Early and Late Stage C-H Activation Protocols for Bioactive Molecules and Direct Conversion of Stilbenes to Diaryl-α-hydroxyacetaldehydes

by

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in

SCIENCE

Under the supervision of

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Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled *"Early and Late Stage C-H Activation Protocols for Bioactive Molecules and Direct Conversion of Stilbenes to Diaryl-α-hydroxyacetaldehydes"* submitted by *Ms. Rupali Gundappa Kalshetti* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.

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Date: 21/05/2021

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Name: Dr. C. V. Ramana
Date : 21/05/2021
Place: Pune

Dedicated to

My Family & Friends

With Lots of Love

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Rupali Kalshetti

ABBREVIATIONS AND ACRONYMS

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
Cat.	Catalytic
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
CH_3CN	Acetonitrile
Conc.	Concentrated
DCE	1,2-Dichloroethane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DMA	Dimethylacetamide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DTBP	Di-tert-butyl peroxide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
PhMgBr	Phenyl magnesium bromide
^{n}BuLi	*n*-Butyl lithium
HRMS	High Resolution Mass Spectrometry
AcOH	Acetic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
NaH	Sodiumhydride
NBS	N-bromosuccinimide
HFIP	Hexafluoro-2-propanol
CTAB	Cetyltrimethylammonium Bromide
Ph	Phenyl
Py	Pyridine

ABBREVIATIONS AND ACRONYMS

AgOAc	Silver acetate
TBHP	*tert*-Butyl hydroperoxide
TIPS	*Triisopropylsilane*
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
TBAI	Tetra-n-butylammonium iodide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
PPh_3	Triphenylphosphine
rt	Room Temperature
sat.	Saturated
^{t}BuOK	Potassium tertiary butoxide
TBAF	Tetra-n-butylammonium fluoride
THF	Tetrahydrofuran
AMLA	Ambiphilic Metal Ligand Activation
CMD	Concerted Metallation-Deprotonation
DG	Directing group

Abbreviations used for NMR spectral informations:

br	broad	s	singlet	dt	doublet of triplets
d	doublet	t	triplet	ddd	doublet of doublet of doublets
m	multiplet	q	quartet	ddt	doublet of doublet of triplets
quint	quintet	sept	septet	tt	triplet of triplets

GENERAL REMARKS

- All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. The anhydrous solvents were distilled prior to use: CH_2Cl_2, DCE and DMF from CaH_2; methanol from Mg cake; THF on Na/benzophenone; triethylamine and pyridine over KOH; acetic anhydride from sodium acetate.

- ^1H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL- 400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL- 100 (100 MHz) and DRX–125 MHz spectrometer.

- High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.

- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I2, and anisaldehyde in ethanol as developing agents.

- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50 °C unless otherwise specified.

- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENT

CONTENT

SYNOPSIS

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	**Ms. Rupali Gundappa Kalshetti**
AcSIR Enrolment No. & Date	**10CC17J26013; January 2017**
Faculty	**Chemical Sciences**
CSIR Lab Affiliated with	**Division of Organic Chemistry, CSIR-NCL, Pune**
Title of the Thesis	**Early and Late Stage C-H Activation Protocols for Bioactive Molecules and Direct Conversion of Stilbenes to Diaryl-α-hydroxyacetaldehydes**
Research Supervisor	**Dr. C. V. Ramana (CSIR-NCL, Pune)**

Keywords: **Ir/Rh catalysed C-H activation, Oxidative Rearrangement**

1. Introduction and Statement of Purpose:

In recent years, transition metal catalysed direct/directed C-H activation strategies have gained importance in synthetic organic chemistry. In particular, directed C-H activation has become a very popular and a useful method to synthesize a large number of aromatic as well as heteroaromatic compounds of interest.[1] In this context, the synthesis of molecules that bear suitable directing groups, particularly their late stage functionalization (LSF) *via* C-H activation strategies has become an important tool to build focused libraries of organic scaffolds of small drug molecules and also of complex polymers.[2]

2,2-diraylacetaldehydes represent a highly functionalized core with the potential for various ring annulations. Despite this, due to their ready deformylation, the methods for their synthesis are scarce and there are only a limited number of reports on their utility in organic synthesis. This warrants the development of reliable methods for their synthesis and the demonstration of their utility in natural product synthesis.[3] One of the simple possibilities in this context is their two carbon Wittig-Gennari olefination and intramolecular lactonization leading to a 5,5-diarybutenolide core – a popular synthetic target in natural products synthesis.[4]

2. Objectives:

a) The synthesis of alkynyl quinozolin-4-ones employing iridium(III) catalysed directed C-H activation.

b) The use of early and late stage C-H activation strategies to build focussed small molecule libraries around the recently launched sickle cell anemia drug Voxelotor (GBT 440).

c) Tuning the oxidative rearrangement of stilbenes towards diarylhydroxyacetaldehydes.

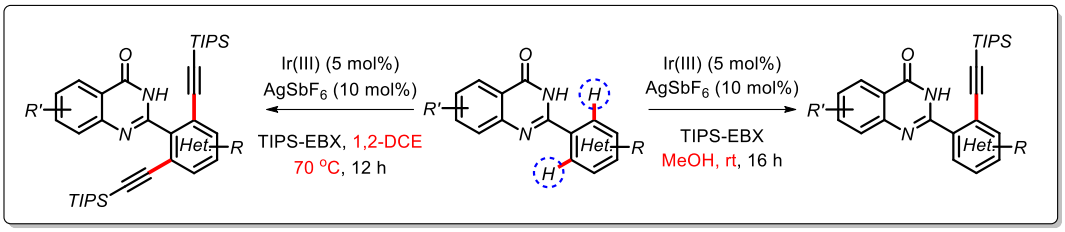
3. Methodology:

This thesis deals with the development of new methodologies that involve C–C/C–heteroatom bond formations. The thesis comprises of three chapters, where the first chapter contains Iridium(III)-catalysed selective mono-/dialkynylation of 2-(hetero)arylquinazolin-4-one scaffolds *via* directed C–H bond activation. The second chapter deals with the building of focused small molecule libraries around the recently launched sickle cell anemia drug Voxelotor (GBT 440) employing early and late-stage C-H functionalization. The third chapter describes the direct conversion of stilbenes to diaryl-α-hydroxyacetaldehydes and their utility in the synthesis of 5,5-diarybutenolides.

Chapter I: <u>Iridium(III)-Catalysed Alkynylation of 2-(Hetero)arylquinazolin-4-one Scaffolds *via* C–H Bond Activation</u>:

Alkynes are an important class of functional groups that can be introduced traditionally, by using transition metal catalyzed cross coupling reactions. Recently, some alternative catalytic reactions have been reported that facilitate C-H bond activation without the necessity of pre-functionalization of the substrate. The directed C-H alkynylation is considered as an important alternative to the Sonogashira reaction.[5] Coming to the directed C–H functionalization of the pendant aryl ring present in the 2-arylquinazolin-4-one core, the latest report of C-H bond activation on 2-(Hetero)arylquinazolin-4-ones was published by Cui *et al.* in 2018, which documented the C-H amination using iridium (III) complexes.[6] Prior to that arylation, alkenylation and cross dehydrogenative coupling with acrylates and acetylation on 2-(Hetero)arylquinazolin-4-ones have been reported using [Pd], [Ru], [Rh] and [Cu]-complexes by various research groups until 2018.[7] This compilation of the C–H functionalization of 2-arylquinazolin-4-ones revealed that the corresponding directed

alkynylation *via* C–H bond functionalization on these scaffolds is unknown, which prompted us to explore in this direction. In this chapter, we have established the directed C–H alkynylation of 2-(hetero)arylquinazolin-4-ones with the ethynylbenziodoxolone reagent (TIPS-EBX) employing an Ir(III)-catalyst. Conditions for both monoalkynylation as well as dialkynylation have been developed with a variety of substrates having higher yields for all the compound synthesized.



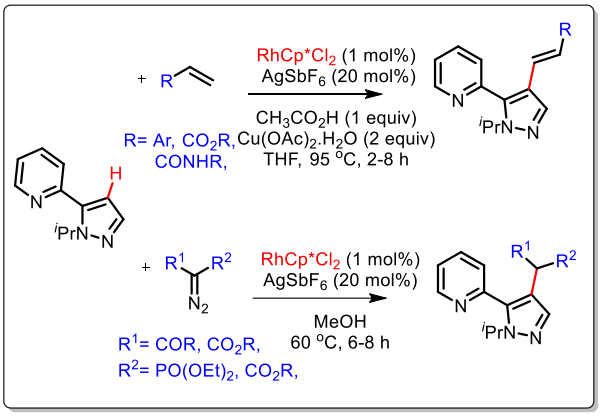
Chapter II: <u>Building focussed small molecule libraries around Voxelotor (GBT 440) *via* early and late stage C-H functionalization</u>:

Sickle-cell anaemia (SCA) is a chronic disorder prevalent mainly in the scheduled population. India is estimated to have the second highest burden of the disease, with highest prevalence in the socioeconomically disadvantaged communities such as the tribal population, which accounts for 8.5% of the total Indian population.[8] Along with the difficulties associated with its diagnosis, the treatment of SCA is hampered because of the lack of available medicines. Hydroxyurea is the only drug that has been used for the treatment of SCA, though paracetamol or ibuprofen is prescribed for pain relief. Voxelotor (GBT 440) is a very recently introduced drug for the treatment of Sickle cell anemia that acts by inhibiting haemoglobin S (HbS) polymerization.[9] In 2017, as part of the GoI National Sickle Cell Anemia Control Program, an initiative has been taken to identify novel drug candidates for SCA. GBT 440, which was in Phase III clinical trials (renamed as Voxelotor after its approval in 2020), has been selected as a promising scaffold in this regard.

The structure of the Voxelotor presents three interesting scaffolds, pyridine, pyrazole and a salicylaldehyde that are linearly linked. Keeping the C-H functionalization as a key tool, we have opted to build GBT 440 like scaffolds by the olefination of the pyrazolylpyridine scaffold and also by the direct late stage functionalization of GBT 440.

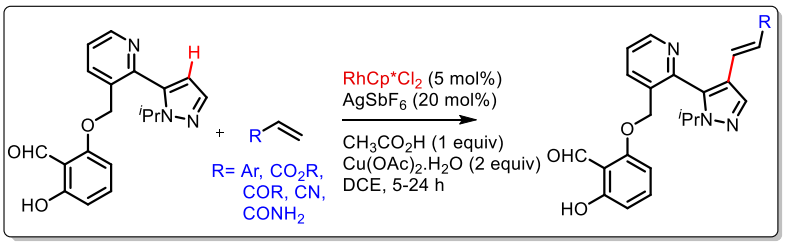
Section I: <u>Rhodium(III)-Catalysed Alkenylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine Scaffolds *via* C–H Bond Activation</u>:

In this section, the directed C–H alkenylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine with the alkenes, acrylates and amides employing a Rh(III)-catalyst has been described. The broad scope of this reaction and the compatibility of various functional groups such as -F, -Cl, -Br, -OMe, -NO_2, alkyl, acrylates and amides has been explored to synthesize a focussed library having functional group variations on the newly introduced styryl ring. Simultaneously, the directed C–H alkylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine has been explored using the corresponding diazo compounds, which include ketoesters, phosphonates, diesters and TIPS-EBX, by employing a Rh(III)-catalyst.



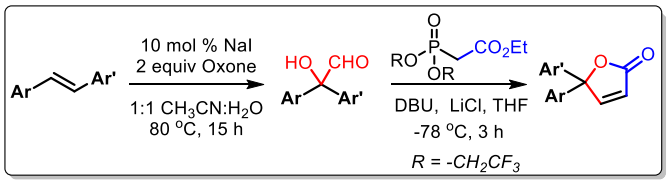
Section II: <u>Functionalization of the Pyrazole unit of GBT 440 *via* C–H Bond Activation</u>:

Considering the possibility that further derivatization of the drug could show better activity than the GBT-440 itself, we began our endeavor by carrying out the directed C–H alkenylation of GBT-440 with alkenes, acrylates, amides etc. by employing a Rh(III)-catalyst. Simultaneously, we also explored the broad scope and compatibility of various functional groups such as -F, -Cl, -Br, -OMe, -NO_2, alkyl, acrylates, amides, ketones, aldehydes etc. Biological evaluation of synthesized compounds revealed good results, especially for a 4-Chloro substituted GBT-440 compound that showed higher activity than the GBT-440 itself.



Chapter III: Oxidative Rearrangement of Stilbenes to 2,2-Diaryl-2-hydroxyacetaldehydes:

In 2012, Fry and coworkers documented the anodic oxidation of diphenylacetaldehyde leading to benzophenone and proposed a mechanism for its formation, with α-hydroxydiphenylacetaldehyde as an intermediate.[10] Given the potential of the α-hydroxydiarylacetaldehyde core as a building block in synthesis and the scarcity of methods available for its synthesis, we speculated on the possibility of synthesizing α-hydroxydiphenylacetaldehyde *via* controlled oxidation of stilbenes. Our successful efforts in this direction culminated in the development of a one-pot iodine-catalyzed oxone-mediated oxidative rearrangement of stilbenes leading to 2,2-diaryl-2-hydroxyacetaldehydes. With the help of control experiments, we have found that the intermediate diarylacetaldehyde undergoes α-hydroxylation, with oxygen being transferred from the water present in the reaction. The resulting α-hydroxy aldehydes have been subjected for a one-pot Stille-Gennari olefination followed by cyclisation leading to 5,5-diaryl-γ-butenolides



4. Summary:

a) Successfully developed [Ir]-catalysed ortho-alkynylation of 2-(hetero)arylquinazolin-4-ones with TIPS-IBX. Suitable conditions for both monoalkynylation as well as dialkynylation have been identified.

b) Established the pyridine directed C-H activation protocol for the selective alkenylation/alkylation of the pyrazole ring using a Rh(III) catalyst.

c) Late stage functionalization of GBT-440 has been successfully executed to synthesise a variety of analogues and potential candidate that is more active than GBT-440 has been identified.

d) Developed a simple methodology for the synthesis of 2,2-diaryl-2-hydroxyacetaldehydes *via* oxidative rearrangement of stilbenes and the utility of these derivatives has been been examined for the synthesis of γ-butenolides.

5. Future direction:

a) As part of the utility of the synthesized alkynylquinozolinones, we have established protocols for regioselective intramolecular cyclizations. Extending the scope of these reactions is expected to deliver diverse tetracyclic scaffolds with potential bioactivity.

b) The late-stage functionalization of GBT-440 is quite successful in identifying a better candidate. This can be further explored to introduce some popular functional groups such as trifluromethyl, fluro and sulphone that are trivially employed in medicinal chemistry programs.

c) The oxidative rearrangement that we have developed is quite novel and has the potential, when explored with other disubstituted olefins, to synthesize highly functionalized carbonyl compounds. In addition, one of the 2,2-diaryl-2-hydroxyacetaldehydes that we have synthesized could be used directly for securing a new synthesis of sacidumlignan D.

6. Publications:

1. Rohokale, R. S.; Kalshetti, R. G.; Ramana, C. V. *J. Org. Chem.* **2019**, *84*, 2951–2961.
2. Kalshetti, R. G.; Ramana, C. V. *ACS Omega* **2020**, *5*, 25199–25208.

7. References:

1. Li, X.; Ouyang, W.; Nie, J.; Ji, S.; Chen, Q.; Huo, Y. *ChemCatChem* **2020**, *12*(9), 2358-2384.
2. Wencel-Delord, J.; Glorius, F. *Nature Chem* **2013**, *5*, 369–375.
3. a) Sharma, A.; Sharma, N.; Kumar, R.; Sharma, U. K.; Sinha, A. K. *Chem. Commun.* **2009**, *35*, 5299–5301. b) Peraka, S.; Reddy, M. M.; Mameda N.; Macharla, A. K.;, Kodumuri, S.; Chevella, D.; Nama, N. *Adv. Synth. Catal.* **2015**, *357*, 1125–1130. (c) Pettit, G. R.; Lippert, J. W.; Herald, D. L. *J. Org. Chem*. **2000**, *65*, 7438.
4. a) Rao, Y. S. *Chemical Reviews*, **1976**, *76*, 5. 625-694. b) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502−10566.
5. (a) Caspers, L. D.; Nachtsheim, B. J. *Chem. Asian J.* **2018**, *13*, 1231–1247. (b) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787. (c) Li, X.; Wu, G.; Liu, X.; Zhu, Z.; Huo, Y.; Jiang H. *J. Org. Chem*. **2017**, *82*, 13003−13011. (d) hen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. *Org. Lett.* **2017**, *19*, 2474−2477.
6. Feng, Y.; Li, Y.; Yu, Y.; Wang, L.; Cui, X. *RSC Advances* **2018**, *8*, 8450–8454.
7. (a)Yu, Y.; Yue, Y.; Wang, D.; Li, X.; Chen, C.; Peng, J. *Synthesis* **2016**, 48, 3941–3950. (b) Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Xuan, L.-J. *Org. Biomol. Chem.* **2015**, *13*, 6474–6478. (c) Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906–8913.

(d) Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem.* **2015**, 7705–7717.

8. (a) Serjeant, G. R.; Ghosh, K.; Patel, J. Indian *J Med Res*. **2016**, 143, 21-24. (b) Colah, R. B.; Mukherjee, M. B.; Martin, S.; Ghosh, K. *Indian J Med Res*. **2015**, *141*, 509-515.
9. (a) Aldallal, S. M. *Cureus* **2020**, *12*, DOI 10.7759/cureus.7105 (b) Han, J.; Saraf, S. L.; Gordeuk, V. R. *Pharmacotherapy* **2020**, *40*, 526-534.
10. Merzel, R. L.; Fry, A. J. *J. Electrochem. Soc.* **2012**, *159*, G117-G122.

CHAPTER I

Iridium(III)-Catalysed Alkynylation of 2-(Hetero)arylquinazolin-4-one Scaffolds *via* C–H Bond Activation

1.1 Introduction:

Nitrogen-containing heterocyclic compounds embrace a large section of biologically important structural motifs abundantly found in natural products, pharmaceuticals and agrochemicals.[1] This, indeed, has been responsible for a larger research focus on the synthesis of N-heterocyclic compounds over the last two centuries.[2] In fact, 60-70% of the currently marketed drug molecules consist of at least one nitrogen-containing heterocyclic unit in their entire structure.[3] Quinazoline is one such privileged skeleton that is widely found in various natural products and is an important heterocyclic moiety that had been explored in various drug discovery programs such as anti-fungal,[4] anti-bacterial,[5] anti-cancer,[6] anti-inflammatory,[7] anti-hypertensive, anti-convulsant,[8] and anti-proliferative[9] chemistry. Interestingly, the quinazoline scaffold was synthesized much earlier by Gries and co-workers in 1869 (4-cyanoquinozolinone was synthesized from the reaction of anthranilic with cyanogens) before the documentation of the first member of this family vasicine, which has its own Indian origin.[10] Vasicine, also known as peganine, was isolated in 1888 from the Indian medicinal tree *Adhatoda vasica* and later from other species. So far, close to 200 quinazoline alkaloids have been isolated, thus making this as a special class of the alkaloids family with broad biological activities displayed, with the quinazoline scaffold being considered as a promising scaffold in drug discovery programs. Some representative examples of the drug molecules and biologically active molecules consisting of the quinazoline or its oxidized version quinazoline-4-one scaffolds are depicted in **Figure F1.1**. From the number of examples provided, it becomes apparent that the quinazoline and quinazolinone are quite popular scaffolds in medicinal chemistry and advancements in this domain, especially in novel approaches to constructing these scaffolds, and also functionalizing these scaffolds are equally important. As the focus of this chapter is going to be mainly on the alkynylation of 2-arylquinazolinones *via* C–H activation, a brief compilation of methods for the synthesis of 2-arylquinazolinones, a brief introduction to C–H activation followed by a brief description about the documented work on the functionalization of 2-arylquinazolinones *via* C–H activation, and finally the details about the alkynylation *via* C–H activation will be presented.

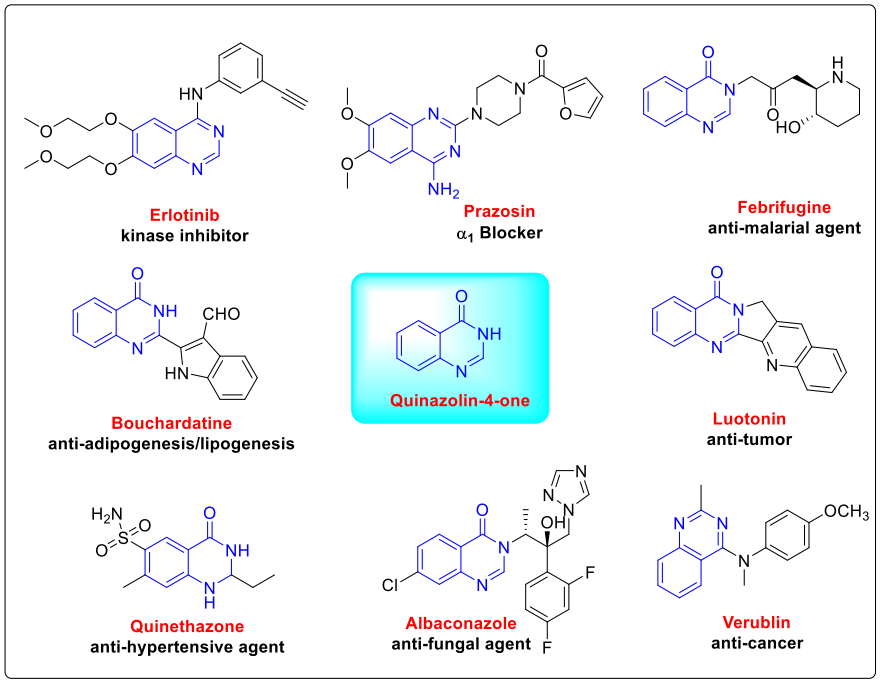


Figure F1.1: *Representative examples of bioactive quinazolinone and quinazoline based molecules, and drugs.*

1.2 Advanced synthetic strategies for building 2-arylquinazolin-4-one scaffolds: The significance of quinazolinone scaffolds in biological and medicinal areas has attracted many a chemist's interest to synthesize compounds containing the quinazolinone ring, as they are the precursors of around 200 naturally found alkaloids. The traditional way to make these quinazolinone rings is to employ the 2-aminobenzoic acids or related derivatives such as 2-amino benzamide, isatoic anhydride, 2-amino benzonitrile, 2-carbomethoxyphenyl isocyanate, N-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as appropriate starting materials that undergo condensation reactions with aldehydes or carboxylic acids in the presence of a dehydrating agent or in some cases by providing heat. Amongst the vast literature documented on the 2-aryl-quinazoline-4-one synthesis, some of the important methods are listed below in **Table T1.1**.

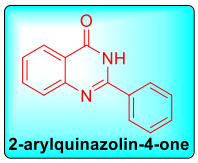
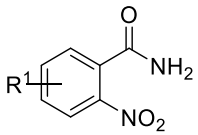
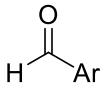
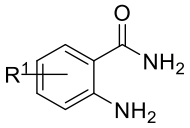
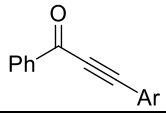
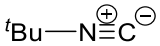
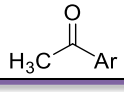
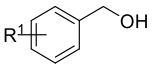
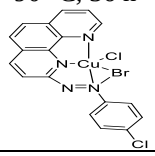
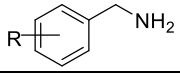
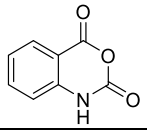
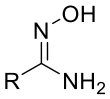
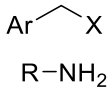
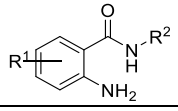
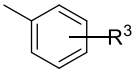
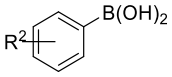
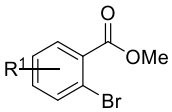
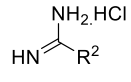
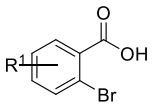
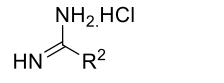
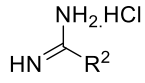
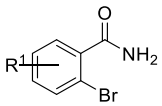
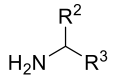
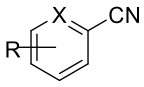
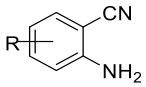
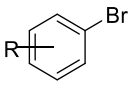
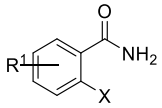
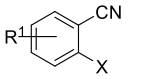
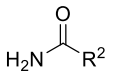
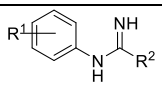
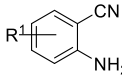
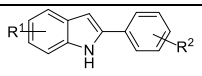
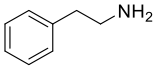
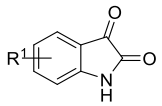
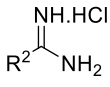
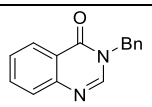


Table T1.1: *Literature reports for the synthesis of 2-aryl quinozoline-4-one*

Sr. No.	Starting material	Coupling partner	Reaction condition	Yield (%)	Reference
1			$Na_2S_2O_4$ DMF-H_2O(9:1) 90 °C, 5 h	65-92	*Synthesis* **2013**, *45*, 2043.
2			$FeCl_3$, TBHP, DMSO, 60 °C, 7 h	37-93	*RSC Adv*. **2014**, *4*, 6486.
3			[Cp*$IrCl_2$], xylene, reflux, 24-120 h	50-94	*J. Org. Chem.* **2011**, *76*, 7730.
4			CuBr, K_2CO_3, DMSO, 120 °C, 24 h	39-99	*Synthesis* **2013**, *45*, 3349.
5			ZnI_2, TBHP, DMSO, 110 °C, 16 h	60-90	*RSC Adv*. **2014**, *4*, 8.
6			α-MnO_2-150, TBHP, chlorobenzene, 80 °C, 16 h	71-99	*Chem. Commun*. **2015**, *51*, 9205.
7			I_2, DMSO, DMC, 100 °C, 12–26 h	41-93	*RSC Adv*. **2013**, *3*, 10817.
8			Pt/HBEA, mesitylene, reflux, 24 h	65-95	*Catal. Sci. Technol.* **2014**, *4*, 1716.
9			$Ru(PPh_3)_3(CO)(H)_2$, xantphos, crotononitrile, toluene, reflux, 24 h	40-85	*Org. Biomol. Chem*. **2012**, *10*, 240.
10			KOH, air, toluene, 90 °C, 20 h	48-98	*Monatsh. Chem*. **2015**, *146*, 1343.
11			$Pd(OAc)_2$, TPPMS, H_2O, 120 °C, 16 h	65-96	*J. Org. Chem*. **2012**, *77*, 7046.
12			I_2, DMSO, 110 °C	48-81	*Org. Lett*. **2013**, *15*, 378.
13			TFA, Toluene, 90 °C, 16 h	45-98	*Org. Chem. Front*. **2015**, *2*, 366.
14		ArBr	$Pd(OAc)_2$, $BuPAd_2$, DMF, DBU, CO, 120 °C, 16 h	43-96	*Chem. Eur. J.* **2013,** *19*, 12635.
15		ArI	 $PdCl_2$, DPPP, $CaCl_2$, ^{t}BuONa, Toluene, 145 °C, 8 h	41-93	*J. Org. Chem*. **2014**, *79*, 5082.
16		ArCHO or Het-CHO	DMSO, 120 °C, 16 h, Open flask	42-86	*Tetrahedron Lett.* **2014**, *55*, 2340.
17			I_2, O_2, DMSO, 110 °C, 16 h	50-82	*J. Org. Chem.* **2015,** *80*, 6915.

18			DMSO, 140 °C, 16 h, O_2, 4-8 h	14-83	*Tetrahedron* **2016**, *72*, 1330.
19			[Ni(MeTAA)] Na^tOBu, Xylene, 100 °C, 36 h	24-90	*J. Org. Chem.* **2017,** *82*, 7165.
20			Toluene, NaOH, 90 °C, 36 h 	35-95	*J. Org. Chem.* **2019**, *84*, 10160.
21		 R = Ar, Het, Nap	$Pd(TFA)_2$, bpy, DMSO, 100 °C, O_2, 12 h	37-85	*Org. Chem. Front.*, **2018**, *5*, 2734.
22			$K_2S_2O_8$ ACN: H_2O, 6 h, rt	72-94	*ChemistrySelect* **2017**, *2*, 4963.
23		ArCHO	$Ga(OTf)_3$, NH_4OAc DMSO, 85 °C 50-70 min,	79-92	*Tetrahedron Lett*. **2008**, *49*, 3814.
24			$FeCl_3$, 1, 4-dioxane, 80 °C, 2-8 h	78-93	*Synlett* **2014,** *25*, 821.
25			K_2CO_3, DMSO, 90 °C, 6 h	90-97	*Synlett* **2012**, *23*, 85.
26			DTBP, TsOH DMSO, 110 °C 20 h	26-92	*Chem. Commun.* **2014**, *50*, 6471.
27		ArCHO	*p*-TsOH, THF, rt, 10 min, PIDA, rt, 1 h	47-92	*Synthesis* **2013,** *45*, 2998.
28			^{t}-Bu-NC $Pd(PPh_3)_2Cl_2$ $Cu(OAc)_2$ DMF, 100 °C	43-97	*J. Org. Chem.* **2018**, *83*, 9201.
29		 R^2 = Me, Pr, Ph	CuI, L-Proline Cs_2CO_3, DMF 80 °C	74-95	*Chem. Commun.* **2008**, 6333
30		 R^2 = alkyl, aryl, amine	CuI, Cs_2CO_3, DMF rt	40-97	*Angew. Chem. Int. Ed*. **2009**, *48*, 348.
31		 R^2 = alkyl, aryl	$FeCl_3$, Cs_2CO_3, DMF, 120 °C	60-82	*J. Comb. Chem.* **2009**, *11*, 653.
32		 R^2 = alkyl, aryl R^3 = COOH	CuBr, K_2CO_3, air, DMSO, 110-120 °C	43-84	*Org. Lett*. **2011**, *13*, 1274. *J. Org. Chem.* **2011**, *76*, 3846.

33		 X = C, N	$Cu(OAc)_2$, ^tBuOK, ^tBuOH, 100 °C, 16 h	25-84	*J. Org. Chem.* **2018**, *83*, 10352.
34		R−CHO R−CH_2OH Ar−CH_3	$TMSN_3$ Air or TBHP CuI, DMSO, 80 °C	41-89	*J. Org. Chem.* **2016**, *81*, 5046.
35			$Pd(OAc)_2$, $BuPAd_2$, K_2CO_3, DMSO/H_2O	55-86	*Green Chem.*, **2014**, *16*, 1336.
36	 X = I, Br, Cl	 R^2 = Me, allyl, Phenyl, benzyl	CuBr, K_2CO_3, air, DMF, 120 °C, 24 h	21-73	*Eur. J. Org. Chem.* **2014**, 2682. *Chin. Chem. Lett.* **2015**, *26*, 369.
37	 X = I, Br, Cl R^1 = H, F, Me, NO_2 OMe, CF_3	 R^2 = alkyl, aryl	CuI, NaOH, NMP, 120 °C, 12 h	52-85	*RSC Adv*. **2014**, *4*, 44811.
38	 R^1 = H, Me, OMe R^2 = alkyl, benzyl, aryl	-	$Pd(OAc)_2$, CuO, CO, AcOH, 110 °C	53-81	*J. Org. Chem.* **2011**, *76*, 6362.
39	 R = H, Me, OMe Cl, F;	ArBr	$Pd(OAc)_2$, $BuPAd_2$, DMSO/H_2O, CO, K_2CO_3, 120 °C, 16 h	30-91	*Green Chem.* **2014**, *16*, 1336.
40			CuBr, NMP, O_2, 80 °C	51-96	*J. Org. Chem.* **2015**, *80*, 7099.
41			TBHP K_3PO_4 DMSO, rt	42-90	*Org. Lett*. **2016**, *18*, 2942.
42		ArI	LiO^tBu CuI $Pd(OAc)_2$ DMF, 120 °C, µW, 10 min	14-96	*Org. Lett*. **2015**, *17*, 1700.

1.3 C–H Activation: In the recent past, catalytic C–H activation has become a broadly applied strategy across various domains of organic synthesis.[11] C–H activation involves activating the non-acidic C–H bond by metal coordination using different mechanisms, depending on the substrate. Ar–Ar coupling *via* C–H activation has been recognized as an alternative sustainable/green approach for the traditional cross-coupling reactions. In addition, a wide range of classical organic reactions such as alkylation, hydroxylation, acylation, alkoxy-carbonylation, alkenylation, amination, amidation, alkynylation, borylation and hydroxyamination have been explored *via* C–H

activation to synthesize a variety of molecules with high diversity. The major difference between traditional cross coupling and cross coupling *via* C–H activation is that the former requires pre-activation while the latter does not, in most of the cases. Although some reactions require one coupling partner to be activated, cross dehydrogenative coupling reactions do not require preactivation of the coupling partners.

C–H bond activation and C–H bond functionalization are two different concepts, as the first reaction is reversible while the second is irreversible. The concept of C–H functionalization when applied to organic molecules precludes the extra efforts required for the prefunctionalization, which avoids generation of waste and thus can be utilized for the synthesis of complex molecules *via* late stage functionalization. There are many transition metals that are used to carry out this type of C–H activation, such as Pd, Ni, Co, Rh, Ir, Ru, Re, Fe, as these metals have high reactivity towards C–H bonds. However, some challenges are also associated with these reactions, as we cannot get the reactivity of the particular C–H bond, which forces us to apply harsh conditions. To avoid such issues researchers have started using directing groups for these transformations.

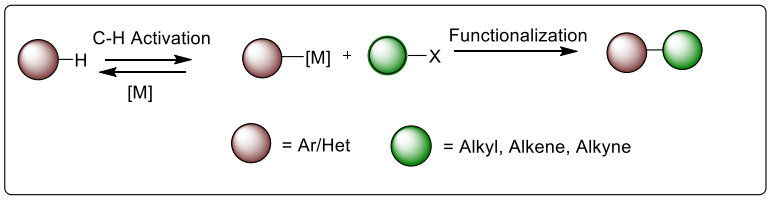


Figure F1.2: Representation of the C–H activation and functionalization concept.

1.4 Direct/Directed C–H Activation:

Direct C–H activation is a concept wherein the reaction proceeds without the involvement of any directing group. Direct C–H activation is a widely used method, as it does not require the addition and removal of directing groups in the reaction, which minimises the reaction steps. Although this method looks easy, it is not very popular, because of the low selectivity of C–H bonds, which results in unwanted products. Therefore, the advanced version of C–H bond activation includes the installation of the directing group to increase the selectivity, and is known as directed C–H bond activation. In this, the metal co-ordinates to the directing group initially and forms the metallacycle, which allows the activation of the proximal C–H bond with ease (**Figure F1.3**). The

advantages associated with this method are: the coordination ability of the metal to the substrate, regioselectivity, and most importantly, activation of the desired C–H bond. Due to these advantages, this method has gained a lot of attention and popularity in the field of synthetic organic chemistry. Even though the installation and removal of the directing groups increases the number of the steps, it is essential to the reaction, as it predominantly gives us the formation of desired products. Nowadays, scientists are exploring new avenues of directed C–H bond activation by using the substrate itself as the directing group for product formation. In this regard, a lot of research has been conducted to design various substrates that will act as directing groups in the reaction, thus avoiding the need to install the directing groups externally. This is possible mainly by the use of heterocyclic substrates that act as directing groups, thereby undergoing the directed C–H activation, which gives rise to the formation of biologically active compounds and analogues of important natural products. Aligning ourselves with these interests and thought processes, we have aimed to employ the directed C–H activation protocol to build a library of biologically active compounds.

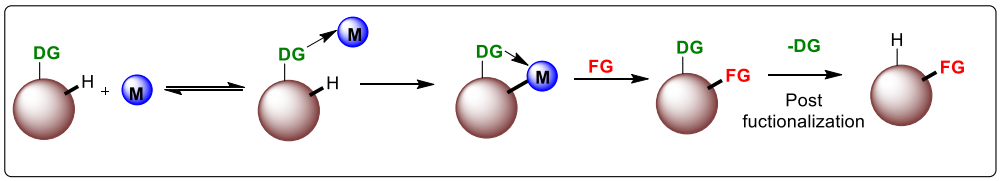


Figure F1.3: *Representation of directing group assisted C–H activation.*

1.5 Directing groups:[12] A potential directing group has various requirements that need to be fulfilled. The main requirement is the strict necessity of proximity of the directing group (DG) to achieve the selective activation of C–H bonds. It must be electron-donating enough for co-ordination with the transition metal. The DGs commonly employed are Lewis bases that should be labile or semi-labile ligands, so that they do not block a coordination site at the metal center permanently. Achieving good reactivity and selectivity in some cases has proved to be very challenging - so the use of donor groups as directing groups is necessarily required in such cases. Nowadays, the trend is to use the directing groups as substrates themselves for conducting the C–H activation, which includes bipyridyl, amides and carbonyls, sulfoxides, quinoline-N-oxide and pyrrole. Till date, a diverse collection of directing groups have been documented that comprise of amides, amines, imines, carboxylic acids, ketones, esters and hydroxyl groups. (**Figure F1.4**) These

directing groups are used to do modifications such as arylations, aminations, alkylations, alkenylations and alkynylation reactions.

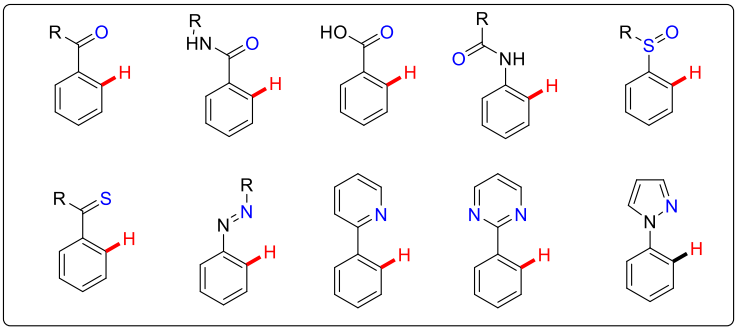
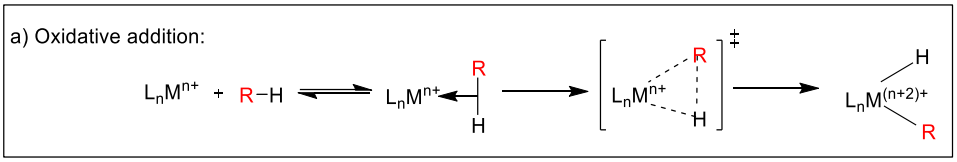


Figure F1.4: *Most used directing groups for C–H activation.*

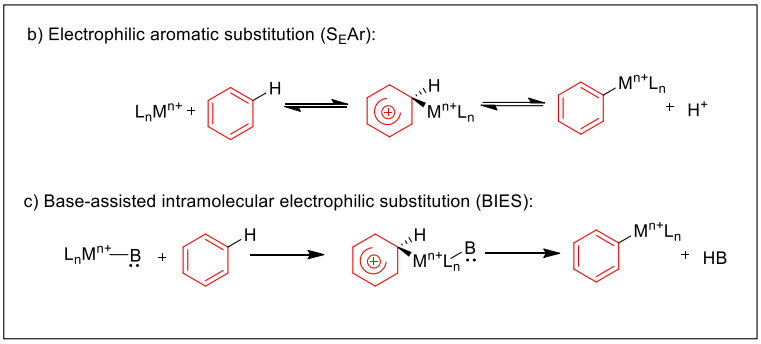
1.6 Mechanism of C–H activation:[13] There are five different types of mechanisms proposed for the activation of the C–H bonds. There are as follows:

1. Oxidative addition: It is the insertion of an electron rich metal between a C–H bond. By interacting strongly in a synergistic fashion, the σ C–H bond coordinates with the metal by dπ-back donation to the σ* C–H orbital, which results in an overall lowering of the bond energy, thus leading to the cleavage of the C–H bond. As the C–H bond cleaves, there is formation of a new M–C bond and M–H bond through a three-membered transition state. This oxidative addition mechanism is mainly for electron-rich, low-valent complexes of the late transition metals (Re, Fe, Ru, Os, Ir, and Pt) as the formation of the new bonds and increase in the oxidation state of the metal in the transition state are energetically favourable.

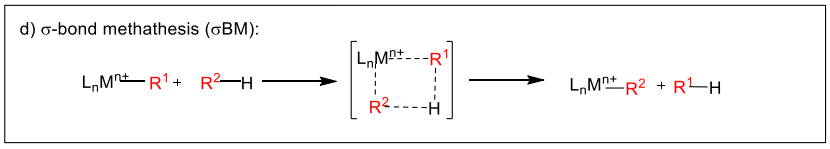


2. Electrophilic aromatic substitution (base-assisted intramolecular electrophilic substitution): This mechanism proceeds through the electronic interaction of the electrophilic metals that behave as Lewis acids, with the π-electronic cloud of the substrate generating the cationic complex C(aryl)–M bond without changing the oxidation state of

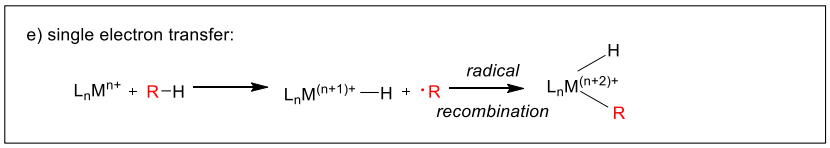
the metal. This leads to an increase in the acidity of the C–H bond, which facilitates the deprotonation by re-aromatization on reacting with the base. Generally, the base is associated at the coordination sphere of the metal complex. This mechanism is also called the base assisted intramolecular electrophilic type substitution.



3. σ–Bond metathesis: This type of mechanism mainly occurs with electron deficient metals having high oxidation states. It proceeds *via* the formation of two new sigma bonds and cleavage of two old sigma bonds through a concerted four-membered transition state without increasing the oxidation state of the metal. In this mechanism, the M–H species is not observed and thus it directly leads to the formation of the M–R^2 and the R^1–H bond.

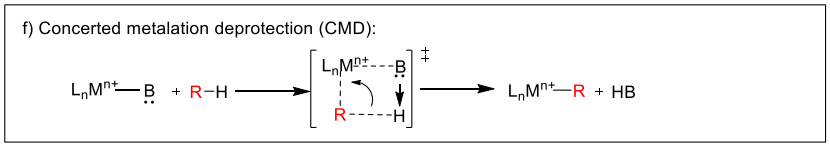


4. Single electron transfer (SET): This mechanism involves the homolytic cleavage of the C–H bond, which results in the formation of a metal hydride and a carbon radical. The carbon radical on recombining with the metal center gives the alkyl or aryl hydride metal oxidized species.



5.Concerted metalation deprotonation (CMD): In this type of mechanism, there is a combined interaction of the metal and ligand with the C–H bond, which results in the deprotonation by the intramolecular base that is associated with the metal center in a

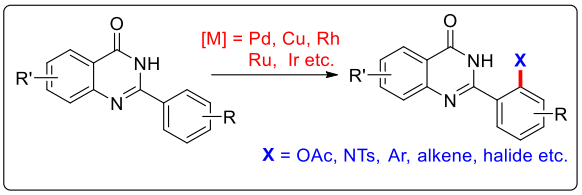
concerted way, so that the M–C bond is formed. Here, the C–H activation occurs on the bond that is present in close proximity to the metal center and the directing group. This type of mechanism is very diverse, as it includes a variety of metals and directing groups.



1.7 Directed C–H activation on the arylquinazolin-4-one scaffold:

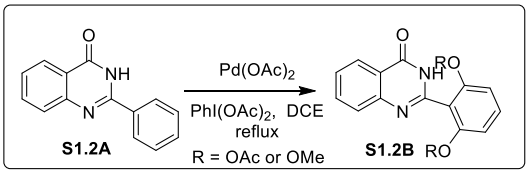
As mentioned previously, the quinazoline and quinazolinone scaffolds have been widely employed by medicinal chemists for the development of new drugs or drug candidates. Integrated with the pyrimidine core and the provision of a fused aryl ring, along with the possible pendant aryl/alkyl groups at C2/N3, these scaffolds offer multiple sites for C–H functionalization with an inbuilt directing group. This allows a handle for the post modification *via* C–H activation. Thus providing an easy approach for generating the focused libraries around these quinazoline/quinazolin-4-one scaffolds. This possibility has been well explored for the arylation, acetoxylation, halogenation, alkenylation and sulphamidation reactions on these scaffolds. Many groups have utilized the pendant aryl ring present in the quinazolin-4-one for the development of new scaffolds by applying the directed C–H activation protocol to enhance the structural diversity and molecular complexity of quinazolines. This has also paved a path for the synthesis of fused N-heterocyclic cores that are found in bioactive quinazolinones and in some natural products.

Directed C–H functionalization of the pendant aryl ring in the 2-arylquinazolin-4-one core has been well explored and, till date, a huge library of compounds containing the quinazolinone core have been synthesized.[14] This was achieved through reactions such as C–H amination, arylation, alkenylation and cross dehydrogenative coupling with acrylates and acetoxylation, documented using [Pd], [Ru], [Rh], [Ir] and [Cu]-complexes. Coming to the reports with [Ir]-complexes, there are very few in this regard (Scheme S1.1). Thus, shown below is a gist of the research work done on quinazolinone rings in the past few years using the directed C–H activation protocol.



Scheme S1.1: *C–H functionalization of 2-Aryl-quinazolin-4-one scaffold by using various transition metals*

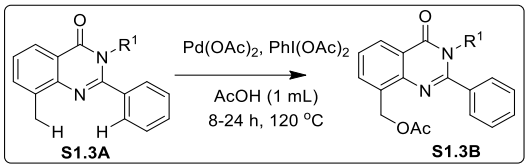
Acetoxylation: The first report of selective oxidative functionalization of aryl-substituted quinazolinones takes into consideration the dual activation of both the amide and the *ortho*-chelating imine group, and was reported by Subba Reddy *et al.* in 2012. They have developed an efficient quinazoline directed acetoxylation and methoxylation of C2-aryl groups using palladium as the catalyst. Here, the acetoxylation was carried out using a 5.0 mol% $Pd(OAc)_2$ catalyst with $PhI(OAc)_2$ as the oxidant in DCE solvent under reflux conditions, to get the monoacetoxylation/methoxylation as well bis-acetoxylation/methoxylation products **S1.2B** in good to excellent yields. (Scheme S1.2).



Scheme S1.2: *Reddy's acetoxy-substituted 4(3H)-quinazolinone synthesis*

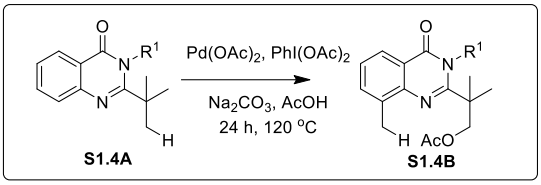
(Reddy, B. V. S.; Narasimhulu, G.; Umadevi, N.; Yadav, J. S. *Synlett* **2012**, *23*, 1364–1370)

Later, in 2017, Mhaske's group developed a complementary method for the acetoxylation of the C8-Me group of the quinazolinone ring. For this transformation, there is a requirement of the protection of the N^3 hydrogen, as it increases the possibility of the acetoxylation of the C8-Me group of the fused aryl ring of the quinazoline instead of the *ortho*-C–H activation of the pendant aryl ring. In this method, the 2-arylquinazolione **S1.3A** undergoes the acetoxylation reaction in the presence of $Pd(OAc)_2$ as catalyst followed by the addition of the $PhI(OAc)_2$ as the oxidant to afford the desired product **S1.3B** in good yields. (Scheme S1.3).



Scheme S1.3: *Mhaske's approach for the C(sp)3 Acetoxylation*
(Garad, D. N.; Mhaske, S. B. *J. Org. Chem.* **2017,** *82*, 10470–10478)

Interestingly, when a *tert*-Bu group is present at the C2 position of the quinazolinone ring, one of its methyl groups gets selectively acetoxylated instead of the C8-Me group (Scheme S1.4).

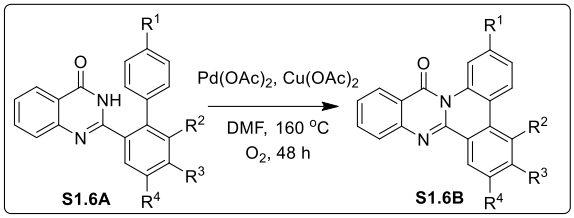


Scheme S1.4: *Mhaske's approach for the C(sp)3 Acetoxylation*
(Garad, D. N.; Mhaske, S. B. *J. Org. Chem.* **2017,** *82*, 10470–10478)

Amination: In 2014, Wu and Chen reported a palladium-catalyzed intramolecular aerobic oxidative C–H amination protocol for the synthesis of indazolo[3,2-b]quinazolinones **S1.5B** from 2-aryl-3-(arylamino)quinazolinones. Detailed mechanistic investigations revealed that the reaction involves the formation of the dimeric palladacycle, which is the key intermediate that undergoes the cascade rollover cyclometalation and C–H amination to derive the product **S1.5B** in good yield. (Scheme S1.5).

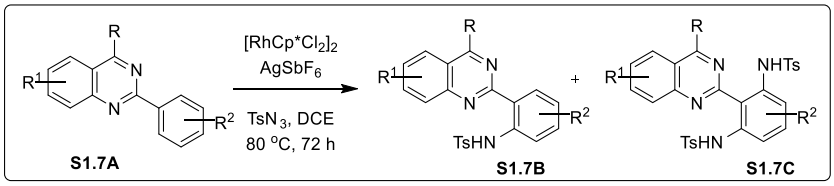
Scheme S1. 5: *Chen & Wu's synthesis of indazolo[3,2-b]quinazolinones*
(Yang, W.; Chen, J.; Huang, X.; Ding, J.; Liu, M.; Wu, H. *Org. Lett*. **2014**, *16*, 5418–5421)

In 2016 Banerji and co-workers disclosed the synthesis of the fused quinazolinones/phenanthridine hetero pentacyclic compounds using Pd-catalyzed aerobic oxidative C–H amination of the strained quinazolinone scaffold **S1.6A**. The utilization of the $Pd(OAc)_2$ and $Cu(OAc)_2$ catalyst combination in DMF as solvent at 160 °C leads to the formation of the fused heterocyclic quinazolinone compounds **S1.6B** in good to excellent yields. (Scheme S1.6).



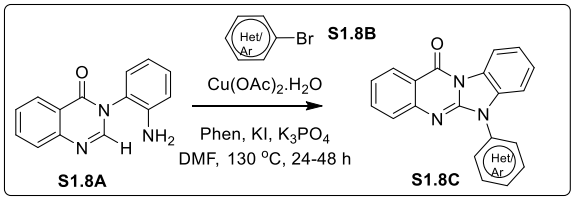
Scheme S1.6: *Banerji's approach for C–H Amination*
(Banerji, B.; Bera, S.; Chatterjee, S.; Killi, S. K.; Adhikary, S. Chem. -Eur. J. 2016, 22, 3506–3512)

In 2015, Peng and co-workers carried out the remarkable rhodium (III) catalyzed C–H amidation of the diarylquinazoline, where sulphonyl azide was used as an amine source to get the regioselective mono or bis amidation of the corresponding quinazoline ring **S1.7A** in DCE as a solvent, which was heated at 80 °C for 72 h to get the required product **S1.7B** or **S1.7C** in good amounts. This reaction showed tolerance of various functional groups such as nitro, fluoro, chloro, and naphthyl during the amidation reaction. (Scheme S1.7).



Scheme S1.7: *Direct C–H Amidation of 2,4-Diarylquinazoline*
(Zhang, C.; Zhou, Y.; Deng, Z.; Chen, X.; Peng, Y. *Eur. J. Org. Chem.* **2015**, 1735–1744)

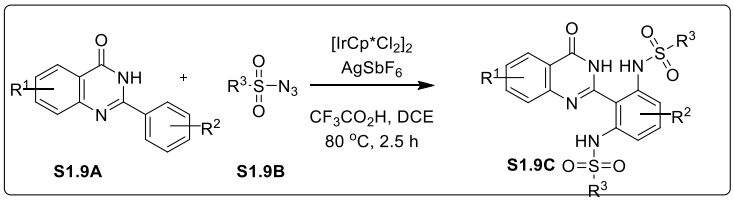
Later in 2016, Kaliappan's group disclosed a copper-catalyzed two-fold cascade C–N bond coupling reaction in between the N-anilinoquinazolinones **S1.8A** and aryl/heteroaryl halides **S1.8B** leading to the formation of N-Aryl benzimidazoquinazolinones **S1.8C**. A variety of benzimidazoquinazolinones have been synthesized in good to excellent yields. (Scheme S1.8).



Scheme S1.8: *Kaliappan's Synthesis of N-Aryl Benzimidazoquinazolinones*
(Banerjee, A.; Subramanian, P.; Kaliappan, K. P. *J. Org. Chem.* **2016**, *81*, 10424–10432)

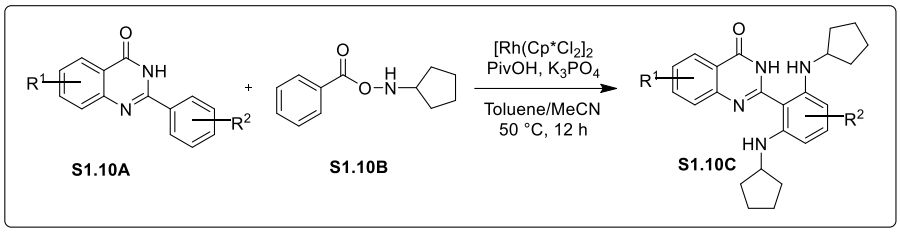
Following this, Cui and co-workers reported a Ir-catalyzed diamination of C2-aryl quinazolin-4-(3*H*)-one **S1.9A** with *para*-toluenesulfonyl azide **S1.9B** leading to the synthesis of

ortho-diamided quinazolinones **S1.9C**. The employed conditions involved the use of an iridium catalyst and $AgSbF_6$ additive in trifluoroacetic acid at 80 °C in 2.5 h and resulted in the formation of a diamide product **S1.9C** in good to excellent yield. In this, the scope of the different substituents present on the quinazolinone, as well as the scope of the substituted sulfonyl azides, has been explored with very good results. (Scheme S1.9).



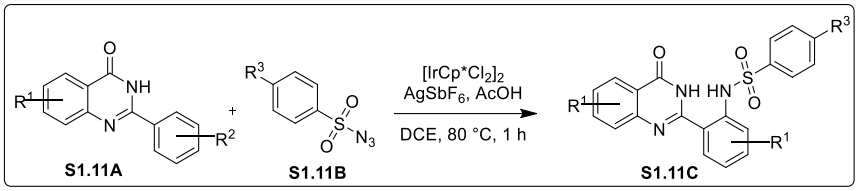
Scheme S1.9: *Iridium catalyzed Direct C–H sulfamidation*
(Feng, Y.; Li, Y.; Yu, Y.; Wang, L.; Cui, X. *RSC Advances* **2018**, *8*, 8450–8454)

In 2018, Peng and co-workers reported the C–H amination of 2-arylquinazolinones **S1.10A**, which reacted with N-alkyl-O-benzoyl-hydroxylamines **S1.10B** in the presence of $[Rh(Cp^*Cl_2)]_2$. PivOH was used as the additive, K_3PO_4 as the base; then the reaction mixture was heated in a toluene/MeCN solvent mixture at 50 °C for 12 h, which resulted in the formation of the diaminated product **S1.10C** in good yields (Scheme S1.10).



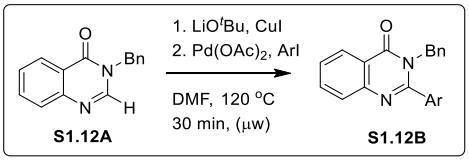
Scheme S1.10: *Rh(III) catalyzed C–H amination of 2-aryl quinazolinones scaffolds*
(Zhang, Y.; Huang, J.; Deng, Z.; Mao, X.; Peng, Y. *Tetrahedron* **2018**, *74*, 2330–2337)

Recently, Cui and co-workers reported the mono-sulfamidation of 2-aryl quinazolinones **S1.11A** using the sulfonyl azide **S1.11B** as the aminating reagent in the presence of an iridium catalyst, with $AgSbF_6$ as the additive in DCE solvent, which was refluxed at 80 °C for 1 h. This resulted in the formation of sulfamidated quinazolinones **S1.11C** in good yields. A series of functionalized mono-sulfamided 2-arylquinazolinones have been synthesized using low catalyst loading. (Scheme S1.11).



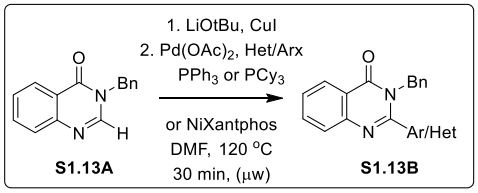
Scheme S1.11: *Iridium catalyzed mono-sulfamidation of 2-aryl quinazolinones scaffolds*
(Feng, Y.; Zhang, Z.; Fua, Q.; Yao, Q.; Huang, H.; Shen, J.; Cui, X. *Chin. Chem. Lett.* **2020**, *31*, 58–60)

Arylation: The Pd catalyzed direct C2-arylation on quinazolinone ring appears to have been unexplored until 2015. The first report came in 2015 from the Fruit and Besson group, who developed a Pd-catalyzed direct C2–H (hetero)arylation of quinazolin-4-one **S1.12A** using aryl iodides. In this method, the N^3 had to be protected with a benzyl group and it could be deprotected using $AlCl_3$ afterwards. The arylation using various aryl iodides required Pd and Cu as the catalyst combination and the use of LiO^tBu as the base in DMF at 120 °C under microwave irradiation (Scheme S1.12).



Scheme S1.12: *Pd catalyzed Direct C–H Arylation*
(Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. Org. Lett. 2015, 17, 1700–1703)

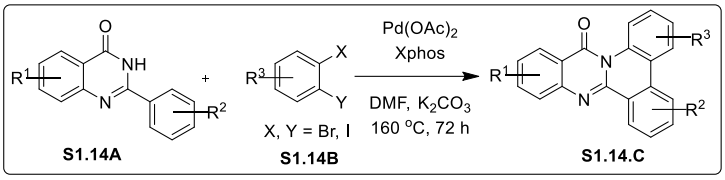
Following this, the same group further extended their work with aryl bromides, as well as with aryl chlorides, using $Pd(OAc)_2$ as the catalyst and PPh_3 or PCy_3 as ligands. Under the same conditions, a variety of hetero halides were also found to be compatible and provided the corresponding C2-heteroarylated quinazolinones in good yields (Scheme S1.13).



Scheme S1.13: *Pd catalyzed Direct C–H Arylation using aryl halides*
(Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. *Eur. J. Org. Chem.* **2015,** 7705–7717)

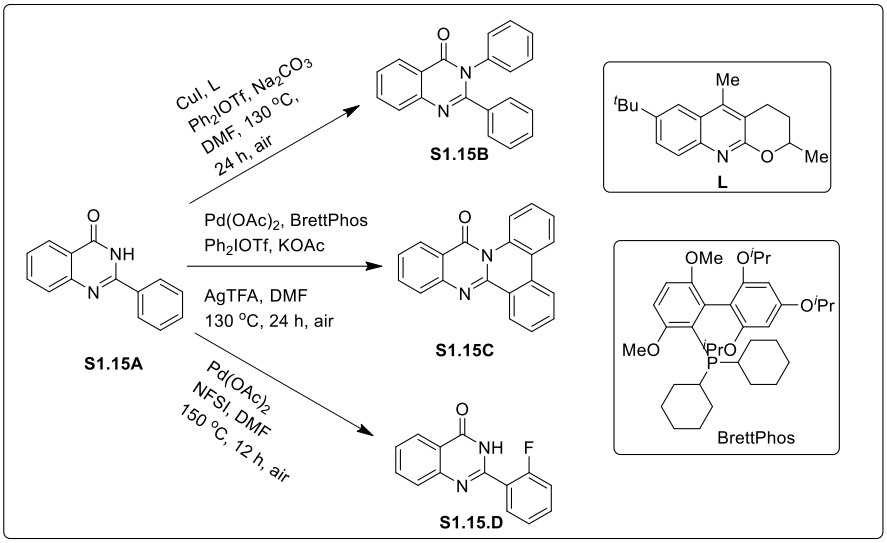
In 2016, Peng and co-workers revealed a novel method for the synthesis of quinazolinone-fused phenanthridinones **S1.14C** from 2-arylquinazolinones using the Pd catalyst. This comprises

of a direct intermolecular C–H arylation of 2-arylquinazolines **S1.14A** with *ortho* di-haloarenes **S1.14B** followed by intramolecular C–N coupling in the presence of a Pd catalyst, Xphos ligand, K_2CO_3 in DMF at 160 °C for 72 h (Scheme S1.14).



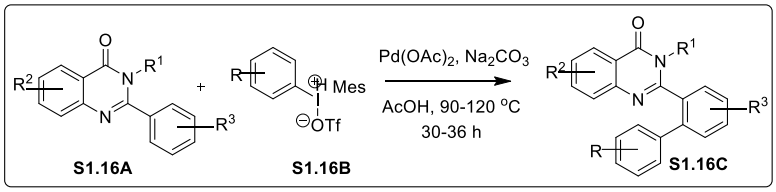
Scheme S1.14: *Pd catalysed Direct C–H Arylation using dihaloarenes*
(Yu, Y.; Yue, Y.; Wang, D.; Li, X.; Chen, C.; Peng, J. *Synthesis* **2016**, *48*, 3941–3950)

In 2017, Park and Hong *et al.* developed a variety of direct functionalization methods on the 2-phenylquinazolin-4(3H)-ones scaffold. Here, the unmasked quinozoline-4-one ring underwent a couple of reactions such as N-arylation, annulative π-extension, and C–H fluorination using the Pd, Cu catalyst. After that, the utility of derived products was shown by preparing the graphene-based non-electronic device, so that it allowed electronic recognition of the real-time Hg^+ ions in the aqueous solution. At first, N-arylation was done by using a copper catalyst, the quinoline-based ligand, with a hypervalent diphenyliodonium triflate used as an aryl source in the presence of K_2CO_3 as the base in DMF solvent at 130 °C in 24 h. This led to the desired N-arylated product **S1.15B** in hand. Next, the annulative π–extension was explored by using $Pd(OAc)_2$ as the catalyst, BrettPhos as the ligand, and Ph_2IOTf_2 as the aryl source. The use of silver trifluoroacetate was found to be the suitable oxidant. Furthermore, the whole mixture was refluxed in DMF solvent at 130 °C for 24 h to obtain the annulated compound **S1.15C** in good yield. Lastly, fluorination of the quinazolinone scaffolds was explored by reacting with N-fluorobenzenesulfonimide as the fluorine source in the presence of the Pd catalyst in DMF solvent at 150 °C in 12 h, leading to the formation of the fluorinated quinazolinone compound **S1.15D** in excellent yield. (Scheme S1.15).



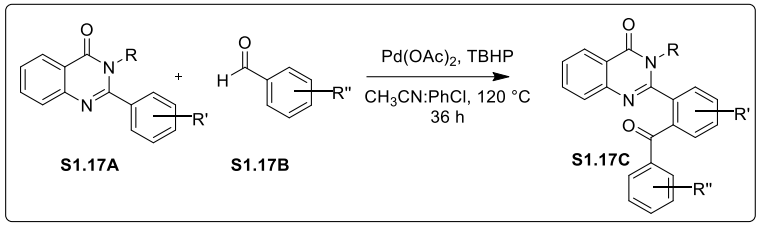
Scheme S1.15: *Pd/Cu catalysed C–H functionalization of 2-aryl-quinazolin-one ring*
(Lee, J. B.; Kang, M. E.; Kim, J.; Lee, C. Y.; Kee, J.-M.; Myung, K.; Park, J.-U.; Hong, S. Y. *Chem. Commun*. **2017**, *53*, 10394–10397)

In the same year, Mhaske *et al.* reported the arylation of the pendant aryl ring of the quinazolin-4-one using a palladium catalyst. Here, the 2-arylquinazolin-4-one **S1.16A** reacts with diphenyliodonium triflates **S1.16B** in the presence of the $Pd(OAc)_2$ catalyst, with Na_2CO_3 as the base heated in AcOH solvent at 90-120 °C for 30–36 h, leading to the formation of the monoarylated quinazolin-4-one compound **S1.16C** in good yields. The scope of the substituent present on the quinazolin-4-one ring, as well as the feasibility of the various diaryliodonium triflates were checked to show the applicability of this method. (Scheme S1.16).



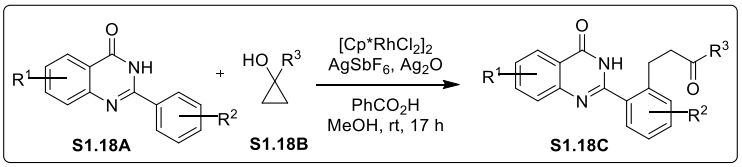
Scheme S1.16: *Pd catalyzed Direct C–H Arylation of pendant aryl ring*
(Garad, D. N.; Viveki, A. B.; Mhaske, S. B. *J. Org. Chem*. **2017**, *82*, 6366–6372)

Recently, in 2020 Khirsagar *et al.* have established the cross dehydrogenative coupling reaction of the aromatic aldehydes **S1.17B** as well as benzyl alcohols with 2-arylquinozoliones **S1.17A** using the Pd catalyst, with TBHP as the oxidant in acetonitrile/chlorobenzene solvent in 1:4 ratio at 120 °C in 36 h, resulting in the formation of the expected ketones **S1.17C** in good yields. (Scheme S1.17).



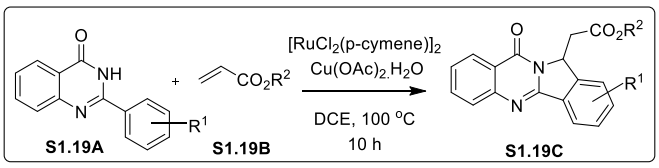
Scheme S1.17: *Pd catalyzed CDC coupling of aldehyde and quinazolinone*
(Kshirsagar, U. A.; Waghmare, D. S.; Tambe, S. D. *New J. Chem.,* **2020**, *44*, 16697)

Alkylation: In 2021, Peng *et al.* reported the alkylation of arylquinazoline-4-one **S1.18A**, which reacts with the cycloproponols **S1.18B** in the presence of $RhCp^*Cl_2$ catalyst, $AgSbF_6$ additive, Ag_2O oxidant, benzoic acid proton source in MeOH solvent at room temperature in 17 h. This resulted in the formation of the quinazolin-4(3H)-one scaffold containing β-aryl ketone **S1.18C** in good yield. (Scheme S1.18)



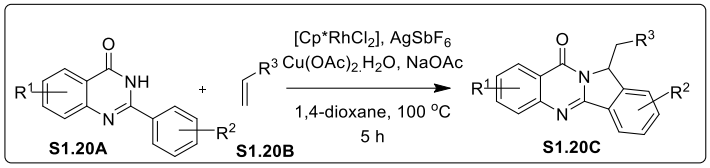
Scheme S1.18: *Rh(III) catalyzed alkylation of arylquinazolin-4-one*
(Chen, M-W.; Lou, M.; Deng, Z.; Yang, Q.; Peng, Y. *Asian J. Org. Chem*. **2021**, *10*, 192–195)

Alkenylation: In 2015, Xuan and co-workers reported the synthesis of the pyrrolo[2,1-b]quinazolin-9(1*H*)-one motif **S1.19C** by the reaction of the arylquinazolin-4-ones **S1.19A** with olefins **S1.19B** in the presence of a ruthenium catalyst and $Cu(OAc)_2$ oxidant in DCE solvent at 100 °C to get the alkenylated/annulated product **S1.19C** in good to moderate yields. The scope of the range of alkenes/acrylates was explored here and this strategy became efficient for the synthesis of the pyrrolo[2,1-b]quinazolin-9(1*H*)-one scaffold. However, the coupling reaction between **S1.19A** and N, N-dimethyl acrylamide, styrenes, methyl methacrylate and vinyl sulphone was found to be incompatible in the current approach. (Scheme S1.19).



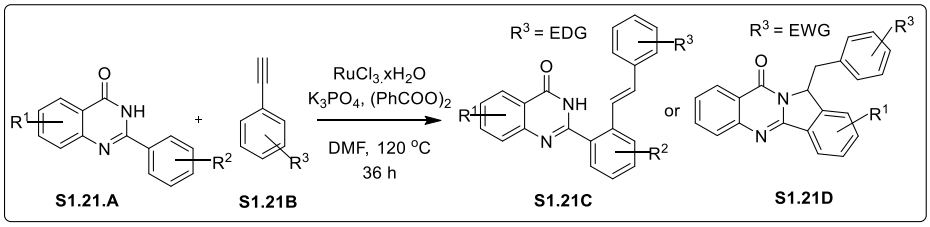
Scheme S1.19: *Ru-catalyzed oxidative coupling of 2-aryl-quinazolinone with olefins*
(Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Xuan, L.-J. *Org. Biomol. Chem*. **2015**, *13*, 6474–6478)

In 2016 Peng and co-workers have reported the quinozoline-one directed and rhodium catalyzed sequential C–H activation followed by the addition with the acrylates to synthesize a variety of pyrrolo[2,1-b]quinazolin-9(1*H*)-one **S1.20C** compounds in one go. The quinozolin-4-one ring **S1.20A** compound was heated in the presence of acrylates **S1.20B**, RhCp*Cl_2 catalyst, $AgSbF_6$ additive, $Cu(OAc)_2$ oxidant and NaOAc base in 1,4-dioxane solvent for 5 h, leading to the formation of the pyrrolo[2,1-b]quinazoli-9(1*H*)-one **S1.20C** derivative in good yields. (Scheme S1.20).



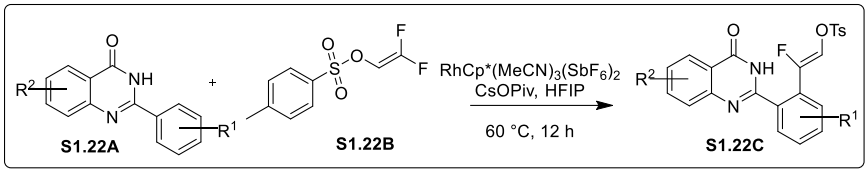
Scheme S1.20: *Ru-catalyzed C–H activation/aza-Michael addition of 2-aryl-quinazolinone with olefin*
(Jiang, X.; Yang, Q.; Yuan, J.; Deng, Z.; Mao, X.; Peng, Y.; Yu, C. *Tetrahedron* **2016**, *72*, 1238–1243)

In 2018, Mhaske *et al.* carried out C–H alkenylation followed by the hydroamidative cyclization of the arylquinazolin-4-one ring **S1.21A** by reacting it with terminal alkynes **S1.21B** in the presence of the $RuCl_3.xH_2O$ catalyst, K_3PO_4 base, and dibenzoyl peroxide aoxidant in DMF solvent heated at 120 °C for 36 h, leading to the formation of the alkenylated compound **S1.21C** in good yield and, in some cases, the annulated product **S1.21D** was also formed in good to moderate yield when electron-withdrawing groups were present on the terminal alkynes. The scope of the different substituted terminal alkynes and various quinazolinones was studied to show the compatibility of this method. (Scheme S1.21).



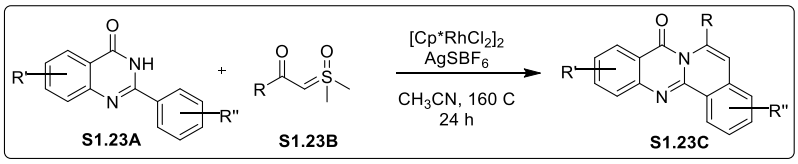
Scheme S1.21: *Ru-catalyzed alkenylation/amidative cyclisation of 2-aryl-quinazolinone with alkynes*
(Viveki, A. B.; Mhaske, S. B. *J. Org. Chem.* **2018**, *83*, 8906–8913)

Recently, in 2020, Peng *et al.* documented the monofluoronation of the quinazolinone rings where the 2-arylquinazolinone ring **S1.22A** reacted with 2,2-difluorovinyl tosylate **S1.22B** in the presence of a RhCp*$(MeCN)_3(SbF_6)_2$ complex, with CsOPiv as the base in HFIP solvent heated at 60 °C for 12 h. This led to the formation of a 2-(o-monofluoroalkenylaryl)quinazolinone **S1.22C** derivative. (Scheme S1.22).



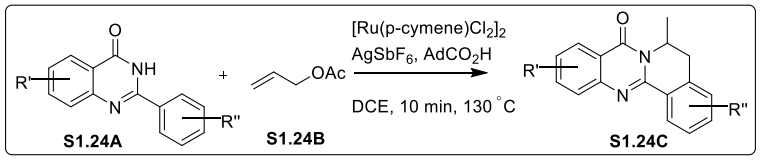
Scheme S1.22: *Rh(III) catalyzed synthesis of monofluoroquinazolinone derivatives*
(Wang, N.; Yang, Q.; Deng, Z.; Mao, X.; Peng, Y. *ACS Omega* **2020**, *5*, 14635–14644)

C–H functionalization/Annulation: Recently in 2020, Ma & Szostak *et al.* reported the Rh(III)-catalyzed C–H activation followed by an annulation reaction of the 2-arylquinazolin-4-one **S1.23A** ring with sulfoxonium ylides **S1.23B** to get the isoquinolino[1,2-b]quinazolines derivatives **S1.23C** in good yields. The scope of the various arylquinazolin-4-ones, as well as the variety of sulfoxonium ylides, was checked. Reaction conditions included the use of CH_3CN as a solvent, which was heated up to 160 °C for 24 h to get the expected product in good to excellent yield. Mainly, the synthesized mono-C6-substituted isoquinolino[1,2-*b*]quinazolines compound showed promising cytotoxic activity. The reported reaction was very eco-friendly, as the byproduct formed after the reaction was only DMSO and H_2O which were released after the reaction. (Scheme S1.23).



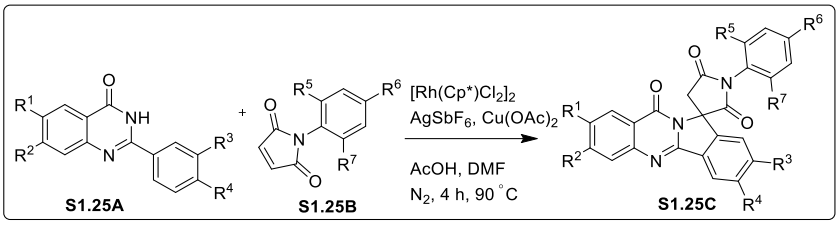
Scheme S1.23: *Rh(III) catalyzed synthesis of Isoquinolino[1,2-b]quinazolines*
(Zhang, J.; Wang, X.; Chen, D.; Kang, Y.; Ma, Y.; Szostak, M. *J. Org. Chem.* **2020,** *85*, 3192–3201)

In 2018, Jana and co-workers reported the Ruthenium(II) catalyzed directed C–H allylation followed by hydroamination of the arylquinazolin-4-one **S1.24A** scaffolds in the presence of $AgSbF_6$ and with adamantine carboxylic acid as the additive. This gave a good result because of less nucleophilicity and better proton donation than the other acids, when stirred in DCE solvent at 130 °C for 10 min to get the dihydroisoquinolino[1,2-b] quinazolinones derivatives **S1.24C** in good yields. (Scheme S1.24).



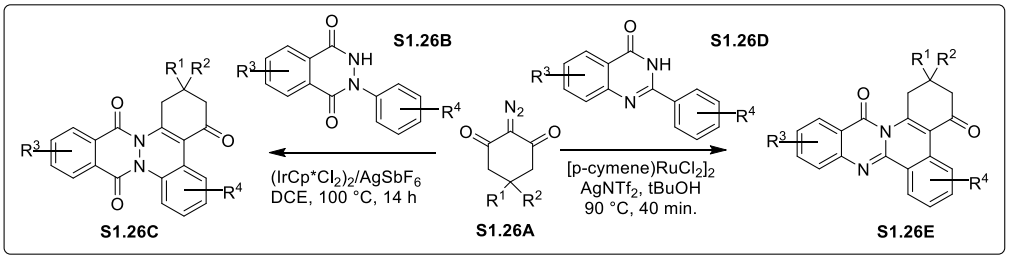
Scheme S1.24: *Ru(II) catalyzed synthesis of Dihydroisoquinolino[1,2-b]quinazolinones*
(Bairy, G.; Das, S.; Begam, H. M.; Jana, R. *Org. Lett.* **2018**, *20*, 7107–7112)

In 2019, Lee and co-workers reported the Rh(III) catalyzed C–H activation of arylquinazolin-4-one ring **S1.25A** reacted with maleimides **S1.25B** in the presence of $AgSbF_6$ as an additive and wth the use of $Cu(OAc)_2$ as the oxidant in DMF solvent heated at 90 °C for 4 h under nitrogen atmosphere to get the spiroisoindoloquinazolinones **S1.25C** in good yields. A variety of substituted arylquinozolin-ones and also maleimides were employed to check the feasibility of the reaction. In one go, the C-C and C-N bond formation took place by using C–H activation followed by aza-Michael addition leading to spirocyclisation of the corresponding compounds. (Scheme S1.25).



Scheme S1.25: *Rh(III) catalyzed synthesis of spiroisoindoloquinazolinones*
(Devkota, S.; Lee, H-J.; Kim, S. H.; Lee, Y. R. *Adv. Synth. Catal.* **2019**, *361*, 5587–5595)

In 2018, Wang and co-workers reported the C–H functionalization of the quinazolinone rings, where in the first case, the 2-arylquinazolinone **S1.26D** ring reacted with a 1,3-diketone-2-diazo **S1.26B** compound in the presence of a Ru(II) catalyst, with $AgNTf_2$ as the additive in ^{t}BuOH solvent at 90 °C for 40 min, resulting in the formation of the annulated 8*H*-isoquinolino[1,2-b]quinazolin-8-ones product **S1.26E** in good yield. In the second case, the diazo compound **S1.26A** reacted with the 2-phenyl-dihydrophthalazine-1,4-dione **S1.26B** in the presence of Ir(III) catalyst, $AgSbF_6$ as the additive in DCE solvent at 100 °C for 14 h, resulting in the formation of phthalazino[2,3-a]cinnoline-8,13-diones **S1.26C** in good yields. In this method, the reaction conditions were mild and favorable for a variety of functionalized diazo ketones, 2-arylquinozolinones as well as with a variety of 2-phenyl-dihydrophthalazine-1,4-diones. (Scheme S1.26).

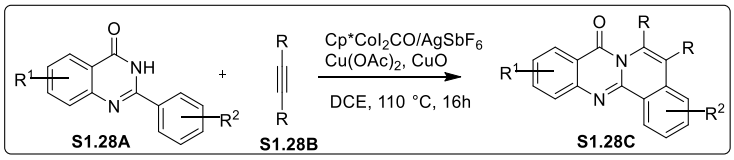


Scheme S1.26: *Ru(II)/Ir(III) catalyzed C–H functionalization of cyclic amides*
(Cai, P.; Zhang, E.; Wu, Y.; Fang, T.; Li, Q.; Yang, C.; Wang, J.; Shang, Y. *ACS Omega* **2018**, *3*, 14575–14584)

In 2019 Dabri and co-workers disclosed the first report of CDC coupling followed by annulation, which gave the formation of hydroxyisoindolo[1,2-b]quinazolinone **S1.27C**. Here, 2-arylquinozolinone **S1.27A** first reacted with aldehydes **S1.27B**, undergoing the CDC reaction in the presence of a Pd catalyst and TBHP oxidant, which led to further intramolecular cyclization, revealing the formation of the expected product in 16 h at 80 °C in good yields. These conversions were applied to a diverse range of aldehydes and quinazolinones and proceeded with high yield and regioselectivity. (Scheme S1.27).

Scheme S1.27: *Pd catalyzed synthesis of Hydroxyisoindolo[1,2-b]quinazolinone*
(Dabiri, M.; Lehi, N. F.; Movahed, S. K.; Khavasi, H. R. *Eur. J. Org. Chem*. **2019**, 2933–2940)

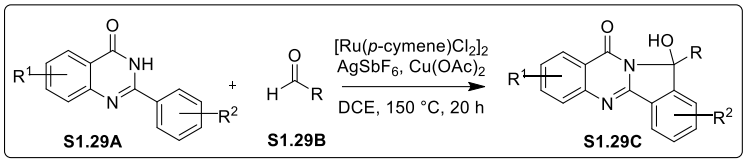
Parthasarathy *et al.* reported the synthesis of tetracyclic quinazolinones using a cobalt catalyst. 2-aryl quinazolinones **S1.28A** react with symmetrically substituted alkynes **S1.28B** in the presence of a cobalt catalyst and $AgSbF_6$ additive, with $Cu(OAc)_2$ as the oxidant in DCE solvent. The system was heated at 110 °C for 16 h, resulting in the formation of the annulated product **S1.28C** in good yields. Quinazolinone containing the electron-donating as well as electron-withdrawing substituents was found to be compatible under these reaction conditions. The scope of unsymmetrically substituted alkynes was also checked. Interestingly, they observed different products and explained the mechanism to show how they were formed. (Scheme S1.28).



Scheme S1.28: *Co catalyzed C–H functionalization of quinazolinones by alkynes*
(Kumaran, S.; Parthasarathy, K. *Eur. J. Org. Chem*. **2020,** 866–869)

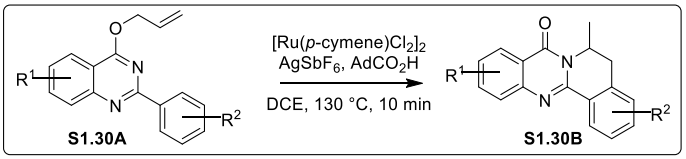
Recently in 2020, Mishra and Kim and co-workers reported the hydroxyalkylation of the 2-aryl quinazolinones ring. Where there is a coupling reaction in between the activated aldehydes **S1.29B** and the 2-aryl quinazolinones **S1.29B** in the presence Ru(II) catalyst, with $Cu(OAc)_2$ as the

oxidant, the reaction mixture was heated in DCE solvent at 150 °C for 20 h, leading to the formation of the tetracyclic isoindoloquinozolinones core **S1.29C** in good to moderate yields. Suitable conditions for both hydroxyalkylation as well for cyclization were established successfully. For the hydroxyalkylation, NaOAc was the best base optimized. (Scheme S1.29).



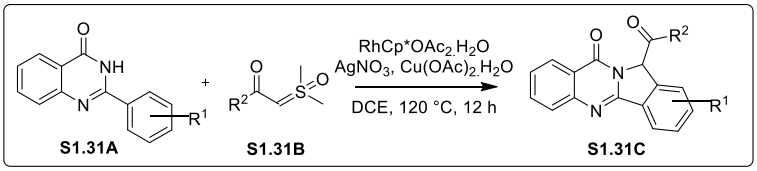
Scheme S1.29: Ru(II) catalyzed synthesis of isoindoloquinazolinones
(Choi, J. H.; Kim, K.; Oh, H.; Han, S.; Mishra, N.K.; Kim, I. S. *Org. Biomol. Chem*. **2020**, *18*, 9611–9622)

In 2019, Jana *et al.* reported allylation followed by the hydroamination reaction of *o*-substituted quinazolinones using a Ru(II) catalyst. Here, the migration of the allyl group from the quinazolinone ring **S1.30A** to the *ortho* position of the aryl ring occurs, which further leads to fast cyclization with the nitrogen of the quinazolinone ring in 10 min at 130 °C in DCE solvent, leading to the synthesis of the rutaecarpine analogs **S1.30B** in good yields. (Scheme S1.30).



Scheme S1.30: *Ru(II) catalyzed C–H allylation/Hydroamination*
(Bairya, G.; Nandia, A.; Mannaa, K.; Jana, R. *Synthesis* **2019**, *51*, 2523–2531)

Recently, Cheng *et al.* reported the 4+1 annulation reaction in between sulfoxonium ylides **S1.31B** and 2-aryl quinazolinones **S1.31A** in the presence of the $RhCp^*OAc_2.H_2O$ catalyst, with $AgNO_3$ as the suitable additive, $Cu(OAc)_2$ as the oxidant in DCE solvent at 120 °C in 12 h, resulting in the formation of the tetracyclic core **S1.31C** in good yields. Different 12-benzoyl isoindolo[1,2-*b*]quinazolin-10 (12*H*)-ones **S1.31C** derivatives were synthesized in good to moderate yields. The scope of the various sulfoxonium ylides and 2-arylquinazolinones were successfully checked to expand the work. (Scheme S1.31).



Scheme S1.31: *Rhodium catalyzed 4+1 annulation reaction of 2-aryl quinazolinones scaffolds*

(Wanga, C.; Qian, P-C.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2020**, *61*, 152441)

From this brief compilation on directed C–H activation of the 2-arylquinazolinones, it becomes apparent that these are very good substrates for post modification and amicable for functionalization with a majority of the electrophiles that have been employed in the C–H activation studies. However, it is interesting to note that the alkynylation of 2-arylquinazolinones has been never explored, despite that fact that these alkynes can be further manipulated for further structural modification and elaborations. This prompted us to look at the documented work on the catalytic C–H alkynylations and brief compilation of the same follows.

1.8 Alkynylation reaction by C–H activation:

Alkynes are an important recurring structural unit widely explored in organic synthesis. "Alkyne" is a unique functional group in organic synthesis that allows the introduction of a wide range of carbon and/or hetero atom centered functional groups that can be easily transformed into carbo-/heterocycles of varying ring sizes.[15] Interestingly, there are many active pharmaceuticals and natural products that contain an alkyne unit. The Corey-Fuchs reaction and the Seyferth-Gilbert homologation are the classical reactions to form terminal C≡C bonds and the alkyne-alkyne cross metathesis forms the internal alkynes. However, in general, the addition of a functionalized alkyne

at the desired carbon center was carried out by employing alkylation, nucleophilic addition to carbonyls or opening of epoxides, as well as cross coupling reactions such as Sonogashira coupling. In recent years, there has been a tremendous interest in the catalytic alkynylation of C–H bonds to avoid pre-functionalization of the reacting substrates.[16] Indeed, the direct/directed alkynylation of sp2 C–H bonds is considered as a reliable alternative to Sonogashira coupling.[17,18] In this pursuit, terminal alkynes,[19] haloalkynes,[20] borane alkynes,[21] and alkynylated hypervalent iodine reagents[22] are the four different types of alkyne precursors used for the directed alkynylation reaction. Among all the alkynylating reagents, cyclic hypervalent iodine reagents are the latest reagents used for efficient transfer of the alkyne group.

Hypervalent Iodine Compounds:[22] The hypervalent iodine compounds have been widely employed for many transformations such as oxidations, single electron transfer, rearrangements and radical reactions in synthetic areas to make the carbon-carbon or carbon-hetero bonds. Recently,

they have also been identified as potent functional group transfer reagents. In 1991, Ochiai first introduced such an alkynyl-substituted member of this family of potent hypervalent iodine reagents. Again in 1996, the Zhadkin group discovered the triisopropylsilylethynyl-1,2-benziodoxol-3(1H)-one (TIPS-EBX) reagent including other cyclic hypervalent iodine reagents of this family.

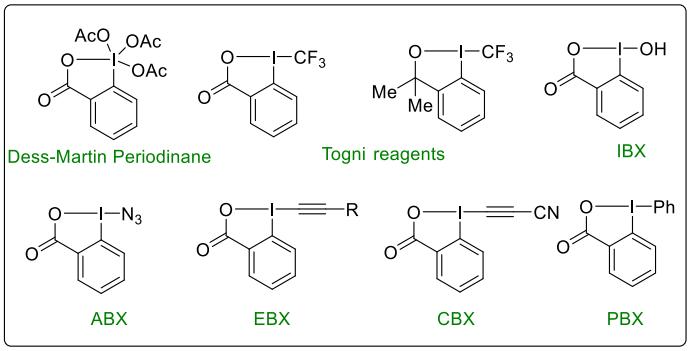


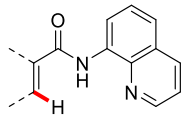
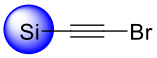
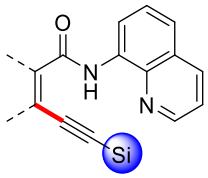
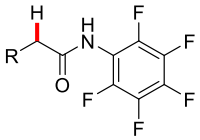
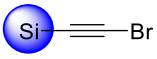
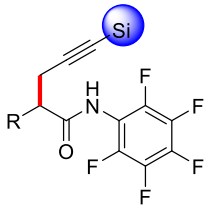
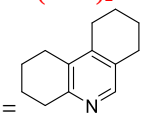
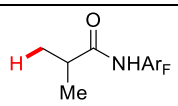
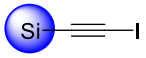
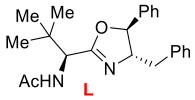
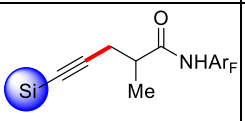
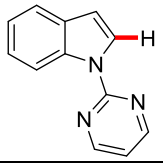
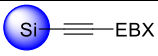
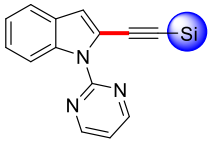
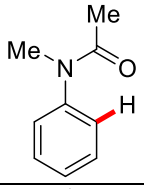
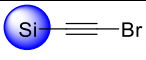
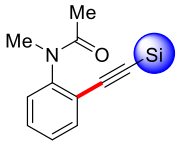
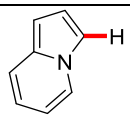
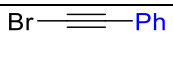
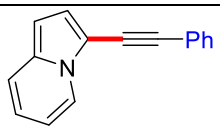
Figure F1.5: *Selected examples of cyclic hypervalent iodine reagents*

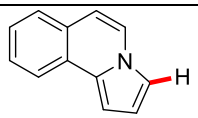
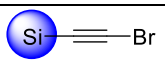
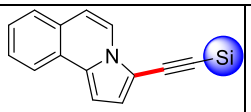
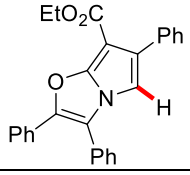
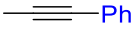
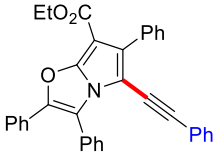
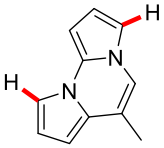
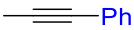
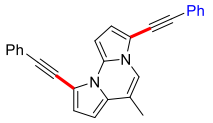
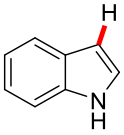
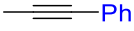
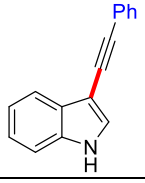
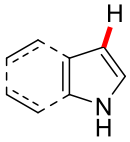
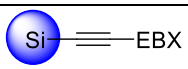
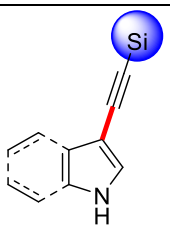
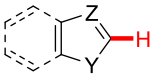
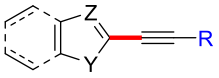
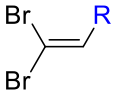
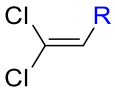
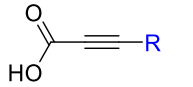
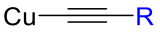
The TIPS-EBX and related EBX reagents in general are prepared by the reaction of 2-iodobenzoic acid with trimethylsilyl triflate, (triisopropylsilyl)(trimethylsilyl)acetylene and pyridine. These reagents show exceptional reactivity as they deliver the electrophilic acetylene group easily under mild reaction conditions, as it is a very stable, active reagent. After its discovery, TIPS-EBX was left unexplored till 2009, when the Waser group used it for the first time for the alkynylation of indoles and pyrroles by using gold catalysis. This pioneering work brought TIPS-EBX and other hypervalent iodine reagents into the limelight, which initiated a lot of research work using these hypervalent reagents to carry out useful electrophilic alkynylation transformations.

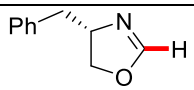
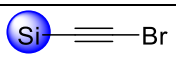
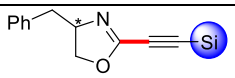
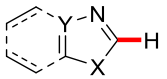
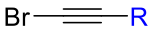
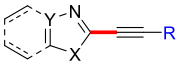
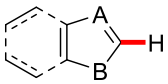
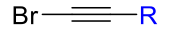
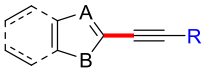
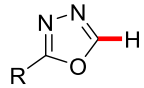
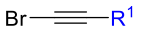
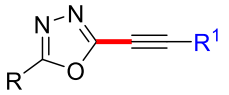
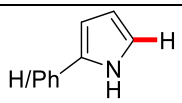
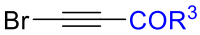
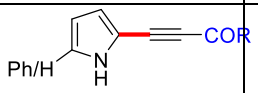
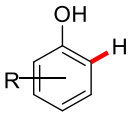
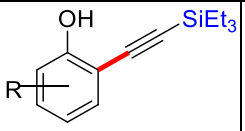
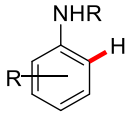
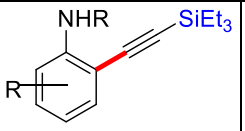
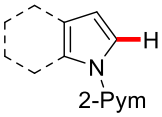
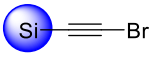
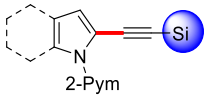
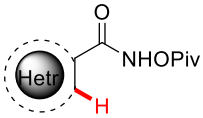
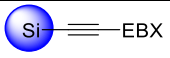
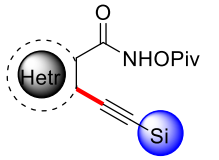
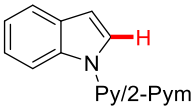
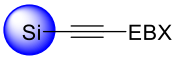
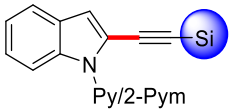
Coming to the alkynylation *via* C–H activation, the directed alkynylation reactions occupy a special role in this regard, as they are regioselective and can be conducted even at room temperature.[18] A variety of functional groups such as amines, amides, anilides, imines, esters, carboxylic acids, ketones, hydroxyls and various heterocycles have been employed as directing groups for directed C–H bond alkynylations. The alkyne sources employed in this pursuit include terminal alkynes,[19] haloalkynes,[20] borane alkynes,[21] and alkynylated hypervalent iodine reagents.[22] There are various inorganic metal complexes (Pd, Ru, Rh, Ir, Co etc.) that have been used to catalyze different types of C–H bond- (sp3, sp2 and sp) activation processes. As this chapter mainly deals with the directed alkynylation reactions *via* C–H activation, a comprehensive

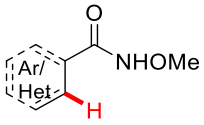
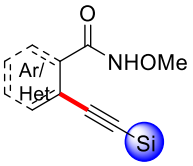
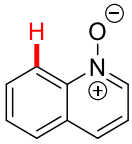
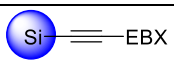
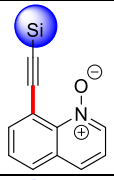
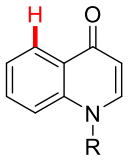
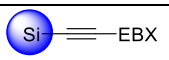
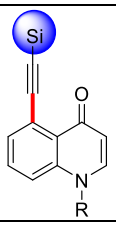
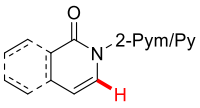
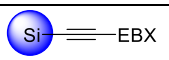
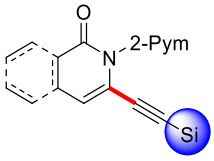
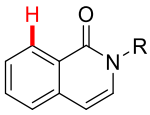
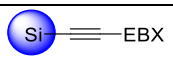
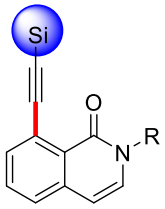
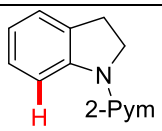
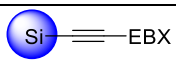
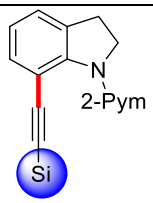
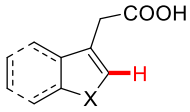
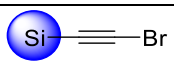
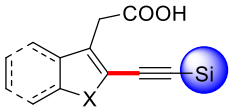
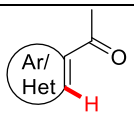
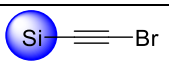
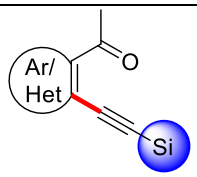
compilation of various reports of the metal catalyzed C–H alkynylation reactions are summarized in the table below.

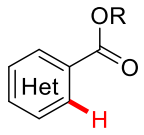
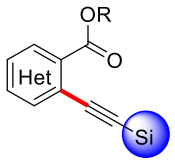
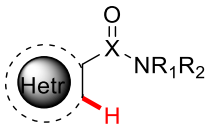
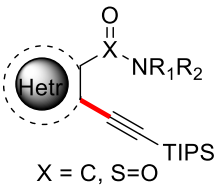
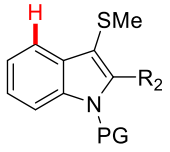
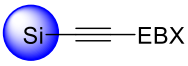
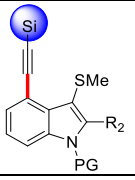
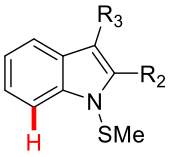
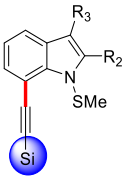
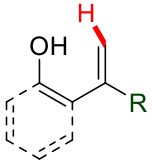
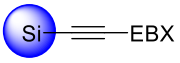
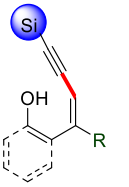
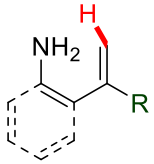
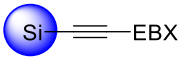
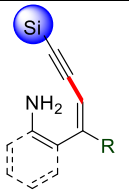
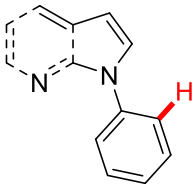
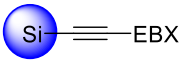
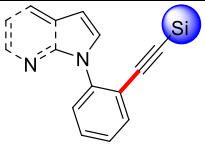
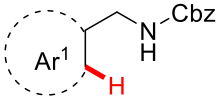
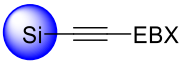
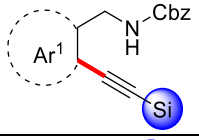
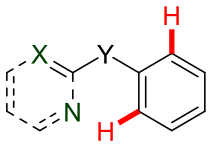
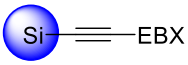
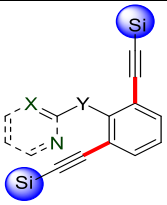
Table T1.2: *Transition metal catalyzed C–H alkynylation by using various directing groups and metals:*

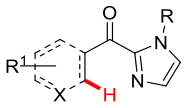
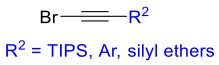
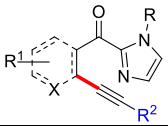
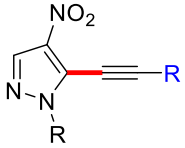
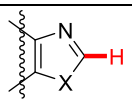
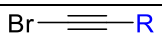
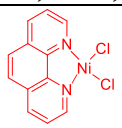
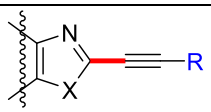
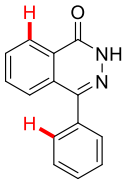
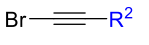
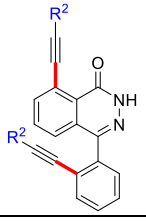
Sr. No	Directing groups	Alkylating reagent	Reactions conditions	Product	Reference
1			$Pd(OAc)_2$ AgOAc LiCl Toluene, 110 °C		*J. Am. Chem. Soc.* **2011**, *133*, 12984.
2			$Pd(OAc)_2$ (cat.) PR_3 or NHC (cat.) Cs_2CO_3 Et2O, 80 °C		*J. Am. Chem. Soc.* **2013**, *135*, 3387.
3			$Pd(OAc)_2$ L =  AgOAc Toluene, 110 °C		*Angew. Chem. Int. Ed.* **2017**, *56*, 1873.
4			$Pd(OAc)_2$ L, Ag_2CO_3, Toluene 50 °C, 48 h 		*Science* **2017**, *355*, 499.
5			$[Cp^*CoCOI_2]$ AgF, $Mg(OCH_3)_2$ TFE, 110 °C, 24 h		*Org. Lett.* **2015**, *17*, 4094.
6			$Pd(OAc)_2$, AgOTf, K_2CO_3, PhMe, 70 °C		*Org. Lett.* **2009**, *11*, 3250.
7			$PdCl_2(PPh_3)_2$ KOAc, 30-80 °C, PhMe		*J. Am. Chem. Soc.* **2007**, *129*, 7742.

8					
9					
10					
11			$PdCl_2(PPh_3)_2$ NaOAc THF, 50 °C		*Tetrahedron Lett.* **2009**, *50*, 763.
12			$AuCl$, Et_2O, 23 °C		*Angew. Chem. Int. Ed.* **2009**, *48*, 9346.
13	 Z = C, N; Y = N, O, S	 R = TIPS or Ph	$Pd(OAc)_2$ Xantphos ^{t}BuOLi Dioxane, 100 °C	 Z = C, N; Y=N, O, S	*Org. Lett.* **2010**, *12*, 1868.
			$CuBr.SMe_2$ DPE-Phos ^{t}BuOLi, Dioxane 120 °C, 2h		*Org. Lett.* **2010**, *12*, 4038.
			$Pd(OAc)_2$ DPE-Phos tBuOLi 1,4-dioxane		*Org. Lett.* **2012**, *14*, 1824.
14		 R = Nap, Ar, ^{n}C$_6$H$_5$, Si(i-Pr)$_3$	$NiBr_2$, dtbpy ^{t}BuOLi diglyme, toluene 100 °C, O_2, 1-3h		*Org. Lett.* **2010**, *12*, 2358.
15		 R = Ar, Nap, ^{n}Pentyl	$PdCl_2$, dppe, Ag_2O 60 °C, 12h		*Eur. J. Org. Chem.* **2013**, 7902.
16		 R = alkyl, Ar	1,10-phenanthroline ^{t}BuOLi, O_2, CH_3CN, rt, 48h		*Org. Lett.* **2014**, *16*, 4488.

17			Pd cat. Ag_2O, Cs_2CO_3 DMF, 85 °C, 6h Or Pd cat. Ag_2O, DMF, 80 °C O_2		*Tetrahedron* **2015**, *71*, 1975.
18			$Pd(OAc)_2$, Xantphos, ^{t}BuOLi Dioxane, 100 °C		*Org. Lett.* **2010**, *12*, 1868.
19	 X = O, S, NPh Y = CH, N	 R = Ph, naphthyl, nC_6H_{13}	$Ni(Cod)_2$, dppbz, ^{t}BuOLi PhMe, reflux, 1 h		*Org. Lett.* **2009**, *11*, 4156.
20	 A = C, N Y = N, O, N	 R = TIPS or Ph	$CuBr.Sme_2$, DPEPhos ^{t}BuOLi Dioxane, 120 °C, 1h		*Angew. Chem. Int. Ed.* **2009**, *48*, 9553.
21	 R = Ph, 1-Naphthyl	 R^1 = Ph, naphthyl, 1-cyclohexenyl TIPS, 4-Me-Ph	CuI, 1,10 phenanthroline ^{t}BuOLi PhMe, 1 h		*J. Org. Chem.* **2010**, *75*, 1764.
22		 R = Ph, 2-thienyl	Al_2O_3, rt		*Tetrahedron Lett.* **2004**, *45*, 6513. *Tetrahedron* **2008**, *64*, 5541.
23			$GaCl_3$, ^{n}BuLi, DtBMP, PhCl, 120 °C		*J. Am. Chem. Soc.* **2002**, *124*, 8528.
24			$GaCl_3$, ^{n}BuLi, DtBMP, PhCl, 120 °C		*Tetrahedron Lett.* **2004**, *45*, 4333.
25	 2-Pym		$[Cp^*CoCOI_2]$ $AgSbF_6$ K_2CO_3 TFE, 25 °C, 18 h	 2-Pym	*Org. Lett.* **2015**, *17*, 5316.
26			$[Cp^*RhCl_2]$ NaOAc DCE, rt, 12h		*Angew. Chem.* **2014**, *53*, 2722.
27	 Py/2-Pym		$[Cp^*RhCl_2]$ $Zn(Otf)_2$ DCE, rt or 80 °C, 16h	 Py/2-Pym	*J. Am. Chem. Soc.* **2014**, *136*, 4780.

28			$[Cp^*IrCl_2]_2$ $AgNTf_2$, DCE 30 °C, 16h		
29			$[Cp^*Rh(MeCN)_3][SbF_6]_2$ PivOH, MS (4 A°), rt, 12h, DCE		*Org. Lett.* **2014**, *16*, 4598.
30			$[Cp^*Rh(MeCN)_3][SbF_6]_2$ Xylene 80 °C, 12h, under air		*Org. Lett.* **2015**, *17*, *1938.*
31			$[Cp^*Rh(MeCN)_3][SbF_6]_2$ Xylene 80 °C, 12h, under air		*Org. Lett.* **2015**, *17*, 1938.
32			$[Cp^*RhCl_2]_2$ $Zn(Otf)_2$ 80 °C, 12h, N_2, DCE		*J. Org. Chem.* **2016**, *81*, 715.
33	 R= alkyl, CH_2Ph, cyclopentane		$[Cp^*RhCl_2]_2$ AgSbF6 80 °C, 16h, DCE		*Org. Lett.* **2016**, *18*, 1056.
34			$[Cp^*IrCl_2]_2$ $AgNTf_2$, EtOH rt, 10h		*J. Org. Chem.* **2015**, *80*, 1946.
35	 X= N, S		$[Cp^*IrCl_2]_2$ $KHCO_3$ t-amyl-OH 70 °C, 24h	 X= N, S	*Org. Lett.* **2017**, *19*, 2474.
36			$[Cp^*IrCl_2]_2$ $AgNTf_2$, NaOAc, AgOAc DCE:HFIP 120 °C, 24h		*J. Org. Chem.* **2017**, *82*, 13003.

37					
38	 X = C, S=O		$[Cp^*IrCl_2]_2$ $AgNTf_2$, NaOAc, AgOAc Cs_2CO_2 DCE:HFIP 100 °C, 12h	 X = C, S=O	*Org. Chem. Front.* **2019**, *6*, 284.
39			$[Cp^*IrCl_2]_2$ AgOTf, $NaOPiv\text{-}H_2O$, TFE 80 °C, 24h		*Angew. Chem. Int. Ed.* **2019**, *58*, 9856.
40			**1.** $[Cp^*IrCl_2]_2$ AgOTf, $NaOPiv\text{-}H_2O$, TFE, 80 °C, 24h 2. KOH, $^tBu_4PBr$, DCM, rt, 15 min		
41	 R = alkyl, aryl		$[Cp^*RhCl_2]_2$ DIPEA MeCN, rt, 2 h	 R = alkyl, aryl	*Angew. Chem. Int. Ed.* **2015**, *54*, 4949.
42	 R = alkyl, aryl		$[IrCp^*Cl_2]_2$, Py, KOAc, DCE, 10 h, rt	 R = alkyl, aryl	*Chem. Eur. J.* **2017**, *23*, 2748.
43			$[IrCp^*Cl_2]_2$, AgNTf2, DCE, 80 °C, 16 h		*Org. Biomol. Chem.*, **2016**, *14*, 2944.
44			$[IrCp^*Cl_2]_2$, PivOH, Cs_2CO_3, 80 °C, 12 h		*Org. Lett.* **2018**, *20*, 2454.
45	 X = CH, N Y = NH, O		$[IrCp^*Cl_2]_2$, AgSBF6, DCE, 18 h, 30 °C		*Org. Biomol. Chem.*, **2016**, *14*, 2898.

46		 R^2 = TIPS, Ar, silyl ethers	$[Cp^*IrCl_2]_2$ LiOAc $NaBAr^F_4$ $AgOAc$ DCE, 100 °C 36 h.		*ACS Catal.* **2020**, *10*, 5173.
47		 R = Ar, alkyl etc.	$Pd(OAc)_2$ PPh_3, $(CH_3)_2CHCO_2H$ Cs_2CO_3 $AgCO_3$ Toluene, 90 °C, 24 h		*Eur. J. Org. Chem.* **2018**, 2645.
48	 X = S, NAr, O R = Aryl	 R = Ar	 ^{t}BuOLi 1, 4-dioxane 130 °C, 12h		*Asian J. Org. Chem.* **2018**, *7*, 1390.
49		 R^2 = TIPS, TES	$[Cp^*RhCl_2]_2$ Ag_2CO_3 $AgSbF_6$ DCE, 100 °C, air, 12 h		*Eur. J. Org. Chem.* **2020**, 1100.

Amongst the documented reports for C–H bond activation, iridium complexes occupy a special place due to their high reactivity towards the C–H bond cleavage.[23] So, coming to the Ir(III)-catalyzed directed alkynylations using EBX-based reagents (**Figure F1.6**),[23a-23i] the Jiang, Zeng, Li and Xie groups reported the carbonyl/carboxylate and pyrimidine directed *ortho* C–H alkynylation of (hetero)aryl rings. The selective terminal alkynylation of 2-vinylanilines has been reported by the Nachtsheim group. Li and co-workers, on the other hand, documented an Ir-catalyzed pyridine directed alkynylation of pendant aryl units of *N*[1]-aryl-7-azaindol derivatives using TIPS-EBX. Very recently, Zhao and co-workers reported the selective ortho-alkynylation of Cbz-protected benzylamines employing bromoalkynes as the electrophilic alkynylating agents, while Nishi & Miura reported the sulfur directed alkynylation of indoles at the C4 and C7 positions in a selective manner.

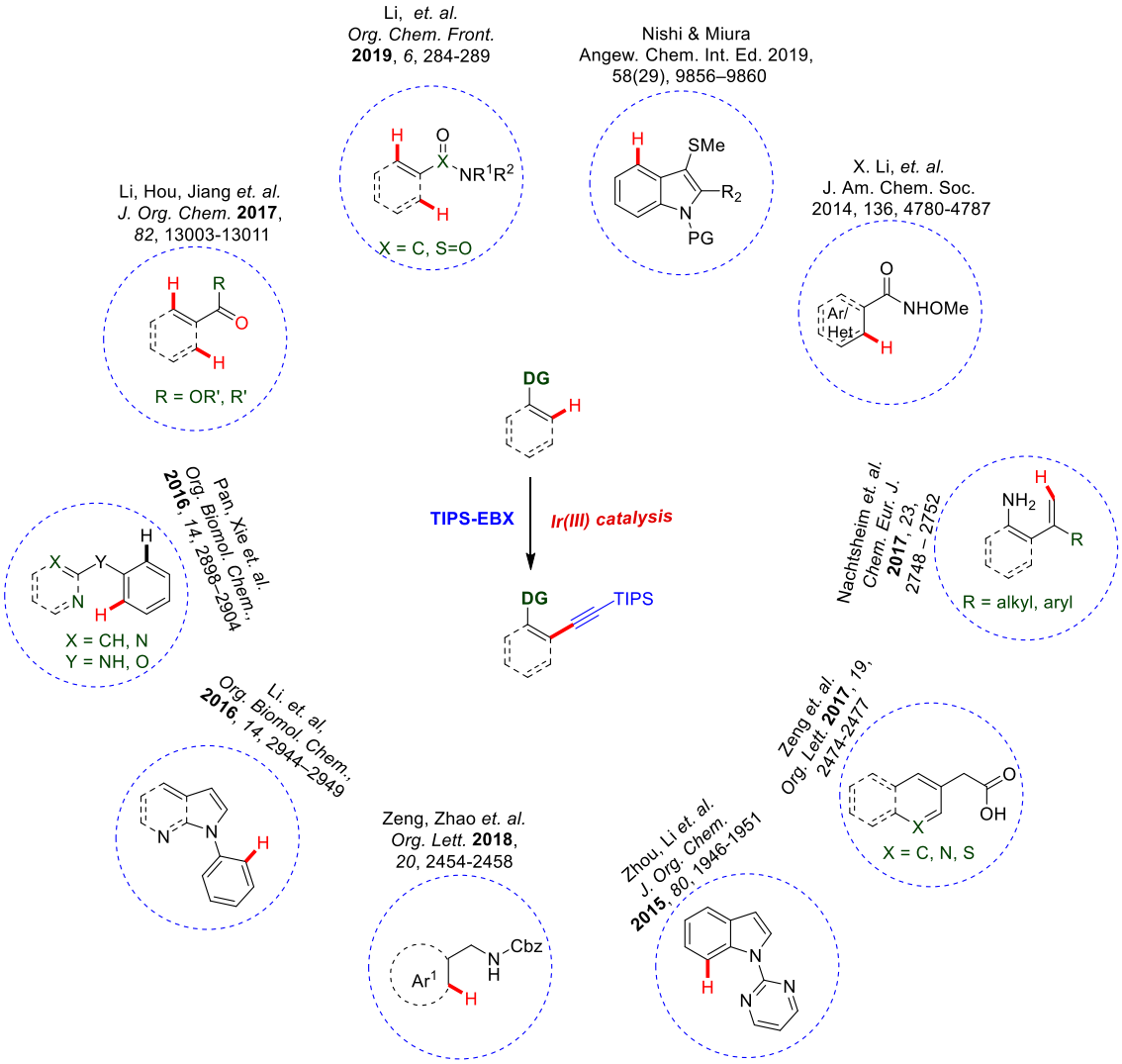


Figure F1.6: *Ir(III) catalyzed alkynylation using different directing groups.*

From the comprehensive compilation provided above, it is evident that the quinazolinone scaffold offers an inbuilt directing group for post-modification, especially for the pendant C2-aryl groups. As mentioned, this has been explored for the functionalization *via* C–H activation with a majority of the electrophiles, although the alkynylation of 2-arylquinazolinones has never been explored despite that fact that these alkynes can be further manipulated for further structural modification and elaborations. In the following section, we will be describing our studies on this aspect, especially employing the [Ir]-complexes, which, as indicated above, have shown superior reactivity.

1.9 Present work:

N-containing heterocyclic compounds such as quinazoline and quinazoline-4-ones are interesting scaffolds ubiquitously present in approved/investigational drug candidates, as well as in many natural products (**Figure F1.7**). Their wide biological activities had drawn significant attention for their construction and also post functionalization.[24] As a part of our ongoing program on C–H activation functionalization at ambient temperatures employing [Ir]-complexes,[25] the directed alkynylation of 2-arylquinazolin-4-ones has been undertaken, considering the fact that it provides a versatile functional group that will allow bringing diversity in the future for quinazolinone derivatives by applying a diverse range of transformations documented with alkynes. Despite several C–H functionalizations reported on the corresponding 2-aryl quinazolinones, interestingly, there is no report till now for a directed alkynylation on the 2-aryl quinazoline-4-one ring. This prompted us to take a chance for developing an efficient methodology for the quinazoline-4-one directed C–H alkynylation of the aryl ring with Ir(III) complexes, and further, to employ the strategy for regioselective intramolecular cyclizations.

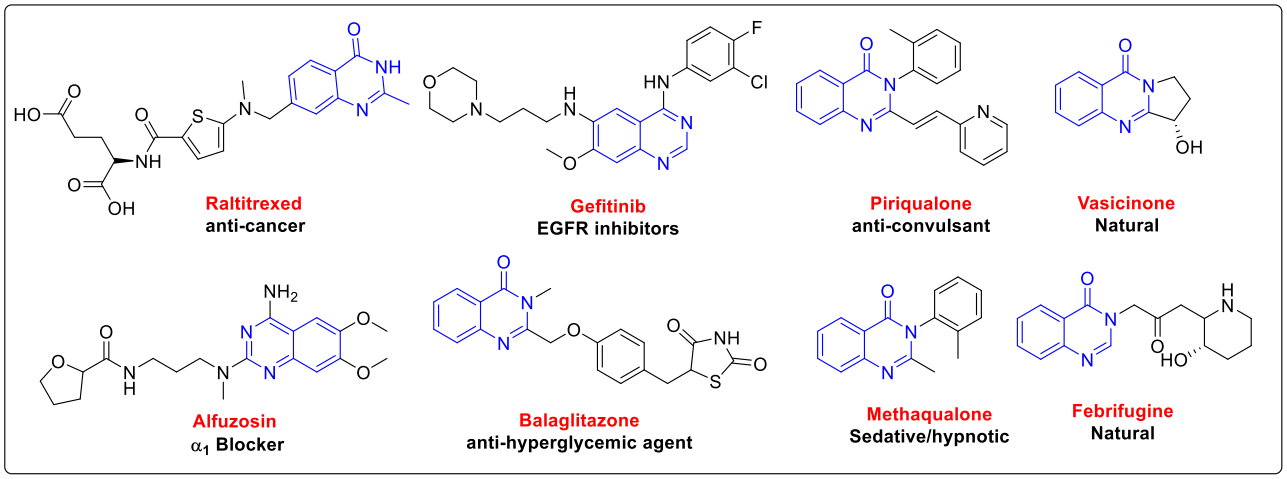


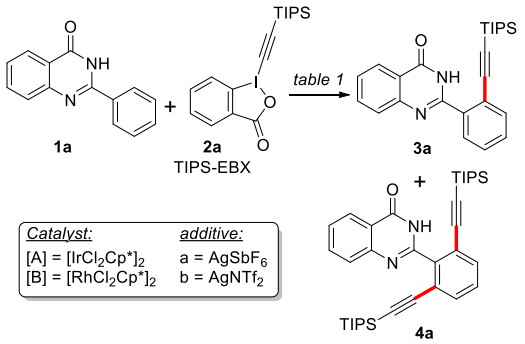
Figure F1. 7: *Pharmacological importance of bioactive quinazolinone and quinazoline based molecules, drugs, and natural products.*

In this context, the preliminary experiments were conducted employing 2-phenylquinazolin-4-one (**1a,** 1 equiv**)** as the model substrate and TIPS-EBX (**2**, 1.2 equiv) as the alkynylating reagent and $[IrCp^*Cl_2]_2$ (5 mol%) and $AgSbF_6$ (10 mol%) as the catalyst systems. Initially, different solvents were screened to see the feasibility of the proposed alkynylation. As shown in Table T1.3, the reaction outcome seems to be solvent dependent. When conducted in CH_3CN at rt, the reaction was sluggish and gave monoalkynylated quinazolin-4-one **3a** (21%), along with dialkynylated quinazolin-4-one **4a** (10%) (Table T1.3, entry 1). The products yield was improved when we switched to other aprotic polar solvents such as THF and dioxane. However, both mono- and dialkynylated products were obtained in varying proportions (Table T1.3, entries 2-3). The structures of the obtained products were established with the help of spectral and analytical data. In the ^1H NMR spectrum of compound **3a**, the characteristic peak of the *ortho* proton of the aryl group of the quinazoline ring disappeared and the multiplet for 21 protons of the TIPS groups was seen to resonate at δ 1.38–0.99 ppm. In the ^{13}C NMR spectrum of compound **3a**, the three methyl groups of the TIPS group appeared as a quartet at δ 18.6 ppm and the three methine carbons resonated at δ 11.2 ppm. A further distinctive acetylene peak of the TIPS-alkyne appeared at δ 104.1 and at δ 100.4, both as singlet carbons. Next, in the HRMS, the calculated accurate mass for the compound was found to be 403.2200 and it was found at 403.2206, thus satisfying the expected monoalkynylation product formation. Next, we analyzed the dialkylated product **4a**. In that case, too, we observed that the two *ortho* protons peak of the aryl group of quinazolinone disappeared completely and the multiplet of 42 protons of the TIPS group were observed to resonate at δ 0.86 ppm. In the ^{13}C NMR spectrum of **4a**, the twelve methyl carbons of the TIPS group appeared as a quartet at δ 18.3 ppm and the six methane carbons resonated at δ 11.0 ppm as a doublet. Further, the four carbons from the acetylene group resonated at 102.6 and 97.2 as the quaternary carbons. HRMS peak at 583.3543 provided additional clues for the dialkynylation product.

With this structure confirmation, we further moved to a detailed examination of the reaction conditions by varying the solvent, temperature and catalyst. Interestingly, when the reactions were conducted in protic solvents such as methanol, ethanol and trifluroethanol at room temperature (Table T1.3, entries 4-8), the dialkynylated product was not observed and the

monoalkynylated product was obtained in varying yields. It was found that methanol was a good choice of solvent for this reaction, giving **3a** in 89% isolated yield (entry 4). At this juncture, to check the possibility of carrying out the dialkynylation exclusively, the reactions were conducted using 2.5 equiv of TIPS-EBX (with respect to **1a**) and different non-polar solvents such as toluene, dichloromethane and dichloroethane at different temperatures. As shown in Table T1.3, the best results were obtained in dichloroethane at 70 °C, resulting in the dialkynylated product **4a** in 94% isolated yield (entry 14). Control experiments revealed that the presence of the Ir-complex was essential and that under similar conditions, the Rh(III) complex performed poorly (entries 15–17).

Table T1.3: *Optimization studies*[a]



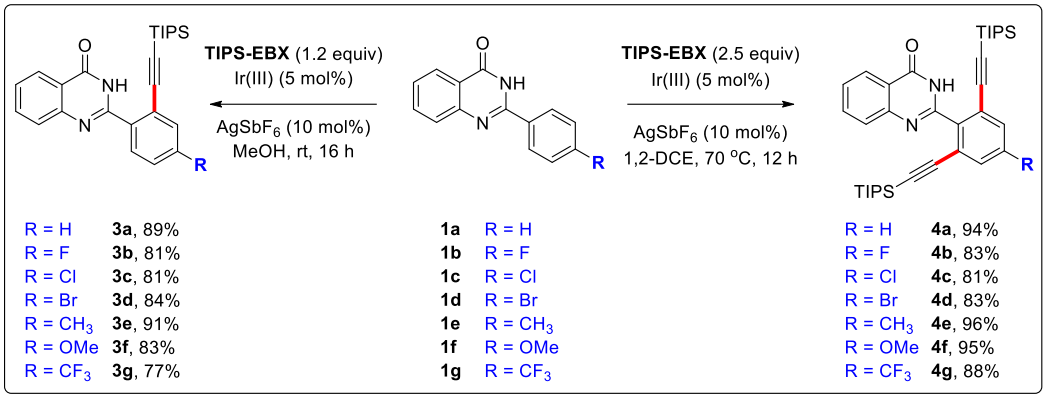
entry	catalyst/ additive	solvent	temp. (°C) time (h)	yield[b] (%) 3a	4a
1	[A]/a	CH_3CN	rt/16	21	10
2	[A]/a	THF	rt/12	42	8
3	[A]/a	Dioxane	rt/16	44	trace
4	**[A]/a**	**MeOH**	**rt/16**	**89**	**trace**
5	[A]/a	EtOH	rt/16	52	trace
6	[A]/a	HFIP	rt/16	36	trace
7	[A]/a	TFE	rt/16	30	trace
8	[A]/a	Toluene	rt/16	35	12
9	[A]/a	DCM	rt/16	38	22

10	[B]/a	DCE	rt/16	27	trace
11	[A]/b	DCE	rt/16	18	43
12	[A]/a	MeOH	70/12	20	53
13	[A]/a	DCM	70/12	12	62
14	**[A]/a**	**DCE**	**70/12**	**--**	**94**
15	[B]/a	DCE	70/12	12	40
16	[B]/b	DCE	70/12	8	32
17	[B]/b	DCE	70/12	trace	28[c]
18	[A]/b	DCE	70/12	8	68
19	[A]/b	DCE	70/12	24	38[c]

[a]Reaction conditions: For entries 1-10: 0.05 mmol of **1a**, 0.06 mmol of **2a**, 5 mol % of catalyst, 10 mol % of additive, dry solvent (1.0 mL), 16 h; for entries 12-19: 0.05 mmol of **1a**, 0.125 mmol of **2a**, 5 mol % of $[IrCp^*Cl_2]_2$, 10 mol % of additives, dry solvent (1.0 mL), 12 h. [b]Isolated yields. [c]NaOAc (1.2 eq.) was used.

Having the complementary conditions for the selective mono- or dialkynylation in hand, we proceeded to explore the scope of the current transformations employing diverse 2-(hetero)arylquinazolin-4-one scaffolds (Scheme S1.32). Initially, we examined the scope of substituents on the *para*-position (F, Cl, Br, Me, OMe, CF_3; respectively **1b**–**1g**). The selective mono-/dialkynylation of these substrates **1b**–**1g** proceeded smoothly with **2** under optimized conditions and provided the corresponding monoalkynylated products **3b**–**3g** (81-91%) and dialkynylated products **4b**–**4g** (77-96%) in good to excellent yields. Coming to the ^{1}H NMR spectrum of compound **3b**, the one *ortho* proton of the aryl group of quinazoline ring was seen to disappear and the multiplet for 21 protons of the TIPS groups was seen to resonate at δ 1.30–1.06 ppm. In the ^{13}C NMR spectrum of compound **3b**, the three methyls from the TIPS group appeared as the quartet at δ 18.6 ppm and three methine carbons resonated at δ 11.1 ppm. A further distinctive acetylene peak of TIPS-alkyne appeared both as a singlet at δ 102.9 and at δ 102.1 ppm. Next, in the HRMS, the calculated accurate mass for the compound was 421.2106 and it was found at 421.2110 thus confirming the monoalkynylation product formation. Similarly, in case of dialkynylated compound **4b**, two *ortho* proton peaks of the aryl group of quinazolinone were seen

to disappear completely and the multiplet of 42 protons of the TIPS group was observed to resonate at δ 0.85 ppm. In the ^{13}C NMR spectrum of compound **4b**, the twelve methyl carbons of the TIPS group appeared as a quartet at δ 18.3 ppm and the six methine carbons resonated at δ 10.9 ppm as a doublet. Furthermore, all the four carbons from the acetylene group were seen as quaternary carbons, out of which two carbons resonated at δ 101.5 with a corresponding fluorine coupling constant value of $J_{C\text{-}F}$ = 3.0 Hz and the other two at δ 98.7 ppm. The HRMS peak at 601.3449 provided additional support for the assigned structure of the dialkynylation product **4b**.

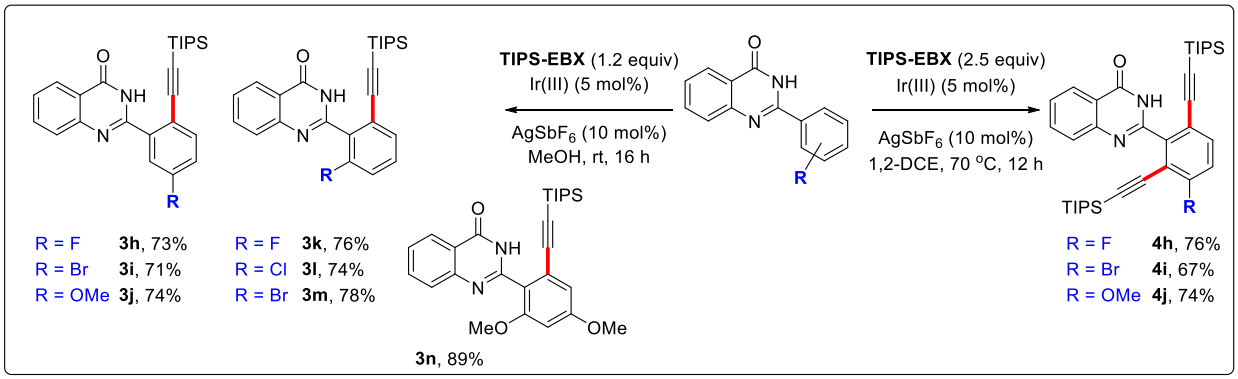


Scheme S1.32: *Selective mono- or dialkynylation of substrates containing substituent at the para-position*

In the ^{1}H NMR spectrum of compound **3f**, the one *ortho* proton of the aryl group of quinazoline ring was seen to disappear and the multiplet for 21 protons of the TIPS groups was seen to resonate at δ 1.29–1.10 ppm. In the ^{13}C NMR spectrum of compound **3f**, the three methyl carbons from the TIPS group appeared as the quartet at δ 18.7 ppm and the three methine carbons resonated at δ 11.2 ppm. A further distinctive quaternary acetylene peak of TIPS-alkyne appeared at δ 102.9 and another at δ 102.1 ppm. Next, in the HRMS, the calculated accurate mass for the compound was 433.2306 and it was found at 433.2310, thus satisfying the expected monoalkynylation product formation. Similarly, in case of the dialkynylated product **4f**, we observed that two *ortho* protons peaks of the aryl group of quinazolinone were missing completely and the TIPS group multiplet integrating for 42 protons was seen to resonate at δ 0.86 ppm. In the

^{13}C NMR spectrum, the twelve methyl carbons of the TIPS group appeared as a quartet at δ 18.3 ppm and the six methine carbons resonated at δ 10.9 ppm as a doublet. Further, out of the four carbons from the acetylene group, two carbons resonate at δ 102.7 and the other two at δ 96.8. All four appeared as the quaternary carbons. An HRMS peak at 613.3649 provided additional evidence for the dialkynylation product **4f**.

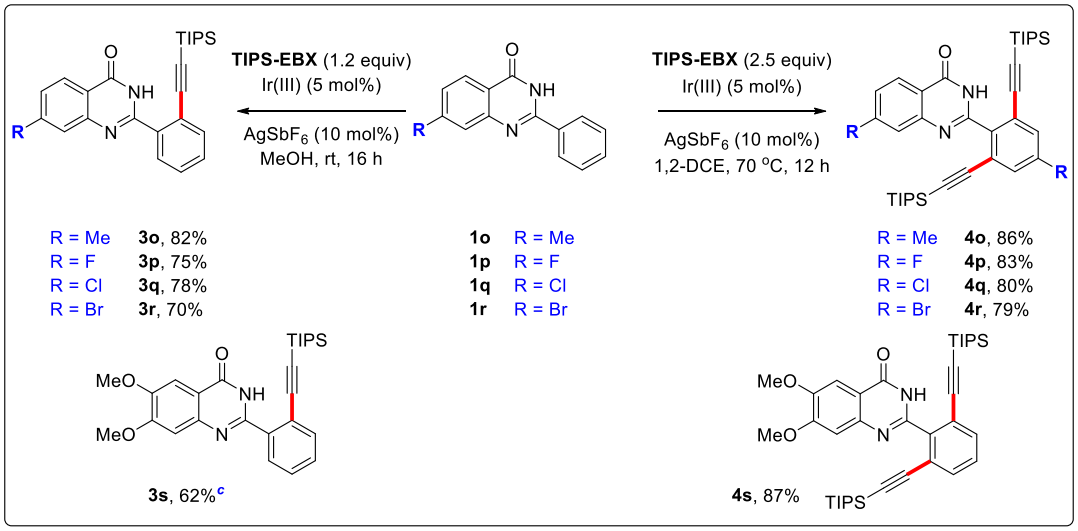
Next, the selective mono-/dialkynylation of substrates **1h**–**1j** having different substituents at the *meta*-position (F, Br, OMe; respectively **1h**–**1j**) was carried out. These reactions proceeded smoothly with **2** under optimized conditions and provided the corresponding monoalkynylated products **3h**–**3j** (71-74%) and dialkynylated products **4h**–**4j** (67-76%) in good to excellent yields. Next, the alkynylation of the *ortho*-substituted derivatives **1k**–**1m** has been carried out to look at the possible steric hindrance of another *ortho*-substitution on the reaction outcome. The reactions proceeded smoothly under the optimized conditions at rt and provided the corresponding alkynylated derivatives **3k**–**3m** in good yields. Even with the 2,4-dimethoxy aryl substrate, the alkynylation reaction proceeded smoothly and provided the corresponding product **3n** in 89% yield (Scheme S1.33).



Scheme S1.33: *Selective mono- or dialkynylation of substrates containing substituent at meta and ortho-position*

After having explored the scope of the reaction with substrates having variations mainly on the pendant aryl rings, we next proceeded further to examine the substrate scope by varying the substitution on the quinazoline aryl ring, along with the changing of the substitution, by also

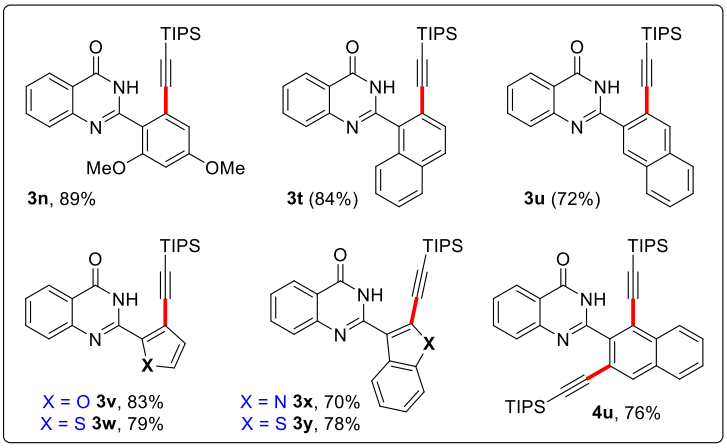
varying the pendant aryl ring. As shown in Scheme S1.34, the selective mono-/dialkynation of the C7–(Me, F, Br or NO_2) substituted 2-phenylquinazolin-4-ones **1o–1r** has been examined initially. In all the cases, the mono- and dialkynylation with **2** proceeded smoothly and provided the corresponding monoalkynylated products **3o–3r** (70-82%) and dialkynylated products **4o–4r** (79-86%) in very good yields. However, the monoalkynylation of 6,7-dimethoxy-2-phenylquinazolin-4(3*H*)-one (**1s**) gave the corresponding monoalkynylated product **3s** in 62% yield, along with the dialkynylated product **4s** in 14% yield.



Scheme S1.34: *Selective mono- or dialkynylation of substrates containing substituents present on* quinazoline aryl ring

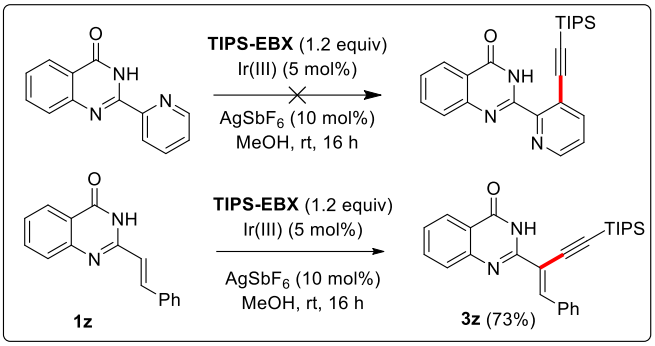
Next, the scope of the alkynylation reaction has been examined by employing quinazolin-4-ones **1t**–**1y** having C2-napthyl and heteroaryl substituents. In case of 2-(1-napthyl) quinazolin-4(3*H*)-one (**1t**), the alkynylation happened as expected at the C2 of the naphthyl ring and gave the corresponding product **3t** in 84% yield. In the ^{1}H NMR spectrum of compound **3t**, the one *ortho* proton of the naphthyl ring was seen to disappear and the multiplet for 21 protons of the TIPS groups was seen to resonate at δ 1.06–0.78 ppm. In the ^{13}C NMR spectrum of compound **3t**, the three methyls from the TIPS group appeared as a quartet at δ 18.4 ppm and the three methine carbons resonated at δ 11.0 ppm. A further distinctive acetylene peak of TIPS-alkyne appeared both as singlet at δ 103.9 and at δ 97.9 ppm. Next, in the HRMS, the calculated accurate mass for the compound was 453.2357 and it was found at 453.2361, thereby confirming the expected

product formation. On the other hand, in case of the isomeric 2-(2-napthyl) quinazolin-4(3*H*)-one (**1u**), the monalkynylation took place selectively at the C3 position instead of C1, resulting in the product **3u**. In the ^{1}H NMR spectrum of compound **3u**, the one *ortho* proton of the naphtyl ring was seen to disappear and the multiplet for 21 protons of the TIPS groups was seen to resonate at δ 1.22–1.09 ppm. In this case, two protons that are at the C1 and C4 positions appeared as two singlets: one at δ 8.73 ppm and another at δ 8.17 ppm. This proves that the alkynylation took place regioselectively at the C3 position rather than at the C1 position due to steric factors. In the ^{13}C NMR spectrum of compound **3u**, the three methyl carbons from the TIPS group appeared as a quartet at δ 18.7 ppm and the three methine carbons resonated at δ 11.2 ppm. A further quaternary acetylene peak of the TIPS-alkyne appeared at δ 104.5 and another at δ 99.1 ppm. Next, in the HRMS, the calculated accurate mass for the compound was found to be 453.2357 and it was found at 453.2355, thus demonstrating the **3u** product formation. This site selectivity seemed to originate from steric hindrance from the fused aromatic ring. The dialkynylation of **1u** was also facile, giving the 1,3-dialkynylated product **4u** in 76% yield. Coming to the alkynylation of 2-heteroaryl quinazolin-4-ones such as (2-furanyl; **1v**), (2-thiophenyl; **1w**), (3-indolyl; **1x**) and (3-benzothiophenyl; **1y**), under the standard reaction conditions, the alkynylation with **2** proceeded smoothly and gave the products **3v-3y** in good yields (70–83%).



Scheme S1.35: *Selective mono- or dialkynylation of substrates containing C2-napthyl and heteroaryl substituents.*

However, 2-(2-pyridyl)quinazolin-4-none was found to be intact under these reaction conditions, suggesting the possible formation of a stable *N*,*N*'-bidentate iridium complex, which seemed to inhibit further reactions. Interestingly, when (*E*)-2-styrylquinazolin-4(3*H*)-one (**1z**) was employed as a substrate, under the standard reaction conditions, the alkynylation with **2** proceeded selectively at the *β*-carbon of the styrene and gave **3z** in 73% yield.

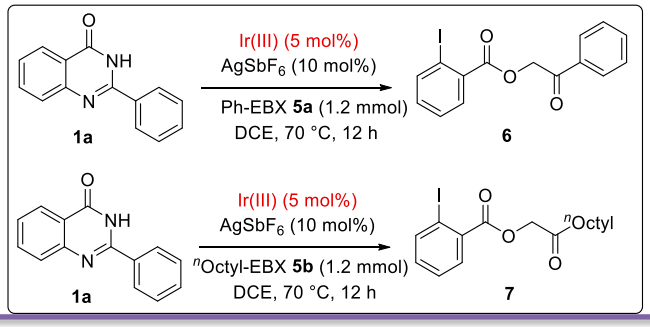


Scheme S1.36: *Selective mono-alkynylation of 2-(2-pyridyl)quinazolin-4-none and (E)-2-styrylquinazolin-4(3H)-one.*

To have a substrate for exploring the synthetic utility, the mono- and dialkynylation of 2-phenylquinazolin-4(3*H*)-one **1a** was carried out on a 1 g scale using 5 mol % of the iridium complex. The reactions proceeded smoothly to afford **3a** (1.5 g) and **4a** (2.3 g) in 82% and 92% yields respectively.

Attempted alkynylation with different R-EBX regents:

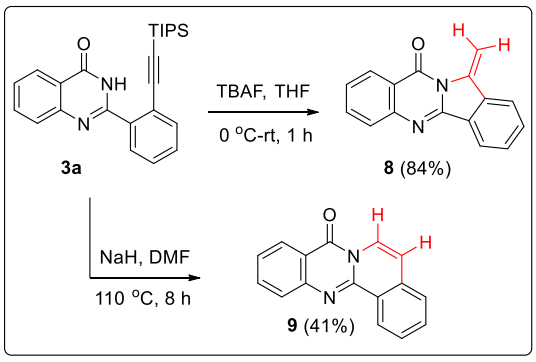
The possibility of using R-EBX (R = *n*-octyl or phenyl) has been examined under both mono and dialkylation conditions. At room temperature, both substrates are intact and when heated, the R-EBX was seen to undergo an internal redox process resulting in the 2-oxo-2-(*n*-octyl or phenyl)ethyl 2-iodobenzoate derivatives (Scheme S1.37).[26-28]



Scheme S1.37: *Alkynylation attempts with R-EBX.*

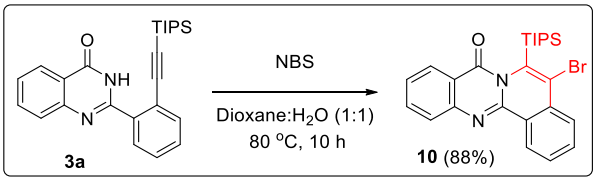
Synthetic utility and gram scale reaction:

Next, to explore the synthetic utility, the complementary 5-*exo*-dig and 6-*endo*-dig cycloisomerization reactions of alkyne **3a** (Scheme S1.38) were carried out by employing, respectively, tetra-*n*-butylammonium fluoride (TBAF) and sodium hydride (NaH) in DMF. The cyclization of alkyne **3a** with TBAF proceeded smoothly and provided the cyclized product **8** in 84% yield. On the other hand, the reaction of alkyne **3a** with NaH, required harsh conditions and the cyclization proceeded in a complementary 6-*exo* dig fashion to provide the known compound **9** in moderate yields.[29] Coming to the structural assignment of compound **8**, in the ^{1}H NMR spectrum, the terminal olefinic methylene protons appeared separately as singlets with a chemical shift difference of 1.03 ppm. One of the protons, which was oriented towards the carbonyl, appeared down field (due to the anisotropic effect of the amide carbonyl oriented *syn* to this proton) at δ 7.07 ppm and another at δ 5.94 ppm, both as singlets. In ^{13}C NMR spectrum of the compound, this methylene carbon appeared as a triplet at δ 101.8 ppm. A further HRMS value calculated for the same was at 247.0866 and it accurately matched with the found value of 247.0865. Coming to the known compound **9**, in the ^{1}H NMR spectrum, the two olefinic protons appeared separately at δ 8.67 ppm and at δ 7.05 ppm, both as doublets with a characteristic cis-olefin coupling constant J = 7.8 Hz. In the ^{13}C NMR of compound **9**, these internal olefin carbons resonated at δ125.8 ppm and δ 113.2 ppm, both as doublets.



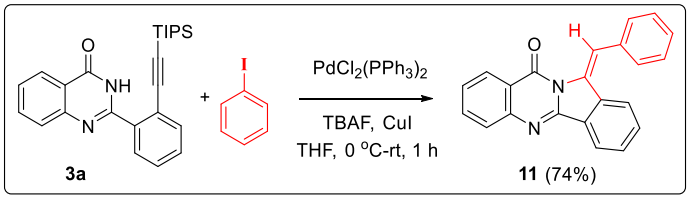
Scheme S1.38: *Selective 5-exo-dig and 6-endo-dig cycloisomerization with TBAF and NaH.*

On the other hand, the electrophilic 6-*endo*-dig bromocyclization of compound **3a** with *N*-bromosuccinimide (NBS) resulted in the formation of **10** in 88% yield. Coming to the structural elucidation, in the ^{1}H NMR spectrum of compound **10**, the TIPS group containing the methyl proton appeared at δ 1.31 ppm as a br. singlet and a methine proton appeared at δ 1.84–1.74 ppm as a multiplet. In the ^{13}C NMR, the methyl carbon from the TIPS group appeared at δ 19.4 ppm as a quartet and the methine carbon appeared at δ 14.2 ppm as doublet. Next, the bromine and TIPS attached two quaternary carbons appeared as singlets at δ 120.0 ppm and at δ 136.7 ppm respectively. A further HRMS value found at 483.1292 confirmed the assigned structure of compound **10**.



Scheme S1.39: *Selective electrophilic 6-endo-dig bromocyclization with NBS.*

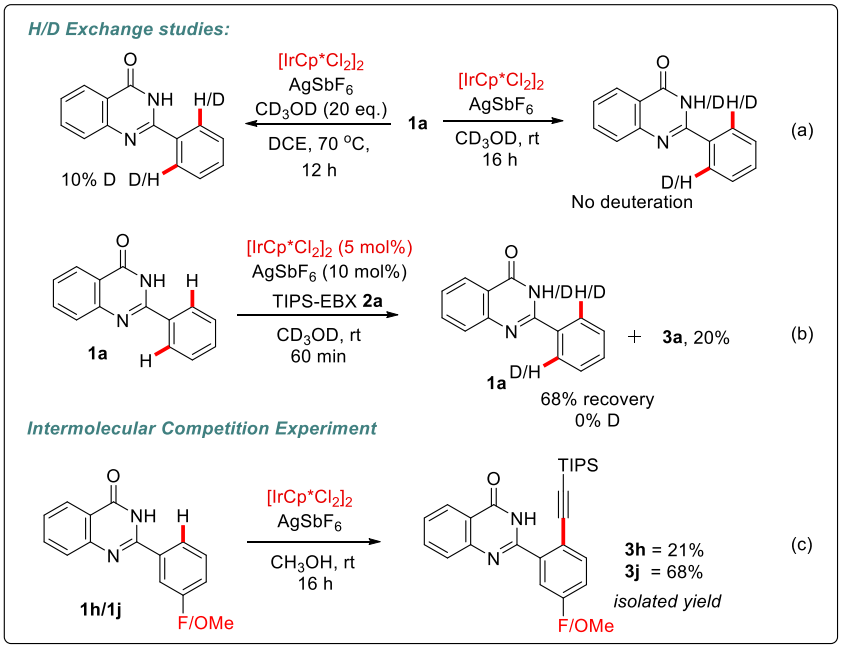
After having explored the possible complementary cycloisomerization with TBAF, NaH and NBS, next we examined the possibility of carrying out the one-pot desilylation with TBAF followed by the [Pd]-catalyzed Sonogashira coupling and intramolecular hydroamination. As shown in Scheme S1.41, the reaction of compound **3a** and iodobenzene, in the presence of $PdCl_2(PPh_3)_2$ (10 mol%) and CuI (30 mol%) along with TBAF (0.4 mL, 1M in THF, 1.2 equiv) in THF at rt, provided a new compound within 1 h, which was characterized as the known compound **11** (Scheme S1.40). The spectral data of compound **11** was in agreement with the data reported by the Wang group.[30] For example, in the ^{1}H NMR spectrum of compound **11**, the terminal olefinic proton resonated down field δ 9.15 ppm as a singlet, thus indicating its orientation syn to the amide carbonyl. In the ^{13}C NMR spectrum, the same olefinic carbon appeared at δ 122.9 ppm as a doublet.



Scheme S1.40: *[Pd]-catalyzed Sonogashira coupling and intramolecular hydroamination.*

Control and competitive experiments:

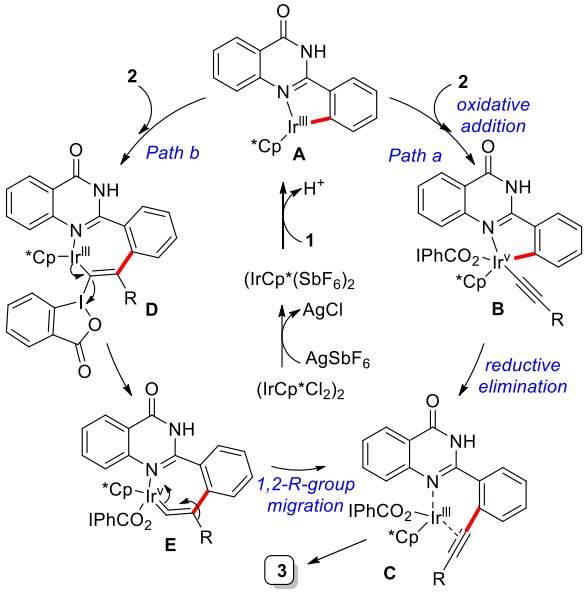
After having established the scope and viability at large scales and also the synthetic utility of the alkynylated products, we next proceeded further to understand the course of the reaction with the help of labeling and control experiments. As shown in Scheme S1.41, no labeling was noticed when the reaction was carried out in CD_3OD at rt. Only nominal 10% deuterium labeling was seen when the reaction was heated in a mixture of DCE and CD_3OD. These labelling experiments revealed that the C−H bond cleavage was a reversible process (Scheme S1.41a). When the reaction was carried out in the presence of **2**, no deuterium incorporation was observed in the recovered **1a**, indicating that the alkynylation process proceeded faster than the deuteration. As expected, the competitive reaction of an equimolar amount of **1h** (3-flurophenyl), **1j** (3-methoxphenyl) and **2** under standard conditions gave **3h** in 21% and **3j** in 68% isolated yield respectively (1:3.2 ratio), indicating that electron-rich phenyl groups underwent alkynylation faster (Scheme S1.41c).



Scheme S1.41: *Control and Competition Experiments.*

Mechanistic Proposal:

Based upon the previous reports,[31-34] we propose the following tentative mechanistic pathway (Scheme S1.42). The catalytic cycle can begin with the formation of the monomeric IrCp*$(SbF_6)_2$ complex, upon reaction of the dimeric iridium complex with $AgSbF_6$. This can undergo a coordinative C–H insertion with 2-arylquinazolin-4-one **1**, resulting in the cyclometalated Ir(III)-complex **A**.[31] There are two possible pathways proposed for the transfer of the alkyne group from the TIPS-EBX to the aryl ring. In one path, the involvement of an intermediate Ir(V) species occurs *via* oxidative addition, resulting in the alkynyl-Ir(V) species **B**, which can undergo a reductive elimination, generating the key Ir(III)-alkyne intermediate **C** (path a). [16b, 32] In another path, the complexation of the intermediate **A** with the alkyne unit TIPS-EBX followed by a regioselective migratory insertion of alkyne results in the intermediate **D** which, upon the α-elimination of 2-iodobenzoic acid, results in the iridium vinylidene species **E**.[33,34b] The intermediate **E** then undergoes a concerted R group-migration followed by elimination, resulting in intermediate **C**, a species that is common in both the pathways a and b. Finally, the alkynylated product **3** and the active Ir(III)-species are generated by the dissociation of alkyne from **C** by complexing with 2-arylquinazolin-4-one **1**, which undergoes a C–H insertion to continue the catalytic cycle.



Scheme S1.42: *Mechanistic Proposal.*

1.10 Conclusions:

In conclusion, [Ir]-catalysed *ortho*-alkynylation of 2-(hetero)arylquinazolin-4-ones with TIPS-EBX has been established. In methanol, selective monoalkynylation has been observed at room temperature. On the other hand, the dialkynylation could be conducted by switching to 1,2-dichloroethane as a solvent and conducting the reaction at 70 °C. A wide-range of mono-/dialkynylated quinazolin-4-ones have been synthesized in good to excellent yields. The synthetic utility of these substrates has been demonstrated by carrying their cycloisomerization with TBAF, NaH and NBS to arrive at complementary cyclization products. In addition, the possibility of Sonogashira coupling and concomitant intramolecular hydroamination has also been demonstrated successfully. Thus, considering the ease of functionalizing the alkyne groups and the importance of the quinazolin-4-one scaffold in new drug discovery programs, this late stage alkynylation provides an attractive handle to synthesize molecules of therapeutic interest.

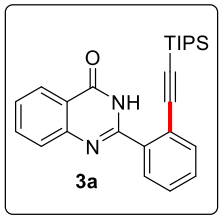
Experimental section:

General procedure for iridium catalyzed C–H monoalkynylation of quinazolin-2-ones: To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added aryl quinqzolinone (0.2 mmol), TIPS-EBX (0.24 mmol), $[IrCp^*Cl_2]_2$ (5 mol%, 8 mg), $AgSbF_6$ (10 mol%, 7 mg), and methanol (3 mL) under air. The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford monoalkynylated quinazolin-2-ones **3**.

General procedure for iridium catalyzed C–H dialkynylation of quinazolin-2-ones: To a screw capped vial with a spinvane triangular shaped teflon stir bar were added quinazolin-4-one (0.2 mmol), TIPS-EBX (0.5 mmol), $[IrCp^*Cl_2]_2$ (5 mol%, 8 mg), $AgSbF_6$ (10 mol%, 7 mg) and 1,2-dichloroethane (3 mL) under air. The reaction mixture was stirred at 70 °C for 12 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (9:1 petroleum ether/EtOAc) to afford dilalkynylated quinazolin-4-ones **4**.

2-(2-((Triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3a):

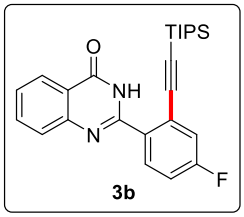
The product was obtained as white solid; Yield: 72 mg (89%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 146–147 °C; IR(neat) ν_{max}: 3022, 2944, 2142, 2863, 2150, 1671, 1563, 1368, 1213, 881, 769, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.34–8.23 (m, 2H), 7.84– 7.72 (m, 2H), 7.69–7.57 (m, 1H), 7.54–7.45 (m, 3H), 1.38–0.99 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 149.1 (s), 134.8 (d), 134.5 (d), 133.7 (s), 130.8 (d), 130.0 (d), 129.2 (d), 128.0 (d), 127.0 (d), 126.5 (d), 121.4 (s), 120.6 (s), 104.1 (s), 100.4 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{31}N_2OSi$ 403.2200, found 403.2206.



3a

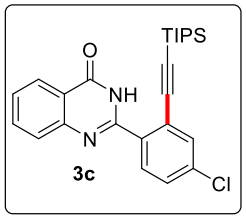
2-(4-Fluoro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3b).

The product was obtained as white solid; Yield: 68 mg (81%). R_f: 0.4 (5:1 petroleum ether/EtOAc) Mp: 154–155 °C; IR(neat) ν_{max}: 2944, 2861, 2155, 1655,1462, 1370, 1223, 876, 768, 637 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ10.71 (s, 1H), 8.42–8.10 (m, 2H), 7.85–7.71 (m, 2H), 7.59–7.43 (m, 1H), 7.32 (dd, J = 8.7, 2.6 Hz, 1H), 7.22 (ddd, J = 8.9, 7.8, 2.7 Hz, 1H), 1.30–1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6 (ds, $J_{C–F}$ = 253.7 Hz), 162.3 (s), 161.3 (s), 150.3 (s), 149.0 (s), 134.6 (d), 132.6(dd, J_{C-F} = 9.2 Hz), 130.0 (ds, J_{C-F} = 2.9 Hz), 128.0 (d), 127.1 (d), 126.5 (d), 122.6 (ds, J_{C-F} = 10.1 Hz) 121.2 (dd, J_{C-F} = 23.6 Hz), 117.1 (dd, J_{C-F} = 21.6 Hz), 102.9 (s), 102.1 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2110.



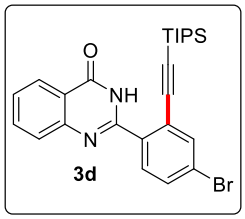
2-(4-Chloro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3c).

The product was obtained as white solid; Yield: 70 mg (81%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 151–152 °C; IR(neat) ν_{max}: 2948, 2860, 2152, 1670, 1463, 1368, 1228, 860, 732, 660 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.29 (dd, J = 8.2, 3.2 Hz, 2H), 7.79 (d, J = 3.8 Hz, 2H), 7.61 (d, J = 2.0 Hz, 1H), 7.49 (ddd, J = 8.6, 6.5, 2.9 Hz, 2H), 1.35–1.04 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 150.2 (s), 149.0 (s), 137.0 (s), 134.7 (d), 134.2 (d), 131.9 (s), 131.5 (d), 129.6 (d), 128.0 (d), 127.2 (d), 126.5 (d), 121.9 (s), 121.4 (s), 102.8 (s), 102.3 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for, $C_{25}H_{30}ClN_2OSi$ 437.1810 found 437.1816.



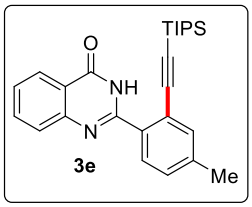
2-(4-Bromo-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3d).

The product was obtained as white solid; Yield: 80 mg (84%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 153–154 °C; IR(neat) ν_{max}: 3281, 2938, 2862, 2146, 1691, 1467, 1372, 1213, 880, 727, 634 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.30 (dt, J = 7.9, 1.1 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 7.89–7.74 (m, 3H), 7.64 (dd, J = 8.6, 2.1 Hz, 1H), 7.57–7.41 (m, 1H), 1.26–0.93 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 150.2 (s), 149.0 (s), 137.1 (d), 134.7 (d), 132.6 (d), 132.3 (s), 131.5 (d), 128.1 (d), 127.2 (d), 126.5 (d), 125.2 (s), 122.1 (s), 121.4 (s), 102.7 (s), 102.5 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1312.



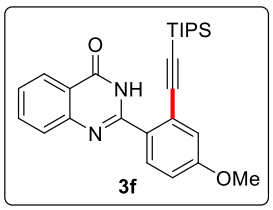
2-(4-Methyl-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3e).

The product was obtained as white solid; Yield: 76 mg (91%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 149–150 °C; IR(neat) ν_{max}: 2944, 2861, 2158, 1680, 1571, 1463, 1369, 1222, 840, 710, 669 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.86–7.64 (m, 2H), 7.54–7.39 (m, 2H), 7.31 (dd, J = 8.2, 1.0 Hz, 1H), 2.41 (s, 3H), 1.76–0.81 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 149.2 (s), 141.4 (s), 135.2 (d), 134.5 (d), 130.7 (s), 130.3 (d), 130.0 (d), 128.0 (d), 126.7 (d), 126.5 (d), 121.3 (s), 120.2 (s), 104.5 (s), 100.1 (s), 21.1 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{33}N_2OSi$ 417.2357, found 417.2362.



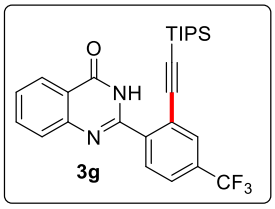
2-(4-Methoxy-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3f).

The product was obtained as white solid; Yield: 72 mg (83%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 150–151 °C; IR(neat) ν_{max}: 2937, 2859, 2143, 1685, 1578, 1460, 1370, 1226, 726, 664 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.32 (d, J = 8.9 Hz, 1H), 8.30–8.26 (m, 1H), 7.79–7.72 (m, 2H), 7.45 (ddd, J = 8.2, 6.0, 2.3 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 7.04 (dd, J = 8.9, 2.7 Hz, 1H), 3.89 (s, 3H), 1.29–1.10 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 161.3 (s), 150.9 (s), 149.3 (s), 134.46 (d), 132.0 (d), 127.8 (d), 126.6 (d), 126.5 (d), 125.9 (s), 121.6 (s), 121.2 (s), 119.3 (d), 115.8 (d), 104.2 (s), 100.6 (s), 55.6 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_2Si$ 433.2306, found 433.2310.



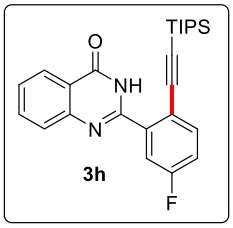
2-(4-(Trifluoromethyl)-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3g).

The product was obtained as white solid; Yield: 74 mg (77%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 169–170 °C; IR(neat) ν_{max}: 2922, 2862, 2140, 1668, 1564, 1464, 1330, 1120, 899, 774, 660 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.42 (d, J = 8.3 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.84–7.77 (m, 2H), 7.74 (dd, J = 8.3, 1.3 Hz, 1H), 7.58–7.47 (m, 1H), 1.46–0.86 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 149.9 (s), 148.8 (s), 136.8 (s), 134.8 (d), 133.0 (s), 132.7 (s), 131.43 (qd, $J_{C\text{-}F3}$ = 3.8 Hz), (q, J = 7.5,Hz), 130.8 (d), 128.2 (d), 127.5 (d), 126.6 (d), 125.6 (qd, $J_{C\text{-}F3}$ = 3.5 Hz), 123.2 (qs, $J_{C\text{-}F3}$ = 273.0 Hz), 121.8 (s), 121.5 (ds, J = 1.2 Hz),



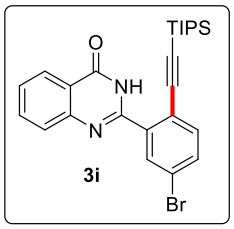
102.6 (s), 18.6 (q, 6C), 11.1 (d, 3C). HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{30}F_3N_2OSi$ 471.2074, found 471.2081.

2-(5-Fluoro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3h).



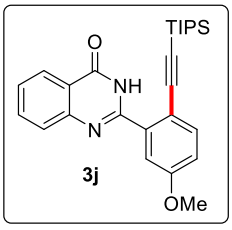
The product was obtained as white solid; Yield: 62 mg (73%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 136–137 °C; IR(neat) ν_{max}: 3296, 2943, 2862, 2150, 1685, 1554, 1462, 1285, 844, 721, 672 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.89–7.71 (m, 2H), 7.57–7.40 (m, 2H), 7.36–7.20 (m, 1H), 1.31–1.02 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2 (ds, $1J_{C–F}$ = 252.7 Hz),161.4 (s), 150.2 (s), 148.9 (s), 135.5 (s), 134.7 (d), 130.0 (dd, $3JC–F$ = 8.7 Hz) , 128.1 (d), 127.2 (d), 126.5 (d), 125.5 (dd, $4J_{C–F}$ = 3.4 Hz), 121.4 (s), 117.8 (dd, $2J_{C–F}$ = 21.8 Hz), 110.0 (ds, $2J_{C–F}$ = 18.8 Hz), 107.2 (s), 96.5 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2107.

2-(5-Bromo-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3i).



The product was obtained as white solid; Yield: 68 mg (71%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 164–165 °C; IR(neat) ν_{max}: 3024, 2939, 2861, 2152, 1665, 1603, 1465, 1291, 878, 767, 658 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.31 (d, J = 7.7 Hz, 1H), 7.86–7.75 (m, 2H), 7.61 (dd, J = 8.3, 2.1 Hz, 1H), 7.54–7.48 (m, 2H), 1.23–1.18 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 149.7 (s), 148.9 (s), 136.0 (d), 134.9 (s), 134.7 (d), 133.9 (d), 132.9 (d), 128.6 (d), 127.32 (d), 126.5 (d), 123.6 (s), 121.4 (s), 119.3 (s), 103.2 (s), 102.2 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1313.

2-(5-Methoxy-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3j).

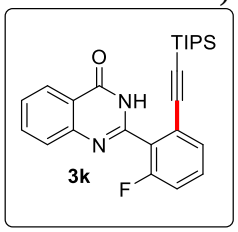


The product was obtained as white solid; Yield: 64 mg (74%). R_f: 0.6 (5:1 petroleum ether/EtOAc) Mp: 122–123 °C; IR(neat) ν_{max}: 2938, 2862, 2150, 1664, 1591, 1463, 1241, 1025, 877, 773, 668 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.84–7.74 (m, 3H), 7.56 (d, J = 8.6 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.01 (dd, J = 8.6, 2.5 Hz, 1H), 3.91 (s, 3H), 1.22–1.01 (m, 21H);

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 160.0 (s), 151.1 (s), 149.1 (s), 136.3 (d), 135.1 (s), 134.5 (d), 128.0 (d), 127.0 (d), 126.5 (d), 121.4 (s), 117.8 (d), 114.1 (d), 112.9 (s), 104.2 (s), 98.4 (s), 55.7 (q), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_2Si$ 433.2306, found 433.2311.

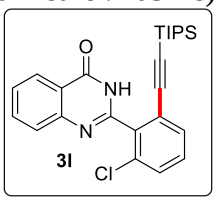
2-(2-Fluoro-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3k).

The product was obtained as white solid; Yield: 62 mg (76%). R_f: 0.4 (5:1 petroleum ether/EtOAc) Mp: 153–154 °C; IR(neat) ν_{max}: 2941, 2863, 2154, 1665, 1467, 1371, 1221, 871, 761, 648 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.91–7.71 (m, 2H), 7.52 (ddd, J = 8.1, 4.8, 3.5 Hz, 1H), 7.47–7.37 (m, 2H), 7.24–7.11 (m, 1H), 0.97–0.74 (m, 21H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3 (s), 159.9 (ds, $J_{C–F}$ = 251.2 Hz), 148.9 (s), 147.6 (s), 134.6 (d), 131.7 (dd, J_{C-F} = 9.2 Hz), 129.3 (dd, J_{C-F} = 3.3 Hz), 128.1 (d), 127.4 (d), 126.4 (d), 125.0 (ds, J_{C-F} = 3.5 Hz), 124.6 (ds, J_{C-F} = 16.4 Hz), 121.4 (s), 116.4(dd, J_{C-F} = 21.6 Hz), 102.2 (ds, J_{C-F} = 3.8 Hz), 97.9 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2107.



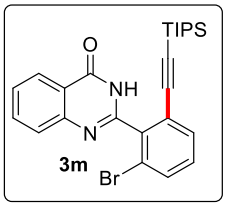
2-(2-Chloro-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3l).

The product was obtained as white solid; Yield: 64 mg (74%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 184–185 °C; IR(neat) ν_{max}: 2943, 2864, 2153, 1670, 1462, 1379, 1228, 860, 738, 661 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.86–7.68 (m, 2H), 7.57–7.48 (m, 2H), 7.46 (dd, J = 8.2, 1.3 Hz, 1H), 7.43–7.34 (m, 1H), 0.87–0.80 (m, 21H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.6 (s), 150.2 (s), 148.9 (s), 135.6 (s), 134.6 (d), 133.1 (s), 131.4 (d), 130.9 (d), 129.7 (d), 128.1 (d), 127.4 (d), 126.3 (d), 125.2 (s), 121.4 (s), 102.3 (s), 97.8 (s), 18.3 (q, 6C), 10.9 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for, $C_{25}H_{30}ClN_2OSi$ 437.1810 found 437.1814.



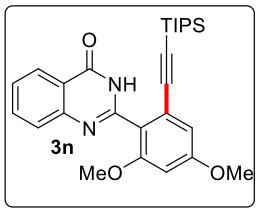
2-(2-Bromo-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3m).

The product was obtained as white solid; Yield: 75 mg (78%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 194–195 °C; IR(neat) ν_{max}: 3222, 2940, 2862, 2148, 1666, 1468, 1370, 1220, 882, 730, 636 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.26 (dd, J = 8.4, 4.5 Hz, 1H), 7.79 (d, J = 3.6 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 7.8, 1.1 Hz, 1H), 7.55–7.49 (m, 1H), 7.32 (t, J = 8.0 Hz, 1H), 1.04–0.71 (m, 21H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 161.9 (s), 151.1 (s), 148.8 (s), 137.4 (s), 134.6 (d), 132.8 (d), 131.9 (d), 131.1 (d), 128.1 (d), 127.4 (d), 126.4 (d), 125.2 (s), 121.8 (s), 121.5 (s), 102.2 (s), 98.0 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1309.



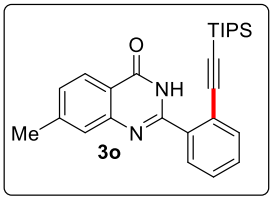
2-(2,4-Dimethoxy-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3n).

The product was obtained as white solid; Yield: 82 mg (89%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 129–130 °C; IR(neat) ν_{max}: 2922, 2860, 2145, 1671, 1596, 1387, 1216, 1021, 861, 734, 643 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 11.3 (s, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.20 (s, 1H), 8.11–7.97 (m, 2H), 7.72 (ddd, J = 8.2, 6.7, 1.6 Hz, 1H), 7.51 (s, 1H), 4.29 (s, 3H), 4.23 (s, 3H), 1.58–1.31 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.9 (s), 150.7 (s), 150.0 (s), 149.2 (s), 134.5 (d), 127.8 (d), 126.7 (d), 126.6 (s), 126.5 (d), 121.2 (s), 116.2 (d), 113.2 (s), 112.1 (d), 104.5 (s), 99.5 (s), 56.2 (q), 56.2 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{35}N_2O_3Si$ 463.2411, found 463.2419.



7-Methyl-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3o).

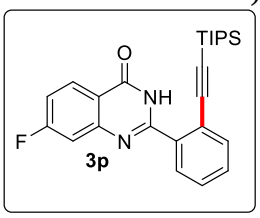
The product was obtained as white solid; Yield: 68 mg (82%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 118–119 °C; IR(neat) ν_{max}: 2935, 2859, 2155, 1655, 1610, 1456, 1216, 880, 791, 666 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.29 (dd, J = 7.4, 1.5 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.65 (dd, J = 7.1, 1.6 Hz, 1H), 7.60 (s, 1H), 7.55–7.45 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 2.52 (s, 3H), 1.49–0.76 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 151.2 (s), 149.3 (s), 145.5 (s), 134.8 (d), 133.7 (s), 130.68 (d), 130.0 (d), 129.2 (d), 128.5 (d), 127.8 (d), 126.3 (d), 120.5 (s), 119.0 (s),



104.2 (s), 100.5 (s), 21.9 (q), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{33}N_2OSi$ 417.2357, found 417.2352.

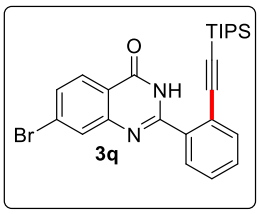
7-Fluoro-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin4(3*H*)-one(3p).

The product was obtained as white solid; Yield: 63 mg (75%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 121–122 °C; IR(neat) ν_{max}: 3283, 2944, 2861, 2143, 1687, 1576, 1373, 1285, 879, 765, 676 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.92 (brs, 1H), 8.33–8.17 (m, 2H), 7.69–7.56 (m, 1H), 7.54–7.48 (m, 2H), 7.43 (d, J = 9.7 Hz, 1H), 7.24–7.13 (m, 1H), 1.31–0.84 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7 (ds, $1J_{C–F}$ = 254.2 Hz), 160.7 (ds, J_{C-F} = 2.6 Hz), 152.4 (s), 151.3(ds, J_{C-F} = 13.2 Hz), 134.9 (d), 133.3 (ds, J_{C-F} = 3.1 Hz), 131.0 (d), 130.0 (d), 129.2 (dd, $J_{C–F}$ = 2.0 Hz), 129.1 (d), 120.7(ds, J_{C-F} = 2.4 Hz), 118.1 (ds, $J_{C–F}$ = 1.8 Hz), 115.7 (dd, $J_{C–F}$ = 23.6 Hz), 113.3 (dd,$J_{C–F}$ = 21.8 Hz), 104.1 (s), 100.7 (s), 18.6 (q, 6C), 11.2 (d, 3C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –103.2.; HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2100.



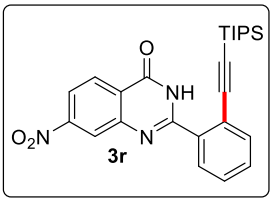
7-Bromo-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3q).

The product was obtained as white solid; Yield: 75 mg (78%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 124–125 °C; IR(neat) ν_{max}: 3308, 2941, 2143, 2864, 1689, 1587, 1462, 1234, 880, 769, 659 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.70–7.62 (m, 1H), 7.58 (dd, J = 8.5, 1.9 Hz, 1H), 7.56–7.45 (m, 2H), 1.56–0.89 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 152.2 (s), 150.1 (s), 135.0 (d), 133.0 (s), 131.1 (d), 130.8 (d), 130.3 (d), 130.1 (d), 129.3 (d), 129.3 (s), 127.9 (d), 120.5 (s), 120.2 (s), 104.1 (s), 101.1 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1298.



7-Nitro-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3r).

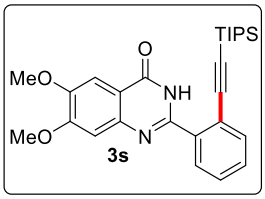
The product was obtained as yellow solid; Yield: 62 mg (70%). R_f: 0.4 (5:1 petroleum ether/EtOAc) Mp: 147–148 °C; IR(neat) ν_{max}: 3261, 2933, 2862, 2150, 1702, 1576, 1347, 1228, 880, 731, 676 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 8.7 Hz, 1H), 8.44–



8.39 (m, 1H), 8.24 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.73–7.66 (m, 1H), 7.62–7.43 (m, 2H), 1.26–1.03 (m, 21H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 160.1 (s), 153.0 (s, 2C), 151.8 (s), 149.7 (s), 135.2 (d), 132.2 (s), 131.6 (d), 130.2 (d), 129.5 (d), 128.4 (d), 125.5 (s), 123.6 (d), 120.5 (d), 104.0 (s), 101.8 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}N_3O_3Si$ 448.2051, found 448.2047.

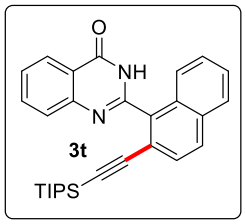
6,7-Dimethoxy-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (3s).

The product was obtained as white solid; Yield: 58 mg (62%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 129–130 °C; IR(neat) ν_{max}: 2942, 2861, 2148, 1656, 1569, 1385, 1269, 1218, 1080, 980, 878, 668 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.33 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.70–7.66 (m, 2H), 7.57–7.48 (m, 2H), 7.29 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 1.33–1.10 (m, 21H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7 (s), 155.1 (s), 149.9 (s), 149.3 (s), 145.4 (s), 134.9 (d), 133.5 (s), 130.6 (d), 129.7 (d), 129.3 (d), 120.3 (s), 114.7 (s), 108.5 (d), 105.5 (d), 104.3 (s), 100.5 (s), 56.4 (q), 56.3 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{35}N_2O_3Si$ 463.2411, found 463.2408.



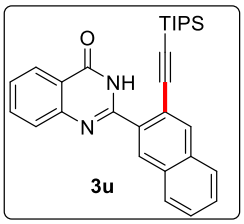
2-(2-((Triisopropylsilyl)ethynyl)naphthalen-1yl)quinazolin-4(3*H*)-one (3t).

The product was obtained as yellow solid; Yield: 76 mg (84%). R_f: 0.6 (5:1 petroleum ether/EtOAc) Mp: 202–203 °C; IR(neat) ν_{max}: 2943, 2858, 2142, 1662, 1466, 1371, 1221, 880, 768, 670, 634 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.29 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.84–7.79 (m, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.58–7.45 (m, 3H), 1.06–0.78 (m, 21H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0 (s), 151.6 (s), 149.0 (s), 134.7 (d), 134.5 (s), 132.9 (s), 130.7 (s), 130.2 (d), 128.7 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.3 (d), 127.2 (d), 126.4 (d), 124.9 (d), 121.5 (s), 121.0 (s), 103.9 (s), 97.9 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{33}N_2OSi$ 453.2357, found 453.2361.



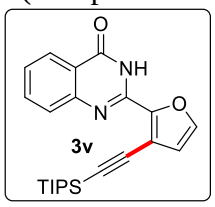
2-(3-((Triisopropylsilyl)ethynyl)naphthalen-2-yl)quinazolin-4(3*H*)-one (3u).

The product was obtained as white solid; Yield: 64 mg (72%). R_f: 0.6 (5:1 petroleum ether/EtOAc) Mp: 194–195 °C; IR(neat) ν_{max}: 2941, 2861, 2148, 1665, 1602, 1462, 1370, 1224, 880, 763, 668, 639 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.73 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H), 7.97 (d, J = 7.1 Hz, 1H), 7.86 (d, J = 7.9 Hz, 2H), 7.83–7.74 (m, 1H), 7.65–7.53 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 1.22–1.09 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 151.6 (s), 149.3 (s), 135.3 (d), 134.3 (d), 133.6 (s), 132.5 (s), 130.8 (d), 130.3 (s), 129.0 (d), 128.5 (d), 128.0 (d), 127.9 (d), 127.4 (d), 126.9 (d), 126.5 (d), 121.3 (s), 117.0 (s), 104.5 (s), 99.1 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{29}H_{33}N_2OSi$ 453.2357, found 453.2355.



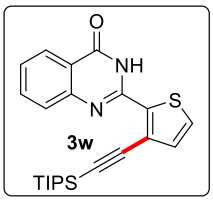
2-(3-((Triisopropylsilyl)ethynyl)furan-2-yl)quinazolin-4(3*H*)-one (3v).

The product was obtained as yellow solid; Yield: 64 mg (83%). R_f: 0.6 (5:1 petroleum ether/EtOAc) Mp: 148–149 °C; IR(neat) ν_{max}: 2924, 2858, 2139, 1655, 1370, 1211, 881, 748, 642 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.29 (dd, J = 8.0, 1.1 Hz, 1H), 7.84 (dd, J = 8.2, 0.7 Hz, 1H), 7.77 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 1.31–1.13 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.7 (s), 148.7 (s), 146.7 (s), 145.2 (d), 143.0 (s), 134.8 (d), 128.1 (d), 127.2 (d), 126.7 (d), 121.8 (s), 115.6 (d), 110.4 (s), 103.9 (s), 96.9 (s), 18.8 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_2Si$ 393.1993, found 393.1995.



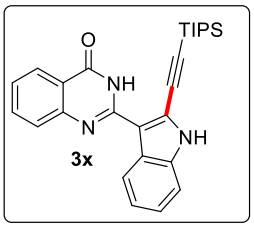
2-(3-((Triisopropylsilyl)ethynyl)thiophen-2-yl)quinazolin-4(3*H*)-one (3w).

The product was obtained as yellow solid; Yield: 64 mg (79%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 136–137 °C; IR(neat) ν_{max}: 2944, 2861, 2141, 1689, 1464, 1348, 1212, 769, 710, 668 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.82–7.61 (m, 2H), 7.49–7.41 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 1.36–1.12 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9 (s), 148.9 (s), 146.8 (s), 138.5 (s), 134.6 (d), 132.5 (d), 129.8 (d), 127.6 (d), 126.7 (d), 126.6 (d), 121.6 (s), 121.2 (s), 102.3 (s), 100.4 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2OSSi$ 409.1764, found 409.1765.



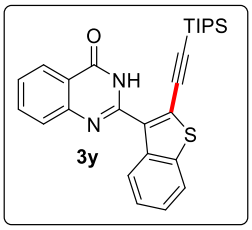
2-(2-((Triisopropylsilyl)ethynyl)-1*H*-indol-3-yl)quinazolin-4(3*H*)-one (3x).

The product was obtained as yellow solid; Yield: 60 mg (70%). R_f: 0.5 (5:1 petroleum ether/EtOAc) Mp: 209–210 °C; IR(neat) ν_{max}: 3254, 2937, 2862, 2139, 1661, 1584, 1418, 1235, 874, 718, 674 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (brs, 1H), 8.89 (d, J = 7.4 Hz, 1H), 8.70 (brs, 1H), 8.30 (dd, J = 7.9, 1.1 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.76 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.43 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 7.40–7.31 (m, 3H), 1.36–1.11 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 149.9 (s), 148.5 (s), 135.8 (s), 134.4 (d), 127.9 (d), 126.5 (d), 126.0 (d), 125.6 (s), 125.5 (d), 123.9 (d), 122.7 (d), 121.3 (s), 118.4 (s), 113.4 (s), 110.8 (d), 105.9 (s), 96.8 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{32}N_3OSi$ 442.2309, found 442.2305.



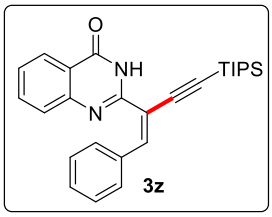
2-(2-((Triisopropylsilyl)ethynyl)benzo[b]thiophen-3-yl)quinazolin-4(3*H*)-one (3y).

The product was obtained as yellow solid; Yield: 72 mg (78%). R_f: 0.6 (5:1 petroleum ether/EtOAc) Mp: 170–171 °C; IR(neat) ν_{max}: 2930, 2861, 2133, 1664, 1594, 1457, 885, 765, 684, cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.83–7.75 (m, 2H), 7.54–7.45 (m, 3H), 1.51–1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 149.0 (s), 147.4 (s), 139.2 (s), 136.7 (s), 134.6 (d), 130.1 (s), 128.2 (d), 127.2 (d), 126.8 (d), 126.6 (d), 126.6 (d), 125.9 (d), 124.8 (s), 121.7 (ds, 2C), 108.9 (s), 97.7 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{31}N_2OSSi$ 459.1921, found 459.1916.



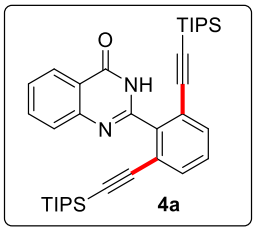
(*Z*)-2-(1-Phenyl-4-(triisopropylsilyl)but-1-en-3-yn-2-yl)quinazolin-4(3*H*)-one (3z).

The product was obtained as yellow thick liquid; Yield: 62 mg (73%). R_f: 0.6 (5:1 petroleum ether/EtOAc) IR(neat) ν_{max}: 3308, 2941, 2864, 1689, 1587, 1462, 1234, 880, 769, 659, cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 11.33 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.79–7.71 (m, 2H), 7.52–7.42 (m, 4H), 7.12 (s, 1H), 1.46–1.09 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0 (s), 150.2 (s), 149.2 (s), 136.9 (s), 134.6 (d), 129.9 (d), 129.0 (s), 128.8 (d, 2C), 127.8 (d), 127.4 (d), 127.24 (d), 126.9 (d, 2C), 126.7 (d), 121.8 (s), 109.5 (s), 102.9 (s), 18.7 (q,



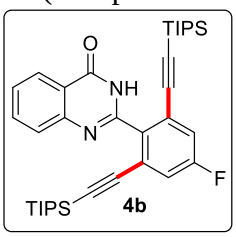
6C), 11.2 (d, 3C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{33}N_2OSi$ 429.2357, found 429.2356.

2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4a).



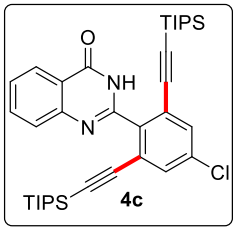
The product was obtained as white solid; Yield: 110 mg (94%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp. 188–189 °C; IR(neat) ν_{max}: 2943, 2862, 2148, 1666, 1459, 1370, 1224, 880, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.75 (dd, J = 4.6, 1.2 Hz, 2H), 7.58–7.54 (m, 2H), 7.52–7.48 (m, 1H), 7.40 (dd, J = 8.3, 7.4 Hz, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 148.9 (s), 138.9 (s), 134.4 (d), 132.7 (d, 2C), 129.8 (d), 128.1 (d), 127.1 (d), 126.2 (d), 123.3 (s, 2C), 121.6 (s), 102.6 (s, 2C), 97.2 (s, 2C), 18.3 (q, 12C),11.0 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{51}N_2OSi_2$ 583.3534, found 583.3543.

2-(4-Fluoro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4b).



The product was obtained as white solid; Yield: 100 mg (83%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 168–169 °C. IR(neat) ν_{max}: 2942, 2863, 2149, 1668, 1464, 1369, 1223, 996, 878, 662 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.88–7.65 (m, 2H), 7.52–7.48 (m, 1H), 7.26 (d, J = 8.6 Hz, 2H), 0.85 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4 (ds, J_{C-F} = 251.7 Hz), 161.6 (s), 150.5 (s), 148.9 (s), 135.5(ds, J_{C-F} = 3.4 Hz), 134.4 (d), 128.1 (d, 2C), 127.3 (d), 126.2 (d), 125.4 (ds, J_{C-F} = 10.9 Hz, 2C), 121.6 (s), 119.7(dd, J_{C-F} = 23.3 Hz), 101.5(ds, J_{C-F} = 3.0 Hz, 2C), 98.7 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3449.

2-(4-Chloro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4c).

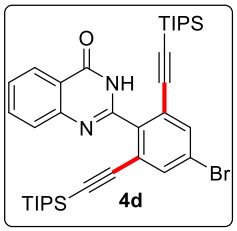


The product was obtained as white solid; Yield: 100 mg (81%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 185–186 °C; IR(neat) ν_{max}: 2942, 2863, 2152, 1664, 1498, 1369, 1212, 999, 772, 662 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.82–7.71 (m, 2H), 7.54 (s, 2H), 7.53–7.48 (m, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.3 (s), 148.8

(s), 137.2 (s), 135.8 (s), 134.4 (d), 132.4 (d, 2C), 128.1 (d), 127.3 (d), 126.2 (d), 124.8 (s, 2C), 121.6 (s), 101.3 (s, 2C), 98.9 (s, 2C), 18.3 (q, 12 C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}ClN_2OSi_2$ 617.3145, found 617.3153.

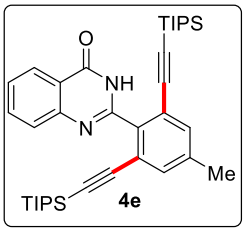
2-(4-Bromo-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4d).

The product was obtained as white solid; Yield: 110 mg (83%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 181–182 °C; IR(neat) ν_{max}: 2942, 2862, 2152, 1667, 1464, 1369, 1213, 939, 773, 670 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.79–7.72 (m, 2H), 7.69 (s, 2H), 7.53–7.49 (m, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.4 (s), 148.8 (s), 137.7 (s), 135.2 (d, 2C), 134.5 (d), 128.1(d), 127.3 (d), 126.2 (d), 124.9 (s, 2C), 123.6 (s), 121.6 (s), 101.2 (s, 2C), 99.1 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$ 661.2640, found 661.2643.



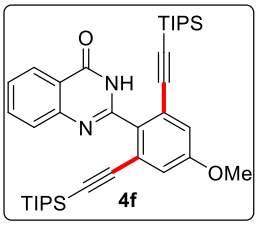
2-(4-Methyl-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4e).

The product was obtained as white solid; Yield: 114 mg (96%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 190–191 °C. IR(neat) ν_{max}: 2970, 2862, 2144, 1668, 1438, 1369, 1212, 901, 653 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 3.8 Hz, 2H), 7.48 (m, 1H), 7.37 (s, 2H), 2.37 (s, 3H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.8 (s), 151.2 (s), 148.9 (s), 140.1 (s), 136.2 (s), 134.3 (d), 133.3 (d, 2C), 128.1 (d), 127.0 (d), 126.1 (d), 123.0 (s, 2C), 121.6 (s), 102.8 (s, 2C), 96.5 (s, 2C), 20.93 (q), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{53}N_2OSi_2$ 597.3691, found 597.3702.



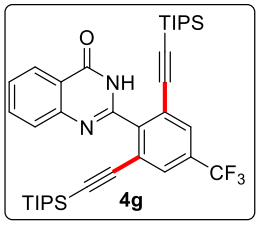
2-(4-Methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4f).

The product was obtained as white solid; Yield: 116 mg (95%). R_f: 0.8 (9:1 petroleum ether/EtOAc) Mp: 183–184 °C; IR(neat) ν_{max}: 2940, 2862, 2144, 1669, 1496, 1369, 1222, 880, 670 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 7.74 (dd, J = 4.6, 1.0 Hz, 2H), 7.54–7.40 (m, 1H), 7.05 (s, 2H), 3.86 (s, 3H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 160.1 (s), 151.1 (s), 149.0 (s), 134.3 (d), 131.9 (s), 128.1 (d), 127.0 (d), 126.1 (d), 124.5 (s,



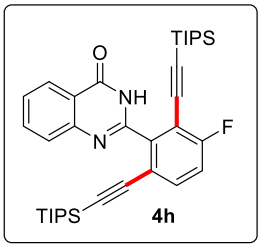
2C), 121.5 (s), 118.3 (d, 2C), 102.7 (s, 2C), 96.8 (s, 2C), 55.8 (q), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{53}N_2O_2Si_2$ 613.3640, found 613.3649.

2-(4-(Trifluoromethyl)-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4g).



The product was obtained as white solid; Yield: 114 mg (88%). R_f: 0.8 (9:1 petroleum ether/EtOAc) Mp: 186–187 °C; IR(neat) ν_{max}: 2942, 2860, 2156, 1670, 1496, 1373, 1232, 950, 880, 674 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.10–7.63 (m, 4H), 7.53–7.49 (m, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 150.1 (s), 148.8 (s), 141.7 (s), 134.5 (d), 132.5 (qs, $2J_{C–F}$ = 33.3 Hz), 129.0 (qd, $3J_{C–F}$ = 3.6 Hz), 128.1 (d), 127.4 (d), 126.2 (d, 2C), 124.5 (s, 2C), 122.9 (qs, $1J_{C–F}$ = 273.2 Hz), 121.7 (s), 101.2 (s, 2C), 99.6 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{50}F_3N_2OSi_2$ 651.3408, found 651.3420.

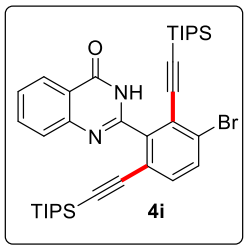
2-(3-Fluoro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4h).



The product was obtained as white solid; Yield: 91 mg (76%). R_f: 0.6 (9:1 petroleum ether/EtOAc) Mp: 178–179 °C; IR(neat) ν_{max}: 2933, 2861, 2140, 1667, 1463, 1370, 1226, 881, 773, 674 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.81–7.68 (m, 2H), 7.56–7.48 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 0.87 (d, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163. 9 (s), 162.7 (ds, J = 252.1 Hz), 161.4 (ds, J_{C-F} = 5.5 Hz), 149.9 (ds, J_{C-F} = 2.2 Hz), 148.8 (s), 140.6 (s), 134.5 (d), 134.1(dd, J_{C-F} = 8.4 Hz), 128.2 (d), 127.4 (d), 126.2 (d), 121.6 (s), 119.3 (ds, J_{C-F} = 4.0 Hz), 117.4 (dd, J_{C-F} = 21.9 Hz), 103.6 (ds, J_{C-F} = 3.6 Hz), 101.7 (s), 96.8 (s), 95.5 (s), 18.3 (dq, J_{C-F} = 2.6 Hz, 12C), 11.0 (dd, J_{C-F} = 4.6 Hz, 6C)^{19}F NMR (376 MHz, $CDCl_3$) δ –105.4.; HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3452.

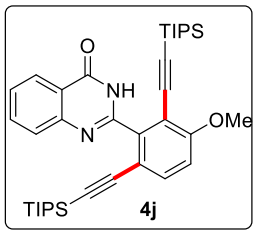
2-(3-Bromo-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4i).

The product was obtained as white solid; Yield: 88 mg (67%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 184–185 °C; IR(neat) ν_{max}: 2940, 2863, 2148, 1681, 1463, 1371, 1209, 991, 879, 669 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.78–7.72 (m, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.51 (ddd, J = 8.2, 6.1, 2.2 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 0.91–0.74 (m, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 150.7 (s), 148.9 (s), 140.5 (s), 134.5 (d), 134.0 (d), 132.9 (d), 128.2 (d), 127.4 (d), 126.3 (d), 122.3 (s), 121.8 (s), 103.5 (s), 101.8 (s), 100.9 (s, 2C), 98.5 (s, 2C), 18.4 (q, 6C), 18.3 (q, 6C), 11.0 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$ 661.2640, found 661.2640.



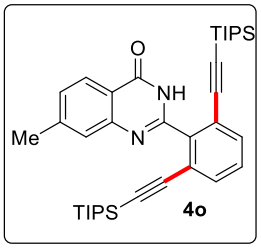
2-(3-Methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3*H*)-one (4j).

The product was obtained as white solid; Yield: 86 mg (74%). R_f: 0.8 (9:1 petroleum ether/EtOAc) Mp: 169–170 °C; IR(neat) ν_{max}: 2942, 2863, 2133, 1669, 1496, 1370, 1232, 880, 670 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 7.76–7.73 (m, 2H), 7.61–7.35 (m, 2H), 6.94 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 0.86 (s, 21H), 0.84 (s, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 160.9 (s), 151.0 (s), 149.0 (s), 140.4 (s), 134.3 (d), 134.0 (d), 128.1 (d), 127.1 (d), 126.1 (d), 121.6 (s), 115.1 (s), 113.1 (s), 112.3 (d), 102.6 (s), 101.8 (s), 98.5 (s), 94.6 (s), 56.4 (q), 18.4 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{53}N_2O_2Si_2$ 613.3640, found 613.3640.



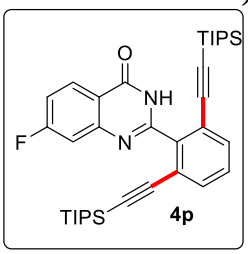
2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-methylquinazolin-4(3*H*)-one (4o).

The product was obtained as white solid; Yield: 102 mg (86%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 202–203 °C; IR(neat) ν_{max}: 2941, 2862, 2141, 1657, 1453, 1370, 1224, 985, 879, 667 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.61–7.55 (m, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 2.49 (s, 3H), 0.87 (s, 42H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.3 (s), 151.1 (s), 149.0 (s), 145.2 (s), 138.9 (s), 132.7 (d, 2C), 129.6 (d), 128.6 (d), 128.0 (d), 126.0 (d), 123.3 (s, 2C), 119.2 (s), 102.6 (s, 2C), 97.1 (s, 2C), 21.9 (q), 18.3 (q, 12C), 11.0 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{37}H_{53}N_2OSi_2$ 597.3691, found 597.3684.



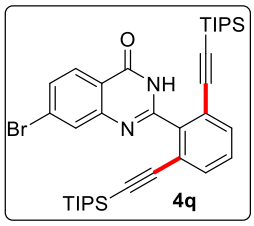
2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-fluoroquinazolin-4(3*H*)-one (4p).

The product was obtained as white solid; Yield: 99 mg (83%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 203–204 °C; IR(neat) ν_{max}: 2940, 2863, 2145, 1663, 1608, 1452, 1370, 1225, 985, 877, 667 cm^{-1} ; ^1H NMR (400 MHz, $CDCL_3$) δ 9.35 (s, 1H), 8.28 (dd, J = 8.7, 6.2 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.44–7.36 (m, 2H), 7.21 (td, J = 8.6, 2.3 Hz, 1H), 0.87 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5 (ds, $J_{C–F}$ = 254.3 Hz), 160.9 (s), 152.7 (s), 151.2 (ds, J_{C-F} = 13.1 Hz), 138.5 (s), 132.7 (d, 2C), 130.0 (d), 128.9 (dd, J_{C-F} = 10.6 Hz), 123.2 (s, 2C), 118.3 (s), 115.8 (dd, J_{C-F} = 23.6 Hz), 113.4 (dd, J_{C-F} = 22.1 Hz), 102.5 (s, 2C), 97.4 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –103.1.; HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3450.



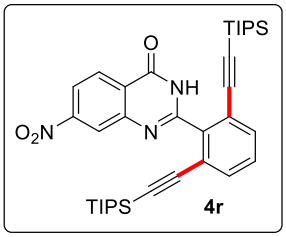
2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-bromoquinazolin-4(3*H*)-one (4q).

The product was obtained as white solid; Yield: 106 mg (80%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 202–203 °C; IR(neat) ν_{max}: 2941, 2862, 2145, 1661, 1596, 1445, 1370, 1225, 986, 881, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 8.5, 1.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.45–7.38 (m, 1H), 0.89 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 152.5 (s), 149.9 (s), 138.4 (s), 132.8 (d, 2C), 130.9 (d), 130.5 (d), 130.0 (d), 129.0 (s), 127.6 (d), 123.2 (s, 2C), 120.5 (s), 102.4 (s, 2C), 97.5 (s, 2C), 18.4 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$ 661.2640, found 661.2637.



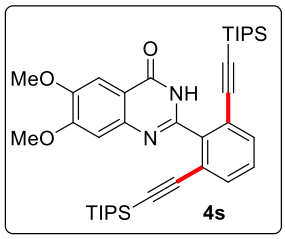
2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-nitroquinazolin-4(3*H*)-one (4r).

The product was obtained as yellow solid; Yield: 98 mg (79%). R_f: 0.6 (9:1 petroleum ether/EtOAc) Mp: 212–213 °C; IR(neat) ν_{max}: 2941, 2862, 2155, 1667, 1606, 1534, 1453, 1346, 1228, 985, 880, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (brs, 1H), 8.59 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.26 (dd, J = 8.7, 2.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4 (s), 153.7 (s), 151.6 (s), 149.6 (s), 137.9 (s), 132.9 (d, 2C), 130.3 (d), 128.1 (d), 125.7 (s), 123.6 (d), 123.1 (s, 2C), 120.8 (d),



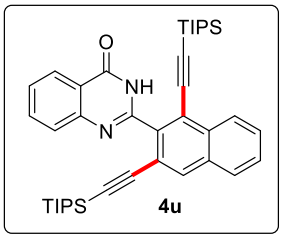
102.4 (s, 2C), 97.7 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{50}N_3O_3Si_2$ 628.3385, found 628.3372.

2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (4s).



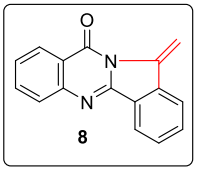
The product was obtained as white solid; Yield: 112 mg (87%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 193–194 °C; IR(neat) ν_{max}: 2940, 2862, 2138, 1647, 1608, 1457, 1385, 1269, 1213, 1093, 980, 878, 666 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.60 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 0.88 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1 (s), 154.8 (s), 149.9 (s), 149.3 (s), 145.3 (s), 138.8 (s), 132.7 (d, 2C), 129.7 (d), 123.3 (s, 2C), 114.9 (s), 108.7 (d), 105.1 (d), 102.7 (s, 2C), 97.0 (s, 2C), 56.4 (q), 56.2 (q), 18.4 (q, 12C), 11.0 (d, 6C); HRMS (ESI–TOF) m/z: $[M]^+$ calcd for $C_{38}H_{54}N_2O_3Si_2$ 642.3667, found 642.3647.

2-(1,3-Bis((triisopropylsilyl)ethynyl)naphthalen-2-yl)quinazolin-4(3*H*)-one (4u).



The product was obtained as white solid; Yield: 96 mg (76%). R_f: 0.7 (9:1 petroleum ether/EtOAc) Mp: 204–205 °C; IR(neat) ν_{max}: 2936, 2862, 2141, 1665, 1606, 1463, 1371, 1023, 881, 665 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.81–7.71 (m, 2H), 7.67–7.55 (m, 2H), 7.53–7.45 (m, 1H), 0.92 (s, 21H), 0.88 (s, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 151.6 (s), 149.0 (s), 136.6 (s), 134.3 (d), 133.3 (d), 133.0 (s), 132.6 (s), 128.6 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.1 (d), 126.8 (d), 126.2 (d), 121.7 (s), 121.7 (s), 119.4 (s), 103.1 (s), 100.7 (s), 96.4 (s, 2C), 18.4 (q, 6C), 18.3 (q, 6C), 11.0 (d, 6C); HRMS (ESI–TOF) m/z: $[M + H]^+$ calcd for $C_{40}H_{53}N_2OSi_2$ 633.3691, found 633.3682.

12-Methyleneisoindolo[1,2-b]quinazolin-10(12*H*)-one (8):

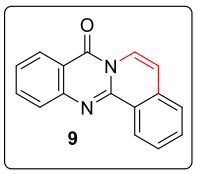


To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in THF (1 mL) was added TBAF (0.24 mL, 0.24 mmol) at 0 °C. After addition, the solution was warmed up to room temperature and stirred for another 1h and quenched with water, extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4. The volatile compounds were removed in vacuo and the residue was subjected to column

chromatography on silica gel to afford **8** (42 mg; 84%). Colorless solid; R_f: 0.5 (5:1 petroleum ether/EtOAc); Mp: 280-282 °C; IR (neat) ν_{max}: 2921, 2552, 1669, 1650, 1602, 1468, 1334, 873, 768, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.4 Hz, 1H), 7.90 – 7.76 (m, 3H), 7.63 (dt, J = 22.0, 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.07 (s, 1H), 5.94 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 151.8 (s), 147.6 (s), 139.7 (s), 135.6 (s), 134.4 (d), 132.4 (d), 130.2 (d), 129.9 (s), 127.6 (d), 127.1 (d), 126.8 (d), 123.0 (d), 121.4 (s), 120.3 (d), 101.8 (t); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{11}ON_2$ 247.0866, found 247.0865.

8*H*-Isoquinolino[1,2-b]quinazolin-8-one (9):

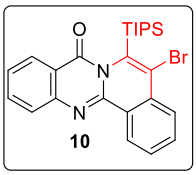
To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in dry DMF (1.5 mL) was added NaH (60%) (4.8 mg, 0.2 mmol) at room temperature. The solution was heated at 80 °C for 10h and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **9** (20 mg 41%). yellow solid; R_f: 0.7 (5:1 petroleum /EtOAc); Mp: 167-169 °C (168–170 °C)[29]; ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.89 (dt, J = 15.0, 7.5 Hz, 2H), 7.77 – 7.72 (m, 1H), 7.67 (dd, J = 12.8, 7.5 Hz, 2H), 7.53 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5 (s), 147.6 (s), 146.2 (s), 134.8 (d), 132.9 (s), 132.2 (d, 2C), 128.5 (d), 127.6 (d), 127.3 (d), 127.3 (d), 126.5 (d), 125.8 (d), 122.0 (s), 117.8 (s), 113.2 (d); LC-MS (ESI) m/z: 247 [M+H].



9

5-Bromo-6-(triisopropylsilyl)-8*H*-isoquinolino[1,2-b]quinazolin-8-one (10):

To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in dioxane:water (1:1) (1.5 mL) was added NBS (53 mg, 0.3 mmol) at room temperature. The solution was heated at 80 °C for 10h and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **10** (85 mg; 88%). yellow solid; R_f: 0.3 (5:1 petroleum /EtOAc); Mp: 180-182 °C; IR (neat) ν_{max}: 2948, 2667, 1676, 1598, 1564, 1466, 1367, 879, 749, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8 Hz, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 1.84 – 1.74 (m, 3H), 1.31 (brs, 18H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 160.0 (s), 145.1 (s), 138.4 (s), 136.7 (s), 132.8 (d), 131.8 (d), 130.5 (s), 129.9

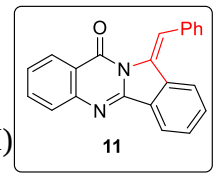


10

(d), 128.5 (d), 125.3 (d), 124.6 (d), 121.9 (d), 121.1 (d), 120.0 (s), 119.9 (s), 19.4 (q, 6C), 14.2 (d, 3C); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{30}ON_2{}^{81}BrSi$ 483.1285, found 483.1292.

(*E*)-12-Benzylideneisoindolo[1,2-b]quinazolin-10(12H)-one (11):

In oven dried Schlenk tube was charged with TIPS-alkyne **3a** (81 mg, 0.2 mmol), aryl iodide (49 mg, 0.24 mmol), $PdCl_2(PPh)_3$ (14 mg, 10 mol%), CuI (11.4 mg, 30 mol%) in sequence. The Schlenk tube was vacuumed and backfilled with nitrogen for three times followed by adding anhydrous THF (1 ml). TBAF (0.4 mL, 1M in THF) was added into the solution at 0 °C and under the protection of nitrogen through syringe and then the Schenk tube was closed tightly. After warming up to room temperature and stirring for 1 hour, water was added and the resulting mixture was extracted with dichloromethane (2×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **11** (48 mg; 74%) as yellow solid.*R_f*: 0.7 (5:1 petroleum /EtOAc); Mp: 184−186 °C (184-185 °C)[30]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1 H) 8.48 (dd, *J*=8.01, 1.14 Hz, 1 H) 8.20 (d, *J*=7.63 Hz, 1 H) 7.83 - 7.88 (m, 1 H) 7.77 - 7.83 (m, 1 H) 7.49-7.56 (m, 4 H) 7.46-7.49 (m, 2H) 7.41-7.46 (m, 1H) 7.33 - 7.38 (m, 1 H) 7.27 - 7.30 (d, *J*= 8.0 Hz, 1 H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.3 (s), 151.4 (s), 147.5 (s), 135.3 (s, 2C), 134.4 (s), 134.3 (d), 131.9 (d), 130.7 (s), 129.6 (d), 129.0 (d, 2C), 128.8 (d, 2C), 128.2 (d), 127.5 (d), 127.2 (d), 126.6 (d), 123.8 (d), 123.2 (d), 122.9 (d), 121.5 (s); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{15}N_2O$ 323.1179, found 323.1179.



11

Procedure for D/H exchange studies in CD_3OD at rt.

A solution of 2-phenylquinazolin-4(3*H*)-one (**1a**, 22.2 mg, 0.10 mmol), $[IrCp^*Cl_2]_2$ (4 mg, 5 mol %), $AgSbF_6$ (3 mg, 10 mol %), CD_3OD (1 mL) was stirred at rt for 16 h. Next, the reaction mixture was filtered through a pad of Celite and then washed with CH_2Cl_2 (5 mL x 3). Solvents were removed under reduced pressure and the compound was analysed by ^{1}H NMR analysis.

Procedure for D/H exchange studies in DCE at 70 °C.

A solution of 2-phenylquinazolin-4(3*H*)-one (**1a**, 22.2 mg, 0.10 mmol), $[IrCp^*Cl_2]_2$ (3.98 mg, 5 mol%), $AgSbF_6$ (3 mg, 10 mol%), 1,2-dichloroethane (0.5 mL) and CD_3OD (0.5 mL) under air. The reaction mixture was stirred at 70 ^{o}C for 12 h. Next, the reaction mixture was filtered through a pad of Celite and then washed with CH_2Cl_2 (5 mL x 3). Solvents were removed under reduced pressure and the compound was analysed by ^{1}H NMR analysis.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.7 Hz, 1H), 8.29 – 8.18 (m, 1.80H), 7.84 (dd, *J* = 9.5, 3.6 Hz, 2H), 7.71 – 7.45 (m, 4H).

Procedure for D/H exchange studies in CD_3OD at rt in the presence of 2.

A solution of 2-phenylquinazolin-4(3*H*)-one (**1a**, 22.2 mg, 0.10 mmol), $[IrCp^*Cl_2]_2$ (4 mg, 5 mol %), $AgSbF_6$ (3 mg, 10 mol %), TIPS-EBX (**2a,** 51 mg, 0.11 mmol), CD_3OD (1 mL) was stirred at rt for 16 h. Next, the reaction mixture was filtered through a pad of Celite and then washed with CH_2Cl_2 (5 mL x 3). Solvents were removed under reduced pressure and the compound was analysed by ^{1}H NMR analysis.

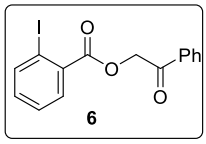
Procedure for doing the Intermolecular competition Experiment.

A solution of equimolar amount of **1h**, **1j** and **2** (0.20 mmol), $[IrCp^*Cl_2]_2$ (8 mg, 5 mol %), $AgSbF_6$ (7 mg, 10 mol %), TIPS-EBX (**2a,** 0.24 mmol), CH_3OH (3 mL) was stirred at rt for 16 h. Next, the reaction mixture was filtered through a pad of Celite and then washed with CH_2Cl_2 (5 mL x 3). Solvents were removed under reduced pressure and the compound was isolated gave **3h** in 21% and **3j** in 68% yield respectively (1:3.2 ratio) and also analysed by ^{1}H NMR analysis.

Procedure for Alkynylation of 1a with Ph-EBX and *n*-Octyl-EBX:

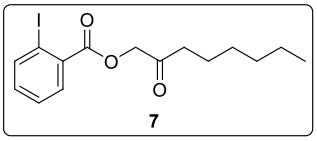
A solution of 2-phenylquinazolin-4(3*H*)-one **1a** (0.2 mmol), Ph-EBX/n-octyl-EBX (0.24 mmol), $[IrCp^*Cl_2]_2$ (5 mol%, 8 mg), $AgSbF_6$ (10 mol%, 7 mg) and 1,2-dichloroethane (3 mL) was stirred at 70 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography (9:1 pet. ether/EtOAc) to afford 2-oxo-2-phenylethyl 2-iodobenzoate (38 mg; 52%) or 2-oxooctyl 2-iodobenzoate (36 mg, 48%) as yellow oils.

2-Oxophenyl 2-iodobenzoate (6):[26-28] R_f: 0.6 (5:1 pet. ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 15.9, 7.8 Hz, 2H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 5.60 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.7 (s), 165.8 (s), 141.5 (d), 134.2 (s), 134.1 (d), 133.1 (d), 131.7 (d), 129.0 (d), 128.1 (d), 127.9 (d), 94.5 (s), 66.7 (t). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}IO_3$ 366.9826, found 366.9829.



6

2-Oxooctyl 2-iodobenzoate (7): R_f: 0.7 (5:1 pet. ether/EtOAc); IR(neat) ν_{max}: 2927, 1725, 1583, 1465, 1247, 1128, 1043, 1014, 739, 637 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.18 (td, *J* = 7.7, 1.5 Hz, 1H), 4.89 (s, 2H), 2.49 (t, *J* = 7.4 Hz, 2H), 1.70 – 1.55 (m, 2H), 1.37 – 1.22 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ 203.6 (s), 165.7 (s), 141.5 (d), 134.0 (s), 133.1 (d), 131.5 (d), 128.0 (d), 94.4 (s), 68.6 (t), 38.9 (t), 31.52 (t), 28.8 (t), 23.2 (t), 22.5 (t), 14.0 (q).; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}IO_3$ 389.0608, found 389.0613.



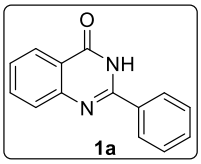
7

5. Experimental Procedure for synthesis of Quinazolinones.

5.1 General Procedure A (for preparing 1a-1g, 1k-1m, 1t, 1v, 1w):[35] A solution of anthranilamide (2.0 mmol; 1.0 equiv) and aryl aldehyde (2.4 mmol; 1.2 equiv) in DMSO (10 mL) was heated at 120 °C for 48 h. After complete consumption of the starting materials as indicated by TLC, the reaction mixture was poured in ice-water; the precipitate was filtered and recrystallized from ethanol.

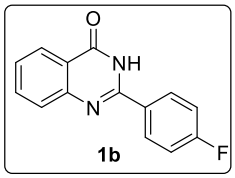
5.2 General Procedure B (for preparing 1h-j, 1n, 1o-s, 1u, 1y, 1z):[36] A solution of amide (2 mmol;1.0 equiv), aldehyde (2.2 mmol; 1.1 equiv.) and *p*-TsOH (0.1 mmol) in THF (20 mL) was stirred at rt for 10 min and then PIDA (3 mmol; 1.5 equiv.) was added portion-wise over 10-15 min and stirring was continued for addition 2h. The reaction mixture was diluted with EtOAc (20 mL) and stirred with sat. aq $NaHCO_3$ solution (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford the desired quinazolinone.

2-Phenylquinazolin-4(3*H*)-one (1a):[35] 392 mg (88%). ^1H NMR (200 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.44 – 8.06 (m, 3H), 8.03 – 7.69 (m, 2H), 7.58 -7.49 (m, 4H).

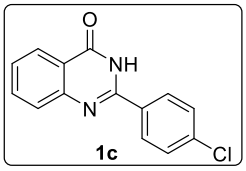


1a

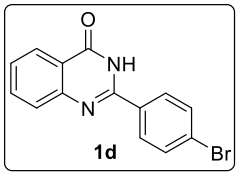
2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (1b):[37] Yield: 442 mg (92%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.59 (s, 1H), 8.25 (dd, *J* = 8.9, 5.5 Hz, 2H), 8.15 (d, *J* = 6.9 Hz, 1H), 7.85 (t, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 8.8 Hz, 2H).



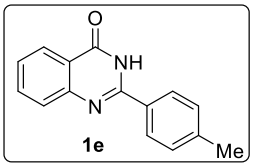
2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (1c):[35] Yield: 452 mg (88%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.6 (s, 1H), 8.28 (dd, *J* = 9.0, 5.4 Hz, 2H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.95 – 7.68 (m, 2H), 7.55 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1H), 7.42 (t, *J* = 8.9 Hz, 2H).



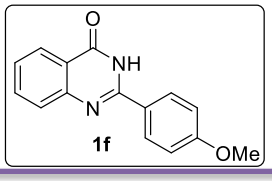
2-(4-Bromophenyl)quinazolin-4(3*H*)-one (1d):[37] Yield: 505 mg (84 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.64 (s, 1H), 8.23 – 8.07 (m, 3H), 7.99 – 7.67 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H).



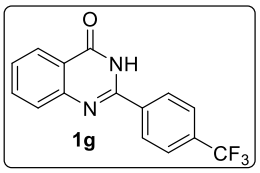
2-(4-Methylphenyl)quinazolin-4(3*H*)-one (1e):[35] Yield: 421 mg (89%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.47 (s, 1H), 8.17 – 8.08 (m, 3H), 7.83 (t, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H).



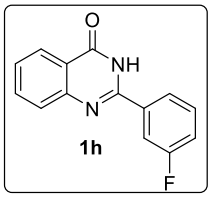
2-(4-Methoxyphenyl)quinazolin-4(*3H*)-one (1f):[35] Yield: 428 mg (85 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.42 (s, 1H), 8.19 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.9 Hz, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H).



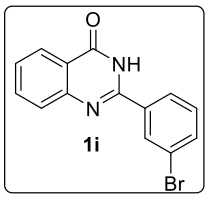
2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (1g):[37] Yield: 540 mg (93%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.77 (s, 1H), 8.40 (d, *J* = 8.2 Hz, 2H), 8.20 (d, *J* = 6.9 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.89-7.78 (m, 2H), 7.66 – 7.49 (m, 1H).



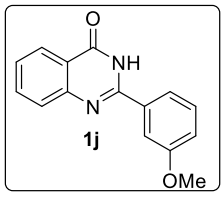
2-(3-Fluorophenyl)quinazolin-4(3*H*)-one (1h):[38] Yield: 360 mg (75 %). ^{1}H NMR (200 MHz, DMSO- d_6) ^{1}H NMR (200 MHz, DMSO-*d*6) δ 12.61 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.03 (t, *J* = 9.8 Hz, 2H), 7.89 -7.73 (m, 2H), 7.66 -7.48 (m, 2H), 7.44 (t, *J* = 8.5 Hz, 1H).



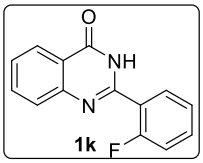
2-(3-Bromophenyl)quinazolin-4(3*H*)-one (1i):[38] Yield: 469 mg (78 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.64 (s, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.06 (t, *J* = 9.6 Hz, 2H), 7.95 – 7.74 (m, 2H), 7.72 – 7.36 (m, 3H).



2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (1j):[39] Yield: 408 mg (81 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.54 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 8.01 – 7.67 (m, 4H), 7.67 – 7.31 (m, 2H), 7.15 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.87 (s, 3H).

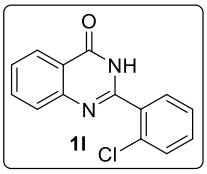


2-(2-Fluorophenyl)quinazolin-4(3*H*)-one (1k):[40] Following the **Method A** procedure, **1k** was obtained as a white solid. Yield: 413 mg (86 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.57 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.93 – 7.66 (m, 3H), 7.67 – 7.46 (m, 2H), 7.45 – 7.25 (m, 2H).



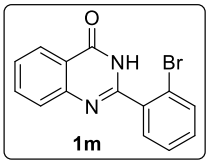
1k

2-(2-Chlorophenyl)quinazolin-4(3*H*)-one (1l):[35] Yield: 395 mg (77 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.65 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.93 – 7.78 (m, 1H), 7.76 – 7.63 (m, 2H), 7.53 – 7.45 (m, 4H).



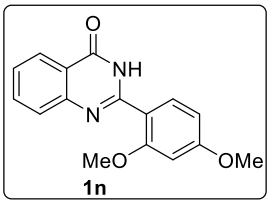
1l

2-(2-Bromophenyl)quinazolin-4(3*H*)-one (1m):[38] Yield: 488 mg (81 %). ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.63 (s, 1H), 8.18 (d, J = 6.8 Hz, 1H), 7.94 – 7.38 (m, 7H).



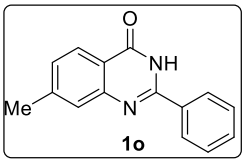
1m

2-(2,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one (1n):[39] Yield: 485 mg (86 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.43 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.97 – 7.63 (m, 4H), 7.60 – 7.39 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H).



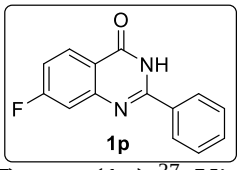
1n

7-Methyl-2-phenylquinazolin-4(3*H*)-one (1o):[37] Yield: 382 mg (81%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.44 (s, 1H), 8.16 (d, J = 7.5 Hz, 2H), 8.02 (d, J = 8.1 Hz, 1H), 7.58 –m 7.52 (m, 4H), 7.32 (d, J = 7.4 Hz, 1H), 2.45 (s, 3H).



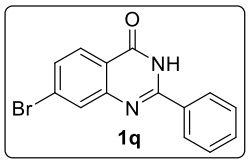
1o

7-Fluoro-2-phenylquinazolin-4(3*H*)-one (1p):[40] Yield: 394 mg (82%). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.64 (s, 1H), 8.50 – 7.96 (m, 3H), 7.67 – 7.47 (m, 4H), 7.38 (td, *J* = 8.7, 2.5 Hz, 1H).



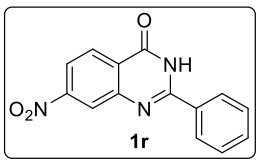
1p

7-Bromo-2-phenylquinazolin-4(3*H*)-one (1q):[37] Yield: 493 mg (82%).^{1}H NMR (200 MHz, DMSO- d_6) δ 12.66 (s, 1H), 8.19 – 8.14 (m, *J* = 7.8, 1.8 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 1.8 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.62 – 7.45 (m, 3H).



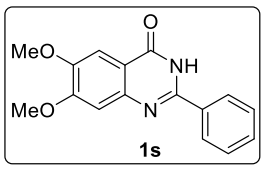
1q

7-Nitro-2-phenylquinazolin-4(3*H*)-one (1r):[40] Yield: 427 mg (80 %).^{1}H NMR (200 MHz, DMSO- d_6) δ 12.92 (s, 1H), 8.43 (d, *J* = 2.1 Hz, 1H), 8.36 (d, *J* = 8.7 Hz, 1H), 8.25 – 8.19 (m, 3H), 7.72 – 7.46 (m, 3H).



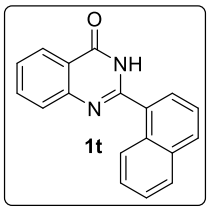
1r

6,7-Dimethoxy-2-phenylquinazolin-4(3*H*)-one (1s):[37] Yield: 440 mg (78 %).^{1}H NMR (200 MHz, DMSO- d_6) δ 12.43 (s, 1H), 8.17 (dd, *J* = 7.3, 2.3 Hz, 2H), 7.65 – 7.37 (m, 4H), 7.22 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H).



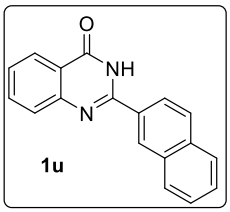
1s

2-(1-Naphthyl)quinazolin-4(3*H*)-one (1t):[35] Yield: 441 mg (81 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.69 (s, 1H), 8.25- 8.03 (m, 4H), 7.93 – 7.51 (m, 7H).

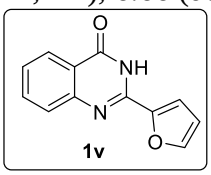


1t

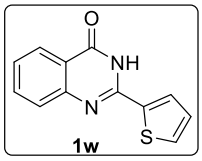
2-(2-Naphthyl)quinazolin-4(3*H*)-one (1u):[35] Yield: 474 mg (87 %). ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.69 (s, 1H), 8.83 (s, 1H), 8.31 (d, *J* = 10.0 Hz, 1H), 8.19 (d, *J* = 7.4 Hz, 1H), 8.15 – 8.00 (m, 3H), 7.93 – 7.76 (m, 2H), 7.72 – 7.45 (m, 3H).



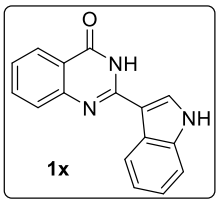
2-(2-Furyl)quinazolin-4(3*H*)-one (1v):[35] Yield: 399 mg (94 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.45 (s, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.68 (d, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 3.6 Hz, 1H), 7.48 (ddd, *J* = 8.2, 5.4, 2.9 Hz, 1H), 6.66 (dd, *J* = 3.6, 1.7 Hz, 1H).



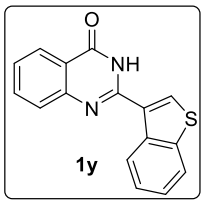
2-(2-Thienyl)quinazolin-4(3*H*)-one (1w):[35] Yield: 410 mg (90 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.25 (d, *J* = 10.0 Hz, 1H), 7.88 – 7.75 (m, 2H), 7.60 – 7.37 (m, 4H).



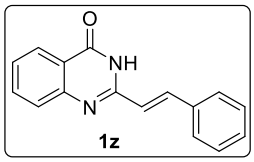
2-(1*H*-indol-3-yl)quinazolin-4(3*H*)-one (1x):[41] Yield: 376 mg (58 %). ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.18 (s, 1H), 11.89 (s, 1H), 8.84 – 8.66 (m, 1H), 8.57 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.77 (q, *J* = 7.7 Hz, 2H), 7.58 – 7.31 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H).



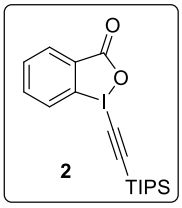
2-(Benzo[b]thiophen-3-yl)quinazolin-4(3*H*)-one (1y):[42] Yield: 395 mg (71 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.54 (s, 1H), 9.01 (d, *J* = 7.4 Hz, 1H), 8.79 (s, 1H), 8.14 (dd, *J* = 13.8, 8.1 Hz, 2H), 7.98 – 7.71 (m, 2H), 7.69 – 7.35 (m, 3H).

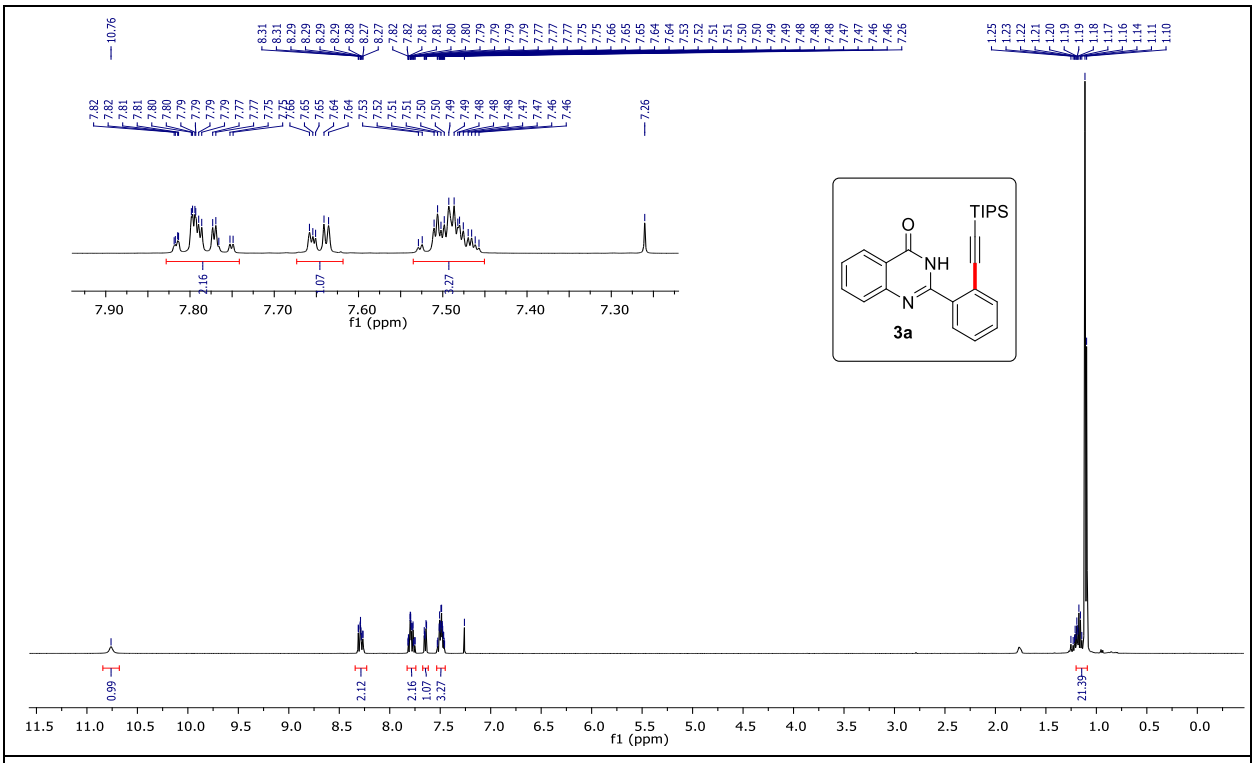


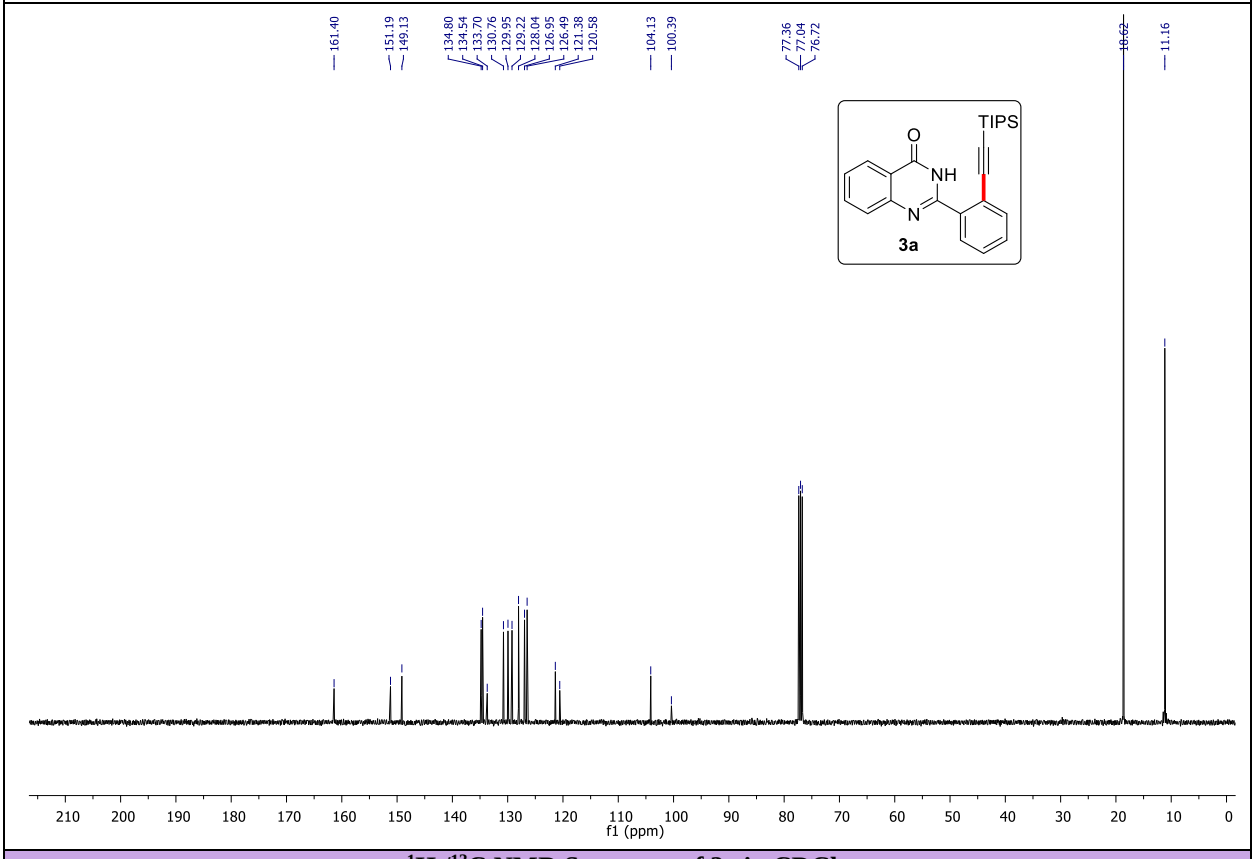
(*E*)-2-(Styryl)quinazolin-4(3*H*)-one (1z):[35] Yield: 377 mg (76 %). ^{1}H NMR (200 MHz, DMSO- d_6) δ 12.35 (s, 1H), 8.11 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 16.2 Hz, 1H), 7.81 (t, *J* = 7.0 Hz, 1H), 7.69- 7.65(m, 3H), 7.58 – 7.37 (m, 4H), 7.01 (d, *J* = 16.2 Hz, 1H).



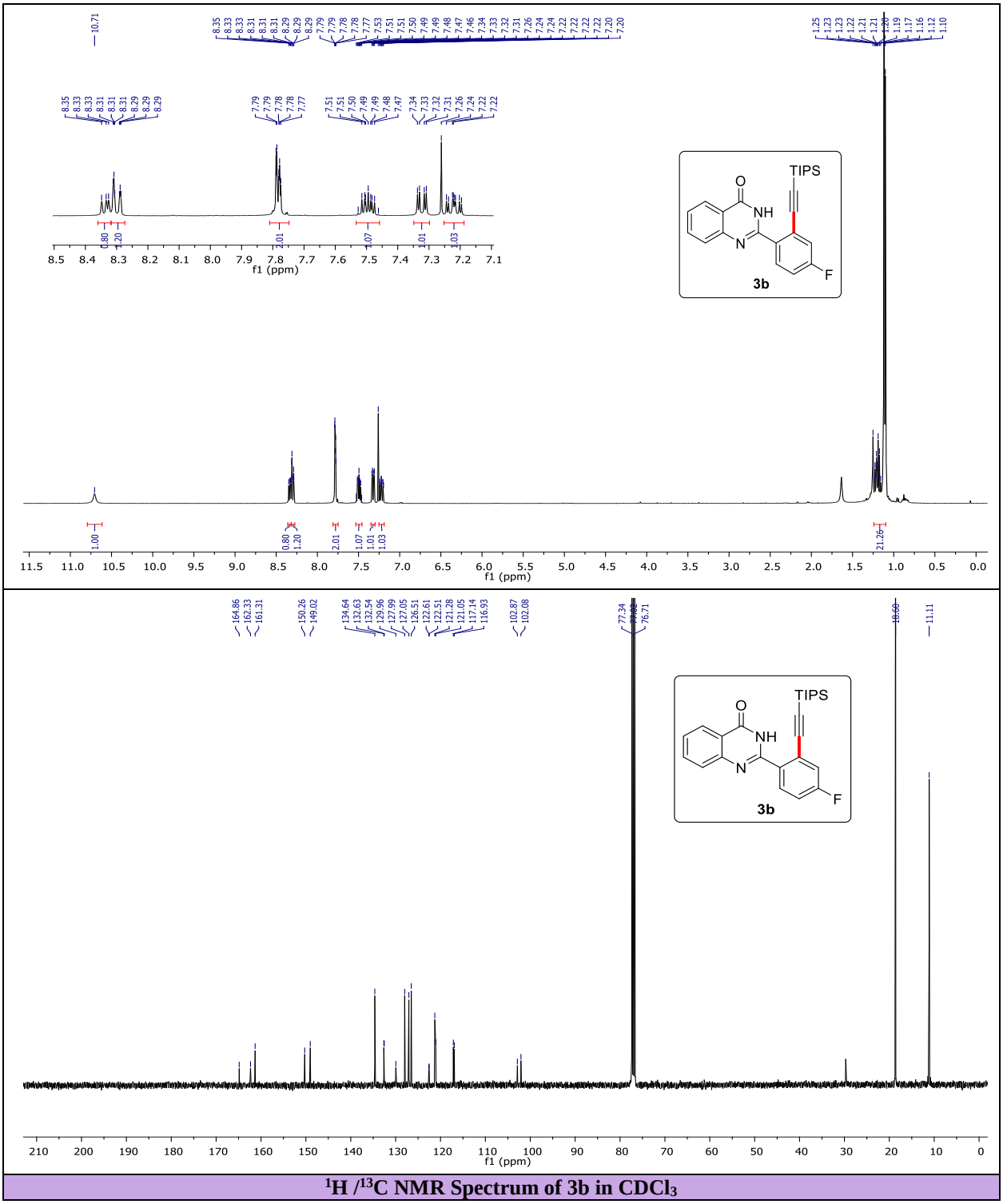
1-[(Tri*iso*propyllsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, (2)):[43] Yield: 36 g (85 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.48 – 8.36 (m, 1H), 8.34 – 8.23 (m, 1H), 7.91 – 7.64 (m, 2H), 1.26 – 0.96 (m, 21H).



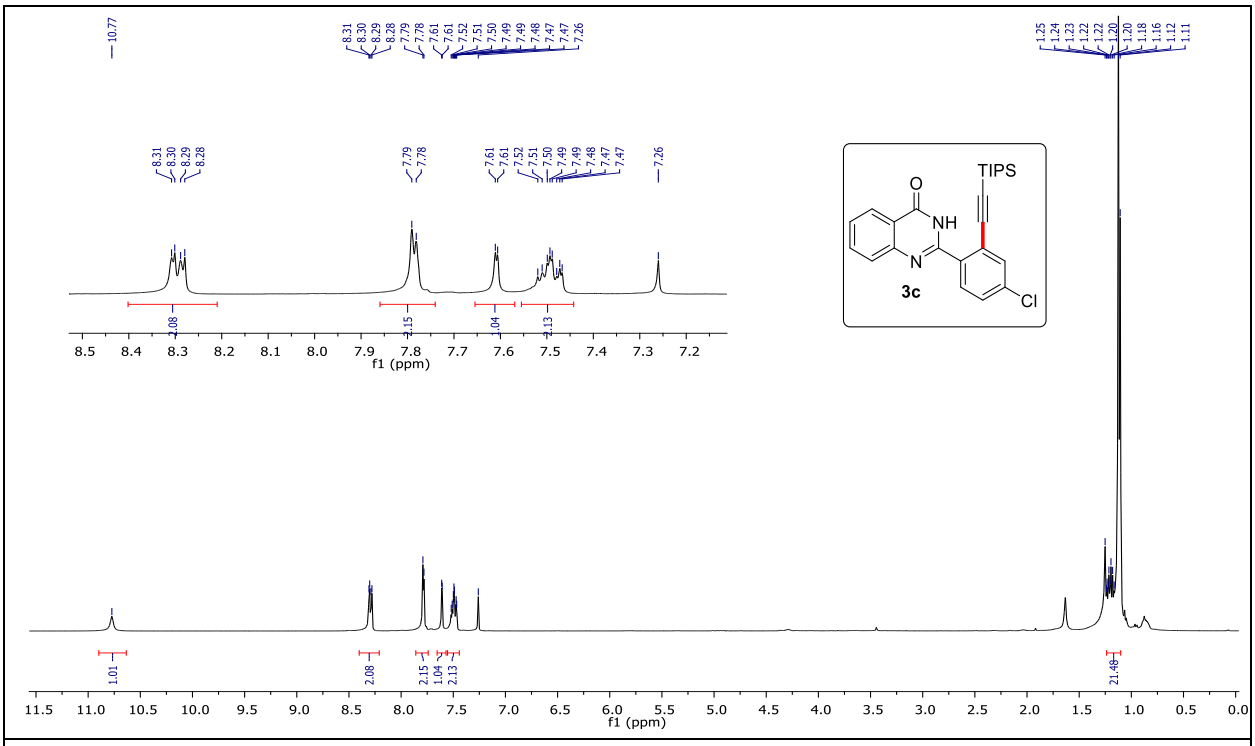


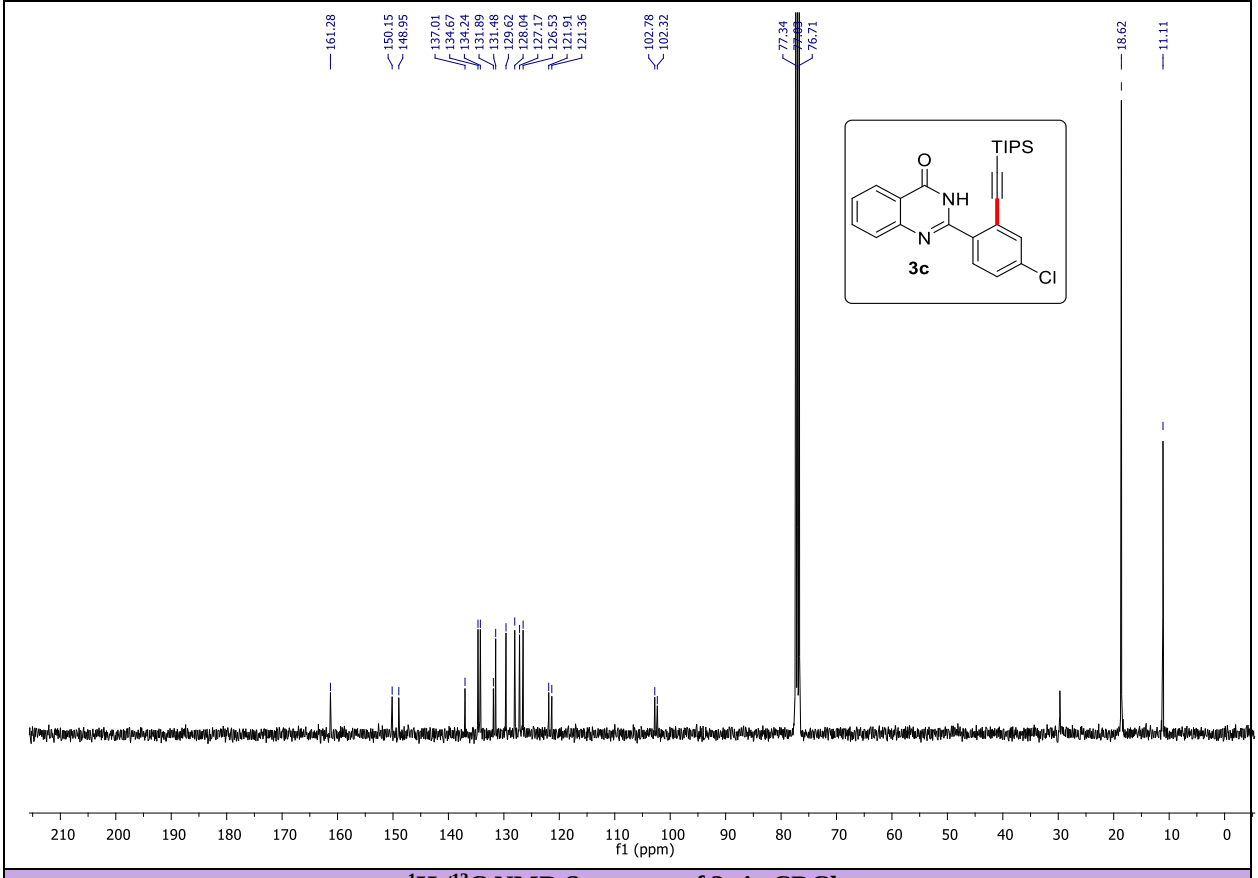


^{1}H /^{13}C NMR Spectrum of 3a in $CDCl_3$

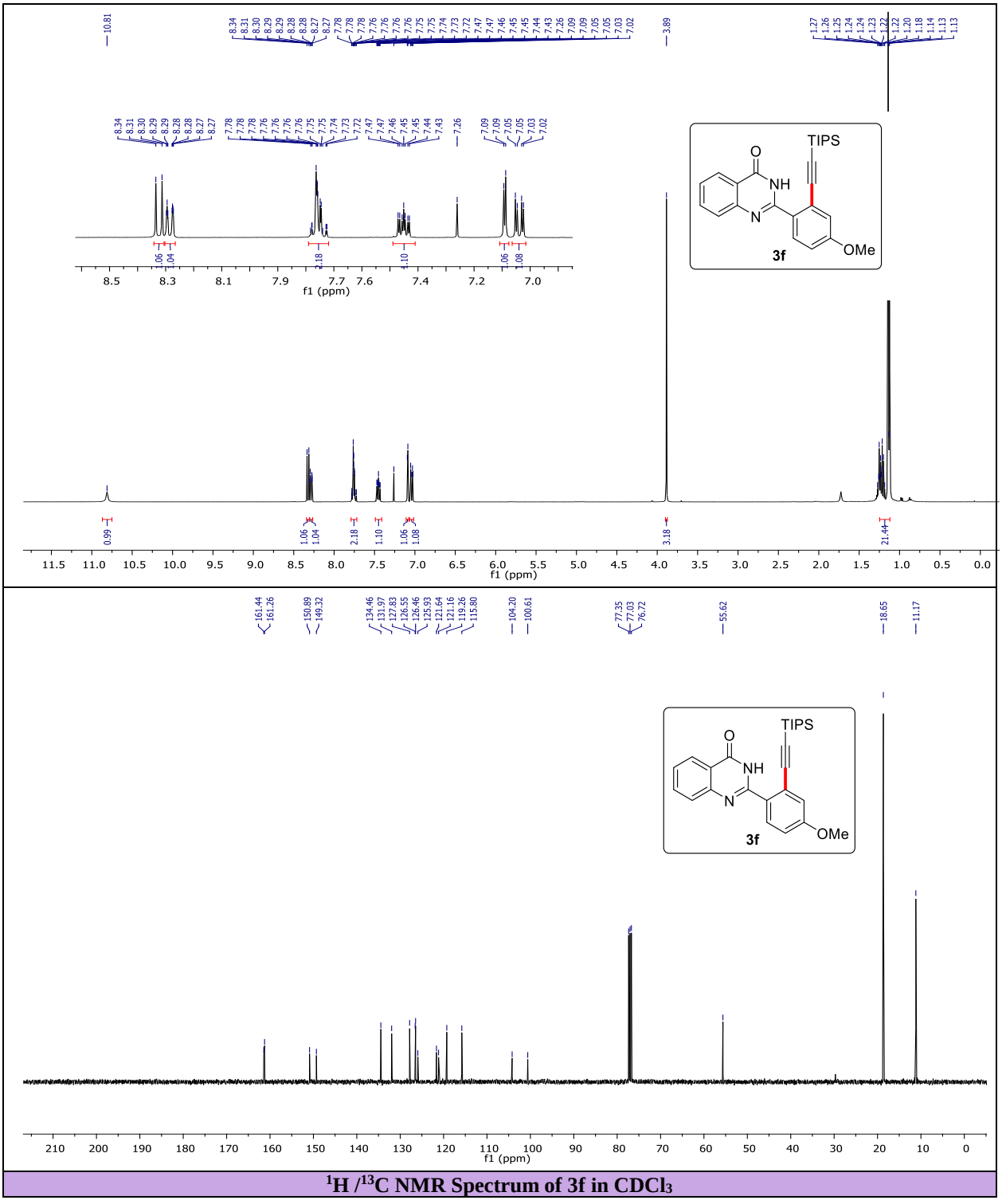


^{1}H /^{13}C NMR Spectrum of 3b in $CDCl_3$

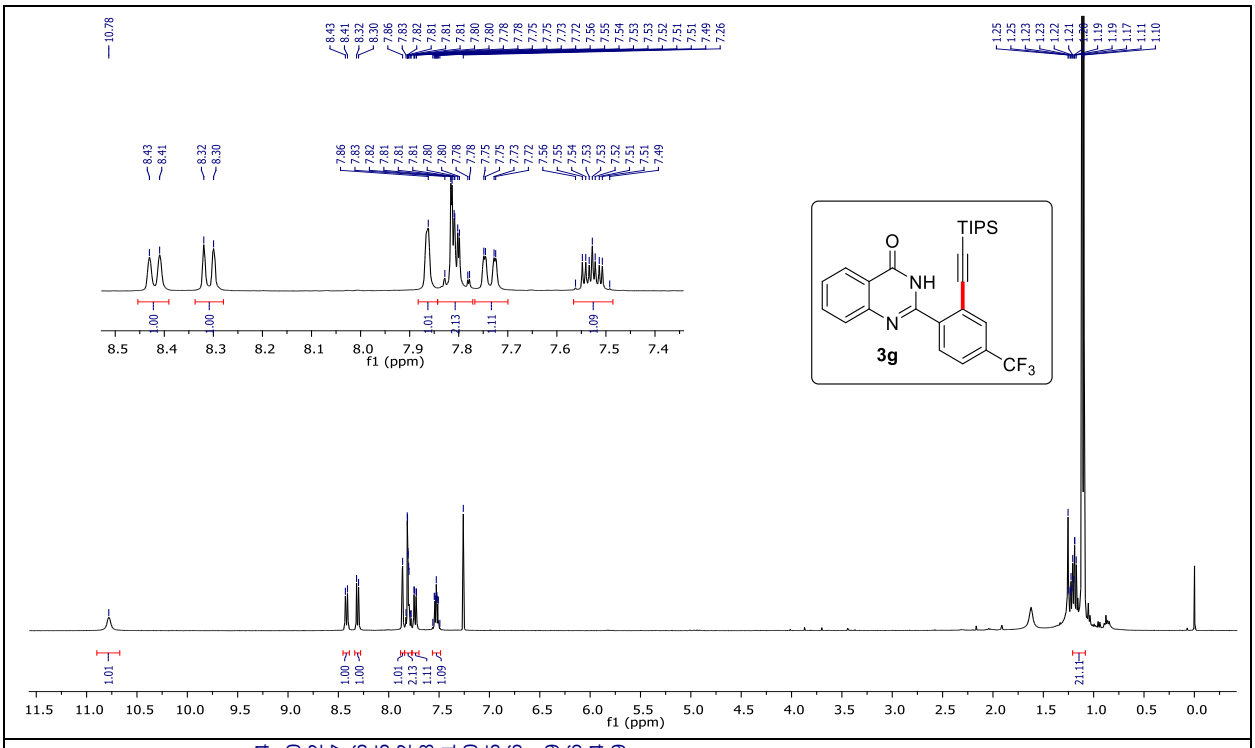


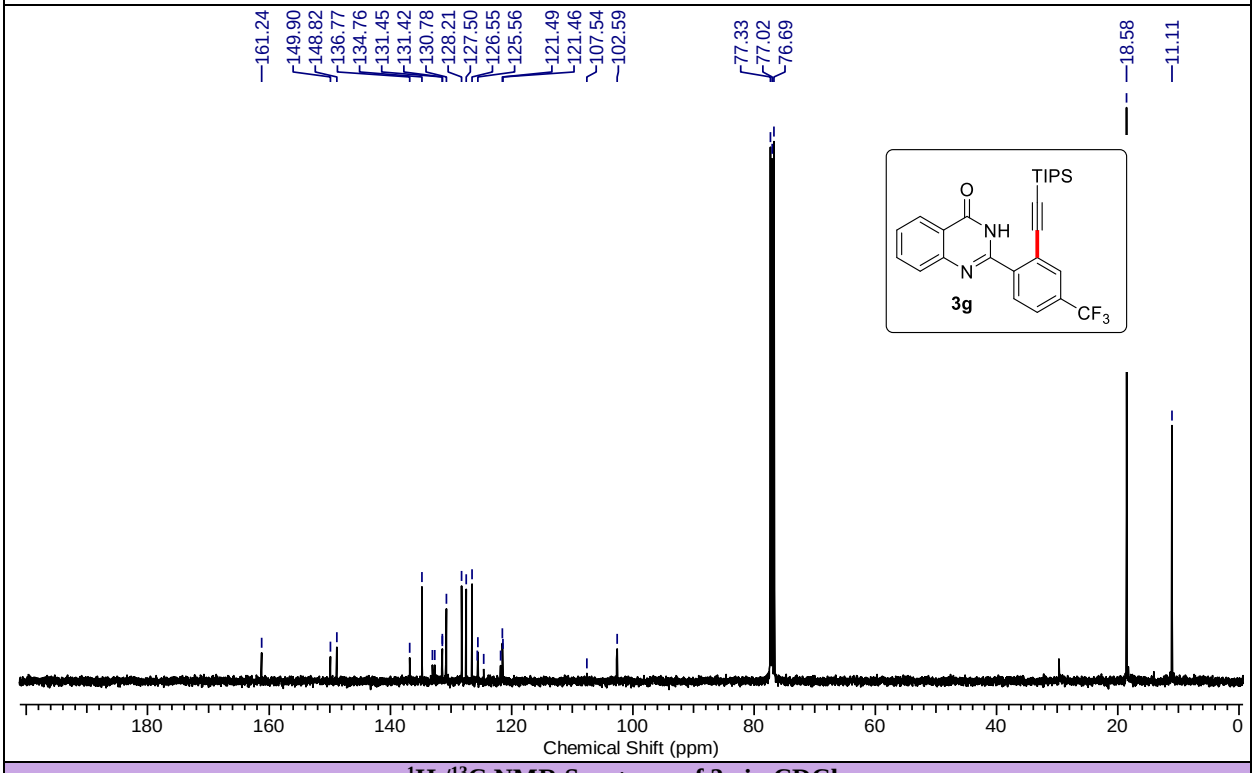


^{1}H /^{13}C NMR Spectrum of 3c in $CDCl_3$

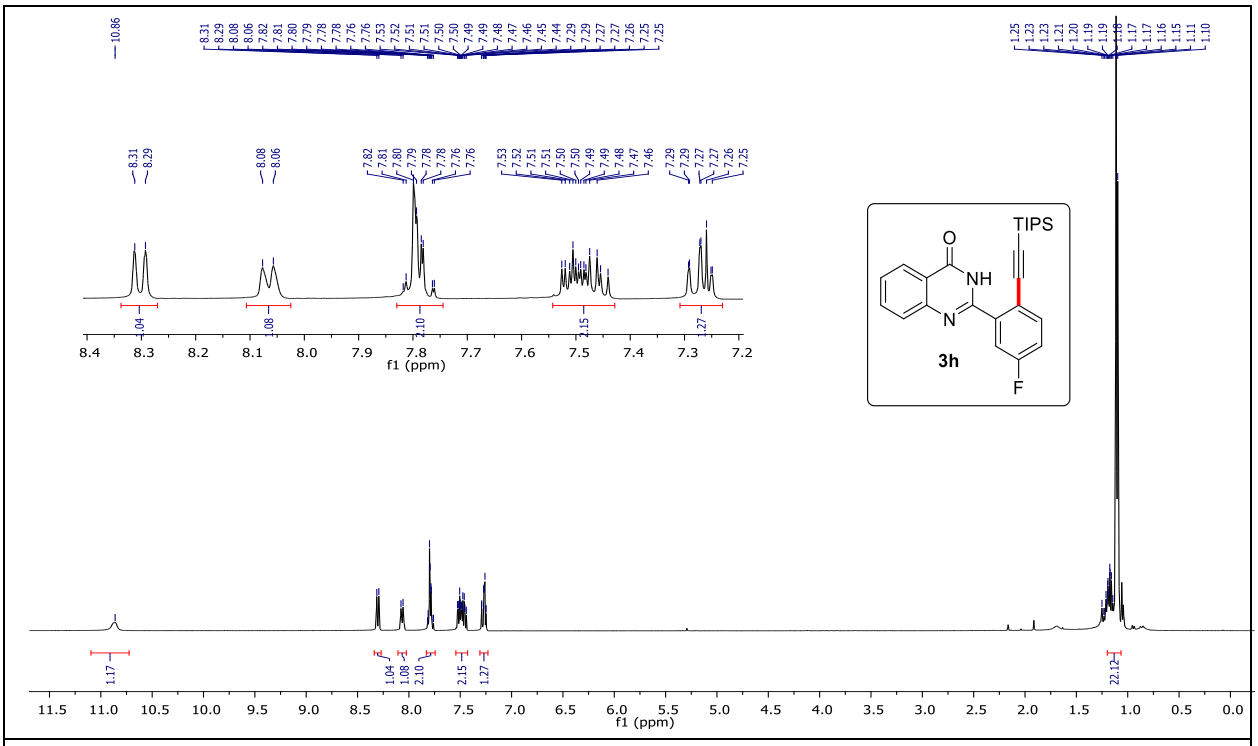


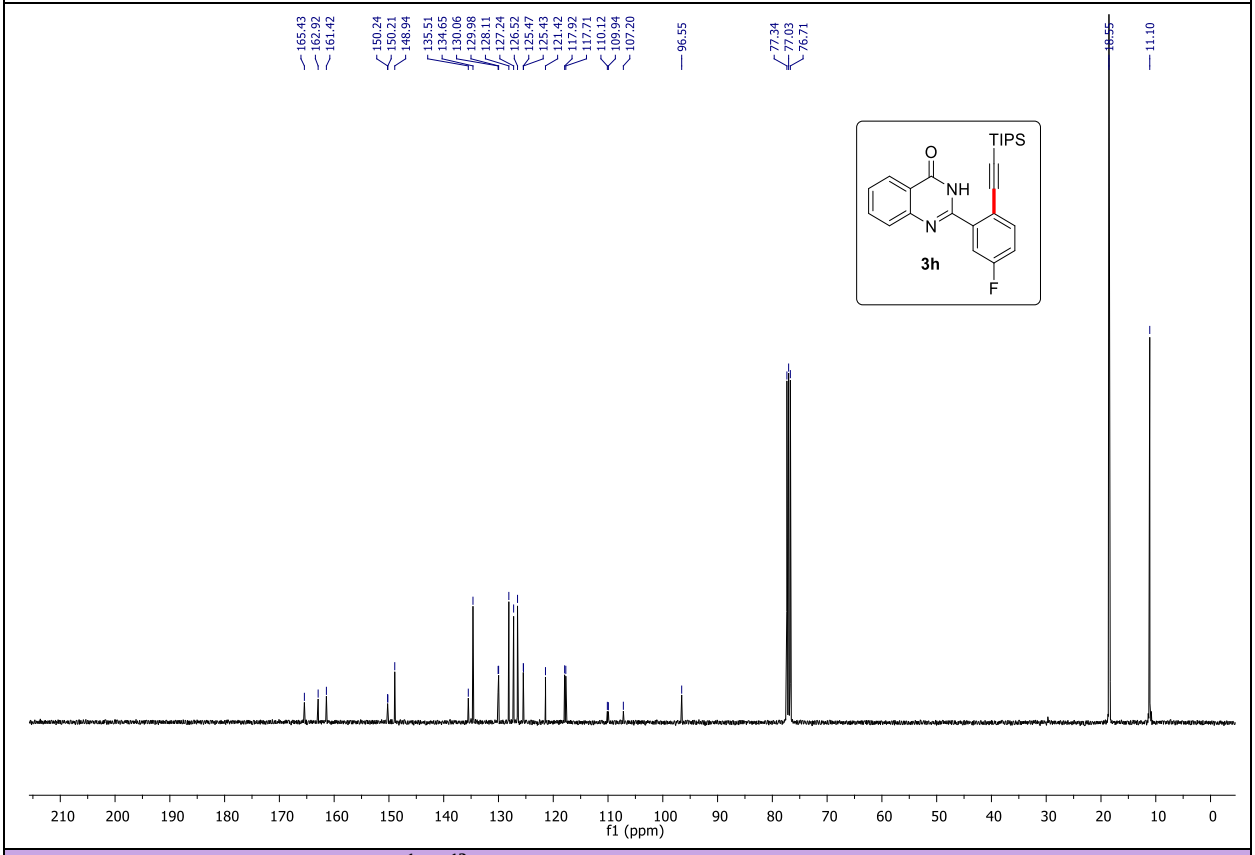
^{1}H /^{13}C NMR Spectrum of 3f in $CDCl_3$



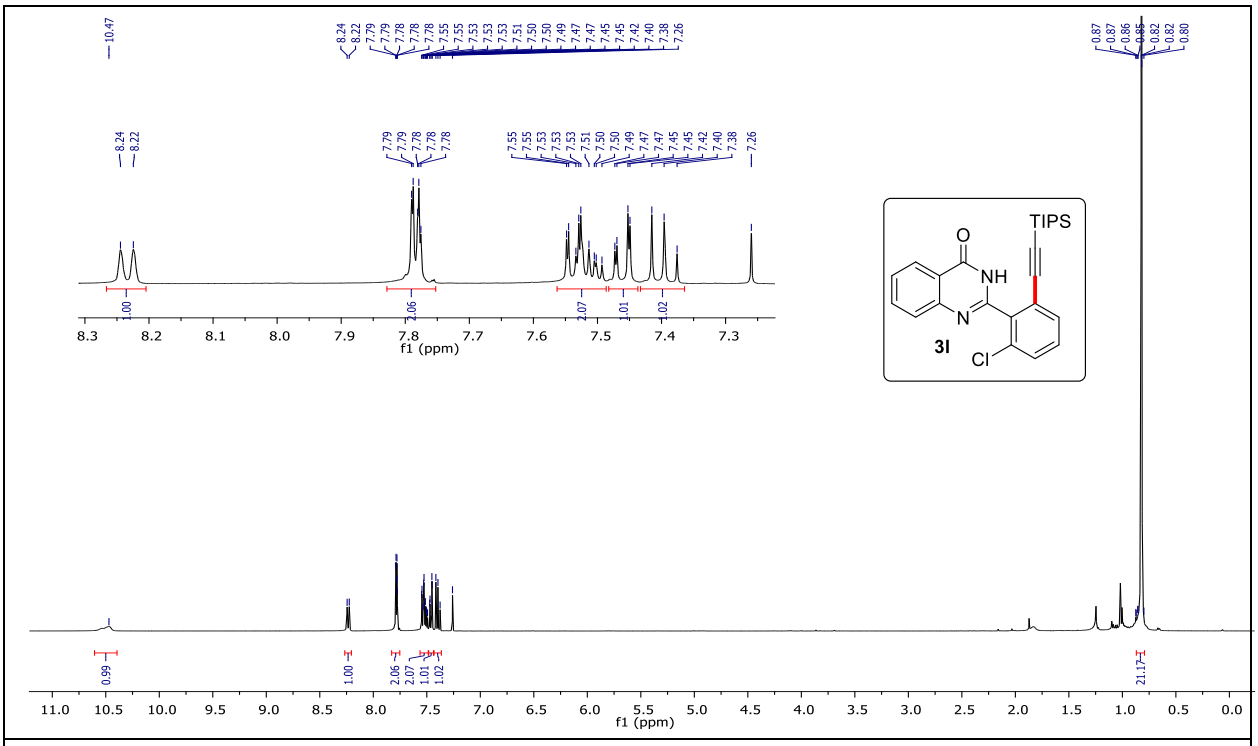


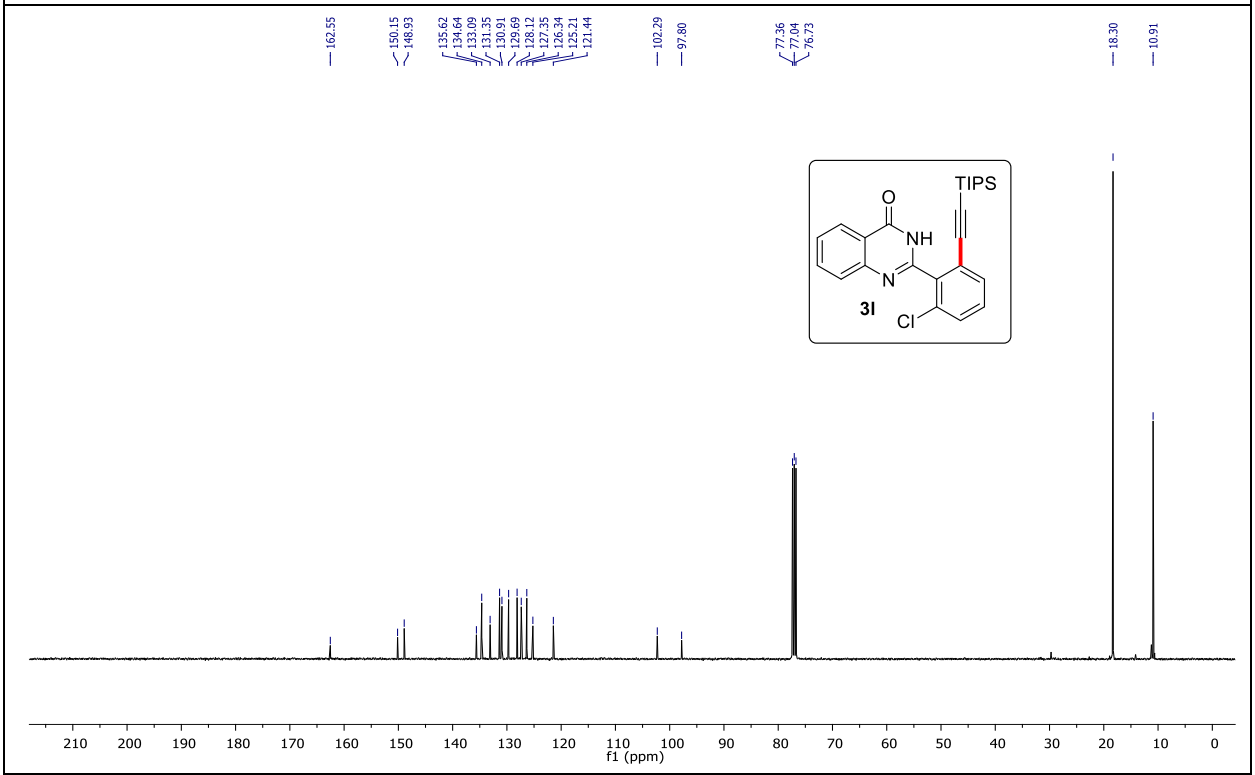
^{1}H /^{13}C NMR Spectrum of 3g in $CDCl_3$



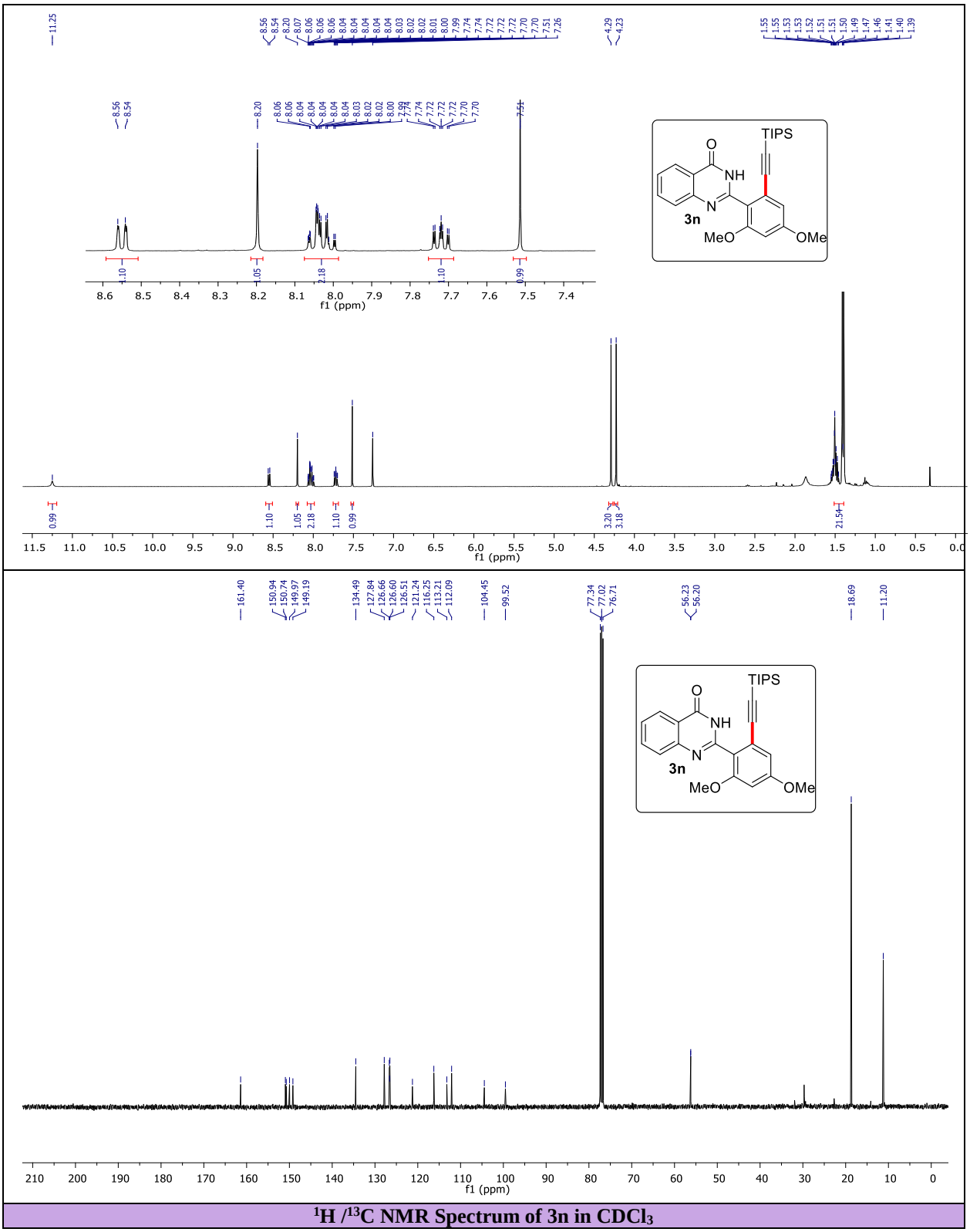


^{1}H /^{13}C NMR Spectrum of 3h in $CDCl_3$

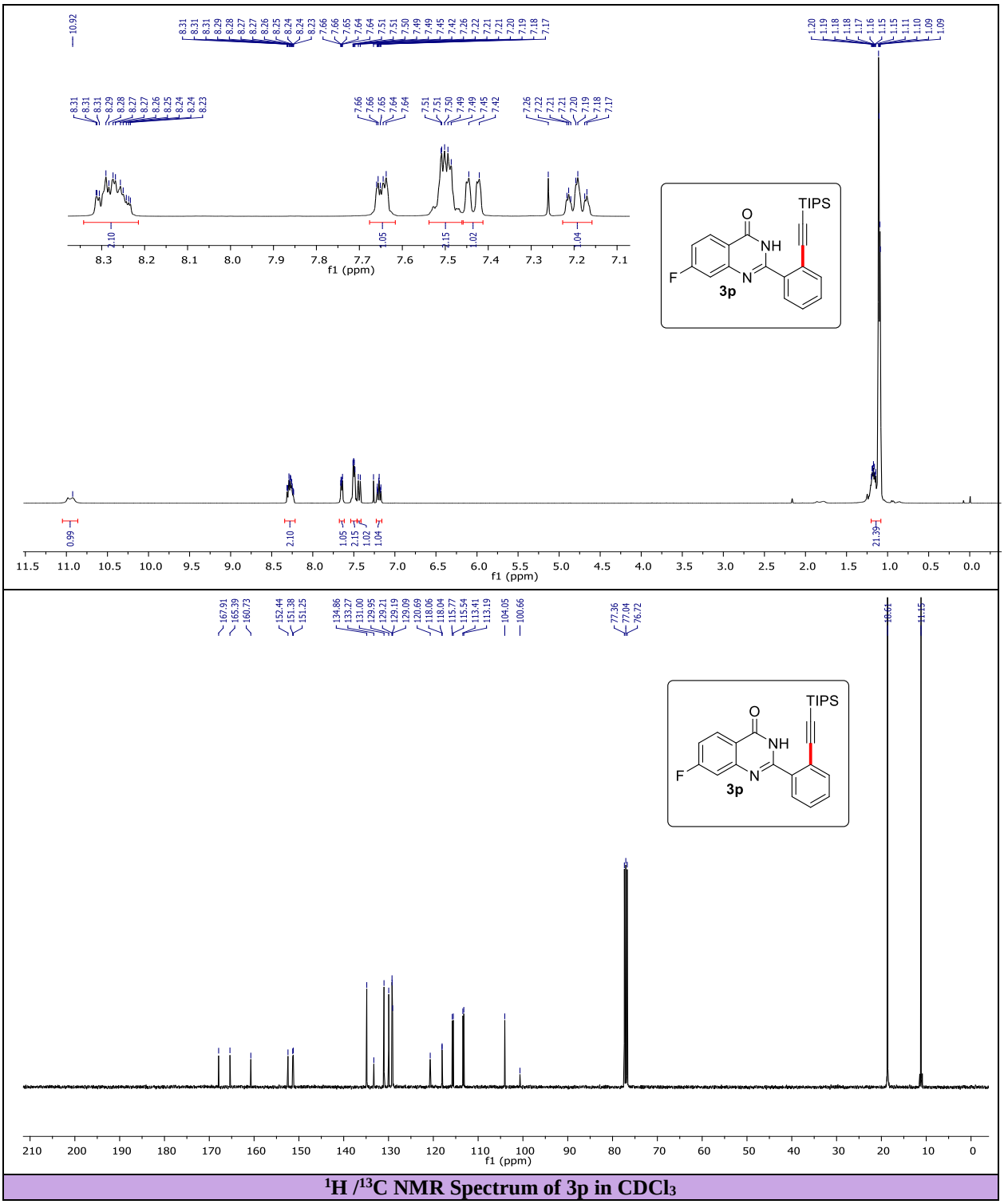




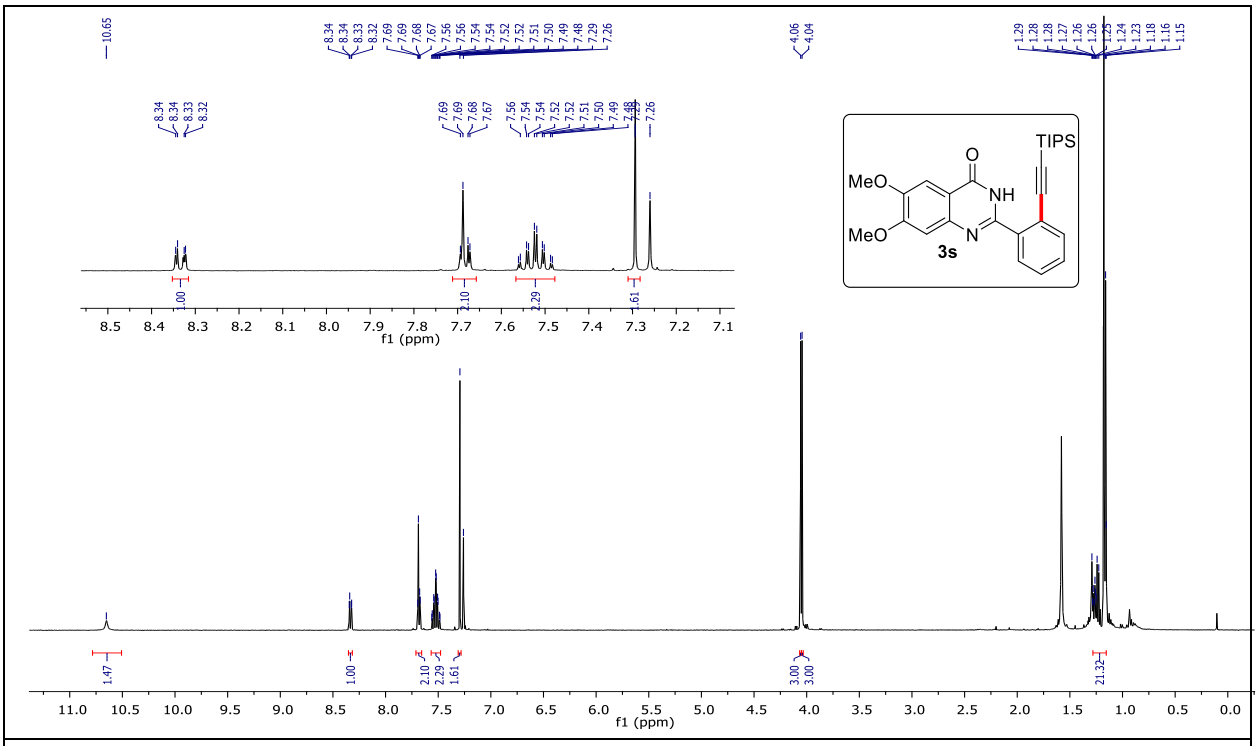
^{1}H /^{13}C NMR Spectrum of 3l in $CDCl_3$

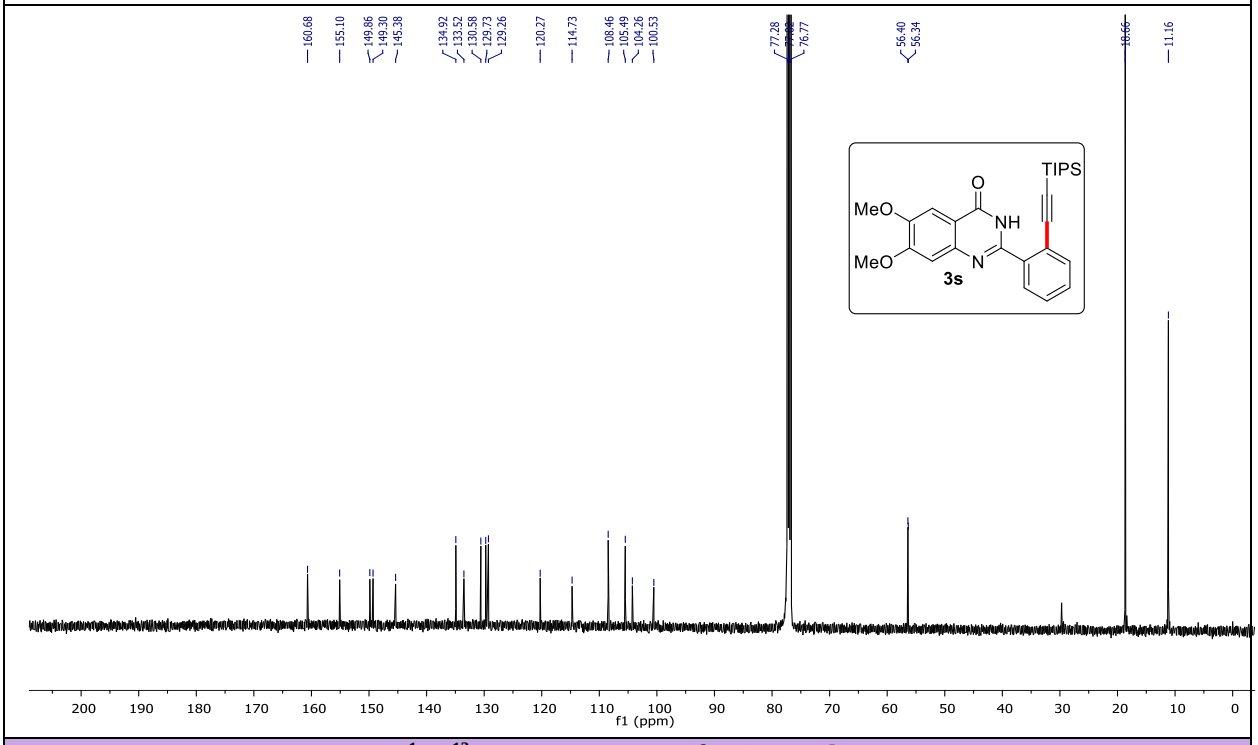


^{1}H /^{13}C NMR Spectrum of 3n in $CDCl_3$

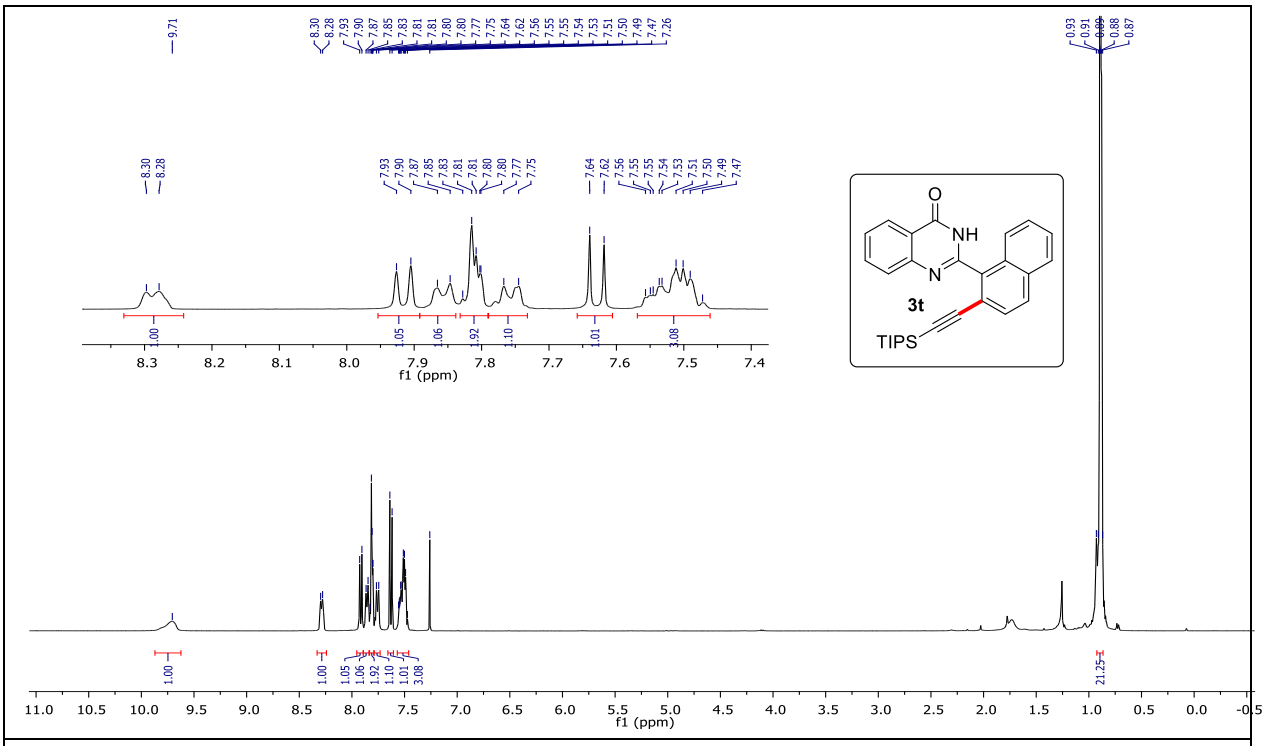


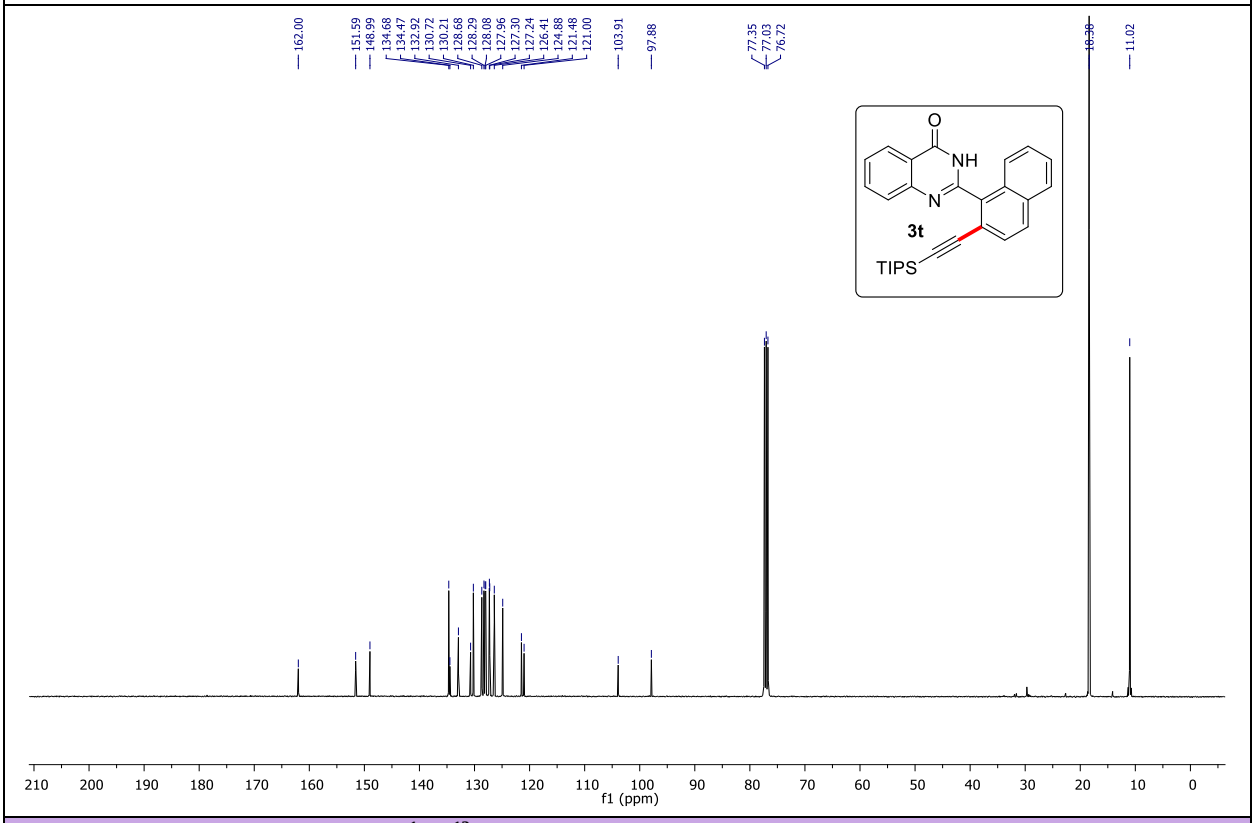
^{1}H /^{13}C NMR Spectrum of 3p in $CDCl_3$



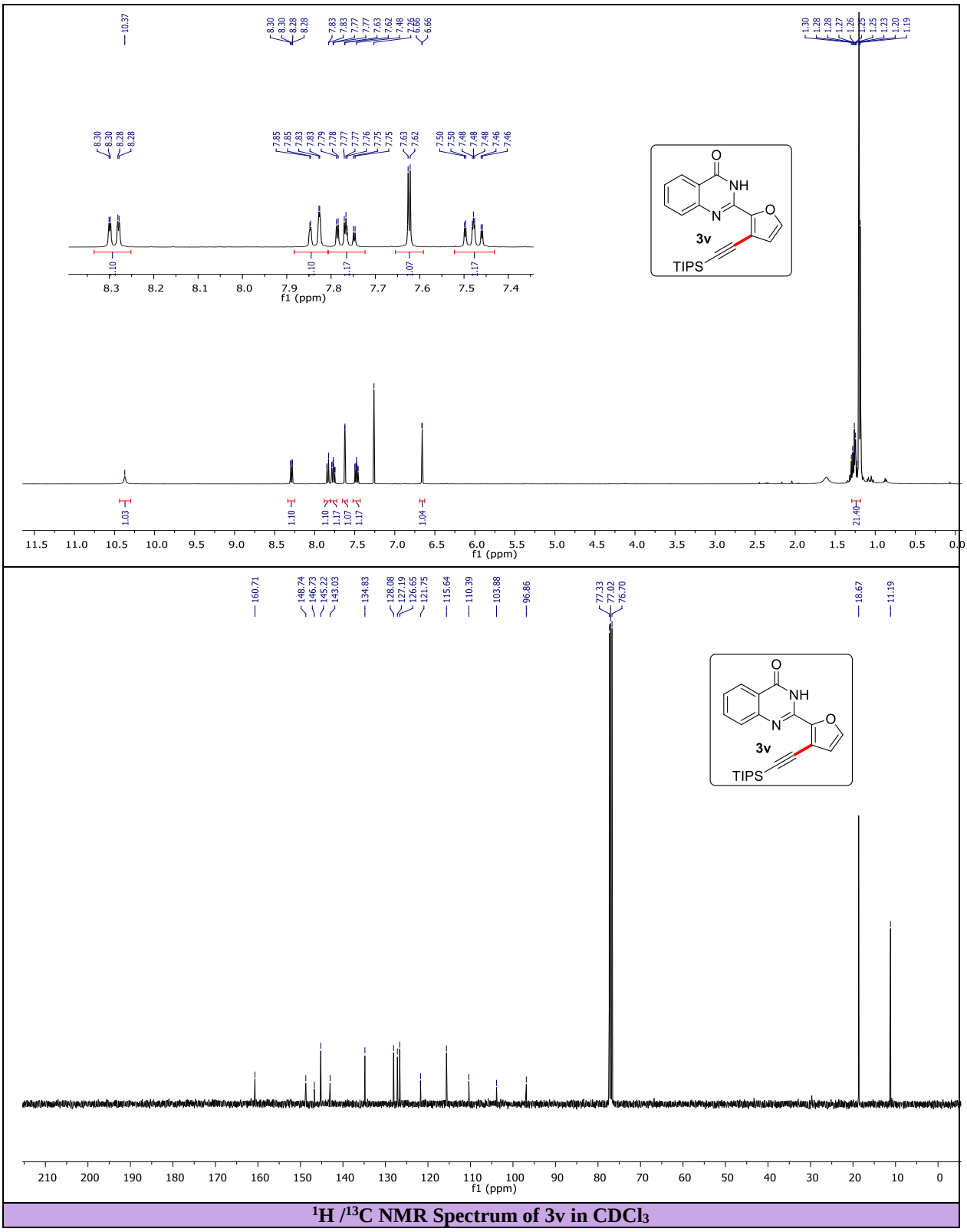


^{1}H /^{13}C NMR Spectrum of 3s in $CDCl_3$

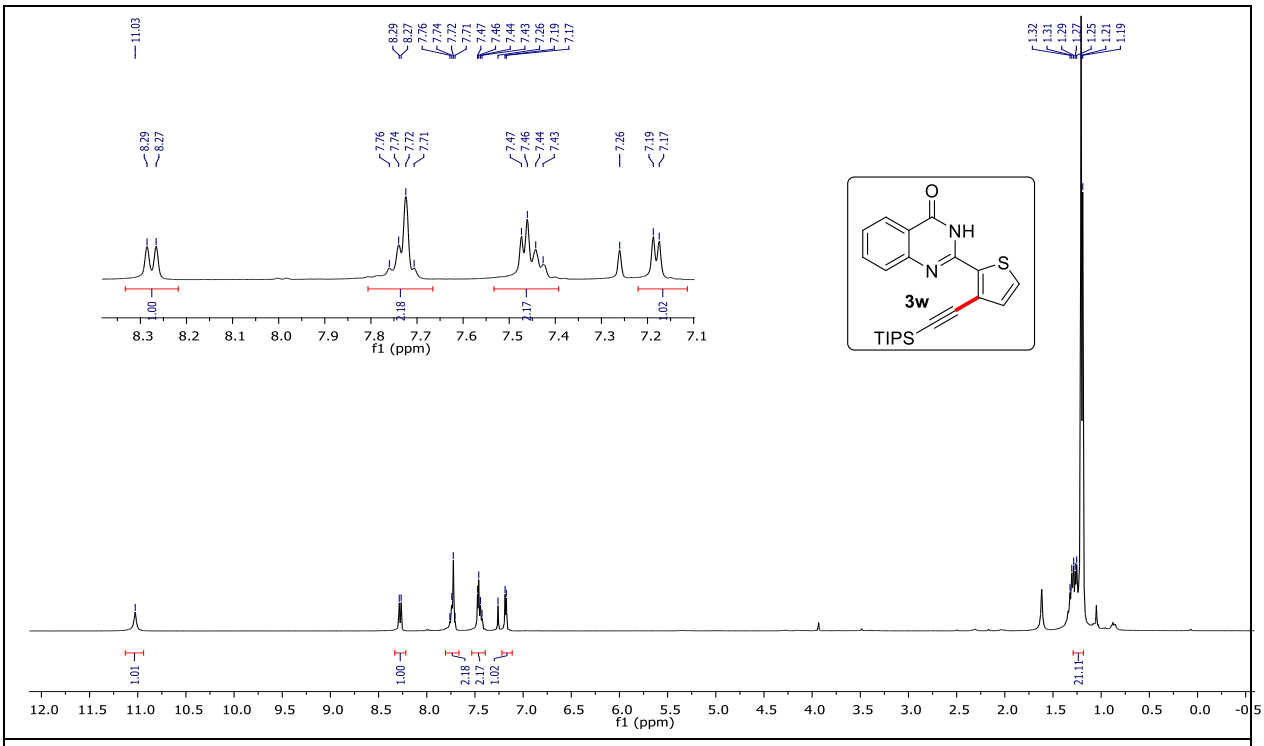


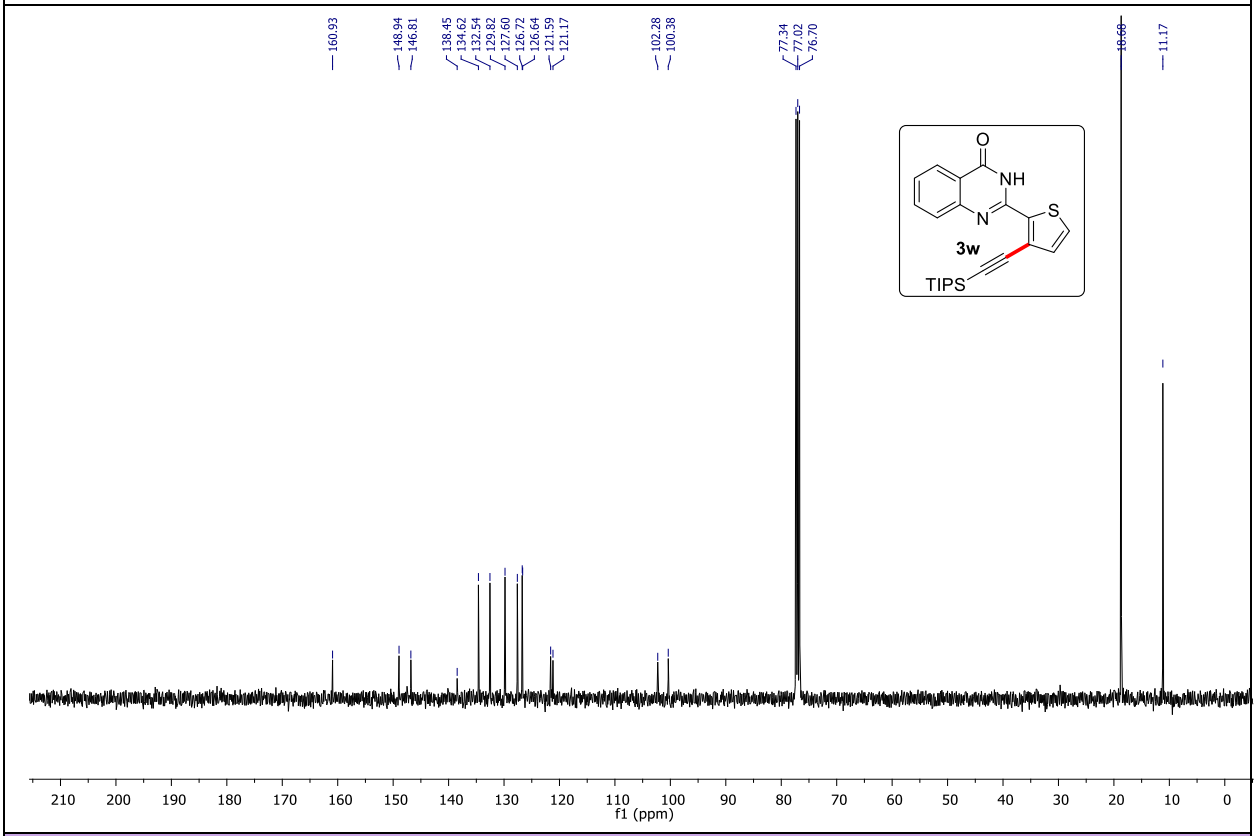


^{1}H /^{13}C NMR Spectrum of 3t in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 3v in $CDCl_3$





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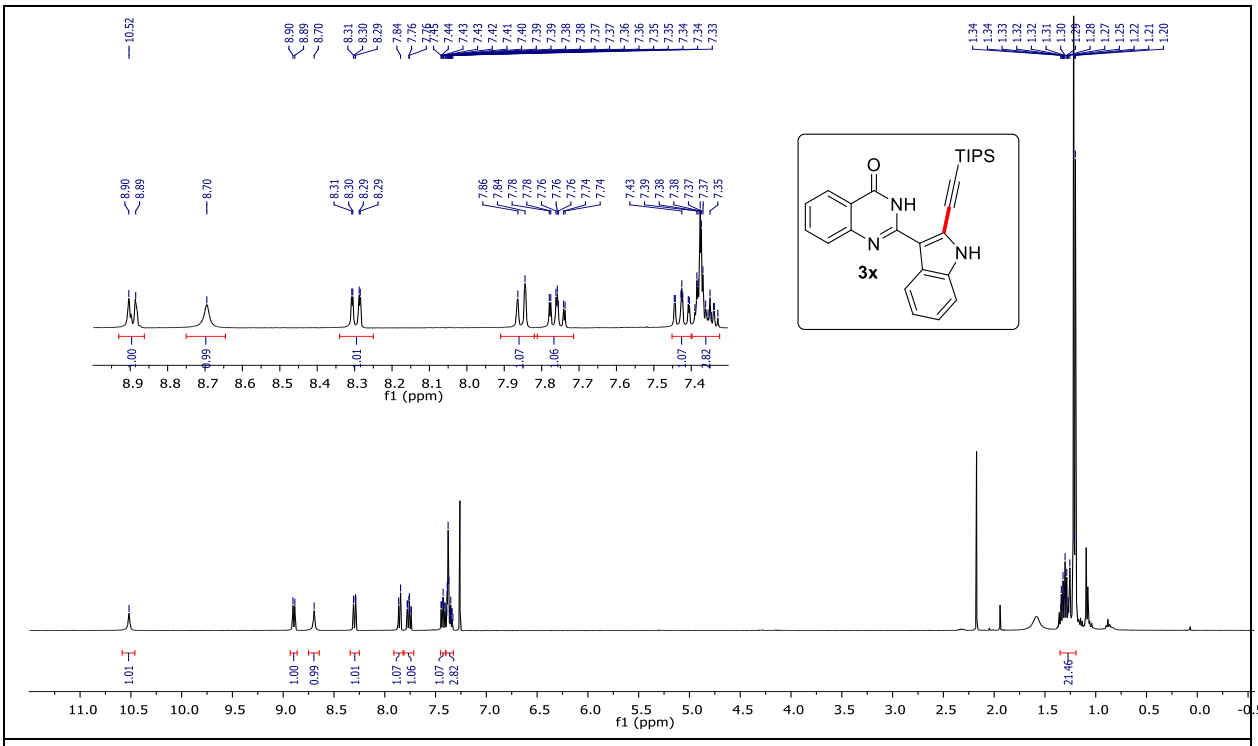
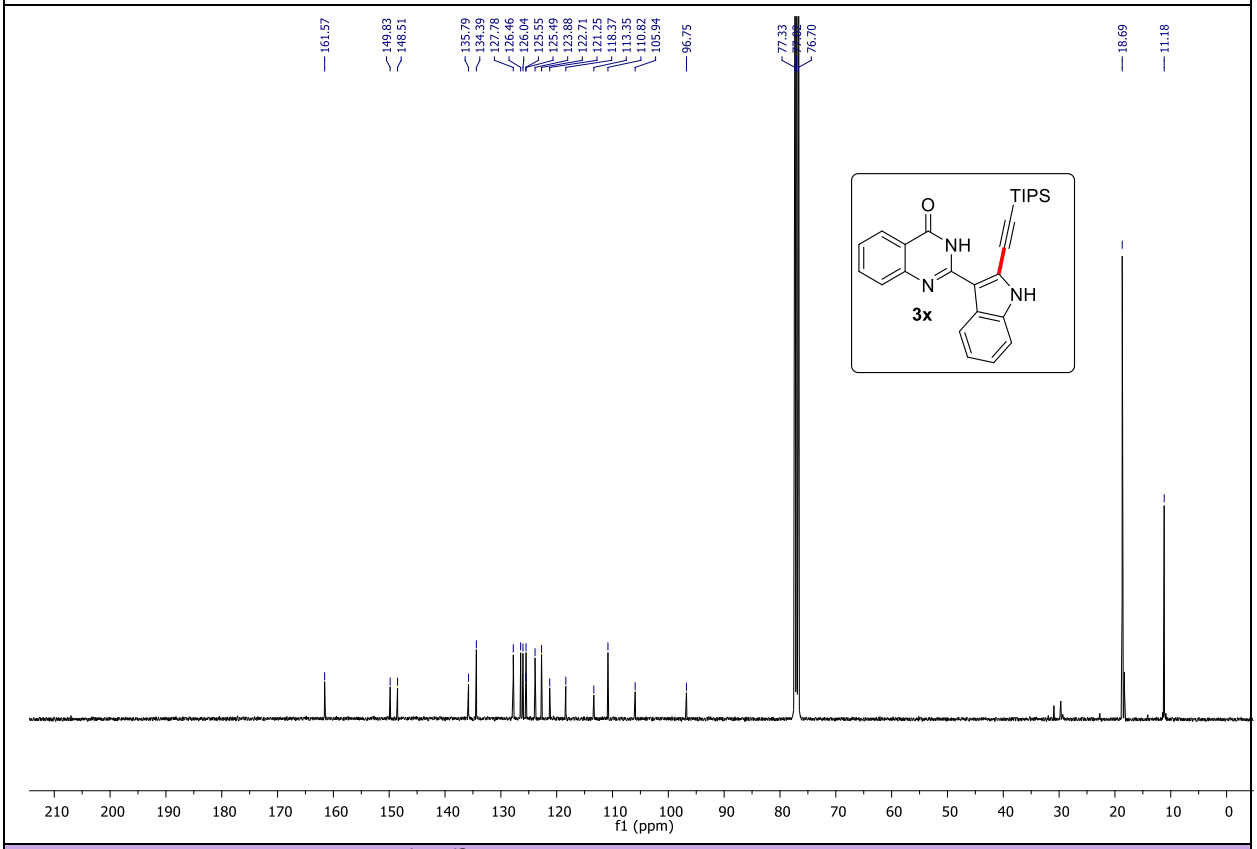
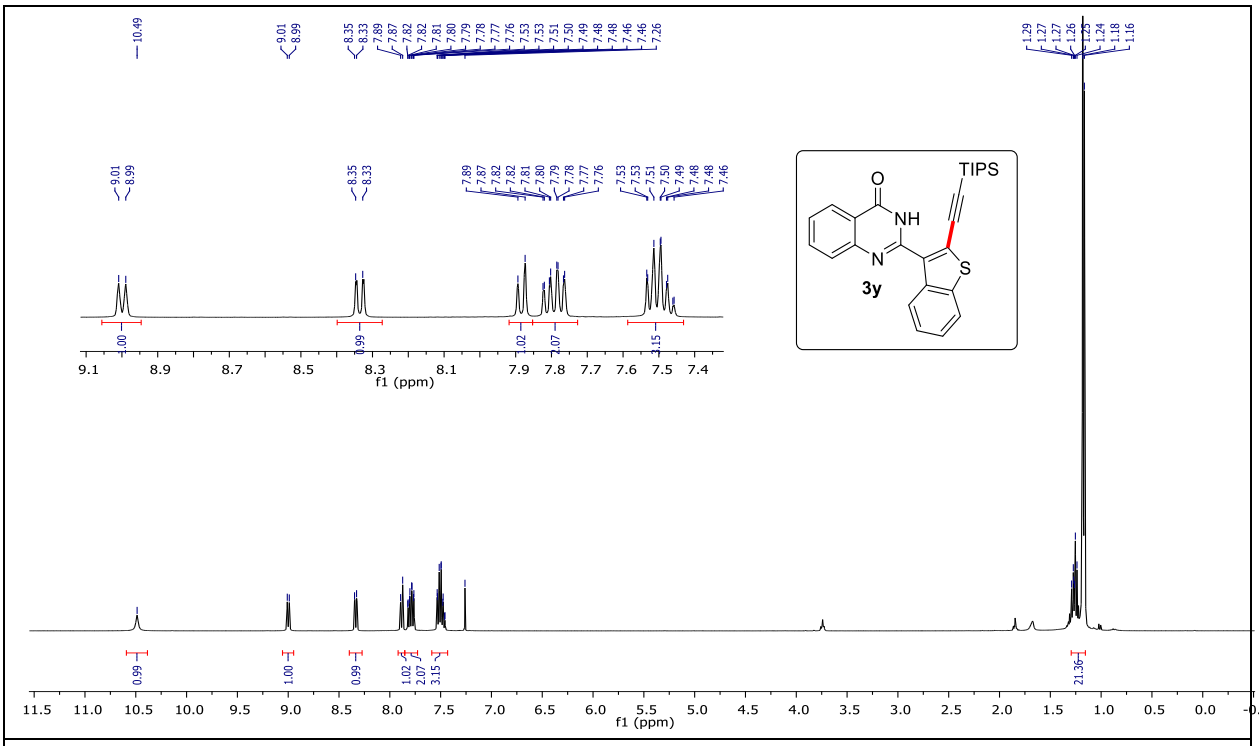
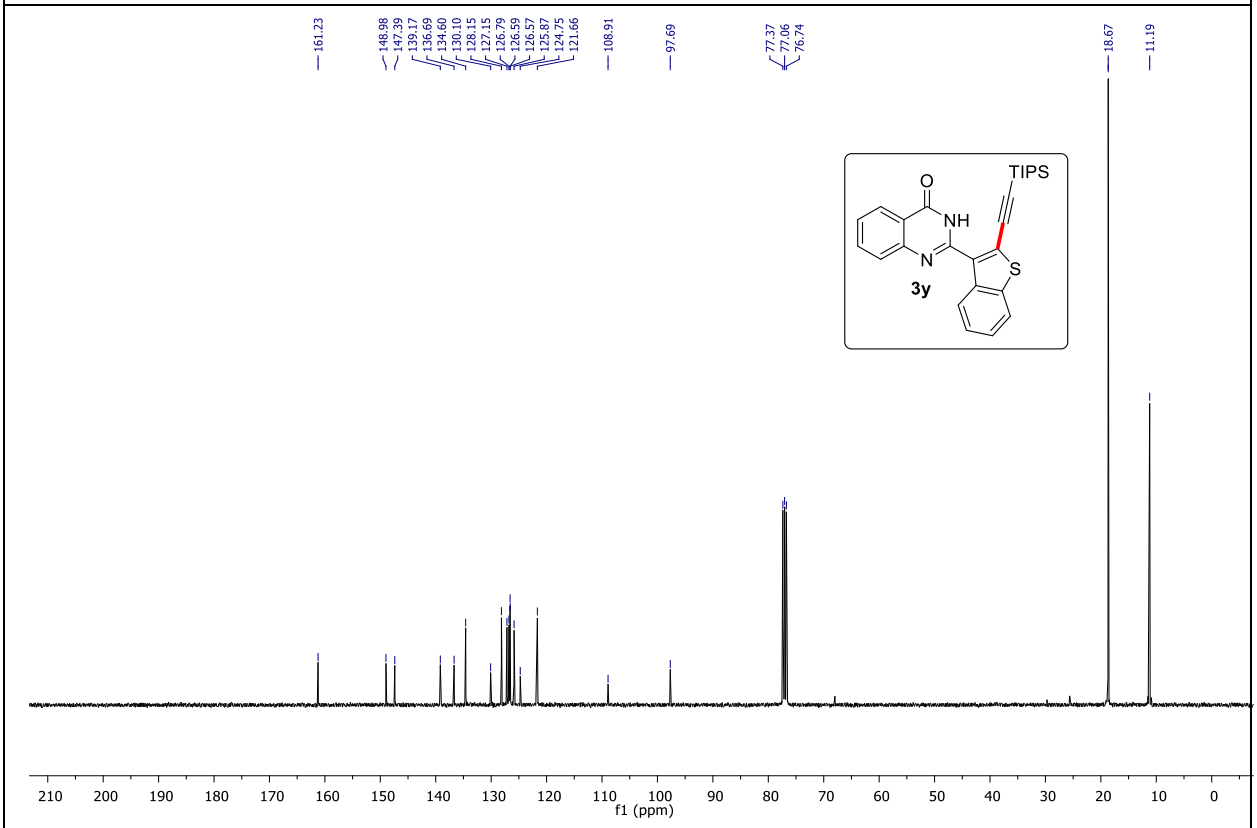


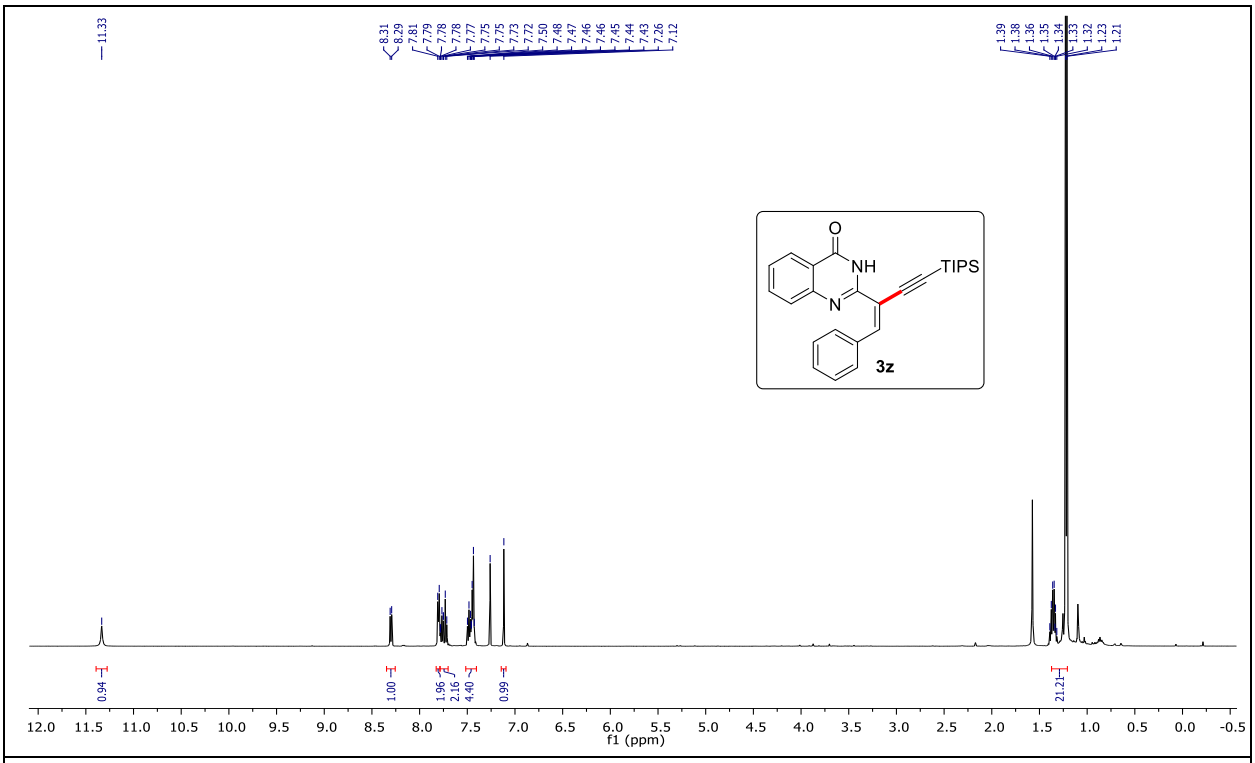


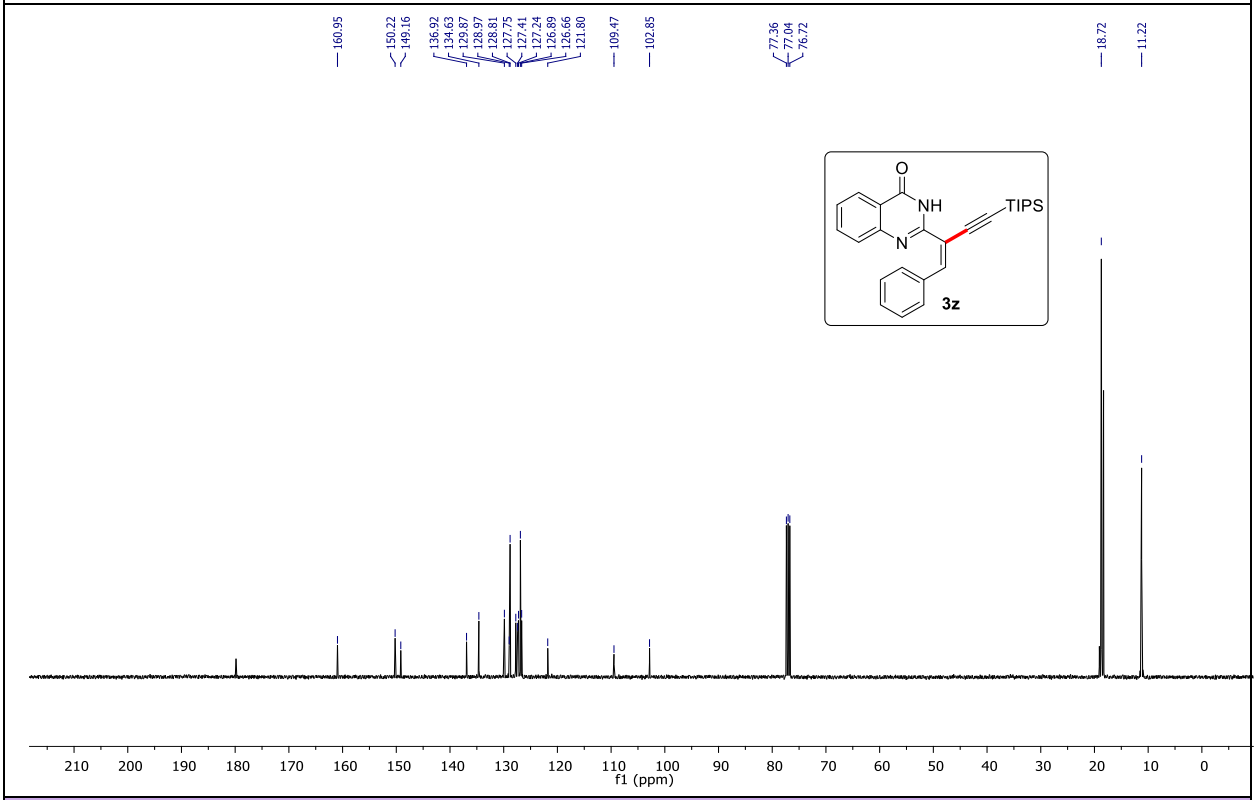
^{1}H /^{13}C NMR Spectrum of 3x in $CDCl_3$



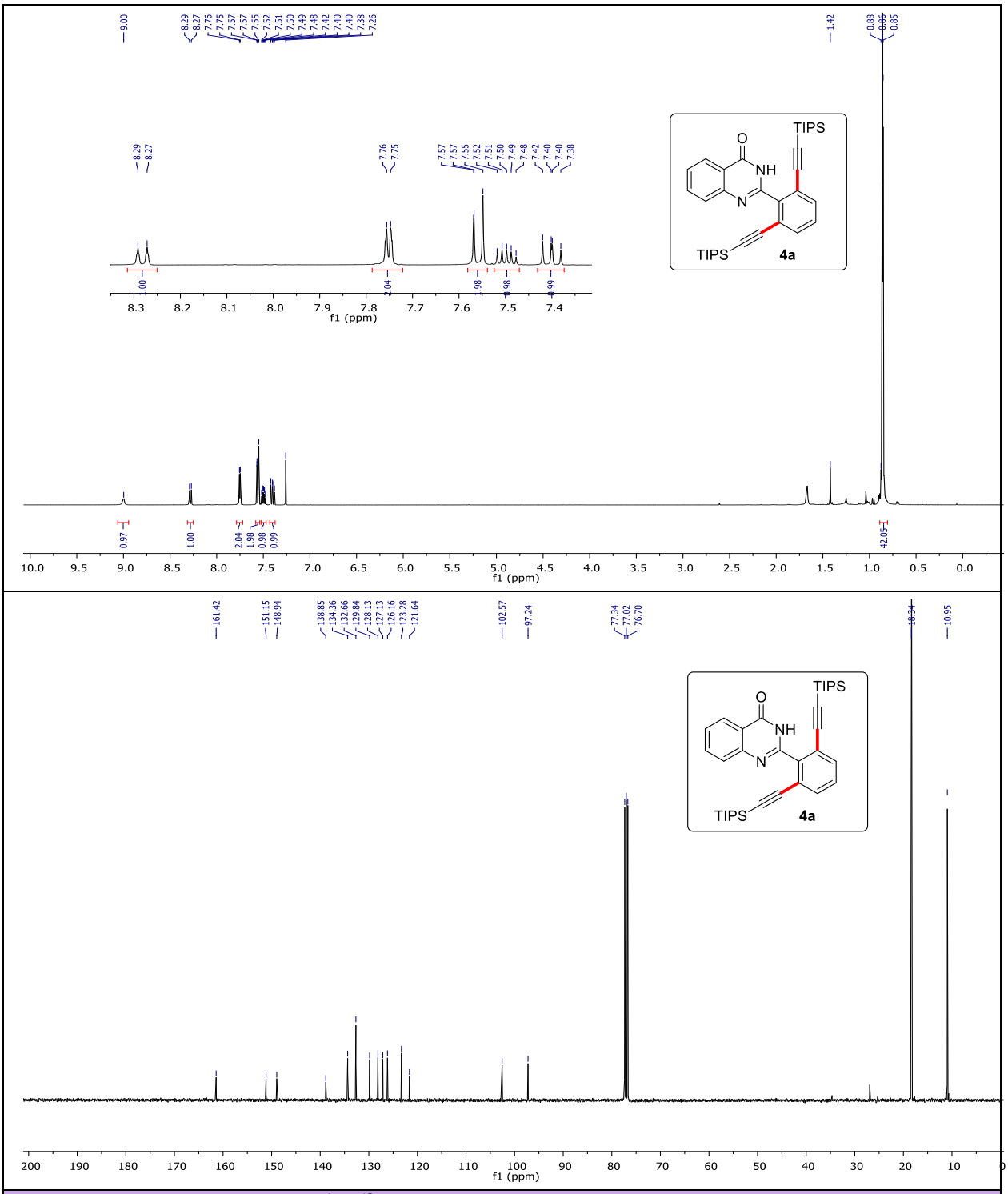


^{1}H /^{13}C NMR Spectrum of 3y in $CDCl_3$

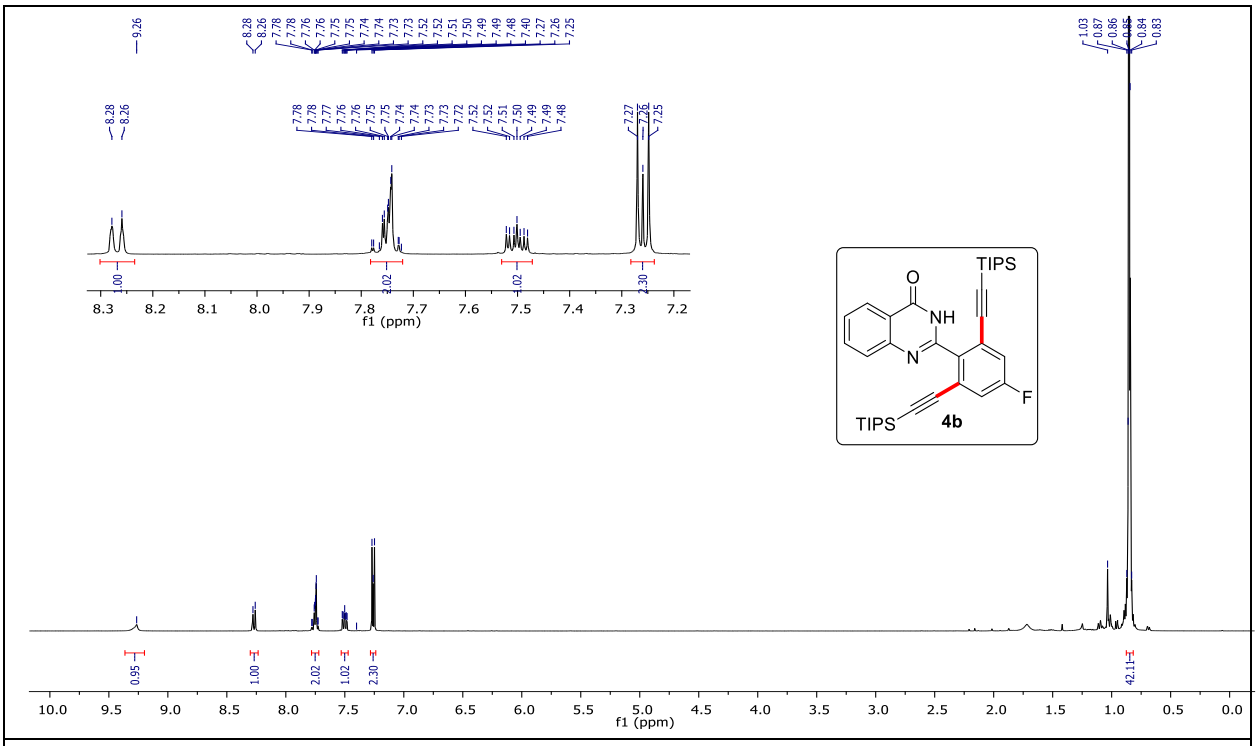


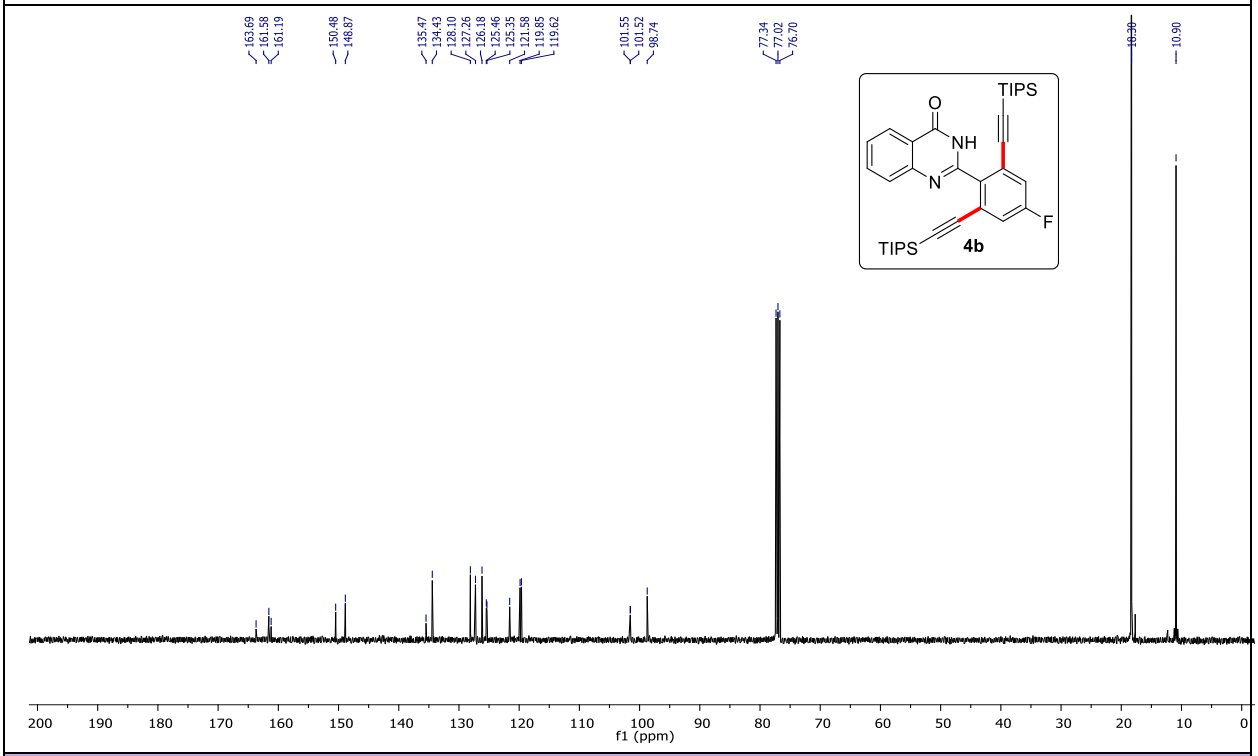


^{1}H /^{13}C NMR Spectrum of 3z in $CDCl_3$

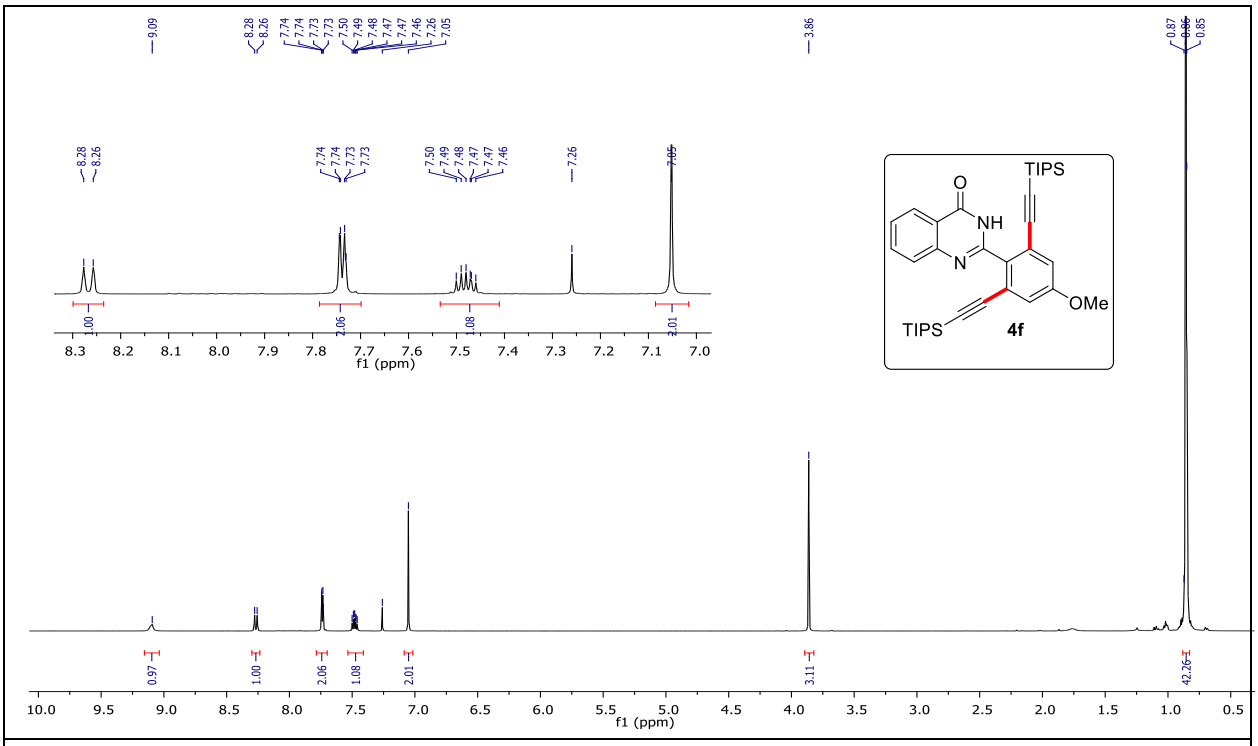


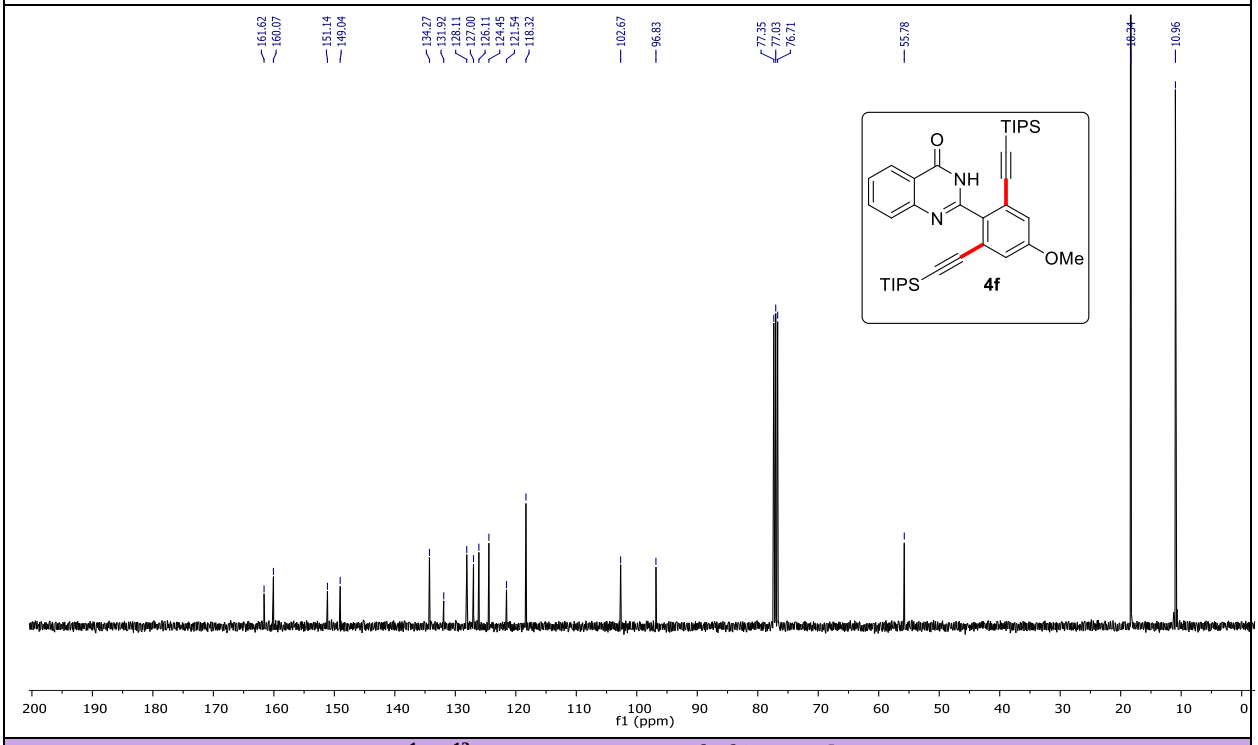
^{1}H /^{13}C NMR Spectrum of 4a in $CDCl_3$



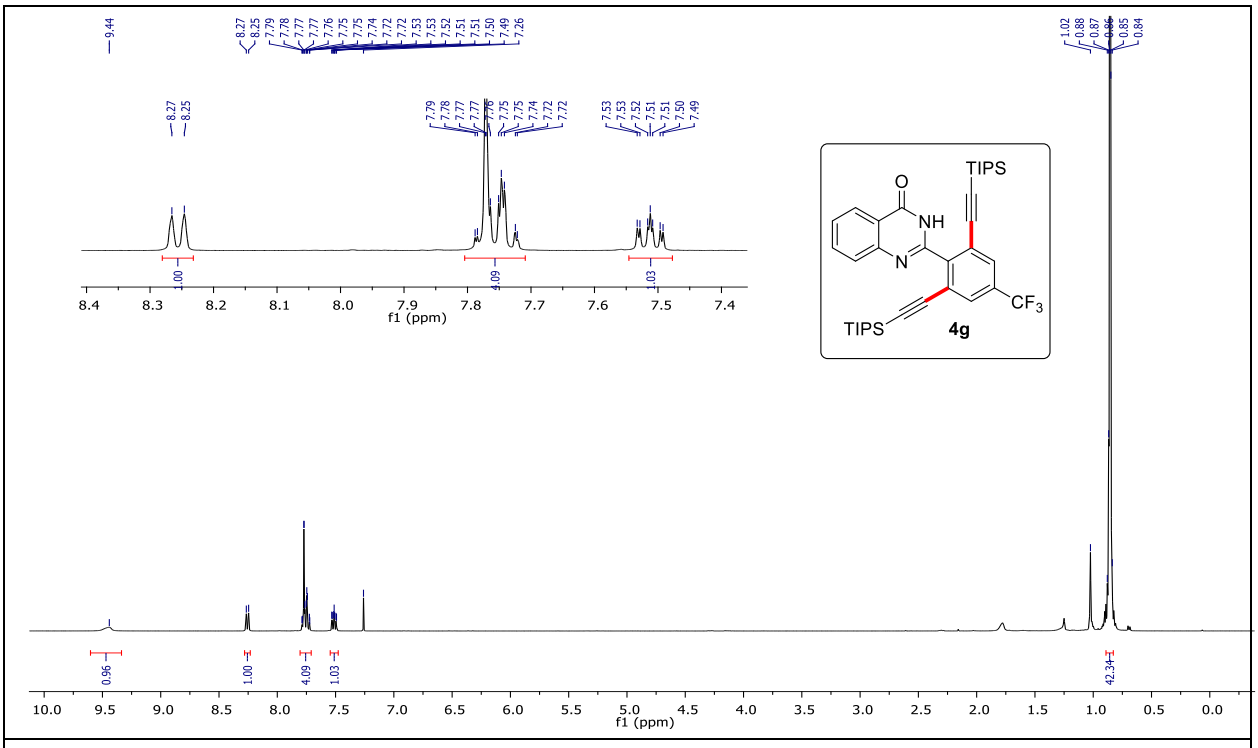


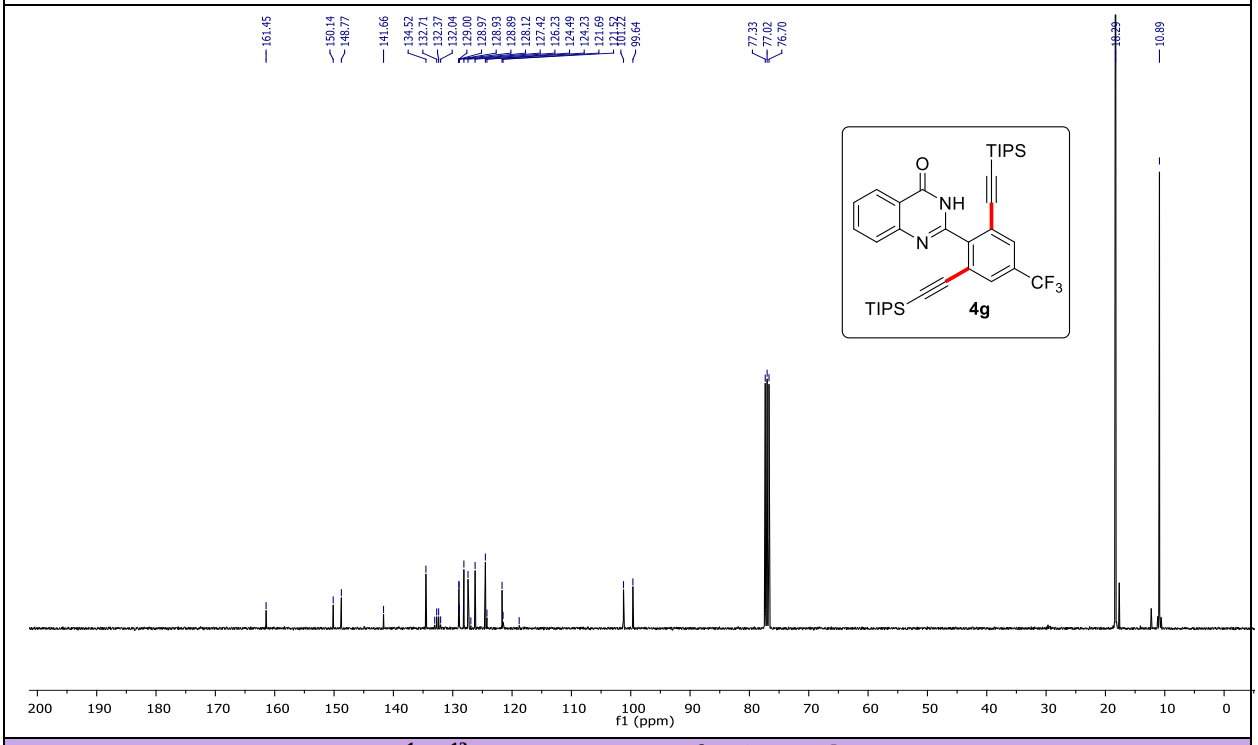
^{1}H /^{13}C NMR Spectrum of 4b in $CDCl_3$



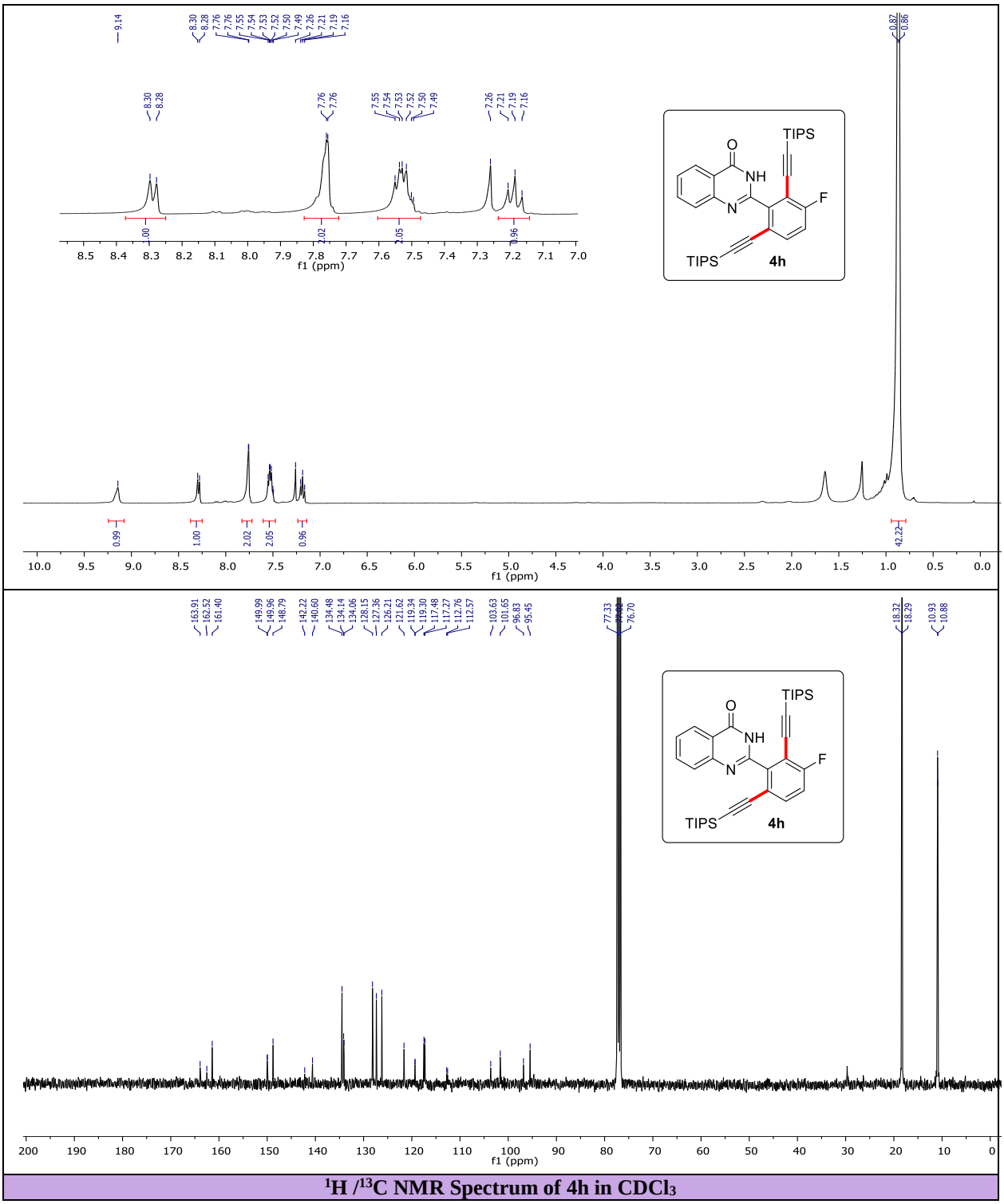


^{1}H /^{13}C NMR Spectrum of 4f in $CDCl_3$

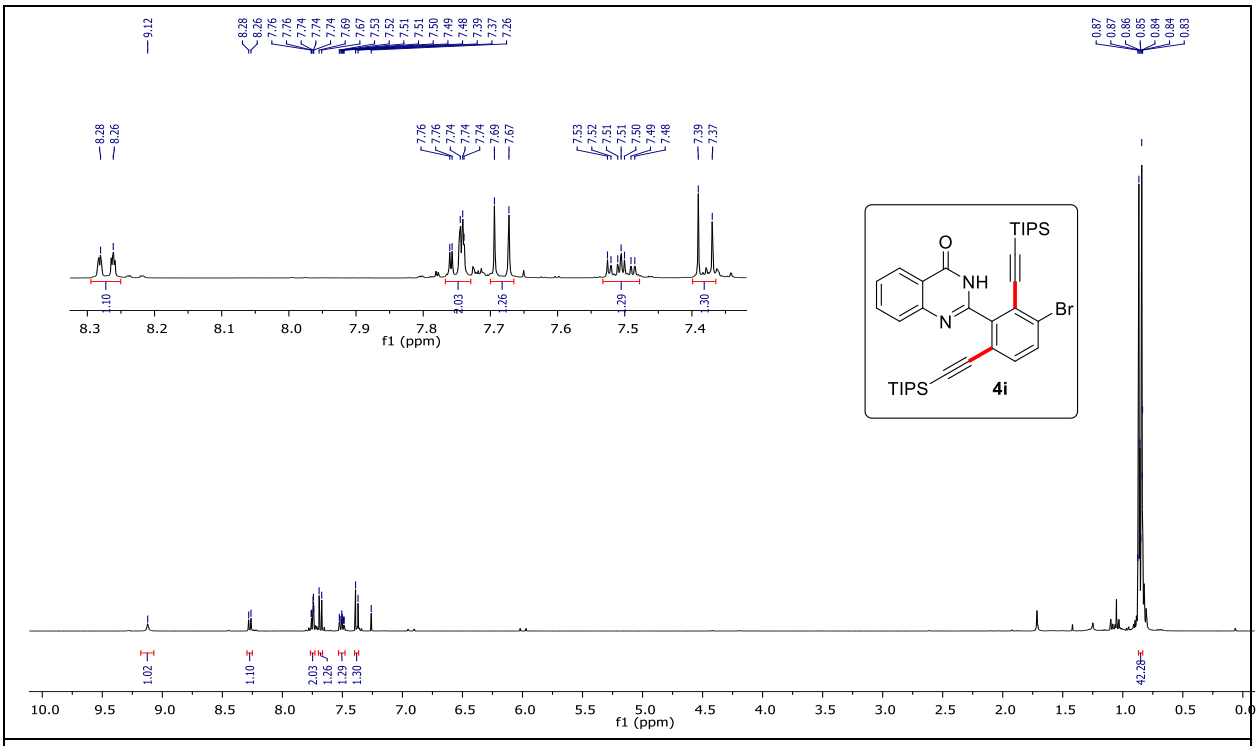


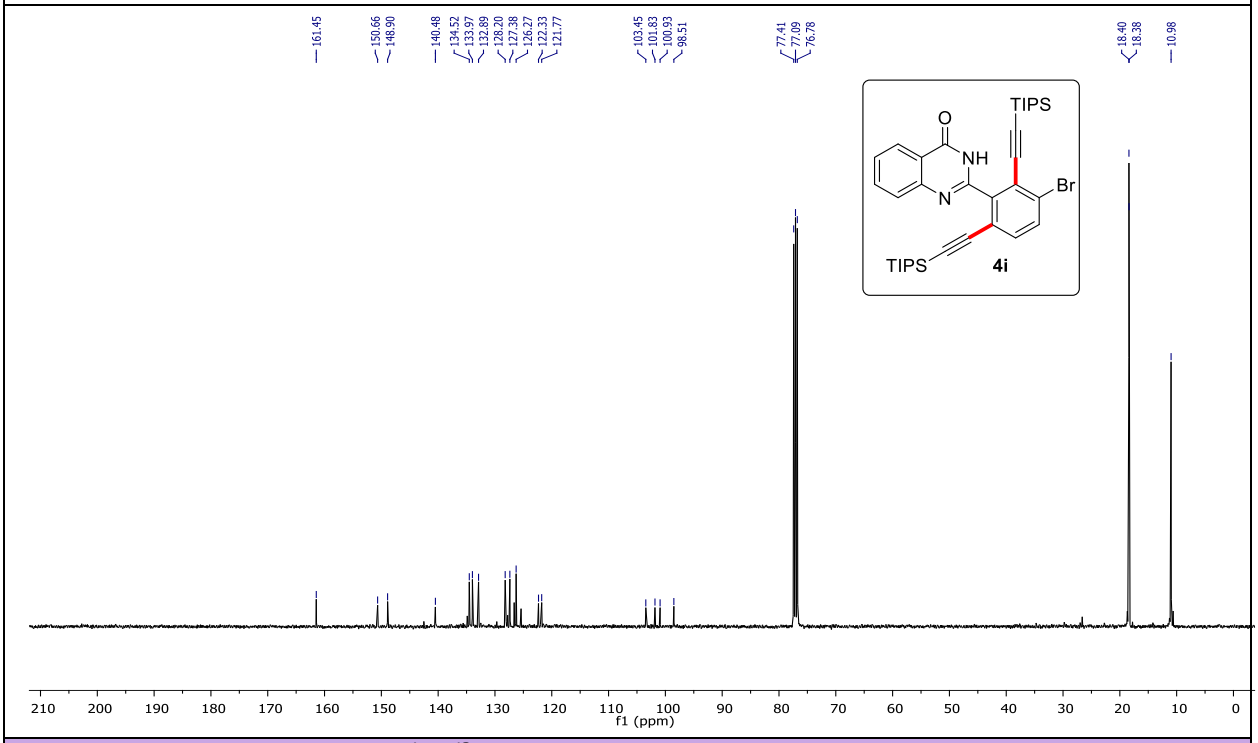


^{1}H /^{13}C NMR Spectrum of 4g in $CDCl_3$

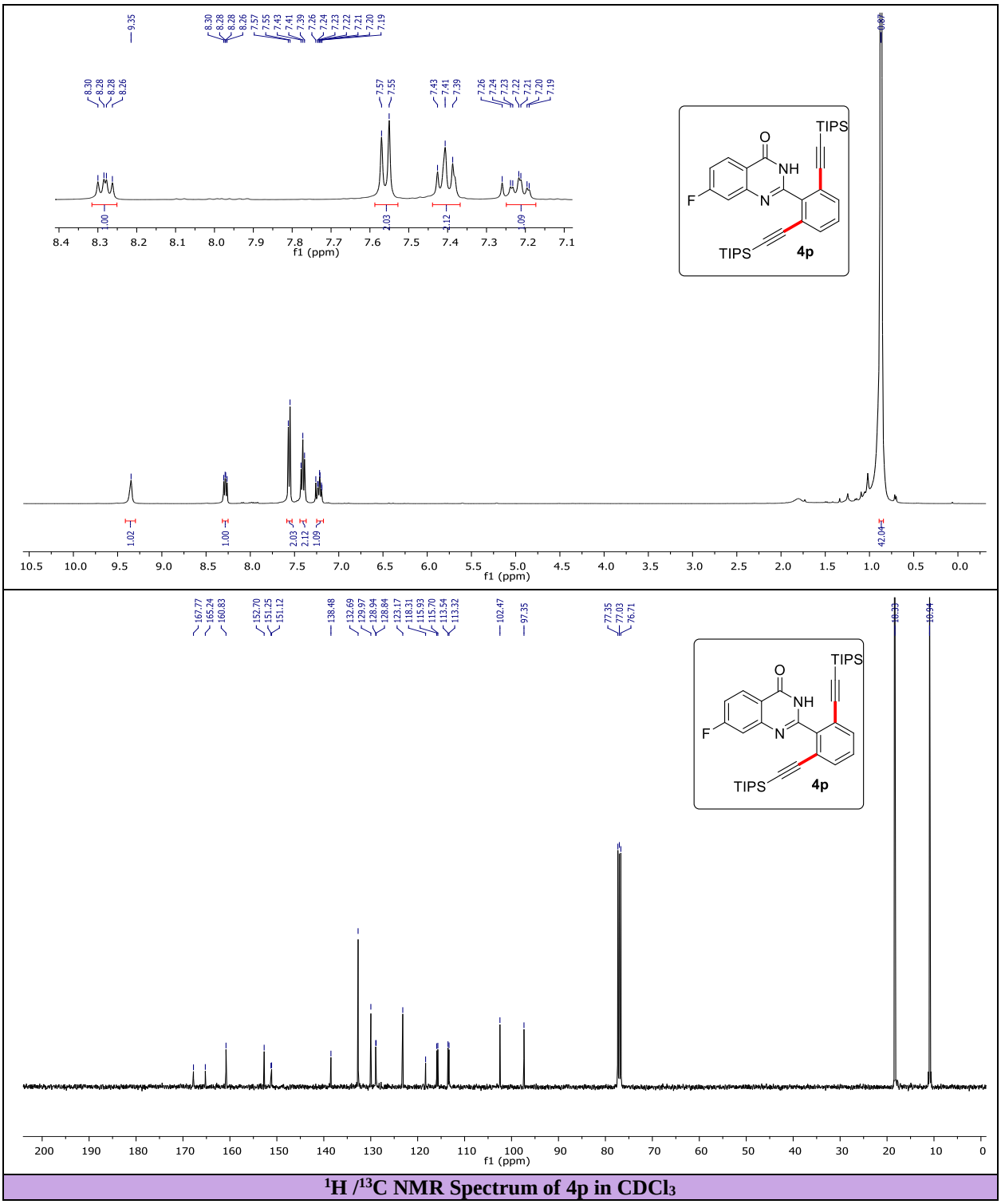


^{1}H /^{13}C NMR Spectrum of 4h in $CDCl_3$

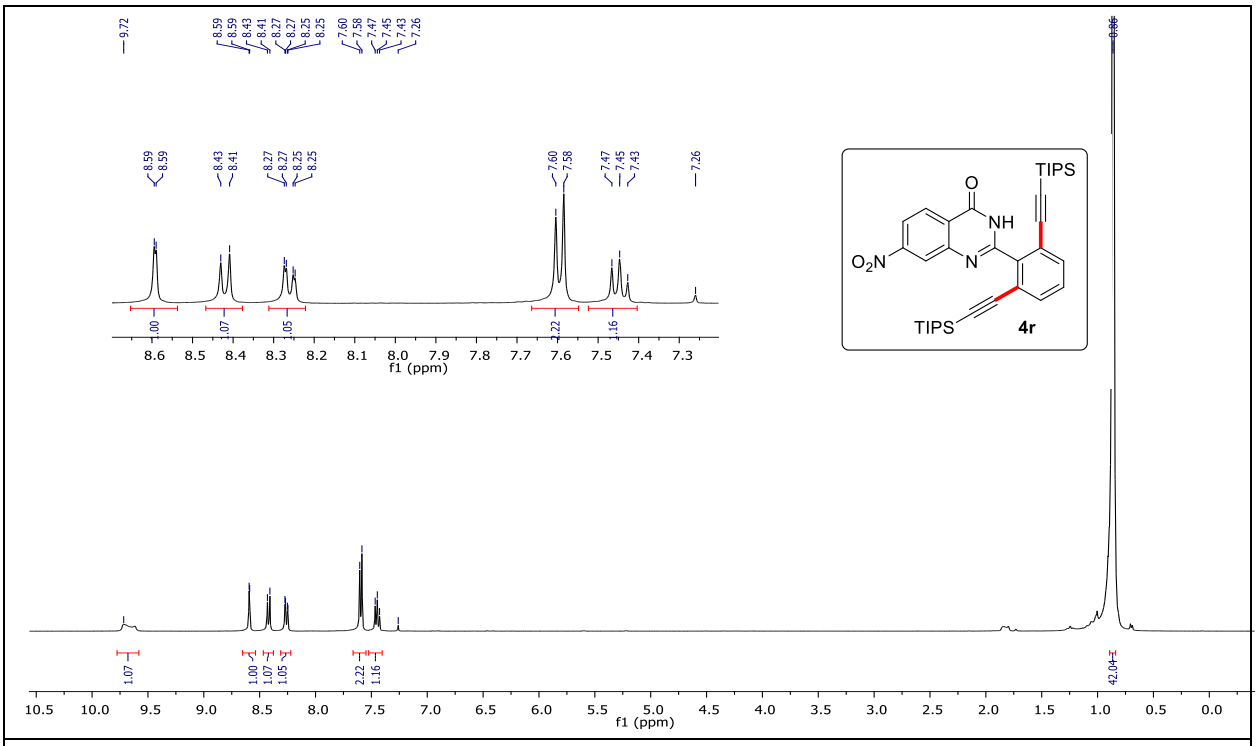


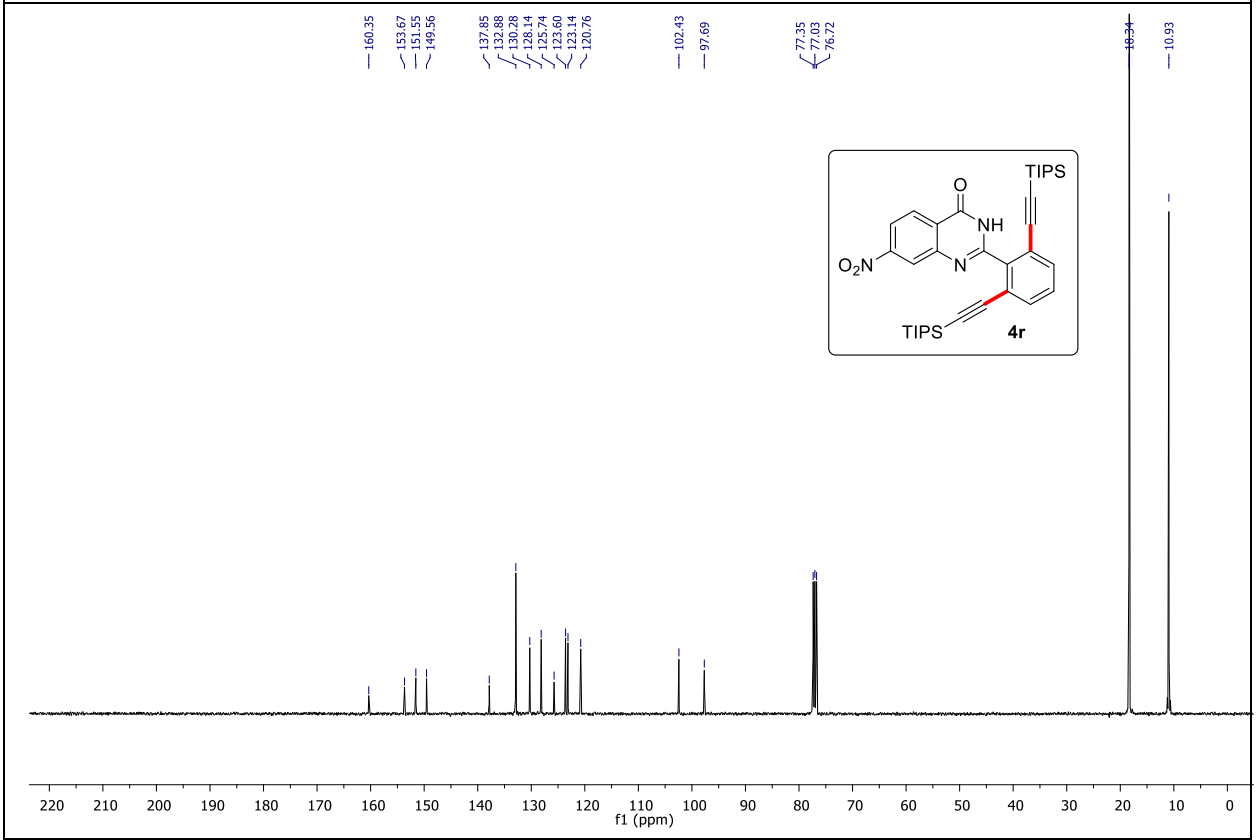


^{1}H /^{13}C NMR Spectrum of 4i in $CDCl_3$

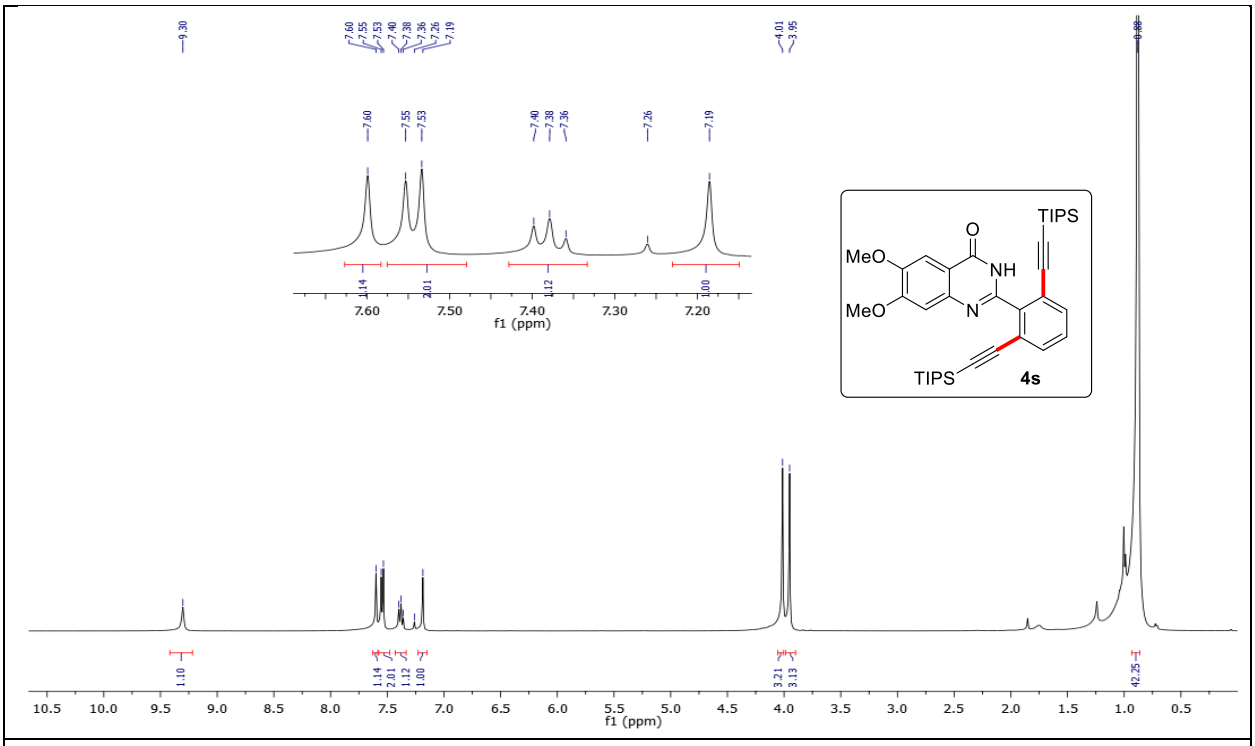


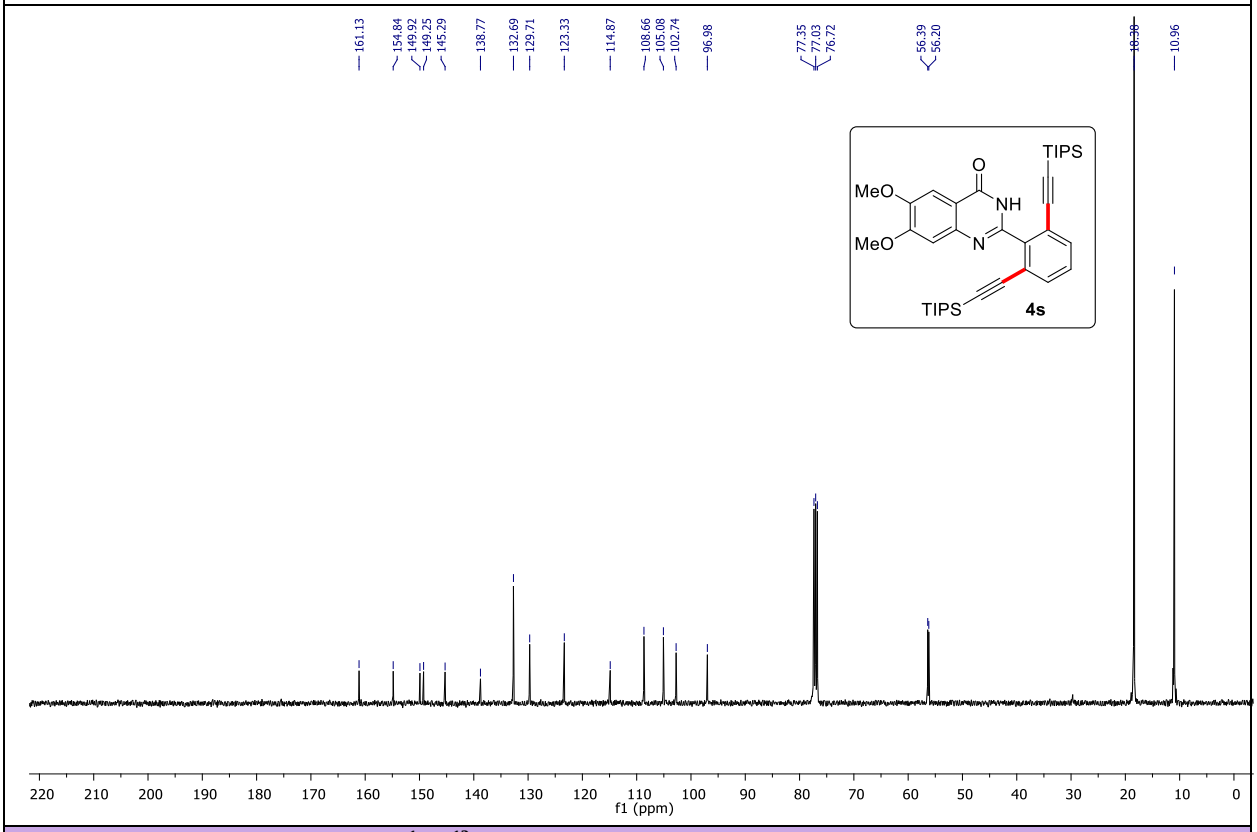
^{1}H /^{13}C NMR Spectrum of 4p in $CDCl_3$



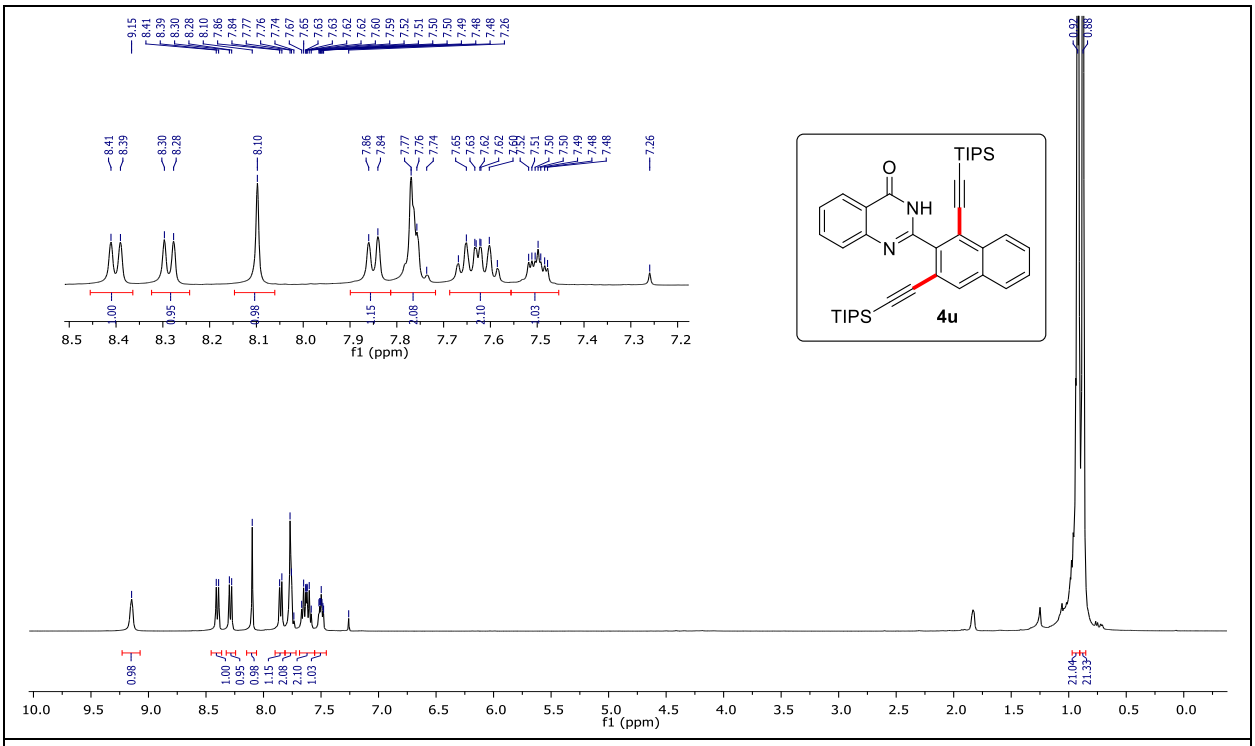


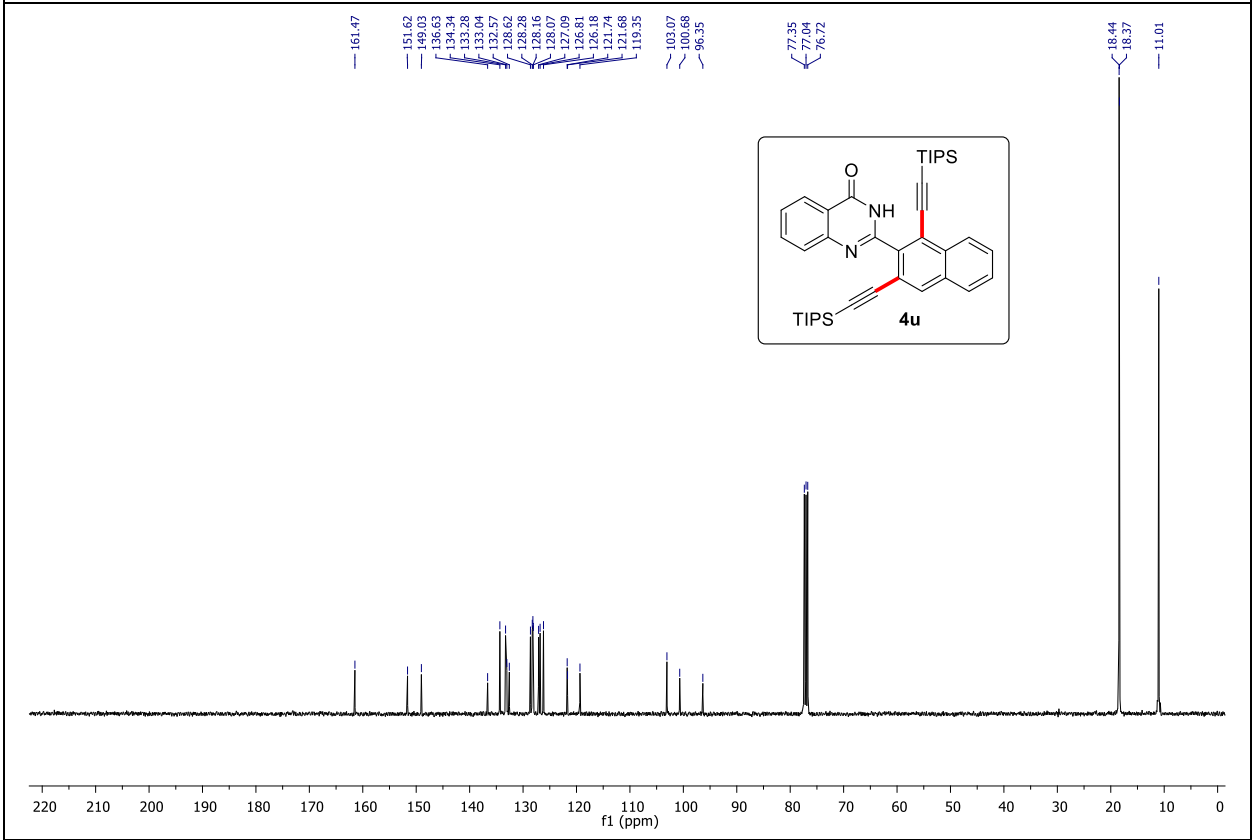
^{1}H /^{13}C NMR Spectrum of 4r in $CDCl_3$



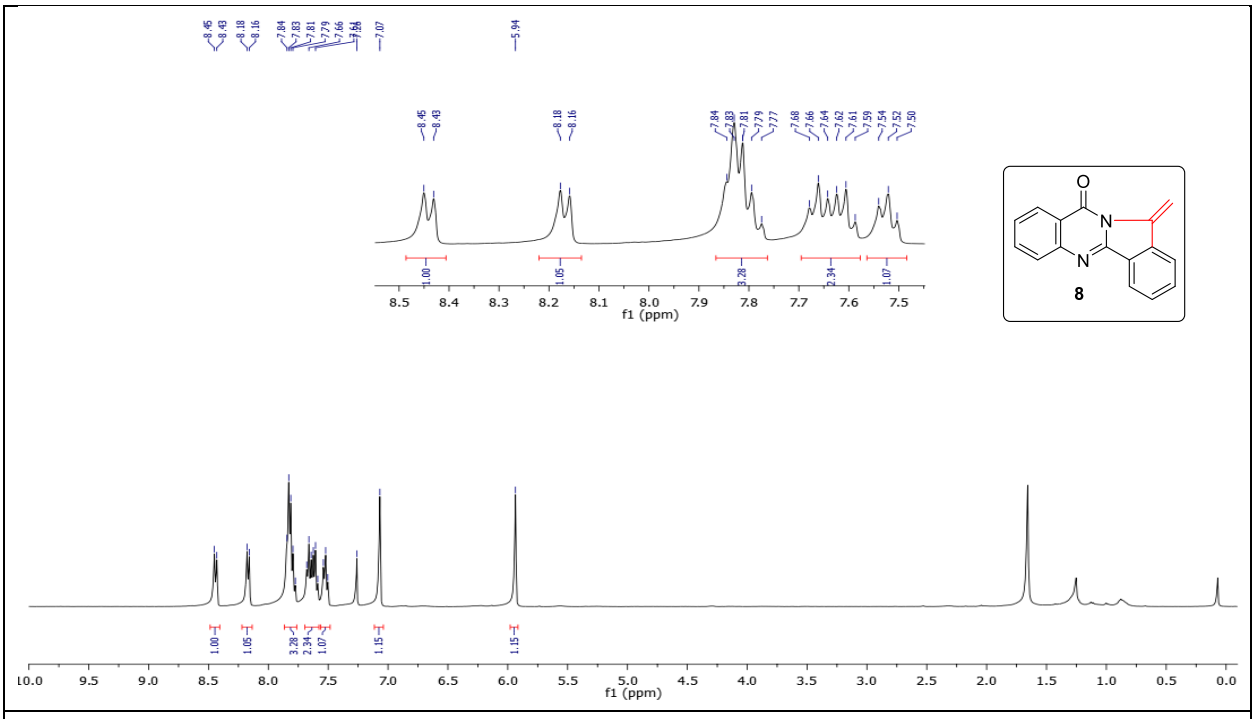


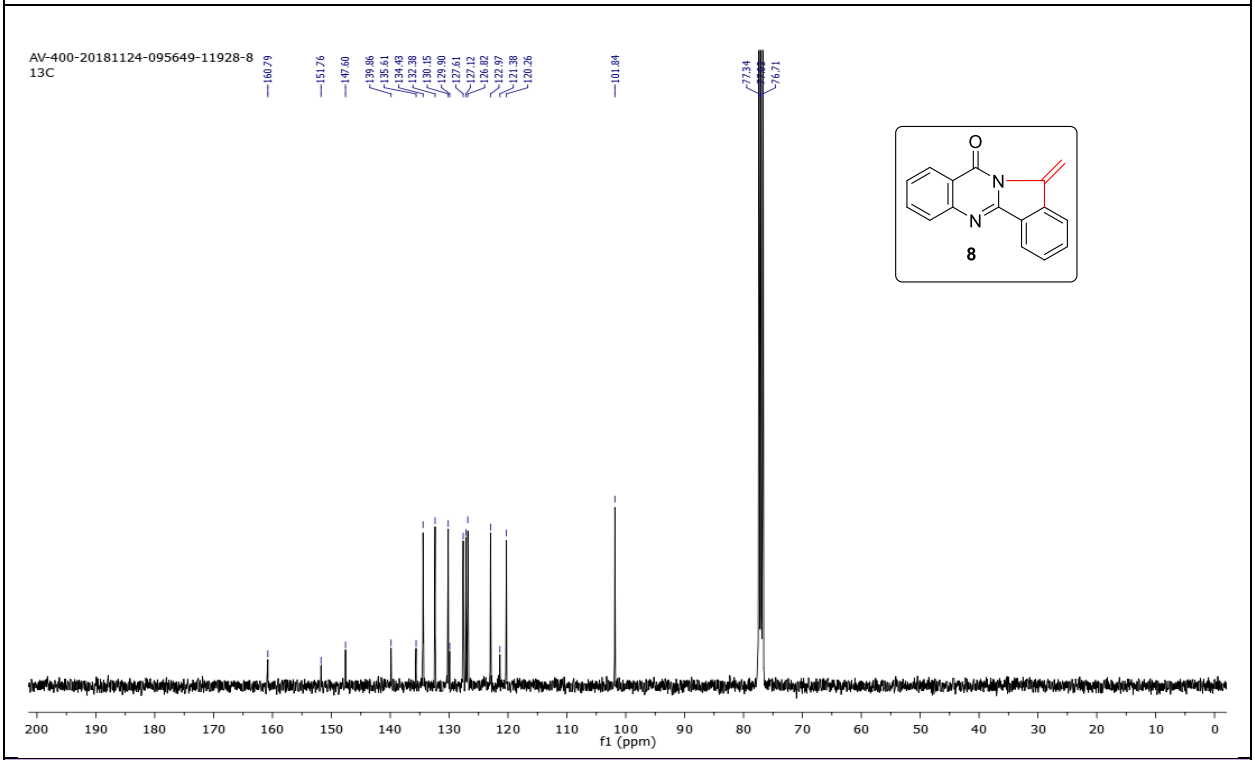
^{1}H /^{13}C NMR Spectrum of 4s in $CDCl_3$



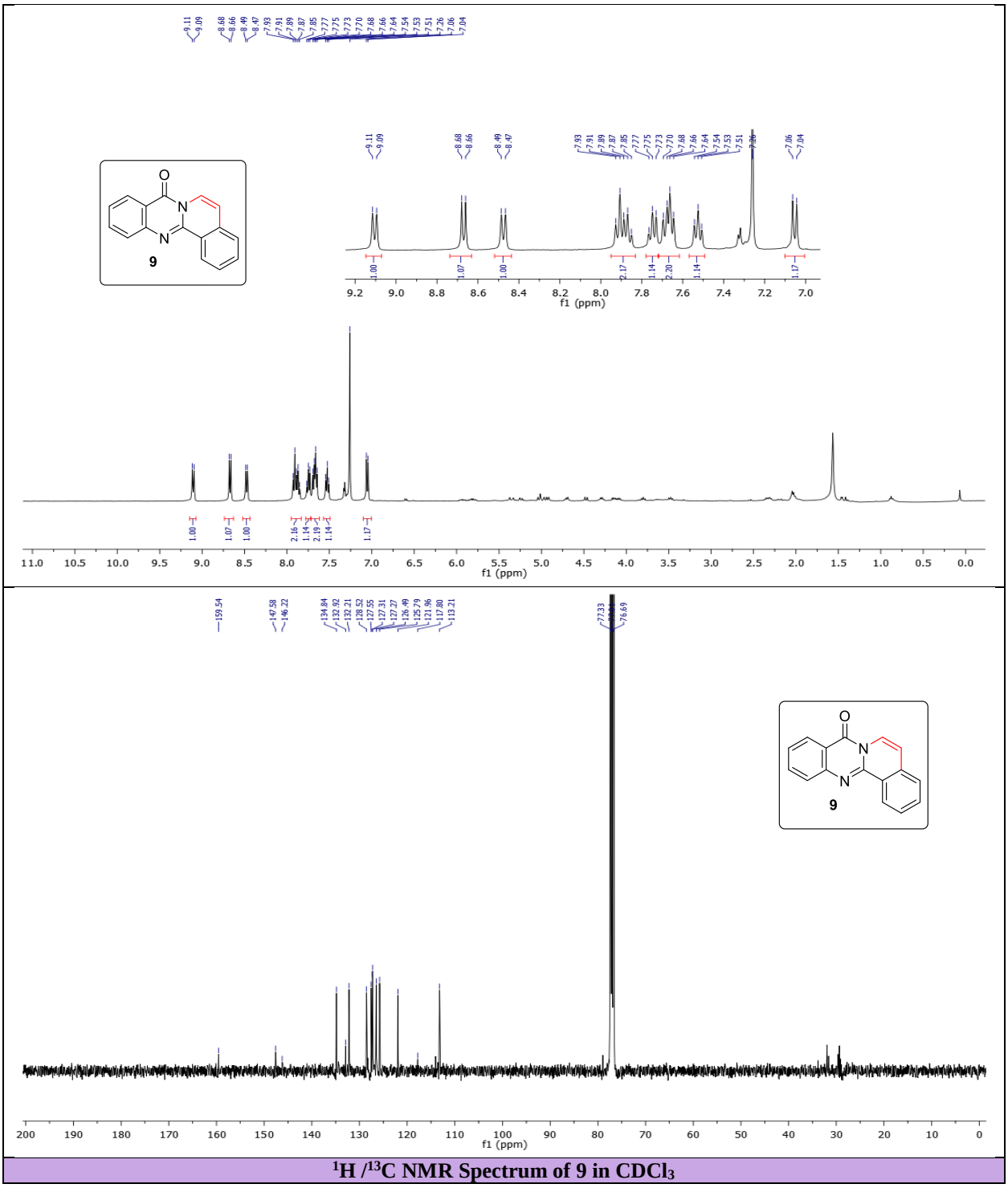


^{1}H /^{13}C NMR Spectrum of 4u in $CDCl_3$

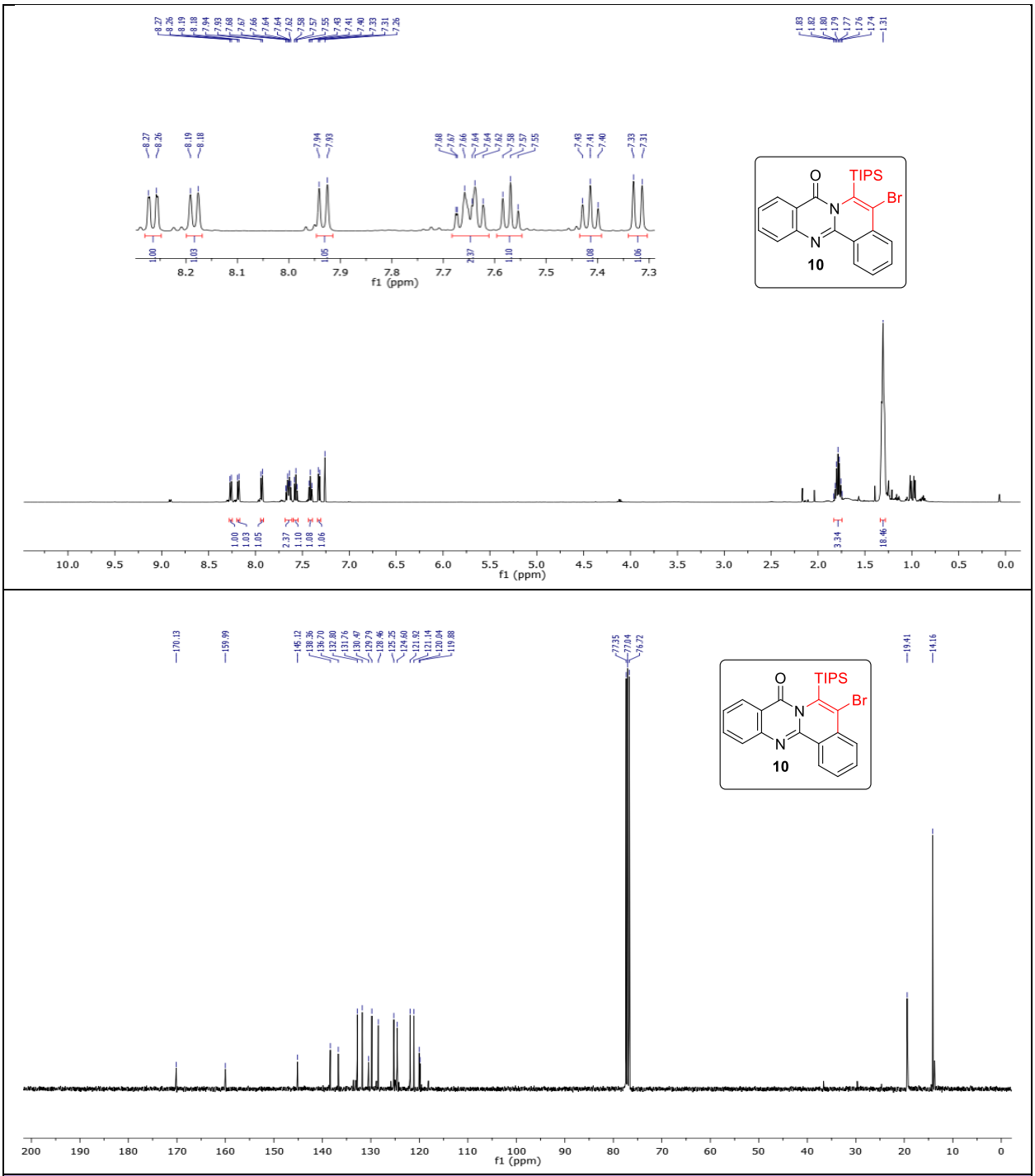




^{1}H /^{13}C NMR Spectrum of 8 in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 9 in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 10 in $CDCl_3$

References:

1. a) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.*, **2016**, *14*, 6611. b) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K. Jonnalagadda, S. B. *Molecules* **2020**, *25*, 1909. c) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *Advan. Biol. Res.* **2011**, *5*, 120. d) Wu, X-F.; Neumann, H.; Beller, M. *Chem. Rev*. **2013**, *113*, 1. e) Lamberth, C. *Pest Manag Sci* **2013**, *69*, 1106. f) Joule, J.A. *Adv Heterocycl Chem*. **2016**, *119*, 81.
2. a) Polshettiwar, V.; Varma, R. S. *Curr Opin Drug Discov Devel*. **2007**, *10*, 723. b) Zhang, B.; Studer, A.; *Chem. Soc. Rev*., **2015**, *44*, 3505. c) Liu, J.; Jiang, J.; Zheng, L.; Liu, Z-Q. *Adv. Synth. Catal*. **2020**, *362*, 4876.
3. a) Heravi, M. M.; Zadsirjan, V. *RSC Adv*., **2020**, *10*, 44247. b) Hosseinzadeh, Z.; Ramazani, A.; Razzaghi-Asl, N. *Curr. Org. Chem.* **2018**, *22*, 2256. c) Ajani, O. O.; Audu, O. Y.; Aderohunmu, D. V.; Owolabi, F. E.; Olomieja, A. O. *Am. J. Drug Discovery Dev*., **2017**, *7*, 1.
4. Chan, J. H.; Hong, J. S.; Kuyper, L. F.; Jones, M. L.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D. *J. Heterocycl. Chem*. **1997**, *34*, 145.
5. a) Currens, M. J.; Gulakowski, R. J.; Mariner, J. M.; Moran, R. A.; Buckheit Jr, R. W.; Gustafson, K. R.; McMahon, J. B.; Boyd, M. R. *J. Pharmacol. Exp. Ther*. **1996**, *279*, 645. b) Gupta, T.; Rohilla, A.; Pathak, A.; Akhtar, M. J.; Haider, M. R.; Yar, M. S.; *Synth. Commun*. **2018**, *48*, 1099.
6. a) Marzaro, G.; Guiotto, A.; Chilin, A. Expert Opin. Ther. Pat. **2012**, *22*, 1099. b) Chandrika, P. M.; Yakaiah, T.; Rao, A. R. R.; Narsaiah, B.; Reddy, N. C.; Sridhar, V.; Rao, J. V. *Eur. J. Med. Chem*., **2008**, *43*, 846.
7. Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem*. **1999**, *42*, 3860.
8. a) Asif, M. *Int. J. Med. Chem*. **2014**, 27 pages, doi.org/10.1155/2014/395637 b) Alagarsamy, V.; Chitra, K.; Saravanan, G.; Solomon, V. R.; Sulthana, M.T.; Narendhar, B. Eur. J. Med. Chem. **2018**, *151*, 628.

9. Palem, J. D.; Alugubelli, G. R.; Bantu, R.; Nagarapu, L.; Polepalli, S.; Jain, S. N.; Bathini, R.; Manga, V. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 3014.
10. a) Eguchi, S. *Top Heterocycl Chem* **2006**, *6*, 113. b) Griess, P. *Ber. Dtsch. Chem. Ges.*, **1869**, *2*, 415.
11. a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. b) Li, X.; Ouyang, W.; Nie, J.; Ji, S.; Chen, Q.; Huo, Y. *ChemCatChem* **2020**, *12*, 2358.
12. Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; , Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev*., **2018**, *47*, 6603.
13. a) Gallego, D.; Baquero, E. A. *Open Chem.*, **2018**; *16*, 1001. b) Basu, D.; Kumar, S.; Sudhir, V. S.; Bandichhor, R. *J. Chem. Sci*. **2018**, *130*, 71.
14. a) Gupta, P. K.; Yadav, N.; Jaiswal, S.; Asad, M.; Kant, R.; Hajela, K. *Chem. -Eur. J.* **2015**, *21*, 13210. b) Dabiri, M.; Lehi, N. F.; Movahed, S. K.; and Khavasi, H. R. *Org. Biomol. Chem.*, **2017**, *15*, 6264. c) Lingayya, R.; Vellakkaran, M.; Nagaiah, K.; Nanubolu, J. *Adv. Synth. Catal.* **2016**, *358*, 81. d) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. *Org. Biomol. Chem.* **2014**, *12*, 758. e) Wei, L.-S.; He, G.-X.; Kong, X.-F.; Pan, C.-X.; Mo, D.-L.; Su, G.-F. *J. Org. Chem.* **2018**, *83*, 6719.
15. a) Trost, B. M.; Li, C.-J. Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations; Wiley: New York, **2014**. b) Stang, P. J.; Diederich, F. Modern Acetylene Chemistry; Wiley: New York, **2008**. c) Diederich, F.; Stang, P. J.; Tykwinski, R. R. Acetylene Chemistry; Wiley: New York, **2005**. d) Schobert, H. *Chem. Rev.* **2014**, *114*, 1743. e) Trotus, I.-T.; Zimmermann, T.; Schuth, F. *Chem. Rev.* **2014**, *114*, 1761. f) Chinchilla, R.; Najera, C. *Chem. Rev.* **2014**, *114*, 1783. g) Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. *Chem. Rev.* **2016**, *116*, 5894.
16. For selected examples of C–H alkynylation and references cited therein: a) Caspers, L. D.; Nachtsheim, B. J. *Chem. Asian J.* **2018**, *13*, 1231. b) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2010**, *49*, 2096.

17. a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467. b) Meijere, A. d.; Diederich, F. *Metal-catalyzed cross–coupling reactions*, 2nd, completely rev. and enl. ed., Wiley-VCH, Weinheim, **2004**. c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4442. d) Plenio, H. *Angew. Chem., Int. Ed*. **2008**, *47*, 6954. e) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

18. a) Negishi, E.; Anastasia, L. *Chem. Rev*. **2003**, *103*, 1979. b) Weng, Y.; Cheng, B.; He, C.; Lei, A. *Angew. Chem., Int. Ed*. **2012**, *51*, 9547. c) Wang, M.; Wang, Z.; Shang. M.; Dai. H. *Chin. J. Org. Chem*. **2015**, *35*, 570. d) Li, C.-J. *Acc. Chem. Res*. **2010**, *43*, 581. e) For recent reviews on transition metal catalysed C-H bond functionalization by the use of diverse directing groups, see: Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843.

19. Selected examples for alkynylation using terminal alkyne reagents: a) Liu, W.; Li, L.; Li, C.-J. *Nat. Commun*. **2015**, *6*, 6526. b) Yi, J.; Lu, X.; Sun, Y.-Y.; Xiao, B.; Liu, L. *Angew. Chem., Int. Ed*. **2013**, *52*, 12409. c) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc*. **2003**, *125*, 13642. d) Tang, S.; Liu, Y.; Gao, X.; Wang, P.; Huang, P.; Lei, A. *J. Am. Chem. Soc.* **2018**, *140*, 6006. e) Wu, X.-X.; Liu, A.; Xu, S.; He, J.; Sun, W.; Chen, S. *Org. Lett.* **2018**, *20*, 1538. f) Luo, F.-X.; Cao, Z.-C.; Zhao, H.-W.; Wang, D.; Zhang, Y.-F.; Xu, X.; Shi, Z.-J. *Organometallics* **2017**, *36*, 18.

20. Selected examples for alkynylation using haloalkyne reagents: a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. b) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. c) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354.

21. Selected examples for alkynylation using boron alkyne reagent: a) Bertolini, F.; Woodward, S. *Synlett* **2009**, 1, 51. b) Molander, G. A.; Traister, K. M. *Org. Lett.* **2013,** *15*, 5052. c) Molander, G. A.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416.

22. For reviews and highlight articles on reactions of hypervalent iodine reagents: a) Ochiai, M.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 5511. b) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547. c) Brand, J.

P.; Waser J. *Chem. Soc. Rev.* **2012**, *41*, 4165. d) Li, Y.; Hari, D. P.; Vita, V. M.; Waser, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 4436. e) Waser, J. *Synlett* **2016**, *27*, 2761. f) Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2015**, *54*, 8876.

23. For selected examples of $[Cp^*IrCl_2]_2$-catalyzed C-H activation, see: a) Li, X.; Wu, G.; Liu, X.; Zhu, Z.; Huo, Y.; Jiang H. *J. Org. Chem.* **2017**, *82*, 13003. b) Chen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. *Org. Lett.* **2017**, *19*, 2474. c) Caspers, L. D.; Finkbeiner, P.; Nachtsheim, B. J. *Chem. Eur. J.* **2017**, *23*, 2748. d) Li, G.; Hu, J.; Zeng, R.; Shi, D-Q.; Zhao, Y. *Org. Lett.* **2018**, *20*, 2454. e) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1946. f) Tang, G.-D.; Pan, C.-L.; Xie, F. *Org. Biomol. Chem.*, **2016**, *14*, 2898. g) Liu, B.; Wang, X.; Ge, Z.; Li, R. *Org. Biomol. Chem.*, **2016**, *14*, 2944. h) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780. i) Kona, C. N.; Nishii, Y.; Miura, M. *Angew.Chem. Int. Ed*. **2019,** *58*, 9856.

24. a) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2008**, *51*, 3367. b) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49. c) Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D. G.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C. Y.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X. G.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A.; Tang, W.; Wang, L.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. *J. Med. Chem.* **2007**, *50*, 5202.

25. a) Phatake, R. S.; Patel, P.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 292. b) Phatake, R. S.; Patel, P.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 2828.

26. Lu, B.; Wu, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 11598.

27. Wu, J.; Yoshikai, N. *Angew. Chem., Int. Ed*. **2015**, *54*, 11107.

28. Roy, A.; Das, M. K.; Chaudhuri, S.; Bisai, A. *J. Org. Chem*. **2018**, *83*, 403.

29. Rao, D. N.; Rasheed, S.; Das, P. *Org. Lett*. **2016**, *18*, 3142.

30. Liu, J. -Q.; Ma, Y. -G.; Zhang, M. -M.; Wang, X. -S. *J. Org. Chem.* **2017**, *82*, 4918.

31. a) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492. b) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414.

32. Li, Y.; Xie, F.; Li, X. *J. Org. Chem.* **2016**, *81*, 715.

33. Finkbeiner, P.; Kloeckner, U.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4949.

34. a) For the synthesis of starting materials see: supporting information. b) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. -Eur. J.* **2012**, *18*, 5655. c) Sun, J.; Tan, Q.; Yang, W.; Liu, B.; Xu, B. *Adv. Synth. Catal.* **2014**, *356*, 388.

35. Kim, N. Y.; Cheon, C.-H. *Tetrahedron Lett*. **2014**, *55*, 2340.

36. Cheng, R.; Guo, T.; Zhang–Negrerie, D.; Du, Y.; Zhao, K. *Synthesis* **2013**, *45*, 2998.

37. Liu, W.; Wu, G.; Gao, W.; Ding, J.; Huang, X.; Liu, M.; Wua, H. *Org. Chem. Front.* **2018**, *5*, 2734.

38. Hudwekar, A. D.; Reddy, G. L.; Verma, P. K.; Gupta, S.; Vishwakarma, R. A.; Sawant, S. D. *ChemistrySelect* **2017**, *2*, 4963.

39. Parua, S.; Das, S.; Sikari, R.; Sinha, S.; Paul, N. D. *J. Org. Chem.* **2017**, *82*, 7165.

40. Wang, Z.-Z.; Tang, Y. *Tetrahedron* **2016**, *72*, 1330.

41. Mason, J. J.; Bergman, J.; Janosik, T. *J. Nat. Prod.* **2008**, *71*, 1447.

42. Li, H.; He, L.; Neumann, H.; Beller, M.; Wu, X-F. *Green Chem.* **2014**, *16*, 1336.

43. Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. -Eur. J.* **2012**, *18*, 5655.

CHAPTER II

Building focussed small molecule libraries around Voxelotor (GBT 440) *via* early and late stage C-H functionalization

1.1 Introduction:

Heterocyclic compounds play a key role in metabolism, which is evident from the presence of these subunits in a wide range of natural products. Nitrogen-containing heterocycles are the basic structures of several biologically active compounds and display various applications in chemical as well as biological fields.[1] Historically, these nitrogen-containing heterocycles were known to be a vital source of therapeutic agents and are a distinctive class of compounds, used to synthesize half of all the organic compounds.[2] Among all heterocyclic compounds, pyrazole is one of the commonly found structural units in many pharmaceutically active compounds, drugs, agrochemical products, and also in ligands employed for transition metal complexes synthesis.[3] In particular, their analogues show various properties such as anti-bacterial, anti-fungal, anti-cancer, anti-depressant, anti-inflammatory, anti-tuberculosis, anti-oxidant, and anti-viral.[4] A recent survey conducted by Richie *et al.* at GlaxoSmithKline revealed that the pyrazole ring is the most common heterocyclic ring in drug molecules.[3a] A few examples of drug molecules holding the pyrazole motif are presented in **Figure F2.1**. According to the research conducted, pyrazole has a good developability score, as a majority of investigational drugs having this core showed fewer pharmaceutical and toxicological problems during the drug development phase.[3b,5] This prompted a significant amount of interest to derive novel synthetic strategies for building the functionalized pyrazole ring or its derivatives.

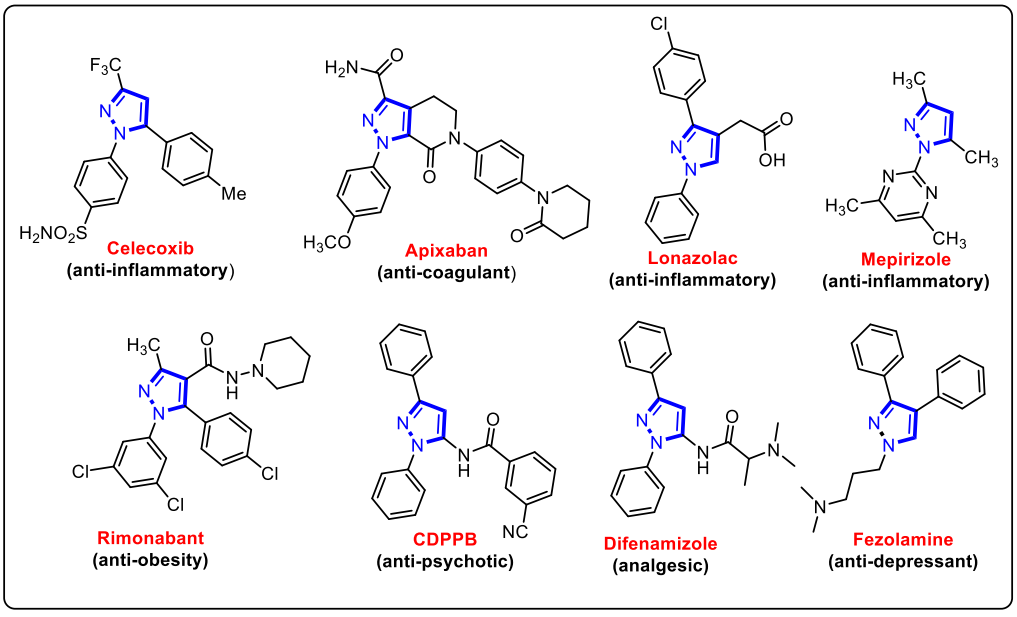


Figure F2.1: *Selected drug molecules holding the pyrazole unit*

Sickle cell disease is a set of autosomal recessive diseases that is caused by a mutation of the single amino acid in the β-chain of haemoglobin and which results in the formation of abnormal sickle hemoglobin (HbS). There are different types of this disease; the more common ones are sickle cell anemia, sickle beta-plus thalassemia, sickle hemoglobin-C disease, and sickle beta-zero thalassemia.[6] Among these, sickle-cell anemia (SCA) is a chronic disorder prevalent mainly in the scheduled population. These abnormal sickle hemoglobin (HbS) undergo polymerization when they are deoxygenated, which results in red-cell sickling and membrane damage. This disease mainly leads to hemolysis, vaso-occlusion, inflammation and chronic anemia, which causes the acute and chronic manifestations of sickle cell disease that substantially shorten the life expectancy by 30 years.[7]

Around 100,000 people in the US are affected by this disease.[6a] After the US, India is estimated to have the second-highest burden of the disease, with the highest prevalence in the socioeconomically disadvantaged communities such as the tribal population, which accounts for 8.5% of the total Indian population.[8] Along with the difficulties associated with its diagnosis, the treatment of SCA is hampered because of the lack of available medicines. The treatment involves mainly maintaining the HbS in the oxygenated state to avoid polymerization, as it occurs only in the deoxygenated state. Approved drugs against sickle cell include hydroxyurea and L-glutamine.[9] Among these approved drugs, hydroxyurea is the one that has been widely used for the treatment of SCA, despite the issues about its safety, especially, proven myelosuppression and teratogenicity.[9c] The L-glutamine is a newly approved drug against SCA. However, it does not fight the underlying issue of this disease and is helpful in controlling the vaso-occlusive crisis – a common painful complication of sickle cell anemia.[9d] In some cases, paracetamol or ibuprofen were prescribed for pain relief. Until the discovery of Voxelotor (GBT-440), there were no approved drugs that could modify the underlying disease mechanism of SCA. Voxelotor (GBT 440) is a very recently introduced drug for the treatment of Sickle cell anemia that acts by inhibiting haemoglobin S (HbS) polymerization.[10] In 2017, as part of the GoI National Sickle Cell Anemia Control Program, an initiative has been taken to identify novel drug candidates for SCA. GBT 440, which was in Phase III clinical trials (renamed as Voxelotor after its approval in 2020), has been selected as a promising scaffold in this regard.

The structure of Voxelotor presents three interesting scaffolds, pyridine, pyrazole, and salicylaldehyde that are linearly linked. Keeping the C–H functionalization as a key tool, we have

opted to build GBT 440 like scaffolds by the C–H functionalization of the simple pyrazolylpyridine scaffold and also by the direct late-stage functionalization of GBT 440 scaffold.

1.2 Pre/Post Drug modifications using early or late stage C–H functionalization:

Four decades ago, the modern concept of using C–H functionalization for developing diverse analogues of complex motifs has been visualized.[11] Nowadays, late stage C–H activation has become an important tool used in medicinal chemistry, as it provides a shortcut compared to other classical methods to bring diversity in drug molecules with an equal ease to synthesize a focused library around the drug molecules. Apart from the medicinal chemistry, the late stage functionalization *via* the C–H activation approach has been amply applied in diverse areas that include the complex large molecules such as polymers.[11c] Coming to the LSF in drug discovery, some of the selected examples of drug modifications using C–H activation are presented in **Figure F1.2**, where all these drugs have been synthesized in large scale using C–H activation protocol. As our work mainly deals with the late stage functionalization of drug molecules, we wish to present some of the key C–H functionalization reactions that are used on large scales during the drug development process.

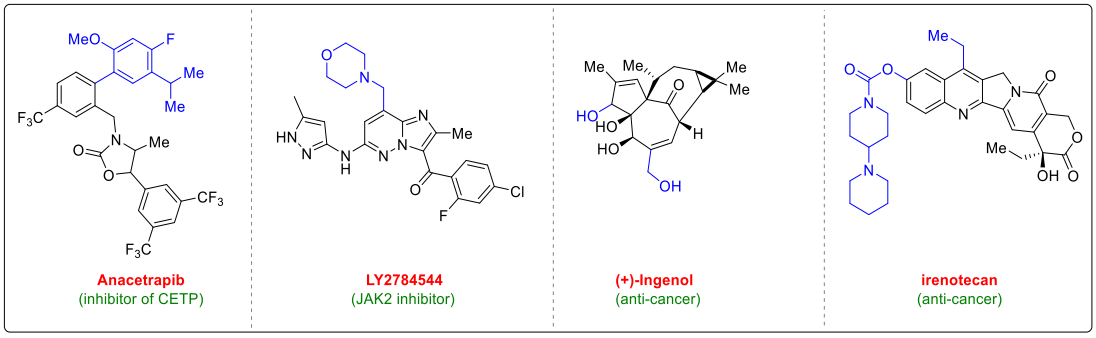
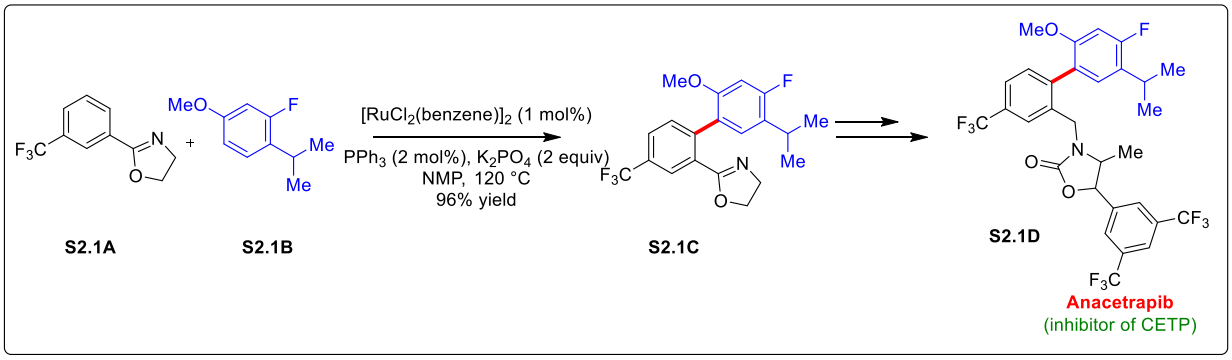


Figure F1.2: *Selective examples of the large scale C–H functionalization of drug molecules.*

Anacetrapib, a selective CETP inhibitor drug which was used for the treatment of hypercholesterolemia is a classic example where the Ru-Catalysed direct C–H arylation protocol has been used to synthesize the biaryl core.[12] In 2010, Ouellet and co-workers documented a robust and high yield protocol that comprises of treating 2-aryloxazoline **S2.1A** with 4-isopropyl-2-bromo-5-fluoroanisole **S2.1B** in the presence of a Ru(II) catalyst, PPh_3 ligand, K_3PO_4 base, and γ-

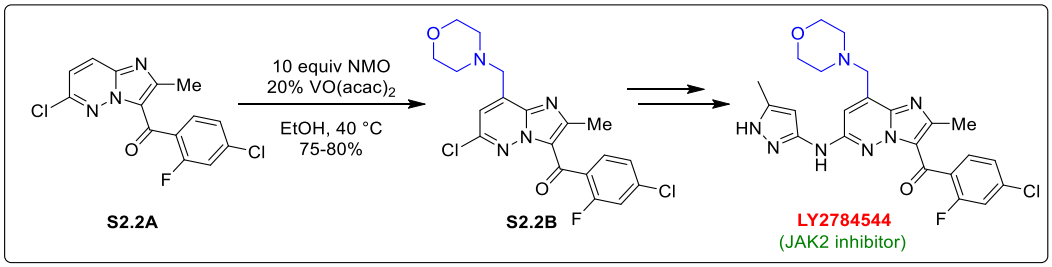
butyrolactone as an important additive in NMP solvent at 120 °C to afford the arylated compound **S2.1C**. It is worth to note that both the coupling partners required for this C–H functionalization reaction were prepared from readily available starting materials and the suitability of this transformation on a large-scale has been successfully demonstrated.



Scheme S2.1: *Ru-Catalysed C–H arylation of 2-aryloxazoline*

(Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 5, 1436–1439)

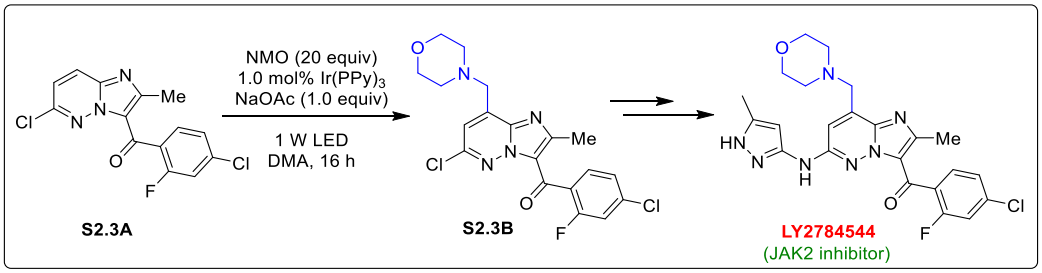
Next, LY2784544, which is a JAK2-V617F inhibitor, has been in clinical trials for the treatment of myeloproliferative disorders. Recently, a large scale synthesis of LY2784544 (100 kg scale) has been executed *via* a C–H functionalization protocol.[13a] In 2012, Mitchell's group reported the $VO(acac)_2$ catalysed addition of N-methylmorpholine N-oxide on **S2.2A** in the presence of excess of NMO and ethanol solvent at 40 °C to synthesize the intermediate **S2.2B** in very good yield. They have conducted this reaction in a large scale, and along with that, they have also prepared other APIs in a pilot-plant scale and reduced the steps required for the synthesis of the final drug molecule.



Scheme S2.2: *Vanadium catalysed addition of N-methylmorpholine N-oxide.*

(Mitchell, D.; Cole, K. P.; Pollock, P. M.; Coppert, D. M.; Burkholder, T. P.; Clayton, J. R. *Org. Process Res. Dev.* **2012**, *16*, 1, 70–81.)

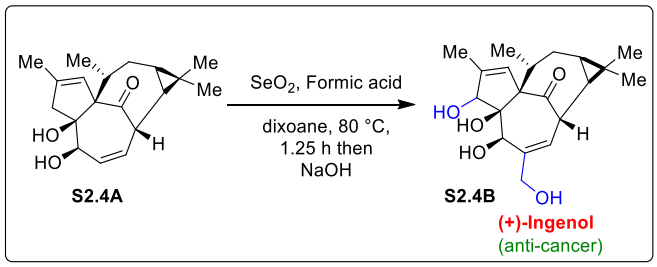
In 2014, Stephenson's group reported a visible light photo-catalysed direct coupling of N-methylmorpholine with unactivated pyridazine **S2.3A** in good yield. Where they conducted the Mannich reaction on imidazopyridazine **S2.3A** in the presence of $Ir(PPy)_3$ catalyst, with sodium acetate as the base in DMA solvent, and irradiated with 1 W LED light, they obtained the expected product **S2.3B** in good yield.[13b]



Scheme S2.3: *Photocatalysed direct coupling of imidazopyridazine with NMO*

(Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *J. Org. Chem.* **2014**, *79*, 11631−11643.)

Further, ingenol, which is a diterpenoid with potent anticancer activity, has been synthesized by utilizing the LSF strategy by conducting the allylic oxidation at the final stages in its total synthesis.[14] In 2013 and 2014, Jørgensen, McKerral, Baran and Co-workers together reported the total synthesis of the ingenol molecule in 14 steps. For its synthesis, they have carried out allylic oxidation **S2.4A** leading to ingenol **S2.4B** in the presence of selenium dioxide, and formic acid heated to 80 °C.

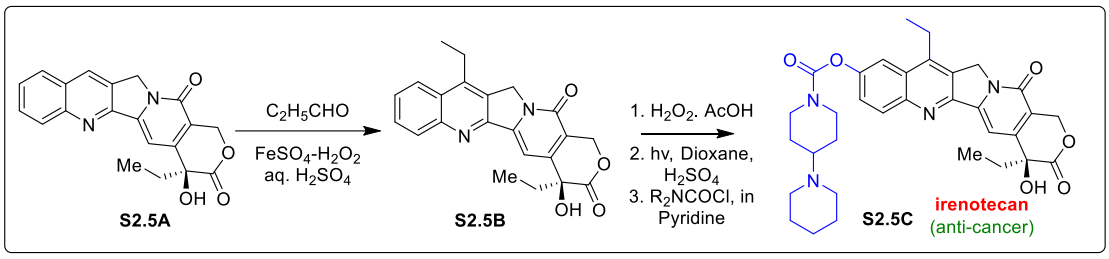


Scheme S2.4: *Synthesis of ingenol using the LSF strategy.*

(Jørgensen, L.; McKerrall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* 2013, *241, 878* and *J. Am. Chem. Soc.* **2014**, *136*, 15, 5799–5810.)

An important innovation in the field of LSF was realized through the synthesis of irenotecan, a drug used to treat leukemia, lymphoma and other cancer diseases, from camptothecin, by using radical alkylation followed by oxidation reaction.[15] In 1991, Sawada *et al.* successfully reported the transformation camptothecin **S2.5A** into irenotecan drug **S2.5C**. The first reaction was conducted in the presence of ferrous sulphate, H_2O_2 and propioaldehyde and resulted in the

formation of the alkylated product **S2.5B**. Further, its N-oxide formation, photochemical aryl ring oxidation and reaction with the chlorocarbonyl derivative of diamine resulted in the formation of the expected product **S2.5C** in good yield. All of these reported examples clearly highlight the importance of LSF in the process innovations.

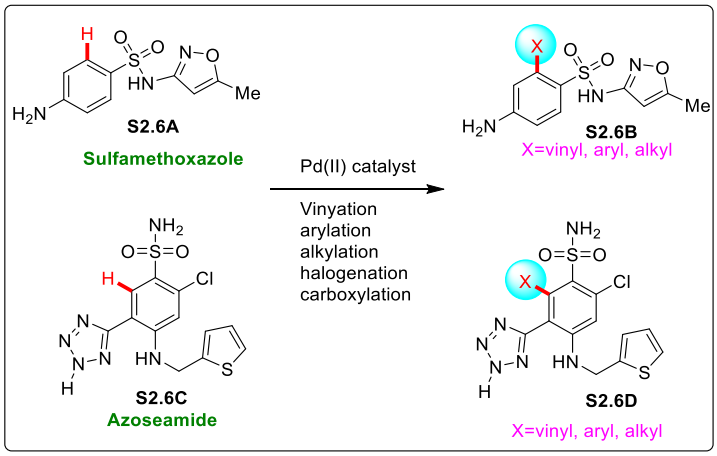


Scheme S2.5: *Synthesis of irinotecan from camptothecin using LSF strategy*

(Sawada, S.; Okajima, S.; Aiyama, R.; Nokata, K.; Furuta, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.*, **1991**, *39*, 1446)

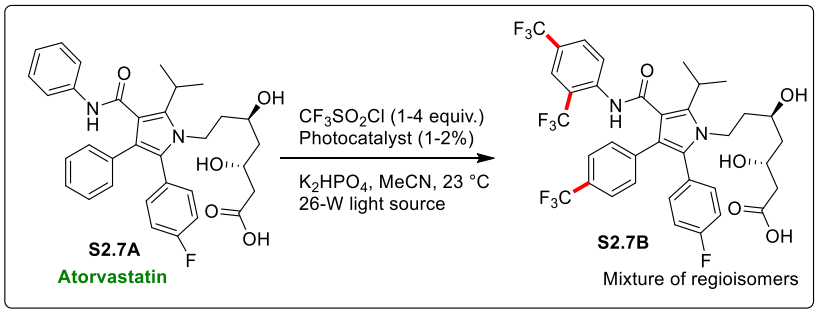
Post drug modification through LSF is basically the derivatization of the drug molecule by selectively activating a C–H bond to synthesize a variety of analogues of interest. The basis of the synthesizing new drug molecules or any biologically active molecule is to look for a compound or an analogue which possesses improved biological activity and thus, can be achieved through slight modifications. Thus, the LSF strategy can be applied actively in drug discovery programs for direct modification of the lead structure and would also be helpful to do diversity oriented synthesis of drug molecules. The advantage of LSF is to introduce a diverse set of (functional) groups in the identified lead without maneuvering the synthesis of the main core. Adding the active functional groups such as halo, carboxy and olefin will allow a functional group handle for further structure activity relationship studies. Some of the recent examples where the LSF has been amply applied in the synthesis of analogues of the identified drugs are presented below.

In 2010, sulfonamide-containing antibacterial drugs such as Sulfamethoxazole **S2.6A** and Azoseamide **S2.6C** have been modified using various C–H functionalization reactions such as arylation, alkylation, carboxylation, halogenation, and vinylation.[16,18]



Scheme S2.6: *Sulfonamide directed C–H functionalization of drug candidates.*

One of the early reports on LSF in drug derivatization was documented by Macmilan in 2011 and comprised of the exhaustive yet regioselective radical trifluoromethylation of atorvastatin aromatic rings, atorvastatin **S2.7A**, where they reacted in the presence of a $Ru(phen)_3Cl_2$ photocatalyst, with triflyl chloride as the fluorinating source, and K_2HPO_4 as base. The trifluoromethylation of the drug molecule gave the *tris*-trifluromethylated compound **S2.7B** in good yield.[17]

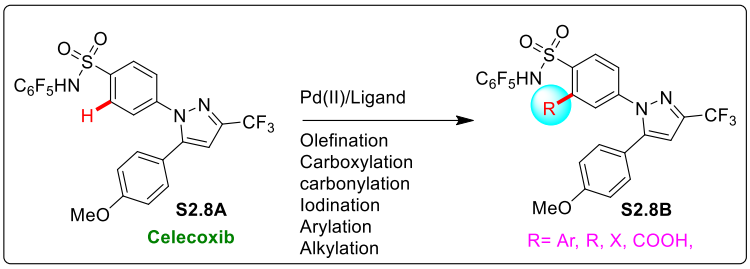


Scheme S2.7: *Photocatalysed trifluromethylation of atorvastatin*

(Nagib, D. A.; MacMillan, D. W. C. *Nature*, **2011**, *480*, 224.)

During the same time, another interesting report for the post drug modification was reported by Yu's group. In 2011, Yu and co-workers reported a successfully Pd-catalyzed C–H functionalization of the anti-inflammatory drug celecoxib **S2.8A** that comprised of alkylation, arylation, olefination, carboxylation, carbonylation, and also halogenation to synthesize a variety of new carbon and heteroatom *ortho*-functionalized and perfluoroaryl analogues of celecoxib **S2.8B**. The C–H activation on Celecoxib was facile due to the presence of a weakly coordinating

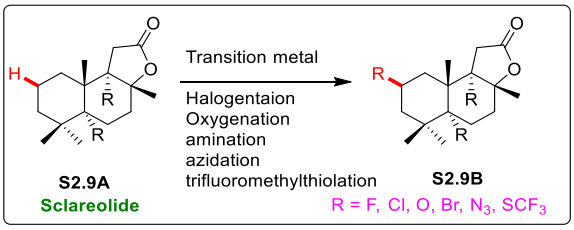
sulfonamide group that served as the directing group, thus making it possible to synthesize all its analogues in very good yield without introducing any external directing group.[18]



Scheme S2.8: *Pd(II)-catalysed Celecoxib C–H functionalization*

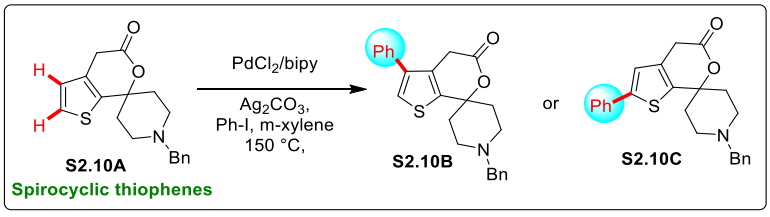
(Dai, H-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y-H.; Yu, J-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228.)

Following this, there appeared several reports on the C–H functionalization of Sclareolide (a fragrance used in cosmetics that gained popularity for its use as a weight loss supplement) **S2.9A** in various drug discovery programs. A wide range of reactions such as amination,[19] bromination,[20] chlorination,[21] oxygenation,[22] azidation,[23] and also trifluoromethylthiolation[24] have been successfully executed on this scaffold.



Scheme S2.9: *Transition metal catalysed sclareolide C–H functionalization.*

In 2012, Itami & Wunsch together reported the arylation of a spirocyclic thiophene derivative **S2.10A**, which had been identified with its high affinity towards the σ1 receptors. In the speculation about whether adding an aryl ring at the C4 position would have a good effect on the reactivity and selectivity of the drug,[25] a number of analogs of α-arylated spirocyclic thiophenes **S2.10B** and **S2.10C** have been synthesized and their biological activity checked.



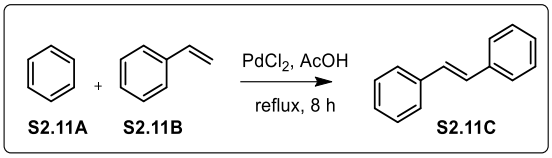
Scheme S2.10: *Pd-catalysed arylation of spirocyclic thoiphenes*

(Meyer, C.; Schepmann, D.; Yanagisawa, S.; Yamaguchi, J.; Itami, K.; Wünsch, B. *Eur. J. Org. Chem.* **2012,** 5972–5979.)

The above selected examples documented in the literature signify the importance of LSF in drug modifications as well as in drug synthesis. This LSF concept is very broad, which extends beyond medicinal chemistry. Interestingly, apart from this field, it has also been applied for the late stage modification of some metal-organic frameworks (MOFs) and also for polymers.[26] Inspired by these reports, we took an initiative to apply this tool on drug molecules to build a library of biologically active compounds. As the majority of our efforts are focused on using directed alkenylation in the context of the synthesis of GBT-440 analogues or their post-modification, a brief account on the alkenylation *via* C–H activation is presented below.

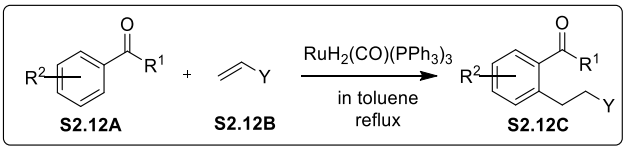
1.3 Alkenylation reaction *via* C–H activation

Alkenes such as vinyl arenes are valuable intermediates, important raw materials used to construct complex molecules in organic synthesis and they are key structural scaffolds abundantly found in many natural products and bioactive compounds,[27] medicinal chemistry,[28] and also in material science.[29] The classical method for their synthesis includes the Wittig reactions, olefin metathesis, Heck reactions, addition to alkynes, and, sometimes, multistep synthesis.[30] Amongst these, the cross-coupling reactions are very popular in the manufacturing of a wide range of drugs.[31] However, the requirement of the pre-activated substrates is one of the concerns. In 1967, Fujiwara and Moritani reported a Pd catalyzed cross-coupling reaction between an aromatic C–H bond with an olefinic C–H bond to generate a new C–C bond – a year before the Heck coupling reaction.[32] This reaction required the addition of an external oxidant to run the reaction catalytically. A general example of this reaction includes the cross-coupling of benzene **S2.11A** with styrene **S2.11B** in the presence of a Pd catalyst to afford the stilbene **S2.11C**. It is one of the most classical ways to make the alkenes using the cross dehydrogenative coupling *via* the C–H activation protocol. However, the Fujiwara–Moritani reaction has not received significant attention until 1990, as the conditions employed were not practical. However, recent advancements have unveiled the potential of the Fujiwara–Moritani reaction to a greater extent and enabled similar transformations on complex substrates, especially as a powerful alternative to the Heck coupling reactions, as it reduced the generation of salt waste to a maximum extent (Scheme S2.11).



Scheme S2.11: *Synthesis of stilbene using Fujiwara-Moritani reaction*
(Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119–1122.)

The direct functionalization of the C–H bond to the C–X bond (X= C, O, N, among others) is a powerful tool and also is a challenging task. Especially, in substrates having several C–H bonds with similar reactivity, addressing the regioselectivity becomes a challenging task. The carbonyl-directed *ortho*-alkylaton of acetophenones **S2.12A** with vinylsilanes **S2.12B** reported by Murai and Chatani is a trendsetter in the history of C–H functionalization in general and in directed C–H activation in particular (**Scheme S2.12**).[33]



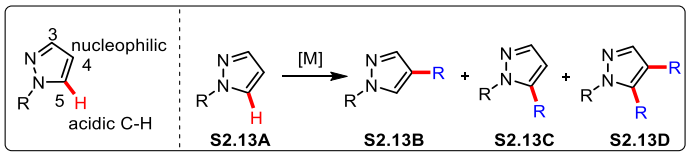
Scheme S2.12: *Ru-Catalysed alkylation of aromatic ketones*
(Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531.)

The directing group assisted *ortho*-selective functionalization *via* C–H activation has been widely explored during the last two decades employing a wide range of metal complexes (Pd, Ru, Rh, Ir, Co), deploying a variety of functional groups such as amine, amide, anilide, imine, ester, carboxylic acid, ketone, hydroxyl, and various heterocycles as directing groups. This is one of the topics that had been covered extensively in regular intervals. As the work embodied in this chapter deals mainly with a Rh-catalyzed directed alkenylation on pyrazole rings and also the alkylation with diazo compounds, some of the recent reports on C–H activation of the pyrazole scaffold are presented below.

1.4 C–H functionalization of pyrazole rings

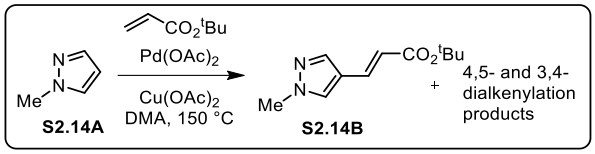
The transition metal catalyzed direct/directed C–H functionalization of pyrazole rings has been well studied during the last two decades.[34] An excellent coverage of the documented reports on the pyrazole functionalization *via* direct and directed C–H activation has appeared recently from Joo and co-workers. There are a couple of interesting reports on the late-stage C–H

functionalization of the pyrazole moiety in the context of the synthesis focused small molecule libraries.[35] The Pd-catalysts were very popular in the context of pyrazole C–H functionalization, especially for the formation of new C–C bonds. In recent years, other transition metals, such as Ir, Rh, Co, Ni, and Au have been explored by several groups to form C–C and C–heteroatom bonds. When compared to the directed synthesis, the direct C–H functionalization of pyrazole rings has been well explored for various types of C–C bond forming reactions such arylation, alkenylation, alkylation and heteroatom bond formations (C–B and C–Si). One of the early reports on the direct C5-arylation of N-arylpyrazole nucleus was documented by the Daugulis group, employing CuI as a catalyst and in the presence of a lithium base.[36] Controlling the regioselectivity is the major problem in this direct C–H functionalization of pyrazoles, and this was systematically studied by the Sames groups during their direct C–H arylation of pyrazoles.[37] After the arylation, the direct alkenylation either with alkenes (cross dehydrogenative coupling) or with alkynes is another reaction that is very popular and various metal complexes showed their viability for this transformation. Interestingly, the direct alkynylation with terminal acetylenes and alkylation with activated alkyl halides under palladium catalysis have been also documented. However, these are under explored reactions. Apart from these, the annulation reactions with alkynes and also the intramolecular direct C–H functionalization reactions have been explored in the context of synthesizing complex fused pyrazole scaffolds.



Scheme S2.13: *Reactivity of the pyrazole unit.*

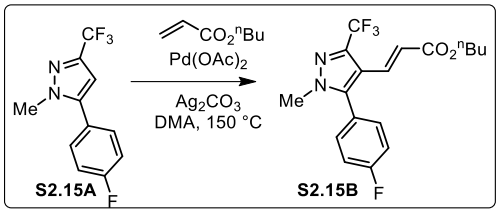
Coming to the alkenylation of the pyrazole ring, both alkenes and alkynes have been employed as alkenyl group donors. Some of the previously known reactions for pyrazole alkenylation include dehydrogenative cross coupling with alkenes in the presence of Pd-catalyst and oxidant.[38] In 2011, Wheeler and co-workers documented the C4-alkenylation of *N*-methyl pyrazole **S2.14A** with ^{t}butyl acrylate in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$ in DMA solvent resulting in **S2.14B** in lower yield along with a mixture of the dialkenylated product (Scheme S2.14).



Scheme S2.14: *Pd-catalyzed alkenylation of N-methylpyrazole*

(Chappell, B.; Dedman, N.; Wheeler, S. *Tetrahedron Lett*. 2011, 52, 3223–3225)

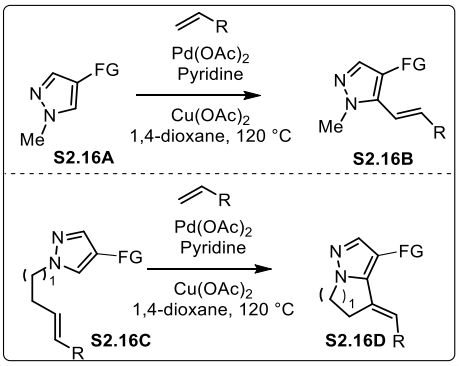
In 2013, Wu's group reported the alkenylation of highly substituted pyrazoles using a Pd catalyst and Ag_2CO_3 as the oxidant. In this particular case, they used 1,3,5-trisubstituted pyrazoles **S2.15A** containing a CF_3 group at the C3 position, which resulted in alkenylation at the C4 position **S2.15B** in good yield (Scheme S2.15).



Scheme S2.15: *Alkenylation of highly substituted pyrazole moiety*

(Wang, X.; Fang, X.; Xiao, H.; Gong, D.; Yang, X.; Wu, F. *Tetrahedron*, **2013**, *69*, 6993–7000.)

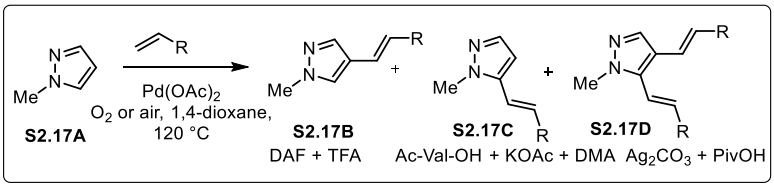
In 2016, Joo and co-workers documented intra and intermolecular alkenylation reactions of 4-substituted pyrazole using the $Pd(OAc)_2$ catalyst, and with pyridine as the ligand to enhance the reaction yield. In the case of intermolecular alkenylation, 4-substituted N-methyl pyrazole **S2.16A** reacts with vinyl arenes, n-butyl acrylate, or acryl amides in the 1,4-dioxane solvent at 120 °C and leads to the formation of the corresponding alkenylated product **S2.16B** in good yield. In intramolecular alkenylation reactions, the corresponding five-, six-, and seven-membered fused pyrazoles rings were formed in good yield. In the case of the styryl group, *E*-alkenes were formed as the major products. In both the reaction conditions, the electron-donating, as well as electron-withdrawing groupw present at the C4 position of pyrazole were well tolerated (Scheme S2.16).



Scheme S2.16: *Inter/intramolecular alkenylation of 4-substituted pyrazoles*

(Han, S. J.; Kim, H. T.; Joo, J. M. *J. Org. Chem.,* **2016**, *81*, 689–698.)

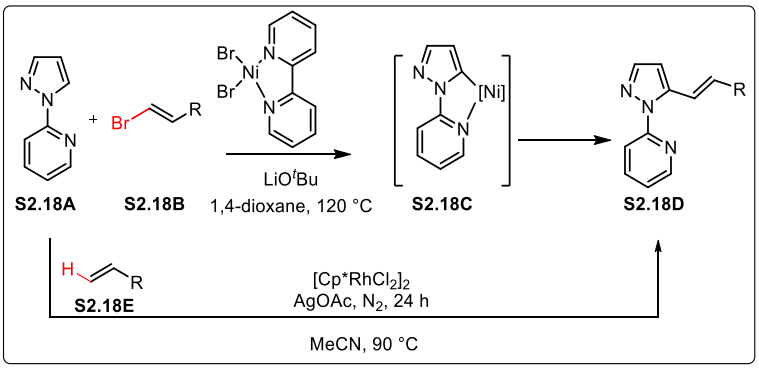
In 2017, Joo Lim and Baik reported a ligand controlled regiodivergent aerobic C–H alkenylation of *N*-alkylpyrazole **S2.17A** using the Pd-catalyst, which resulted in the C4 or C5, and C4,C5di-alkenylation of pyrazole ring in a controlled way. Selectivity at the C4 position was successfully achieved using the palladium complex, which was prepared from a 4,5-diazafluoren-9-one (DAF) ligand and trifluoroacetic acid. Interestingly, the selectivity can be switched to the C5 position by addition of appropriate bases/ligands. The combination of an N-acetyl valine ligand and KOAc was found to be the best for the selective C5 alkenylation. Next, the use of PivOH and silver carbonate afforded the corresponding dialkenylated product in good yield (Scheme S2.17).



Scheme S2.17: *Ligand-controlled C–H alkenylation of pyrazoles*

(Kim, H. T.; Ha, H.; Kang, G.; Kim, O. S.; Ryu, H.; Biswas, A. K.; Lim, S. M.; Baik, M-H.; Joo, J. M. *Angew. Chem. Int. Ed.,* **2017**, *56*, 16262–16266.)

In 2019, Punji's group disclosed the use of a 2-pyridyl ring as the directing group for selective C5 functionalization of the pyrazole ring. The C5-alkenylation reaction of the 2-pyridyl substituted pyrazole ring **S2.18A** has been carried out using the Ni-bipyridine complex, with lithium ^{t}butoxide as the base, and 1-bromostyrene as the alkenylating agent (Scheme S2.18). Recently, Zhu's group reported an advanced protocol for a similar alkenylation **S2.18A**, employing Rh-complexes, albeit directly with the styrenes **S2.18E**.



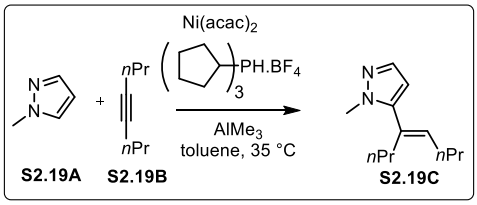
Scheme S2.18: *Directing-group-assisted C–H alkenylation using an alkenyl bromide*

(Jagtap, R. A.; Vinod, C. P.; Punji, B. *ACS Catal.,* **2019**, *9*, 431–441.)

Scheme S2.18: *Rh(III) catalysed alkenylation of 2-(1H-pyrazol-1-yl)pyridine with alkenes*
(Meng, H.; Yang, F.; Chen, M.; Chen, C.; Zhu, B. *Org. Chem. Front.*, **2021**, *8*, 773–777.)

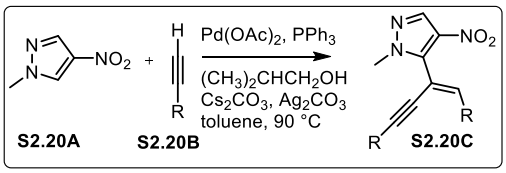
1.5 Alkenylation using alkynes:

In 2007, Hiyama and co-workers documented a Ni-catalyzed direct C5-alkenylation of *N*-methylpyrazole using internal alkynes. The simple and air-stable $Ni(acac)_2$ complex has been employed as the catalyst along with the tricyclopentylphosphonium tetrafluoroborate ligand, and $AlMe_3$ in toluene solvent at 35 °C to obtain the corresponding alkenylated product **S2.19C** in good yield (Scheme S2.19).



Scheme S2.19: *Ni-catalyzed hydroarylation of 4-octyne*
(Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Heterocycles*, 2007, 72, 677–680)

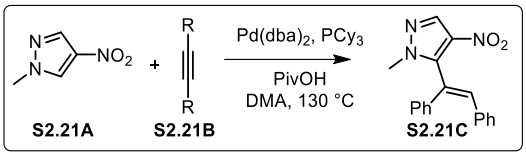
In 2018, while dealing with pyrazole alkynylation, Joo and co-workers discovered the homocoupling of terminal alkynes followed by hydroarylation of the resulting 1,3-diynes with pyrazole. For example, the reaction of 4-nitro pyrazole **S2.20A** with terminal alkynes **S2.20B** in the presence of a $Pd(OAc)_2$ catalyst, the PPh_3 ligand, cesium carbonate and silver carbonate in toluene solvent at 90 °C gave the alkenylated product **S2.20C** in good yield. As this reaction is limited for 4-nitro substituted pyrazoles the substrate scope has been limited mainly in terms of the terminal alkynes employed (Scheme S2.20).



Scheme S2.20: *Coupling of 4-nitropyrazoles and terminal alkynes*
(Ha, H.; Shin, C.; Bae, S.; Joo, J. M. *Eur. J. Org. Chem.*, **2018**, 2645–2650.)

A year later, the same group established the hydroarylation reaction of pyrazole with internal alkynes using Pd-complexes. As shown in Scheme S2.21, the 4-nitropyrazole **S2.21A**

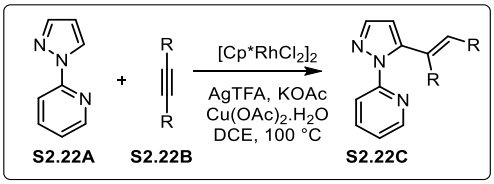
reacts with diaryl alkynes **S2.21B** in the presence of the $Pd(dba)_2$ catalyst, and the PCy_3 ligand in DMA at 130 °C to provide the alkenylated pyrazole product **S2.21C** in good yield.



Scheme S2.21: *Pd-catalyzed hydroarylation of diphenyl acetylene*

(Lee, W.; Shin, C.; Park, S. E. Joo, J. M. *J. Org. Chem.*, **2019**, *84*, 12913─12924)

In 2020, Zhu and co-workers documented a pyridine-directed Rh(III)-catalyzed C–H alkenylation of pyrazole scaffolds with internal alkynes *via* a rollover cyclometalation strategy. The reaction of (1*H*-pyrazol-1-yl)pyridine **S2.22A** with diarylacetylene **S2.22B** in the presence of $[Cp^*RhCl_2]_2$ catalyst, AgTFA, KOAc, and $Cu(OAc)_2$ in DCE at 100 °C resulted in the formation of the corresponding alkenylated product **S2.22C** in good yield. In this case, the choice of DCE solvent was too difficult for enhancing the hydroarylation reaction, rather than annulation in DMF solvent. A control experiment carried out using the pre- and post-rollover intermediates suggested that the reaction involves the rollover pathway (Scheme S2.22).

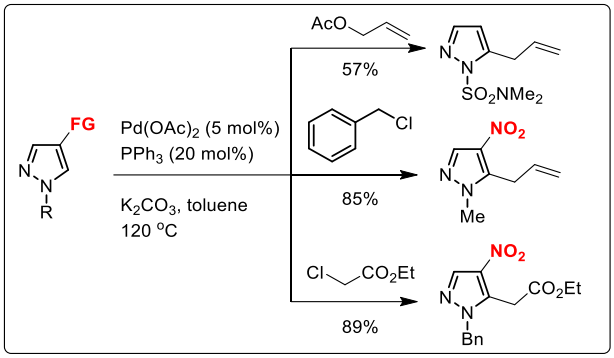


Scheme S2.22: *Directing-group-assisted hydroarylation of internal alkynes*

(Wu, S.; Wang, Z.; Ma, D.; Chen, C.; Zhu, B. *Org. Chem. Front.*, **2020**, *7*, 1158─1163.)

1.6 Direct Alkylation of Pyrazoles:

Unlike alkenylation, the alkylation of pyrazole scaffold was less explored and there is a single report by Joo's group.[39] The direct C5–H alkylation of pyrazoles with allylacetates and benzyl halides has been accomplished by employing $Pd(OAc)_2$ as a catalyst in the presence of PPh_3 and K_2CO_3. The presence of electron-withdrawing groups such as chloro, nitro or a carboxylate groups at the C4 position seems to be important. In addition, for allylation reactions, a sulphonyl protection of the pyrazole nitrogen is required (also see Scheme S2.23). A similar methodology has been extended by this group with α-chloroacetates and acetamides as incoming electrophiles to prepare α-pyrazolyl acetic acid.



Scheme S2.23: *Pd-Catalysed alkylation of pyrazole ring*

From the reports provided above, it is evident that the direct alkenylation of the pyrazole ring is well precedented. Coming to the directed alkylation, the reports are limited mainly to pyridine as a directing group that also place one of the pyrazole nitrogen at the C2 of pyridine so that this directing group could be easily removed. When it comes to alkylation, there is only a single report on the direct alkylation of nitro-substituted pyrazoles with activated halides. Coming to the C4-functionalization *via* C–H activations, this is not well explored. Thus, the pyrazolylpyridine core present in the GBT-440 is well suited for the directed C4-functionalization *via* C–H activation and importantly, if successful, it provides an easy access for the corresponding analogues. In addition, this will lay the platform for post modification of GBT-440.

CHAPTER II (Section-I)

Rhodium(III)-Catalysed Alkenylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine Scaffolds *via* C–H Bond Activation

1.7 Present work

Heterocyclic scaffolds like pyridine and pyrazole are the most privileged scaffolds present in many drug molecules. Interestingly, there are some approved drugs having both pyridine and pyrazole scaffolds and the selected examples are depicted in **Figure F2.3.** The Voxelotor (also known as GBT-440) is one of the recently approved drugs for the treatment of Sickle Cell Anemia (SCA) that contains a 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine core. Voxelotor, sold under the brand name OXBYTA was discovered by Global Blood Therapeutics. The US FDA has approved this drug for using against sickle cell disease on a fast track mode in May, 2020. GBT-440 is a hemoglobin S polymerization inhibitor directed for the treatment of SCA in adults and pediatric patients of twelve years of age and older.

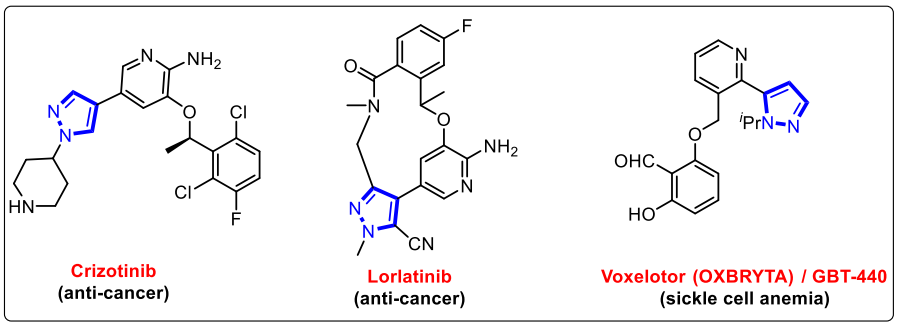


Figure F2.3: *Examples of pyrazole-pyridine scaffold containing drug molecules.*

Sickle Cell Anemia (SCA) is a red blood disorder in which no healthy red blood cells are present to supply the oxygen to the whole body. In SCA, the blood cells are like sickles that are not flexible, not allowing the round red blood cells to move easily in the blood vessels. GBT-440 prevents the sickling of red blood cells and thus, it interferes with the underlying pathology by modifications in the disease outcome.[10] It reacts through the formation of a covalent bond with the amino acid valine, which is present at the N terminal of the α chain of Hb and which leads to allosteric changes of Hb and increases the affinity between oxygen and Hb. Indeed, GBT-440 has been discovered in the process of developing derivatives of the naturally occurring molecule vanillin that was known to form a Schiff base with the N-terminal Val of the α-chains of Hb and stabilize oxy HbS, which resulted in decreased p50 (the oxygen pressure (mmHg) at which 50% of the Hb in a given blood is oxygenated). Tucaresol is one of the earlier candidates that has been developed in this context. However, it was not able to cross the Phase I clinical trials. On similar

lines 5-(hydroxymethyl)furfural (5-HMF) has also been explored and could only reach the critical Phase 2 trials. GBT-440 has shown improved potency with a 1:1 stoichiometric binding efficiency with HbS tetramers and a substantial increase in Hb levels. Due to the immediate requirement of the therapy against SCA, the FDA has conducted the trials on a fast track and then this drug became a breakthrough therapy recently.[40]

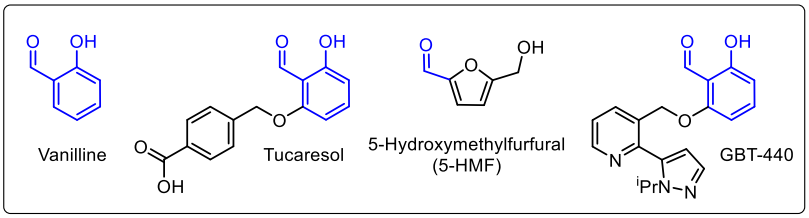
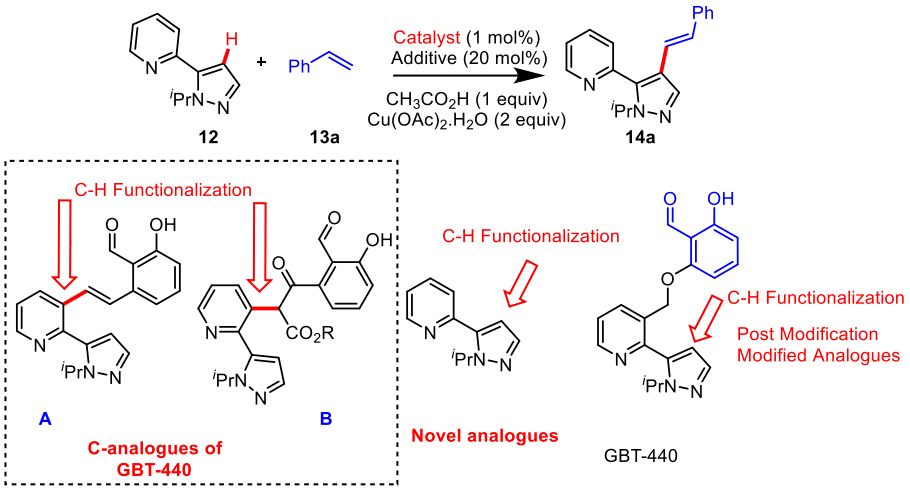


Figure F2.4. Known covalent HbS modulators and proposal of synthesizing GBT-440 analogues and post modification of GBT-440 *via* C-H functionalization of pyrazole at C4-H

As mentioned previously, India is estimated to have the second-highest burden of the disease.[8] As a part of management of sickle cell anemia disease in India, a mission aimed at the development of new chemical compounds which can modulate the known or validated drug targets related to the management of the SCA has been formulated in 2017 by CSIR. GBT-440, which was in Phase III clinical trials (renamed as Voxelotor after its approval in 2020), has been selected as a promising scaffold in this regard.

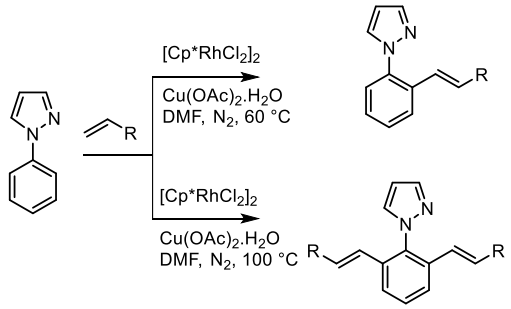


Scheme S2.24: *C-H functionlisation and post modification of GBT-440*

GBT-440 is characterized with the 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine core and a salicylaldehyde unit connected with a hydroxymethylether with the pyridine C3. After the initial inspection of the core structure of GBT-440, the pyrazolylpyridine unit present in GBT-440 has been identified as a potential handle for adding various carbon-centered electrophiles *via* C–H activation. Considering this, we have devised a project that comprises of building focused small molecule libraries *via* C–H functionalization of the pyrazole unit of GBT-440. One of the initial objectives was replacing the hydroxymethylether (that connects the pyridine and salicylaldehyde core) with an olefin or keto ester by pyrazole-directed C–H activation.[41] However, our initial experiments have revealed that the pyridine directed the same on the pyrazole ring. As some of these initially synthesized derivatives showed a promising prevention of the sickling of red blood cells, this has been continued further to synthesize a large set of derivatives by playing around the simple pyrazolylpyridine unit and later, the same has been extended for the late-stage modification directly on GBT-440.

1.8 Results and discussion:

Keeping the objective, our initial focus was on carrying out the cross dehydrogenative coupling with styrene on the pyridine core. In 2009, Satoh, Miura and co-workers documented the pyrazole directed mono- and di-vinylation of 1-phenylpyrazoles employing the Rh(III)-catalyzed oxidative C–H coupling with alkenes (Scheme S2.25).[41]

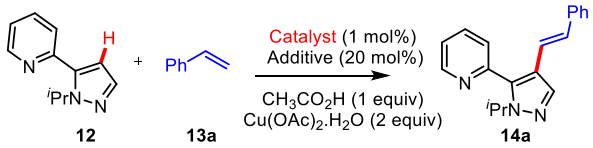


Scheme S2.25: *Rh(III) catalysed mono- and di-vinylation of 1-phenylpyrazoles.*

Indeed, this report served as a starting point for our initial thoughts of functionalizing the pyridine core. Our preliminary study began with conducting the reaction of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine **12a** with styrene as the model substrate employing $[RhCp^*Cl_2]_2$ (1 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2.6H_2O$ (2 equiv), and AcOH (1 equiv) combined in CH_3CN solvent at 95 °C for 2 h, which resulted in the formation of a new product **14a** in 57% yield. Though the

vinylation on the pyridine core was our desired target, when we looked at the ^{1}H NMR spectrum of compound **14a**, the characteristic proton peak of pyrazole ring was seen to disappear and the adjacent pyrazole proton appeared as a singlet at δ 7.89 ppm, revealing the C–H functionalization of pyrazole unit, and the participation of pyridine as a directing group. The observed large coupling constant J = 16.0 Hz between the olefinic-H which appeared as doublets at δ 6.95–6.88 ppm and at δ 6.88–6.81 ppm revealed the exclusive formation of the *trans*-olefin. In the ^{13}C NMR spectrum of compound **14a**, the alkene peaks appeared as doublets at δ 135.8 ppm and at δ 126.9 ppm. Next, in the HRMS, the calculated accurate mass for the compound was 290.1652 and it was found at 290.1652, thus confirming the constitution of the assigned structure.

Table T2.1: *Optimization studies.*

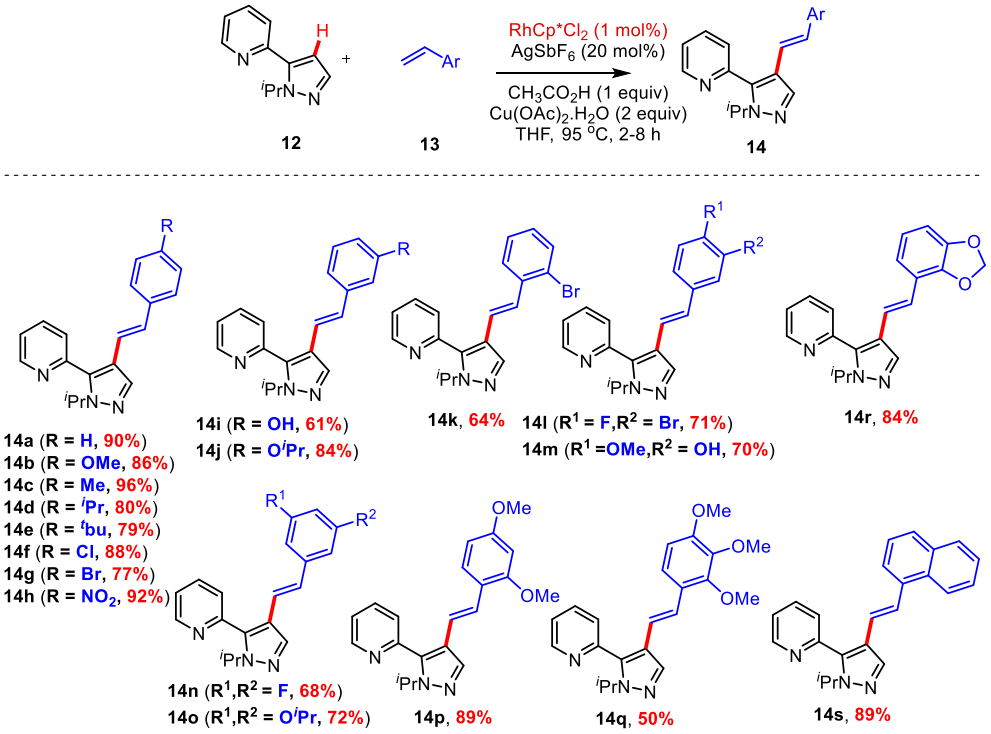


Entry	Catalyst	Additives	Solvent	temp. (°C) time (h)	Yield (%)[b] 14a
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$	CH_3CN	95/2	57
2	$[RhCp^*Cl_2]_2$	$AgSbF_6$	Dioxane	95/2	60
3	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6$**	**THF**	**95/2**	**89**
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	95/2	86
5	$[RhCp^*Cl_2]_2$	$AgSbF_6$	Toluene	95/2	35
6	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCM	95/2	38
7	$[IrCp^*Cl_2]_2$	$AgSbF_6$	THF	95/2	57

[a]Reaction conditions: 0.2 mmol (1 equiv) of **12**, 0.3 mmol (1.2 equiv) of **13a**, 1 mol % of catalyst, 20 mol % of additives, dry solvent (1.0 mL), [b]Isolated yields.

Though the selectivity was undesired, we failed in our attempts to obtain the desired selectivity by employing other metal complexes such as Pd, Ru and Co. They were found to be either unsuitable or gave the formation of **14a** in yields that were much inferior when compared to the initially obtained yields with the Rh-complex. This has prompted us to explore the current reaction in the direction of developing a focused library around the GBT-440 core.

Having this initial result in hand, we moved further to optimize the reaction by varying the solvents. As shown in **Table T2.1**, the reaction outcome seems to be solvent-dependent. In dioxane solvent, the reaction proceeded with a moderate increase in the product yield (entry 2). Interestingly when the reaction was conducted in THF, product **14a** was obtained in 89% yield (Table T2.1 entry 3). Further screening of the solvents revealed that 1,2-DCE, DCM, and toluene were not compatible for the current transformation (entries 4-6). In addition, control experiments revealed that the presence of the Rh-complex was essential and that under similar conditions, the Ir(III) complex performed poorly (entry 7).

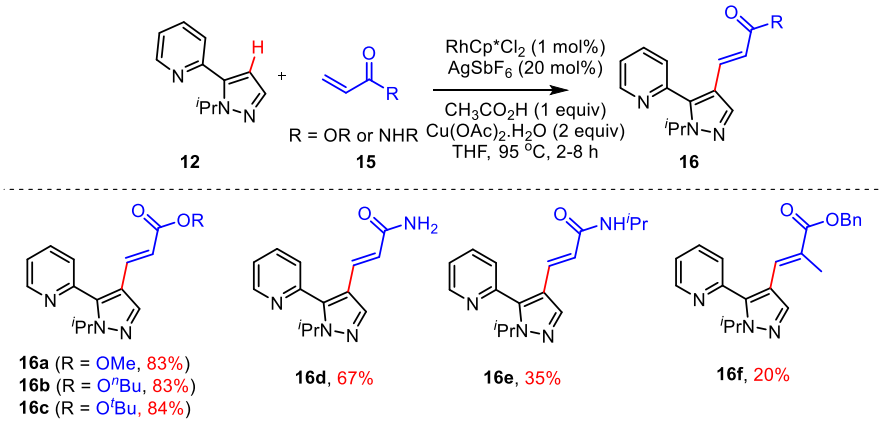


Scheme S2.26: *Substrate scope using substituted styrenes.*

In order to explore the generality of the present reaction, a variety of substituted styrenes containing electron-donating as well as electron-withdrawing substrates were coupled with pyrazolylpyridine scaffolds using the optimized conditions to afford alkenylated products in good yields. In all the cases, we observed excellent selectivity and very good yields. (Scheme S2.26). Initially, we employed a diverse set of styrene derivatives **13b**–**13h** having different substituents at the *para*-position such as -OMe, -Me, ^{i}-Pr, ^{t}-Bu, Cl, Br, NO_2. In all the cases, the reaction proceeded smoothly and provided the corresponding products **14b**–**14h** in very good yields (77-

96%). Next, the reactions with *meta*-hydroxy/isopropyloxy styrenes gave the corresponding alkenylated products **14i** and **14j** respectively in 61% and 84% yields. Similarly, the reaction with 2-bromostyrene also proceeded smoothly and provided **14k** in 64% yield. Further, a diverse set of di-/trisubstituted styrenes were employed as substrates to synthesize compounds **14l-14p**. Only in case of the trimethoxy styrene **13q**, the corresponding product **14q** was obtained in a moderate yield of 50%. On the other hand, with the piperonaldehyde derived alkene **13r**, the product **14r** was obtained in 84% yield. Even with 1-vinylnaphthalene, the reaction was facile and provided the corresponding product **14s** in excellent yield.

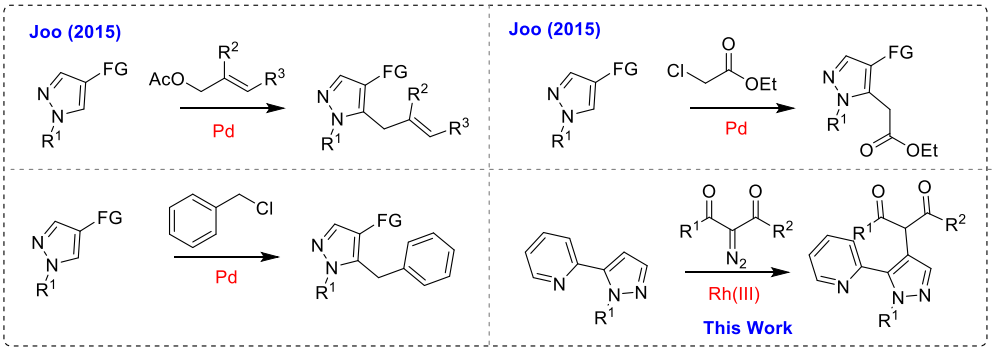
Further, to expand the scope of this reaction, we employed various conjugated olefins in the current reaction. As shown in Scheme S2.27, the reaction with simple acrylates such as methyl, n-butyl, t-butyl acrylates was facile and provided the corresponding alkenylated products **16a-16c** in 83-84% yield. However, when the olefin was substituted with a methyl, the reactions were sluggish with benzyl methacrylate, with the required alkenylated **16f** being obtained in 20% yield and methyl crotonate being found to not be compatible for the current alkenylation. With the unsubstituted acryl amide as well, the C–H alkenylation reaction was facile and gave the corresponding product **16d** in 67% yield. However, with *N*-isopropylacrylamide, the reaction was sluggish and resulted in the desired product **16e** in 35% yield. (Scheme S2.27).



Scheme S2.27: *Substrate scope using the substituted acrylates and amides.*

Having synthesized a diverse set of alkenylated compounds, we next proceeded for the alkylation with the diazocarbonyl compounds. As indicated earlier, the pyrazole alkylation was underexplored till date. Mainly, activated alkyl halides have been used for the alkylation by using

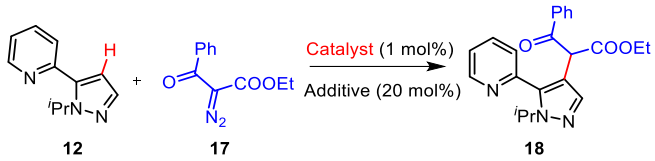
the palladium catalyst. In that context in 2015, Joo *et al.* disclosed the first report of pyrazole alkylation with the help of this allyl or benzyl group, which can be introduced at the C5 position.[39a] Further, Joo and co-workers expanded their work by synthesizing the α-pyrazolyl acetic acid from α-chloroacetates and acetamides.[39b] Similarly, Kalyani *et al.* have carried out the functionalization of nitropyrazoles with benzyl acetate using the $Pd(OAc)_2$ catalyst and the XPhos ligand (Scheme S2.28).[39c] Comparing all these alkylation reports reveals to us that pyrazole alkylation should be explored in a simple and effective way using the directed C-H activation protocol. Hence, this developed protocol can be applied in the area of total synthesis of the bioactive molecule *via* late-stage functionalization.



Scheme S2.28: *Reported alkylation on the pyrazole scaffold.*

Coming to the desired alkylation with the diazo compounds, Cp*Rh(III) and Cp*Ir(III) complexes have been well explored for C−H carbenoid functionalization.[42] Keeping this in mind, our initial experiments on the C-H alkylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine started with employing the benzoyl substituted diazo β-keto ester **17** for optimizing the reaction conditions. The results are summarized in **Table T2.2**. Initially, when the reaction was conducted using the $IrCp^*Cl_2$ catalyst and the $AgSbF_6$ additive in methanol solvent, we did not observe the formation of any new product (entry 1). Interestingly, when the reaction was carried out in 1,2-DCE at 80 °C for 2 h, the desired product **18** was obtained in 29% yield (entry 3). The attempted optimization of the reaction by varying solvents was found to be futile. At this juncture, when we switched to Rh-complexes, the reaction with $RhCp^*Cl_2$ (1 mol%) in the presence of $AgSbF_6$ (20 mol%) additive in methanol at 60 °C in 2 h provided the desired compound **18** in 90% yield (entry 6). As a control, we looked at the compatibility of other Rh-catalysts, additives, solvent and temperature, which revealed that the initial conditions were much superior (entry 2, 4, 5).

Table T2.2: *Optimization studies.*

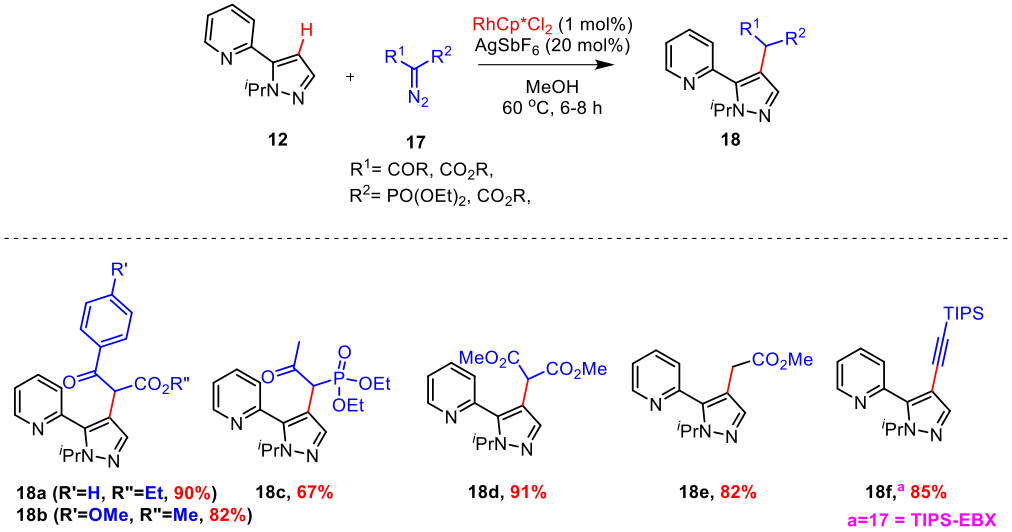


12 17 18

Entry	Catalyst	Additives	Solvent	temp.(°C) time (h)	Yield (%)[b] 18a
1	$[IrCp^*Cl_2]_2$	$AgSbF_6$	MeOH	rt/12	NR
2	$[IrCp^*Cl_2]_2$	$AgNTf_2$	MeOH	rt/12	NR
3	$[IrCp^*Cl_2]_2$	$AgSbF_6$	DCE	80/2	29
4	$[IrCp^*Cl_2]_2$	$AgSbF_6$	EtOH	80/2	10
5	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	60/6	45
6	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6$**	**MeOH**	**60/6**	**90**

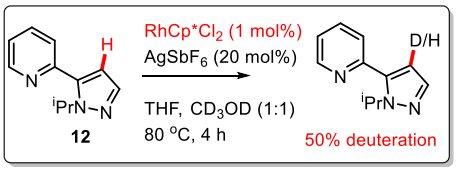
[a]Reaction conditions: 0.2 mmol (1 equiv) of **12**, 0.3 mmol (1.2 equiv) of **17**, 1 mol % of catalyst, 20 mol % of additives, dry solvent (1.0 mL), [b]Isolated yields.

Next, the scope of the reaction has been explored by using different diazo compounds (Scheme S2.29). One of the problems with the resulting β-ketoesters **18a** and **18b** was that they existed as a mixture of keto-enol tautomers, thus resulting in a complex NMR spectra. Next, other popular diazo compounds were employed in the carbene C–H insertion reactions, such as Ohiram-Bestmann's diazophosphonate, diazo derivatives of dimethylmalonate, Meldrum's acid and finally, simple ethyl diazoacetate. In all the cases the reactions proceeded smoothly and provided the corresponding alkylated products in good to excellent yields. Interestingly, when the TIPS-EBX reagent was employed for the alkynylation under the current optimized conditions, it afforded the alkynylated compound **18f** in 85% yield.



Scheme S2.29: *Substrate scope using diazocarbonyl compounds and TIPS-EBX regent.*

Deuterium labelling experiment: After exploring both alkenylation and alkylation, we proceeded further to understand the reaction mechanism. First, to check the reversibility of the C-H metalation, deuterium labelling experiments were carried out. When **12** was subjected to the same catalytic system in the absence of alkene in a mixture of CD_3OD /THF (1:1) at 80 °C for 4 h, about 50% deuteration was observed at the expected site of the recovered starting material. This revealed that a reversible C–H bond cleavage process was involved in this transformation.

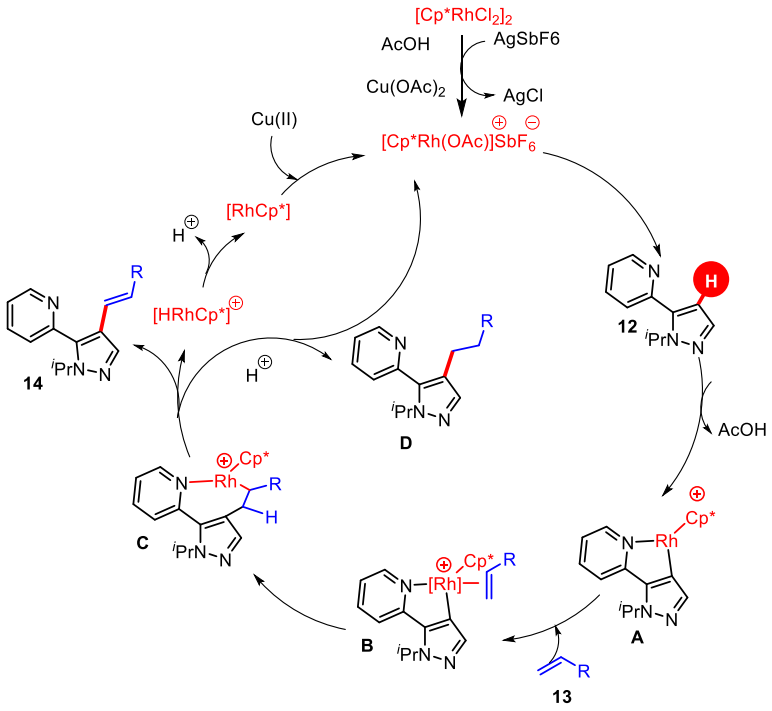


Scheme S2.30: *Deuterium labelling experiment of* ***12***

1.9 Mechanistic Proposal:

Based on the literature precedent,[43] a plausible mechanism for alkenylation was proposed (Scheme S2.31). The reaction proceeded with the generation of a cationic Rh(III)-complex followed by coordinative C–H insertion, mainly *via* a base-assisted internal electrophilic substitution reaction.[43b] Good site selectivity was achieved by the preference of the rhodium complex to the strongly coordinating pyridine nitrogen. The protic medium may play a role in facilitating this step, which leads to the formation of the cyclometallated complex **A**. After that,

coordination of the olefin to the cyclometallated intermediate forms the complex **B**, followed by carbo-rhodation to give the complex **C** and subsequent β-hydride elimination to yield the proximal C−H alkenylated product **14**. In some exceptional cases, protonation of the complex **C** took place instead of β-hydride elimination and resulted in the formation of alkylated product **D** instead of the alkenylated product **14**.



Scheme S2.31: *Mechanistic Proposal.*

CHAPTER II (Section-II)

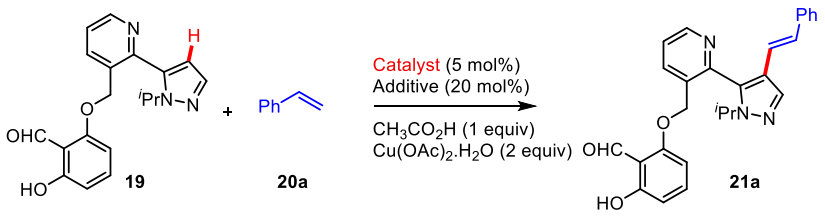
Functionalization of the Pyrazole unit of GBT 440 *via* C–H Bond Activation

1.10 Alkenylation of GBT440:

Having established the alkenylation and alkylation of the basic pyridylpyrazole scaffold, we next proceeded to extend this chemistry employing GBT440 as a substrate. However, as indicated in the table, the reaction required re-optimization of the conditions, which might be due to the steric crowding around the pyrazole unit and also the presence of free –OH and carbaldehyde groups. Under standard conditions, [$RhCp^*Cl_2$ (1 mol%) catalyst, $AgSbF_6$ (20 mol%) as the additive, AcOH (1 equiv), and $Cu(OAc)_2$ (2 equiv), heating at 95 °C in THF for 2 h] employed previously, the reaction between GBT440 **19** and styrene **20a** gave compound **21a** in 10% yield (entry 1). The structure of the resulting product **21a** was established with the help of spectral and analytical data. In the ^1H NMR spectrum of compound **21a**, the pyrazole proton appeared as a singlet at δ 7.86 ppm. The newly formed olefin protons appeared as doublets at δ 6.72 ppm and δ 6.60 ppm with a characteristic *trans*-coupling constant J = 16.0 Hz. In the ^{13}C NMR spectrum of compound **21a**, the alkene carbons appeared as doublets at δ 136.3 ppm and at δ 124.1 ppm.

Next, we proceeded for the optimization of the reaction conditions. When we replaced THF with acetonitrile (entry 2), the yield was improved to 26%. At this point, a quick screening of solvents with increased catalyst loading (5 mol%) and time has been carried out. As shown in the table, the yield was further improved in dioxane solvent (entry 3). On the other hand, the reaction in THF solvent resulted in the compound **21a** in 69% yield (entry 4). Finally, in 1,2-DCE, the compound **21a** was obtained in 81% yield (Table T2.3, Entry 5). The use of a low boiling solvent such as DCM resulted in low yields (entry 6). The same reaction employing $IrCp^*Cl_2$ as a catalyst did not result in a favorable outcome: the requisite product **21a** was obtained in 40% yield (entry 7). Overall, when compared with the alkenylation of the parent pyridylpyrazole, the alkenylation of GBT440 required more catalyst loading and also a prolonged reaction time.

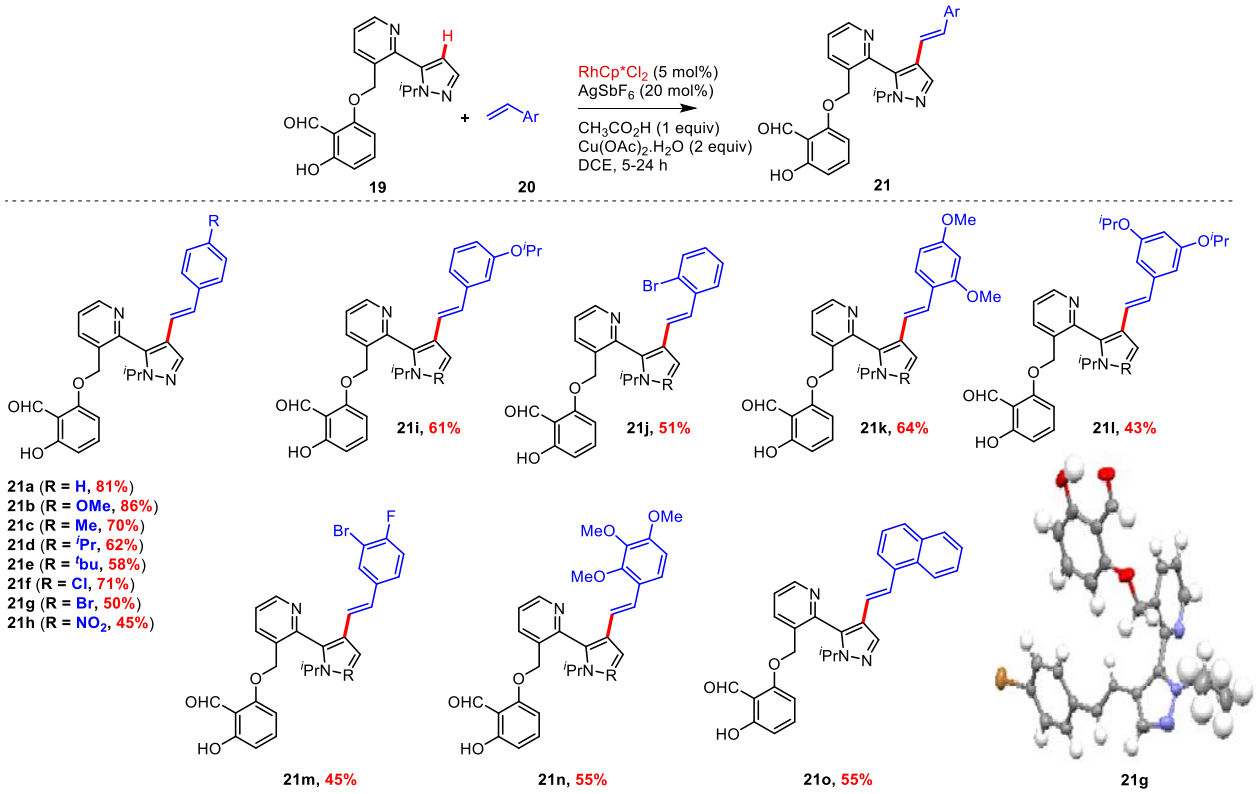
Table T2.3: Optimization studies.



Entry	Catalyst	Additives	Solvent	temp. (°C) time (h)	Yield (%)[b] 21a
1[c]	$[RhCp^*Cl_2]_2$	$AgSbF_6$	THF	95/2	10
2[c]	$[RhCp^*Cl_2]_2$	$AgSbF_6$	CH_3CN	95/15	26
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$	Dioxane	95/15	50
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$	THF	95/20	69
5	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6$**	**DCE**	**95/15**	**81**
6	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCM	50/2	12
7	$[IrCp^*Cl_2]_2$	$AgSbF_6$	THF	95/15	40

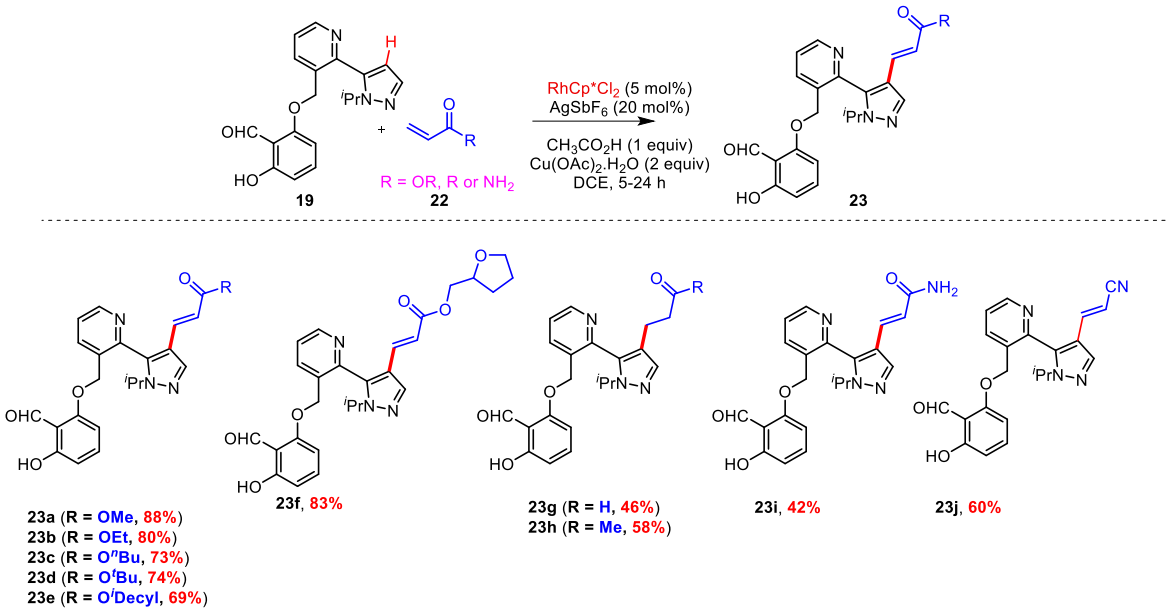
[a]Reaction conditions: 0.2 mmol (1 equiv) of **19**, 0.3 mmol (1.2 equiv) of **20a**, 5 mol % of catalyst, 20 mol % of additives, dry solvent (1.0 mL), [b]Isolated yields. [c]1 mol % of catalyst.

Next, the scope of this direct alkenylation of GBT440 was examined by using the previously employed substituted styrenes. As shown in Scheme S2.32, in general, the reactions were facile and the requisite products were obtained in moderate to good yields. Coming to the reactions with the *p*-substituted styrenes **20a**–**20h**, the corresponding alkenylated products **21a-21ah** were formed in 45-86% yield. Only in case of *p*-nitrostyrene, the yields were poor. With 3-isopropoxy styrene, the requisite alkenylated product **21i** was obtained in 61% yield. Similarly, with 2-bromo styrene, the yield of the corresponding alkenylated product **21j** dropped to 51%. When it comes to the reactions with disubstituted styrenes **20k–20m**, the yields were moderate to good. Remarkably, the reaction with the trimethoxystyrene **20n** was also facile and provided the alkenylated product **21n** in 55% yield. Even the reaction was also facile with 1-vinylnaphthalene and provided the corresponding product **21o** in good yield.



Scheme S2.32: *Substrate scope using substituted styrenes.*

In substrate scope, we also elaborated our study using the acrylates by applying the same reaction conditions as mentioned above and we got very good results for all the acrylates used (Scheme S2.33). So, the treatment of **19** with several acrylates **22a-22e** bearing different ester groups (methyl, ethyl, *n*-butyl, *t*-butyl, and *i*-decyl respectively) under optimized conditions provided the desired products **23a-23e** in excellent yields (69-88%). Interestingly, furfural acrylate **22f** also performed well in these conditions and resulted in the formation of **23f** product in 83% yield. In the case of the acrylamides, the reaction was feasible but not up to the mark and we ended up with a moderate yield for the formed compound **23i** (42% yield). This may be due to C–H alkenylation side reactions that are possible in the presence of aldehyde and amine groups. Next, we examined the compatibility of acrolein (**22g**), methylvinyl ketone (**22h**) and acrylonitrile (**22j**), under the optimized conditions. Interestingly, with acrolein and methylvinyl ketone the corresponding alkylated products **23g** (46%), and **23h** (58%) were obtained.



Scheme S2.33: *substrate scope using substituted acrylates and amide.*

1.11 Biological Evaluation: Having a good number of compounds synthesized from the parent pyridylpyrazole **12** and GBT440, we next proceeded for the measuring of the oxygen binding efficiency of the hemoglobin isolated from the sickled red blood cells treated with these compounds (1 μmol). The parent GBT440 has been used as a control endowed with 100% oxygen binding efficiency (Figures F2.5 and Scheme S2.34).

As presented in Figure F2.5, the majority of the compounds derived from pyridylpyrazole **12** did not show good activity when compared to GBT440. Interestingly, in case of the phosponate **18c** derived from the directed alkylation with the Ohira-Bestmann reagent, showed significant enhancement in the oxygen binding efficiency of the sickled hemoglobin with a relative efficiency of 75% compared to that of GBT440. Whereas the compounds derived from the GBT440 directly, showed more promising activity. Amongst all, the compounds NCL-SA-88 (**23c**), NCL-SA-97 (**21k**), NCL-SA-91 (**21c**), NCL-SA-98 (**21b**), and NCL-SA-95 (**21f**) showed relatively closer or better activity compared to GBT-440. Amongst all of these compounds **NCL-SA-95 (21f)** showed slightly higher activity than the GBT-440, which warrants further validation. Further characterization of these compounds for their sHb modulating activity is under progress.

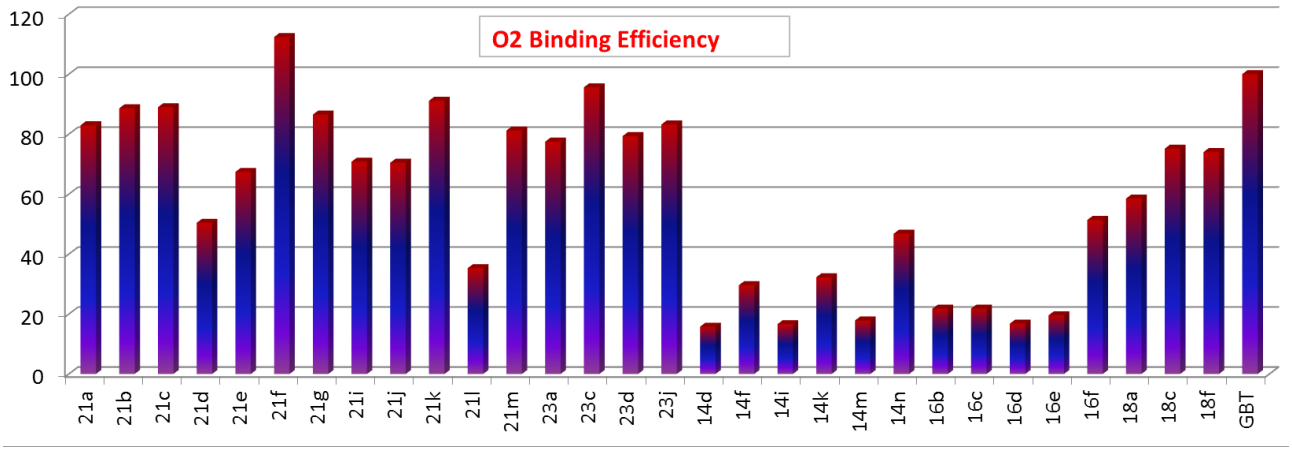
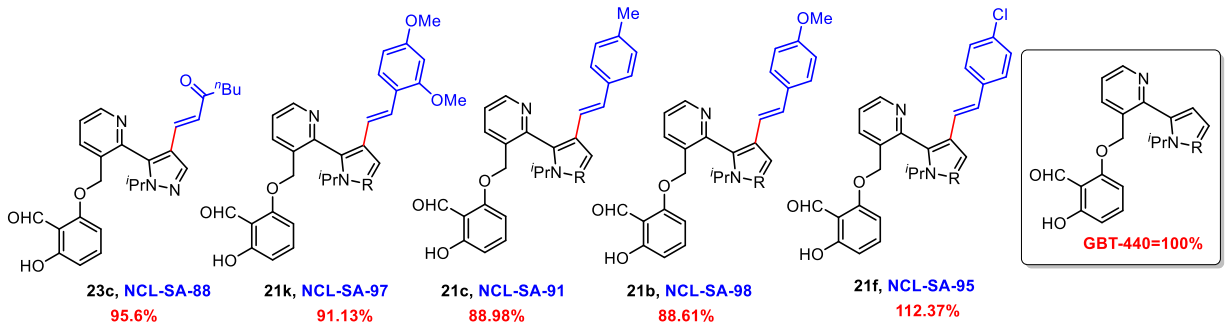


Figure F2.5: *Graphical representation of biological activity of the synthesized compounds against SCA Vs GBT-440.*



Scheme S2.34: *Biological activity of selected compounds against SCA vs GBT-440.*

1.12 Conclusion

The possibility of carrying the directed alkenylation/alkylation of pyrazolylpyridine **12** and **GBT440** has been executed successfully *via* rhodium(III) catalyzed C–H functionalization. In both the instances, the proximal site selectivity has been achieved by the cationic nature of the catalyst and the strong coordination of the pyridine nitrogen to the catalyst. Initially, the feasibility of both alkenylation and alkylation has been explored with the basic pyridylpyrazole core **12** employing a diverse range of styrenes substituted with electron-donating, as well as electron-withdrawing groups such as -F, -Cl, -Br, -OMe, -NO_2 for the alkenylation. In a majority of the cases, the alkenylation products were obtained in good to excellent yields. Even with the acrylates/acrylamides, the cross dehydrogenative coupling was the major event with compound **12**. Subsequently, the direct alkylation of **12** was explored with various diazo compounds. Next,

we have extended the alkenylation protocol with GBT-440 as a substrate. Unlike with the parent scaffold 12, the directed C–H alkenylation of GBT with both substituted styrenes and conjugated olefins required excess catalyst loading as well as prolonged reaction times. Interestingly, in case of conjugated acrylates and amides, among others, instead of cross dehydrogenative coupling that was noticed with **12**, with **GBT440** the alkylation was seen to take place exclusively. All the compounds synthesized from the C–H functionalization of **12** and GBT440 have been screened for the oxygen binding affinity for the hemoglobin isolated from the sickle blood cells treated with these compounds, keeping the parent GBT440s as 100%. In case of the compounds derived from **12**, the phosphonate showed promising activity (75%). Coming to the GBT440 analogues, a good number of the compounds showed similar activity like GBT440 and one compound showed increased activity (112%). Currently, work in the direction of extending the C–H functionalization on GBT440 with other electrophiles is in progress.

Experimental Section:

General procedure for the Rh-catalyzed C–H Bond Activation of 12: In general, all reactions were carried out employing 50 mg of **12**.

To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added pyrazolyl pyridine **12** (50 mg, 1 equiv, 0.267 mmol), styrene **13** (55.6 mg, 2 equiv, 0.534 mmol), $[RhCp^*Cl_2]_2$ (1.7 mg, 0.01 equiv, 1 mol%), $AgSbF_6$ (18 mg, 0.20 equiv, 20 mol%), $Cu(OAc)_2.H_2O$ (107 mg, 2 equiv, 0534 mmol), AcOH (16 mg, 1 equiv, 0.267) and THF (4 mL) under air. The reaction mixture was stirred at 95 °C for 2-6 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **14**.

Representative procedure for 0.5 mmol scale:

To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added pyrazolyl pyridine **12** (100 mg, 1 equiv, 0.534 mmol), styrene **13** (111 mg, 2 equiv, 1.07 mmol), $[RhCp^*Cl_2]_2$ (3.3 mg, 0.01 equiv, 1 mol%), $AgSbF_6$ (37 mg, 20 mol%,), $Cu(OAc)_2.H_2O$ (213 mg, 2 equiv, 1.07 mmol) AcOH (32 mg, 1 equiv, 0.534 mmol) and THF (10 mL) under air. The reaction mixture was stirred at 95 °C for 2 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **14**.

General procedure for the Rh-catalyzed C–H Bond Activation of 12 using acrylates or acryl amide 15: In general, all reactions were carried out employing 50 mg of **12**.

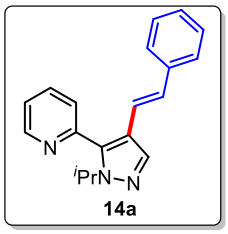
To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added pyrazolyl pyridine **12** (50 mg, 1 equiv, 0.267 mmol), acrylates or acryl amide **15** (46 mg, 2 equiv, 0.534 mmol), $[RhCp^*Cl_2]_2$ (1.7 mg, 0.01 equiv, 1 mol%), $AgSbF_6$ (18 mg, 0.20 equiv, 20 mol%), $Cu(OAc)_2.H_2O$ (107 mg, 2 equiv, 0534 mmol), AcOH (16 mg, 1 equiv, 0.267 mmol) and THF (4 mL) under air. The reaction mixture was stirred at 95 °C for 2-8 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried

(Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **16**.

General procedure for the Rh-catalyzed C–H Bond Activation of 12 with β-ketoesters or diazoesters or diazophosphate or TIPS-EBX 17: In general, all reactions were carried out employing 50 mg of **12**.

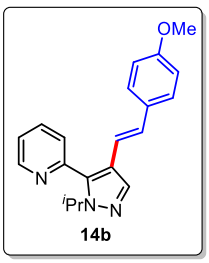
To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added pyrazolyl pyridine **12** (50 mg, 1 equiv), β-ketoesters or diazoesters or diazophosphate **17** (2 equiv), $[RhCp^*Cl_2]_2$ (1.7 mg, 1 mol%), $AgSbF_6$ (18 mg, 20 mol%), and MeOH (4 mL) under air. The reaction mixture was stirred at 60 °C for 2–6 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkylated product **18**.

(E)-2-(1-Isopropyl-4-styryl-1*H*-pyrazol-5-yl)pyridine (14a): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 77 mg (90%); colorless solid; mp: 130–132 °C; IR(neat) ν_{max} 2976, 1587, 1484, 1451, 1404, 1278, 1196, 1061, 1002, 959, 839, 793, 748, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 3.8 Hz, 1H), 7.89 (s, 1H), 7.87–7.82 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.40–7.34 (m, 3H), 7.30 (t, J = 7.6 Hz, 2H), 7.23–7.17 (m, 1H), 6.95–6.88 (d, J = 16.0 Hz, 1H), 6.88–6.81 (d, J = 16.8 Hz, 1H), 4.86 (spt, J = 6.6 Hz, 1H), 1.50 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1 (d) 149.6 (s) 138.4 (s) 137.7 (s) 136.6 (d) 135.8 (d) 128.5 (d, 2C) 127.7 (d) 126.9 (d) 125.9 (d, 2C) 125.7 (d) 122.9 (d) 119.2 (s) 118.6 (d) 50.7 (d) 22.627 (q, 2C) ppm; HRMS (ESI) calcd. for $C_{19}H_{20}N_3$: 290.1652 $[M + H]^+$; found 290.1652.



14a

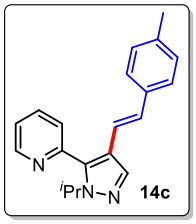
(E)-2-(1-isopropyl-4-(4-methoxystyryl)-1*H*-pyrazol-5-yl)pyridine (14b): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 73 mg (86%); colorless solid; mp: 98–100 °C; IR(neat) ν_{max} 3030, 1605, 1510, 1352, 1247, 1033, 841, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 3.8 Hz, 1H), 7.87–7.79 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.38–7.28 (m, 3H), 6.89–6.82 (m, J = 16.02 Hz, 3H), 6.74–6.66 (d, J = 16.0 Hz, 1H), 4.86 (spt, J = 6.6 Hz, 1H), 3.80 (s, 3H), 1.49 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (s), 150.1 (d), 149.7 (s), 138.0 (s), 136.6 (d), 135.6 (d), 130.6 (s), 127.3 (d), 127.1 (d, 2C), 125.6 (d), 122.8 (d),



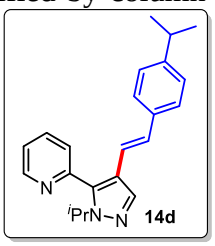
14b

119.5 (s), 116.5 (d), 114.0 (d, 2C), 55.3 (d), 50.6 (q), 22.6 (q, 2C) ppm; HRMS (ESI) m/z: calcd. for $C_{20}H_{22}N_3O$: 320.1757 $[M + H]^+$; found: 320.1765.

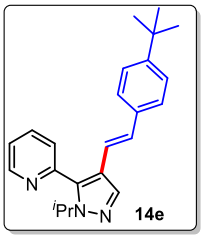
(E)-2-(1-isopropyl-4-(4-methylstyryl)-1*H*-pyrazol-5-yl)pyridine (14c): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 78 mg (96%); colorless solid; mp: 94–96 °C; IR(neat) ν_{max} 2997, 1587, 1485, 1421, 1206, 965, 842, 791, 744, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 3.8 Hz, 1H), 7.86 (s, 1H), 7.82 (dt, J = 1.9, 7.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.33 (dd, J = 3.8, 7.6 Hz, 1H), 7.29–7.23 (d, J = 8.4 Hz, 2H), 7.12–7.06 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 16.8 Hz, 1H), 6.78 (d, J = 16.0 Hz, 1H), 4.85 (spt, J = 6.6 Hz, 1H), 2.31 (s, 3H), 1.48 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1 (d), 149.8 (s), 138.3 (s), 136.9 (s), 136.7 (d), 135.9 (d), 135.1 (s), 129.4 (d, 2C), 127.7 (d), 125.9 (d, 2C), 125.6 (d), 122.8 (d), 119.3 (s), 117.6 (d), 50.6 (d), 22.6 (q), 21.1 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{20}H_{22}N_3$: 304.1808 $[M+H]^+$; found: 304.1818.



(E)-2-(1-isopropyl-4-(4-isopropylstyryl)-1*H*-pyrazol-5-yl)pyridine (14d): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 71 mg (80%); gum; IR(neat) ν_{max} 2958, 1586, 1486, 1422, 1196, 1055, 1002, 962, 842, 792, 699, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 4.3 Hz, 1H), 7.88 (s, 1H), 7.86–7.78 (t, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.38–7.30 (m, 3H), 7.17 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 16.5 Hz, 1H), 6.80 (d, J = 16.5 Hz, 1H), 4.88 (spt, J = 6.5 Hz, 1H), 2.89 (spt, J = 6.8 Hz, 1H), 1.50 (d, J = 6.7 Hz, 6H), 1.25 (d, J = 7.3 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1 (d), 149.7 (s), 147.9 (s), 138.2 (s), 136.6 (d), 135.7 (d), 135.4 (s), 127.7 (d), 126.6 (d, 2C), 126.0 (d, 2C), 125.7 (d), 122.8 (d), 119.4 (s), 117.8 (d), 50.6 (d), 33.8 (d), 23.9 (q, 2C), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{22}H_{26}N_3$: 332.2121 $[M+H]^+$; found: 332.2124.

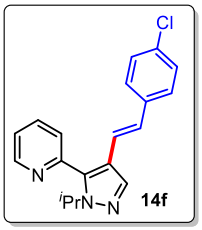


(E)-2-(4-(4-(tert-butyl)styryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14e): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 73 mg (79%); yellow syrup/gum; IR(neat) ν_{max} 2963, 1586, 1485, 1405, 1364, 1298, 1196, 1061, 1002, 961, 843, 816, 792, 746, 700, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 3.8 Hz, 1H), 7.86 (s, 1H), 7.81 (dt, J = 1.5, 7.6 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.37–7.23 (m, 5H), 6.89 (d, J = 16.0 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 4.93–4.78 (spt, 1H), 1.48 (d, J = 6.9 Hz, 6H), 1.30 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):

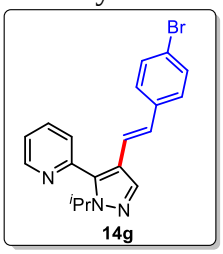


δ 150.1 (d), 149.6 (s), 138.2 (s), 136.6 (d, 2C), 135.7 (d), 135.0 (s), 127.6 (d), 125.7 (d, 2C), 125.4 (d, 2C), 122.8 (d), 119.4 (s, 2C), 117.9 (d), 50.6 (d), 34.5 (s), 31.2 (q, 2C), 22.6 (q, 3C) ppm; HRMS (ESI): calcd. for $C_{23}H_{28}N_3$:346.2278 $[M+H]^+$; found: 346.2285.

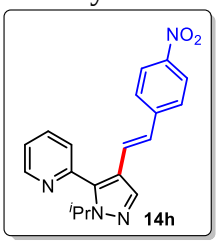
(E)-2-(4-(4-chlorostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14f): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 76 mg (88%); colorless solid; mp: 110–112 °C; IR(neat) ν_{max} 3010, 1587, 1483, 1404, 1196, 1090, 1004, 959, 792, 750, 717, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.79 (d, J = 4.6 Hz, 1H), 7.86 (s, 1H), 7.84–7.79 (m, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 4.6, 7.6 Hz, 1H), 7.25 (q, J = 8.4 Hz, 4H), 6.86–6.81 (d, J = 16.0 Hz, 1H), 6.81–6.76 (d, J = 16.7 Hz, 1H), 4.81 (spt, J = 6.6 Hz, 1H), 1.47 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2 (d), 149.4 (s), 138.6 (s), 136.7 (d), 136.2 (s), 135.8 (d), 132.4 (s), 128.6 (d, 2C), 127.1 (d, 2C), 126.3 (d), 125.6 (d), 123.0 (d), 119.2 (d), 118.9 (s), 50.7 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{19}N_3Cl$: 324.1262 $[M+H]^+$; found: 324.1267.



(E)-2-(4-(4-bromostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14g): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 76 mg (77%); colorless solid; mp: 108–110 °C; IR(neat) ν_{max} 2928, 1639, 1587, 1483, 1405, 1197, 1070, 1005, 960, 793, 749, 714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84–8.78 (d, J = 3.0 Hz, 1H), 7.87 (s, 1H), 7.87–7.82 (dd, J = 1.5 Hz, 1H), 7.46–7.34 (m, 4H), 7.23 (d, J = 8.4 Hz, 2H), 6.83 (s, 2H), 4.90-4.76 (spt, J = 6.8 Hz, 1H), 1.49 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (d), 149.5 (s), 138.6 (s), 136.7 (d), 136.7 (s), 135.8 (d), 131.6 (d, 2C), 127.4 (d, 2C), 126.3 (d), 125.6 (d), 123.0 (d), 120.5 (s), 119.4 (d), 118.9 (s), 50.7 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{19}N_3Br$:368.0757 $[M+H]^+$; found: 368.0765.

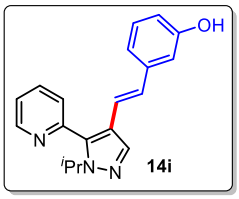


(E)-2-(1-isopropyl-4-(4-nitrostyryl)-1*H*-pyrazol-5-yl)pyridine (14h): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 82 mg (92%); yellow solid; mp: 108–110 °C; IR(neat) ν_{max} 2925, 1591, 1512, 1337, 1260, 1109, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, J = 4.6 Hz, 1H), 8.14 (d, J = 9.2 Hz, 2H), 7.93 (s, 1H), 7.89 (dt, J = 1.9, 7.8 Hz, 1H), 7.50–7.37 (m, 4H), 7.06–7.00 (d, J = 16.0 Hz, 1H), 6.96–6.89 (d, J = 16.0 Hz, 1H), 4.80 (spt, J = 6.6 Hz, 1H), 1.50 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4 (d), 149.1 (s), 146.2 (s),

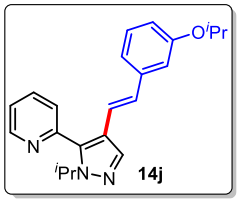


144.4 (s), 139.4 (s), 136.8 (d), 136.1 (d), 126.2 (d, 2C), 125.6 (d), 125.0 (d), 124.0 (d, 2C), 123.5 (d), 123.3 (d), 118.4 (s), 50.9 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{19}N_4O_2$: 335.1503 $[M+H]^+$; found: 335.1506.

(E)-3-(2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)vinyl)phenol (14i): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 50 mg (61%); colorless solid; mp: 170–172 °C; IR(neat) ν_{max} 2924, 2854, 1589, 1488, 141, 1424, 1369, 1262, 1155, 1063, 1009, 958, 869, 791, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.81–8.72 (d, J = 2.2 Hz, 1H), 7.85 (s, 1H), 7.84–7.80 (dd, J = 1.5 Hz, 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 5.3, 6.9 Hz, 1H), 7.14–7.07 (t, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.81–6.76 (d, J = 16.7 Hz, 2H), 6.75–6.69 (d, J = 16. Hz, 1H), 6.66 (dd, J = 2.3, 7.6 Hz, 1H), 4.83–4.69 (spt, J = 6.8 Hz, 1H), 1.45 (d, J = 6.9 Hz, 6H), 1.23 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (s), 150.0 (d), 149.2 (s), 139.2 (s), 138.3 (s), 137.0 (d), 135.8 (d), 129.6 (d), 127.9 (d), 125.9 (d), 123.2 (d), 119.4 (s), 118.4 (d), 118.3 (d), 114.4 (d), 112.7 (d), 50.9 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{20}N_3O$: 306.1601 $[M+H]^+$; found:306.1609.

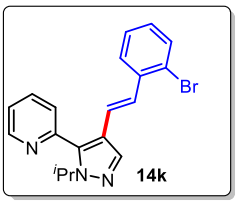


(E)-2-(4-(3-isopropoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14j): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 78 mg (84%); colorless syrup/gum; IR(neat) ν_{max} 2976, 1587, 1484, 1450, 1423, 1382, 1257, 1154, 1115, 1061, 1001, 958, 882, 791, 742, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 5.3 Hz, 1H), 7.87 (s, 1H), 7.86–7.81 (dt, J = 2.0 Hz, 7.63 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.39–7.33 (m, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.92–6.89 (m, 1H), 6.84 (d, J = 7.6 Hz, 2H), 6.75 (dd, J = 2.3, 8.4 Hz, 1H), 4.86 (spt, J = 6.6 Hz, 1H), 4.55 (spt, J = 6.0 Hz, 1H), 1.49 (d, J = 6.9 Hz, 6H), 1.33 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0 (s), 150.1 (d), 149.5 (s), 139.3 (s), 138.4 (s), 136.6 (d), 135.8 (d), 129.4 (d), 127.6 (d), 125.7 (d), 122.9 (d), 119.1 (s), 118.8 (d), 118.6 (d), 114.1 (d), 113.6 (d), 69.7 (d), 50.7 (d), 22.6 (q, 2C), 22.0 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{22}H_{26}N_3O$: 348.2070 $[M+H]^+$; found: 348.2077.

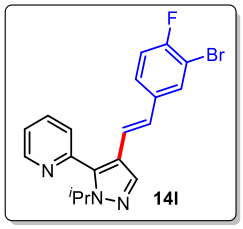


(E)-2-(4-(2-bromostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14k): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 63 mg (64%); colorless syrup; IR(neat) ν_{max} 2994, 1634, 1586, 1487, 1462, 1198, 1060, 1022, 1002, 958, 836, 793, 745, 718, 663

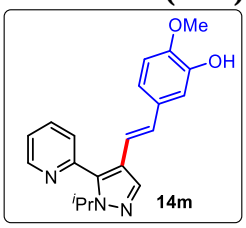
cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.81 (d, J = 4.6 Hz, 1H), 7.91 (s, 1H), 7.84 (dt, J = 1.9, 7.8 Hz, 1H), 7.53 (d, J = 6.9 Hz, 1H), 7.49–7.43 (t, J = 7.6 Hz, 2H), 7.39–7.33 (m, 1H), 7.25–7.16 (m, J = 16.0 Hz, 2H), 7.07–7.01 (dt, J = 1.5 Hz, 6.9 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 4.82 (spt, J = 6.7 Hz, 1H), 1.50 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2 (d), 149.4 (s), 138.7 (s), 137.5 (s), 136.7 (d), 136.3 (d), 132.9 (d), 128.2 (d), 127.3 (d), 126.3 (d), 126.2 (d), 125.7 (d), 123.5 (d), 123.0 (s), 121.4 (d), 118.9 (s), 50.7 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{19}N_3Br$: 368.0757 $[M+H]^+$; found: 368.0765.



(E)-2-(4-(3-bromo-4-fluorostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14l): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 73 mg (71%); yellowish syrup; IR(neat) ν_{max} 2978, 1587, 1483, 1422, 1245, 1198, 1043, 1002, 960, 881, 792, 747, 708, 676, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 3.8 Hz, 1H), 7.88–7.80 (m, 2H), 7.51 (d, J = 6.9 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.38–7.33 (m, 1H), 7.26–7.18 (m, 1H), 7.01 (t, J = 8.4 Hz, 1H), 6.80–6.75 (d, J =16.8 Hz, 1H), 6.75–6.68 (d, J = 16.0 Hz, 1H), 4.79 (spt, J = 6.9 Hz, 1H), 1.47 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9 (ds, $^1J_{C-F}$ = 247.3 Hz), 150.3 (d), 149.4 (s), 138.7 (s), 136.7 (d), 135.8 (d), 135.5 (ds, $^4J_{C-F}$ = 3.8 Hz), 130.4 (d), 126.4 (dd, $^3J_{C-F}$ = 6.7 Hz), 125.6 (d), 125.0 (d), 123.0 (d), 119.7 (d), 118.6 (s), 116.4 (dd, $^2J_{C-F}$ = 23 Hz), 109.2 (ds, $^2J_{C-F}$ = 22.1 Hz), 50.8 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd for $C_{19}H_{18}BrFN_3$: 386.0663 [M+H]+; found: 386.0679.

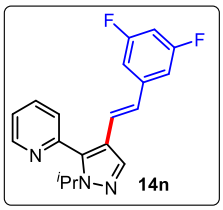


(E)-5-(2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)vinyl)-2-methoxyphenol (14m): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 63 mg (70%); colorless solid; mp: 122–124 °C; IR(neat) ν_{max} 2926, 1587, 1510, 1270, 1130, 1027, 959, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 4.6 Hz, 1H), 7.86 (s, 1H), 7.85–7.81 (dd, J = 1.5 Hz, 6.1 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.36 (dd, J = 4.6, 7.6 Hz, 1H), 7.01 (d, J = 1.5 Hz, 1H), 6.86–6.76 (m, J = 16.7 Hz, 3H), 6.71–6.65 (d, J = 16.0 Hz, 1H), 5.76 (br. s., 1H), 4.89–4.78 (spt, J = 6.9 Hz, 1H), 3.87 (s, 3H), 1.48 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1 (d), 149.5 (s), 146.0 (s), 145.6 (s), 138.1 (s), 136.7 (d), 135.6 (d), 131.5 (s), 127.3 (d), 125.7 (d),

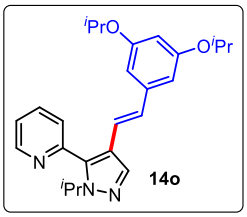


122.8 (d), 119.4 (d), 118.9 (s), 116.9 (d), 111.0 (d), 110.6 (d), 55.9 (d), 50.6 (q), 22.6 (q, 2C)ppm; HRMS (ESI): calcd. for $C_{20}H_{22}O_2N_3$: 336.1707 $[M+H]^+$; found: 336.1708.

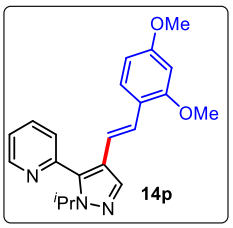
(E)-2-(4-(3,5-difluorostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14n): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 59 mg (68%);colorless solid; mp: 86–88 °C; IR(neat) ν_{max} 2995, 1587, 1483, 1422, 1245, 1198, 1043, 1002, 958, 881, 792, 747, 708, 675, 624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.80 (d, J = 3.8 Hz, 1H), 7.88–7.84 (dd, J = 1.9 Hz, 8.0 Hz, 1H), 7.84 (s, 1H), 7.51 (dd, J = 2.3, 6.9 Hz, 1H), 7.46–7.31 (m, 2H), 7.26–7.19 (m, 1H), 7.01 (t, J = 8.4 Hz, 1H), 6.80–6.75 (d, J = 16.8 Hz, 1H), 6.74–6.69 (d, J = 16.8 Hz, 1H), 4.79 (spt, J = 6.6 Hz, 1H), 1.47 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0 (ds, $^1J_{C\text{-}F}$ = 247.3 Hz), 150.3 (d), 149.4 (s), 138.7 (s), 136.7 (d), 135.8 (d), 135.6 (ds, $^3J_{C\text{-}F}$ = 3.8 Hz), 130.5 (d), 126.4 (dd, $^2J_{C\text{-}F}$ = 6.7 Hz), 125.6 (d), 125.0 (d), 123.1 (d), 119.7 (dd, $^4J_{C\text{-}F}$ = 2.9 Hz), 118.7 (s), 116.4 (dd, $^2J_{C\text{-}F}$ = 23 Hz), 109.2 (ds, $^3J_{C\text{-}F}$ = 21.1 Hz), 50.8 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{18}N_3F_2$: 326.1463 $[M+H]^+$; found: 326.1477.



(E)-2-(4-(3,5-diisopropoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14o): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 78 mg (72%); yellow syrup; IR(neat) ν_{max} 2976, 1584, 1452, 1382, 1288, 1181, 1151, 1112, 1038, 959, 792, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 3.8 Hz, 1H), 7.87–7.85 (s, 1H), 7.84–7.81 (dd, J = 1.5 Hz, 7.6 Hz,1H), 7.43 (d, J = 7.6 Hz, 1H), 7.38–7.33 (m, 1H), 6.80 (d, J = 1.5 Hz, 2H), 6.50 (d, J = 2.3 Hz, 2H), 6.32 (t, J = 2.3 Hz, 1H), 4.85 (spt, J = 6.6 Hz, 1H), 4.52 (spt, J = 6.0 Hz, 2H), 1.48 (d, J = 6.9 Hz, 6H), 1.32 (d, J = 6.1 Hz, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0 (s, 2C), 150.1 (d), 149.5 (s), 139.7 (s), 138.4 (s), 136.7 (d), 135.8 (d), 127.8 (d), 125.7 (d), 122.9 (d), 119.1 (d), 118.9 (s), 106.1 (d, 2C), 102.4 (d), 69.8 (d, 2C), 50.6 (d), 22.6 (q, 2C), 22.0 (q, 4C) ppm; HRMS (ESI): calcd. for $C_{25}H_{32}N_3O_2$: 406.2489 $[M+H]^+$; found: 406.2497.

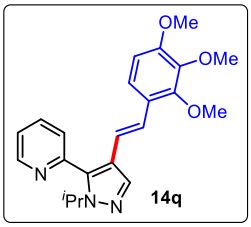


(E)-2-(4-(2,4-dimethoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14p): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 83 mg (89%); colorless solid; mp: 124–126 °C; IR(neat) ν_{max} 2935, 1605, 1501, 1455, 1421, 1261, 1206, 1157, 1117, 1032, 1002, 964, 834, 792, 734, 665, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 4.3 Hz, 1H), 7.88 (s,

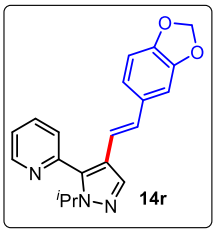


1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.35–7.29 (m, 2H), 7.16 (d, *J* = 16.5 Hz, 1H), 6.75 (d, *J* = 16.5 Hz, 1H), 6.50–6.39 (m, 2H), 4.98–4.79 (spt, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 1.48 (d, *J* = 6.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0 (s), 157.6 (s), 149.9 (d), 149.8 (s), 137.8 (s), 136.5 (d), 135.7 (d), 126.8 (d), 125.7 (d), 122.6 (d), 122.5 (d), 120.1 (s), 120.0 (s), 117.1 (d), 104.8 (d), 98.4 (d), 55.4 (q), 55.3 (q), 50.6 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{21}H_{24}O_2N_3$: 350.1863 $[M+H]^+$; found: 350.1868.

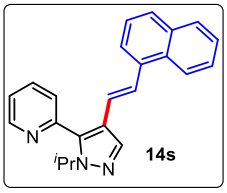
(E)-2-(1-isopropyl-4-(2,3,4-trimethoxystyryl)-1*H*-pyrazol-5-yl)pyridine (14q): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 51 mg (50%); colorless solid; mp: 105–107 °C; IR(neat) ν_{max} 2926, 1583, 1454, 1421, 1238, 1127, 1006, 794 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 3.8 Hz, 1H), 7.85 (s, 1H), 7.83 - 7.79 (dd, *J* = 2.3 Hz, 7.6 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.37–7.32 (m, 1H), 6.82 (d, *J* = 16.0 Hz, 1H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.58 (s, 2H), 4.83 (spt, *J* = 6.4, 13.2 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 1.47 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3 (s, 2C), 150.2 (d), 149.6 (s), 138.3 (s), 137.5 (s), 136.6 (d), 135.8 (d), 133.6 (s), 127.8 (d), 125.7 (d), 122.9 (d), 119.1 (s), 118.2 (d), 103.2 (d, 2C), 60.9 (d), 56.1 (q, 2C), 50.7 (q), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{22}H_{26}N_3O_3$: 380.1969 $[M+H]^+$; found: 380.1972.



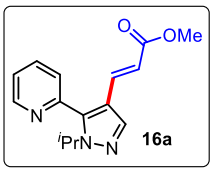
(E)-2-(4-(2-(benzo[d][1,3]dioxol-5-yl)vinyl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridine (14r): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 75 mg (84%); colorless syrup; IR(neat) ν_{max} 2926, 1587, 1482, 1444, 1248, 1191, 1036, 1002, 957, 929, 791, 747, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, *J*=6.1 Hz, 1H), 7.79–7.88 (m, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33–7.38 (m, 1H), 6.91 (d, *J* = 1.5 Hz, 1H), 6.78–6.85 (m, *J* = 16.8 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 16.8 Hz, 1H), 5.94 (s, 2H), 4.85 (spt, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1 (d), 149.6 (s), 147.9 (s), 146.8 (s), 138.2 (s), 136.6 (d), 135.6 (d), 132.3 (s), 127.4 (d), 125.6 (d), 122.8 (d), 120.7 (d), 119.2 (s), 116.9 (d), 108.3 (d), 105.1 (d), 101.0 (t), 50.7 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{20}H_{20}N_3O_2$: 334.1550 $[M+H]^+$; found: 334.1552.



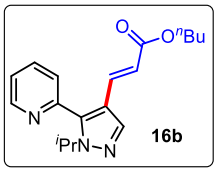
(E)-2-(1-isopropyl-4-(2-(naphthalen-1-yl)vinyl)-1*H*-pyrazol-5-yl)pyridine (14s): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 81 mg (89%); colorless solid; mp: 148–150 °C; IR(neat) ν_{max} 2976, 1587, 1487, 1404, 1196, 1061, 1002, 957, 887, 851, 792, 744, 666, 621 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, J = 4.6 Hz, 1H), 7.96 (s, 1H), 7.87 (dt, J = 1.9, 7.8 Hz, 1H), 7.82–7.72 (m, 4H), 7.59 (dd, J = 1.5, 8.4 Hz, 1H), 7.51–7.35 (m, 4H), 7.09 (d, J = 16.0 Hz, 1H), 6.98 (d, J = 16.0 Hz, 1H), 4.88 (spt, J = 6.6 Hz, 1H), 1.52 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2 (d), 149.6 (s), 138.5 (s), 136.7 (d), 135.8 (d), 135.2 (s), 133.7 (s), 132.7 (s), 128.1 (d), 127.8 (d), 127.8 (d), 127.6 (d), 126.2 (d), 125.7 (d), 125.7 (d), 125.6 (d), 123.2 (d), 122.9 (d), 119.3 (s), 118.9 (d), 50.7 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{23}H_{22}N_3$: 340.1808 $[M+H]^+$; found: 340.1816.



methyl (E)-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acrylate (16a): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 60 mg (83%); colorless syrup; IR(neat) ν_{max} 2932, 1710, 1633, 1587, 148, 1427, 1317, 1267, 1169, 999, 854, 795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 4.3 Hz, 1H), 7.92–7.80 (m, 2H), 7.47 (d, J = 15.9 Hz, 1H), 7.42–7.36 (m, 2H), 6.23 (d, J = 15.9 Hz, 1H), 4.88–4.67 (spt, J = 6.7 Hz, 1H), 3.74 (s, 3H), 1.48 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (s), 150.4 (d), 148.5 (s), 140.9 (s), 137.0 (d), 136.9 (d), 135.3 (d), 125.8 (d), 123.5 (d), 116.7 (s,), 115.8 (d), 51.4 (d), 51.1 (q), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{15}H_{18}N_3O_2$: 272.1394 $[M+H]^+$; found: 272.1395.

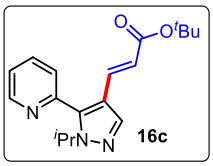


butyl (E)-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acrylate (16b): Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 69 mg (83%); colorless syrup; IR(neat) ν_{max} 2960, 1705, 1633, 1587, 1432, 1385, 1312, 1259, 1162, 1062, 982, 850, 793, 749, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 3.8 Hz, 1H), 7.87 (s, 1H), 7.86–7.82 (dd, J = 1.9 Hz, 8.0 Hz, 1H), 7.46 (d, J = 16.0 Hz, 1H), 7.42–7.35 (m, 2H), 6.23 (d, J = 15.3 Hz, 1H), 4.79 (spt, J = 6.4 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 1.69–1.58 (pent, J = 6.9 Hz, 2H), 1.47 (d, J = 6.1 Hz, 6H), 1.43–1.35 (hext, J = 7.6 Hz, 2H), 0.93 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5 (s), 150.3 (d), 148.5 (s), 140.9 (s), 137.0 (d), 136.9 (d), 135.1 (d), 125.8 (d), 123.4 (d), 116.7 (s), 116.2 (d), 64.1 (t), 51.0 (d), 30.7 (t),

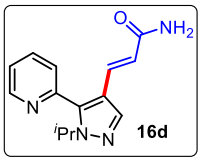


22.5 (q, 2 C), 19.1 (t), 13.7 (q) ppm; HRMS (ESI): calcd. for $C_{18}H_{24}N_3O_2$: 314.1863 $[M+H]^+$; found: 314.1866.

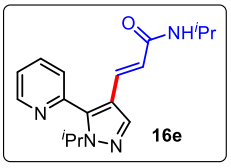
tert-butyl (E)-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acrylate (16c): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 70 mg (84%); colorless solid; mp: 82–84 °C; IR(neat) ν_{max} 2977, 1701, 1633, 1587, 1366, 1317, 1242, 1142, 1060, 980, 858, 792, 748, 715, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 3.8 Hz, 1H), 7.84 (s, 1H), 7.83–7.78 (d, J = 7.6 Hz,1H), 7.41–7.31 (m, J = 16.8 Hz, 3H), 6.16 (d, J = 16.0 Hz, 1H), 4.77 (spt, J = 6.6 Hz, 1H), 1.45 (s, 12H), 1.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (s), 150.4 (d), 148.7 (s), 140.9 (s), 137.0 (d), 136.9 (d), 134.2 (d), 125.9 (d), 123.5 (d), 118.1 (d), 116.9 (s), 80.2 (s), 51.1 (d), 28.3 (q, 4C), 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{18}H_{24}N_3O_2$: 314.1863 $[M+H]^+$; found: 314.1866.



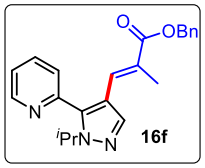
(E)-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acrylamide (16d): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 46 mg (67%); colorless solid; mp: 180–182 °C; IR(neat) ν_{max} 3335, 3205, 1665, 1606, 1454, 1388, 1198, 980, 795, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, J = 4.3 Hz, 1H), 7.91–7.75 (m, 2H), 7.49–7.29 (m, J = 15.3 Hz, 3H), 6.27 (d, J = 15.9 Hz, 1H), 5.78 (br. s., 2H), 4.78 (spt, J = 6.7 Hz, 1H), 1.46 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (s), 150.3 (d), 148.5 (s), 140.9 (s), 137.0 (d), 136.7 (d), 132.9 (d), 125.9 (d), 123.4 (d), 117.7 (d), 116.7 (s), 51.0 (d), 22.6 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{14}H_{17}N_4O$: 257.1397 $[M+H]^+$; found: 257.1400.



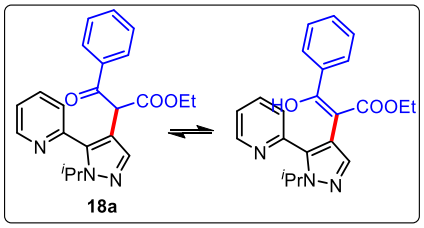
(E)-N-isopropyl-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acrylamide (16e): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 28 mg (35%); colorless gum; IR(neat) ν_{max} 3330,2972, 2927, 1658, 1614, 1551, 1487, 1453, 1424, 1353, 1200, 1127, 998, 850, 793, 718, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, J = 4.6 Hz, 1H), 7.87–7.84 (dd, J = 2.3 Hz, 7.6 Hz, 1H), 7.83 (s, 1H), 7.45–7.33 (m, J = 15.3 Hz, 3H), 6.17 (d, J = 15.3 Hz, 1H), 5.37 (d, J = 7.6 Hz, 1H), 4.82 (spt, J = 6.6 Hz, 1H), 4.16 (spt, J = 6.8 Hz, 1H), 1.47 (d, J = 6.1 Hz, 6H), 1.18 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4 (s), 150.3 (d), 148.7 (s), 140.7 (s), 137.1 (d), 136.5 (d), 131.2 (d), 126.0 (d), 123.4 (d), 119.3 (d), 117.1 (s), 51.0 (d), 41.5 (d), 22.9 (q, 2C), 22.7 (q, 2C); HRMS (ESI): calcd. for $C_{17}H_{23}N_4O$: 299.1866 $[M+H]^+$; found: 299.1868



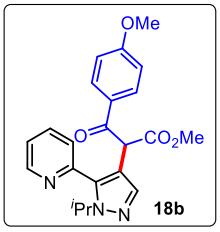
benzyl (E)-3-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)-2-methylacrylate (16f): Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 19 mg (20%); colorless solid; mp: 100–102 °C; IR(neat) ν_{max} 2925, 1703, 1633, 1587, 1486, 1453, 1270, 1237, 1210, 1111, 790, 749, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.79 (dt, J = 1.5, 3.1 Hz, 1H), 7.88 (s, 1H), 7.82 (dt, J = 1.5, 7.6 Hz, 1H), 7.46 (s, 1H), 7.40–7.29 (m, 7H), 5.19 (s, 2H), 4.93–4.83 (spt, J = 6.1 Hz, 1H), 2.18 (s, 3H), 1.50 (d, J = 6.1 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 (s), 150.3 (d), 148.9 (s), 141.3 (s), 138.6 (d), 136.8 (d), 136.6 (d), 130.0 (d), 128.5 (d, 2C), 128.0 (s), 127.7 (d, 2C), 126.1 (d), 125.0 (s), 123.3 (d), 116.9 (s), 66.3 (t), 51.1 (d), 22.7 (q, 2C), 14.5 (q) ppm; HRMS (ESI): calcd. for $C_{22}H_{24}N_3O_2$: 362.1863 $[M+H]^+$; found: 362.1866.



ethyl 2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)-3-oxo-3-phenylpropanoate (18a): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 91 mg (90%); colorless gum; IR(neat) ν_{max} 3735, 3675, 3567, 2984, 1737, 1684, 1591, 1415, 1247, 1180, 1011, 750, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 13.55 (br, s. 1H), 8.81–8.69 (m, 2H), 8.32 (s, 1H), 8.16–8.00 (m, 1H), 7.91–7.77 (m, 4H), 7.74 (s, 1H), 7.67–7.43 (m, 3H), 7.43–7.30 (m, 6H), 7.23 - 6.98 (m, 2H), 5.59 (s, 1H), 4.71–4.47 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.20–4.13 (m, 2H), 1.49–1.42 (m, 12H), 1.32 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3 (s), 178.5 (s), 173.5 (s), 171.9 (s), 169.0 (s), 162.6 (s), 150.3 (d), 149.7 (d), 149.2 (s), 148.2 (s), 144.6 (s), 142.6 (d), 139.3 (d), 136.9 (d), 136.5 (d), 135.6 (s), 133.4 (d), 128.9 (d, 4C), 128.6 (d, 4C), 127.6 (d), 126.5 (d), 125.2 (d), 124.1 (d), 123.2 (d), 117.0 (s), 112.2 (s), 94.6 (s), 62.2 (t), 61.7 (t), 51.5 (d), 51.0 (d, 2C), 22.8 (q), 22.7 (q), 22.4 (q, 2C), 14.0 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{22}H_{24}O_3N_3$: 378.1812 $[M+H]^+$; found: 378.1817.

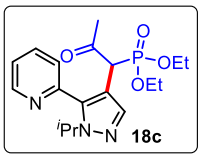


Methyl-3-(4-fluorophenyl)-2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)-3-oxopropanoate (18b): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 86 mg (82%); colorless syrup; IR(neat) ν_{max} 3739, 2967, 1742, 1676, 1594, 1428, 1252, 1168, 1016, 846, 792, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (td, J = 1.6, 4.3 Hz, 1H), 7.86–7.80 (m, 3H), 7.72 (s, 1H), 7.39–7.35 (m, 2H), 6.85–6.80 (m, 2H), 5.59 (s, 1H), 4.68–4.56 (spt, J = 6.6 Hz, 1H),

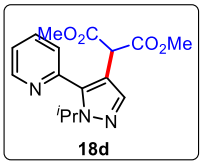


3.83 (s, 3H), 3.71 (s, 3H), 1.45 (dd, J = 2.4, 6.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9 (s) 169.8 (s) 163.8 (s) 150.3 (d) 149.3 (s) 139.3 (d) 139.0 (s) 136.9 (d) 131.4 (d, 2C) 128.3 (s) 125.2 (d) 123.2 (d) 113.8 (d, 2C) 112.4 (s) 55.5 (d) 52.7 (q) 50.9 (d) 50.5 (q) 22.8 (q) 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{22}H_{24}O_4N_3$: 394.1761 $[M+H]^+$; found: 394.1769.

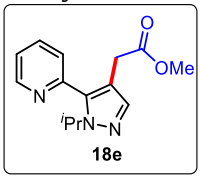
Diethyl (1-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)-2-oxopropyl)phosphonate (18c): Purified by column chromatography (50% EtOAc in petroleum ether, R_f = 0.5); yield: 68 mg (67%); yellowish syrup; IR(neat) ν_{max} 3903, 3802, 2989, 1718, 1427, 1366, 1232, 1030, 963, 745, 663 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (d, J = 4.3 Hz, 1H), 7.92 (s, 1H), 7.84 (t, J = 7.0 Hz, 1H), 7.47 (d, J = 7.3 Hz, 1H), 7.38–7.32 (m, 1H), 4.65 (spt, J = 6.7 Hz, 1H), 4.41–4.35 (s, 1H), 4.12–4.00 (q, 4H), 2.29 (s, 3H), 1.48–1.43 (d, J = 6.1 Hz, 6H), 1.27–1.20 (t, J = 7.3 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5 (s), 150.3 (d), 148.9 (s), 139.1 (d), 139.0 (s), 136.9 (d), 125.2 (d), 123.2 (d), 109.6 (s), 63.3, 63.3, 63.0, 62.9 (t, 2C), 51.0 (d), 50.6- 49.2 (d), 30.1 (q), 22.7 -22.6 (q, 2C), 16.3, 16.2, 16.2, 16.2 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{18}H_{27}O_4N_3P$: 380.1734 $[M+H]^+$; found: 380.1740.



dimethyl 2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)malonate (18d): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 77 mg (91%); yellow solid; mp: 96–98 °C; IR(neat) ν_{max} 3868, 3733, 2973, 1742, 1589, 1435, 1234, 1163, 1013, 796, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 3.8 Hz, 1H), 7.82 (dt, J = 1.5, 7.6 Hz, 1H), 7.77 (s, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.34 (dd, J = 6.1, 7.6 Hz, 1H), 4.67 (spt, J = 6.1 Hz, 1H), 4.59 (s, 1H), 3.71 (s, 6H), 1.45 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (s, 2C), 150.3 (d), 149.0 (s), 139.7 (s), 138.7 (d), 136.9 (d), 125.3 (d), 123.3 (d), 111.3 (s), 53.0 (d), 51.0 (d), 48.2 (q, 2C), 22.8 (q, 2C) ppm; HRMS (ESI): calcd for $C_{16}H_{20}O_4N_3$: 318.1448 $[M+H]^+$; found: 318.1454.

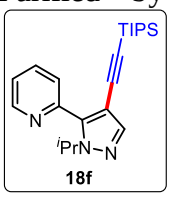


methyl 2-(1-isopropyl-5-(pyridin-2-yl)-1*H*-pyrazol-4-yl)acetate (18e): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 57 mg (82%); yellow solid; mp: 110–112 °C; IR(neat) ν_{max} 3734, 2970, 2927, 2371, 1724, 1597, 1422, 1259, 1193, 1010, 796, 709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.6 Hz, 1H), 7.83 (dt, J = 1.5, 7.6 Hz, 1H), 7.58 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.36–7.30 (m, 1H), 4.77–4.66 (spt, J = 6.1 Hz, 1H), 3.65 (s, 3H), 3.48 (s, 2H), 1.46 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (s), 150.1 (d), 149.5 (s), 139.2 (s), 139.0 (d), 137.0 (d),



125.2 (d), 123.0 (d), 112.2 (s), 52.1 (d), 50.9 (q), 30.1 (t), 22.8 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{14}H_{18}O_2N_3$: 260.1394 $[M+H]^+$; found: 260.1394.

2-(1-isopropyl-4-((triisopropylsilyl)ethynyl)-1*H*-pyrazol-5-yl)pyridine (18f): Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 83 mg (85%); yellowish gum; IR(neat) ν_{max} 3873, 3732, 3621, 3396, 2941, 2867, 2374, 2154, 1729, 1583, 1255, 1060, 999, 880 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.75–8.70 (dd, J = 4.9 Hz, 1H), 8.08–8.02 (m, 1H), 7.79–7.73 (m, 1H), 7.73–7.68 (m, 1H), 7.29 (dd, J = 5.1, 7.4 Hz, 1H), 5.40–5.32 (spt, J = 6.5 Hz, 1H), 1.53–1.48 (m, J = 6.5 Hz, 6H), 1.09 (dd, J = 2.7, 5.3 Hz, 21H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3 (d), 148.8 (s), 142.2 (d), 141.6 (s), 136.3 (d), 125.3 (d), 122.8 (d), 103.4 (s), 99.1 (s), 92.8 (s), 51.5 (d), 22.6 (q, 2C), 18.6 (d, 3C), 11.3 (q, 6C)ppm; HRMS (ESI): calcd. for $C_{22}H_{34}N_3Si$: 368.2517 $[M+H]^+$; found: 368.2528.



18f

General procedure for the Rh-catalyzed C–H Bond Activation of 19: In general, all reactions were carried out employing 50 mg of **19**.

To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added GBT-440 **19** (50 mg, 1 equiv, 0.148 mmol), styrene **20** (30.9 mg, 2 equiv, 0296 mmol), $[RhCp^*Cl_2]_2$ (4.6 mg, 5 mol%, 0.05 equiv), $AgSbF_6$ (10 mg, 20 mol%, 0.20 equiv), $Cu(OAc)_2.H_2O$ (59 mg, 2 equiv, 296 mmol), AcOH (9 mg, 1 equiv, 0.148 mmol) and DCE (4 mL) under air. The reaction mixture was stirred at 95 °C for 15-24 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **21**.

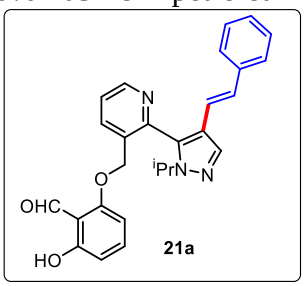
Representative procedure for 0.5 mmol scale:

To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added GBT-440 **19** (180 mg, 1 equiv, 0.534 mmol), styrene **20a** (111 mg, 2 equiv, 1.07 mmol), $[RhCp^*Cl_2]_2$ (16.5 mg, 5 mol%, 0.05 equiv), $AgSbF_6$ (36 mg, 20 mol%, 0.20 equiv), $Cu(OAc)_2.H_2O$ (213 mg, 2 equiv, 1.07 mmol) AcOH (32 mg, 1 equiv, 0.534 mmol) and DCE (10 mL) under air. The reaction mixture was stirred at 95 °C for 15 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **21**.

General procedure for the Rh-catalyzed C–H Bond Activation of 19 using acrylates or acryl amide 22: In general, all reactions were carried out employing 50 mg of **19**.

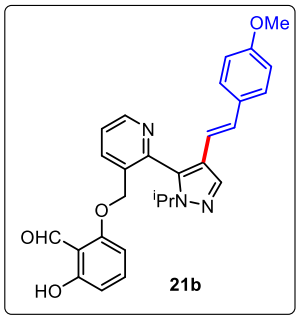
To a screw capped vial with a spinvane triangular–shaped Teflon stir bar were added GBT 440 **19** (50 mg, 1 equiv, 0.148 mmol), acrylates, aldehyde/ketone or acryl amide **22** (25.5 mg, 2 equiv, 0.296 mmol), $[RhCp^*Cl_2]_2$ (4.6 mg, 5 mol%, 0.05 equiv), $AgSbF_6$ (10 mg, 20 mol%, 0.20 equiv), $Cu(OAc)_2.H_2O$ (59 mg, 2 equiv, 296 mmol), AcOH (9 mg, 1 equiv, 0.148 mmol) and DCE (4 mL) under air. The reaction mixture was stirred at 95 °C for 2-24 h. After completion, the reaction mixture was diluted with ethyl acetate and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the alkene **23**.

(E)-2-hydroxy-6-((2-(1-isopropyl-4-styryl-1*H*-pyrazol-5-yl)pyridin-3 yl)methoxy)benzaldehyde (21a): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 46 mg (70%); colorless solid; mp: 118–120 °C; IR(neat) ν_{max} 2980, 1641, 1456, 1398, 1313, 1236, 1075, 1002, 960, 836, 781, 691, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.86 (s, 1H), 10.32 (s, 1H), 8.84 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.02 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.86 (s, 1H), 7.52 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.25 (d, *J* = 4.6 Hz, 4H), 7.23–7.15 (m, 2H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.64–6.55 (d, *J* = 16.0 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.14 (d, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 4.91 (d, *J* = 13.0 Hz, 1H), 4.31 (spt, *J* = 6.6 Hz, 1H), 1.55 (d, *J* = 6.1 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (d), 163.7 (s, 2C), 160.6 (s), 150.1 (d), 147.9 (s), 138.3 (d), 137.2 (s), 136.4 (d), 136.3 (d), 135.9 (s), 132.4 (s), 128.6 (d, 2C), 128.3 (d), 127.3 (d), 125.9 (d, 2C), 124.1 (d), 119.6 (s), 117.7 (d), 110.7 (d), 101.8 (d), 66.7 (t), 51.1 (d), 22.7 (q), 22.6 (q) ppm; HRMS (ESI) calcd. for $C_{27}H_{26}O_3N_3$: 440.1969 $[M + H]^+$; found 440.1971.



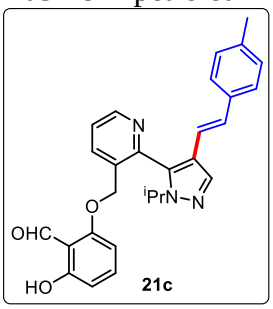
21a

(E)-2-hydroxy-6-((2-(1-isopropyl-4-(4-methoxystyryl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21b): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 60 mg (86%); colorless gum; IR(neat) ν_{max} 2927, 1641, 1510, 1457, 1239, 1173, 1077, 1033, 962, 783, 718, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.88 (s, 1H), 10.33 (s, 1H), 8.85 (d, *J* = 3.8 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.53 (dd, *J* = 5.0, 7.6 Hz, 1H), 7.26–7.16 (m, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.53–6.44 (m, *J* = 16.4 Hz, 2H), 6.16 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.92 (d, *J* = 12.6 Hz, 1H), 4.33 (spt, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 1.57 (d, *J* = 6.5 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.7 (s, 2C), 160.7 (s), 159.1 (s), 150.0 (d), 148.0 (s), 138.4 (d), 136.4 (d), 136.1 (d), 135.5 (s), 132.5 (s), 130.1 (s), 128.0 (d), 127.1 (d, 2C), 124.1 (d), 119.9 (s), 115.6 (d), 114.0 (d, 2C), 110.7 (d), 101.9 (d), 66.8 (t), 55.3 (d), 51.1 (q), 22.6 (q, 2C) ppm; HRMS (ESI) m/z: calcd. for $C_{28}H_{28}O_4N_3$: 470.2074 $[M + H]^+$; found: 470.2077.



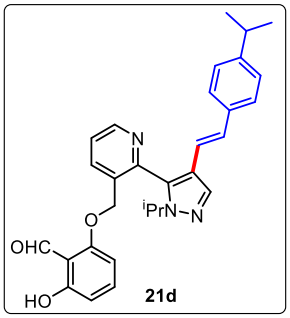
21b

(E)-2-hydroxy-6-((2-(1-isopropyl-4-(4-methylstyryl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21c): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 47 mg (70%); Yellowish solid; mp: 88–92 °C IR(neat) ν_{max} 2925, 1641, 1576, 1457, 1398, 1313, 1237, 1077, 1002, 963, 782, 717, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.87 (s, 1H), 10.32 (s, 1H), 8.84 (br. s., 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.52 (dd, *J* = 4.2, 6.5 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 7.17–7.12 (d, *J* = 7.6 Hz, 2H), 7.08–7.03 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 16.8 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 4.90 (d, *J* = 13.0 Hz, 1H), 4.37–4.25 (spt, *J* = 6.9 Hz, 1H), 2.31 (s, 3H), 1.56 (d, *J* = 6.1 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7 (d), 163.8 (s, 2C), 160.7 (s), 150.1 (d), 148.0 (s), 138.5 (d), 137.3 (s, 2C), 136.5 (d), 136.3 (d), 134.6 (s), 132.6 (s), 129.4 (d, 2C), 128.4 (d), 125.9 (d, 2C), 124.2 (d), 119.9 (s), 116.8 (d), 110.8 (d), 101.9 (d), 66.8 (t), 51.2 (q), 22.8 (q) 22.7 (q), 21.3 (q) ppm; HRMS (ESI): calcd. for $C_{28}H_{28}O_3N_3$: 454.2125 $[M+H]^+$; found: 454.2126.



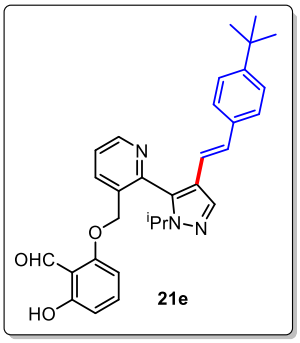
21c

(E)-2-hydroxy-6-((2-(1-isopropyl-4-(4-isopropylstyryl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21d): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 44 mg (62%); Yellowish syrup; IR(neat) ν_{max} 2962, 1642, 1457, 1237, 1077, 963, 783, 734, 663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.87 (s, 1H), 10.33 (s, 1H), 8.83 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.02 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.85 (s, 1H), 7.51 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.23–7.16 (m, 3H), 7.14–7.09 (m, 2H), 6.70 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 16.8 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.13 (d, *J* = 7.6 Hz, 1H), 5.06 (d, *J* = 13.0 Hz, 1H), 4.90 (d, *J* = 13.0 Hz, 1H), 4.36–4.27 (spt, *J* = 6.9 Hz, 1H), 2.86 (spt, *J* = 6.9 Hz, 1H), 1.56 (d, *J* = 6.1 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7 (d), 163.8 (s, 2C), 160.7 (s), 150.1 (d), 148.4 (s), 148.1 (s), 138.5 (d), 136.4 (d), 136.4 (d), 135.8 (s), 135.0 (s), 132.5 (s), 128.4 (d), 126.7 (d, 2C), 126.0 (d, 2C), 124.2 (d), 119.9 (s), 116.9 (d), 110.8 (d), 101.9 (d), 66.8 (t), 51.2 (d), 33.9 (d), 24.0 (q, 2C), 22.8 (q), 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{30}H_{32}O_3N_3$: 482.2438 $[M+H]^+$; found:482.2443.



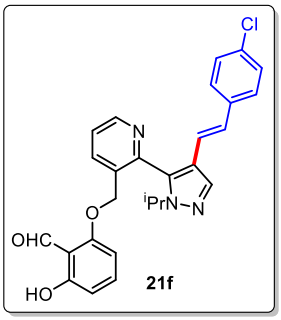
21d

(E)-2-((2-(4-(4-(tert-butyl)styryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21e): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 43 mg (58%); yellow syrup; IR(neat) ν_{max} 2960, 1642, 1577, 1457, 1367, 1237, 1077, 1002, 963, 838, 782, 715, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.88 (br. s., 1H), 10.34 (br. s., 1H), 8.85 (br. s., 1H), 8.03 (d, *J* = 6.7 Hz, 1H), 7.87 (br. s., 1H), 7.53 (br. s., 1H), 7.28 (br. s., 2H), 7.22 (br. s., 3H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 6.15 (d, *J* = 7.9 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.91 (d, *J* = 12.8 Hz, 1H), 4.42–4.26 (m, 1H), 1.57 (d, *J* = 5.5 Hz, 3H), 1.39 (d, *J* = 5.5 Hz, 3H), 1.31 (br. s., 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.7 (s), 160.7 (s), 150.5 (s), 150.0 (d), 148.0 (s), 138.4 (d), 136.3 (d, 2C), 135.8 (s), 134.5 (s), 132.5 (s), 128.2 (d), 125.7 (d, 2C), 125.5 (d, 2C), 124.1 (d), 119.8 (s), 117.0 (d), 110.7 (s), 110.7 (d), 101.9 (d), 66.7 (t), 51.1 (d), 34.6 (q, 3C), 31.3 (s), 22.7 (q), 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{31}H_{34}O_3N_3$:496.2595 $[M+H]^+$; found: 496.2597.



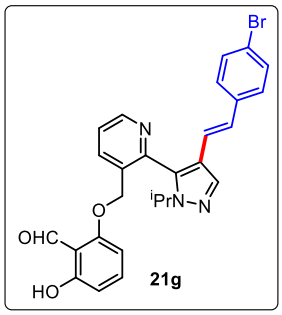
21e

(E)-2-((2-(4-(4-chlorostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21f): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 50 mg (71%); colorless solid; mp: 120–122 °C; IR(neat) ν_{max} 2925, 1641, 1483, 1457, 1399, 1313, 1237, 1077, 1006, 962, 782, 716, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.85 (s, 1H), 10.30 (s, 1H), 8.84 (d, *J* = 4.6 Hz, 1H), 8.03 (d, *J* = 6.9 Hz, 1H), 7.85 (s, 1H), 7.53 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.25–7.13 (m, 5H), 6.66 (d, *J* = 16.8 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 1H), 4.89 (d, *J* = 12.2 Hz, 1H), 4.29 (spt, *J* = 6.6 Hz, 1H), 1.54 (d, *J* = 6.1 Hz, 3H), 1.39 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6 (d), 163.8 (s), 160.7 (s), 150.3 (d), 148.0 (s), 138.4 (d), 136.7 (d), 136.4 (d), 136.2 (s), 135.9 (s), 132.9 (s), 132.5 (s), 128.8 (d, 2C), 127.1 (d, 2C), 127.0 (d), 124.3 (d), 119.4 (s), 118.4 (d), 110.9 (d), 110.8 (s), 101.8 (d), 66.8 (t), 51.3 (d), 22.9 (q), 22.6 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{25}O_3N_3Cl$: 474.1579 $[M+H]^+$; found:474.1580.

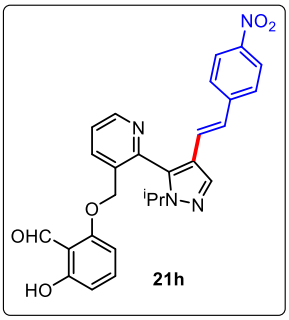


21f

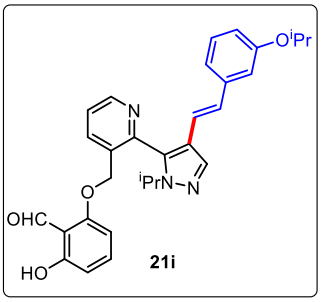
(E)-2-((2-(4-(4-bromostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21g): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 38 mg (50%); colorless solid; mp: 145–147 °C; IR(neat) ν_{max} 2925, 1641, 1482, 1457, 1398, 1313, 1236, 1073, 1005, 962, 782, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.83 (s, 1H), 10.28 (s, 1H), 8.82 (d, *J* = 3.1 Hz, 1H), 8.01 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.84 (s, 1H), 7.52 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.36–7.31 (d, *J* = 8.4 Hz, 2H), 7.26–7.18 (m, 1H), 7.10–7.04 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 16.7 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 12.2 Hz, 1H), 4.27 (spt, *J* = 6.6 Hz, 1H), 1.51 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6 (d), 163.8 (s), 160.7 (s), 150.3 (d), 147.9 (s), 138.4 (d), 136.7 (d), 136.4 (d), 136.3 (s), 136.21 (s), 132.5 (s), 131.7 (d, 2C), 127.4 (d, 2C), 127.0 (d), 124.4 (d), 121.0 (s), 119.4 (s), 118.5 (d), 110.9 (d), 110.8 (s), 101.8 (d), 66.8 (t), 51.3 (d), 22.8 (q), 22.6 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{25}O_3N_3Br$:518.1074 $[M+H]^+$; found: 518.1078.



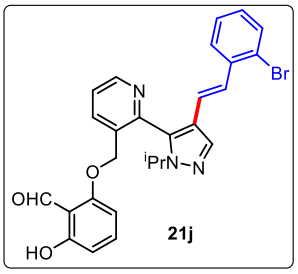
(E)-2-hydroxy-6-((2-(1-isopropyl-4-(4-nitrostyryl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21h): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 32 mg (45%); yellowish gum; IR(neat) ν_{max} 2933, 1640, 1592, 1513, 1458, 1338, 1238, 1078, 785 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.84 (s, 1H), 10.31 (s, 1H), 8.91 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 8.10 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.95 (s, 1H), 7.61 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.37 (d, *J* = 9.2 Hz, 2H), 7.31 - 7.28 (m, 1H), 6.78 (s, 2H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.19 (d, *J* = 8.4 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 4.93 (d, *J* = 12.2 Hz, 1H), 4.31 (spt, *J* = 6.7 Hz, 1H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.45 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4 (d), 163.8 (s), 160.6 (s), 150.4 (d), 147.8 (s), 146.4 (s), 143.9 (s), 138.2 (d), 137.0 (d), 136.7 (d), 132.4 (s), 126.2 (d, 2C), 125.5 (d), 124.5 (d), 124.1 (d, 2C), 123.8 (s), 122.5 (d), 118.9 (s), 111.0 (d), 110.7 (s), 101.6 (d), 66.8 (t), 51.4 (d), 22.8 (q), 22.4 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{25}O_5N_4$: 485.1819 $[M+H]^+$; found: 485.1821.



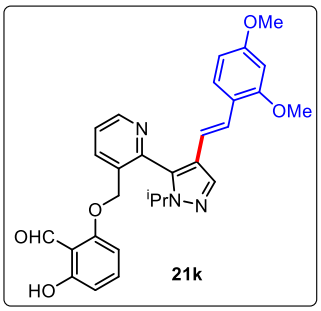
(E)-2-hydroxy-6-((2-(4-(3-isopropoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21i): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 45 mg (61%); yellowish gum; IR(neat) ν_{max} 2925, 1642, 1457, 1372, 1314, 1237, 1115, 1078, 1002, 781, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.87 (s, 1H), 10.32 (s, 1H), 8.84 (br. s., 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 7.58–7.48 (m, 1H), 7.22 (t, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.78 (br. s., 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.67 (d, *J* = 16.4 Hz, 1H), 6.57 (d, *J* = 16.4 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 5.05 (d, *J* = 13.0 Hz, 1H), 4.90 (d, *J* = 12.6 Hz, 1H), 4.52 (spt, *J* = 5.7 Hz, 1H), 4.31 (spt, *J* = 5.7 Hz, 1H), 1.55 (d, *J* = 6.1 Hz, 3H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 5.7 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.7 (s), 160.7 (s), 158.1 (s), 150.1 (d), 147.9 (s), 138.8 (s), 138.4 (d), 136.4 (d), 136.4 (s), 132.5 (s), 129.5 (d, 2C), 128.3 (d), 124.2 (d), 119.6 (s), 118.5 (d), 117.9 (d), 114.1 (d), 113.8 (d), 110.8 (s), 110.8 (d), 101.9 (d), 69.8 (d), 66.7 (t), 51.2 (d), 22.7 (q), 22.6 (q), 22.1 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{30}H_{32}O_4N_3$: 498.2387 $[M+H]^+$; found:498.2391.



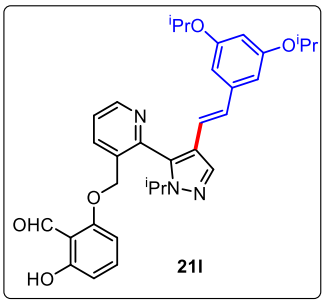
(E)-2-((2-(4-(2-bromostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21j): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 39 mg (51%); yellowish solid; mp: 78–80 °C; IR(neat) ν_{max} 2925, 1640, 1577, 1458, 1313, 1236, 1076, 1022, 961, 836, 782, 748, 717, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.82 (s, 1H), 10.26 (s, 1H), 8.83 (d, *J* = 3.8 Hz, 1H), 8.01 (d, *J* = 6.9 Hz, 1H), 7.83 (s, 1H), 7.50 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.26–7.20 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.04–6.97 (m, 1H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.59 (d, *J* = 16.8 Hz, 1H), 6.47 (d, J = 9.2 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 4.88 (d, *J* = 12.2 Hz, 1H), 4.35– 4.24 (spt, *J* = 6.9 Hz, 1H), 1.54 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.7 (s), 160.7 (s), 150.3 (d), 148.1 (s), 138.5 (d), 137.3 (d), 137.2 (s), 136.9 (d), 136.2 (s), 133.0 (d), 132.5 (s), 128.6 (d), 127.6 (d), 126.8 (d), 126.1 (d), 124.3 (d), 123.6 (s), 120.8 (d), 119.3 (s), 110.8 (d), 110.7 (s), 101.9 (d), 66.8 (t), 51.3 (d), 22.8 (q), 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{25}O_3N_3Br$: 518.1074 $[M+H]^+$; found: 518.1075.



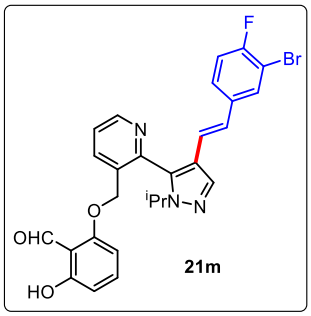
(E)-2-((2-(4-(2,4-dimethoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21k): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 47 mg (64%); colorless gum; IR(neat) ν_{max} 2962, 1643, 1513, 1460, 1263, 1079, 1026, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.85 (s, 1H), 10.31 (s, 1H), 8.84 (d, *J* = 6.1 Hz, 1H), 8.02 (d, *J* = 6.1 Hz, 1H), 7.83 (s, 1H), 7.54–7.50 (m, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 6.82–6.73 (m, 3H), 6.64 (d, *J* = 16.8 Hz, 1H), 6.51–6.43 (m, *J* = 16.0 Hz, 2H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.05 (d, *J* = 13.0 Hz, 1H), 4.90 (d, *J* = 13.0 Hz, 1H), 4.34–4.24 (spt, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 1.55 (d, *J* = 6.9 Hz, 3H), 1.38 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.8 (s, 2C), 160.7 (s), 150.1 (d), 149.1 (s), 148.8 (s), 148.2 (s), 138.4 (d), 136.5 (d), 136.4 (d), 135.7 (s), 132.6 (s), 130.6 (s), 128.4 (d), 124.2 (d), 119.9 (s), 118.9 (d), 116.1 (d), 111.3 (d), 110.8 (d), 109.0 (d), 101.9 (d), 66.8 (t), 56.0 (q), 56.0 (q), 51.2 (d), 22.8 (q), 22.7 (q) ppm; HRMS (ESI): calcd. for $C_{29}H_{30}O_5N_3$: 500.2180 $[M+H]^+$; found: 500.2183.



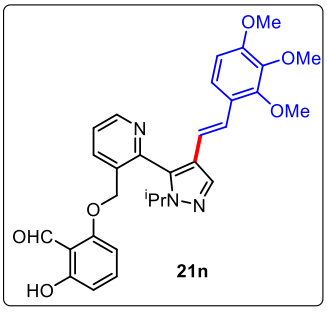
(E)-2-((2-(4-(3,5-diisopropoxystyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21l): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 35 mg (43%); brownish gum; IR(neat) ν_{max} 2979, 1643, 1583, 1458, 1334, 1313, 1239, 1171, 1078, 784, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.87 (s, 1H), 10.31 (s, 1H), 8.81 (dd, *J* = 1.5, 4.6 Hz, 1H), 7.99 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.82 (s, 1H), 7.50 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.28–7.17 (m, 1H), 6.63–6.56 (d, *J* = 16.0 Hz, 1H), 6.55–6.49 (d, *J* = 16.8 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 2H), 6.28 (t, *J* = 2.3 Hz, 1H), 6.11 (d, *J* = 8.4 Hz, 1H), 5.02 (d, *J* = 13.0 Hz, 1H), 4.87 (d, *J* = 13.0 Hz, 1H), 4.52–4.41 (m, 2H), 4.27 (td, *J* = 6.3, 13.4 Hz, 1H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.29 (dd, *J* = 2.3, 6.1 Hz, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7 (d), 163.8 (s), 160.7 (s), 159.2 (s, 2C), 150.1 (d), 147.9 (s), 139.4 (s), 138.5 (d), 136.5 (d), 136.4 (d), 136.0 (s), 132.6 (s), 128.4 (d), 124.3 (d), 119.6 (s), 118.1 (d), 110.8 (d), 110.8 (s), 106.2 (d, 2C), 102.4 (d), 102.0 (d), 69.9 (d, 2C), 66.8 (t), 51.2 (d), 22.8 (q, 2C), 22.7 (q, 2C), 22.1 (q, 2C) ppm; HRMS (ESI): calcd for $C_{33}H_{38}O_5N_3$: 556.2806 [M+H]+; found: 556.2811.



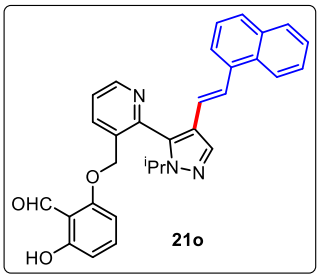
(E)-2-((2-(4-(3-bromo-4-fluorostyryl)-1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (21m): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 36 mg (45%); yellowish gum; IR(neat) ν_{max} 2930, 1642, 1485, 1458, 1397, 1314, 1240, 1078, 961, 783, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.82 (s, 1H), 10.26 (s, 1H), 8.82 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.52 (dd, *J* = 4.6, 7.6 Hz, 1H), 7.37 (dd, *J* = 2.3, 6.1 Hz, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 7.10 (ddd, *J* = 2.3, 4.6, 8.4 Hz, 1H), 6.95 (t, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.50–6.42 (m, *J* = 16.0 Hz, 2H), 6.12 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 12.2 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.25 (spt, *J* = 6.5 Hz, 1H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.36 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6 (d), 163.8 (s), 160.7 (s), 158.2 (ds, $^1J_{C-F}$ = 247.3 Hz), 150.3 (d), 147.9 (s), 138.4 (d), 136.9 (d), 136.4 (d), 136.3 (s), 135.2 (ds, $^4J_{C-F}$= 3.8 Hz), 132.5 (s), 130.5 (d), 126.4 (dd, $^3J_{C-F}$ =6.7 Hz), 125.6 (d), 124.5 (d), 119.2 (s), 118.9 (dd, $^3J_{C-F}$ =1.9 Hz), 116.6 (dd, $^2J_{C-F}$ = 22 Hz), 110.9 (d), 110.8 (s), 109.4 (ds, $^2J_{C-F}$ =22.1 Hz), 101. 8 (d), 66.8 (t), 51.3 (d), 22.9 (q), 22.6 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{24}O_3N_3BrF$: 536.0980 $[M+H]^+$; found:536.0981.



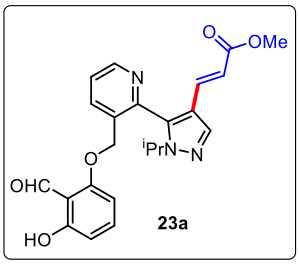
(E)-2-hydroxy-6-((2-(1-isopropyl-4-(2,3,4-trimethoxystyryl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21n): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 43 mg (55%); yellowish gum; IR(neat) ν_{max} 2926, 1642, 1581, 1458, 1421, 1337, 1238, 1127, 1078, 1005, 784, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.86 (s, 1H), 10.30 (s, 1H), 8.87 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.14–8.00 (m, 1H), 7.85 (s, 1H), 7.55 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.25 (t, *J* = 8.4 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.54–6.44 (m, *J* =15.3 Hz, 4H), 6.16 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 4.91 (d, *J* = 12.2 Hz, 1H), 4.31 (spt, *J* = 6.6 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 6H), 1.56 (d, *J* = 6.5 Hz, 3H), 1.40 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 193.4 (d), 163.7 (s), 160.7 (s), 153.3 (s), 150.1 (d), 148.1 (s), 138.3 (d), 137.9 (s), 136.5 (d), 136.5 (d), 135.8 (s), 133.2 (s), 132.5 (s), 128.5 (d), 128.4 (d), 127.6 (s), 124.2 (d), 119.6 (s), 117.3 (d), 110.8 (d), 110.8 (s), 103.3 (d), 101.8 (d), 66.8 (t), 60.9 (d), 56.2 (q, 2C), 51.2 (q), 22.8 (q), 22.6 (q) ppm; HRMS (ESI): calcd. for $C_{30}H_{32}O_6N_3$: 530.2286 $[M+H]^+$; found: 530.2289.



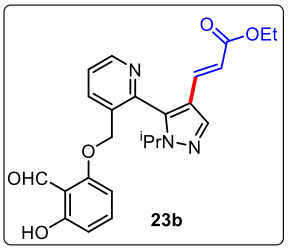
(E)-2-hydroxy-6-((2-(1-isopropyl-4-(2-(naphthalen-1-yl)vinyl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (21o): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 40 mg (55%); yellowish gum; IR(neat) ν_{max} 2925, 1641, 1457, 1313, 1237, 1077, 961, 783, 717, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 11.73 (s, 1H), 10.24 (s, 1H), 8.78 (dd, *J* = 1.5, 4.6 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.72–7.57 (m, 3H), 7.55–7.42 (m, 2H), 7.41–7.28 (m, 3H), 7.21–7.02 (m, 1H), 6.81(d, *J* = 16.4 Hz, 1H), 6.63 (d, *J* = 16.4 Hz, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 6.06 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 12.7 Hz, 1H), 4.84 (d, *J* = 12.7 Hz, 1H), 4.24 (spt, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (d), 163.7 (s, 2C), 160.7 (s), 150.1 (d), 148.0 (s), 138.3 (d), 136.4 (d), 136.4 (d), 136.0 (s), 134.8 (s), 133.6 (s), 132.8 (s), 132.5 (s), 128.4 (d), 128.2 (d), 127.8 (d), 127.7 (d), 126.4 (d), 125.9 (d), 125.8 (d), 124.2 (d), 123.0 (d), 119.7 (s), 118.1 (d), 110.8 (d), 101.8 (d), 66.8 (t), 51.2 (d), 22.8 (q), 22.6 (q) ppm; HRMS (ESI): calcd. for $C_{31}H_{28}O_3N_3$: 490.2125 $[M+H]^+$; found: 490.2125.



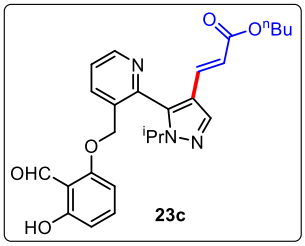
Methyl (E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23a) : Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (88%); colorless solid; mp: 118–120 °C; IR(neat) ν_{max} 2924, 1708, 1640, 1457, 1314, 1237, 1076, 979, 783, 716, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.92 (s, 1H), 10.29 (s, 1H), 8.80 (dd, *J* = 1.5 Hz, 4.6 Hz, 1H), 7.98–8.05 (dd, *J* = 1.5 Hz, 7.6 Hz, 1H), 7.85 (s, 1H), 7.52 (dd, *J* =4.6 Hz, 8.4 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 3.8 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 6.01 (d, *J* = 16.0 Hz, 1 H), 4.92 (d, *J* = 12.2 Hz, 1H), 4.82 (d, *J* = 12.2 Hz, 1H), 4.23 (spt, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 1.50 (d, *J* = 6.9 Hz, 3H), 1.35 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7 (d), 167.5 (s), 163.9 (s), 160.7 (s), 150.5 (d), 147.3 (s), 138.6 (s), 138.5 (d), 137.7 (d), 137.1 (d), 134.4 (d), 132.5 (s), 124.7 (d), 117.3 (s), 116.1 (d), 111.1 (d), 110.8 (s), 101.8 (d), 66.7 (t), 51.7 (d), 51.6 (q), 22.8 (q), 22.5 (q) ppm; HRMS (ESI): calcd. for $C_{23}H_{24}O_5N_3$: 422.1710 $[M+H]^+$; found: 422.1716.



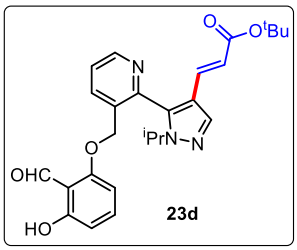
Ethyl (E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23b): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 52 mg (80%); reddish solid; mp: 104–106 °C; IR(neat) ν_{max} 2391, 1704, 1639, 1458, 1312, 1237, 1173, 1075, 785, 717, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.94 (s, 1H), 10.31 (s, 1H), 8.83 (br. s., 1H), 8.05 (br. s., 1H), 7.87 (s, 1H) 7.55 (br. s., 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 15.3 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.17 (d, *J* = 7.6 Hz, 1H), 6.04 (d, *J* = 15.3 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.84 (d, *J* = 10.7 Hz, 1H), 4.26 (br. s., 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 1.52 (br. s., 3H), 1.37 (br. s., 3H), 1.27–1.23 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (d), 167.2 (s), 163.8 (s, 2C), 160.7 (s), 150.5 (d), 147.2 (s), 138.5 (d), 137.7 (d), 137.3 (d), 134.2 (d), 132.5 (s), 124.9 (d), 117.4 (s), 116.6 (d), 111.0 (d), 110.8 (s), 101.8 (d), 66.8 (t), 60.5 (t), 51.8 (d), 22.9 (q), 22.6 (q), 14.4 (q) ppm; HRMS (ESI): calcd. for $C_{24}H_{26}O_5N_3$: 436.1867 $[M+H]^+$; found: 436.1864.



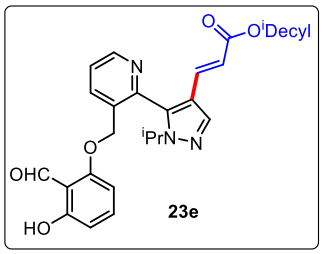
Butyl (E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23c): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 50 mg (73%); colorless solid; mp: 112–114 °C; IR(neat) ν_{max} 2927, 1705, 1639, 1457, 1384, 1311, 1236, 1167, 1075, 980, 782, 716, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.94 (s, 1H), 10.31 (s, 1H), 8.82 (dd, *J* = 1.9, 5.0 Hz, 1H), 8.03 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.87 (s, 1H), 7.54 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 15.3 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.17 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.84 (d, *J* = 12.2 Hz, 1H), 4.26 (spt, *J* = 6.6 Hz, 1H), 4.10 (t, *J* = 6.9 Hz, 2H), 1.65–1.56 (m, 2H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.42–1.30 (m, 5H), 0.95–0.89 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7 (d), 167.3 (s), 163.9 (s), 160.7 (s), 150.4 (d), 147.2 (s), 138.6 (s), 138.4 (d), 137.6 (d), 137.0 (d), 134.1 (d), 132.5 (s), 124.7 (d), 117.4 (s), 116.6 (d), 111.0 (d), 110.8 (s), 101.8 (d), 66.8 (t), 64.4 (t), 51.6 (d), 30.8 (t), 22.8 (q), 22.5 (q), 19.2 (t), 13.8 (q) ppm; HRMS (ESI): calcd. for $C_{26}H_{30}O_5N_3$: 464.2180 $[M+H]^+$; found: 464.2184.



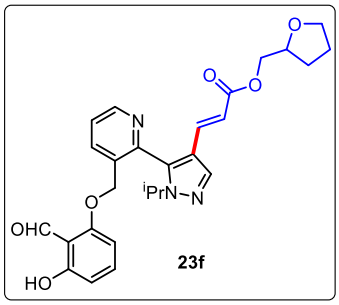
Tert-butyl (E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23d): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 51 mg (74%); colorless solid; mp: 138–140 °C; IR(neat) ν_{max} 2924, 1701, 1640, 1457, 1368, 1315, 1237, 1146, 1076, 980, 858, 782, 716, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.92 (s, 1H), 10.31 (s, 1H), 8.78 (br. s., 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.52 (br. s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.12 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.15 (d, J = 8.4 Hz, 1H), 6.01 (d, J = 16.0 Hz, 1H), 4.95 (d, J = 12.2 Hz, 1H), 4.82 (d, J = 12.2 Hz, 1H), 4.24 (td, J = 6.5, 13.0 Hz, 1H), 1.49 (d, J = 6.1 Hz, 3H), 1.42 (s, 9H), 1.34 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (d), 166.6 (s), 163.8 (s), 160.7 (s), 150.4 (d), 147.3 (s), 138.4 (d), 137.8 (s), 137.4 (d), 137.0 (d), 133.1 (d), 132.5 (s), 124.7 (d), 118.4 (d), 117.5 (s), 111.0 (d), 110.8 (s), 101.8 (d), 80.4 (s), 66.8 (t), 51.6 (d), 28.2 (q, 3C), 22.8 (q), 22.5 (q) ppm; HRMS (ESI): calcd. for $C_{26}H_{30}O_5N_3$: 464.2180 $[M+H]^+$; found: 464.2177.



8-methylnonyl (E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23e): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 40 mg (69%); yellowish gum; IR(neat) ν_{max} 2957, 1706, 1641, 1459, 1383, 1313, 1239, 1171, 1078, 784, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.92 (s, 1H), 10.29 (s, 1H), 8.80 (d, J = 3.1 Hz, 1H), 8.01 (dd, J = 1.5, 7.6 Hz, 1H), 7.86 (s, 1H), 7.52 (dd, J = 4.6, 7.6 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.20 (d, J = 16.0 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 6.15 (d, J = 8.4 Hz, 1H), 6.09–5.98 (m, J = 16.0 Hz, 1H), 4.93 (d, J = 12.2 Hz, 1H), 4.81 (d, J = 12.2 Hz, 1H), 4.24 (spt, J = 6.9 Hz, 1H), 4.14–4.02 (m, 2H), 1.64–1.52 (m, 2H), 1.50 (d, J = 6.9 Hz, 3H), 1.35 (d, J = 6.1 Hz, 3H), 1.29–1.18 (m, 5H), 1.12–1.02 (m, 2H), 0.91–0.69 (m, 10H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8 (d), 167.3 (s), 163.9 (s, 2C), 160.6 (s), 150.5 (d), 147.2 (s), 138.5 (d), 137.6 (d), 137.1 (d), 134.1 (d), 132.5 (s), 124.8 (d), 117.4 (s), 116.7 (d), 111.0 (d), 110.8 (s), 101.8 (d), 66.8 (t), 65.0 (t), 64.7 (t), 63.2 (t), 51.7 (d), 29.8 (t, 2C), 29.2 (t), 26.3 (t), 22.8 (q), 22.8 (d), 22.6 (q, 3C)ppm; HRMS (ESI): calcd. for $C_{32}H_{42}O_5N_3$: 548.3119 $[M+H]^+$; found: 548.3118.

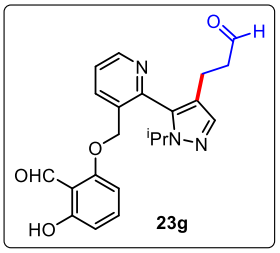


(tetrahydrofuran-2-yl)methyl (*E*)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylate (23f): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 60 mg (83%); colorless solid; mp: 100–102 °C IR(neat) ν_{max} 2927, 1708, 1640, 1458, 1313, 1239, 1171, 1077, 786, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.94 (s, 1H), 10.31 (s, 1H), 8.81 (dd, *J* = 1.5, 5.3 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 1H), 7.87 (s, 1H), 7.54 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 16.0 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.17 (d, *J* = 8.4 Hz, 1H), 6.11 (d, *J* = 16.0 Hz, 1H), 4.94 (d, *J* = 12.2 Hz, 1H), 4.83 (d, *J* = 12.2 Hz, 1H), 4.29–4.22 (spt, *J* = 6.1 Hz, 1H), 4.22–4.07 (m, 2H), 4.06–3.98 (m, 1H), 3.90–3.83 (m, 1H), 3.82–3.73 (m, 1H), 2.05–1.95 (m, 1H), 1.94–1.84 (m, 2H), 1.60 (td, *J* = 7.4, 12.6 Hz, 1H), 1.51 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7 (d), 167.1 (s), 163.8 (s), 160.7 (s), 150.4 (d), 147.2 (s), 138.6 (s), 138.5 (d), 137.7 (d), 137.1 (d), 134.7 (d), 132.5 (s), 124.7 (d), 117.3 (s), 116.1 (d), 111.0 (d), 110.8 (s), 101.8 (d), 76.7 (d), 68.5 (t), 66.7 (t), 66.6–66.5 (t), 51.6 (d), 28.0 (t), 25.7 (t), 22.8 (q), 22.5 (q) ppm; HRMS (ESI): calcd. for $C_{27}H_{30}O_6N_3$: 492.2129 $[M+H]^+$; found: 492.2127



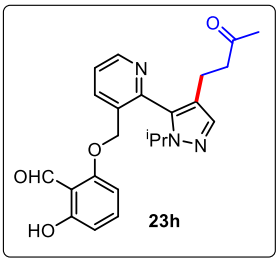
23f

2-hydroxy-6-((2-(1-isopropyl-4-(3-oxopropyl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (23g): Purified by column chromatography (40% EtOAc in petroleum ether, R_f = 0.5); yield: 27 mg (46%); colorless syrup; IR(neat) ν_{max} 2926, 1722, 1642, 1458, 1239, 1076, 785, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.92 (s, 1H), 10.35 (s, 1H), 9.71 (s, 1H), 8.79 (dd, *J* = 1.5, 4.6 Hz, 1H), 8.02 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.54–7.45 (m, 2H), 7.38 (t, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.26 (d, *J* = 8.4 Hz, 1H), 4.98 (d, *J* = 11.4 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.13 (spt, *J* = 6.5 Hz, 1H), 2.76–2.46 (m, 4H), 1.42 (d, *J* = 6.1 Hz, 3H), 1.37 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4 (d), 193.7 (d), 163.9 (s, 2C), 160.9 (s), 150.2 (d), 148.6 (s), 138.6 (d), 137.9 (d), 136.8 (d), 136.4 (s), 132.4 (s), 124.2 (d), 118.7 (s), 111.0 (d), 101.8 (d), 66.9 (t), 51.2 (d), 44.5 (t), 23.0 (q), 22.5 (q), 16.4 (t) ppm; HRMS (ESI): calcd. for $C_{22}H_{24}O_4N_3$: 394.1761 $[M+H]^+$; found: 394.1762.



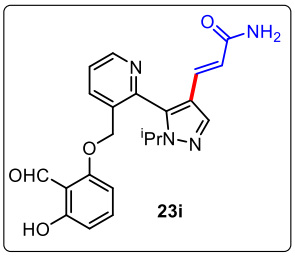
23g

2-hydroxy-6-((2-(1-isopropyl-4-(3-oxobutyl)-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (23h): Purified by column chromatography (40% EtOAc in petroleum ether, R_f = 0.5); yield: 35 mg (58%); colorless syrup; IR(neat) ν_{max} 2929, 1712, 1641, 1458, 1342, 1238, 1169, 1076, 786, 719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.90 (s, 1H), 10.32 (s, 1H), 8.74 (d, J = 4.6 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 5.0, 8.0 Hz, 1H), 7.43 (s, 1H), 7.35 (t, J = 8.4 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.24 (d, J = 8.4 Hz, 1H), 4.97 (d, J = 11.4 Hz, 1H), 4.83 (d, J = 12.2 Hz, 1H), 4.10 (spt, J = 6.6 Hz, 1H), 2.72–2.52 (m, 3H), 2.46–2.38 (m, 1H), 2.03 (s, 3H), 1.40 (d, J = 6.1 Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9 (s), 193.7 (d), 163.8 (s, 2C), 160.9 (s), 150.1 (d), 148.7 (s), 138.6 (d), 137.8 (d), 136.7 (d), 136.3 (s), 132.4 (s), 124.2 (d), 119.2 (s), 111.0 (d), 101.9 (d), 66.9 (t), 51.2 (d), 44.1 (t), 30.0 (q), 23.0 (q), 22.5 (q), 17.8 (t) ppm; HRMS (ESI): calcd. for $C_{23}H_{26}O_4N_3$: 408.1918 $[M+H]^+$; found: 408.1921.



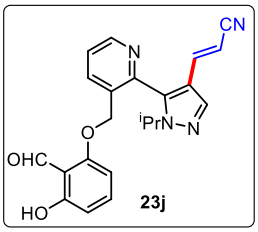
23h

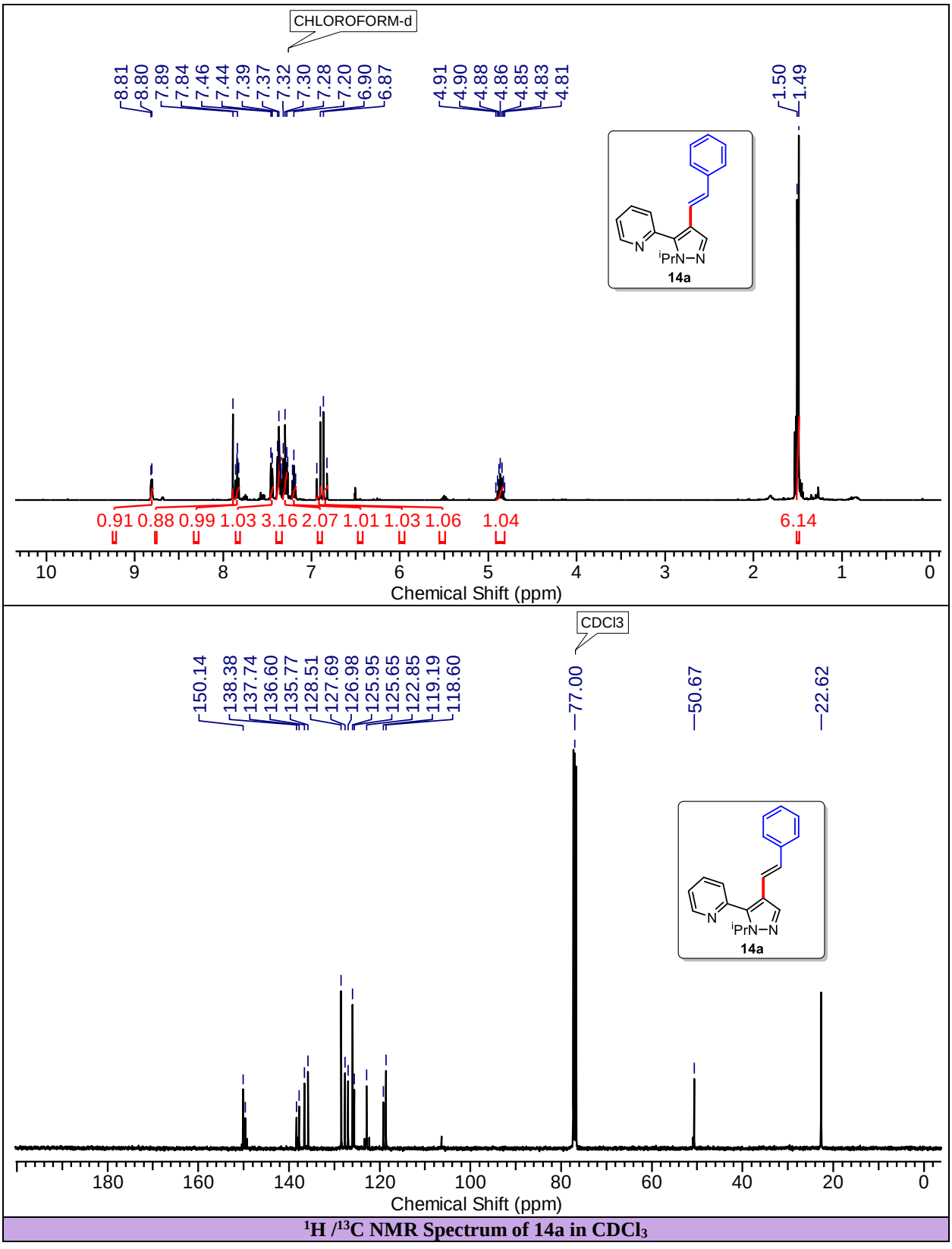
(E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylamide (23i): Purified by column chromatography (80% EtOAc in petroleum ether, R_f = 0.5); yield: 25 mg (42%); yellowish solid; mp: 175–177 °C; IR(neat) ν_{max} 3300, 2925, 1640, 1459, 1391, 1238, 1078, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.90 (br. s., 1 H), 10.25 (s, 1H), 8.76 (dd, J = 1.4, 4.8 Hz, 1H), 7.99 (dd, J = 1.1 Hz, 7.9 Hz, 1H), 7.82 (s, 1H), 7.49 (dd, J = 4.8, 8.0 Hz, 1H), 7.30 (t, J = 8.4 Hz, 1H), 7.13 (d, J = 15.5 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 6.17–6.09 (m, J = 15.4 Hz, 2H), 4.93 (d, J = 12.3 Hz, 1H), 4.80 (d, J = 12.3 Hz, 1 H), 4.21 (spt, J = 6.6 Hz, 1H), 1.98 (br. s., 2H), 1.47 (d, J = 6.6 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8 (d), 168.5 (s), 163.8 (s), 160.6 (s), 150.2 (d), 147.1 (s), 138.5 (d), 138.5 (s), 137.1 (d, 2C), 132.5 (s), 131.8 (d), 124.7 (d), 118.1 (d), 117.3 (s), 110.9 (d), 110.7 (s), 101.8 (d), 66.7 (t), 51.5 (d), 22.7 (q), 22.4 (q) ppm; HRMS (ESI): calcd. for $C_{22}H_{23}O_4N_4$: 407.1714 $[M+H]^+$; found: 407.1711.



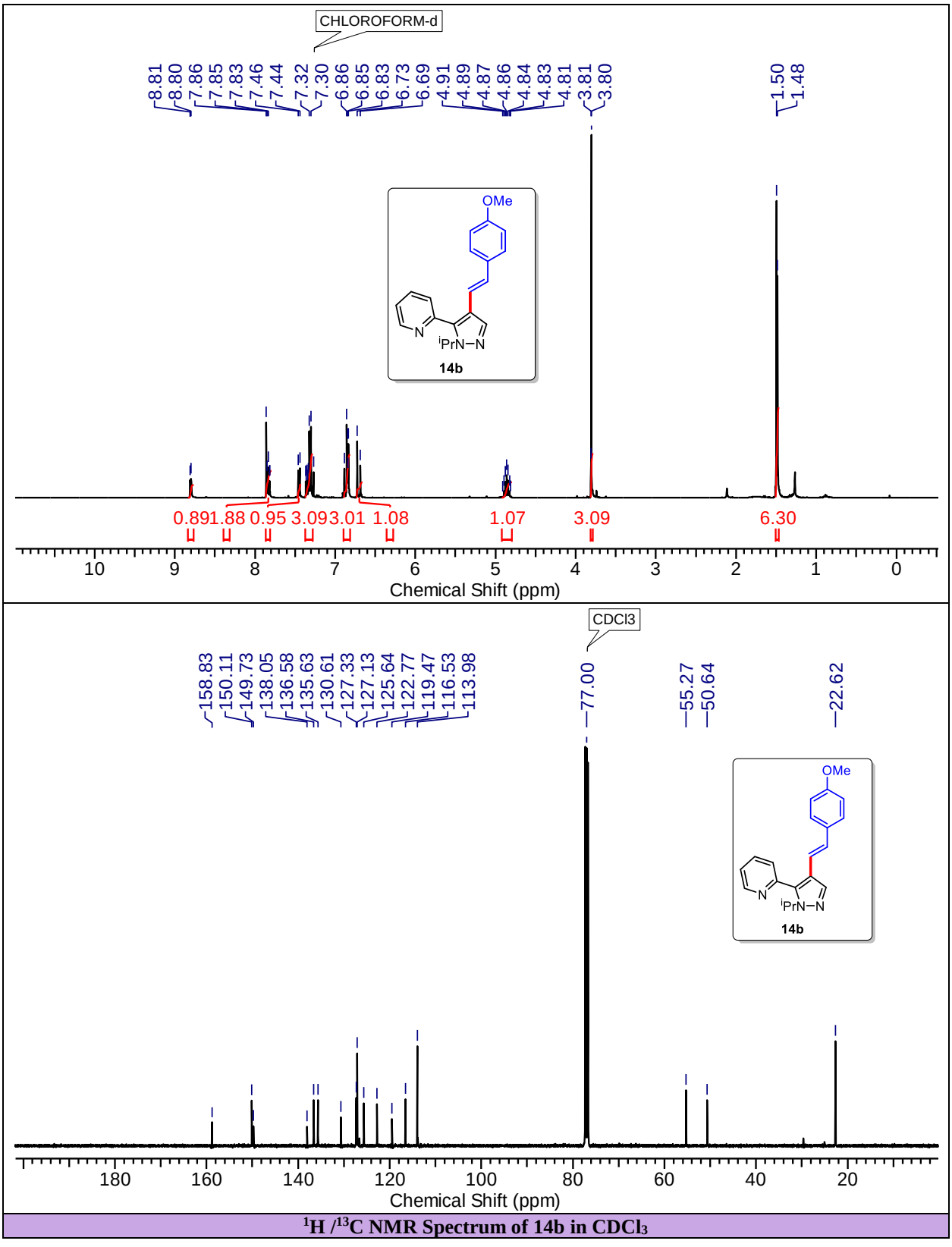
23i

(E)-3-(5-(3-((2-formyl-3-hydroxyphenoxy)methyl)pyridin-2-yl)-1-isopropyl-1*H*-pyrazol-4-yl)acrylonitrile (23j): Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 35 mg (60%); yellowish gum; IR(neat) ν_{max} 2925, 2213, 1618, 1577, 1457, 1401, 1313, 1236, 1076, 965, 783, 716, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 11.90 (d, J = 9.9 Hz, 1H), 10.31 (d, J = 5.3 Hz, 1H), 8.83 (t, J = 5.0 Hz, 1H), 8.06 (ddd, J = 1.5, 3.4, 8.0 Hz, 1H), 7.84 (s, 1H), 7.61–7.53 (m, 1H), 7.41–7.34 (m, 1H), 6.90 (d, J = 16.8 Hz, 1H), 6.62–6.47 (m, J = 14.5 Hz, 1H), 6.19 (t, J = 8.4 Hz, 1H), 5.40 (d, J = 16.8 Hz, 1H), 4.99–4.75 (m, J =12.2 Hz, 2H), 4.29–4.16 (spt, J = 6.9 Hz, 1H), 1.50–1.45 (t, J = 6.9 Hz, 3H), 1.40 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5 (d), 163.9 (s), 160.5 (s), 150.7–150.5 (d), 146.7 (s), 140.2 (d), 139.7 (s), 138.7–138.5 (d), 138.1–138.0 (d), 137.3–137.1 (d), 132.7–132.5 (s), 125.1–124.9 (d), 118.5–118.0 (s), 116.8 (s), 111.3 (d), 110.8 (s), 101.8–101.7 (d), 94.0–92.4 (d), 66.7 (t), 52.0–51.9 (d), 22.9 (q), 22.4–22.3 (q) ppm; HRMS (ESI): calcd. for $C_{22}H_{21}O_3N_4$: 389.1608 $[M+H]^+$; found: 389.1610.

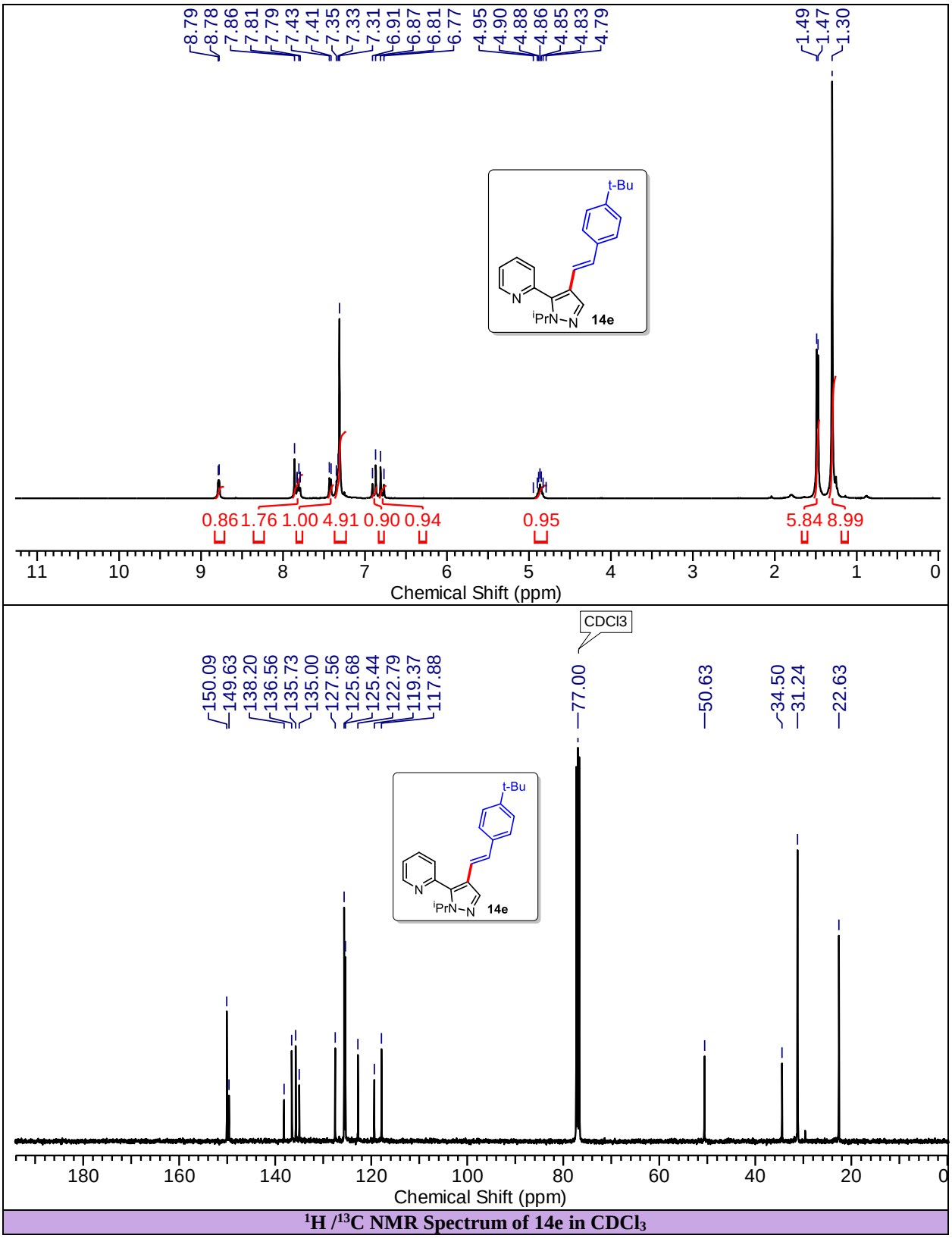




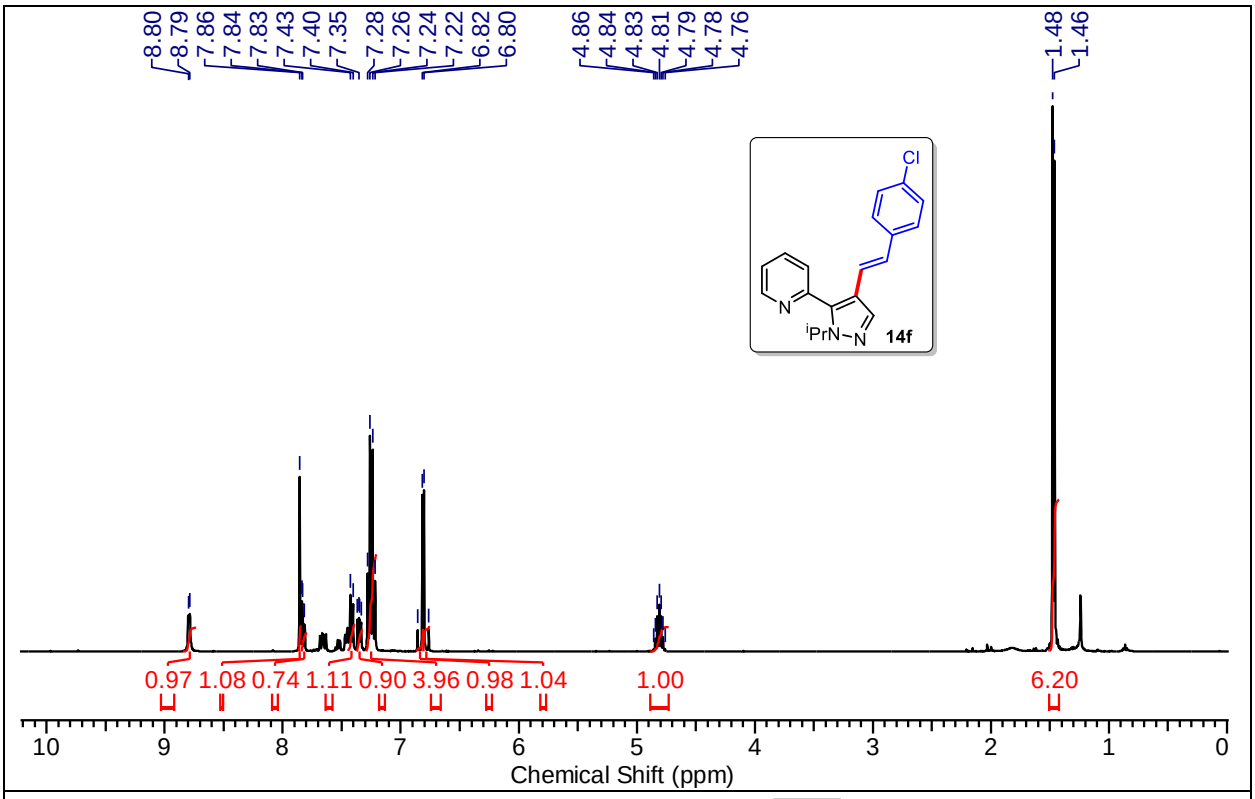
^{1}H /^{13}C NMR Spectrum of 14a in $CDCl_3$

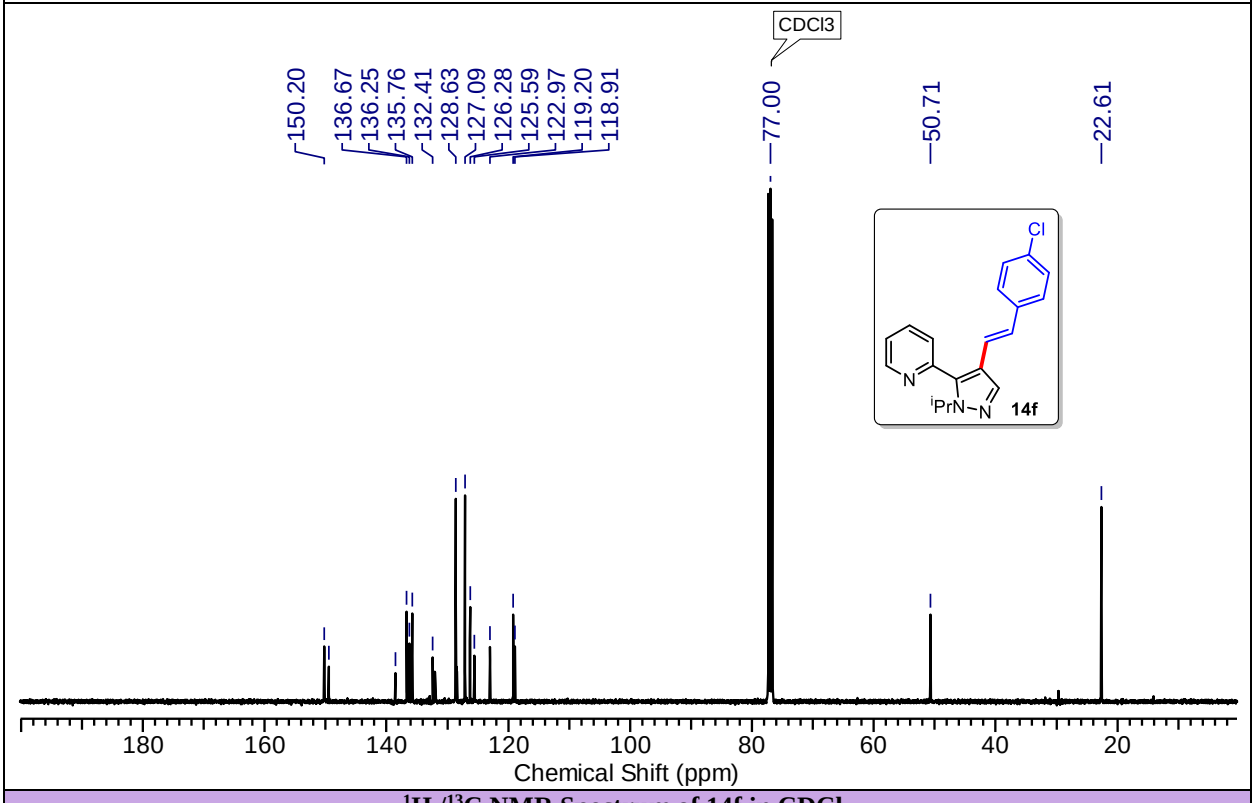


^{1}H /^{13}C NMR Spectrum of 14b in $CDCl_3$

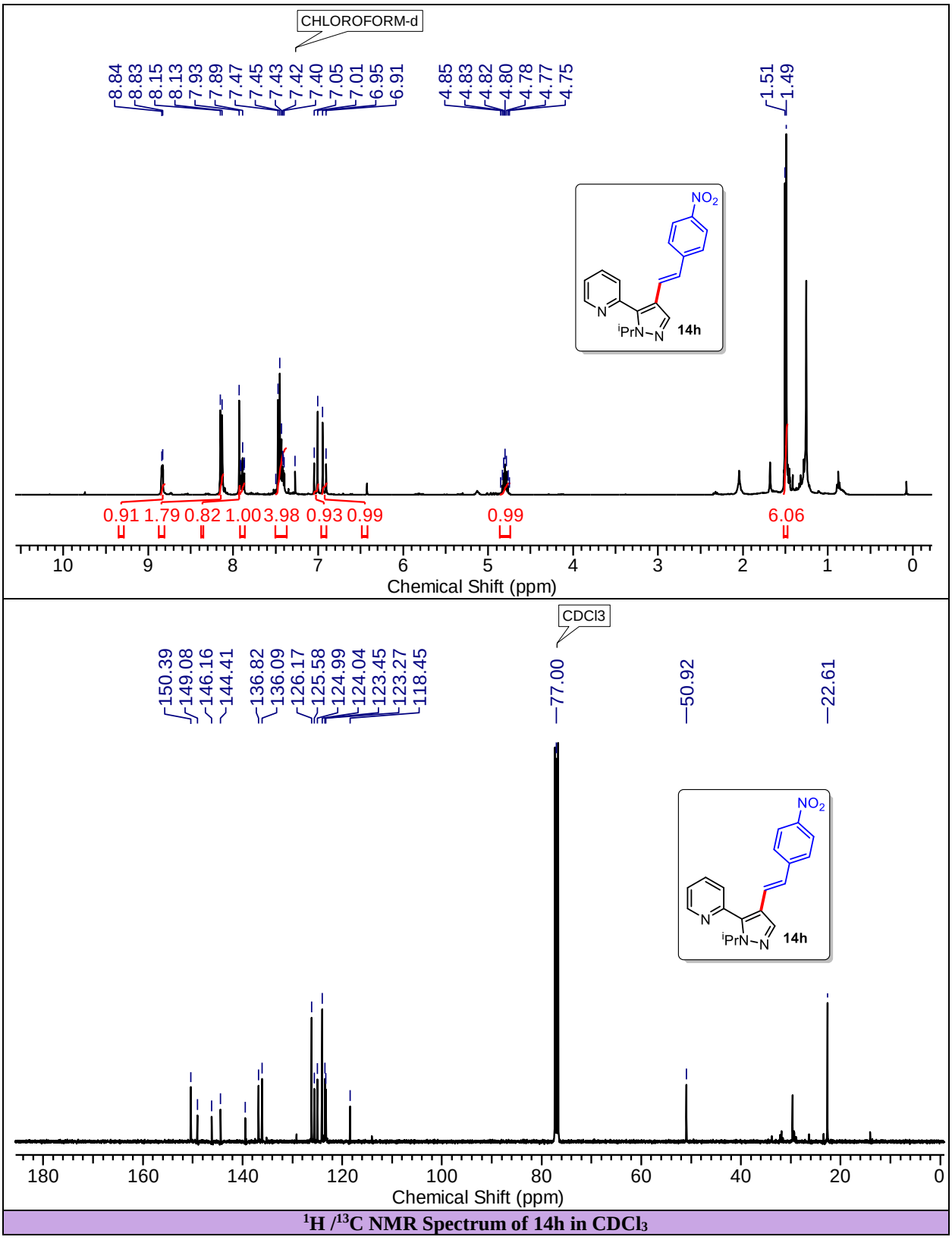


^{1}H /^{13}C NMR Spectrum of 14e in $CDCl_3$

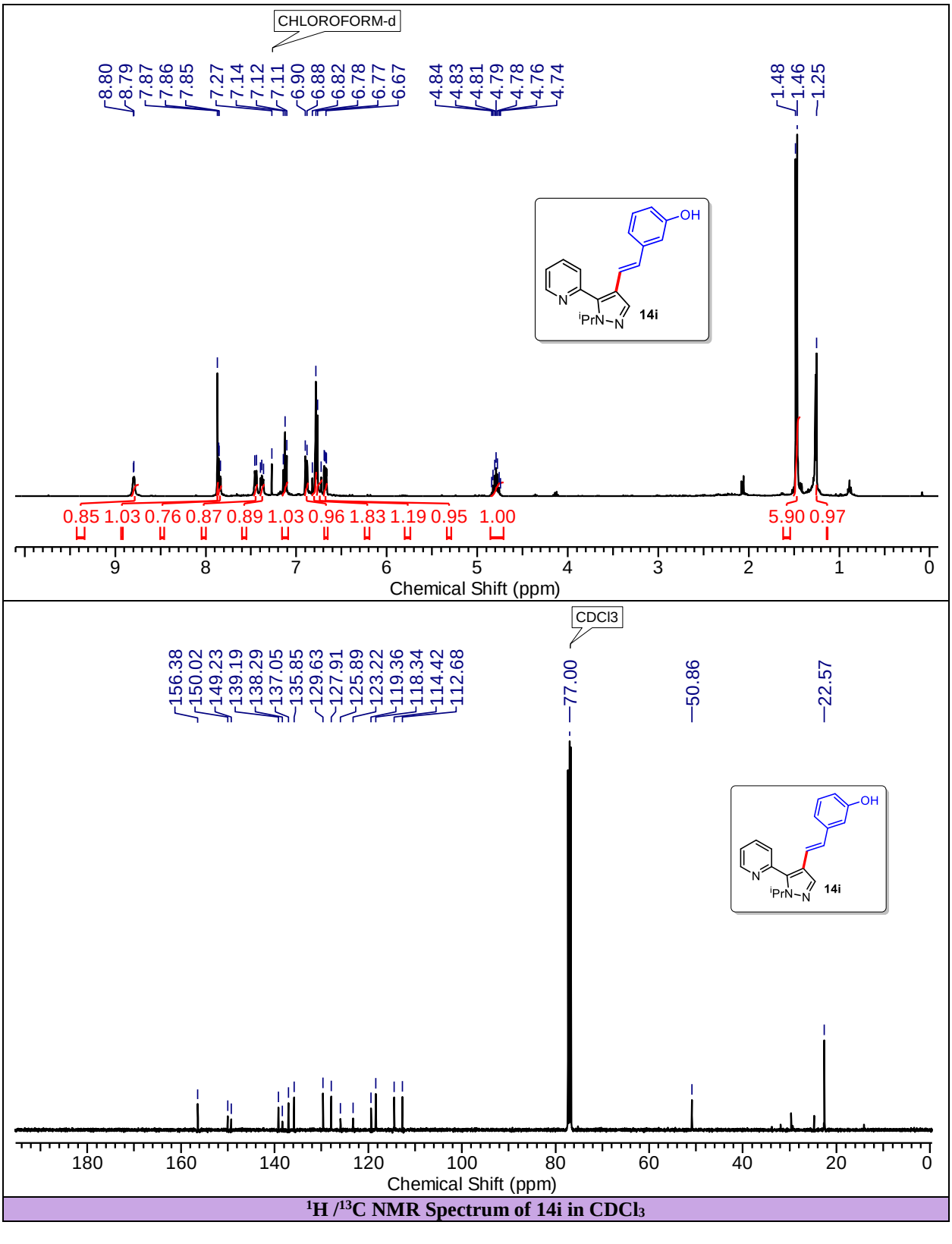




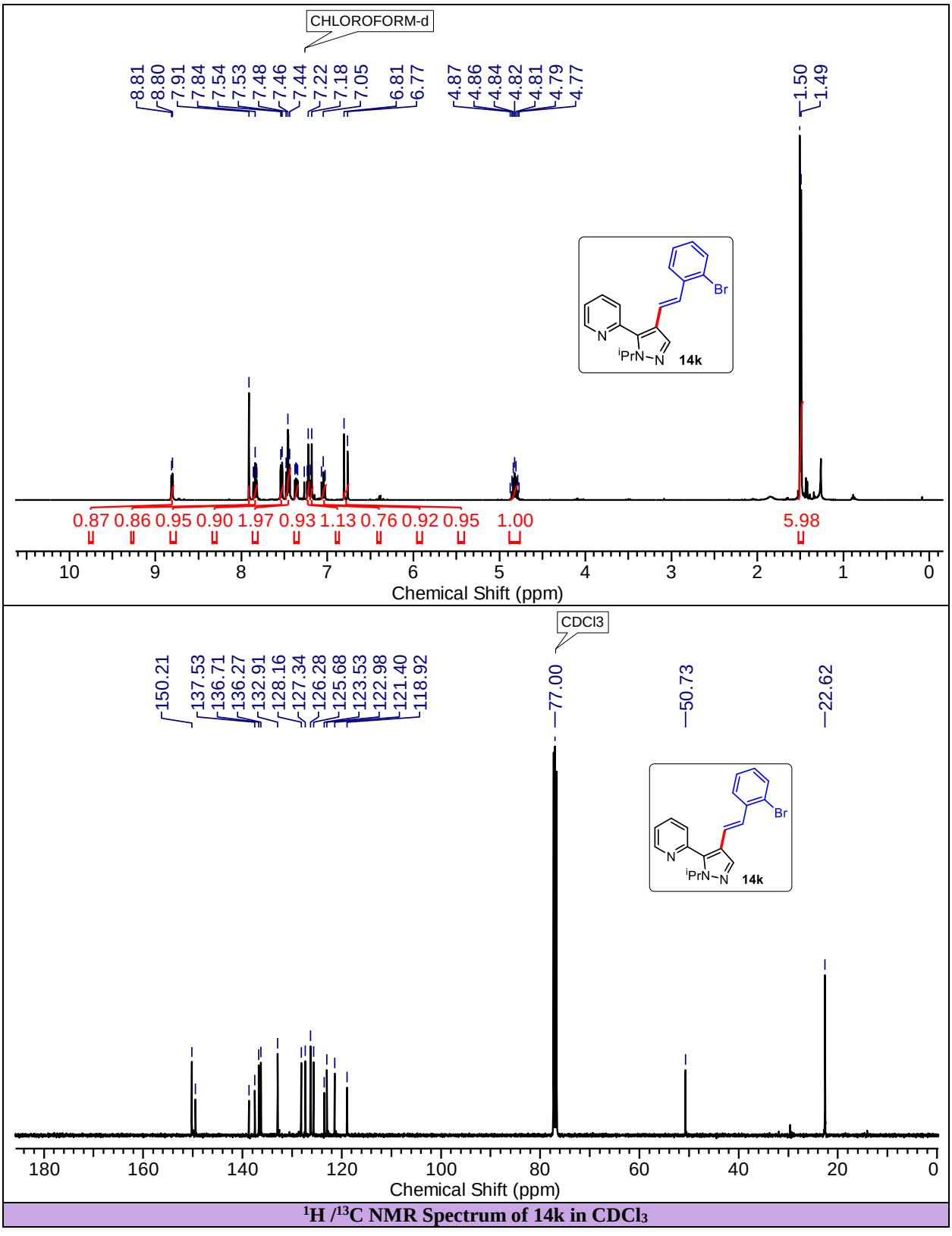
^{1}H /^{13}C NMR Spectrum of 14f in $CDCl_3$



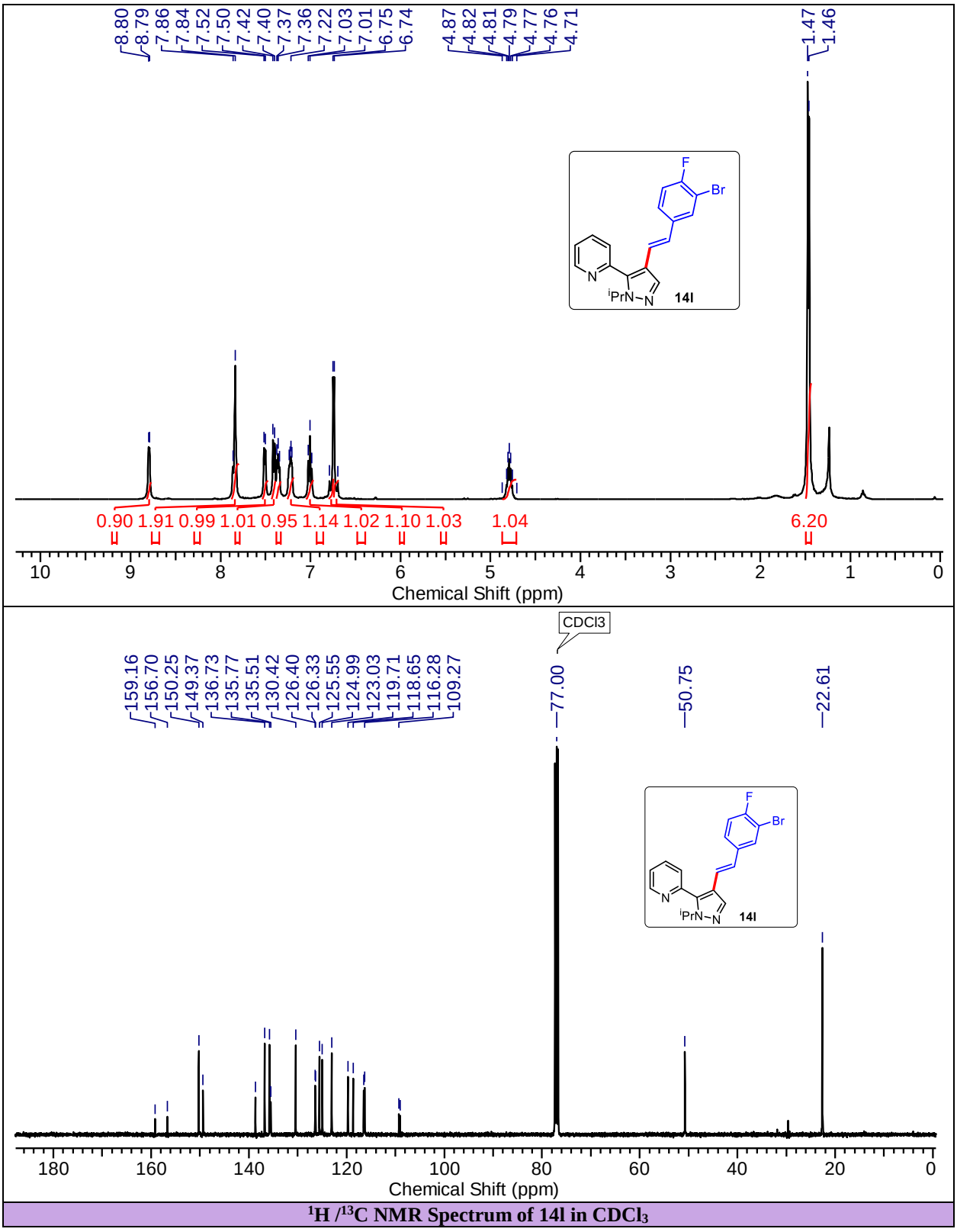
^{1}H /^{13}C NMR Spectrum of 14h in $CDCl_3$



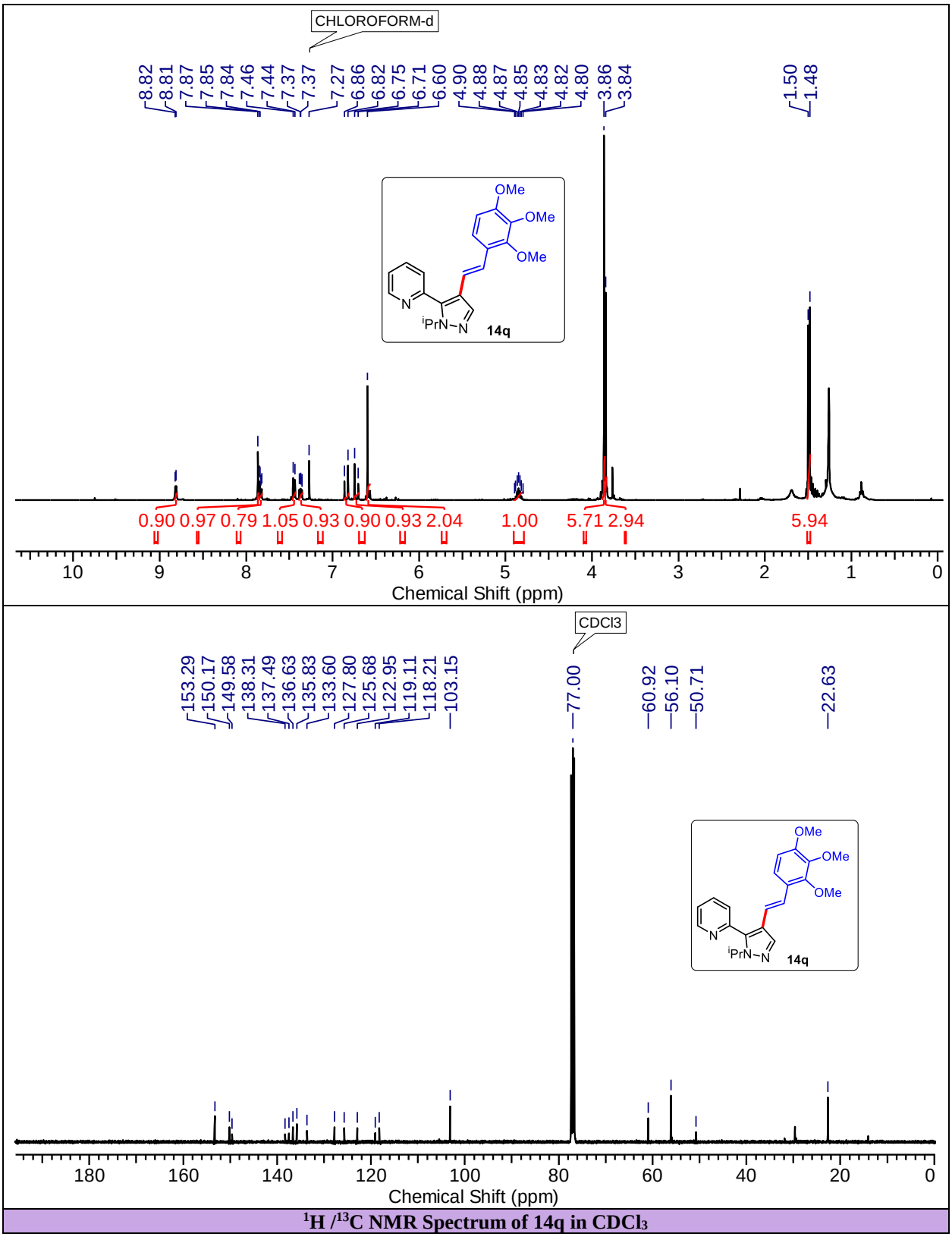
^{1}H /^{13}C NMR Spectrum of 14i in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 14k in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 14l in $CDCl_3$



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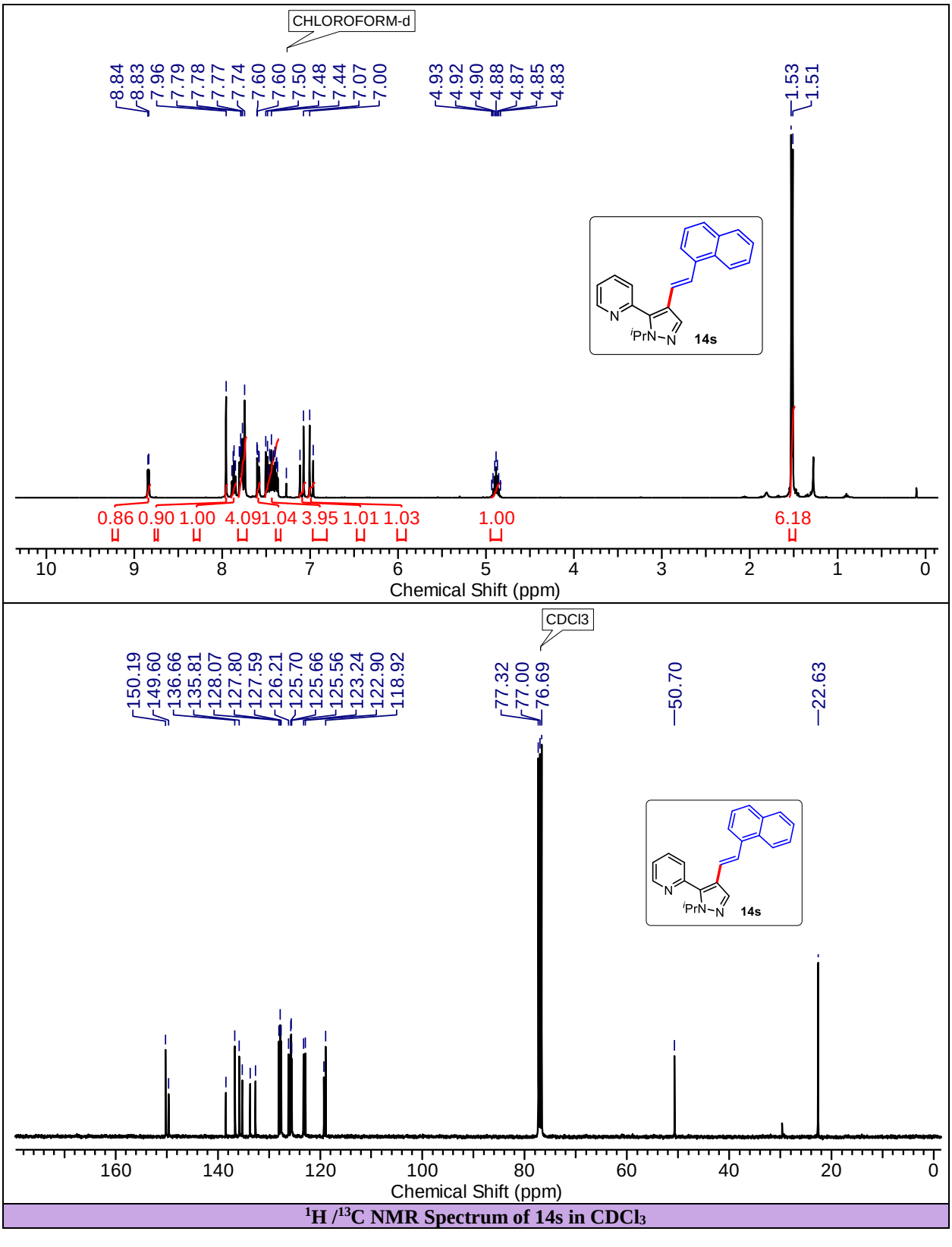

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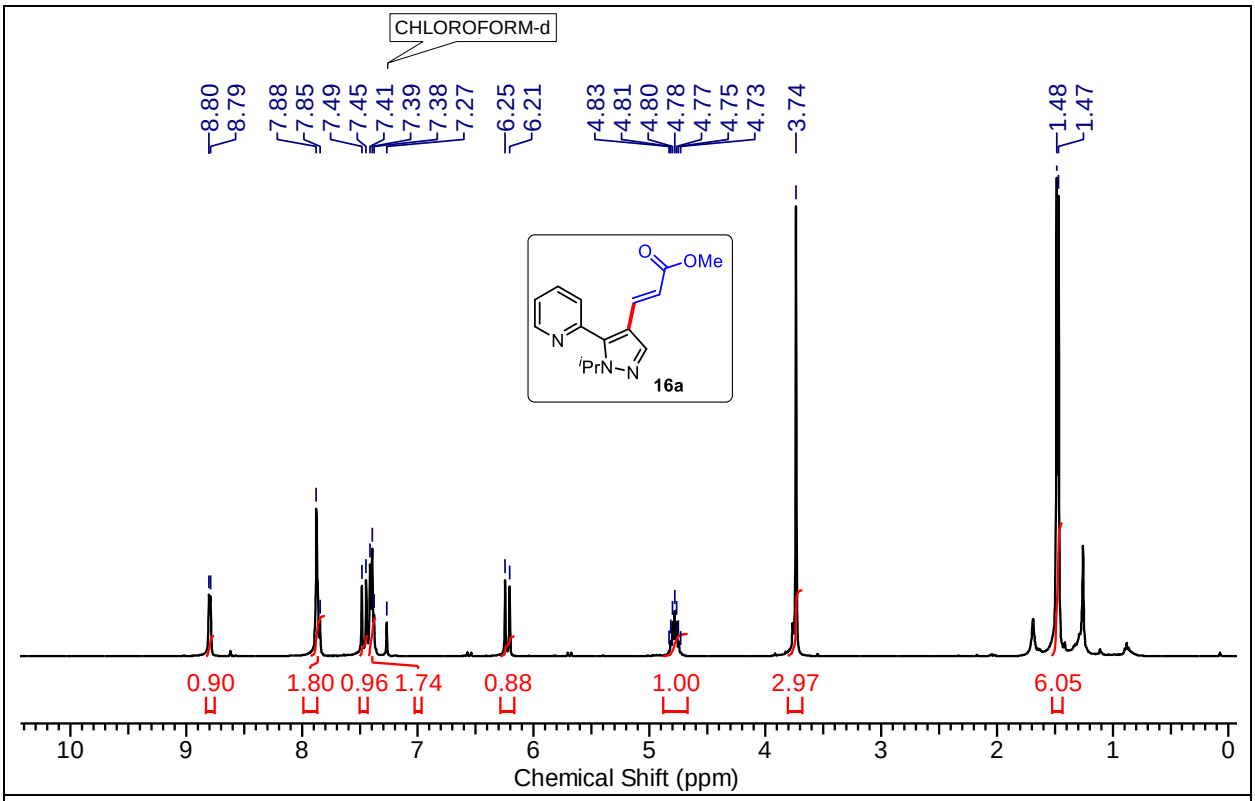
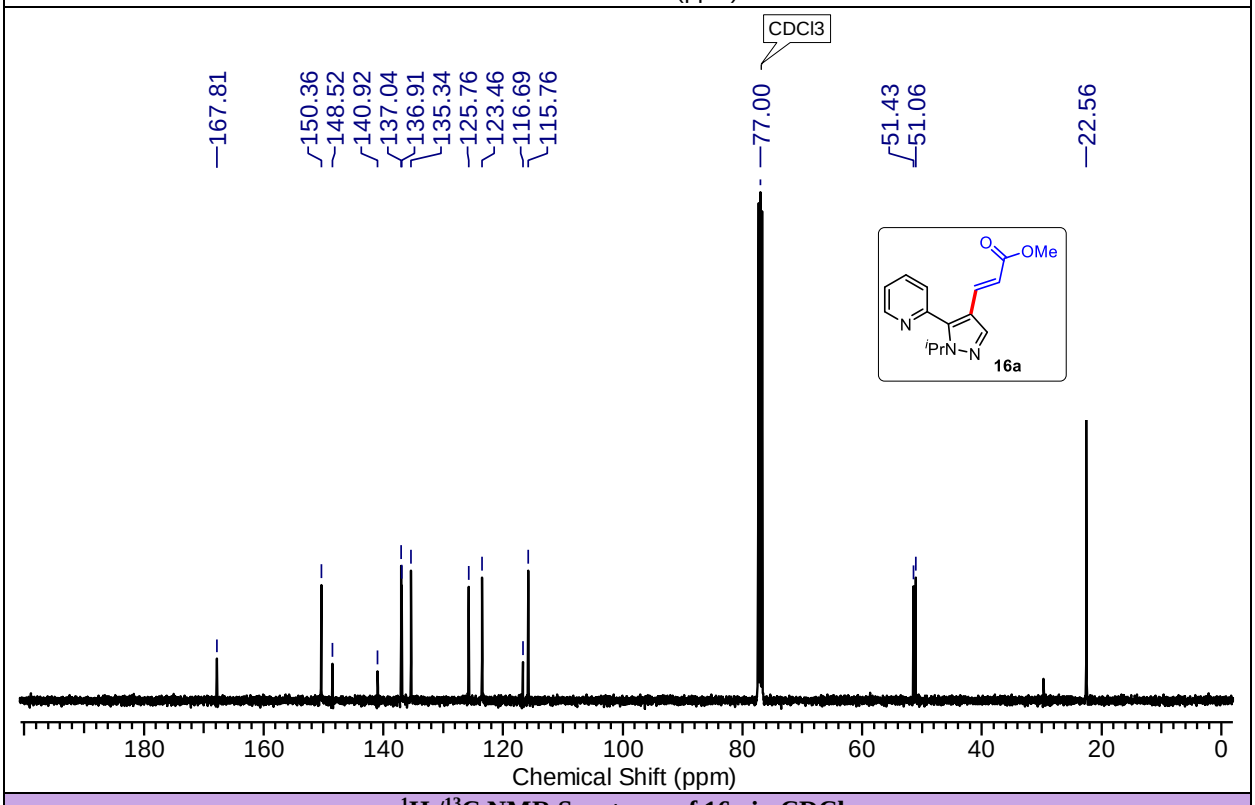
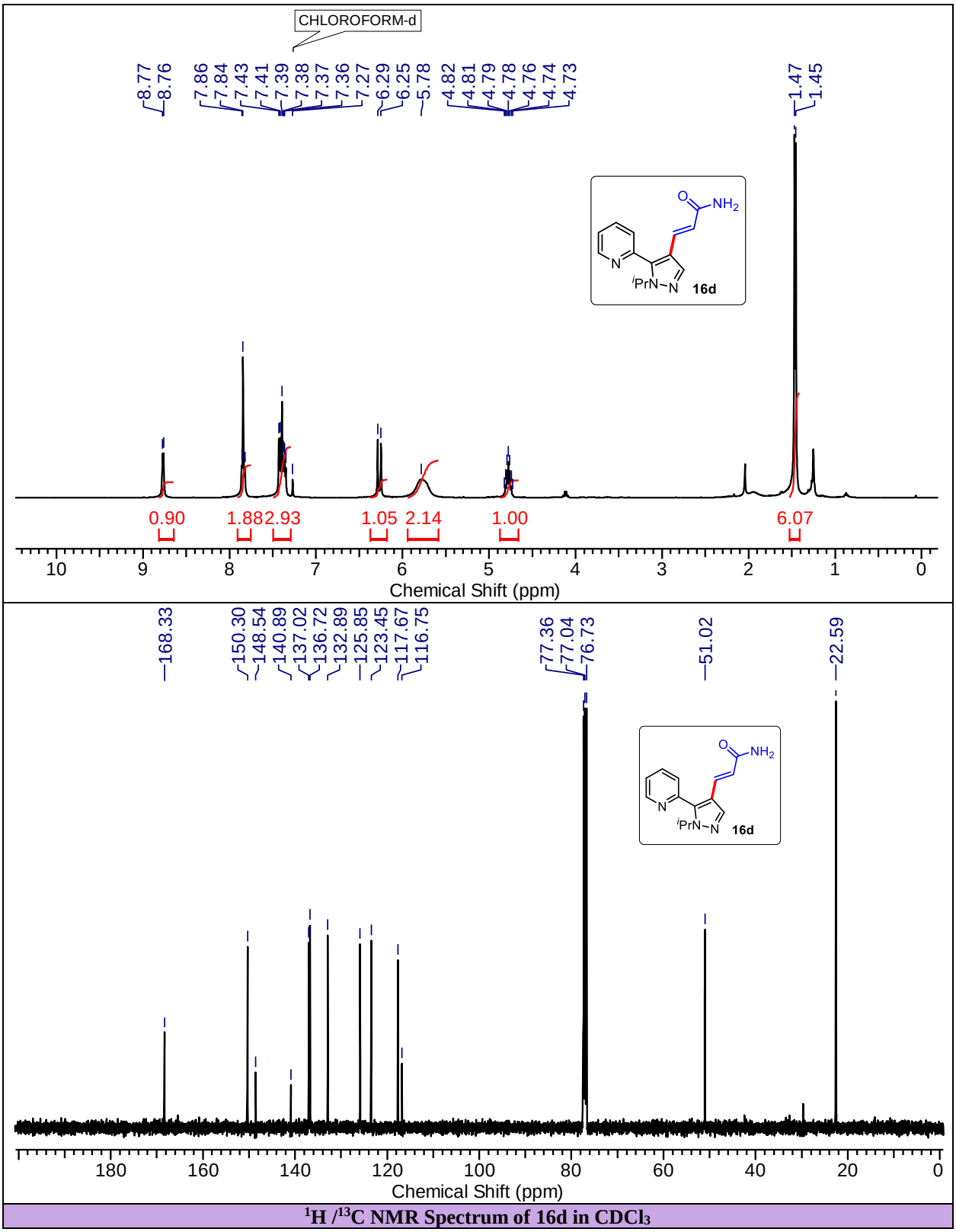




^{1}H /^{13}C NMR Spectrum of 16a in $CDCl_3$



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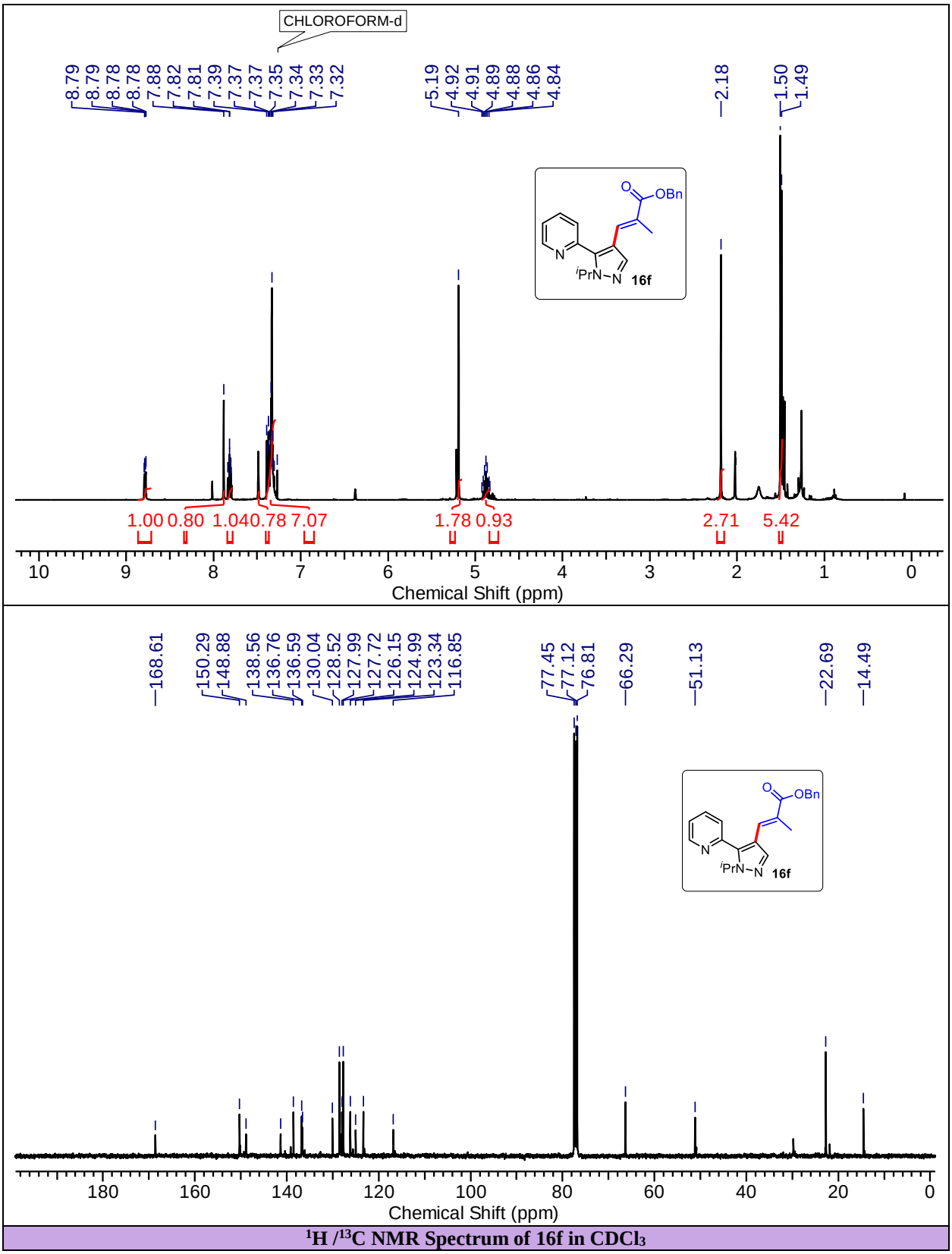
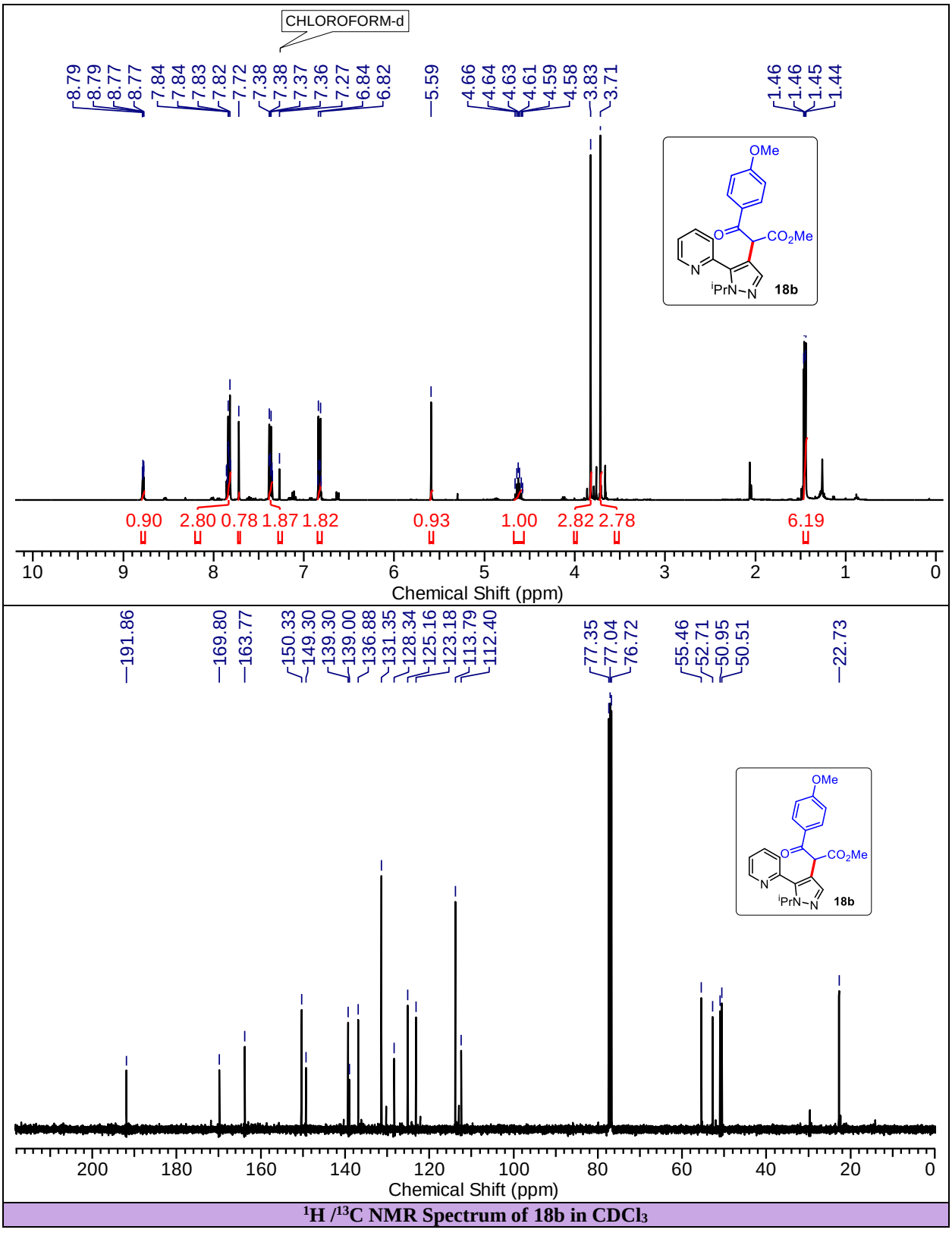


^{1}H /^{13}C NMR Spectrum of 16f in $CDCl_3$



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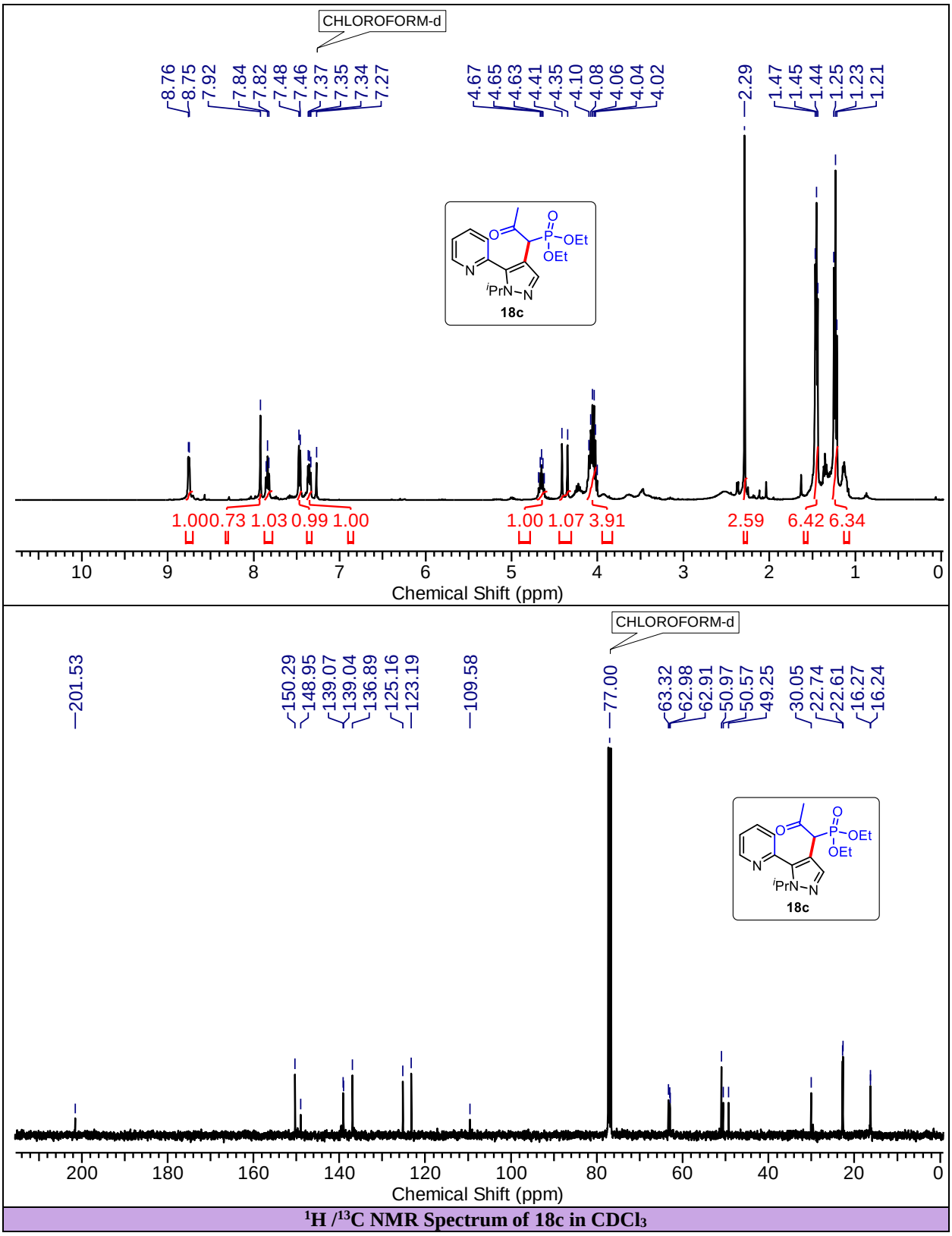

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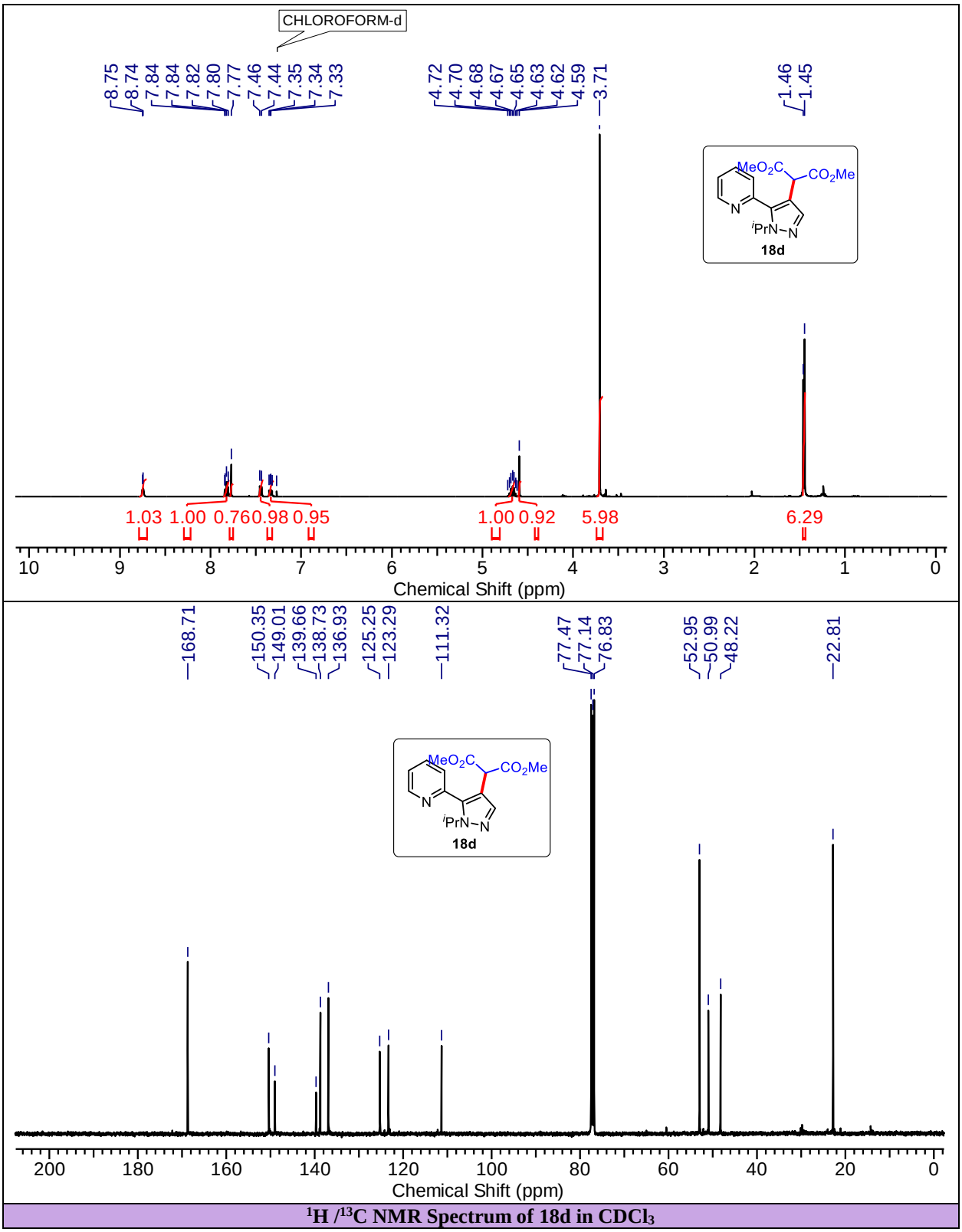

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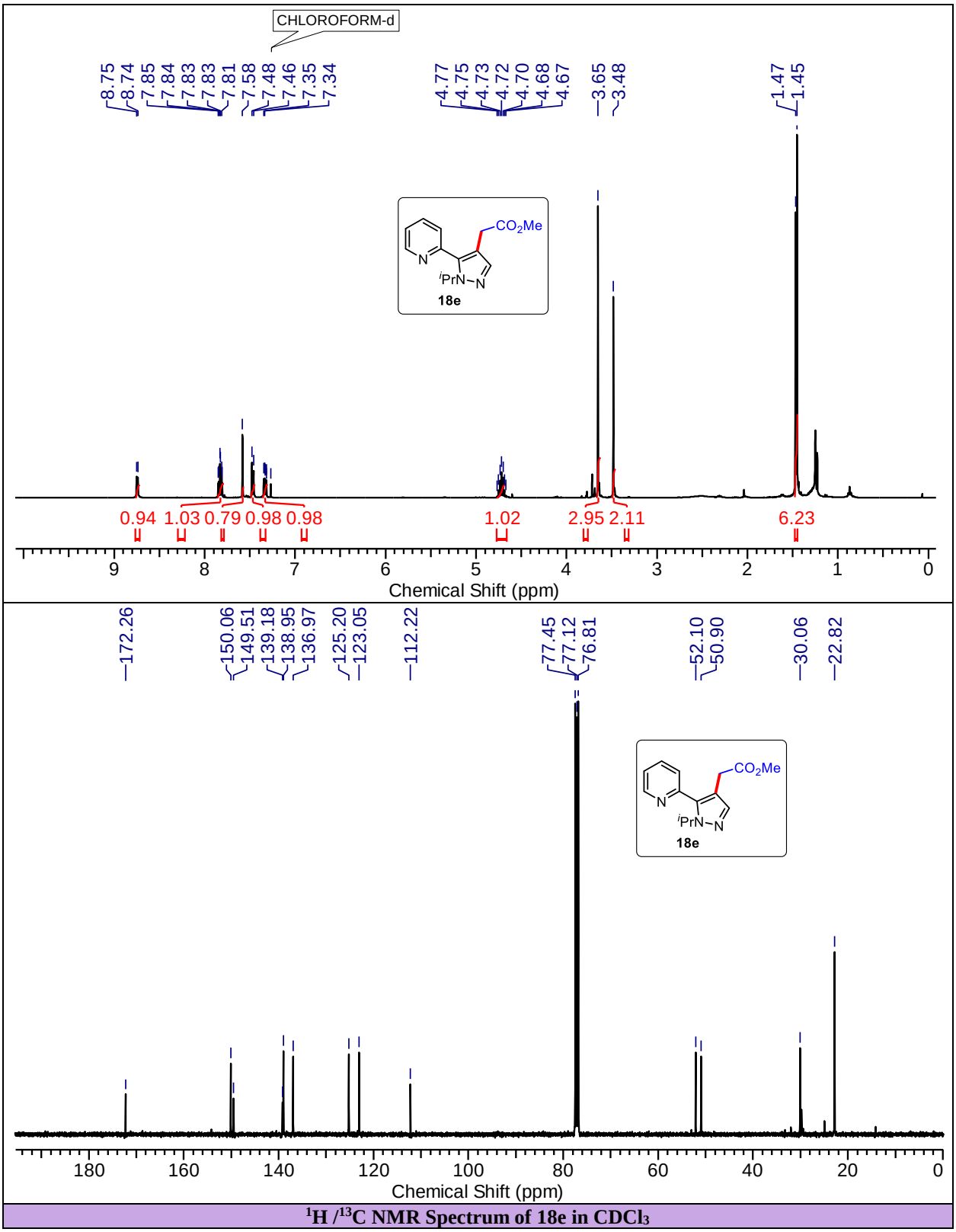

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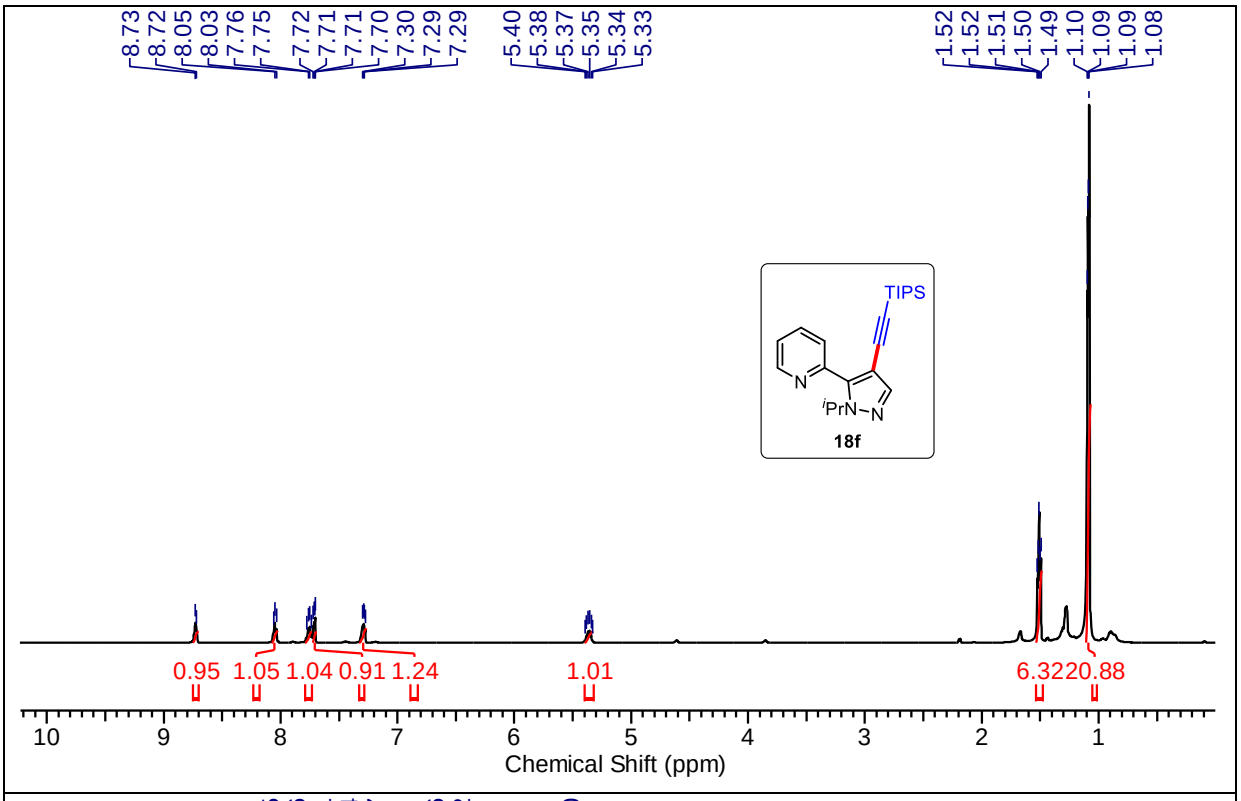
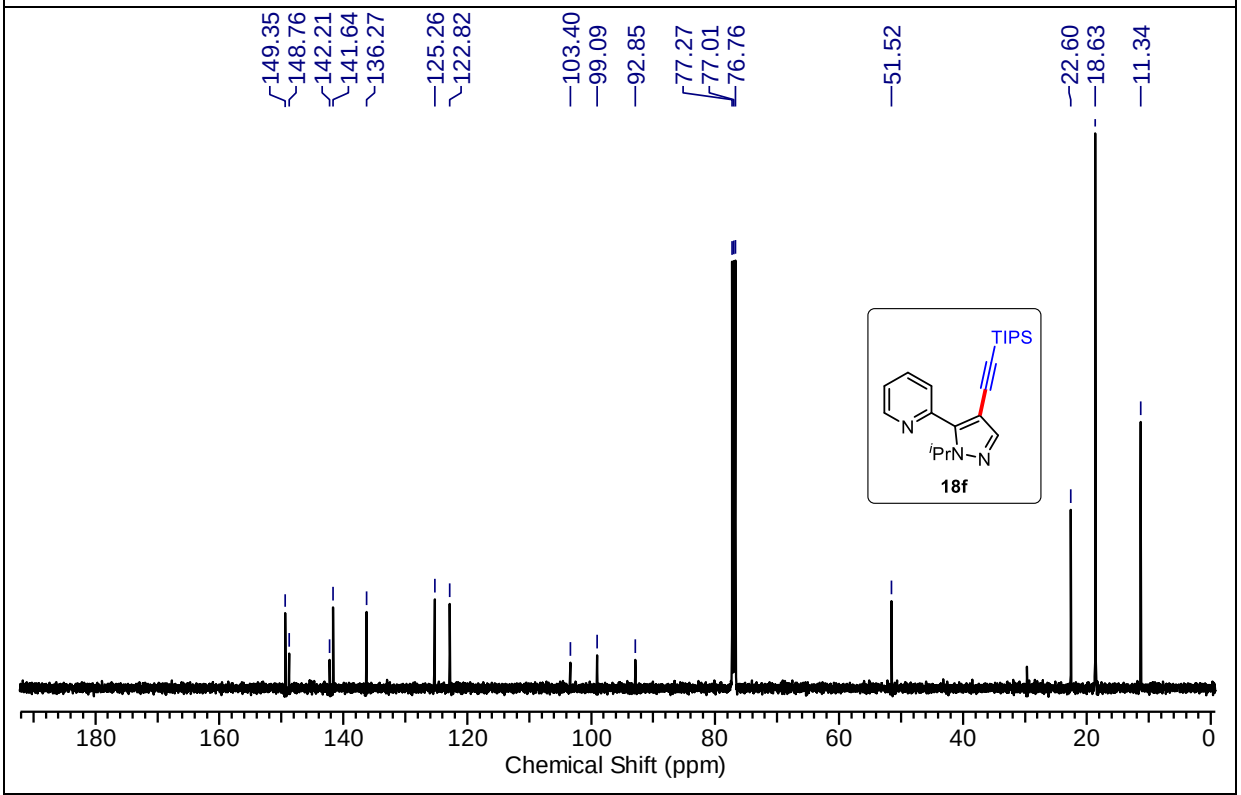
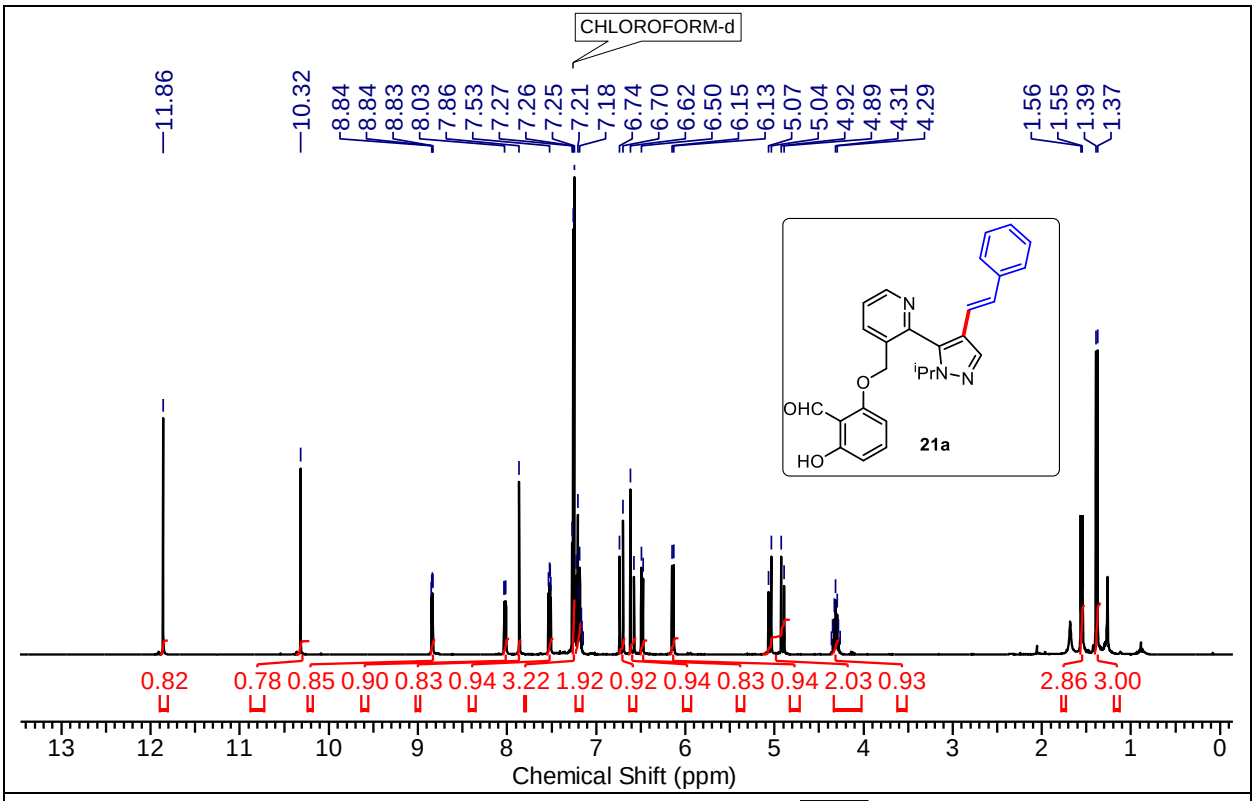
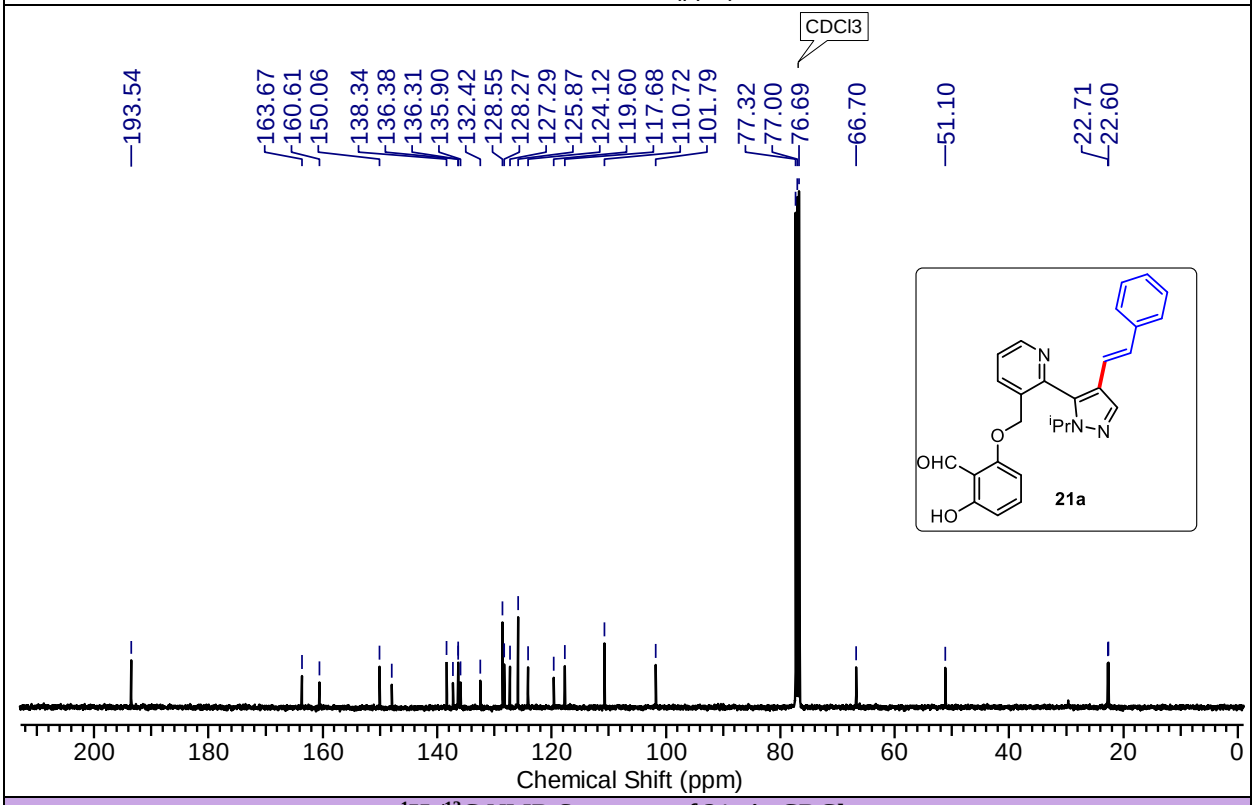




^{1}H /^{13}C NMR Spectrum of 18f in $CDCl_3$





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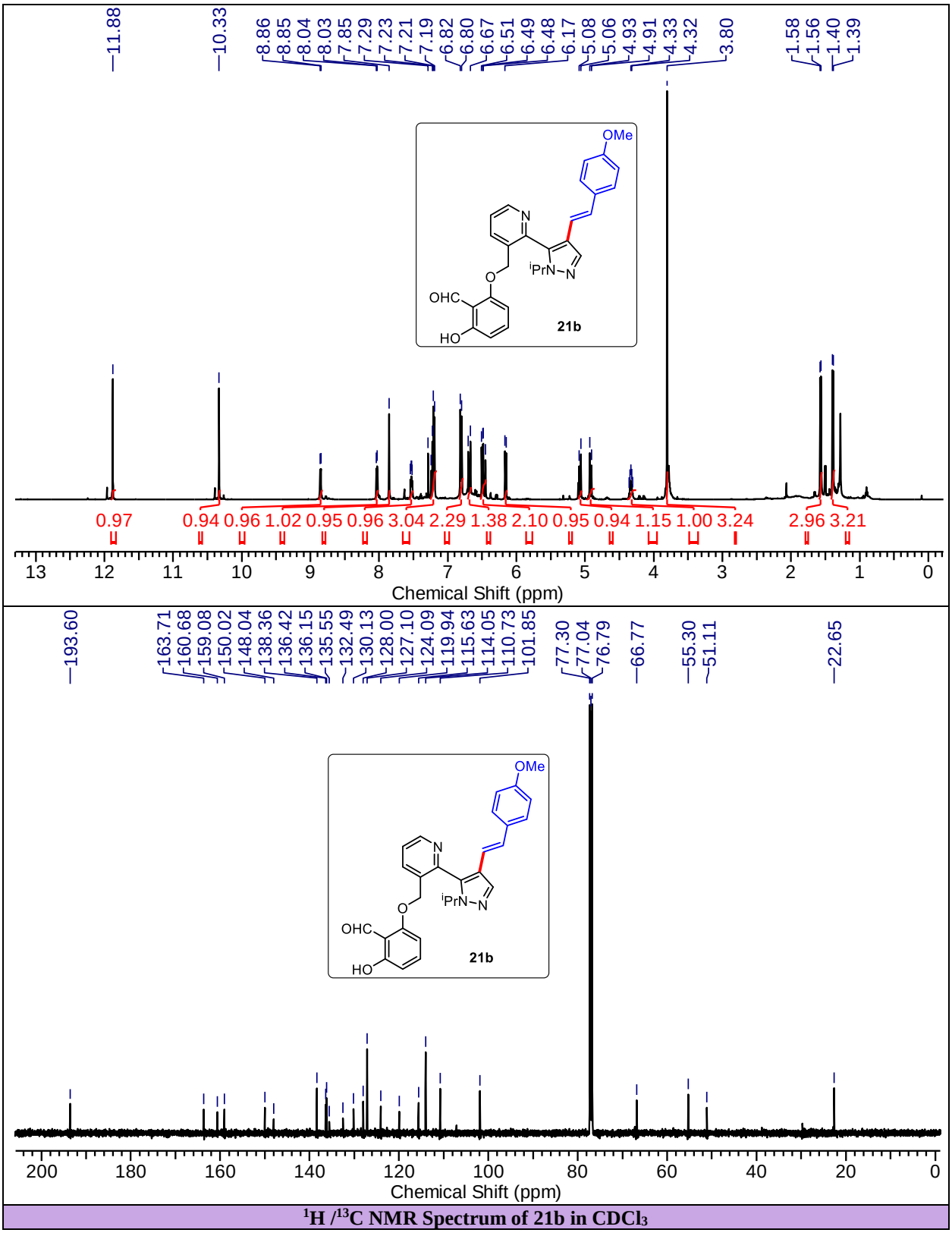

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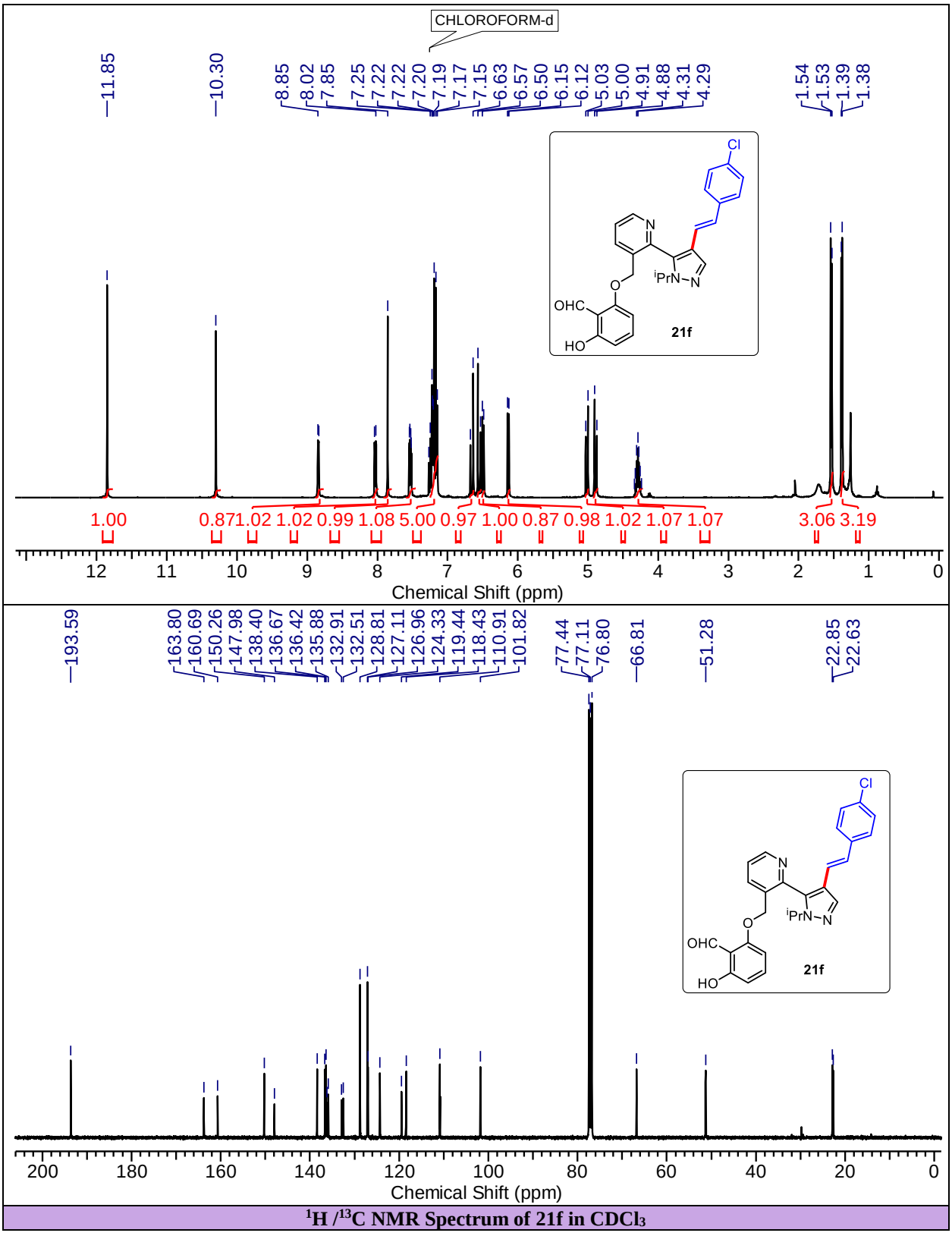

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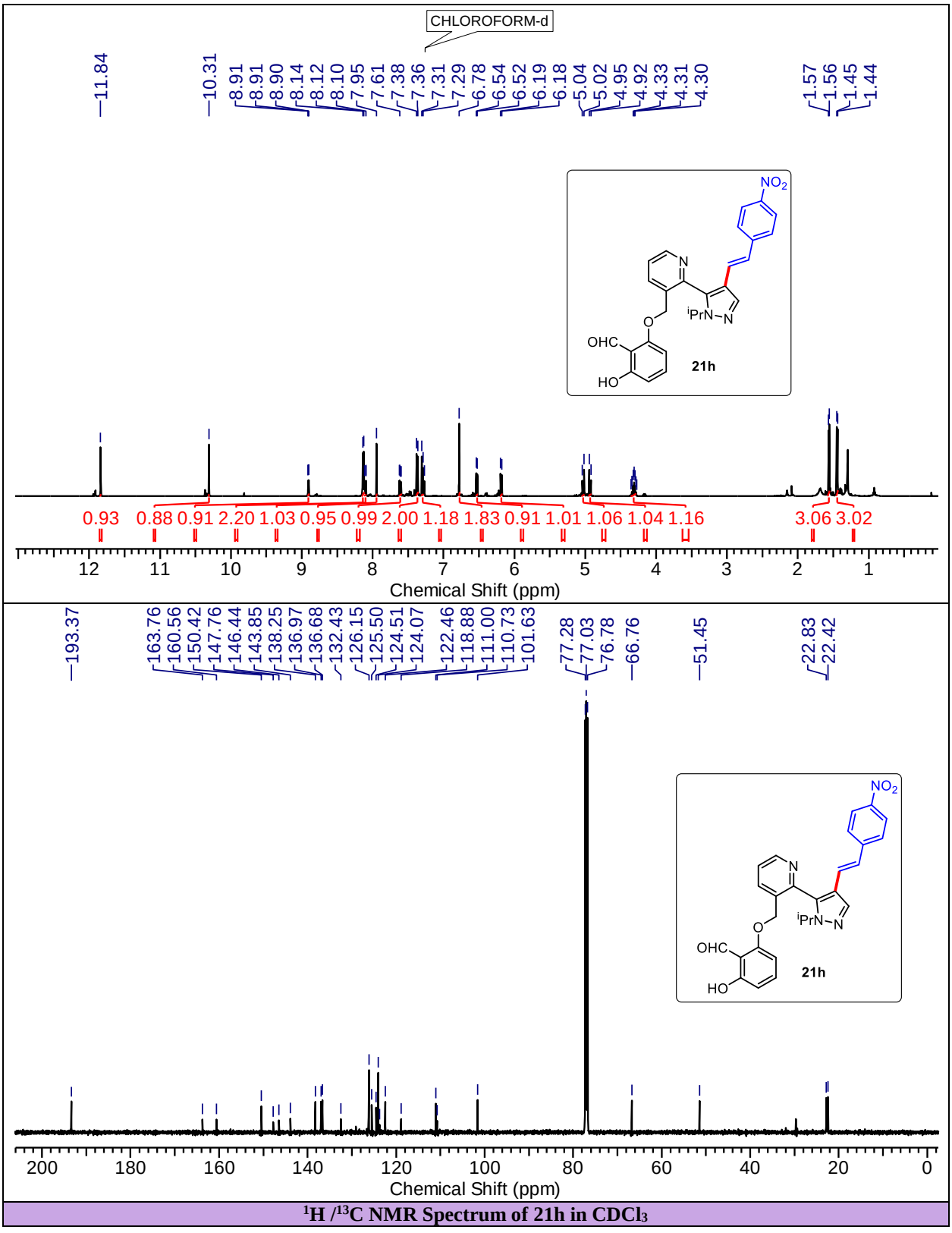
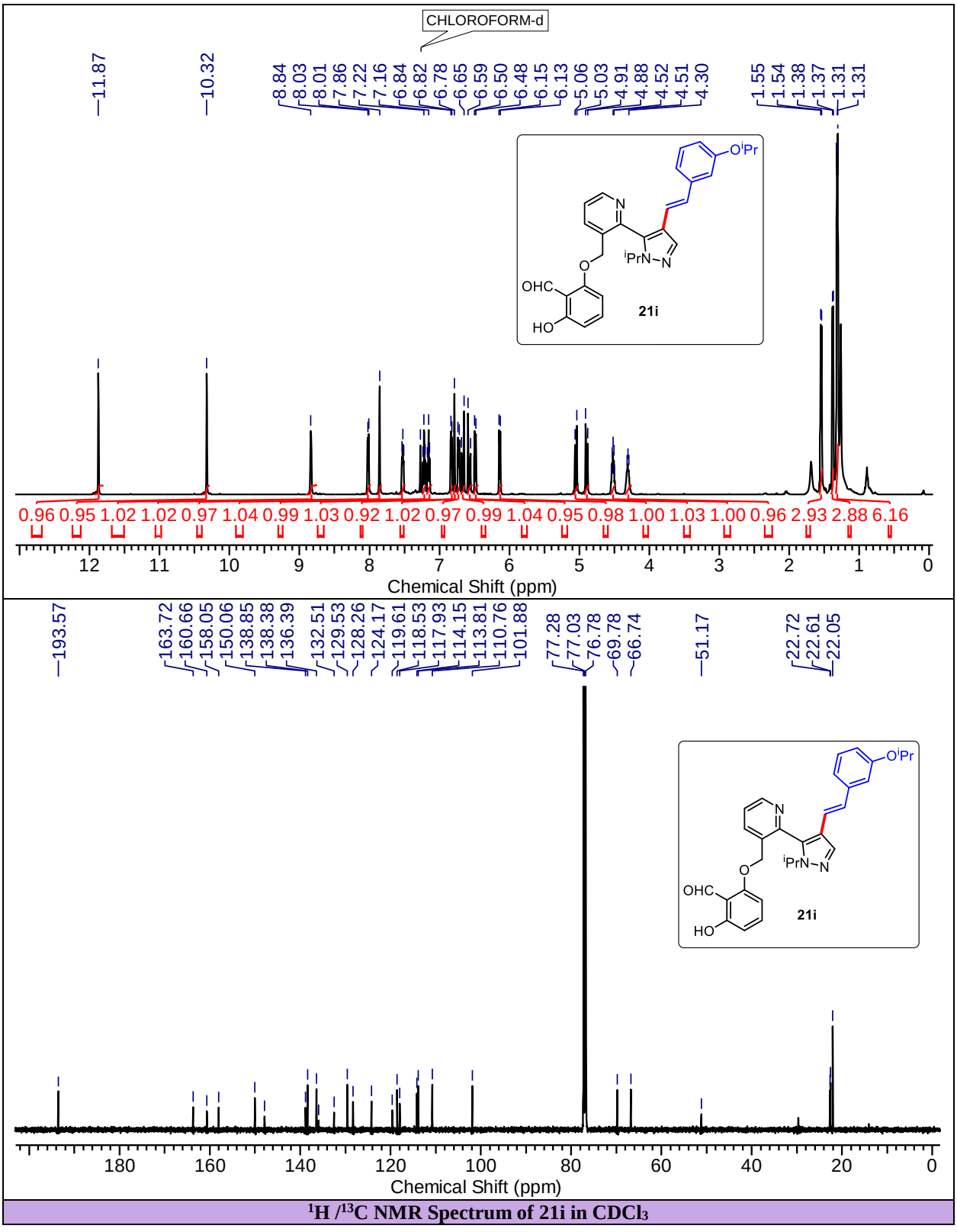
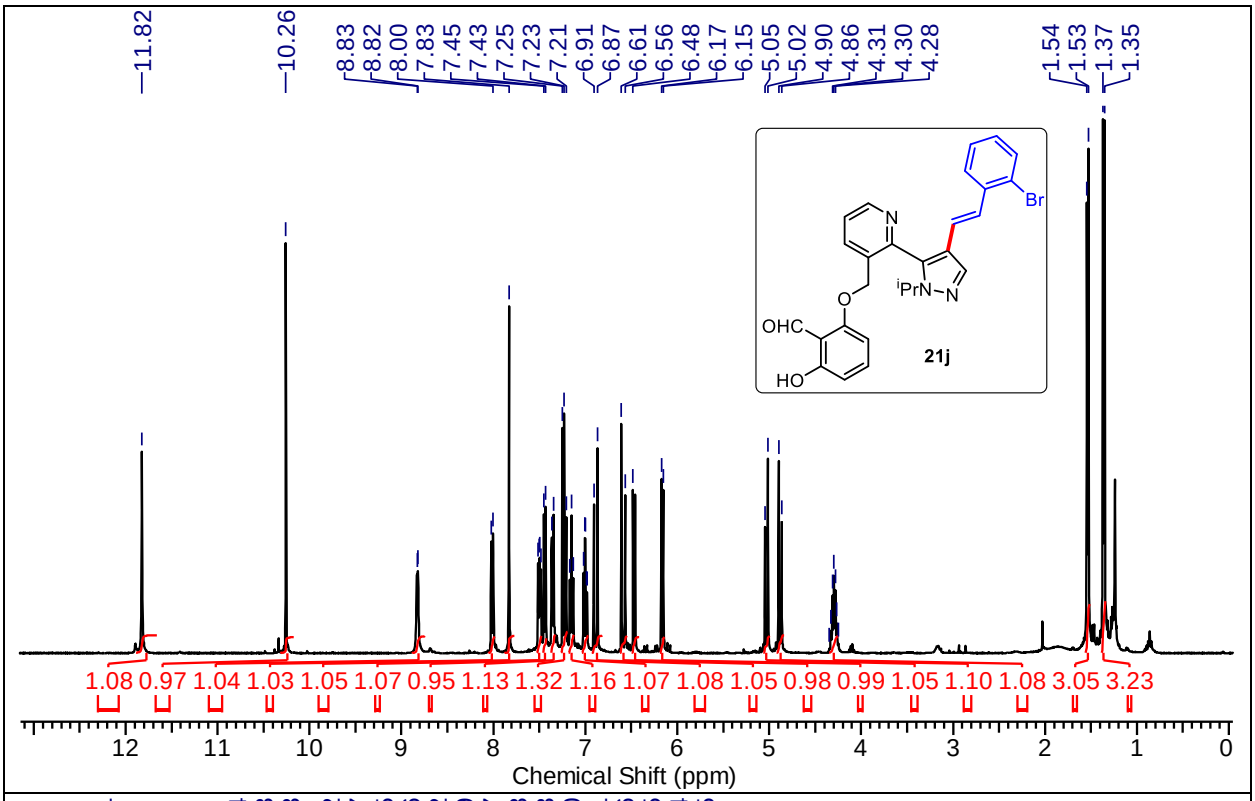
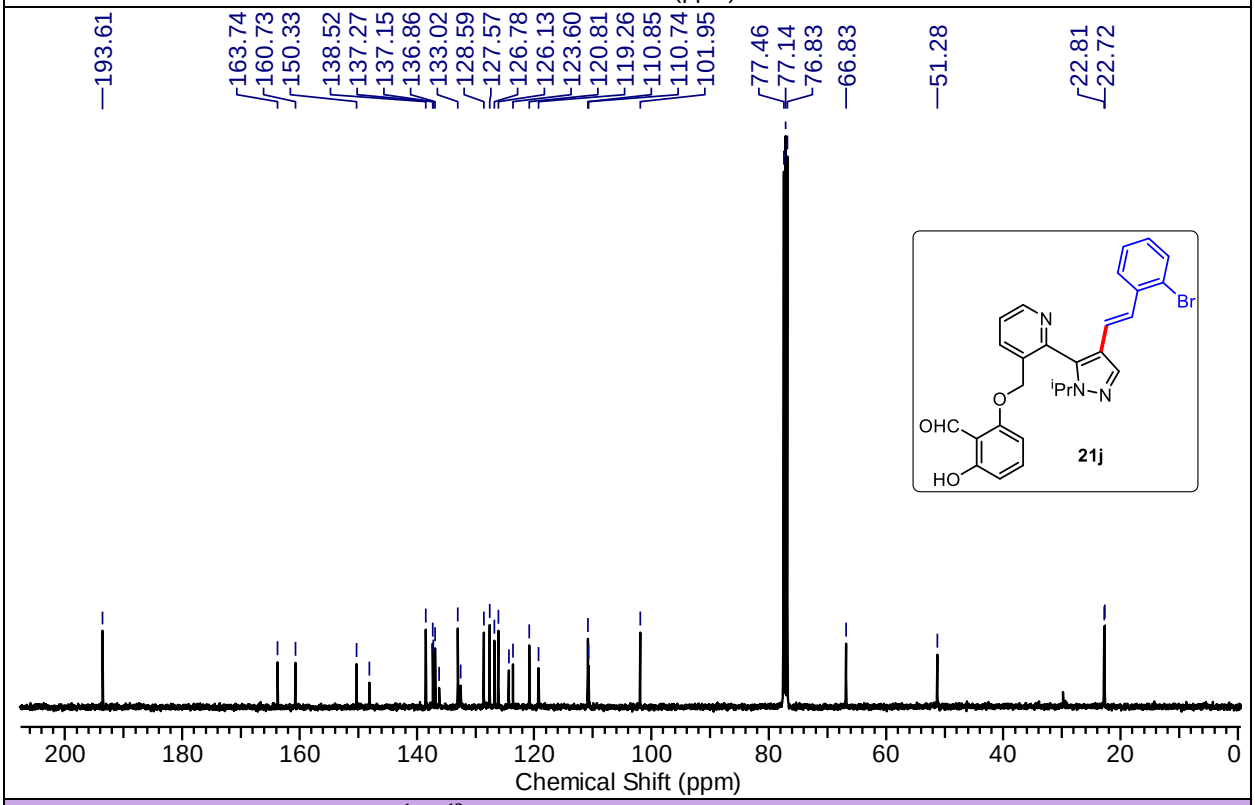


^{1}H /^{13}C NMR Spectrum of 21h in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 21i in $CDCl_3$





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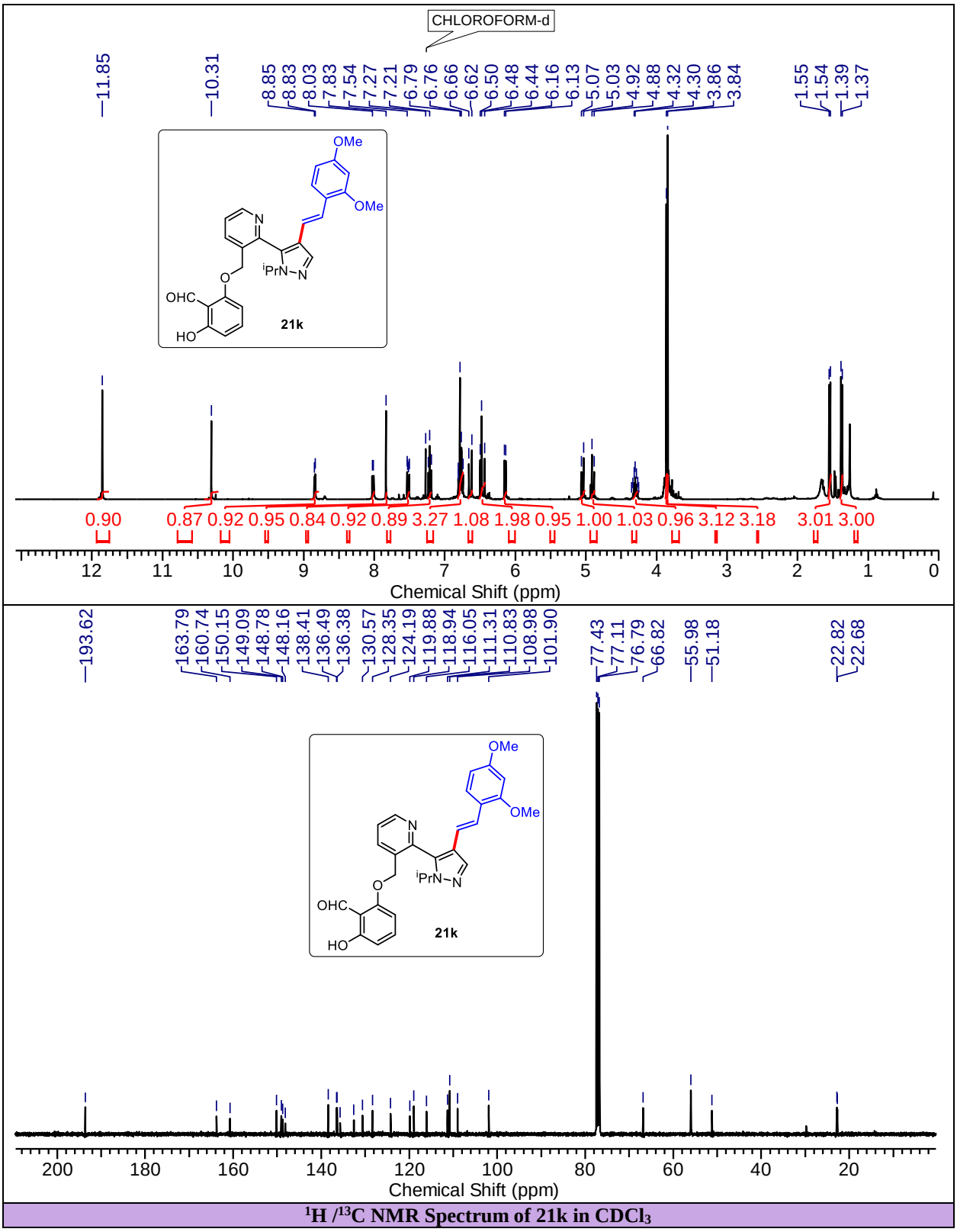
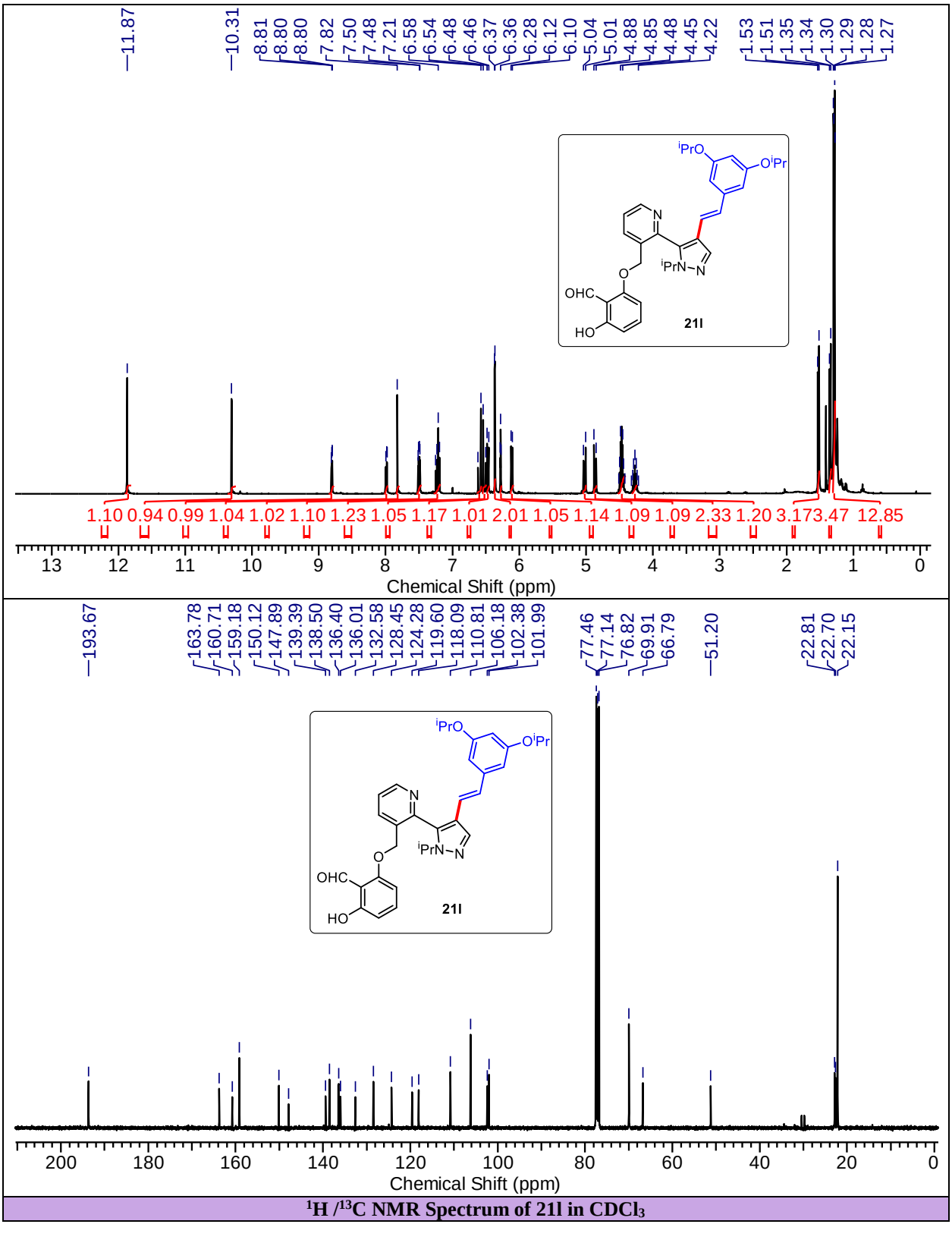
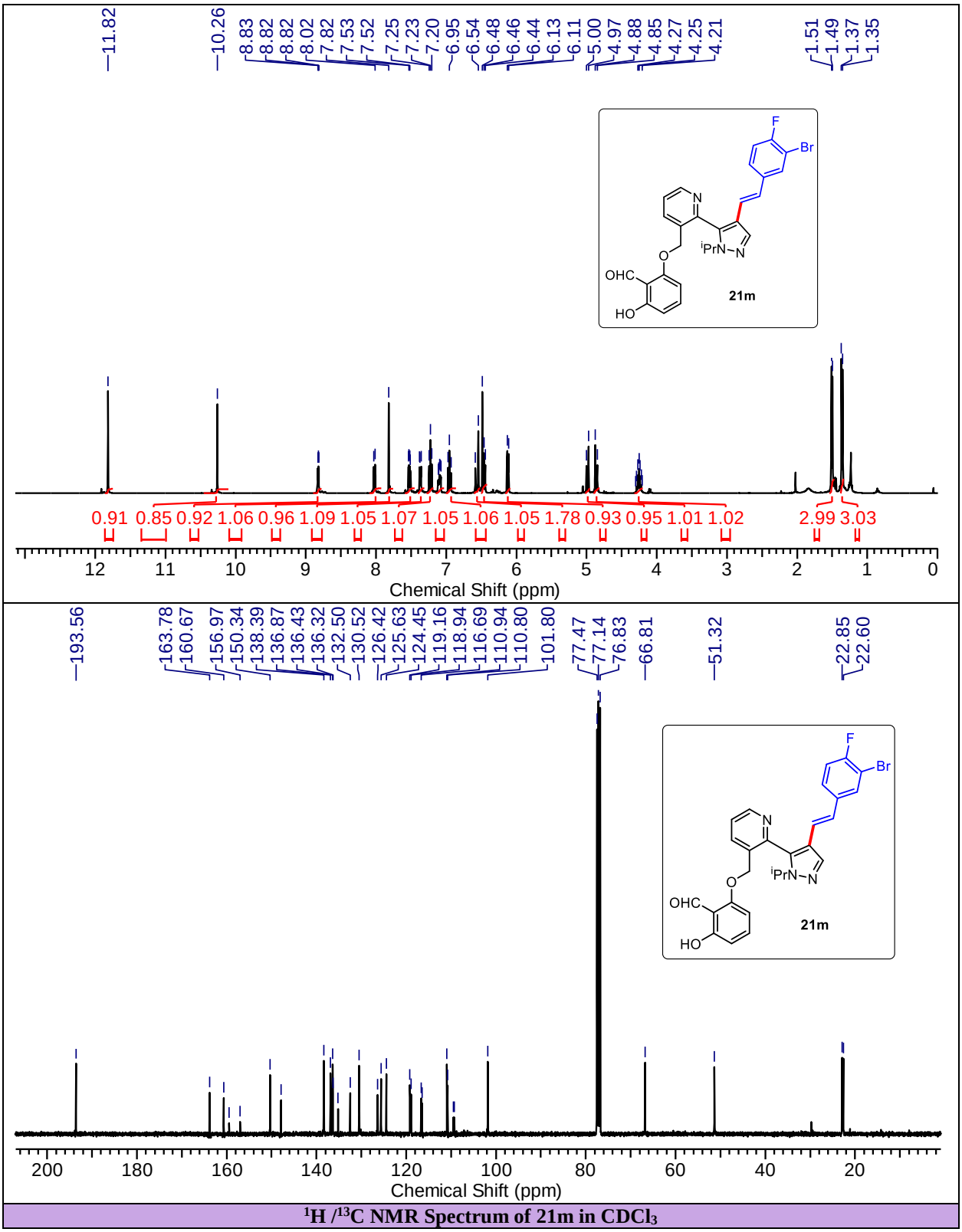


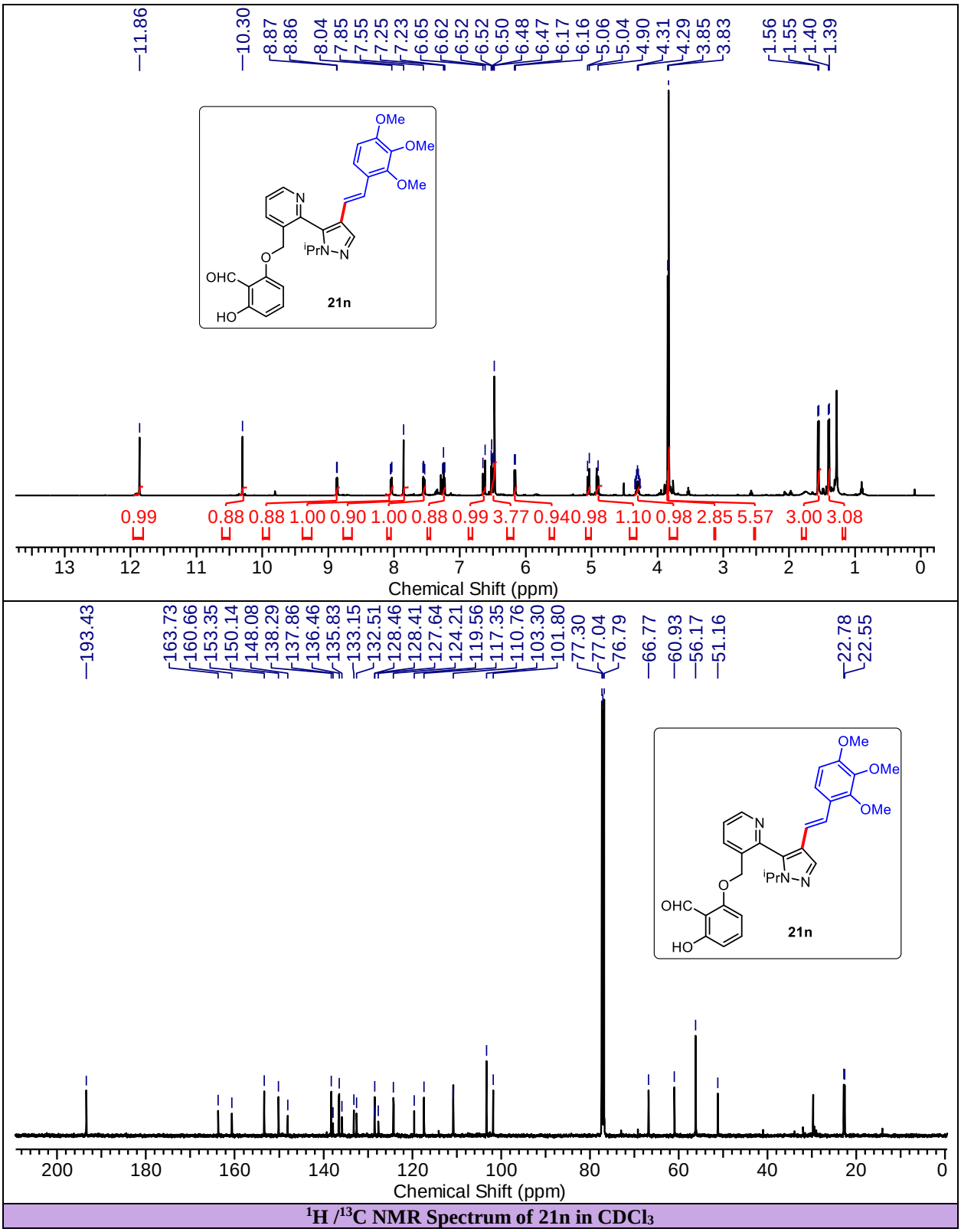
^{1}H /^{13}C NMR Spectrum of 21k in $CDCl_3$



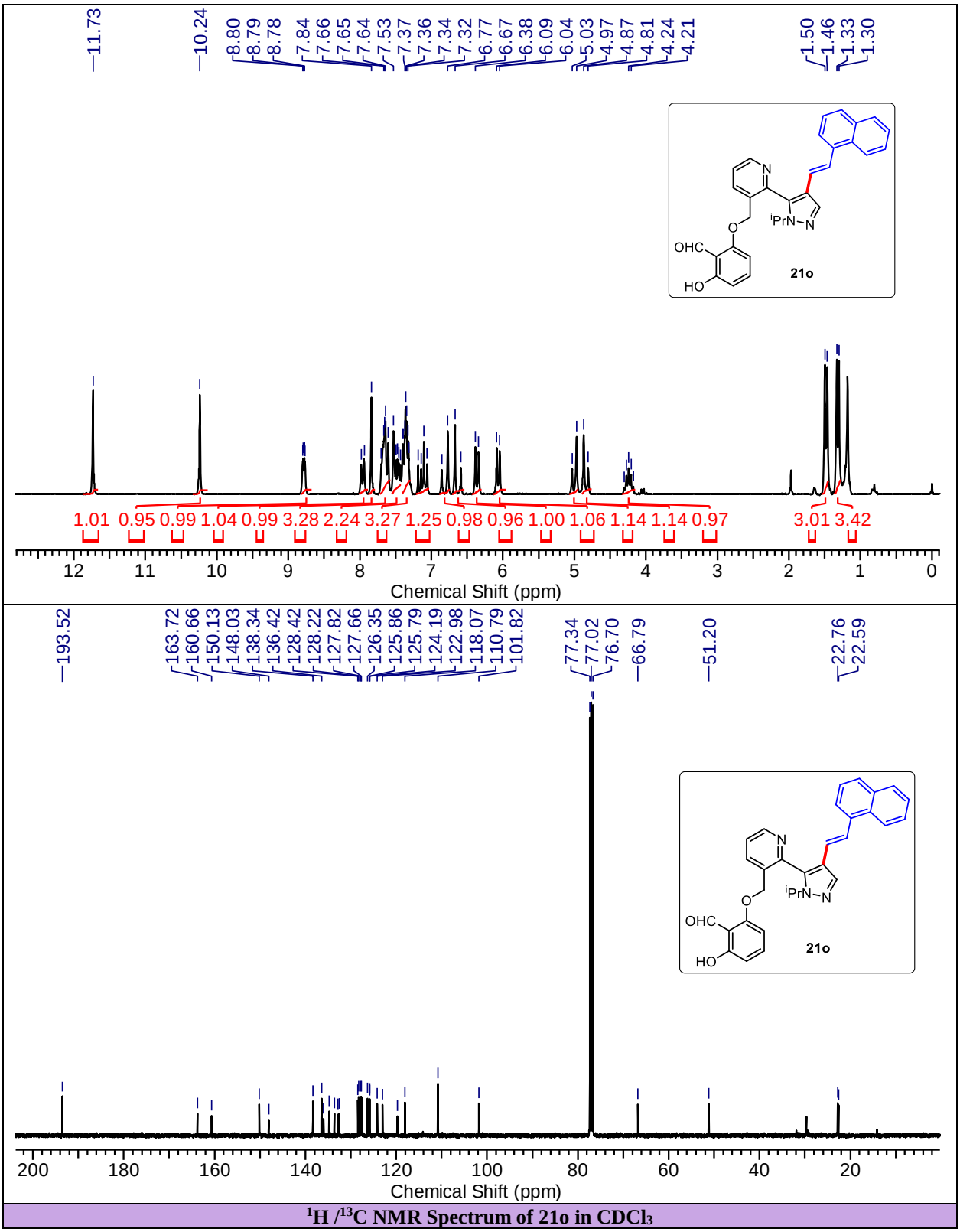
^{1}H /^{13}C NMR Spectrum of 21l in $CDCl_3$



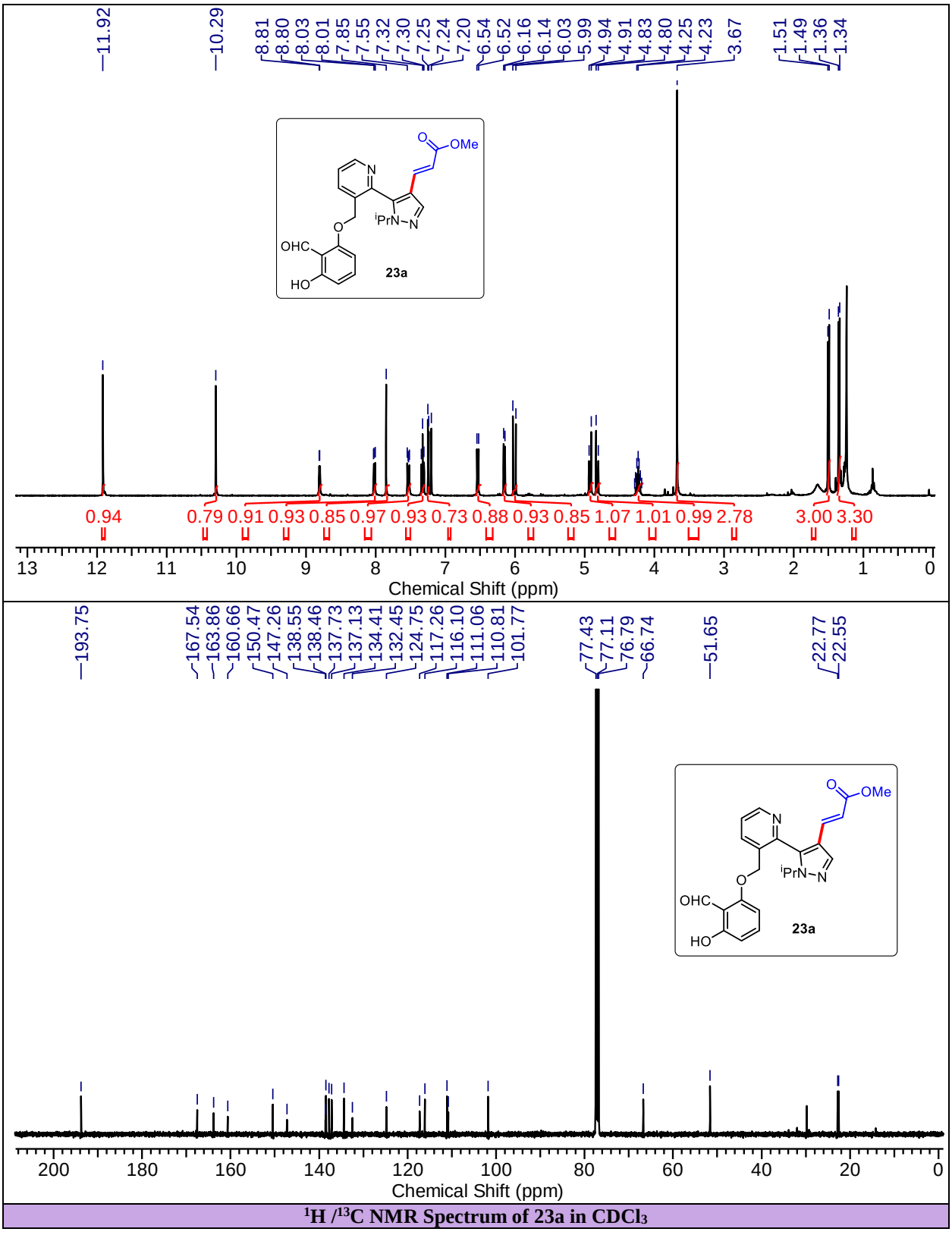
^{1}H /^{13}C NMR Spectrum of 21m in $CDCl_3$



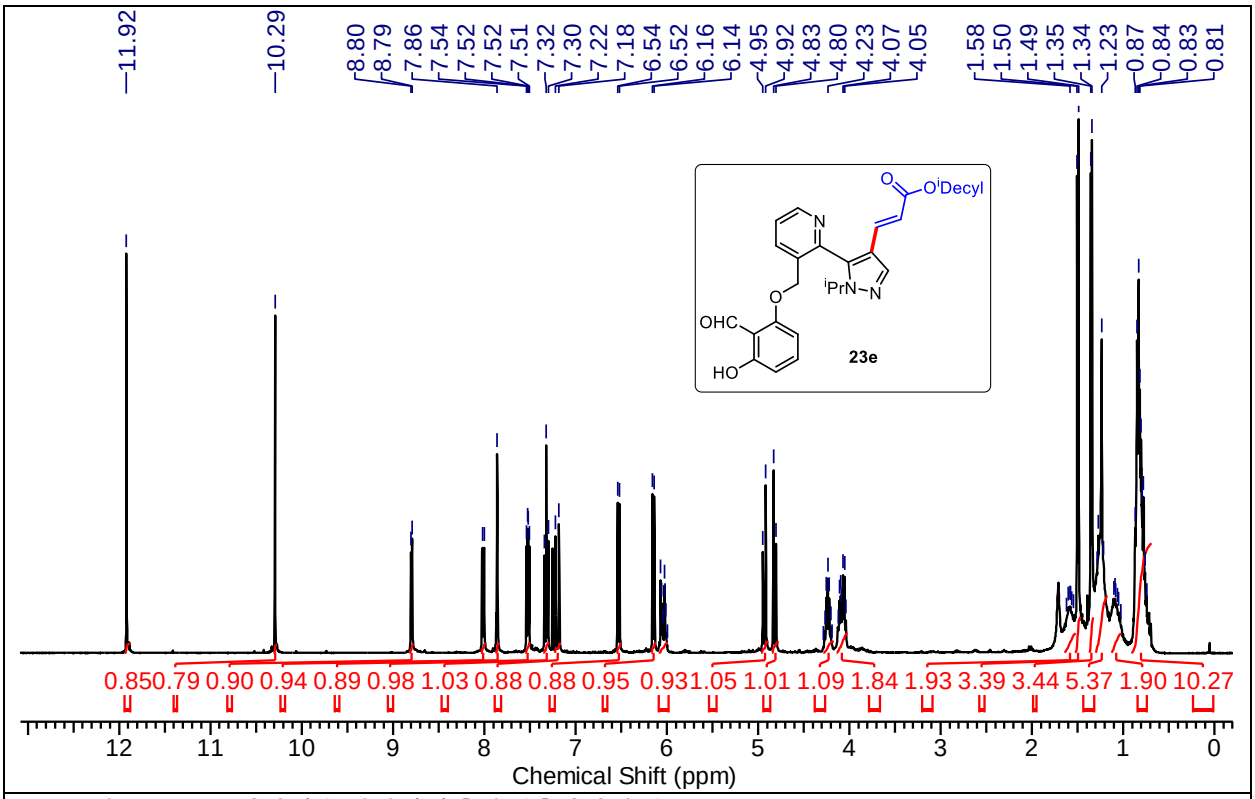
^{1}H /^{13}C NMR Spectrum of 21n in $CDCl_3$

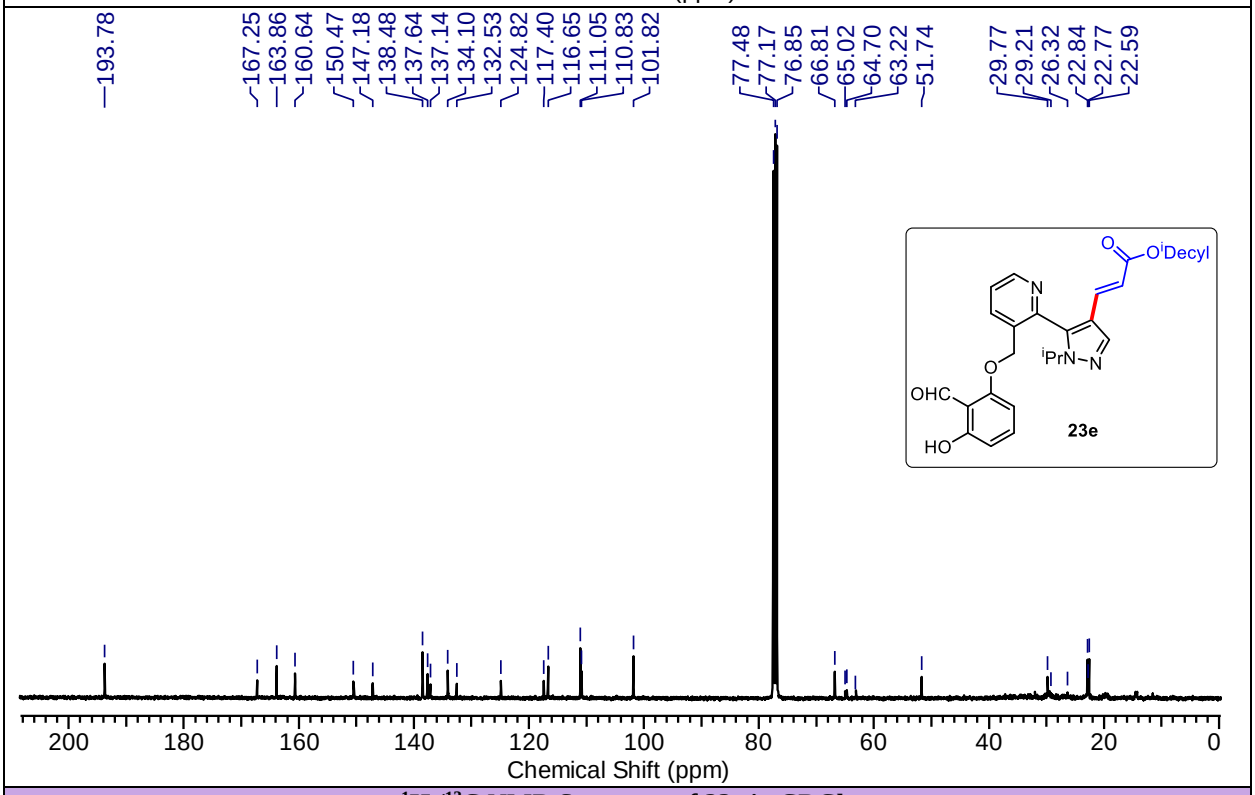


^{1}H /^{13}C NMR Spectrum of 21o in $CDCl_3$

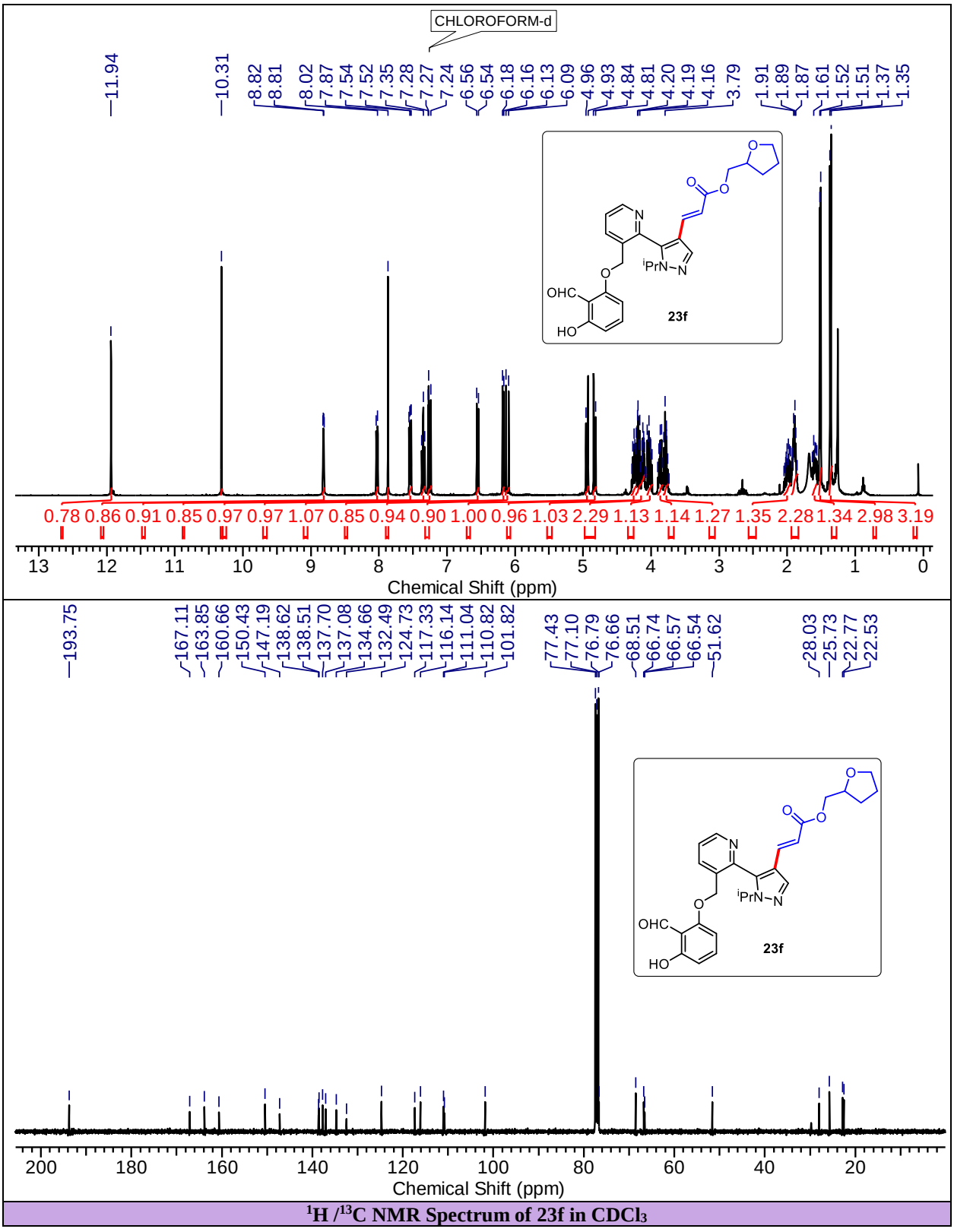


^{1}H /^{13}C NMR Spectrum of 23a in $CDCl_3$

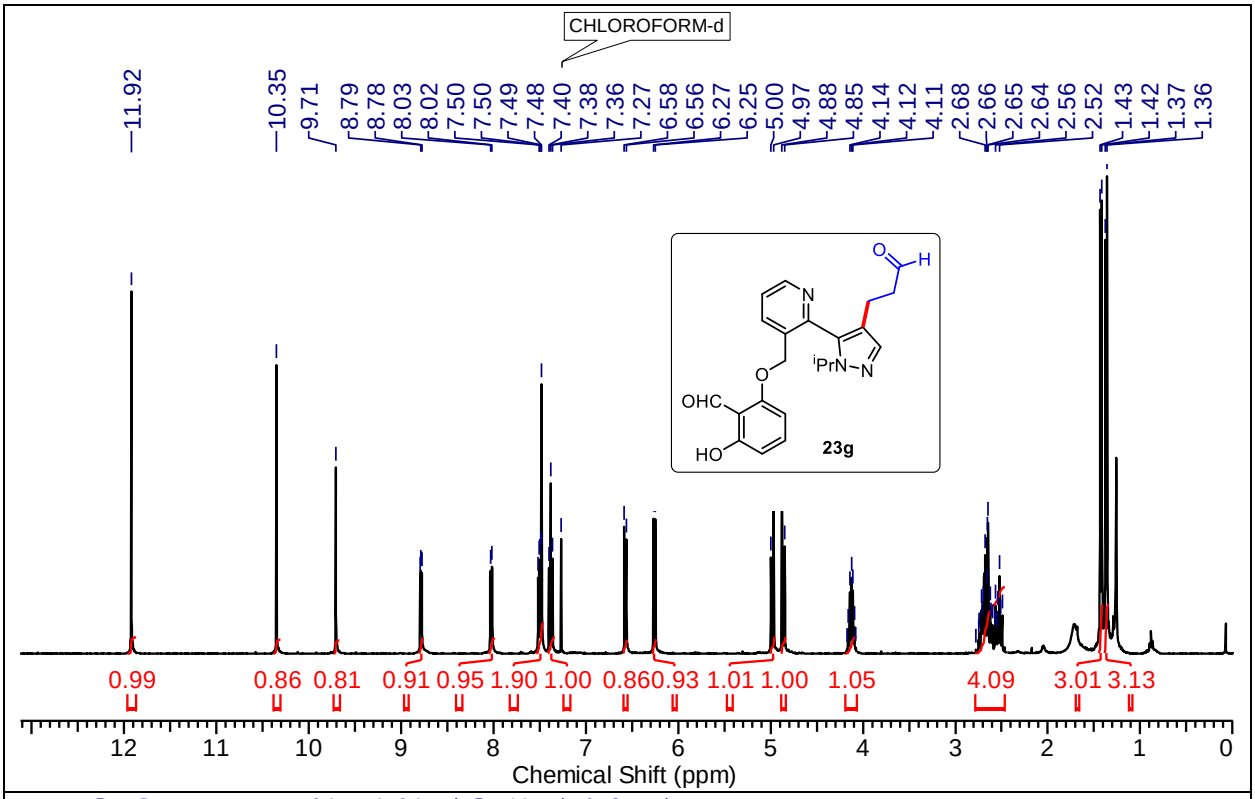


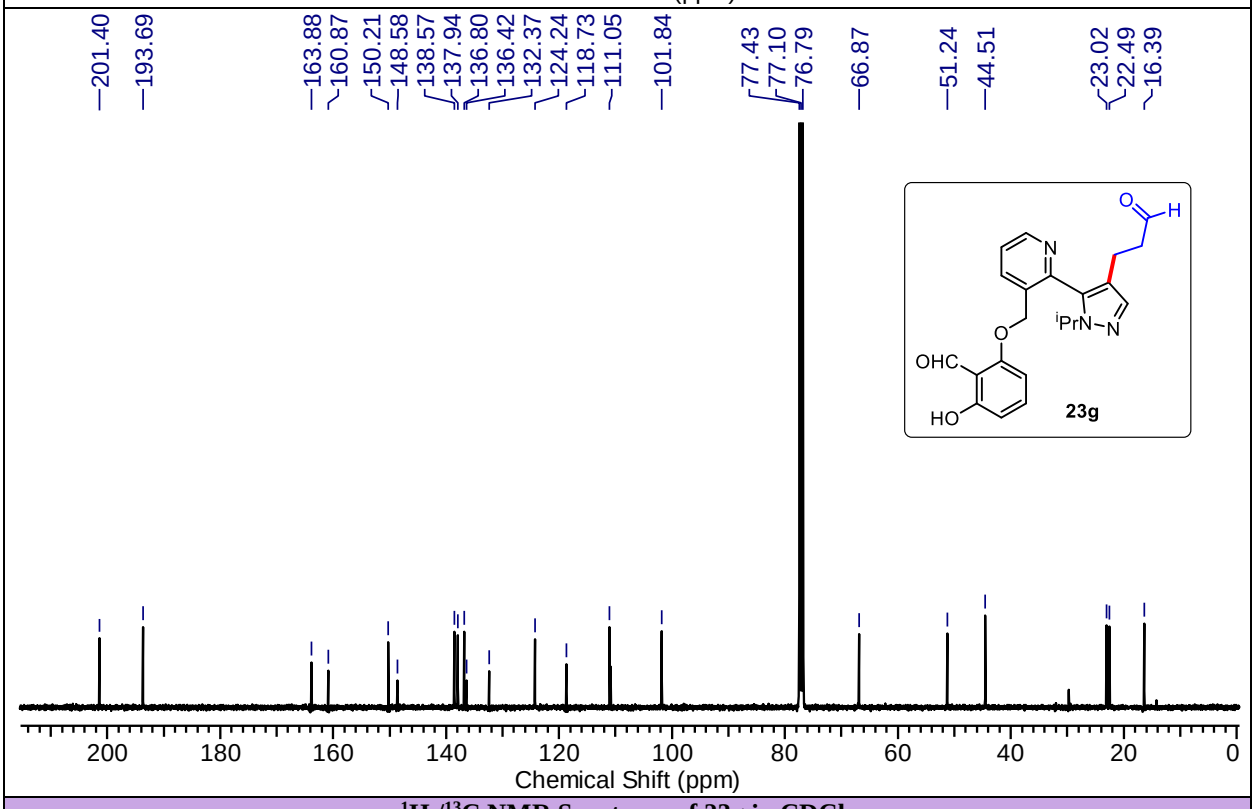


^{1}H /^{13}C NMR Spectrum of 23e in $CDCl_3$

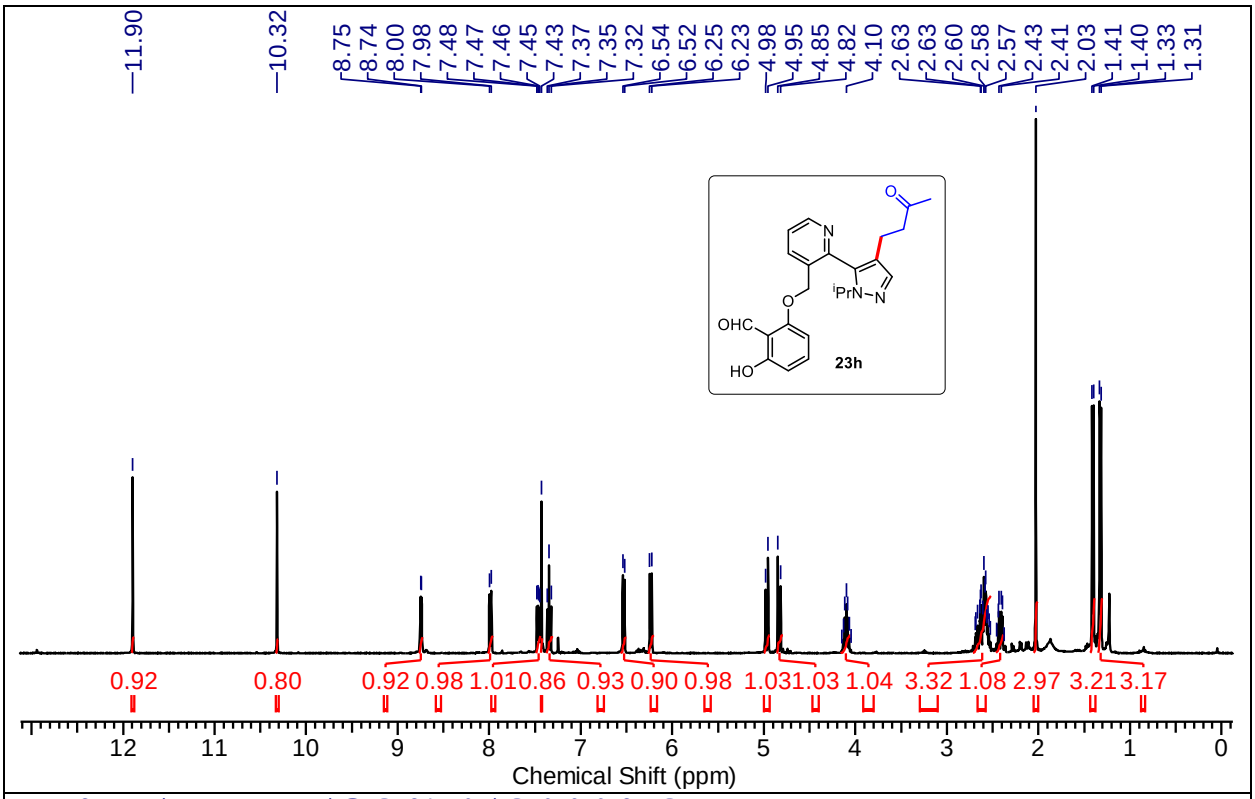


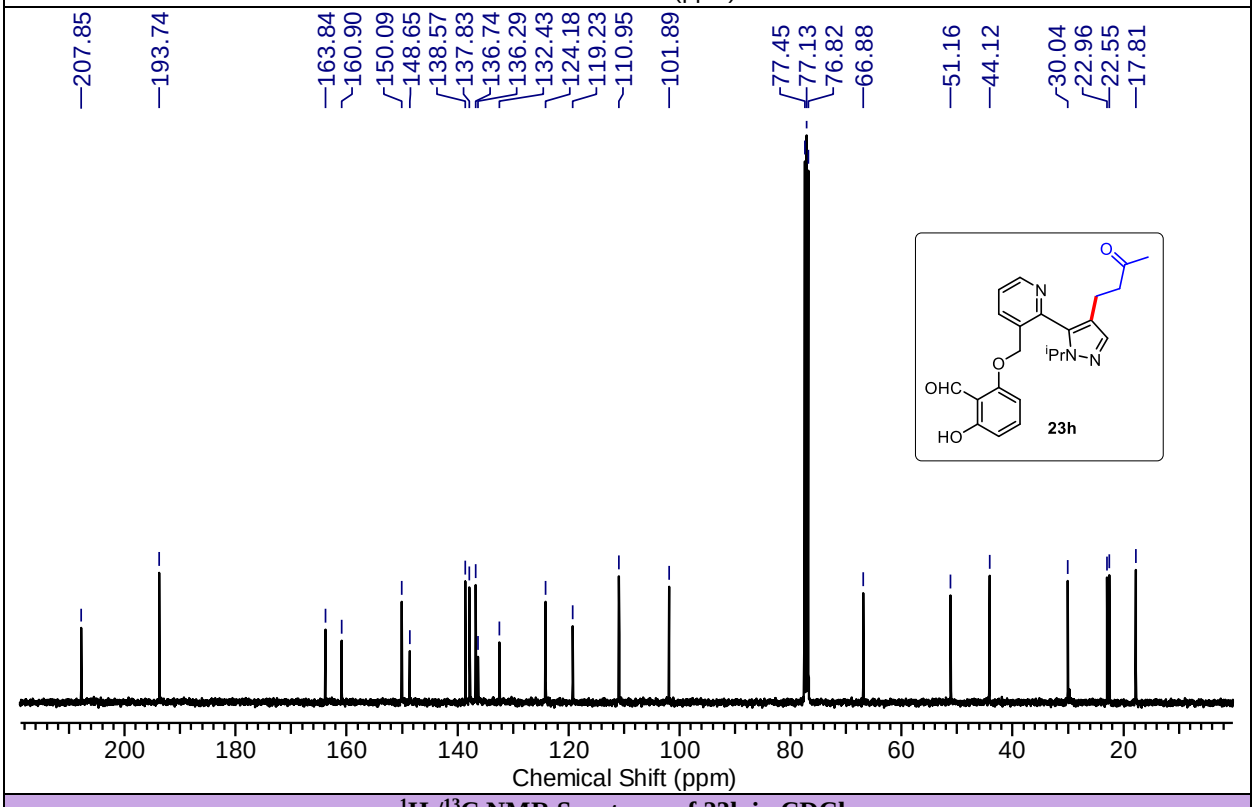
^{1}H /^{13}C NMR Spectrum of 23f in $CDCl_3$



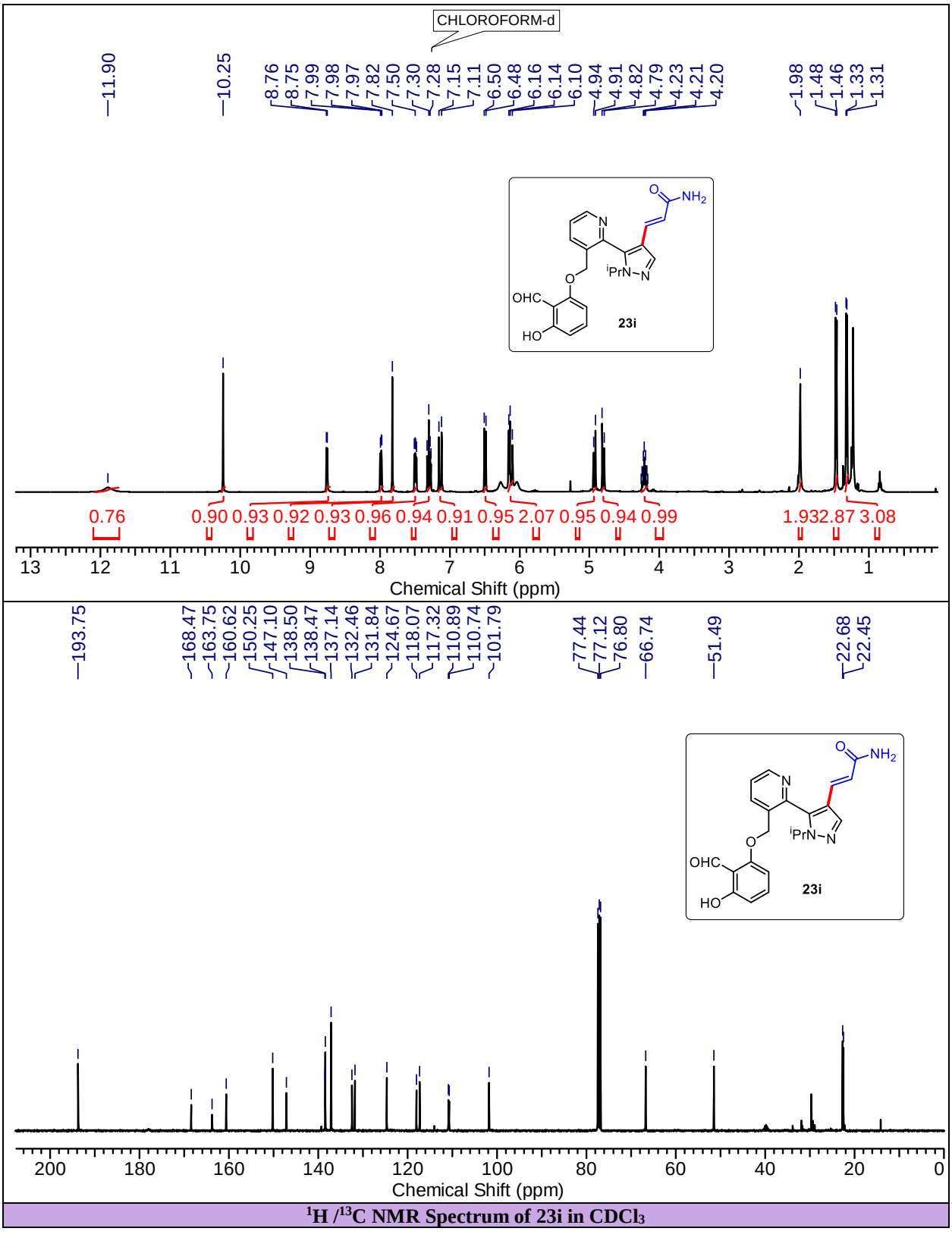


^{1}H /^{13}C NMR Spectrum of 23g in $CDCl_3$

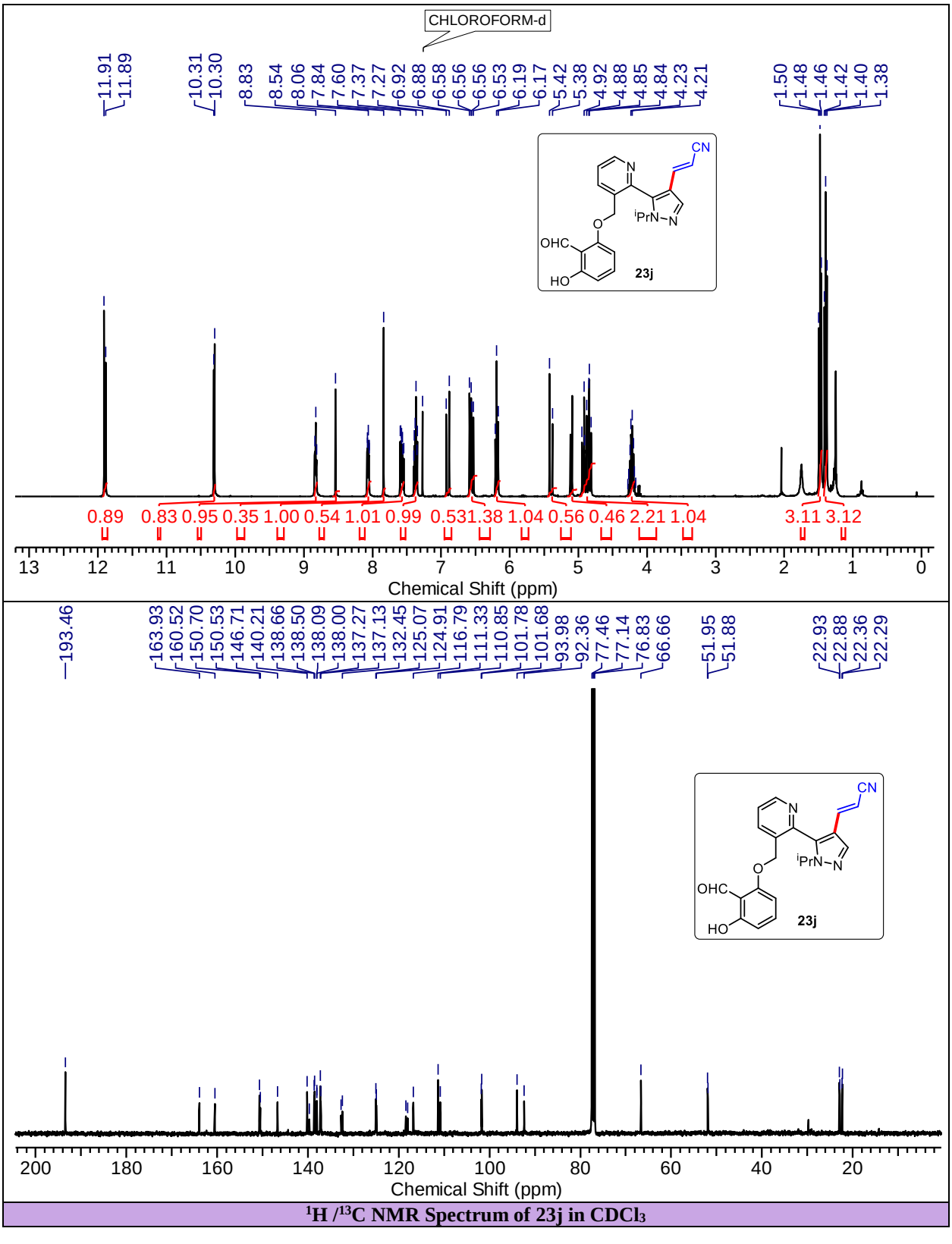




^{1}H /^{13}C NMR Spectrum of 23h in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 23i in $CDCl_3$



^{1}H /^{13}C NMR Spectrum of 23j in $CDCl_3$

1. a) Ju, Y.; Varma, R. S. *J. Org. Chem.*, **2006**, *71*, 135. b) Noga, E. J.; Barthalmus, G. T.; Mitchell, M. K. *Cell Biology Int. Rep.* **1986**, *10*, 239. c) Craig, P. N. In Comprehensive Medicinal Chemistry; Drayton, C. J., Ed.; Pergamon Press: New York, **1991**; Vol. 8. d) Katritzky, A. R.; Pozharskii, A. F. Handbook of Heterocyclic Chemistry: 2000, 2nd ed.; Pergamon Press: New York, **2000**. e) Padwa, A.; Bur, S. *Chem. ReV*. **2004**, *104*, 2401.
2. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.*, **2013**, *113*, 2958.
3. a) Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N. *Med. Chem. Commun.*, **2012**, *3*, 1062. b) Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, N. Y.; Al-aizari, A. F.; Ansar, M. H. *Molecules*, **2018**, *23*, 134. c) Trofimenko, S. *Chem. Rev.*, **1993**, *93*, 943. d) Yet, L. Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor Eds. R. J. K. Pyrazoles. In Comprehensive Heterocyclic Chemistry; Elsevier: Oxford, U.K., **2008**, 4, 1. e) Khan, M. F.; Alam, M. M.; Verma, G.; Akhtar, W.; Akhter, M.; Shaquiquzzaman, M. *Eur. J. Med. Chem.* **2016**, *120*, 170.
4. a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. b) Ansari, A.; Ali, A.; Asif, M. *New J. Chem.* **2017**, *41*, 16.
5. Naim, M. J.; Alam, O.; Nawaz, F.; Alam, Md. J.; Alam, P. *J Pharm Bioallied Sci.* **2016**, *8*, 2.
6. a) Piel, F. B.; Steinberg, M. H.; Rees, D. C. *N Engl J Med.* **2017**, *376*, 1561. b) Ware, R. E.; de Montalembert, M.; Tshilolo, L.; Abboud, M. R. *Lancet.* **2017**, 390, 311. c) Kato, G. J.; Piel, F. B.; Reid, C. D. *Nat Rev Dis Primers*. **2018**, *4*, 18010.
7. a) Rees, D. C.; Williams, T. N.; Gladwin, M. T. *Lancet* **2010**, *376*, 2018. b) Gladwin, M. T. *Lancet*. **2016**, *387*, 2565. c) Vichinsky, E.; Hoppe, C. C.; Ataga, K. I. *N Engl J Med*. **2019**, *381*, 509.
8. a) Serjeant, G. R.; Ghosh, K.; Patel, J. *Indian J Med Res* **2016**, *143*, 21. b) Colah, R. B.; Mukherjee, M. B.; Martin, S.; Ghosh, K. *Indian J Med Res* **2015**, *141*, 509.
9. a) Charache, S.; Terrin, M. L.; Moore, R. D.; Dover, G. J.; Barton, F. B.; Eckert, S. V.; McMahon, R. P.; Bonds, D. R. *N. Engl. J. Med.* **1995**, *332*, 1317. b) Torres, L.; Conran, N. *Expert Opin Pharmacother*. **2019**, *20*, 173. c) Charache, S.; Terrin, M. L.; Moore, R. D.; *N Engl J Med.* **1995**, *332*, 1317. d) Niihara, Y.; Miller, S. T.; Kanter, J. *N Engl J Med.* **2018**, *379*, 226.

10. a) Aldallal, S. M. *Cureus* **2020**, *12*, DOI 10.7759/cureus.7105 b) Han, J.; Saraf, S. L.; Gordeuk, V. R. *Pharmacotherapy* **2020**, *40*, 526. c) Vichinsky, E.; Hoppe, C. C.; Ataga, K. I.; Ware, R. E.; Nduba, V.; El-Beshlawy, A.; Hassab, H.; Achebe, M. M.; Alkindi, S.; Clark Brown, R.; Diuguid, D. L.; Telfer, P.; Tsitsikas, D. A.; Elghandour, A.; Gordeuk, V. R.; Kanter, J.; Abboud, M. R.; Lehrer-Graiwer, J.; Tonda, M.; Intondi, A.; Tong, B.; Howard, J. *N Engl J Med.* **2019**, *381*, 509. d) Torres, L.; Conran, N.; *Expert Opin Pharmacother*. **2019**, *20*, 173.
11. a) Moir, M.; Danon, J. J.; Reekie, T. A.; Kassiou, M. *Expert Opin Drug Discov* **2019,** *14*, 1137. b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev*., **2016**, *45*, 546. c) Kondo, Y.; García-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 7, 1164.
12. Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem*., **2011**, *76*, 1436.
13. a) Mitchell, D. K.; Cole, P.; Pollock, P. M.; Coppert, D. M.; Burkholder, T. P.; Clayton, J. R. *Org. Process Res. Dev*., **2012**, *16*, 213. b) Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *J. Org. Chem*., **2014**, *79*, 11631.
14. a) McKerrall, S. J.; Jørgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S.; *J. Am. Chem. Soc*., **2014**, *136*, 5799.
15. Sawada, S.; Okijima, S.; Aiyama, R.; Nokata, K.; Furuta, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K.; Miyasaka, T. *Chem. Pharm. Bull.*, **1991**, *39*, 1446.
16. a) Kalgutkar, A.; Jones, R.; Sawant, A. In Metabolism Pharmacokinetics and Toxicity of Functional Groups; Smith, D. A., Ed.; RSC: Cambridge, UK, 2010; RSC Drug Discovery Series No. 1, Chapter 5. b) Hansch, C.; Sammes, P. G.; Taylor, J. B. Comprehensive Medicinal Chemistry; Pergamon Press: Oxford, UK, 1990; Vol. 2, Chapter 7.1
17. Nagib, D. A.; MacMillan, D. W. C. *Nature*, **2011**, *480*, 224
18. Dai, H-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y-H.; Yu, J-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
19. Chen, K.; Eschenmoser, A.; Baran, P. S. *Angew. Chem., Int. Ed.,* **2009**, *48*, 9705.
20. Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.,* **2014**, *136*, 14389.
21. Liu, W.; Groves, J. T. *J. Am. Chem. Soc*., **2010**, *132*, 12847.

22. a) Chen, M. S.; White, M. C. *Science*, **2010**, *327*, 566. b) Go´mez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M. *J. Org. Chem.*, **2013**, *78*, 1421. c) Choudhary, M. I.; Musharraf, S. G.; Sami, A.; Atta-ur-Rahman, *Helv. Chim. Acta*, **2004**, *87*, 2685.
23. Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.*, **2015**, *137*, 5300.
24. Guo, S.; Zhang, X.; Tang, P. *Angew. Chem., Int. Ed.*, **2015**, *54*, 4065.
25. Meyer, C.; Schepmann, D.; Yanagisawa, S.; Yamaguchi, J.; Itami, K.; Wünsch, B. *Eur. J. Org. Chem.* **2012**, 5972.
26. a) Dröge, T.; Notzon, A.; Fröhlich, R.; Glorius, F. *Chem. Eur. J.* **2011**, *17*, 11974. b) Kondo, Y.; García-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 1164.
27. a) Cheel, J.; Theoduloz, C.; Rodríguez, J.; Saud, G.; Caligari, P. D. S.; Schmeda-Hirschmann, G. *J. Agric. Food Chem.*, **2005**, *53*, 8512. b) Siddiqui, B. S.; Aslam, H.; Begum, S.; Ali, S. T. *Nat. Prod. Res.*, **2007**, *21*, 736. c) Lee, Y.; Park, B.; Lyoo, W. *Synthesis*, **2009**, 2146. d) Chae, S. W.; Han, A.-R.; Park, J. H.; Rhie, J. Y.; Lim, H.-J.; Seo, E.-K.; Lee, H. J. *J. Nat. Prod.*, **2013**, *76*, 2277. e) Nguyen, P.-H.; Yang, J.-L.; Uddin, M. N.; Park, S.-L.; Lim, S.-I.; Jung, D.-W.; Williams, D. R.; Oh, W.-K. *J. Nat. Prod.*, **2013**, *76*, 2080.
28. a) Patel, K.; Karthikeyan, C.; Hari Narayana Moorthy, N. S.; Deora, G. S.; Solomon, V. R.; Lee. H.; Trivedi, P. *Med. Chem. Res.* **2011**, *21*, 1780. b) Sharma, N.; Mohanakrishnan, D.; Shard, A.; Sharma, A.; Sinha, A. K.; Sahal, D. *J. Med. Chem.*, **2012**, *55*, 297. c) Singh, R. S. P.; Michel, D.; Das, U.; Dimmock, J. R.; Alcorn, J. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 5199. d) Chuprajob, T.; Changtam, C.; Chokchaisiri, R.; Chunglok, W.; Sornkaew, N.; Suksamrarn, A.; *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 2839.
29. a) Kraft, A.; Grimsdale, A.; Holmes, A. *Angew. Chem., Int. Ed.*, **1998**, *37*, 403. b) Garay-Jimenez, J.; Gergeres, C. D.; Young, A.; Lim, D. V.; Turos, E.; *Nanomed: Nanotech. Biol. Med.* **2009**, *5*, 443. c) Grimsdale, A. C.; Leok Chan, K.; Martin, R. E.; Jokisz, P. G.; Holmes, A. B. *Chem. Rev.*, **2009**, *109*, 897. d) Jiang, Q.; Lei, Z. *Biotechnol. Bioprocess Eng.*, **2011**, *16*, 1187. e) Wencel-Delord, J.; Glorius, F. *Nat. Chem.*, **2013**, *5*, 369.
30. a) Wang, J. Stereoselective alkene synthesis, Springer Verlag, Heidelberg, New York, **2012**. b) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; Vicente, J. *J. Am. Chem. Soc.*, **2003**, *125*, 6034. c) Taber, D. F.; Nelson, C. G. *J. Org. Chem.*, **2006**, *71*, 8973. d) El-Batta,

A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. *J. Org. Chem.*, **2007**, *72*, 5244. e) Taber, D. F.; Sheth, R. B. *J. Org. Chem.*, **2008**, *73*, 8030. f) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.*, **2010**, *132*, 5018.

31. a) Metal-Catalyzed Cross-Coupling Reactions, ed. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, 1998. b) Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis, ed. J. Tsuji, Wiley, New York, 2000. c) Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn, 2004.
32. a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.*, **2001**, *34*, 633. b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.*, **2007**, *107*, 5318. c) Vasil'ev, A. V. *Russ. J. Org. Chem.*, **2009**, *45*, 1. d) Bellina, F.; Rossi, R.; Lessi, M. *Synthesis* **2010**, 4131. e) Le Bras, J.; Muzart, J. *Chem. Rev.*, **2011**, *111*, 1170.
33. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.
34. a) Faisal, M.; Saeed, A.; Hussain, S.; Dar, P.; Larik, F. A. *J. Chem. Sci.* **2019**, *131*, 70. b) Castillo, J-C.; Portilla, J.; *Italian Society of Chemistry* ISBN: 1724. c) Dar, A. M.; Shamsuzzaman. *J Nucl Med Radiat Ther* **2015**, *5*, 250.
35. Wencel-Delord, J.; Glorius, F. *Nat. Chem.*, **2013**, 5, 369.
36. Do, H-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, *45*, 15185.
37. Goikhman, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, *8*, 3042.
38. a) Le Bras, J.; Muzart, J. *Chem. Rev.*, **2011**, *111*, 1170–1214. b) Lee Bras, J.; Muzart, J. *Catalysts*, **2020**, *10*, 571.
39. a) Bae, S.; Jang, H.-L.; Jung, H.; Joo, J. M. *J. Org. Chem.*, **2015**, *80*, 690. b) Jang, H.-L.; Kim, H. T.; Cho, E. J.; Joo, J. M. *Asian J. Org. Chem.* **2015**, *4*, 1386. c) Yi, Z.; Aschenaki, Y.; Daley, R.; Davick, S.; Schnaith, A.; Wander, R.; Kalyani, D.; *J. Org. Chem.*, **2017**, *82*, 6946.
40. a) Piel, F. B.; Steinberg, M. H.; Rees, D. C. *N Engl J Med*. **2017**, *376*, 1561. b) Gopalsamy, A.; Aulabaugh, A. E.; Barakat, A.; Beaumont, K. C.; Cabral, S.; Canterbury, D. P.; Casimiro-Garcia, A.; Chang, J. S.; Chen, M. Z.; Choi, C.; Dow, R. L.; Fadeyi, O. O.; Feng, X.; France, S. P.; Howard, R. M.; Janz, J. M.; Jasti, J.; Jasuja, R.; Jones, L. H.; King-Ahmad, A.; Knee, K. M.; Kohrt, J. T.; Limberakis, C.; Liras, S.; Martinez, C. A.; McClure,

K. F.; Narayanan, A.; Narula, J.; Novak, J. J.; O'Connell, T. N.; Parikh, M. D.; Piotrowski, D. W.; Plotnikova, O.; Robinson, R. P.; Sahasrabudhe, P. V.; Sharma, R.; Thuma, B. A.; Vasa, D.; Wei, L.; Wenzel, A. Z.; Withka, J. M.; Xiao, J.; Yayla, H. G. *J. Med. Chem.* **2021**, *64*, 326.

41. Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2009**, *74*, 7094.
42. a) Kumar, S.; Nunewar, S.; Oluguttula, S.; Nanduri, S.; Kanchupalli, V. *Org. Biomol. Chem.*, **2021**. *19*, 1438. b) Nunewar, S.; Kumar, S.; Talakola, S.; Nanduri, S.; Kanchupalli, V. *Chem Asian J*. **2021**, *16*, 443. c) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.*, **2015**, *51*, 7986.
43. a) Kumar, P.; Kapur, M. *Org. Lett*. **2019**, *21*, 2134. b) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal*. **2016**, *6*, 498. c) Wu, S.; Wang, Z.; Ma, D.; Chen, C.; Zhu, B. *Org. Chem. Front*., **2020**, *7*, 1158. d) Zhou, J.; Li, B.; Qian, Z.-C.; Shi, B.-F. *Adv. Synth. Catal*. **2014**, *356*, 1038. e) Kim, H.; Thombal, R. S.; Khanal, H. D.; Lee, Y. R. *Chem. Commun*., **2019**, *55*, 13402. f) Lu, P.; Feng, C.; Loh, T.-P. *Org. Lett.*, **2015**, *17*, 3210.

CHAPTER III

Oxidative Rearrangement of Stilbenes to 2,2-Diaryl-2-hydroxyacetaldehydes

1.1 Introduction:

Stilbenes and their derivatives are part of an important class of plant polyphenols that have attracted enormous importance due to their diverse biological activities, such as anti-inflammatory,[1] anti-cancer,[2] anti-proliferative,[3] anti-microbial,[4] anti-HIV,[5] anti-herpes simplex virus,[6] and anti-angiogenesis.[7,3b] Stilbenes are mainly divided into two classes, namely, monomeric and oligomeric stilbenes, where oligomeric stilbenes have complex configurations/diverse oligomerizations formed by the combination of the homogenous or heterogeneous monomeric stilbenes.[8] Till date, there are more than 400 naturally occurring biologically active stilbenes isolated and identified.[9] Stilbenes exist in *E* or *Z* form. According to the study, *E* or *trans* isomers are biologically more active than the *Z or cis*-isomer as the *trans* isomers are thermodynamically more stable than the *cis* isomers. The resveratrol, oxyresveratrol, pterostilbene, combretastatin, etc. (**Figure F3.1**) are some of the *trans*-stilbenes that are very popular due to their inherent biological activity.[10]

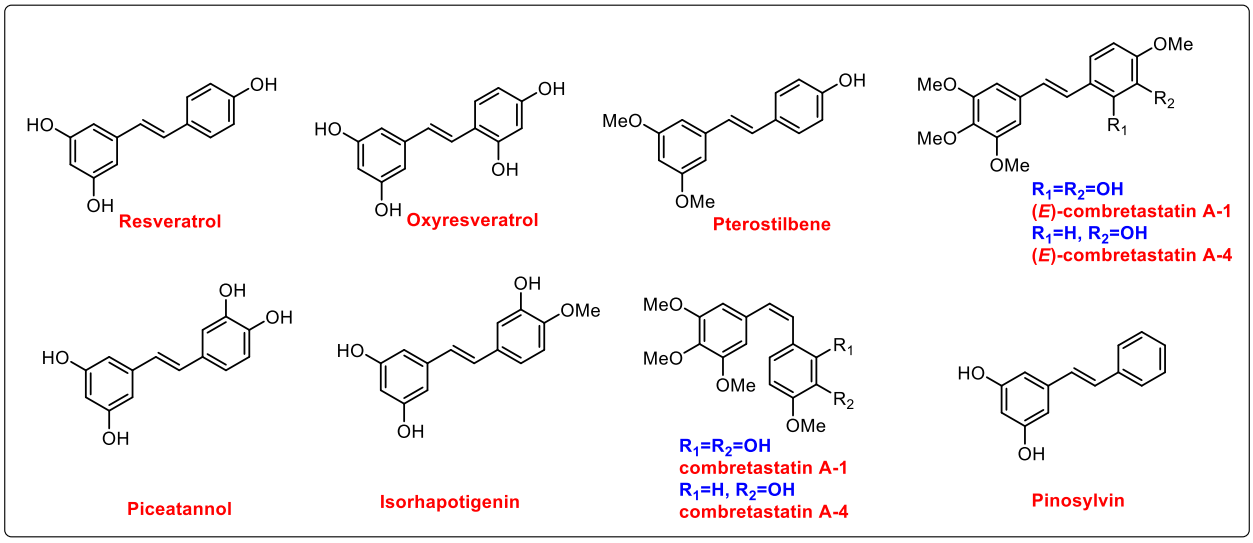


Figure F3.1: *Naturally occurring biologically active stilbene derivatives.*

Resveratrol is the most popular and widely studied stilbene, as it gives protection against pathogens, and is also effective against cancer and AIDS while having estrogenic potency.[11] Coming to the biosynthesis of stilbenes, stilbenes are synthesized in the plants *via* the phenyl propanoid pathway from phenylalanine.[12] Due to the reduced availability of the naturally occurring

stilbenes in adequate quantity, many synthetic methods such as Wittig-Horner olefination reaction, McMurry coupling reaction, Perkin aldol condensation, Sonogashira reaction, Mizoroki–Heck, Negishi, Stille, Suzuki–Miyaura, Grubbs, Knoevenagel–Doebner, and the Ramberg–Bucklund reactions have been deployed in their preparation.[13] In addition, a good number of novel methodologies have also developed to synthesize various stilbene derivatives.[14]

On the other hand, the oxidative cleavage of the C=C bond for the construction of new carbon-carbon and carbon-hetero bonds using a suitable oxidant is a very important synthetic transformation in organic chemistry, as it has broad applications mainly in the field of the total synthesis of natural products.[15] Oxidative scission of double bonds is a fundamental concept in organic synthesis and leads to the formation of functionalized carbonyl compounds such as aldehydes, ketones, and carboxylic acids, which are the key precursors for further transformations. Generally, the classical way to break the double bond of olefin is by utilizing ozonolysis[16] or the Lemieux-Johnson reaction.[17] Next, the transition metal-catalyzed olefin cleavage is also well known with metals such as Ru,[18] Pd,[19] Au,[20] and Os[21] with the suitable co-oxidant combination.

In recent years, due to the safety concerns associated with the metals, the use of alternative catalysts such as iodine in combination with safer oxidizing agents (*via* hypervalent iodine intermediate formation) has attracted a great deal of attention.[22,23] These iodine-catalyzed reactions are said to be an alternative to the transition metal-catalyzed reactions. This hypervalent iodine reagent is a nontoxic, environmentally friendly, versatile reagent. Taking into consideration the immense utility of these stilbenes and also our interest in the olefin functionalization using oxone, we aimed to utilize this stilbene for oxidative rearrangements, especially leading to the 2-diarylacetaldehydes. The 2-diarylacetaldehyde core represents a highly functionalized core having the potential for various ring annulations. Reports for the synthesis of such diarylacetaldehydes are very limited, because the fast oxidation that leads to decarboxylation forms the diarylketones.[24] This prompted us to explore in this direction employing stilbenes and to show their utility in providing advanced intermediates for natural product synthesis, which otherwise require a multistep synthetic sequence. In particular keeping the objective of synthesizing diaryl acetaldehydes from stilbenes en route to the synthesis of 4,4-diaryl-γ-butenolides in mind, the following introductory part will focus briefly on the oxidative rearrangements mediated by hypervalent iodine compounds, followed by the synthesis of diarylacetaldehydes and

diarylhydroxyacetaldehydes and finally on how the targeted 4,4-diaryl-γ-butenolides are synthesized in general.

1.2 Hypervalent Iodine Compounds: Hypervalent iodine compounds are easily available, non-toxic, safe to handle, high stability, environmentally friendly reagents widely used in organic chemistry to acquire unique transformations without the involvement of transition metals.[25] Their electrophilic nature and their potential as good leaving groups single them out as suitable reagents for generating cationic intermediates, especially from olefins, and importantly, when an oxidative rearrangement leading to the rearranged products is a pre-requisite. There are two types of migration reactions that are generally observed: C-N and C-C bond migration reactions. Particularly, the C-C bond migration reaction is facile due to the electrophilic nature of the hypervalent iodine reagent which activates the double bond in the olefin so that it leads to oxidative rearrangement reactions such as ring expansion, ring contraction, or the aryl ring migration.[26] There are two types of hypervalent reagents that are well known in the literature depending upon their oxidation states, such as Iodine (III) and Iodine (V). As our work mainly deals with the hypervalent Iodine (III) compound formation, most of these used reagents are presented in **Figure F3.2**.

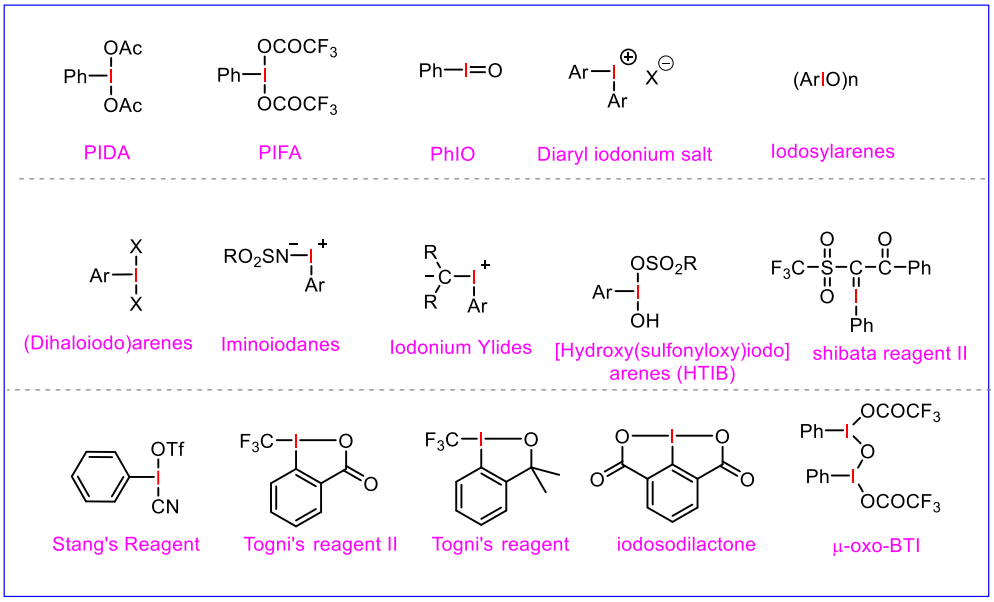


Figure F3.2: *A variety of hypervalent Iodine (III) compounds.*

1.3 Oxidative rearrangement: Coming to the hypervalent iodine catalyzed rearrangement reactions,[27] the most popular are 1,2-migration, Beckmann rearrangement, Hoffmann rearrangement, ring contraction and ring expansions (**Figure F3.3**).[28] Importantly, these hypervalent iodine reagents can mediate the 1,2 aryl group shift due to their electrophilic nature. As our work contributes towards the 1,2 migration through the *in situ* formed hypervalent iodine intermediate, we have presented a brief collection of the literature reports that include the reactions involving the hypervalent iodine catalyzed oxidative 1,2 rearrangements of alkyl or aromatic groups. Many of the presented reports are based on the direct use of the hypervalent iodine reagent for this transformation, followed by some examples that include the *in situ* formation of a hypervalent iodine intermediate (formed by a catalytic amount of iodine and a stoichiometric amount of oxidizing agent) during this conversion, similar to our case.

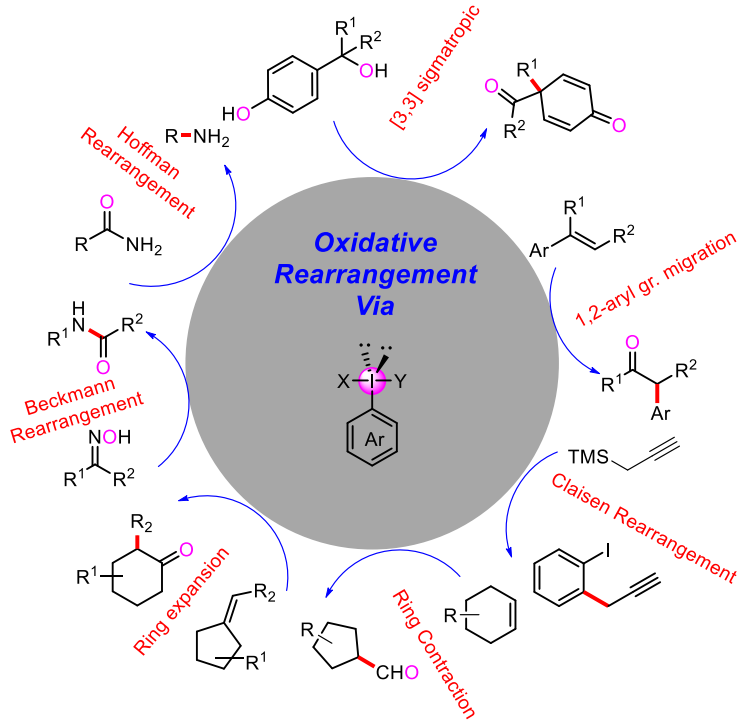
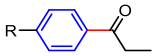
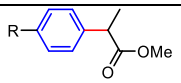
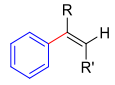
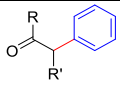
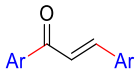
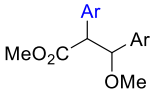
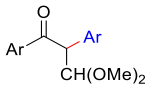
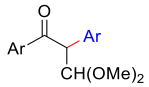
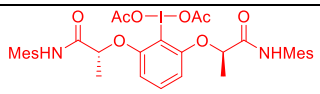
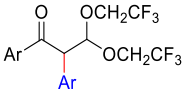
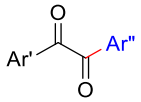
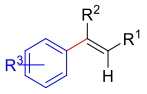
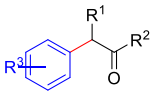
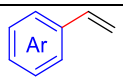
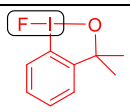
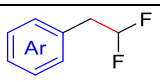
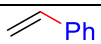
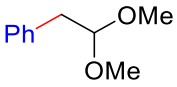
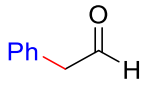
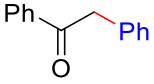
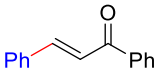
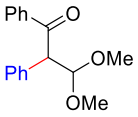
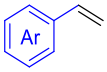
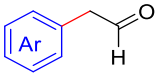
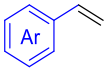
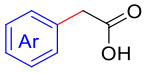
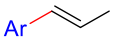
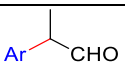
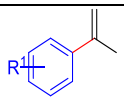
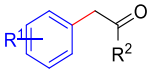
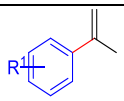
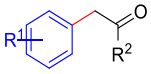
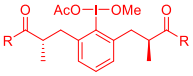
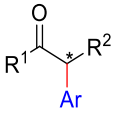
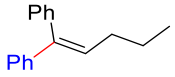
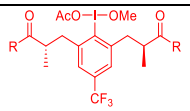
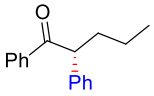
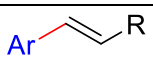
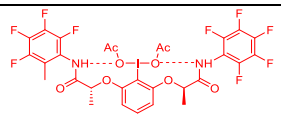
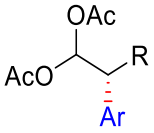


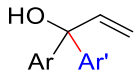
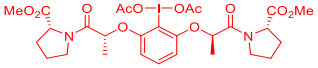
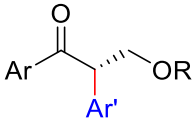
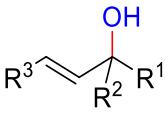
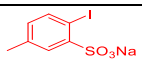
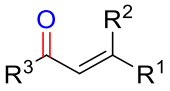
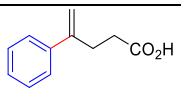
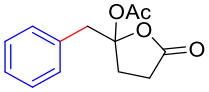
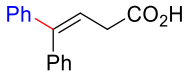
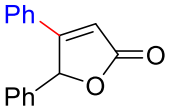
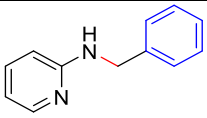
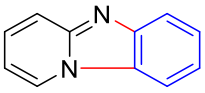
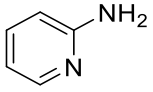
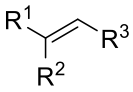
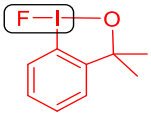
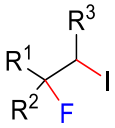
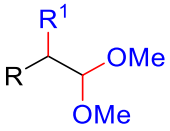
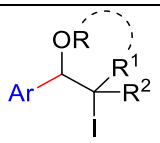
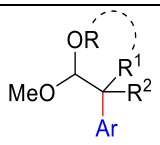
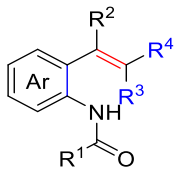
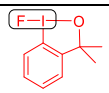
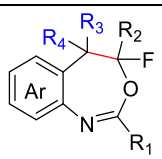
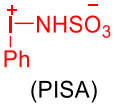
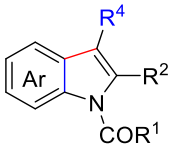
Figure F3.3: *HVI catalyzed oxidative rearrangement reactions.*

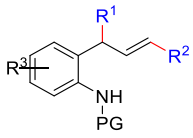
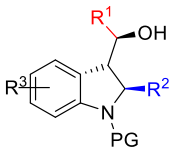
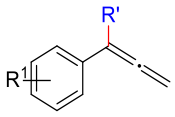
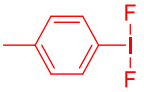
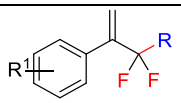
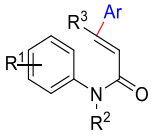
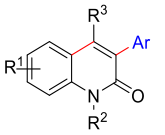
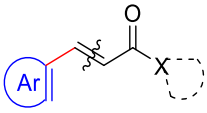
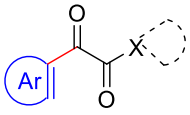
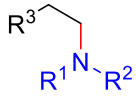
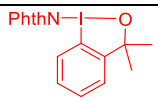
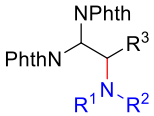
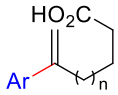
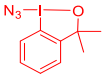
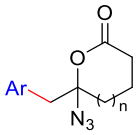
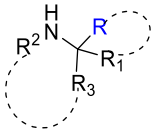
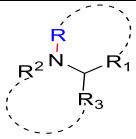
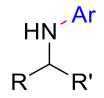
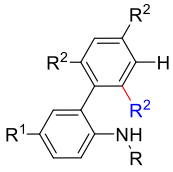
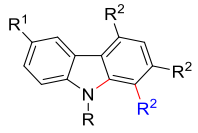
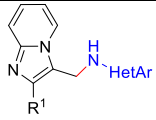
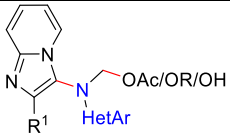
1.2-Migration Reactions: This type of reaction includes 1,2 aryl ring migration, 1,2 alkyl group migration, or the 1,2-carbon-nitrogen migration. The 1,2 rearrangement of the groups present on the alkene are the most popular. A compilation of the literature reports that cover the hypervalent iodine catalysed oxidative rearrangement reactions is presented in **Table T3.1**.

Table T3.1. *Literature reports on hypervalent iodine mediated 1,2-oxidative rearrangements.*

Sr. No.	Starting	Reaction conditions	Product	Reference
1		$PhI(OAc)_2$, $(Me_3O)_3CH$, H_2SO_4, 60 °C, 10 min		*Synthesis*, **1984**, 231.
2	 R = H, CH_3, R' = H R = H, R' = Aroyl R' = OH; R' = H	C_6H_5IO, MeOH, CF_3SO_3H, FSO_3H, $BF_3.Oet_2$		*Tetrahedron Lett.* **1985**, *26*, 2961.
3		$PhI(OAc)_2$, $(Me_3O)_3CH$ H_2SO_4, rt, 20 h		*Synthesis*, **1990**, 1025.
4		$PhI(OCOCF_3)_2$ (PIFA) MeOH, rt		*J. Chem. Soc., Perkin Trans. 1*, **1998**, 2533.
6		MW, HTIB/BTIB, MeOH, $CHCl_3$, 60 °C, 12 min.		*Tetrahedron* **2006**, *62*, 8625.
7		 TMSOTf, DCM/TFE, -40 °C, 1 h, then -15 °C, 14 h		*Angew. Chem., Int. Ed.*, **2013**, *52*, 7018.
8		I_2, TBHP, DMSO, 120 °C, 36 h		*ACS Omega* **2019**, *4*, 9636.
9	 R^1 = H, alkyl, R^2 = H, alkyl, aryl, R^3 = H, Cl, Me, OMe	$PhI(OAc)_2$, MeOH H_2SO_4, rt, 20 h		*Russ. Chem. Bull., Int. Ed.*, **2004**, *53*, 1735.
10		 $AgBF_4$, $CDCl_3$, 40 °C, 18 h		*Angew. Chem., Int. Ed.*, **2014**, *53*, 12897.

11		$PhI(OAc)_2$, MeOH H_2SO_4, -20 °C, 20 min		*Russ. J. Org. Chem.* **2001**, *37*, 1179.
12		$PhI(OAc)_2$, H_2O, MeCN, H_2SO_4, -15 °C, 20 min		
13		$PhI(OAc)_2$, MeOH, H_2SO_4, -15 °C, 30 min		
14		$PhI(OAc)_2$, MeOH, H_2SO_4, 25 °C, 320 min		
15		NH_4I, Oxone, SDS, H_2O, rt, 0-3 h		*Adv. Synth. Catal.* **2015**, *357*, 1125.
16		I_2, Oxone, DME-H2O, rt, 4 h		*RSC Adv.*, **2016**, *6*, 6719.
17		I_2, Ag_2O, Dioxane-H_2O, rt, 7-24 h		*Chem. Lett.* ***1984***, *13*, 341.
18		 4-Me-IBS Triton-X 405TM Oxone, MTBE, ^{i}PrOH, Na_2SO_3, NaOH, $NaHSO_3$		*Org. Lett.*, **2013**, *15*, 1650.
19		NaI, Oxone, CH_3CN:H_2O, rt, 20 h.		*Chin. Chem. Lett.* **2015**, *26*, 248.
20		 TsOH, MeOH CH_2Cl_2/TFE, -78 °C		*Chem. – Eur. J.*, **2016**, *22*, 4030.
21		 TsOH. H_2O, MeOH, CH_2Cl_2/CF_3CH_2OH, -78 °C, rt, 12 h		*J. Org. Chem.*, **2020**, *85*, 10175.
22	 R = Me, Et, Pr, iBu	 Yb(Otf)$_3$, DCM/AcOH, 12 h,		

23		 TsOH.H_2O, Selectflour, ROH/MeCN, 25 °C, 8 h	 R = Me, Et, ^{n}Bu, ^{t}Bu, $ArCH_2$	*Angew. Chem., Int. Ed.*, **2019**, *58*, 7450.
24		 Oxone, Bu_4NHSO_4, K_2CO_3, EtOAc, Na_2SO_4, 60 °C,		*Org. Lett.*, **2009**, *11*, No. 15, 3470.
25		PhI(OAc)$_2$, CH_2Cl_2, rt, 2h		*Org. Lett.*, **2003**, *5*, 2157.
26		PhI(OCOCF$_3$)$_2$, TMSOTf, MeCN, rt, 30 min		*ChemistryOpen*, **2012**, *1*, 245.
27		PhI(OPiv)$_2$, HFIP, 25 °C, air, 7 h		*Org. Lett.*, **2013**, *15*, 3476.
28		 PhI(OPiv)$_2$, HFIP, 40 °C, air, 12 h		*Angew. Chem., Int. Ed.*, **2014**, *53*, 8163.
29		 PdX_2 (X = TFA, OAc, $(BF_4)(MeCN)_2$, $CDCl_3$,		*ACS Catal.*, **2016**, *6*, 447.
30	 R = aryl/alkyl R^1 = H/aryl/alkyl/COPh/NO_2	NH_4I, Oxone, MeOH, 30 °C		*RSC Adv., 2015, 5, 73732.*
31		IPy_2BF_4 $BF_3.OEt_2$ MeOH, CH_2Cl_2 rt, 15 min		*Chem. Eur. J. 2005, 11, 5938.*
32		 4 A° MS, MeCN, rt, 5 min		*Chem. Eur. J.* **2016,** *22*, 3660.
33		 (PISA) $MeCN/H_2O$, 60 °C, 2h		*Org. Lett.*, **2018**, *20*, 4052.

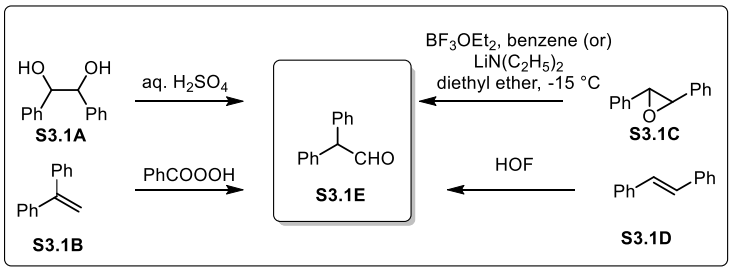
34		PhI, mCPBA, HFIP/H_2O, 0 °C		*Org. Lett.*, **2017**, *19*, 6478.
35		 $BF_3.OEt_2$ DCE, reflux, 10-30 min		*Angew. Chem. Int. Ed.* **2017**, *56*, 11620.
36		PIFA, TFA, BF_3OEt_2, DCE, 0 °C, rt,		*Org. Lett.*, **2013**, *15*, 2906.
37		PIFA, Conc. H_2SO_4, TFA, EtOH, $BF_3.OEt_2$ Reflux, 10 h		*Org. Lett.*, **2014**, *16*, 5772.
38		 CH_3CN, 60 °C, 12 h		*Angew. Chem., Int. Ed.*, **2015,** *54*, 13719.
39		 $Pd(hfacac)_2$, MeCN, 3h, rt		*Chem. – Eur. J.*, **2017**, *23*, 9501.
40		$PhI(OAc)_2$, $NaCNBH_3$, TFE, 0 °C, rt		*Org. Lett.* **2018**, *20*, 2333.
41		$PhI(OAc)_2$, Cs_2CO_3, $NaBH_4$ MeOH, 0 °C, rt		*Org. Lett.* **2019**, 21, 3023.
42		$PhI(OAc)_2$, TFE, rt, 3 h or PhI, *m*CPBA, TFE, rt, 3 h		*J. Org. Chem.*, **2018**, *83*, 11278.
43		$PhI(OAc)_2$, Toluene or R-OH, 50 °C, 3 h.		*J. Org. Chem.*, **2020**, *85*, 7309.

1.4 Synthesis of diarylacetaldehydes

The diarylacetaldehydes are an important class of intermediate used in various fields, such as in medicinal chemistry, in industry and also in natural product syntheses.[29] Previously, these

aryl acetaldehydes were synthesized by doing the oxidation of the corresponding alcohols (derived from terminal olefins) or *via* hydroformylation. Another important approach for their synthesis was the rearrangement of epoxides, diols and the Meinwald rearrangement of halohydrins.[30] In recent years, hypervalent iodine catalyzed oxidation of olefin leading to the synthesis of mono-/diarylacetaldehyde has also attracted the attention of synthetic chemists.[31]

One of the earliest methods reported for the synthesis of diphenylacetaldehyde was the sulphuric acid mediated rearrangement of diphenylethane-1,2-diol (typically known as hydrobenzoin, Zincke, Th. *Ber. Dtsch. Chem. Ges*. **1876**, *9*, 1761-1775), diphenylethylenoxides (Klages, A. Kessler, J. *Ber. Dtsch. Chem. Ges*. **1906**, *39*, 1753-1756) or the direct oxidative rearrangement of 1,2-diphenylethylene employing perbenzoic acid (Newbold, G. T.; Spring, F. S. *J. Chem. Soc*. **1945**, 247–248). In 1955, the House acid catalyzed rearrangement of the stilbene oxide led to diphenyl acetaldehyde (Scheme S3.1). Next, in 1958, Cope and co-workers reported a similar kind of rearrangement of the *trans*-stilbene oxide **S3.1C** in the presence of dry lithium diethylamide in diethyl ether solvent at -15 °C, leading to diphenylacetaldehyde **S3.1E** in good yield. Following these two inaugural reports, there were several advances documented for these rearrangements employing a wide range of Lewis/solid acid catalysts and also bases.



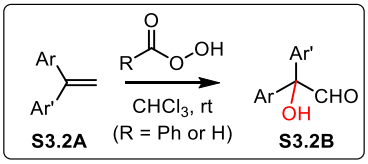
Scheme S3.1: *Known methods for the synthesis of diphenylacetaldehyde*

Coming to the direct conversion of stilbene to diphenylacetaldehyde, in 1984, Bonneti and co-workers documented the conversion of aromatic olefins with hypofluorous acid leading to the formation of aldehydes. Here, the *trans*-stilbene **S3.1D** underwent the flurohydration reaction in the presence of hypofluorous acid followed by 1,2 phenyl shift to give the diphenylacetaldehyde **S3.1E** (Andrews, L. E.; Bonneti, R. *Tetrahedron Lett.* **1984**, *41*, 781–784). There are a couple of reports where the epoxidation of stilbene employed either Mn-Salen complexes or Fe-Porphyrin

complexes; in these cases, the formation of diphenylacetaldehyde as a side product has been noticed. A similar conversion was documented in 2009 by Sinha and co-workers employing NIS in the presence of a cationic surfactant CTAB in DMSO-Water under microwave heating at 115 °C (Sharma, A.; Sharma, N.; Kumar, R.; Sharma, U.K.; Sinha, A. K. *Chem. Commun*., **2009**, 5299–5301). Very recently, Liu and co-workers reported the oxidative iodofunctionalization in the presence of I_2O_5 as the oxidant, lithium iodide as the iodine source in acetone-water condition, which unexpectedly resulted in the formation of the diarylacetaldehyde **S3.1E** compound (*via* the pinacol rearrangement reaction of the *in situ* formed iodohydrin intermediate) (Yi, W.; Wang, P-F.; Lu, M.; Liu, Q-Q.; Bai, X.; Chen, K-D.; Zhang, J-W.; Liu, G-Q. *ACS Sustainable Chem. Eng.* **2019**, *7*, 16777−16785).

1.5 Synthesis of hydroxydiarylacetaldehydes

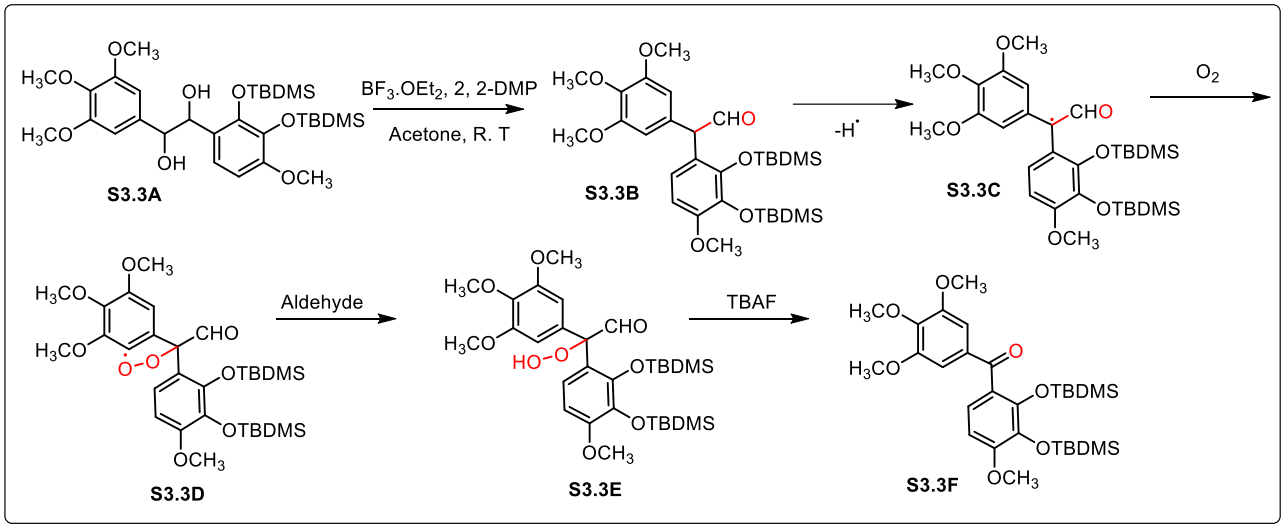
There are only a few reports on the synthesis of hydroxydiarylacetaldehydes. In 1952, Weisenborn and Curtin *et al.* documented the formation of α-hydroxydiphenylacetaldehyde **S3.2B** during the epoxidation of the 1,1'-diarylethylenes **S3.2A** for the first time. In this case, the epoxidation reaction was carried out in the presence of perbenzoic acid followed by hydride elimination, giving the hydroxydiphenylacetaldehyde as the intermediate (Scheme S3.2). Further, the compound **S3.2B** again oxidized in the presence of perbenzoic acid followed by reduction using $LiAlH_4$ to deliver the diol as the final product.



Scheme S3.2: *Hydroxydiphenylacetaldehyde formation from peroxide*
(Weisenborn, F. L.; Taub, D. *J. Am. Chem. Soc*. **1952**, *74*, 1329-1330)

In 2002, Petit *et al.* showed a radical pathway for the formation of a α-hydroperoxido-diphenylacetaldehyde compound from the corresponding diol. This diol **S3.3A** undergoes oxidative rearrangement in the presence of $BF_3.OEt_2$ to give the diarylacetaldehyde **S3.3B.** Furthermore, in order to get the benzophenone product, the radical reaction occurred and the free radical of diarylacetaldehyde **S3.3C** was formed. This radical seemed to be stable, as there was a

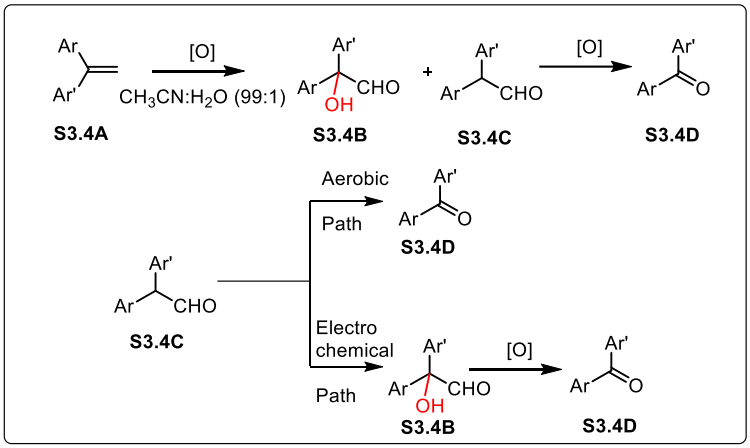
conjugation of the two aryl and carbonyl groups which allowed favorable delocalization. So, next this radical abstracted one proton from another molecule of diphenylacetaldehyde and then α-hydroperoxido-diphenylacetaldehyde **S3.3E** was formed. Finally, this hydroperoxide reacted with the fluoride ion from TBAF, which resulted in benzophenone **S3.3F** formation with the elimination of a carbonyl carbon (Scheme S3.3).



Scheme S3.3: *Synthesis of hydroxyphenstatin by the radical pathway.*

(Pettit, G. R.; Lippert, J. W.; Herald, D. L. *J. Org. Chem.* **2000**, *65*, 7438-7444)

Later, Fry and co-workers studied the anodic conversion of diphenylacetaldehyde **S3.4C** to benzophenone **S3.4D** in the presence of atmospheric oxygen and discussed two paths. The first involved an electrochemical pathway that controlled the potential anodic oxidation of **S3.4C** and was carried out under nitrogen. α-hydroxydiphenylacetaldehyde **S3.4B** was observed as the intermediate, which further converted to benzophenone. The second was the chemical path, which involved the direct conversion of 1,1-diphenylethylene **S3.4A** to benzophenone **S3.4D** in the presence of air where the molecular oxygen or the reagent grade acetonitrile was the source of the oxygen atom for benzophenone formation (Scheme S3.4). Overall, the labelling experiments were carried out to understand the mechanism and proved that the first diphenylacetaldehyde was formed, which further oxidized to give the hydroxydiphenylacetaldehyde intermediate and finally after oxidation, resulted in the benzophenone formation with the removal of the carbonyl carbon.



Scheme S3.4: *Anodic oxidation study of diphenylacetaldehyde*
(Merzel, R. L.; Fry, A. J. *J. Electrochem. Soc.* **2012**, *159* (10), G117-G122)

Hence, what one can conclude from the above paragraphs is that the reports for the synthesis of hydroxydiarylacetaldehyde are very scarce and most of them were isolated as intermediates instead of the main product. Although there are concerns regarding the stability of the formed hydroxydiarylacetaldehyde, its utility in natural product synthesis and possible derivatization/ring annulation, developing methods for the synthesis of hydroxydiarylacetaaldehydes is important. One of the reasons for our entry in this domain was due to the need of developing simple methods for the synthesis of the 4,4-diaryl-γ-butenolide core in dealing with the synthesis of Sacidumulignans.

1.6 γ-butenolides:

Lactones are important structural motifs due to their widespread occurrence in many natural products with a wide range of biological activities.[32] In particular, γ-butyrolactones and their unsaturated analogues γ–butenolides are popular synthetic targets in natural product synthesis and also the building blocks for many biologically active compounds (**Figure F3.4**).[33]

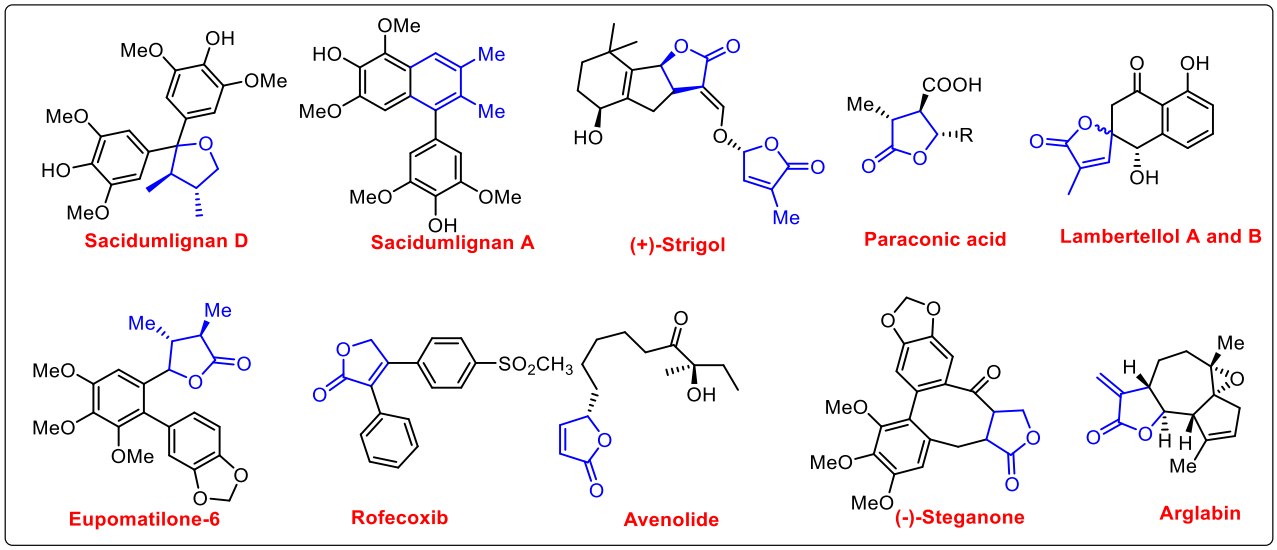
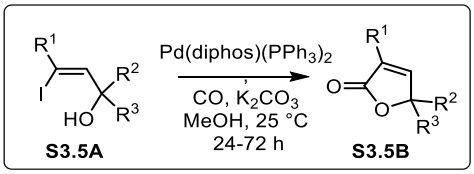


Figure F3.4: *Naturally occurring products having the γ–butenolide or γ–butyrolactone core.*

Due to the presence of a highly versatile functional group, the γ-butenolide core can undergo numerous transformations, which has warranted the development of simple methods for the synthesis of these important building blocks. One of the conventional methods for their synthesis consists of the cyclization of α-hydroxyl acid to lactones. Recently, there has been a great deal of attention on the involvement of transition metals for the preparation of γ,γ-disubstituted α,β-unsaturated-γ-lactones,[34] as this framework forms part of the structure of the natural bioactive compounds. A brief literature collection of their synthesis is presented below.[35]

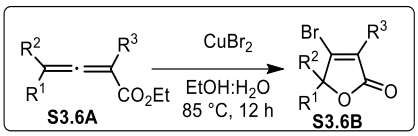
1.7 Literature reports for γ,γ-disubstituted α,β-unsaturated-γ- butenolide synthesis:

In 1980 Stille's group reported the Palladium(0) catalyzed synthesis of 4,4-disubstituted γ-butenolides by applying the carbonylation strategy on halo-alcohols. The reaction started with *Z*-vinyl iodoalcohol **S3.5A** which underwent the carbonylation in the presence of Pd(0) catalyst in methanol solvent heated at 25-35 °C for 24-72 h to give the γ-butenolides **S3.5B** in good yield (Scheme S3.5). The catalytic cycle starts with the oxidative addition of halide to Pd(0) followed by the formation of a palladium-carbon bond by the insertion of the carbon monoxide. Next, an alcohol facilitates the reductive elimination. Importantly, in this type of reaction, the presence of a base is essential to keep the catalyst active and also to activate the hydroxyl group.



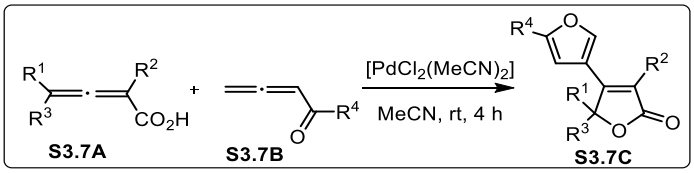
Scheme S3.5: *Synthesis of γ- butenolides by a Pd(0) catalyst.*
(Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193-4198)

Ma and co-workers developed an efficient method for making the γ- butenolides from allenoates. Differently substituted allenoates **S3.6A** reacted with copper bromide at 85 °C in aq. ethanol solvent for 12 h to deliver the corresponding γ-bromobutenolides **S3.6B** in good to moderate yields (Scheme S3.6).



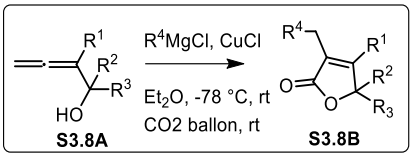
Scheme S3.6: *$CuBr_2$ mediated synthesis of γ- butenolides.*
(Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075–4077)

Later, the same group reported the Pd-catalysed oxidative cyclization and dimerization reaction of 2,3-allenoic acids **S3.7A** and 1,2-allenyl ketones **S3.7B** leading to polysubstituted γ-butenolides **S3.7C** in good to excellent yields (Scheme S3.7).



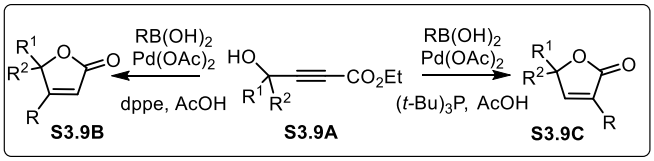
Scheme S3.7: *Pd catalyzed synthesis of highly functionalized the γ- butenolides*
(Ma, S.; Yu, Z. *Angew. Chem. Int. Ed.* **2002**, *41*, 1775-1778)

Very recently, this group documented the carbomagnesiation of 2,3-allenols using a Grignard reagent, which further reacted with carbon dioxide to give the functionalized furanones (Scheme S3.8). The strategy utilized the reaction of substituted allenols **S3.8A** with the Grignard reagent in the presence of CuCl, leading to carbometallation followed by the reaction with carbon dioxide at room temperature at -78 °C to synthesize the γ-butyrolactones **S3.8B**. Here, the use of chiral allenols led to the synthesis of optically active furanones. When the reaction was carried out with RMgCl, it provided better yields than the RMgBr reagent.



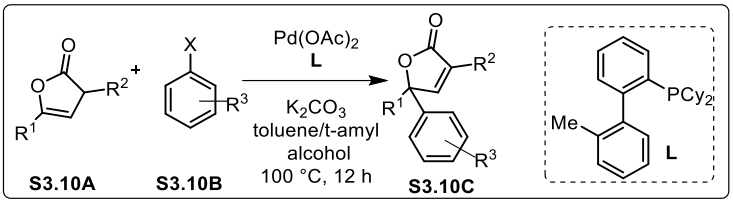
Scheme S3.8: *Synthesis of γ-Butyrolactones via carboxylation of 2,3-Allenols.*
(Li, S.; Miao, B.; Yuan, W.; Ma, S. *Org. Lett.* **2013**, 15, 977–979)

Oh and co-workers have explored the possibility of the regioselective Pd-catalyzed coupling reaction followed by lactonization in between the hydroxyl carboxylates and organoboronic acids (Scheme S3.9). For that purpose, in the first case, they have treated the hydroxyl carboxylate compound **S3.9A** with alkenyl or aryl boronic acid in the presence of $Pd(OAc)_2$ catalyst, dppe ligand, and acetic acid. In the second case, they used $Pd(OAc)_2$ as the catalyst, $(t\text{-}Bu)_3P$ as the ligand, and acetic acid. For both the transformations to occur, different solvents were employed depending upon the substrate, such as THF, 1, 4-dioxane, chloroform heated in the range of 50-100 °C for 4-24 h, to get a variety of functionalized lactones **S3.9B** or **S3.9C** in good yields.



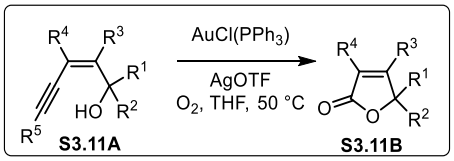
Scheme S3.9: *Pd catalyzed coupling of organoboronic acids with hydroxy esters*.
(Oh, C. H.; Park, S. J.; Ryu, J. H.; Gupta, A. K. *Tetrahedron Lett.* **2004**, *45* 7039–7042)

Buchwald *et al.* developed the Pd-catalyzed arylation reaction on butenolides using different aryl halides to create quaternary centers (Scheme S3.10). In this, the study began with the reaction of simple α,γ-unsaturated butyrolactones **S3.10A** with aryl halide **S3.10B** in the presence of $Pd(OAc)_2$ catalyst, and K_2CO_3 base in toluene/t-amyl alcohol solvent heated up to 100 °C for 12 h to afford the arylated α,β-unsaturated butyrolactone **S3.10C** in good yield. The further utility of this method was proven using the synthesis of the tricyclic tetrahydroisoquinolinone core using α-angelicalactone as the starting material.



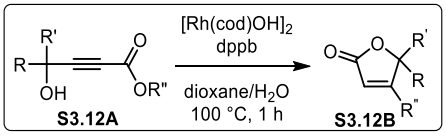
Scheme S3.10: *Pd- catalyzed synthesis of 5,5 di-substituted butenolides.*
(Hyde, A. M. Buchwald S. L. *Org. Lett*., **2009**, *11*, 2663-2666)

Liu *et al.* have determined the feasibility of the cyclization/oxidative cleavage process of the *Z*-enynols using gold catalysis (Scheme S3.11). In that regard, they have chosen *Z*-enynols **S3.11A** as the starting substrates that were treated in the presence of $AuCl(PPh_3)$/AgOTf catalyst system, where oxygen was bubbled into the reaction mixture containing THF solvent, which underwent an easy cleavage of the triple bond at 50 °C in 2-42 h to give butenolides **S3.11B** as the major product in very good yield.



Scheme S3.11: *Au-catalyzed synthesis of butenolides.*
(Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332-11333)

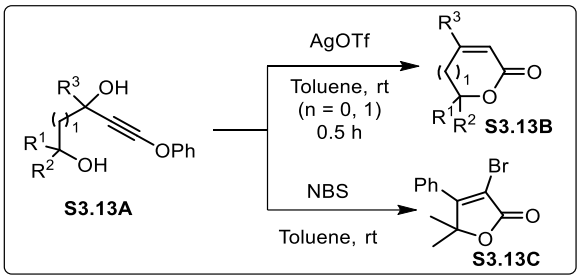
Arcadi *et al.* reported the sequential Rh-catalyzed addition of the organoboron reagent to hydroxyl alkynoates (Scheme S3.12). Aryl boronic acids underwent the addition/lactonization reaction with a variety of hydroxyl alkynoates **S3.12A** in the presence of a rhodium catalyst in dioxane/H_2O solvent heated up to 100 °C for 1 h to lead to the formation of functionalized furanones **S3.12B** in good yields. Mainly, the substrates containing a tertiary propargylic alcohol group resulted in the reversal of the regioselectivity, as the compounds containing the secondary propargylic alcohol group were not affected with regard to regioselectivity. $[Rh(cod)OH]_2$ was seen to be the best catalyst for this transformation but other additional products were also observed and the use of $Rh(acac)(C_2H_4)_2$/dppf as the catalyst system for this reaction resulted in better selectivity than the others.



Scheme S3.12: *Rh catalyzed synthesis of furanones.*

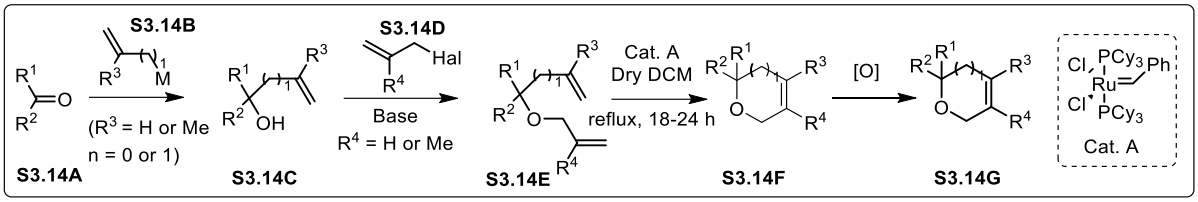
(Alfonsi, M.; Arcadi, A.; Chiarini, M.; Marinelli, F. *J. Org. Chem.* **2007**, *72*, 9510-9517)

Egi and Akai *et al.* reported the silver triflate catalyzed synthesis of multisubstituted α,β-unsaturated-γ-lactones **S3.13B** *via* intramolecular cyclization of phenoxyethynyl diols **S3.13A** using mild conditions. Next, they have also disclosed one other similar kind of cyclization that proceeded using an equivalent amount of NBS instead of AgOTf to afford the bromo substituted α, β-unsaturated-γ-lactones **S3.13C**. The reactivity of diverse phenoxyethynyl diols was also checked. In all the cases, they observed good results for the compounds they synthesized. Although this method required a lengthy means of preparing the starting material the reaction proceeded faster with this reaction to deliver the product in the presence of a catalytic amount of AgOTf, in comparison to other methods (Scheme S3.13).



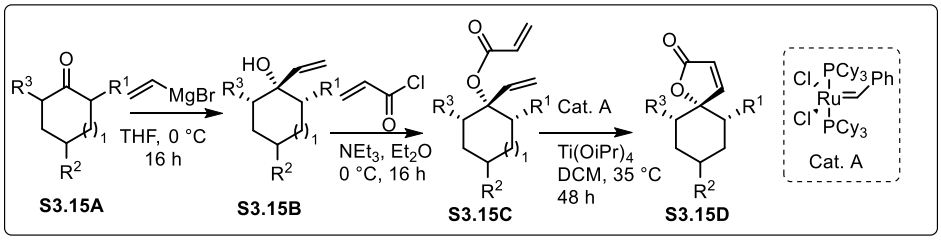
Scheme S3.13: *Ag-catalyzed synthesis of multisubstituted α, β-unsaturated lactones.*
(Egi, M.; Ota, Y.; Nishimura, Y.; Shimizu, K.; Azechi, K.; Akai, S. *Org. Lett.*, **2013,** *15*, 4150-4153)

Merco and Carda *et al.* developed the ring closing metathesis oxidation sequence for the synthesis of five and six-membered cyclic lactones from aldehyde and ketones. In this report, first the carbonyl compounds **S3.14A** were subjected to *C*-allylation using the vinyl magnesium bromide **S3.14B** in dry THF solvent to give allyl carbinols **S3.14C** in more than 80 % yield. After that, *O*-allylation of allyl carbinols was carried out by reacting with base KH and allyl bromide **S3.14D** in THF solvent, which resulted in the formation of the expected ethers **S3.14E**. Next, RCM was performed using the catalyst A in dry DCM solvent heated up to reflux for 18-24 h to give the cyclic ether **S3.14F** in good yield. Finally, allylic oxidation using chromium trioxide in dry DCM at 0 °C in 1 h furnished the final six or five-membered lactones **S3.14G** in good yield (Scheme S3.14).



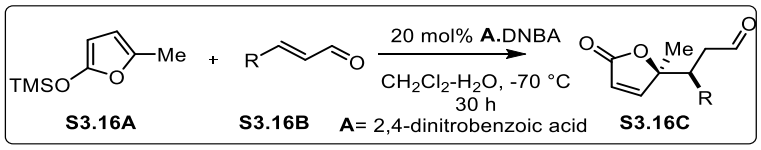
Scheme S3.14: *RCM strategy for the synthesis of 6 or 5-membered lactones*
(Marco, J. A.; Carda, M.; Rodrı´guez, S.; Castillob, E.; Kneeteman, M. *Tetrahedron* **2003**, *59*, 4085–4101)

Langer *et al.* have successfully utilized the ring closing metathesis strategy for the synthesis of spirocyclic butenolides (Scheme S3.15). Here, first the cyclic ketone **S3.15A** underwent the Grignard reaction with vinyl magnesium bromide to get the alcohol **S3.15B** in hand. After that, the same alcohol was subjected to acrylic acid chloride in order to transform it to esters. Later, from the compound **S3.15C,** the ester and the side alkene functionality underwent ring-closing metathesis in the presence of Grubbs 1st generation catalyst with a catalytic amount of $Ti(O^iPr)_4$ in DCM solvent at 35 °C in 48 h afford the formation of spirocyclic butenolides **S3.15D** in good yield.



Scheme S3.15: *Spirocyclic butenolides synthesis by using ring closing metathesis*
(Albrechta, U.; Langer, P. *Tetrahedron* **2007**, *63*, 4648–4654)

Macmillan and co-workers in 2003 reported the synthesis of γ-butenolides by using first the enantioselective organocatalytic Mukaiyama Michael reaction. Silyloxy furan **S3.16A** underwent enantioselective organocatalytic 1,4 addition in the presence of amine salt **A** (2,4-dinitrobenzoic acid) in DCM:H_2O solvent at -78 °C in 30 h, which resulted in the formation of α,β-unsaturated γ-butenolides **S3.16C** in good yield with excellent *ee* (Scheme S3.16).

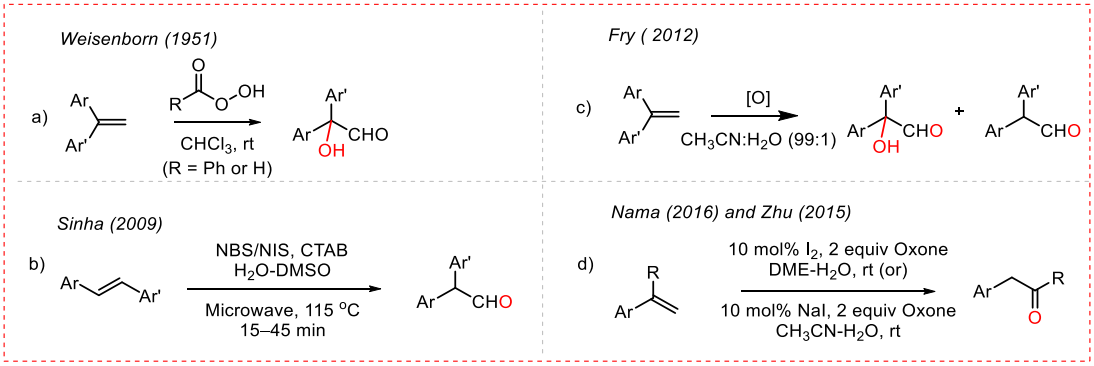


Scheme S3.16: *Organocatalyzed addition of silyloxy Furan*
(Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 1192-1194)

From the above compilation on the synthesis of the 5,5-disubstituted α,β-unsaturated-γ-butenolide and 5,5-disubstituted γ-butyrolactones motifs, it becomes clear that methods based on transition metal-catalysis have dominated this domain and that they require multiple steps for the starting material synthesis. Hence, there is a scope for developing the methods for the synthesis of the γ-butenolide core without the involvement of transition metals and toxic chemicals. This indeed served as one of the starting points of our intention to develop a simple method for the synthesis of diarylhydroxyacetaldehydes and extend their utility for the synthesis of the γ-butenolide core. Our successful endeavor in this regard will be described in the next part.

1.8 Present work:

The oxidation/rearrangement/oligomerization of stilbenes is an important biochemical transformation that has inspired great innovation and the use of various oxidizing agents.[9] The direct oxidation of stilbenes resulting in epoxides and/or vicinal diols is well established and their acid/base catalyzed rearrangements are well-studied reactions.[32,36,37] There are occasions where the rearrangement of initially formed epoxides/diols has been observed during the oxidation of stilbenes.[38] In this context, the House rearrangement of stilbene oxides leading to diarylacetaldehyde is a well-studied reaction.[2,36] In parallel, the Meinwald rearrangement of halohydrins or a one-pot halohydrin synthesis and its rearrangement has been established as important alternatives for the synthesis of diarylacetaldehyde without involving the epoxides.[30,31c, 39] The diarylacetaldehydes are known to undergo decarbonylation resulting in the corresponding benzophenones under oxidative and halogenation conditions.[40,24] The possibility of combining all these events *i.e.* olefin oxidation, pinacol rearrangement and/or oxidative decarbonylation is interesting and this has been executed very recently for the direct synthesis of carbonyl compounds from styrenes/stilbenes (**Scheme S3.17**).[29c, 41]

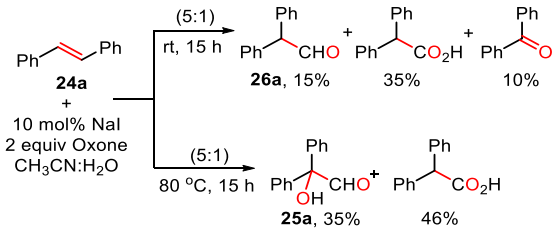


Scheme S3.17*. Selected oxidative rearrangement of stilbenes/arylalkenes*

In this chapter, we document the direct conversion of stilbenes **24** to α-hydroxy diarylacetaldehydes **25**. The possibility of obtaining α-hydroxydiarylacetaldehyde **25** from stilbenes was speculated considering a recent report from Fry and coworkers on the anodic oxidation of diphenylacetaldehyde leading to benzophenone, which indicated the occurrence of α-hydroxydiphenylacetaldehyde as an intermediate.[42] Earlier, Weisenborn and Curtin have documented the isolation of α-hydroxydiarylacetaldehydes during the epoxidation of the 1,1'-

diaryethylenes.[43] This option was employed with the idea of developing a general method for the synthesis of a 5,5-diaryl-γ-butenolide core,[44] where the Stille-Gennari olefination of a α-hydroxydiarylacetaldehyde **25** and subsequent lactonization was a direct proposition.[45]

With this speculation, documented methods for the direct conversion of aryl alkenes to carbonyl compounds have been examined. Among these, the reports of Sinha,[31] Zhu[39c] and Nama[39d] groups are interesting. Sinha and co-workers reported the conversion of stilbenes to diarylacetaldehydes employing NBS in the presence of a cationic surfactant under microwave irradiation.[31] The Nama and Zhu groups reported the iodine catalyzed oxidative rearrangement of aryl alkenes to β-arylketones.[39c,39d] A close examination of these reports prompted the exploration of the NaI and Oxone combination in our pursuit. Initial experiments employing simple stilbene as a substrate under Zhu conditions (10 mol% NaI, 2 equiv Oxone in a 5:1 CH_3CN/H_2O at rt) gave a mixture of diphenylacetaldehyde **26a** (15%), diphenylacetic acid (35%) and benzophenone (10%). This prompted us to do a parallel screening of reaction conditions by varying the reaction temperature and solvent ratio. Initial experiments with temperature variation revealed the formation of the requisite 2-hydroxy-2,2-diphenylacetaldehyde (**25a**). For example, when carried out at 80 °C with the same composition of the reaction contents, the required hydroxyacetaldehyde **25a** was obtained in 35% yield along with 46% of diphenyl acetic acid. As shown in Scheme S3.18, changing the solvent composition also had some positive effect on the reaction outcome. When the reaction was conducted in a 1:1 mixture at rt, the formation of **26a** in 42% yield along with 12% benzaldehyde was observed.

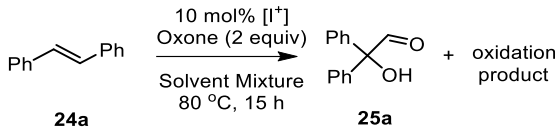


Scheme S3.18: *Selected conditions for the oxidative rearrangement of stilbene **24a**.*

The best results were obtained when the reaction was conducted at 80 °C in a 1:1 CH_3CN/H_2O mixture for 15 h. The starting stilbene was completely consumed and the required 2,2-diaryl-2-hydroxyacetaldehyde (66%) was obtained as the major product and a mixture of benzaldehyde/benzophenone (10%) was also isolated. Under similar conditions, when different

iodine sources such as I_2, KI, CuI, NIS, NH_4I were employed, the required 2,2-diaryl-2-hydroxyacetaldehyde was obtained in 19–55% yield along with the benzaldehyde and/or benzophenone as the minor products (entries 3–7). Furthermore, when NBS was used as the halogen source, benzoin was obtained in 40% yield (entry 8). Decreasing or increasing the amount of oxone was not encouraging (entries 9 and 10). Further experiments were carried out to shift the reaction outcome completely towards the formation of the required product **25a**, by changing the solvent combination, using additives and by the use of microwave. The results were not satisfactory.

Table T3.2.[a] Optimisation.



24a 25a

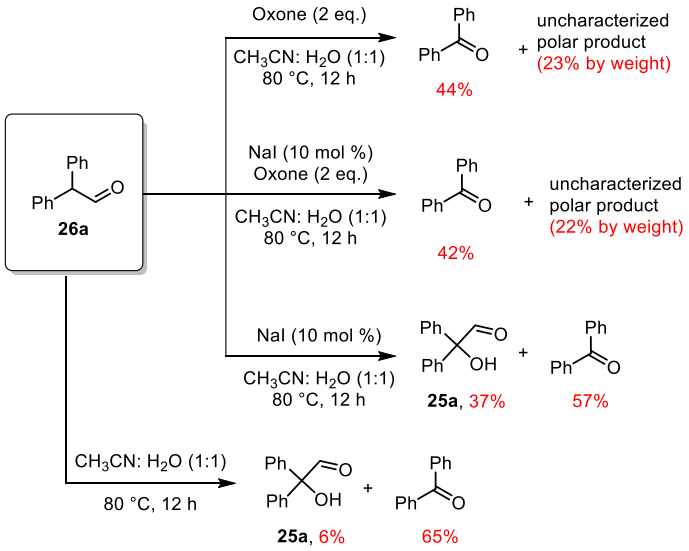
Entry	Iodine Source	Solvent ratio	Yield[b] 25a
1	NaI	5:1	35[c]
2	**NaI**	**1:1**	**66**
3	I_2	1:1	47
4	KI	1:1	48
5	CuI	1:1	42
6	NIS	1:1	19
7	NH_4I	1:1	55
8	NBS	1:1	40[d]
9	NaI[e]	1:1	23
10	NaI[f]	1:1	48
11	I_2	dioxane:H_2O	46
12	NaI	DMSO:H_2O	NR
13	NaI	MeOH:H_2O	2
14	NaI	DME:H_2O	5
15	NaI	DMF:H_2O	30
16	NaI	acetone:H_2O	**1** + diketone
17	NaI+CTAB	1:1	56
18	NaI+TBAI	1:1	48
19	NaI[g]	1:1	28

[a]all reactions were carried out on approximately a 0.5 mmol scale, 2 equiv of oxidant and 0.1 equiv of iodine source, all reagent and substrate additions were done at room temperature (25 °C), with stirring for the next 15 h at 80 °C; [b]isolated yields, [c]diphenyl acetic acid as the major product; [d]benzoin as the major product; [e]1 equiv of oxone; [f]2.5 equiv of oxone used. [g]reaction was carried out in MW at 100 °C.

Next, the structure of compound **25a** was established with the help of ^{1}H and ^{13}C NMR spectral and analytical data. Coming to the ^{1}H NMR spectrum of compound **25a**, all the aromatic protons resonated at δ 7.3 ppm, with the aldehyde group at δ 9.9 ppm. The OH proton appeared as a broad singlet at δ 3.9 ppm. In the ^{13}C NMR spectrum of compound **25a**, the aliphatic quaternary carbon peak appeared at δ 83.4 ppm as a singlet and also the carbonyl aldehyde resonated at δ 198.0 ppm as a doublet. The further HRMS value calculated for compound **25a** was 235.0730 and the peak was found at 235.0729, which supported the constitution of the hydroxyacetaldehyde product **25a**.

1.9 Control Experiments:

Having realized the possibility of synthesising 2,2-diphenyl-2-hydroxyacetaldehyde directly from stilbene, we next looked at the course of the reaction. The immediate concern was the hydroxylation reaction and the role of the Oxone or the by-products resulting after the initial oxidation. In order to understand this, we conducted a set of control experiments employing freshly prepared diphenylacetaldehyde **26a** with the exclusion of the reaction components one after the other (Scheme S3.19).

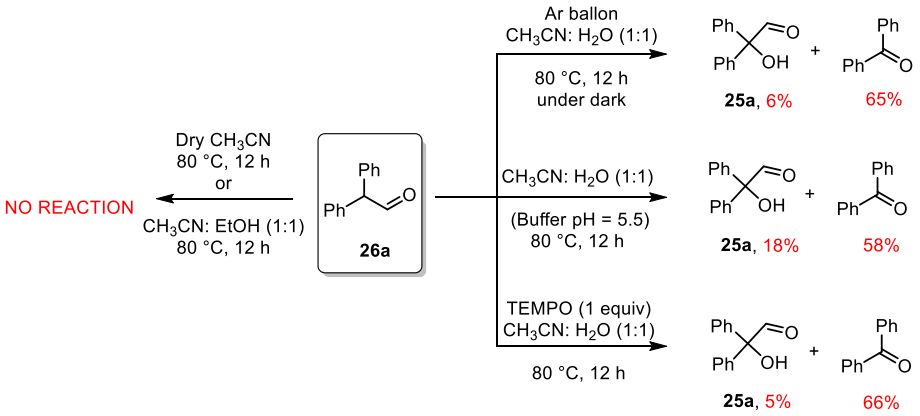


Scheme S3.19: *Control experiments.*

As shown in Scheme S3.46, when **26a** was refluxed under the employed conditions in the presence of Oxone and NaI in a mixture of 1:1 acetonitrile/water, benzophenone in 42%

yield and diphenylhydroxy acetic acid in 22% yield were isolated. Next, a similar outcome was noticed when the reaction was carried out in the absence of NaI. Interestingly, when only Oxone was replaced, the requisite hydroxyaldehyde **25a** was isolated in 37% yield, along with 57% benzophenone, indicating that NaI was playing a role in the α-hydroxylation. Next, when diphenylacetaldehyde **26a** was heated in a mixture of 1:1 acetonitrile/water in the absence of both Oxone and NaI, the formation of hydroxyaldehyde **25a** (6%) and benzophenone (65%) was noticed and when water was also removed, the starting **26a** was seen to be intact. These experiments revealed that the presence of water was essential.

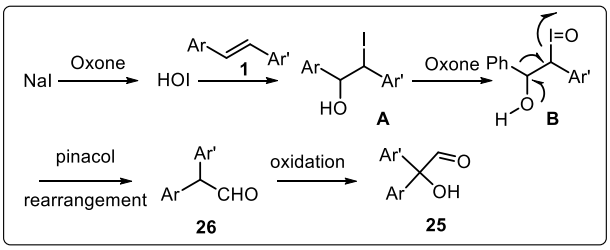
In addition, a separate experiment was carried out where the solution of **26a** in a mixture of 1:1 acetonitrile/water was purged with argon for fifteen minutes and heated under argon atmosphere under dark in a closed flask covered with silver foil (Scheme S3.20). In this case too, complete conversion of the starting diphenyl acetaldehyde was noticed and resulted in the isolation of **25a** in 6% and benzophenone in 65% yields. Interestingly, when the reaction was carried out by adjusting the pH to 5.5 (measured for normal optimized conditions), the yield of hydroxy aldehyde was improved to 18%. However, the benzophenone (58%) was the major product, indicating that the pH of the reaction medium plays a role on determining the stability of the intermediate hydroxyacetaldehyde. As a control, when we replaced the water with ethanol as a proton source or in dry acetonitrile, there was no formation of **25a** or benzophenone. Finally, to examine the possibility of a radical pathway, the reaction was carried out in the presence of TEMPO as a radical suppresser. This resulted in the isolation **25a** in 5% yield and benzophenone in 66% yield.



Scheme S3.20: *Control experiments.*

All these results indicate that the reaction is proceeding *via* oxidation of diphenylacetaldehyde to hydroxyaldehyde; that any external oxidant may not be required for the α-hydroxylation; [43,46] that the presence of water is important and that it does not follow the radical pathway. This is in accordance with earlier reports where water was found to be the source of oxygen for the oxidation of diphenylacetaldehyde to hydroxyaldehyde.[42a] The ready deformylation of the hydroxyaldehyde to the benzophenone under neutral conditions and the isolation of the hydroxyacetaldehyde in moderate yields when conducted in the presence of acidic buffer suggests that the deformylation is pH sensitive. Also, though the role of NaI on the α-hydroxylation step is not clear, its presence appears to be important.

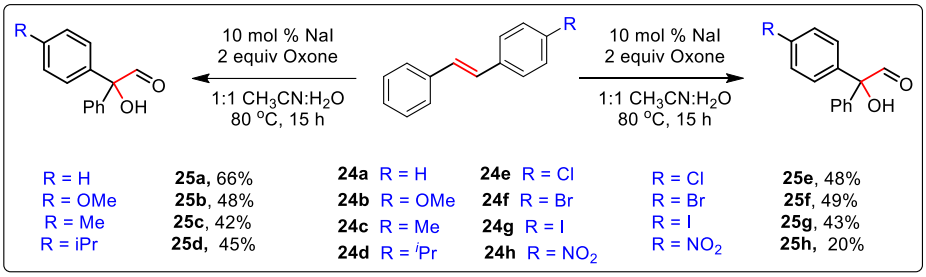
Coming to α-hydroxylation of **26a**, as discussed previously, there are two proposals postulated. One is a radical pathway comprising of oxygen abstracting the α-hydrogen followed by recombination of the carbon centered and peroxide radicals, which would result in the α-hydroperoxido-diphenylacetaldehyde.[41a,29c] The other one is an anodic oxidation pathway that involves the addition of water to a cationic radical generated after adding an electron to the enol of the diphenylacetaldehyde.[42] The preliminary results in our case favor the second pathway; however, further studies are warranted to understand the course of oxidation and are currently in progress. With this information in hand and with help of earlier proposals on the iodine-mediated oxidative rearrangements,[39] we propose the following tentative mechanism (Scheme S3.21). Initially, NaI is oxidized to HOI, which adds to the alkene in the presence of water to form the iodohydrin A. Further oxidation of iodine with Oxone leads to the unstable hypervalent iodine intermediate B, which undergoes aryl ring migration to form the diphenylacetaldehyde **26**, which subsequently undergoes oxidation leading to the corresponding hydroxyaldehyde **25**.



Scheme S3.21: *Tentative mechanism.*

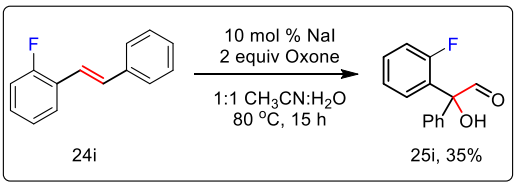
Next, the compatibility of various stilbenes under the current conditions has been examined. In general, substituted stilbenes having either electron donating or electron withdrawing groups on the benzene ring are found to be compatible (Scheme S3.22). However, the yields are moderate to good. In all cases, the corresponding cleaved aldehyde(s), and, in some cases, the corresponding acid[47] and/or benzophenone were obtained as minor products. Initially, stilbenes **24b**–**24h** having substituents at the *p*-position (OMe, Me, *iso*-propyl, Cl, Br, I, NO_2 respectively) on one of the aryl rings have been employed. The reactions proceeded smoothly and provided the corresponding 2,2-diaryl-2-hydroxyacetaldehydes **25b**–**25h** in moderate yields (20–49%) (Scheme S3.22). Coming to the ^{1}H NMR spectrum of compound **25b,** one of the aromatic ring protons resonated at δ 7.38–7.45 ppm as a multiplet of five protons and another 1,4-disubstituted aromatic ring resonated at δ 7.29 and 6.95 ppm as a doublet of doublet for 4 protons. Next, the characteristic aldehyde proton appeared at δ 9.9 ppm, the methoxy proton was seen to resonate at δ 3.84 and the hydroxy proton appeared at δ 4.23 ppm as a singlet. In the ^{13}C NMR spectrum of compound **25b,** the aliphatic quaternary carbon peak appeared at δ 83.1 ppm and the carbonyl aldehyde resonated at δ 198.0 ppm. Furthermore, the HRMS value calculated for compound **25b** was 265.0835 and the peak was found at 265.0832, thereby providing the additional confirmation to the assigned structure of hydroxyacetaldehyde **25b**.

Next, in the ^{1}H NMR spectrum of compound **25h**, the characteristic *trans*-olefin peak disappeared completely and the aldehyde proton resonated at δ 10.01 ppm and the hydroxy proton was seen at δ 4.48 ppm as singlets. Next, out of two aryl rings, the protons of one aromatic ring appeared at δ 8.26 and 7.63 ppm as a doublet of doublet for four protons and the protons of the other aromatic ring resonated at δ 7.35–7.50 and 7.30 ppm as multiplets integrating together for five protons. In the ^{13}C NMR spectrum of compound **25h**, the carbonyl carbon appeared at δ 197.0 ppm and the aliphatic quaternary carbon peak appeared at δ 83.2 ppm. Furthermore, the HRMS value calculated for compound **25h** was 258.0761 and the peak was found at 258.0752, providing further support for the assigned structure of the hydroxyaldehyde product **25h.**



Scheme S3.22: *Substrate scope of para-substituted stilbenes.*

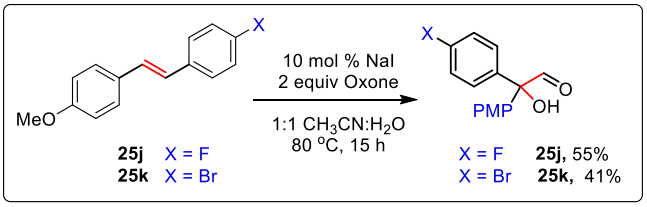
Next, the *ortho*-substituted stilbene **24i** employed for the same reaction conditions and the corresponding *ortho*-substituted hydroxyacetaldehyde **25i** were obtained in 35% yield. Coming to the ^{1}H NMR spectrum of compound **25i**, the aldehyde proton resonated at δ 10.06 ppm as a singlet and the hydroxy proton was seen as a broad singlet at δ 4.65 ppm. Next, two aromatic ring protons appeared in the range of δ 7.38–7.17 ppm as a multiplet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 196.7 ppm with a corresponding fluorine coupling constant value of $^{4}J_{C\text{-}F}$ = 5.4 Hz. Then, the quaternary carbon holding the aryl, aldehyde, and hydroxy groups resonated at δ 82.1 ppm, along with a fluorine coupling constant value of $^{4}J_{C\text{–}F}$ = 3.1 Hz. The further HRMS value calculated for compound **25i** was 231.0816 and the peak was found at 231.0805, providing additional confirmation of the formed hydroxyacetaldehyde product **25i**.



Scheme S3.23: *Substrate scope of ortho-substituted stilbenes.*

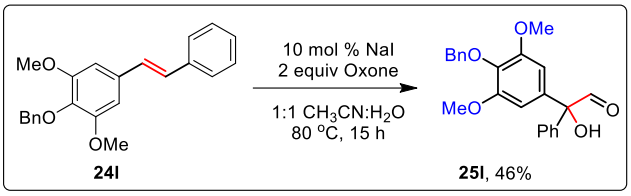
Similarly, the oxidative rearrangement of unsymmetrical stilbenes **24j**–**24k** having different substituents on both aryl rings gave the requisite hydroxyacetaldehydes **25j**–**25k** in moderate yields (41–55%; Scheme S3.24). Coming to the ^{1}H NMR spectrum of compound **25j**, the distinguishing *trans*-olefin peak disappeared completely and the important aldehyde proton resonated at δ 9.91 ppm as a singlet and the hydroxy proton was also seen at δ 3.83 ppm. Next, one of the aromatic ring protons appeared at δ 7.38 and 7.27 ppm as a doublet of doublet for four protons. Along with this, the other aromatic ring resonated at δ 7.11 and 6.95 ppm as a multiplet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 197.6 ppm and the

quaternary peak appeared at δ 82.7 ppm. The fluorine attached quaternary carbon resonated at δ 162.6 ppm with the corresponding fluorine coupling constant $^{1}J_{C-F}$ = 248.0 Hz. The further HRMS value calculated for compound **25j** was 261.0921 and the peak was found at 261.0914, providing the supplementary confirmation to the formed hydroxyacetaldehyde product **25j**.



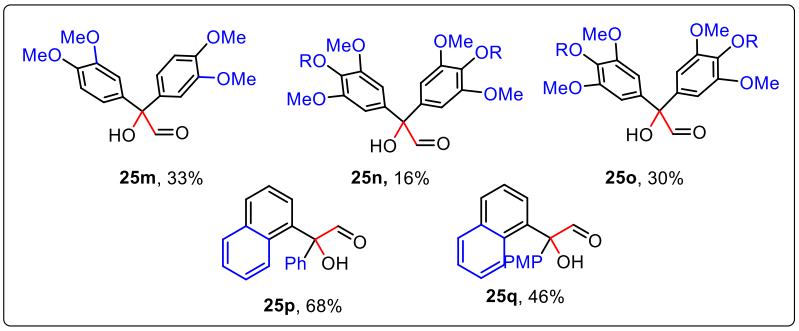
Scheme S3.24: *Substrate scope of unsymmetrical stilbenes*

Next, we examined a benzyloxy protected stilbene **24l**, which gave product **25l** in 46% yield. The structure of the compound **25l** was established with the help of NMR spectral data. For example, in the ^{1}H NMR spectrum of compound **25l**, the typical aldehyde proton resonated at δ 9.87 ppm as a singlet and the hydroxy proton was seen at δ 4.33 ppm as a broad singlet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 197.6 ppm and the quaternary carbon resonated at δ 83.4 ppm. Further HRMS value for compound **25l** was found at 401.1349, providing the supportive confirmation to the formed hydroxyacetaldehyde product **25l**.



Scheme S3.25: *Oxidative rearrangement of benzyloxy protected stilbene.*

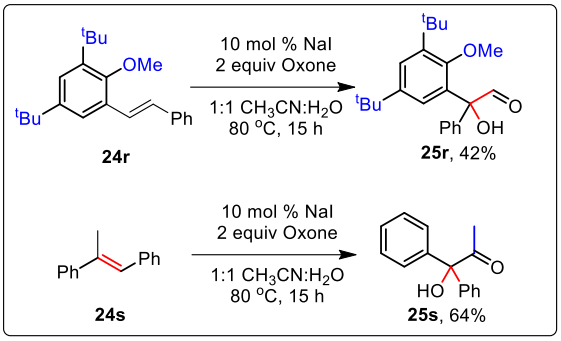
However, increase in the number of methoxy groups on the aryl ring of stilbenes **24m**–**24o** resulted in lower yields of the corresponding α-hydroxydiarylaldehydes **25m**–**25o** in 16–33% yield. This may be due to increased resonance stabilization, which may favour the cleavage of the double bond. Next, the scope of oxidation was further examined employing stilbenes **24p** and **24q** having a naphthalene ring on one side. Here too, the oxidative rearrangement was facile and provided the hydroxyaldehydes **25p** and **25q** in good yields (Scheme S3.26).



Scheme S3.26: *Oxidative rearrangement of the highly substituted/naphthalene substituted stilbene.*

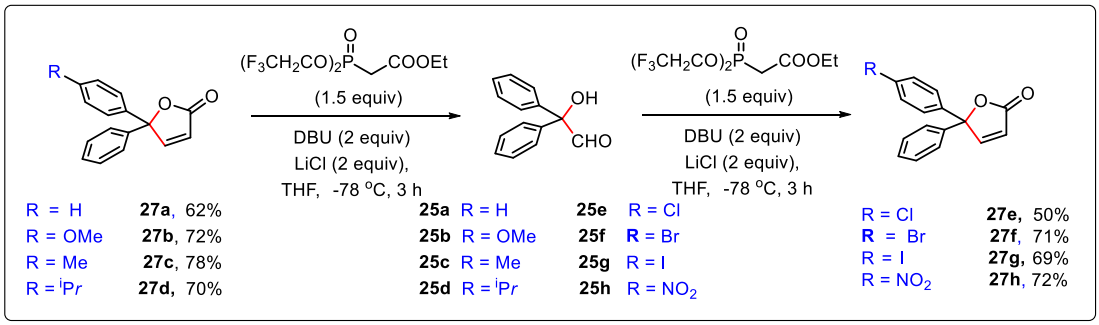
Coming to the ^{1}H NMR spectrum of the symmetric diaryl hydroxyacetaldehyde **25o**, the aromatic ring protons appeared at δ 6.57 ppm as a singlet for four protons. Next, the aldehyde proton appeared at δ 9.91 ppm and the hydroxy proton resonated at δ 4.42 ppm as a singlet. In the ^{13}C NMR spectrum, the quaternary carbon peak appeared at δ 83.5 ppm and also the carbonyl aldehyde was seen to resonate at δ 197.2 ppm. The further HRMS value calculated for compound **25o** was 449.2170 and the peak found at 449.2166, providing the extra confirmation to the formed hydroxyacetaldehyde product **25o**.

The stilbene **24r** having a *tert*-butyl group on one side of the aryl ring was also compatible under these conditions and gave the corresponding oxidation product **25r** (42%). Interestingly, the oxidative rearrangement of stilbene **24s** having a methyl substitution on alkene was also facile and the hydroxyketone **25s** was formed in 64% yield (Scheme S3.27). The exclusive formation of **25s** revealed that the phenyl group was more prone to migration over the methyl group. Coming to the ^{1}H NMR spectrum of compound **25s**, all the aromatic protons resonated at δ 7.28 ppm as a multiplet. The hydroxy proton was seen at δ 4.76 ppm as a singlet and the methyl attached to the ketone resonated as a singlet at δ 2.17 ppm. In the ^{13}C NMR spectrum, the ketone carbon appeared at δ 208.7 ppm and the quaternary carbon was seen to resonate at δ 85.8 ppm as a singlet. The further HRMS value calculated for compound **25s** was 249.0886 and the peak found at 249.0884, providing the supportive confirmation to the formed hydroxyacetaldehyde product **25s**.



Scheme S3.27: *Oxidation of tert-butyl and methyl group substituted stilbenes.*

Having access to a good number of α-hydroxydiarylacetaldehydes, we proceeded further to synthesize γ,γ-diaryl-γ-butenolides employing the Still-Gennari Wittig olefination followed by cyclisation. Generally employed methods for their synthesis involve either adding the aryl Grignard reagents to lactones/esters or starting with the benzophenones. These methods require multiple steps.[44] After screening a couple of conditions reported for *cis*-Wittig olefination,[45] the treatment of hydroxyaldehyde **25a** with ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]acetate in the presence of DBU and LiCl at –78 °C gave the required diaryl-γ-butenolide **27a** in very good yields.

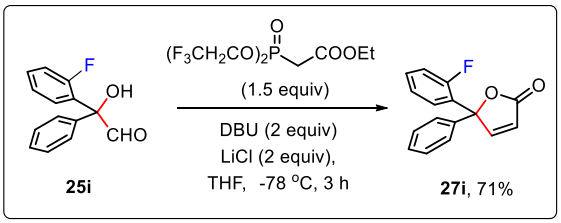


Scheme S3.28: *Substrate scope of γ,γ-diaryl-γ-butenolides containing a para-substituent.*

The structure of the product obtained was established with the help of NMR and HRMS analysis. For example, in the ^{1}H NMR spectrum of compound **27a,** the characteristic *cis*-olefin protons appeared as doublets at δ 7.96 ppm and r at δ 6.20 ppm with a coupling constant of 5.49 Hz. In the ^{13}C NMR spectrum, the five-membered ester carbonyl peak resonated at δ 172.1 ppm and the quaternary carbon holding two aryl groups resonated at δ 92.2 ppm. Later, the HRMS value of compound **27a** was found 237.0908, thus confirming the assigned constitution of the product **27a**.

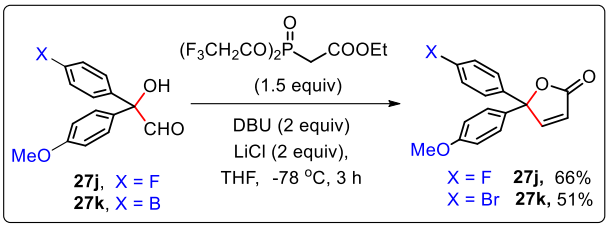
Inspired with this initial success, all the earlier synthesised 2,2-diaryl-2-hydroxyacetaldehydes were subjected for the *cis*-Wittig olefination followed by cyclization to obtain the corresponding lactones in moderate to good yields. It was notable that all the diarylhydroxyaldehydes with electron-donating groups, as well as electron-withdrawing groups on the benzene ring, gave similar yields. When the *para*-substituted hydroxy aldehydes **25b**–**25h** were subjected to this lactonisation conditions, the corresponding lactones **27b**–**27h** were obtained in good yields (50–78%) (Scheme S3.28).

Further hydroxy aldehyde **25i** holding *ortho*-substituents have been employed for the same reaction conditions to obtain the corresponding *ortho*-substituted γ–butenolides **27i** in 71% yield (Scheme S3.29). Coming to the structural characterization, in the ^{1}H NMR spectrum of compound **27i**, the olefin peaks appeared as doublets, one at δ 8.18 ppm and other at δ 6.23 ppm with the coupling constant of δ 5.3 Hz. In the ^{13}C NMR spectrum, the ester carbonyl peak resonated at δ 171.7 ppm and the quaternary carbon holding two aryl groups was detected at δ 90.0 ppm. Next, the aromatic carbon attached to fluorine atom resonated at δ 159.3 ppm with the fluorine coupling constant $^{1}J_{C\text{-}F}$ = 247 Hz. The observed HRMS value of compound **27i**: 255.0815 (calcd. 255.0816) was supportive of the assigned constitution of **27i**.



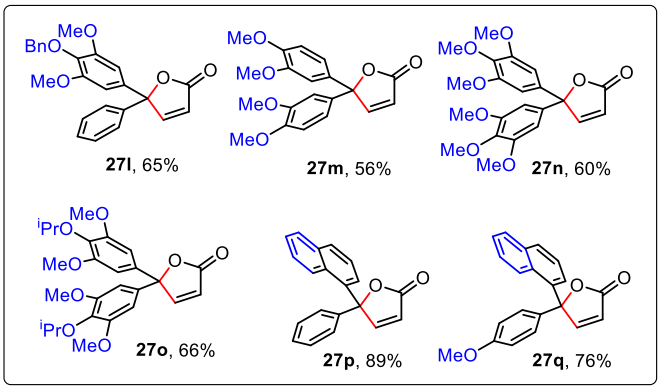
Scheme S3.29: *Synthesis of ortho-substituted γ,γ-diaryl-γ-butenolide.*

Similarly, the unsymmetrically substituted hydroxy aldehydes **25j** & **25k** led to the synthesis of the lactones **27j** and **27k** in good yields (66% and 51%). We checked the feasibility of having an electron donating group attached to one side of the aromatic ring and electron withdrawing groups attached to the other side of the ring and observed good results. (Scheme S3.30).



Scheme S3.30: *Synthesis of unsymmetrically substituted γ,γ-diaryl-γ-butenolide.*

Further, highly/naphthalene γ–butenolides (**27l**–**27o**) having multiple alkoxy groups on the aromatic ring have been successfully prepared in good yields (56–66%) using the corresponding aldehydes **25l**–**25o**. Similarly, olefination cum lactonization of the naphthalene substituted hydroxy aldehydes **25p** and **25q** proceeded smoothly to provide the corresponding lactones **27p** (76%) and **27q** (89%) in excellent yields (Scheme S3.31). The structures of all the compounds synthesized have been established with the help of spectral and analytical data.



Scheme S3.31: *Synthesis of highly/naphthalene substituted γ,γ-diaryl-γ-butenolide.*

1.10 Conclusions

In conclusion, an unprecedented NaI-catalyzed Oxone-mediated oxidative rearrangement of stilbenes to 2,2-diaryl-2-hydroxyacetaldehydes has been documented. With the help of control experiments, a tentative mechanism postulating the possible oxygen transfer from the water to the initial formed diarylacetaldehyde for the final α-hydroxylation has been proposed. These diarylhydroxyacetaldehydes have been converted to 5,5-diaryl-γ-butenolides by employing a two-carbon cis-Wittig reaction and intramolecular lactonization. Currently, work in the direction of understanding the mechanism of α-hydroxylation is in progress.

Experimental Section: All starting stilbenes were prepared according to well–known literature procedures.[48]

General procedure for the oxidation of stilbenes 24: In general, all reactions were carried out employing 100 mg of stilbene **24**.

At rt, a solution of stilbene **24** (100 mg, 0.55 mmol, 1 equiv) in a 1:1 CH_3CN:H_2O system (4 mL) was treated with sodium iodide (8.3 mg, 0.05 mmol, 10 mol %) and stirred for 5 min and then Oxone (337 mg, 1.1 mmol, 2 equiv) was added slowly. The resulting suspension was heated at 80 °C for 15 h by which time the TLC showed the complete disappearance of the starting stilbene. The reaction mixture was concentrated under reduced pressure and partitioned between EtOAc (20 ml) and water (10 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with $Na_2S_2O_8$ (3 x 20 mL), brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford the hydroxyaldehyde **25** along with small amounts of side product aldehyde and sometimes the ketone.

Representative procedure for 5 mmol scale:

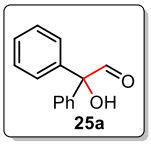
At rt, a solution of Stilbene **24a** (900 mg, 5 mmol) in 1:1 CH_3CN:H_2O (40 mL), was added sodium iodide (75 mg, 0.5 mmol) then stirred for 5 min followed by addition of Oxone (3072 mg, 10 mmol) was done slowly at 25 °C and the contents were heated at 80 ^oC for 15 h. Usual workup followed by purification by column chromatography afforded compound **25a** (699 mg, 66% yield) as white solid.

General Procedure for the **preparation of γ,γ-disubstituted α,β-unsaturated-γ-lactones** ***27:*** In general all reactions were carried out employing 100 mg of hydroxy aldehyde **25**.

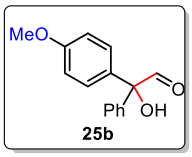
To a suspension of anhydrous lithium chloride (2 equiv) in dry THF (5 mL) under a nitrogen atmosphere, ethyl [bis(2,2,2-trifluoroethoxy)phosphinyl]acetate (1.5 equiv) was added and stirred for 15 min at 25 °C. Then the reaction mixture was cooled to 0 °C and treated with DBU (2 equiv) and stirred at the same temperature for additional 30 min. Next, the reaction mixture was cooled to –78 °C and a solution of the aldehyde **25** (1 equiv) in THF (5 mL) was added dropwise and continued stirring for 3 h. Then the reaction mixture was warmed to 0 °C and quenched by adding sat. NH_4Cl and concentrated on a rotary evaporator under reduced pressure.

The crude was dissolved in ethyl acetate (20 mL) and was washed with H_2O (10 mL) followed by brine and concentrated. The crude was purified by column chromatography to procure the γ,γ-disubstituted α,β-unsaturated-γ-lactone product **27**.

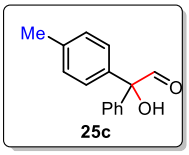
2-Hydroxy-2,2-diphenylacetaldehyde (25a). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 78 mg (66%); colorless solid; mp: 55–57 °C (*Lit.*[49] 52–55 °C); IR(neat) ν_{max} 3477, 2925, 1723, 1491, 1448, 1336, 1176, 962, 794, 754, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.9 (s, 1H), 7.3 (s, 10H), 3.9 (br. s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0 (d), 139.3 (s, 2C), 128.8 (d, 4C), 128.5 (d, 2C), 127.4 (d, 4C), 83.4 (s) ppm; HRMS (ESI) calcd. for $C_{14}H_{12}O_2Na$: 235.0730 $[M + Na]^+$; found 235.0729.



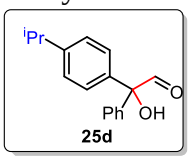
2-Hydroxy-2-(4-methoxyphenyl)-2-phenylacetaldehyde (25b). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (48%); colorless solid; mp: 72–74 °C (*Lit.*[43b] 73–74 °C); IR(neat) ν_{max} 3477, 2951, 1721, 1608, 1511, 1448, 1302, 1252, 1173, 102, 964, 831, 751, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.0 (s, 1H), 7.38–7.45 (m, 5H), 7.29 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 4.38 (s, 1H), 3.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0 (d), 159.6 (s), 139.3 (s), 131.3 (s), 128.7 (d, 2C), 128.7 (d, 2C), 128.3 (d), 127.3 (d, 2C), 114.1 (d, 2C), 83.1 (s), 55.2 (q) ppm; HRMS (ESI) m/z: calcd. for $C_{15}H_{14}O_3Na$: 265.0835 $[M + Na]^+$; found: 265.0832.



2-Hydroxy-2-phenyl-2-(*p*-tolyl)acetaldehyde (25c).[50] Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 49 mg (42%); colorless syrup; IR(neat) ν_{max} 3477, 2921, 1720, 1512, 1448, 1173, 1014, 815, 751, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.29 (s, 5H), 7.14 (d, J = 2.4 Hz, 4H), 4.29 (s, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2 (d), 139.5 (s), 138.4 (s), 136.5 (s), 129.6 (d, 2C), 128.8 (d, 2C), 128.5 (d), 127.5 (d, 2C), 127.4 (d, 2C), 83.4 (s), 21.2 (q) ppm; HRMS (ESI): calcd. for $C_{15}H_{14}O_2Na$: 249.0886 $[M+Na]^+$; found: 249.0883.

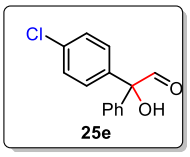


2-Hydroxy-2-(4-isopropylphenyl)-2-phenylacetaldehyde (25d). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 51 mg (45%); colorless solid;; mp: 50–52 °C; IR(neat) ν_{max} 3482, 2951, 1720, 1509, 1450, 1338, 1175, 1014, 829, 793, 741, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.31 (s, 5H), 7.18 (s, 4H), 4.28 (s, 1H), 2.84 (quin, J = 6.9 Hz, 1H), 1.17 (d, J = 6.9 Hz,



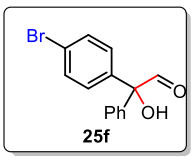
6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1 (s), 149.3 (s), 139.4 (s), 136.7 (s), 128.8 (d, 2C), 128.4 (d, 2C), 127.4 (d, 3C), 126.9 (d, 2C), 83.3 (s), 33.8 (d), 23.9 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{17}H_{18}O_2Na^+$: 277.1199 $[M+Na]^+$; found: 277.1196.

2-chloro-2-(4-chlorophenyl)-2-phenylacetaldehyde (25e).[51] Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (45%); yellow syrup; IR(neat) ν_{max} 3466, 2922, 1720, 1490, 1400, 1092, 1011, 823, 823, 792, 758, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.28–7.55 (m, 9H), 4.41 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5 (d), 139.0 (s), 137.7 (s), 134.6 (s), 129.0 (d, 2C), 128.9 (d, 2C), 128.8 (d), 128.7 (d, 2C), 127.3 (d, 2C), 83.0 (s) ppm; HRMS (ESI): calcd. for $C_{14}H_{10}O_2Cl$:245.0373 [M–H]+; found: 245.0364.



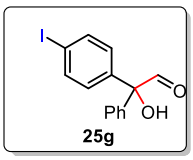
25e

2-(4-Bromophenyl)-2-hydroxy-2-phenylacetaldehyde (25f). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (49%); colorless syrup; IR(neat) ν_{max} 3451, 2922, 1720, 1487, 1448,1395, 1153, 1072, 1006, 898, 817, 791, 756, 697, 653 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.40–7.46 (m, 3H), 7.35–7.37 (m, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.41 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5 (d), 138.9 (s), 138.3 (s), 132.0 (d, 2C), 129.1 (d, 2C), 129.0 (d), 128.7 (d, 2C), 127.3 (d, 2C), 122.8 (s), 83.0 (s) ppm; HRMS (ESI): calcd. for $C_{14}H_{10}O_2Br$: 288.9871 $[M–H]^+$; found: 288.9859.



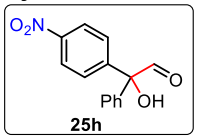
25f

2-Hydroxy-2-(4-iodophenyl)-2-phenylacetaldehyde (25g). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 47 mg (43%); colorless syrup; IR(neat) ν_{max} 3463, 2921, 1721, 1484, 1448, 1392, 1174, 1003, 817, 789, 755, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.95 (s, 1H) 7.75 (d, J = 7.93 Hz, 2H), 7.38–7.43 (m, 3H), 7.34 (d, J = 7.32 Hz, 2H), 7.14 (d, J = 8.55 Hz, 2H), 4.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6 (d), 139.0 (s), 138.0 (d, 2C), 129.4 (d, 2C), 129.1 (d, 2C), 128.9 (d), 128.6 (s), 127.5 (d, 2C), 94.8 (s), 83.3 (s) ppm; HRMS (ESI): calcd. for $C_{14}H_{12}O_2I$: 338.9876 $[M+H]^+$; found: 338.9868.



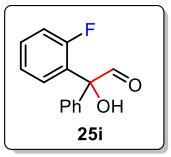
25g

2-Hydroxy-2-(4-nitrophenyl)-2-phenylacetaldehyde (25h). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 23 mg (20%); yellow syrup; IR(neat) ν_{max} 3492, 2923, 1720, 1603, 1518, 1345, 1176, 852, 791, 751, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.26 (d, J = 8.39 Hz, 2H), 7.63 (d, J = 9.16 Hz, 2H), 7.35–7.50 (m, 3H), 7.30 (d, J = 6.87 Hz, 2H) 4.48 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0 (d), 147.9 (s), 146.2 (s), 138.8 (s), 129.3 (d, 2C), 129.2 (d, 2C), 128.5 (d, 2C), 127.3 (d), 124.0 (d, 2C), 83.2 (s) ppm; HRMS (ESI): calcd. for $C_{14}H_{12}O_4N$: 258.0761 $[M+H]^+$; found: 258.0752.



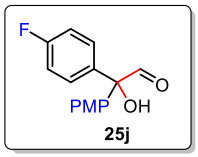
25h

2-(2-Fluorophenyl)-2-hydroxy-2-phenylacetaldehyde (25i). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 41 mg (35%); colorless gum; IR(neat) ν_{max} 3492, 2962, 1721, 1485, 1450, 1337, 1175, 962, 755, 699, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.06 (d, J = 5.49 Hz, 1H), 7.38–7.49 (m, 7H), 7.20–7.26 (m, 1H), 7.10–7.17 (m, 1H), 4.65 (br. s., 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7 (dd, $^4J_{C-F}$ = 5.4 Hz), 159.8 (ds, $^1J_{C-F}$ = 246.6 Hz), 137.9 (s), 130.8 (dd, $^3J_{C-F}$ = 8.5 Hz), 129.9 (dd $^4J_{C-F}$ = 3.9 Hz), 128.8 (d, 2C), 128.6 (d), 127.5 (ds, $^2J_{C-F}$ = 13.9 Hz), 126.9 (d, 2C), 124.8 (dd, $^4J_{C-F}$ = 3.1 Hz), 115.9 (dd, $^2J_{C-F}$ = 22.4 Hz), 82.1 (ds, $^4J_{C-F}$ = 3.1 Hz) ppm; HRMS (ESI): calcd. for $C_{14}H_{12}O_2F$: 231.0816 $[M+H]^+$; found:231.0805.



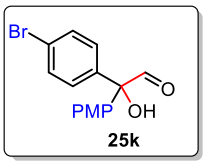
25i

2-(4-fluorophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetaldehyde (25j). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 64 mg (55%); colorless syrup; IR(neat) ν_{max} 3509, 2962, 1719, 1603, 1506, 1302, 1250, 1159, 1031, 828, 774.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.38 (dd, J = 8.39, 5.34 Hz, 2H), 7.27 (d, J = 8.77 Hz, 2H), 7.11 (t, J = 8.58 Hz, 2H), 6.95 (d, J = 8.77 Hz, 2H), 4.43 (s, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.6 (d), 162.6 (ds, $^1J_{C-F}$ = 248.0 Hz), 159.7 (s), 135.2 (s), 131.1 (s), 129.3 (dd, 2C, $^3J_{C-F}$ = 8.6 Hz), 128.6 (d, 2C), 115.6 (dd, 2C, $^2J_{C-F}$ = 22.0 Hz), 114.2 (d, 2C), 82.7 (s), 55.2 (q) ppm; HRMS (ESI): calcd. for $C_{15}H_{14}O_3$: 261.0921 $[M+H]^+$; found: 261.0914.

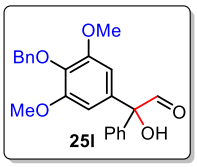


25j

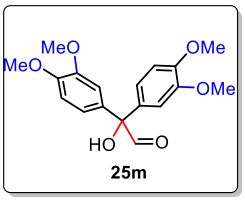
2-(4-Bromophenyl)-2-hydroxy-2-(4-methoxyphenyl)acetaldehyde (25k). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 46 mg (41%); colorless syrup; IR(neat) ν_{max} 3492, 2925, 1719, 1650, 1602, 1510, 1253, 1172, 1072, 1009, 828, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.46 (d, J = 8.59 Hz, 2H), 7.03–7.27 (m, 4H), 6.84 (d, J = 8.84 Hz, 2H), 4.27 (s, 1H), 3.74 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4 (d), 159.9 (s), 138.4 (s), 131.9 (d, 2C), 131.0 (s), 129.1 (d, 2C), 128.73 (d, 2C), 122.8 (s), 114.4 (d, 2C), 82.8 (s), 55.4 (q) ppm; HRMS (ESI): calcd. for $C_{15}H_{14}O_3Br$: 321.0121 $[M+H]^+$; found: 321.0107.



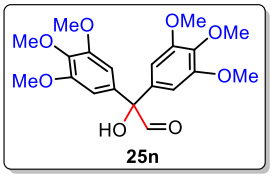
2-(4-(benzyloxy)-3,5-dimethoxyphenyl)-2-hydroxy-2-phenylacetaldehyde (25l). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 50 mg (46%); colorless solid; mp: 98–100 °C; IR(neat) ν_{max} 3493, 2952, 1720, 1588, 1502, 1454, 1414, 1324, 1236, 1125, 981, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.18–7.43 (m, 10H), 6.49 (s, 2H), 4.94 (s, 2H), 4.33 (s, 1H), 3.69 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6 (s), 153.8 (s, 2C), 139.2 (s), 137.7 (s), 137.2 (s), 134.5 (s) 128.9 (d, 2C), 128.6 (d), 128.4 (d, 2C), 128.2 (d, 2C), 127.9 (d), 127.5 (d, 2C), 104.8 (d, 2C), 83.4 (s), 75.0 (t), 56.2 (q, 2C) ppm; HRMS (ESI): calcd for $C_{23}H_{22}O_5Na$: 401.1359 [M+Na]+; found: 401.1349.



2,2-Bis(3,4-dimethoxyphenyl)-2-hydroxyacetaldehyde (25m). Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 37 mg (33%); colorless solid; mp: 132–134 °C; IR(neat) ν_{max} 3492, 2958, 1720, 1592, 1509, 1460, 1413, 1255, 1135, 1021, 864, 811, 759, 645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.89 (s, 1H), 6.92 (d, J = 1.3 Hz, 2H), 6.84–6.90 (m, 4H), 4.34 (br. s, 1H), 3.89 (s, 6H), 3.83 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.5 (d), 149.4 (s, 2C), 149.2 (s, 2C), 131.7 (s, 2C), 120.1 (d, 2C), 111.0 (d 2C), 110.5 (d, 2C), 83.0 (s), 56.0 (q, 4C) ppm; HRMS (ESI): calcd. for $C_{18}H_{20}O_6Na$: 335.1152 $[M+Na]^+$; found: 335.1148.

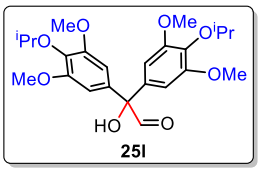


2-Hydroxy-2,2-bis(3,4,5-trimethoxyphenyl)acetaldehyde (25n). Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 17 mg (16%); yellow syrup; IR(neat) ν_{max} 3492, 2925, 1720, 1588, 1504, 1456, 1414, 1324, 1237, 1124, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.90



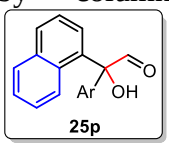
(s, 1H), 6.59 (s, 4H), 4.39 (s, 1H) 3.87 (s, 6H) 3.83 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.0 (d), 153.6 (s, 4C), 138.4 (s, 2C), 134.2 (s, 2C), 104.9 (d, 4C), 83.5 (s), 60.9 (s, 2C), 56.3 (s, 4C) ppm; HRMS (ESI): calcd. for $C_{20}H_{23}O_8$: 391.1387 $[M–H]^+$; found: 391.1384.

2-Hydroxy-2,2-bis(4-isopropoxy-3,5-dimethoxyphenyl)acetaldehyde (25o). Purified by column chromatography (20% EtOAc in petroleum ether, R_f = 0.5); yield: 32 mg (30%); yellow syrup; IR(neat) ν_{max} 3492, 2974, 1719, 1585, 1500, 1457, 1413, 1322, 1231, 1103, 929, 839, 733, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 6.57 (s, 4H), 4.42 (s, 1H), 4.34–4.41 (hept, 2H), 3.78 (s, 12H), 1.31 (s, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2 (d), 154.0 (s, 4C), 136.3 (s, 2C), 133.8 (s, 2C), 104.8 (d, 4C), 83.5 (s), 75.4 (d, 2C), 56.1 (q, 4C), 22.5 (q, 4C) ppm; HRMS (ESI): calcd. for $C_{24}H_{33}O_8$: 449.2170 $[M+H]^+$; found: 449.2166.



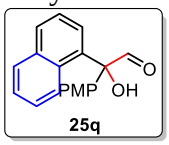
25l

2-Hydroxy-2-(naphthalen-1-yl)-2-phenylacetaldehyde (25p).[52] Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 77 mg (68%); colorless solid; mp: 92–94 °C; IR(neat) ν_{max} 3462, 2925, 1717, 1509, 1448, 1345, 1166, 1059, 947, 776, 745, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 7.78–8.04 (m, 3H), 7.14–7.65 (m, 9H), 4.70 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5 (s), 139.3 (s), 136.6 (s), 135.2 (s), 131.0 (s), 130.0 (d), 129.1 (d, 2C), 128.9 (d), 128.5 (d), 127.0 (d, 2C), 126.7 (d), 126.2 (d), 125.9 (d), 125.4 (d), 124.6 (d), 84.1 (s) ppm; HRMS (ESI): calcd. for $C_{18}H_{14}O_2Na$: 285.0886 $[M+Na]^+$; found: 285.0881.



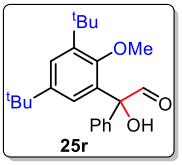
25p

2-Hydroxy-2-(4-methoxyphenyl)-2-(naphthalen-1-yl)acetaldehyde (25q). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 54 mg (46%); colorless solid; mp: 128–130 °C; IR(neat) ν_{max} 3492, 2963, 1716, 1604, 1507, 1507, 1460, 1301, 1249, 1173, 1104, 1029, 951, 832, 802, 778, 647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (d, J = 1.4 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.81–7.89 (m, 2H), 7.38–7.46 (m, 3H), 7.23–7.33 (m, 3H), 6.88 (d, J = 9.2 Hz, 2H), 4.60 (d, J = 1.4 Hz, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1 (s), 159.6 (s), 136.5 (s), 135.0 (s), 131.0 (s), 130.9 (s), 129.9 (d, 1C), 128.8 (d, 1C), 128.2 (d, 2C), 126.7 (d, 1C), 126.0 (d, 1C), 125.8 (d, 1C), 125.2 (d, 1C), 124.5 (d, 1C), 114.4 (d, 2C), 83.6 (s), 55.2 (s) ppm; HRMS (ESI): calcd. for $C_{19}H_{17}O_3$: 293.1172 $[M+H]^+$; found: 293.1159.

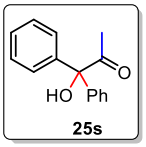


25q

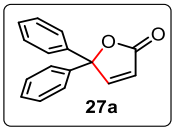
2-(3,5-Di-tert-butyl-2-methoxyphenyl)-2-hydroxy-2-phenylacetaldehyde (25r). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 42 mg (42%); colorless solid; mp: 132–134 °C; IR(neat) ν_{max} 3492, 2958, 1715, 1475, 1363, 1229, 1164, 1135, 998, 887, 799, 756, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 7.74–7.94 (m, 7H), 5.20 (s, 1H), 4.08 (s, 3H), 1.94 (s, 9H), 1.63 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7 (s), 155.2 (s), 146.7 (s), 141.9 (s), 139.4 (s), 135.7 (s), 128.3 (d, 2C), 127.9 (d, 1C), 127.2 (d, 2C), 127.0 (d, 1C), 125.9 (d, 1C), 82.6 (s), 63.4 (q, 1C), 35.6 (s), 34.5 (s), 31.7 (q, 3C), 31.2 (q, 3C) ppm; HRMS (ESI): calcd. for $C_{23}H_{31}O_3$: 355.2268 $[M+H]^+$; found: 355.2262.



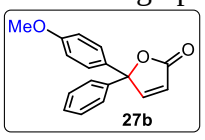
1-Hydroxy-1,1-diphenylpropan-2-one (25s). Purified by column chromatography (5% EtOAc in petroleum ether, R_f = 0.5); yield: 75 mg (64%); colorless solid; mp: 64–66 °C (*Lit.*[46] 64–66 °C); IR(neat) ν_{max} 3462, 2925, 1706, 1492, 1447, 1335, 1157, 1055, 754, 696 cm^{-1}; cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 10H), 4.76 (s, 1H), 2.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7 (s), 141.4 (s, 2C), 128.5 (d, 4C), 128.3 (d, 4C), 128.1 (d, 2C), 85.8 (s), 26.3 (q) ppm; HRMS (ESI): calcd. for $C_{15}H_{14}O_2Na$: 249.0886 $[M+Na]^+$; found: 249.0884.



5,5-Diphenylfuran-2(5*H*)-one (27a). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 69 mg (62%); colorless solid; mp: 134–136°C (*Lit.*[44e] 133–134 °C); IR(neat) ν_{max} 2925, 1760, 1449, 1211, 1095, 985, 921, 818, 759, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 5.49 Hz, 1H), 7.30–7.43 (m, 10H), 6.20 (d, J = 5.49 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (s), 158.8 (d), 139.2 (s, 2C), 128.7 (d, 4C), 128.6 (d, 2C), 126.6 (d, 4C), 119.7 (d), 92.2 (s) ppm; HRMS (ESI): calcd. for $[C_{16}H_{13}O_2+H]^+$: 237.0910 $[M+H]^+$; found: 237.0908.

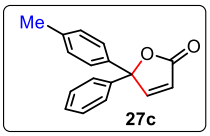


5-(4-Methoxyphenyl)-5-phenylfuran-2(5*H*)-one (27b). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 79 mg (72%); colorless solid; mp: 118–120 °C (*Lit.*[53] 118.6–119.6 °C); IR(neat) ν_{max} 2951, 1762, 1609, 1512, 1254, 1179, 1092, 1032, 918, 832, 758, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 5.49 Hz, 1H), 7.30–7.40 (m, 5H), 7.22 (d, J = 9.16 Hz, 2H), 6.88 (d, J = 9.16 Hz, 2H), 6.18 (d, J = 5.49 Hz, 1H), 3.81 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (s), 159.8 (s), 159.0

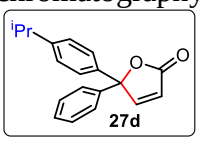


(d), 139.4 (s), 131.3 (s), 128.7 (d, 2C), 128.6 (d), 128.1 (d, 2C), 126.5 (d, 2C), 119.5 (d), 114.0 (d, 2C), 92.2 (s), 55.3 (q) ppm; HRMS (ESI): calcd. for $C_{17}H_{15}O_3$: 267.1016 $[M+H]^+$; found: 267.1012.

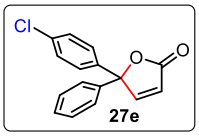
5-Phenyl-5-(p-tolyl)furan-2(5*H*)-one (27c). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 86 mg (78%); colorless solid; mp: 70–72 °C; IR(neat) ν_{max} 2921, 1764, 1211, 1092, 919, 820, 757, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 5.49 Hz, 1H), 7.35 (d, J = 6.71 Hz, 5H), 7.16–7.22 (m, 4H), 6.18 (d, J = 5.49 Hz, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (s), 158.9 (d), 139.4 (s), 138.6 (s), 136.3 (s), 129.4 (d, 2C), 128.7 (d, 2C), 128.6 (d, 2C), 126.8 (d), 126.5 (d, 2C), 119.6 (d), 92.2 (s), 21.1 (s) ppm; HRMS (ESI): calcd. for $C_{17}H_{15}O_2$: 251.1067 $[M+H]^+$; found: 251.1064.



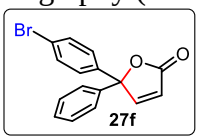
5-(4-Isopropylphenyl)-5-phenylfuran-2(5*H*)-one (27d). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 77 mg (70%); colorless solid; mp: 88–90 °C; IR(neat) ν_{max} 2951, 1766, 1092, 919, 818, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 5.5 Hz, 1H), 7.33–7.38 (m, 5H), 7.23 (s, 4H), 6.19 (d, J = 5.5 Hz, 1H), 2.91 (hept, J = 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (s), 158.9 (d), 149.5 (s), 139.4 (s), 136.5 (s), 128.7 (d, 2C), 128.5 (d), 126.8 (d, 2C), 126.6 (d, 2C), 126.5 (d, 2C), 119.5 (d), 92.3 (s), 33.8 (d), 23.8 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{19}H_{19}O_2$: 279.1380 $[M+H]^+$; found: 279.1378.



5-(4-Chlorophenyl)-5-phenylfuran-2(5*H*)-one (27e). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (50%); colorless gum; IR(neat) ν_{max} 2950, 1761, 1491, 1208, 1092, 1055, 985, 915, 815, 761, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 5.5 Hz, 1H), 7.26–7.40 (m, 9H), 6.23 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (s), 158.3 (d), 138.8 (s), 137.8 (s), 134.8 (s), 128.9 (d, 2C), 128.9 (d), 128.9 (d, 2C), 128.0 (d, 2C), 126.5 (d, 2C), 120.0 (d), 91.6 (s) ppm; HRMS (ESI): calcd. for $C_{16}H_{12}O_2Cl$: 271.0520 $[M+H]^+$; found: 271.0520.

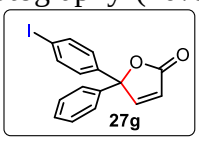


5-(4-Bromophenyl)-5-phenylfuran-2(5*H*)-one (27f). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 77 mg (71%); colorless solid; mp: 72–74 °C; IR(neat) ν_{max} 2925, 1767, 1488, 1209, 1091, 918, 821, 760, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.34–7.40 (m,

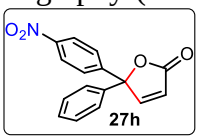


3H), 7.29–7.32 (m, 2H), 7.20 (m, *J* = 8.8 Hz, 2H), 6.21 (d, *J* = 5.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7 (s), 158.2 (d), 138.7 (s), 138.4 (s), 131.9 (d, 2C), 128.9 (d), 128.8 (d, 2C), 128.3 (d, 2C), 126.5 (d, 2C), 122.9 (s), 120.0 (d), 91.6 (s) ppm; HRMS (ESI): calcd. for $C_{16}H_{12}O_2Br$: 315.0015 $[M+H]^+$; found: 315.0009.

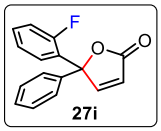
5-(4-Iodophenyl)-5-phenylfuran-2(5*H*)-one (27g). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 74 mg (69%); colorless solid; mp: 80–82 °C, IR(neat) ν_{max} 2951, 1758, 1484, 1393, 1202, 1090, 985, 816, 759, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 5.3 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.35–7.39 (m, 3H), 7.28–7.31 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 5.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7 (s), 158.2 (d), 139.1 (s), 138.8 (s), 137.9 (d, 2C), 128.9 (d), 128.9 (d, 2C), 128.4 (d, 2C), 126.5 (d, 2C), 120.0 (d), 94.67 (s), 91.74 (s) ppm; HRMS (ESI): calcd. for $C_{16}H_{12}O_2I$: 362.9876 $[M+H]^+$; found: 362.9879.



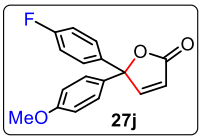
5-(4-Nitrophenyl)-5-phenylfuran-2(5*H*)-one (27h). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 79 mg (72%); colorless gum; IR(neat) ν_{max} 2920, 1759, 1519, 1347, 1207, 1091, 915, 851, 815, 760, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 9.2 Hz, 2H), 7.97 (d, *J* = 5.3 Hz, 1H), 7.53–7.57 (d, *J* = 8.9 Hz, 2H), 7.38–7.44 (m, 3H), 7.28–7.33 (m, 2H), 6.29 (d, *J* = 5.3 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1 (s), 157.4 (d), 147.9 (s), 146.2 (s), 138.2 (s), 129.3 (d), 129.1 (d, 2C), 127.5 (d, 2C), 126.5 (d, 2C), 124.0 (d, 2C), 120.7 (d), 91.2 (s) ppm; HRMS (ESI): calcd. for $C_{16}H_{12}O_4N$: 282.0761 $[M+H]^+$; found: 282.0750.



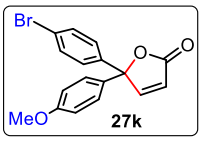
5-(2-Fluorophenyl)-5-phenylfuran-2(5*H*)-one (27i). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 78 mg (71%); colorless solid; mp: 120–122 °C; IR(neat) ν_{max} 2924, 1761, 1486, 1451, 1219, 1087, 984, 915, 820, 758, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 5.6, 3.38 Hz, 1H), 7.64–7.71 (m, 1H), 7.33–7.46 (m, 4H), 7.15–7.33 (m, 3H), 7.08 (dd, *J* =11.3, 8.3 Hz, 1H), 6.23 (d, *J* = 5.3 Hz, 1 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7 (s), 159.3 (ds, $^1J_{C\text{-}F}$ = 247 Hz), 157.6 (dd, $^3J_{C\text{-}F}$ = 6.3 Hz), 138.3 (s), 130.7 (dd, $^3J_{C\text{-}F}$ = 8.5 Hz), 129.0 (d) 128.8 (d, 2C), 127.6 (dd, $^4J_{C\text{-}F}$ = 3.1 Hz), 126.8 (ds, $^3J_{C\text{-}F}$ = 12.3 Hz), 126.8 (d, 2C) 124.8 (dd, $^4J_{C\text{-}F}$ = 3.1 Hz), 120.1 (d), 116.2 (dd, $^2J_{C\text{-}F}$ = 22.4 Hz), 90.0 (s) ppm; HRMS (ESI): calcd. for $C_{16}H_{12}O_2F$: 255.0816 $[M+H]^+$; found: 255.0815.



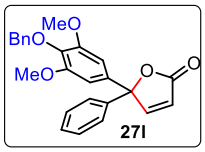
5-(4-Fluorophenyl)-5-(4-methoxyphenyl)furan-2(5*H*)-one (27j). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 72 mg (66%); colorless solid; mp: 96–98 °C; IR(neat) ν_{max} 2933, 1764, 1606, 1510, 1304, 1232, 1181, 1086, 1032, 964, 918, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 6.0 Hz, 1H), 7.30 (dd, J = 9.0, 5.26 Hz, 2H), 7.21 (m, J = 8.3 Hz, 2H), 7.04–7.09 (m, 2H), 6.90 (m, J = 9.0 Hz, 2 H), 6.20 (d, J = 5.3 Hz, 1H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (s), 163.4 (ds, $^1J_{C\text{-}F}$ = 248.9 Hz), 159.9 (s), 158.7 (d), 135.3 (s), 131.0 (s), 128.5 (dd, $^3J_{C\text{-}F}$ =8.5 Hz, 2C), 128.0 (d, 2C), 119.6 (d), 115.7 (dd, $^2J_{C\text{-}F}$ = 21.6, 2C), 114.1 (d, 2C), 91.64 (s), 55.33 (q) ppm; HRMS (ESI): calcd. for $C_{17}H_{14}O_3F$: 285.0921 $[M+H]^+$; found:285.0918.



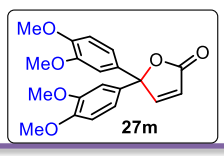
5-(4-Bromophenyl)-5-(4-methoxyphenyl)furan-2(5*H*)-one (27k). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 55 mg (51%); colorless solid; mp: 90–92 °C; IR(neat) ν_{max} 2930, 1762, 1607, 1511, 1305, 1253, 1179, 1085, 1031, 982, 919, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 5.7 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.14–7.21 (m, 4H), 6.88 (d, J = 9.2 Hz, 2H), 6.19 (d, J = 5.7 Hz, 1H), 3.81 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9 (s), 159.9 (s), 158.4 (d), 138.5 (s), 131.8 (d), 130.7 (s), 128.2 (d), 128.1 (d), 122.8 (s), 119.8 (d), 114.1 (d), 91.6 (s), 55.3 (s) ppm; HRMS (ESI): calcd. for $C_{17}H_{14}O_3$: 345.0121 $[M+H]^+$; found: 345.0107.



5-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-5-phenylfuran-2(5*H*)-one (27l). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 69 mg (65%); colorless solid; mp: 124–126 °C; IR(neat) ν_{max} 2921, 1760, 1589, 1503, 1453, 1414, 1328, 1214, 1126, 970, 920, 835, 734, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 5.7 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.27–7.41 (m, 8H), 6.51 (s, 2H), 6.20 (d, J = 5.7 Hz, 1H), 5.01 (s, 2H), 3.77 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (s), 158.7 (d), 153.7 (s, 2C), 139.1 (s), 137.7 (s), 137.3 (s), 134.7 (s), 128.8 (d), 128.7 (d, 2C), 128.4 (d, 2C), 128.2 (d, 2C), 127.9 (d), 126.6 (d, 2C), 119.7 (d), 104.3 (d, 2C), 90.2 (s), 75.0 (t), 56.3 (q, 2C) ppm; HRMS (ESI): calcd for $C_{25}H_{23}O_5$: 403.1540 $[M+H]^+$; found: 403.1538.

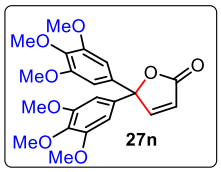


5,5-Bis(3,4-dimethoxyphenyl)furan-2(5*H*)-one (27m). Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 60 mg (56%); yellow solid; mp: 113–115 °C; IR(neat) ν_{max} 2931, 1762, 1515, 1463, 1414, 1263, 1143,

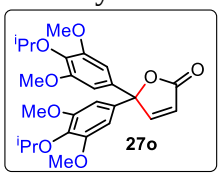


1025, 922, 840, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 5.5 Hz, 1H), 6.82 (s, 6H), 6.17 (d, J = 5.5 Hz, 1H), 3.88 (s, 6H), 3.82 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (s), 159.0 (d), 149.3 (s, 2C), 149.1 (s, 2C), 131.6 (s, 2C), 119.2 (d, 2C), 110.7 (d, 4C), 109.8 (d), 92.1 (s), 56.0 (q, 4C) ppm; HRMS (ESI): calcd. for $C_{20}H_{21}O_6$: 357.1333 $[M+H]^+$; found: 357.1328.

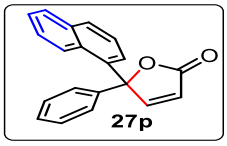
5,5-Bis(3,4,5-trimethoxyphenyl)furan-2(5*H*)-one (27n). Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 64 mg (60%); yellow solid; mp: 166–168 °C; IR(neat) ν_{max} 2922, 1766, 1590, 1507, 1459, 1416, 1329, 1242, 1128, 1004, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 5.5 Hz, 1H), 6.51 (s, 4H), 6.20 (d, J = 5.5 Hz, 1H), 3.82 (s, 12H), 3.86 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (s), 158.6 (d, 2C), 153.3 (s, 4C), 138.4 (s, 2C), 134.4 (s), 119.6 (d), 104.1 (d, 4C), 92.1 (s), 60.9 (q, 3C), 56.3 (q, 3C) ppm; HRMS (ESI): calcd. for $C_{22}H_{25}O_8$: 417.1544 $[M+H]^+$; found: 417.1539.



5,5-Bis(4-isopropoxy-3,5-dimethoxyphenyl)furan-2(5*H*)-one (27o). Purified by column chromatography (30% EtOAc in petroleum ether, R_f = 0.5); yield: 69 mg (66%); colorless solid; mp: 160–162 °C; IR(neat) ν_{max} 2925, 1729, 1587, 1501, 1459, 1415, 1325, 1236, 1125, 926, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 6.1 Hz, 1H), 6.49 (s, 4H), 6.20 (d, J = 5.5 Hz, 1H), 4.37 (hept, J = 12.2, 6.10 Hz, 2H), 3.77 (s, 12H), 1.29 (d, J = 6.1 Hz, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (s), 158.7 (d), 153.9 (s, 4C), 136.5 (s, 2C), 133.9 (s, 2C), 119.4 (d), 104.2 (d, 4C), 92.3 (s), 75.4 (d, 2C), 56.2 (q, 4C), 22.43 (q, 4C) ppm; HRMS (ESI): calcd. for $C_{26}H_{33}O_8$: 473.2170 $[M+H]^+$; found: 473.2166.

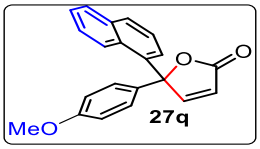


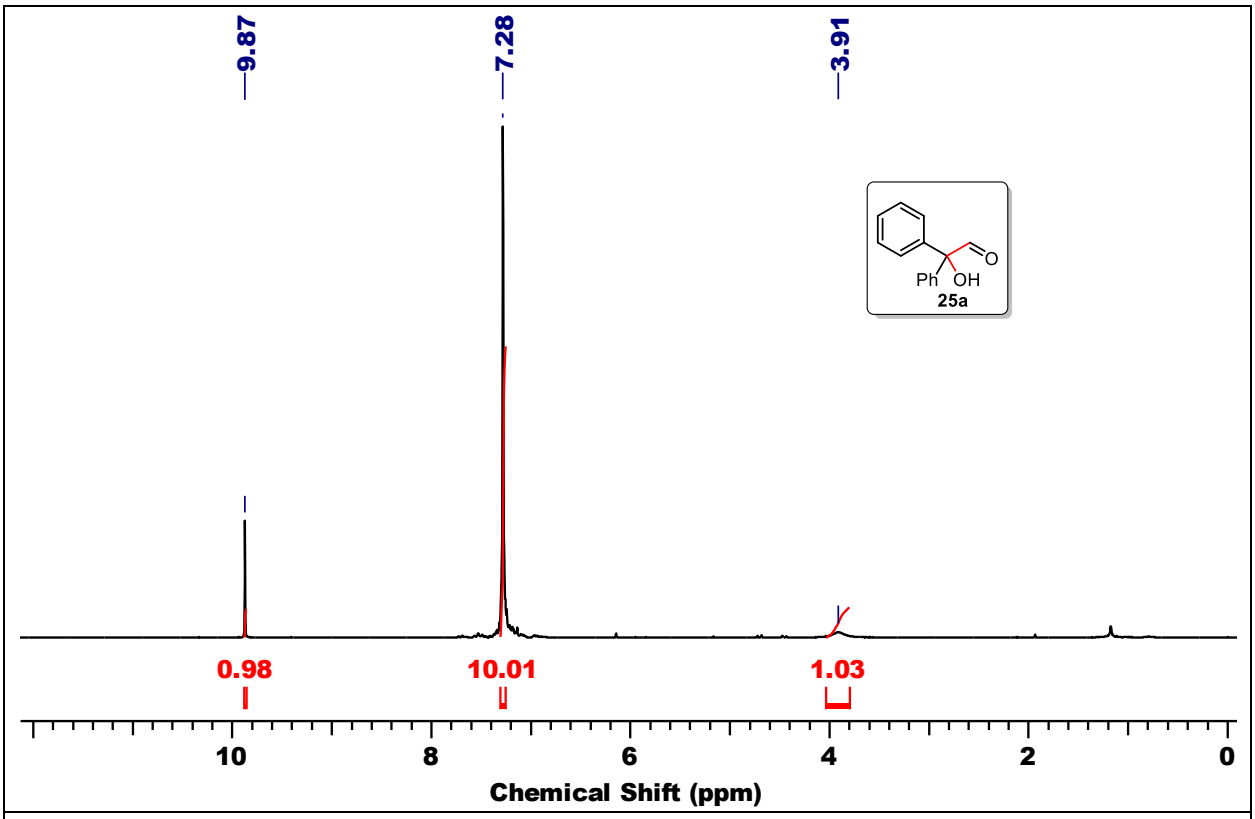
5-(Naphthalen-1-yl)-5-phenylfuran-2(5*H*)-one (27p). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 97 mg (89%); colorless solid; mp: 184–186 °C; IR(neat) ν_{max} 2925, 1763, 1199, 1089, 969, 924, 778, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 5.5 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 7.3 Hz, 1H), 7.49–7.55 (m, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.24–7.38 (m, 6H), 6.23 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (s), 159.5 (d), 139.3 (s), 134.7 (s), 134.6 (s), 130.5 (d), 130.3 (s), 129.0 (d, 2C), 128.8 (d), 128.6 (d),

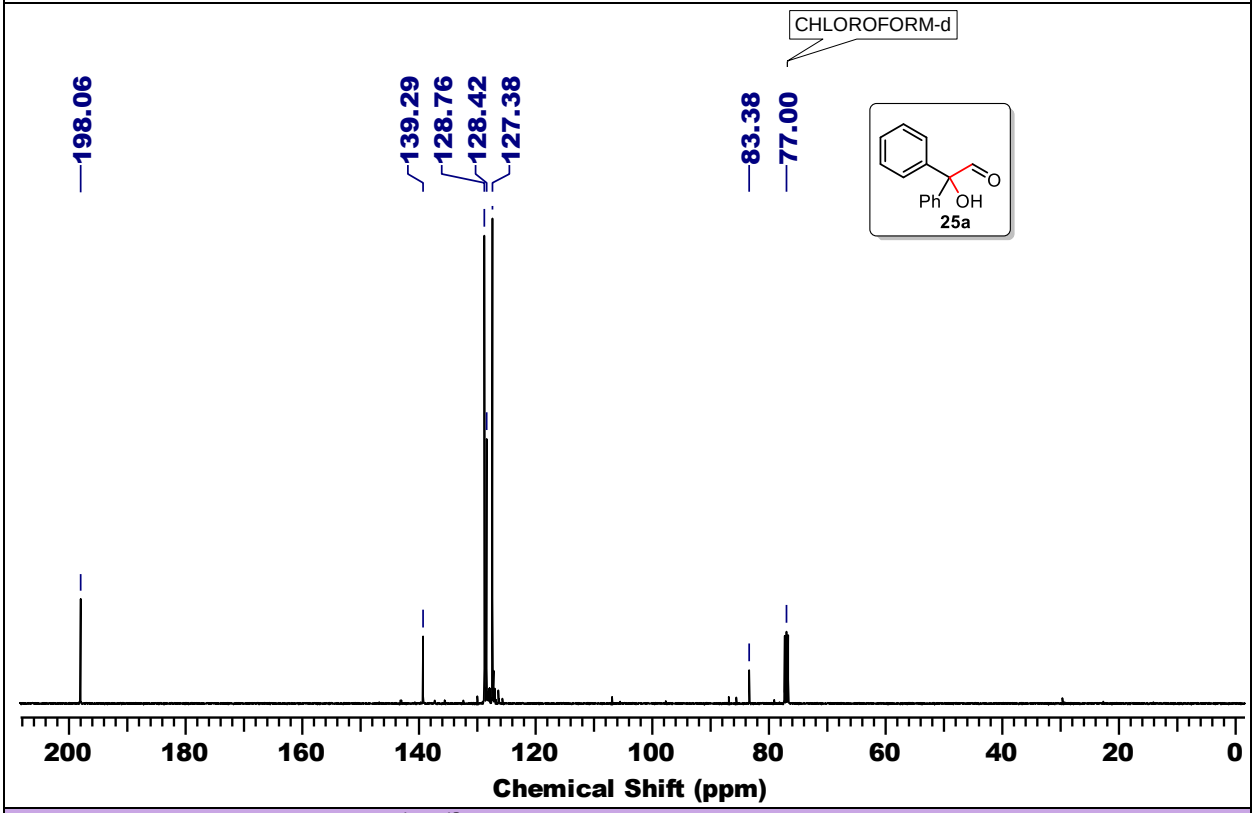


126.4 (d), 126.2 (d), 125.8 (d), 125.7 (d, 2C), 125.2 (d), 124.6 (d), 119.1 (d), 92.9 (s) ppm; HRMS (ESI): calcd. for $C_{20}H_{14}O_2Na$: 309.0886 $[M+H]^+$; found: 309.0873.

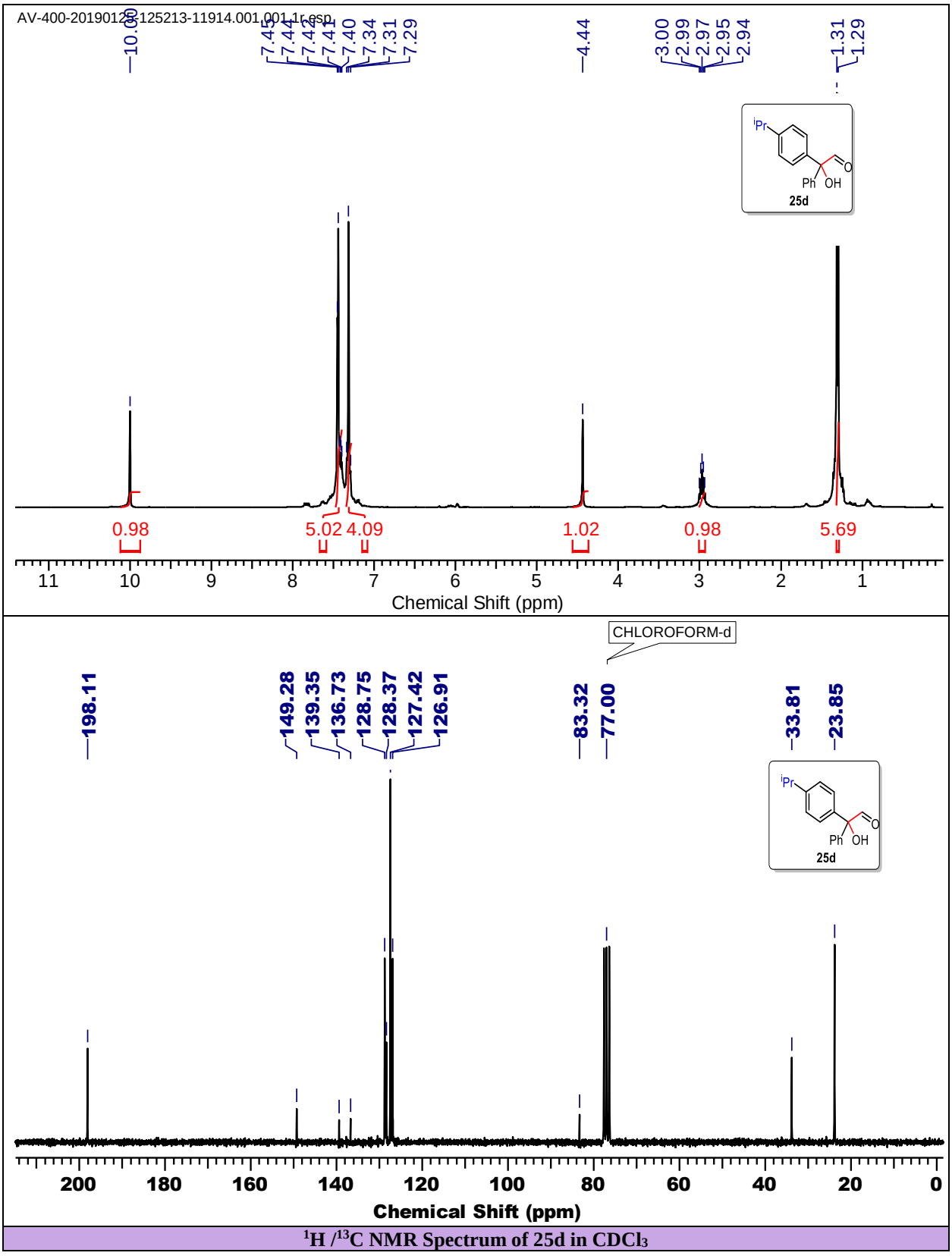
5-(4-Methoxyphenyl)-5-(naphthalen-1-yl)furan-2(5*H*)-one (27q). Purified by column chromatography (10% EtOAc in petroleum ether, R_f = 0.5); yield: 82 mg (76%); colorless solid; mp: 100–102 °C; IR(neat) ν_{max} 2921, 1763, 1607, 1511, 1253, 1178, 1087, 1032, 919, 832, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 6.0 Hz, 1H), 7.80– 7.98 (m, 3H), 7.70 (d, J = 7.5 Hz, 1H), 7.40–7.54 (m, 2H), 7.25–7.37 (m, 1H), 7.16 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 6.21 (d, J = 5.3 Hz, 1H), 3.78 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2 (s), 159.8 (s), 159.4 (d), 134.8 (s), 134.6 (s), 131.1 (s), 130.5 (s), 130.2 (d), 128.8 (d), 127.3 (d, 2C), 126.4 (d), 126.2 (d), 125.8 (d), 125.0 (d), 124.7 (d), 119.1 (d), 114.3 (d, 2C), 92.9 (s), 55.3 (q) ppm; HRMS (ESI): calcd. for $C_{21}H_{17}O_3$: 317.1172 $[M+H]^+$; found: 317.1169.



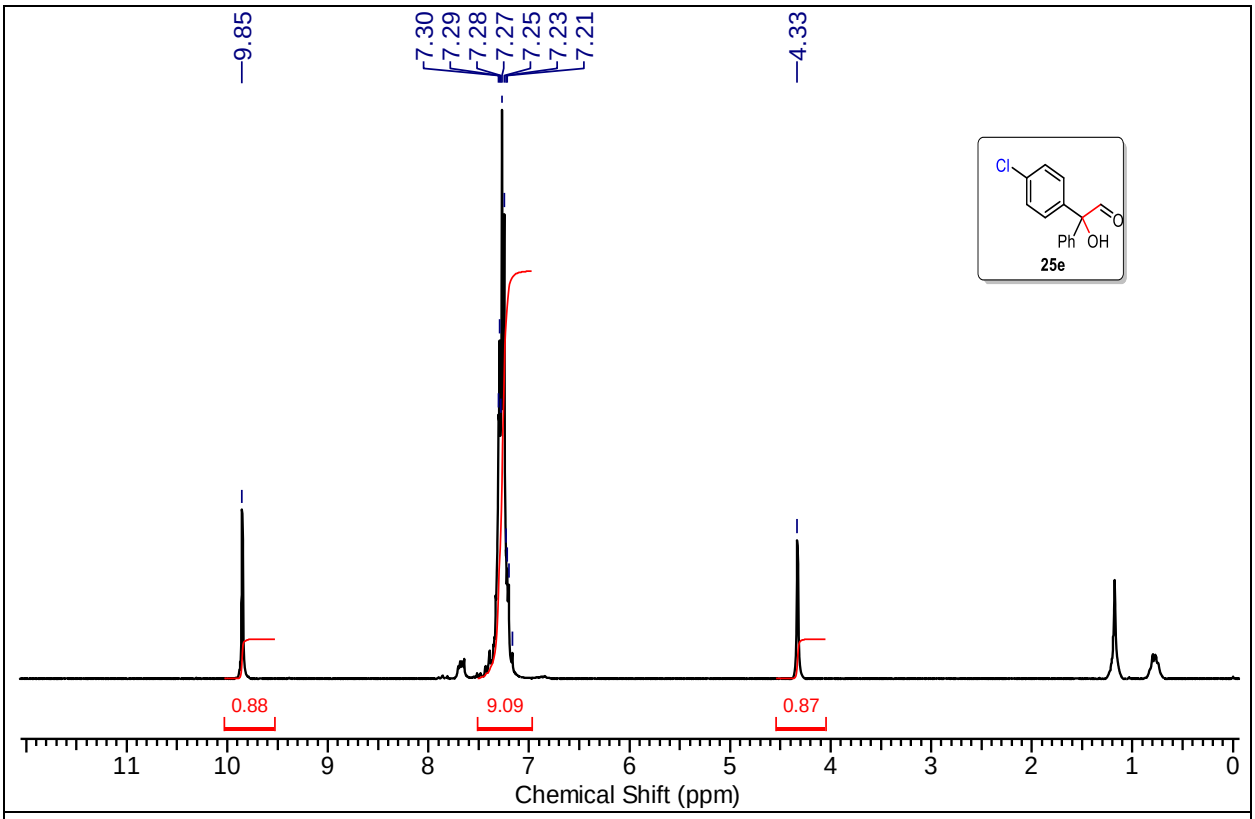


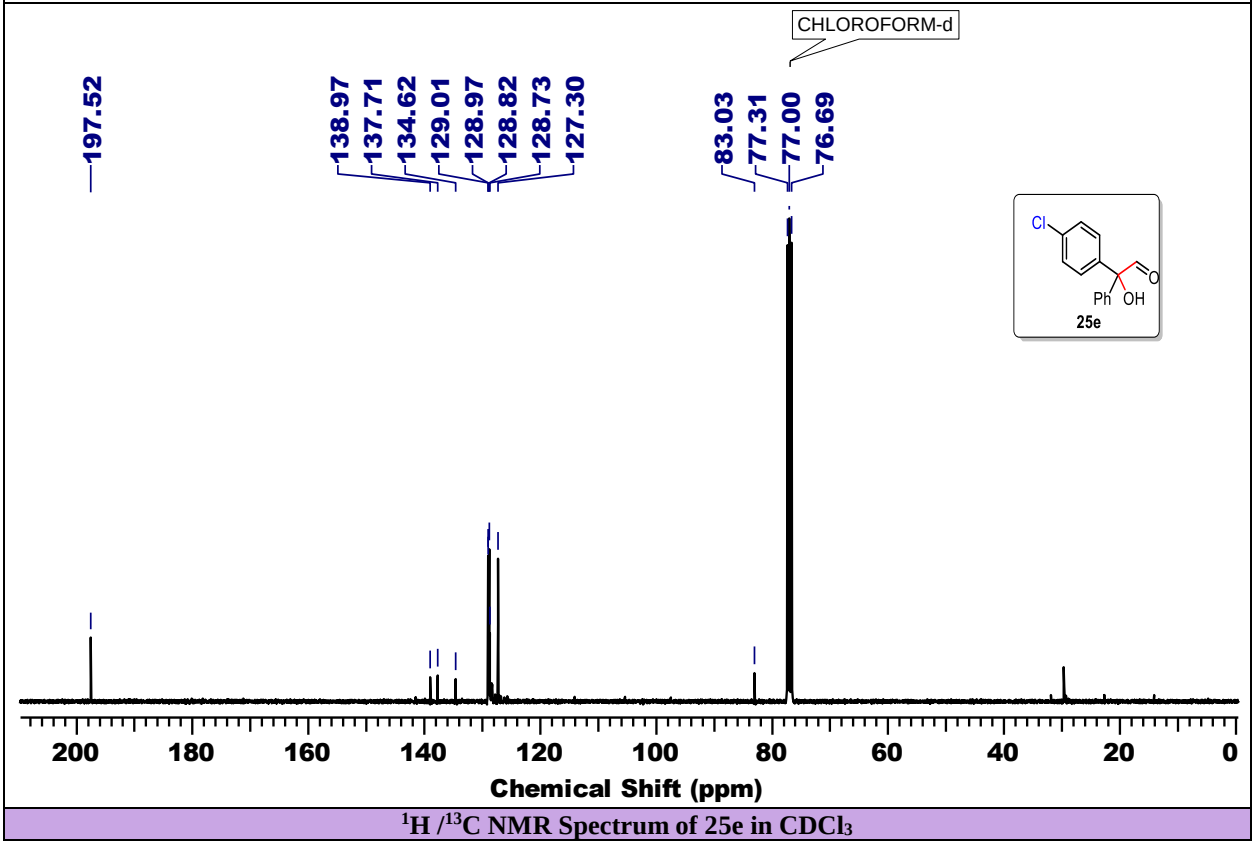


^{1}H /^{13}C NMR Spectrum of 25a in $CDCl_3$

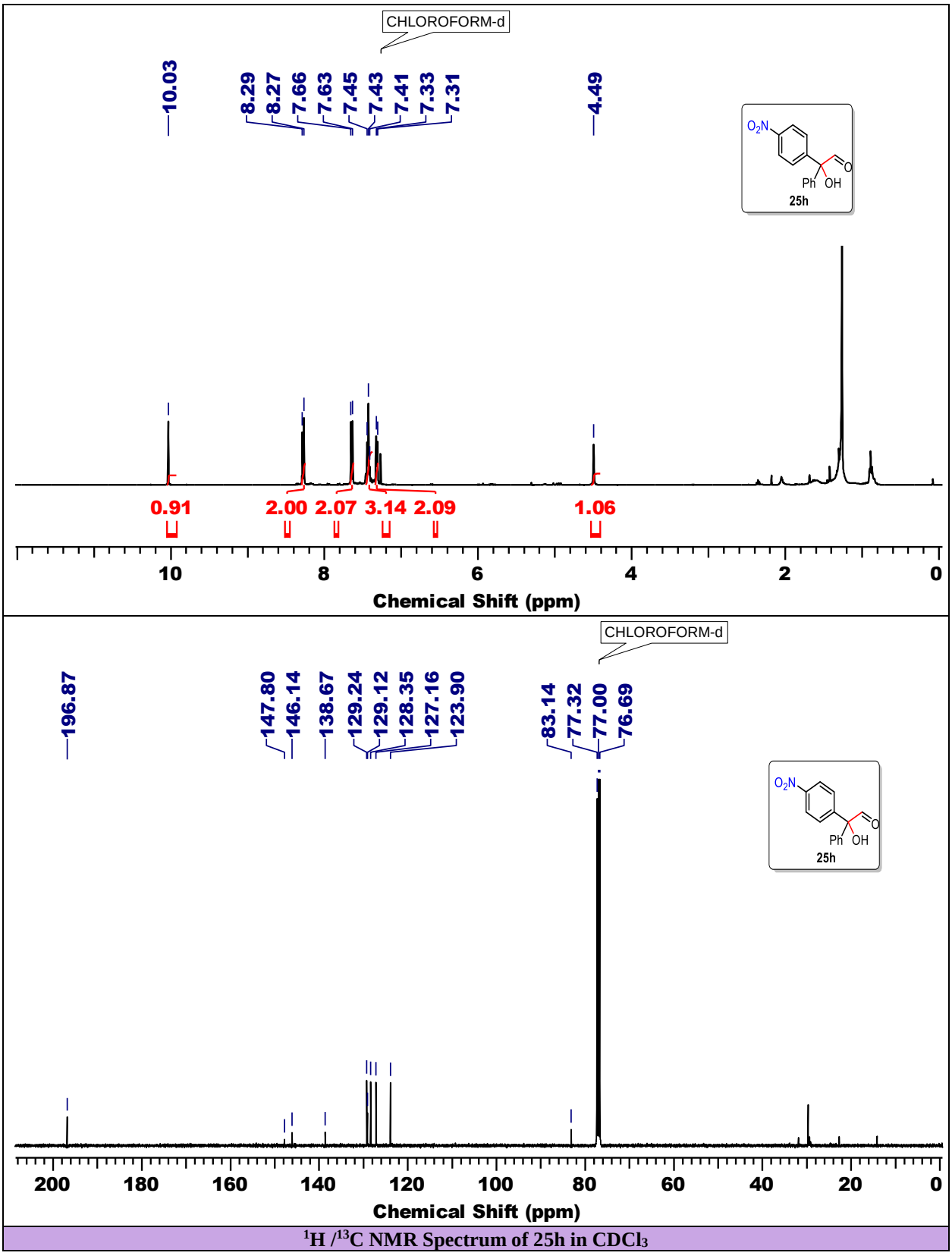


^{1}H /^{13}C NMR Spectrum of 25d in $CDCl_3$

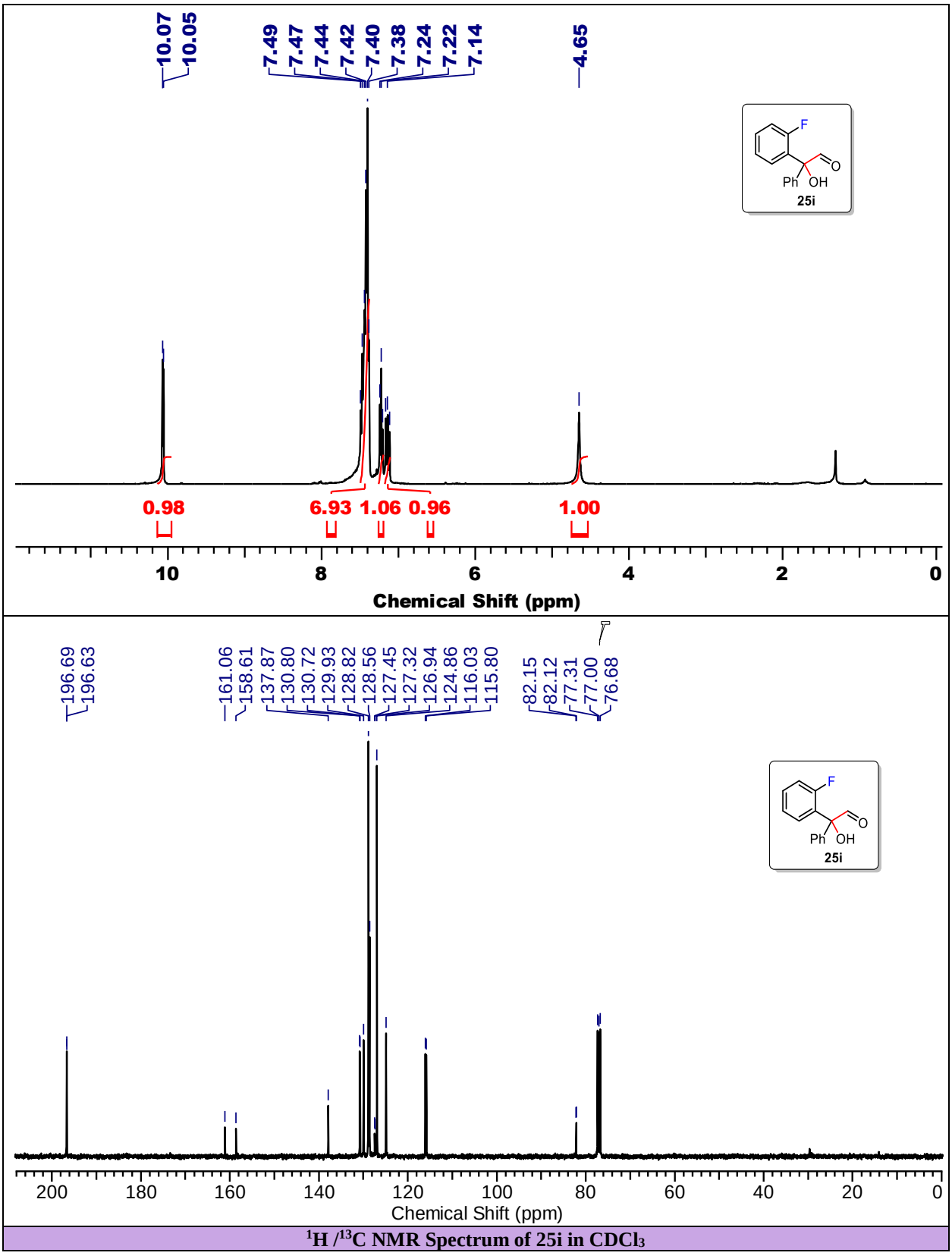




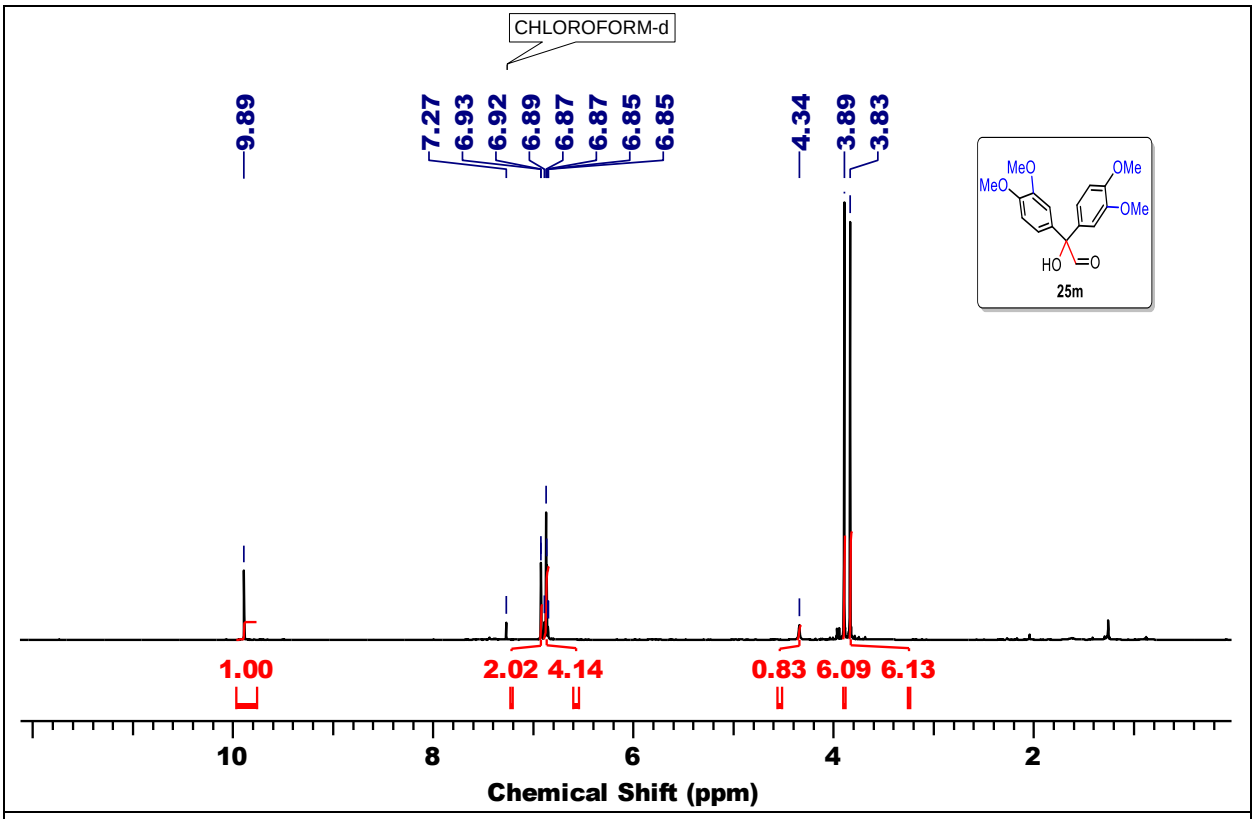
^{1}H /^{13}C NMR Spectrum of 25e in $CDCl_3$

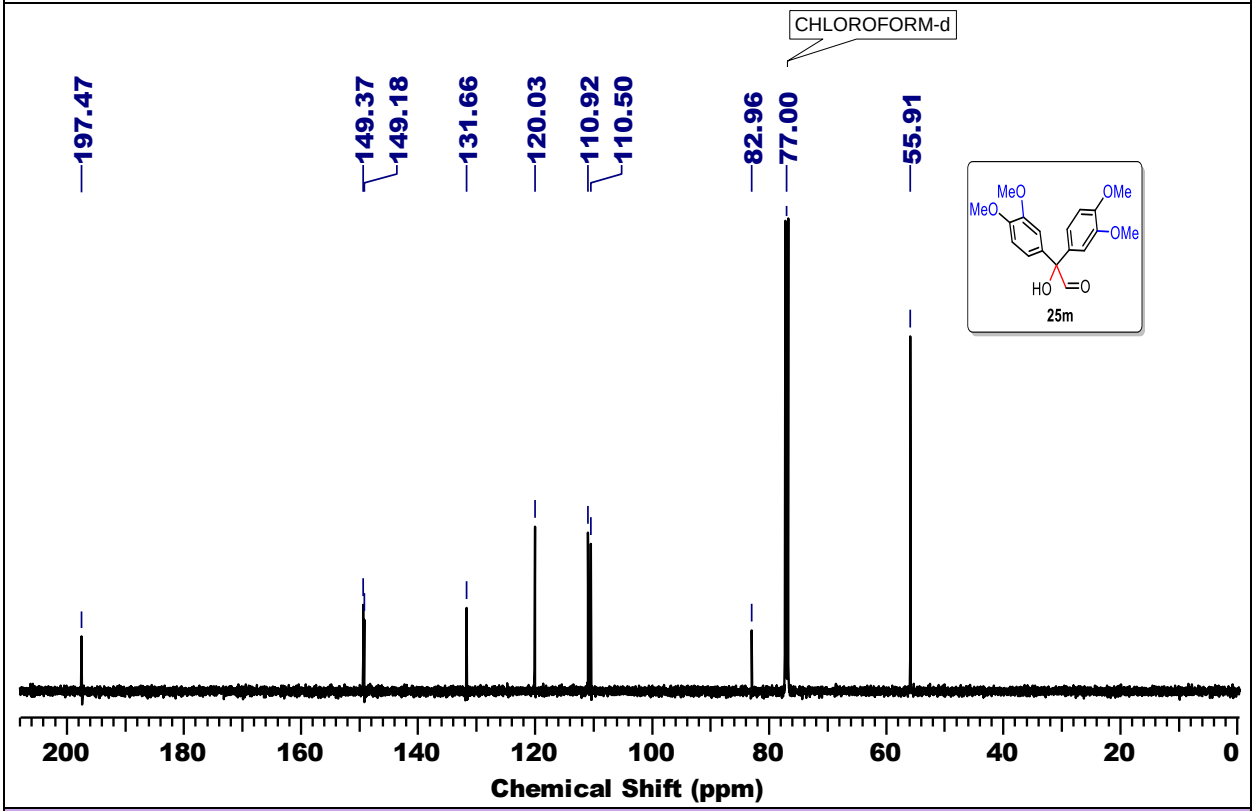


^{1}H /^{13}C NMR Spectrum of 25h in $CDCl_3$

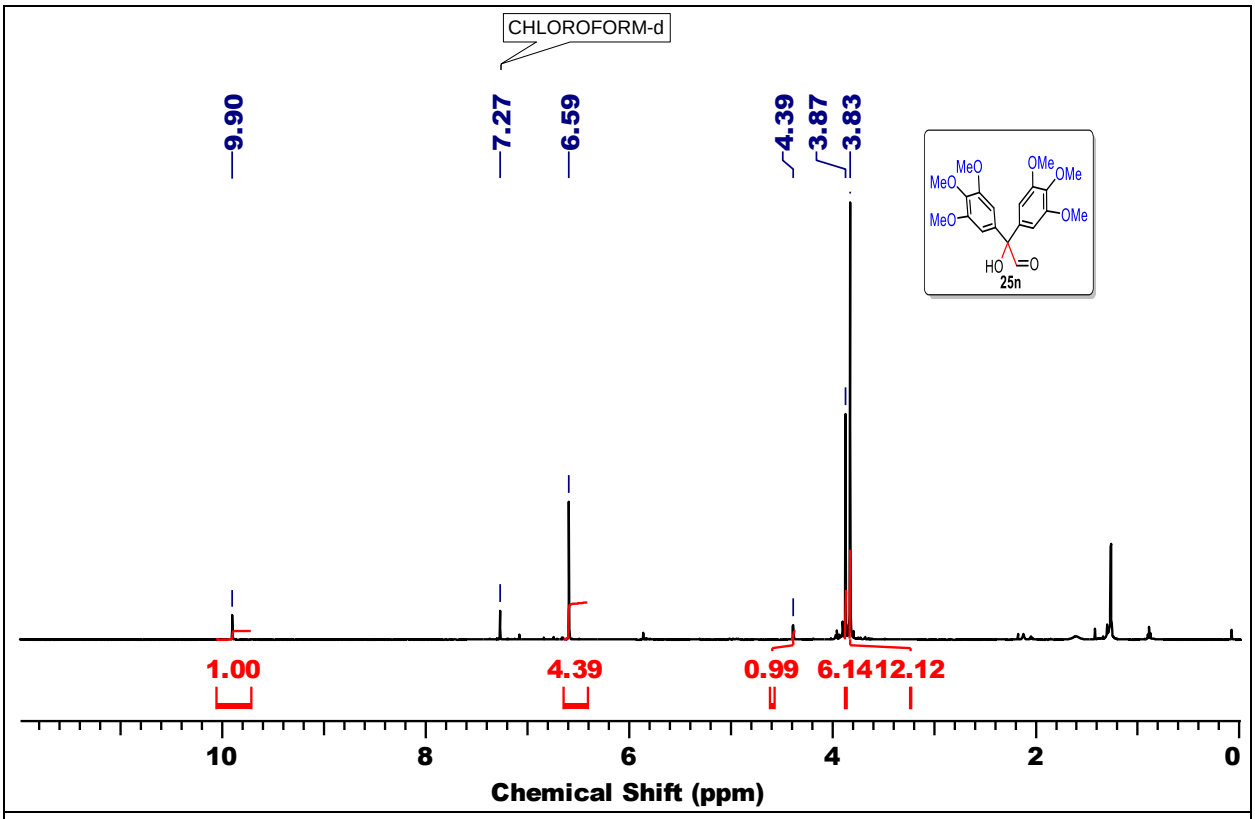


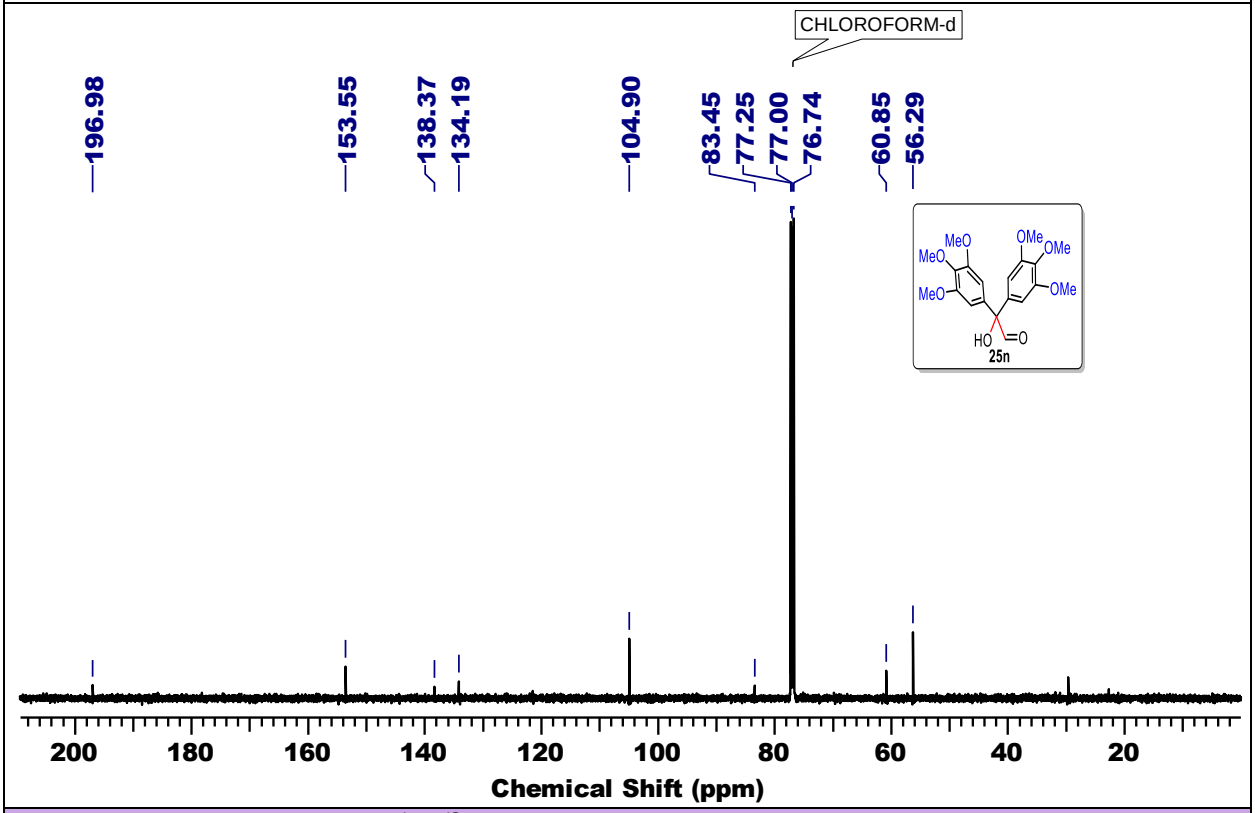
^{1}H /^{13}C NMR Spectrum of 25i in $CDCl_3$



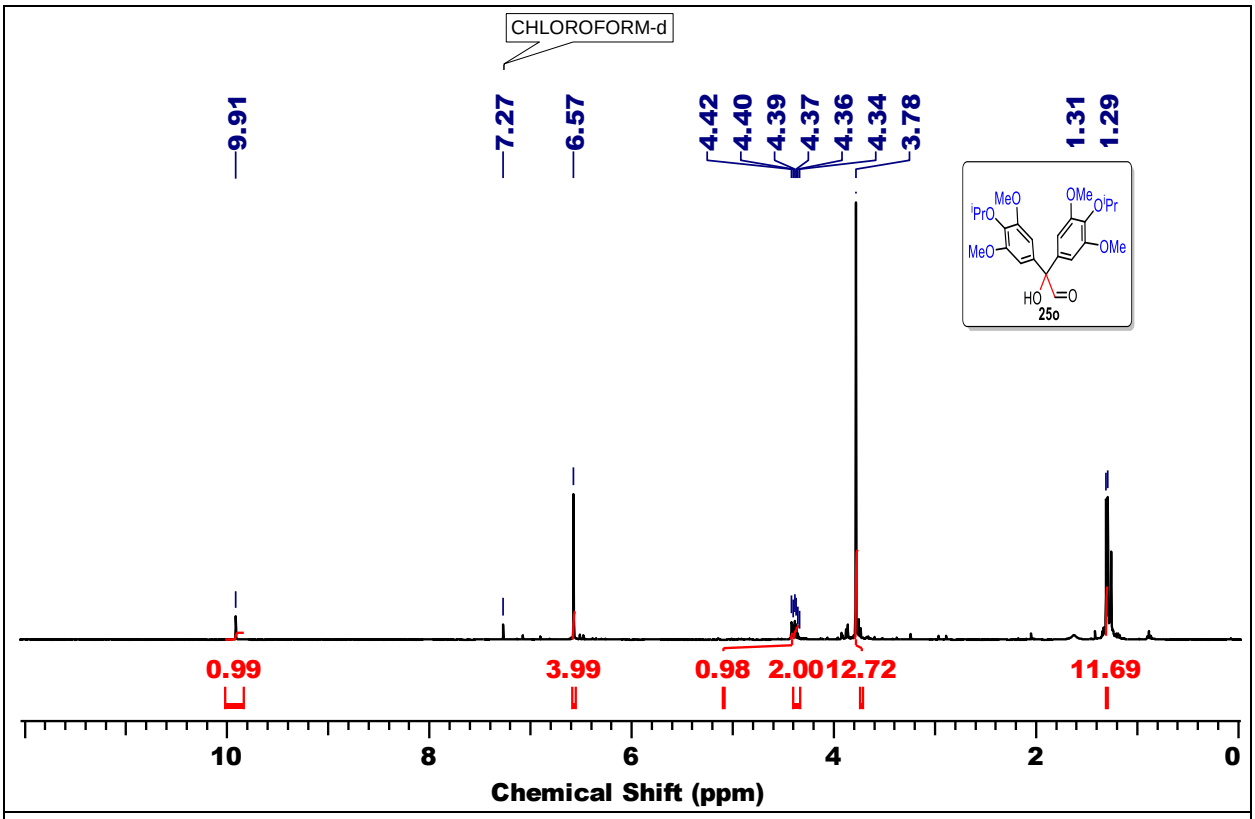


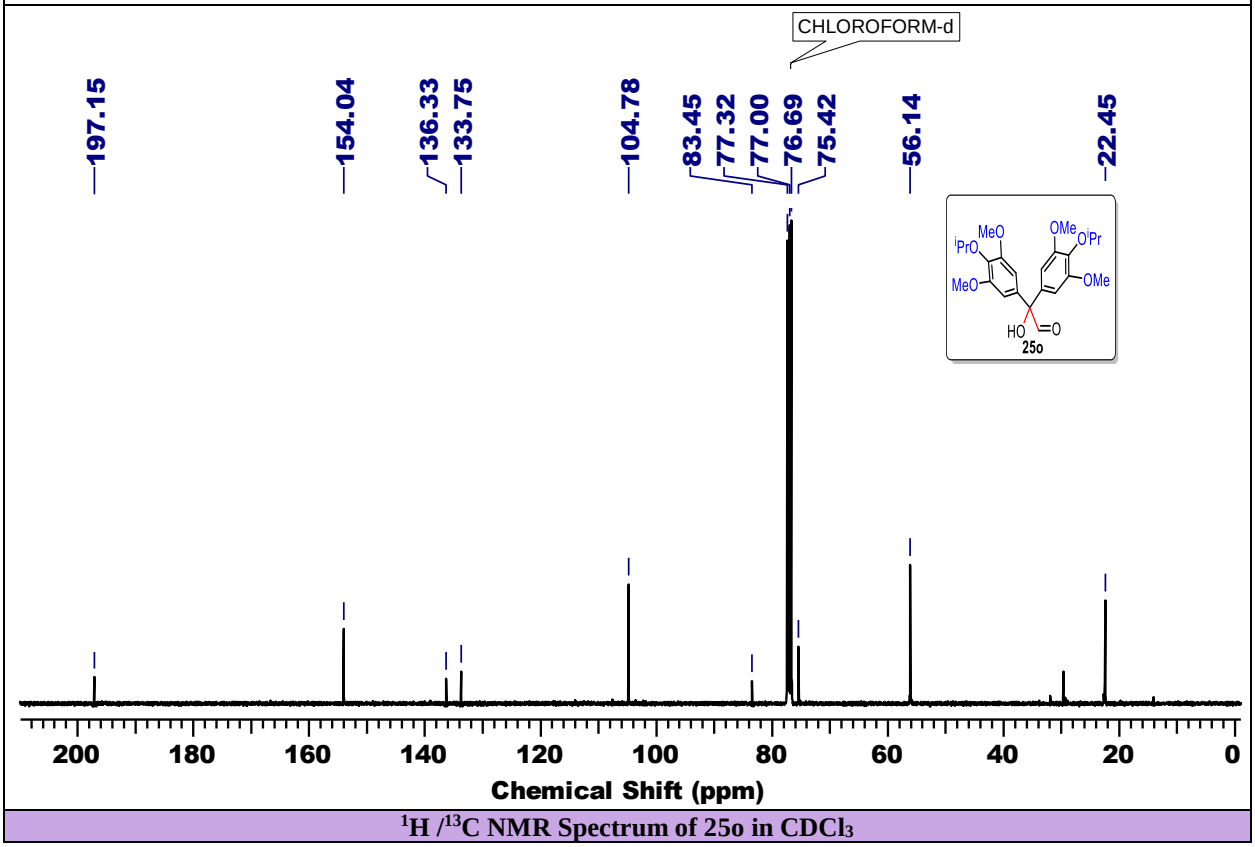
^{1}H /^{13}C NMR Spectrum of 25m in $CDCl_3$



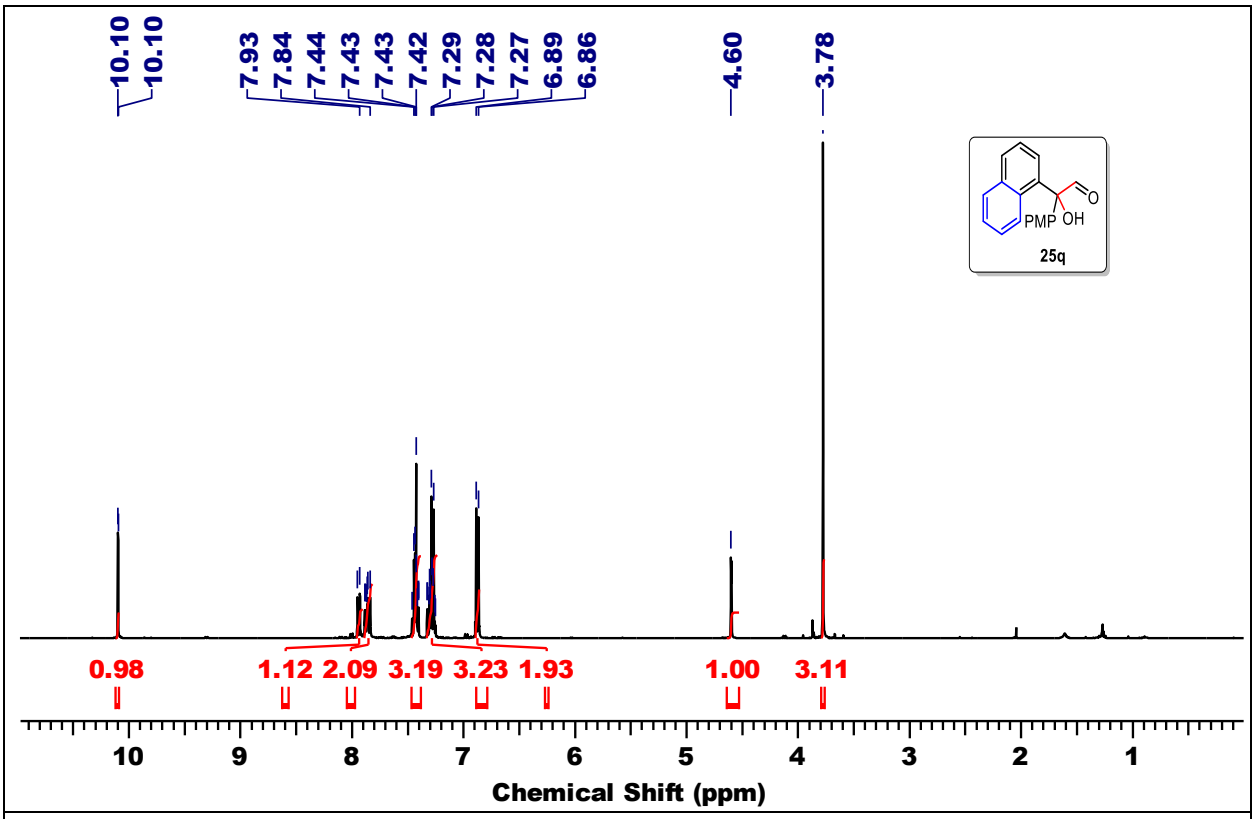


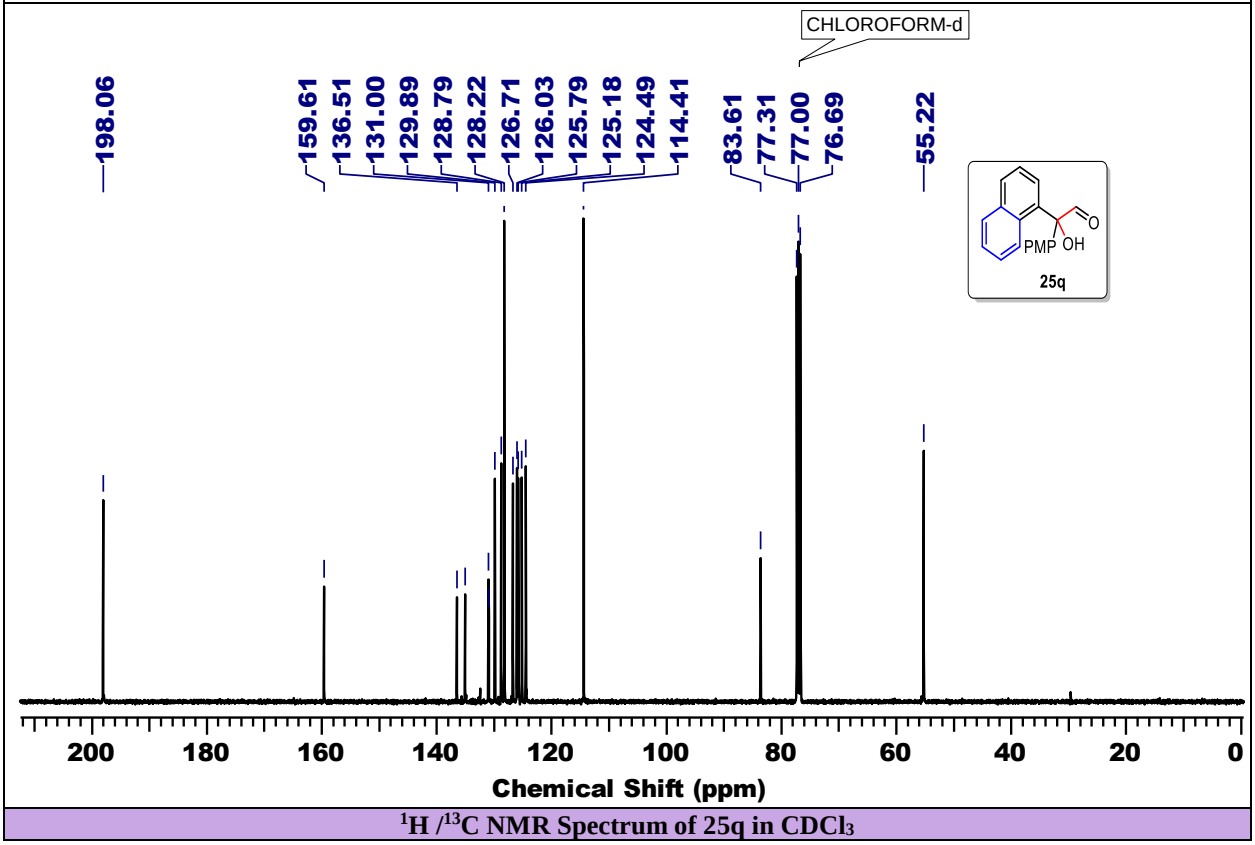
^{1}H /^{13}C NMR Spectrum of 25n in $CDCl_3$



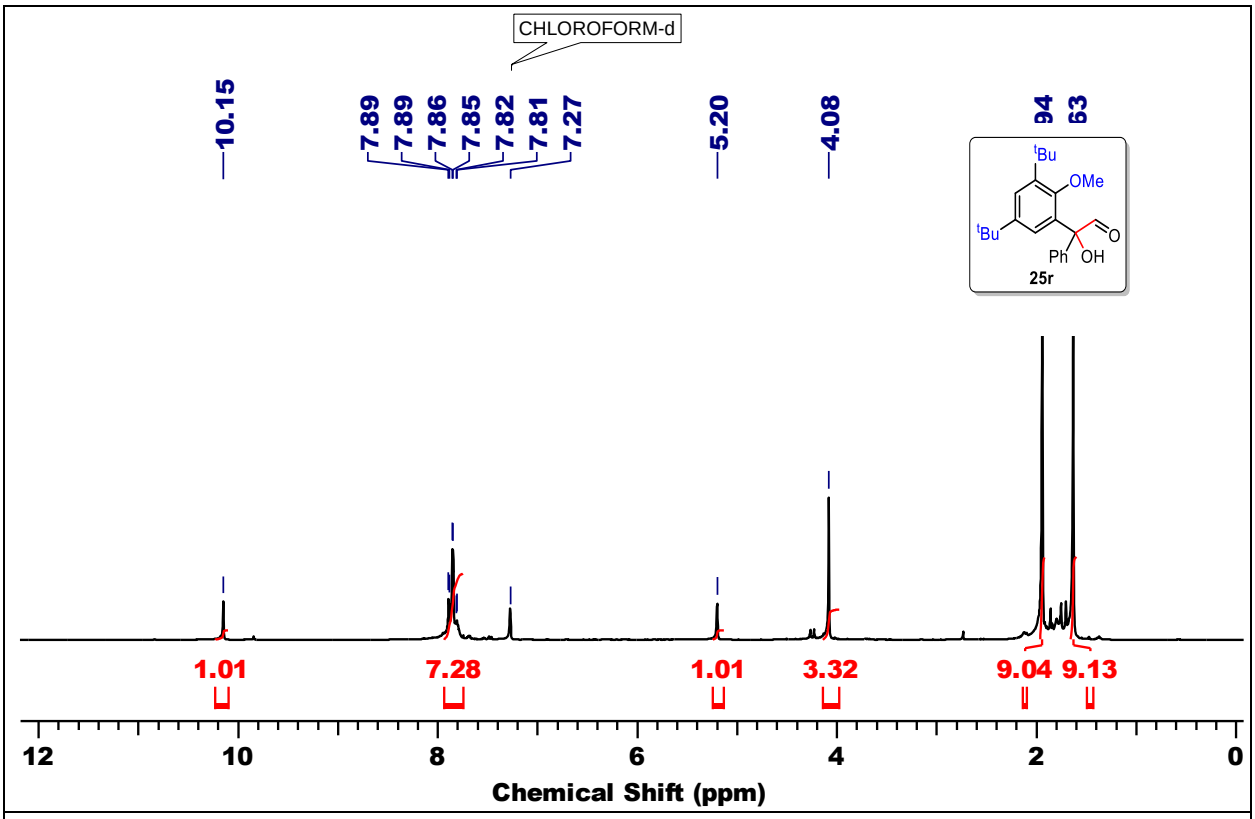


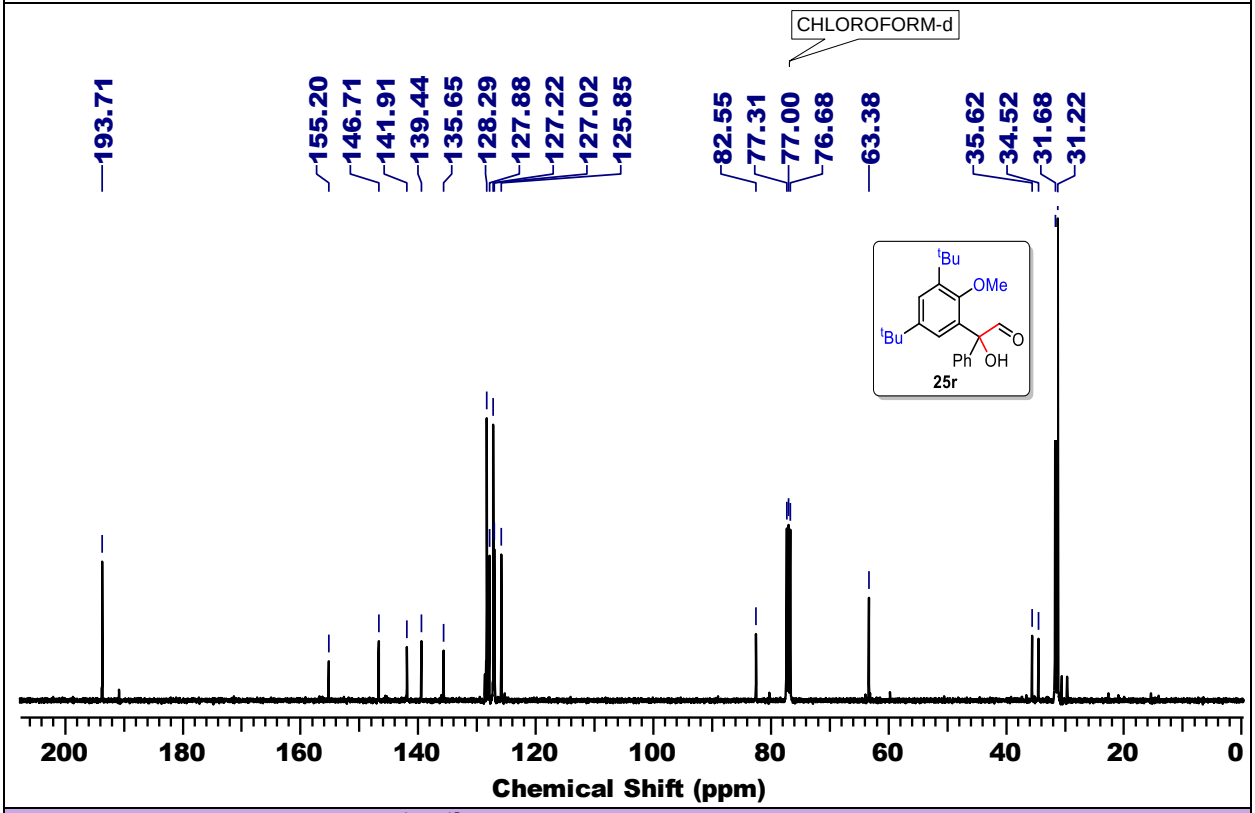
^{1}H /^{13}C NMR Spectrum of 25o in $CDCl_3$



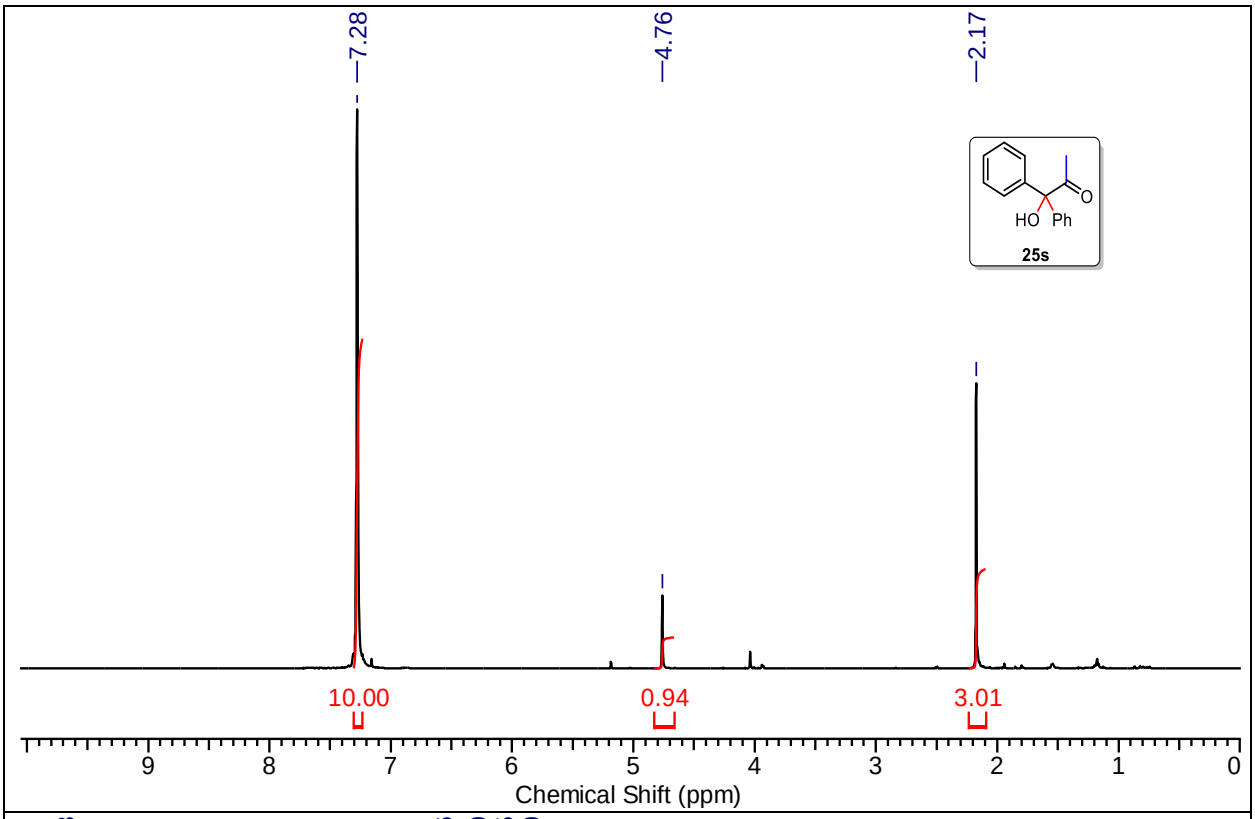


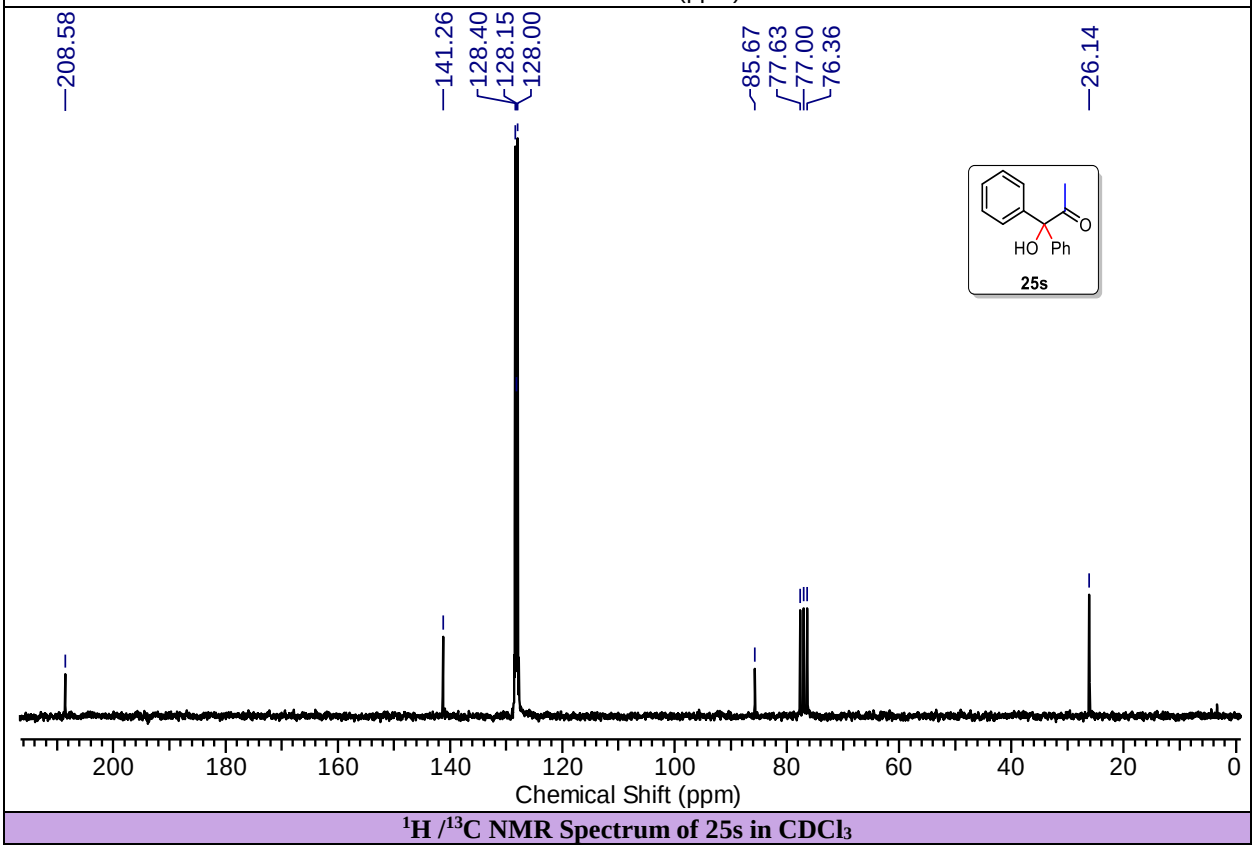
^{1}H /^{13}C NMR Spectrum of 25q in $CDCl_3$



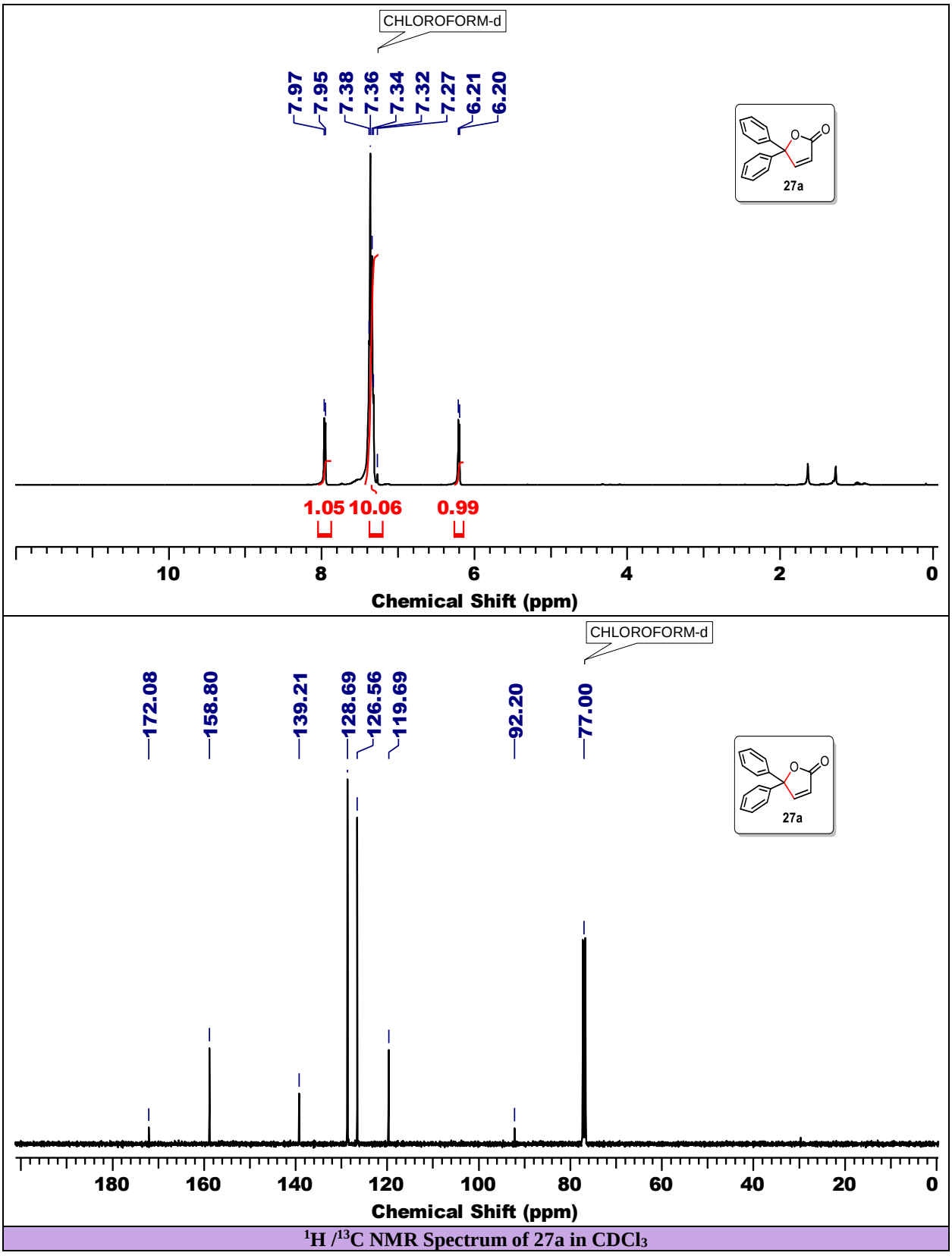


^{1}H /^{13}C NMR Spectrum of 25r in $CDCl_3$

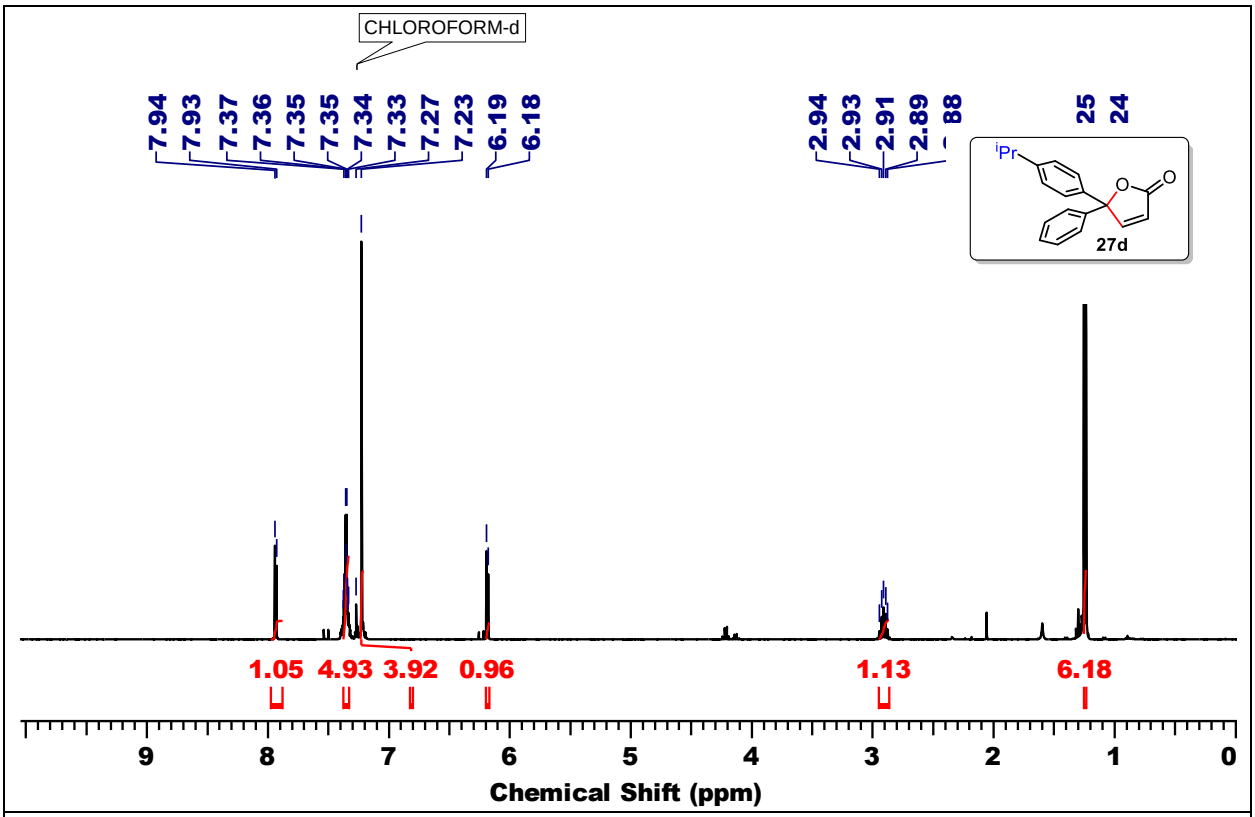


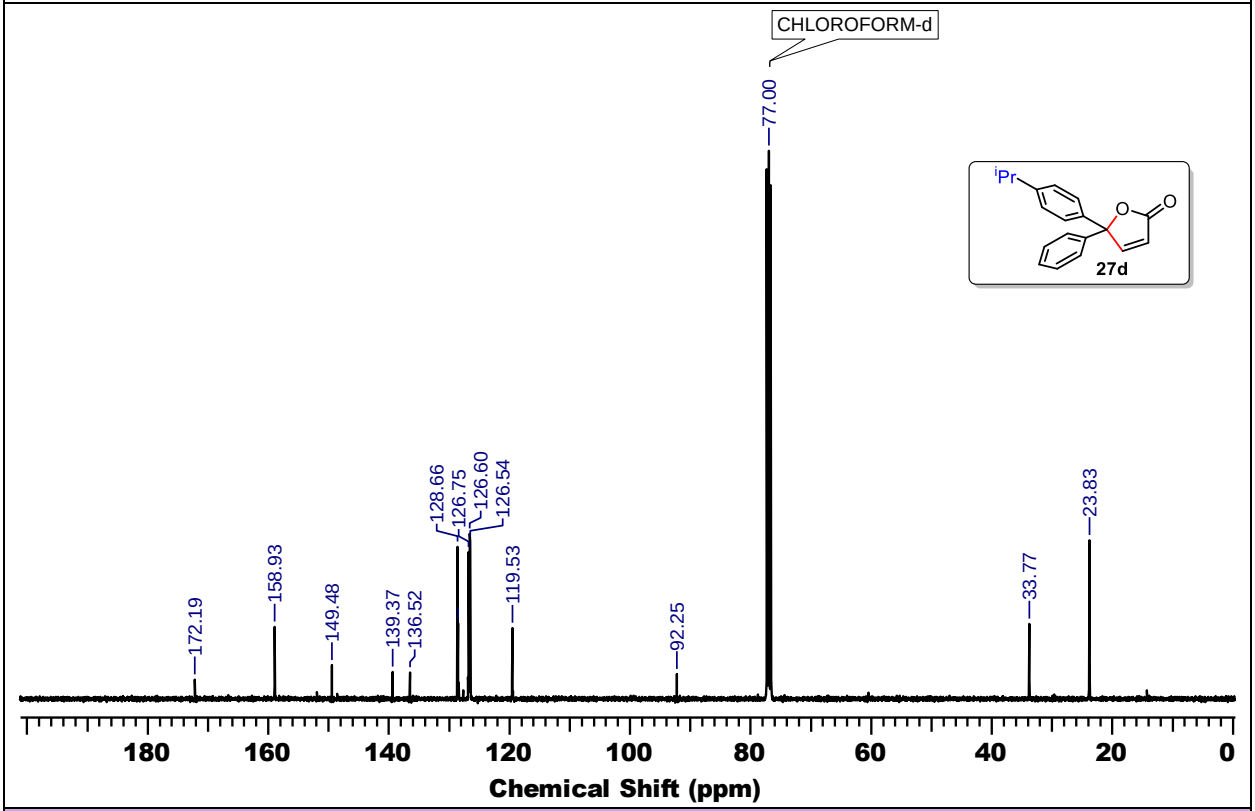


^{1}H /^{13}C NMR Spectrum of 25s in $CDCl_3$

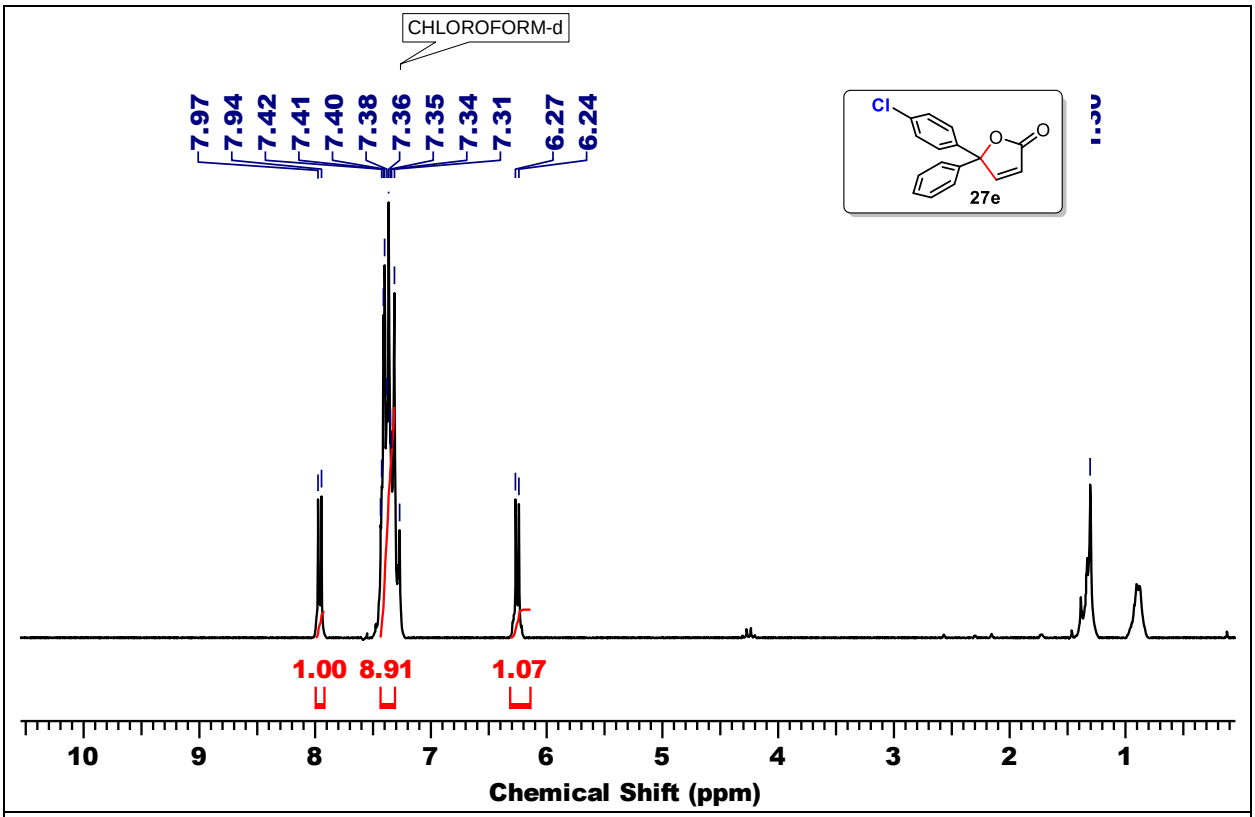


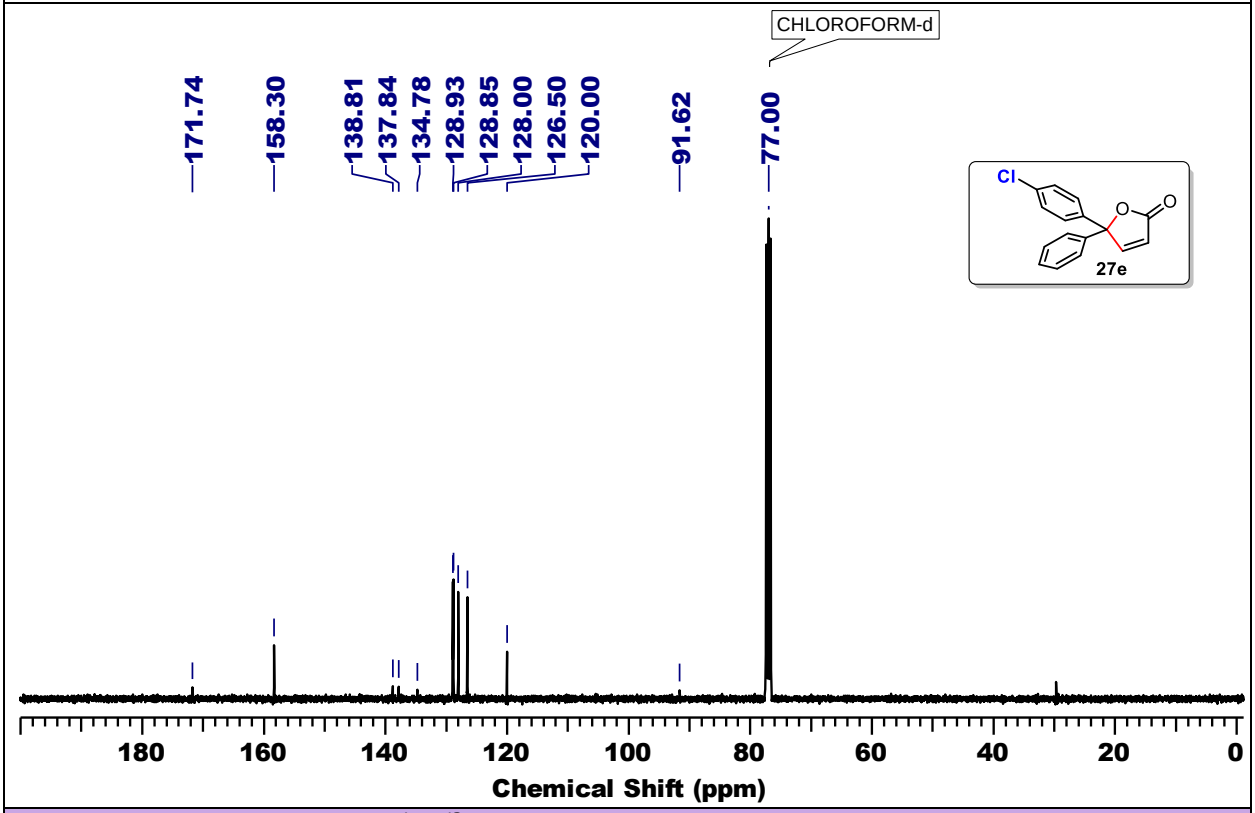
^{1}H /^{13}C NMR Spectrum of 27a in $CDCl_3$



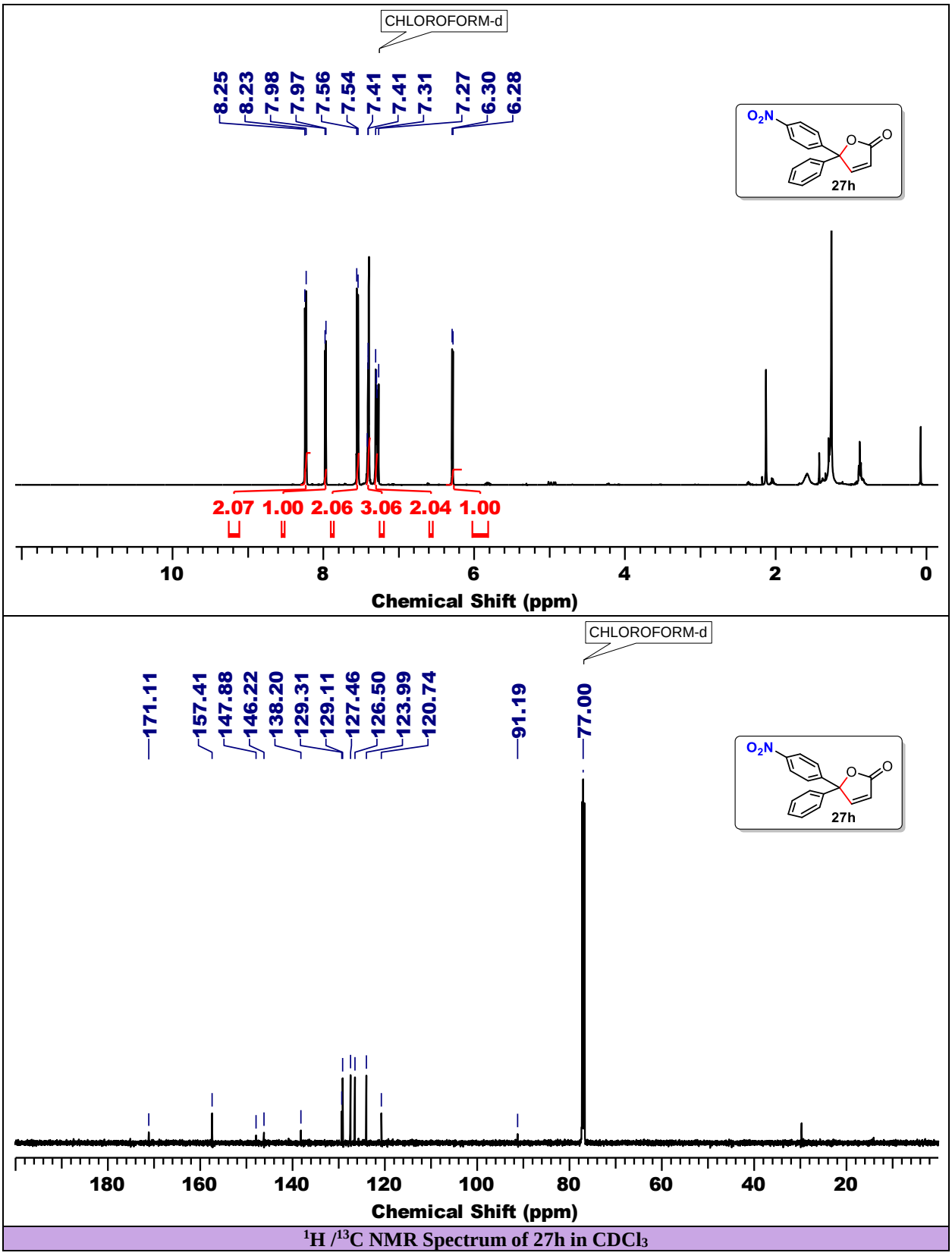


^{1}H /^{13}C NMR Spectrum of 27d in $CDCl_3$

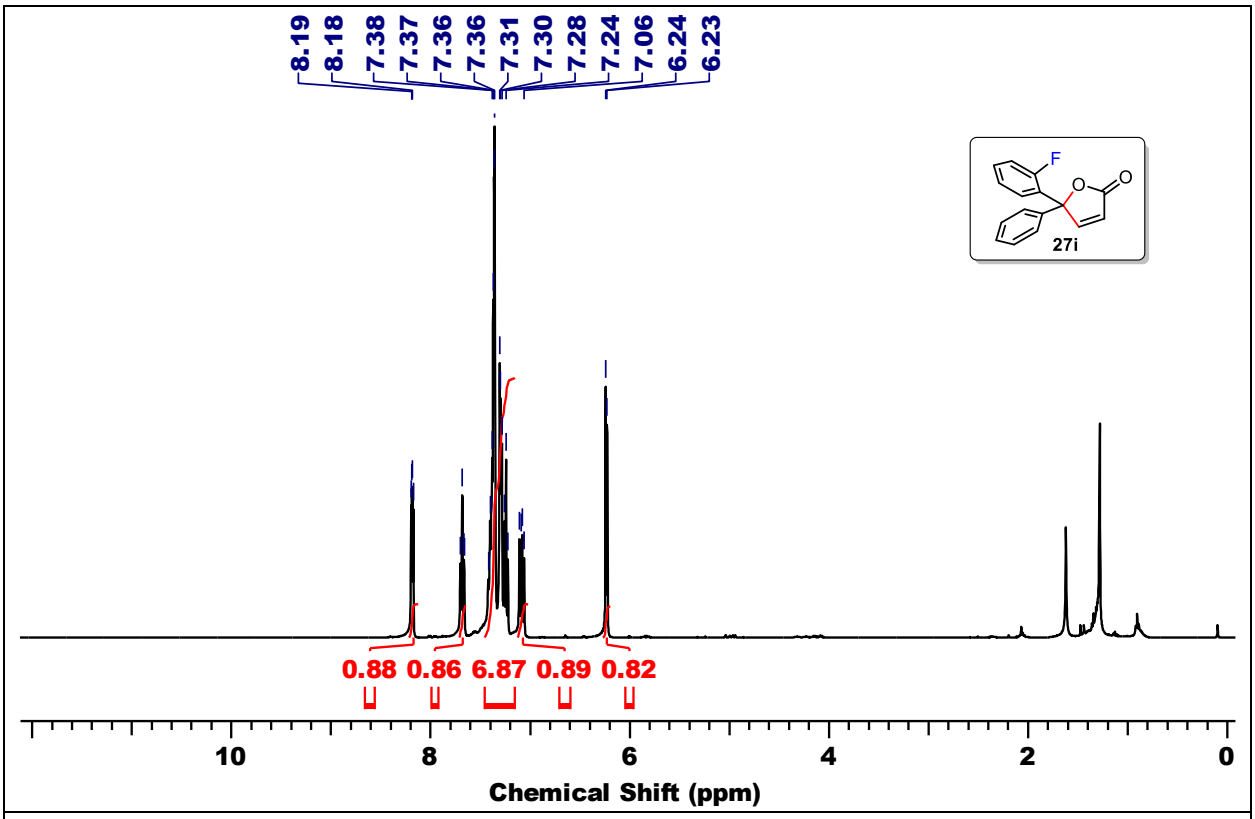


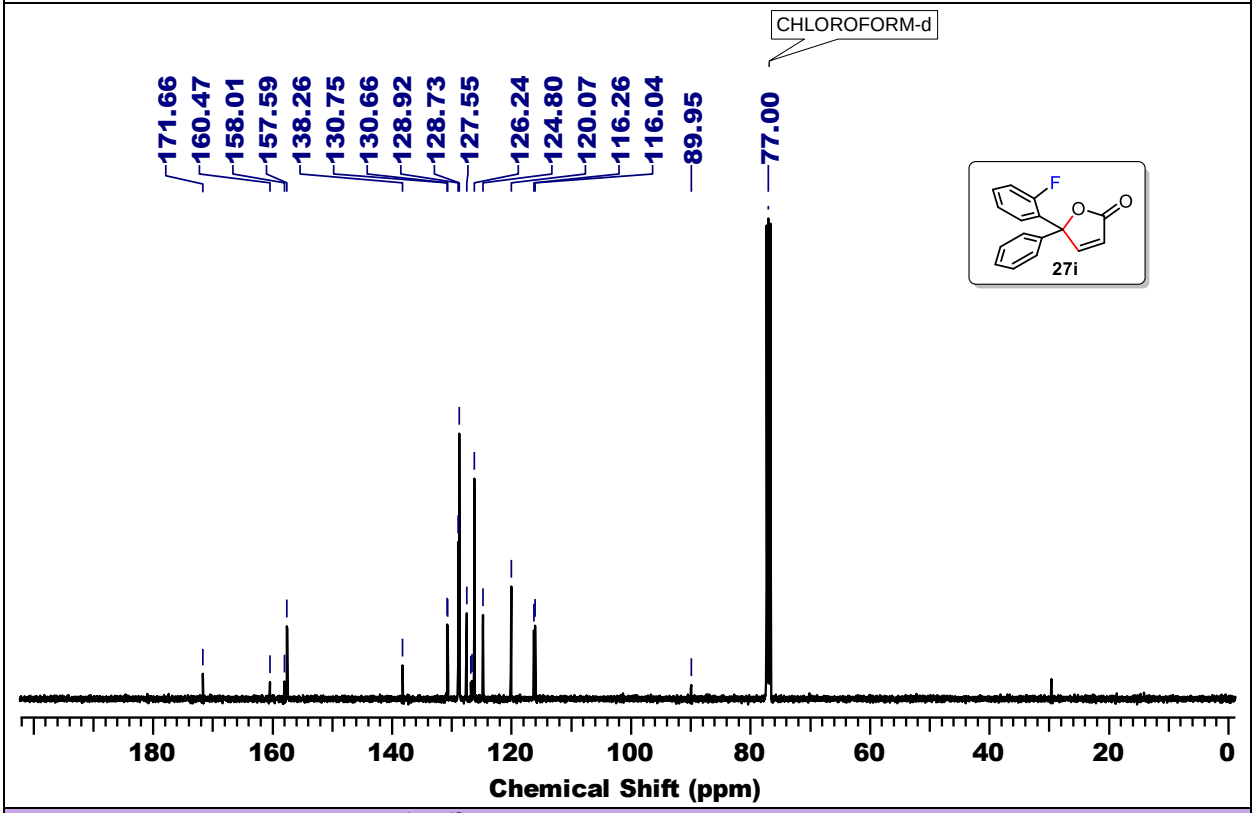


^{1}H /^{13}C NMR Spectrum of 27e in $CDCl_3$

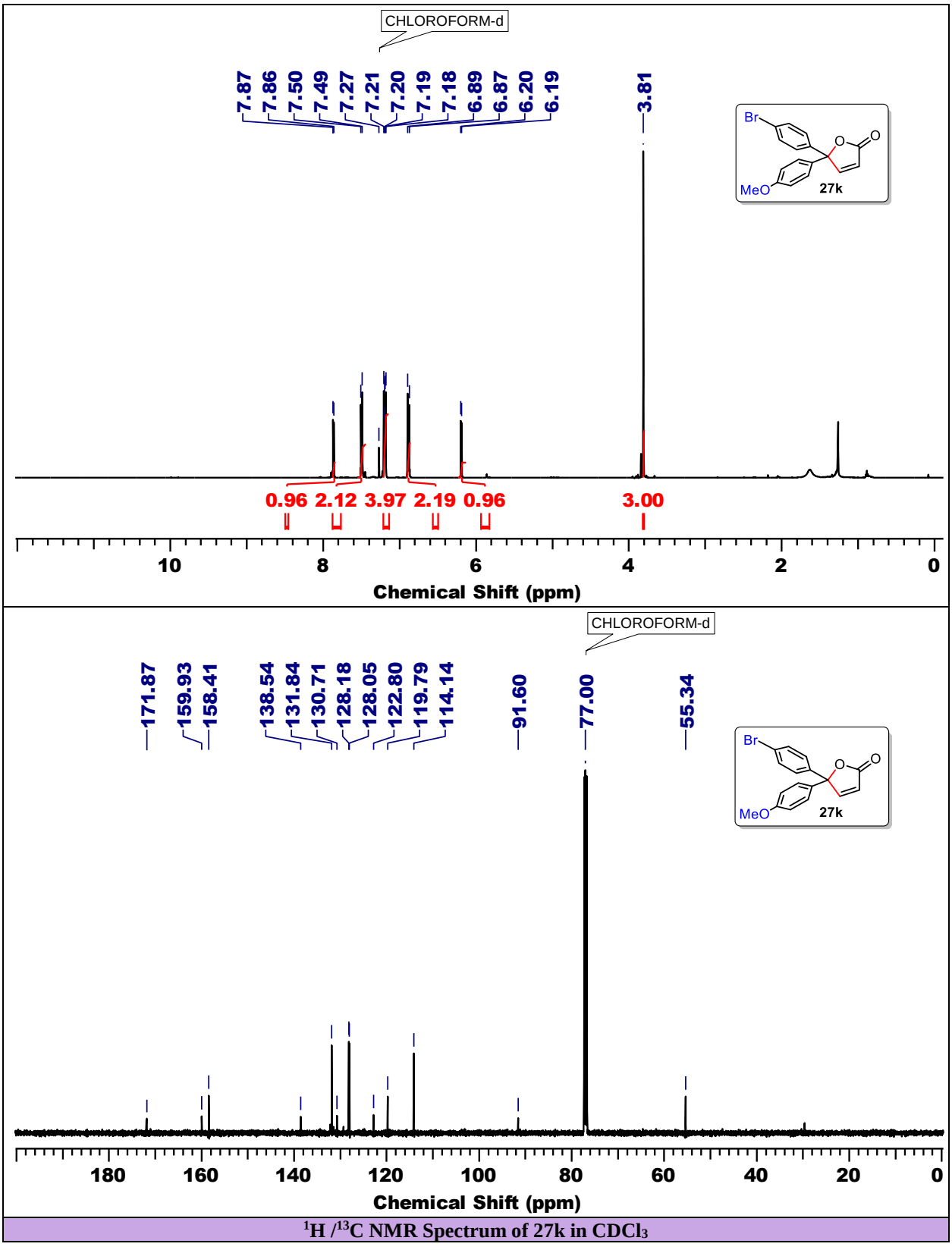


^{1}H /^{13}C NMR Spectrum of 27h in $CDCl_3$

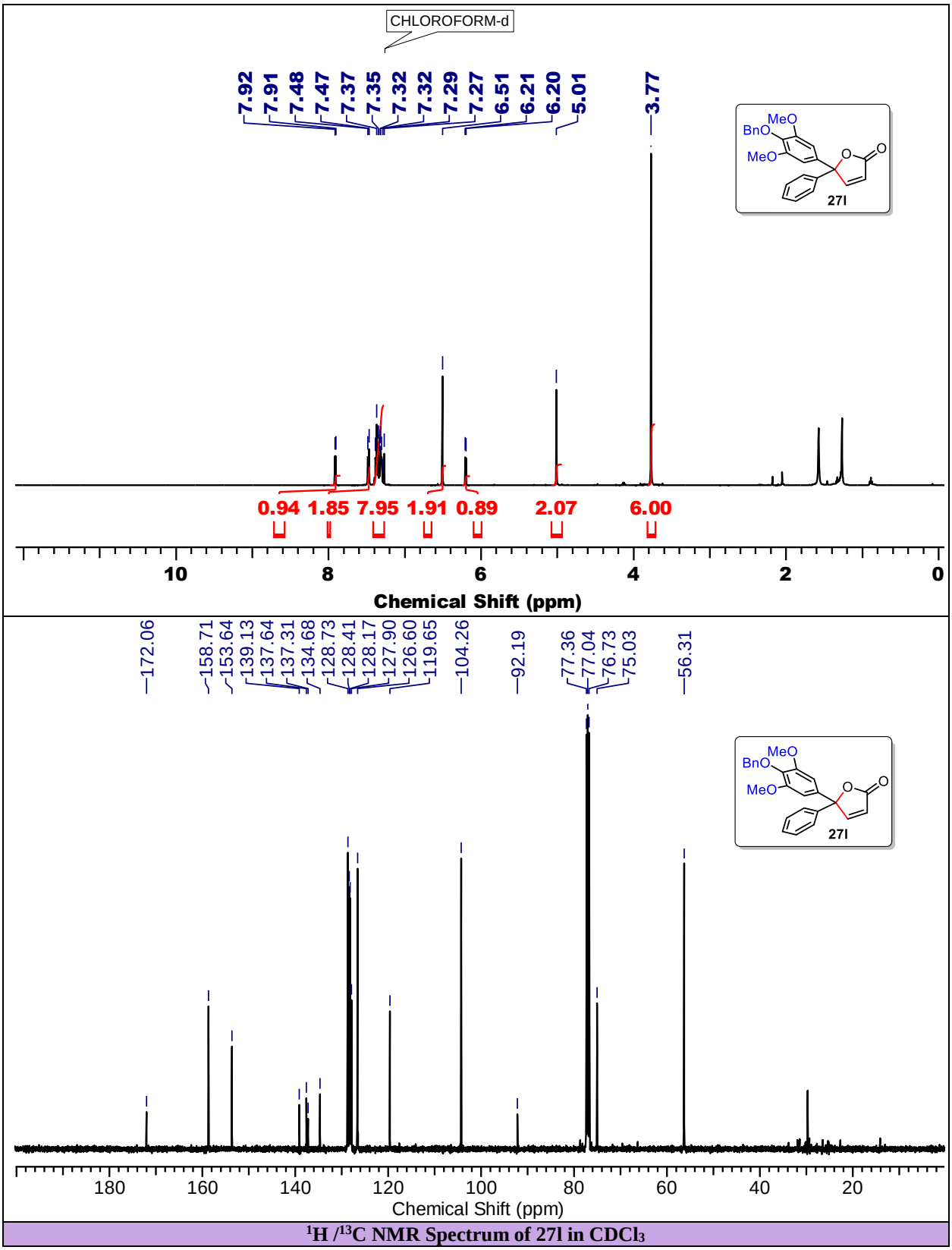




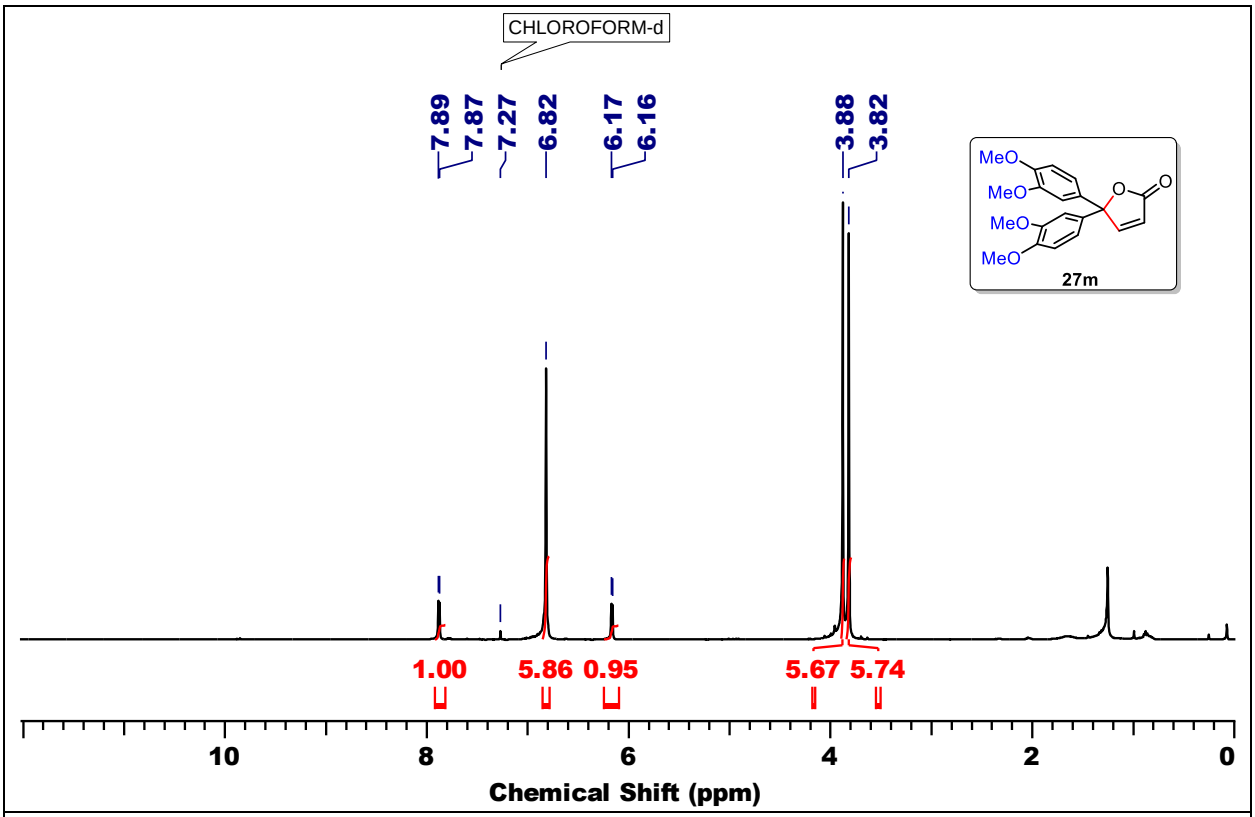
^{1}H /^{13}C NMR Spectrum of 27i in $CDCl_3$

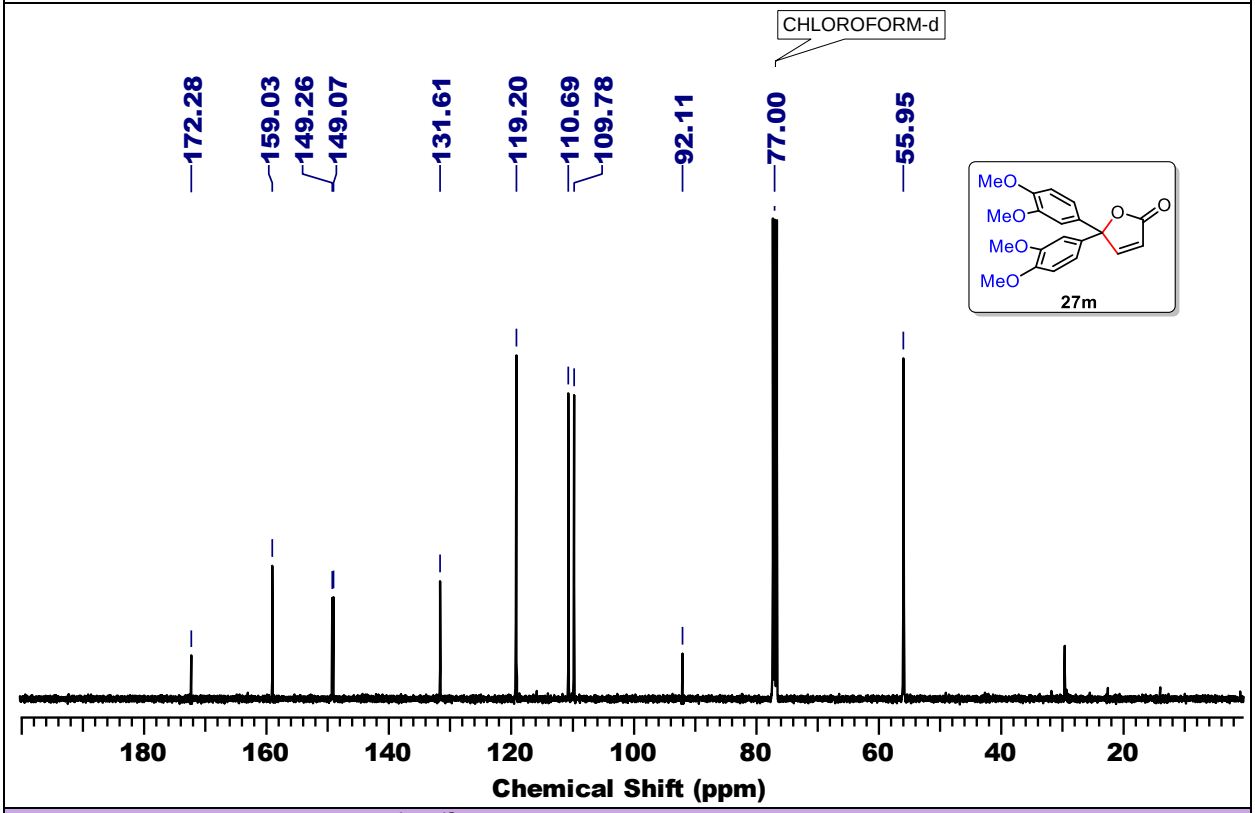


^{1}H /^{13}C NMR Spectrum of 27k in $CDCl_3$

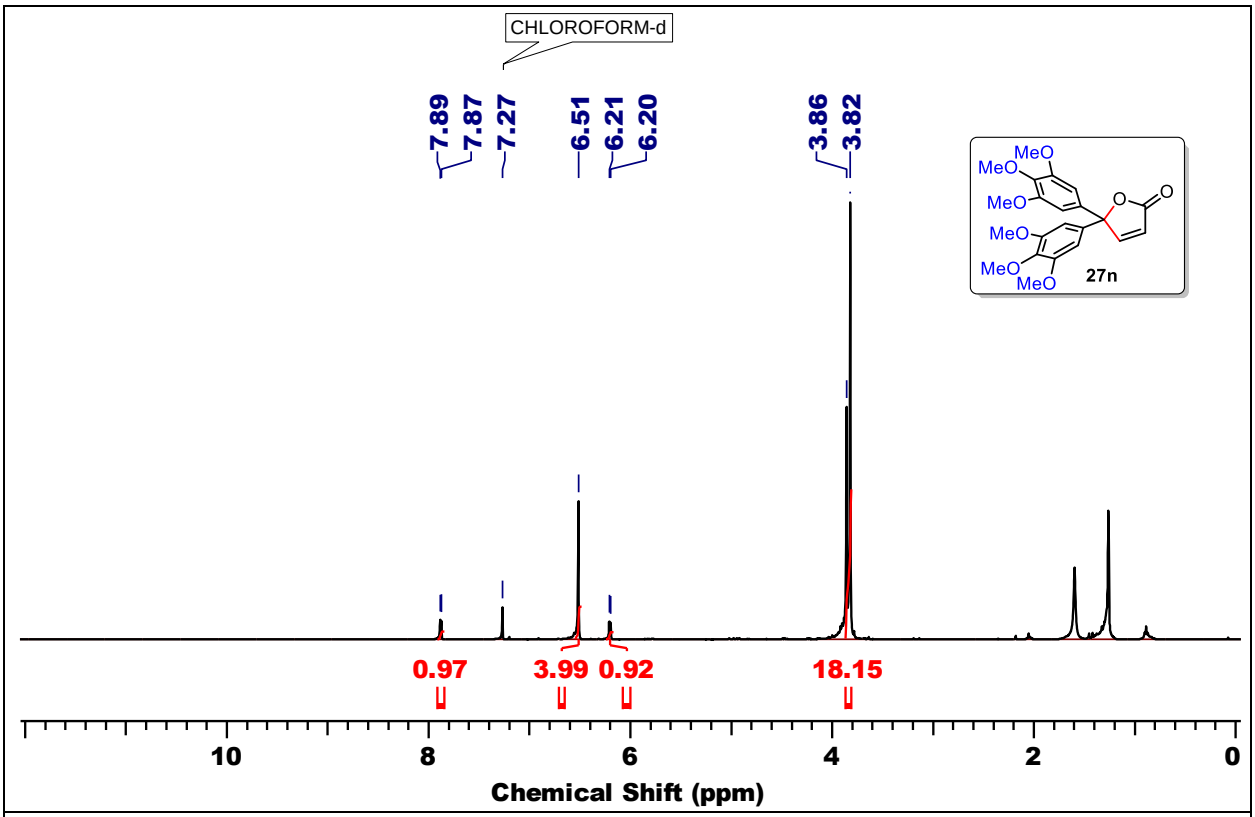


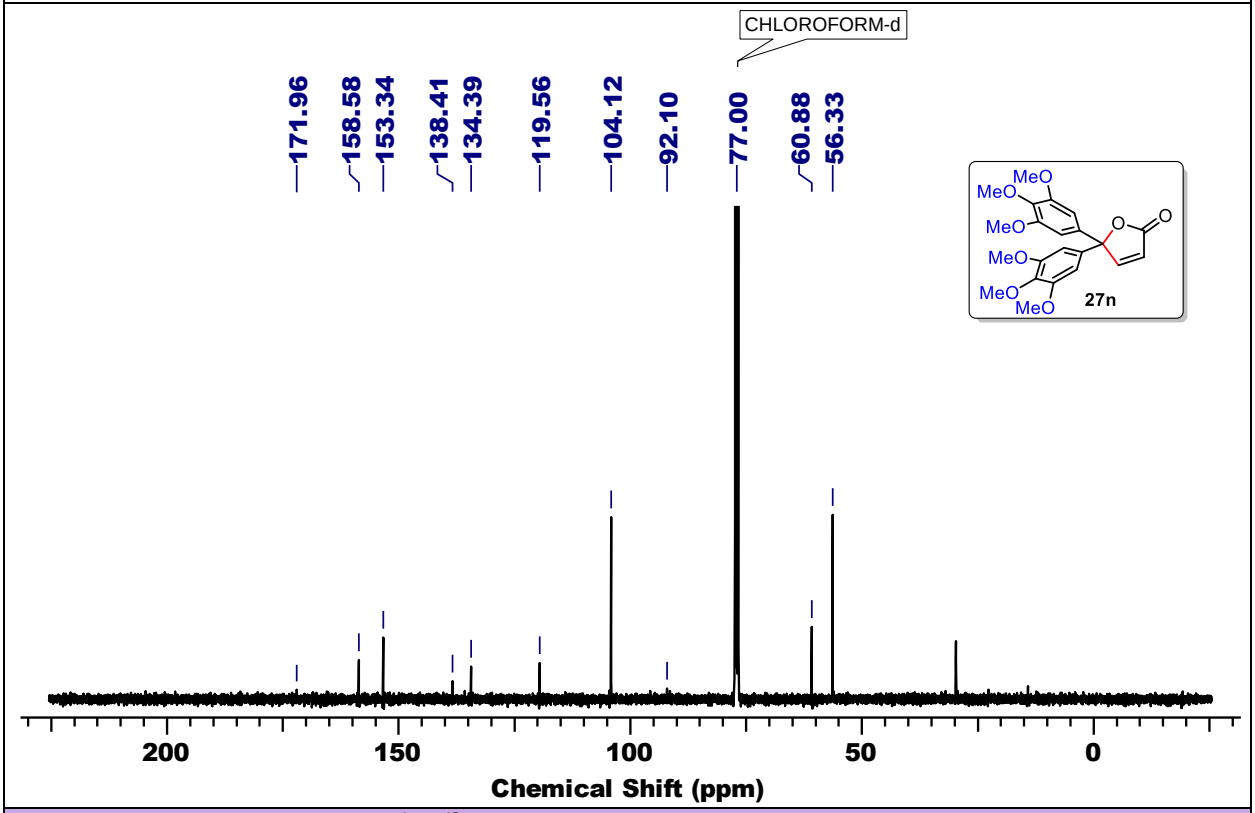
^{1}H /^{13}C NMR Spectrum of 27l in $CDCl_3$



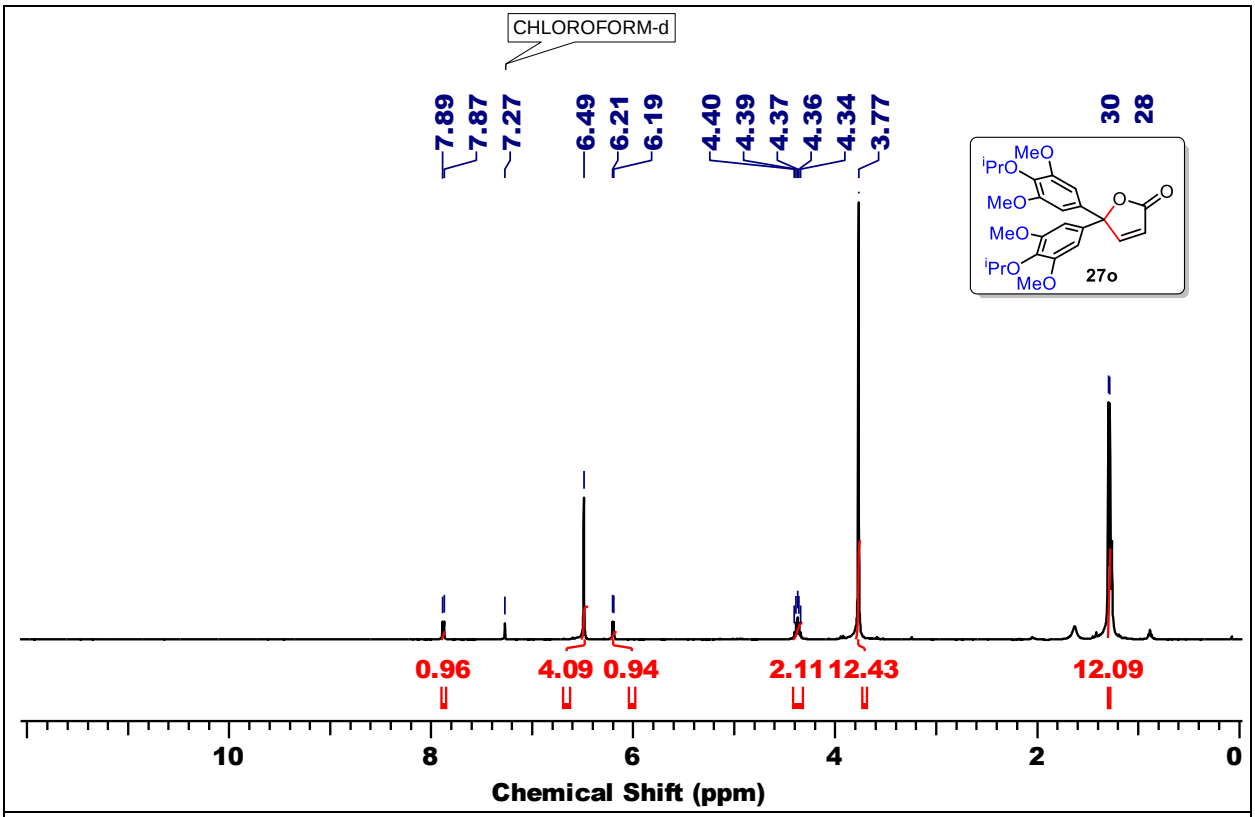


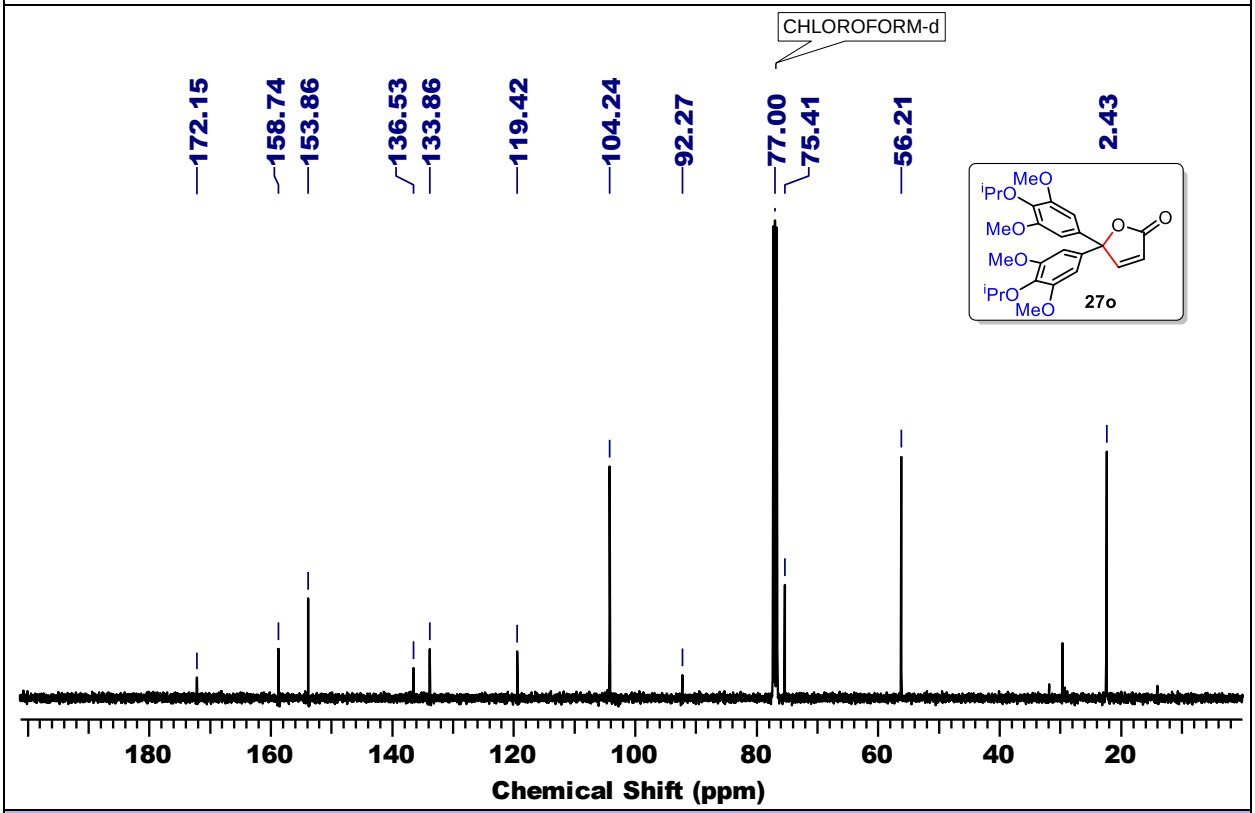
^{1}H /^{13}C NMR Spectrum of 27m in $CDCl_3$



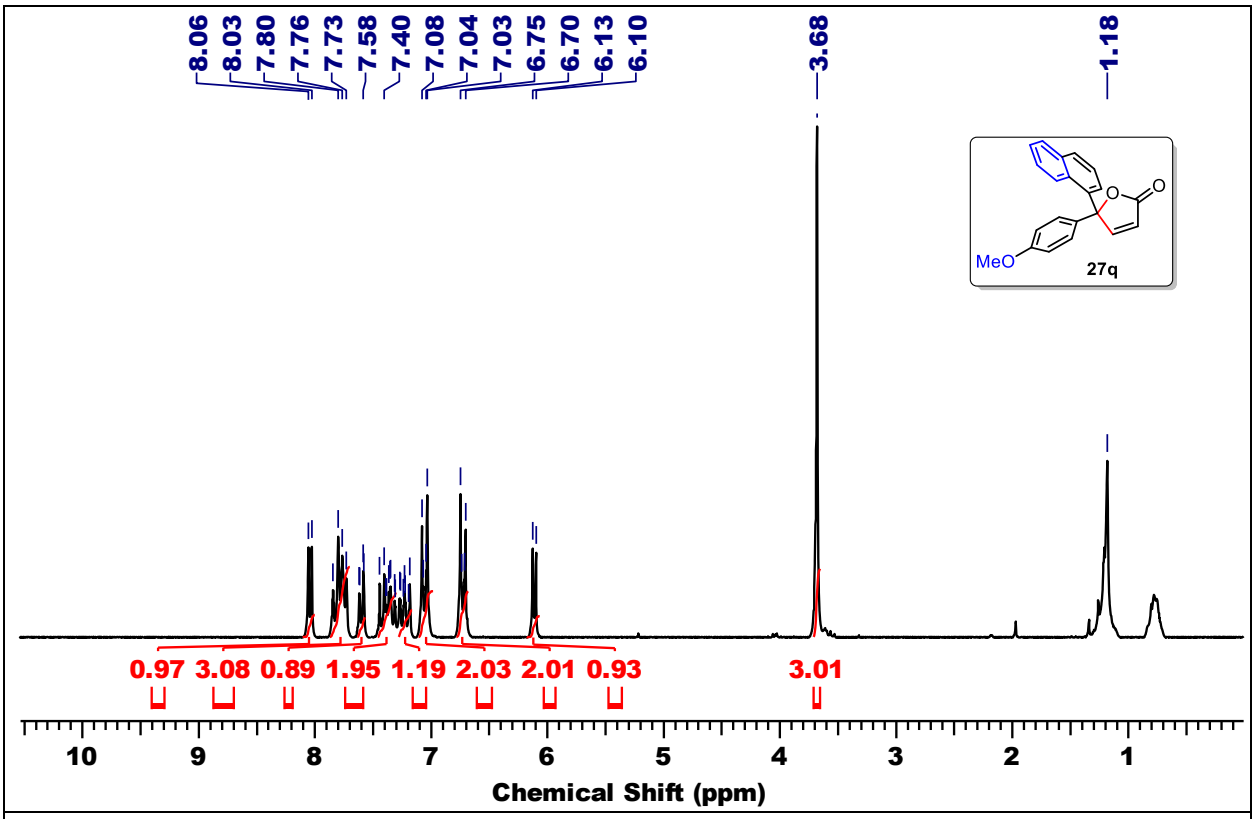


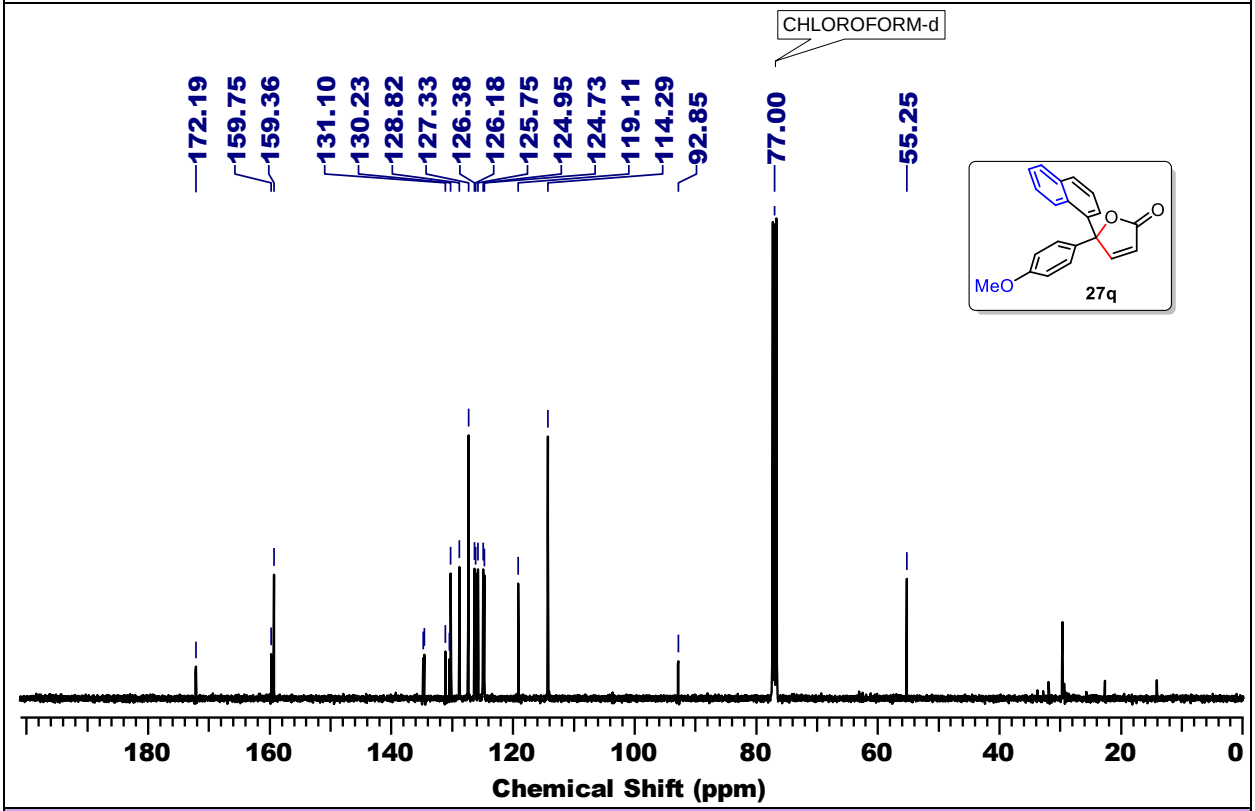
^{1}H /^{13}C NMR Spectrum of 27n in $CDCl_3$





^{1}H /^{13}C NMR Spectrum of 27o in $CDCl_3$





^{1}H /^{13}C NMR Spectrum of 27q in $CDCl_3$

References:

1) Gao, M.; Wang, M.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D.; Zheng, Q. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5767.
2) a) Inayat-Hussain, S.H.; Thomas, N. F. *Expert Opin Ther Pat* 2004, *14*, 819. b) Hart, J. H. *Annu Rev Phytopathol* **1981**, *19*, 437. c) Roman, B. I.; De Coen, L. M.; Thérèse F C Mortier, S.; De Ryck, T.; Vanhoecke, B. W. A.; Katritzky, A. R.; Bracke, M. E.; Stevens, C. V. *Bioorg Med Chem* **2013**, *21*, 5054. d) Gosslau, A.; Pabbaraja, S.; Knapp, S.; Chen, K. Y. *Eur J Pharmacol* **2008**, *587*, 25. e) Kumar, A. S.; Reddy, M. A.; Jain, N.; Kishor, C.; Murthy, T. R.; Ramesh, D.; Supriya, B.; Addlagatta, A.; Kalivendi S. V.; Sreedhar, B. *Eur J Med Chem* **2013**, *60*, 305.
3) a) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W.; Fong, H. H.; Farnworth, N. R.; Kinghorn, A. D.; Metha, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218–220. b) Pettit, G. R.; Rhodes, M. R.; Herald, D. L.; Hamel, E.; Schmidt, J. M.; Pettit, R. K. *J Med Chem* **2005**, *48*, 4087.
4) a) Kabir, M. S.; Monte, A.; Cook, J. M. *Tetrahedron Lett.* **2007**, *48*, 7269. b) Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem Pharm Bull* **1992**, *40*, 1130. c) Boonlaksiri, C.; Oonanant, W.; Kongsaeree, P.; Kittakoop, P.; Tanticharoen, M.; Thebtaranonth, Y. *Phytochem* **2000**, *54*, 415. d) Gao, M.; Wang, M.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D.; Zheng, Q. H. *Bioorg Med Chem Lett* **2006**, *16*, 5767.
5) a) Wang, L. X.; Heredia, A.; Song, H.; Zhang, Z.; Yu, B.; Davis, C.; Redfield, R. *J Pharm Sci* **2004**, *93*, 2448. b) Likhitwitayawuid, K.; Sritularak, B.; Benchanak, K.; Lipipun, V.; Mathew, J.; Schinazi, R. F. *Nat Prod Res* **2005**, *19*, 177.
6) Docherty, J. J.; Fu, M. M.; Stiffler, B. S.; Limperos, R. J.; Pokabla, C. M.; De Lucia, A. L. *Antivir Res* **1999**, *43*, 145.
7) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W.; Fong, H. H.; Farnworth, N. R.; Kinghorn, A. D.; Metha, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218.
8) Riviere, C.; Pawlus, A. D.; Merillon, J-M. *Nat. Prod. Rep.*, **2012**, *29*, 1317.
9) a) Shen, T.; Wang, X. N.; Lou, H. X. Natural stilbenes: an overview. *Nat. Prod. Rep.* **2009**, *26*, 916. b) Chong, J.; Poutaraud, A.; Hugueney, P. *Science* **2009**, *177*, 143. c) Jorgensen,

K. B. *Molecules* **2010**, *15*, 4334. d) Keylor, M. H.; Matsurra, B. S.; Stephenson, C. R. J. *Chem. Rev.* **2015**, *115*, 8976.

10) a) de Lima, D. P.; Rotta, R.; Beatriz, A.; Marques, M. R.; Montenegro, R. C.; Vasconcellos, M. C.; Pessoa, C.; de Moraes, M. O.; Costa-Lotufo, L. V.; Sawaya, A. C. H. F.; Eberlin, M. N. *Eur J Med Chem* **2009**, *44*, 701. b) Xiao, C. F.; Tao, L. Y.; Sun, H. Y.; Wei, W.; Chen, Y.; Fu, L. W.; Zou, Y. *Chin Chem Lett* **2010**, *21*, 1295. c) Giraud, A.; Provot, O.; Hamze, A.; Brion, J. D.; Alami, M. *Tetrahedron Lett* **2008**, *49*, 1107.

11) a) Larrosa, M.; Tomas-Barberan, F. A.; Espin, J. C. *J Agric Food Chem* **2003**, *51*, 4576. b) Simoni, D.; Invidiata, F. P.; Eleopra, M.; Marchetti, P.; Rondanin, R.; Baruchello, R.; Grisolia, G.; Tripathi, A.; Kellogg, G. E.; Durrant, D.; Lee, R. M. *Bioorg Med Chem* **2009**, *17*, 512.

12) Yu, O.; Jez, J.M. *Plant J.* **2008**, *54*, 750.

13) a) Sinha, A. K.; Kumar, V.; Sharma, A.; Sharma, A.; Kumar, R. *Tetrahedron* **2007**, *63*, 11070. b) Robinson, J. E.; Taylor, R. J. K. *Chem Commun* **2007**, *16*, 1617. c) Alonso, F.; Riente, P.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 3070. d) Khan, Z. A.; Iqbal, A.; Shahzad, S. A. *Mol Divers* **2017**, *21*, 483.

14) a) Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323. b) Zhang, N.; Quan, Z-J.; Zhang, Z.; Da, Y-X.; Wang, X-C. *Chem. Commun.*, **2016**, *52*, 14234.

15) a) Lee, D. G.; Chen, T. Comprehensive Organic Synthesis, 1st ed. (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, *7*, 541. b) Kuhn, F. E.; Fischer, R. W.; Herrmann, W. A.; Weskamp, T. Transition Metals for Organic Synthesis (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, Germany, **2004,** *2*, 427. c) Green, M. E.; Rech, P. J. C.. E. Floreancig, *Angew. Chem. Int. Ed.* **2008**, *47*, 7317.

16) a) Criegee, R.; Angew. Chem., Int. Ed., 1975, *14*, 745. b) P. S. Bailey, Ozonization in Organic Chemistry, Academic Press, O'Brien, New York, 1978. c) C. E. Schiaffo and P. H. Dussault, *J. Org. Chem.*, **2008,** *73*, 4688. d) Baxendale, M. I. R.; and S. V. Ley, Org. Lett., **2010**, *12*, 1596. e) R. Willand-Charnley, Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.*, **2012,** *14*, 2242. f) Ornum, S. G. V.; Champeau, R. M.; Pariza, R. *Chem. Rev.*, **2006**, *106*, 2990. g) Larock, R. C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, **1999**, 1213.

17) a) Pappo, R.; Allen, D.; Lemieux, Jr. R.; Johnson, W. S. *J. Org. Chem.*, **1956**, *21*, 478. b) Shing, T. K. M. in: Comprehensive Organic Synthesis, 1st ed. (Eds.: B. M. Trost, I. Flemming), Pergamon Press, Oxford, **1991**, *7*, 703.

18) a) Griffith, W. P.; Shoair, A. G.; Suriaatmaja, M. *Synth. Commun.*, **2000**, *30*, 3091. b) Plietker, B. *J. Org. Chem.*, **2003**, *68*, 7123 c) Ho, C-M.; Yu, W-Y.; Che, C-M. *Angew. Chem., Int. Ed.*, **2004**, *43*, 3303 d) Yang, D.; Zhang, C. *J. Org. Chem.*, **2001**, *66*, 4814.

19) Wang, A.; Jiang, H. *J. Org. Chem.*, **2010**, *75*, 2321.

20) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.*, **2006**, *8*, 693.

21) Travis, B. R.; Narayan, R. S.; Borhan, B. J. *J. Am. Chem. Soc.*, **2002**, *124*, 3824.

22) a) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177. b) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, *45*, 979. c) Liu, D.; Lei, A. *Chem. Asian J.* **2015**, *10*, 806.

23) a) Uyanik, M.; Ishihara, K. *Chimica Oggi* **2011,** *9*, 18. b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5331. c) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H. *Chem. Eur. J.* **2011**, *17*, 4085. d) Li, X.; Zhou, C. Xu, X. *ARKIVOC* (ix) **2012**, 150. e) Yusubova, M. S.; Zhdankin, V. V. *Resource-Efficient Technologies 1* **2015**, 49–67.

24) Tian, X.; Ren, Y-L.; Cheng, X.; Lu, Weiwei. *Chemistry Select*. **2019**, *4*, 11496.

25) a) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.*, **2016**, *116*, 3328. b) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.*, **2015**, *115*, 650. c) Singh, F. V.; Wirth, T. *Chem. – Asian J.*, **2014**, *9*, 950. d) Zhdankin, V. V. *Chem. Rev.*, **2008**, *108*, 5299.

26) a) Silva, L. F.; Vasconcelos, R. S.; Nogueira, M. A. *Org. Lett.*, **2008**, *10*, 1017. b) Abo, T.; Sawaguchi, M.; Senboku, H.; Hara, S. *Molecules*, **2005**, *10*, 183. b) Silva, L. F.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Dorigutto, A. C. *Org. Lett.*, **2007**, *9*, 1433. c) Yusubov, M. S.; Zholobova, G. A.; Filimonova, I. L.; Chi, K. *Russ. Chem. Bull. Int. Ed.*, **2004**, *53*, 1735. d) Kameyama, M.; Siqueira, F. A.; Gracia-Mijares, M.; Silva, L. F.; Silva, M. T. A.; *Molecules*, **2011**, *16*, 9421. e) Farid, U.; Malmedy, F.; Claveau, R.; Albers, L.; Wirth, T. *Angew. Chem., Int. Ed.*, **2013**, *52*, 7018. f) Boye, A. C.; Meyer, D. C.; Ingison, K.; French, A. N.; Wirth, T. *Org. Lett.*, **2003**, *5*, 2157.

27) a) Singh, F. V.; Wirth, T. *Synthesis*, **2013**, 2499. b) Maertens. G.; Canesi, S. *Top. Curr. Chem.*, **2016**, *373*, 223. c) Wengryniuk, S. E.; Canesi, S. Rearrangements and

Fragmentations Mediated by Hypervalent Iodine Reagents, PATAI'S Chemistry of Functional Groups, *John Wiley & Sons, Ltd, Chichester, UK*, **2018**, 665.

28) Zhang, B.; Li, X.; Guo, B.; Du, Y. *Chem. Commun*., **2020**, *56*, 14119.

29) a) C. A. Dvorak, US Pat., 4395571, **1983**. b) Stille, J. K.; Parrinello, G. Eur. Pat., 314759, **1989**. c) Pettit, G. R.; Lippert, J. W. Herald, D. L. *J. Org. Chem.*, **2000**, *65*, 7438. d) Baumann, T.; Bachle, M.; Brase, S. *Org. Lett.*, **2006**, *8*, 3797. e) Brase, S.; Baumann, T.; Dahmenb, S.; Vogt, H. *Chem. Commun.*, **2007**, 1881. f) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.*, **2003**, *68*, 929. g) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.*, **2007**, *46*, 7236.

30) a) Robinson, M. W. C.; Davies, A. M.; Buckle, R.; Mabbett, I.; Taylor, S. H.; Graham, A. E. *Org. Biomol. Chem.* **2009**, *7*, 2559. b) Shi, H.; Du, C.; Zhang, X.; Xie, F.; Wang, X.; Cui, S.; Peng, X.; Cheng, M.; Lin, B.; Liu, Y. *J. Org. Chem.* **2018**, *83*, 1312. c) Wang, Z.; Li, M.; Zhang, W.; Jia, J.; Wang, F.; Xue, S. *Tetrahedron Lett.* **2011**, *52*, 5968.

31) Sharma, A.; Sharma, N.; Kumar, R.; Sharma, U. K.; Sinha, A. K. *Chem. Commun*., **2009**, 5299.

32) a) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908. b) Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429. c) Xie, X.; Yoneyama, K.; Kusumoto, D.; Yamada, Y.; Takeuchi, Y.; Sugimoto, Y.; Yoneyama, K. *Tetrahedron Lett.* **2008**, *49*, 2066. d) Flematti, G. R.; Ghisalberti, E. L.; Dixon, K. W.; Trengove, R. D. Science 2004, *305*, 977. e) Murakami, T.; Morikawa, Y.; Hashimoto, M.; Okuno, T.; Harada, Y. *Org. Lett.* **2004**, *6*, 157. f) Alali, F.Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504.

33) a) Rao, Y. S. *Chem. Rev*. **1964**, *64*, 353. b) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. c) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans.* **2002**, *21*, 2324. d) Gil, S.; Parra, M.; Rodriguez, P.; Segura, J. *Mini-Rev. Org. Chem.* **2009**, *6*, 345. e) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43. f) Miyabe, H.; Fujji, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. g) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675. h) Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Rev.* **2017**, *117*, 10502. i) Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 1566.

34) a) Ugurchieva, T. M.; Veselovsky, V. V. *Russ. Chem. Rev.* **2009**, *78*, 337. b) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans.1* **2002**, 2324. Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346. c) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295. d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525. e) Villalobos, M. N.; Wood, J. L.; Jeong, S.; Benson, C. L.; Zeman, S. M.; McCarty, C.; Weiss, M. M.; Salcedo, A.; Jenkins, J. *Tetrahedron* **2009**, *65*, 8091. f) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 1277. g) Adrio, J.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 778. h) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431. i) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun*. **2005**, 3295. j) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. k) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2003**, *42*, 2892. l) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2003**, *42*, 1955.

35) Bartoli, A.; Rodier, F.; Commeiras, L.; Parrain, J.-L.; Chouraqui, G. *Nat. Prod. Rep.* **2011**, *28*, 763.

36) a) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070. b) Cope, A. C.; Trumbull, P. A.; Trumbull, E. R. *J. Am. Chem. Soc.* **1958**, *80*, 2844. c) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582. d) Crandall, J. K.; Apparu, M. Base-promoted isomerizations of epoxides. Organic Reactions (Hoboken, NJ, United States) **1983**, Vol. 29. e) Mathew, W.C.; Robinson, K. S.; Pillinger, I. M.; David, A. T.; Graham, A. E. *Tetrahedron* **2010**, *66*, 8377. f) Roy, S.; Banerjee, R.; Nangia, A.; Kruger, G. J. *Chem.–Eur. J.* **2006**, *12*, 3777. g) Cavdar, H.; Saracoglu, N. *Tetrahedron*, **2009**, *65*, 985.

37) a) Zincke, Th. Benzylisoxylene and benzylisophthalic acid. *Ber. Dtsch. Chem. Ges*. **1876**, *9*, 1761. b) Ben Alloum, A.; Labiad, B.; Villemin, D. *J. Chem. Soc., Chem. Commun.* **1989**, *7*, 386.

38) a) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. b) Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* **1988**, *29*, 3941. c) Kim, T.; Mirafzal, G. A.; Liu, J.; Bauld, N. L. *J. Am. Chem. Soc.* **1993**, *115*, 7653. d) Mesbahi, E.; Safari, N.; Gheidi, M. *J. Porphyr. Phthalocyanines* **2014**, *18*, 354.

39) a) Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* **1984**, 341. b) Andrews, L. E.; Bonnett, R.; Appelman, E. H. *Tetrahedron* **1985**, *41*, 781. b) Peraka, S.; Reddy, M. M.; Mameda N.;

Macharla, A. K.;, Kodumuri, S.; Chevella, D.; Nama, N. *Adv. Synth. Catal.* **2015**, *357*, 1125. c) Zhu, M.; Zhao, Y. *Chin. Chem. Lett.* **2015**, *26*, 248. d) Kodumuri S.; Peraka, S.; Mameda, N.; Chevella, D.; Banothua, R.; Nama, N. *RSC Adv.* **2016**, *6*, 6719. e) Yi, W.; Wang, P-F.; Lu, M.; Liu, Q-Q.; Bai, X.; Chen, K-D.; Zhang, J-W.; Liu, G-Q. *ACS Sustain. Chem. Eng.* **2019**, *7*, 16777.

40) a) Danilov, S.; Venus-Danilova, E. *Ber. Dtsch. Chem. Ges [Abteilung] B: Abhandlungen.* **1926**, *59B*, 1032. b) Frimer, A. A.; Gilinsky-Sharon, P.; Aljadeff, G.; Gottlieb, H. E.; Hameiri-Buch, J.; Marks, V.; Philosof, R.; Rosental, Z. *J. Org. Chem*. **1989**, *54*, 4853. d) Welch, J. T.; Seper, K.W. *Syn. Commun.* **1984**, *14*, 933. e) Althaus, M; Togni, A; Mezzetti, A. *J. Fluor. Chem.* **2009**, *130*, 702. f) Havare, N.; Plattner, D. A. *Org. Lett*. **2012**, *14*, 5078. g) Hu, G.; Ramakumar, K.; Brenner-Moyer, S. E. *J. Org. Chem*. **2017**, *82*, 6972. h) Shipilovskikh, S. A.; Rubtsov, A. E.; Malkov, A. V. *Org. Lett*. **2017**, *19*, 6760.

41) a) Sharma, N.; Sharma, A.; Kumar, R.; Shard, A.; Sinha, A. K. *Eur. J. Org. Chem*. **2010**, 6025. b) Zeng, X.; Xu D.; Miao, C.; Xiaa, C.; Sun, Wei. *RSC Adv*. **2014**, *4*, 46494. c) Fraile, J.; García, N.; Mayoral, J. A.; Santomauro, F. G.; Guidotti, M. *ACS Catal.* **2015**, *5*, 3552.

42) a) Merzel, R. L.; Fry, A. J. *J. Electrochem. Soc.* **2012**, *159*, G117. b) Ogibin, Y. N., Ilovaisky, A. I.; Nikishin, G. I. *Russ. Chem. Bull.* **1997**, *46*, 2089.

43) Possible α-hydroxylation of intermediate diaryl acetaldehydes with peroxides has been postulated earlier by: a) Weisenborn, F. L.; Taub, D. *J. Am. Chem. Soc*. **1952**, *74*, 1329. b) Curtin, D. Y.; Bradley, A. *J. Am. Chem. Soc*. **1954**, *76*, 5777.

44) Some selected methods for synthesis of 5,5-diary-γ-butenolide core see: a) Grandguillot, J. C.; Rouessac, F. *Synthesis* **1979**, 607. b) Lehmann, J.; Gossen, A. Lactones. XIV.. *Arch. Pharm. (Weinheim)* **1987**, *320*, 1059. c) Kothiyal, D. P.; Chamoli, R. P. *Ind. J. Chem., Sec. B.* **1990**, *29B*, 166. d) Kondo, T.; Kodoi, K.; Mitsudo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 755. e) Tnay, Y. L.; Chiba, S. *Chem.– Asian J.* **2015**, *10*, 873.

45) a) Franci, X.; Martina, S. L. X.; McGrady, J. E.; Webb, M. R.; Donald, C.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7735. b) Devalankar, D. A.; Chouthaiwale, P. V.; Sudalai, A. *Tetrahedron: Asymm.* **2012,** *23*, 240.

46) Liang, Y-F.; Jiao, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 548.

47) Parida, K. N.; Moorthy, J. N. *Tetrahedron* **2014**, *70*, 2280.

48) a) Sarabia, F. J.; Ferreira, E. M. *Org. Lett*. **2017**, *19*, 2865. b) Baker, R.; Sims, R. J. *Synthesis* **1981**, *2*, 117. c) Shen, X.; Liu, P.; Liu, Y.; Dai, B. *Lett. Org. Chem*. **2018**, *15*, 709–715. d) Wen, X-M.; Tao, L.; Xiang, Y-Z.; Fang, Y-G.; Yu, X-Q. *ARKIVOC*. **2005**, (xiii), 169. e) Roy, X.; Schenck, C. L.; Ahn, S.; Lalancette, R. A.; Venkataraman, L.; Nuckolls, C.; Steigerwald, M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12473. f) Zhang, J.; Peng, Y.; Leng, W.; Gao. Y.; Xu, F.; Chai, J. *Chin. J. Catal*. **2016**, *37*, 468. g) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758. h) Heynekamp, J. J.; Weber, W. M.; Hunsaker, L. A.; Gonzales, A. M.; Orlando, R. A.; Deck, L. M.; Vander Jagt, D. L. *J. Med. Chem*. **2006**, *49*, 7182. i) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett*. **2010**, *39*, 68. j) Azzena, U.; Dettori, G.; Idini, M. V.; Pisano, L.; Sechi, G. *Tetrahedron* **2003**, *59*, 7961. k) Niwa, T.; Nakada, M. *J. Am. Chem. Soc.* **2012**, *134*, 13538. l) Nishinaga, A.; Iwasaki, H.; Shimizu, T.; Toyoda, Y.; Matsuura, T. *J. Org. Chem*. **1986**, *51*, 2257.

49) Zhang, X.; Staples, R. J.; Rheingoldb, A. L.; Wulff, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 13971.

50) Mukaiyama,T.; Sakito, Y.; Asami, M. EP0011417B1.

51) Schlegel, M.; Schneider, C. *Chem. Commun.* **2018**, *54*, 11124.

52) Hou, Z.; Wakatsuki, Y. Product Class 12: Organometallic Complexes of Scandium, Yttrium, and the Lanthanides. *Science of Synthesis* **2003**, *2*, 849.

53) Fujimoto, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 3161.

ABSTRACT

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Title of the thesis: Early and Late Stage C-H Activation Protocols for Bioactive Molecules and Direct Conversion of Stilbenes to Diaryl-α-hydroxyacetaldehydes

In recent years, transition metal catalysed directed C-H activation has become a very popular and a useful method to synthesize a large number of aromatic as well as heteroaromatic compounds of interest. In this context, the synthesis of molecules that bear suitable directing groups, particularly their late stage functionalization (LSF) *via* C-H activation strategies has become an important tool to build focused libraries of organic scaffolds of drug molecules. On the other hand, 2,2-diarylacetaldehydes represent a highly functionalized core with the potential for various ring annulations. Despite this, due to their ready deformylation, the methods for their synthesis are scarce and very limited number of reports are present on their utility in organic synthesis. This warrants the development of reliable methods for their synthesis and the demonstration of their utility in natural product synthesis. One of the simple possibilities in this context is their two carbon Wittig-Gennari olefination and intramolecular lactonization leading to a 5,5-diarylbutenolide core – a popular synthetic target in natural products synthesis.

Chapter I includes the directed C–H alkynylation of 2-(hetero)arylquinazolin-4-ones with the ethynylbenziodoxolone reagent (TIPS-EBX) employing an Ir(III)-catalyst. Then Chapter II deals with the directed C–H alkenylation/alkylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine/ functionalization of the Pyrazole unit of GBT 440 scaffold with the alkenes, acrylates, amides, and diazocarbonyl compounds using Rh(III)-catalyst. Overall chapter-II deals with the building of focused small molecule libraries around the recently launched sickle cell anemia drug Voxelotor (GBT 440) employing early and late stage C-H functionalization. In chapter III, we developed one-pot iodine-catalysed oxone-mediated oxidative rearrangement of stilbenes leading to 2,2-diaryl-2-hydroxyacetaldehydes. The resulting α-hydroxy aldehydes have been subjected for a one-pot Stille-Gennari olefination followed by cyclisation leading to 5,5-diaryl-γ-butenolides.

LIST OF PUBLICATIONS

List of Publications Emanating from the Thesis work

1. Rohokale, R. S.; **Kalshetti, R. G.**; Ramana, C. V. Iridium(III)-Catalyzed Alkynylation of 2-(Hetero)arylquinazolin-4-one Scaffolds via C–H Bond Activation; *J. Org. Chem.* **2019**, *84*, 2951–2961.

2. More, G. V.; Malekar, P. V.; **Kalshetti, R. G.**; Shinde, M. H.; Ramana, C. V. Ru-catalyzed asymmetric transfer hydrogenation of α-acyl butyrolactone via dynamic kinetic resolution: Asymmetric synthesis of bis-THF alcohol intermediate of darunavir;. *Tetrahedron Lett.* **2021**, *66*, 5283.

3. **Kalshetti, R. G.**; Ramana, C. V. Rhodium(III)-Catalysed Alkenylation/Alkylation of 2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridine Scaffolds *via* C–H Bond Activation. (Manuscript under preparation)

4. **Kalshetti, R. G.**; Ramana, C. V. Rhodium(III)-Catalysed Alkenylation of 2-hydroxy-6-((2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde/ GBT-440 Scaffolds *via* C–H Bond Activation. (Manuscript under preparation)

List of Publications Non-Emanating from the Thesis Work

5. **Kalshetti, R. G.**; Venkataramasubramanian, V.; Kamble, S.; Sudalai, A. Concise enantioselective synthesis of (+)-sertraline and (-)-CP-52002 using proline catalysis; *Tetrahedron Lett.* **2016**, *57*, 1053–1055.

6. Prasad, P. K.; **Kalshetti, R. G.**; Reddi, R. N.; Kamble, S. P.; Sudalai, A.; I_2-Mediated Regioselective C-3 Azidation of Indoles. *Org. Biomol. Chem.*, **2016**, *14*, 3027–3030.

7. Reddi, R. N.; Prasad, P. K.; **Kalshetti, R. G.**; Sudalai, A. A Concise Enantioselective Synthesis of 1,4-Dideoxy-1,4-imino-D-Arabinitol using Co (III) (salen)-catalyzed HKR of Two-Stereocentered anti-Azido Epoxide. *Tetrahedron: Asymmetry,* **2017**, *28*, 162–165.

8. **Kalshetti, R. G.**; Ramana, C. V. Oxidative Rearrangement of Stilbenes to 2,2-Diaryl-2-hydroxyacetaldehydes; *ACS Omega* **2020**, *5*, 25199–25208.

9. **Kalshetti**, **R. G.**; Mandle, R. D.; Kamble, S. P.; Sudalai, A. P_2O_5-mediated Friedel-Crafts acylation of activated arenes with carboxylic acid as acylating agent; *Indian J. Chem*. **2020**, *59B*, 1861–1867.

Patents

1. **Rupali kalshetti**.; V. Venkataramasubramanian.; Arumugam Sudalai.Novel organocatalytic asymmetric syntheses of antidepressants- (+)-sertraline and Tametraline. **WO2015/193921A1**

2. Sudalai, Arumugam; Prasad, Pragati Kishore; **Kalshetti, Rupali**; Reddi, Rambabu Indole derivatives, preparation and use thereof. **WO 2017163263 A1**

List of Posters presented with details

1. 26th ISHC Congress International conference held at University of Regensburg, Germany. (3–8 Sep **2017**)

   Title: Proline Catalyzed Sequential Reactions for the Synthesis of 1,2-syn, 1,4-anti Diamino Alcohols

   Abstract: an unprecedented, one-pot procedure for a sequential α-amination/ Prins/ Ritter amidation of aldehydes that leads to the synthesis of functionalized THP units in good yields with excellent enantio- and diastereoselectivities. To demonstrate the application of this one-pot method we synthesized 1,2-syn, 1,4-anti diamino alcohol *via* reductive ring opening of THP unit. The salient features of the methodology are (1) easy availability of starting materials, (2) simple environmentally friendly procedure, and (3) availability of proline in both enantiomeric forms

2. National Science Day Celebration held at CSIR-NCL, Pune, India. (24–25 Feb **2017**)

   Title: A concise enantioselective synthesis of 1,4-dideoxy-1,4-imino-d-arabinitol using Co(III)(salen)-catalyzed hydrolytic kinetic resolution of a two-stereocentered anti-azido epoxide

   Abstract: A concise enantioselective synthesis of 1,4-dideoxy-1,4-imino-d-arabinitol, (+)-DAB-1, has been described in good overall yield (18.1%) and with high enantiomeric purity (up to 98% ee) starting from a simple raw material, cis-

2-butene-1,4-diol. The Co-catalyzed hydrolytic kinetic resolution of a two-stereocentered racemic azido epoxide followed by asymmetric dihydroxylation of the alkene and 'one pot' reductive cyclisation of the azido diol are key reactions in the synthetic sequence.

3. National Science Day Celebration held at CSIR-NCL, Pune, India. (24–25 Feb **2019**)

   Title: Iodine Catalyzed Oxidative Rearrangement of Stilbenes: Application towards the Synthesis of 5,5-Diaryl-γ-butenolides

   Abstract: A Simple iodine-catalysed oxidative rearrangement of stilbenes to 2,2-diaryl-2-hydroxyacetaldehydes has been developed by employing Oxone in CH_3CN/H_2O (1:1, V/V). Further the synthesis of 5,5-diaryl-γ-butenolides from these diaryl hydroxyacetalehydes has been developed under mild conditions by employing Stille-Gennari olefination followed by cyclisation in single step

List of Conference Attended with Details

26^{th} ISHC Congress International conference held at University of Regensburg, Germany. (3–8 Sep **2017**)

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Iridium(III)-Catalyzed Alkynylation of 2-(Hetero)arylquinazolin-4-one Scaffolds via C−H Bond Activation

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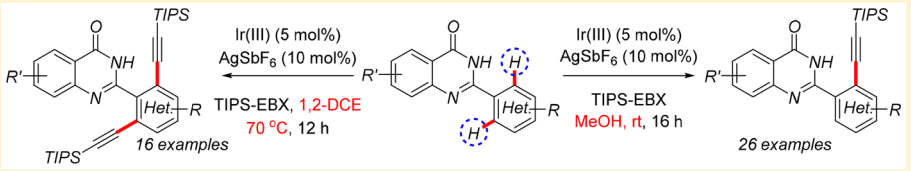
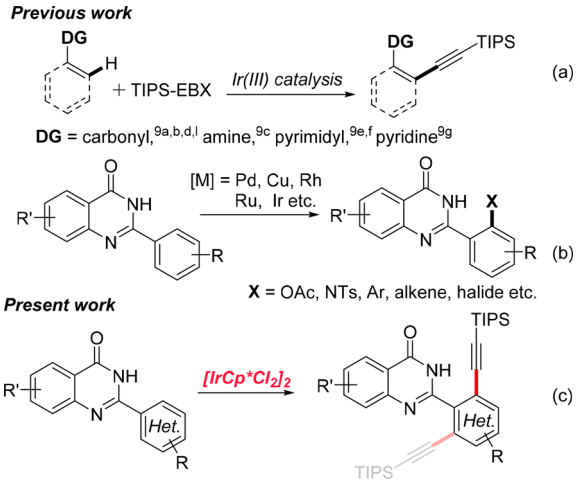
Supporting Information



ABSTRACT: The directed C−H alkynylation of 2-(hetero)arylquinazolin-4-ones has been explored with the ethynylbenziodoxolone reagent TIPS-EBX employing an Ir(III) catalyst. Complementary conditions for either monoalkynylation or dialkynylation have been developed. Also demonstrated is the broad scope of this reaction and the compatibility of various functional groups such as −F, −Cl, −Br, $-CF_3$, −OMe, $-NO_2$, and alkyl, etc.

"Alkyne" is a unique functional group in organic synthesis that allows the introduction of a wide range of carbon- and/or heteroatom-centered functional groups that can be easily transformed into carbo-/heterocycles of varying ring sizes.[1] There are several methods based on either functional group manipulation or cross-coupling reactions to construct or introduce an alkyne unit. In recent years, there has been tremendous interest in the catalytic alkynylation of C−H bonds to avoid prefunctionalization of the reacting substrates.[2] Indeed, the direct/directed alkynylation of sp^2 C−H bonds is considered as a reliable alternative to Sonogashira coupling.[3,4] The directed alkynylation reactions occupy a special role in this regard as they are regioselective and can be conducted even at room temperature.[4] A variety of functional groups such as amine, amide, anilide, imine, ester, carboxylic acid, various heterocycles, hydroxyl, and ketone groups have been employed as directing groups for directed C−H bond alkynylations. The alkyne sources employed in this pursuit include terminal alkynes,[5] haloalkynes,[6] borane alkynes,[7] and alkynylated hypervalent iodine reagents.[8] There are various inorganic metal complexes (Pd, Ru, Rh, Ir, Co, etc.) that have been employed for the different types of C−H bond- activation processes (sp^3, sp^2, and sp). Among these, iridium complexes occupy a special place due to the high reactivity of the Ir(III) species toward C−H bond cleavage.[9] Coming to the Ir(III)-catalyzed directed alkynylations using EBX-based reagents (Scheme 1a),[9a−g] the Jiang, Zeng, Li, and Xie groups reported, respectively, the carbonyl/carboxylate and pyrimidine-directed *ortho* C−H alkynylation of (hetero)aryl rings. The selective terminal alkynylation of 2-vinylanilines has been reported by the Nachtsheim group. Li and co-workers, on the other hand, documented an Ir-catalyzed pyridine-directed alkynylation of pendant aryls units of N^1-aryl-7-azaindole derivatives using TIPS-EBX. Very recently, Zhao and co-workers reported the selective *ortho*-alkynylation of Cbz-protected benzylamines employing bromoalkynes as the electrophilic alkynylating agents.

Scheme 1. Transition-Metal-Catalyzed Alkynylation Reactions



As part of our ongoing program on C−H activation functionalization at ambient temperatures employing [Ir] complexes,[10] the directed alkynylation of 2-arylquinazolinones has been undertaken considering the fact that quinazolin-4-one is a privileged structural unit widely found in natural products and in some approved/investigational drug candidates.[11] Anticancer drugs like erlotinib, gefitinib, and prazosin, which have been used to cure high blood pressure, anxiety and panic

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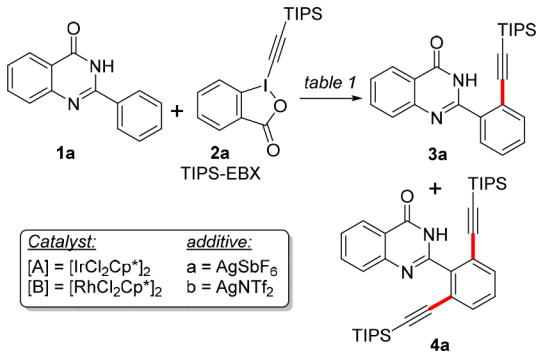
disorder, are representative quinazolin-4-one-based marketed drugs.

The directed C−H functionalization of the pendant aryl ring in the 2-arylquinazolin-4-one core has been well explored.[12] C−H amination,[13] arylation,[14] alkenylation,[15] and cross-dehydrogenative coupling[16] with acrylates and aceotxylation[17] have been documented using [Pd], [Ru], [Rh], and [Cu] complexes (Scheme 1b). Coming to the reports with [Ir] complexes, there are very few in this regard. The mono-/bis-sulfamidation of the aryl ring in 2-arylquinazolin-4-one using sulfonyl azides was recently reported by Cui and co-workers, and the reactions were carried out at elevated temperatures.[13e] This compilation on C−H functionalization of 2-arylquinazolin-4-ones revealed that the corresponding directed alkynylation via C−H bond functionalization on these scaffolds is missing. This prompted us to conduct explorations in this direction.

In this context, the preliminary experiments were conducted employing 2-phenylquinazolin-4-one **1a**(0.05 mmol) and TIPS-EBX **2** (0.06 mmol) as substrates and $[IrCp^*Cl_2]_2$(5 mol %) and $AgSbF_6$ (10 mol %) as the catalyst system. Initially, different solvents were screened to see the feasibility of the proposed alkynylation. As shown in Table 1, the reaction outcome seems to be solvent dependent. When conducted in CH_3CN at rt, the reaction was sluggish and gave mono-alkynylated quinazolin-4-one **3a**(21%) along with dialkynylated quinazolin-4-one **4a** (10%) (Table 1, entry 1). The product yield was improved when we switched to other aprotic polar solvents such as THF and dioxane. However, both mono- and dialkynylated products were obtained in varying proportions (Table 1, entries 2 and 3). Interestingly, when the reactions were conducted in protic solvents such as methanol, ethanol, and trifluoroethanol at room temperature (Table 1, entries 4−8), the dialkynylated product was not observed and the monoalkynylated product was obtained in varying yields. It was found that methanol was a good choice of solvent for this reaction, giving **3a** in 89% isolated yield (entry 4). At this juncture, to check the possibility of carrying out the dialkynylation exclusively, the reactions were conducted using 2.5 equiv of TIPS-EBX (with respect to **1a**), and different nonpolar solvents such as toluene, dichloromethane, and dichloroethane were screened at different temperatures. As shown in Table 1, the best results were obtained in dichloroethane at 70 °C, resulting in the dialkynylated product **4a** in 94% isolated yield (entry 14). Control experiments revealed that the presence of the Ir complex is essential and that under similar conditions the Rh(III) complex performed poorly (entries 15−17).

Having the complementary conditions for the selective mono- or dialkynylation in hand, we proceeded to explore the scope of the current transformations employing diverse 2-(hetero)arylquinazolin-4-one scaffolds (Scheme 2). Initially, we examined the scope of substituents on the *para*-position (F, Cl, Br, Me, OMe, CF_3; respectively **1b−g**) and the *meta*-position (F, Br, OMe; respectively **1h−j**). The selective mono-/dialkynylation of these substrates **1b−j** proceeded smoothly with **2** under optimized conditions and provided the corresponding monoalkynylated products **3b−j** (73−91%) and dialkynylated products **4b−j** (67−96%) in good to excellent yields. The catalytic *ortho*-C−H alkynylation was not affected by the steric hindrance of another *ortho*-substitution (**1k−m**). Even when methoxy groups were placed at the *ortho*- and *para*-positions, the alkynylation reaction proceeded smoothly and provided the corresponding product **3n** in 89% yield.

Table 1. Optimization Studies[a]



entry	catalyst/ additive	solvent	temp (°C)/time (h)	yield[b] (%) 3a	4a
1	[A]/a	CH_3CN	rt/16	21	10
2	[A]/a	THF	rt/12	42	8
3	[A]/a	dioxane	rt/16	44	trace
4	[A]/a	**MeOH**	**rt/16**	**89**	**trace**
5	[A]/a	EtOH	rt/16	52	trace
6	[A]/a	HFIP	rt/16	36	trace
7	[A]/a	TFE	rt/16	30	trace
8	[A]/a	toluene	rt/16	35	12
9	[A]/a	DCM	rt/16	38	22
10	[B]/a	DCE	rt/16	27	trace
11	[A]/b	DCE	rt/16	18	43
12	[A]/a	MeOH	70/12	20	53
13	[A]/a	DCM	70/12	12	62
14	[A]/a	**DCE**	**70/12**	–	**94**
15	[B]/a	DCE	70/12	12	40
16	[B]/b	DCE	70/12	8	32
17	[B]/b	DCE	70/12	trace	28[c]
18	[A]/b	DCE	70/12	8	68
19	[A]/b	DCE	70/12	24	38[c]

[a]Reaction conditions: for entries 1−10, 0.05 mmol of **1a**, 0.06 mmol of **2a**, 5 mol % of catalyst, 10 mol % of additive, dry solvent (1.0 mL), 16 h; for entries 12−19, 0.05 mmol of **1a**, 0.125 mmol of **2a**, 5 mol % of $[IrCp^*Cl_2]_2$, 10 mol % of additives, dry solvent (1.0 mL), 12 h. [b]Isolated yields. [c]NaOAc (1.2 equiv) was used.

Next, we examined the scope of substituents on the aryl ring of the quinazolin-4-one core by employing the C7-(Me, F, Br or NO_2)-substituted 2-phenylquinazolin-4-ones **1o−r**. In all cases, the mono- and dialkynylation with **2** proceeded smoothly and provided the corresponding monoalkynylated products **3o−r** (70−82%) and dialkynylated products **4o−r** (79−86%) in very good yields. However, the monoalkynylation of 6,7-dimethoxy-2-phenylquinazolin-4(3*H*)-one (**1s**) gave the corresponding monoalkynylated product **3s** in 62% yield, along with the dialkynylated product **4s** in 14% yield.

The scope of the alkynylation reaction has been further examined by employing quinazolin-4-ones **1t−z** having C2-naphthyl and heteroaryl substituents. In the case of 2-(1-naphthyl)quinazolin-4(3*H*)-one (**1t**), the alkynylation proceeded as expected at the C2 of the naphthyl ring and gave the corresponding product **3t** in 84% yield. On the other hand, in the case of the isomeric 2-(2-naphthyl) quinazolin-4(3*H*)-one (**1u**), the monoalkynylation took place selectively at the C3 position instead of C1, resulting in the product **3u**. This site

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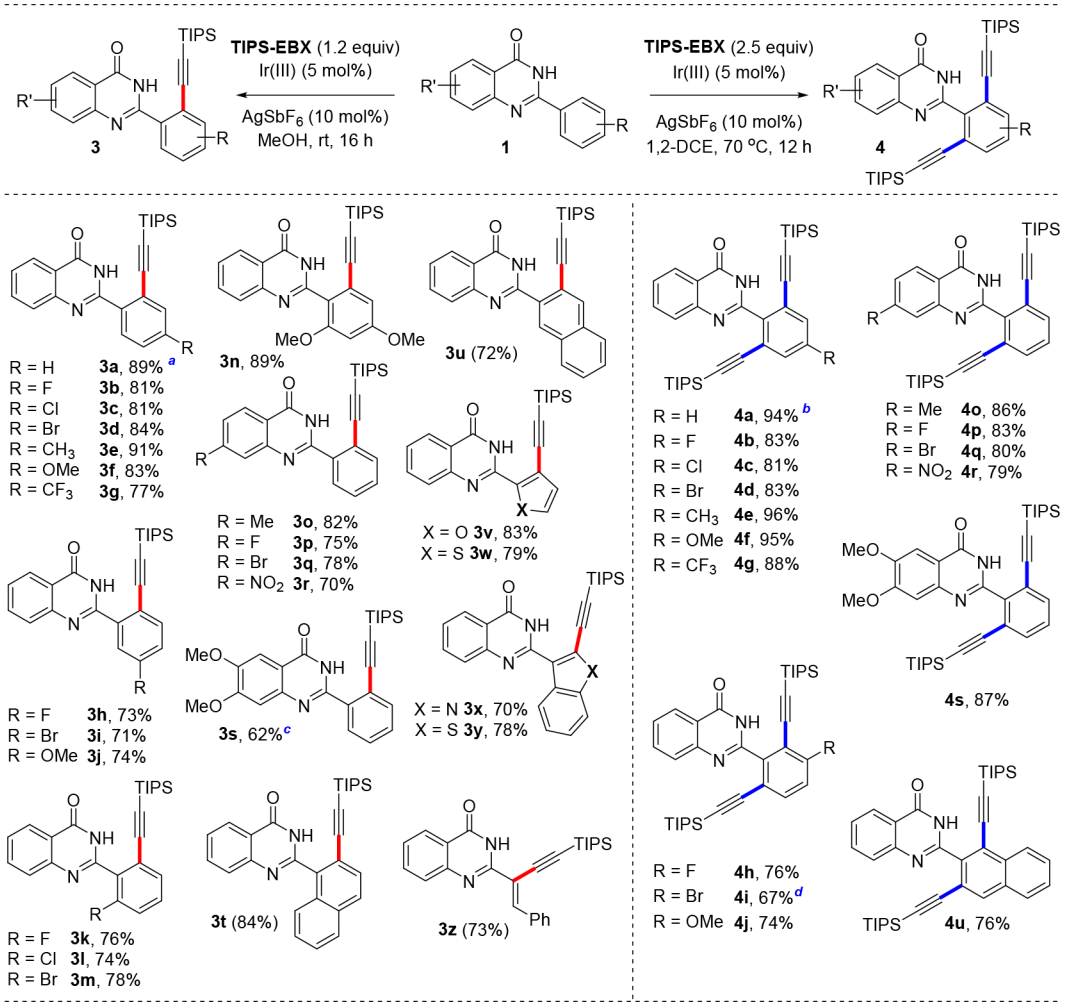
Scheme 2. Ir(III)-Catalyzed C−H Mono-/Dialkynylation of 2-(Hetero)arylquinazolin-4-one Scaffolds[a]



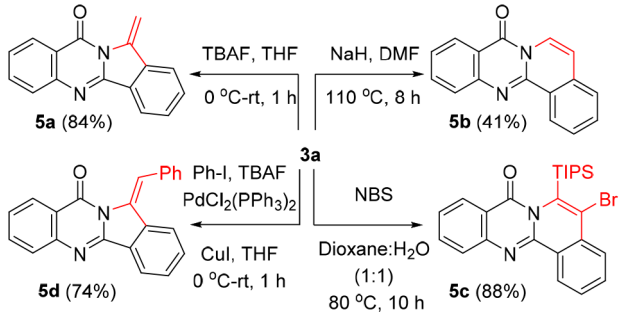
[a]Conditions: (a) 82% on 1 g scale; (b) 92% on 1 g scale; (c) 14% of **4s** was isolated; (d) 12% of **3i** was isolated.

selectivity seems to originating from steric hindrance by the fused aromatic ring. The dialkynylation of **1u** is also facile, giving the 1,3-dialkynylated product **4u** in 76% yield. Coming to the alkynylation of 2-heteroaryl quinazolin-4-ones such as (2-furanyl, **1v**), (2-thiophene-yl, **1w**), (3-indolyl, **1x**), and (3-benzothiophene-yl, **1y**), under the standard reaction conditions, the alkynylation with **2** proceeded smoothly and gave the products **3v−y** in good yields (70−83%). However, 2-(2-pyridyl)quinazolin-4-one was found to be intact under these reaction conditions, suggesting the possible formation of a stable *N*,*N*′-bidentate iridium complex which seems to inhibit further reactions. Interestingly, when (*E*)-2-styrylquinazolin-4(3*H*)-one (**1z**) was employed as a substrate, under the standard reaction conditions, the alkynylation with **2** proceeded selectively at the *β*-carbon of the styrene and gave **3z** in 73% yield. To obtain a substrate for exploring the synthetic utility, the mono- and dialkynylation of 2-phenylquinazolin-4(3*H*)-one **1a** was carried out on 1 g scale using 5 mol % of the iridium complex. The reactions proceeded smoothly to afford **3a** (1.5 g) and **4a** (2.3 g) in 82% and 92% yields respectively.

The possibility of using R-EBX (R = *n*-octyl or phenyl) has been examined under both mono- and dialkylation conditions. At room temperature, both substrates are intact, and when heated the R-EBX undergoes an internal redox process resulting in the 2-oxo-2-(*n*-octyl or phenyl)ethyl 2-iodobenzoate derivatives (see Scheme S1).

Next, the synthetic utility of alkyne **3a** (Scheme 3) was demonstrated by subjecting it to cycloisomerization employing

Scheme 3. Synthetic Utility of 3a



tetra-*n*-butylammonium fluoride (TBAF) and sodium hydride (NaH) in DMF to obtain the complementary 5-*exo*-*dig*-and 6-*endo*-*dig*-cyclized products **5a** and **5b** with simultaneous TIPS deprotection, respectively, in 84% and 41% yield. On the other hand, the electrophilic 6-*endo*-*dig* bromocyclization of compound **3a** with *N*-bromosuccinimide (NBS) resulted in the

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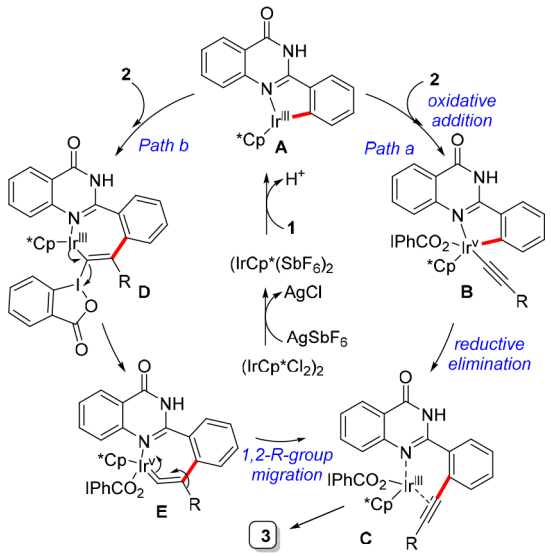
formation of **5c** in 88% yield and the one-pot desilylation with TBAF and [Pd]-catalyzed Sonogashira/hydroamination afforded cyclized product **5d** in 74% yield.

Next, control experiments have been carried out to understand the course of the reaction in general and the complementary mono- vs dialkynylation. Deuterium-labeling experiments employing CD_3OD (10% in the *ortho*-position of the phenyl group under heating in DCE and no labeling when carried out in CD_3OD at rt) revealed that the C−H bond cleavage was a reversible process (see Schemes S3 and S4). When the reaction was carried out in the presence of **2** (Scheme S5), no deuterium incorporation was observed in the recovered **1a**, indicating that the alkynylation process proceeds faster than the deuteration. As expected, the competitive reaction of an equimolar amount of **1h** (3-fluorophenyl), **1j** (3-methoxphenyl), and **2** under standard conditions gave **3h** in 21% and **3j** in 68% isolated yield respectively (1:3.2 ratio), indicating that electron-rich phenyl groups undergo alkynylation faster (see Scheme S6).

Based upon the previous reports,[18−21] we propose the following tentative mechanistic pathway (Scheme 4). The

Scheme 4. Mechanistic Proposal



catalytic cycle starts with the formation of the monomeric $IrCp^*(SbF_6)_2$ complex upon reaction of the dimeric iridium complex with $AgSbF_6$. This undergoes a coordinative C−H insertion with 2-arylquinazolin-4-one **1**, resulting in the cyclometalated Ir(III) complex **A**.[18] There are two possible pathways proposed for the transfer of the alkyne group from the TIPS-EBX to the aryl ring. In one path, the involvement of an intermediate Ir(V) species occurs via the oxidative addition resulting in the alkynyl-Ir(V) species **B**, which undergoes a reductive elimination, generating the key Ir(III)-alkyne intermediate **C** (path a).[2b,19] In another path, the complexation of the intermediate **A** with the alkyne unit TIPS-EBX followed by a regioselective migratory insertion of alkyne results in the intermediate **D** which, upon α-elimination of 2-iodobenzoic acid, results in the iridium vinylidene species **E**.[20,21b] The intermediate **E** then undergoes a concerted R group migration followed by elimination, resulting in intermediate **C**, a species that is common in both the pathways a and b. Finally, the alkynylated product **3** and the active Ir(III) species are generated by the dissociation of alkyne from **C** by complexing with 2-arylquinazolin-4-one **1**, which undergoes a C−H insertion to continue the catalytic cycle.

In conclusion, [Ir]-catalyzed *ortho*-alkynylation of 2-(hetero)arylquinazolin-4-ones with TIPS-EBX has been established. In methanol, selective monoalkynylation has been observed at room temperature. On the other hand, the dialkynylation could be conducted by switching to 1,2-dichloroethane as a solvent and conducting the reaction at 70 °C. A wide-range of mono-/dialkynylated quinazolin-4-ones have been synthesized in good to excellent yields. Considering the ease of functionalizing the alkyne groups and the importance of the quinazolin-4-one scaffold in new drug discovery programs, this late-stage alkynylation provides an attractive handle to synthesize molecules of therapeutic interest.

EXPERIMENTAL SECTION

General Information. The reactions were carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. All anhydrous solvents were distilled prior to use: dichloromethane, DCE, and CH_3CN from CaH_2; methanol from Mg cake; THF on Na/benzophenone. Commercial reagents were used without any purification. Column chromatography was carried out by using silica gel (60−120, 100−200, 230−400 mesh). ^1H and ^{13}C NMR chemical shifts are reported in ppm relative to chloroform-*d* (δ = 7.26) or TMS, and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations have been used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, hept = septet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on a Q Exactive Hybrid Quadrupole Orbitrap mass spectrometer, where the mass analyzer used for analysis is orbitrap. Melting points were recorded on a digital microscopic melting apparatus and are uncorrected. Infrared spectra were recorded on an ATR, and only major peaks are reported in cm^{-1}. All starting quinazolin-2-ones[21a] and ethynyl benziodoxolones[21b] were prepared according to well−known literature procedures.

General Procedure for Iridium Catalyzed C−H Monoalkynylation of Quinazolin-2-ones. To a screw-capped vial with a spinvane triangular−shaped Teflon stir bar were added aryl quinqzolinone (0.2 mmol), TIPS-EBX (0.24 mmol), $[IrCp^*Cl_2]_2$ (5 mol %, 8 mg), $AgSbF_6$ (10 mol %, 7 mg), and methanol (3 mL) under air. The reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and washed with satd $NaHCO_3$ followed by brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford monoalkynylated quinazolin-2-ones **3**.

General Procedure for Iridium-Catalyzed C−H Dialkynylation of Quinazolin-2-ones. To a screw-capped vial with a spinvane triangular shaped Teflon stir bar were added quinazolin-4-one (0.2 mmol), TIPS-EBX (0.5 mmol), $[IrCp^*Cl_2]_2$ (5 mol %, 8 mg), $AgSbF_6$ (10 mol %, 7 mg), and 1,2-dichloroethane (3 mL) under air. The reaction mixture was stirred at 70 °C for 12 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and washed with satd $NaHCO_3$ followed by brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude was purified by column chromatography (9:1 petroleum ether/EtOAc) to afford dilalkynylated quinazolin-4-ones **4**.

*2-(2-((Triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3a**).* The product was obtained as a white solid: yield 72 mg (89%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 146−147 °C; IR (neat) ν_{max} 3022, 2944, 2142, 2863, 2150, 1671, 1563, 1368, 1213, 881, 769, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.34−8.23 (m, 2H), 7.84−7.72 (m, 2H), 7.69−7.57 (m, 1H), 7.54−7.45 (m, 3H), 1.38−0.99 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 149.1 (s), 134.8 (d), 134.5 (d), 133.7 (s), 130.8 (d), 130.0 (d), 129.2 (d), 128.0 (d), 127.0 (d), 126.5 (d), 121.4 (s), 120.6 (s),

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104.1 (s), 100.4 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{31}N_2OSi$ 403.2200, found 403.2206.

*2-(4-Fluoro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3b**).* The product was obtained as a white solid: yield 68 mg (81%); R_f 0.4 (5:1 petroleum ether/EtOAc); mp 154−155 °C; IR (neat) ν_{max} 2944, 2861, 2155, 1655, 1462, 1370, 1223, 876, 768, 637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.42−8.10 (m, 2H), 7.85−7.71 (m, 2H), 7.59−7.43 (m, 1H), 7.32 (dd, J = 8.7, 2.6 Hz, 1H), 7.22 (ddd, J = 8.9, 7.8, 2.7 Hz, 1H), 1.30−1.06 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6 (ds, $^1J_{C-F}$ = 253.7 Hz), 161.3 (s), 150.3 (s), 149.0 (s), 134.6 (d), 132.6 (dd, $^3J_{C-F}$= 9.2 Hz), 130.0 (ds, $^4J_{C-F}$ = 2.9 Hz), 128.0 (d), 127.1 (d), 126.5 (d), 122.6 (ds, $^3J_{C-F}$ = 10.1 Hz), 121.3 (s), 121.2 (dd, $^2J_{C-F}$ = 23.6 Hz), 117.1 (dd, $^2J_{C-F}$ = 21.6 Hz), 102.9 (s), 102.1 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2110.

*2-(4-Chloro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3c**).* The product was obtained as a white solid: yield 70 mg (81%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 151−152 °C; IR (neat) ν_{max} 2948, 2860, 2152, 1670, 1463, 1368, 1228, 860, 732, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.29 (dd, J = 8.2, 3.2 Hz, 2H), 7.79 (d, J = 3.8 Hz, 2H), 7.61 (d, J = 2.0 Hz, 1H), 7.49 (ddd, J = 8.6, 6.5, 2.9 Hz, 2H), 1.35−1.04 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 150.2 (s), 149.0 (s), 137.0 (s), 134.7 (d), 134.2 (d), 131.9 (s), 131.5 (d), 129.6 (d), 128.0 (d), 127.2 (d), 126.5 (d), 121.9 (s), 121.4 (s), 102.8 (s), 102.3 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}ClN_2OSi$ 437.1810 found 437.1816.

*2-(4-Bromo-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3d**).* The product was obtained as a white solid: yield 80 mg (84%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 153−154 °C; IR (neat) ν_{max} 3281, 2938, 2862, 2146, 1691, 1467, 1372, 1213, 880, 727, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.30 (dt, J = 7.9, 1.1 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H), 7.89−7.74 (m, 3H), 7.64 (dd, J = 8.6, 2.1 Hz, 1H), 7.57−7.41 (m, 1H), 1.26−0.93 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 150.2 (s), 149.0 (s), 137.1 (d), 134.7 (d), 132.6 (d), 132.3 (s), 131.5 (d), 128.1 (d), 127.2 (d), 126.5 (d), 125.2 (s), 122.1 (s), 121.4 (s), 102.7 (s), 102.5 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1312.

*2-(4-Methyl-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3e**).* The product was obtained as a white solid: yield 76 mg (91%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 149−150 °C; IR (neat) ν_{max} 2944, 2861, 2158, 1680, 1571, 1463, 1369, 1222, 840, 710, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.30 (d, J = 7.7 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.86−7.64 (m, 2H), 7.54−7.39 (m, 2H), 7.31 (dd, J = 8.2, 1.0 Hz, 1H), 2.41 (s, 3H), 1.76−0.81 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 149.2 (s), 141.4 (s), 135.2 (d), 134.5 (d), 130.7 (s), 130.3 (d), 130.0 (d), 128.0 (d), 126.7 (d), 126.5 (d), 121.3 (s), 120.2 (s), 104.5 (s), 100.1 (s), 21.1 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{33}N_2OSi$ 417.2357, found 417.2362.

*2-(4-Methoxy-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3f**).* The product was obtained as a white solid: yield 72 mg (83%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 150−151 °C; IR (neat) ν_{max} 2937, 2859, 2143, 1685, 1578, 1460, 1370, 1226, 726, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.32 (d, J = 8.9 Hz, 1H), 8.30−8.26 (m, 1H), 7.79−7.72 (m, 2H), 7.45 (ddd, J = 8.2, 6.0, 2.3 Hz, 1H), 7.09 (d, J = 2.6 Hz, 1H), 7.04 (dd, J = 8.9, 2.7 Hz, 1H), 3.89 (s, 3H), 1.29−1.10 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 161.3 (s), 150.9 (s), 149.3 (s), 134.46 (d), 132.0 (d), 127.8 (d), 126.6 (d), 126.5 (d), 125.9 (s), 121.6 (s), 121.2 (s), 119.3 (d), 115.8 (d), 104.2 (s), 100.6 (s), 55.6 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_2Si$ 433.2306, found 433.2310.

*2-(4-(Trifluoromethyl)-2-((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**3g**).* The product was obtained as a white solid: yield 74 mg (77%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 169−170 °C; IR (neat) ν_{max} 2922, 2862, 2140, 1668, 1564, 1464, 1330, 1120, 899, 774, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.42 (d, J = 8.3 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.84−7.77 (m, 2H), 7.74 (dd, J = 8.3, 1.3 Hz, 1H), 7.58−7.47 (m, 1H), 1.46−0.86 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 149.9 (s), 148.8 (s), 136.8 (s), 134.8 (d), 133.0 (qs, $^2J_{C-F}$ = 33.8 Hz), 131.43 (qd, $^3J_{C-F}$ = 11.0 Hz), 130.8 (d), 128.2 (d), 127.5 (d), 126.6 (d), 125.6 (qd, $^3J_{C-F}$ = 10.3 Hz), 124.5 (qs, $^1J_{C-F}$ = 273.0 Hz), 121.5 (ds, $^4J_{C-F}$ = 2.9 Hz), 121.5 (s), 107.5 (s), 102.6 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{30}F_3N_2OSi$ 471.2074, found 471.2081.

*2-(5-Fluoro-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3h**).* The product was obtained as a white solid: yield 62 mg (73%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 136−137 °C; IR (neat) ν_{max} 3296, 2943, 2862, 2150, 1685, 1554, 1462, 1285, 844, 721, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.89−7.71 (m, 2H), 7.57−7.40 (m, 2H), 7.36−7.20 (m, 1H), 1.31−1.02 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2 (ds, $^1J_{C-F}$ = 252.7 Hz), 161.4 (s), 150.2 (s), 148.9 (s), 135.5 (s), 134.7 (d), 130.0 (dd, $^3J_{C-F}$ = 8.7 Hz), 128.1 (d), 127.2 (d), 126.5 (d), 125.5 (dd, $^4J_{C-F}$ = 3.4 Hz), 121.4 (s), 117.8 (dd, $^2J_{C-F}$ = 21.8 Hz), 110.0 (ds, $^2J_{C-F}$ = 18.8 Hz), 107.2 (s), 96.5 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2107.

*2-(5-Bromo-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3i**).* The product was obtained as a white solid: yield 68 mg (71%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 164−165 °C; IR (neat) ν_{max} 3024, 2939, 2861, 2152, 1665, 1603, 1465, 1291, 878, 767, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.31 (d, J = 7.7 Hz, 1H), 7.86−7.75 (m, 2H), 7.61 (dd, J = 8.3, 2.1 Hz, 1H), 7.54−7.48 (m, 2H), 1.23−1.18 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3 (s), 149.7 (s), 148.9 (s), 136.0 (d), 134.9 (s), 134.7 (d), 133.9 (d), 132.9 (d), 128.6 (d), 127.32 (d), 126.5 (d), 123.6 (s), 121.4 (s), 119.3 (s), 103.2 (s), 102.2 (s), 18.6 (q, 6C), 11.1 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1313.

*2-(5-Methoxy-2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3j**).* The product was obtained as a white solid: yield 64 mg (74%); R_f 0.6 (5:1 petroleum ether/EtOAc); mp 122−123 °C; IR (neat) ν_{max} 2938, 2862, 2150, 1664, 1591, 1463, 1241, 1025, 877, 773, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.84−7.74 (m, 3H), 7.56 (d, J = 8.6 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 7.01 (dd, J = 8.6, 2.5 Hz, 1H), 3.91 (s, 3H), 1.22−1.01 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 160.0 (s), 151.1 (s), 149.1 (s), 136.3 (d), 135.1 (s), 134.5 (d), 128.0 (d), 127.0 (d), 126.5 (d), 121.4 (s), 117.8 (d), 114.1 (d), 112.9 (s), 104.2 (s), 98.4 (s), 55.7 (q), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_2Si$ 433.2306, found 433.2311.

*2-(2-Fluoro-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3k**).* The product was obtained as a white solid: yield 62 mg (76%); R_f 0.4 (5:1 petroleum ether/EtOAc); mp 153−154 °C; IR (neat) ν_{max} 2941, 2863, 2154, 1665, 1467, 1371, 1221, 871, 761, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.91−7.71 (m, 2H), 7.52 (ddd, J = 8.1, 4.8, 3.5 Hz, 1H), 7.47−7.37 (m, 2H), 7.24−7.11 (m, 1H), 0.97−0.74 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3 (s), 159.9 (ds, $^1J_{C-F}$ = 251.2 Hz), 148.9 (s), 147.6 (s), 134.6 (d), 131.7 (dd, $^3J_{C-F}$ = 9.2 Hz), 129.3 (dd, $^4J_{C-F}$ = 3.3 Hz), 128.1 (d), 127.4 (d), 126.4 (d), 125.0 (s), 124.6 (ds, $^2J_{C-F}$ = 16.4 Hz), 121.4 (s), 116.4 (dd, $^2J_{C-F}$ = 21.6 Hz), 102.2 (ds, $^4J_{C-F}$ = 3.8 Hz), 97.9 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2107.

*2-(2-Chloro-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3l**).* The product was obtained as a white solid: yield 64 mg (74%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 184−185 °C; IR (neat) ν_{max} 2943, 2864, 2153, 1670, 1462, 1379, 1228, 860, 738, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.86−7.68 (m, 2H), 7.57−7.48 (m, 2H), 7.46 (dd, J = 8.2, 1.3 Hz, 1H), 7.43−7.34 (m, 1H), 0.87−0.80 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.6 (s), 150.2 (s), 148.9 (s), 135.6 (s), 134.6 (d), 133.1 (s), 131.4 (d), 130.9 (d), 129.7 (d), 128.1 (d), 127.4 (d), 126.3 (d), 125.2 (s), 121.4 (s), 102.3 (s), 97.8 (s), 18.3 (q, 6C),

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10.9 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}ClN_2OSi$ 437.1810 found 437.1814.

*2-(2-Bromo-6-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3m**).* The product was obtained as a white solid: yield 75 mg (78%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 194−195 °C; IR (neat) ν_{max} 3222, 2940, 2862, 2148, 1666, 1468, 1370, 1220, 882, 730, 636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.26 (dd, J = 8.4, 4.5 Hz, 1H), 7.79 (d, J = 3.6 Hz, 2H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (dd, J = 7.8, 1.1 Hz, 1H), 7.55−7.49 (m, 1H), 7.32 (t, J = 8.0 Hz, 1H), 1.04−0.71 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.9 (s), 151.1 (s), 148.8 (s), 137.4 (s), 134.6 (d), 132.8 (d), 131.9 (d), 131.1 (d), 128.1 (d), 127.4 (d), 126.4 (d), 125.2 (s), 121.8 (s), 121.5 (s), 102.2 (s), 98.0 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1309.

*2-(2,4-Dimethoxy-6-((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**3n**).* The product was obtained as a white solid: yield 82 mg (89%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 129−130 °C; IR (neat) ν_{max} 2922, 2860, 2145, 1671, 1596, 1387, 1216, 1021, 861, 734, 643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (s, 1H), 8.55 (d, J = 7.9 Hz, 1H), 8.20 (s, 1H), 8.11−7.97 (m, 2H), 7.72 (ddd, J = 8.2, 6.7, 1.6 Hz, 1H), 7.51 (s, 1H), 4.29 (s, 3H), 4.23 (s, 3H), 1.58−1.31 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.9 (s), 150.7 (s), 150.0 (s), 149.2 (s), 134.5 (d), 127.8 (d), 126.7 (d), 126.6 (s), 126.5 (d), 121.2 (s), 116.2 (d), 113.2 (s), 112.1 (d), 104.5 (s), 99.5 (s), 56.2 (q), 56.2 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{35}N_2O_3Si$ 463.2411, found 463.2419.

*7-Methyl-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3o**).* The product was obtained as a white solid: yield 68 mg (82%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 118−119 °C; IR (neat) ν_{max} 2935, 2859, 2155, 1655, 1610, 1456, 1216, 880, 791, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.29 (dd, J = 7.4, 1.5 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H), 7.65 (dd, J = 7.1, 1.6 Hz, 1H), 7.60 (s, 1H), 7.55−7.45 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 2.52 (s, 3H), 1.49−0.76 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 151.2 (s), 149.3 (s), 145.5 (s), 134.8 (d), 133.7 (s), 130.68 (d), 130.0 (d), 129.2 (d), 128.5 (d), 127.8 (d), 126.3 (d), 120.5 (s), 119.0 (s), 104.2 (s), 100.5 (s), 21.9 (q), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{33}N_2OSi$ 417.2357, found 417.2352.

*7-Fluoro-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin4(3H)-one (**3p**).* The product was obtained as a white solid: yield 63 mg (75%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 121−122 °C; IR (neat) ν_{max} 3283, 2944, 2861, 2143, 1687, 1576, 1373, 1285, 879, 765, 676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (brs, 1H), 8.33−8.17 (m, 2H), 7.69−7.56 (m, 1H), 7.54−7.48 (m, 2H), 7.43 (d, J = 9.7 Hz, 1H), 7.24−7.13 (m, 1H), 1.31−0.84 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7 (ds, $^1J_{C-F}$ = 254.2 Hz), 160.7 (s), 152.4 (s), 151.3 (ds, $^3J_{C-F}$ = 13.2 Hz), 134.9 (d), 133.3 (ds, $^4J_{C-F}$ = 3.1 Hz), 131.0 (d), 130.0 (d), 129.2 (d), 129.1 (dd, $^3J_{C-F}$ = 11.0 Hz), 120.7 (s), 118.1 (s,), 115.7 (dd, $^2J_{C-F}$ = 23.6 Hz), 113.3 (dd, $^2J_{C-F}$ = 21.8 Hz), 104.1 (s), 100.7 (s), 18.6 (q, 6C), 11.2 (d, 3C); ^{19}F NMR (377 MHz, $CDCl_3$) δ −103.2.; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}FN_2OSi$ 421.2106, found 421.2100.

*7-Bromo-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3q**).* The product was obtained as a white solid: yield 75 mg (78%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 124−125 °C; IR (neat) ν_{max} 3308, 2941, 2143, 2864, 1689, 1587, 1462, 1234, 880, 769, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.31 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H), 7.70−7.62 (m, 1H), 7.58 (dd, J = 8.5, 1.9 Hz, 1H), 7.56−7.45 (m, 2H), 1.56−0.89 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 152.2 (s), 150.1 (s), 135.0 (d), 133.0 (s), 131.1 (d), 130.8 (d), 130.3 (d), 130.1 (d), 129.3 (d), 129.3 (s), 127.9 (d), 120.5 (s), 120.2 (s), 104.1 (s), 101.1 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}BrN_2OSi$ 481.1305, found 481.1298.

*7-Nitro-2-(2-((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**3r**).* The product was obtained as a yellow solid: yield 62 mg (70%); R_f 0.4 (5:1 petroleum ether/EtOAc); mp 147−148 °C; IR (neat) ν_{max} 3261, 2933, 2862, 2150, 1702, 1576, 1347, 1228, 880, 731, 676 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.64 (d, J = 2.1 Hz, 1H), 8.46 (d, J = 8.7 Hz, 1H), 8.44−8.39 (m, 1H), 8.24 (dd, J = 8.7, 2.1 Hz, 1H), 7.73−7.66 (m, 1H), 7.62−7.43 (m, 2H), 1.26−1.03 (m, 21H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.1 (s), 153.0 (s, 2C), 151.8 (s), 149.7 (s), 135.2 (d), 132.2 (s), 131.6 (d), 130.2 (d), 129.5 (d), 128.4 (d), 125.5 (s), 123.6 (d), 120.5 (d), 104.0 (s), 101.8 (s), 18.6 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}N_3O_3Si$ 448.2051, found 448.2047.

*6,7-Dimethoxy-2-(2-((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**3s**).* The product was obtained as a white solid: yield 58 mg (62%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 129−130 °C; IR (neat) ν_{max} 2942, 2861, 2148, 1656, 1569, 1385, 1269, 1218, 1080, 980, 878, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.33 (dd, J = 7.6, 1.5 Hz, 1H), 7.70−7.66 (m, 2H), 7.57−7.48 (m, 2H), 7.29 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 1.33−1.10 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7 (s), 155.1 (s), 149.9 (s), 149.3 (s), 145.4 (s), 134.9 (d), 133.5 (s), 130.6 (d), 129.7 (d), 129.3 (d), 120.3 (s), 114.7 (s), 108.5 (d), 105.5 (d), 104.3 (s), 100.5 (s), 56.4 (q), 56.3 (q), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{35}N_2O_3Si$ 463.2411, found 463.2408.

*2-(2-((Triisopropylsilyl)ethynyl)naphthalen-1yl)quinazolin-4(3H)-one (**3t**).* The product was obtained as a yellow solid: yield 76 mg (84%); R_f 0.6 (5:1 petroleum ether/EtOAc); mp 202−203 °C; IR (neat) ν_{max} 2943, 2858, 2142, 1662, 1466, 1371, 1221, 880, 768, 670, 634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.29 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.84−7.79 (m, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.58−7.45 (m, 3H), 1.06−0.78 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.0 (s), 151.6 (s), 149.0 (s), 134.7 (d), 134.5 (s), 132.9 (s), 130.7 (s), 130.2 (d), 128.7 (d), 128.3 (d), 128.1 (d), 128.0 (d), 127.3 (d), 127.2 (d), 126.4 (d), 124.9 (d), 121.5 (s), 121.0 (s), 103.9 (s), 97.9 (s), 18.4 (q, 6C), 11.0 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{29}H_{33}N_2OSi$ 453.2357, found 453.2361.

*2-(3-((Triisopropylsilyl)ethynyl)naphthalen-2-yl)quinazolin-4(3H)-one (**3u**).* The product was obtained as a white solid: yield 64 mg (72%); R_f 0.6 (5:1 petroleum ether/EtOAc); mp 194−195 °C; IR (neat) ν_{max} 2941, 2861, 2148, 1665, 1602, 1462, 1370, 1224, 880, 763, 668, 639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.73 (s, 1H), 8.31 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H), 7.97 (d, J = 7.1 Hz, 1H), 7.86 (d, J = 7.9 Hz, 2H), 7.83−7.74 (m, 1H), 7.65−7.53 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 1.22−1.09 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 151.6 (s), 149.3 (s), 135.3 (d), 134.3 (d), 133.6 (s), 132.5 (s), 130.8 (d), 130.3 (s), 129.0 (d), 128.5 (d), 128.0 (d), 127.9 (d), 127.4 (d), 126.9 (d), 126.5 (d), 121.3 (s), 117.0 (s), 104.5 (s), 99.1 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{29}H_{33}N_2OSi$ 453.2357, found 453.2355.

*2-(3-((Triisopropylsilyl)ethynyl)furan-2-yl)quinazolin-4(3H)-one (**3v**).* The product was obtained as a yellow solid: yield 64 mg (83%); R_f 0.6 (5:1 petroleum ether/EtOAc); mp 148−149 °C; IR (neat) ν_{max} 2924, 2858, 2139, 1655, 1370, 1211, 881, 748, 642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.29 (dd, J = 8.0, 1.1 Hz, 1H), 7.84 (dd, J = 8.2, 0.7 Hz, 1H), 7.77 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.62 (d, J = 1.9 Hz, 1H), 7.48 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 1.31−1.13 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7 (s), 148.7 (s), 146.7 (s), 145.2 (d), 143.0 (s), 134.8 (d), 128.1 (d), 127.2 (d), 126.7 (d), 121.8 (s), 115.6 (d), 110.4 (s), 103.9 (s), 96.9 (s), 18.8 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{29}N_2O_2Si$ 393.1993, found 393.1995.

*2-(3-((Triisopropylsilyl)ethynyl)thiophene-2-yl)quinazolin-4(3H)-one (**3w**).* The product was obtained as a yellow solid: yield 64 mg (79%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 136−137 °C; IR (neat) ν_{max} 2944, 2861, 2141, 1689, 1464, 1348, 1212, 769, 710, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.03 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.82−7.61 (m, 2H), 7.49−7.41 (m, 2H), 7.18 (d, J = 5.1 Hz, 1H), 1.36−1.12 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9 (s), 148.9 (s), 146.8 (s), 138.5 (s), 134.6 (d), 132.5 (d), 129.8 (d), 127.6 (d), 126.7 (d), 126.6 (d), 121.6 (s), 121.2 (s), 102.3 (s),

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100.4 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{29}N_2OSSi$ 409.1764, found 409.1765.

*2-(2-((Triisopropylsilyl)ethynyl)-1H-indol-3-yl)quinazolin-4(3H)-one (**3x**).* The product was obtained as a yellow solid: yield 60 mg (70%); R_f 0.5 (5:1 petroleum ether/EtOAc); mp 209−210 °C; IR (neat) ν_{max} 3254, 2937, 2862, 2139, 1661, 1584, 1418, 1235, 874, 718, 674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (brs, 1H), 8.89 (d, J = 7.4 Hz, 1H), 8.70 (brs, 1H), 8.30 (dd, J = 7.9, 1.1 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.76 (ddd, J = 8.3, 7.1, 1.6 Hz, 1H), 7.43 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 7.40−7.31 (m, 3H), 1.36−1.11 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 149.9 (s), 148.5 (s), 135.8 (s), 134.4 (d), 127.9 (d), 126.5 (d), 126.0 (d), 125.6 (s), 125.5 (d), 123.9 (d), 122.7 (d), 121.3 (s), 118.4 (s), 113.4 (s), 110.8 (d), 105.9 (s), 96.8 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{32}N_3OSi$ 442.2309, found 442.2305.

*2-(2-((Triisopropylsilyl)ethynyl)benzo[b]thiophene-3-yl)-quinazolin-4(3H)-one (**3y**).* The product was obtained as a yellow solid: yield 72 mg (78%); R_f 0.6 (5:1 petroleum ether/EtOAc); mp 170−171 °C; IR (neat) ν_{max} 2930, 2861, 2133, 1664, 1594, 1457, 885, 765, 684, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.83−7.75 (m, 2H), 7.54−7.45 (m, 3H), 1.51−1.06 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.2 (s), 149.0 (s), 147.4 (s), 139.2 (s), 136.7 (s), 134.6 (d), 130.1 (s), 128.2 (d), 127.2 (d), 126.8 (d), 126.6 (d), 126.6 (d), 125.9 (d), 124.8 (s), 121.7 (ds, 2C), 108.9 (s), 97.7 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{31}N_2OSSi$ 459.1921, found 459.1916.

*(Z)-2-(1-Phenyl-4-(triisopropylsilyl)but-1-en-3-yn-2-yl)-quinazolin-4(3H)-one (**3z**).* The product was obtained as yellow thick liquid: yield 62 mg (73%); R_f 0.6 (5:1 petroleum ether/EtOAc) IR (neat) ν_{max} 3308, 2941, 2864, 1689, 1587, 1462, 1234, 880, 769, 659, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.33 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.79−7.71 (m, 2H), 7.52−7.42 (m, 4H), 7.12 (s, 1H), 1.46−1.09 (m, 21H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.0 (s), 150.2 (s), 149.2 (s), 136.9 (s), 134.6 (d), 129.9 (d), 129.0 (s), 128.8 (d, 2C), 127.8 (d), 127.4 (d), 127.24 (d), 126.9 (d, 2C), 126.7 (d), 121.8 (s), 109.5 (s), 102.9 (s), 18.7 (q, 6C), 11.2 (d, 3C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{33}N_2OSi$ 429.2357, found 429.2356.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4a**).* The product was obtained as a white solid: yield 110 mg (94%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 188−189 °C; IR (neat) ν_{max} 2943, 2862, 2148, 1666, 1459, 1370, 1224, 880, 669 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.75 (dd, J = 4.6, 1.2 Hz, 2H), 7.58−7.54 (m, 2H), 7.52−7.48 (m, 1H), 7.40 (dd, J = 8.3, 7.4 Hz, 1H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 151.2 (s), 148.9 (s), 138.9 (s), 134.4 (d), 132.7 (d, 2C), 129.8 (d), 128.1 (d), 127.1 (d), 126.2 (d), 123.3 (s, 2C), 121.6 (s), 102.6 (s, 2C), 97.2 (s, 2C), 18.3 (q, 12C),11.0 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{51}N_2OSi_2$ 583.3534, found 583.3543.

*2-(4-Fluoro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4b**).* The product was obtained as a white solid: yield 100 mg (83%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 168−169 °C. IR (neat) ν_{max} 2942, 2863, 2149, 1668, 1464, 1369, 1223, 996, 878, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.88−7.65 (m, 2H), 7.52−7.48 (m, 1H), 7.26 (d, J = 8.6 Hz, 2H), 0.85 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4 (ds, $^1J_{C-F}$ = 251.7 Hz), 161.6 (s), 150.5 (s), 148.9 (s), 135.5 (ds, $^4J_{C-F}$ = 3.4 Hz), 134.4 (d), 128.1 (d), 127.3 (d), 126.2 (d), 125.4 (ds, $^3J_{C-F}$ = 10.9 Hz, 2C), 121.6 (s), 119.7 (dd, $^2J_{C-F}$ = 23.3 Hz, 2C), 101.5 (ds, $^4J_{C-F}$ = 3.0 Hz, 2C), 98.7 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3449.

*2-(4-Chloro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4c**).* The product was obtained as a white solid: yield 100 mg (81%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 185−186 °C; IR (neat) ν_{max} 2942, 2863, 2152, 1664, 1498, 1369, 1212, 999, 772, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.82−7.71 (m, 2H), 7.54 (s, 2H), 7.53−7.48 (m, 1H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.3 (s), 148.8 (s), 137.2 (s), 135.8 (s), 134.4 (d), 132.4 (d, 2C), 128.1 (d), 127.3 (d), 126.2 (d), 124.8 (s, 2C), 121.6 (s), 101.3 (s, 2C), 98.9 (s, 2C), 18.3 (q, 12 C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{50}ClN_2OSi_2$617.3145, found 617.3153.

*2-(4-Bromo-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4d**).* The product was obtained as a white solid: yield 110 mg (83%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 181−182 °C; IR (neat) ν_{max} 2942, 2862, 2152, 1667, 1464, 1369, 1213, 939, 773, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.79−7.72 (m, 2H), 7.69 (s, 2H), 7.53−7.49 (m, 1H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 150.4 (s), 148.8 (s), 137.7 (s), 135.2 (d, 2C), 134.5 (d), 128.1(d), 127.3 (d), 126.2 (d), 124.9 (s, 2C), 123.6 (s), 121.6 (s), 101.2 (s, 2C), 99.1 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$661.2640, found 661.2643.

*2-(4-Methyl-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4e**).* The product was obtained as a white solid: yield 114 mg (96%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 190−191 °C. IR (neat) ν_{max} 2970, 2862, 2144, 1668, 1438, 1369, 1212, 901, 653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.27 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 3.8 Hz, 2H), 7.48 (m, 1H), 7.37 (s, 2H), 2.37 (s, 3H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.8 (s), 151.2 (s), 148.9 (s), 140.1 (s), 136.2 (s), 134.3 (d), 133.3 (d, 2C), 128.1 (d), 127.0 (d), 126.1 (d), 123.0 (s, 2C), 121.6 (s), 102.8 (s, 2C), 96.5 (s, 2C), 20.93 (q), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{37}H_{53}N_2OSi_2$ 597.3691, found 597.3702.

*2-(4-Methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**4f**).* The product was obtained as a white solid: yield 116 mg (95%); R_f 0.8 (9:1 petroleum ether/EtOAc); mp 183−184 °C; IR (neat) ν_{max} 2940, 2862, 2144, 1669, 1496, 1369, 1222, 880, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 7.74 (dd, J = 4.6, 1.0 Hz, 2H), 7.54−7.40 (m, 1H), 7.05 (s, 2H), 3.86 (s, 3H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6 (s), 160.1 (s), 151.1 (s), 149.0 (s), 134.3 (d), 131.9 (s), 128.1 (d), 127.0 (d), 126.1 (d), 124.5 (s, 2C), 121.5 (s), 118.3 (d, 2C), 102.7 (s, 2C), 96.8 (s, 2C), 55.8 (q), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{37}H_{53}N_2O_2Si_2$ 613.3640, found 613.3649.

*2-(4-(Trifluoromethyl)-2,6-bis((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**4g**).* The product was obtained as a white solid: yield 114 mg (88%); R_f 0.8 (9:1 petroleum ether/EtOAc); mp 186−187 °C; IR (neat) ν_{max} 2942, 2860, 2156, 1670, 1496, 1373, 1232, 950, 880, 674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.10−7.63 (m, 4H), 7.53−7.49 (m, 1H), 0.86 (s, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 150.1 (s), 148.8 (s), 141.7 (s), 134.5 (d), 132.5 (qs, $^2J_{C-F}$ = 33.3 Hz), 129.0 (qd, $^3J_{C-F}$ = 3.6 Hz, 2C), 128.1 (d), 127.4 (d), 126.2 (d), 124.5 (s, 2C), 122.9 (qs, $^1J_{C-F}$ = 273.2 Hz), 121.7 (s), 101.2 (s, 2C), 99.6 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{37}H_{50}F_3N_2OSi_2$651.3408, found 651.3420.

*2-(3-Fluoro-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4h**).* The product was obtained as a white solid: yield 91 mg (76%); R_f 0.6 (9:1 petroleum ether/EtOAc); mp 178−179 °C; IR (neat) ν_{max} 2933, 2861, 2140, 1667, 1463, 1370, 1226, 881, 773, 674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.81−7.68 (m, 2H), 7.56−7.48 (m, 2H), 7.18 (t, J = 8.5 Hz, 1H), 0.87 (d, 42H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.9 (ds, $^1J_{C-F}$ = 257.4 Hz), 161.4 (s), 149.9 (s), 148.8 (s), 140.6 (s), 134.5 (d), 134.1 (dd, $^3J_{C-F}$ = 8.4 Hz), 128.2 (d), 127.4 (d), 126.2 (d), 121.6 (s), 119.3 (ds, $^4J_{C-F}$ = 4.0 Hz), 117.4 (dd, $^2J_{C-F}$ = 21.9 Hz), 112.7 (ds, $^2J_{C-F}$ = 18.49 Hz), 103.6 (s), 101.7 (s), 96.8 (s), 95.5 (s), 18.3 (dq, $^4J_{C-F}$ = 2.6 Hz, 12C), 11.0 (dd, $^4J_{C-F}$ = 4.6 Hz, 6C)^{19}F NMR (376 MHz, $CDCl_3$) δ −105.4.; HRMS (ESI−TOF) m/z [M + H]$^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3452.

*2-(3-Bromo-2,6-bis((triisopropylsilyl)ethynyl)phenyl)quinazolin-4(3H)-one (**4i**).* The product was obtained as a white solid: yield 88 mg (67%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 184−185 °C; IR (neat) ν_{max} 2940, 2863, 2148, 1681, 1463, 1371, 1209, 991, 879, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.27 (d, J = 7.5

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Hz, 1H), 7.78−7.72 (m, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.51 (ddd, J = 8.2, 6.1, 2.2 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 0.91−0.74 (m, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 150.7 (s), 148.9 (s), 140.5 (s), 134.5 (d), 134.0 (d), 132.9 (d), 128.2 (d), 127.4 (d), 126.3 (d), 122.3 (s), 121.8 (s), 103.5 (s), 101.8 (s), 100.9 (s, 2C), 98.5 (s, 2C), 18.4 (q, 6C), 18.3 (q, 6C), 11.0 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$661.2640, found 661.2640.

*2-(3-Methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)-quinazolin-4(3H)-one (**4j**).* The product was obtained as a white solid: yield 86 mg (74%); R_f 0.8 (9:1 petroleum ether/EtOAc); mp 169−170 °C; IR (neat) ν_{max} 2942, 2863, 2133, 1669, 1496, 1370, 1232, 880, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 7.76−7.73 (m, 2H), 7.61−7.35 (m, 2H), 6.94 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 0.86 (s, 21H), 0.84 (s, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (s), 160.9 (s), 151.0 (s), 149.0 (s), 140.4 (s), 134.3 (d), 134.0 (d), 128.1 (d), 127.1 (d), 126.1 (d), 121.6 (s), 115.1 (s), 113.1 (s), 112.3 (d), 102.6 (s), 101.8 (s), 98.5 (s), 94.6 (s), 56.4 (q), 18.4 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{37}H_{53}N_2O_2Si_2$ 613.3640, found 613.3640.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-methylquinazolin-4(3H)-one (**4o**).* The product was obtained as a white solid: yield 102 mg (86%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 202−203 °C; IR (neat) ν_{max} 2941, 2862, 2141, 1657, 1453, 1370, 1224, 985, 879, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.61−7.55 (m, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 2.49 (s, 3H), 0.87 (s, 42H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.3 (s), 151.1 (s), 149.0 (s), 145.2 (s), 138.9 (s), 132.7 (d, 2C), 129.6 (d), 128.6 (d), 128.0 (d), 126.0 (d), 123.3 (s, 2C), 119.2 (s), 102.6 (s, 2C), 97.1 (s, 2C), 21.9 (q), 18.3 (q, 12C), 11.0 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{37}H_{53}N_2OSi_2$ 597.3691, found 597.3684.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-fluoroquinazolin-4(3H)-one (**4p**).* The product was obtained as a white solid: yield 99 mg (83%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 203−204 °C; IR (neat) ν_{max} 2940, 2863, 2145, 1663, 1608, 1452, 1370, 1225, 985, 877, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCL_3$) δ 9.35 (s, 1H), 8.28 (dd, J = 8.7, 6.2 Hz, 1H), 7.56 (d, J = 7.8 Hz, 2H), 7.44−7.36 (m, 2H), 7.21 (td, J = 8.6, 2.3 Hz, 1H), 0.87 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5 (ds, $^1J_{C-F}$ = 254.3 Hz),160.9 (s), 152.7 (s), 151.2 (ds, $^3J_{C-F}$ = 13.1 Hz), 138.5 (s), 132.7 (d, 2C), 130.0 (d), 128.9 (dd, $^3J_{C-F}$ = 10.6 Hz), 123.2 (s, 2C), 118.3 (s), 115.8 (dd, $^2J_{C-F}$ = 23.6 Hz), 113.4 (dd, $^2J_{C-F}$ = 22.1 Hz), 102.5 (s, 2C), 97.4 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.1; HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{50}FN_2OSi_2$ 601.3440, found 601.3450.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-bromoquinazolin-4(3H)-one (**4q**).* The product was obtained as a white solid: yield 106 mg (80%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 202−203 °C; IR (neat) ν_{max} 2941, 2862, 2145, 1661, 1596, 1445, 1370, 1225, 986, 881, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 8.5, 1.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.45−7.38 (m, 1H), 0.89 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 152.5 (s), 149.9 (s), 138.4 (s), 132.8 (d, 2C), 130.9 (d), 130.5 (d), 130.0 (d), 129.0 (s), 127.6 (d), 123.2 (s, 2C), 120.5 (s), 102.4 (s, 2C), 97.5 (s, 2C), 18.4 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{50}BrN_2OSi_2$661.2640, found 661.2637.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-7-nitroquinazolin-4(3H)-one (**4r**).* The product was obtained as a yellow solid: yield 98 mg (79%); R_f 0.6 (9:1 petroleum ether/EtOAc); mp 212−213 °C; IR (neat) ν_{max} 2941, 2862, 2155, 1667, 1606, 1534, 1453, 1346, 1228, 985, 880, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (brs, 1H), 8.59 (d, J = 1.8 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.26 (dd, J = 8.7, 2.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 0.86 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4 (s), 153.7 (s), 151.6 (s), 149.6 (s), 137.9 (s), 132.9 (d, 2C), 130.3 (d), 128.1 (d), 125.7 (s), 123.6 (d), 123.1 (s, 2C), 120.8 (d), 102.4 (s, 2C), 97.7 (s, 2C), 18.3 (q, 12C), 10.9 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{50}N_3O_3Si_2$ 628.3385, found 628.3372.

*2-(2,6-Bis((triisopropylsilyl)ethynyl)phenyl)-6,7-dimethoxyquinazolin-4(3H)-one (**4s**).* The product was obtained as a white solid: yield 112 mg (87%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 193−194 °C; IR (neat) ν_{max} 2940, 2862, 2138, 1647, 1608, 1457, 1385, 1269, 1213, 1093, 980, 878, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.60 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 0.88 (s, 42H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1 (s), 154.8 (s), 149.9 (s), 149.3 (s), 145.3 (s), 138.8 (s), 132.7 (d, 2C), 129.7 (d), 123.3 (s, 2C), 114.9 (s), 108.7 (d), 105.1 (d), 102.7 (s, 2C), 97.0 (s, 2C), 56.4 (q), 56.2 (q), 18.4 (q, 12C), 11.0 (d, 6C); HRMS (ESI−TOF) m/z $[M]^+$ calcd for $C_{38}H_{54}N_2O_3Si_2$ 642.3667, found 642.3647.

*2-(1,3-Bis((triisopropylsilyl)ethynyl)naphthalen-2-yl)quinazolin-4(3H)-one (**4u**).* The product was obtained as a white solid: yield 96 mg (76%); R_f 0.7 (9:1 petroleum ether/EtOAc); mp 204−205 °C; IR (neat) ν_{max} 2936, 2862, 2141, 1665, 1606, 1463, 1371, 1023, 881, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.81−7.71 (m, 2H), 7.67−7.55 (m, 2H), 7.53−7.45 (m, 1H), 0.92 (s, 21H), 0.88 (s, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5 (s), 151.6 (s), 149.0 (s), 136.6 (s), 134.3 (d), 133.3 (d), 133.0 (s), 132.6 (s), 128.6 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.1 (d), 126.8 (d), 126.2 (d), 121.7 (s), 121.7 (s), 119.4 (s), 103.1 (s), 100.7 (s), 96.4 (s, 2C), 18.4 (q, 6C), 18.3 (q, 6C), 11.0 (d, 6C); HRMS (ESI−TOF) m/z $[M + H]^+$ calcd for $C_{40}H_{53}N_2OSi_2$ 633.3691, found 633.3682.

*12-Methyleneisoindolo[1,2-b]quinazolin-10(12H)-one (**5a**).* To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in THF (1 mL) was added TBAF (0.24 mL, 0.24 mmol) at 0 °C. After addition, the solution was warmed to room temperature, stirred for another 1 h, quenched with water, and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. The volatile compounds were removed in vacuo, and the residue was subjected to column chromatography on silica gel to afford **5a** (42 mg; 84%): colorless solid; R_f 0.5 (5:1 petroleum ether/EtOAc); mp 280−282 °C; IR (neat) ν_{max} 2921, 2552, 1669, 1650, 1602, 1468, 1334, 873, 768, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.4 Hz, 1H), 7.90−7.76 (m, 3H), 7.63 (dt, J = 22.0, 7.3 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.07 (s, 1H), 5.94 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8 (s), 151.8 (s), 147.6 (s), 139.7 (s), 135.6 (s), 134.4 (d), 132.4 (d), 130.2 (d), 129.9 (s), 127.6 (d), 127.1 (d), 126.8 (d), 123.0 (d), 121.4 (s), 120.3 (d), 101.8 (t); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{11}ON_2$ 247.0866, found 247.0865.

*8H-Isoquinolino[1,2-b]quinazolin-8-one (**5b**).* To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in dry DMF (1.5 mL) was added NaH (60%) (4.8 mg, 0.2 mmol) at room temperature. The solution was heated at 80 °C for 10 h and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **5b** (20 mg 41%) as a yellow solid: R_f 0.7 (5:1 petroleum/EtOAc); mp 167−169 °C (168−170 °C);[22] ^1H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 8.0 Hz, 1H), 8.67 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.89 (dt, J = 15.0, 7.5 Hz, 2H), 7.77−7.72 (m, 1H), 7.67 (dd, J = 12.8, 7.5 Hz, 2H), 7.53 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5 (s), 147.6 (s), 146.2 (s), 134.8 (d), 132.9 (s), 132.2 (d, 2C), 128.5 (d), 127.6 (d), 127.3 (d), 127.3 (d), 126.5 (d), 125.8 (d), 122.0 (s), 117.8 (s), 113.2 (d); LC−MS (ESI) m/z 247 $[M + H]^+$.

*5-Bromo-6-(triisopropylsilyl)-8H-isoquinolino[1,2-b]quinazolin-8-one (**5c**).* To a solution of TIPS-alkyne **3a** (81 mg, 0.2 mmol) in dioxane/water (1:1) (1.5 mL) was added NBS (53 mg, 0.3 mmol) at room temperature. The solution was heated at 80 °C for 10 h and then extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **5c** (85 mg; 88%) as a yellow solid: R_f 0.3 (5:1 petroleum/EtOAc); mp 180−182 °C; IR (neat) ν_{max} 2948, 2667, 1676, 1598, 1564, 1466, 1367, 879, 749, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 7.8

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Hz, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74−7.62 (m, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 1.84−1.74 (m, 3H), 1.31 (brs, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.1 (s), 160.0 (s), 145.1 (s), 138.4 (s), 136.7 (s), 132.8 (d), 131.8 (d), 130.5 (s), 129.9 (d), 128.5 (d), 125.3 (d), 124.6 (d), 121.9 (d), 121.1 (d), 120.0 (s), 119.9 (s), 19.4 (q, 6C), 14.2 (d, 3C); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{30}ON_2{}^{81}BrSi$ 483.1285, found 483.1292.

(E)-12-Benzylideneisoindolo[1,2-b]quinazolin-10(12H)-one (**5d**). An oven-dried Schlenk tube was charged with TIPS-alkyne **3a** (81 mg, 0.2 mmol), aryl iodide (49 mg, 0.24 mmol), $PdCl_2(PPh)_3$ (14 mg, 10 mol %), and CuI (11.4 mg, 30 mol %) in sequence. The Schlenk tube was vacuumed and backfilled with nitrogen three times followed by addition of anhydrous THF (1 mL). TBAF (0.4 mL, 1 M in THF) was added into the solution at 0 °C and under the protection of nitrogen through syringe, and then the Schlenk tube was closed tightly. After the solution was warmed to room temperature and stirred for 1 h, water was added, and the resulting mixture was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography on silica gel to afford **5d** (48 mg; 74%) as a yellow solid: R_f 0.7 (5:1 petroleum/EtOAc); mp 184−186 °C (184−185 °C);[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.15 (s, 1 H) 8.48 (dd, J = 8.01, 1.14 Hz, 1 H) 8.20 (d, J = 7.63 Hz, 1 H) 7.83−7.88 (m, 1 H) 7.77−7.83 (m, 1 H) 7.49−7.56 (m, 4 H) 7.46−7.49 (m, 2H) 7.41−7.46 (m, 1H) 7.33−7.38 (m, 1 H) 7.27−7.30 (d, J = 8.0 Hz, 1 H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 161.3 (s), 151.4 (s), 147.5 (s), 135.3 (s, 2C), 134.4 (s), 134.3 (d), 131.9 (d), 130.7 (s), 129.6 (d), 129.0 (d, 2C), 128.8 (d, 2C), 128.2 (d), 127.5 (d), 127.2 (d), 126.6 (d), 123.8 (d), 123.2 (d), 122.9 (d), 121.5 (s); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_2O$ 323.1179, found 323.1179.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02738.

^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Trost, B. M.; Li, C.-J. *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Wiley: New York, 2014. (b) Stang, P. J.; Diederich, F. *Modern Acetylene Chemistry*; Wiley: New York, 2008. (c) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Acetylene Chemistry*; Wiley: New York, 2005. (d) Schobert, H. Production of Acetylene and Acetylene-based Chemicals from Coal. *Chem. Rev.* **2014**, *114*, 1743−1760. (e) Trotus, I.-T.; Zimmermann, T.; Schuth, F. Catalytic Reactions of Acetylene: A Feedstock for the Chemical Industry Revisited. *Chem. Rev.* **2014**, *114*, 1761−1782. (f) Chinchilla, R.; Najera, C. Chemicals from Alkynes with Palladium Catalysts. *Chem. Rev.* **2014**, *114*, 1783−1826. (g) Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. Alkenylation of Arenes and Heteroarenes with Alkynes. *Chem. Rev.* **2016**, *116*, 5894−5986.

(2) For selected examples of C−H alkynylation: (a) Caspers, L. D.; Nachtsheim, B. J. Directing-Group-mediated C−H Alkynylations. *Chem. - Asian J.* **2018**, *13*, 1231−1247 and references cited therein . (b) Xie, F.; Qi, Z.; Yu, S.; Li, X. Rh(III)- and Ir(III)-Catalyzed C−H Alkynylation of Arenes under Chelation Assistance. *J. Am. Chem. Soc.* **2014**, *136*, 4780−4787. (c) Dudnik, A. S.; Gevorgyan, V. Formal Inverse Sonogashira Reaction: Direct Alkynylation of Arenes and Heterocycles with Alkynyl Halides. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096−2098.

(3) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467−4470. (b) Meijere, A. d.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489. (d) Plenio, H. Catalysts for the Sonogashira Coupling-The Crownless Again Shall Be King. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954−6956. (e) Chinchilla, R.; Najera, C. Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **2011**, *40*, 5084−5121.

(4) (a) Negishi, E.; Anastasia, L. Palladium−Catalyzed Alkynylation. *Chem. Rev.* **2003**, *103*, 1979−2018. (b) Weng, Y.; Cheng, B.; He, C.; Lei, A. Rational Design of a Palladium-Catalyzed Csp−Csp Cross-Coupling Reaction Inspired by Kinetic Studies. *Angew. Chem., Int. Ed.* **2012**, *51*, 9547−9551. (c) Wang, M.; Wang, Z.; Shang, M.; Dai, H. Transition Metal Catalyzed C−H Alkynylation. *Youji Huaxue* **2015**, *35*, 570−577. (d) Li, C.-J. The Development of Catalytic Nucleophilic Additions of Terminal Alkynes in Water. *Acc. Chem. Res.* **2010**, *43*, 581−590. (e) For recent reviews on transition-metal-catalyzed C−H bond functionalization by the use of diverse directing groups, see: Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. Recent advances in directed C−H functionalizations using monodentatenitrogen-based directing groups. *Org. Chem. Front.* **2014**, *1*, 843−895.

(5) Selected examples for alkynylation using terminal alkyne reagents: (a) Liu, W.; Li, L.; Li, C.-J. Empowering a transition-metal-free coupling between alkyne and alkyl iodide with light in water. *Nat. Commun.* **2015**, *6*, 6526. (b) Yi, J.; Lu, X.; Sun, Y.-Y.; Xiao, B.; Liu, L. Nickel-Catalyzed Sonogashira Reactions of Non-activated SecondaryAlkyl Bromides and Iodides. *Angew. Chem., Int. Ed.* **2013**, *52*, 12409−12413. (c) Eckhardt, M.; Fu, G. C. The First Applications of Carbene Ligands in Cross-Couplings of Alkyl Electrophiles: Sonogashira Reactions of Unactivated Alkyl Bromides and Iodides. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (d) Tang, S.; Liu, Y.; Gao, X.; Wang, P.; Huang, P.; Lei, A. Multi-Metal-Catalyzed Oxidative Radical Alkynylation with TerminalAlkynes: A New Strategy for C(sp^3)−C(sp) Bond Formation. *J. Am. Chem. Soc.* **2018**, *140*, 6006−6013. (e) Wu, X.-X.; Liu, A.; Xu, S.; He, J.; Sun, W.; Chen, S. Palladium-Catalyzed Domino Cyclization/Alkylation of Terminal Alkynes: Synthesis of Alkynyl-Functionalized Azaindoline Derivatives. *Org. Lett.* **2018**, *20*, 1538−1541. (f) Luo, F.-X.; Cao, Z.-C.; Zhao, H.-W.; Wang, D.; Zhang, Y.-F.; Xu, X.; Shi, Z.-J. Nickel-Catalyzed Oxidative Coupling of Unactivated C(sp^3)−H Bonds in Aliphatic Amides with Terminal Alkynes. *Organometallics* **2017**, *36*, 18−21.

(6) Selected examples for alkynylation using haloalkyne reagents: (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. Direct Palladium-Catalyzed Alkynylation of *N*-Fused Heterocycles. *J. Am. Chem. Soc.* **2007**, *129*, 7742−7743. (b) Tobisu, M.; Ano, Y.; Chatani, N. Palladium-Catalyzed Direct Alkynylation of C−H Bonds in Benzenes. *Org. Lett.* **2009**, *11*, 3250−3252. (c) Ano, Y.; Tobisu, M.; Chatani, N. Palladium-Catalyzed Direct *ortho*−Alkynylation of Aromatic Carboxylic Acid Derivatives. *Org. Lett.* **2012**, *14*, 354−357.

DOI: 10.1021/acs.joc.8b02738
J. Org. Chem. 2019, 84, 2951−2961

(7) Selected examples for alkynylation using boron alkyne reagent: (a) Bertolini, F.; Woodward, S. Rapid 1,4-Alkynylation of Acyclic Enones Using K[F_3BCCR]. *Synlett* **2009**, *2009*, 51−54. (b) Molander, G. A.; Traister, K. M. Pd-Catalyzed Alkynylation of 2-Chloroacetates and 2-Chloroacetamides with Potassium Alkynyltrifluoroborates. *Org. Lett.* **2013**, *15*, 5052−5055. (c) Molander, G. A.; Katona, B. W.; Machrouhi, F. Development of the Suzuki-Miyaura Cross-Coupling Reaction: Use of Air-Stable Potassium Alkynyltrifluoroborates in Aryl Alkynylations. *J. Org. Chem.* **2002**, *67*, 8416−8423.

(8) For reviews and highlight articles on reactions of hypervalent iodine reagents, see: (a) Brand, J. P.; Waser, J. Electrophilic alkynylation: the dark side of acetylene chemistry. *Chem. Soc. Rev.* **2012**, *41*, 4165−4179. (b) Li, Y.; Hari, D. P.; Vita, V. M.; Waser, J. Cyclic Hypervalent Iodine Reagents for Atom-TransferReactions: Beyond Trifluoromethylation. *Angew. Chem., Int. Ed.* **2016**, *55*, 4436−4454. (c) Waser, J. Benziodoxol(on)e Reagents as Tools in Organic Synthesis: The Background behind the Discovery at the Laboratory of Catalysis and Organic Synthesis. *Synlett* **2016**, *27*, 2761−2773. (d) Kaschel, J.; Werz, D. B. Ethynyl Benziodoxolone (EBX): Installing Alkynes the Reversed Way. *Angew. Chem., Int. Ed.* **2015**, *54*, 8876−8878.

(9) For selected examples of [Cp*$IrCl_2$]$_2$-catalyzed C−H activation, see: (a) Li, X.; Wu, G.; Liu, X.; Zhu, Z.; Huo, Y.; Jiang, H. Regioselective C−H Bond Alkynylation of Carbonyl Compounds through Ir(III) Catalysis. *J. Org. Chem.* **2017**, *82*, 13003−13011. (b) Chen, C.; Liu, P.; Tang, J.; Deng, G.; Zeng, X. Iridium-Catalyzed, Weakly Coordination-Assisted *Ortho*-Alkynylation of (Hetero)-aromatic Carboxylic Acids without Cyclization. *Org. Lett.* **2017**, *19*, 2474−2477. (c) Caspers, L. D.; Finkbeiner, P.; Nachtsheim, B. J. Direct Electrophilic C−H Alkynylation of Unprotected 2-Vinylanilines. *Chem. - Eur. J.* **2017**, *23*, 2748−2752. (d) Li, G.; Hu, J.; Zeng, R.; Shi, D.-Q.; Zhao, Y. Direct *ortho*-Selective C−H Functionalization of Carboxybenzyl-Protected Arylalkylamines via Ir(III)-Catalyzed C−H Activation. *Org. Lett.* **2018**, *20*, 2454−2458. (e) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. Iridium(III)-Catalyzed C-7 Selective C−H Alkynylation of Indolines at Room Temperature. *J. Org. Chem.* **2015**, *80*, 1946−1951. (f) Tang, G.-D.; Pan, C.-L.; Xie, F. Ir(III)-catalyzed C−H alkynylation of arenes under chelation assistance. *Org. Biomol. Chem.* **2016**, *14*, 2898−2904. (g) Liu, B.; Wang, X.; Ge, Z.; Li, R. Regioselective Ir(III)-catalyzed C−H alkynylation directed by 7-azaindoles. *Org. Biomol. Chem.* **2016**, *14*, 2944−2949. (h) Pan, S.; Shibata, T. Recent Advances in Iridium-Catalyzed Alkylation of C−H and N−H Bonds. *ACS Catal.* **2013**, *3*, 704−712. (i) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. Ir(III)-Catalyzed Mild C−H Amidation of Arenes and Alkenes: An Efficient Usage of Acyl Azides as the Nitrogen Source. *J. Am. Chem. Soc.* **2013**, *135*, 12861. (j) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. Iridium-Catalyzed Intermolecular Amidation of sp^3 C−H Bonds: Late-Stage Functionalization of an Unactivated Methyl Group. *J. Am. Chem. Soc.* **2014**, *136*, 4141−4144. (k) Zhou, T.; Li, L.; Li, B.; Song, H.; Wang, B. Ir(III)-Catalyzed Oxidative Coupling of NH Isoquinolones with Benzoquinone. *Org. Lett.* **2015**, *17*, 4204−4207. (l) Wu, G.; Ouyang, W.; Chen, Q.; Huo, Y.; Li, X. Cross-dehydrogenative alkynylation of sulfonamides and amides with terminal alkynes via Ir(III) catalysis. *Org. Chem. Front.* **2019**, *6*, 284.

(10) (a) Phatake, R. S.; Patel, P.; Ramana, C. V. Ir(III)-Catalyzed Synthesis of Isoquinoline *N*-Oxides from Aryloxime and α−Diazocarbonyl Compounds. *Org. Lett.* **2016**, *18*, 292−295. (b) Phatake, R. S.; Patel, P.; Ramana, C. V. Ir(III)-Catalyzed Carbenoid Functionalization of Benzamides: Synthesis of *N*-Methoxyisoquinolinediones and *N*-Methoxyisoquinolinones. *Org. Lett.* **2016**, *18*, 2828−2831.

(11) (a) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Sarma, J. A. R. P.; Dayam, R.; Neamati, N. Discovery of Novel Small-Molecule Inhibitors of Human Epidermal Growth Factor Receptor-2: Combined Ligand and Target-Based Approach. *J. Med. Chem.* **2008**, *51*, 3367−3377. (b) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, B. N.; Palmer, M. J. 2,4-Diamino-6,7-dimethoxyquinazolines. 2-[4-(1,4-Benzodioxan-2-ylcarbonyl)piperazin-1-yl] derivatives as α_1Adrenoceptor Antagonists and Antihypertensive agents. *J. Med. Chem.* **1987**, *30*, 49−57. (c) Rudolph, J.; Esler, W. P.; O'Connor, S.; Coish, P. D. G.; Wickens, P. L.; Brands, M.; Bierer, D. E.; Bloomquist, B. T.; Bondar, G.; Chen, L.; Chuang, C. Y.; Claus, T. H.; Fathi, Z.; Fu, W.; Khire, U. R.; Kristie, J. A.; Liu, X. G.; Lowe, D. B.; McClure, A. C.; Michels, M.; Ortiz, A. A.; Ramsden, P. D.; Schoenleber, R. W.; Shelekhin, T. E.; Vakalopoulos, A.; Tang, W.; Wang, L.; Yi, L.; Gardell, S. J.; Livingston, J. N.; Sweet, L. J.; Bullock, W. H. Quinazolinone Derivatives as Orally Available Ghrelin Receptor Antagonists for the Treatment of Diabetes and Obesity. *J. Med. Chem.* **2007**, *50*, 5202−5216.

(12) (a) Gupta, P. K.; Yadav, N.; Jaiswal, S.; Asad, M.; Kant, R.; Hajela, K. Palladium-Catalyzed Synthesis of Phenanthridine/Benzoxazine Fused Quinazolinones by Intramolecular C−H Bond Activation. *Chem. - Eur. J.* **2015**, *21*, 13210−13215. (b) Dabiri, M.; Lehi, N. F.; Movahed, S. K.; Khavasi, H. R. Pd-Catalyzed regioselective C−H halogenation ofquinazolinones and benzoxazinones. *Org. Biomol. Chem.* **2017**, *15*, 6264−6268. (c) Lingayya, R.; Vellakkaran, M.; Nagaiah, K.; Nanubolu, J. Rhodium(II) Catalyzed Carbenoid Insertion of *N* Tosylhydrazones into Amide N−H Bonds: An Efficient Approach to N^3 Benzyl/Alkyl 2 arylquinazolinones. *Adv. Synth. Catal.* **2016**, *358*, 81−89. (d) Lu, H.; Yang, Q.; Zhou, Y.; Guo, Y.; Deng, Z.; Ding, Q.; Peng, Y. Cross-coupling/annulations of quinazolones with alkynes for access to fused polycyclic heteroarenes under mild conditions. *Org. Biomol. Chem.* **2014**, *12*, 758−764. (e) Wei, L.-S.; He, G.-X.; Kong, X.-F.; Pan, C.-X.; Mo, D.-L.; Su, G.-F. Gold(III)-Catalyzed Selective Cyclization of Alkynyl Quinazolinone-Tethered Pyrroles: Synthesis of Fused Quinazolinone Scaffolds. *J. Org. Chem.* **2018**, *83*, 6719−6727.

(13) (a) Yang, W.; Chen, J.; Huang, X.; Ding, J.; Liu, M.; Wu, H. Pd-Catalyzed Intramolecular Aerobic Oxidative C−H Amination of 2-Aryl-3-(arylamino)quinazolinones: Synthesis of Fluorescent Indazolo-[3,2-*b*]quinazolinones. *Org. Lett.* **2014**, *16*, 5418−5421. (b) Banerji, B.; Bera, S.; Chatterjee, S.; Killi, S. K.; Adhikary, S. Regioselective Synthesis of Quinazolinone-/Phenanthridine Fused Heteropolycycles by Pd-Catalyzed Direct Intramolecular Aerobic Oxidative C−H Amination from Aromatic Strained Amides. *Chem. - Eur. J.* **2016**, *22*, 3506−3512. (c) Banerjee, A.; Subramanian, P.; Kaliappan, K. P. Copper-Catalyzed Cascade Amination Route to *N*-Aryl Benzimidazoquinazolinones. *J. Org. Chem.* **2016**, *81*, 10424−10432. (d) Zhang, C.; Zhou, Y.; Deng, Z.; Chen, X.; Peng, Y. Rhodium-Catalyzed Regioselective Direct C−H Amidation of 2,4-Diarylquinazoline with Sulfonyl Azides: An Example of Steric Hindrance Regulated Mono- and Diamidation Selectivity. *Eur. J. Org. Chem.* **2015**, *2015*, 1735−1744. (e) Feng, Y.; Li, Y.; Yu, Y.; Wang, L.; Cui, X. Iridium-catalysed direct sulfamidation of quinazolinones. *RSC Adv.* **2018**, *8*, 8450−8454.

(14) (a) Yu, Y.; Yue, Y.; Wang, D.; Li, X.; Chen, C.; Peng, J. Modular Synthesis of Quinazolinone-Fused Phenanthridinones by a Palladium-Catalyzed Cascade C−H/N−H Arylation Process. *Synthesis* **2016**, *48*, 3941−3950. (b) Laclef, S.; Harari, M.; Godeau, J.; Schmitz-Afonso, I.; Bischoff, L.; Hoarau, C.; Levacher, V.; Fruit, C.; Besson, T. Ligand-Free Pd-Catalyzed and Copper-Assisted C−H Arylation of Quinazolin-4-ones with Aryl Iodides under Microwave Heating. *Org. Lett.* **2015**, *17*, 1700−1703. (c) Godeau, J.; Harari, M.; Laclef, S.; Deau, E.; Fruit, C.; Besson, T. Cu/Pd Catalyzed C2−H Arylation of Quinazolin 4(3*H*) ones with (Hetero)aryl Halides. *Eur. J. Org. Chem.* **2015**, *2015*, 7705−7717. (d) Lee, J. B.; Kang, M. E.; Kim, J.; Lee, C. Y.; Kee, J.-M.; Myung, K.; Park, J.-U.; Hong, S. Y. Direct diversification of unmasked quinazolin-4(3*H*)-ones through orthogonal reactivity modulation. *Chem. Commun.* **2017**, *53*, 10394−10397. (e) Garad, D. N.; Viveki, A. B.; Mhaske, S. B. Pd-Catalyzed Regioselective Mono-Arylation: Quinazolinone as the Inherent Directing Group for C(sp^2)−H Activation. *J. Org. Chem.* **2017**, *82*, 6366−6372.

(15) (a) Zheng, Y.; Song, W.-B.; Zhang, S.-W.; Xuan, L.-J. Ruthenium-catalyzed oxidative coupling of 2-aryl-4-quinazolinones with olefins: synthesis of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one motifs. *Org. Biomol. Chem.* **2015**, *13*, 6474−6478. (b) Viveki, A. B.; Mhaske,

DOI: 10.1021/acs.joc.8b02738
J. Org. Chem. 2019, 84, 2951−2961

S. B. Ruthenium-Catalyzed Regioselective Alkenylation/Tandem Hydroamidative Cyclization of Unmasked Quinazolinones Using Terminal Alkynes. *J. Org. Chem.* **2018**, *83*, 8906−8913.
(16) Jiang, X.; Yang, Q.; Yuan, J.; Deng, Z.; Mao, X.; Peng, Y.; Yu, C. Rhodium-catalyzed tandem C−H activation and aza-Michael addition of 2-arylquinazolin-4-ones with acrylates for the synthesis of pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one derivatives. *Tetrahedron* **2016**, *72*, 1238−1243.
(17) Reddy, B. V. S.; Narasimhulu, G.; Umadevi, N.; Yadav, J. S. Quinazolinone-Directed C−H Activation: A Novel Strategy for the Acetoxylation-Methoxylation of the Arenes. *Synlett* **2012**, *23*, 1364−1370.
(18) (a) Li, L.; Brennessel, W. W.; Jones, W. D. C−H Activation of Phenyl Imines and 2-Phenylpyridines with $[Cp^*MCl_2]_2$ (M = Ir, Rh): Regioselectivity, Kinetics, and Mechanism. *Organometallics* **2009**, *28*, 3492−3500. (b) Li, L.; Brennessel, W. W.; Jones, W. D. An Efficient Low-Temperature Route to Polycyclic Isoquinoline Salt Synthesis via C−H Activation with $[Cp^*MCl_2]_2$ (M = Rh, Ir). *J. Am. Chem. Soc.* **2008**, *130*, 12414−12419.
(19) Li, Y.; Xie, F.; Li, X. Formal Gold- and Rhodium-Catalyzed Regiodivergent C−H Alkynylation of 2-Pyridones. *J. Org. Chem.* **2016**, *81*, 715−722.
(20) Finkbeiner, P.; Kloeckner, U.; Nachtsheim, B. J. OH-Directed Alkynylation of 2-Vinylphenols with Ethynyl Benziodoxolones: A Fast Access to Terminal 1,3-Enynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 4949−4952.
(21) (a) For the synthesis of starting materials, see the Supporting Information. (b) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. Ethynyl Benziodoxolones for the Direct Alkynylation of Heterocycles: Structural Requirement, Improved Procedure for Pyrroles, and Insights into the Mechanism. *Chem. - Eur. J.* **2012**, *18*, 5655−5666. (c) Sun, J.; Tan, Q.; Yang, W.; Liu, B.; Xu, B. Copper-Catalyzed Aerobic Oxidative Annulation and Carbon-Carbon Bond Cleavage of Arylacetamides: Domino Synthesis of Fused Quinazolinones. *Adv. Synth. Catal.* **2014**, *356*, 388−394.
(22) Nageswar Rao, D.; Rasheed, S.; Das, P. Palladium/Silver Synergistic Catalysis in Direct Aerobic Carbonylation of C(sp2)−H Bonds Using DMF as a Carbon Source: Synthesis of Pyrido-Fused Quinazolinones and Phenanthridinones. *Org. Lett.* **2016**, *18*, 3142−3145.
(23) Liu, J.-Q.; Ma, Y.-G.; Zhang, M.-M.; Wang, X.-S. Consecutive Sonogashira Coupling and Hydroamination Cyclization for the Synthesis of Isoindolo[1,2-b]quinazolin-10(12*H*)-ones Catalyzed by CuI/L-Proline. *J. Org. Chem.* **2017**, *82*, 4918−4923.

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Ru-catalyzed asymmetric transfer hydrogenation of α-acyl butyrolactone *via* dynamic kinetic resolution: Asymmetric synthesis of *bis*-THF alcohol intermediate of darunavir

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ABSTRACT

The Ru-catalyzed *enantio*- and diastereoselective dynamic kinetic resolution of α-(benzyloxy/benzoyloxy)acyl-γ-butyrolactones has been examined *via* transfer hydrogenation. Employing the in situ prepared (*R*,*R*)-Ru-FsDPEN catalyst, the transfer hydrogenation of using formic acid/triethylamine at rt gave the corresponding (*S*)-3-((*S*)-2-(benzyloxy/benzoyloxy)-1-hydroxyethyl)dihydrofuran-2(3*H*)-one with good to excellent diastereo- and enantioselectivity. One of the resulting hydrogenation product prepared on gram scales was utilized for the synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3–*b*]furan-3-ol (**1**), a key synthetic intermediate of various HIV protease inhibitors such as darunavir with excellent *enantio*- (95% *ee*) and diastereoselectivities (dr 95:5).

Introduction

Acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV) damages the immune system of human beings which eventually leads to death [1]. For the last couple of decades, the HIV protease inhibitors have been employed as effective antiretroviral drugs (ARV) and are important constituents of combination therapy or highly active anti-retroviral therapy (HAART) to treat HIV-AIDS [2]. The synthetic intermediate (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3–*b*]furan-3-ol (**1**), which is trivially known as *bis*-THF alcohol **1** is a key unit in various HIV protease inhibitors like darunavir and brecanavir (Fig. 1) [3–6]. Due to its significant utility in various HIV PIs, the *bis*-THF alcohol unit **1** has gained considerable synthetic attention and numerous methods have been reported for its synthesis [7–10]. Amongst these, the traditional L-glyceraldehyde based approaches and those of the enzymatic dynamic kinetic resolution of α-benzyloxyacyl-γ-butyrolactones are of commercial significance [8–10]. Though the former has stood the test of time, the latter is a relatively new approach invented by Lonza Ltd. [11] and seems to be popular among the Chinese manufacturers who supply to the majority of the generic retroviral API manufacturers (Scheme 1).

Interestingly, the catalytic asymmetric hydrogenation via dynamic kinetic resolution of related α-benzyloxyacyl-γ-butyrolactones (**3**) was documented by the Sumitomo Chemical Company, Limited in 2003 (Scheme 1) [12]. However, this suffered from drawbacks of low diastereo- or enantioselectivity, the use of expensive phosphine-based ligands and the conducting of the hydrogenation at higher pressure and temperature, which seems to be a limiting factor for its practical applications. Considering all these drawbacks, we wondered about the catalytic dynamic kinetic resolution of these lactones **2** and **3** under asymmetric transfer hydrogenation conditions. The asymmetric transfer hydrogenation of racemic compounds via dynamic kinetic resolution (ATH-DKR) is an elegant and powerful method for the preparation of various optically active compounds containing two stereocenters [13]. ATH-DKR processes have gained a lot of interest over the past few years because of their operationally simpler approach than molecular hydrogenation as well as due to high diastereo- and enantioselectivities notices [14]. Herein, we describe the first enantioselective ATH-DKR of α-(benzyloxy/benzoyloxy)acyl-γ-butyrolactones, a transformation that (1) uses readily available and inexpensive starting materials, (2) requires low catalyst loading, (3) has in situ catalyst formation, and (4) after transformation

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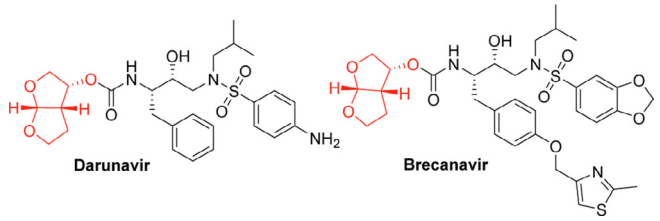
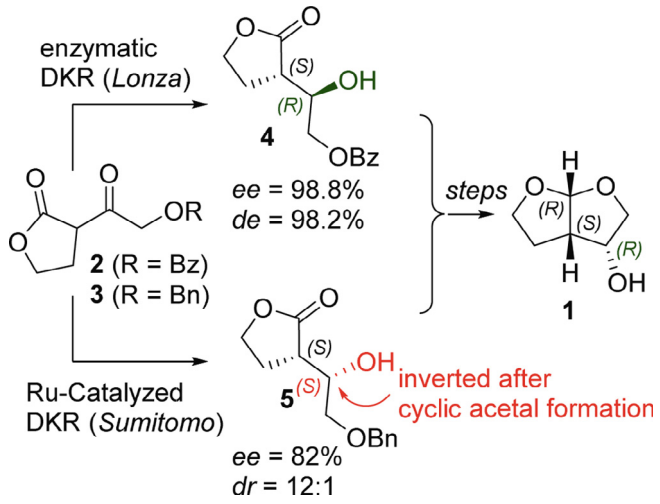


Fig. 1. Structures of HIV-protease inhibitors with the *bis*-THF alcohol **1** structural unit.



Scheme 1. Methods reported for DKR of α-acyl-γ-butyrolactones **2** and **3**.

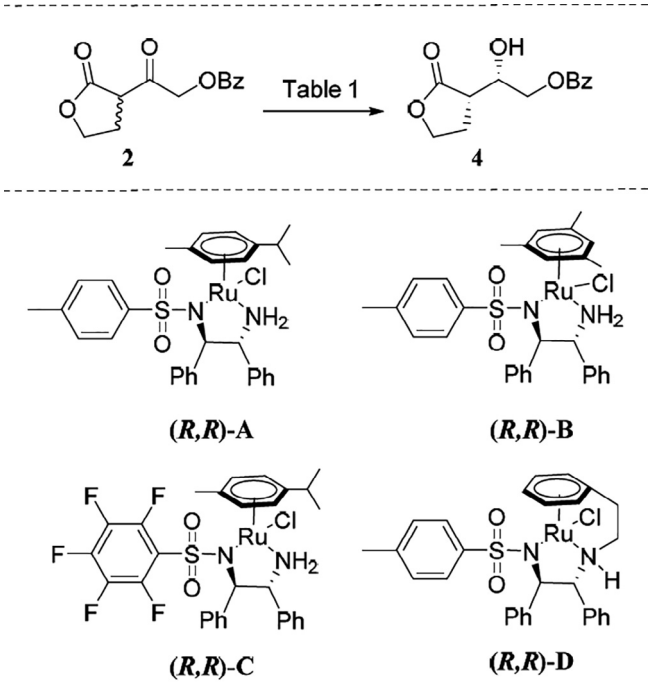
forms *bis*-THF alcohol having three contiguous stereo-centers with up to 95% enantiomeric excess (*ee*) and 95/05 diastereomer ratio (dr).

Results and discussion

Having mentioned the importance of the ATH-DKR and to examine its suitability with lactones **2** and **3**, the work in the direction commenced to identify the optimal substrate/conditions. Our initial optimization experiments started with the lactone **2** and the RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] (**A**). As shown in Table 1, using a mixture of HCO_2H/Et_3N (5:2) as hydrogen source in dichloromethane, the hydrogenation proceeded smoothly at rt and provided the product **4** in 73% *ee* and 78:22 dr ratio (Table 1, entry 1). In the process of optimizing the reaction conditions, initially, different solvents as well as a combination of solvents have been screened employing catalyst **A**. As shown below, in all solvents, the reactions ended up with high conversion; however, without any further improvement in *ee*/dr (Table 1, entries 2–11). This prompted us to examine the other complexes (RuCl[(*R*,*R*)-TsDPEN]-(mesitylene)) (**B**), (RuCl[(*R*,*R*)-FsDPEN](*p*-cymene)) (**C**), and (RuCl [(*R*,*R*)-Teth-TsDPEN] (**D**), in this pursuit.

Initial experiments with complexes **B**, **C** and **D** (Table 1, entries 12–14) in dichloromethane as solvent revealed that the catalyst **C** was found to improve diastereoselectivity up to 86/14, with no change in % *ee* (Table 1, entry 13). For further improvement in % *ee* of the desired product, the reaction was examined in different solvents and solvent combinations using catalyst **C** (Table 1, entries 15–19). These experiments revealed that the reaction in $CHCl_3$ resulted in high dr ratio (92/08) but lower % *ee* (73%) (Table 1, entry 17) and the same in *t*-amyl alcohol as solvent gave high % *ee* (78%) and lower dr (86:14) (Table 1, entry 19).

Table 1
Catalyst and solvent screening on substrate **2**.

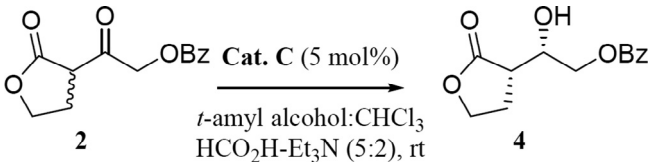


entry	Catalyst	Solvent	Conv. (%)[b]	*syn*/*anti*[b]	*ee* (%)[b]
1	**A**	DCM	99	78/22	73
2	**A**	ACN	99	51/49	67
3	**A**	MeOH	89	62/38	39
4	**A**	EtOAc	99	74/26	76
5	**A**	MTBE	97	35/65	54
6	**A**	DMSO	99	24/76	59
7	**A**	IPA	99	67/33	49
8	**A**	$CHCl_3$	99	88/12	64
9	**A**	EtOAc + DCM	99	70/30	69
10	**A**	$CHCl_3$ + THF	99	74/26	67
11	**A**	DCM + THF	99	72/28	68
12	**B**	DCM	99	71/29	17
13	**C**	DCM	99	86/14	73
14	**D**	DCM	99	64/36	1.4
15	**C**	DCE	99	81/19	74
16	**C**	DCM + THF	99	79/ 21	79
17	**C**	$CHCl_3$	99	92/08	73
18	**C**	$CHCl_3$ + THF	99	80/20	75
19	**C**	*t*-amyl alcohol	99	86/14	78
20	**C**	*t*-amyl alcohol + $CHCl_3$	99	90/10	78
21	**C**[c]	*t*-amyl alcohol + $CHCl_3$	99	90/10	72
22	**C**[d]	*t*-amyl alcohol + $CHCl_3$	99	86/14	67

[a]Conditions: 0.1 mmol of 2, 5 mol % of catalyst, and 0.1 mL of FA/TEA (5:2) were added to the solvent (2 mL), and the mixture was stirred at 27 °C for 48 h. [b]-Conversions, dr, and *ee* were calculated from chiral HPLC. [c]FA/DIPEA (5:2), [d] FA/DBU (5:2) used instead of FA/TEA (5:2).

With this clue, we next examined the reaction in a 70:30 mixture of *t*-amyl alcohol/$CHCl_3$, which resulted in a high dr ratio (90/10) with good % *ee* (78%) (Table 1, entry 20) as compared to other solvents. At this juncture, we screened the mixture of HCO_2H/ DIPEA (5:2) and HCO_2H/ DBU (5:2), which were used as hydrogen source to check its effect on % *ee* and dr ratio but we ended up with a lower % *ee* in both the cases (Table 1, entries 21 and 22). With these results in hand, the next set of reactions have been carried out by varying the percentage from 10 to 50% of $CHCl_3$ in *t*-amyl alcohol (Table 2, entries 1–6). At the outset, the solvent combination of *t*-amyl alcohol and $CHCl_3$ in 1.6:0.4 mL ratio proved to be the better with improved *ee* (78%) and dr (91:9) of the desired product (Table 2, entry 3). From these results, it was evident that

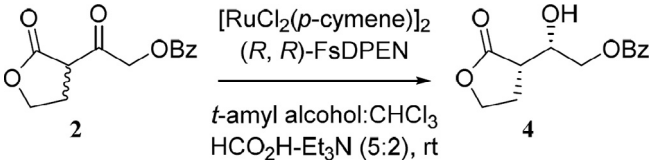
Table 2
Screening of *t*-amyl alcohol:$CHCl_3$ solvent ratio.



Entry	*t*-amyl alcohol (mL)	$CHCl_3$ (mL)	Conv. (%)[b]	*syn/anti*[b]	*ee* (%)[b]
1	1.8	0.2	99	86/14	78
2	1.6	0.4	99	89/11	77
3	1.4	0.6	99	91/09	78
4	1.2	0.8	99	91/09	77
5	1.0	1.0	99	88/12	75
6	0.8	1.2	99	83/16	72

[a]Conditions: 0.1 mmol of 2, 5 mol % of catalyst, and 0.1 mL of FA/TEA (5:2) were added to the solvent (2.0 mL). [b]Conversions, dr and *ee* were calculated from chiral HPLC.

Table 3
Screening of in situ complex/varying the catalyst loading.



Entry	Catalyst (mol %)	Conv. (%)[b]	*syn/anti*[b]	*ee* (%)[b]
1[c]	5	99	90/10	77
2[d]	5	99	91/09	78
3[d]	2	99	88/12	78
4[d]	1	99	91/09	76

[a]Conditions: 0.5 mmol of 2, and 0.5 mL of FA/TEA (5:2) were added to the solvent (10.0 mL). [b]Conversions, dr ratio and ee were calculated from chiral HPLC. [c]Ligand: [Ru]-complex proportion 1:1, [d]Ligand: [Ru]-complex proportion 1:2.

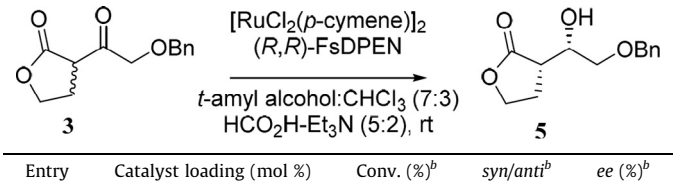
the % *ee* and dr outcome seems to be dependent on the combination of solvents and their respective concentrations.

At this stage, to avoid the use of commercial Ru-complexes that are very expensive, the possibility of employing in situ generated (RuCl[(*R*,*R*)-FsDPEN](*p*-cymene)) was explored (Table 3, entries 1–4) by varying the catalyst loading from 5 to 1 mol% (Table 3, entries 1–4). These experiments revealed that 5 mol% catalyst (Ru: Ligand ratio 1:2) gave the best results with a complete conversion of **2** resulting in the desired product **4** with 78% *ee* and 91/09 dr ratio (Table 3, entry 2). The decrease in catalyst loading resulted in a nominal decrease in the % *ee* and dr ratio (Table 3, entries 3–4).

Based on these detailed experiments with the benzoyl substrate **2**, we next moved to examine the compatibility of benzyl lactone **3** under the optimized conditions. As shown in Table 4, the results are encouraging. With 5 mol% in situ generated catalyst **C** (Ru: ligand ratio = 1:2) the complete conversion of the substrate was noticed within 12 h at room temperature and the corresponding hydroxyl lactone **5** was obtained with good enantioselectivity (91% *ee*) and diastereoselectivity (91/09) (Table 4, entry 1). This inspired us to further investigate the catalyst loading (Table 4, entries 2–5). Gratifyingly, even with 0.5 mol% catalyst, the reaction proceeded smoothly, with increased 95% *ee* and 95/05 dr ratio (Table 4, entry 4). Decreasing the catalyst loading to 0.2 mol% resulted in a lower conversion with no loss of *ee* and dr ratio (Table 4, entry 5).

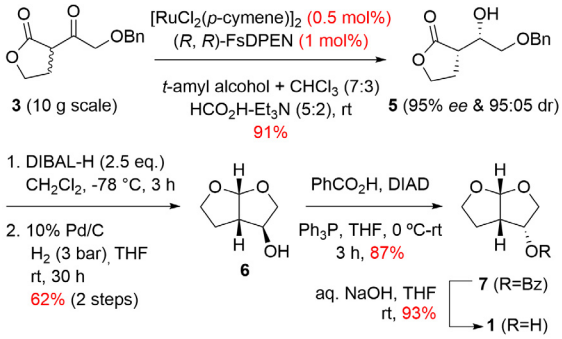
The efficiency of this ATH-DKR process developed has been examined by conducting the reaction on a 10 g scale, under optimized reaction conditions. This gave the desired product **5** with 95% *ee* and 95/05 dr ratio (Scheme 2). This compound 5 has been

Table 4
DKR of benzyloxylactone 3 under optimized conditions 2.



Entry	Catalyst loading (mol %)	Conv. (%)[b]	*syn/anti*[b]	*ee* (%)[b]
1	5	99	91/09	91
2	2	99	95/05	94
3	1	99	95/05	95
4	0.5	99	95/05	95
5	0.2	60	94/06	95

[a]Conditions: 1 mmol of 3, and 1 mL of FA/TEA (5:2) were added to the solvent. [b]Conversion, dr ratio, and *ee* were calculated from chiral HPLC.



Scheme 2. Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3–*b*]furan-3-ol (1).

further advanced to the benzoate **7** of the key Darunavir intermediate **1** by following the established 3 step sequence [7f,9b] and its absolute configuration/enatioselectivity (*ee*: 95%; dr: 95/05) has been established by comparing with the authentic benzoate prepared from the commercial **1**. Finally, saponification of **7** with aq. NaOH in THF provided the *bis*-THF alcohol **1**.

Conclusion

In conclusion, the dynamic kinetic resolution of benzoyloxy/benzyloxy α-acyl-γ-butyrolactone *via* asymmetric transfer hydrogenation has been examined for the first time employing chiral Ruthenium complexes. The best results were obtained with the benzylated substrate. After substantial optimization, the ATH reaction was successfully carried out employing 0.5 mol% of in situ prepared (*R*,*R*)-Ru-FsDPEN complex and using HCO_2H/Et_3N mixture as a hydrogen source. With both substrates, the ATH-DKR reactions have been executed on gram scales and obtained good to excellent diastereo and enantioselectivities (up to dr = 95:5 and *ee* = 95%) and one of the intermediate has been advanced to synthesize *bis*-THF alcohol intermediate of darunavir on a multi gram scale.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152831.

References

[1] (a) R.A. Weiss, Science 260 (1993) 1273–1279;
(b) D.C. Douek, M. Roederer, R.A. Koup, Annu. Rev. Med. 60 (2009) 471–484.
[2] (a) J. Pokorná, L. Machala, P. Řezáčová, J. Konvalinka, Viruses 1 (2009) 1209–1239;
(b) A.K. Ghosh, B.D. Chapsal, I.T. Weber, H. Mitsuya, Acc. Chem. Res. 41 (2008) 78–86;
(c) F. Berti, V. Frecer, S. Miertus, Curr. Pharm. Des. 20 (2014) 3398–3411;
(d) A.K. Ghosh, H.L. Osswald, G. Prato, J. Med. Chem. 59 (2016) 5172–5208;
(e) A.K. Ghosh, D.D. Anderson, I.T. Weber, H. Mitsuya, Angew. Chem., Int. Ed. 51 (2012) 1778–1802;
(f) Z. Lv, Y. Chu, Y. Wang, HIV/AIDS 7 (2015) 95–104.
[3] (a) E. De Clercq, Int. J. Antimicrob. Agents 33 (2009) 307–320;
(b) K. McKeage, C.M. Perry, S.J. Keam, Drugs 69 (2009) 477–503;
(c) E.D. Deeks, Drugs 74 (2014) 99–125.
[4] (a) M.H. Hanlon, D.J.T. Porter, E.S. Furfine, A. Spaltenstein, H. Luke Carter, D. Danger, A.Y.L. Shu, I.W. Kaldor, J.F. Miller, V.A. Samano, Biochemistry 43 (2004) 14500–14507;
(b) J.F. Miller, C.W. Andrews, M. Brieger, E.S. Furfine, M.R. Hale, M.H. Hanlon, R. J. Hazen, I. Kaldor, E.W. McLean, D. Reynolds, D.M. Sammond, A. Spaltenstein, R. Tung, E.M. Turner, R.X. Xu, R.G. Sherrill, Bioorg. Med. Chem. Lett. 16 (2006) 1788–1794.
[5] T. Cihlar, G.X. He, X. Liu, J.M. Chen, M. Hatada, S. Swaminathan, M.J. McDermott, Z.Y. Yang, A.S. Mulato, X. Chen, S.A. Leavitt, K.M. Stray, W.A. Lee, J. Mol. Biol. 363 (2006) 635–647.
[6] Martin McDermott, Gilead Sciences, Inc Patent US 2005/0136396 A1.
[7] Selected reports on the synthesis of 1. (a) M. Uchiyama, M. Hirai, M. Nagata, R. Katoh, R. Ogawa, A. Ohta, Tetrahedron Lett. 42 (2001) 4653−4656. (c) A.K. Ghosh, S. Leshchenko, M. Noetzel, J. Org. Chem. 69 (2004) 7822−7829. (c) A.K. Ghosh, J. Li, R.S.A. Perali, Synthesis 18 (2006) 3015−3018. (d) R.H. Yu, R.P. Polniaszek, M.W. Becker, C.M. Cook, L.H.L. Yu, Org. Process Res. Dev. 11 (2007) 972−980. (e) W.L. Canoy, B.E. Cooley, J.A. Corona, T.C. Lovelace, A. Millar, A.M. Weber, S. Xie, Y. Zhang, Org. Lett. 10 (2008) 1103−1106. (f) D.M. Black, R. Davis, B.D. Doan, T.C. Lovelace, A. Millar, J.F. Toczko, S. Xie, Tetrahedron Asymm. 19 (2008) 2015−2019. (g) P.R. Sridhar, G.M. Reddy, K. Seshadri, Eur. J. Org. Chem. (2012) 6228−6235. (h) Y. Hayashi, T. Aikawa, Y. Shimasaki, H. Okamoto, Y. Tomioka, T. Miki, M. Takeda, T. Ikemoto, Org. Process Res. Dev. 20 (2016) 1615−1620. (i) T. Kanemitsu, M. Inoue, N. Yoshimura, K. Yoneyama, R. Watarai, M. Miyazaki, Y. Odanaka, K. Nagata, T.A. Itoh, Eur. J. Org. Chem. (2016) 1874−1880. (j) Smithkline Beecham Corporation, USA. Patent WO2003024974A2. (b) A. Sevenich, G.Q. Liu, A.J. Arduengo, B.F. Gupton, T.J. Opatz, Org. Chem. 82 (2017) 1218−1223.
[8] (a) A.K. Ghosh, Y. Chen, Tetrahedron Lett. 36 (1995) 505−508. (b) D.L.N.G. Surleraux, A. Tahri, W.G. Verschueren, G.M.E. Pille, H.A. De Kock, T.H.M. Jonckers, A. Peeters, S. De Meyer, H. Azijn, R. Pauwels, M.P. De Bethune, N.M. King, M. Prabu-Jeyabalan, C.A. Schiffer, P.B.T.P. Wigerinck, J. Med. Chem. 48 (2005) 1813−1822. (c) Y.L. Khmelnitsky, P.C. Michels, I.C. Cotterill, M. Eissenstat, V. Sunku, V.R. Veeramaneni, H. Cittineni, G.R. Kotha, S.R. Talasani, K.K. Ramanathan, V.K. Chitineni, B.R. Venepalli, Org. Process Res. Dev. 15 (2011) 279−283. (d) SmithKline Beecham Corporation, USA; Martin, M. T. Patent WO2005000249A2. (e) A.K. Ghosh, S.B. Markad, W.L. Robinson, J. Org. Chem. 86 (2021) 1216–1222.
[9] (a) P.J.L.M. Quaedflieg, B.R.R. Kesteleyn, P.B.T.P. Wigerinck, N.M.F. Goyvaerts, R.J. Vijn, C.S.M. Liebregts, J.H.M.H. Kooistra, C. Cusan, Org. Lett. 7 (2005) 5917–5920;
(b) M.G. Kulkarni, Y.B. Shaikh, A.S. Borhade, A.P. Dhondge, S.W. Chavhan, M.P. Desai, D.R. Birhade, N.R. Dhatrak, R. Gannimani, Tetrahedron Asymm. 21 (2010) 2394–2398;
(c) A.K. Ghosh, C.D. Martyr, M. Steffey, Y.-F. Wang, J. Agniswamy, M. Amano, I. T. Weber, H. Mitsuya, ACS Med. Chem. Lett. 2 (4) (2011) 298–302.
[10] A.K. Ghosh, J.F. Kincaid, D.E. Walters, Y. Chen, N.C. Chaudhuri, W.J. Thompson, C. Culberson, P.M.D. Fitzgerald, H.Y. Lee, S.P. McKee, P.M. Munson, T.T. Duong, P.L. Darke, J.A. Zugay, W.A. Schleif, M.G. Axel, J. Lin, J.R. Huff, J. Med. Chem. 39 (1996) 3278–3290.
[11] Lonza Ltd. 4052 Basel (CH), EP 2 634 180 A1.
[12] Sumitomo Chemical Company, Limited, Tokyo; USA. Patent US 2005/0256322 Al.
[13] (a) R. Noyori, M. Tokunaga, M. Kitamura, Bull. Chem. Soc. Jpn. 68 (1995) 36–55;
(b) R. Noyori, S. Hashiguchi, Acc. Chem. Res 30 (1997) 97–102;
(c) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 118 (1996) 2521–2522;
(d) V. Parekh, J.A. Ramsdenb, M. Wills, Catal. Sci. Technol. 2 (2012) 406–414;
(e) A. Kišić, M. Stephan, B. Mohar, Org. Lett. 15 (2013) 1614–1617.
[14] Selected papers and reviews for DKR-ATH: (a) N.J. Alcock, I. Mann, P. Peach, M. Wills, Tetrahedron Asymm. 13 (2002) 2485−2490. (b) S. Liu, J.H. Xie, L.X. Wang, Q.L. Zhou, Angew. Chemie - Int. Ed. 2007; 46: 7506−7508. (c) S. Liu, J.H. Xie, W. Li, W.L. Kong, L.X. Wang, Q.L. Zhou, Org. Lett. 11 (2009) 4994−4997. (d) Z. Ding, J. Yang, T. Wang, Z. Shen, Y. Zhang, Chem. Commun. (2009) 571−573. (e) D. Cartigny, K. Püntener, T. Ayad, M. Scalone, V. Ratovelomanana-Vidal, Org. Lett. 12 (2010) 3788−3791. (f) M.T. Corbett, J.S. Johnson, J. Am. Chem. Soc. 135 (2013) 594−597. (g) L. Monnereau, D. Cartigny, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, Chem. - A Eur. J. 21 (2015) 11799−11806. (h) T. Cheng, Q. Ye, Q. Zhao, G. Liu, Org. Lett. 17 (2015) 4972−4975. (i) D. Wang, D. Astruc, Chem. Rev. 115 (2015) 6621−6686. (j) P.G. Echeverria, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, Synthesis 48 (2016) 2523−2539. (k) Q. Hu, J. Chen, Z. Zhang, Y. Liu, W. Zhang, Org. Lett. 18 (2016) 1290−1293. (l) Y.M. Zhang, Q.Y. Zhang, D.C. Wang, M.S. Xie, G.R. Qu, H.M. Guo, Org. Lett. 21 (2019) 2998−3002. (m) G. Sun, W. Jian, Z. Luo, T. Sun, C. Li, J. Zhang, Z. Wang, Org. Process Res. Dev. 23 (2019) 1204−1212. (n) Z. Luo, Z. Wang, G. Sun, W. Jian, F. Jiang, B. Luan, R. Li, L. Zhang, Org. Lett. 22 (2020) 4322−4326. (o) F. Wang, L.-S. Zheng, Q.-W. Lang, C. Yin, T. Wu, P. Phansavath, G.-Q. Chen, V. Ratovelomanana-Vidal, X. Zhang, Chem. Commun. 56 (2020) 3119−3122.

Erratum

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