"Isatogens: Reactions and Synthetic Utility"

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO

SAVITRIBAI PHULE PUNE UNIVERSITY

BY

V. S. Kumar Chepuri

Dr. C. V. Ramana

(Research Guide)

ORGANIC CHEMISTRY DIVISION
CSIR-NATIONAL CHEMICAL LABORATORY
PUNE–411008

November–2014

Dedicated To

MY Mother

With tons of love

DECLARATION

The research work embodied in this thesis has been carried out at CSIR-National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune – 411008
March–2014 **(V. S. Kumar Chepuri)**

Dr. C. V. Ramana

Phone: +91–20–25902577
+91–20–25902455
E–mail: vr.chepuri@ncl.res.in

CERTIFICATE

The research work presented in thesis entitled "**Isatogens: Reactions and Synthetic Utility**" has been carried out under my supervision and is a bonafide work of **Mr. V. S. Kumar Chepuri**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008
November – 2014

Dr. C. V. Ramana
(Research Guide)

Acknowledgements

This thesis represents the amalgamation of my work with the good and bad moments in the past six years in Organic Chemistry Division, NCL. Dozens of people have helped and taught me immensely in life as well as during my PhD tenure, I would like to take this as an opportunity to thank all those people.

First of all, I'd like to give my sincere thanks to my honorific supervisor **Dr. C. V. Ramana**, for giving me an opportunity for doing the PhD and he deserves a lot of credit for any of my success in research. His scientific curiosity in teaching the students in the form of conducting group meetings have inspired and driven me to learn many aspects of chemistry. And the work discipline whatever he taught me I will continue throughout my life.

I also thank the current Head of the OCD, Dr. Pradeep K. Tripathi and the former Head of the OCD, Dr. Ganesh Pandey and the Director of NCL for providing infrastructural facilities. I gratefully acknowledge the valuable suggestions and timely help of Dr. Srinivas Hotha, Dr. D. S. Reddy, Dr B.L.V. Prasad, Dr. Vanka Kumar, Dr. Thulsiram, and Dr. Borate. Suggestions offered during assessments and other presentations, by scientists namely, Dr. Nitin Patil, Dr. S.P. Chavan, Prof. M. G. Kulkarni, Prof. D. D. Dhavale, Dr. (Mrs.) Radhika S. Kusurkar and Dr (Mrs.) Vaishali Shinde are also gratefully acknowledged.

I need to thank specially my teacher Dhanalakshmi garu, without her generous support and encouragement I might not continued my higher education, also the Ph.D. And Venkateswararao master, Nageswararao anna, Rajarao sir, Suryarao Sir, Satyavathi teacher, Dr. Jaya Prakash for their inspirational teaching, honorable ethics and firm discipline. I am highly thankful to Dr. Ravindranath sir, Dr. J. Venkateswararao sir, Dr. Prasadarao sir, for their sincere efforts and motivation towards research during my stay at the Chemistry Department, from Bapatla Engineering College.

My sincere thanks to the people in various parts of the institute, Mrs. Katharine Raphel, Mrs. Pooja Kulkarni and all OCD office staff for their cooperation. Help from the spectroscopy, analytical and mass group is gratefully acknowledged. I also thank Dr. Rajmohan, NMR division and his group. For HRMS Mrs. Santha kumari, Swamy, Deepika, Mital and Swapnil for their unhesitant support and assistance. And special thanks to X-ray crystallographic analysis, Dr. Rajesh, Dr. Vedavati Puranik and Sridhar.

I would like to offer thanks to my friends and beloved seniors Neelarapu Sridhar, Yadagiri, Chandrababu Naidu, Manoj, Ramireddy, Dr. Sreedhar Reddy, Dr. Swaroop, for their love and affection. I also greatly thankful to families of my friends Vilas anna-Sunitha vadina, Rajender anna-Yogitha vadina, Santhosh anna-Uma vadina, Raju anna (bio) for creating family atmosphere.

I gratefully acknowledge the training and support extended by my senior colleagues Dr. Sharad, Dr. Kulbhushan, Dr. Giri, Dr. Pandey, Dr. Pitambar, Dr. Rahul, Dr. Sachin, Dr. Rosy, Dr. Sahoo, Dr. Vikhe and B. Senthil kumar, who taught me various techniques and encouraged me at several point of time during the tenure as a PhD student. I would like to thank all my colleagues for always maintaining cheerful and healthy work environment inside as well as outside the Lab. My special thanks to Narendraprasad reddy, Srinivas, Venkannababu, Mangesh, Yogesh, Shyam, Ketan, Jitu, Paresh, Atul, Ravindra, Ajay, Dinesh, Anuradha, Anand, Mahesh Patil, Vivek, Mahesh Shinde, Santhosh, Anand, Sravani, Friedi, Mishel, Amala, Jamsheena, ketan (Ju), manu Thomas, pathan, Jahnavi and Hema whom I shared my most precious moments during my PhD.

I also consider myself blessed in that I got to spend a major chunk of my time at NCL with all telugu mithra mandali Venu, Chaithanya, Dr. Ravi, Durgaprasad, Shiva, Janakiram, Narsimha Rao Kanna, Bogesh, Ramireddy, Bala, Rambabu, Chaithanya krishna, Shanthivardan, Chaitanya (IIT G), Ravi, Hanuman, Laxmi Prasad, Deva datta, Innaiah, Srikanth, Nagendra, Trinadh, Sathish Bhattu, Suresh, Seetharam sing, Sathish, Kumar raja, Kasinath, Naresh killi, Hari, Tharun, Eswar, Nookaraju, Dr. Sudhakar, Dr. Eshwar, Dr. srikanth (Late), Dr. B. Srinivas, Dr. Ramesh and Dr. V. Srinivas Rao. They have always been and will continue to be an inspiration to me. I always enjoy their company and they are my strength for many things. I am lucky to have such a big family, which I have got kind gift in NCL. I also thank my friends in IISER. Rajesh, Krishna, Ravi kiran, Venkateshwar rao, Kishor, Bapu, Satish.

My family is always source of inspiration and great moral support for me in perceiving my education, I used thank god of almighty for providing me such a beautiful family. The words are insufficient to express my sense of gratitude for my family. Though, I take this opportunity to my sense of gratitude to my parents, Bharathi and Srirama Murthi (late) for their tons of love, sacrifice, blessings, unconditional support and encouragement. I express my deep and paramount gratitude to my sister Jyothi and brother-in-Law Ramanjaneyulu without their constant support, encouragement I cannot stand with this dissertation. I am lucky to have lovely niece Swetha, Keerthi I always enjoy their company even at short stays at home.

I am also thankful to CSIR, New Delhi for the financial assistance in the form of fellowship. At last but not the least, I thank whole heartedly, the omnipotent God, the illimitable superior spirit, for the strength and determination to put my chin up when faced with hardships in life.

V. S. Kumar Chepuri

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
Boc	–	Tert-Butyl oxy carbonyl
Ms	–	Methanesulphonyl chloride
Ts	–	Toluenesulphonyl chloride
Bu	–	Butyl
^{t}BuOH	–	Tertiary butyl alcohol
Cat.	–	Catalytic/catalyst
DCM	–	Dichloromethane
Conc.	–	Concentrated
DMP	–	2,2'-Dimethoxypropane
DMF	–	*N,N*-Dimethylformamide
DMAP	–	*N,N'*-Dimethylaminopyridine
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EC	–	Effictive concentration
HRMS	–	High Resolution Mass Spectroscopy
IBX	–	2-Iodobenzoic acid
Liq.	–	Liquid
Me	–	Methyl
NMR	–	Nuclear Magnetic Resonance
Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
i-PrOH	–	*iso*-Propanol
rt	–	Room Temperature
Sat.	–	Saturated
TBAF	–	Tetra-*n*-butylammonium fluoride
THF	–	Tetrahydrofuran

Abbreviations used for NMR spectral informations:

br	Broad	q	Quartet
d	Doublet	s	Singlet
m	Multiplet	t	Triplet

GENERAL REMARKS

- ^{1}H 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.
- Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 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}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- 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, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

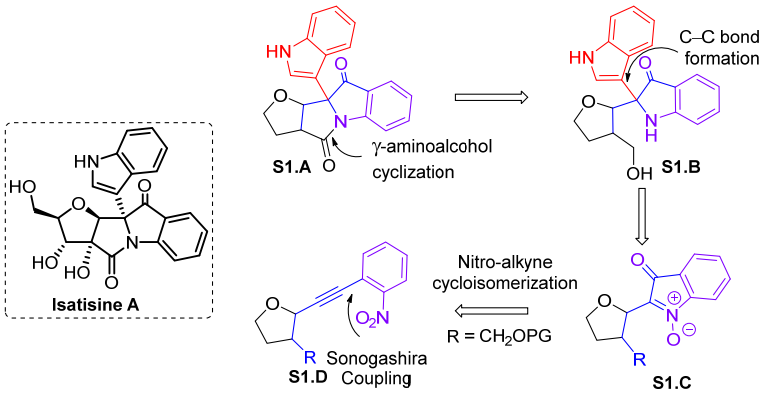
The thesis entitled "**Isatogens: Reactions and Synthetic Utility**" consists of three chapters followed by the Experimental Section, References and NMR Spectra. Chapter One provides the information about isatogens, such as the methods for the synthesis and some reported examples on the reactions of isatogens (nucleophilic additions and [3+2]-dipolar cycloadditions). Chapter two deals with the development of complementary methods for the addition of indole to isatogens with a complete regioselectivity at both the reacting partners and the synthesis of a diverse set of 2,2-disubstituted indolin-3-ones. The applicability of this method has been demonstrated by completing the total synthesis of 13-*deoxy* Isatisine A. In the third Chapter was presented the work that has been carried out in the context of the total synthesis of Austamide. A novel cascade reaction comprising of the "Au-catalyzed nitroalkyne cycloisomerization and intramolecular [3+2]-dipolar cycloaddition" has been developed for the synthesis of the central tricyclic core of Austamide. Another one-pot reaction comprising "inter molecular [3+2]-dipolar cycloaddition of isatogens with olefins and the Ru-catalyzed redox-neutral N–O cleavage" leading to the *β*-amino ketones has also been developed.

Chapter 1: Synthesis and reactions of Isatogens

Introduction: The 3-oxo-3H-indole-1-oxides, trivially known as isatogen, is an unnatural scaffold and characterized by the presence of both nitrone and keto units. Isatogens readily undergo nucleophilic attack at the C2 and C3 positions forming 2,2-disubstituted indolin-3-one and tertiary alcohol skeletons. Considering the widespread occurrence of the 2,2-disubstituted and (2,2)-*spiro* pseudoindoxyl skeletons in natural products and the easy access to isatogens that we have provided recently, methods for the development of the regioselective C2-functionalization of isatogens either with nucleophiles or *via* dipolar cycloaddition has been planned.

Chapter 2: Total Synthesis of 13-*deoxy* Isatisine A

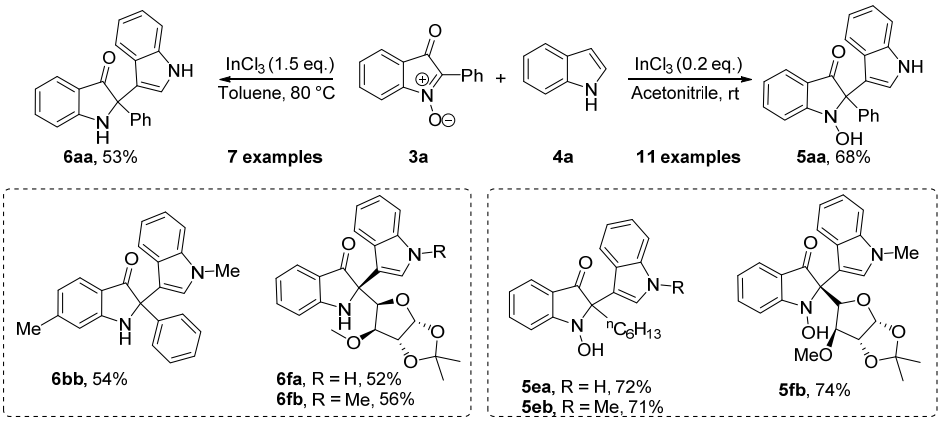
Isatisine A is a complex bisindole alkaloid isolated by Chen and co-workers in 2007 from the leaves of *Isatis indigotica Fort*, a herbaceous plant species. Its acetonide derivative is an artifact during the isolation and was found to exhibit cytotoxicity against C8166 with CC_{50} = 302 μM and anti-HIV-1 activity of EC_{50} = 37.8 μM.



Scheme 1: Retrosynthetic disconnections for the central core of Isatisine A

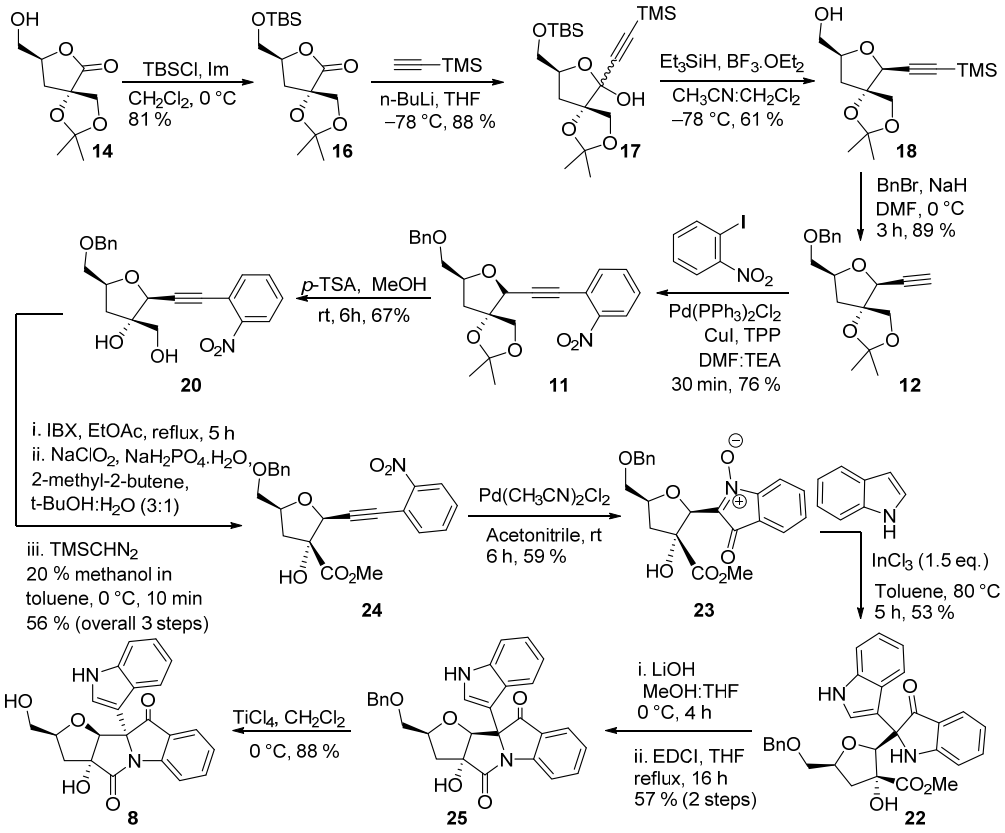
The tentative disconnections for the central tetracyclic system of the Isatisine A feature three metal mediated reactions such as – i. the regioselective C–C bond formation between the indole C3 and isatogen C2 positions; ii. construction of the isatogen *via* nitroalkyne cycloisomerization; and iii. the preparation of nitroalkyne by the Sonogashira coupling process (Scheme 1).

As a part of this strategy, our exploratory experiments with various Lewis acids led to the development of methods for the addition of indoles to isatogens leading selectively to either 2,2-disubstituted-*N*-hydroxy-indolin-3-one (**5**) or 2,2-disubstituted-indolin-3-one (**6**) compounds employing $InCl_3$ as a catalyst or as the reagent. The scope of these reactions has been amply demonstrated with six different isatogens and employed for the addition reactions with simple indole and *N*-methyl indole under two different conditions (Scheme 2).



Scheme 2: Scope of the $InCl_3$-mediated C–C bond formation reaction

To demonstrate its viability, the synthesis of 13-*deoxy*-Isatisine A has been completed in ten steps from a known and easily available lactone **14**. The primary alcohol group in lactone **14** was protected as its TBS ether using TBSCl/imidazole in CH_2Cl_2 at 0 °C. The lactone **16** was subjected to alkyne addition with trimethylsilyl acetylene and *n*-BuLi in THF at –78 °C to give the lactols **17** in 10:1 ratio with 88% yield. The reduction of the lactols **17** with Et_3SiH and $BF_3.OEt_2$ in acetonitrile and dichloromethane at –78 °C gave the alkynol **18** resulting from the deoxygenation and the TBS-group deprotection in 61% yield. The anomeric configuration was fixed as β with the help of the 2D NMR spectroscopic analysis of the corresponding acetate **18-Ac**.



Scheme 3: Total synthesis of 13-*deoxy* Isatisine A

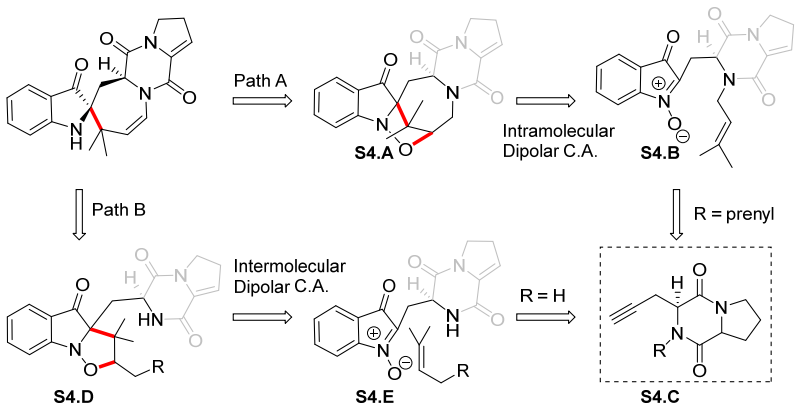
Next, the free alcohol in compound **18** was subjected for benzylation using BnBr and NaH in DMF at 0 °C. The C-trimethylsilyl group was also found to be deprotected under the same conditions to give the compound **12** in 89% yield. The Sonogashira coupling of **12** with *o*-iodonitrobenzene was performed using

$Pd(PPh_3)_2Cl_2$ and CuI in 1:3 ratio of DMF-Et_3N solvent to afford the key nitroalkyne **11** in 76% yield. Due to the formation of nitro enolether **19** in the Pd-mediated cycloisomerization with compounds **11** and **20**, the strategy has been revised by keeping the amine-ester coupling to lactam at the final stage. Compound **11** was subjected for acetonide hydrolysis by employing catalytic amounts of *p*-TSA in methanol at room temperature to afford the diol **20** in 67% yield. Next, the nitroalkyne ester **24** was synthesized by functional group transformations. The nitroalkyne cycloisomerization of **24** with $Pd(CH_3CN)_2Cl_2$ in acetonitrile gave the corresponding isatogen **23**. The isatogen was treated with indole and 1.5 eq. of $InCl_3$ in toluene at 80 °C to afford the indolin-3-one compound **22** in moderate yield. The hydrolysis of ester to carboxylic acid, followed by intramolecular amidation using EDCI gave the lactam **25**. The stereochemistry of the quaternary center of formed lactam was established with COSY\NOESY analysis. Finally, the lactam was subjected to debenzylation using $TiCl_4$ in CH_2Cl_2 to afford the 13-*deoxy* Isatisine A (**8**) in 88% yield (Scheme 3).

Chapter 3: Towards the total synthesis of Austamide

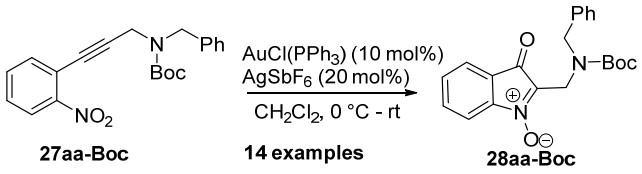
Austamide was isolated in 1971 from *Aspergillus ustus* CSIR 1128 by Styne and co-workers. The toxic maize-meal cultures of *A. ustus* were extracted and fractionated led to the isolation of Austamide, a toxic metabolite. Coming to the structural features of the Austamide, (i) it is an unprecedented pentacyclic skeleton, (ii) has two stereocenters, one at the *spiro*-junction and other at the diketopiperazine junction, (iii) has a typical pseudoindoxyl chromophore and (iv) it has two labile enamide functionalities.

The C–C bond formation (at the C2-position of pseudoindoxyl core) *via* the intra or intermolecular [3+2]-cycloaddition of nitrone has been identified as the key transformation in our planned total synthesis of Austamide. As shown in Scheme 4, the intramolecular *endo*-selective cycloaddition, the N–O bond cleavage in the resulting isoxazolidine and subsequent dehydration was the initial plan. Considering the possibility of intramolecular cycloaddition resulting in undesired regioselectivity, the intermolecular cycloaddition (Path B) has also been considered as an alternative.



Scheme 4: Approach for the synthesis of *spiro*-pseudoindoxyl skeletons

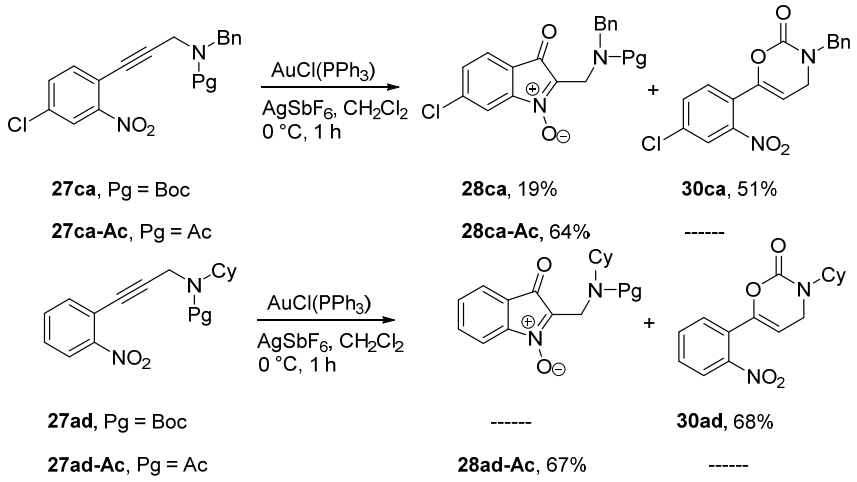
Our work in this direction started with a hypothesis that both the cycloisomerization (leading to isatogen) and the [3+2]-cycloaddition could be carried out in one-pot. In addition, we also assumed that, the presence of an electron withdrawing group such as nitrogen on the alkyne chain should promote the 5-*exo* dig mode of cyclization to lead to the isatogen with both the Pd- and Au-complexes. Early, investigations on the Au-catalyzed cycloisomerization of the nitroalkyne **27aa-Boc** has indeed revealed that with the majority of the Au-complexes employed, the isatogen **28aa-Boc** formation was the major event and the best results were obtained when 10 mol% of $AuCl(PPh_3)$ was employed along with 20 mol% of $AgSbF_6$ (Scheme 5). The scope of this reaction has been established by employing various nitroalkynes, especially by varying (i) the amine protecting group and (ii) substituents on aromatic as well as on the amine unit.



Scheme 5: Au-catalysed synthesis of isatogens

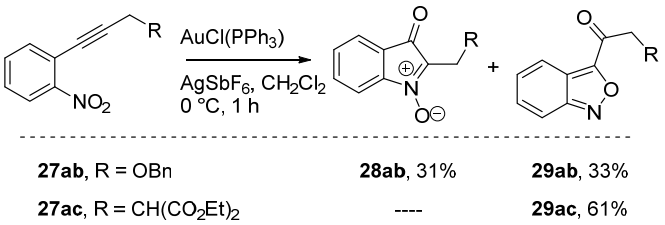
As shown in Scheme 5, in many of the cases the isatogen formation was the exclusive event. In case of the substrate **27ca** and **27ad** respectively having a Cl-group on aryl ring or a bulky cyclohexyl group on nitrogen, the participation of the –Boc group in the cyclization leading to the cyclic carbamate was noticed. However,

the cyclization of the corresponding *N*-acetyl compounds provided isatogens exclusively (Scheme 6).



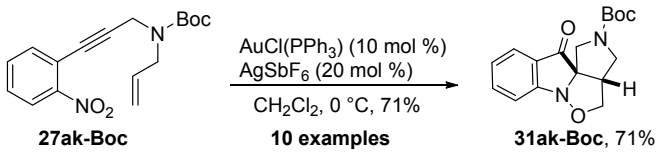
Scheme 6: Influence of the substituents on Au-catalysed cycloisomerization

The control experiments with the nitroalkynes **27ab** and **27ac** derived respectively from the benzylpropargyl ether and diethylpropargyl malonate revealed that the mode of cyclization is dependent upon the presence/absence of a heteroatom at the propargylic position and the magnitude of the –I effect that it can insert (Scheme 7).



Scheme 7: Control experiments for Au-catalysed cycloisomerization

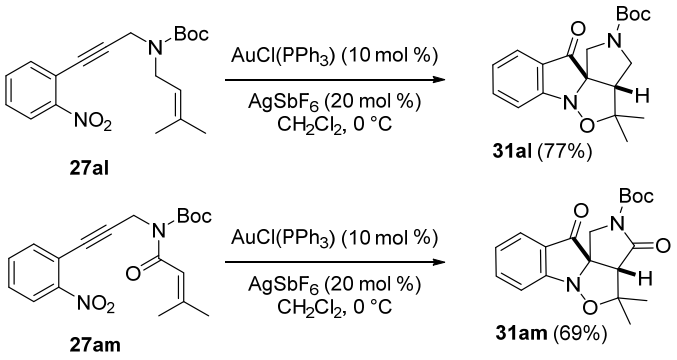
Next, the possibility of the proposed cycloisomerization-cycloaddition cascade has been examined by subjecting the *o*-nitro propargl-*N*-allyl derivative **27ak-Boc** to the conditions that were employed for the isatogen synthesis. The tetracyclic isoxazolidine **31ak-Boc** was obtained in 71% yield, with a net creation of three rings in one go (Scheme 8).



27ak-Boc **10 examples** **31ak-Boc**, 71%

Scheme 8: Au-catalyzed cyclization-cycloaddition cascade for synthesis of *spiro*-pseudoindoxyl tricyclic core

This reaction has been generalized by employing various *N*-allyl, *N*-prenyl and *N*-(3,3-dimethylacryloyl) derivatives (Scheme 9).

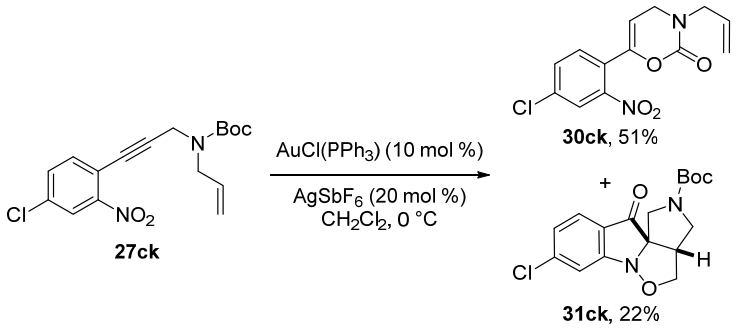


27al **31al** (77%)

27am **31am** (69%)

Scheme 9: Au-catalysed cyclization-cycloaddition cascade process with *N*-prenyl and *N*-(3,3-dimethylacryloyl) derivatives

As expected, with the substrate **27ck** having a Cl-group, the participation of the –Boc group in the cyclization leading to the cyclic carbamate **30ck** was the major event (Scheme 10).

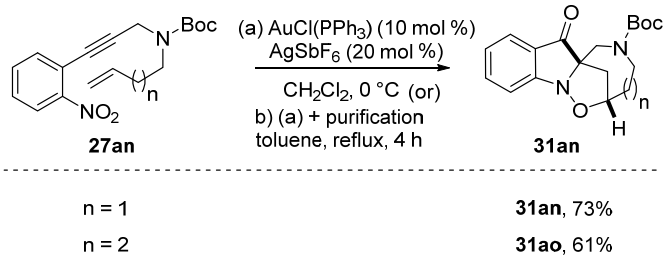


27ck **30ck**, 51% **31ck**, 22%

Scheme 10: The competing cyclization process

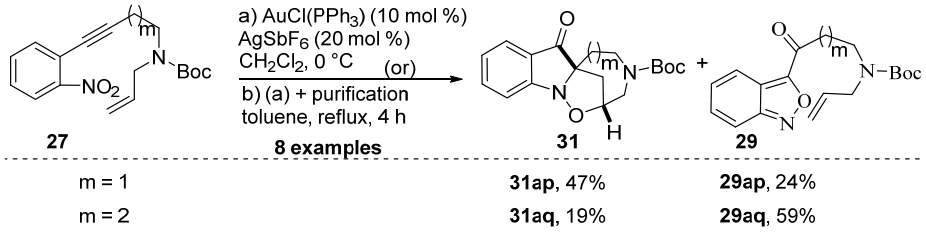
Subsequently, the synthesis of higher annulated ring systems has been explored by employing the substrates with differing chain length between the nitrogen and the alkyne/alkene units. First, the cycloisomerization of the substrates having variable number of intervening carbons between the nitrogen and alkene terminus was

verified. When n = 1, cycloisomerization and cycloaddition were spontaneous and the cycloaddition was *endo*-selective and led to the formation of the [4,2,1]-bridged bicyclic skeleton **31an**. On the other hand, when n = 2, the cycloaddition was not spontaneous; the obtained alkenyl isatogen had to be isolated and then subjected for the cycloaddition in refluxing toluene (Scheme 11). In this case too, the cycloaddition was completely *endo*-selective.



Scheme 11: Au-catalysed synthesis of higher annulated ring systems

Next were employed the substrates having a variable number of carbons between the nitrogen and alkyne termini, with the *N*-allyl unit kept consistent. When m = 1, the cycloisomerization was not selective and delivered the mixture of anthranil **29ap** and [4,2,1]-bridged bicyclic skeleton **31ap**. In case of the substrate where the m = 2, the selectivity of the cycloisomerization further dropped and also the cycloaddition had to be conducted separately with the isolated isatogen in refluxing toluene (Scheme 12).

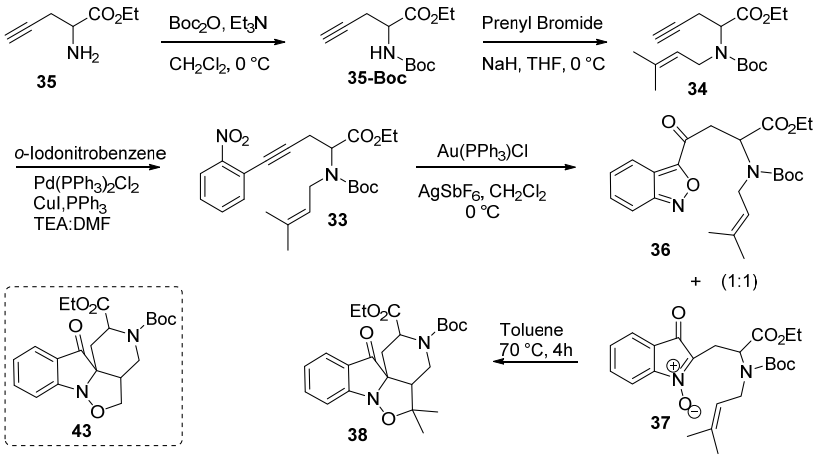


Scheme 12: Au-catalysed synthesis of higher annulated ring systems

Attempts towards the total synthesis of Austamide:

Having established the one-pot cycloisomerization-cycloaddition cascade and with the promising *endo*-selective cycloaddition with the substrates **27an** and **27ap**, the total synthesis of the Austamide was started. The work in this direction started with the preparation of propargylated ethyl glycinate **35** through the benzophenone Schiff's base by following literature reports. Protection of free amine with $(Boc)_2O$,

Et_3N followed by the alkylation with prenyl bromide by using NaH in THF at 0 °C produced enynamide **34** in 79% yield. Finally, the Sonogashira coupling of enynamide **34** with *o*-iodonitrobenzene delivered the key substrate **33** in 75% yield.



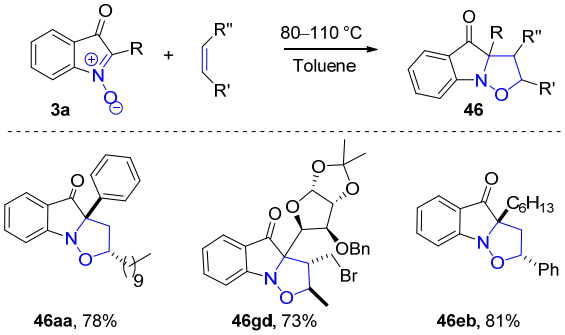
Scheme 13: Approach towards the synthesis of Austamide

This *o*-nitro enynamide **33** was treated with the $AuCl(PPh_3)\backslash AgSbF_6$ catalytic system in CH_2Cl_2 at 0 °C for 3 h and delivered a 1:1 mixture of anthranil **36** and alkenyl isatogen **37** (the cycloaddition was not spontaneous). The cycloaddition of the intermediate alkenyl isatogen **37** was carried out in toluene at 70 °C. Unfortunately, the resulted isoxazolidine **38** was found to have a fused bicyclic system resulting from the *exo*-selective cycloaddition. As a control, the cycloaddition of the corresponding *N*-allyl ynamide was also examined. Once again, the fused bicyclic compound **43** was obtained exclusively. It seems that the presence of carboxylate hinders the formation of the bridged bicyclic skeleton. These early failures with the intramolecular cycloaddition have warranted proceeding with the alternative intermolecular [3+2]-dipolar cycloaddition strategy.

C–C bond formation issue – Intermolecular [3+2]-Dipolar cycloaddition

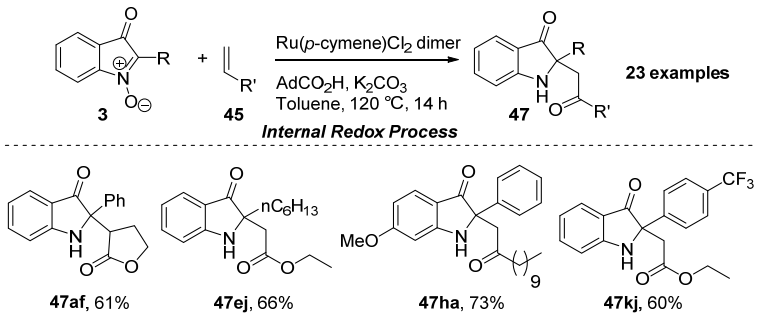
Our investigations in this context started with examining the regioselectivity of the projected intermolecular [3+2]-dipolar cycloaddition of isatogens with various olefins. Initial experiments on the cycloaddition of 2-phenyl isatogen **3a** and 1-dodecene **45a** revealed that the reaction proceeds smoothly in refluxing toluene in a sealed tube for 8 h and provides the isoxazolidine **46aa** in 78% yield. Further experiments on the cycloaddition of **3a** revealed that various other olefins, including the allyl bromide **45c**, were compatible under these conditions and the corresponding

cycloaddition products were obtained with good regio-/stereo selectivity. When 2-hexyl isatogen **3e** and 2-furanosyl isatogen **3g** were employed as the substrates, the thermal cycloaddition reaction was facile at 80 °C (Scheme 14). In case of the sugar isatogen **3g**, the cycloaddition resulted in a 20:1 regioselectivity.



Scheme 14: Thermal cycloaddition of isatogens and olefins

Having understood the reactivity/selectivity of the intermolecular cycloaddition employing the three representative isatogens, we next explored the possibility of a one-pot cycloaddition/cleavage of the N–O bond in the resulting isoxazolidine derivatives. Our initial experiments in this context employed the intermediate isoxazolidine as a substrate and examined various Ru-complexes. Interestingly, these experiments revealed that the nature of the products obtained depends upon the complex employed and also the additives present. And importantly, these early experiments indicated that the isoxazolidines **46** can be directly converted into the corresponding *β*-aminoketo derivative **47** which is unprecedented. Optimization of this reaction led to the identification of the exact conditions to convert **46** into the corresponding ketone **47**. Later, we realized that cycloaddition and internal redox can happen in one pot in a cascade fashion.



Scheme 15: Ru-mediated [3+2]-dipolar cycloaddition *cum* internal redox process

Next, the compatibility of various alkenes towards this cascade has been studied systematically. As shown in Scheme 15, this reaction proceeds smoothly with simple and electron rich olefins. In case of conjugated olefins such as butyl acrylate and ethylvinyl ketone, due to their self-oligomerization, the reaction results in a mixture of products and the separation of the desired product in pure form was found to be a difficult task. However, in case of methacrylate **45g**, two products resulting from the reductive N–O bond cleavage **48ag** and subsequent lactamization **48ag'** were obtained. Interestingly, when *N*-vinylpyrrolidinone was employed as the substrate, the substituted *N*-vinylpyrrolidinone was obtained exclusively. The formation of **49ap** revealed that the intermediate hemiaminal had undergone dehydration without any further oxidation. The scope of these transformations has been generalized by employing these alkenes and a broad range of isatogens. To our delight, the functional groups such as –Cl, –F and $–CF_3$ on either side of the aromatic rings are also compatible and furnished the corresponding pseudoindoxyl derivatives in moderate to good yields.

In conclusion, the selective functionalization of C2 of isatogen has been explored in inter and intramolecular fashion. Two complementary methods have been developed for the addition of indole to isatogen leading to the synthesis of either 2,2-disubstituted-*N*-hydroxy-indolin-3-one (**5**) or 2,2-disubstituted-indolin-3-one (**6**) by employing $InCl_3$ as a catalyst or reagent. The applicability of this method has been demonstrated by executing the total synthesis of 13-*deoxy* Isatisine A. Next, the Au-catalyzed cycloisomerization-cycloaddition cascade has been established for the construction of *spiro*-pseudoindoxyl skeletons such as the central tricyclic core of the Austamide. However, with the original substrate designed for the total synthesis of Austamide, the regioselectivity was undesired during this intramolecular cascade reaction, which led us to revise the strategy, opting for an intermolecular [3+2]-dipolar cycloaddition. As a part of this, the direct conversion of the isoxazolidine unit (resulting from the cycloaddition) to *β*-aminoketo derivatives has been developed by employing Ru-mediated N–O bond cleavage followed by the oxidation of the *in situ* generated alcohol.

CHAPTER I:

Synthesis and reactions of Isatogens

Introduction

The chemistry of the organic compounds having Zwitterionic octet/sextet structures, trivially known as 1,3-dipoles, has been known even back in the nineteenth century.[1] However, the fruitful application of these compounds in organic synthesis has been achieved only in the last few decades. A majority of the known 1,3-dipoles are constituted with the first row elements especially carbon, nitrogen and oxygen, with the nitrogen occupying the central place in more than 60% of the known 1,3-dipoles. These 1,3-dipoles can be represented as either an allyl-type or a propargyl/allenyl-type zwitterionic structures. There are a total of 18 second-row 1,3-dipoles in which 12 are allyl type and 6 are propargyl type. The delocalization of the negative or positive charges on to any terminus of a 1,3-dipole is possible.

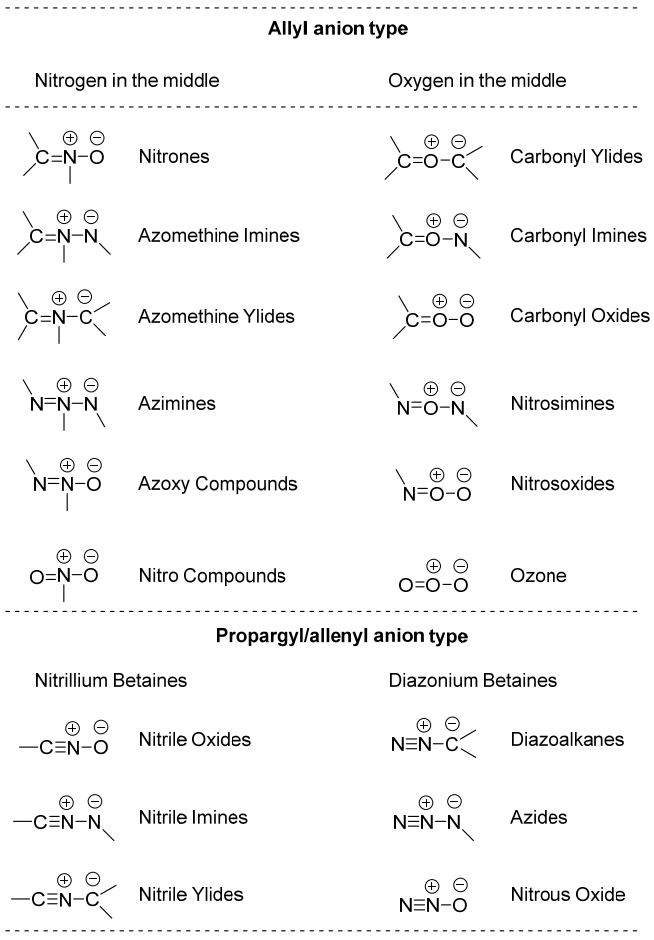


Figure 1: Classification of the 1,3-dipoles

However, it is influenced by the nature of the connected atoms and their electronic preferences. The termini of a 1,3-dipole can be treated as both nucleophilic

and/or electrophilic. Thus they can display reactivity with both nucleophiles and electrophiles.[2] However, one of the most important reactions of these 1,3-dipoles is the cycloaddition that bears their name – 1,3-dipolar cycloaddition. Figure 1 provides known dipoles of the first row.

Nitrone is one of earliest reported 1,3-dipoles. Beckmann was the first to observe the nitrones as by-products in the alkylation of oximes and a first report documenting its cycloaddition appeared in 1890.[3] Quite interestingly, in 1881, during the course of his classic research on indigo, Baeyer reported the first member of an interesting class of compounds trivially known as isatogens (isatin + gen) which are the cyclic version of these nitrones and are isomeric to isatin.[4] Ethyl isatogenate was synthesized by Bayer by the cycloisomerization of *o*-nitrophenylpropiolates by the treatment of cold concentrated sulphuric acid. Later, Pfeiffer and Ruggli have explored this class of compounds systematically and provided some important methodologies for their synthesis.[5] The isatogens are 3-oxo-3H-indole 1-oxides which are unnatural scaffolds and are characterized by the presence of both nitrone and keto units. The structure of the isatogen is shown below along with its three canonical forms (Figure 2).

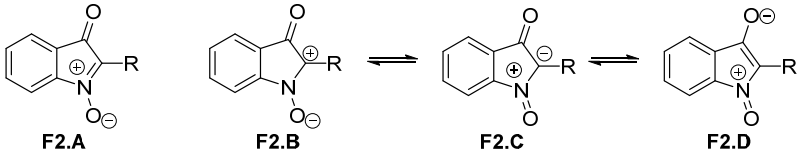
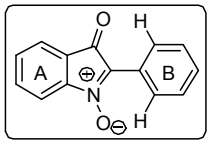


Figure 2: Canonical forms of isatogens

The first canonical structure shows the possibility of the addition of nucleophiles and dipolarophiles, whereas the back polarization represented in the second form is well known in cyclic nitrone and aromatic N-oxides. Coming to the characteristic features of isatogens, in the IR spectra, the strong absorption at 1700-1720 cm^{-1} is characteristic of conjugated carbonyl groups in the five membered ring compounds. A band at 1175 cm^{-1} has been assigned to the N–O stretching vibrations. In the NMR spectra, isatogens are characterized by the four protons in ring A having the equivalent values, because of the similar effects of carbonyl and nitrone groups. For example, 2-arylisatogens having the four protons of ring **A** form as multiplet whereas the ortho protons of ring **B** are more deshielded by the carbonyl and nitrone groups.

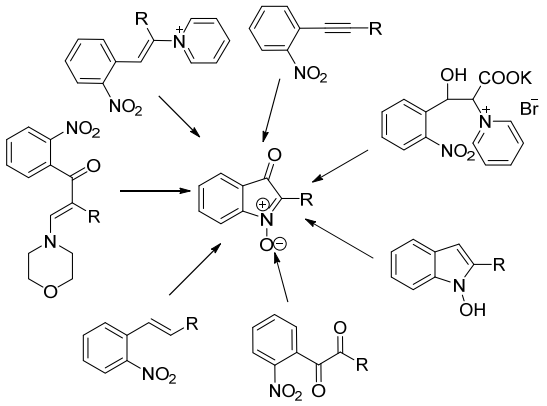


1.1 Biological properties of isatogens:

Coming to the biological activity, 2-aryl isatogens inhibits the uptake of phosphate, glutamate and calcium ions into mitochondria. Whereas, 2-phenyl carbamoylisatogen (R = CONHPh) behaves as a classical uncoupling agent and releases the inhibition of ATP synthesis caused by the 2-phenylisatogen and oligomycin. Isatogens can form spin trap adducts with hydroxyl and superoxide radicals and these are the inhibitors of ROS mediated cell death.[6]

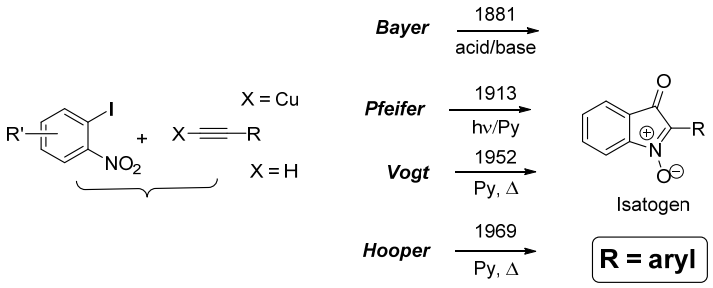
1.2 General synthesis of isatogens:

Mainly two methods have been reported in literature for the syntheses of isatogens, i) oxidation of a 1-hydroxy-2-substituted indole which is applicable to both alkyl and aryl substituted isatogens but requires multiple steps for the preparation of the starting material;[7] ii) involves the intramolecular cyclization of an *ortho*-substituted nitrobenzene but is limited to the synthesis of 2-arylisatogens. Recent developments include the use of metal mediated cycloisomerization of *o*-nitroalkyne benzene derivatives for the synthesis of isatogens. A brief account of the reported methods for the synthesis of isatogens has been described below (Scheme 1).[8]



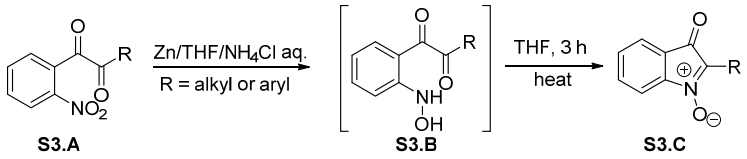
Scheme 1: Available approaches for synthesis of isatogens

Amongst these, the inaugural synthesis of isatogens was reported by Baeyer in 1881 of *o*-nitro propiolates using cold conc. H_2SO_4.[4] The synthesis includes the base-mediated cycloisomerization of *o*-nitroalkyne derivatives under sunlight and pyridine,[9] refluxing the compound in neat pyridine[10] and treatment of *o*-nitroalkyne with nitroso benzene in chloroform at room temperature (Scheme 2).[11]



Scheme 2: Nitroalkyne cycloisomerization based methods for the synthesis of 2-arylisatogens

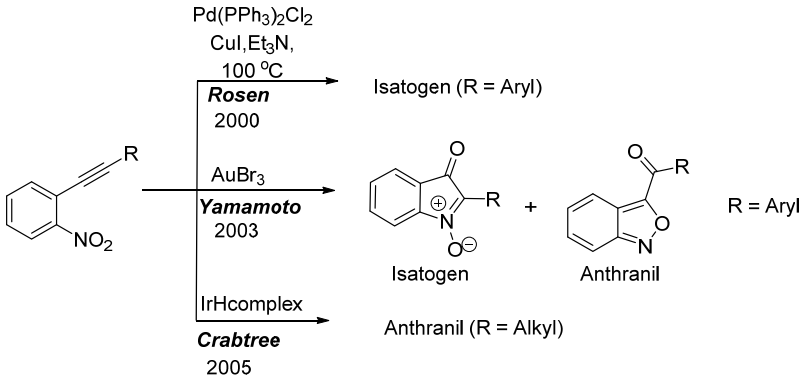
Another method for the synthesis of isatogens involves the reductive cyclization of 2-nitrobenzyl **S3.A** to give the intermediate hydroxyl amino compound **S3.B** which is further heated for 3 h in THF.[12] Though this method is multi-step in nature and requires harsh conditions, this is the only method that can be adopted for the synthesis of both aryl as well as alkyl substituted isatogens **S3.C** (Scheme 3).



Scheme 3: Reductive cyclization of 2-nitrobenzyl for the synthesis of isatogens

1.3 Metal-catalyzed nitroalkyne cycloisomerization:

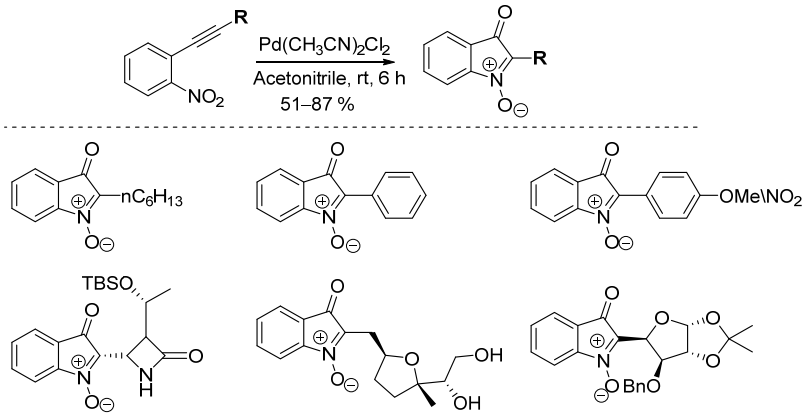
Recent advances in the nitroalkyne cycloisomerization involve the utilization of the mild conditions such as a gold(III)bromide[13] or an iridium hydride complex.[14]



Scheme 4: Transition metal catalyzed nitroalkyne cycloisomerization

However, the outcome of the cyclization is dictated by the nature of the alkyne substituent: *o*-(arylalkynyl)nitrobenzenes, for instance, were seen to give a mixture of isatogen and anthranil in the presence of catalytic amounts of gold(III) bromide. On the other hand, anthranils were formed exclusively from *o*-(alkylalkynyl) nitrobenzenes in the presence of either gold(III)bromide or an iridium hydride complex (Scheme 4).

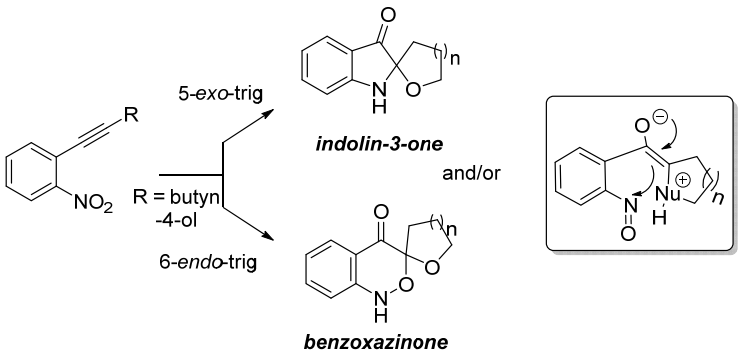
In 2010, we documented a general, mild and substituent independent method for the synthesis of isatogen by [Pd]-catalyzed nitroalkyne cycloisomerization. We have also studied in detail the mechanistic aspects by density functional theory (DFT) and reasoned that the formation of α-oxo metal carbenoids occurs by the 5-*exo* mode of cyclization of the nitro group on the alkyne, which subsequently undergoes $6e^-$ electro cyclization to isatogen. We have executed this method for the synthesis of alkyl- as well as aryl-isatogens and successfully explored the reaction to diverse range of substrates having different C2-substituents such as β-lactams, sugar and with different protecting groups (Scheme 5).[15]



Scheme 5: Pd-catalyzed nitroalkyne cycloisomerization

After successful demonstration of the [Pd]-mediated nitroalkyne cycloisomerization for the synthesis of isatogens, we further explored the reaction by placing the nucleophile intramolecularly. We hypothesized that the presence of the internal nucleophile in the cycloisomerization will lead to the formation of *N*-hydroxy *spiro*-indolin-3-one and/or *spiro*-benzoxazinone. For this, we have chosen the 6-(2-nitrophenyl)hex-5-yn-1-ol as a model substrate and subjected it to the Pd(II) and Au(III) catalysts in acetonitrile. We observed the formation of the *spiro*-indolin-3-one

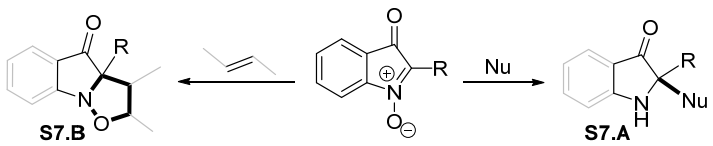
as the sole product in the case of $Pd(CH_3CN)_2Cl_2$, whereas *spiro*-benzoxazinone was obtained as the major product and anthranil derivative as the minor product in the case of $AuBr_3$. The diversity in the product formation is mainly due to the mode of cyclization involved in the reaction. When Pd-catalyst was employed, the reaction likely proceeded through the 5-*exo* dig mode of cyclization to form the indolin-3-one derivative, whereas when Au-catalyst was employed, the reaction took the 6-*endo* dig mode of cyclization and formed the benzoxazinone derivative (Scheme 6).[16]



Scheme 6: Transition metal catalyzed *o*-nitroalkynol cycloisomerization

1.4. Reactions of isatogens:

Coming to the chemical reactivity of isatogens, these are characterized by the presence of nitrone and ketone functionalities. Isatogens undergo photochemical reactions to form the rearranged products and are also susceptible to various reducing agents. Isatogens undergo nucleophilic additions at the C2- and C3-positions, forming 2,2-disubstituted indolin-3-one and tertiary alcohol skeletons. They are known to undergo [3+2]-dipolar cycloadditions with dipolarophiles to obtain the isoxazolidine derivatives. On the whole, functionalization at the C2-position of isatogens either by nucleophilic addition or by cycloaddition generates the synthetically demanding 2,2-disubstituted 1,2-dihydro-3H-indolin-3-one (trivially known as pseudoindoxyl) skeletons having the quaternary (stereogenic) center at the C2-position (Scheme 7).

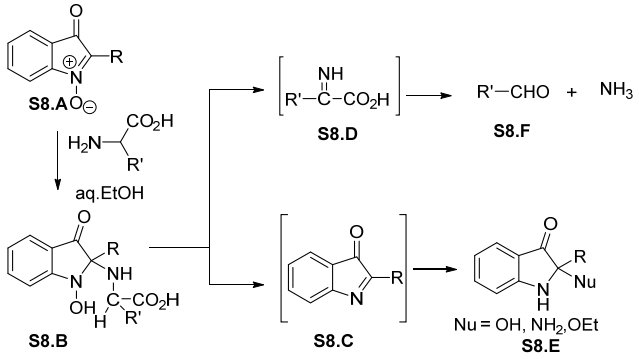


Scheme 7: Reactions of isatogens

1.4.1. Nucleophilic additions on isatogens:

1.4.1.1. Addition of heteroatom centered nucleophiles:

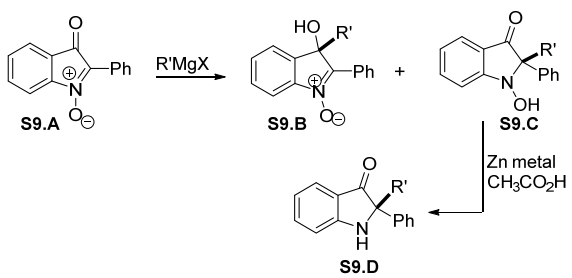
The reactivity of isatogens as well as their biological activity was studied systematically by the group of Hooper. Isatogen was subjected to the nucleophilic addition in ethanol with the weak nucleophiles such as amino acids that formed the corresponding adducts at the C2-position. The formed adduct decomposed to the indolone **S8.C** and α-imino carboxylic acid **S8.D**. Indol-3-one rapidly reacts with either ethanol or water and forms the corresponding adducts **S8.E** (Nu = OEt, OH) (Scheme 8).[17]



Scheme 8: Heteroatom centered nucleophilic addition

1.4.1.2. Addition of carbon centered nucleophiles:

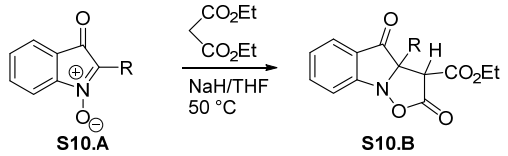
In 1975, Marchetti and co-workers have synthesized the aminoxyls by the application of organometallic reagents on isatogens. Grignard reagents as well as the organolithium reagents react with isatogens **S9.A** leading to the formation of C3- and C2- addition products, which are, respectively, a 3°-alcohol **S9.B** and N–OH **S9.C**. The regioselectivity is poor and the product distribution depends on the Grignard reagent used and to some extent on the reaction medium.



Scheme 9: Grignard addition on the isatogen

On the other hand, the addition of benzyl and *tert*-butyl Grignard reagents to the isatogen affords the 2-benzyl-(or *tert*-butyl)-2-phenyl-1,2-dihydro-3*H*-indol-3-ones as the exclusive product. They proposed the single electron-transfer mechanism to account for this divergence in product formation.The reduction of C2-attacked hydroxylamine with Zn provides the requisite 2,2-disubstituted pseudoindoxyl derivatives **S9.D** (Scheme 9).[18]

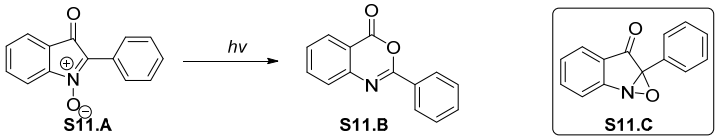
Greci and co-workers reported the addition of the diethyl malonate anion to the C2-position of the isatogen yielding the intermediate N-oxide that subsequently undergoes cyclization and forms the isoxazolidone **S10.B** (Scheme 10).[19]



Scheme 10: Carbon centered nucleophilic addition

1.4.2. Photochemical rearrangement of isatogens:

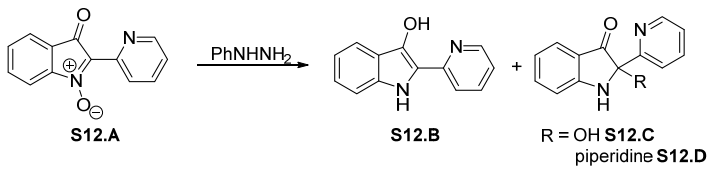
The photochemical behavior of the 2-phenylisatogen was studied by Eckroth's group. The irradiation of 2-phenyl isatogen **S11.A** in various solvents with a Hanovia 450tv high pressure immersion lamp (no filter) for 1–2 h gave the 2-phenyl-4H-3,l-benzoxazin-4-one **S11.B**. The progress of the reaction and yield of the product formed are solvent dependent. The reaction proceeds in better yield with non-polar solvents, probably indicating a diradical mechanism in operation (Scheme 11).[20]



Scheme 11: Photochemical isomerisation of isatogens

1.4.3. Reductions of isatogens:

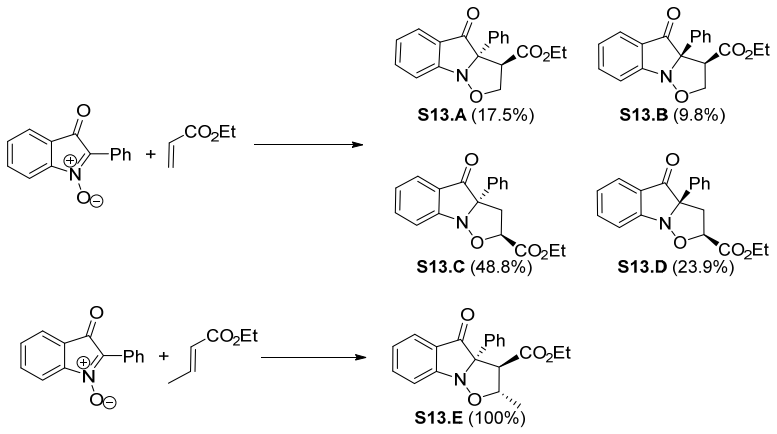
Inspired by the *in vitro* anti-bacterial activity of 2,2'-pyridylisatogen, Wibberley and co-workers have synthesized its derivatives by the reduction of isatogen. The reduction of 2,2'-pyridylisatogen **S12.A** with phenyl hydrazine yielded the 2,2'-pyridyl indoxyl **S12.B** and indolone hydrate **S12.C**. The structure of indolone hydrate has been proposed from its similarity with that of the piperidine adduct of indolone **S12.D** (Scheme 12).[21]



Scheme 12: Reduction of isatogen with phenyl hydrazine

1.4.4. [3+2]-Dipolar cycloadditions with the isatogens:

In 2001, Greci and co-workers have revealed the dipolar cycloaddition of isatogen with alkenes and verified the regio- as well as the diastereoselectivity. The cycloaddition of 2-phenylisatogen with ethyl acrylate was found to be non-selective and delivered all the four possible isomers **S13.A-D**. On the other hand, with ethyl crotonate or ethyl cinnamate having the *trans*-configuration, the cycloaddition reaction proceeded with complete regio- and stereoselectivity and provided a single product, where the newly formed C–C bond is at the α-position to the carboxylate group and has a *trans-trans* relative stereochemistry on the oxazolidine ring **S13.E**. *ab initio* calculations have revealed that the product distribution may be influenced by kinetic rather than thermo chemical factors (Scheme 13).[22]



Scheme 13: [3+2]-Dipolar cycloaddition of isatogens with dipolarophiles

Thus, a close examination of literature on the synthetic utility of isatogens has revealed that there are very few reports on the intermolecular functionalization of isatogens either by nucleophilic addition or by dipolar cycloaddition and the potential of these compounds *en route* to the synthesis of pseudoindoxyl skeletons has not yet been explored. The major limitations associated with isatogens were their synthesis, on the one hand, and the poor regioselectivity in intermolecular reactions on the other. Quite interestingly, the intramolecular functionalization of isatogens has never been

attempted, despite the fact that it can provide *spiro*-pseudoindoxyl skeletons rapidly. Considering these factors, we have started a program on developing the practical methods for the synthesis of isatogens and their subsequent functionalization to address the total synthesis of the pseudoindoxyl class of natural products.[23] Pseudoindoxyl natural products are one of the subgroups present in the widely distributed indole class of alkaloids and are characterized by the presence of a 2,2-disubstituted indolin-3-one substructure. The structural complexity and the diverse biological activities reported for these pseudoindoxyl class of natural products has attracted the attention of synthetic chemists for a long time and various methods have been successfully developed for constructing this core and some of them have found applicability in the total synthesis. Quite interestingly, despite the fact that the isatogen nucleus displays an immediate and isolable synthon in constructing this core, as mentioned above, there has not been a single report so far on the use of isatogens in total synthesis, until our group had entered in this area. In the following sections of this chapter, some of the important methods that have been developed for the synthesis of pseudoindoxyl skeletons especially in the context of natural products synthesis will be discussed briefly in chronological order.

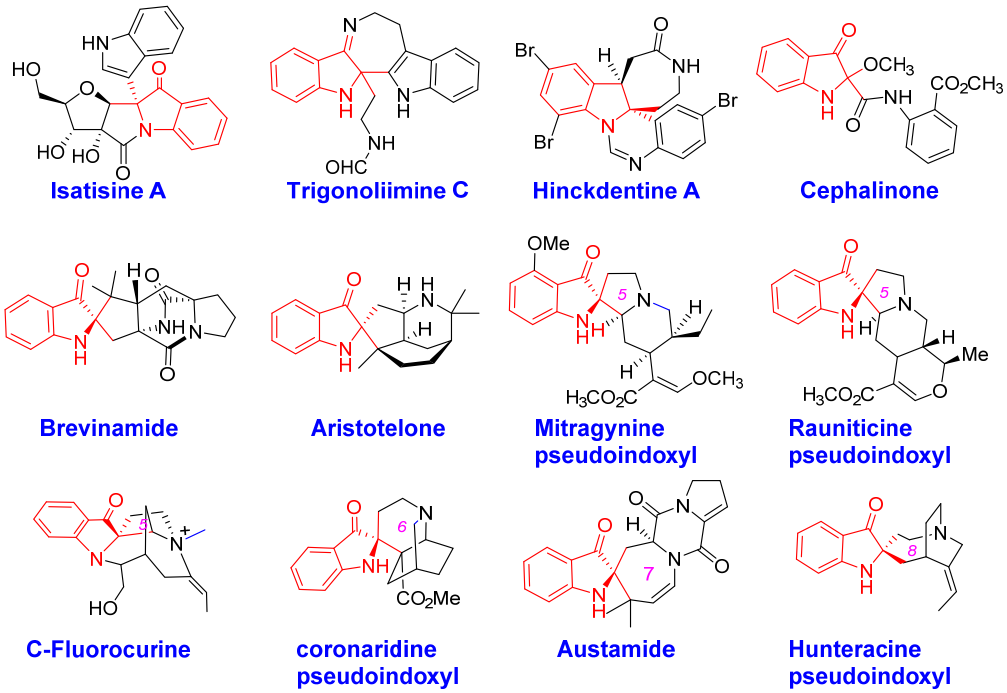


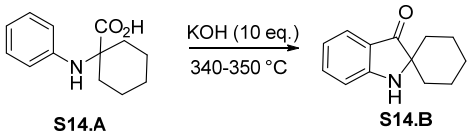
Figure 3: Representative pseudoindoxyl natural products

The pseudoindoxyl natural products are characterized by the presence of complex molecular architectures with the central 2,2-disubstituted or (2,2)-*spiro*-pseudoindoxyl skeletons having the carbogenic and heterogenic *spiro*-cycles with varying ring sizes from 5 to 8 and also possessing significant biological properties. The challenging structural features and prominent biological properties of these natural products have attracted the synthetic community towards engineering new methods for forging this skeleton. Figure 3 presents some of the important natural products of this class.[24] Coming to the synthesis of these complex frameworks, the only method employed for the construction of central 2,2-disubstituted or (2,2)-*spiro*-pseudoindoxyl skeletons is limited mainly to the oxidative rearrangement of the corresponding indole compounds.

1.5. Approaches for the synthesis of 2,2-disubstituted pseudoindoxyl skeletons:

1.5.1. Condensation method:

In 1928, Plant and co-workers synthesized the *spiro*-pseudoindoxyl cyclohexane from the l-anilino-1-cyclohexane carboxylic acid **S14.A**.[25] The mixture of carboxylic acid and KOH were heated at 340–350 °C for 30 min to obtain the *spiro*-pseudoindoxyl compound **S14.B** in 13 % yield (Scheme 14).

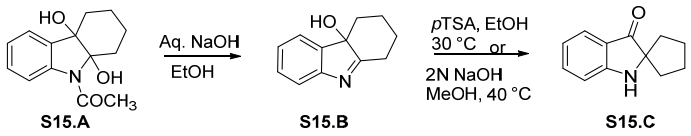


S14.A S14.B

Scheme 14: The synthesis of pseudoindoxyl derivatives

1.5.2. Rearrangement of dihydroxy carbazole:

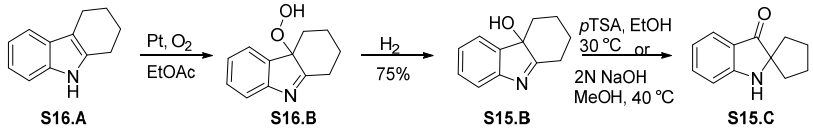
In 1950, Witkop and co-workers have documented the first examples of the synthesis of *spiro*-pseudoindoxyl skeletons involving the acid catalyzed rearrangement of 2,3-disubstituted-3H-indol-3-ol derivatives.[26] Thus the deacetylation of the 9-acetyl-10,11-dihydroxy carbazole **S15.A** and subsequent acid- or base-catalyzed rearrangement of the intermediate indol-3-ol **S15.B** led to the formation of the *spiro*-pseudoindoxyl skeleton **S15.C** (Scheme 15).



Scheme 15: Rearrangement of dihydroxycarbazole derivative

1.5.3. Oxidative rearrangement:

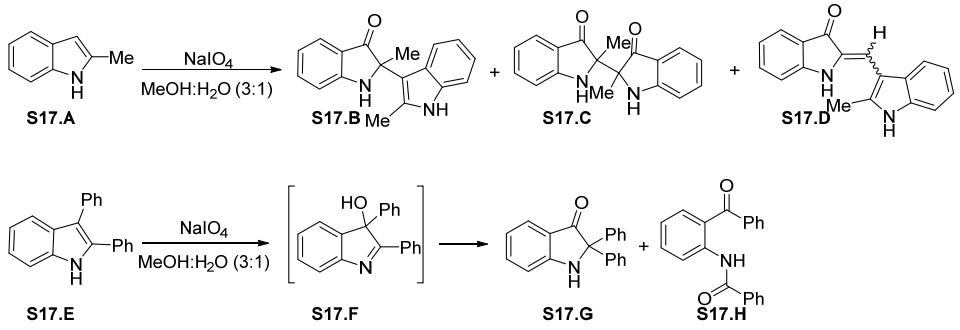
Later, in 1952, the same group documented the oxidative rearrangement of tetrahydrocarbazoles.[27] The catalytic oxidation of tetrahydrocarbazole **S16.A** on the platinum catalyst in ethyl acetate, followed by the subsequent hydrogenation of the intermediate peroxide **S16.B** provided the 11-hydroxytetrahydrocarbazolenine **S15.B**, which, upon acid or base mediated rearrangement, gave the *spiro*-[cyclopentane-1,2'-indolin]-3'-one **S15.C** (Scheme 16).



Scheme 16: Oxidative rearrangement of tetrahydrocarbazole

1.5.4. Oxidation of indole derivatives with $NaIO_4$:

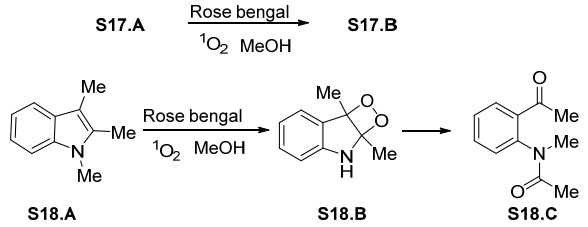
In 1970, Dolby and co-workers reported the peroxidation of indole derivatives.[28] The treatment of 2-methyl indole with $NaIO_4$ in a 3:1 ratio of methanol and water delivered the indoxyl dimers **S17.B**, **S17.C** and **S17.D** in 39%, 33% and 4% yield respectively; whereas the oxidation of 2,3-diphenyl indole **S17.E** produced the 2,2-diphenyl indoxyl **S17.G** and the *o*-benzamido benzophenone **S17.H**, with the intermediate 3-hydroxy-2,3-diphenyl indolenin **S17.F** in 8% and 42% yield respectively (Scheme 17).



Scheme 17: Oxidation of the indole derivative with $NaIO_4$

1.5.5. Oxidation of indole derivatives with singlet oxygen:

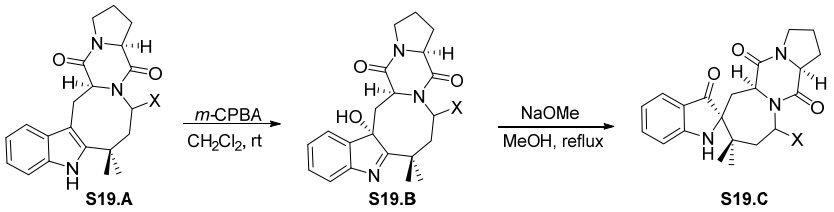
In 1972, Matsuura and co-workers have disclosed the indole oxidation employing singlet oxygen.[29] The 2-methylindole, when subjected to irradiation in the presence of the rose-bengal in methanol, led to the indoxyl dimer being obtained in quantitative yield. On the other hand, under the same conditions, 1,2,3-trimethylindole **S18.A** gave the acetophenone **S18.C** exclusively (Scheme 18).



Scheme 18: Oxidation of indole derivative with singlet oxygen

1.5.6. Kishi's method:

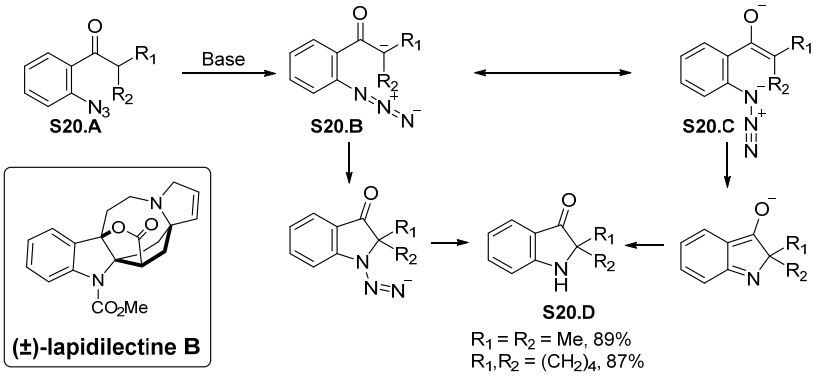
In 1978, Kishi and co-workers documented the total synthesis of austamide A employing a two step strategy for installing the (2,2)-*spiro*-pseudoindoxyl scaffold at the final stage.[30] The carbazole derivative **S19.A** was subjected to oxidation with *m*-CPBA to provide the intermediate 3H-indol-3-ol **S19.B**, which subsequently underwent pinacol-like rearrangement when refluxed with NaOMe to furnish the (2,2)-*spiro*-pseudoindoxyl skeleton **S19.C** in 53% overall yield (Scheme 19).



Scheme 19: Oxidation followed by the pinacol-like rearrangement

1.5.7. Smalley cyclization:

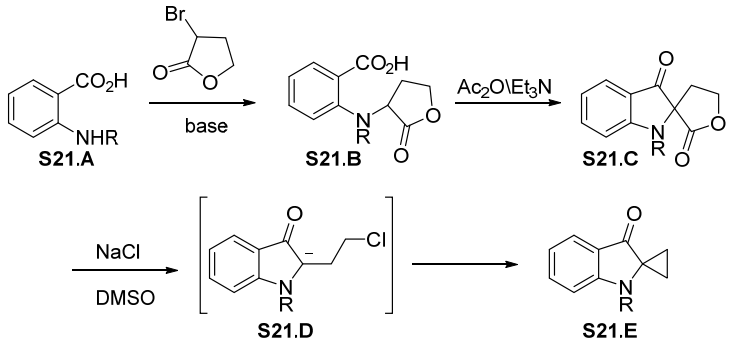
In 1979, Smalley and co-workers reported the base induced cyclization of *o*-azidophenyl alkyl ketone **S20.A** at room temperature for the formation of 2,2-dialkylindoxyls or (2,2)-*spiro*-pseudoindoxyl skeletons **S20.D** in high yield.[31] Later, in 2001, Pearson's group employed this cyclization in the total synthesis of lapidilectine B (Scheme 20).[32]



Scheme 20: Smalley cyclization of *o*-azidophenyl alkyl ketones

1.5.8. Spiroannulation:

In 1981, Kawada and co-workers documented a three step protocol for the synthesis of *spiro*-cycloalkyl pseudoindoxyl skeleton from the anthranilic acid. The condensation of anthranilic acid **S21.A** with *α*-bromo-*γ*-butyrolactone in the presence of a base followed by the *spiro*-annulation with acetic anhydride and triethylamine provided the *spiro*-lactone derivative **S21.C**. The decarboxylation of lactone in the presence of NaCl in DMSO gave the *sprio*-cyclopropane pseudoindoxyl skeleton **S21.E** (Scheme 21).[33]



Scheme 21: Synthesis of the *spiro*-cyclopropane pseudoindoxyl skeleton

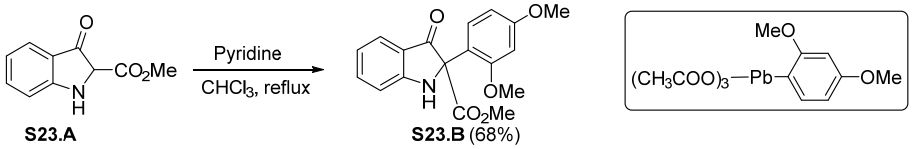
1.5.9. Oxidation of indole derivatives with *N*-chlorobenzotriazole:

In 1982, Greci and co-workers reported the chlorination of indole derivatives with *N*-chlorobenzotriazole (NCBT).[34] The treatment of 2-phenyl indole **S22.A** with NCBT in methanol or aqueous acetonitrile gave the 3-chloro derivative **S22.B** and the dimeric indoxyl product **S22.C** in 64% and 22% yields respectively (Scheme 22).

Scheme 22: Oxidation of indole derivative with *N*-chloro benzotriazole

1.5.10. Arylation of 3-indolinones with aryllead triacetate:

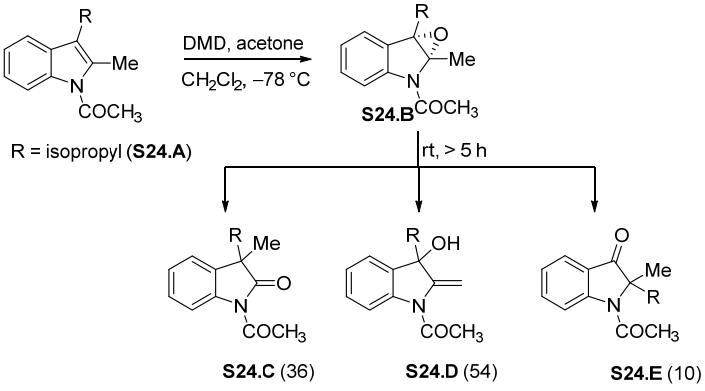
In 1992, Mérour and co-workers furnished the C-arylation of *N*-protected *β*-ketoester **S23.A** with aryllead (IV) triacetates. The 2-alkoxycarbonyl-3-oxo-2,3-dihydroindole was refluxed with the 2,4-dimethoxyphenyllead triacetate in $CHC1_3$ and pyridine for 5 h to obtain the methyl 2-(2,4-dimethoxyphenyl)-3-oxoindoline-2-carboxylate **S23.B** (Scheme 23).[35]



Scheme 23: Arylation of oxindole with the aryllead(IV) triacetate reagent

1.5.11. Oxidation of indole derivatives with dimethyldioxirane:

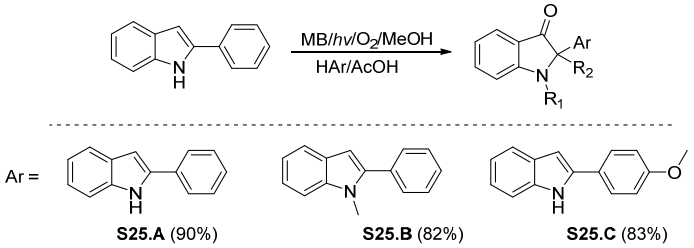
In 1993, Foote and co-workers have developed a method for the oxidation of the indole derivative with dimethyldioxiranes (DMDO).[36] Treatment of the indole derivative **S24.A** with DMDO in acetone and CH_2Cl_2 at –78 °C produced the intermediate epoxide derivative **S24.B**. When this reached the room temperature, it delivered the three products **S24.C**, **S24.D** and **S24.E** (Scheme 24).



Scheme 24: Oxidation of indole derivative with DMDO

1.5.12. Singlet oxygenation of 2-aryl indoles:

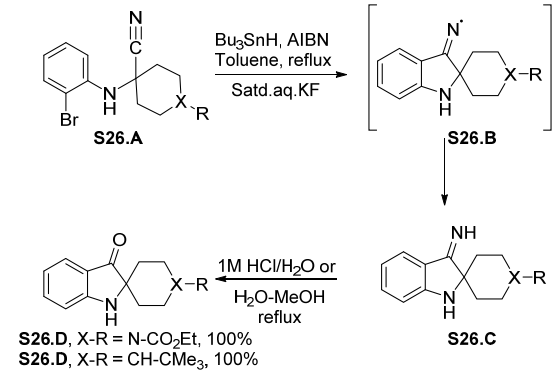
In 1996, Quing have attempted a two step protocol involving singlet oxygenation followed by acid-catalyzed nucleophilic substitution of the 2-arylindoles for the synthesis of 2,2-diaryl-1,2-dihydro-3H-indol-3-one.[37] The reaction was performed by the irradiation of 2-arylindole, methylene blue and pyridine in methanol with a 1000 W tungsten halogen lamp operated at 180 V through a cutoff light filter under oxygen bubbling at 20 °C for 1.5–2 h. Subsequently, acetic acid and aryl nucleophiles were added to the mixture and refluxed for 1–2 h to synthesize the 2,2-diaryl-1,2-dihydro-3H-indol-3-ones (Scheme 25).



Scheme 25: Singlet oxygenation followed by the nucleophilic addition

1.5.13. Radical cyclization:

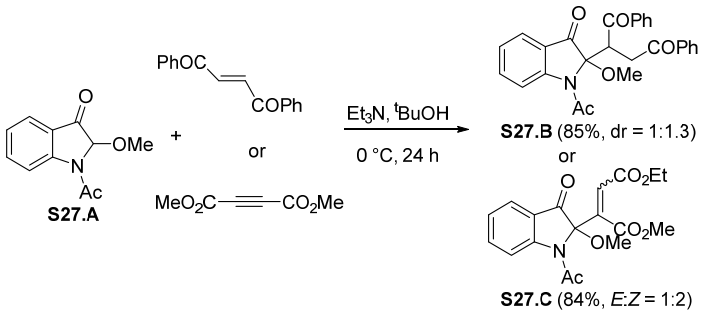
In 1999, Sulsky and co-workers have designed a radical cyclization of anilinonitrile **S26.A** to synthesize the *spiro*-indoxyl skeletons. The reaction involved the generation of the aryl radical, which underwent 5-*exo*-dig cyclization followed by reduction to form the *spiro*-pseudoindoxyl imine derivative **S26.C**. Subsequent hydrolysis of the imine provided the desired *spiro*-pseudoindoxyl skeleton **S26.D** in good yield (Scheme 26).[38]



Scheme 26: Radical cyclization for the synthesis of *spiro*-indoxyl skeletons

1.5.14. Michael addition of oxindoles:

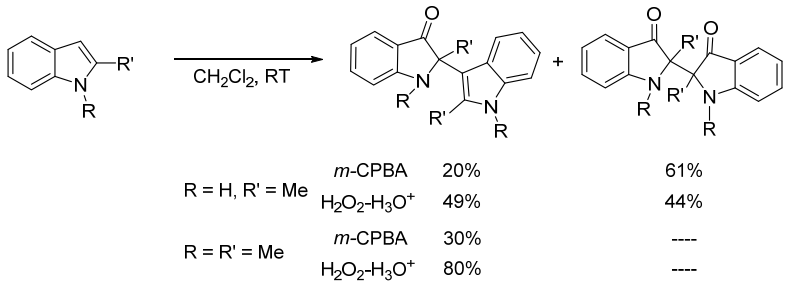
In 1999, Sakamoto and co-workers have developed a Michael addition strategy for the functionalization of indol-3-one with α,β-unsaturated carbonyl compounds.[39] Thus, the treatment of 1-acetyl-1,2-dihydro-3H-indol-3-one **S27.A** with diphenylbutene dione or dimethyl but-2-ynedioate in the presence of triethylamine in *t*-butanol at 0 °C for 24 h provided the indolinones **S27.B** and **S27.C** in good yields (Scheme 27).



Scheme 27: Michael addition of oxindole to ethylenic and acetylenic carbonyl compounds

1.5.15. Oxidation of indole derivatives with *m*-CPBA and H_2O_2:

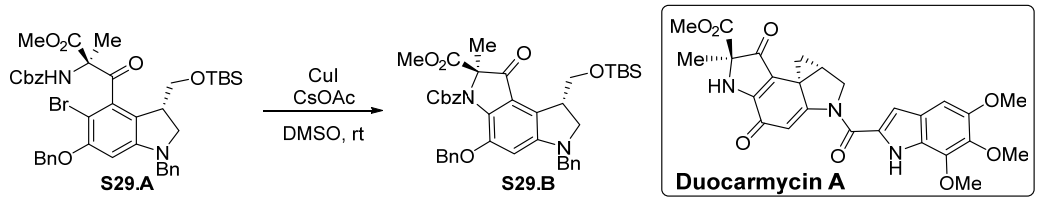
In 2001, Greci and co-workers demonstrated the oxidation of indole derivatives with different oxidizing agents.[40] When 2-methyl indole was subjected to the oxidation with either *m*-CPBA or H_2O_2 it delivered the mixture of dimeric indole derivatives, whereas the reaction of 1,2-dimethylindole on oxidation with either *m*-CPBA or H_2O_2 produced dimer as the sole product (Scheme 28).



Scheme 28: Oxidation of indole derivative with *m*-CPBA and H_2O_2

1.5.16. Fukuyama's indolin-3-one synthesis:

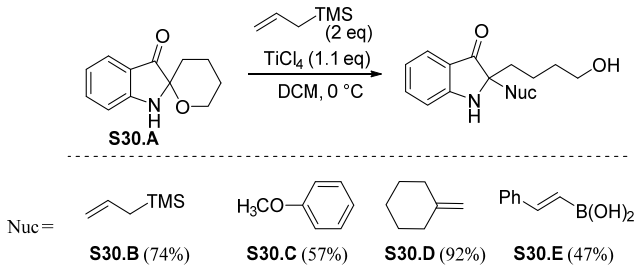
In 2003, Fukuyama and co-workers indigenously developed the CuI catalyzed intramolecular amination, which was a key step in the total synthesis of the Duocarmycin A.[41] The treatment of the amide derivative **S29.A** with CuI and excess CsOAc in DMSO at room temperature led to the 2,2-disubstituted indolin-3-one **S29.B** in quantitative yield (Scheme 29).



Scheme 29: CuI-catalyzed 2,2-disubstituted indolin-3-one synthesis

1.5.17. Activation followed by the alkylation on N,O-Acetals:

In 2007, Kobayashi and co-workers have disclosed the oxidation of 2-substituted indole followed by Lewis acid catalyzed alkylation to access a variety of 2,2-disubstituted indolin-3-ones. Stable masked indolone was synthesized by the multi-oxidation of 2-(hydroxylalkyl)indoles using *m*-CPBA (Scheme 30).



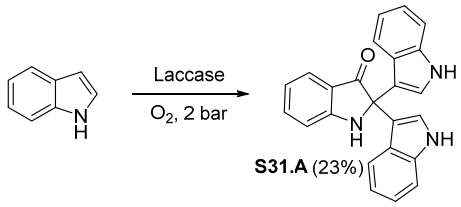
Scheme 30: $TiCl_4$ mediated alkylation of *spiro*-indolin-3-one

The obtained *spiro-N,O*-ketal **S30.A** was treated with different nucleophiles (allyltrimethylsilane **S30.B**, Fridel–Craft's reaction with anisole **S30.C**, aza-prins reaction with alkene **S30.D** and petasis condensation with boronic acid **S30.E**) in the presence of a Lewis acid to obtain a variety of 2,2-disubstituted indolin-3-ones in good yields.[42]

1.5.18. Trimerization of indoles:

In 2008, Iacazio and co-workers have synthesized the 2,2-bis(3'-indolyl)-indoxyl **S31.A**, which is a natural compound isolated from the bacterial source. Indole

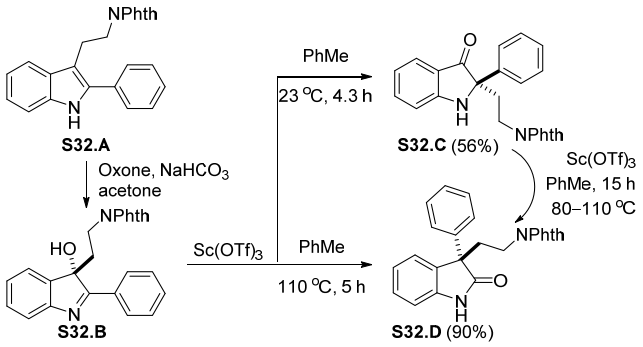
subjected to the Laccase enzyme under O_2 with 2 bar pressure forms the trimerized indole compound.[43] Later, the indole oxidative trimerization has been documented by employing simple oxidants such as TEMPO in air, $NaNO_2$ in pyridine; and $CuCl_2$ and TEMPO (Scheme 31).[44]



Scheme 31: Trimerization of indole

1.5.19. $Sc(OTf)_3$-Catalyzed oxidative rearrangement of indolin-3-ols:

In 2008, Movassaghi and co-workers have introduced $Sc(OTf)_3$ as a catalyst for the rearrangement of indolin-3-ols to prepare either C3- or C2-oxindoles. The 2-phenyltryptamine **S32.A** was subjected to oxidation by oxone and $NaHCO_3$ in acetone followed by a stereoselective rearrangement with $Sc(OTf)_3$ in toluene to provide the 3-oxindole **S32.C** at 23 °C and 2-oxindole **S32.D** at 110 °C (Scheme 32).[45]

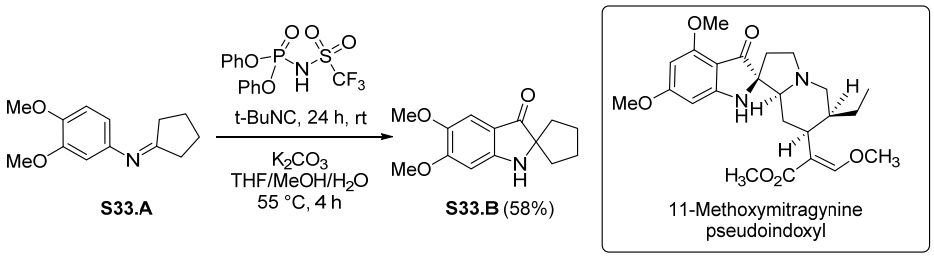


Scheme 32: Oxidative rearrangement of 2-aryl tryptamine with $Sc(OTf)_3$

1.5.20. Sorensen's interrupted Ugi reaction:

In 2009, Sorensen and co-workers reported a novel method for the synthesis of pseudoindoxyl skeletons that comprises of an interrupted Ugi reaction and the Houben–Hoesch cyclization.[46] The treatment of electron rich and sterically hindered imine **S33.A** with an isocyanide in the presence of a strong Bronsted acid gave directly the pseudoindoxyl imine which was subjected for base hydrolysis to provide the corresponding indoxyl **S33.B** in high yields. This methodology has been

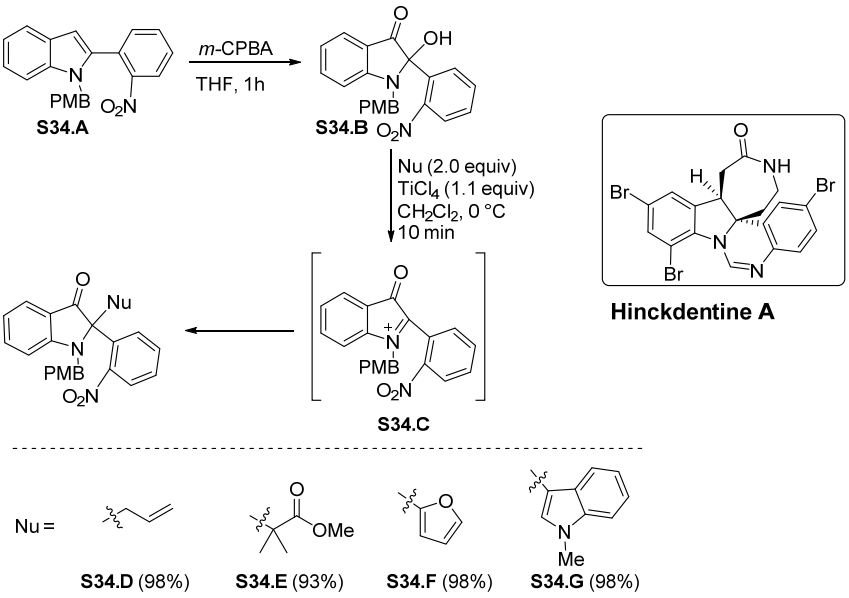
employed as a key step in the total synthesis of the 11-Methoxymitragynine pseudoindoxyl natural product (Scheme 33).



Scheme 33: Interrupted Ugi reaction on the electron rich imines

1.5.21. Mannich type reaction:

In 2010, Kawasaki and co-workers have developed a two-step protocol for the synthesis of pseudoindoxyls comprising the oxidative rearrangement of 2-substituted indoles followed by the Mannich reaction with the carbon nucleophiles (Scheme 34).

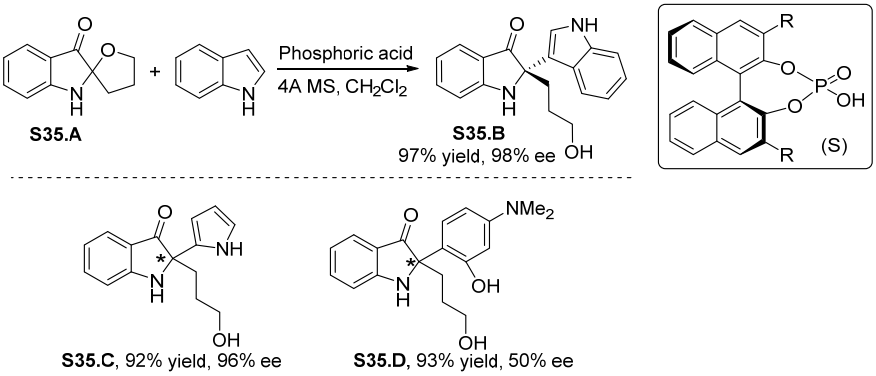


Scheme 34: Oxidation followed by the nucleophilic addition

Thus, the oxidation of 2-aryl indole **S34.A** with *m*-CPBA oxidation followed by the Mannich reaction of the resulting 2-hydroxy-1,2-dihydro-3H-indol-3-one **S34.B** with various carbon nucleophiles (such as allyl boronic ester, silylketenacetal, furan and *N*-Me indole) produced the 2,2-disubstituted indolin-3-one **S34.D**. This methodology has been successfully employed in the total synthesis of the marine bryozoan alkaloid Hinckdentine A.[47]

1.5.22. Chiral phosphoric acid-catalysed Friedel–Crafts alkylation reaction of indoles:

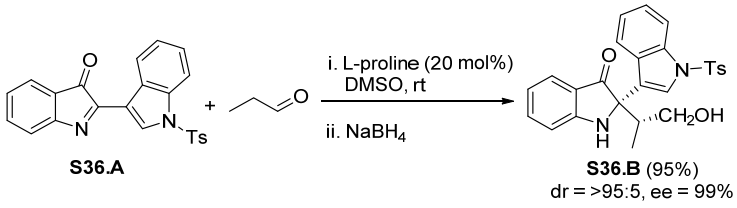
In 2011, You and co-workers have reported a method with the racemic *spiro*-*N*,*O*-acetals using the chiral phosphoric acid.[48] The Friedel–Crafts alkylation reaction of indoles, pyrrole and 3-(dimethylamino)phenol with racemic *spiro*-indolin-3-one **S35.A** was catalysed by the chiral phosphoric acid to obtain the 2,2-disubstituted indolin-3-ones **S35.B** having a quaternary stereocenter with upto 99% yield and 99% *ee* (Scheme 35).



Scheme 35: The chiral phosphoric acid catalyzed addition of indole to *spiro*-indolin-3-one

1.5.23. Enantioselective asymmetric Mannich reaction:

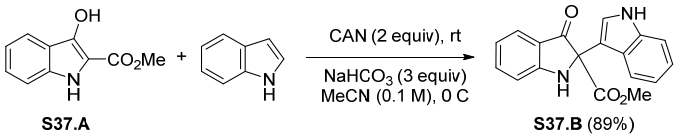
In 2011, Xie and co-workers have developed a proline catalyzed enantioselective asymmetric Mannich reaction of ketimine with aldehyde for the creation of the chiral quaternary center.[49] For example, the treatment of 2,3'-biindol-3-one **S36.A** with acetaldehyde in the presence of *L*-proline in DMF followed by the $NaBH_4$ reduction gave the 2,2-disubstituted indolin-3-one **S36.B** in excellent yield and enantioselectivities (Scheme 36).



Scheme 36: The proline-catalyzed Mannich reaction of indolones

1.5.24. Oxidative coupling of indoles with 3-oxindoles:

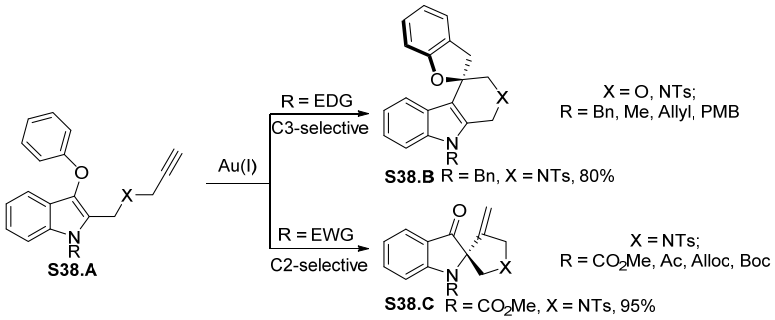
In 2011, Baran and co-workers employed the oxidative coupling method for combining 3-oxindoles with indoles.[50] The 3-oxindole-2-carboxylate **S37.A** was oxidized with CAN in presence of an indole and $NaHCO_3$ in acetonitrile at room temperature to obtain the pseudoindoxyl **S37.B** bearing a carboxy group at the C2-position (Scheme 37).



Scheme 37: Oxidative coupling with oxindoles

1.5.25. Gold-catalyzed annulations:

In 2011, Tu and co-workers have developed the *N*-protecting group dependent gold-catalyzed regiodivergent annulation of alkynylindoles. The treatment of 3-phenoxy alkynylindole **S38.A** having an electron-donating group on the nitrogen with the Au(I) catalyst in CH_2Cl_2 at room temperature gave the tetrahydro-*β*-carboline **S38.B**, whereas 3-phenoxy alkynyl indole having an electron-withdrawing group produces the *spiro*-pseudoindoxyl derivative **S38.C** (Scheme 38).[51]

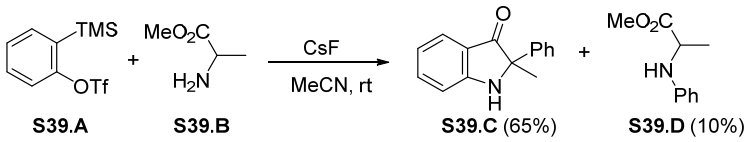


Scheme 38: Regiodivergent annulation of *N*-protected alkynylindoles

1.5.26. Reaction of arynes with the amino acid ester:

In 2011, Okamura and co-workers reported a novel methodology for the synthesis of pseudoindoxyls comprising of the cycloaddition of amino acid methyl esters with benzyne. For example, the treatment of 2-(trimethylsilyl)phenyl triflate **S39.A** with CsF in the presence of L-alanine methyl ester **S39.B** in acetonitrile at

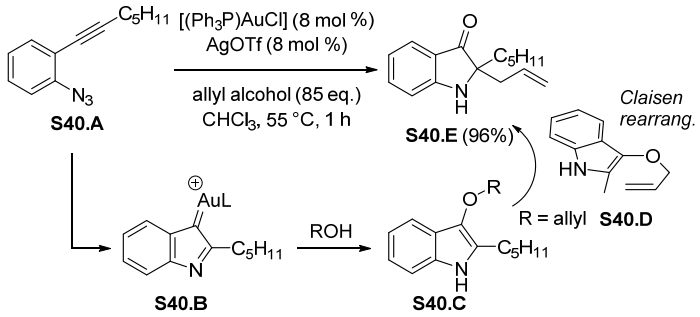
room temperature gave 2-methyl 2-phenylindolin-3-one **S39.C** in 65% yields (Scheme 39).[52]



Scheme 39: Cycloaddition of benzyne and the substituted amino acid

1.5.27. 2-Alkynyl arylazides to the pseudoindoxyl frameworks:

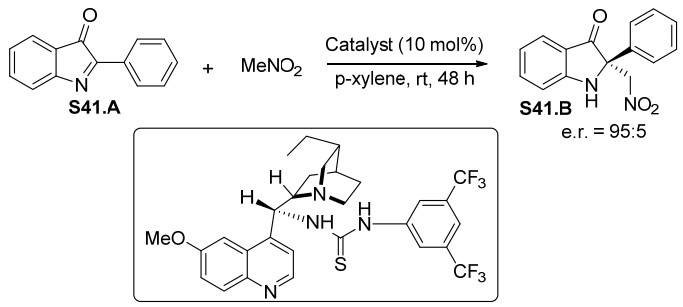
In 2011, Gagosz and co-workers utilized gold(I)-catalysis for the synthesis of indolin-3-ones from the 2-alkynyl arylazides.[53] When Au(I) was employed on 2-alkynyl arylazides **S40.A**, it formed the *α*-imino gold carbene **S40.B**, which was subsequently trapped with alcohol to deliver the indole derivative **S40.C**. If the alcohol has the possibility to undergo Claisen rearrangement then it forms the 2,2-disubstituted pseudoindoxyl derivative **S40.E**, otherwise it forms the 3-substituted indole derivative **S40.D** (R = Et, 99% yield). The diversity in the product formation depends on the nucleophile involved in the reaction (Scheme 40).



Scheme 40: Gold-catalyzed synthesis of pseudoindoxyl derivatives

1.5.28. Enantioselective aza-Henry reaction:

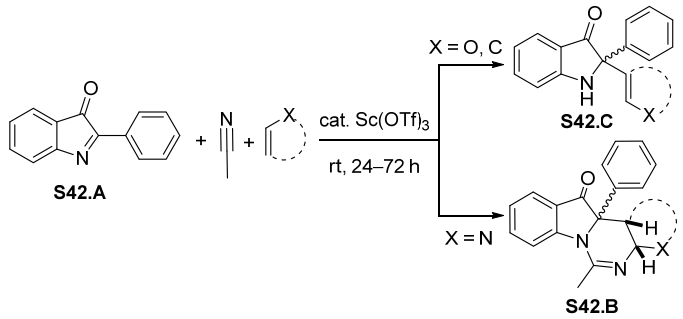
In 2012, Alemán and co-workers have disclosed the enantioselective aza-Henry reaction of cyclic *α*-carbonyl ketimines under bifunctional catalysis. The reaction involved the addition of nitromethane to 2-phenyl-3H-indol-3-one **S41.A** in *p*-xylene by using the thiourea catalyst. The 2,2-disubstituted indol-3-one **S41.B** was obtained in 90% yield with excellent enantioselectivity (Scheme 41).[54]



Scheme 41: Enantioselective Aza-Henry reaction of indolones

1.5.29. Multicomponent Mannich-Ritter transformation:

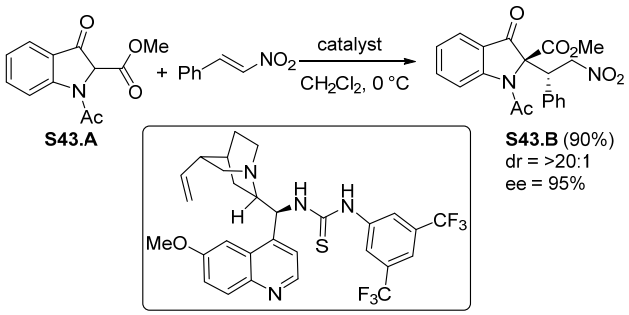
In 2012, Lavilla and co-workers documented the Lewis acid catalyzed multicomponent Mannich-Ritter reaction on 3-indolone.[55] The product diversity was shown to be dependent on the alkene partner employed in the reaction. The treatment of 2-phenyl indolone with dihydropyran and nitrile in the presence of 20 mol% $Sc(OTf)_3$ at room temperature provided the MCR adduct **S42.B**, whereas in case of vinylamine derivatives, the 2,2-disubstituted pseudoindoxyl skeleton **S42.A** was obtained (Scheme 42).



Scheme 42: Multi-component Mannich-Ritter transformation of indolones

1.5.30. Organocatalytic asymmetric Michael addition of oxindoles:

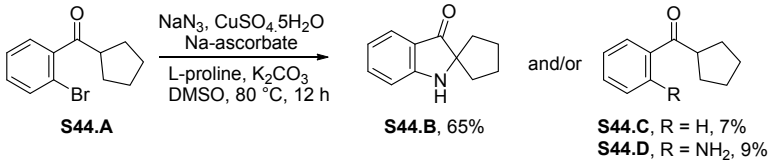
In 2012, Xu and co-workers has developed the organocatalytic version of the Michael addition of oxindoles to nitroolefin using a bi-functional thiourea-catalyst.[56] The treatment of methyl 1-acetyl-3-oxo indolin-2-carboxylate with *β*-nitrostyrene in the presence of 10 mol % of thiourea catalyst in CH_2Cl_2 at 0 °C afforded the 2,2-disubstituted indolin-3-one derivatives with a chiral quaternary stereocenter in high yield and with excellent stereoselectivity (Scheme 43).



Scheme 43: Organocatalytic Michael addition of oxindole on to nitroolefins

1.5.31. S_NAr *cum* Smalley cyclization:

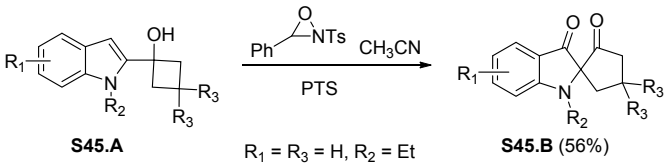
In 2013, our group established a simple protocol composed of the sequential S_NAr reaction followed by Smalley cyclization.[57] This transformation utilized the catalytic Cu(I)-ascorbate redox system for the conversion of the α-bromophenyl derivative **S44.A** to the α-azidophenyl derivative by S_NAr. In the same conditions, the base induced enolate addition to azide takes place to afford either the 2,2-disubstituted or (2,2)-*spiro*-pseudoindoxyl derivative **S44.B** (Scheme 44).



Scheme 44: Sequential S_NAr and Smalley cyclization of α-bromophenyl derivatives

1.5.32. Oxidative dearomatization/semipinacol rearrangement:

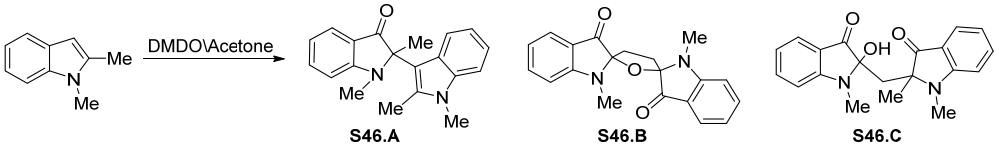
In 2013, Zhang and co-workers developed a cascade consisting of oxidative dearomatization and semipinacol rearrangement of indol-2-yl cyclobutanol for the synthesis of the (2,2)-*spiro*-pseudoindoxyl skeleton.[58] The oxidation of indol-2-yl cyclobutanol **S45.A** with *N*-sulfonyl oxaziridine in acetonitrile at room temperature gave the dearomatized intermediate, which underwent semipinacol rearrangement in the presence of PTS.H_2O to provide the 2-*spiro*-cyclo-3-oxindole **S45.B** (Scheme 45).



Scheme 45: Oxidative dearomatization followed by the semipinacol rearrangement

1.5.33. Oxidation of indole derivatives with DMDO:

In 2013, Rodríguez and co-workers has re-examined the oxidation of indole derivatives with dimethyldioxirane.[59] The treatment of 1,2-dimethyl indole with DMDO in acetone delivered the dimeric products **S46.A**, **S46.B** and **S46.C** in the ratio 34%, 26% and 22%, along with some minor compounds (Scheme 46).



Scheme 46: Oxidation of indole derivative with DMDO

CHAPTER II:

Total synthesis of 13-*deoxy* Isatisine A

SECTION A

[In]-mediated C3-alkylation of Indoles with Isatogens

2.1. Isolation and structural elucidation of Isatisine A:

Isatisine A was isolated by Chen and co-workers in 2007 from the leaves of *Isatis indigotica Fort* (Cruciferae).[24t] It is a biennial herbaceous plant species widely distributed and cultivated in Anhui province, China. "Ban-Lan-Gen" and "Da-Qing-Ye" are the commercial trade names in Chinese for the roots and leaves of *I. indigotica* (Figure 4). These have been used as a traditional Chinese medicine for the treatment of viral diseases including influenza, viral pneumonia, mumps, and hepatitis for several centuries in China. Due to promising biological activity and the generation of diverse structures, *I. indigotica* has become an attractive source for the research community. In search of anti-HIV active compounds, the leaves of this plant have been analyzed. These investigations have rendered a unique alkaloid; its structure was elucidated through extensive spectroscopic analyses and single crystal X-ray crystallography.

Figure 4: (a) Leaves of *Isatis Indigotica* Fort; (b) Commercial Ban-Lan-Gen Tea

The isolation process was carried out by refluxing the 50 kg air-dried and powdered leaves in 80% EtOH for 2 h. Evaporation and extraction provided 120 g of the crude. This was chromatographed on silica gel and eight fractions of this crude were collected. Repetitive column chromatography of a promising fraction provided 64 mg of compound **1** (Figure 2), This was obtained as yellow needle crystals and showed the optical rotation of $[\alpha]_D^{25}$= –283.15 (*c* 0.46, MeOH). As the structural characterization of this compound through the 1D and 2D NMR spectra data turned out to be a difficult proposition, it was established with the help of the single crystal X-ray analysis which confirmed this compound **1** as shown in Figure 5, revealing an unique alkaloid skeleton isolated for the first from *I. indigotica* and, interestingly, with an acetonide group. However, a comparison of the original EtOAc fraction with

that of authentic compound **1** using TLC and HPLC techniques suggested that compound **1** was an artifact resulting during the purification process. Finally, the acid-hydrolysis of compound **1** afforded Isatisine A (**2**, $C_{22}H_{18}N_2O_6$). The relative stereochemistry of Isatisine A at C-2, 9, 10, 12, and 13 has been established as R*, S*, R*, S*, and S*.

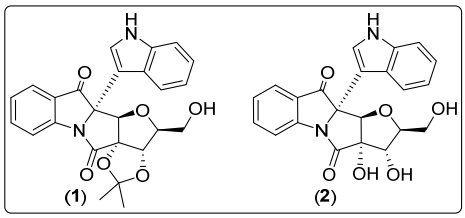


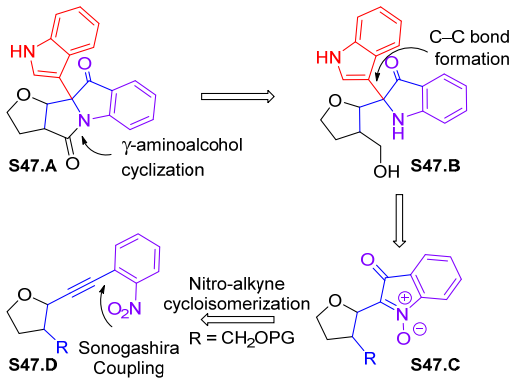
Figure 5: Proposed structures of the Isatisine A and its acetonide

Coming to the structural features, Isatisine A is an unprecedented fused tetracyclic framework with five contiguous stereocenters, among which two are fully substituted. Isatisine A comprises of a densely functionalized tetrahydrofuran core and indolin-3-one units connected through a C-anomeric linkage at the C2 position of the indolin-3-one; an amide bridge between the C2 of furanose and nitrogen of the indolinone forms the central bridging γ-lactam ring. There has an indole unit as a substituent at the C2 position of indolinone connected with its C3. Coming to its biological activity, its acetonide derivative, which is formed as an artifact during the isolation, was found to exhibit cytotoxicity against C8166 with CC_{50} = 302 μM and anti-HIV-1activity of EC_{50} = 37.8 μM.

2.2. Retrosynthetic disconnections:

Intrigued by the promising biological activities and the challenging structural features of Isatisine A, a project aiming at its total synthesis has been taken up immediately after its isolation. As shown in Scheme 47, our intended strategy features the construction of the central tetracyclic core of the Isatisine A featuring four late stage transformations that address the key C–C and C–N formations.[60] There are namely – i. the dehydrogenative cyclization of a γ-aminoalcohol to construct the central lactam ring (using Rh/Ru); ii. the addition of indole to isatogen (Lewis Acid?); iii. the nitro-alkyne cycloisomerization to construct the isatogen nucleus (metal?) and iv. Sonogashira coupling for synthesizing the key nitroalkyne (Pd). Out of these four key reactions, two of them are characterized with a flexibility window to alter the

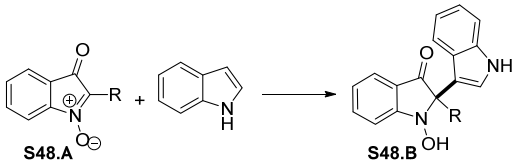
functional groups on either of the indole rings. The first one is the Sonogashira coupling and the second one is the addition of indole to isatogen. We have intended to develop catalytic methods for the two key reactions – nitroalkyne cycloisomerization and the subsequent addition of indole to this isatogen.



Scheme 47: Retrosynthetic disconnections for the central tetracyclic core

2.3. Construction of central 2,2-disubstituted indolin-3-one skeleton:

One of the bottlenecks that we have realized immediately after starting this program was the metal-catalyzed nitroalkyne cycloisomerization. As we discussed in the Introduction, these cyclizations are suitable only for the synthesis of 2-arylisatogens. This problem has been solved by one of our group members, who developed a practical and general method for the synthesis of isatogens by employing Pd-complexes.[15] In parallel, the next problem, *i.e.*, the C–C bond formation between the C3 of indole and the C2 of isatogen has been taken up.



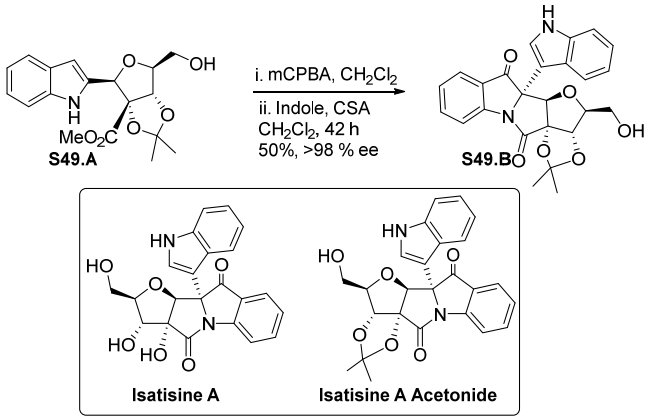
Scheme 48: Key C-C bond formation for the synthesis of central indolin-3-one

The objective of this chapter was to develop the methods for the regioselective addition of nucleophile at the C2-position of isatogen **S48.A**, leading to the synthesis of 2,2-disubstituted indolin-3-one **S48.B** (Scheme 48) and explore its applicability in the total synthesis of Isatisine A. As has been revealed earlier, the addition of nucleophiles to isatogens is non-regioselective and takes place at the C2 as well as the C3-positions and that there was no single report on the addition of indole to isatogens.

Before we completed our synthesis of 13-*deoxy* Isatisine A as a model for the total synthesis of Isatisine A, Kerr, followed by Panek's group reported the total synthesis of *ent*-Isatisine A and established its absolute configuration. Following this, the Jiang group reported the total synthesis of naturally occurring Isatisine A. Following our model synthesis, there have been another two total syntheses - one from our group and another from Xie's group. Below, is a short description about how the construction of the central indolin-3-one skeleton has been addressed by these four groups.

2.3.1. Kerr approach:

In 2010, Kerr and co-workers documented the first total synthesis of (+)-Isatisine A and revised its absolute configuration. The central tetracyclic core was synthesized by the oxidation of the indole derivative **S49.A** using *m*-CPBA in CH_2Cl_2 to form the 2-hydroxy indolin-3-one. This was subjected to the indole addition with the camphor sulphonic acid in CH_2Cl_2 for 42 h to obtain **S49.B** in 50 % yield with >98% *ee* (Scheme 49). Finally, the acetonide group was deprotected to complete the total synthesis of *ent*-Isatisine A.[61]

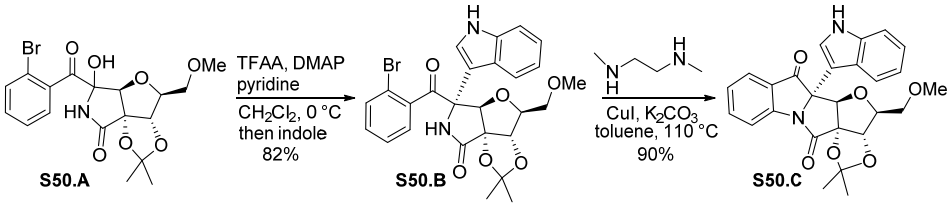


Scheme 49: Kerr approach for the central core and the revised structures of Isatisine A

2.3.2. Panek approach:

Immediately after Kerr's report, Panek and co-workers also reported the total synthesis of (+)-Isatisine A. The central core was constructed by converting aminal **S50.A** to the easily leaving acetate derivative using the TFAA\DMAP\pyridine followed by the addition of indole in CH_2Cl_2 at 0 °C. This furnished the indole adduct

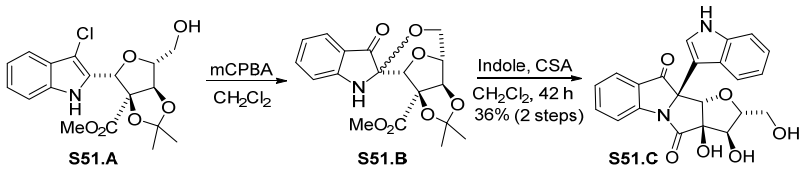
S50.B in 82% yield. This was subjected for the CuI-mediated modified Buchwald amidation in toluene at 110 °C to afford the central tetracyclic skeleton **S50.C** of Isatisine A in 90% yield (Scheme 50).[62]



Scheme 50: Panek approach for the central core of Isatisine A

2.3.3. Liang approach:

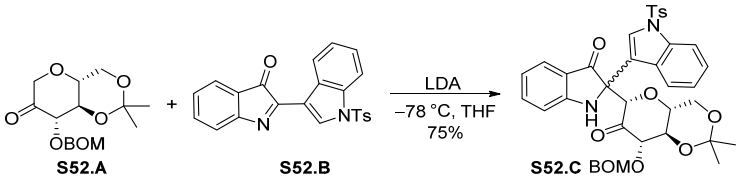
In 2011, Liang and co-workers have synthesized the naturally occurring Isatisine A. The central tetracyclic framework was constructed by following relatively the same procedure as followed by the Kerr group. Oxidation of the indole derivative **S51.A** followed by addition of indole with camphor sulphonic acid provided the central core of Isatisine A **S51.C** in 36% yield over 2 steps (Scheme 51).[63]



Scheme 51: Liang approach for the central core of Isatisine A

2.3.4. Xie approach:

In 2012, Xie and co-workers have documented the biomimetic synthesis of Isatisine A, which was exemplified as a short sequence. The central tetracyclic core of Isatisine A **S52.C** was devised by the nucleophilic addition of the ketone compound **S52.A** to the indolone unit **S52.B** (Scheme 52).[64]



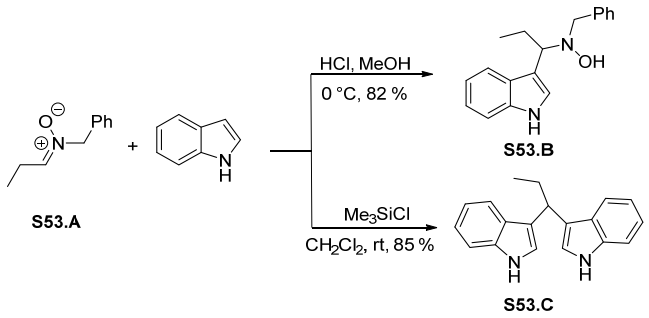
Scheme 52: Xie approach for the central core of Isatisine A

2.4. C-C bond formation reaction:

Our studies in this direction started with addressing the key issue of the addition of indole to isatogen. Although there is no report for the addition of indole to isatogen in the literature, there are two reports where the addition of indole to nitrone was documented using either Bronsted acid or microwave conditions.

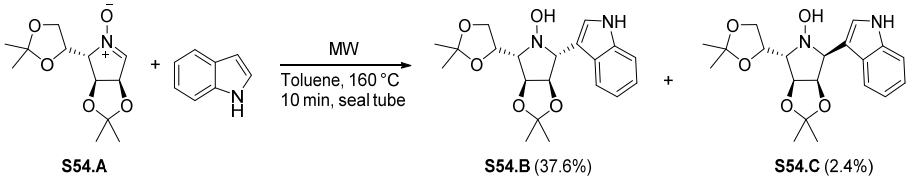
2.4.1 Addition of indole to nitrone:

In 1997, Valiée and co-workers have reported the Friedel-Crafts type reaction of nitrone **S53.A** on indole to synthesize either indolyl *N*-hydroxylamine or symmetrical diindolyl alkanes depending on the reagent used. When the reaction was performed with methanolic HCl in CH_2Cl_2 at 0 °C, it formed the indolyl *N*-hydroxyl amines **S53.B** in 82% yield. On the other hand, in the case of Me_3SiCl in CH_2Cl_2, symmetrical diindolylalkane **S53.C** was obtained in 85% yield (Scheme 53).[65]



Scheme 53: Friedel-Crafts type addition of indole to the nitrone

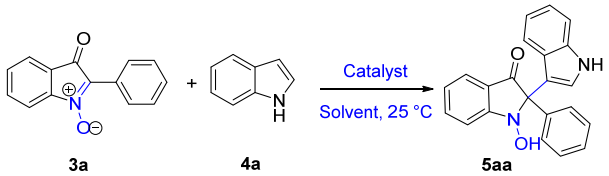
In 2011, Li and co-workers documented an advanced method for the addition of pyrrole/indole to nitrones (Scheme 54). The reaction of furanose nitrone **S54.A** and indole was carried out under the microwave irradiation in toluene and in a sealed tube at 160 °C to obtain the 2`,3`-*trans*-isomer **S54.B** in predominant quantities over 2`,3`-*cis*-isomer **S54.C**. The dominance in product distribution is presumably because of the favorable *exo*-attack.[66]



Scheme 54: Microwave assisted indole addition to nitrone

As a whole, the addition of indole to nitrones has been reported under harsh reaction conditions. Considering the fact that the substrate that we will be employing in the total synthesis of Isatisine A is going to carry sensitive functional/protecting groups, we have been forced to identify mild catalyst/conditions for the addition of indole to isatogen to make it compatible in the planned total synthesis. Our investigations in this regard began with the finding of a suitable catalyst for the addition of indole **4a** to 2-phenyl isatogen **3a** in acetonitrile and employed 20 mol% catalyst. Table 1 succinctly describes our exploratory experiments with different Lewis acids such as $Sc(OTf)_3$, Ag(OTf), $Zn(OTf)_2$ and $FeCl_3$ in CH_3CN solvent. In all the cases, the reactions were found to be sluggish even after 24 h. A similar trend was noticed when camphor sulphonic acid (CSA) was employed as the catalyst. In case of $InCl_3$, the reaction was completed in 3 h and provided the *N*-hydroxy indolin-3-one **5aa** in 68% yield, which guided the identification of $InCl_3$ as the catalyst of choice in this regard and acetonitrile as the suitable solvent. When $InCl_3.4H_2O$ and $In(OTf)_3$ were employed as catalysts, the reaction was slow in the former case (incomplete even after 48 h) whereas, in the latter case, the reaction was completed within 4 h and provided the hydroxylamine **5aa** in yields comparable with that of the $InCl_3$ mediated reaction.[67]

Table 1: Optimization of the reaction with different Lewis acids



3a **4a** **5aa**

entry	catalyst	time (h)	yield %
1	$Sc(OTf)_3$	24	34
2	Ag(OTf)	19	33
3	$Zn(OTf)_2$	20	39
4	CSA	42	41
5	$FeCl_3$	15	31
6	**$InCl_3$**	**3**	**68**
7	$In(OTf)_3$	4	49
8	$InCl_3.4H_2O$	48	--

The optimized conditions involve the treatment of 2-phenyl isatogen (**3a**, 1 eq.) and indole (**4a**, 1 eq.) in CH_3CN with $InCl_3$ (20 mol%) under argon atmosphere at 25 °C for 3 h to provide the *N*-hydroxyindolin-3-one derivative **5aa** in 68% yields. The melting point of compound **5aa** is 265–267 °C and is characterized by the analytical techniques such as the NMR and Mass spectrometry. Compound **5aa** was scanned in 3:2 mixture of methanol-d_4 and $CDCl_3$ solvents because of the poor solubility of the compound in the $CDCl_3$ alone. Two ortho protons (nitrone) in the 8.61–8.66 ppm region of compound **3a** were absent in the ^{1}H-NMR spectra of compound **5aa** and shifted to upfield, which demonstrated that the reaction has taken place at the nitrone end. The appearance of a quaternary carbon at 80.0 ppm in the ^{13}C NMR spectrum of **5aa** and a downfiled shift of the carbonyl group from 186.7 to 197.6 ppm indicated the loss of conjugation which is present in the isatogen. The constitution of **5aa** has been confirmed as $C_{22}H_{17}N_2O_2$ by the HRMS ($[M+H]^+$) found as 341.1290.

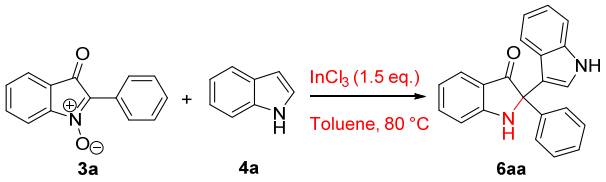
Next, we examined the $InCl_3$-mediated indole addition reaction in different solvents. As shown in Table 2, in polar aprotic solvents like DMF and DMSO, the starting compounds are completely intact even after prolonged stirring at room temperature. The reaction was also found to be slow in non-polar solvents such as toluene, benzene and dichloromethane and the same trend was observed in polar protic solvents like methanol and ethanol.

Table 2: Optimization of the reaction with different solvents

S.No	Solvent	Time(h)	Yield %
1	Acetonitrile	4	68
2	DCM	5	49
3	DMF	48	N.R.
4	DMSO	48	N. R.
5	Toluene	8	18

When the reaction was performed in toluene, the reaction conversion was poor (<35%) and the required product **5aa** was obtained in only 18% yield. We reasoned that this was because of the poor solubility of $InCl_3$ in toluene. In this regard, the reaction temperature was gradually increased from room temperature to 80 °C. Interestingly, we observed the formation of a new compound **6aa** in lesser amounts. We determined the obtained compound through TLC and found that it was different

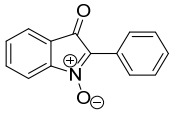
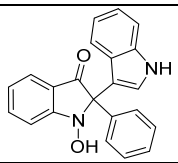
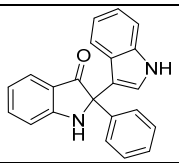
from compound **5aa**. The structure of compound **6aa** was analyzed by spectroscopic techinques such as NMR and Mass spectrometry. Unlike *N*-hydroxylamine compound **5aa**, compound **6aa** showed the excellent solubility in $CDCl_3$ alone. Two ortho protons (nitrone) in 8.61–8.66 ppm region of compound **3a** were absent in the ^{1}H-NMR spectrum of compound **6aa** and they shifted to upfield. A broad singlet peak at 5.37 ppm in the ^{1}H NMR spectrum indicated the presence of the NH group. The appearance of a quaternary carbon at 71.3 ppm in the ^{13}C NMR spectrum of compound **6aa** is indicative of the indolin-3-one junction and the carbonyl group was moved from 186.7 to 200.5 ppm. The downfiled shift of the carbonyl group indicated the loss of conjugation which is present in the isatogen. The constitution of **6aa** has been confirmed as $C_{22}H_{17}N_2O$ by the HRMS ($[M+H]^+$) found as 325.1316.



Scheme 55: C–C bond formation followed by the N–O bond reduction

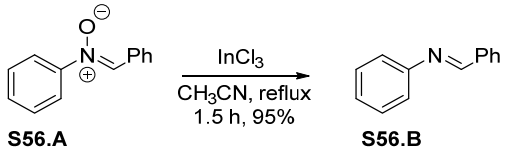
Thus, the structure of compound **6aa** was established as shown in Scheme 55 which has resulted from the indole addition followed by the N–O bond cleavage[68] at 80 °C temperature. Later, the optimization experiments with varying amounts of $InCl_3$ revealed that with 1.5 eq. of the $InCl_3$, the conversion of the starting isatogen was complete and gave the compound **6aa** in 53% yield. A comparative description of the NMR data of compounds **3a**, **5aa** and **6aa** has been shown in Table 3.

Table 3: ^{1}H and ^{13}C NMR chemical shifts of compounds **3a**, **5aa** and **6aa**

Isatogen **3a**	Compound **5aa**	Compound **6aa**
		
(200 MHz, $CDCl_3$)	(500 MHz, 3:2 Methanol-d_4+$CDCl_3$)	(500 MHz, $CDCl_3$)
		5.37 (br s, 1H) (NH)
7.45-7.50 (m, 3H)	6.86 (t, J = 7.6 Hz, 1H)	6.88 (t, J = 7.6 Hz, 1H)
	7.00 (t, J = 6.6 Hz, 1H)	6.92 (d, J = 8.3 Hz, 1H)
7.53-7.57 (m, 1H) 7.61-7.65 (m, 1H)	7.03–7.11 (m, 3H) 7.24 (d, J = 7.1 Hz, 1H)	6.98 (t, J = 7.5 Hz, 1H) 7.12–7.18 (m, 3H)
7.67-7.70 (m, 2H)	7.27–7.35 (m, 4H)	7.26–7.31 (m, 3H) 7.36 (d, J = 8.2 Hz, 1H)

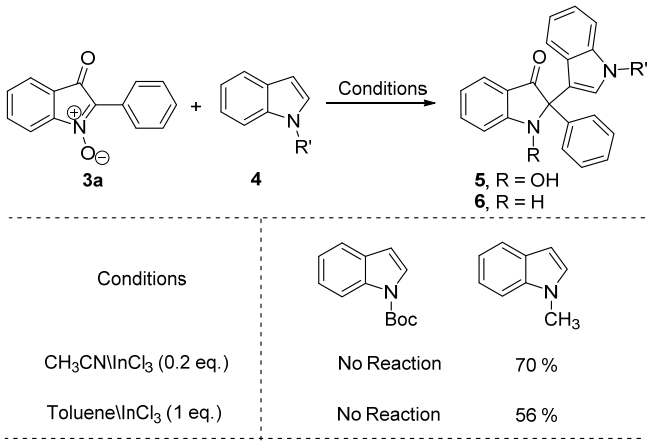
8.61-8.66 (m, 2H)		7.50 (s, 2H) 7.60 (t, *J* = 7.7 Hz, 1H)	7.49 (t, *J* = 7.7 Hz, 1H) 7.55 (dd, *J* = 1.8, 8.1 Hz, 2H)
		7.68 (d, *J* = 6.2 Hz, 1H)	7.68 (d, *J* = 8.0 Hz, 1H)
			8.18 (br s, 1H) (NH)
C2	147.9 (s)	80.0 (s)	71.3 (s)
C3	186.7 (s)	197.6 (s)	200.5 (s)

A literature search on the In-mediated reduction of nitrones has revealed an early report by Sandhu and co-workers that details the reduction of nitrone **S56.A** to imine **S56.B** employing 1 eq. of $InCl_3$ in refluxing CH_3CN (Scheme 56).[69] A control experiment was performed in this context, to find out whether the indole addition occurs prior to the N–O reduction[70] or later. In this regard, isatogen **3a** was heated in toluene with 1.5 eq. $InCl_3$ at 80 ºC for 8 h and it was observed that **3a** was intact.



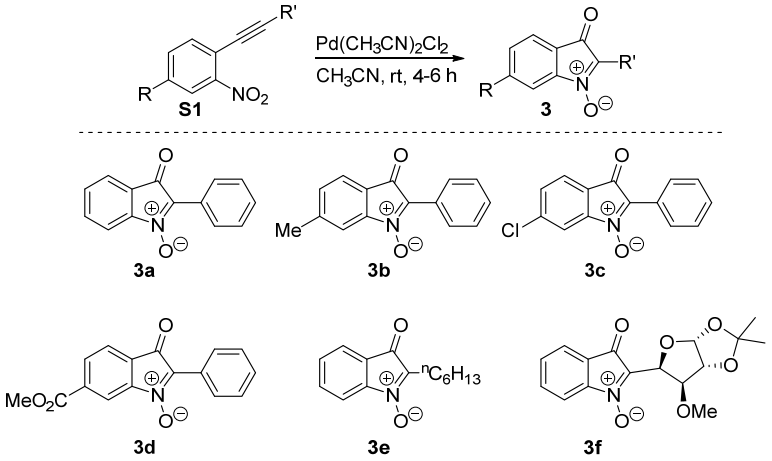
Scheme 56: Reduction of nitrone with $InCl_3$

Next, the compatibility of other indoles in these transformations was examined by employing *N*-methylindole **4b** and *N*-Boc indole **4c**. It has been found that the reaction was facile under both the conditions with **4b**, whereas the *N*-Boc indole was completely inactive in either of the conditions (Scheme 57).



Scheme 57: Reaction with different indoles

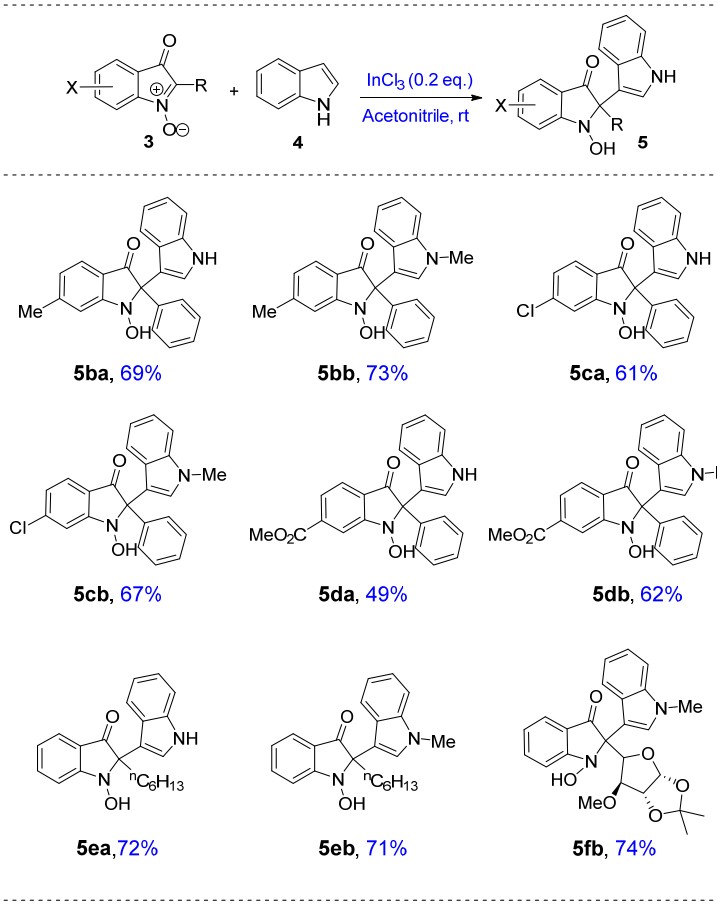
To generalize these two complementary reactions, isatogens **3b**–**3f** having substituents such as aryl, alkyl- and sugar units at the C(2)-position and also different substituents such as Me, Cl, CO_2Me on the phenyl ring at the *para*-position to the keto group were selected as the representative substrates and synthesized by employing the indigenous Pd-mediated nitroalkyne cycloisomerization (Scheme 58).



Scheme 58: Nitroalkyne cycloisomerization for the synthesis of isatogens

2.9. Scope for the $InCl_3$-mediated C–C bond formation:

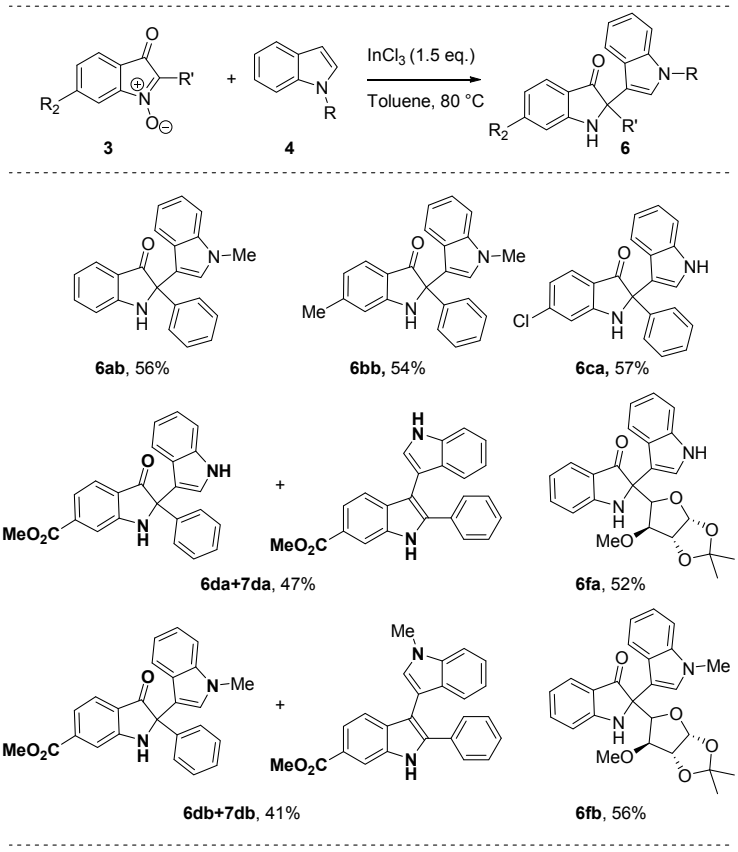
Scheme 59, exemplifies the scope of the addition of simple indole and *N*-Me indole to isatogens **3b** – **3f** by using $InCl_3$ (20 mol %) as a catalyst at room temperature in acetonitrile. The reaction of Me-isatogen under the above conditions provided the indolin-3-one compound in 69% yield, whereas the reaction with the isatogens having the electron withdrawing groups such as –Cl and $–CO_2Me$ formed the corresponding adduct in slightly lesser yields (61% and 49% respectively). Further, the reaction with alkyl isatogen was quite good and formed compound **5ea** in 72% yield. Coming to the sugar isatogens **3f**, it was observed that the reaction was fast and gave the addition compound **5fb** in 74% yield. Also, the reactions with *N*-methylindole proceeded smoothly and provided the corresponding 2,2-disubstituted indolin-3-ones in better yields than with the simple indole.



Scheme 59: Scope of the $InCl_3$ mediated addition of indoles to isatogens

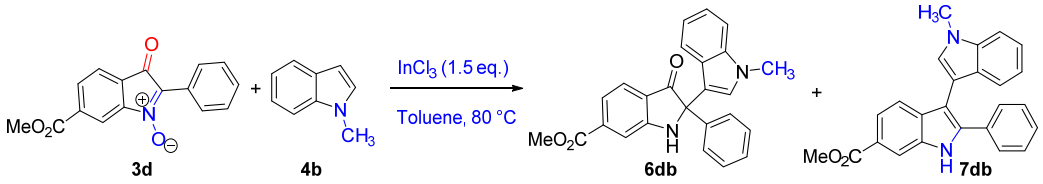
2.10. Scope for the $InCl_3$-mediated C–C bond formation *cum* N–O bond reduction:

Scheme 60 illustrates the scope of the one-pot addition of indoles **4a**/**4b** to isatogens **3b** – **3f** and subsequent N–O reduction employing 1.5 eq. of $InCl_3$ in toluene at 80 °C. The reactions proceeded smoothly and provided the corresponding indolin-3-ones in moderate to good yields.



Scheme 60: Scope of the $InCl_3$-mediated addition of indole to isatogen and N–O reduction

When a carboxylate group was present *para* to the carbonyl of isatogen, under the conditions employed for addition/N–O reduction, along with the expected **6db**, unsymmetrical bis-indole molecule **7db** was obtained as the minor product. The structure of **7db** was established with the help of spectral and analytical data. We observed the appearance of a new –NH peak at 8.61 ppm in the ^{1}H NMR spectrum of compound **6db+7db** (Scheme 61). The extra carbonyl group at ~200.0 ppm in the ^{13}C NMR spectrum was absent. The assigned structure of compound **7db** was further confirmed by the single crystal X-ray structural analysis (Figure 6).



Scheme 61: Synthesis of bis-indole molecule

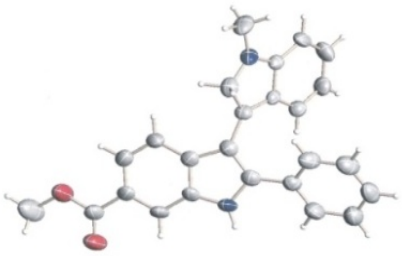
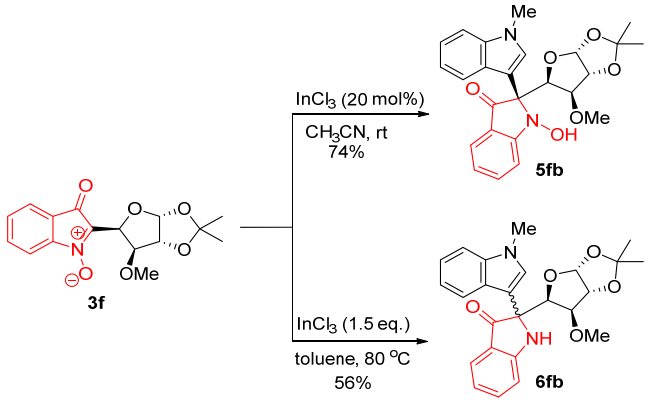


Figure 6: Single crystal X-ray diffraction of compound **7db**

Another set of reactions that needs a special mention are the reactions of the sugar isatogen **3f** with **4b**. Under catalytic conditions at room temperature, the reaction was completely regio and diastereoselective and provided exclusively the corresponding N–OH derivative **5fb**. The structure of **5fb** has been established with the help of single crystal *X*-ray analysis (Figure 7).[71] When it comes to the reactions in toluene at 80 ºC with 1.5 eq. of $InCl_3$, a 2:1 inseparable epimeric mixture of the corresponding indolin-3-one derivatives, along with some other unidentified products were obtained (Scheme 62).



Scheme 62: Reaction of sugar isatogen **3f** in different conditions

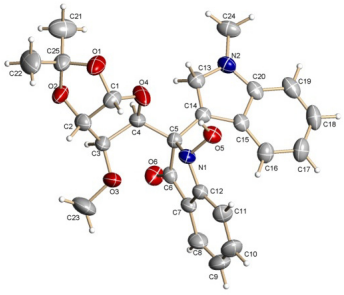


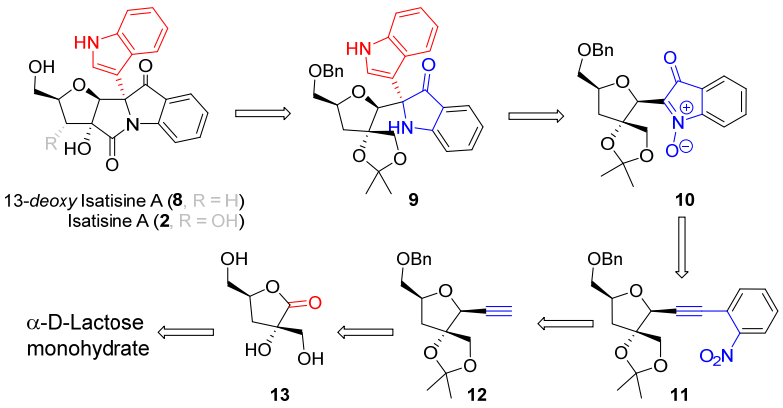
Figure 7: Single crystal X-ray diffraction of the **5fb**

SECTION B

The total synthesis of 13-*deoxy* Isatisine A

2.12. Retrosynthetic disconnections:

Having generalized complementary methods for the addition of indole on isatogen to achieve the regioselective C–C bond formation for the construction of central indolin-3-one skeleton, we next focused our attention on the compatibility of these reactions in the total synthesis. The synthesis of 13-*deoxy* Isatisine A (**8**) has been planned as a model study in the pursuit of total synthesis of Isatisine A (**2**) considering the fact that the lactone **13** could be prepared in bulk quantities in one step from lactose.[72] Scheme 63 reveals the key disconnections in this context. The final amide unit installation has been planned by the dehydrogenative coupling of γ-aminoalcohol **9** which in turn can be obtained by the regioselective addition of indole to the isatogen **10**. The isatogen derivative was planned from the Pd-mediated nitroalkyne cycloisomerization of the nitroalkyne **11**. The synthesis of the key alkyne **12** was planned from the known isosaccharino lactone **13** following the Kishi's alkynylation-reductive etherification approach reported for the synthesis of *β*-C-glycosides.[73]

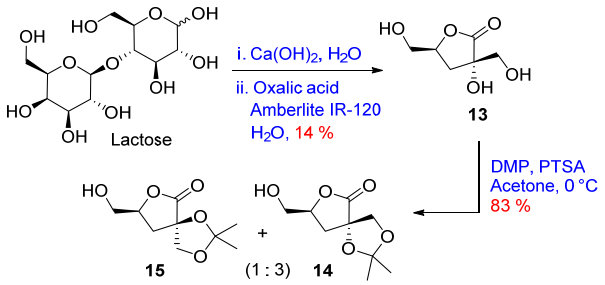


Scheme 63: Retrosynthetic disconnections for the 13-*deoxy* Isatisine A

2.13. Synthesis of isosaccharino lactone 13:

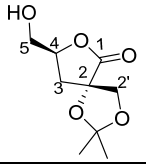
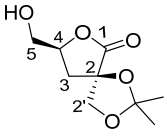
The synthesis commenced with the preparation of lactone **13** from the *α*-D-Lactose monohydrate according to the established procedure. Lactose monohydrate was subjected for the base hydrolysis with $Ca(OH)_2$ in water for 3 days. The obtained calcium salt of isosaccharino lactone was acidified with the oxalic acid liberated the lactone triol in 14% yield. Acetonide protection of lactone **13** using DMP/*p*TSA in acetone at 0 °C gave the known compound **14** along with its C2-epimer **15** in a 3:1

ratio (83% overall yield). It was quite surprising to notice that the compound **14** has been prepared by several groups and widely used in organic synthesis. However, nobody has reported the isolation of epimeric **15**. As shown in Table 4, a comparison of both the lactones has clearly revealed that, both are γ-lactones and are epimeric at C2 (Scheme 64).



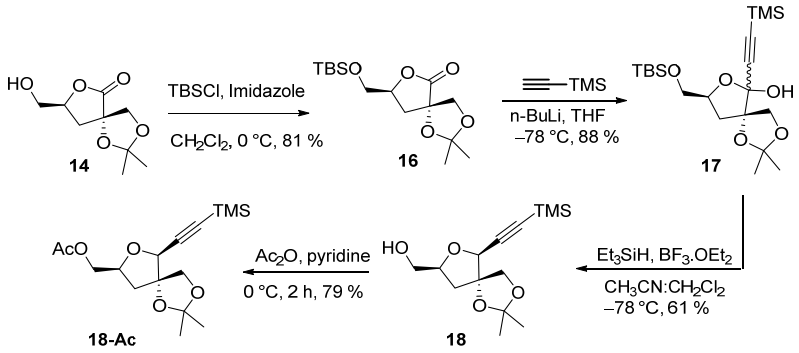
Scheme 64: Synthesis of staring lactone **13**

Table 4: NMR description of two epimeric lactones

		
C3–H	2.34 (dd, *J* = 6.6, 13.8 Hz, 1H) 2.46 (dd, *J* = 7.3, 13.8 Hz, 1H)	2.34–2.38 (m, 2H)
C2'–H	3.58 (dd, *J* = 2.9, 12.7 Hz, 1H) 3.95 (dd, *J* = 2.0, 12.7 Hz, 1H)	3.69 (dd, *J* = 12.8, 5.5 Hz, 1H) 3.88 (dd, *J* = 12.7, 2.9 Hz, 1H)
C5–H	4.10 (d, *J* = 9.2 Hz, 1H) 4.30 (d, *J* = 9.2 Hz, 1H)	4.07 (d, *J* = 8.9 Hz, 1H) 4.19 (d, *J* = 8.9 Hz, 1H)
C4–H	4.62–4.72 (m, 1H)	4.48 (tdd, *J* = 7.7, 7.7, 5.3, 3.1 Hz)
C3	35.6 (t)	35.3 (t)
C2'	62.9 (t)	63.5 (t)
C5	71.6 (t)	71.9 (t)
C4	77.9 (d)	77.3 (d)
C1	176.1 (s)	175.5 (s)

2.14. Synthesis of nitroalkyne fragment:

We proceeded with compound **14** to synthesize the key alkyne fragment **12**. The primary alcohol group in compound **14** was protected as its TBS ether using TBSCl/imidazole in CH_2Cl_2 at 0 °C to provide the compound **16** in 81% yield. This was characterized by the appearance of TBS- protons at 0.05, 0.06 and 0.87 ppm in the ^{1}H NMR spectrum of **16**. The lactone **16** was subjected to alkyne addition with trimethylsilyl acetylene and *n*-BuLi in THF at –78 °C to give the lactols **17** in 10:1 ratio with 88% yield. The hydroxyl proton appeared as the broad singlet at 4.46 ppm and TMS group at 0.16 ppm in the ^{1}H NMR spectrum of lactols **17**. The carbonyl peak at 175.7 ppm was disappeared in the ^{13}C NMR spectrum. HRMS analysis showed the formation of ($[M+Na]^+$) with the constitution $C_{20}H_{38}O_5Si_2Na$ found as 437.2156. The reduction of the obtained alkynol **17** with Et_3SiH and $BF_3.OEt_2$ in acetonitrile and dichloromethane at –78 °C gave the alkynol **18**, resulting from the deoxygenation and the TBS-group deprotection in 61% yield. The anomeric proton at 4.52 ppm appeared as singlet in the ^{1}H NMR spectrum of **18** and the formation of a methine carbon at 76.8 ppm was noticed in the ^{13}C NMR spectrum. For characterization and to fix the stereochemistry of the newly created center, the alkynol **18** was converted to the corresponding acetate **18-Ac** by treating with Ac_2O and pyridine at 0 °C (Scheme 65).



Scheme 65: *β-C*-alkynylation of lactone **13**

The stereochemistry of the anomeric center was established with the help of 2D NMR spectra analysis (Figure 8). For example, in the NOESY of **18-Ac**, the observed cross peaks between the C(1)–H and C(4)–H, and between the C(1)–H and one of the acetonide methyl group indicate that they are all on the same side of the

ring. As we know that the C(4)–H has an α-configuration, the anomeric configuration was fixed as β.[74]

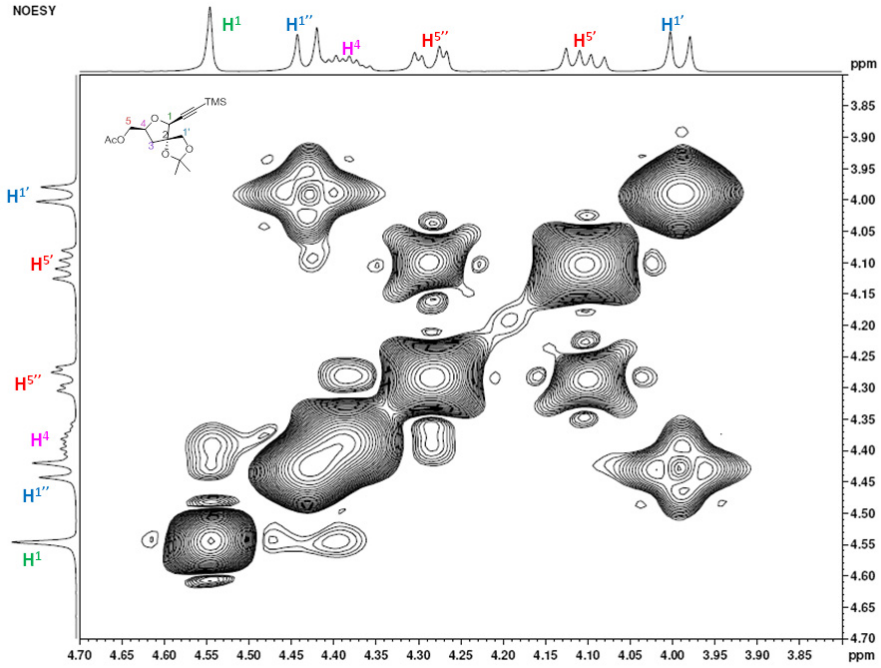
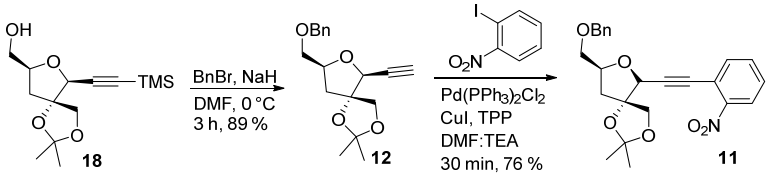


Figure 8: NOESY spectral analysis of **18-Ac**

Next, the free alcohol in compound **18** was subjected for benzylation using BnBr and NaH in DMF at 0 °C. The C-trimethylsilyl group was also found to be deprotected under the same conditions to give the compound **12** in 89% yield. In the ^{1}H NMR spectrum of compound **12**, the C–TMS group at 0.16 ppm was absent and a terminal alkyne proton was seen to resonate at 2.56 ppm. In addition, a singlet at 4.59 ppm integrating for two H, and a doublet of anomeric C–H at 4.52 ppm (singlet before benzylation) were noticed. In the ^{13}C NMR spectrum of compound **12**, the acetylenic carbon doublet was observed at 76.0 ppm along with the benzylic triplet.

The Sonogashira coupling of **12** with *o*-iodonitrobenzene was performed using $Pd(PPh_3)_2Cl_2$ and CuI in 1:3 DMF-Et_3N solvent to afford the key nitroalkyne **11** in 76% yield (Scheme 66).[75] In the ^{1}H NMR spectrum of compound **11**, the anomeric C–H shifted to down field (4.52 to 4.80 ppm) and also there was a 0.1 ppm difference of the remaining peaks of compound **11** from that of compound **12**. Coming to the ^{13}C NMR spectrum of compound **11**, the acetylenic –CH at 76.0 ppm of compound **12**

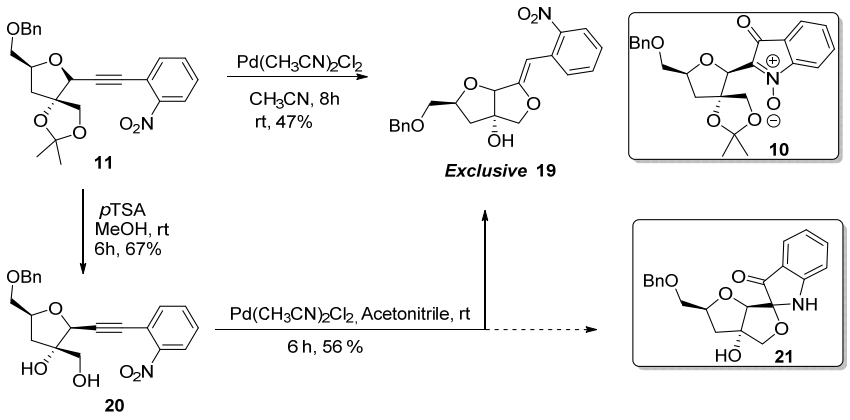
became a singlet (-C) at 82.5 ppm. The constitution of compound **11** was determined as $C_{24}H_{25}NO_6Na$ from the HRMS ($[M+Na]^+$) found as 446.1587.



Scheme 66: Synthesis of nitroalkyne intermediate

2.15. Pd-mediated nitroalkyne cycloisomerization:

Having the key nitroalkyne **11** in hand, our next concern was its cycloisomerization leading to the requisite isatogen **10**. The cycloisomerization of **11** was examined with $Pd(CH_3CN)_2Cl_2$ in acetonitrile at room temperature which resulted in the formation of a new product **19** in 47% yield. The spectral data analysis of compound **19** revealed that a 5-*exo*-dig alkynol[76] cycloisomerization instead of the nitroalkyne cycloisomerization had taken place, resulting in the enol ether derivative **19** (Scheme 67). For example, in the ^{1}H NMR spectrum of compound **19**, the methyl signals corresponding to the acetonide are absent and a singlet at the characteristic enol-ether proton has been noticed at 5.98 ppm. In addition, in the ^{13}C NMR spectrum of compound **19**, two olefinic carbons resonating at 96.8 and 158.4 ppm were noticed. Finally, the observed peak at 406.1283 in the HRMS ($[M+Na]^+$) of compound **19** provided further support for the assigned structure.

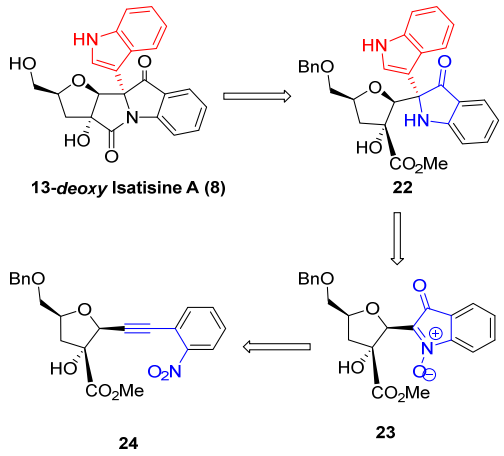


Scheme 67: Attempts for the synthesis of isatogen or *spiro*-indolin-3-one

This unexpected result has led to a revision of our strategy featuring the synthesis of the *spiro*-indolin-3-one derivative **21** by nitroalkynol cycloisomerization that had been established earlier in our group. Accordingly, the compound **11** was subjected for acetonide hydrolysis employing catalytic amounts of *p*-TSA in methanol at room temperature to afford the diol **20** in 67% yield. The resulting diol **20** when treated with $Pd(CH_3CN)_2Cl_2$ in acetonitrile at room temperature provided exclusively the enol ether **19** in 69% yield (Scheme 67).

2.16. Revised strategy:

As the approaches to synthesize either isatogen or *spiro*-indolin-3-one by Pd-mediated nitroalkyne cycloisomerization with the substrates **11** and **20** failed, the plan has been revised. As shown in Scheme 68, the synthesis of lactam has been changed from the dehydrogenative coupling of γ-aminoalcohol to an intramolecular amide bond formation that has been established in case of the total synthesis of Isatisine A by Kerr's group.[61b] This led to the identification of the synthesis of amino-ester **22** from isatogen **23** which in turn was intended from the Pd-mediated nitroalkyne cycloisomerization of the newly designed nitroalkyne **24**.

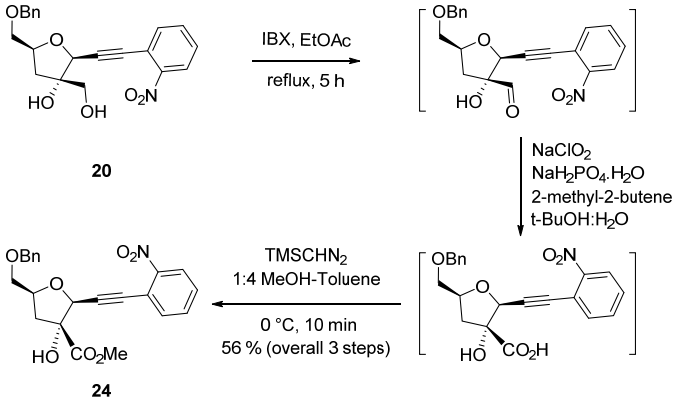


Scheme 68: Revised strategy and the expected retrosynthetic disconnections

2.17. Synthesis of nitroalkyne ester:

According to the revised plan, the synthesis of the key nitroalkyne ester **24** was intended from nitroalkynediol **20**. The oxidation of diol **20** was carried out with IBX in EtOAc at reflux to afford the intermediate aldehyde that was immediately subjected for further oxidation under Pinnic conditions employing $NaClO_2$/

$NaH_2PO_4.H_2O$ and 2-methyl-2-butene as a chloride ion scavenger in *tert*-BuOH and H_2O.[77] The resulting crude carboxylic acid was esterified under neutral conditions[78] employing $TMSCHN_2$ in 20% methanol in toluene at 0 °C to afford the key nitroalkyne ester **24** in 56% overall yield for 3 steps. In the ^1H NMR spectrum of compound **24**, the characteristic doublets of $–CH_2$ are absent and a methyl singlet at 3.83 ppm was observed. In addition the anomeric-H shifted downfield (4.79 to 4.85 ppm) because of the transformation from $–CH_2OH$ to $–CO_2Me$. In the ^{13}C NMR spectrum of compound **24**, the carbonyl singlet was seen to resonate at 173.2 ppm and the quaternary carbon of furan ring was shifted from 93.8 to 91.4 ppm**.** The constitution of compound **24** was determined as $C_{22}H_{21}NO_7Na$ from the HRMS where the peak corresponding to ($[M+Na]^+$) was found at 434.1230 (Scheme 69).

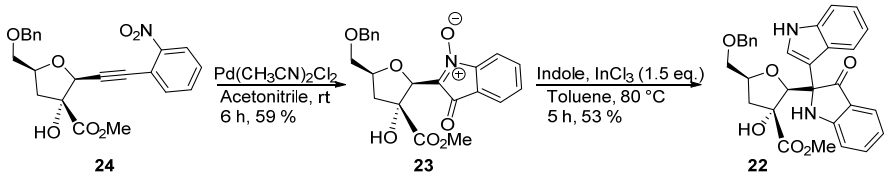


Scheme 69: Synthesis of key nitroalkyne **24**

2.18. The nitroalkyne cycloisomerization and $InCl_3$-mediated C–C bond formations:

Having the key nitroalkyne **24** in hand, our next concern was about its cycloisomerization and subsequent addition of indole employing $InCl_3$. Gratifyingly, the nitroalkyne cycloisomerization of **24** with $Pd(CH_3CN)_2Cl_2$ in acetonitrile proceeded smoothly and provided the corresponding isatogen **23** in 59% yield (Scheme 70). The formation of isatogen is apparent from the appearance of four aromatic protons collectively as a multiplet at 7.29–7.35 ppm in the ^1H NMR spectrum of compound **23**. In addition, two new singlets at 148.0 and 185.9 ppm have been noticed in the ^{13}C NMR spectrum of compound **23** which further confirmed the assigned structure. Next, the attempted addition of indole to isatogen **23** using 1.5 eq. of $InCl_3$ in toluene at 80 °C gave the required 2,2-disubstituted indolin-3-one

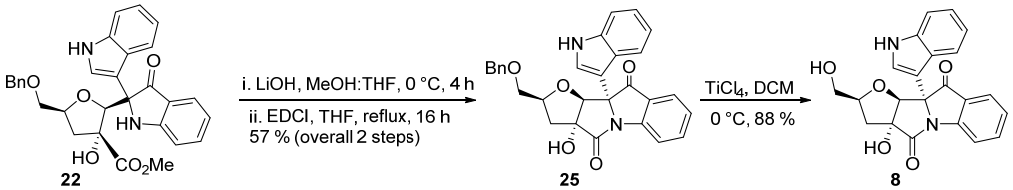
derivative **22**, though the yield was poor (Scheme 24). Subsequently, this reaction was performed in a stepwise manner - i. the addition of indole to isatogen at room temperature with 20 mol% of $InCl_3$; ii. after complete consumption of **23**, an additional 1.3 eq. of $InCl_3$ was added and then heated at 80 °C for 5 h in toluene. Under these conditions, the pseudoindoxyl **22** was obtained in 53% yield as a single diastereomer. The structure of compound **22** was established with the help of spectral and analytical data. For example, in the ^{1}H NMR spectrum of compound **22**, the peak corresponding to –NH appeared as a broad singlet at 6.01 ppm. On the other hand, in the ^{13}C NMR of **22**, the appearance of a quaternary center (C2) at 83.2 ppm and the shifting of the carbonyl group from 185.9 to 200.7 ppm clearly indicated the presence of a 2,2-disubstituted pseudoindoxyl core. Finally, a peak at m/z 535.1838 ($[M+Na]^+$) supported the assigned constitution for **22**.



Scheme 70: Synthesis for central skeleton of 13-*deoxy* Isatisine A

2.19. Synthesis of 13-*deoxy* Isatisine A:

Having the penultimate intermediate **22** in hand, now the stage was set for the construction of central lactam ring following the Kerr's protocol.[61b] Accordingly, the hydrolysis of the ester group in compound **22** was carried out using $LiOH.H_2O$ in mixture of MeOH:THF in 1:3 ratio, to obtain the corresponding carboxylic acid. The crude acid was subjected for the subsequent intramolecular amidation using EDCI under high dilution conditions in THF at reflux to procure the lactam **25** in 57% yield over the 2 steps (Scheme 71). The stereochemistry of the newly generated quaternary center (during the indole addition) of lactam **25** was established with the help of COSY\NOESY analysis.



Scheme 71: Synthesis of 13-*deoxy* Isatisine A

Figure 9 summarizes the salient features of the 1D/2D spectra of compound **25**. In the ^{1}H NMR spectrum of compound **25**, the anomeric C10–H resonated at 4.93 ppm and showed through space interaction with the C2'–H (next to the nitrogen) of pendant indole ring that appeared at 7.27 ppm. In addition, there was a strong NOESY peak between the C4'–H (8.14 ppm) of indole and C12–H (4.43 ppm), C4–H of the furanose ring. In addition, the C(12)–H has also shown a cross-peak with the C2'–H of indole, which collectively indicate the presence of C12–H, C10–H and C2'–H in the α-face of furanose ring and that the stereochemistry at the quaternary center is the same as that in Isatisine A.

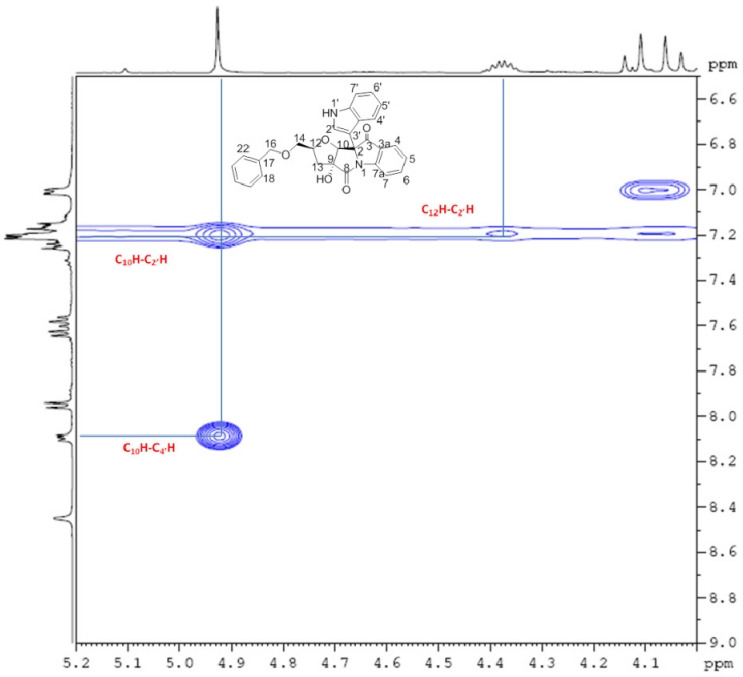
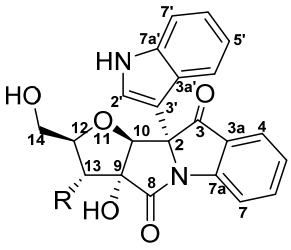


Figure 9: NOESY analysis of the lactam **25**

After having established the stereochemistry of the newly created center in the lactam **25** and confirmed that it was as required in Isatisine A, we proceeded for the debenzylation using $TiCl_4$ in CH_2Cl_2 at 0 °C to afford the 13-*deoxy* Isatisine A (**8**) in 88% yield (Scheme 71).[79] The structure of the 13-*deoxy* Isatisine A was established with the help of spectral and analytical data (Table 5). The optical rotation of 13-*deoxy* Isatisine A was found as $[\alpha]_D^{25} = -157.7$ (*c* 0.95, CH_3OH).

In conclusion, we have developed two complementary methods for the addition of C3 of indole to isatogen and executed the total synthesis of 13-*deoxy* Isatisine A to establish the compatibility of these methods in a complex synthesis. With these promising results, the total synthesis of Isatisine A has also been executed successfully employing the same reaction for the key C–C bond formation.

Table 5: Comparison of ^{1}H NMR (CD_3OD, 500 MHz) data of isolated and synthetic molecule



R = OH, Isatisine A (2)
R = H, 13-*deoxy* Isatisine A (8)

	Isatisine A (^{1}H)	**13-*deoxy* Isatisine A (^{1}H)**
H-13	4.05 (d, *J* = 4.0 Hz, 1H)	2.17 (dd, *J* = 8.5, 13.4 Hz, 1H) 2.47 (dd, *J* = 6.3, 13.5 Hz, 1H)
H-14	3.38 (dd, *J* = 11.5, 4.5 Hz, 1H) 3.33 (dd, *J* = 11.5, 4.5 Hz, 1H)	3.27 (dd, *J* = 3.9, 4.9 Hz, 2H)
H-12	3.83 (m, 1H)	4.21–4.27 (m, 1H)
H-10	4.63 (s, 1H)	4.91 (br s, 3H)
H-5′	7.05 (dd, *J* = 7.5, 7.5 Hz, 1H)	7.07 (ddd, *J* = 0.9, 6.9, 8.0 Hz, 1H)
H-6′	7.12 (dd, *J* = 8.0, 7.0 Hz, 1H)	7.14 (ddd, *J* = 1.1, 6.9, 8.0 Hz, 1H)
H-2′	7.28 (s, 1H)	7.27 (s, 1H)
H-5 H-7′	7.32 (dd, *J* = 7.5, 7.5 Hz, 1H) 7.33 (d, *J* = 8.0 Hz, 1H)	7.31–7.36 (m, 2H)
H-4	7.63 (d, *J* = 7.5 Hz, 1H)	7.64 (d, *J* = 7.5 Hz, 1H)
H-6	7.77 (dd, *J* = 7.5, 7.5 Hz, 1H)	7.80 (ddd, *J* = 1.2, 7.4, 8.4 Hz, 1H)
H-4′	7.93 (d, *J* = 8.0 Hz, 1H)	7.93 (d, *J* = 8.0 Hz, 1H)
H-7	7.99 (d, *J* = 8.5 Hz, 1H)	8.0 (d, *J* = 8.1 Hz, 1H)

CHAPTER III:

Towards the total synthesis of Austamide

SECTION A

[Au]-catalyzed cycloisomerization/cycloaddition cascade for the central tricyclic core of *spiro*-pseudoindoxyl natural products

Introduction

In 1971, Styne and co-workers reported the isolation of Austamide from the toxic maize-meal cultures of *Aspergillus ustus* CSIR 1128.[24d] The structure of Austamide (**26**) was elucidated with the help of spectroscopic techniques as well as with the degradation experiments. Austamide appears as a yellow amorphous compound with an intense green fluorescence. Coming to the structural features, Austamide is characterized with an unprecedented pentacyclic skeleton featuring a *spiro*-pseudoindoxyl chromophore and two labile enamide functionalities. It has two stereogenic centers, one at the *spiro*-junction and other at the diketopiperizine junction. There are two total syntheses reported so far for Austamide (Figure 10).

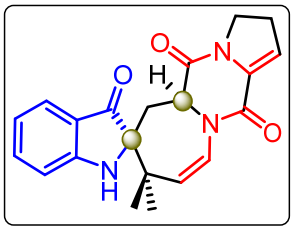
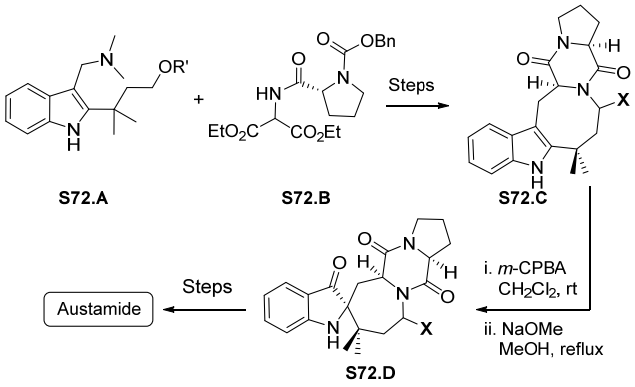


Figure 10: Structure of Austamide, a pseudoindoxyl natural product

In 1979, Kishi and co-workers have reported the first synthesis of racemic Austamide in 29 steps. This was the occasion, where the oxidative rearrangement of indoles was optimized, and employed as a key step in the total synthesis.[80]

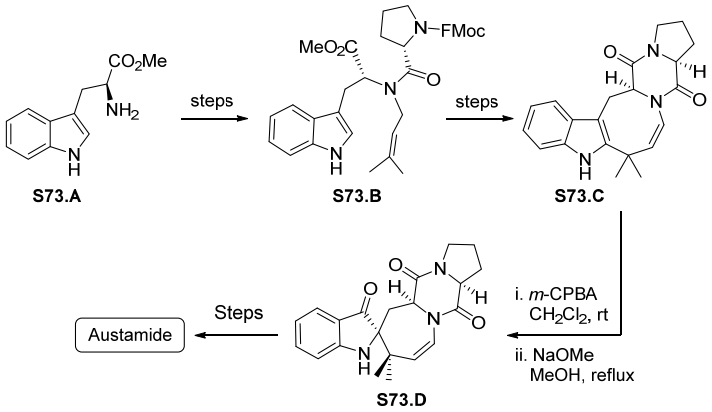


Scheme 72: Kishi's approach for the total synthesis of Austamide

First, the coupling of the indole derivative **S72.A** with the proline derivative **S72.B**; then the subsequent functional group modifications led to the synthesis of the indole derivative **S72.C**. This was subjected for the oxidation with *m*-CPBA followed by the pinacol-type rearrangement of the resulting 3-hydroxy indolenine with NaOMe in methanol led to the construction of the key pseudoindoxyl skeleton. It was

mentioned that the stereo-chemical outcome of this rearranged product is determined by the stereochemistry of oxidation (Scheme 72).

In 2002, Corey and Baran have documented the first enantioselective total synthesis of (+)-Austamide in a relatively short way. This synthesis has its own origin from the biosynthetic proposal by Harrison[81] for the construction of the indoloazocene precursor **S73.C** from an *N*-prenylated tryptophan derivative using Pd-catalysis. The resulting indoloazocene **S73.C** has been subjected for Kishi's oxidative rearrangement to construct the key *spiro*-pseudoindoxyl skeleton (Scheme 73).[82]

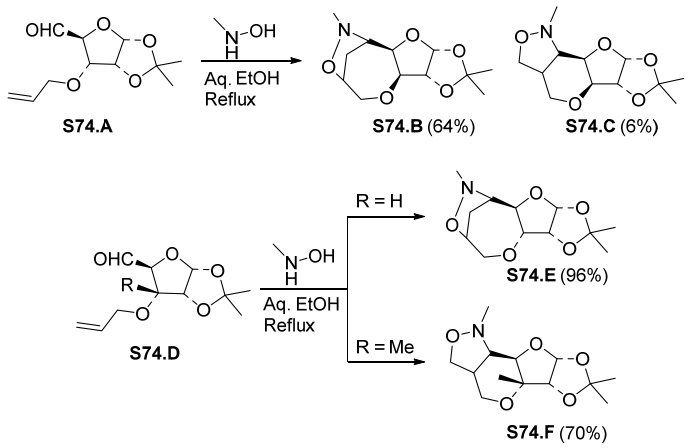


Scheme 73: Corey's approach for the total synthesis of Austamide

Given the current interest of our group on pseudoindoxyl natural products, the total synthesis of Austamide has been considered with the keen objective of expanding our isatogen approach for the central indolinone core. The construction of the key *spiro*-indoxyl has been planned at the final stage featuring one of the C–C bond formations through the intramolecular nitrone cycloaddition.[83]

Coming to the cycloaddition of isatogens, there are a couple of reports in the literature that have been mentioned in the previous section about the regioselectivity issues associated with the reported cases. The intramolecular version has not yet been documented, as the reliable methods for the synthesis of isatogens are limited. One of the reasons for selecting the intramolecular cycloaddition in the context of the tricyclic *spiro*-pseudoindoxyl core, especially of Austamide, was considering the corresponding intramolecular nitrone cycloadditions and especially the report from Shing and co-workers.[84] In 1994, Shing's group documented the intramolecular nitrone cycloadditions on sugar templates and the dependence of regioselectivity towards either oxepanes or tetrahydropyrans on the stereochemical issues. For

example, the treatment of aldehyde (R = H) **S74.D** with the *N*-methyl hydroxylamine in refluxing aqueous ethanol furnished the oxepane derivative **S74.E** whereas, with the aldehyde where R = Me, it provided the tetrahydropyran derivative **S74.F** because of the steric hindrance from the methyl group (Scheme 74).



Scheme 74: Intramolecular nitrone cycloadditions

Considering this, we hypothesized that, the intramolecular [3+2]-dipolar cycloaddition of isatogen should provide a general approach for the construction of the central core of various *spiro*-pseudoindoxyl natural products by changing the number/nature of the atoms between the dipole and the pendant olefin and also changing the substituents to tune the regioselectivity.[85] If we can combine both the isatogen formation with the cycloaddition, this process could lead to the creation of three stereogenic centers from a simple linear substrate with complete atom economy (Figure 11).[86] The design and development of such cascade transformation is significant due to the beneficial outcomes like generation of molecular diversity, structural and stereo-chemical complexity in a short span. [87]

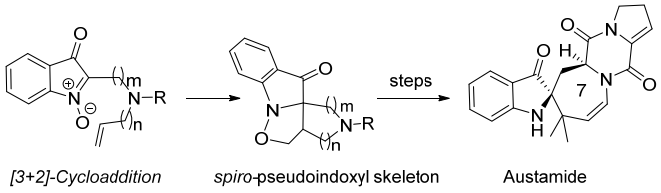
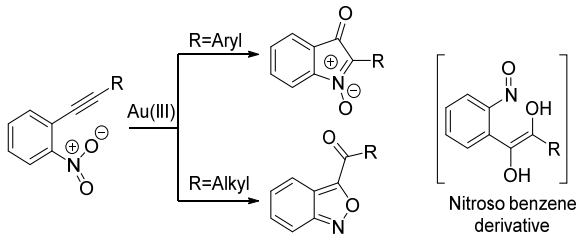


Figure 11: *Spiro*-pseudoindoxyl skeleton construction via nitroalkyne cycloisomerization and subsequent [3+2]-cycloaddition

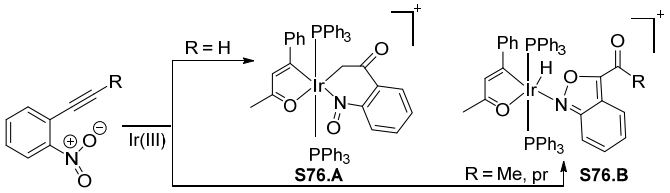
However, one major problem is the regioselectivity of the cycloisomerization.[88] In 2003, Yamamoto and co-workers have employed Au(III)

complexes for doing nitroalkyne cycloisomerization. The regioselectivity of the cyclization depends upon the substituents present. A 5-*exo*-dig cyclization leads to the isatogen and 6-*endo*-dig cyclization delivers the isomeric anthranil. If the alkyne bear an aryl substituent, a mixture of both isatogen and anthranil were formed when Au[III]Br_3 was employed as the catalyst – the isatogen being the major product. On the other hand, if the substituent is an alkyl group, under similar conditions, exclusive formation anthranil was noticed (Scheme 75).[13]



Scheme 75: Au-catalyzed synthesis of isatogens and anthranils

Later, in 2005, Crabtree and co-workers have employed the iridium hydride complex for this nitroalkyne cycloisomerization. They demonstrated the formation of the iridium nitroso complex **S76.A** and the iridium hydride anthranil complex **S76.B** with alkyl substituted nitroalkyne (Scheme 76).[14]

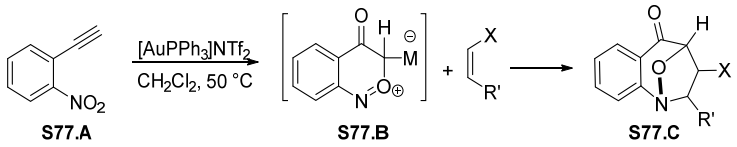


Scheme 76: Ir-catalyzed nitroalkyne cycloisomerization

In 2010, we revealed that when $PdCl_2$ was employed as the catalyst, without any bias, the cyclization occurs exclusively in a 5-*exo*-dig fashion and provides the isatogens. However, the yields are moderate to good. Later, we documented a novel (Pd- or Au-) catalyst dependent complementary cyclization of nitroalkynols leading to either *spiro*-indolinone or benzoxazinone depending upon whether the initial cyclization is occurring respectively in a 5-*exo*-dig (with Pd) or 6-*endo*-dig (with Au) fashion.[16]

Subsequently, in 2011, Liu and co-workers reported the Au[I]-catalyzed cycloisomerization of terminal nitroalkynes and the trapping of the intermediate α-oxo gold carbenoids[89] with external olefins *via* [3+2]-cycloaddition (Scheme 77). As

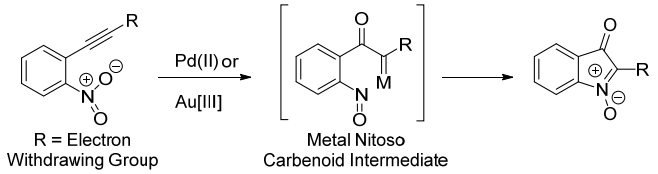
expected, with this complex too, with internal alkynes, the anthranil was formed exclusively.[90]



Scheme 77: Au-catalyzed synthesis of azacyclic skeletons

Results and Discussion:

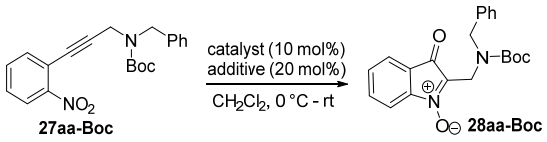
Thus, one of the bottlenecks in our proposal was about the regioselectivity of nitroalkyne cycloisomerization. In order to proceed with the proposed cyclization-cycloisomerization, our initial hypothesis was that when an electron withdrawing group such as nitrogen is present on the pendant chain, it should promote the 5-*exo*-dig mode of cyclization *inter alia* the isatogen formation even when a gold-complex was employed as the catalyst (Scheme 78).[91] Although with Pd-complex, the cyclization should proceed with the desired regioselectivity, the substrates that we employ for the proposed cascade cyclization are going to be demanding, since they carry an internal olefin in close proximity to the alkyne and also the presence of the hetero atoms in between, such as oxygen or nitrogen, might lead to some unwanted side reactions. Indeed, our earlier efforts with this complex were met with complex mixtures.



Scheme 78: Synthesis of isatogen *via* metal nitroso carbenoid intermediate

To proceed in this direction, the *N*-Boc-benzylpropargyl amine was subjected for the Sonogashira coupling to obtain the model nitroalkyne **27aa-Boc** and was subjected initially for the Pd-mediated cycloisomerization employing $Pd(CH_3CN)_2Cl_2$ in CH_3CN at room temperature. As anticipated, the reaction gave a complex mixture. Next, the possibility of nitroalkyne cycloisomerization of **27aa-Boc** has been examined with various Au-complexes for which the results are summarized in Table 6.

Table 6: Optimization of the reaction with Au-combinations

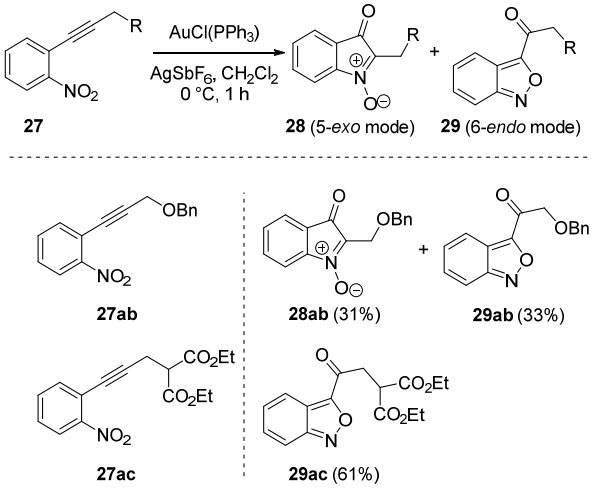


entry	catalyst	additive	time h	% yield[a]
1	$AuBr_3$	--	3	44
2	$AuCl(PMe_3)$	$AgSbF_6$	3	47
3	**$AuCl(PPh_3)$**	**$AgSbF_6$**	**2**	**68**
4	$AuCl(BiPh^tBu_2P)$	$AgSbF_6$	4	10
5[b]	$AuCl(PPh_3)$	AgOTf	7	22
6	**$AuCl(PPh_3)$**	**$AgNTf_2$**	**3**	**60**
7	**$AuCl(PPh_3)$**	**$AgBF_4$**	**3**	**62**
8[b]	$AuCl(PPh_3)$	$AgOCOCF_3$	24	25
9[b]	$AuCl(PPh_3)$	AgOAc	24	18
10	$AuCl(PPh_3)$	$AgNO_3$	48	N.R.
11	$AuCl(PPh_3)$	$AgCO_3$	48	N.R.

a. isolated yields; *b*. yield with respect to the recovered starting material; N.R. = No Reaction.

As shown in Table 6, it was observed that the formation of isatogen was the major pathway with the majority of the Au-complexes, with only variations in the isolated yields. When the combination of $AuCl(PPh_3)$ with $AgSbF_6$ was employed as the catalyst, best results were obtained in terms of the yields. $AuBr_3$ also delivered the isatogen but with moderate yield. We observed the slow consumption of nitroalkyne in case of the catalysts $AuCl(PMe_3)$ and $AuCl(BiPh^tBu_2P)$. On the other hand, complete conversion of the starting material was took place with $AuCl(PPh_3)$ in combination with other silver salts such as $AgBF_4$ and $AgNTf_2$ afforded the isatogen in good to excellent yields. However, the reaction with AgOTf, AgOAc and $AgOCOCF_3$ combinations found the high recovery of starting material. In contrast, $AgCO_3$ and $AgNO_3$ combinations are completely inactive for this transformation.

The constitution of isatogen was established with the help of spectral and analytical techniques. The 1:2:1 proton pattern in aromatic region of compound **27aa-Boc** was transformed as a bunch between 7.43-7.58 ppm region in ^{1}H NMR spectra of the **28aa-Boc** which is the characteristic of the fused aryl ring of the isatogen. Two alkyne carbons (at 80.7 and 93.3 ppm) of compound **27aa-Boc** were shifted to downfield, one peak at 146.9 ppm (C2-of isatogen) and other at 185.4 ppm (carbonyl of isatogen) in the ^{13}C NMR of compound **28aa-Boc**. The constitution of **28aa-Boc** has been same as that of **27aa-Boc** and confirmed as $C_{21}H_{23}N_2O_4$ by the $[M+H]^+$ peak in the HRMS found as 367.1652.

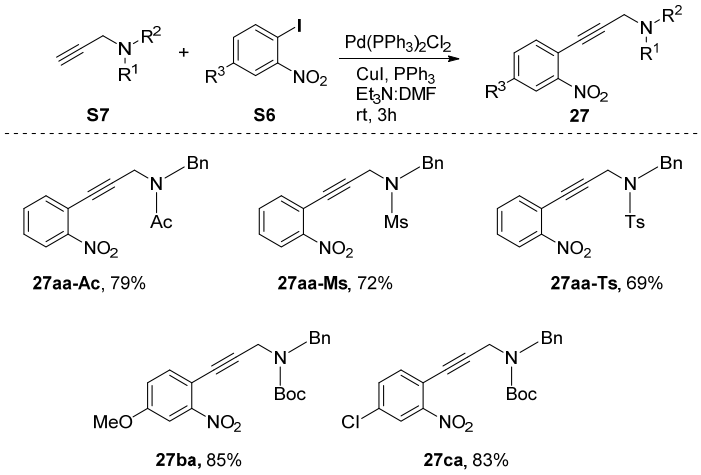


Scheme 79: Control experiments in the Au-catalyzed nitroalkyne cycloisomerization

Next, we prepared the nitroalkynes **27ab** and **27ac** respectively from benzylpropargyl ether and diethyl propargylmalonate and examined their Au[I]-catalyzed nitroalkyne cycloisomerization. The cyclization of nitroalkyne derived from the propargyl benzylether **27ab**, gave a mixture of isatogen **28ab** and anthranil **29ab** in 1:1 yield. These two products were separated by flash silica column chromatography and the structures were determined with the help of NMR. In case of the nitroalkyne **27ac**, the Au[I]-catalyzed cycloisomerization led exclusively to the corresponding anthranil **29ac** (Scheme 79). In the ^{1}H NMR spectra of **29ac**, the 1:2:1 proton pattern of compound **27ac** in aromatic region has been transformed as four separate peaks appearing in between 7.22–8.00 ppm. Two alkyne carbons of compound **27ac** were shifted to downfield and appeared at 158.8, 186.2 ppm in the ^{13}C NMR spectra of compound **29ac**. The constitution of **29ac** found to be same as that of **27ac** and

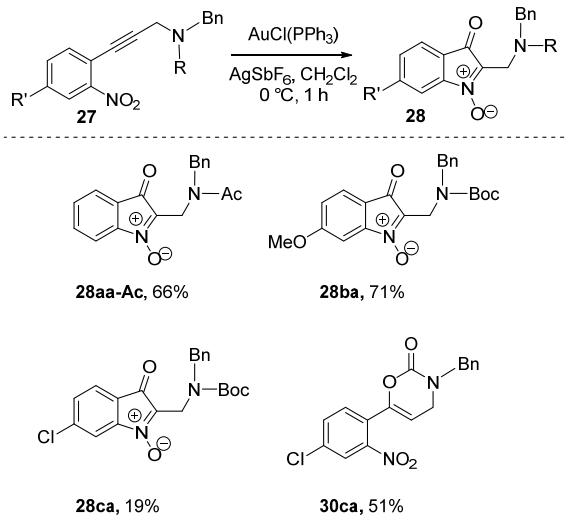
confirmed as $C_{16}H_{18}NO_6$ by the $[M+H]^+$ peak found at 320.1129 in the HRMS. Overall, these results clearly indicate that the mode of cyclizations, *i.e.* either 5-*exo* or 6-*endo* is dependent upon the presence/absence of a hetero-atom at the propargylic position and the magnitude of the –I effect that it can insert.

Next, we have synthesized various *o*-nitroalkynes by the Sonogashira coupling of terminal alkynes and *o*-iodo nitrobenzenes (Scheme 80). The variations specifically involved (i) the amine protection with –Boc, –Ac, –Ts, –Ms and (ii) the substituents on the aromatic ring such as –OMe, –Cl.



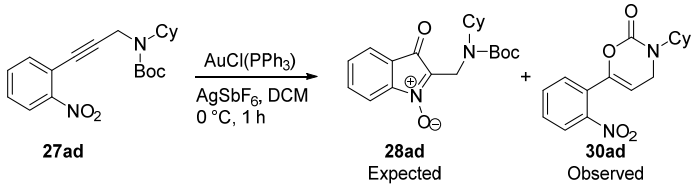
Scheme 80: Synthesis of various nitroalkynes by Sonogashira coupling

As shown in Scheme 81, the cycloisomerization of the propargyl amine having *N*-Ac group under the standard conditions produced isatogen exclusively in 66% yield. In contrast, when the reaction was carried out with *N*-Ms and *N*-Ts derivatives, the nitroalkynes were found to be intact even after a prolonged reaction time. One more observation in Au-catalyzed nitroalkyne cycloisomerization is that the outcome and yield of the reaction was influenced by the nature of the substituents on the nitroaryl ring. When we employed the substrates having electron donating groups such as –OMe under Au(I) catalytic conditions, the reactions were smooth and the yields were good. On the other hand, with substrates having electron withdrawing group like –Cl, we observed the formation of isatogen as a minor product and the participation of the *N*-Boc group in a 6-*endo*-dig fashion leading to cyclic carbamates **30ca** as the major product.



Scheme 81: Optimization of the reaction with variable protecting groups and substituents

The formation of cyclic carbamate **30ca** (white color charring spot) can be easily identified from that of the starting nitroalkyne by TLC and the reaction mixture was purified by flash silica column chromatography. We have observed the clear solubility of this compound in $CDCl_3$. The obtained cyclic carbamate was characterized with the help of analytical techniques such as NMR and mass spectrometry. The *tert*-butyl group at 1.51 ppm has been disappeared in the ^1H NMR spectrum of compound **30ca** and a proton appeared at 5.98 ppm (triplet) indicated the presence of internal olefinic proton. A doublet peak at 95.7 ppm in the ^{13}C NMR spectra of compound **30ca** is indicative of olefinic carbon of enol ether. The constitution of compound **30ca** has been confirmed as $C_{17}H_{14}ClN_2O_4$ by the $[M+H]^+$ found at 345.0637 in the HRMS.

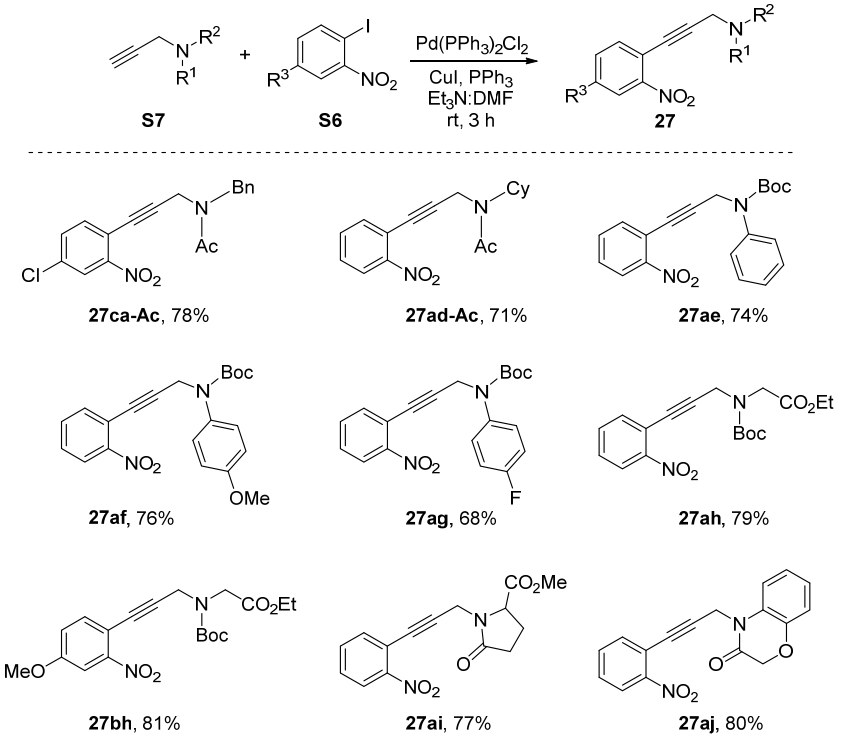


Scheme 82: Synthesis of cyclic carbamate with the *N*-bulky cycloalkyl groups

Furthermore, the reaction of the substrate having a bulky cycloalkyl group on the nitrogen under similar conditions delivered the cyclic carbamate **30ad** as a sole product in 68% yield (Scheme 82). From these studies, it is clear that electronic perturbations on the aryl ring or the steric crowding around the nitrogen can strongly

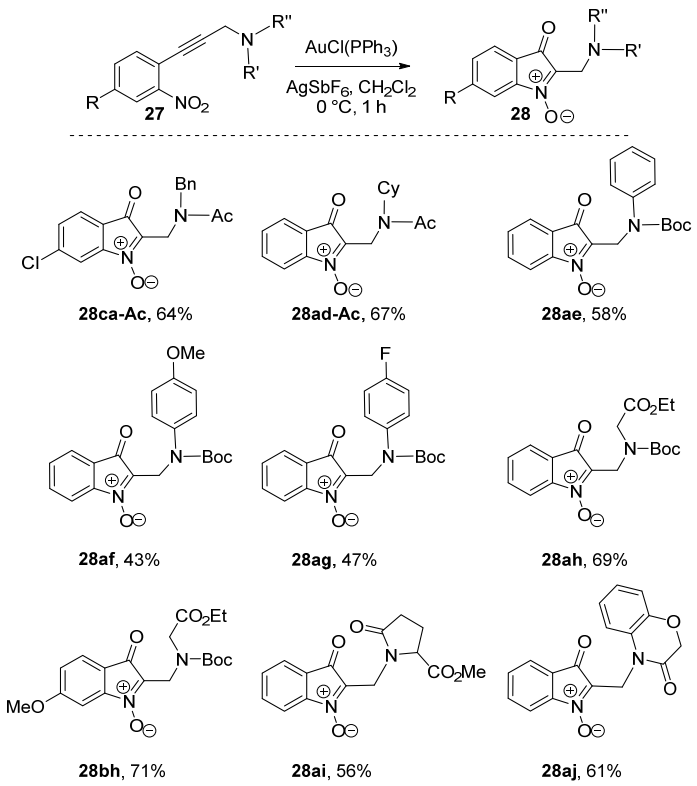
influence and switch the reacting nucleophiles and the outcome (Isatogen or Cyclic carbamate) of the reaction.

Coming to the problems associated with the *N*-Boc protected substrates having the Cl-group on the aromatic ring as well as bulky groups on the nitrogen atom, reactions lead to the formation of the cyclic carbamate derivative. We expected that, the replacement of the –Boc group with –Ac should lead to the formation of isatogen. Additionally, we have also scrutinized the compatibility of the reaction by synthesizing several other nitroalkynes having the *N*-substituents such as *N*-aryl derivatives as well as cyclic lactams by the similar procedure (Scheme 83).



Scheme 83: Synthesis of various nitroalkynes by Sonogashira coupling

Scheme 84 demonstrates the applicability of the standardized reaction conditions to various substrates prepared in the above Scheme 83. The reaction of the *N*-Ac compounds of **27ca** and **27ad** led to the corresponding isatogens exclusively in excellent yields. Furthermore, the cyclization of the *N*-propargyl simple aniline substrate **27ae** proceeded smoothly and provided the isatogen **28ae** in moderate yield.

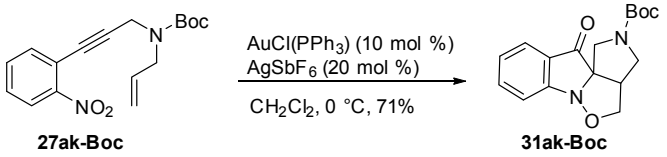


Scheme 84: Scope of the Au-catalyzed isatogen synthesis

On the other hand, with the substrates having –F and –OMe groups on the *N*-aryl ring, the reactions were sluggish and the corresponding isatogens **28af** and **28ag** are obtained in 43% and 47%yields. Further, the reaction with the *N*-propargyl glycinate derivative underwent the cyclization to form isatogen in 69% yields. Not only propargyl *N*-Boc derivatives, the reaction with propargylated amides as well are facile for the synthesis of isatogen. The cycloisomerization of cyclic amides such as pyrrolidone **27ai** and benzomorpholine **27aj** derivatives also proceeded smoothly and provided the corresponding isatogens **28ai** and **28aj** in 56% and 61% yields respectively.

After the successful demonstration of our hypothesis on Au-catalyzed nitroalkyne cycloisomerization for the isatogen preparation, next we have focussed on its subsequent cycloaddition with a suitably positioned olefin leading to the synthesis of C2-*spiro*-pseudoindoxyl frameworks. In this regard, we have synthesized the simple *o*-nitro enynamide **27ak-Boc** through the Sonogashira coupling of enyne carbamate **S7** and *o*-iodo nitro benzene **S6** (Scheme 83). This cycloisomerization of *o*-nitro enynamide **27ak-Boc** under the standardized reaction conditions at 0 °C for 4 h

gave exclusively a single product in 71% yield. The structure of the resulting **31ak-Boc** as the expected tricyclic pseudoindoxyl isoxazolidine has been elucidated with the help of NMR data. This has concluded our objective of converting a simply accessible linear enyne chain into the tricyclic pseudoindoxyl skeleton which has been realized. Importantly, this cascade process involves the construction of one C–C, one C–N, and two C–O bonds in a single pot with a net formation of three rings and two contiguous stereogenic centers (Scheme 85). The 1:2:1 pattern of aromatic protons was transformed as 2:1:1 pattern in the ^{1}H NMR spectrum of compound **31ak-Boc**. In the ^{13}C NMR of compound **31ak-Boc**, the two characteristic carbons of indolinone unit were appeared at 80.1 and 197.5 ppm. In addition, the two carbon signals at 51.5 (doublet) and 72.5 (triplet) ppm suggested that –CH was connected to the *spiro*-junction and –CH_2 to the oxygen of nitrone. The constitution of **31ak-Boc** has been found to be same as that of **27ak-Boc** and confirmed as $C_{17}H_{20}N_2O_4Na$ by the $[M+Na]^+$ found as 339.1315 in the HRMS. The relative stereochemistry of **31ak-Boc** has been established with the help of single crystal X-ray diffraction analysis (Figure 12).



27ak-Boc 31ak-Boc

Scheme 85: Au-catalyzed synthesis of *spiro*-pseudoindoxyl isoxazolidine skeletons

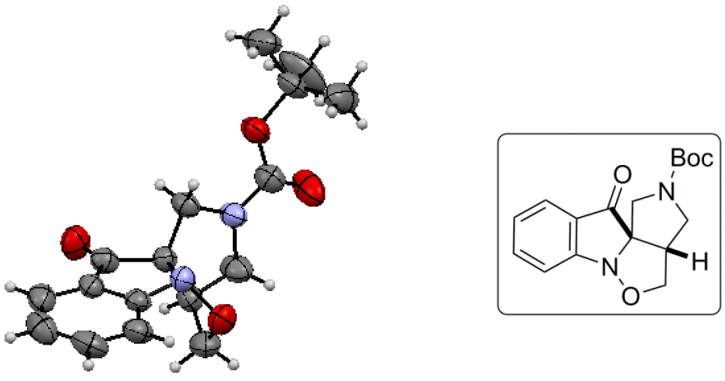
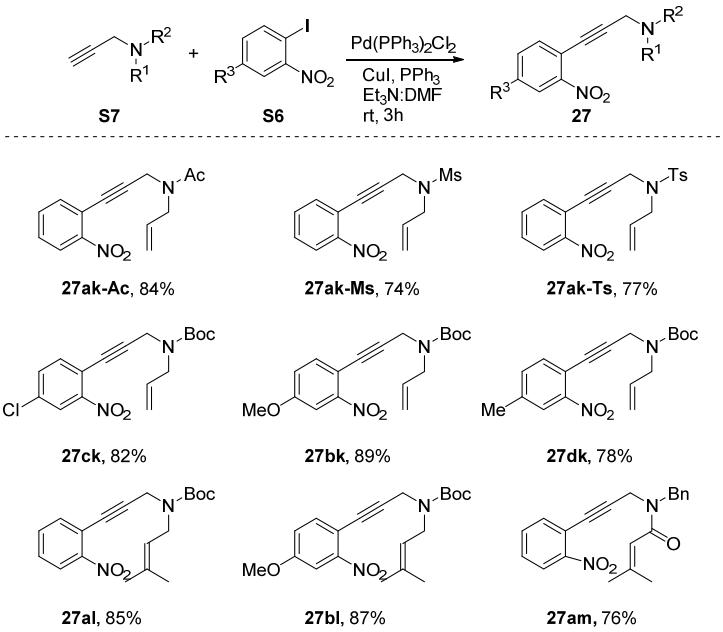


Figure 12: Single crystal X-ray diffraction of **31ak-Boc**

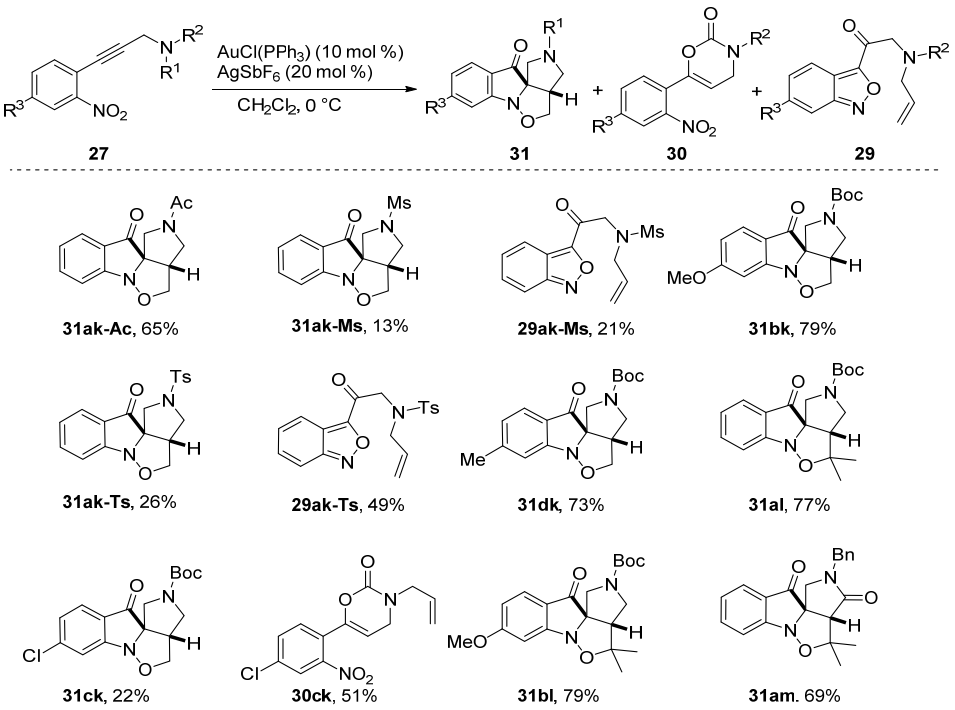
Next, to generalize the scope of this gold mediated cycloisomerization *cum* cycloaddition, a wide range of 3-(2-nitrophenyl)prop-2-yn-1-amine derivatives have been prepared by following simple synthetic transformations and the final

Sonogashira coupling with selected nitroalkynes. The variations that we incorporated in these substrates mainly are: (i) protecting groups on the nitrogen, (ii) substituents on the aromatic ring and (iii) different substituents on the *N*-alkenyl group (Scheme 86).



Scheme 86: Sonogashira coupling for the synthesis of various *o*-nitro enynamides

Scheme 87 describes the cyclization of these substrates under the standardised conditions. Similar to the *N*-Boc derivative, the reaction of the *N*-Ac derivative **27ak-Ac** under Au(I)-catalytic systems was rapid and provided the tricyclic isoxazolidine in 65% yield. Quite interestingly, the reaction of substrates with *N*-Ms and *N*-Ts derivatives **27ak-Ms** and **27ak-Ts** was also facile; the however formation of the anthranil was predominant over the isatogen that subsequently underwent cycloaddition and led to the formation of isoxazolidine. In case of the *N*-Ms derivative, the conversion was poor and the majority of the starting material was recovered. As mentioned earlier, in case of simple nitroalkynes **27aa-Ms** and **27aa-Ts**, under the same conditions, the starting compounds were completely intact. Thus, the facile cyclization of *N*-Ms and *N*-Ts derivatives **27ak-Ms** and **27ak-Ts** revealed that there is a synergetic effect of alkene π-coordination on the internal nitroalkyne redox processes mediated by the Au-complex.[92]



Scheme 87: Scope of the Au-catalysis on *o*-nitro enynamide derivatives

Further, we pursued the reaction of the substrates having the electron donating substituents such as MeO- and Me- on the aryl ring (**27bk** and **27dk**). The rate and yields were enhanced with these substrates and the reactions delivered the corresponding isoxazolidines **31bk** and **31dk** in 79% and 73% yields. On the other hand, the reaction of the substrates with electron withdrawing groups like –Cl on the aryl ring (**27ck**) reduced the rate of the reaction. We obtained the cyclic carbamate **30ck** as a major product in 51% yield and isoxazolidine **31ck** as a minor product in 22% yield. When we employed the reaction with the substrate having a prenyl group **27al** as the alkene partner, the rate and yield of the reaction were enhanced and isoxazolidine **31al** was liberated in 77% yield. To our delight, we also succeeded with the substrate having an amide group **27am** instead of *N*-Boc and procured the corresponding isoxazolidine **31am** in 69% yield. On the whole, we could successfully demonstrate the proposed cycloisomerization-cycloaddition cascade by employing Au-catalyst with the majority of propagylamine derivatives for the construction of the central tricyclic core having a 5-membered azacyclic ring in good yields.

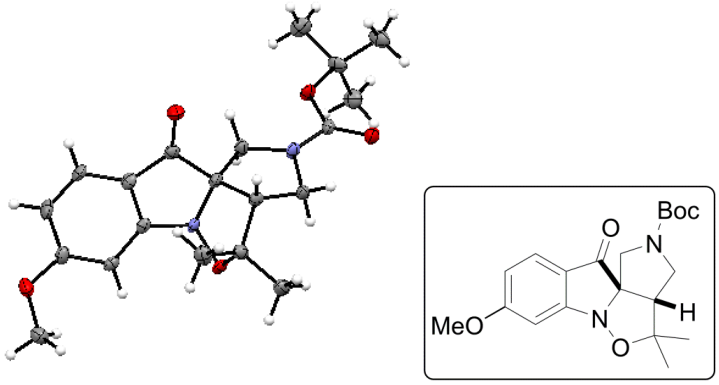
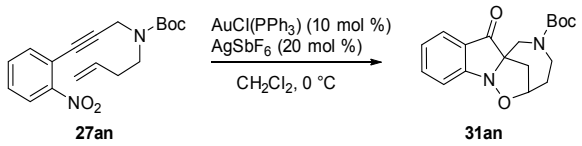


Figure 13: Single crystal X-ray diffraction of the **31bl**[93]

Next, to demonstrate the diversity and efficiency of this cascade transformation, we have taken up the synthesis of higher annulated ring systems employing the nitroalkyne substrates with varied chain lengths (of alkyne and alkene) on nitrogen. This is an important aspect in the context of the Austamide synthesis and also in the context of understanding how the regioselectivity will be dictated by the ring size during the cycloaddition. In this regard, the *o*-nitro propargyl-*N*-butenyl substrate **27an** has been prepared by following simple chemical manipulations and its cycloisomerization has been performed under the standard conditions. The reaction proceeded smoothly in 4 h to deliver a single isoxazolidine product **31an** in 73% yield. A detailed analysis of the NMR spectra of the resulting compound **31an** revealed that it has a [4,2,1]-bridged bicylic skeleton resulting from the *endo*-selective cycloaddition of the intermediate isatogen (Scheme 88).[94]



Scheme 88: Synthesis of higher annulated skeleton

In the ^{1}H NMR spectrum of compound **31an**, the aromatic–H appeared in a characteristic 2:1:1 pattern and there is one C–H that appeared in the down field (ppm) as a multiple at 4.92 ppm and the CH_2 protons were appeared range in upfield at 3.00–3.33 ppm range. In the ^{13}C NMR of compound **31an**, the two alkyne carbons of **27an** (at 80.2 and 93.6 ppm) have been replaced with two new quarterly peaks at 78.8 and 196.8 ppm. In addition, two olefinic carbons of compound **27an** have been

replaced with two new peaks at 51.4 (t) and 82.4 (d) ppm in the ^{13}C NMR spectrum of compound **31an**. These chemical shifts suggested that –CH was connected to the oxygen of nitrone and $–CH_2$ to the *spiro*-junction thus indicating a [4.2.1]-bridged bicyclic system *inter alia* an *endo*-selective [3+2]-cycloaddition. The constitution of **31an** found to be same as that of **27an** and confirmed as $C_{18}H_{22}N_2O_4Na$ by $[M+Na]^+$ peak found as 353.1472 in the HRMS. The assigned structure of compound **31an** was further established with the help of single crystal X-ray diffraction analysis (Figure 14).[95]

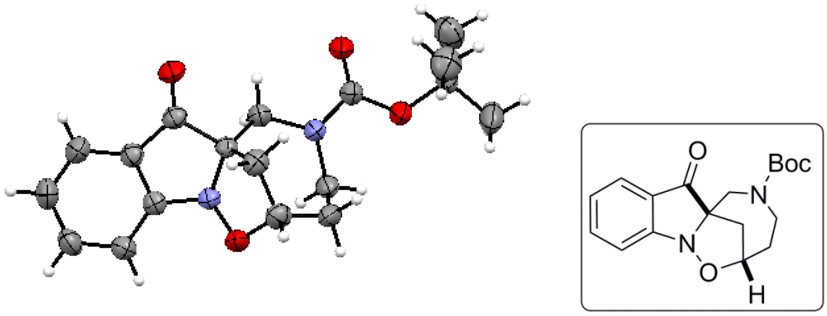
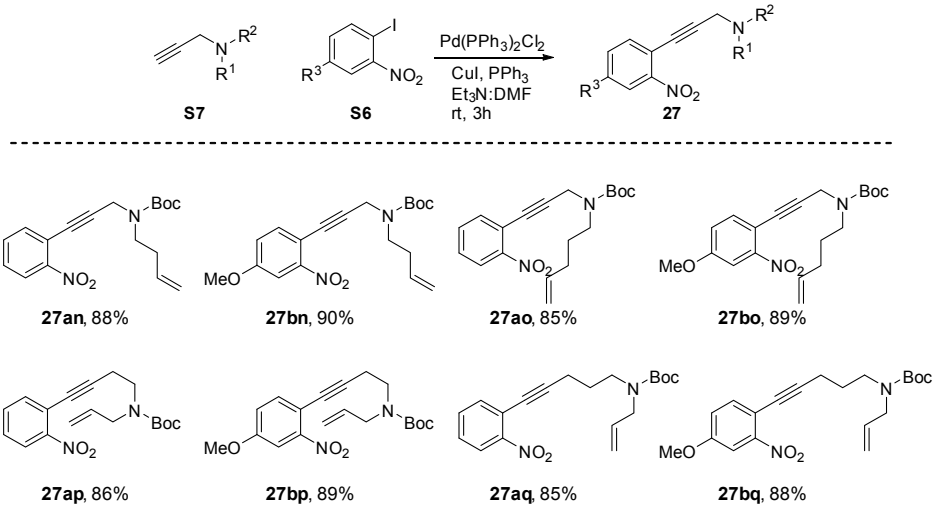


Figure 14: Single crystal X-ray diffraction of compound **31an**

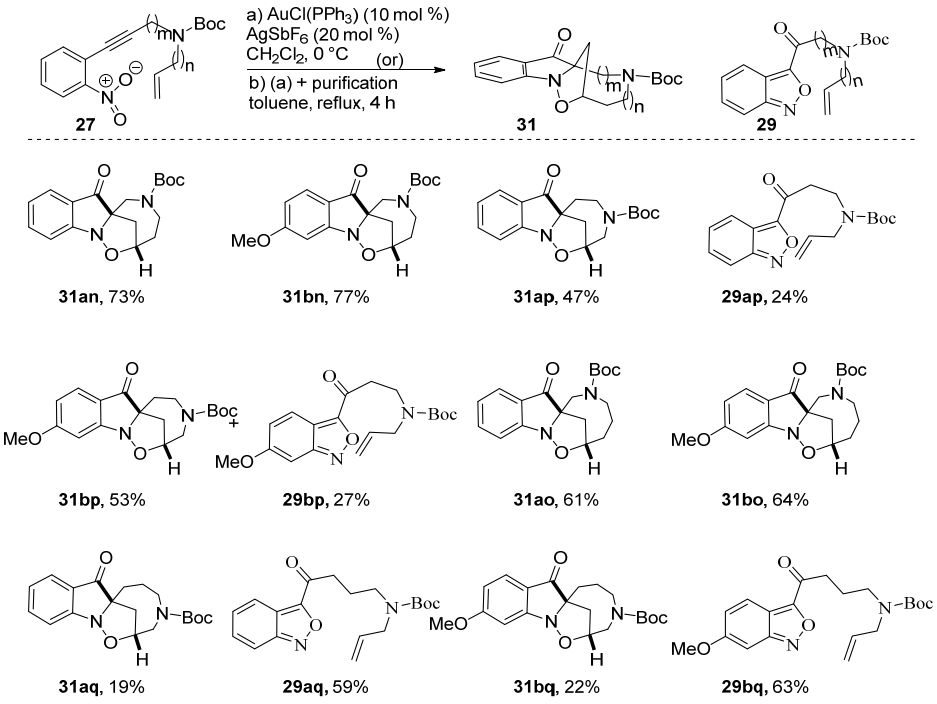


Scheme 89: Synthesis of *o*-nitro enynamides through the Sonogashira coupling

Intrigued by the above result, next we have synthesized various *o*-nitro enynamide substrates for further exploration of this cascade transformation. We have chosen the variations in position of the central nitrogen atom (distance from either alkyne or alkene terminus) for scrutinizing the applicability of the cascade reaction (Scheme 89). In this regard, *o*-nitro derivatives of propargyl-*N*-pentenyl, butynyl-*N*-allyl and

pentynyl-*N*-allyl substrates were synthesized according to the standard protocol (Sonogashira coupling).

The results of the above synthesized substrates towards the Au-catalyzed transformation have been summarized in Scheme 90. First, we treated the propargyl-*N*-pentenyl derivative **27ao** to the reaction conditions, realized the formation of the alkenyl isatogen **28ao** (the nitroalkyne cycloisomerization only taken place), where the cycloaddition was not instantaneous. The intermediate isatogen was isolated and then subjected for the cycloaddition in refluxing toluene for 4 h to obtain the isoxazolidine **31ao** in 61% yield. With the help of NMR data, the structure of the compound **31ao** was established (like above) as the [5,2,1]-bridged bicyclic product with the net annulation of a 8-membered heterocyclic ring.



Scheme 90: Scope of Au-catalysis on the *o*-nitro enynamide derivatives

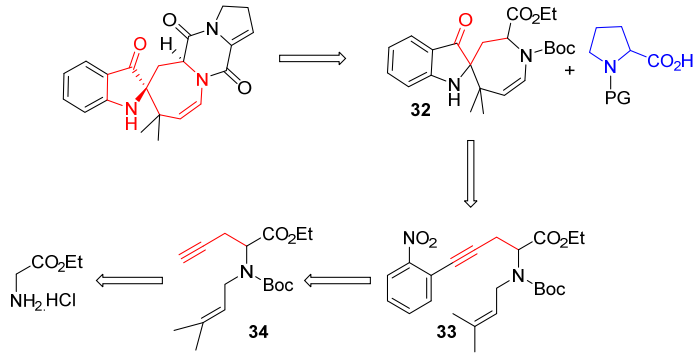
Next, we performed the reaction of the *o*-nitro butynyl-*N*-allyl derivative **27ap** which is the positional isomer of **27an**, where the nitrogen has been moved two carbons away from the alkyne terminus. The result was surprising but not unanticipated. The cycloisomerization was not selective and provided the corresponding bridged *spiro*-pseudoindoxyl derivative **31ap** (cycloaddition of the intermediate isatogen was spontaneous) and anthranil **29ap** in 47% and 24% yields respectively. We reasoned

that this may be because the influence of directing –I (–NBoc) group was decreased, thereby making the cycloisomerization non-selective (5-*exo* + 6-*endo*) leading to the formation of the isoxazolidine as well as anthranil skeletons. Both products could be distinguished with the R_f difference on TLC from that of the starting nitroalkyne compound. With the help of NMR spectral data, the structure of **31ap** could be established as the [4,2,1]-bridged bicyclic system with the net annulations of 7-membered azacyclic ring.

Next, we performed the reaction of the *o*-nitro pentynyl-*N*-allyl derivative **27aq**, where the number of linking carbons between the nitrogen and the alkyne terminus was increased to three. The cyclization of **27aq**, under standard conditions, delivered the alkenyl isatogen **28aq** and the anthranil **29aq** in a 1:3 ratio revealing that the 5-*exo*-dig selectivity during the cyclization, had dropped further. In this case too, the subsequent intramolecular cycloaddition of alkenyl isatogen **28aq** was carried out separately at elevated temperatures to obtain the *spiro*-pseudoindoxyl product **31aq** in 19% yield. The structure of the obtained compound was established as a [5,2,1]-bridged bicyclic skeleton (*endo*-selectivity) with the help of NMR spectral data analysis.

The cyclization-cycloaddition cascade approach towards the total synthesis of Austamide:

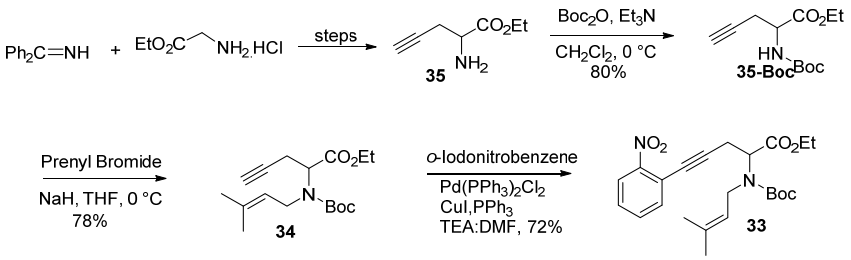
Having been established a two-step strategy for the central tricyclic core present in various *spiro*-pseudoindoxyl natural products;[96] our next concern was its applicability in the total synthesis of Austamide. Scheme 91, saliently describes our retrosynthetic disconnections featuring the synthesis of the diketopiperazine moiety,[97] which could be obtained by coupling the tricyclic pseudoindoxyl amine unit **32** and Boc-protected proline. The synthesis of the tricyclic intermediate **32** was planned from the established cascade reaction of *o*-nitroenynamide derivative **33** which, in turn, was planned by the Sonogashira coupling of *N*-prenyl ethynylalanine **34** and *o*-iodonitrobenzene.



Scheme 91: Key retrosynthetic disconnections for the Austamide

The synthesis was commenced with the preparation of the propargylated ethyl glycinate **35** through the benzophenone Schiff's base by following the literature reports.[98] Ethyl glycinate hydrochloride was treated with benzophenoneimine in CH_2Cl_2 for the transimination which led to the formation of imino ethylglycinate. This was subjected to the alkylation with propargyl bromide with NaH in THF:DMF (9:1) conditions. Then acidic hydrolysis of the imine followed by the neutralization with K_2CO_3 produced the propargylated ethyl glycinate **35**. Boc-protection of free amine was carried out with $(Boc)_2O$ and triethylamine in CH_2Cl_2 at 0 °C and delivered compound **35-Boc** in 80% yield. The Boc-protected amine **35-Boc** was alkylated with prenyl bromide by using NaH in THF at 0 °C which produced the enyne **34** in 78% yield. The structure of the enyne **34** was established with the help of NMR data. The broad singlet at 5.3 ppm was disappeared in the ^1H NMR spectra of compound **34** and a triplet at 5.1 ppm was confirmed as internal olefinic proton. A doublet peak at 121.1

ppm and two methyl groups as quartets at 17.7 and 25.7 ppm were observed in ^{13}C NMR spectrum of compound **34**. Then the subsequent Sonogashira coupling of this terminal alkyne with the *o*-iodo nitrobenzene provided the key intermediate **33** (Scheme 92).



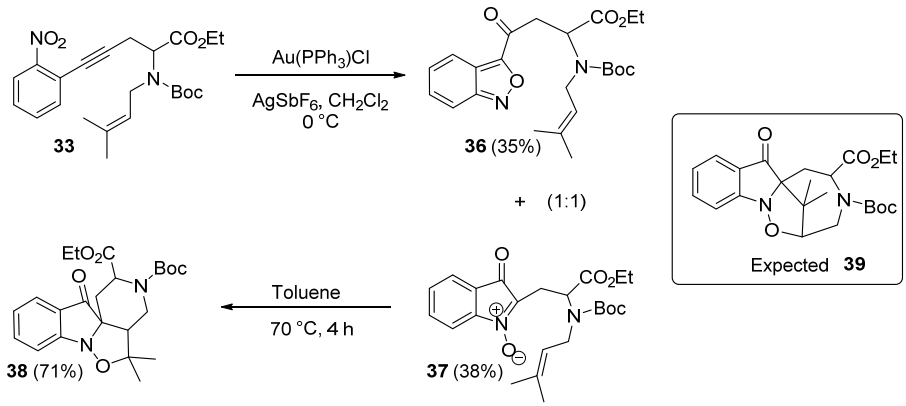
Scheme 92: Synthesis of the *o*-nitro enynamide derivative

The acetylenic proton at 2.00 ppm of the compound **34** was missed in the ^{1}H NMR spectrum of compound **33**. Acetylenic –CH at 81.3 (d) ppm of compound **34** was transformed to the quaternary carbon, and appeared at 80.7 ppm in the ^{13}C NMR of compound **33**. Also internal alkyne carbon was shifted to downfield (70.1 to 95.7 ppm) because of the attached nitrophenyl group on the other end of alkyne. Next, we executed the cycloisomerization-cyclization cascade of *o*-nitroenynamide **33** employing the $AuCl(PPh_3)\backslash AgSbF_6$ catalytic system in CH_2Cl_2 at 0 °C. The reaction was completed within 3 h and delivered a 1:1 mixture of anthranil **36** and alkenyl isatogen **37** (the cycloisomerization was not selective and the cycloaddition was not spontaneous). The structure of compound **36** was established with the help of NMR spectral data analysis.

Next, the cycloaddition of the intermediate alkenyl isatogen **37** was carried out in toluene at 70 °C to obtain the isoxazolidine **38**. The compound **38** was subjected for extensive NMR investigations to elucidate its structure. In the ^{1}H NMR spectrum of compound **38**, the triplet peak of olefinic -CH (5.1 ppm) in the compound **33** was absent and a new C–H peak was appeared as a doublet of doublet at 2.59 ppm. In addition there are two doublet of doublet peaks of $–CH_2$ present at 3.33 and 4.85 ppm. Also, the 1:2:1 pattern (present in **33**) of aromatic protons was changed to a 2:1:1 pattern. In the ^{13}C NMR spectrum of compound **38**, the characteristic quaternary carbon of the *gem*-dimethyl group was appeared as a singlet at 88.1 ppm (isoxazolidine ring) and there are two CH_2 triplets one at 51.4 ppm and the other one at 52.3 ppm. In addition the characteristic carbons of the indolinone unit were

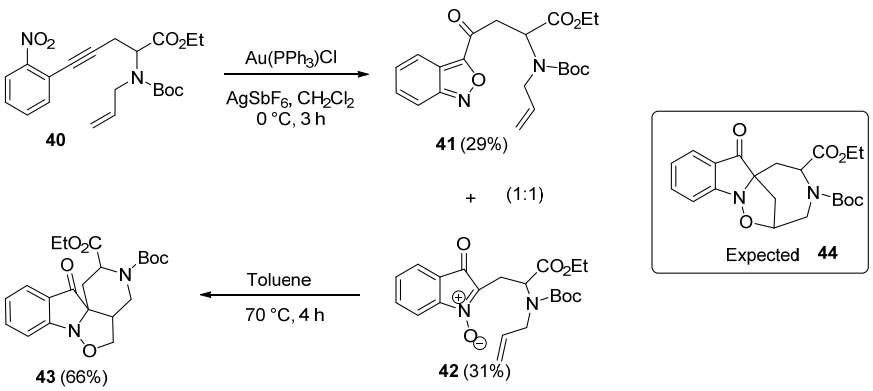
appeared at 75.4 and 201.8 ppm. The appearance of a quaternary carbon at down field and of the –CH at relative up filed (51.4 ppm) clearly indicated the presence of fused bicyclic skeleton in compound **38** and that the cycloaddition occurred completely in an *exo*-selective fashion.

Thus, this detailed analysis has revealed that the intramolecular [3+2]-cycloaddition of isatogen **37** occurred with undesired *exo*-selectivity resulting in a [6.5.6.5]-fused bicyclic skeleton with the net annulations of the 6-membered azacyclic ring. This was not encouraging. However, it suggests that maybe this undesired selectivity was due to the dimethyl group that hindering the formation of the bridged bicyclic skeleton during the cycloaddition (Scheme 93).



Scheme 93: Au-mediated nitroalkyne cycloisomerization *cum* [3+2]-cycloaddition

To answer this, we have synthesized the corresponding *N*-allyl derivative **40** following a similar sequence as employed in the preparation of enynamide **33** and subjected it for the Au-catalyzed cycloisomerization under standard conditions. The cyclization of **40** proceeded smoothly and provided a 1:1 mixture of anthranil **41** and alkenyl isatogen **42**. Finally, the cycloaddition of **42** in toluene at 70 °C resulted in the isolation of a single product in very good yield. Quite surprisingly, a detailed analysis of the spectral data of **43** revealed that it has the undesired [6.5.6.5]-fused bicyclic skeleton resulting from the *exo*-selective cycloaddition (Scheme 94). This result is quite surprising as the similar substrate **27ap** which has the exact connectivity except that there was no carboxylate group next to the amine, gave exclusively the [4,2,1]-bridged bicyclic system with the net annulations of 7-membered azacyclic ring. However, this indicates that in case of the isatogen **42**, the carboxylate group played a crucial role in directing the cycloaddition with complete *exo*-selectivity.



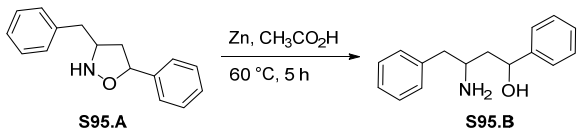
Scheme 94: Control experiments with the *N*-Allyl derivative **40**

Thus, despite the fact that the results with the model substrate have led to the identification of this cyclization-cycloaddition as an elegant tool to proceed for the total synthesis, however, when it was employed with the original substrate the outcome was completely unexpected. This led us to doubt the feasibility of this intramolecular cycloaddition approach in the projected total synthesis of Austamide and thus forced us to revise our strategy. Without moving away from our initial objective of using isatogen nucleus as the direct synthon for the central indolinone core of Austamide, we revised our strategy with a simple modification – an intermolecular [3+2] cycloaddition to construct a 2,2-disubstituted pseudoindoxyl and subsequent construction of the central 7-membered ring either by imine formation or an *N*-alkylation.

SECTION B

[Ru]-catalyzed intermolecular cycloadditions with isatogens for the synthesis of 2,2-disubstituted pseudoindoxyl skeletons

Another important aspect in this context was the N–O bond cleavage in the resulting isoxazolidine ring.[99,100] Among the many methods that are available for the cleavage of isoxazolidine to *β*-aminoalcohol, the Zn/CH_3CO_2H was the popular one (Scheme 95). Other methods employing Pd/C, phosphorous compounds, trialkylamine–SO_2 complex, aluminum iodide, tin reagents and SmI_2 etc have also been documented.



Scheme 95: Cleavage of isoxazolidine motifs

To minimize the number of steps and also to avoid the harsh conditions reported for the N–O bond cleavage, we intended to explore the possibility of [3+2]-dipolar cycloaddition of isatogen with alkene followed by N–O bond cleavage employing transition metal complexes.[101]

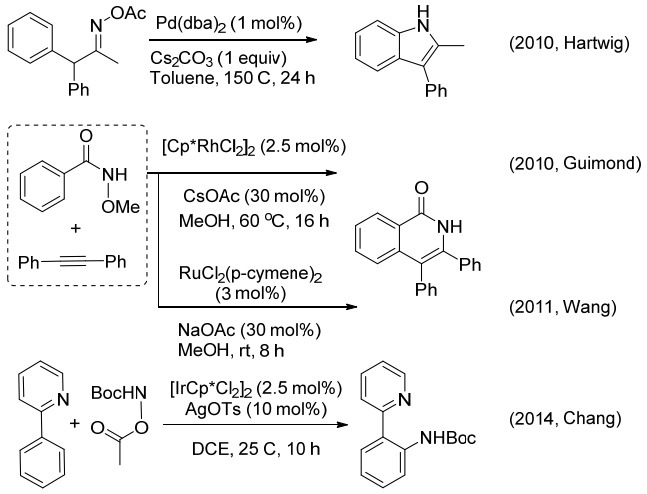
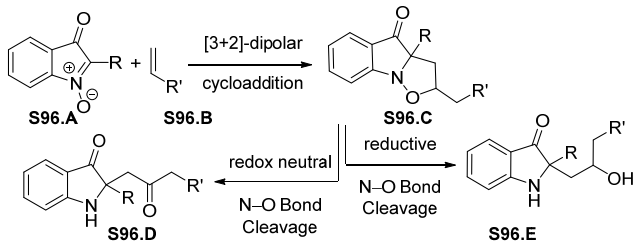


Figure 15: Representative C–H activation and functionalization of substrate endowed with N–O group as an internal oxidant

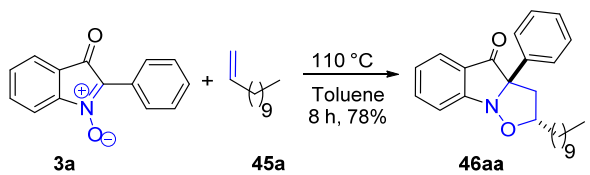
This proposal was founded upon the recent disclosures on the oxidative addition of various metal complexes across the N–O bond that subsequently avoided the use of external oxidant for the catalyst regeneration in the most challenging C–H activation and functionalization reactions. Figure 15 provides some salient developments in this area that have occurred during last four years.

To proceed in the direction of realizing the main objective of construction of the *spiro*-pseudoindoxyl core through the intramolecular [3+2]-dipolar cycloaddition of isatogen, the development of a one-pot procedure for intermolecular cycloaddition of isatogens with alkene followed by N–O bond cleavage employing transition metal complexes was a first step in this direction. There exists two possibilities for N–O bond cleavage – either reductive or redox neutral cleavage,[102] the latter being expected as the predominant path (Scheme 96). In addition, our recent observation of large Stoke shifts[103] that these pseudoindoxyl compounds displayed, led us to reason that if this one-pot protocol is realized, it provides a great avenue for the easy construction of a large set of compounds[104] and an opportunity to conjugate a fluorophore to olefin bearing biologically important molecules[105] and also to polymer materials.



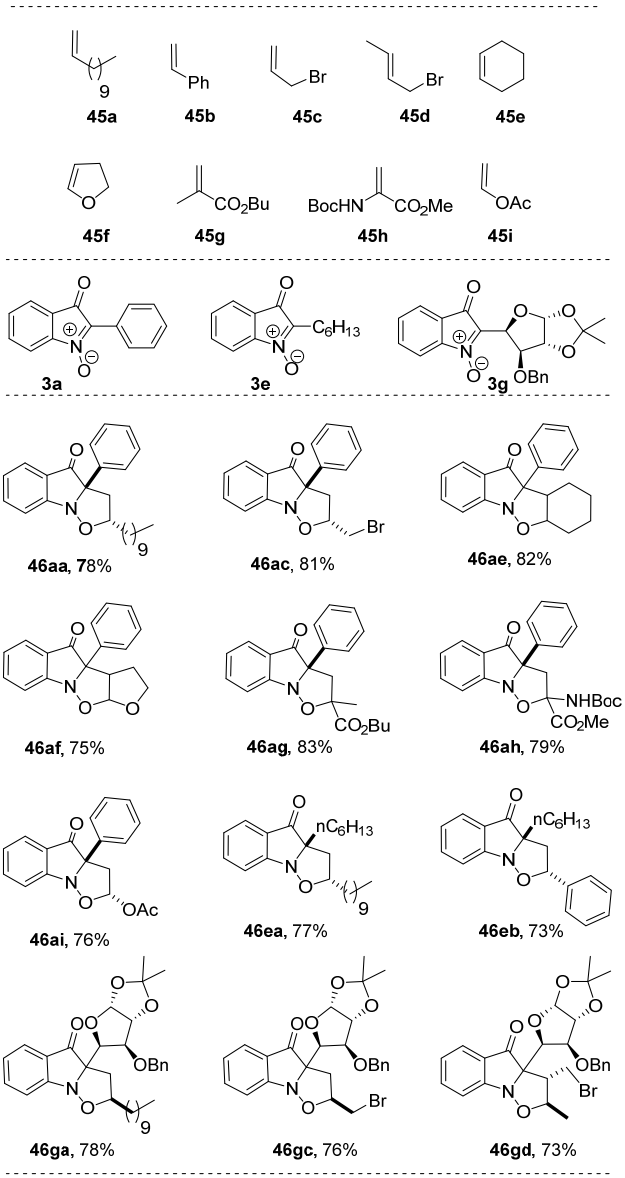
Scheme 96: The intended one-pot cycloaddition and reductive/redox neutral N–O bond cleavage

Having set this initial objective, the work in this direction started with the examination of the feasibility of [3+2]-dipolar cycloaddition of easily accessible 2-phenylisatogen with a diverse set of olefins that bear sensitive functional groups and/or that have not been explored earlier. Our early experiments in this context involved heating a solution of 2-phenylisatogen **3a** and 1-dodecene **45a** in toluene at reflux in a sealed tube. The complete consumption of **3a** has been noticed within 8 h and provided exclusively **46aa** in 78% yield (Scheme 97).



Scheme 97: Thermal cycloaddition of isatogen **3a** with and dodec-1-ene

The obtained compound **46aa** was clearly soluble in $CDCl_3$. The two ortho-protons of the phenyl ring in compound **3a** (8.63 ppm) were shifted to up field (7.55 ppm) in the ^1H NMR spectrum of compound **46aa**. A doublet of quartet (dq) at 3.88 ppm and two doublets of doublets (dd) peaks at 2.35, 2.95 ppm were assigned as the CH_2 of 1-dodecene connected at the nitrone junction. In the ^{13}C NMR spectrum of compound **46aa**, a doublet (-CH) at 79.8 ppm and a triplet ($-CH_2$) at 47.5 ppm indicated that the oxygen of nitrone was connected to –CH of dodecene unit. The constitution of **46aa** has been confirmed as $C_{26}H_{33}NO_2Na$ by $[M+Na]^+$ appeared at 414.2404 in the HRMS.



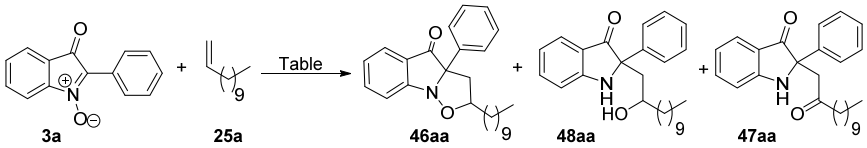
Scheme 98: Scope of the [3+2]-dipolar cycloaddition

To extend the scope of this approach, the sensitive alkenes such as styrene, allyl bromide, crotyl bromide and Boc-protected 2-aminoacrylate have been selected as the substrates and further examination was their cycloaddition with the three representative isatogens **3a**, **3e** and **3g** bearing respectively, a phenyl, alkyl and furanosyl substituents at C2 of the nitrone unit. The reaction of isatogen **3a** with allyl bromide at 110 °C proceeded smoothly and provided the corresponding isoxazolidine in excellent yield without any damage to the pendant bromo-group. The structure of **46ac** was established with the help of single crystal X-ray structural analysis. In case of isatogens **3e** and **3g**, the cycloaddition reactions are facile even at 80 °C and provided the corresponding isatogens in very good yields. Coming to the reactions with isatogen **3g**, in general an inseparable mixture of diastereomers in a 20:1 ratio was obtained (Scheme 98). The fixing of the relative stereochemistry of the newly generated stereocenters in the resulting compounds was found to be difficult by 2D NMR.

One-pot Cycloaddition and N–O Cleavage:

Next we examined conducting both dipolar cycloaddition and N–O bond cleavage in a single pot. The 2-phenyl isatogen and 1-dodecene have been selected as the representative substrates and some of the commercially available Ru-complexes under various conditions were employed to achieve the cycloaddition *cum* N–O bond cleavage.[106] Table 7 saliently describes the exploratory experiments that were conducted in this context. In general, the reactions were carried out in a sealed tube in toluene at 120 ^{o}C and 5 mol% of catalyst was used along with 30 mol% of adamantine carboxylic acid ($AdCO_2H$) as an additive and 3 eq. base. As an initial attempt, with $Ru(PPh_3)_3Cl_2$ as a catalyst, under these conditions, a mixture of the cycloaddition product **46aa** in 62% and *β*-amino ketone product **47aa** in 12% yield were obtained. This early result was promising and suggested that the proposed N–O bond cleavage with a concomitant C–O bond oxidation is possible. Gratifyingly, when employing Ru(*p*-cymene)Cl_2 dimer as a catalyst, the keto compound **47aa** was obtained exclusively in 74% yield. Even for the reaction with the $Ru_3(CO)_{12}$ complex **47aa** was the only product, albeit the yield was not comparable and also required longer reaction time (36 h) for the complete consumption of the starting isatogen.

Table 7: Optimization of catalysts and additives

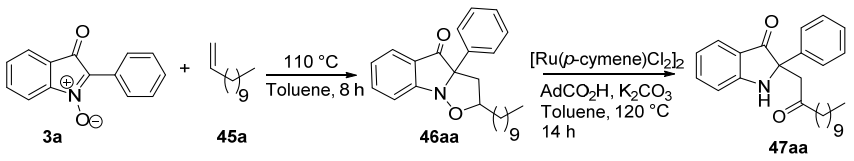


entry	catlalyst	additive	base	yield (%) **46**:**48**:**47**
1	$Ru(PPh_3)_3Cl_2$	$AdCO_2H$	K_2CO_3	62:0:12
2	**[Ru(*p*-cymene)Cl_2]$_2$**	**$AdCO_2H$**	**K_2CO_3**	**0:0:74**
3	$Ru_3(CO)_{12}$	$AdCO_2H$	K_2CO_3	0:0:58
4	[Ru(*p*-cymene)Cl_2]$_2$	$Cu(OAc)_2.H_2O$	K_2CO_3	19:15:29
5	[Ru(*p*-cymene)Cl_2]$_2$	CH_3CO_2H	K_2CO_3	0:0:69
6	[Ru(*p*-cymene)Cl_2]$_2$	Cl_3CCO_2H	K_2CO_3	22:0:18
7	[Ru(*p*-cymene)Cl_2]$_2$	$AdCO_2H$	$NaHCO_3$	0:0:67
8	------	$AdCO_2H$	K_2CO_3	82:0:0

These experiments resulted in the discovery of a catalytic 'Internal Redox' method for isoxazolidine cleavage, which involved the one pot N–O bond cleavage and subsequent oxidation of the *in situ* generated alcohol unit into a *β*-aminoketone derivative. Further exploration was continued with different additives and bases along with Ru(*p*-cymene)Cl_2 dimer as catalyst. We inspected this reaction with different additives like $Cu(OAc)_2.H_2O$, acetic acid and Cl_3CCO_2H. The results indicated that the reaction with $AdCO_2H$ delivered **47aa** in good yields and without any other side products. The same reaction in the presence of $Cu(OAc)_2.2H_2O$ provided three products **46aa**, **48aa**, **47aa** in 19:15:29% yields respectively. Subsequently, we inspected the reaction with bases like $NaHCO_3$ and NaOAc in order to improve the efficiency of this transformation. There is not much improvement of yield observed when compared to K_2CO_3 for this reaction. As expected, the cycloaddition product

46aa was left unchanged when $AdCO_2H$ and K_2CO_3 were employed without using the catalyst Ru(*p*-cymene)Cl_2 dimer.

We also conducted a reaction; first isatogen **3a** and dodecene were heated in refluxing toluene to obtain the cycloaddition product. Subsequently, were added the catalyst, additive and base and the heating was continued. As expected, the *β*-aminoketone derivative **47aa** was obtained in nearly same yields (Scheme 99).



Scheme 99: Sequential [3+2]-dipolar cycloaddition *cum* internal redox reaction

In the ^{1}H NMR spectrum of compound **47aa,** the two *ortho*-protons of the phenyl ring were shifted to up field (7.55 ppm) and there are two –CH_2 peaks, one appeared as a multiplet of two protons at 2.09–2.41 ppm and the other one as two doublet peaks at 2.58, 3.62 ppm. A broad singlet at 6.15 ppm in the ^{1}H NMR spectrum was indicated the presence of NH proton. The two carbonyl peaks have been identified separately in the ^{13}C NMR of the compound **47aa** – one at 200.4 ppm and the other newly generated carbonyl at 209.3 ppm. The constitution of **47aa** has been confirmed as $C_{26}H_{34}NO_2$ by $[M+H]^+$ peak found as 392.2584 in the HRMS.

Next, the scope of the olefins in this one-pot reaction has been explored employing various electron rich and electron deficient olefins such as styrene, ethylvinyl ether, dihydrofuran, 4-methyl styrene, allylbenzyl ether, cyclohexene, *tert*-butyl methacrylate, *tert*-butyl acrylate, ethylvinyl ketone, cyclohexenone and vinyl pyrrolidone (Figure 16).

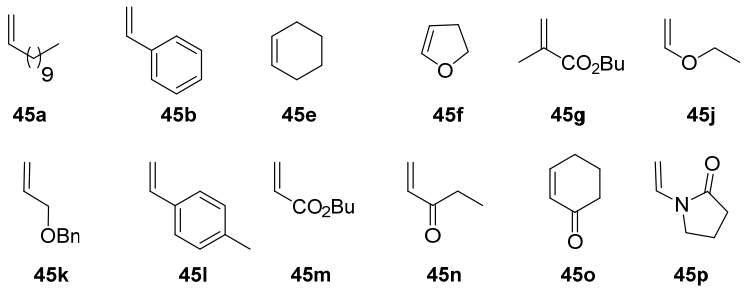
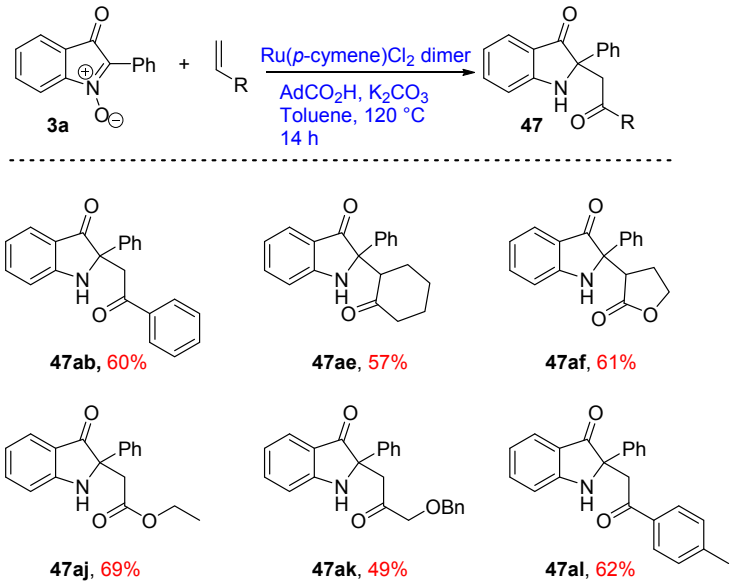


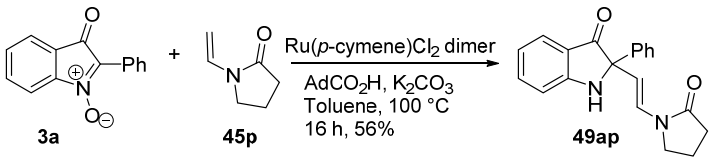
Figure 16: Various alkenes subjected to the cascade process

Schemes 100 – 102 summarize the reaction with three types of olefins. As given in Scheme 100, the reaction of 2-phenyl isatogen **3a** with simple olefins such as styrene, 4-methylstyrene, cyclohexene and benzylallyl ether proceeded smoothly and provided the corresponding ketones exclusively. In case of the reactions with electron rich olefins, such as ethylvinyl ether and dihydrofuran, the corresponding ester or lactones were obtained.



Scheme 100: Scope of the [3+2]-dipolar cycloaddition *cum* internal redox with various olefins

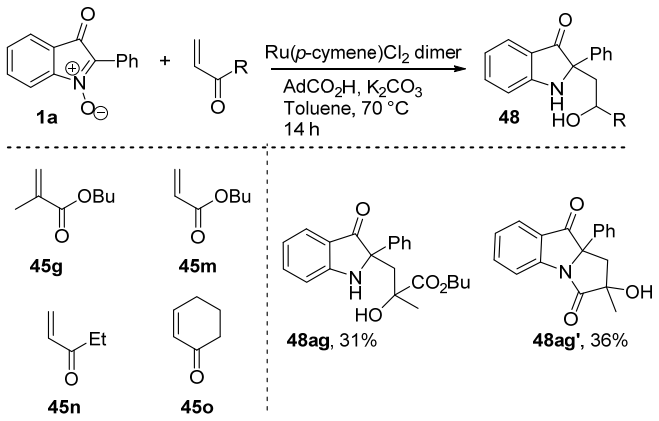
Interestingly, when *N*-vinylpyrrolidinone **45p** was employed as the substrate, the substituted *N*-vinylpyrrolidinone was obtained exclusively. The formation of **49ap** revealed that the intermediate hemiaminal has undergone dehydration without any further oxidation (Scheme 101).



Scheme 101: Reaction with conjugated olefins

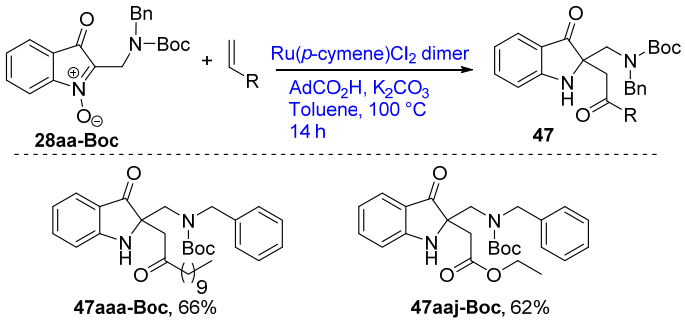
Scheme 102, illustrates the reaction of 2-phenyl isatogen with conjugated olefins under the standard reaction conditions. In these cases, the reaction was performed at lower temperatures. The solution of **3a** and conjugated olefin were heated in toluene

at 70 °C until the complete consumption of the starting isatogen (6 h) and then the catalyst and additives were added and the heating was continued at 70 °C for an additional 12 h. The reaction results in mixture of products and separation of desired product in pure was found to be a difficult task, due to the self-oligomerization of olefin. On the other hand, in case of butyl methacrylate **g**, the *β*-aminoalcohol and cyclic lactam were obtained in 31% and 36% yield respectively.



Scheme 102: Reaction with conjugated olefins

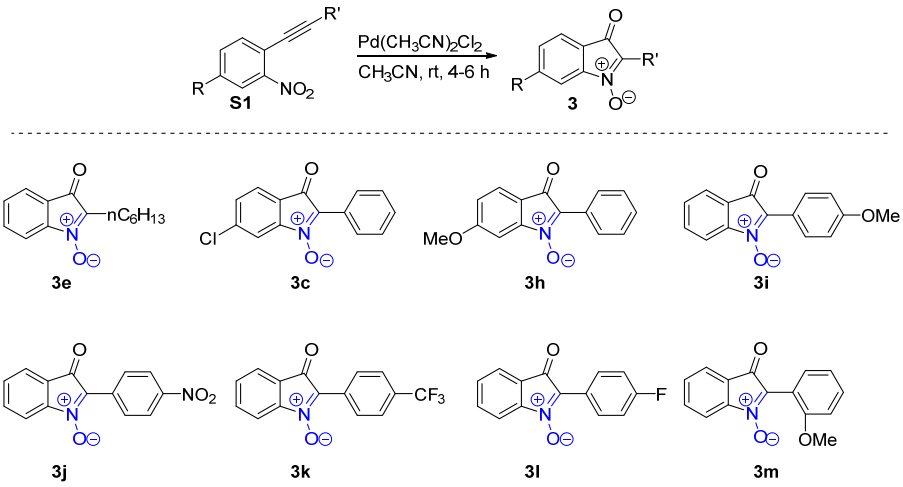
It has been noticed that, Boc-protection also survives under the reaction conditions. Treatment of compound **28aa-Boc** with 1-dodecene and ethylvinylether, delivered the corresponding *β*-aminoketo and ester compounds **47aaa-Boc**, **47aaj-Boc** in 66%, 62% yields respectively (Scheme 103).



Scheme 103: Compatibility with Boc-protected isatogens

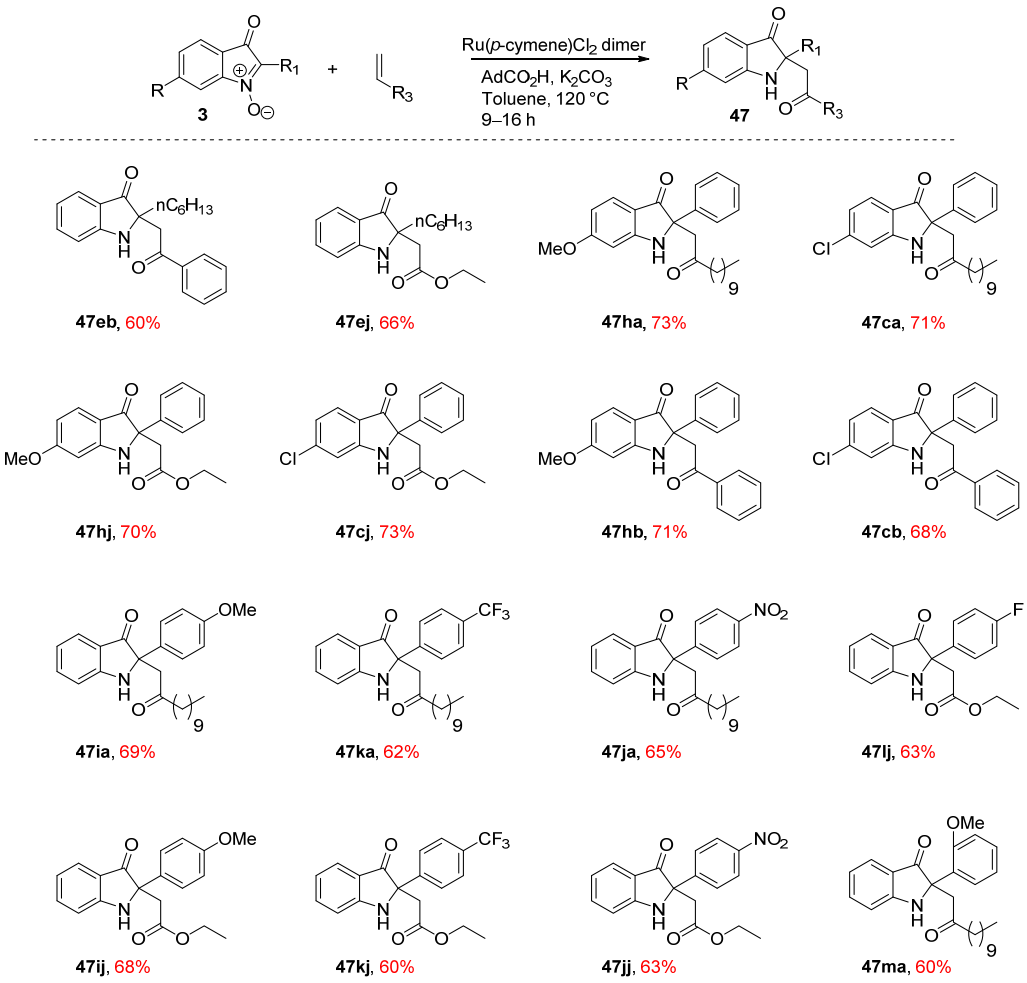
Next, we explored the scope of the reaction with various other isatogens, which were synthesized according to the previously established methods. These isatogens had a variation of substituents - i. at the C2 (alkyl or aryl); ii. at the *para*-

position to the keto group such as –Cl, –OMe and iii. at the *para*-position of C2-aryl group such as $–NO_2$, –OMe, –F, $–CF_3$ and *o*-OMe (Scheme 104).



Scheme 104: Synthesis of isatogens by Pd-mediated cycloisomerization

As shown in Scheme 105, the 2-hexyl isatogen **3e** with ethyl vinyl ether and styrene underwent the [3+2]-cycloaddition *cum* internal redox cascade and provided the C2-alkylated pseudoindoxyl **47ej** and **47eb** in 66% and 60% yields respectively. The treatment of 2-phenyl isatogen having electron withdrawing substituent (e.g., chloro) at the *para*-position to the keto group with the 1-dodecene, ethyl vinylether and styrene led to a facile reaction and provided the C2-alkylated products **47ca**, **47cj** and **47cb** in 71%, 73% and 68% yields respectively. Also with electron donating substituent such as the methoxy group provided **47ha**, **47hj** and **47hb** in 73%, 70% and 71% yields respectively. These results indicated that electronic perturbation at the keto-group does not have any influence on the reaction outcome. In case of the isatogens having electron withdrawing substituent like $–NO_2$ (**3j**), $–CF_3$ (**3k**) and –F (**3l**) group at *para*-position, their one-pot reaction with 1-dodecene, ethyl vinyl ether have proceeded smoothly and provided the correspond keto products in good yields. A similar trend was observed when the isatogens having electron donating groups such as –OMe on the aryl rings were employed. Furthermore, the effect of steric hindrance was also verified by performing the reaction with the 2-(*o*-MeOPh) isatogen **3m** with the 1-dodecene which procured the C2-alkylated pseudoindoxyl **47ma** in 60% yield (Scheme 105).



Scheme 105: Scope of [3+2]-dipolar cycloaddition *cum* internal redox with various isatogens

It is speculated that the fluorescence in the 1,2-dihydroindol-3-one core structure is mainly because of the auxochrome, *viz* the amino group which acts as a donor and the carbonyl group as an acceptor which are connected via a benzene ring. The λ_{max} and λ_{em} of the substrates depends mainly on the nature of donor and acceptor parts of the substrate. The observed optical data revealed that the compounds with a methoxy group (**47ij**) on the phenyl ring showed absorption and emission at longer wavelengths than those substrates having no substituent or other substituent on the benzene ring (Table 8). A trend was noticed in the Stokes shifts (ranging from 71 nm – 94 nm) displayed by these indol-3-ones.

Table 8: Optical properties of *β*-aminoketo compounds

Compound	Absorption	Emission	Stoke shift
47aa	394	480	86
47ab	395	480	85
47ae	405	479	74
47af	400	479	79
47aj	394	481	87
47ak	392	481	89
47al	400	483	83
47ap	398	489	91
47eb	392	476	84
47ej	391	479	88
47ha	375	461	86
47ca	397	473	76
47hj	375	460	85
47cj	391	473	82
47hb	382	463	85
47cb	398	472	74
47ia	401	486	85
47ka	400	481	81
47ja	399	470	71
47ij	396	490	94
47kj	393	477	84
47jj	395	484	89
47ma	396	486	90

In summary, as a part of our ongoing Austamide total synthesis program, a couple of new methods have been established mainly addressing the selective C2-functionalization of isatogens. We developed a simple domino process "comprising Au-catalyzed nitroalkyne redox leading to isatogen and its subsequent [3+2]-cycloaddition with a suitably positioned olefin" - for the construction of the tricyclic core present in the Austamide and related *spiro*-pseudoindoxyl natural products. Subsequently, we attempted to apply this protocol for the synthesis of the key seven membered *spiro*-pseudoindoxyl building block that was designed as an intermediate in the total synthesis of Austamide. However, due to the undesired regioselectivity of the key cycloaddition, we were forced to revise our strategy featuring an intermolecular [3+2]-cycloaddition to arrive at a suitably functional pseudoindoxyl and subsequent intramolecular imine formation. As part of this, our early investigation on the one-pot [3+2]-cycloaddition and N–O bond cleave have led us to identify a novel Ru-catalyzed redox-neutral N–O cleavage in isoxalidines leading to *β*-aminoketones. Further work on the total synthesis of Austamide employing this [3+2]-cycloaddition approach is currently under progress.

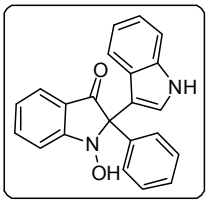
EXPERIMENTAL SECTION

General Methods

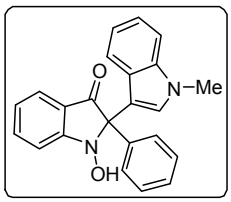
Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven-dried glassware. All anhydrous solvents were distilled prior to use: acetonitrile, dichloromethane and DMF from CaH_2; methanol from Mg cake; THF and toluene on Na/benzophenone; triethylamine and pyridine over KOH; Ac_2O over NaOAc; EtOAc over K_2CO_3; Commercial reagents were used without purification. Column chromatography was carried out by using spectrochem silica gel (60–120, 100–200, 230–400 mesh). Optical rotations were determined on a Jasco DIP-370 digital polarimeter. Specific optical rotations $[\alpha]^D$ are given in 10^{-1} x deg x cm^2 x g^{-1}. ^1H and ^{13}C NMR spectroscopy measurements were carried out on Bruker AC 200 MHz or Bruker DRX 400 or Bruker DRX 500 MHz spectrometers, and TMS was used as an internal standard. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield from Chloroform-d (δ = 7.25) or TMS and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The Multiplicity of ^{13}C NMR signals was assigned with the help of DEPT spectra and the abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, represent C (quaternary), CH, CH_2 and CH_3 respectively. Mass spectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) and 4800 plus MALDI TOF/TOF Applied Biosystem spectrometer. High Resolution Mass Spectral analysis (HRMS) was performed on SYNAPT G2 High Difinition Mass Spectrometry (HDMS) and micromass ESI-TOF MS.

General procedure for cat.$InCl_3$-mediated indole additions: To a solution of isatogen (1 eq.) in acetonitrile (4 mL) was added indole (1 eq.) and the reaction mixture was degassed under argon atmosphere. To this solution, anhy.$InCl_3$ (0.2 eq.) was added and then degassed under argon atmosphere. The reaction mixture was stirred for 2–4 h at rt. After completion of the reaction as indicated by TLC, the contents are concentrated and purified by silica gel (100–200 mesh) column chromatography (30% → 50% ethyl acetate in petroleum ether).

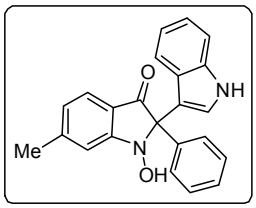
1-Hydroxy-2-phenyl-2,3'-biindolin-3-one (**5aa**): Yellow solid; 68%; (R_f = 0.35, 30% AcOEt/pet.ether); m.p. 265–267 °C; ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ6.86 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 6.6 Hz, 1H), 7.03–7.11 (m, 3H), 7.24 (d, J = 7.1 Hz, 1H), 7.27–7.35 (m, 4H), 7.50 (s, 2H), 7.60 (t, J = 7.7 Hz, 1H), 7.68 (d, J = 6.2 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ80.0 (s), 111.2 (d), 112.2 (s), 112.6 (d), 118.9 (d), 119.6 (s), 121.1 (d), 121.4 (d), 124.0 (d), 125.3 (d), 126.4 (s), 127.4 (d), 127.8 (d, 2C), 128.1 (d, 2C), 136.2 (s), 137.3 (s), 137.3 (d), 161.6 (s), 197.6 (s) ppm; IR ($CHCl_3$): ν bar = 3390, 3016, 2923, 1700, 1544, 1216, 1030, 669 cm^{-1}; ESI-MS: *m/z* (%): 363.30 (50) [M+Na]$^+$, 379.47 (25) [M+K]$^+$; HRMS: calcd. for $C_{22}H_{17}N_2O_2$ (M^++H): 341.1290, found 341.1290.



1-Hydroxy-1'-methyl-2-phenyl-2,3'-biindolin-3-one (**5ab**): Yellow solid; 70%; (R_f = 0.55, 30% AcOEt/pet.ether); m.p. 207–209°C; ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ3.69 (s, 3H), 6.84 (ddd, J = 0.7, 6.9, 7.8 Hz, 1H), 6.93 (s, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.10 (ddd, J = 0.9, 7.0, 8.1 Hz, 1H), 7.23 (dd, J = 8.6, 11.1 Hz, 2H), 7.26 (dd, J = 1.6, 4.9 Hz, 2H), 7.39 (t, J = 1.7 Hz, 1H), 7.48 (m, 2H), 7.58 (ddd, J = 1.1, 7.0, 8.2 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ32.3 (q), 80.0 (s), 108.9 (d), 111.4 (s), 112.6 (d), 118.7 (d), 119.5 (s), 120.9 (d), 121.2 (d), 121.8 (d), 123.9 (d), 127.1 (s), 127.4 (d), 127.7 (d, 2C), 128.1 (d, 2C), 129.3 (d), 137.0 (s), 137.3 (d), 137.6 (s), 161.9 (s), 197.9 (s) ppm; IR ($CHCl_3$): ν bar = 3384, 3021, 2923, 1686, 1384, 1215, 665 cm^{-1}; ESI-MS: *m/z* (%): 377.20 (100) [M+Na]$^+$; HRMS: calcd. for $C_{23}H_{19}N_2O_2$ (M^++H): 355.1446, found 355.1424**.**

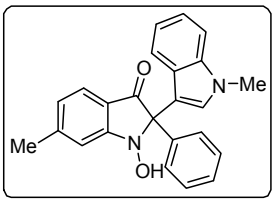


1-Hydroxy-2-(1H-indol-3-yl)-6-methyl-2-phenylindolin-3-one (**5ba**): Brown gum; 69%; (R_f = 0.30, 30% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ2.42 (s, 3H), 6.79 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 7.01 (dd, J = 4.6, 8.2 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 7.24–7.29 (m, 3H), 7.32 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 4.0 Hz, 2H), 7.52 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ21.2 (q), 79.9 (s), 110.5 (d), 112.0 (s), 112.0 (d), 116.8 (s), 117.9 (d), 120.5 (d), 121.0 (d), 122.0 (d), 123.1 (d), 124.6 (d), 126.2 (s), 126.7 (d),

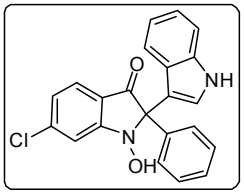


127.1 (d, 2C), 127.7 (d, 2C), 136.1 (s), 137.5 (s), 148.9 (s), 162.1 (s), 197.4 (s) ppm; IR ($CHCl_3$): *v* bar = 3398, 2926, 1703, 1495, 1119, 1031, 696 cm^{-1}; ESI-MS: *m/z* (%): 377.12 (100) $[M+Na]^+$, 393.15 (5) $[M+K]^+$; HRMS: calcd. for $C_{23}H_{19}N_2O_2$ (M^++H): 355.1446, found 355.1424**.**

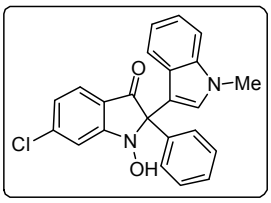
1-Hydroxy-6-methyl-2-(1-methyl-1H-indol-3-yl)-2-phenylindolin-3-one (**5bb**): Brown oil; 73%; (R_f = 0.55, 30% AcOEt/pet.ether); ^1H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ2.41 (s, 3H), 3.69 (s, 3H), 6.82 (t, *J* = 8.4 Hz, 2H), 6.93 (s, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 7.03 (s, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.23–7.28 (m, 4H), 7.48 (dd, *J* = 3.6, 7.4 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ22.8 (q), 33.0 (q), 81.2 (s), 109.8 (d), 112.6 (s), 113.6 (d), 118.2 (s), 119.5 (d), 122.1 (d), 122.8 (d), 123.5 (d), 124.5 (d), 128.2 (d), 128.5 (d, 2C), 128.7 (s), 129.0 (d, 2C), 130.2 (d), 138.0 (s), 138.8 (s), 150.3 (s), 163.5 (s), 198.6 (s) ppm; IR ($CHCl_3$): *v* bar = 3369, 3018, 2852, 1693, 1449, 1215, 1043, 699 cm^{-1}; ESI-MS: *m/z* (%): 391.16 (100) $[M+Na]^+$; HRMS: calcd. for $C_{24}H_{21}N_2O_2$ (M^++H): 369.1603, found 369.1594.



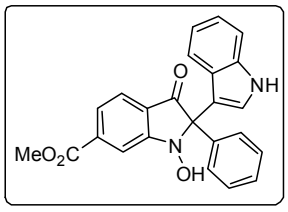
5-Chloro-1-hydroxy-2-phenyl-2,3'-biindolin-3-one (**5ca**): Pale yellow gum; 61%; (R_f = 0.30, 30% AcOEt/pet.ether); ^1H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ6.80 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 7.19 (s, 1H), 7.28 (m, 3H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.46 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ80.1 (s), 95.3 (s), 110.5 (d), 111.3 (d), 117.2 (s), 118.0 (d), 120.4 (d), 120.6 (d), 120.8 (d), 124.5 (d), 124.7 (d), 126.0 (s), 126.9 (d), 127.1 (d, 2C), 127.6 (d, 2C), 136.2 (s), 136.9 (s), 143.4 (s), 161.7 (s), 196.3 (s) ppm; IR ($CHCl_3$): *v* bar = 3399, 3019, 1701, 1602, 1316, 1215, 1108, 699 cm^{-1}; ESI-MS: *m/z* (%): 375.50 (15) $[M+H]^+$; HRMS: calcd. for $C_{22}H_{15}ClN_2O_2Na$ (M^++Na): 397.0720, found 397.0721.



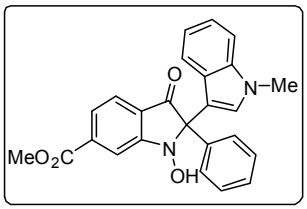
5-Chloro-1-hydroxy-1'-methyl-2-phenyl-2,3'-biindolin-3-one (**5cb**): Pale yellow liquid; 67%; (R_f = 0.40, 30% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$, 25°C, TMS): δ3.69 (s, 3H), 6.86 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.94 (s, 1H), 7.02 (d, J = 8.1 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 7.19 (s, 1H), 7.23–7.27 (m,4H), 7.43–7.47 (m, 2H), 7.55 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ32.4 (q), 80.3 (s), 109.0 (d), 110.8 (s), 112.1 (d),117.7 (s), 118.8 (d), 121.3 (d), 121.3 (d), 121.7 (d), 125.1 (d), 126.9 (s), 127.5 (d), 127.8 (d, 2C), 128.0 (d, 2C), 129.4 (d), 136.9 (s), 137.1 (s), 143.9 (s), 161.9 (s), 196.3 (s) ppm; IR ($CHCl_3$): v bar = 3439, 3019, 1680, 1599, 1215, 1045, 669 cm^{-1}; ESI-MS: *m/z* (%): 411.20 (1) $[M+Na]^+$; HRMS: calcd. for $C_{23}H_{18}ClN_2O_2$ (M^++H): 389.1057, found 389.1057.



Methyl 1-hydroxy-3-oxo-2-phenyl-2,3'-biindoline-6-carboxylate (**5da**): Yellow liquid; 49%; (R_f = 0.30, 30% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ3.92 (s, 3H), 6.82 (t, J = 7.7 Hz, 1H), 7.02 (d, J = 4.6 Hz, 1H), 7.04 (t, J = 7.9 Hz, 1H), 7.07 (s, 1H), 7.28 (m, 3H), 7.32 (d, J = 8.1 Hz, 1H), 7.45–7.49 (m, 2H), 7.51 (s, 1H), 7.58 (dd, J = 1.2, 8.1 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ52.0 (q), 80.7 (s), 110.9 (d), 111.5 (t), 113.2 (d), 118.5 (d), 121.0 (s), 121.1 (d), 121.2 (d), 122.3 (t), 123.7 (d), 125.1 (d), 126.2 (s), 127.3 (d), 127.6 (d, 2C), 128.0 (d, 2C), 136.3 (s), 137.0 (s), 137.4 (s), 161.2 (s), 166.4 (s), 197.6 (s) ppm; IR ($CHCl_3$): v bar = 3410, 3020, 2934, 1769, 1618, 1330, 1217, 1093, 1045, 667 cm^{-1}; ESI-MS: *m/z* (%): 421.10 (100) $[M+Na]^+$, 437.34 (10) $[M+K]^+$; HRMS: calcd. for $C_{24}H_{19}N_2O_4$ (M^++H): 399.1345, found 399.1345**.**

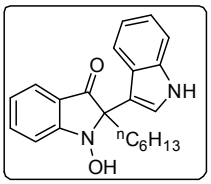


Methyl 1-hydroxy-1'-methyl-3-oxo-2-phenyl-2,3'-biindoline-6-carboxylate (**5db**): Yellow gum; 62%; (R_f = 0.50, 30% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ3.71 (s, 3H), 3.93 (s, 3H), 6.85 (t, J = 7.5 Hz, 1H), 6.96 (s, 1H), 7.01 (d, J = 7.9 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.26–7.32 (m, 4H), 7.45–7.49 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.85 (s, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ32.1 (q), 52.0 (q), 80.4

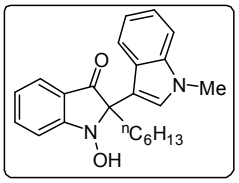


(s), 108.8 (d), 110.6 (s), 113.3 (d), 118.5 (d), 121.1 (d), 121.5 (d), 122.2 (s), 123.7 (d), 126.8 (s), 127.3 (d), 127.5 (d, 2C), 127.9 (d, 2C), 129.2 (d), 136.8 (s), 137.0 (s), 137.4 (s), 161.2 (s), 166.3 (s), 171.5 (s), 197.3 (s) ppm; IR ($CHCl_3$): *v* bar = 3443, 2989, 1735, 1650, 1615, 1375, 1243, 1097, 635 cm^{-1}; ESI-MS: *m/z* (%): 435.20 (100) $[M+Na]^+$, 451.25 (50) $[M+K]^+$; HRMS: calcd. for $C_{25}H_{21}N_2O_4$ (M^++H): 413.1501, found 413.1507.

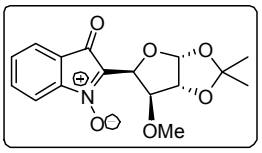
2-Hexyl-1-hydroxy-2,3'-biindolin-3-one (**5ea**): Brown gum; 72%; (R_f = 0.40, 25% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ0.80 (t, *J* = 6.4 Hz, 3H), 1.13–1.30 (m, 8H), 2.35–2.45 (m, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 7.1 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.30 (t, *J* = 3.4 Hz, 2H), 7.61 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ13.0 (q), 21.8 (t), 23.4 (t), 28.9 (t), 30.8 (t), 33.6 (t), 76.4 (s), 110.7 (d), 111.6 (d), 112.6 (s), 118.3 (d), 119.4 (d), 119.9 (d), 120.0 (s), 120.8 (d), 122.7 (d), 123.6 (d), 124.9 (s), 136.2 (s), 137.0 (d), 162.3 (s), 201.4 (s) ppm; IR ($CHCl_3$): *v* bar = 3340, 2928, 1677, 1458, 1205, 1020, 655 cm^{-1}; ESI-MS: *m/z* (%): 349.60 (20) $[M+H]^+$, 371.20 (100) $[M+Na]^+$; HRMS: calcd. for $C_{22}H_{25}N_2O_2$ (M^++H): 349.1916, found 349.1916**.**



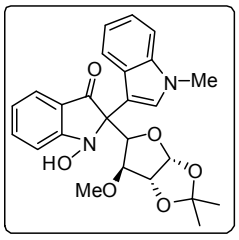
2-Hexyl-1-hydroxy-1'-methyl-2,3'-biindolin-3-one (**5eb**): Pale yellow solid; 71%; m.p. 131–133°C; (R_f = 0.60, 25% AcOEt/pet.ether); ^{1}H NMR (400 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ0.80 (t, *J* = 6.4 Hz, 3H), 1.13–1.30 (m, 8H), 2.39 (t, *J* = 7.6 Hz, 2H), 3.74 (s, 3H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.15–7.26 (m, 4H), 7.62 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ13.1 (q), 21.9 (t), 23.5 (t), 29.0 (t), 31.0 (t), 32.0 (q), 33.8 (t), 76.5 (s), 108.7 (d), 111.7 (d), 111.9 (s), 118.5 (d), 119.9 (d), 120.0 (s), 120.1 (d), 121.0 (d), 122.9 (d), 125.6 (s), 127.9 (d), 136.8 (s), 137.2 (d), 162.4 (s), 201.3 (s) ppm; IR ($CHCl_3$): *v* bar = 3393, 3018, 2856, 1698, 1541, 1376, 1216, 1017, 668 cm^{-1}; ESI-MS: *m/z* (%): 385.70 (10) $[M+Na]^+$; HRMS: calcd. for $C_{23}H_{27}N_2O_2$ (M^++H): 363.2072, found 363.2072**.**



2-(6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-oxo-3H-indole 1-oxide (**3f**): Yellow solid; (R_f = 0.40, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.53 (s, 3H), 3.30 (s, 3H), 4.21 (d, J = 5.1 Hz, 1H), 3.91 (d, J = 3.9 Hz, 1H), 5.65 (d, J = 5.1 Hz, 1H), 6.17 (d, J = 3.9 Hz, 1H), 7.53–7.65 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.7 (q), 27.3 (q), 58.2 (q), 74.3 (d), 82.8 (d), 85.4 (d), 105.7 (d), 112.7 (s, 2C), 113.9 (d), 121.8 (d), 123.4 (s), 131.6 (d), 134.2 (d), 146.7 (s), 184.2 (s) ppm; ESI-MS: *m/z* (%): 342.04 (100) $[M+Na]^+$; HRMS: calcd. for $C_{16}H_{17}NO_6Na$ (M^++Na): 342.0954, found 342.0916.



1-Hydroxy-2-(6-methoxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-1'-methyl-2,3'-biindolin-3-one (**5fb**): Yellow crystalline solid; 74%; m.p. 235–237°C; (R_f = 0.60, 50% AcOEt/pet.ether); ^{1}H NMR (500 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ 1.34 (s, 3H), 1.50 (s, 3H), 2.96 (s, 3H), 3.73 (s, 3H), 3.86 (d, J = 3.8 Hz, 1H), 4.59 (d, J = 3.8 Hz, 1H), 5.19 (d, J = 3.9 Hz, 1H), 6.10 (d, J = 3.8 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 9.3 Hz, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 3.2 Hz, 1H); ^{13}C NMR (125 MHz, 3:2 Methanol-d_4+$CDCl_3$): δ 25.1 (q), 25.8 (q), 31.6 (q), 56.2 (q), 75.7 (s), 80.9 (d), 82.7 (d), 84.5 (d), 104.5 (d), 108.6 (d), 109.7 (s), 111.2 (s), 112.5 (d), 118.5 (d), 120.1 (d), 120.2 (d), 120.5 (s), 120.8 (d), 122.0 (d), 125.6 (s), 129.5 (d), 136.5 (s), 136.6 (d), 161.7 (s), 198.5 (s) ppm; IR ($CHCl_3$): ν bar = 3408, 3017, 2930, 2855, 1712, 1610, 1475, 1376, 1162, 1019, 887 cm^{-1}; ESI-MS: *m/z* (%): 451.70 (10) $[M+H]^+$, 473.66 (5) $[M+Na]^+$; HRMS: calcd. for $C_{25}H_{26}N_2O_6Na$ (M^++Na): 473.1689, found 473.1668.



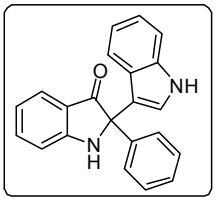
Crystal Data: Data for the compound was collected at T = 296 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Oscillation / frame –0.3º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration. The structure was solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarisation and absorption effects. SADABS correction was applied. SHELX-97 (ShelxTL)[27] was used for structure solution and full matrix least squares

refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

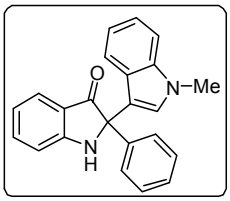
Compound (**5fb**) $C_{25}H_{27}N_2O_6$: Single crystals of the complex were grown by slow evaporation of the solution a mixture of methanol and pet-ether. Pale yellow needle crystal of approximate size 0.19 x 0.15 x 0.11 mm^3, was used for data collection. Hemisphere data acquisition. Total scans = 3, total frames = 1271, exposure / frame = 10.0 sec / frame, θ range = 1.57 to 25.0 º, completeness to θ of 25.0 º is 99.6%. $C_{25}H_{27}N_2O_6$, M = 451.49. Crystals belong to Monoclinic, space group $P2_1$, a = 12.180 (1) , b = 7.0359 (6) , c = 13.294 (1) Å, V = 1112.80 (17) $Å^3$, Z = 2, D_c = 1.347 g /cc, μ (Mo–Kα) = 0.097 mm^{-1}, 5646, reflections measured, 3418 unique [I>2σ(I)], R value 0.0454, wR2 = 0.1096, Largest diff. peak and hole 0.212 and –0.406 e. $Å^{-3}$.

General procedure for $InCl_3$-mediated indole addition cum N–O reductions: A throughly degassed solution of isatogen (1 eq.) and indole (1.5 eq.) and anhydrous $InCl_3$ (1.5 eq.) in toluene (6 mL) was was stirred for 4–8 h at 80 °C. After completion of the reaction as indicated by TLC, the contents were concentrated under reduced pressured and the crude was purified by silicagel (100–200 mesh) column chromatography (20% → 40% ethyl acetate in petroleum ether).

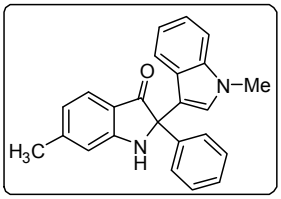
2-(1H-Indol-3-yl)-2-phenylindolin-3-one (**6aa**): Brown liquid; 53%; (R_f = 0.45, 25% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ5.37 (br s, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.12–7.18 (m, 3H), 7.26–7.31 (m, 3H), 7.36 (d, J = 8.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.55 (dd, J = 1.8, 8.1 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 8.18 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ71.3 (s), 102.6 (s), 111.6 (d), 112.9 (d), 115.6 (s), 119.5 (s), 119.6 (d), 119.7 (d), 120.1 (d), 122.5 (d), 123.7 (d), 125.6 (d), 126.8 (d, 2C), 127.7 (d), 128.4 (d, 2C), 136.9 (s), 137.5 (d), 139.5 (s), 160.5 (s), 200.5 (s) ppm; IR ($CHCl_3$): v bar = 3411, 3019, 2927, 1707, 1450, 1215, 758 cm^{-1}; ESI-MS: m/z (%): 325.25 (20) $[M+H]^+$, 347.22 (50) $[M+Na]^+$; HRMS: calcd. for $C_{22}H_{17}N_2O$ (M^++H): 325.1341, found 325.1316.



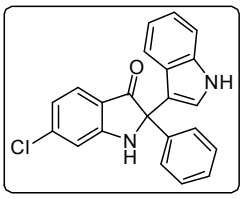
1'-Methyl-2-phenyl-2,3'-biindolin-3-one (**6ab**): Brown gum; 56%; (R_f = 0.55, 25% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ3.73 (s, 3H), 5.35 (br s, 1H), 6.88 (d, J = 7.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 7.02 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.26–7.31 (m, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.56 (dd, J = 1.5, 8.0 Hz, 2H), 7.69 (d, J = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ32.8 (q), 71.3 (s), 109.7 (d), 112.9 (d), 113.9 (s), 119.6 (d, 2C), 119.8 (d), 122.1 (d), 125.6 (d), 126.1 (s), 126.8 (d, 2C), 127.7 (d), 128.3 (d), 128.4 (d, 2C), 137.5 (d), 137.8 (s), 139.6 (s), 160.5 (s), 200.6 (s) ppm; IR ($CHCl_3$): v bar = 3377, 3058, 2926, 1698, 1615, 1467, 1326, 1217, 1031, 698 cm^{-1}; ESI-MS: *m/z* (%): 339.28 (20), $[M+H]^+$, 361.36 (10) $[M+Na]^+$; HRMS: calcd. for $C_{23}H_{19}N_2O$ (M^++H): 339.1497, found 339.1471.



6-Methyl-2-(1-methyl-1H-indol-3-yl)-2-phenylindolin-3-one (**6bb**): Yellow liquid; 54%; (R_f = 0.65, 25% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ2.36 (s, 3H), 3.72 (s, 3H), 5.27 (br s, 1H), 6.71 (d, J = 6.0 Hz, 2H), 6.96 (t, J = 7.5 Hz, 1H), 7.02 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.27 (dd, J = 1.8, 4.1 Hz, 2H), 7.28 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 4.4 Hz, 1H), 7.55 (dd, J = 1.8, 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ22.5 (q), 32.8 (q), 71.5 (s), 109.7 (d), 112.9 (d), 114.1 (s), 117.4 (s), 119.5 (d), 119.8 (d), 121.4 (d), 122.0 (d), 125.3 (d), 126.1 (s), 126.8 (d, 2C), 127.6 (d), 128.3 (d, 3C), 137.7 (s), 139.8 (s), 149.2 (s), 161.0 (s), 199.8 (s) ppm; IR ($CHCl_3$): v bar = 3464, 2985, 1742, 1466, 1374, 1242, 1047, 938 cm^{-1}; ESI-MS: *m/z* (%): 351.10 (5) $[M+H]^+$, 375.09 (100) $[M+Na]^+$, 391.07 (20) $[M+K]^+$; HRMS: calcd. for $C_{24}H_{21}N_2O$ (M^++H): 353.1654, found 353.1678.

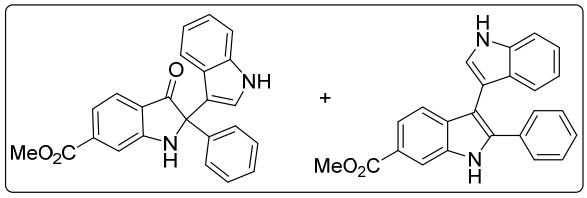


6-Chloro-2-(1H-indol-3-yl)-2-phenylindolin-3-one (6ca): Yellow liquid; 57%; (R_f = 0.50, 25% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ5.46 (br s, 1H), 6.84 (dd, J = 1.3, 8.2 Hz, 1H), 6.91 (d, J = 1.2 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.4 Hz, 3H), 7.17 (s, 1H), 7.28 (s, 2H), 7.36 (d, J = 7.5, 1H), 7.52 (dd, J = 1.7, 7.5 Hz, 2H), 7.59 (d, J = 8.2 Hz, 1H), 8.21 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ71.8 (s), 111.7 (d), 112.6 (d), 115.2 (s), 118.0 (s), 119.6 (d), 120.2 (d),

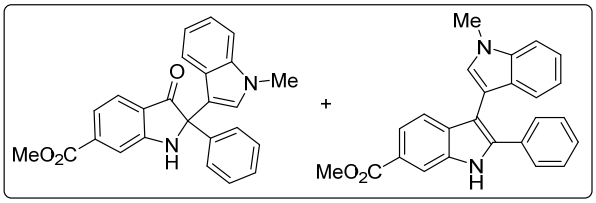


120.4 (d), 122.7 (d), 123.8 (d), 126.6 (d), 126.7 (d, 2C), 127.9 (d), 128.1 (d), 128.5 (d, 2C), 136.9 (s), 139.0 (s), 144.0 (s), 160.6 (s), 199.0 (s) ppm; IR ($CHCl_3$): ν bar = 3410, 3020, 2934, 1769, 1618, 1330, 1217, 1093, 1045, 667 cm^{-1}.

Methyl 3-oxo-2-phenyl-2,3'-biindoline-6-carboxylate (**6da+7da**): Brown gum; 47%; ^1H NMR (500 MHz, $CDCl_3$): δ3.92 (s, 1.4H), 3.94 (s, 3H), 5.49 (br s, 0.34H), 6.98 (d, J = 3.6 Hz, 0.51H), 7.02 (d, J = 7.6 Hz, 1H), 7.11 (m, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.21 (s, 1H), 7.27–7.29 (m, 3H), 7.37 (d, J = 8.3 Hz, 0.69H), 7.45 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 2.4, 7.8 Hz, 2H), 7.53 (t, J = 2.2 Hz, 0.66H), 7.54 (s, 1H), 7.60 (d, J = 13.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 0.48H), 7.79 (dd, J = 1.3, 8.3 Hz, 1H), 8.19 (br s, 0.37H), 8.21 (br s, 1H), 8.30 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ52.0 (q), 52.6 (q), 71.9 (s), 77.2 (d), 96.1 (s), 108.0 (s), 109.5 (s), 111.1 (d), 111.7 (d), 113.2 (d), 114.1 (d), 115.3 (s), 119.7 (d), 119.9 (d), 120.2 (d), 120.3 (d), 120.7 (d), 121.1 (d), 122.1 (d), 122.6 (s), 122.7 (d), 123.5 (d), 123.7 (d), 123.9 (s), 125.4 (s), 125.5 (d), 126.7 (d), 127.2 (s), 127.7 (d, 2C), 128.0 (d), 128.5 (d), 128.7 (d, 2C), 132.5 (s), 133.6 (s), 135.3 (s), 136.3 (s), 137.8 (s), 138.0 (s), 139.0 (s), 166.4 (s), 168.2 (s), 200.3 (s) ppm; IR ($CHCl_3$): ν bar = 3469, 3017, 2851, 1701, 1495, 1450, 1216, 1091, 861, 669 cm^{-1}; ESI-MS: *m/z* (%): 405.07 (100) $[M+Na]^+$, 421.07 (99) $[M+K]^+$; HRMS: calcd. for $C_{24}H_{19}N_2O_3$ (M^++H): 383.1395, found 383.1401.

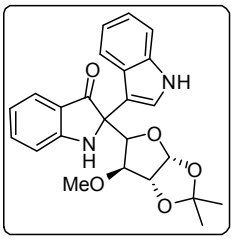


Methyl 1'-methyl-3-oxo-2-phenyl-2,3'-biindoline-6-carboxylate (**6db+7db**): Brown gum; 41%; ^1H NMR (500 MHz, $CDCl_3$): δ3.73 (s, 1H), 3.85 (s, 3H), 3.92 (s, 1H), 3.94 (s, 1H), 5.47 (br s, 1H), 6.97 (dd, J = 0.9, 2.6 Hz, 0.46H), 6.99 (s, 1H), 7.08 (s, 1H), 7.12 (d, J = 7.8 Hz, 0.59H), 7.20 (d, J = 8.4 Hz, 0.47H), 7.22 (s, 0.45H), 7.24 (s, 1H), 7.26 (d, J = 1.6 Hz, 2H), 7.29 (d, J = 3.3 Hz, 2H), 7.32 (d, J = 7.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.52 (dd, J = 1.9, 7.7 Hz, 2H), 7.54–7.56 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 0.42H), 7.79 (dd, J = 1.3, 8.4 Hz, 1H), 8.20 (br s, 1H), 8.61 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ32.8 (q), 32.9 (q), 52.0 (q), 52.6 (q), 72.0 (s), 77.2 (d), 107.8 (s), 108.1 (s), 109.2 (d), 109.8

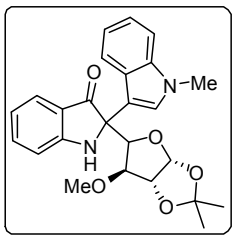


(d), 113.1 (d), 113.5 (s), 114.1 (d), 119.1 (d), 119.7 (d), 119.9 (d), 120.3 (d), 120.8 (d), 121.0 (d), 121.6 (d), 122.2 (d), 122.5 (s), 123.9 (s), 125.5 (d), 125.9 (s), 126.8 (d), 127.6 (s), 127.6 (d, 2C), 127.9 (d), 128.0 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.7 (d, 2C), 132.5 (s), 133.6 (s), 135.2 (s), 137.2 (s), 137.5 (s), 137.8 (s), 138.0 (s), 139.1 (s), 159.8 (s), 166.4 (s), 168.2 (s), 200.4 (s) ppm; IR ($CHCl_3$): *v* bar = 3351, 3017, 2928, 2852, 1702, 1618, 1451, 1217, 1091, 697 cm^{-1}; ESI-MS: *m/z* (%): 397.33 (20) $[M+H]^+$, 419.33 (40) $[M+Na]^+$, 435.26 (100) $[M+K]^+$; HRMS: calcd. for $C_{25}H_{20}N_2O_3Na$ (M^++Na): 419.1372, found 419.1380**.**

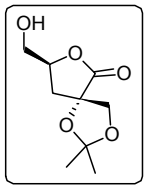
2-(6-Methoxy-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-2,3'-biindolin-3-one (**6fa**): Brown gum; 52%; (R_f = 0.30, 40% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ1.27 (s, 2H), 1.30 (s, 3H), 1.45 (s, 3H), 1.53 (s, 1.62H), 2.81 (s, 3H), 3.12 (s, 1.65H), 3.59 (d, *J* = 3.2 Hz, 0.55H), 3.83 (d, *J* = 3.2 Hz, 1H), 4.42 (d, *J* = 3.8 Hz, 0.56H), 4.46 (d, *J* = 3.8 Hz, 1H), 5.07 (d, *J* = 3.3 Hz, 1H), 5.13 (d, *J* = 3.3 Hz, 0.56H), 5.48 (br s, 1H), 5.85 (d, *J* = 3.7 Hz, 0.54H), 6.01 (d, *J* = 3.8 Hz, 1H), 6.11 (br s, 0.51H), 6.76 (t, *J* = 7.5 Hz, 0.59H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 0.56H), 7.02 (ddd, *J* = 1.2, 7.2, 7.9 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.13–7.16 (m, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.39 (d, *J* = 2.6 Hz, 1H), 7.41–7.44 (m, 1H), 7.45 (d, *J* = 2.9 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 0.63 H), 7.66 (t, *J* = 7.3 Hz, 2H), 8.11 (d, *J* = 7.9 Hz, 0.63), 8.13 (br s, 1H), 8.20 (br s, 0.57H); ^{13}C NMR (125 MHz, $CDCl_3$): δ26.3 (q), 26.5 (q), 26.9 (q), 27.1 (q), 57.6 (q), 57.8 (q), 68.6 (s), 69.8 (s), 80.6 (d), 81.6 (d), 82.2 (d), 82.7 (d), 84.8 (d), 85.5 (d), 105.0 (d), 105.3 (d), 111.2 (d), 111.3 (d), 112.0 (s), 112.0 (s), 112.3 (d), 112.9 (s), 113.0 (s), 115.0 (s), 118.5 (d), 118.8 (d), 119.9 (d), 119.9 (d), 120.0 (s), 120.6 (d), 121.5 (s), 121.7 (d), 122.0 (d), 122.2 (d), 122.3 (d), 123.4 (d), 124.5 (d), 125.0 (s), 125.1 (s), 125.3 (d), 136.8 (s), 137.0 (s), 137.1 (d), 137.1 (d), 162.0 (s), 162.1 (s), 201.4 (s), 201.5 (s) ppm; IR ($CHCl_3$): *v* bar = 3409, 3019, 2853, 1701, 1618, 1457, 1216, 1081, 757 cm^{-1}; ESI-MS: *m/z* (%): 421.12 (3) $[M+H]^+$, 443.15 (100) $[M+Na]^+$, 459.13 (10) $[M+K]^+$; HRMS: calcd. for $C_{24}H_{25}N_2O_5$ (M^++H): 421.1763, found 421.1755.



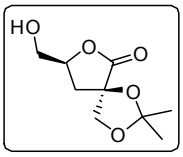
2-(Tetrahydro-6-methoxy-2,2-dimethylfuro[2,3-d][1,3]dioxol-5-yl)-2-(1-methyl-1H-indol-3-yl)indolin-3-one (**6fb**): Brown liquid; 56%; (R_f = 0.45, 40% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ1.27 (s, 3H), 1.53 (s, 3H), 3.14 (s, 3H), 3.61 (d, J = 3.1 Hz, 1H), 3.74 (s, 3H), 4.43 (d, J = 3.9 Hz, 1H), 5.07 (d, J = 3.1 Hz, 1H), 5.84 (d, J = 3.8 Hz, 1H), 6.12 (br s, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.26 (s, 1H), 7.37 (s, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ26.5 (q), 27.1 (q), 32.9 (q), 57.8 (q), 69.7 (s), 80.5 (d), 82.9 (d), 85.4 (d), 105.3 (d), 109.3 (d), 110.9 (s), 112.0 (s), 112.3 (d), 118.5 (d), 119.4 (d), 120.0 (s), 121.6 (d), 121.8 (d), 125.3 (d), 125.7 (s), 127.0 (d), 137.0 (d), 137.5 (s), 161.9 (s), 201.5 (s) ppm; IR ($CHCl_3$): v bar = 3439, 3019, 2928, 2852, 1605, 1450, 1215, 1090, 669 cm^{-1}; ESI-MS: *m/z* (%): 457.20 (100) $[M+Na]^+$, 473.22 (20) $[M+K]^+$; HRMS: calcd. for $C_{25}H_{27}N_2O_5$ (M^++H): 435.1920, found 435.1920.



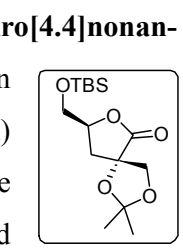
(5S,8S)-8-(Hydroxymethyl)-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonan-6-one (**14**): The crude compound (2.0 g, 12.3 mmol) was dissolved in acetone (30 mL) and cooled to 0 °C. After adding the 2,2-dimethoxypropane (3 mL, 1.23 mmol), catalytic amount of *p*-TSA was added and allowed to stir for overnight. The reaction was quenched with triethylamine at 0 °C. Acetone was removed through vacuum and crude was subjected to column chromatography to yield (0.4 g) as a colorless liquid. (R_f = 0.40, 50% ethyl acetate/pet. ether); $[\alpha]_D^{25}$ = +32.2 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ1.40 (s, 3H), 1.44 (s, 3H), 2.34 (dd, J = 6.6, 13.8 Hz, 1H), 2.46 (dd, J = 7.3, 13.8 Hz, 1H), 3.14 (br s, 1H), 3.58 (dd, J = 2.9, 12.7 Hz, 1H), 3.95 (dd, J = 2.0, 12.7 Hz, 1H), 4.10 (d, J = 9.2 Hz, 1H), 4.30 (d, J = 9.2 Hz, 1H), 4.62–4.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ25.6 (q), 26.3 (q), 35.6 (t), 62.9 (t), 71.6 (t), 77.9 (d), 80.9 (s), 112.2 (s), 176.1 (s) ppm; IR ($CHCl_3$): v bar = 3447, 2990, 2884, 1776, 1457, 1254, 1061, 1008 cm^{-1}; ESI-MS (*m/z*): 225.46 (100) $[M+Na]^+$, HRMS (ESI+): calcd. for $C_9H_{14}O_5Na$ (M^++Na): 225.0739, found 225.0768.



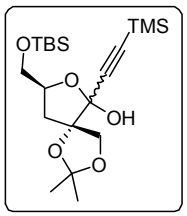
(5R,8S)-8-(Hydroxymethyl)-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonan-6-one (**15**)**:** (R_f = 0.35, 50% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.52 (s, 3H), 2.34–2.38 (m, 2H), 3.69 (dd, J = 12.8, 5.5 Hz, 1H), 3.88 (dd, J = 12.7, 2.9 Hz, 1H), 4.07 (d, J = 8.9 Hz, 1H), 4.19 (d, J = 8.9 Hz, 1H), 4.48 (tdd, J = 7.7, 5.3, 3.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5 (q), 26.4 (q), 35.3 (t), 63.5 (t), 71.9 (t), 77.3 (d), 80.9 (s), 112.5 (s), 175.5 (s) ppm.



8-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonan-6-one (**16**): At 0 °C, a solution of alcohol **14** (5.65 g, 27.9 mmol) in CH_2Cl_2 (60 mL) was treated with imidazole (2.86 g, 41.8 mmol) followed by TBDMSCl (5.06 g, 33.5 mmol) and stirred for 4 h at the same temperature. After the completion of the reaction, ice was added to the reaction mixture and stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2 (60 mL) and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated. The crude was purified by flash column chromatography (2% → 5% AcOEt/pet.ether) to yield compound **16** (7.12 g, 81%) as colorless oil. (R_f = 0.60, 10% AcOEt/pet.ether); $[\alpha]_D^{25}$ = +25.5 (c = 0.51 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.43 (s, 3H), 1.49 (s, 3H), 2.37 (dd, J = 5.6, 13.8 Hz, 1H), 2.50 (dd, J = 8.0, 13.9 Hz, 1H), 3.66 (dd, J = 2.7, 11.5 Hz, 1H), 3.93 (dd, J = 2.9, 11.5 Hz, 1H), 4.12 (d, J = 8.9 Hz, 1H), 4.30 (d, J = 8.9 Hz, 1H), 4.59–4.68 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ –5.5 (q), –5.4 (q), 18.5 (s), 25.6 (q), 25.9 (q, 3C), 26.5 (q), 36.3 (t), 64.1 (t), 72.5 (t), 77.0 (d), 80.8 (s), 112.1 (s), 175.7 (s) ppm; IR ($CHCl_3$): ν bar = 2989, 2886, 1784, 1463, 1253, 1095, 1061, 837, 758 cm^{-1}; ESI-MS: *m/z* (%): 339.14 (75) $[M+Na]^+$; HRMS: calcd. for $C_{15}H_{29}O_5Si$ (M^++H): 317.1784, found 317.1789**.**

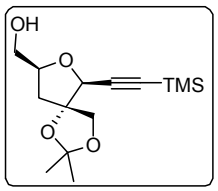


8-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-6-((trimethylsilyl)ethynyl)-1,3,7-trioxaspiro [4.4]nonan-6-ol (**17**): A solution of trimethylsilyl acetylene (2.2 mL, 15.7 mmol) in THF (7 mL) was cooled to –78 °C under argon atmosphere and treated with *n*BuLi (6.8 mL, 1.6 M in hexane) and stirred at –78 °C for 45 min. To this, a solution of lactone **16** (1.0 g, 3.15 mmol) in THF (5 mL) was added dropwise at



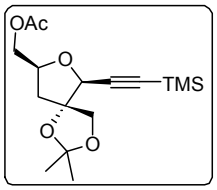
the same temperature and stirring was continued for another 1 h at –78°C. The reaction mixture was quenched with saturated aq.NH_4Cl solution and warmed to rt. The contents were partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethylacetate (2 x 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude by silicagel (100 – 200 Mesh) column chromatography (2% → 5% AcOEt/pet.ether) gave **17** (1.0 g, 88%) as a colorless liquid. (R_f = 0.50, 10% AcOEt/pet.ether); $[\alpha]_D^{25}$ = −34.5 (*c* = 0.93 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ0.07 (s, 6H), 0.16 (s, 9H), 0.87 (s, 9H), 1.43 (s, 3H), 1.49 (s, 3H), 2.18 (dd, *J* = 7.4, 13.1 Hz, 1H), 2.33 (dd, *J* = 8.4, 13.1 Hz, 1H), 3.50 (dd, *J* = 1.8, 10.9 Hz, 1H), 3.86 (dd, *J* = 2.7, 10.9 Hz, 1H), 4.02 (d, *J* = 9.4 Hz, 1H), 4.31 (d, *J* = 9.4 Hz, 1H), 4.46 (s, 1H), 4.51–4.61 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ –5.8 (q), –5.5 (q), –0.5 (q), –0.4 (q, 3C), 18.3 (s), 25.8 (q, 3C), 25.9 (q), 26.2 (q), 27.0 (q), 35.3 (t), 63.4 (t), 68.2 (t), 78.4 (d), 92.0 (s), 99.4 (s), 111.6 (s) ppm; IR ($CHCl_3$): *v* bar = 3381, 2956, 2931, 1463, 1252, 1115, 1064, 843 cm^{-1}; ESI-MS: *m/z* (%): 437.20 (100) $[M+Na]^+$, 453.17 (5) $[M+K]^+$; HRMS: calcd. for $C_{20}H_{38}O_5Si_2Na$ (M^++Na): 437.2155, found 437.2156.

(2,2-Dimethyl-6-((trimethylsilyl)ethynyl)-1,3,7-trioxaspiro[4.4]nonan-8-yl)methanol (**18**): At –78 °C, a solution of lactols **17** (500 mg, 1.2 mmol) in CH_2Cl_2:CH_3CN (1:1 ratio, 6 mL) was treated with Et_3SiH (0.57 mL, 3.61 mmol) followed by $BF_3.OEt_2$ (0.46 mL, 3.61 mmol) and stirred for 1h at the same temperature. The reaction mixture was quenched with saturated aq.$NaHCO_3$ solution and was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was subjected to (100 – 200 Mesh) column chromatography (20%→25% AcOEt/pet.ether) to afford **18** (0.21 g, 61%) as a colorless liquid. (R_f = 0.40, 30% AcOEt/pet.ether); $[\alpha]_D^{25}$ = −38.5 (*c* = 0.38 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ0.16 (s, 9H), 1.40 (s, 6H), 2.08 (dd, *J* = 6.4, 12.9 Hz, 1H), 2.25 (dd, *J* = 9.7, 12.9 Hz, 1H), 3.57 (dd, *J* = 3.1, 12.1 Hz, 1H), 3.84 (dd, *J* = 2.8, 12.1 Hz, 1H), 4.00 (d, *J* = 9.3 Hz, 1H), 4.25–4.33 (m, 1H), 4.37 (d, *J* = 9.3 Hz, 1H), 4.52 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ0.4 (q, 3C), 26.4 (q), 26.4 (q), 37.1 (t), 63.4 (t), 69.3 (t), 76.8 (d),

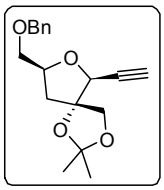


79.5 (d), 90.0 (s), 93.7 (s), 102.1 (s), 110.7 (s) ppm; IR ($CHCl_3$): ν bar = 3420, 2960, 2928, 1714, 1382, 1252, 1048, 847 cm^{-1}; ESI-MS: *m/z* (%): 285.24 (2) $[M+H]^+$, 307.14 (100) $[M+Na]^+$, 323.51 (10) $[M+K]^+$; HRMS: calcd. for $C_{14}H_{24}O_4SiNa$ (M^++Na): 307.1342, found 307.1335.

(2,2-Dimethyl-6-((trimethylsilyl)ethynyl)-1,3,7-trioxaspiro[4.4]nonan-8-yl)methyl acetate (**18-Ac**): At 0 °C, a solution of compound **18** (565 mg, 1.98 mmol) in acetic anhydride (1.87 mL, 19.8 mmol) was cooled and pyridine (1.6 mL, 19.8 mmol) was added dropwise and stirred for 2h at the same temperature. The reaction mixture was poured into $CuSO_4.7H_2O$ solution (20 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layer was washed again with $CuSO_4.7H_2O$ solution (2 x 15 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude was subjected for purification by flash column chromatography (2% → 6% AcOEt/pet.ether) to procure compound **18-Ac** (0.51 g, 79%) as colorless liquid. (R_f = 0.45, 10% AcOEt/pet.ether); $[\alpha]_D^{25}$ = −29.6 (*c* = 0.24 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ0.15 (s, 9H), 1.39 (s, 6H), 1.98 (dd, *J* = 9.8, 12.9 Hz, 1H), 2.08 (s, 3H), 2.21 (dd, *J* = 6.4, 12.9 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 4.09 (dd, *J* = 6.3, 11.7 Hz, 1H), 4.27 (dd, *J* = 3.4, 11.7 Hz, 1H), 4.37 (m, 1H), 4.41 (d, *J* = 9.2 Hz, 1H), 4.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ0.3 (q, 3C), 20.9 (q), 26.4 (q, 2C), 39.0 (t), 66.0 (t), 69.6 (t), 76.3 (d), 76.6 (d), 89.1 (s), 93.3 (s), 101.6 (s), 110.7 (s), 170.9 (s) ppm; IR ($CHCl_3$): ν bar = 2960, 2174, 1783, 1715, 1370, 1252, 1047, 848 cm^{-1}; ESI-MS: *m/z* (%): 365.11 (25) $[M+K]^+$; HRMS: calcd. for $C_{16}H_{26}O_5SiNa$ (M^++Na): 349.1448, found 349.1446.

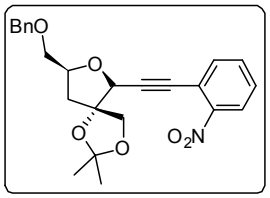


8-(Benzyloxymethyl)-6-ethynyl-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonane (**12**): A solution of compound **18** (500 mg, 1.76 mmol) in DMF (10 mL) was cooled to 0 °C and treated with NaH (60% in oil, 106 mg, 2.64 mmol) and stirred for 45 min. To this, benzyl bromide (0.3 mL, 2.64 mmol) was added and stirring was continued for 3 h at 0°C. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (4 x 30 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude was subjected for purification by flash column chromatography (4% → 7% AcOEt/pet.ether) to procure compound **12**



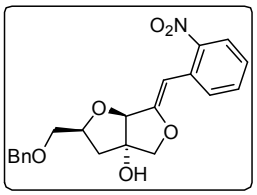
(0.47 g, 89%) as colorless liquid. (R_f = 0.45, 10% AcOEt/pet.ether); $[\alpha]_D^{25}$ = −38.3 (*c* = 0.77 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.41 (s, 3H), 2.04 (dd, *J* = 9.5, 12.9 Hz, 1H), 2.24 (dd, *J* = 6.3, 12.9 Hz, 1H), 2.56 (d, *J* = 2.2 Hz, 1H), 3.57 (dd, *J* = 2.9, 8.7 Hz, 1H), 3.65 (dd, *J* = 5.3, 10.4 Hz, 1H), 3.97 (d, *J* = 9.3 Hz, 1H), 4.29–4.37 (m, 1H), 4.43 (d, *J* = 9.3 Hz, 1H), 4.52 (d, *J* = 2.2 Hz, 1H), 4.59 (s, 2H), 7.30–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.2 (q), 26.4 (q), 39.3 (t), 69.8 (t), 72.0 (t), 73.3 (t), 76.0 (d, 2C), 77.8 (d), 80.3 (s), 89.1 (s), 110.4 (s), 127.5 (d), 127.6 (d, 2C), 128.2 (d, 2C), 138.1 (s) ppm; IR ($CHCl_3$): *v* bar = 3063, 2986, 1724, 1454. 1372, 1215, 1028, 698 cm^{-1}; ESI-MS: *m/z* (%): 325.16 (100) $[M+Na]^+$; HRMS: calcd. for $C_{18}H_{22}O_4Na$ (M^++Na): 325.1416, found 325.1394.

8-(Benzyloxymethyl)-2,2-dimethyl-6-((2-nitrophenyl)ethynyl)-1,3,7-trioxaspiro-[4.4] nonane (**11**): To a solution of alkyne **12** (0.85 g, 2.81 mmol), *o*-iodonitrobenzene (1.049 g, 4.21 mmol) in Et_3N:DMF (2:1, 12 mL) PPh_3 (73 mg, 0.28 mmol) was added and the solution was degassed under argon atmosphere for 10 min. To this, $Pd(PPh_3)_2Cl_2$ (98 mg, 0.14 mmol) was introduced and the reaction mixture was degassed with argon for 10 min and CuI (107 mg, 0.56 mmol) was added and the contents stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and water and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). Combined ethyl acetate layer was washed with brine, dried over (Na_2SO_4), concentrated and the residue obtained was purified by silicagel (100 – 200 Mesh) column chromatography (12% → 16% AcOEt/pet.ether) to afford the compound **11** (0.92 g, 76 %) as yellow oil. (R_f = 0.45, 20% AcOEt/pet.ether); $[\alpha]_D^{25}$ = +57.7 (*c* = 0.69 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.44 (s, 3H), 2.14 (dd, *J* = 3.4, 12.6 Hz, 1H), 2.25 (dd, *J* = 6.4, 12.8 Hz, 1H), 3.60 (dd, *J* = 4.8, 10.6 Hz, 1H), 3.67 (dd, *J* = 5.5, 10.4 Hz, 1H), 4.08 (d, *J* = 9.5 Hz, 1H), 4.39–4.47 (m, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.59 (s, 2H), 4.80 (s, 1H), 7.27–7.34 (m, 5H), 7.46–7.50 (m, 1H), 7.54–7.56 (m, 2H), 8.04 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.3 (q), 26.4 (q), 39.2 (t), 69.3 (t), 72.3 (t), 73.3 (t), 76.6 (d), 78.3 (d), 82.5 (s), 89.8 (s), 93.8 (s), 110.7 (s), 117.7 (s), 124.6 (d), 127.5 (d), 127.6 (d, 2C), 128.2 (d, 2C), 129.1 (d), 132.9 (d), 135.1 (d), 138.2 (s), 149.4 (s) ppm; IR ($CHCl_3$): *v* bar = 2985, 2924, 2853, 1734, 1707, 1607, 1527, 1062 cm^{-1}; ESI-MS: *m/z* (%): 446.17 (100) $[M+Na]^+$,

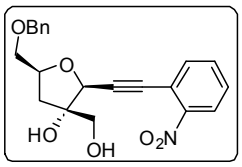


462.18 (3) $[M+K]^+$; HRMS: calcd. for $C_{24}H_{25}NO_6Na$ (M^++Na): 446.1580, found 446.1587.

(2S,3aS,6aR)-2-((Benzyloxy)methyl)-6-((E)-2-nitrobenzylidene) tetrahydrofuro [3,4-b]furan-3a(4H)-ol (19): The compound **11** (120 mg, 0.28 mmol) was dissolved in acetonitrile (7 mL) and degassed under argon atmosphere for 10 min and $Pd(CH_3CN)_2Cl_2$ (3.7 mg, 5 mol%) was added and stirred for 6 h at room temperature. The reaction mixture filtered (*Celite*) and concentrated under reduced pressure. The crude was subjected to (230 – 400 Mesh) column chromatography (25% → 35% AcOEt/pet.ether) purification to procure enolether **19** (51 mg, 47%) as yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (dd, J = 7.9, 1.8 Hz, 2H), 2.41 (br s, 1H), 3.52 (d, J = 4.6 Hz, 2H), 4.19 (d, J = 9.5 Hz, 1H), 4.36 (d, J = 9.5 Hz, 1H), 4.50 (s, 2H), 4.51–4.56 (m, 1H), 4.60 (s, 1H), 5.98 (s, 1H), 7.19 (s, 1H), 7.19–7.22 (m, 1H), 7.22–7.26 (m, 4H), 7.38–7.45 (m, 1H), 7.73 (dd, J = 8.3, 1.2 Hz, 1H), 7.96–8.03 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 39.5 (t), 71.7 (t), 73.5 (t), 80.0 (t), 80.9 (d), 85.8 (s), 89.5 (d), 96.8 (d), 124.3 (d), 126.2 (d), 127.7 (d), 127.8 (d, 2C), 128.4 (d, 2C), 129.8 (s), 130.8 (d), 132.2 (d), 137.9 (s), 147.5 (s), 158.4 (s) ppm. HRMS: calcd. for $C_{21}H_{21}NO_6Na$ (M^++Na): 406.1267, found 406.1283.

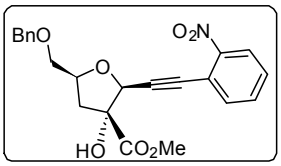


8-(Benzyloxymethyl)-2,2-dimethyl-6-((2-nitrophenyl)ethynyl)- 1,3,7-trioxaspiro [4.4] nonane (**20**): At 0 °C, a solution of compound **11** (920 mg, 2.17 mmol) in MeOH (15 mL) was treated with *p*-TSA (0.1 mmol) and stirred for at rt 8 h. The reaction was neutralized with triethylamine (the pH was adjusted to 7) and concentrated. The residue was purified by column chromatography to (60% → 70% AcOEt/pet.ether) to obtain diol **20** (565 mg, 67%) as yellow oil. (R_f = 0.30, 70% AcOEt/pet.ether); $[\alpha]_D^{25}$ = +3.4 (c = 1.5 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (dd, J = 9.7, 13.1 Hz, 1H), 2.14 (dd, J = 6.4, 13.1 Hz, 1H), 2.98 (br s, 1H), 3.66 (dd, J = 4.3, 10.4 Hz, 1H), 3.74 (dd, J = 5.8, 10.5 Hz, 2H), 3.84 (d, J = 11.6 Hz, 1H), 4.19 (d, J = 11.5 Hz, 1H), 4.52–4.60 (m, 1H), 4.64 (s, 2H), 4.85 (s, 1H), 7.27–7.40 (m, 5H), 7.46–7.55 (m, 1H), 7.58 (dd, J = 3.6, 4.9 Hz, 1H), 7.63 (dd, J = 4.5, 5.4 Hz, 1H), 8.06–8.10 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 38.2 (t), 66.0 (t), 72.3 (t), 73.3 (t), 77.3 (d), 78.4 (d), 82.9 (s), 84.0 (s), 93.8 (s), 117.7 (s), 124.6 (d),



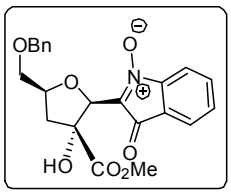
127.5 (d), 127.7 (d, 2C), 128.2 (d, 2C), 129.1 (d), 133.1 (d), 135.2 (d), 138.0 (s), 149.1 (s) ppm; IR ($CHCl_3$): *v* bar = 3419, 2924, 1716, 1608, 1225, 1344, 1262, 1099 cm^{-1}; ESI-MS: *m/z* (%): 406.09 (100) $[M+Na]^+$, 422.04 (3) $[M+K]^+$; HRMS: calcd. for $C_{21}H_{21}NO_6Na$ (M^++Na): 406.1267, found 406.1283.

Methyl 5-(benzyloxymethyl)-3-hydroxy-2-((2-nitrophenyl) ethynyl)tetrahydro-furan-3-carboxylate (**24**): To a solution of alcohol **20** (70 mg, 0.18 mmol) in ethyl acetate (5 mL), IBX (56 mg, 0.2 mmol) was added and heated to reflux. After 6 h, the reaction mixture was cooled and filtered (*Celite*) and concentrated. To a cooled solution of above crude aldehyde in *t*BuOH and H_2O (2:1, 8 mL), $NaH_2PO_4.2H_2O$ (80 mg, 0.55 mmol dissolved in 15 ml water, pH 7) was added. To this, sodium chlorite (54 mg, 0.55 mmol) was added slowly followed by 2-methyl-2-butene (0.6 mL, 5.5 mmol) and the stirring was continued at rt for additional 10 h. After the reaction was complete, solid $NaHCO_3$ was added and the reaction mixture was partitioned between ethyl acetate and water. The aqeous layer was extracted with the ethyl acetate (2 x 10 mL) and the combined organic layer was dried (Na_2SO_4) and concentrated. The resulting crude acid was dissolved in toluene:MeOH (4:1, 5 mL), cooled to 0°C and treated with an hexane solution of $TMSCHN_2$ (1.1–1.5 mmol) dropwise until the yellow color persisted. Stirring was continued for 20 min at 0°C. The reaction was quenched with ice at 0°C and was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude was subjected to silicagel (100 – 200 Mesh) column chromatography (15% → 25% AcOEt/pet.ether) to afford compound **24** (42 mg, 56% over three steps) as a colorless gum. (R_f = 0.45, 30% AcOEt/pet.ether); $[\alpha]_D^{25}$ = +95.5 (*c* = 0.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ2.22 (dd, *J* = 6.5, 13.3 Hz, 1H), 2.50 (dd, *J* = 9.7, 13.3 Hz, 1H), 3.66 (dd, *J* = 4.1, 10.5 Hz, 1H), 3.74 (dd, *J* = 6.4, 10.5 Hz, 1H), 3.79 (br s, 1H), 3.83 (s, 3H), 4.47–4.52 (m, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.64 (d, *J* = 12.1 Hz, 1H), 4.79 (s, 1H), 7.30–7.36 (m, 5H), 7.48 (ddd, *J* = 2.3, 6.8, 8.4 Hz, 1H), 7.53–7.57 (m, 2H), 8.02 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ39.7 (t), 53.4 (q), 71.7 (t), 73.5 (t), 78.7 (d), 78.9 (d), 83.1 (s), 84.4 (s), 91.4 (s), 117.4 (s), 124.6 (d), 127.6 (d), 127.8 (d, 2C), 128.3 (d, 2C), 129.2 (d), 132.8 (d), 135.1 (d), 138.1 (s), 149.6 (s), 173.2 (s) ppm; IR ($CHCl_3$): *v* bar = 3447,

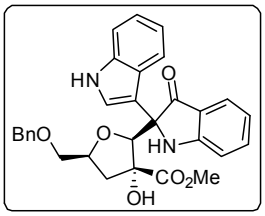


2922, 1736, 1527, 1345, 1235, 1091, 745 cm^{-1}; ESI-MS: *m/z* (%): 434.05 (100) $[M+Na]^+$; HRMS: calcd. for $C_{22}H_{21}NO_7Na$ (M^++Na): 434.1216, found 434.1230**.**

2-(5-(Benzyloxymethyl)-3-hydroxy-3-(methoxycarbonyl)tetrahydrofuran-2-yl)-3-oxo-3H-indole 1-oxide (**23**): The compound **24** (300 mg, 0.73 mmol) was dissolved in acetonitrile (15 mL) and degassed under argon atmosphere for 10 min and $Pd(CH_3CN)_2Cl_2$ (9.4 mg, 5 mol%) was introduced and stirred for 8 h at room temperature. The reaction mixture filtered (*Celite*) and concentrated under reduced pressure. The crude was subjected to (100 – 200 Mesh) column chromatography (15% → 25% AcOEt/pet.ether) purification to procure isatogen **23** (177 mg, 59%) as yellow oil. (R_f = 0.35, 30% AcOEt/pet.ether); $[\alpha]_D^{25}$ = +166.1 (*c* = 0.38 in $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4): δ2.19 (dd, *J* = 4.9, 12.6 Hz, 1H), 2.58 (t, *J* = 12.2 Hz, 1H), 3.54 (s, 3H), 3.79 (dd, *J* = 3.8, 10.6 Hz, 1H), 3.96 (dd, *J* = 7.1, 10.4 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 2H), 4.61–4.62 (m, 1H), 5.34 (s, 1H), 7.29–7.35 (m, 5H), 7.60–7.66 (m, 3H), 7.76 (dd, *J* = 7.0, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, Methanol-d_4): δ41.9 (t), 53.2 (q), 73.0 (t), 74.3 (t), 81.2 (d), 81.8 (d), 85.8 (s), 115.0 (d), 122.7 (d), 124.3 (s), 128.7 (d), 128.9 (d, 2C), 129.3 (d, 2C), 133.2 (d), 136.0 (d), 136.4 (s), 139.6 (s), 148.0 (s), 172.9 (s), 185.9 (s) ppm; IR ($CHCl_3$): *v* bar = 3337, 3020, 2927, 1735, 1618, 1215, 1100, 698 cm^{-1}; ESI-MS: *m/z* (%): 434.08 (100) $[M+Na]^+$; HRMS: calcd. for $C_{22}H_{21}NO_7Na$ (M^++Na): 434.1216, found 434.1226**.**

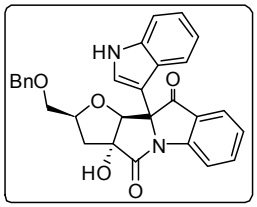


Methyl 5-(benzyloxymethyl)-3-hydroxy-2-(3-oxo-2,3'-biindolin-2-yl)tetrahydrofuran-3-carboxylate (**22**): To a solution of compound **23** (50 mg, 0.12 mmol), indole (22 mg, 0.18 mmol) in acetonitrile (4 mL) was added anhy. $InCl_3$ (6 mg, 0.02 mmol) and degassed with argon atmosphere for 10 min and stirred at rt for 5 h. After the reaction was complete as indicated by TLC, acetonitrile was evaporated under reduced pressure and crude was dissolved in acetonitrile:toluene (1:5, 5 mL). To this additional anhy. $InCl_3$ (35 mg, 0.16 mmol) was added and the reaction mixture was allowed to stir at 80 °C under argon atmosphere for 4 h. Solvent was removed under reduced pressure and the crude was purified by silicagel (60 – 12 Mesh) column chromatography (40% → 50% AcOEt/pet.ether) to afford compound **22** (33 mg, 53%) as red gum. (R_f = 0.4, 60%



AcOEt/pet.ether); $[\alpha]_D^{25}$ = +12.5 (*c* = 0.23 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ2.10 (dd, *J* = 5.0, 12.7 Hz, 1H), 2.50 (dd, *J* = 11.2, 12.7 Hz, 1H), 2.95 (s, 3H), 3.44 (dd, *J* = 5.2, 11.2 Hz, 1H), 3.55 (dd, *J* = 3.7, 11.2 Hz, 1H), 3.59 (br s, 1H), 4.23 (d, *J* = 12.3 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 4.37–4.42 (m, 1H), 5.12 (s, 1H), 6.01 (br s, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.11–7.13 (m, 2H), 7.21–7.27 (m, 5H), 7.46 (ddd, *J* = 1.2, 7.0, 8.3 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 8.28 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ42.9 (t), 52.7 (q), 70.5 (s), 70.8 (t), 73.3 (t), 78.6 (d), 83.2 (s), 93.8 (d), 110.9 (s), 111.3 (d), 111.5 (d), 118.4 (d), 119.7 (s), 120.1 (d), 120.9 (d), 122.3 (d), 122.9 (d), 124.8 (s), 125.4 (d), 127.4 (d), 127.5 (d, 2C), 128.3 (d, 2C), 136.3 (s), 137.4 (d), 138.3 (s), 161.7 (s), 173.9 (s), 200.7 (s) ppm; IR ($CHCl_3$): *v* bar = 3414, 2926, 1734, 1618, 1488, 1374, 1100, 1044, 753 cm^{-1}; ESI-MS: *m/z* (%): 535.19 (100) $[M+Na]^+$, 551.17 (84) $[M+K]^+$; HRMS: calcd. for $C_{30}H_{28}N_2O_6Na$ (M^++Na): 535.1845, found 535.1838**.**

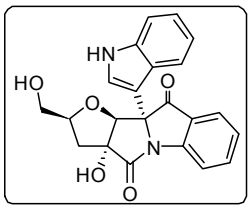
15-O-Benzyl-13-deoxy-Isatisine A (**25**): At 0 °C, a solution of ester **22** (30 mg, 0.06 mmol) in THF:MeOH (3 mL, 3:2) was treated with $LiOH.H_2O$ (9 mg, 0.23 mmol) and stirred at rt for 8 h. The reaction mixture was concentrated under reduced pressure and the crude was filtered through a short silica gel column using 10% MeOH/CH_2Cl_2 as eluent.



To a solution of above acid in THF (20 mL) was added EDCI (16 mg, 0.10 mmol) and the reaction mixture was heated to reflux for 18 h. The reaction mixture was concentrated under reduced pressure and crude was diluted with ethyl acetate (20 mL). The ethyl acetate solution was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude was subjected for purification by silicagel column chromatography (35% → 45% AcOEt/pet.ether) to yield lactam **25** (16 mg, 57%, 2 steps) as yellow gum. (R_f = 0.6, 60% AcOEt/pet.ether); $[\alpha]_D^{25}$ = –123.5 (*c* = 0.35 in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ2.27 (dd, *J* = 9.1, 13.4 Hz, 1H), 2.67 (dd, *J* = 5.4, 13.4 Hz, 1H), 3.20 (dd, *J* = 4.4, 10.7 Hz, 1H), 3.28 (dd, *J* = 4.0, 10.6 Hz, 1H), 4.06 (d, *J* = 12.4 Hz, 1H), 4.13 (d, *J* = 12.5 Hz, 1H), 4.38–4.43 (m, 1H), 4.93 (s, 1H), 7.01 (d, *J* = 1.6 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 7.19–7.22 (m, 5H), 7.25 (s, 1H), 7.30–7.34 (m, 2H), 7.64 (ddd, *J* = 1.2, 7.4, 8.5 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 8.14 (dd, *J*

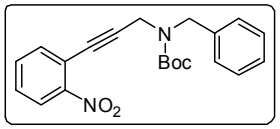
= 2.5, 6.8 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ38.6 (t), 71.0 (t), 73.1 (t), 74.4 (s), 78.6 (d), 85.1 (d), 89.9 (d), 111.3 (s), 111.7 (d), 116.4 (d), 120.8 (d), 120.9 (d), 122.2 (d), 123.2 (d), 124.4 (s), 125.5 (d), 125.6 (d), 125.7 (s), 127.4 (d), 127.5 (d, 2C), 128.2 (d, 2C), 136.5 (d), 137.2 (s), 137.9 (s), 150.3 (s), 173.2 (s), 194.3 (s) ppm; IR ($CHCl_3$): *v* bar = 3393, 2926, 1715, 1698, 1602, 1467, 1094, 750 cm^{-1}; ESI-MS: *m/z* (%): 503.24 (100) $[M+Na]^+$, 519.18 (5) $[M+K]^+$; HRMS: calcd. for $C_{29}H_{24}N_2O_5Na$ (M^++Na): 503.1583, found 503.1586**.**

13-*deoxy*-Isatisine A (**8**): At 0 °C, a solution of lactam **25** (21 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) was treated with a CH_2Cl_2 solution of $TiCl_4$ (0.04 mL, 0.44 mmol) and stirred at the same for 1 h. The reaction mixture was quenched with ice and warmed to rt. The contents were partitioned between ethyl acetate and water and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude was subjected to (100 – 200 Mesh) column chromatography (50% → 60% AcOEt/pet.ether) to obtain **8** (15 mg, 88%) as colorless gum. (R_f = 0.6, 70% AcOEt/pet.ether); $[\alpha]_D^{25}$ = −157.7 (*c* = 0.95 in CH_3OH); ^{1}H NMR (500 MHz, Methanol-d_4): δ2.17 (dd, *J* = 8.5, 13.4 Hz, 1H), 2.47 (dd, *J* = 6.3, 13.5 Hz, 1H), 3.27 (dd, *J* = 3.9, 4.9 Hz, 2H), 4.21–4.27 (m, 1H), 4.61 (br s, 3H), 7.07 (ddd, *J* = 0.9, 6.9, 8.0 Hz, 1H), 7.14 (ddd, *J* = 1.1, 6.9, 8.0 Hz, 1H), 7.27 (s, 1H), 7.31–7.36 (m, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.80 (ddd, *J* = 1.2, 7.4, 8.4 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.0 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (125 MHz, Methanol-d_4): δ39.8 (t), 65.0 (t), 76.1 (s), 80.9 (d), 86.2 (d), 90.6 (s), 110.8 (s), 112.8 (d), 117.7 (d), 120.5 (d), 121.4 (d), 123.0 (d), 124.4 (d), 125.9 (s), 126.2 (d), 126.8 (d), 127.2 (s), 137.8 (d), 139.0 (s), 151.9 (s), 175.4 (s), 196.7 (s) ppm; IR (CH_3OH): *v* bar = 3400, 2935, 1709, 1658, 1467, 1299, 1020, 750 cm^{-1}; ESI-MS: *m/z* (%): 413.10 (100) $[M+Na]^+$; HRMS: calcd. for $C_{22}H_{18}N_2O_5Na$ (M^++Na): 413.1113, found 413.1099**.**

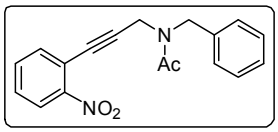


General Procedure A: To a solution of alkyne **S7** (1 eq.), *o*-iodonitrobenzene **S6** (1.3 eq.) in Et_3N:DMF (2:1), PPh_3 (0.2 eq.) was added. To this, $Pd(PPh_3)_2Cl_2$ (0.05 eq.) was added and the reaction mixture was degassed with argon for 10 min and CuI (0.1 eq.) was added and degassed again and the contents stirred at room temperature for 1–3 h. The reaction mixture was partitioned between ethyl acetate and water and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). Combined ethyl acetate layer was washed with brine, dried over Na_2SO_4, concentrated and the residue obtained was purified by flash silicagel column chromatography to afford the compound **27**.

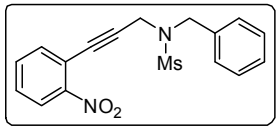
***tert*-Butyl benzyl(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27aa-Boc):** Yellow oil; 83%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (s, 9H), 4.22 (br s, 1H), 4.33 (br s, 1H), 4.67 (s, 2H), 7.28–7.37 (m, 5H), 7.41–7.51 (m, 1H), 7.52–7.60 (m, 2H), 8.04 (d, J = 8.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 36.1 (t), 49.3 (t), 80.7 (s, 2C), 93.3 (s), 118.2 (s), 124.5 (d), 127.3 (d), 127.8 (s), 128.5 (d, 3C), 128.6 (d), 132.7 (d), 134.9 (d), 137.5 (s), 149.9 (s), 155.1 (s) ppm. $C_{21}H_{22}N_2O_4$



N-Benzyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)acetamide (27aa-Ac): Brownish oil; 79%; (R_f = 0.6, 40% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.33 (s, 2H), 4.23 (s, 1H), 4.51 (s, 2H), 4.78 (s, 1H), 4.80 (s, 2H), 7.25–7.37 (m, 8H), 7.37–7.52 (m, 3H), 7.52–7.59 (m, 3H), 8.04 (d, J = 8.1 Hz, 1.7H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5, 21.6 (q), 34.6, 38.1 (t), 48.3, 50.8 (t), 79.0, 79.5 (s), 91.4 , 92.6 (s), 117.4, 118.0 (s), 124.5, 124.6 (d), 126.7, 128.3 (d, 2C), 127.4, 127.7 (d), 128.5, 128.8 (d, 2C),128.6, 129.0 (d), 132.8 (d), 134.7 (d), 135.9, 136.7 (s), 149.6 (s), 170.6 (s) ppm. $C_{18}H_{16}N_2O_3$

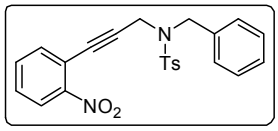


N-Benzyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)methanesulfonamide (27aa-Ms): Brownish gum; 72%; (R_f = 0.4, 30% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06–3.15 (m, 3H), 4.20 (s, 2H), 4.58 (s, 2H), 7.25 (d, J = 8.2 Hz, 1H), 7.35–7.41 (m, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.50–7.55 (m, 1H), 7.61–7.64 (m, 2H), 8.11 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 36.3 (t), 38.3 (q), 50.0 (t), 81.5 (s), 90.5 (s),

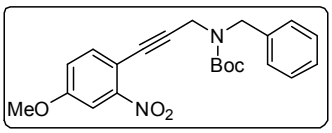


117.4 (s), 124.7 (d), 128.2 (d), 128.7 (d, 4C), 129.3 (d), 133.2 (d), 134.8 (d), 134.8 (d), 149.5 (s) ppm. $C_{17}H_{16}N_2O_4S$

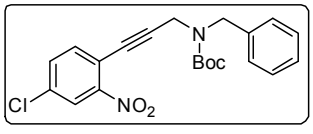
N-Benzyl-4-methyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)benzenesulfonamide (27aa-Ts): Brownish oil; 69%; (R_f = 0.6, 30% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.19 (s, 2H), 4.50 (s, 2H), 7.18 (d, J = 8.2 Hz, 2H), 7.24–7.29 (m, 2H), 7.35 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 7.8 Hz, 3H), 7.50–7.56 (m, 1H), 7.79 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.3 (q), 36.5 (t), 50.2 (t), 81.2 (s), 89.9 (s), 117.6 (s), 124.5 (d), 127.1 (s), 127.8 (d, 2C), 128.1 (d), 128.7 (d, 2C), 128.8 (d), 128.9 (d, 2C), 129.4 (d, 2C), 132.7 (d), 134.6 (d), 134.9 (s), 135.6 (s), 143.6 (s), 149.3 (s) ppm. $C_{23}H_{20}N_2O_4S$



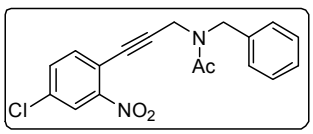
***tert*-Butyl benzyl(3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ba):** Yellow oil; 85%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 3.88 (s, 3H), 4.31 (br s, 2H), 4.66 (s, 2H), 7.09 (dd, J = 8.7, 2.7 Hz, 1H), 7.28–7.37 (m, 5H), 7.45 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 2.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 36.0 (t), 49.2 (t), 55.9 (q), 80.5 (s, 2C), 91.0 (s), 109.2 (d), 110.2 (s), 119.5 (d), 127.3 (d, 2C), 128.5 (d, 3C), 135.7 (d), 137.5 (s), 150.7 (s), 155.1 (s), 159.4 (s) ppm. $C_{22}H_{24}N_2O_5$



***tert*-Butyl benzyl(3-(4-chloro-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ca):** Yellow gum; 83%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 4.30 (br s, 2H), 4.64 (s, 2H), 7.28–7.37 (m, 5H), 7.44–7.56 (m, 2H), 8.03 (d, J = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3 (q, 3C), 35.9 (t), 49.4 (t), 80.7 (s), 94.5 (s), 116.7 (s), 124.8 (d), 127.4 (d), 128.5 (d, 4C), 132.9 (d), 134.5 (s), 135.7 (d), 137.4 (s), 150.0 (s), 155.0 (s) ppm. $C_{21}H_{21}ClN_2O_4$

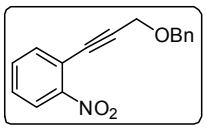


N-Benzyl-N-(3-(4-chloro-2-nitrophenyl)prop-2-yn-1-yl)acetamide (27ca-Ac): Brownish gum; 78%; (R_f = 0.6, 40% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 2.31 (s, 1.7H), 4.21 (s, 1H), 4.49 (s, 2H), 4.75 (s, 1H), 4.77 (s, 2H), 7.25–7.30 (m, 3H), 7.30–7.34 (m, 3H), 7.35–7.41 (m, 2H), 7.42–7.49 (m, 1.7H), 7.51–7.57

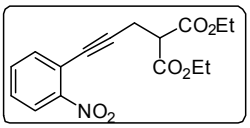


(m, 1.7H), 8.04 (d, J = 1.9 Hz, 1H), 8.05 (d, J = 1.9 Hz, 0.5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.6, 21.7 (q), 34.7, 38.2 (t), 48.5, 51.0 (t), 78.2, 78.7 (s), 92.7, 94.0 (s), 116.1, 116.6 (s), 124.9, 125.0 (d), 126.7 (d, 2C), 127.6, 127.8 (d), 128.4, 128.6, 129.0 (d, 2C), 133.1 (d), 134.6, 135.1 (s), 135.7 (d), 135.9, 136.8 (s), 150.0 (s), 170.5, 170.6 (s) ppm. $C_{18}H_{15}ClN_2O_3$

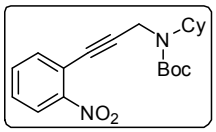
1-(3-(Benzyloxy)prop-1-yn-1-yl)-2-nitrobenzene (27ab): Red colored oil; 91%; (R_f = 0.6, 10% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (s, 2H), 4.93–4.99 (m, 2H), 7.26–7.46 (m, 7H), 7.72 (d, J = 9.6 Hz, 1H), 8.05 (dd, J = 8.7, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 57.5 (t), 71.5 (t), 81.6 (s), 93.3 (s), 117.8 (s), 124.4 (d), 127.7 (d), 128.1 (d, 2C), 128.3 (d, 2C), 128.7 (d), 132.7 (d), 134.7 (d), 137.1 (s), 149.5 (s) ppm. $C_{16}H_{13}NO_3$



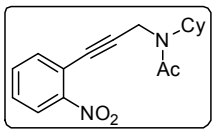
Diethyl 2-(3-(2-nitrophenyl)prop-2-yn-1-yl)malonate (27ac): yellow colored oil; 88%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–1.32 (m, 6H), 3.06–3.11 (m, 2H), 3.70 (td, J = 7.8, 0.9 Hz, 1H), 4.23–4.30 (m, 4H), 7.39–7.46 (m, 1H), 7.51–7.59 (m, 2H), 7.99 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9, 14.0 (q, 2C), 19.7, 21.1 (t), 47.0, 51.0 (d), 61.9 (d, 2C), 77.7 (s), 94.2 (s), 113.8, 118.5 (s), 121.6, 124.4 (d), 128.4 (d), 131.3, 132.6 (d), 134.4, 134.8 (d), 149.9 (s), 167.8 (s, 2C) ppm. $C_{16}H_{17}NO_6$



***tert*-Butyl cyclohexyl(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ad):** Yellow oil; 78%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31–1.37 (m, 2H), 1.46–1.48 (m, 2H), 1.49 (s, 9H), 1.64 (d, J = 11.9 Hz, 1H), 1.83 (s, 5H), 1.80 (s, 2H), 3.98 (br s, 1H), 4.17 (br s, 2H), 7.39–7.46 (m, 1H), 7.49–7.58 (m, 2H), 7.96–8.02 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.5 (t, 2C), 26.0 (t, 2C), 28.4 (q, 3C), 31.1 (t), 33.0 (t), 55.0 (d), 80.1 (s, 2C), 95.8 (s), 118.6 (s), 124.4 (d), 128.4 (d), 132.6 (d), 134.8 (d), 149.8 (s), 154.9 (s) ppm. $C_{20}H_{26}N_2O_4$

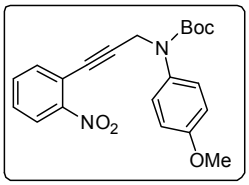


N-Cyclohexyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)acetamide (27ad-Ac):



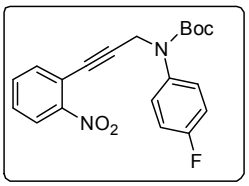
Brownish gum; 71%; (R_f = 0.5, 40% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.28 (m, 3.5H), 1.28–1.52 (m, 7H), 1.60–1.73 (m, 4.5H), 1.73–1.85 (m, 4.5H), 1.90 (d, J = 11.0 Hz, 4.5H), 2.17 (s, 3H), 2.27 (s, 3H), 3.60 (t, J = 12.4 Hz, 1H), 4.21 (s, 2H), 4.36 (s, 2H), 4.48 (t, J = 12.4 Hz, 1H), 7.38–7.50 (m, 2H), 7.50–7.63 (m, 4H), 7.98 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 22.4 (q), 25.2, 25.5, 25.7 (t, 2C), 25.9 (t, 2C), 30.6, 30.9 (t), 31.6, 34.2 (t), 53.0, 58.3 (d), 78.4 (s), 93.7, 95.3 (s), 117.8 (s), 124.3, 124.6 (d), 128.4, 128.9 (d), 132.6, 132.8 (d), 134.8, 135.0 (d), 170.0, 170.4 (s) ppm. $C_{17}H_{20}N_2O_3$

***tert*-Butyl (4-methoxyphenyl)(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27af):**



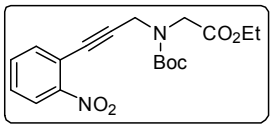
Brown oil; 76%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (br s, 9H), 3.72–3.87 (m, 3H), 4.60 (s, 2H), 6.80–6.94 (m, 2H), 7.23–7.36 (m, 2H), 7.42 (ddd, J = 8.0, 5.5, 3.0 Hz, 1H), 7.47–7.61 (m, 2H), 7.99 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.2 (q, 3C), 41.0 (t), 55.3 (q), 78.8 (s), 80.8 (s), 93.9 (s, 2C), 113.9 (d, 2C), 118.2 (s), 124.4 (d, 2C), 128.5 (d), 132.6 (d, 2C), 134.8 (d), 149.6 (s), 154.4 (s), 157.9 (s) ppm. $C_{21}H_{22}N_2O_5$

***tert*-Butyl (4-fluorophenyl)(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ag):**



Yellow oil; 68%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 4.62 (s, 2H), 7.00–7.10 (m, 2H), 7.33–7.42 (m, 2H), 7.43–7.48 (m, 1H), 7.52–7.57 (m, 2H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.1 (q, 3C), 40.7 (t), 79.0 (s), 81.1 (s, 2C), 115.3 (d), 115.6 (d), 117.9 (s), 124.4 (d, 2C), 128.6 (d), 132.7 (d, 2C), 134.7 (d), 137.8 (s), 149.5 (s), 154.0 (s, 2C) ppm. $C_{20}H_{19}FN_2O_4$

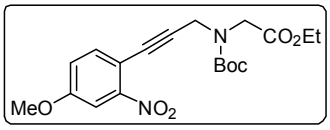
Ethyl N-(tert-butoxycarbonyl)-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)glycinate (27ah):



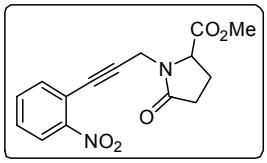
Yellow oil; 79%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22–1.29 (m, 3H), 1.44–1.51 (m, 9H), 4.15–4.27 (m, 4H), 4.42–4.55 (m, 2H), 7.47 (dd, J = 8.0, 2.3 Hz, 1 H), 7.55–7.61 (m, 2H), 8.03 (dd, J = 7.5, 0.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 28.2 (q, 3C), 37.6 (t), 38.2 (t), 47.6 (t), 61.0 (t), 81.0 (s, 2C),

92.5 (s), 124.6 (d), 128.8 (d), 132.8 (d), 134.8 (d), 138.6 (s), 154.7 (s), 169.8 (s) ppm. $C_{18}H_{22}N_2O_6$

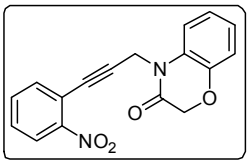
Ethyl N-(tert-butoxycarbonyl)-N-(3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl) glycinate (27bh): Brownish oil; 81%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.29 (m, 3H), 1.45 (d, J = 2.8 Hz, 9H), 3.89 (s, 3H), 4.14–4.23 (m, 4H), 4.41–4.52 (m, 2H), 7.10 (dd, J = 8.7, 2.7 Hz, 1H), 7.47–7.56 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 28.2 (q, 3C), 37.6 (t), 38.2 (t), 47.5 (t), 56.0 (q), 61.0 (t), 80.9 (s, 2C), 90.3 (s), 109.3 (d), 119.7 (d), 135.7 (d), 150.7 (s), 154.8 (s), 159.6 (s), 169.9 (s) ppm. $C_{19}H_{24}N_2O_7$



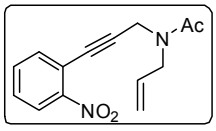
Methyl (R)-1-(3-(2-nitrophenyl)prop-2-yn-1-yl)-5-oxopyrrolidine-2-carboxylate (27ai): Brownish gum; 77%; (R_f = 0.5, 40% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42–2.49 (m, 2H), 3.76 (s, 3H), 4.03 (d, J = 18.2 Hz, 1H), 4.62 (td, J = 4.6, 2.4 Hz, 1H), 4.91 (d, J = 18.2 Hz, 1H), 7.40–7.52 (m, 1H), 7.54–7.63 (m, 2H), 7.98–8.08 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.7 (t), 29.3 (t), 32.1 (t), 52.4 (d), 58.2 (q), 80.0 (s), 90.8 (s), 117.6 (s), 124.5 (d), 128.9 (d), 132.9 (d), 134.6 (d), 149.6 (s), 172.0 (s), 174.5 (s) ppm. $C_{15}H_{14}N_2O_5$



4-(3-(2-Nitrophenyl)prop-2-yn-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (27aj): Brownish oil; 80%; (R_f = 0.6, 40% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.66 (s, 2 H), 4.97 (s, 2 H), 7.00–7.06 (m, 2 H), 7.07–7.15 (m, 2 H), 7.32–7.37 (m, 1 H), 7.52–7.57 (m, 2 H), 7.96–8.07 (m, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.6 (t), 67.5 (t), 79.2 (s), 90.8 (s), 115.5 (d), 116.8 (d), 117.5 (s), 122.9 (d), 124.2 (d), 124.5 (d), 127.8 (s), 129.0 (d), 132.8 (d), 135.0 (d), 145.0 (s), 145.8 (s), 164.1 (s) ppm. $C_{17}H_{12}N_2O_4$

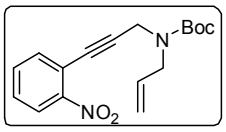


N-Allyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)acetamide (27ak-Ac): Brown oil; 84%; (R_f = 0.5, 50% pet.ether/AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.25 (s, 1H), 4.11–4.16 (m, 3H), 4.27 (s, 1H), 4.49 (s, 2H), 5.17–5.28 (m, 3H), 5.72–5.90 (m, 1.4H), 7.40–7.50 (m, 1.4H), 7.51–7.61 (m, 3H), 7.97–8.05 (m, 1.3H); ^{13}C NMR (101 MHz,

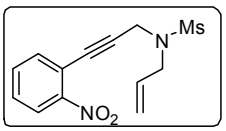


$CDCl_3$): δ 21.1, 21.6 (q), 34.7, 38.1 (t), 47.8, 49.8 (t), 78.6, 79.2 (s), 91.6, 92.8 (s), 117.1, 118.0 (t), 117.4, 117.9 (s), 124.4, 124.5 (d), 128.6, 129.0 (d), 132.0, 132.6 (d), 132.7, 132.8 (d), 134.7 (d), 149.6 (s), 170.2, 170.4 (s) ppm. $C_{14}H_{14}N_2O_3$

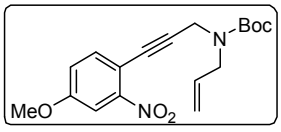
***tert*-Butyl allyl(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ak-Boc):** Yellow colored oil; 87%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 4.03 (d, J = 5.8 Hz, 2H), 4.31 (br s, 2H), 5.14–5.31 (m, 2H), 5.70–5.93 (m, 1H), 7.38–7.49 (m, 1H), 7.49–7.64 (m, 2H), 7.96–8.05 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3 (q, 3C), 43.0 (t), 48.6 (t), 80.4 (s), 93.4 (s), 115.6 (t), 117.0 (s), 118.2 (s), 124.5 (d), 128.6 (d), 132.7 (d), 133.2 (d), 134.8 (d), 149.8 (s), 155.7 (s) ppm; ESI-MS: *m/z* (%): 338.84 (100) $[M+Na]^+$; HRMS: calcd. for $C_{17}H_{20}N_2O_4Na^+$ 339.1315, found 339.1315.



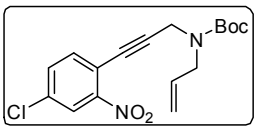
N-Allyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)methanesulfonamide (27ak-Ms): Brown colored oil; 74%; (R_f = 0.6, 30% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.03 (s, 3H), 4.01 (d, J = 6.3 Hz, 2H), 4.36 (s, 2H), 5.28–5.50 (m, 2H), 5.74–5.96 (m, 1H), 7.49–7.57 (m, 1H), 7.59–7.66 (m, 1H), 8.08 (dt, J = 8.0, 0.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.5 (t), 38.3 (q), 49.2 (t), 81.2 (s), 90.6 (s), 117.4 (s), 120.2 (t), 124.7 (d), 129.3 (d), 131.8 (d), 133.1 (d), 134.8 (d), 149.5 (s) ppm; ESI-MS: *m/z* (%): 316.88 (100) $[M+Na]^+$.



***tert*-Butyl allyl(3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27bk):** Brownish gum; 89%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.87 (s, 3H), 4.02 (d, J = 5.8 Hz, 2H), 4.29 (br s, 2H), 5.12–5.29 (m, 2H), 5.71–5.92 (m, 1H), 7.09 (dd, J = 8.7, 2.7 Hz, 1H), 7.45–7.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 36.3 (t), 48.5 (t), 55.9 (q), 78.4 (s), 80.3 (s), 91.3 (s), 109.2 (d), 110.3 (s), 117.1 (t), 119.6 (d), 133.3 (d), 135.7 (d), 150.8 (s), 154.9 (s), 159.4 (s) ppm; HRMS: calcd. for $C_{18}H_{22}N_2O_5Na^+$ 369.1422, found 369.1421.

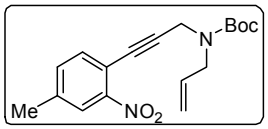


***tert*-Butyl allyl(3-(4-chloro-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27ck):** Brownish oil; 82%; (R_f = 0.6, 20% pet.ether/AcOEt);^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 4.00 (d, J = 5.9 Hz, 2H), 4.29 (br s, 2H), 5.14–5.26 (m, 2H), 5.70–5.91 (m, 1H), 7.52 (d,

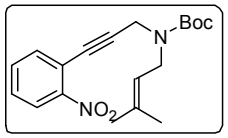


J = 1.3 Hz, 2H), 8.00 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.2 (q, 3C), 36.0, 36.5 (t), 48.6 (t), 80.4 (s), 94.6 (s), 116.7 (s), 117.0 (t), 124.7 (d), 128.3 (s), 128.5 (s), 131.4, 131.5 (d), 132.9 (d), 134.4 (s), 135.6 (d), 150.0 (s) ppm. $C_{17}H_{19}ClN_2O_4$

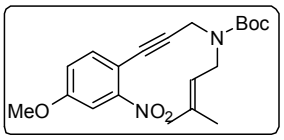
***tert*-Butyl allyl(3-(4-methyl-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27dk):** Brownish oil; 78%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.41 (s, 3H), 4.01 (d, *J* = 5.8 Hz, 2H), 4.28 (br s, 2H), 5.10–5.29 (m, 2H), 5.69–5.91 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.1 (q), 28.2 (q, 3C), 35.9 (t), 48.5 (t), 80.3 (s), 92.2 (s), 115.2 (s), 116.9 (t), 117.5 (s), 124.7 (d), 133.2 (d), 133.5 (d), 134.4 (d), 139.5 (s), 149.6 (s), 154.9 (s) ppm; ESI-MS: *m/z* (%): 353.04 (75) $[M+Na]^+$; HRMS: calcd. for $C_{18}H_{22}N_2O_4Na^+$ 353.1469, found 353.1472.



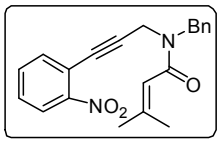
***tert*-Butyl (3-methylbut-2-en-1-yl)(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27al):** Yellow colored oil; 85%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.66–1.78 (m, 6H), 4.03 (d, *J* = 7.1 Hz, 2H), 4.27 (br s, 2H), 5.19 (t, *J* = 7.1 Hz, 1H), 7.38–7.52 (m, 1H), 7.52–7.64 (m, 2H), 8.02 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8 (q), 25.7 (q), 28.4 (q, 3C), 35.9 (t), 43.5 (t), 78.1 (s), 80.2 (s), 93.9 (s), 118.4 (s), 119.8 (d), 124.5 (d), 128.5 (d), 132.6 (d), 134.8 (d), 136.5 (s), 149.9 (s), 155.0 (s) ppm; ESI-MS: *m/z* (%): 366.91 (100) $[M+Na]^+$; HRMS: calcd. for $C_{19}H_{24}N_2O_4Na^+$ 367.1628, found 367.1628.



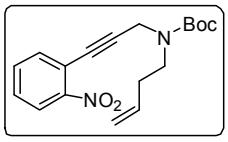
***tert*-Butyl (3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl)(3-methylbut-2-en-1-yl)carbamate (27bl):** Brwonish oil; 87%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.66–1.83 (m, 6H), 3.88 (s, 3H), 4.02 (d, *J* = 6.8 Hz, 2H), 4.25 (br s, 2H), 5.19 (ddd, *J* = 7.1, 5.7, 1.3 Hz, 1H), 7.09 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.41–7.59 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8 (q), 25.7 (q), 28.4 (q, 3C), 35.8 (t), 43.4 (t), 55.9 (q), 80.1 (s, 2C), 91.8 (s), 109.2 (d), 110.4 (s), 119.6 (d), 119.8 (d), 135.7 (d), 136.4 (s), 150.7 (s), 155.0 (s), 159.3 (s) ppm; ESI-MS: *m/z* (%): 397.02 (100) $[M+Na]^+$; HRMS: calcd. for $C_{20}H_{26}N_2O_5Na^+$ 397.1735, found 397.1734.



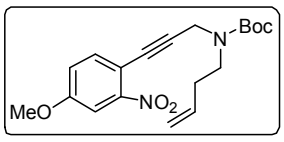
N-Benzyl-3-methyl-N-(3-(2-nitrophenyl)prop-2-yn-1-yl)but-2-enamide (27am): Yellow colored oil; 76%; (R_f = 0.5, 30% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78–1.95 (m, 3H), 2.03 (br s, 3H), 4.27 (s, 1H), 4.49 (s, 1H), 4.82 (s, 2H), 5.85–6.07 (m, 1H), 7.19–7.42 (m, 5H), 7.42–7.70 (m, 3H), 8.04 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.3 (q), 26.4 (q), 34.0 (t), 50.5 (t), 78.9 (s), 93.0 (s), 117.1 (d), 124.5 (d), 127.0 (d), 127.6 (d), 128.5 (d), 128.6 (d), 128.8 (d), 132.8 (d, 2C), 134.8 (d, 2C), 136.4 (s), 149.1 (s), 149.8 (s), 168.2 (s) ppm; ESI-MS: *m/z* (%): 370.99 (100) $[M+Na]^+$; HRMS: calcd. for $C_{21}H_{20}N_2O_3Na^+$ 371.1367, found 371.1366.



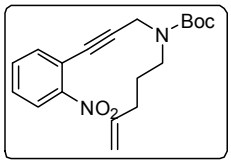
***tert*-Butyl but-3-en-1-yl(3-(2-nitrophenyl)prop-2-yn-1-yl)carbamate (27an):** Orange oil; 89%; (R_f = 0.5, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.37 (q, J = 7.1 Hz, 2H), 3.41–3.52 (dd, J = 6.9, 8.4 Hz, 2H), 4.34 (br s, 2H), 4.95–5.17 (m, 2H), 5.69–5.92 (m, 1H), 7.38–7.49 (m, 1H), 7.50–7.63 (m, 2H), 8.00 (dd, J = 7.6, 0.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9 (t), 28.3 (q, 3C), 32.6 (t), 46.0 (t), 80.2 (s, 2C), 93.6 (s), 116.6 (t), 118.2 (s), 124.5 (d), 128.6 (d), 132.7 (d), 134.8 (d), 135.3 (d), 149.9 (s), 154.9 (s) ppm; ESI-MS: *m/z* (%): 352.93 (100) $[M+Na]^+$; HRMS: calcd. for $C_{18}H_{22}N_2O_4Na^+$ 353.1471, found 353.1472.



***tert*-Butyl but-3-en-1-yl(3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl)carbamate (27bn):** Brown oil; 90%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.35 (q, J = 7.1 Hz, 2H), 3.38–3.52 (m, 2H), 3.85 (s, 3H), 4.19–4.39 (m, 2H), 4.93–5.15 (m, 2H), 5.68–5.91 (m, 1H), 7.07 (dd, J = 8.7, 2.7 Hz, 1H), 7.42–7.52 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8 (t), 28.3 (q, 3C), 32.6 (t), 45.9 (t), 55.9 (q), 80.0 (s, 2C), 91.3 (s), 109.2 (d), 110.2 (s), 116.5 (t), 119.5 (d), 135.4 (d), 135.6 (d), 150.7 (s), 154.9 (s), 159.4 (s) ppm; ESI-MS: *m/z* (%): 382.91 (100) $[M+Na]^+$; HRMS: calcd. for $C_{19}H_{24}N_2O_5Na^+$ 383.1577, found 383.1577.

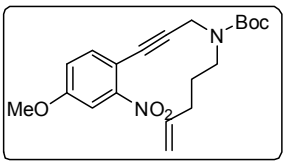


***tert*-Butyl (3-(2-nitrophenyl)prop-2-yn-1-yl)(pent-4-en-1-yl)carbamate (27ao):** Yellow oil; 85%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.67–1.82 (m, 2H), 2.01–2.17 (m, 2H), 3.34–3.48 (m, 2H), 4.34 (br s, 2H), 4.92–5.11 (m, 2H), 5.84

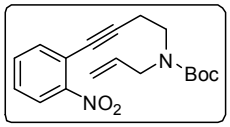


(ddt, J = 17.0, 10.3, 6.5, 6.5 Hz, 1H), 7.40–7.54 (m, 1H), 7.54–7.65 (m, 2H), 8.03 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.2 (t), 28.4 (q, 3C), 30.9 (t, 2C), 46.2 (t), 80.2 (s, 2C), 93.8 (s), 114.9 (t), 122.6 (s), 124.5 (d), 128.6 (d), 132.7 (d), 134.8 (d), 138.0 (d), 149.9 (s), 155.2 (s) ppm; HRMS: calcd. for $C_{19}H_{24}N_2O_4Na^+$ 367.1625, found 367.1628.

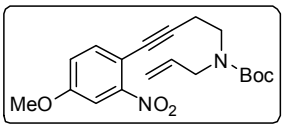
***tert*-Butyl (3-(4-methoxy-2-nitrophenyl)prop-2-yn-1-yl)(pent-4-en-1-yl) carbamate (27bo):** Brown gum; 89%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.69 (quin, J = 7.4 Hz, 2H), 1.96–2.15 (m, 2H), 3.29–3.45 (m, 2H), 3.85 (s, 3H), 4.29 (br s, 2H), 4.84–5.10 (m, 2H), 5.80 (ddt, J = 17.0, 10.3, 6.6, 6.6 Hz, 1H), 7.06 (dd, J = 8.7, 2.7 Hz, 1H), 7.40–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 27.1 (t), 28.3 (q, 3C), 30.8 (t), 36.6 (t), 37.4 (t), 46.0 (t), 55.9 (q), 80.0 (s), 91.4 (s), 109.1 (d), 110.2 (s), 114.8 (t), 119.5 (d), 135.6 (d), 137.9 (d), 150.6 (s), 154.8 (s), 155.2 (s), 159.3 (s) ppm; HRMS: calcd. for $C_{20}H_{26}N_2O_5Na^+$ 397.1733, found 397.1734.



***tert*-Butyl allyl(4-(2-nitrophenyl)but-3-yn-1-yl)carbamate (27ap):** Yellow oil; 86%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.71 (t, J = 6.6 Hz, 2H), 3.45 (br s, 2H), 3.93 (br s, 2H), 5.13 (d, J = 10.4 Hz, 2H), 5.68–5.91 (m, 1H), 7.34–7.46 (m, 1H), 7.47–7.61 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.6 (t), 19.9 (t), 28.3 (q, 3C), 45.4 (t), 45.5 (t), 49.9 (t), 50.5 (t), 79.7 (s), 79.8 (s), 95.9 (s), 96.4 (s), 116.0 (t), 116.7 (t), 118.7 (s), 118.8 (s), 124.3 (d), 128.1 (d), 132.5 (d), 133.9 (d), 134.0 (d), 134.7 (s), 134.8 (s), 149.8 (s), 155.1 (s), 155.2 (s) ppm; ESI-MS: *m/z* (%): 352.93 (50) $[M+Na]^+$; HRMS: calcd. for $C_{18}H_{22}N_2O_4Na^+$ 353.1471, found 353.1472.

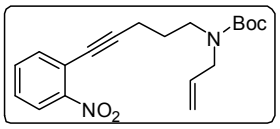


***tert*-Butyl allyl(4-(4-methoxy-2-nitrophenyl)but-3-yn-1-yl)carbamate (27bp):** Brownish gum; 89%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.69 (t, J = 6.6 Hz, 2H), 3.44 (br s, 2H), 3.87 (s, 3H), 3.93 (br s, 2H), 5.14 (d, J = 10.7 Hz, 2H), 5.69–5.92 (m, 1H), 7.07 (dd, J = 8.7, 2.6 Hz, 1H), 7.40–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 19.6 (t), 19.9 (t), 28.3 (q, 3C), 45.5 (t), 49.9 (t), 50.6 (t), 55.9 (q), 79.7 (s), 79.9 (s), 93.7 (s), 94.3 (s), 109.0 (d), 110.9 (s), 111.1 (s), 116.0

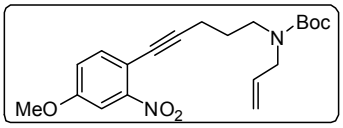


(t), 116.7 (t), 119.6 (d, 2C), 134.0 (d), 135.6 (d), 150.7 (s), 155.2 (s), 159.0 (s) ppm; ESI-MS: *m/z* (%): 382.96 (100) $[M+Na]^+$; HRMS: calcd. for $C_{19}H_{24}N_2O_5Na^+$ 383.1577, found 383.1577.

***tert*-Butyl allyl(5-(2-nitrophenyl)pent-4-yn-1-yl)carbamate (27aq):** Yellow syrup; 85%; (R_f = 0.6, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.85 (t, J = 7.1 Hz, 2H), 2.48 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 7.1 Hz, 2H), 3.80–3.91 (m, 2H), 5.05–5.19 (m, 2H), 5.69–5.90 (m, 1H), 7.34–7.44 (m, 1H), 7.47–7.61 (m, 2H), 7.91–8.00 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.3 (t), 27.1 (t), 28.3 (q, 3C), 45.9 (t), 50.0 (t), 79.5 (s, 2C), 98.2 (s), 116.1 (t), 119.0 (s), 124.3 (d), 127.9 (d), 132.5 (d), 134.1 (d), 134.7 (d), 150.0 (s), 155.5 (s) ppm; ESI-MS: *m/z* (%): 367.08 (100) $[M+Na]^+$; HRMS: calcd. for $C_{19}H_{24}N_2O_4Na^+$ 367.1626, found 367.1628.

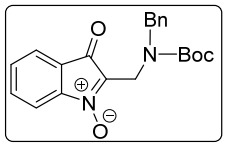


***tert*-Butyl allyl(5-(4-methoxy-2-nitrophenyl)pent-4-yn-1-yl)carbamate (27bq):** Brownish oil; 88%; (R_f = 0.4, 20% pet.ether/AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.75–1.91 (m, 2H), 2.37–2.51 (m, 2H), 3.32 (t, J = 7.1 Hz, 2H), 3.84 (s, 5H), 5.03–5.18 (m, 2H), 5.67–5.89 (m, 1H), 7.05 (dd, J = 8.7, 2.7 Hz, 1H), 7.45 (dd, J = 5.7, 3.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 17.2 (t), 27.0 (t), 27.2 (t), 28.3 (q, 3C), 45.7 (t), 49.4 (t), 50.1 (t), 55.8 (q), 76.0 (s), 79.4 (s), 95.8 (s), 108.9 (d), 111.1 (s), 115.9 (t), 116.4 (t), 119.5 (d, 2C), 134.1 (d), 135.5 (d), 150.6 (s), 155.4 (s), 158.8 (s) ppm; ESI-MS: *m/z* (%): 397.15 (100) $[M+Na]^+$; HRMS: calcd. for $C_{20}H_{26}N_2O_5Na^+$ 397.1733, found 397.1734.

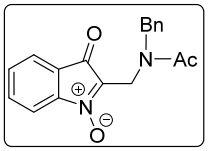


General Procedure B: The *o*-nitroalkyne or *o*-nitroenyne carbamate **27** (1 eq.) was dissolved in anhydrous CH_2Cl_2 (4 mL) was added the catalyst $AuCl(PPh_3)$ (10 mol %), and $AgSbF_6$ (20 mol %) at 0 °C and reaction mixture was warmed to room temperature, then allowed to stir for 4 h. After completion, the reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography (flash silica gel) to procure the isatogen **28** or isoxazolidine **31**.

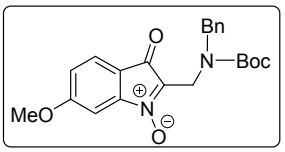
2-((Benzyl(*tert*-butoxycarbonyl)amino)methyl)-3-oxo-3H-indole 1-oxide (28aa-Boc): Yellow gum; 68%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47–1.56 (m, 9H), 4.36–4.50 (m, 2H), 4.58 (d, J = 16.9 Hz, 2H), 7.17–7.29 (m, 5H), 7.43–7.58 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 37.5 (t), 51.0 (t), 80.7 (s), 113.8 (d), 121.3 (d), 123.0 (s), 127.1 (d), 128.3 (d, 4C), 131.3 (d), 134.2 (d), 135.0 (s), 137.9 (s), 146.9 (s), 155.3 (s), 185.4 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{21}H_{23}N_2O_4$ (M^++H): 367.1658, found 367.1652.



2-((*N*-Benzylacetamido)methyl)-3-oxo-3H-indole 1-oxide (28aa-Ac): Highly viscous yellow oil; 66%; (R_f = 0.3, 40% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.51 (s, 3H), 4.50 (s, 2H), 4.54 (s, 2H), 4.67 (s, 2H), 4.77 (s, 2H), 7.11 (t, J = 7.3 Hz, 2H), 7.18–7.39 (m, 8H), 7.48–7.66 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.2, 21.9 (q), 37.8, 38.6 (t), 49.0, 53.7 (t), 113.8, 114.0 (d), 121.5 (d), 122.6, 123.0 (s), 126.3, 126.9 (d), 127.6 (d, 2C), 128.2 (d), 128.8 (d), 131.3, 131.7 (d), 133.9, 134.7 (s), 134.2, 134.4 (d), 136.3, 137.3 (s), 146.7, 146.8 (s), 171.1 (s), 185.2, 185.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{17}N_2O_3$ (M^++H):309.1239, found 309.1234.

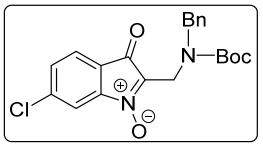


2-((Benzyl(*tert*-butoxycarbonyl)amino)methyl)-6-methoxy-3-oxo-3H-indole 1-oxide (28ba): Brown oil; 71%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.47 (m, 9H), 3.82 (s, 3H), 4.32 (m, 2H), 4.50 (d, J = 18.8 Hz, 2H), 6.80 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 7.09–7.25 (m, 5H), 7.33 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.2 (q, 3C), 37.5 (t), 50.9 (t), 56.2 (q), 80.6 (s), 101.2 (d), 115.0 (d), 123.1 (d), 127.0 (d, 2C), 127.6 (s), 128.3 (d, 3C),

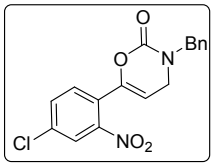


135.7 (s), 137.8 (s), 149.5 (s), 155.3 (s), 165.0 (s), 184.3 (s) ppm; HRMS (ESI^+): calcd. for $C_{22}H_{24}N_2O_5Na$ (M^++Na): 419.1583, found 419.1577.

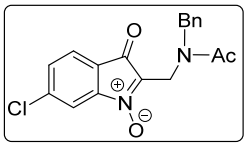
2-((Benzyl(*tert*-butoxycarbonyl)amino)methyl)-6-chloro-3-oxo-3H-indole 1-oxide (28ca): Yellow oil; 19%; (R_f = 0.5, 20% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 9H), 4.43 (br s, 2H), 4.57 (br s, 2H), 7.07–7.26 (m, 5H), 7.39–7.45 (m, 1H), 7.45–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3 (q, 3C), 37.6, 38.0 (t), 51.0, 52.0 (t), 80.8 (s), 115.0 (d), 122.3 (d), 127.1 (d), 127.6 (d), 128.3 (d, 3C), 131.2 (d), 135.9 (s), 137.8 (s, 2C), 140.4 (s), 147.8 (s), 155.3 (s), 184.0 (s) ppm; HRMS (ESI^+): calcd. for $C_{21}H_{21}ClN_2O_4Na$ (M^++Na): 423.1088, found 423.1082.



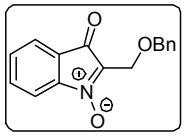
3-Benzyl-6-(4-chloro-2-nitrophenyl)-3,4-dihydro-2H-1,3-oxazin-2-one (30ca): Yellow solid; 51%; (R_f = 0.4, 20% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 4.22 (d, J = 2.1 Hz, 2H), 4.52 (s, 2H), 5.98 (t, J = 2.1 Hz, 1H), 7.24–7.41 (m, 5H), 7.51 (dd, J = 8.5, 2.1 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 47.8 (t), 48.4 (t), 95.7 (d), 124.5 (d), 126.3 (s), 128.2 (d, 2C), 128.4 (d), 129.0 (d, 2C), 132.0 (d), 132.7 (s), 132.9 (d), 134.3 (s), 145.9 (s), 147.2 (s), 154.5 (s) ppm; HRMS (ESI^+): calcd. for $C_{17}H_{14}ClN_2O_4$ (M^++H): 345.0642, found 345.0637.



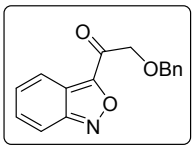
2-((*N*-Benzylacetamido)methyl)-6-chloro-3-oxo-3H-indole 1-oxide (28ca-Ac): Brown gum; 64%; (R_f = 0.5, 50% AcOEt/pet.ether) found as rotameric mixture; ^1H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.47 (s, 2.4H), 4.47 (s, 1.5H), 4.48 (s, 2H), 4.62 (s, 1.5H), 4.73 (s, 2H), 6.96 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1.7H), 7.15–7.25 (m, 4.7H), 7.27–7.34 (m, 2.4H), 7.9 (d, J = 7.7Hz, 1H), 7.42–7.54 (m, 4.5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.1, 21.8 (q), 37.9, 38.7 (t), 49.1, 53.7 (t), 114.9, 115.1 (d), 120.9, 121.3 (s), 122.4, 122.5 (d), 126.3, 126.9 (d, 2C), 127.5, 127.7 (d), 128.1, 128.8 (d, 2C), 131.2, 131.5 (d), 134.7, 135.6, 136.2 (s), 137.3 (s), 140.4, 140.6 (s), 147.5, 147.7 (s), 171.0, 171.1 (s), 183.7, 184.2 (s) ppm; HRMS (ESI^+): calcd. for $C_{18}H_{16}ClN_2O_3$ (M^++H): 343.0849, found 343.0844.



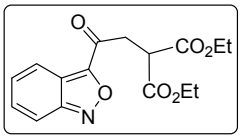
2-((Benzyloxy)methyl)-3-oxo-3H-indole 1-oxide (28ab): Yellow oil; 31%; (R_f = 0.3, 10% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 2H), 4.63 (s, 2H), 7.19–7.39 (m, 5H), 7.53–7.69 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 56.9 (t), 73.6 (t), 114.3 (d), 121.6 (d), 123.0 (s), 127.7 (d, 2C), 127.8 (d), 128.3 (d, 2C), 131.8 (d), 134.4 (d), 134.9 (s), 137.6 (s), 147.1 (s), 185.9 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{16}H_{13}NO_3Na$ (M^++Na): 290.0793, found 290.0788.



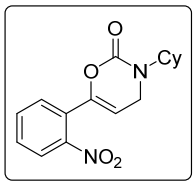
1-(Benzo[c]isoxazol-3-yl)-2-(benzyloxy)ethan-1-one (29ab): Yellow oil; 33%; (R_f = 0.5, 10% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (s, 2H), 4.93–4.98 (m, 2H), 7.26–7.46 (m, 7H), 7.72 (d, J = 9.6 Hz, 1H), 8.05 (dd, J = 8.7, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 72.5 (t), 73.7 (t), 115.9 (d), 119.7 (s), 120.8 (d), 128.1 (d, 2C), 128.1 (d), 128.5 (d, 2C), 128.9 (d), 131.5 (d), 136.9 (s), 157.3 (s), 158.1 (s), 185.9 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{16}H_{13}NO_3Na$ (M^++Na): 290.0793, found 290.0788.



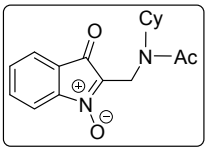
Diethyl 2-(2-(benzo[c]isoxazol-3-yl)-2-oxoethyl)malonate (29ac): Yellow oil; 61%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 6H), 3.83 (d, J = 6.9 Hz, 2H), 4.10 (dd, J = 7.5, 6.8 Hz, 1H), 4.20–4.33 (m, 4H), 7.22–7.33 (m, 1H), 7.41 (ddd, J = 9.0, 6.5, 1.1 Hz, 1H), 7.74 (dd, J = 9.0, 1.0 Hz, 1H), 8.00 (dt, J = 8.7, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9 (q, 2C), 38.7 (t), 46.4 (d), 61.9 (t, 2C), 116.0 (s), 119.3 (s), 120.8 (s), 128.8 (s), 131.3 (s), 157.4 (s), 158.8 (s), 168.3 (s, 2C), 186.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{16}H_{18}NO_6$ (M^++H): 320.1134, found 320.1129.



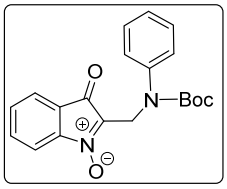
3-Cyclohexyl-6-(2-nitrophenyl)-3,4-dihydro-2H-1,3-oxazin-2-one (30ad): Yellow gum; 68%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.40 (m, 6H), 1.80–1.86 (m, 4H), 3.72–3.78 (m, 1H), 4.33 (d, J = 2.3 Hz, 2H), 6.06 (t, J = 2.1 Hz, 1H), 7.27–7.33 (m, 1H), 7.50–7.55 (m, 2H), 7.86 (dd, J = 8.2, 1.4 Hz, 1H), 8.00–8.04 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.0 (t), 25.1 (t, 2C), 30.1 (t, 2C), 45.3 (t), 52.6 (d), 96.2 (d), 121.4 (s), 124.3 (d), 127.1 (d), 127.9 (s), 130.9 (d), 132.8 (d), 146.0 (s), 154.0 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{16}H_{19}N_2O_4$ (M^++H): 303.1345, found 303.1339.



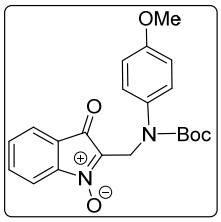
2-((*N*-Cyclohexylacetamido)methyl)-3-oxo-3H-indole 1-oxide (28ad-Ac): Yellow gum; 67%; (R_f = 0.5, 40% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17–1.38 (m, 3.8H), 1.39–1.52 (m, 2H), 1.61 (d, J = 13.5 Hz, 2.8H), 1.82 (t, J = 9.9 Hz, 4H), 2.11 (s, 3H), 2.28 (s, 1H), 3.49–3.68 (m, 1H), 4.40 (s, 2H), 7.44–7.57 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.3, 22.8 (q), 25.0, 25.7 (t, 3C), 29.9, 31.1 (t, 2C), 34.4, 36.6 (t), 53.8, 58.1 (d), 113.4, 114.0 (d), 121.3, 121.7 (d), 122.6, 123.0 (s), 130.9, 131.7 (d), 134.1, 134.5 (d), 135.3 (s), 146.5, 146.6 (s), 170.5, 170.9 (s), 184.7, 185.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{17}H_{21}N_2O_3$ (M^++H): 301.1552, found 301.1547.



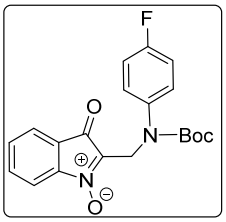
2-(((*tert*-Butoxycarbonyl)(phenyl)amino)methyl)-3-oxo-3H-indole 1-oxide (28ae): Yellow oil; 58%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 4.89 (s, 2H), 7.17 (td, J = 5.7, 2.7 Hz, 1H), 7.28–7.34 (m, 4H), 7.49–7.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.2 (q, 3C), 42.2 (t), 81.0 (s), 113.8 (d), 121.6 (d), 123.0 (s), 126.4 (d), 126.7 (d, 2C), 128.7 (d, 2C), 131.4 (d), 134.3 (d), 134.6 (s), 142.1 (s), 146.8 (s), 154.3 (s), 185.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{20}H_{20}N_2O_4Na$ (M^++ Na): 375.1321, found 375.1315.



2-(((*tert*-Butoxycarbonyl)(4-methoxyphenyl)amino)methyl)-3-oxo-3H-indole 1-oxide (28af): Brown oil; 43%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 3.75 (s, 3H), 4.84 (s, 2H), 6.75–6.84 (m, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.50–7.64 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.2 (q, 3C), 42.2 (t), 55.3 (q), 80.8 (s), 113.8 (d), 113.9 (d), 121.5 (d), 123.1 (s), 128.0 (d, 3C), 131.4 (d), 134.3 (d), 134.6 (s), 135.0 (s), 146.9 (s), 154.6 (s), 157.9 (s), 185.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{21}H_{22}N_2O_5Na$ (M^++Na): 405.1426, found 405.1421.

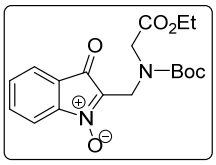


2-(((*tert*-Butoxycarbonyl)(4-fluorophenyl)amino)methyl)-3-oxo-3H-indole 1-oxide (28ag): Yellow gum; 47%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 4.84 (s, 2H), 6.92–7.03 (m, 2H), 7.24–7.33 (m, 2H), 7.51–7.66 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.2 (q, 3C), 42.1 (t), 81.2 (s), 113.9 (d), 115.4

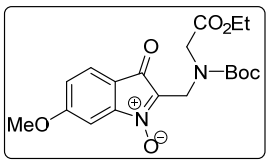


(d), 115.6 (d), 121.6 (d), 123.0 (s), 128.6 (d), 128.7 (d), 131.5 (d), 134.4 (d), 138.0 (s), 146.8 (s), 154.2 (s), 159.7 (s), 162.1 (s), 185.3 (s) ppm; HRMS (ESI^+): calcd. for $C_{20}H_{19}FN_2O_4Na$ (M^++ Na): 393.1227, found 393.1221.

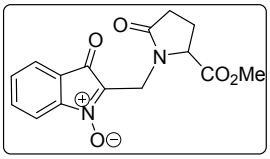
2-(((*tert*-Butoxycarbonyl)(2-ethoxy-2-oxoethyl)amino)methyl)-3-oxo-3H-indole 1-oxide (28ah): Highly viscous yellow oil; 69%; (R_f = 0.4, 20% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.16–1.24 (m, 3H), 1.40–1.48 (m, 9H), 4.09–4.20 (m, 4H), 4.51 (d, J = 5.7 Hz, 2H), 7.55–7.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 28.2 (q, 3C), 38.7 (t), 50.0 (t), 61.0 (t), 81.3 (s), 112.6 (s), 114.1 (d), 121.6 (d), 131.6 (d), 134.4 (d), 134.8 (s), 147.1 (s), 170.0 (s, 2C), 185.5 (s) ppm; HRMS (ESI^+): calcd. for $C_{18}H_{22}N_2O_6Na$ (M^++Na): 385.1376, found 385.1370.



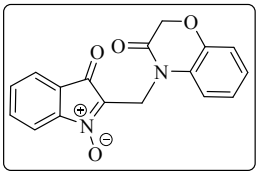
2-(((*tert*-Butoxycarbonyl)(2-ethoxy-2-oxoethyl)amino)methyl)-6-methoxy-3-oxo-3H-indole 1-oxide (28bh): Brown oil; 71%; (R_f = 0.3, 20% AcOEt/pet.ether); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18–1.23 (m, 3H), 1.38–1.48 (m, 9H), 3.87–3.95 (m, 3H), 4.01–4.21 (m, 4H), 4.39–4.54 (m, 2H), 6.86–6.99 (m, 1H), 7.14 (dd, J = 2.9, 5.9 Hz, 1H), 7.43–7.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9, 14.0 (q), 28.0, 28.1 (q, 3C), 38.7, 38.8 (t), 49.8, 50.6 (t), 56.2 (q), 60.2, 60.9 (t), 80.8, 81.2 (s), 101.5 (d), 101.5 (s), 115.1, 115.2 (d), 123.4, 123.4 (d), 135.3, 135.4 (s), 149.7 (s), 154.6, 154.9 (s), 165.1, 165.1 (s), 169.9, 169.9 (s), 184.3 (s) ppm; HRMS (ESI^+): calcd. for $C_{19}H_{25}N_2O_7$ (M^++H): 393.1662, found 393.1656



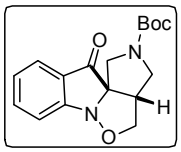
(R)-2-((2-(Methoxycarbonyl)-5-oxopyrrolidin-1-yl)methyl)-3-oxo-3H-indole 1-oxide (28ai): Brown gum; 56%; (R_f = 0.4, 40% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 2.07–2.15 (m, 1H), 2.31–2.48 (m, 3H), 3.76 (s, 3H), 4.23 (d, J = 16.0 Hz, 1H), 4.31–4.44 (m, 1H), 4.88 (d, J = 16.2 Hz, 1H), 7.54–7.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0 (t), 28.7 (t), 33.1 (t), 52.6 (q), 60.3 (d), 114.0 (d), 121.8 (d), 123.0 (s), 131.7 (d), 133.4 (s), 134.5 (d), 154.0 (s), 172.1 (s), 175.1 (s), 185.2 (s) ppm; HRMS (ESI^+): calcd. for $C_{15}H_{15}N_2O_5$ (M^++H): 303.0981, found 303.0975.



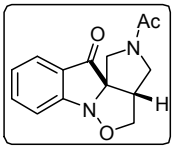
3-Oxo-2-((3-oxo-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-3H-indole 1-oxide (28aj): Brown oil; 61%; (R_f = 0.4, 40% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.68–4.76 (m, 2H), 5.23 (s, 2H), 6.97 (s, 4H), 7.50–7.58 (m, 2H), 7.58–7.73 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.7 (t), 67.4 (t), 114.0 (d), 114.4 (d), 117.2 (d), 121.8 (d), 122.9 (d), 122.9 (s), 124.2 (d), 128.0 (s), 131.8 (d), 132.6 (s), 134.6 (d), 145.2 (s), 146.7 (s), 164.7 (s), 184.7 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{17}H_{13}N_2O_4$ (M^++H): 309.0875, found 309.0870.



***tert*-Butyl 11-oxo-3a,4-dihydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indole-2(3H)-carboxylate (31ak-Boc):** Yellow solid; 71%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.20 (br s, 1H), 3.50 (br s, 1H), 3.64 (dd, J = 9.2, 5.0 Hz, 1H), 3.84–3.97 (m, 2H), 3.97–4.06 (m, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.66–7.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.4 (q, 3C), 51.2 (t), 51.5 (d), 53.1 (t), 72.5 (t), 80.1 (s, 2C), 118.8 (d), 123.6 (d), 123.6 (s), 126.4 (d), 137.5 (d), 153.5 (s), 161.6 (s), 197.5 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{17}H_{20}N_2O_4Na$ (M^++Na): 339.1315, found 339.1315.



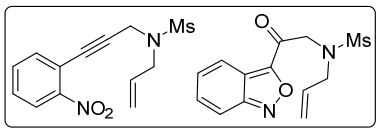
2-Acetyl-2,3,3a,4-tetrahydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indol-11-one (31ak-Ac): Brown oil; 65%; (R_f = 0.3, 50% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.16–3.43 (m, 1H), 3.57–3.71 (m, 2H), 3.88–4.19 (m, 4H), 7.29–7.40 (m, 1H), 7.45–7.53 (m, 1H), 7.66–7.81 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.2, 22.2 (q), 50.5, 52.3 (t), 51.0, 52.4 (d), 52.5, 53.9 (t), 71.8, 72.4 (t), 83.3, 84.8 (s), 118.6, 118.8 (d), 123.5, 123.6 (d), 125.4, 125.6 (s), 126.4, 126.4 (d), 137.5, 137.7 (d), 161.3, 161.4 (s), 168.4, 168.6 (s), 196.6, 197.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{14}H_{14}N_2O_3Na$ (M^++Na): 281.0894, found 281.0897.



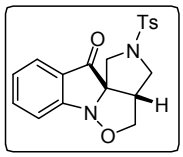
2-(Methylsulfonyl)-2,3,3a,4-tetrahydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a] indol-11-one (31ak-Ms): Brown oil; 13%; (R_f = 0.3, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.06 (s, 3H), 3.26 (dt, J = 8.6, 5.7 Hz, 1H), 3.43–3.54 (m, 1H), 3.67 (dd, J = 9.7, 5.1 Hz, 1H), 3.82–4.08 (m, 4H), 7.29–7.39 (m, 1H), 7.44–7.51 (m, 1H), 7.65–7.81 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.2 (q), 53.0 (d), 53.1 (t), 54.5 (t), 72.0 (t), 84.7

(s), 118.6 (d), 123.8 (d), 125.4 (s), 126.6 (d), 137.8 (d), 161.3 (s), 206.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{14}N_2O_4SNa$ (M^++Na): 317.0563, found 317.0566.

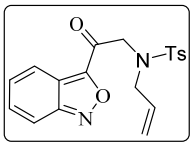
N-Allyl-N-(2-(benzo[c]isoxazol-3-yl)-2-oxoethyl)methanesulfonamide (27ak-Ms + 29ak-Ms): Dark brown oil; 54% (mixture); (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.04 (s, 3H), 3.15 (s, 1.3H), 4.02 (d, J = 6.3 Hz, 2.8H), 4.37 (s, 2H), 4.98 (s, 0.8H), 5.20–5.52 (m, 2.9H), 5.74–5.98 (m, 1.4H), 7.30–7.46 (m, 0.7H), 7.48–7.59 (m, 1H), 7.60–7.67 (m, 2H), 7.74–7.80 (dt, J = 1.1, 2.0, 8.8 Hz, 0.4H), 7.98–8.04 (dt, J = 1.1, 2.3, 8.8 Hz, 0.4H), 8.05–8.14 (dt, J = 1.0, 2.1, 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 36.5 (t), 38.3 (q), 40.5 (q), 49.2 (t), 50.7 (t), 52.9 (t), 81.2 (s), 90.6 (s, 2C), 116.1 (d), 117.4 (s), 120.0 (t), 120.2 (t), 120.4 (d), 124.7 (d), 129.3 (d), 129.4 (d), 131.6 (d), 131.8 (d), 132.3 (d), 133.1 (d), 134.8 (d), 149.5 (s), 157.3 (s), 157.8 (s), 185.0 (s) ppm.



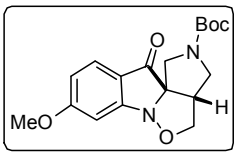
2-Tosyl-2,3,3a,4-tetrahydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indol-11-one (31ak-Ts): Yellow oil; 26%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.04–3.17 (m, 1H), 3.20–3.30 (m, 1H), 3.47–3.76 (m, 4H), 3.88 (d, J = 9.5 Hz, 1H), 7.25–7.31 (m, 1H), 7.32–7.46 (m, 3H), 7.62–7.71 (m, 2H), 7.75 (d, J = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.6 (q), 52.2 (d), 52.9 (t), 54.3 (t), 72.1 (t), 83.8 (s), 118.3 (d), 123.8 (d), 125.1 (s), 126.3 (d), 128.1 (d, 2C), 129.8 (d, 2C), 131.6 (s), 137.6 (d), 144.2 (s), 161.3 (s), 196.1 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{18}N_2O_4SNa$ (M^++Na): 393.0877, found 393.0879.



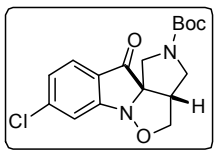
***N*-Allyl-N-(2-(benzo[c]isoxazol-3-yl)-2-oxoethyl)-4-methylbenzenesulfonamide (29ak-Ts):** Yellow oil; 49%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.99 (d, J = 6.6 Hz, 2H), 4.86 (s, 2H), 5.15 (ddt, J = 13.5, 2.5, 1.4 Hz, 2H), 5.61–5.82 (m, 1H), 7.30–7.35 (m, 2H), 7.37–7.47 (m, 1H), 7.65–7.84 (m, 4H), 7.98 (dt, J = 8.7, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.5 (q), 51.1 (t), 52.3 (t), 115.9 (d), 119.8 (s), 120.1 (t), 120.7 (d), 127.3 (d, 2C), 129.0 (d), 129.6 (d, 2C), 131.5 (d), 132.1 (d), 136.5 (s), 143.6 (s), 157.2 (s), 158.0 (s), 183.8 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{18}N_2O_4SNa$ (M^++Na): 393.0874, found 393.0879.



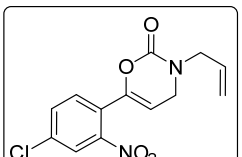
***tert*-Butyl 8-methoxy-11-oxo-3a,4-dihydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo [2,3-a]indole-2(3H)-carboxylate (31bk):** Brown gum; 79%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 3.09–3.26 (m, 1H), 3.39–3.55 (m, 1H), 3.63 (dd, J = 9.3, 4.9 Hz, 1H), 3.81–4.02 (m, 7H), 6.77–6.87 (m, 2H), 7.55 (dd, J = 8.3, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3 (q, 3C), 51.1 (t), 52.0 (d), 53.1 (t), 55.9 (q), 72.6 (t), 79.9 (s), 85.2 (s), 100.8 (d), 115.9 (d), 118.7 (s), 125.0 (d), 153.7 (s), 164.4 (s), 167.7 (s), 195.0 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{22}N_2O_5Na$ (M^++Na): 369.1418, found 369.1421.



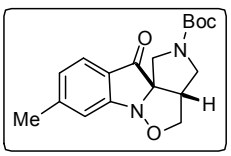
***tert*-Butyl 8-chloro-11-oxo-3a,4-dihydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indole-2(3H)-carboxylate (31ck):** Yellow gum; 22%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 3.12–3.26 (m, 1H), 3.50 (dd, J = 11.0, 5.9 Hz, 1H), 3.61–3.70 (m, 1H), 3.84–3.99 (m, 4H), 7.27 (dd, J = 8.3, 1.7 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.4 (q, 3C), 51.2 (t), 53.0 (t), 72.9 (t), 80.2 (s, 2C), 118.9 (d), 124.0 (s), 124.6 (d), 125.9 (s), 127.2 (d), 144.1 (s), 153.7 (s), 162.5 (s), 196.1 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{17}H_{19}ClN_2O_4Na$ (M^++Na): 373.0931, found 373.0926.



3-Allyl-6-(4-chloro-2-nitrophenyl)-3,4-dihydro-2H-1,3-oxazin-2-one (30ck): Yellow solid; 51%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.97 (d, J = 6.2 Hz, 2H), 4.33 (d, J = 2.1 Hz, 2H), 5.25–5.38 (m, 2H), 5.69–5.91 (m, 1H), 6.04 (t, J = 2.1 Hz, 1H), 7.52 (dd, J = 8.7, 2.2 Hz, 1H), 7.88 (d, J = 2.3 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 46.4 (t), 48.5 (t), 95.7 (d), 119.8 (t), 124.5 (d), 126.3 (s), 130.7 (d), 132.0 (d), 132.7 (s), 132.9 (d), 146.0 (s), 147.2 (s), 154.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{12}ClN_2O_4$ (M^++H): 295.0486, found 295.0480.

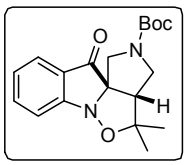


***tert*-Butyl 8-methyl-11-oxo-3a,4-dihydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indole-2(3H)-carboxylate (31dk):** Yellow gum; 73%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.45 (s, 3H), 3.08–3.25 (m, 1H), 3.47 (dd, J = 11.1, 6.1 Hz, 1H), 3.61 (dd, J = 9.3, 4.9 Hz, 1H), 3.79–4.04 (m, 4H), 7.05–7.14 (m, 1H), 7.24



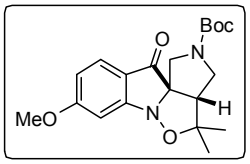
(s, 1H), 7.53 (d, J = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.3 (q), 28.2 (q, 3C), 51.1 (t), 52.1 (d), 53.0 (t), 72.2 (t), 79.8 (s), 84.9 (s), 118.6 (d), 123.2 (d), 123.3 (s), 127.7 (d), 149.4 (s), 153.5 (s), 161.9 (s), 196.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{22}N_2O_4Na$ (M^++Na): 353.1472, found 353.1472.

***tert*-Butyl 4,4-dimethyl-11-oxo-3a,4-dihydro-1H,11H-pyrrolo[3',4':3,4]isoxazolo[2,3-a]indole-2(3H)-carboxylate (31al):**



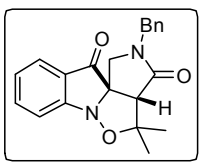
Yellow gum; 77%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.33 (s, 3H), 1.46 (s, 9H), 2.84 (dd, J = 7.8, 3.4 Hz, 1H), 3.52 (dd, J = 12.0, 7.8 Hz, 1H), 3.75–4.01 (m, 3H), 7.22 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.59–7.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.5 (q), 28.3 (q, 3C), 30.6 (q), 47.3 (t), 53.5 (t), 58.8 (d), 80.1 (s), 85.7 (s), 89.3 (s), 118.0 (d), 123.1 (s), 124.2 (d), 125.2 (d), 137.2 (d), 153.8 (s), 164.6 (s), 198.9 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_4Na$ (M^++Na): 367.1631, found 367.1628.

***tert*-Butyl 8-methoxy-4,4-dimethyl-11-oxo-3a,4-dihydro-1H,11H-pyrrolo [3',4':3,4]isoxazolo[2,3-a]indole-2(3H)-carboxylate (31bl):**



Colorless solid; 79%; (R_f = 0.6, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.32 (s, 3H), 1.45 (s, 9H), 2.83 (dd, J = 7.9, 3.5 Hz, 1H), 3.51 (dd, J = 11.7, 8.1 Hz, 1H), 3.73–3.93 (m, 6H), 6.70–6.85 (m, 2H), 7.55 (d, J = 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.5 (q), 28.3 (q, 3C), 30.5 (q), 47.4 (t), 53.7 (t), 55.9 (d), 58.3 (d), 80.0 (s), 86.0 (s), 89.3 (s), 100.3 (d), 114.8 (d), 116.1 (s), 125.6 (d), 153.8 (s), 167.3 (s), 167.5 (s), 196.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{20}H_{26}N_2O_5Na$ (M^++Na): 397.1734, found 397.1734.

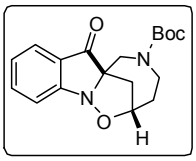
2-Benzyl-4,4-dimethyl-1,2,3a,4-tetrahydro-3H,11H-pyrrolo[3',4':3,4]isoxazolo [2,3-a] indole-3,11-dione (31am):



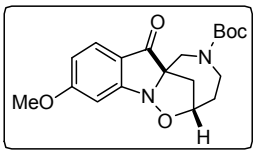
Brown oil; 69%; (R_f = 0.3, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (s, 3H), 1.43 (s, 3H), 3.09 (s, 1H), 3.56 (d, J = 10.5 Hz, 1H), 3.69 (d, J = 10.5 Hz, 1H), 4.29 (d, J = 14.9 Hz, 1H), 4.73 (d, J = 14.9 Hz, 1H), 7.11–7.42 (m, 7H), 7.52–7.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.3 (q), 30.9 (q), 46.8 (t), 53.0 (t), 62.0 (d), 78.3 (s), 89.7 (s), 117.8 (d), 122.7 (s), 124.3 (d), 125.4 (d), 127.8 (d), 127.9 (d, 2C), 128.9 (d, 2C), 135.2 (s), 137.5 (d), 164.8 (s), 169.1

(s), 197.5 (s) ppm; HRMS (ESI^+): calcd. for $C_{21}H_{20}N_2O_3Na$ (M^++Na): 371.1366, found 371.1366.

***tert*-Butyl 7-oxo-3,4-dihydro-2H,7H-2,6a-methano[1,2,5]oxadiazocino[2,3-a]indole-5(6H)-carboxylate (31an):** Yellow solid; 73%; (R_f = 0.5, 30% AcOEt/pet.ether) found as rotameric mixture; ^1H NMR (200 MHz, $CDCl_3$): δ 1.52 (br s, 9H), 1.83 (br s, 2H), 1.93–2.14 (m, 1H), 2.16–2.39 (m, 1H), 3.00–3.33 (m, 2H), 3.87–4.25 (m, 1H), 4.80 (d, J = 13.8 Hz, 1H), 4.92 (br s, 1H), 7.21–7.32 (m, 1H), 7.35–7.46 (m, 1H), 7.65 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3, 28.4 (q, 3C), 33.1, 34.0 (t), 37.2, 37.3 (t), 41.8, 42.1 (t), 50.3, 51.4 (t), 78.7, 78.8 (s), 79.9, 80.3 (s), 82.0, 82.4 (d), 113.9 (d), 118.6 (d), 122.0, 122.1 (s), 124.2, 124.3 (d), 136.9, 137.1 (d), 154.9, 155.2 (s), 163.5, 163.6 (s), 196.4, 196.8 (s) ppm; HRMS (ESI^+): calcd. for $C_{18}H_{22}N_2O_4Na$ (M^++Na): 353.1477, found 353.1472.



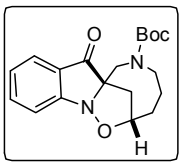
***tert*-Butyl 10-methoxy-7-oxo-3,4-dihydro-2H,7H-2,6a-methano[1,2,5] oxadiazocino [2,3-a]indole-5(6H)-carboxylate (31bn):** Brown gum; 77%; (R_f = 0.4, 30% AcOEt/pet.ether) found as rotameric mixture; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37–1.55 (m, 9H), 1.73–1.90 (m, 2H), 2.02 (dd, J = 12.2, 7.6 Hz, 1H), 2.15–2.31 (m, 1H), 2.93–3.37 (m, 2H), 3.78–3.92 (m, 3H), 3.92–4.16 (m, 1H), 4.51–4.82 (m, 1H), 4.82–4.98 (m, 1H), 6.66–6.88 (m, 2H), 7.53 (d, J = 8.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.4 (q, 3C), 33.2, 34.0 (t), 37.3 (t), 41.8, 42.1 (t), 50.4, 51.5 (t), 55.8 (q), 79.1 (s), 79.9, 80.2 (s), 82.0, 82.3 (d), 100.8 (d), 115.1 (s), 115.1 (d), 125.6 (d), 154.9, 155.2 (s), 166.1, 166.3 (s), 167.3, 167.4 (s), 194.2, 194.5 (s) ppm; HRMS (ESI^+): calcd. for $C_{19}H_{24}N_2O_5Na$ (M^++Na): 383.1577, found 383.1577.



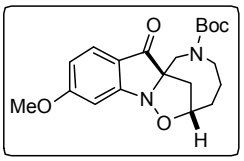
General Procedure C for 27ao, 27bo, 27aq, 27bq: The *o*-nitroenyne carbamate **27** (1 eq.) was dissolved in anhydrous CH_2Cl_2 (4 mL) was added the catalyst $AuCl(PPh_3)$ (10 mol %), and $AgSbF_6$ (20 mol %) at 0 °C and the reaction mixture was warmed to room temperature, then allowed to stir for 4 h. After completion, the reaction mixture was concentrated under reduced pressure and the crude was purified by column chromatography (flash Silica gel) to procure the anthranil **29** and alkenyl isatogen **28**. This alkenyl isatogen was subjected for the next reaction. The solution of alkenyl isatogen **28** (1eq.) in toluene was taken in a sealed tube and heated to reflux for 4–6 h.

After completion, the reaction mixture was evoperated under reduced pressure and subjected for the flash coloumn chromatography to obtain the isoxazolidine **31**.

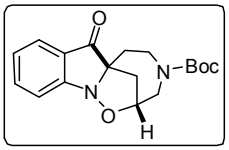
***tert*-Butyl 8-oxo-2,3,4,5-tetrahydro-8H-2,7a-methano[1,2,5]oxadiazonino [2,3-a] indole-6(7H)-carboxylate (31ao):** Yellow oil; 61%; (R_f = 0.5, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (s, 9H), 1.73–1.92 (m, 2H), 2.02–2.34 (m, 4H), 3.17–3.51 (m, 2H), 3.54 (br s, 1H), 4.29–4.44 (m, 1H), 4.75–4.89 (m, 1H), 7.15–7.26 (m, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.57–7.70 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.3, 22.7 (t), 28.4 (q, 3C), 31.3, 31.8 (t), 39.1, 40.3 (t), 46.0, 46.1 (t), 50.8, 51.4 (t), 78.7, 78.8 (s), 79.9, 80.3 (s), 81.2, 81.6 (d), 117.9, 118.3 (d), 121.9, 122.0 (s), 124.2, 124.4 (d), 125.2, 125.4 (d), 136.6, 136.9 (d), 155.9, 156.1 (s), 163.5, 163.7 (s), 197.6, 198.5 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_4Na$ (M^++Na): 367.1627, found 367.1628.



***tert*-Butyl 11-methoxy-8-oxo-2,3,4,5-tetrahydro-8H-2,7a-methano [1,2,5] oxadiazonino[2,3-a]indole-6(7H)-carboxylate (31bo):** Brown gum; 64%; (R_f = 0.4, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (d, J = 6.1 Hz, 9H), 1.60–1.70 (m, 1H), 1.77–1.91 (m, 1H), 2.06–2.16 (m, 1H), 2.16–2.38 (m, 3H), 3.22–3.35 (m, 1H), 3.40–3.60 (m, 1H), 3.72–3.83 (m, 1H), 3.85–3.96 (m, 3H), 4.33 (d, J = 15.3 Hz, 1H), 4.80–4.89 (m, 1H), 6.67–6.87 (m, 2H), 7.54 (d, J = 8.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.4, 22.8 (t), 28.4 (q, 3C), 31.3, 31.9 (t), 39.3, 40.5 (t), 46.0, 46.1 (t), 51.0, 51.6 (t), 55.9 (q), 79.0, 79.2 (s), 79.9, 80.3 (s), 81.3, 81.6 (d), 100.3, 100.5 (d), 114.7, 114.8 (s), 114.9, 115.1 (d), 125.6, 125.8 (d), 155.9, 156.0 (s), 166.2, 166.4 (s), 167.1, 167.3 (s), 195.5, 196.5 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{20}H_{26}N_2O_5Na$ (M^++Na): 397.1736, found 397.1734.

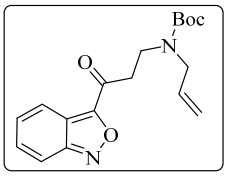


***tert*-Butyl 7-oxo-2,3,5,6-tetrahydro-4H,7H-2,6a-methano[1,2,6]oxadiazocino [2,3-a]indole-4-carboxylate (31ap):** Yellow gum; 47%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36–1.54 (m, 9H), 1.76 (d, J = 14.1 Hz, 1H), 1.99–2.36 (m, 3H), 3.15–3.46 (m, 2H), 3.86–4.14 (m, 2H), 4.93 (dd, J = 7.5, 4.0 Hz, 1H), 7.14–7.25 (m, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.54–7.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 30.9, 31.5 (t), 37.0 (t), 43.1, 43.4 (t), 51.6, 52.6 (t), 80.1 (s), 83.3, 83.7 (d), 83.7 (s),

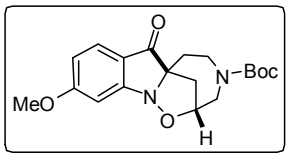


117.6 (d), 121.3 (s), 124.5 (d), 125.0 (d), 136.7 (d), 155.3 (s), 162.9 (s), 197.8 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{22}N_2O_4Na$ (M^++Na): 353.1472, found 353.1472.

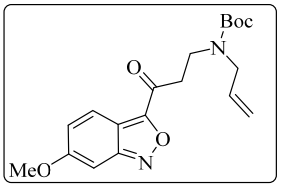
***tert*-Butyl allyl(3-(benzo[c]isoxazol-3-yl)-3-oxopropyl)carbamate (29ap):** Yellow gum; 24%; (R_f = 0.6, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.36 (br s, 2H), 3.55–3.71 (m, 2H), 3.84 (br s, 2H), 4.96–5.21 (m, 2H), 5.60–5.86 (m, 1H), 7.15–7.27 (m, 1H), 7.27–7.41 (m, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.96 (dd, J = 8.7, 0.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.3 (q, 3C), 39.5 (t), 42.0 (t), 49.8, 50.7 (t), 79.9 (s), 116.0 (d), 116.3, 117.0 (t), 119.1 (s), 121.1 (d), 128.6 (d), 131.3 (d), 134.0 (d), 155.2 (s), 157.5 (s), 159.5 (s), 188.5 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{22}N_2O_4Na$ (M^++Na): 353.1472, found 353.1472.



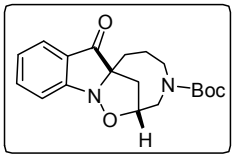
***tert*-Butyl 10-methoxy-7-oxo-2,3,5,6-tetrahydro-4H,7H-2,6a-methano[1,2,6] oxadiazocino [2,3-a]indole-4-carboxylate (31bp):** Brown gum; 53%; (R_f = 0.3, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38–1.57 (m, 9H), 1.81 (br s, 1H), 2.01–2.35 (m, 3H), 3.20–3.45 (m, 2H), 3.88 (s, 3H), 3.91–4.14 (m, 2H), 4.95 (dd, J = 7.4, 3.9 Hz, 1H), 6.64–6.87 (m, 2H), 7.50–7.59 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.4 (q, 3C), 31.1, 31.7 (t), 37.2 (t), 43.1, 43.5 (t), 51.6, 52.6 (t), 55.9 (q), 77.4, 77.5 (s), 80.1, 80.2 (s), 83.4, 83.8 (d), 100.1 (d), 114.4, 114.5 (d), 125.9 (d), 125.9 (s), 154.6, 155.4 (s), 165.5, 165.7 (s), 167.2, 167.2 (s), 195.9 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_5Na$ (M^++Na): 383.1575, found 383.1577.



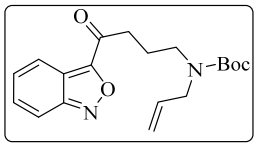
***tert*-Butyl allyl(3-(6-methoxybenzo[c]isoxazol-3-yl)-3-oxopropyl) carbamate (29bp):** Brown gum; 27%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 3.37 (br s, 2H), 3.57–3.73 (m, 2H), 3.88 (s, 5H), 5.02–5.27 (m, 2H), 5.65–5.94 (m, 1H), 6.78 (s, 1H), 6.85–7.01 (m, 1H), 7.86 (d, J = 9.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (q, 3C), 39.4 (t), 41.9 (t), 49.9 (t), 55.5 (q), 79.9 (s), 90.2 (d), 116.1 (t), 121.7 (s), 121.7 (d), 125.8 (d), 134.0 (d), 155.2 (s), 158.6 (s), 158.9 (s), 161.7 (s), 188.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_5Na$ (M^++Na): 383.1578, found 383.1577.



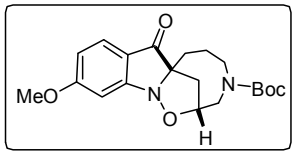
***tert*-Butyl 8-oxo-2,3,6,7-tetrahydro-8H-2,7a-methano[1,2,7]oxadiazonino[2,3-a]indole-4(5H)-carboxylate (31aq):** Yellow oil; 19%; (R_f = 0.3, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42–1.53 (m, 9H), 1.93–2.15 (m, 4H), 2.19–2.28 (m, 2H), 3.08–3.45 (m, 2H), 3.63–3.88 (m, 1H), 3.94 (dd, J = 15.3, 4.0 Hz, 1H), 4.74–4.89 (m, 1H), 7.14–7.24 (m, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.55–7.68 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.2 (t), 28.4 (q, 3C), 29.9 (t), 39.0, 39.8 (t), 45.5, 47.6 (t), 50.4, 51.1 (t), 76.7 (s), 80.0 (s), 83.6, 84.0 (d), 117.4 (d), 121.1 (s), 123.8, 124.5 (d), 124.9 (d), 136.5, 137.1 (d), 156.3 (s), 162.9 (s), 199.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_4Na$ (M^++Na): 367.1630, found 367.1628.



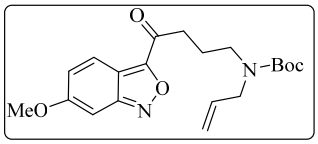
***tert*-Butyl allyl(4-(benzo[c]isoxazol-3-yl)-4-oxobutyl)carbamate (29aq):** Yellow oil; 59%; (R_f = 0.5, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37–1.50 (m, 9H), 2.05 (quin, J = 7.0 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H), 3.36 (t, J = 6.9 Hz, 2H), 3.85 (br s, 2H), 5.06–5.24 (m, 2H), 5.71–5.93 (m, 1H), 7.22–7.33 (m, 1H), 7.41 (dd, J = 8.8, 6.4 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.7, 21.9 (t), 28.2 (q, 3C), 37.1 (t), 45.5 (t), 49.2, 49.7 (t), 79.5 (s), 115.8 (d), 116.6 (t), 119.0 (s), 121.1 (d), 128.4 (d), 131.2 (d), 134.0 (d), 155.4 (s), 157.4 (s), 159.5 (s), 189.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{24}N_2O_4Na$ (M^++Na): 367.1628, found 367.1628.



***tert*-Butyl 11-methoxy-8-oxo-2,3,6,7-tetrahydro-8H-2,7a-methano [1,2,7] oxadiazonino[2,3-a]indole-4(5H)-carboxylate (31bq):** Brown gum; 22%; (R_f = 0.3, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.58 (m, 9H), 1.91–2.10 (m, 3H), 2.12–2.35 (m, 3H), 3.14–3.27 (m, 1H), 3.34–3.41 (dt, J = 5.9, 11.7 Hz, 1H), 3.65–3.77 (m, 1H), 3.77–3.96 (m, 4H), 4.77–4.89 (m, 1H), 6.72 (dd, J = 8.6, 2.0 Hz, 1H), 6.76–6.83 (m, 1H), 7.52 (d, J = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.7, 24.4 (t), 28.4 (q, 3C), 30.1 (t), 39.1, 40.0 (t), 45.5, 45.6 (t), 50.4, 51.1 (t), 55.8 (q), 80.1 (s), 83.8, 84.0 (d), 99.9, 100.1 (d), 113.8 (s), 114.3 (d), 125.3, 125.9 (d), 125.9 (s), 155.4, 156.3 (s), 165.6 (s), 167.1 (s), 197.8 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{20}H_{26}N_2O_5Na$ (M^++Na): 397.1734, found 397.1734.

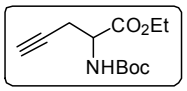


***tert*-Butyl allyl(4-(6-methoxybenzo[c]isoxazol-3-yl)-4-oxobutyl)carbamate (29bq):** Brown gum; 63%; (R_f = 0.5, 30% AcOEt/pet.ether) found as rotameric mixture; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 9H), 1.98 (quin, J = 7.1 Hz, 2H), 3.11 (t, J = 7.2 Hz, 2H), 3.30 (t, J = 7.0 Hz, 2H), 3.76–3.84 (m, 2H), 3.86 (s, 3H), 4.98–5.21 (m, 2H), 5.62–5.90 (m, 1H), 6.74 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 9.3, 2.0 Hz, 1H), 7.83 (dd, J = 9.3, 0.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.8 (t), 28.2 (q, 3C), 37.0 (t), 45.6 (t), 49.4 (t), 55.4 (q), 79.5 (s), 90.1 (s), 90.1 (d), 116.0, 116.3 (t), 121.7 (d), 125.5 (d), 134.0 (d), 155.4 (s), 158.6 (s), 158.8 (s), 161.6 (s), 189.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{20}H_{26}N_2O_5Na$ (M^++Na): 397.1734, found 397.1734.

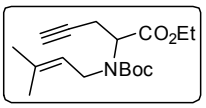


Boc-protection and alkylation of amine were carriedout by followed the literature know procedures.

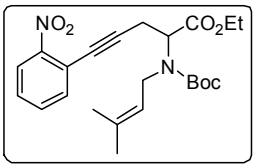
Ethyl 2-((*tert*-butoxycarbonyl)amino)pent-4-ynoate (35-Boc): Colorless oil; 80%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (td, J = 7.1, 2.3 Hz, 3H), 1.41 (d, J = 2.7 Hz, 9H), 2.00–2.02 (m, 1H), 2.67–2.73 (m, 2H), 4.17–4.24 (m, 2H), 4.36–4.44 (m, 1H), 5.36 (d, J = 8.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 22.7 (t), 28.1 (q, 3C), 51.8 (d), 61.6 (t), 71.4 (s), 78.5 (d), 79.9 (s), 155.0 (s), 170.4 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{12}H_{19}NO_4Na$ (M^++Na): 264.1212, found 264.1206.



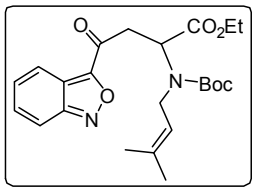
Ethyl 2-((*tert*-butoxycarbonyl)(3-methylbut-2-en-1-yl)amino)pent-4-ynoate (34): Brown oil; 78%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22–1.31 (m, 3H), 1.38–1.49 (m, 9H), 1.66 (s, 3H), 1.70–1.78 (m, 3H), 2.00 (t, J = 2.5 Hz, 1H), 2.75–2.96 (m, 2H), 3.77–4.03 (m, 2H), 4.07–4.33 (m, 3H), 5.27 (t, J = 6.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 17.7 (q), 19.7, 20.5 (t), 25.7 (q), 28.3 (q, 3C), 46.0 (t), 57.8, 58.2 (d), 61.2, 61.3 (t), 69.8, 70.1 (s), 80.2, 80.7 (s), 81.0, 81.3 (d), 120.4, 121.1 (d), 134.4, 135.9 (s), 154.4, 155.0 (s), 170.4 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{27}NO_4Na$ (M^++Na): 332.1838, found 332.1832.



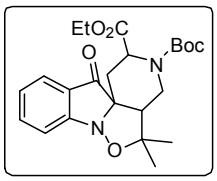
Ethyl 2-((*tert*-butoxycarbonyl)(3-methylbut-2-en-1-yl)amino)-5-(2-nitrophenyl) pent-4-ynoate (33): Yellow oil; 72%; (R_f = 0.6, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24–1.32 (m, 3H), 1.43 (s, 9H), 1.65 (s, 3H), 1.67 (s, 3H), 3.07–3.28 (m, 2H), 3.95 (d, J = 6.1 Hz, 1H), 4.03–4.23 (m, 4H), 5.27 (d, J = 6.3 Hz, 1H), 7.36–7.46 (m, 1H), 7.48–7.61 (m, 2H), 7.92–8.03 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 17.7 (q), 21.1, 22.0 (t), 25.7 (q), 28.2 (q, 3C), 46.1 (t), 58.0, 58.4 (d), 61.2, 61.3 (t), 80.2, 80.7 (s, 2C), 95.3, 95.7 (s), 118.7, 118.8 (s), 120.3, 121.1 (d), 124.4 (d), 128.1, 128.2 (d), 132.5, 132.6 (d), 134.9 (d), 135.9 (s), 149.8 (s), 154.4, 155.1 (s), 170.3 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{30}N_2O_6Na$ (M^++Na): 453.2002, found 453.1996.



Ethyl 4-(benzo[c]isoxazol-3-yl)-2-((tert-butoxycarbonyl)(3-methylbut-2-en-1-yl) amino)-4-oxobutanoate (36): Brown gum; 35%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.26 (m, 3H), 1.45–1.52 (m, 9H), 1.65 (s, 3H), 1.70 (s, 3H), 3.33–3.51 (dd, J = 6.1, 17.1 Hz, 1H), 3.92–4.02 (m, 1H), 4.04–4.25 (m, 4H), 4.59 (m, 1H), 5.15–5.28 (m, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.38–7.46 (m, 1H), 7.74 (d, J = 9.2 Hz, 1H), 8.03–8.07 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 17.8 (q), 25.7 (q), 28.3 (q, 3C), 40.9, 41.5 (t), 45.9, 46.3 (t), 55.1, 55.5 (d), 61.4, 61.6 (t), 80.4, 81.1 (s), 116.0 (d), 119.3 (s), 119.9 (d), 120.5, 121.1 (d), 128.5, 128.7 (d), 131.2, 131.3 (d), 135.4, 136.7 (s), 154.5 (s), 157.6 (s), 159.4 (s), 171.0 (s), 187.1, 187.2 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{30}N_2O_6Na$ (M^++Na): 453.2002, found 453.1996.

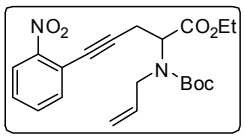


3-(*tert*-Butyl) 2-ethyl 5,5-dimethyl-12-oxo-1,2,4a,5-tetrahydro-12H-pyrido [4',3':3,4] isoxazolo[2,3-a]indole-2,3(4H)-dicarboxylate (38): Yellow gum; 71%; (R_f = 0.5, 40% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 1.45–1.51 (m, 9H), 2.29–2.36 (m, 2H), 2.59 (dd, J = 12.4, 5.9 Hz, 1H), 3.33 (t, J = 12.9 Hz, 1H), 4.15–4.26 (m, 3H), 4.85 (dd, J = 11.8, 6.8 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.60–7.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.3 (q), 28.2 (q, 3C), 30.1 (t), 30.9 (q), 38.0 (t), 51.4 (d), 52.3 (d), 61.1 (t), 75.4 (s), 80.9 (s), 88.1 (s), 118.1 (d), 122.9 (s), 124.3 (d), 125.2 (d),

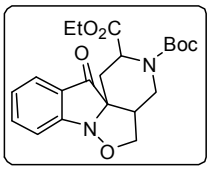


137.3 (d), 154.8 (s), 164.7 (s), 172.4 (s), 201.8 (s) ppm. HRMS (ESI^+): calcd. for $C_{23}H_{30}N_2O_6Na$ (M^++Na): 453.2002, found 453.1996.

Ethyl 2-(allyl(tert-butoxycarbonyl)amino)-5-(2-nitrophenyl)pent-4-ynoate (40): Yellow oil; 74%; (R_f = 0.4, 30% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.23–1.30 (m, 3H), 1.45 (s, 9H), 3.07–3.31 (m, 2H), 3.76–3.99 (m, 1H), 4.04–4.34 (m, 4H), 5.04–5.40 (m, 2H), 5.78–6.06 (m, 1H), 7.37–7.49 (m, 1H), 7.50–7.63 (m, 2H), 7.99 (d, J = 7.96 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 21.2, 22.0 (s), 28.3 (q, 3C), 51.5 (t), 58.2 (d), 61.5 (t), 81.1 (s), 95.1 (s), 116.8, 118.0 (t), 124.4 (d), 128.3 (d), 129.1 (s), 132.6 (d), 134.2 (d), 134.7 (s), 134.9 (d), 149.9 (s), 154.3 (s), 170.1 (s) ppm. HRMS (ESI^+): calcd. for $C_{21}H_{26}N_2O_6Na$ (M^++Na): 425.1689, found 425.1683.

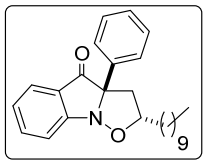


3-(*tert*-Butyl) 2-ethyl 12-oxo-1,2,4a,5-tetrahydro-12H-pyrido[4',3':3,4] isoxazolo [2,3-a]indole-2,3(4H)-dicarboxylate (43): Yellow gum; 66%; (R_f = 0.5, 40% AcOEt/pet.ether); ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 3H), 1.46 (s, 9H), 2.28–2.36 (m, 1H), 2.41–2.48 (m, 1H), 2.77 (dt, J = 11.9, 5.9 Hz, 1H), 3.31 (t, J = 13.0 Hz, 1H), 3.67–3.76 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.29 (dd, J = 13.4, 6.1 Hz, 1H), 4.92 (dd, J = 13.0, 5.4 Hz, 1H), 7.28–7.31 (m, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2 (q), 28.2 (q, 3C), 29.1 (t), 39.8 (t), 45.9 (d), 52.3 (d), 61.1 (t), 70.4 (t), 74.0 (s), 80.9 (s), 118.0 (d), 124.0 (d), 124.9 (s), 126.2 (d), 137.4 (d), 154.6 (s), 161.3 (s), 172.5 (s), 199.8 (s) ppm. HRMS (ESI^+): calcd. for $C_{21}H_{26}N_2O_6Na$ (M^++Na): 425.1689, found 425.1683.

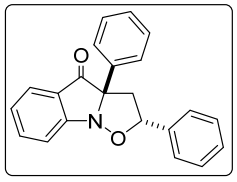


General Procedur for [3+2]-Dipolar Cycloaddition: A solution of isatogen **3** (1 equvi.) and alkene **45** (5 equvi.) in toluene (3 mL) were heated to reflux (alkyl or sugar isatogens were heated at 80 °C) for 6–8 h in a sealed tube. After completion of the reaction, contents were concentrated and the residue obtained was purified by flash silicagel column chromatography to afford the compound **46**.

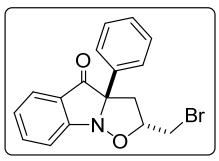
2-Decyl-3a-phenyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46aa): Yellow solid; 78%; (R_f = 0.6, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82–0.93 (m, 3H), 1.22 (s, 16H), 1.51–1.68 (m, 2H), 2.35 (dd, J = 12.6, 10.9 Hz, 1H), 2.95 (dd, J = 12.5, 5.4 Hz, 1H), 3.88 (dq, J = 11.4, 5.8 Hz, 1H), 7.23–7.42 (m, 4H), 7.53–7.77 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 26.1 (t), 29.3 (t, 3C), 29.4 (t), 29.5 (t), 31.8 (t), 32.0 (t), 47.5 (t), 79.8 (d), 80.7 (s), 118.8 (d), 124.0 (d), 125.1 (s), 125.8 (d), 126.1 (d, 2C), 127.7 (d), 128.5 (d, 2C), 137.3 (d), 139.7 (s), 162.5 (s), 199.9 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{26}H_{33}NO_2Na$ (M^++Na): 414.2409, found 414.2404.



2,3a-Diphenyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46ab): Brown solid; 77%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.76 (dd, J = 12.8, 11.1 Hz, 1H), 3.25 (dd, J = 12.9, 5.8 Hz, 1H), 4.87 (dd, J = 11.0, 5.8 Hz, 1H), 7.29 (s, 5H), 7.32 (d, J = 2.8 Hz, 1H), 7.33–7.45 (m, 3H), 7.59–7.67 (m, 1H), 7.68–7.81 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 49.8 (t), 81.1 (d), 81.3 (s), 119.1 (d), 124.2 (d), 125.3 (s), 126.2 (d), 126.2 (d), 126.9 (d, 3C), 127.8 (d), 128.6 (d, 4C), 128.8 (d), 136.2 (s), 137.5 (d), 139.3 (s), 162.2 (s), 199.5 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{22}H_{17}NO_2Na$ (M^++Na): 350.1157, found 350.1152.

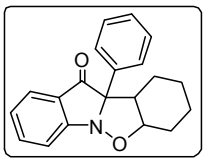


2-(Bromomethyl)-3a-phenyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46ac): Colorless solid; 81%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.59 (dd, J = 13.0, 9.9 Hz, 1H), 3.05 (dd, J = 13.0, 6.0 Hz, 1H), 3.35 (dd, J = 10.7, 6.1 Hz, 1H), 3.44 (dd, J = 10.8, 5.3 Hz, 1H), 4.23 (dq, J = 9.9, 5.8 Hz, 1H), 7.29–7.34 (m, 2H), 7.36–7.41 (m, 2H), 7.59 (d, J = 8.2 Hz, 1H), 7.65–7.71 (m, 3H), 7.74 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.9 (t), 46.4 (t), 79.1 (d), 80.5 (s), 118.9 (d), 124.3 (d), 124.5 (s), 126.1 (d, 2C), 126.3 (d), 127.9 (d), 128.6 (d, 2C),

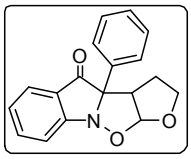


137.4 (d), 138.8 (s), 161.8 (s), 198.6 (s) ppm. HRMS (ESI^+): calcd. for $C_{17}H_{14}BrNO_2Na$ (M^++Na): 366.0106, found 366.0100.

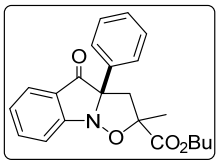
11a-Phenyl-2,3,4,4a,11a,11b-hexahydrobenzo[4,5]isoxazolo[2,3-a]indol-11(1H)-one (46ae): Pale yellow solid; 82%; (R_f = 0.5, 20% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 0.97–1.17 (m, 2H), 1.35–1.51 (m, 3H), 1.70 (br s, 1H), 1.80–2.03 (m, 2H), 2.88 (ddd, J = 11.8, 6.0, 3.7 Hz, 1H), 3.97 (d, J = 2.9 Hz, 1H), 7.27–7.34 (m, 3H), 7.46–7.51 (m, 1H), 7.56–7.66 (m, 2H), 7.70–7.75 (m, 1H), 7.76–7.82 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.1 (t), 24.4 (t), 25.1 (t), 25.6 (t), 48.0 (d), 75.3 (d), 84.2 (s), 121.4 (d), 123.4 (d), 126.8 (d), 127.3 (d, 2C), 127.6 (d), 128.1 (d, 2C), 128.6 (s), 135.4 (s), 137.2 (d), 162.2 (s), 203.7 (s) ppm. HRMS (ESI^+): calcd. for $C_{20}H_{20}NO_2$ (M^++H): 306.1494, found 306.1489.



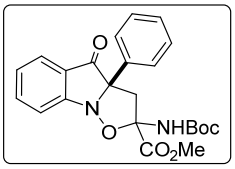
3b-Phenyl-2,3,3a,10a-tetrahydrofuro[3',2':4,5]isoxazolo[2,3-a]indol-4(3bH)-one (46af): Brown solid; 75%; (R_f = 0.5, 30% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.75–1.83 (m, 1H), 1.94–2.00 (m, 1H), 3.66–3.81 (m, 1H), 3.81–3.93 (m, 2H), 5.83 (d, J = 5.1 Hz, 1H), 7.21–7.28 (m, 1H), 7.29–7.35 (m, 1H), 7.35–7.42 (m, 2H), 7.54–7.62 (m, 1H), 7.62–7.76 (m, 2H), 7.86–7.96 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3 (t), 54.3 (d), 69.6 (t), 81.3 (s), 100.0 (s), 110.3 (d), 118.5 (d), 123.2 (s), 124.5 (d), 125.9 (d), 127.4 (d, 2C), 128.0 (d), 128.3 (d, 2C), 137.4 (d), 162.2 (s), 199.6 (s) ppm. HRMS (ESI^+): calcd. for $C_{18}H_{16}NO_3$ (M^++H): 294.1130, found 294.1184.



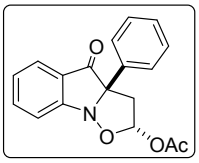
Butyl 2-methyl-4-oxo-3a-phenyl-2,3,3a,4-tetrahydroisoxazolo[2,3-a]indole-2-carboxylate (46ag): Pale brown solid; 83%; (R_f = 0.5, 30% AcOEt /pet.ether); ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 7.3 Hz, 3H), 1.20–1.28 (m, 2H), 1.33–1.42 (m, 2H), 1.48 (s, 3H), 2.61 (d, J = 12.8 Hz, 1H), 3.44–3.51 (m, 1H), 3.65 (dt, J = 10.8, 6.8 Hz, 1H), 3.74 (d, J = 13.3 Hz, 1H), 7.20–7.25 (m, 1H), 7.28–7.33 (m, 1H), 7.35–7.40 (m, 2H), 7.56–7.61 (m, 2H), 7.62–7.67 (m, 1H), 7.67–7.72 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (q), 18.9 (t), 23.6 (q), 30.1 (t), 49.5 (t), 65.4 (t), 80.5 (s), 87.5 (s), 120.0 (d), 124.0 (d), 124.2 (s), 126.0 (d, 3C), 127.9 (d), 128.6 (d, 2C), 136.4 (d), 138.9 (s), 161.7 (s), 172.7 (s), 198.5 (s) ppm. HRMS (ESI^+): calcd. for $C_{22}H_{23}NO_4Na$ (M^++Na): 388.1525, found 388.1519.



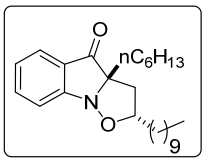
Methyl 2-((tert-butoxycarbonyl)amino)-4-oxo-3a-phenyl-2,3,3a,4-tetrahydro isoxazolo[2,3-a]indole-2-carboxylate (46ah): Brown gum; 79%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26 (s, 9H), 3.18 (d, J = 4.5 Hz, 2H), 3.43 (s, 3H), 5.13 (br s, 1H), 7.14–7.24 (m, 2H), 7.30–7.35 (m, 2H), 7.54 (d, J = 4.8 Hz, 1H), 7.57–7.64 (m, 2H), 7.64–7.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.0 (q, 3C), 47.4 (t), 53.1 (q), 79.8 (s, 2C), 81.2 (s), 94.8 (s), 118.8 (d), 122.1 (s), 124.6 (d), 125.9 (d), 126.3 (d, 2C), 128.3 (d), 128.7 (d, 2C), 136.9 (d), 153.0 (s), 161.7 (s), 168.3 (s), 196.2 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{24}N_2O_6Na$ (M^++Na): 447.1532, found 447.1527.



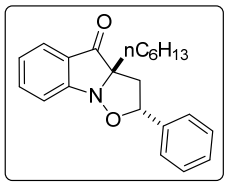
4-Oxo-3a-phenyl-2,3,3a,4-tetrahydroisoxazolo[2,3-a]indol-2-yl acetate (46ai): Yellow solid; 76%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.66 (dd, J = 13.5, 4.9 Hz, 1H), 2.99 (d, J = 13.5 Hz, 1H), 6.58 (d, J = 4.7 Hz, 1H), 7.29–7.46 (m, 4H), 7.54–7.60 (m, 1H), 7.63–7.70 (m, 2H), 7.76–7.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 20.7 (q), 44.5 (t), 77.9 (s), 99.3 (d), 119.3 (d), 122.1 (s), 124.8 (d), 125.9 (s), 126.4 (d, 2C), 126.5 (d), 127.9 (d), 128.2 (d, 2C), 137.2 (d), 161.8 (s), 169.6 (s), 196.2 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{15}NO_4Na$ (M^++Na): 332.0899, found 332.0893.



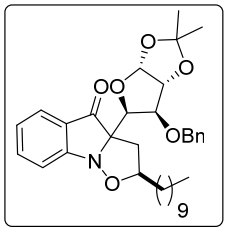
2-Decyl-3a-hexyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46ea): Brown oil; 77%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (d, J = 7.3 Hz, 6H), 1.16 (s, 24H), 1.41–1.54 (m, 2H), 1.80 (dd, J = 12.5, 11.0 Hz, 2H), 1.90–2.02 (m, 1H), 2.32 (dd, J = 12.8, 5.8 Hz, 1H), 3.52–3.72 (m, 1H), 7.11–7.21 (m, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.53–7.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 14.1 (q), 22.5 (t), 22.6 (t), 24.4 (t), 26.1 (t), 29.3 (t), 29.4 (t), 29.4 (t, 3C), 29.5 (t), 31.5 (t), 31.8 (t), 32.2 (t), 36.5 (t), 44.7 (t), 79.2 (d), 79.4 (s), 118.6 (d), 123.3 (d), 125.4 (d), 126.2 (s), 137.0 (d), 163.2 (s), 202.9 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{26}H_{41}NO_2Na$ (M^++Na): 422.3035, found 422.3030.



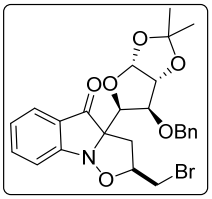
3a-Hexyl-2-phenyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46eb): Brown gum; 73%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81–0.90 (m, 3H), 1.21–1.37 (m, 7H), 1.59 (s, 2H), 1.91–2.21 (m, 2H), 2.22–2.37 (m, 1H), 2.72 (dd, J = 13.1, 6.1 Hz, 1H), 4.68 (dd, J = 10.9, 6.1 Hz, 1H), 7.25–7.31 (m, 1H), 7.34 (s, 4H), 7.49–7.56 (m, 1H), 7.66–7.77 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0 (q), 22.5 (t), 24.6 (t), 29.5 (t), 31.6 (t), 36.6 (t), 47.2 (t), 80.0 (d), 80.7 (s), 119.0 (d), 123.5 (d), 125.8 (d), 126.5 (s), 126.6 (d), 126.7 (d, 2C), 128.7 (d, 2C), 136.7 (s), 137.2 (d), 162.9 (s), 202.4 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{22}H_{26}NO_2$ (M^++H): 336.1964, found 336.1958.



3a-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3] dioxol-5-yl)-2-decyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46ga): Brown oil; 78%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J = 6.4 Hz, 3H), 1.19–1.27 (m, 15H), 1.31 (s, 3H), 1.49 (s, 3H), 1.92 (d, J = 2.8 Hz, 2H), 2.33–2.57 (m, 2H), 3.59–3.77 (m, 1H), 4.15–4.25 (m, 2H), 4.35–4.46 (m, 1H), 4.52 (d, J = 3.9 Hz, 1H), 4.62 (d, J = 4.0 Hz, 1H), 6.09 (d, J = 3.8 Hz, 1H), 6.89–7.00 (m, 2H), 7.06–7.23 (m, 4H), 7.35–7.45 (m, 3H), 7.54–7.65 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 26.1 (t), 26.4 (q), 27.0 (q), 29.3 (t), 29.4 (t, 2C), 29.5 (t), 31.9 (t), 32.0 (t), 36.4 (t), 38.6 (t), 72.3 (t), 79.3 (d), 82.4 (d, 2C), 82.5 (d), 85.3 (s), 105.5 (d), 111.8 (s), 118.5 (d), 123.2 (d), 125.5 (d), 127.4 (s), 127.5 (d), 127.7 (d, 2C), 128.1 (d, 2C), 136.1 (d), 136.6 (s), 160.9 (s), 199.4 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{34}H_{45}NO_6Na$ (M^++Na): 586.3145, found 586.3139.

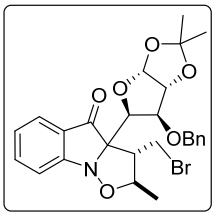


3a-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3] dioxol-5-yl)-2-(bromomethyl)-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46gc): Yellow gum; 76%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.48 (s, 3H), 2.46–2.75 (m, 2H), 3.35–3.52 (m, 2H), 3.91–4.08 (m, 1H), 4.17–4.33 (m, 2H), 4.40–4.49 (m, 1H), 4.54 (d, J = 3.8 Hz, 1H), 4.64 (d, J = 4.0 Hz, 1H), 6.08 (d, J = 3.8 Hz, 1H), 6.91–7.04 (m, 2H), 7.10–7.25 (m, 4H), 7.38–7.49 (m, 2H), 7.57–7.67 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.4 (q), 27.0 (q), 30.1 (t), 41.4 (t), 72.3 (t), 76.8 (s), 78.4 (d), 82.3 (d), 82.4 (d), 84.3 (d), 105.4 (d), 112.0 (s),



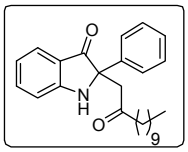
118.6 (d), 123.4 (d), 126.0 (d), 126.7 (s), 127.6 (d), 127.7 (d, 2C), 128.2 (d, 2C), 136.4 (d), 136.6 (s), 160.4 (s), 198.2 (s) ppm. HRMS (ESI^+): calcd. for $C_{25}H_{26}BrNO_6Na$ (M^++Na): 538.0841, found 538.0836.

3a-((3aR,5R,6S,6aR)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3] dioxol-5-yl)-3-(bromomethyl)-2-methyl-3,3a-dihydroisoxazolo[2,3-a]indol-4(2H)-one (46gd): Yellow gum; 73%; (R_f = 0.4, 30% AcOEt/pet.ether); ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.49 (s, 3H), 1.65 (d, J = 6.6 Hz, 3H), 2.60 (dd, J = 13.6, 6.3 Hz, 1H), 2.79 (dd, J = 13.6, 10.3 Hz, 1H), 3.79 (dt, J = 10.3, 6.6 Hz, 1H), 4.08 (quin, J = 6.8 Hz, 1H), 4.22 (d, J = 4.0 Hz, 1H), 4.28 (d, J = 11.4 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 3.7 Hz, 1H), 4.66 (d, J = 4.0 Hz, 1H), 6.09 (d, J = 3.8 Hz, 1H), 6.97 (dd, J = 6.2, 2.7 Hz, 2H), 7.12–7.24 (m, 4H), 7.37–7.50 (m, 2H), 7.57–7.68 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0 (q), 26.4 (q), 27.1 (q), 41.4 (t), 47.2 (d), 72.3 (t), 77.2 (s), 82.3 (d, 3C), 83.0 (d), 105.5 (d), 112.0 (s), 118.5 (d), 123.5 (d), 126.0 (d), 126.7 (s), 127.6 (d), 127.7 (d, 2C), 128.2 (d, 2C), 136.4 (d), 136.7 (s), 160.4 (s), 198.3 (s) ppm. HRMS (ESI^+): calcd. for $C_{26}H_{28}BrNO_6Na$ (M^++Na): 552.0998, found 552.0992.

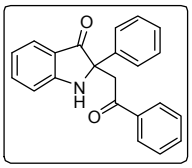


General Procedure for Ru-Catalysed [3+2]-Dipolar Cycloaddition *cum* internal redox process: A solution of isatogen **3** (1 equvi.) and alkene **45** (5 equvi.) in toluene (3 mL) was treated with the Ru(*p*-cymene)Cl_2 dimer (5 mol%), Ad-CO_2H (30 mol%) and K_2CO_3 (3 equvi). The reaction mixture was heated at 120 °C for 8–15 h in a sealed tube. The contents were filtered (*celite*) after completion of the reaction; filterate was concentrated under reduced pressure and the obtained crude was purified using flash silica column chromatography to procure the compound **47**.

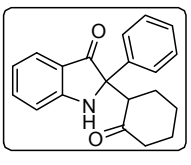
2-(2-Oxododecyl)-2-phenylindolin-3-one (47aa): Dark brown solid; 74%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.72–0.86 (m, 3H), 1.03–1.20 (m, 14H), 1.31–1.44 (m, 2H), 2.09–2.41 (m, 2H), 2.58 (d, J = 17.2 Hz, 1H), 3.62 (d, J = 17.1 Hz, 1H), 6.15 (br s, 1H), 6.64–6.75 (m, 1H), 6.85 (d, J = 8.2 Hz, 1H), 7.13–7.27 (m, 3H), 7.33–7.51 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.3 (t), 28.9 (t), 29.2 (t, 2C), 29.3 (t), 29.5 (t), 31.8 (t), 44.2 (t), 48.7 (t), 69.0 (s), 111.9 (d), 118.2 (d), 118.8 (s), 125.4 (d, 2C), 125.4 (d), 127.6 (d), 128.6 (d, 2C), 137.6 (d), 137.9 (s), 160.0 (s), 200.4 (s), 209.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{26}H_{34}NO_2$ (M^++H): 392.2590, found 392.2584.



2-(2-Oxo-2-phenylethyl)-2-phenylindolin-3-one (47ab): Green solid; 60%; (R_f = 0.6, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.17 (d, J = 17.9 Hz, 1H), 4.44 (d, J = 18.1 Hz, 1H), 6.36 (s, 1H), 6.73–6.84 (m, 1H), 6.94 (d, J = 8.2 Hz, 1H), 7.18–7.33 (m, 3H), 7.35–7.48 (m, 3H), 7.48–7.62 (m, 4H), 7.84–7.94 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 44.7 (t), 69.2 (s), 111.8 (d), 118.1 (s), 118.8 (d), 125.3 (d, 2C), 125.5 (d), 127.5 (d), 128.0 (d, 2C), 128.6 (d, 4C), 133.6 (d), 136.5 (s), 137.7 (d), 138.0 (s), 160.2 (s), 197.7 (s), 200.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{22}H_{18}NO_2$ (M^++H): 328.1338, found 328.1332.

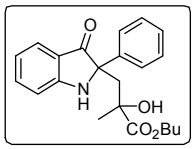


2-(2-Oxocyclohexyl)-2-phenylindolin-3-one (47ae): Yellow solid; 57%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47–1.75 (m, 4H), 2.00–2.09 (m, 2H), 2.25–2.45 (m, 2H), 3.78 (dd, J = 12.1, 5.1 Hz, 1H), 5.98 (s, 1H), 6.69–6.78 (m, 1H), 6.89–6.99 (m, 1H), 7.22–7.34 (m, 3H), 7.40–7.56 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 25.1 (t), 28.9 (t), 29.9 (t), 43.6 (t), 57.5 (d), 72.1 (s), 111.1 (d), 118.4 (d), 118.9 (s), 124.9 (d, 2C),

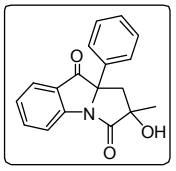


125.2 (d), 127.3 (d), 128.5 (d, 2C), 137.7 (d), 138.8 (s), 161.0 (s), 200.8 (s), 212.2 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{20}H_{20}NO_2$ (M^++H): 306.1494, found 306.1489.

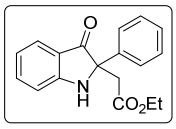
Butyl 2-hydroxy-2-methyl-3-(3-oxo-2-phenylindolin-2-yl)propanoate (48ag): Yellow gum; 31%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81–0.92 (m, 3H), 1.21 (s, 3H), 1.23–1.36 (m, 2H), 1.39–1.58 (m, 2H), 2.54–2.79 (m, 2H), 3.46 (s, 1H), 3.64 (dt, J = 10.7, 6.6 Hz, 1H), 3.95 (dt, J = 10.7, 6.8 Hz, 1H), 6.09 (s, 1H), 6.79 (td, J = 7.4, 0.8 Hz, 1H), 6.93 (dt, J = 8.2, 0.8 Hz, 1H), 7.22–7.33 (m, 3H), 7.39–7.47 (m, 1H), 7.48–7.55 (m, 1H), 7.59–7.68 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (q), 18.9 (t), 27.5 (q), 30.2 (t), 45.3 (t), 66.0 (t), 69.9 (s), 74.6 (s), 112.3 (d), 118.8 (s), 119.1 (d), 125.3 (d), 125.5 (d, 2C), 127.5 (d), 128.5 (d, 2C), 137.3 (d), 140.3 (s), 160.2 (s), 176.7 (s), 201.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{22}H_{25}NO_4Na$ (M^++Na): 390.1681, found 390.1676.



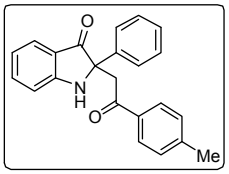
2-Hydroxy-2-methyl-9a-phenyl-1,9a-dihydro-3H-pyrrolo[1,2-a]indole-3,9(2H)-dione (48ag'): Brown gum; 36%; (R_f = 0.3, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 3H), 2.34 (br s, 1H), 2.51 (d, J = 13.8 Hz, 1H), 2.89 (d, J = 13.8 Hz, 1H), 7.23–7.38 (m, 4H), 7.53–7.67 (m, 3H), 7.68–7.80 (m, 1H), 8.01 (d, J = 8.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.6 (q), 45.2 (t), 73.3 (s), 79.5 (s), 117.2 (d), 125.3 (d, 2C), 125.3 (s), 125.6 (d), 125.9 (d), 128.3 (d), 129.0 (d, 2C), 137.2 (d), 138.1 (s), 149.7 (s), 173.4 (s), 198.8 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{15}NO_3Na$ (M^++Na): 316.0950, found 316.0944.



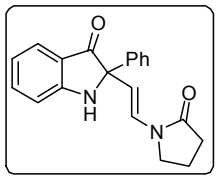
Ethyl 2-(3-oxo-2-phenylindolin-2-yl)acetate (47aj): Dark brown solid; 69%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (t, J = 7.1 Hz, 3H), 2.81 (d, J = 16.0 Hz, 1H), 3.39 (d, J = 15.9 Hz, 1H), 3.99 (qd, J = 7.2, 1.4 Hz, 2H), 6.09 (s, 1H), 6.75–6.85 (m, 1H), 6.95 (dt, J = 8.2, 0.7 Hz, 1H), 7.23–7.36 (m, 3H), 7.42–7.59 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8 (q), 42.0 (t), 60.8 (t), 68.7 (s), 111.9 (d), 118.5 (s), 119.0 (d), 125.5 (d, 3C), 127.8 (d), 128.6 (d, 2C), 137.6 (d), 137.6 (s), 160.1 (s), 170.6 (s), 199.8 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{18}NO_3$ (M^++H): 296.1287, found 296.1281.



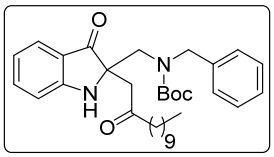
2-(2-Oxo-2-(p-tolyl)ethyl)-2-phenylindolin-3-one (47al): Yellow solid; 62%; (R_f = 0.6, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.12 (d, J = 17.9 Hz, 1H), 4.41 (d, J = 17.9 Hz, 1H), 6.39 (s, 1H), 6.71–6.85 (m, 1H), 6.93 (d, J = 8.3 Hz, 1H), 7.17–7.31 (m, 5H), 7.40–7.50 (m, 1H), 7.51–7.61 (m, 3H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.6 (q), 44.4 (t), 69.3 (s), 111.7 (d), 118.0 (s), 118.7 (d), 125.3 (d, 2C), 125.5 (d), 127.4 (d), 128.1 (d, 2C), 128.6 (d, 2C), 129.3 (d, 2C), 134.0 (s), 137.6 (d), 138.1 (s), 144.6 (s), 160.2 (s), 197.3 (s), 200.7 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{23}H_{19}NO_2Na$ (M^++Na): 364.1313, found 364.1308.



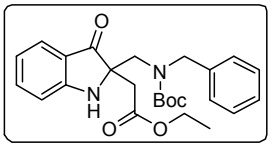
(E)-2-(2-(2-Oxopyrrolidin-1-yl)vinyl)-2-phenylindolin-3-one (49ap): Brown oil; 56%; (R_f = 0.4, 40% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.02–2.17 (m, 2H), 2.39–2.51 (m, 2H), 3.49–3.60 (m, 2H), 5.26 (s, 1H), 5.46 (d, J = 14.4 Hz, 1H), 6.78–6.88 (m, 1H), 6.91 (d, J = 8.2 Hz, 1H), 7.27–7.37 (m, 3H), 7.38–7.52 (m, 4H), 7.60 (d, J = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 17.4 (t), 31.1 (t), 45.4 (t), 71.7 (s), 111.3 (d), 112.5 (d), 118.9 (s), 119.4 (d), 124.4 (d), 125.5 (d), 126.2 (d, 2C), 128.1 (d), 128.8 (d, 2C), 137.6 (d), 140.0 (s), 160.1 (s), 173.5 (s), 200.8 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{20}H_{18}N_2O_2Na$ (M^++Na): 341.1266, found 341.1260.



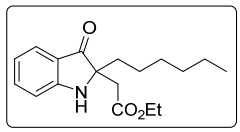
***tert*-Butyl benzyl((3-oxo-2-(2-oxododecyl)indolin-2-yl)methyl)carbamate (47aaa-Boc):** Brown gum; 66%; (R_f = 0.6, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, J = 6.3 Hz, 3H), 1.22 (br s, 14H), 1.33 (s, 9H), 1.49 (br s, 2H), 2.27–2.42 (m, 2H), 2.70 (d, J = 17.1 Hz, 1H), 2.90 (d, J = 17.2 Hz, 1H), 3.20 (d, J = 14.1 Hz, 1H), 3.78 (d, J = 15.8 Hz, 1H), 4.03 (d, J = 14.1 Hz, 1H), 4.32 (d, J = 15.7 Hz, 1H), 5.92 (s, 1H), 6.79–6.89 (m, 2H), 7.08 (d, J = 6.8 Hz, 2H), 7.25 (d, J = 4.5 Hz, 3H), 7.40–7.49 (m, 1H), 7.65 (d, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 27.8 (q), 28.1 (q, 2C), 29.0 (t), 29.2 (t), 29.4 (t), 29.5 (t), 31.8 (t), 36.4 (t), 38.6 (t), 43.3 (t), 46.7 (t), 51.8 (t), 51.9 (t), 69.4 (s), 80.6 (s), 112.6 (d), 118.9 (d, 2C), 121.6 (s), 124.2 (d), 127.2 (d, 2C), 128.4 (d, 2C), 137.1 (d), 137.8 (s), 157.3 (s), 161.9 (s), 203.8 (s), 207.0 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{33}H_{46}N_2O_4Na$ (M^++Na): 557.3355, found 557.3350.



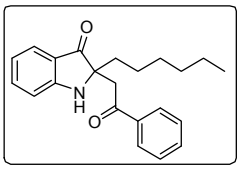
Ethyl 2-(2-((benzyl(*tert*-butoxycarbonyl)amino)methyl)-3-oxoindolin-2-yl)acetate (47aaj-Boc): Brown gum; 62%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99–1.06 (m, 3H), 1.33 (s, 9H), 2.61–2.82 (m, 2H), 3.24 (d, J = 14.1 Hz, 1H), 3.79 (d, J = 16.0 Hz, 1H), 3.95–4.08 (m, 3H), 4.32 (d, J = 15.9 Hz, 1H), 5.92 (s, 1H), 6.87 (d, J = 7.6 Hz, 2H), 7.09 (d, J = 7.3 Hz, 2H), 7.23–7.29 (m, 3H), 7.40–7.49 (m, 1H), 7.65 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8 (q), 28.1 (q, 3C), 39.7 (t), 51.9 (t), 52.0 (t), 60.7 (t), 69.3 (s), 80.8 (s), 112.8 (d), 119.1 (d), 121.8 (s), 124.2 (d), 127.2 (d, 2C), 127.3 (d), 128.4 (d, 2C), 137.2 (d), 137.7 (s), 157.4 (s), 162.2 (s), 169.5 (s), 203.4 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{30}N_2O_5Na$ (M^++Na): 461.2052, found 461.2047.



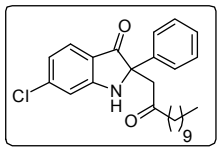
Ethyl 2-(2-hexyl-3-oxoindolin-2-yl)acetate (47ej): Highly viscous yellow oil; 66%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.77–0.87 (m, 3H), 1.08–1.28 (m, 11H), 1.70–1.84 (m, 2H), 2.52 (d, J = 15.7 Hz, 1H), 2.72 (d, J = 15.7 Hz, 1H), 4.02–4.15 (m, 2H), 5.35 (br s, 1H), 6.74–6.89 (m, 2H), 7.44 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9 (q), 14.0 (q), 22.5 (t), 23.0 (t), 29.4 (t), 31.5 (t), 36.2 (t), 41.2 (t), 60.8 (t), 67.1 (s), 112.2 (d), 118.6 (d), 120.6 (d), 124.6 (s), 137.3 (d), 160.4 (s), 171.0 (s), 203.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{26}NO_3$ (M^++H): 304.1913, found 304.1907.



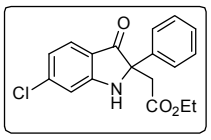
2-Hexyl-2-(2-oxo-2-phenylethyl)indolin-3-one (47eb): Yellow solid; 60%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.75–0.87 (m, 3H), 1.08–1.35 (m, 8H), 1.77–2.00 (m, 2H), 2.89 (d, J = 17.6 Hz, 1H), 3.64 (d, J = 17.4 Hz, 1H), 5.75 (s, 1H), 6.73–6.83 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.39–7.52 (m, 3H), 7.53–7.65 (m, 2H), 7.89–7.99 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9 (q), 22.5 (t), 23.2 (t), 29.4 (t), 31.5 (t), 35.8 (t), 43.8 (t), 67.8 (s), 112.0 (d), 118.2 (d), 120.1 (s), 124.6 (d), 128.1 (d, 2C), 128.7 (d, 2C), 133.6 (d), 136.9 (s), 137.4 (d), 160.5 (s), 198.6 (s), 204.1 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{22}H_{26}NO_2$ (M^++H): 336.1964, found 336.1958.



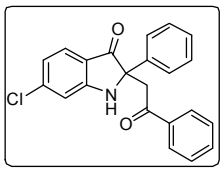
6-Chloro-2-(2-oxododecyl)-2-phenylindolin-3-one (47ca): Brown gum; 71%; (R_f = 0.6, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85–0.91 (m, 3H), 1.13-1.29 (m, 14H), 1.39–1.49 (quin, J = 7.4, 14.7 Hz, 2H), 2.23–2.44 (m, 2H), 2.67 (d, J = 17.4 Hz, 1H), 3.64–3.75 (d, J = 17.4 Hz, 1H), 6.30 (s, 1H), 6.73–6.78 (m, 1H), 6.92–6.96 (m, 1H), 7.21–7.34 (m, 3H), 7.46 (d, J = 8.2 Hz, 1H), 7.49–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.4 (t), 28.9 (t), 29.3 (t, 2C), 29.4 (t), 29.5 (t), 31.8 (t), 44.3 (t), 48.6 (t), 69.5 (s), 111.8 (d), 116.8 (s), 119.7 (d), 125.2 (d, 2C), 126.5 (d), 127.8 (d), 128.7 (d, 2C), 137.5 (s), 144.2 (s), 160.2 (s), 199.0 (s), 209.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{26}H_{33}ClNO_2$ (M^++H): 426.2200, found 426.2194.



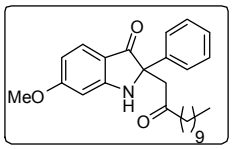
Ethyl 2-(6-chloro-3-oxo-2-phenylindolin-2-yl)acetate (47cj): Yellow solid; 73%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, J = 7.1 Hz, 3H), 2.81 (d, J = 16.2 Hz, 1H), 3.38 (d, J = 16.0 Hz, 1H), 3.92–4.11 (m, 2H), 6.23 (s, 1H), 6.77 (dd, J = 8.3, 1.6 Hz, 1H), 6.92–7.01 (m, 1H), 7.25–7.38 (m, 3H), 7.43–7.56 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8 (q), 41.9 (t), 61.0 (t), 69.2 (s), 111.8 (d), 117.0 (s), 119.8 (d), 125.4 (d, 2C), 126.5 (d), 128.0 (d), 128.7 (d, 2C), 137.2 (s), 144.1 (s), 160.3 (s), 170.5 (s), 198.4 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{16}ClNO_3Na$ (M^++Na): 352.0716, found 352.0711.



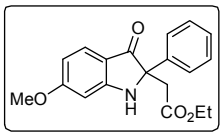
6-Chloro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one (47cb): Brown gum; 68%; (R_f = 0.5, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.19 (d, J = 18.1 Hz, 1H), 4.43 (d, J = 18.1 Hz, 1H), 6.43 (s, 1 H), 6.76 (dd, J = 8.3, 1.7 Hz, 1H), 6.96 (d, J = 1.4 Hz, 1H), 7.20–7.32 (m, 3H), 7.39–7.59 (m, 6H), 7.86–7.95 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 44.6 (t), 69.7 (s), 111.6 (d), 116.6 (s), 119.6 (d), 125.2 (d, 2C), 126.6 (d), 127.7 (d), 128.1 (d, 2C), 128.7 (d, 2C), 128.8 (d, 2C), 133.8 (d), 136.4 (s), 137.6 (s), 144.2 (s), 160.4 (s), 197.6 (s), 199.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{22}H_{16}ClNO_2Na$ (M^++Na): 384.0767, found 384.0762.



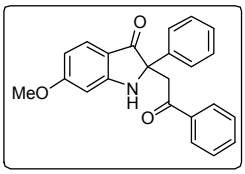
6-Methoxy-2-(2-oxododecyl)-2-phenylindolin-3-one (47ha): Pale yellow solid; 73%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83–0.91 (m, 3H), 1.11–1.29 (m, 14H), 1.38–1.51 (m, 2H), 2.22–2.43 (m, 2H), 2.64 (d, J = 16.9 Hz, 1H), 3.71 (d, J = 16.9 Hz, 1H), 3.85 (s, 3H), 6.28 (s, 1H), 6.34–6.39 (m, 2H), 7.19–7.25 (m, 1H), 7.27–7.33 (m, 2H), 7.45 (d, J = 8.7 Hz, 1H), 7.51–7.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.3 (t), 28.9 (t), 29.2 (t, 2C), 29.4 (t), 29.5 (t), 31.8 (t), 44.3 (t), 48.7 (t), 55.6 (q), 69.5 (s), 94.0 (d), 108.9 (d), 111.5 (s), 125.3 (d, 2C), 126.9 (d), 127.5 (d), 128.5 (d, 2C), 138.3 (s), 162.3 (s), 168.1 (s), 198.0 (s), 209.7 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{27}H_{36}NO_3$ (M^++H): 422.2695, found 422.2690.



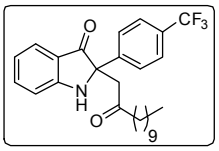
Ethyl 2-(6-methoxy-3-oxo-2-phenylindolin-2-yl)acetate (47hj): White solid; 70%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H), 2.77 (d, J = 16.5 Hz, 1H), 3.40 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H), 4.00 (dtt, J = 10.6, 7.1, 7.1, 3.6 Hz, 2H), 6.17 (s, 1H), 6.31–6.45 (m, 2H), 7.21–7.27 (m, 1H), 7.28–7.33 (m, 2H), 7.46 (d, J = 8.2 Hz, 1H), 7.51–7.56 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8 (q), 41.9 (t), 55.5 (q), 60.8 (t), 69.2 (s), 94.1 (d), 109.0 (d), 111.7 (s), 125.4 (d, 2C), 126.9 (d), 127.6 (d), 128.5 (d, 2C), 138.0 (s), 162.4 (s), 168.0 (s), 170.8 (s), 197.4 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{20}NO_4$ (M^++H): 326.1392, found 326.1387.



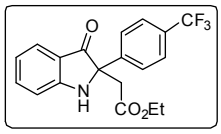
6-Methoxy-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one (47hb): Pale yellow solid; 71%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.15 (d, J = 17.9 Hz, 1H), 3.81 (s, 3H), 4.45 (d, J = 17.9 Hz, 1H), 6.31–6.41 (m, 2H), 6.46 (s, 1H), 7.16–7.32 (m, 3H), 7.34–7.60 (m, 6H), 7.85–7.93 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 44.6 (t), 55.5 (q), 69.7 (s), 93.8 (d), 108.8 (d), 111.3 (s), 125.2 (d, 2C), 126.9 (d), 127.3 (d), 128.0 (d, 2C), 128.5 (d, 2C), 128.6 (d, 2C), 133.6 (d), 136.5 (s), 138.4 (s), 162.5 (s), 168.1 (s), 197.9 (s), 198.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{23}H_{19}NO_3Na$ (M^++Na): 380.1263, found 380.1257.



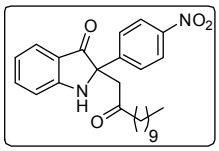
2-(2-Oxobutyl)-2-(4-(trifluoromethyl)phenyl)indolin-3-one (47ka): Brown gum; 62%; (R_f = 0.6, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83–0.91 (m, 3H), 1.11–1.28 (m, 14H), 1.45 (dt, J = 14.1, 7.2 Hz, 2H), 2.28–2.42 (m, 2H), 2.69 (d, J = 17.7 Hz, 1H), 3.72 (d, J = 17.6 Hz, 1H), 6.27 (s, 1H), 6.77–6.87 (m, 1H), 6.97 (d, J = 8.2 Hz, 1H), 7.45–7.52 (m, 1H), 7.52–7.59 (m, 3H), 7.66–7.76 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.4 (t), 28.9 (t), 29.2 (t, 2C), 29.3 (t), 29.5 (t), 31.8 (t), 44.2 (t), 48.9 (t), 68.8 (s), 112.1 (d), 117.9 (s), 119.3 (d), 125.5 (d), 125.6 (d), 125.6 (s), 126.0 (d, 3C), 126.0 (s),138.0 (d), 142.2 (s), 160.0 (s), 199.6 (s), 209.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{27}H_{32}F_3NO_2Na$ (M^++Na): 482.2283, found 482.2277.



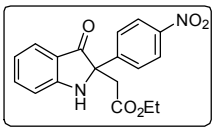
Ethyl 2-(3-oxo-2-(4-(trifluoromethyl)phenyl)indolin-2-yl)acetate (47kj): Brown gum; 60%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.07 (t, J = 7.1 Hz, 3H), 2.76 (d, J = 16.3 Hz, 1H), 3.41 (d, J = 16.3 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 6.18 (s, 1H), 6.80–6.88 (m, 1H), 6.96–7.05 (m, 1H), 7.47–7.62 (m, 4H), 7.68–7.77 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.8 (q), 42.1 (t), 61.2 (t), 68.5 (s), 112.2 (d), 118.1 (s), 119.5 (d), 125.5 (d), 125.5 (d), 125.7 (d), 125.7 (s), 126.2 (d, 2C), 126.2 (s), 138.0 (d), 141.8 (s), 160.1 (s), 170.5 (s), 199.0 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{16}F_3NO_3Na$ (M^++Na): 386.0980, found 386.0974.



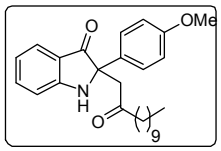
2-(4-Nitrophenyl)-2-(2-oxododecyl)indolin-3-one (47ja): Brown gum; 65%; (R_f = 0.5, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 6.1 Hz, 3H), 1.11–1.27 (m, 14H), 1.35–1.54 (m, 2H), 2.25–2.46 (m, 2H), 2.73 (d, J = 17.8 Hz, 1H), 3.74 (d, J = 17.8 Hz, 1H), 6.32 (s, 1H), 6.83 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.44–7.61 (m, 2H), 7.70–7.84 (m, 2H), 8.09–8.22 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 23.3 (t), 28.9 (t), 29.2 (t, 2C), 29.3 (t), 29.4 (t), 31.8 (t), 43.9 (t), 49.1 (t), 68.8 (s), 112.2 (d), 117.6 (s), 119.5 (d), 123.6 (d, 2C), 125.6 (d), 126.6 (d, 2C), 138.2 (d), 145.6 (s), 147.3 (s), 159.9 (s), 198.9 (s), 209.0 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{26}H_{32}N_2O_4Na$ (M^++Na): 459.2260, found 459.2254.



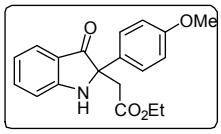
Ethyl 2-(2-(4-nitrophenyl)-3-oxoindolin-2-yl)acetate (47jj): Brown solid; 63%; (R_f = 0.4, 30% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (t, J = 7.1 Hz, 3H), 2.77 (d, J = 16.4 Hz, 1H), 3.42 (d, J = 16.4 Hz, 1H), 4.01 (qd, J = 7.1, 1.3 Hz, 2H), 6.23 (s, 1H), 6.79–6.92 (m, 1H), 7.01 (dt, J = 8.2, 0.8 Hz, 1H), 7.46–7.61 (m, 2H), 7.73–7.86 (m, 2H), 8.12–8.23 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9 (q), 42.2 (t), 61.3 (t), 68.6 (s), 112.4 (d), 117.9 (s), 119.8 (d), 123.6 (d, 2C), 125.7 (d), 126.9 (d, 2C), 138.2 (d), 145.2 (s), 147.5 (s), 160.0 (s), 170.3 (s), 198.3 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{16}N_2O_5Na$ (M^++Na): 363.0957, found 363.0951.



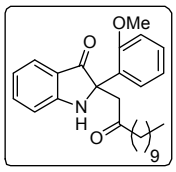
2-(4-Methoxyphenyl)-2-(2-oxododecyl)indolin-3-one (47ia): Dark brown gum; 69%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83–0.91 (m, 3H), 1.13–1.30 (m, 14H), 1.45 (dt, J = 14.1, 7.3 Hz, 2H), 2.33 (q, J = 6.9 Hz, 2H), 2.63 (d, J = 17.1 Hz, 1H), 3.65 (d, J = 17.1 Hz, 1H), 3.75 (s, 3H), 6.18 (s, 1H), 6.73–6.88 (m, 3H), 6.93 (d, J = 8.2 Hz, 1H), 7.42–7.51 (m, 3H), 7.54 (d, J = 7.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1 (q), 22.7 (t), 23.4 (t), 29.0 (t), 29.3 (t, 2C), 29.4 (t), 29.5 (t), 31.9 (t), 44.4 (t), 48.6 (t), 55.2 (q), 68.6 (s), 112.0 (d), 114.0 (d, 2C), 118.4 (s), 118.8 (d), 125.5 (d), 126.6 (d, 2C), 129.9 (s), 137.6 (d), 159.1 (s), 160.0 (s), 200.8 (s), 209.6 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{27}H_{36}NO_3$ (M^++H): 422.2695, found 422.2690.



Ethyl 2-(2-(4-methoxyphenyl)-3-oxoindolin-2-yl)acetate (47ij): Brown gum; 68%; (R_f = 0.3, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (t, J = 7.1 Hz, 3H), 2.77 (d, J = 15.9 Hz, 1H), 3.35 (d, J = 15.9 Hz, 1H), 3.76 (s, 3H), 4.01 (qd, J = 7.1, 1.5 Hz, 2H), 6.00 (s, 1H), 6.80–6.88 (m, 3H), 6.95 (d, J = 8.3 Hz, 1H), 7.41–7.53 (m, 3H), 7.53–7.59 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.9 (q), 42.0 (t), 55.2 (q), 60.9 (t), 68.3 (s), 112.0 (d), 114.0 (d, 2C), 118.6 (s), 119.1 (d), 125.6 (d), 126.7 (d, 2C), 129.6 (s), 137.6 (d), 159.2 (s), 160.1 (s), 170.7 (s), 200.2 (s) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{19}NO_4Na$ (M^++Na): 348.1212, found 348.1206.



2-(2-Methoxyphenyl)-2-(2-oxododecyl)indolin-3-one (47ma): Brown gum; 60%; (R_f = 0.4, 20% AcOEt/pet.ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.83–0.91 (m, 3H), 1.23 (br s, 14H), 1.50 (t, J = 6.9 Hz, 2H), 2.31–2.44 (m, 2H), 2.98 (d, J = 16.9 Hz, 1H), 3.65 (d, J = 17.1 Hz, 1H), 3.86 (s, 3H), 6.12 (br s, 1H), 6.76–6.86 (m, 2H), 6.86–7.00 (m, 2H), 7.19–7.33 (m, 2H), 7.40 (td, J = 7.6, 1.3 Hz, 1H), 7.65–7.74 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 23.5 (t), 29.1 (t), 29.3 (t), 29.35 (t), 29.40 (t), 29.5 (t), 31.9 (t), 43.2 (t), 48.7 (t), 55.5 (q), 68.9 (s), 111.8 (d), 112.3 (d), 118.6 (d), 120.9 (d), 121.0 (s), 124.6 (d), 126.3 (s), 127.4 (d), 129.1 (d), 136.8 (d), 157.5 (s), 159.8 (s), 201.6 (s), 207.8 (s) ppm. HRMS (ESI$^+$): calcd. for $C_{27}H_{35}NO_3Na$ (M^++Na): 444.2515, found 444.2509.



REFERENCES

(1) (a) Angeli *Ber.* **1892**, 26B, 1960; (b) Angeli *Gam. chim. ital.* **1892**, *22*, 11, 451; (c) Angeli *Ber.* **1893**, 26B, 593.

(2) (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565–598; (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633–645; (c) Fireston, R.A. *J. Org. Chem.* **1968**, *33*, 2285; (d) Harcourt, R. D. *J. Mol. Structure* **1972**, *12*, 351–366; (e) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401–6402; (f) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863-909.

(3) (a) E. Beckmann, *Chem. Ber.* **1890**, *23*, 3332; (b) Beckmann, E.; Fellrath, E. *Justus Liebigs Ann. Chem.* **1893**, *1,* 273; (c) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.* **1969**, *102*, 926; Nitrones in the synthesis of natural products: (d) Padwa A., Pearson W. H.: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; John Wiley & Sons: New York, NY, 2002, chapter 1, page 1–82; For synthesis and reactivity of nitrones: (e) Feuer, H. in Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, WILEY-VCH, Weinheim, 2008.

(4) (a) Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1741–1746; (b) Baeyer, A. *Ber. Dtsch. Chem. Ges.***1882**, *15*, 50–61.

(5) (a) Pfeiffer, P. *Justus Liebigs Ann. Chem.* **1916**, *72*, 411; (b) Ruggli, P.; Bolliaer, A. *ibid.* **1921**, *4,* 626; (c) Ruggli, P.; Casper, E.; Hegedus, B. *Helv. Chim. Acta* **1937**, *20*, 250; (d) Ruggli, P.; Cuenin, H. *ibid.* **1944**, *27*, 649.

(6) Fiers, W.; Beyaert, R.; Declercq, W.; Vandenabeele, P. *Oncogene* **1999**, *18*, 7719–7730.

(7) Bond, C. C.; Hooper, M. *Synthesis* **1974**, 443–443.

(8) (a) Preston, P. N.; Tennant, G. *Chem. Rev.* **1972**, *72*, 627–677; (b) Hiremath, S. P.; Hooper, M. *Adv. Heterocycl. Chem.* **1978**, *22*, 123–181; (c) Slatt, J.; Bergman, J. *Tetrahedron* **2002**, *58*, 9187–9191; (d) Söderberg, B. C. G.; Gorugantula, S. P.; Howerton, C. R.; Petersen, J. L.; Dantale, S. W. *Tetrahedron* **2009**, *65*, 7357–7363; (e) Nepveu, F.; Kim, S.; Boyer, J.; Chatriant, O.; Ibrahim, H.; Reybier, K.; Monje, M.-C.; Chevalley, S.; Perio, P.; Lajoie, B. H.; Bouajila, J.; Deharo, E.; Sauvain, M.; Tahar, R.; Basco, L.; Pantaleo, A.; Turini, F.; Arese, P.; Valentin, A.; Thompson, E.; Vivas, L.; Petit, S.; Nallet, J.-P. *J. Med. Chem.* **2010**, *53*, 699–714.

(9) Splitter, J. S.; Calvin, M. *J. Org. Chem.* **1955**, *20*, 1086–1115.

(10) Bond, C. C.; Hooper, M. *J. Chem. Soc. C* **1969**, 2453–2460.

(11) (a) Aleisandri, L. *Gazz. Chim. Ital.* **1927**, *57*, 195; (b) *Chem. Abstr* **1927**, *21*, 2127; (c) *Gazz. Chim. Ital.* **1928**, *58*, 551; (d) *Chem. Abstr*. **1929**, *23*, 1635; (e) *Gazz. Chim. Ztal.* **1928**, *58,* 738; (f) *Chem. Abstr.* **1929**, *23*, 3690; (g) Rosen, G. M.; Tsai, P.; Barth, E. D.; Dorey, G.; Casara, P.; Spedding, M.; Halpern, H. J. *J. Org. Chem.* **2000**, *65*, 4460–4463.

(12) Ruggli, P.; Hegedus, *Helv. Chim. Acta* **1939**, *22*, 147.

(13) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675–5677.

(14) Li, X. W.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066–3073.

(15) Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B. C.; Degterev, A. *Eur. J. Org. Chem.* **2010**, 5955–5966.

(16) Patel, P.; Ramana, C. V. *Org. Biomol. Chem.* **2011**, *9*, 7327–7334.

(17) (a) Bunney, J. E.; Hooper, M. *Tetrahedron Lett.* **1966**, 3857–3860; (b) Hooper, M.; Robertson, J. W. *Tetrahedron Lett.* **1971**, 2139–2140.

(18) (a) Berti, C.; Colonna, M.; Greci, L.; Marchetti, L. *Tetrahedron* **1975**, *31*, 1745–1753; (b) Berti, C.; Greci, L.; Marchetti, L. *J. Chem. Soc. Perkin Trans 2* **1977**, 1032–1035; (c) Berti, C.; Greci, L.; Marchetti, L. *J. Chem. Soc. Perkin Trans 2* **1979**, 233–236; (d) Liu, Y.; McWhorter, W. W. *J. Org. Chem.* **2003**, *68*, 2618–2622.

(19) Tommasi, G.; Bruni, P.; Greci, L.; Sgarabotto, P.; Righi, L. *J. Chem. Soc. Perkin Trans 1* **1999**, 681–686.

(20) (a) Eckroth, D. R.; Squir, R. H. *Chem. Commun.* **1969**, 312; (b) Eckroth, D. R.; Squire, R. H. *J. Org. Chem.* **1971**, *36*, 224–226.

(21) Patterson, D. A.; Wibberley, D. G. *J. Chem. Soc.* **1965**, 1706–1711.

(22) (a) Greci, L.; Tommasi, G.; Bruni, P.; Sgarabotto, P.; Righi, L. *Eur. J. Org. Chem.* **2001**, 3147–3153. (b) Astolfi, P.; Bruni, P.; Greci, L.; Stipa, P.; Righi, L.; Rizzoli, C. *Eur. J. Org. Chem.* **2003**, 2626–2634.

(23) **Indoxyl in natural product synthesis:** (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 3871–3877; (b) P. CapdevieUe, M. Maumy, *Tetrahedron Lett.* **1993**, *34*, 2953–2956; (c) R. Giiller, H.-J. Borschberg, *Helv. Chim. Acta* **1993**, *76*, 1847–1862; (d) Guller, R.; Borschberg, H. J. *Tetrahedron Lett.* **1994**, *35*, 865–868; (e) S. Y. Ryabova, V. G. Granik, *Pharma. Chem. J.* **1995**, *29*, 809–840; (f) Takayama, H.; Kurihara, M.; Subhadhirasakul, S.; Kitajima, M.; Aimi, N.; Sakai, S. *Heterocycles* **1996**, *42*, 87–92; (g) Borschberg, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1465–1491; (h) X.

Qi, H. Bao, U. K. Tambar, *J. Am. Chem. Soc.* **2011**, *133*, 10050–10053; (i) S. Liu, X.-J. Hao, *Tetrahedron Lett.* **2011**, *52*, 5640–5642; (j) S. Han, M. Movassaghi, *J. Am. Chem. Soc.* **2011**, *133*, 10768–10771.

(24) **Natural Products Isalations: Fluorocurine:** (a) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1947**, *30*, 2081–2091; **Coronaridine pseudoindoxyl:** (b) Hwang, B.; Weisbach, J. A.; Douglas, B.; Raffauf, R.; Cava, M. P.; Bessho, K. *J. Org. Chem.* **1969**, *34*, 412–415; **Brevianamide:** (c) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329–2344; **Austamide:** (d) Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331–3334; **Hunteracine Pseudoindoxyl:** (e) Burnell, R. H.; Chapelle, A.; Khalil, M. F. *Can. J. Chem.* **1974**, *52*, 2327–2330; **Aristoteline:** (f) Hesse, M.; Philipsborn, W. v.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W. I.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1964**, *47*, 878–911; (g) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574–575; **Rupicoline:** (h) Niemann, C.; Kessel, J. W. *J. Org. Chem.* **1966**, *31*, 2265–2269; **Raunicine Pseudoindoxyl:** (i) Phillipson, J. D.; Supavita, N. *Phytochemistry* **1983**, *22*, 1809–1813;**aristolarine:**(j) Rolf, K.; Emanuel, S.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 804–814; **Holothurian:** (k) Wang, F. Z.; Fang, Y. C.; Zhu, T. J.; Zhang, M.; Lin, A. Q.; Gu, Q. Q.; Zhu, W. M. *Tetrahedron* **2008**, *64*, 7986–7991; (l) Guller, R.; Borschberg, H. J. *Helv. Chim. Acta.* **1993**, *76*, 1847–1862; **Iboluteine:** (m) Bickel, H.; Giesbrecht, E.; Kebrle, J.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1954**, *37*, 553–565; (n) Dickel, D. F.; Holden, C. L.; Maxfield, R. C.; Paszek, L. E.; Taylor, W. I. *J. Am. Chem. Soc.* **1958**, *80*, 123–125; (o) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564–568; **Duocarmycin A:** (p) Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1915–1917; **Peronatins**: (q) Stachel, S. J.; Nilges, M.; VanVranken, D. L. *J. Org. Chem.* **1997**, *62*, 4756–4762; **Cephalinones** isolation: (r) Wu, P. L.; Hsu, Y. L.; Jao, C. W. *J. Nat. Prod.* **2006**, *69*, 1467–1470; **Laundrines:** (s) Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745; **Isatisine A** isolation: (t) Liu, F.; Jiang, Z. Y.; Wang, R. R.; Zheng, Y. T.; Chen, J. J.; Zhang, X. M.; Ma, Y. B. *Org. Lett.* **2007**, *9*, 4127–4129; **Notoamide O** isolation: (u) Tsukamoto, S.; Umaoka, H.; Yoshikawa, K.; Ikeda, T.; Hirota, H. *J. Nat. Prod.* **2010**, *73*, 1438–1440.

(25) **Condensation:** (a) Betts, R. L.; Muspratt, R.; Plant, S. G. P. *J. Chem. Soc.* **1927**, 1310–1314; (b) Beer, R. J. S.; McGrath, L.; Robertson, A.; Woodier, A. B. *Nature* **1949**, *164*, 362–363; (c) Plant, S. G. P.; Robinson, R. *Nature* **1950**, *165*, 36–37; (d) Plant, S. G. P.; Robinson, R.; Tomlinson, M. *Nature* **1950**, *165*, 928.

(26) (a) Patrick, J. B.; Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 633–634; (1) Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 614–620; (2) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 1558–1564; (3) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2572–2576.

(27) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188–2195.

(28) Dolby, L. J.; Rodia, R. M. *J. Org. Chem.* **1970**, *35*, 1493–1496.

(29) Saito, I.; Imuta, M.; Matsuura, T. *Chem. Lett.* **1972**, 1173–1176.

(30) Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, 539–542

(31) (a) Ardakani, M. A.; Smalley, R. K. *Tetrahedron Lett.* **1979**, 4769–4772.

(32) (a) Pearson, W. H.; Mi, Y.; Lee, I. Y.; Stoy, P. *J. Am. Chem. Soc.* **2001**, *123*, 6724–6725; (b) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109–9122.

(33) Kawada, M.; Kawano, Y.; Sugihara, H.; Takei, S.; Imada, I. *Chem. Pharm. Bull.* **1981**, *29*, 1900–1911.

(34) Berti, C.; Greci, L.; Andruzzi, R.; Trazza, A. *J. Org. Chem.* **1982**, *47*, 4895–4899.

(35) Merour, J. Y.; Chichereau, L.; Finet, J. P. *Tetrahedron Lett.* **1992**, *33*, 3867–3870.

(36) Zhang, X. J.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867–8868.

(37) Ling, K. Q. *Syn. Commun.* **1996**, *26*, 149–152.

(38) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504–5510.

(39) Kawasaki, T.; Tang, C. Y.; Nakanishi, H.; Hirai, S.; Ohshita, T.; Tanizawa, M.; Himori, M.; Satoh, H.; Sakamoto, M.; Miura, K.; Nakano, F. *J. Chem. Soc. Perkin Trans 1* **1999**, 327–333.

(40) Astolfi, P.; Greci, L.; Rizzoli, C.; Sgarabotto, P.; Marrosu, G. *j. Chem. Soc. Perkin Trans 2* **2001**, 1634–1640.

(41) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630–6631.

(42) Buller, M. J.; Cook, T. G.; Kobayashi, Y. *Heterocycles* **2007**, *72*, 163–166.

(43) Ganachaud, C.; Garfagnoli, V.; Tron, T.; Iacazio, G. *Tetrahedron Lett.* **2008**, *49*, 2476–2478.

(44) (a) Qin, W. B.; Chang, Q.; Bao, Y. H.; Wang, N.; Chen, Z. W.; Liu, L. X. *Org. Biomol. Chem.* **2012**, *10*, 8814–8821; (b) Kong, Y. B.; Zhu, J. Y.; Chen, Z. W.; Liu, L. X. *Can. J. Chem.* **2014**, *92*, 269–273; (c) Xue, J.; Bao, Y. H.; Qin, W. B.; Zhu, J. Y.; Kong, Y. B.; Qu, H. G.; Chen, Z. W.; Liu, L. X. *Syn. Commun.* **2014**, *44*, 2215–2221.

(45) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009–4012.

(46) (a) Schneekloth, J. S.; Kim, J.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 3096–3101; (b) Kim, J.; Schneekloth, J. S.; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849–2852.

(47) (a) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197–199; (b) Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236–1243.

(48) Yin, Q.; You, S. L. *Chem. Sci.* **2011**, *2*, 1344–1348.

(49) (a) Li, L. Q.; Han, M. Y.; Xiao, M. X.; Xie, Z. X. *Synlett* **2011**, 1727–1730; (b) Rueping, M.; Rasappan, R.; Raja, S. *Helv. Chim. Acta* **2012**, *95*, 2296–2303.

(50) Jessing, M.; Baran, P. S. *Heterocycles* **2011**, *82*, 1739–1745.

(51) (a) Zhang, Y. Q.; Zhu, D. Y.; Jiao, Z. W.; Li, B. S.; Zhang, F. M.; Tu, Y. Q.; Bi, Z. G. *Org. Lett.* **2011**, *13*, 3458–3461; (b) Cheng, B.; Huang, G.; Xu, L.; Xia, Y. *Org. Biomol. Chem.* **2012**, *10*, 4417–4423.

(52) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822–5824.

(53) Wetzel, A.; Gagosz, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7354–7358.

(54) Parra, A.; Alfaro, R.; Marzo, L.; Moreno-Carrasco, A.; Ruano, J. L. G.; Aleman, J. *Chem. Commun.* **2012**, *48*, 9759–9761.

(55) Preciado, S.; Vicente-Garcia, E.; Llabres, S.; Luque, F. J.; Lavilla, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 6874–6877.

(56) Jin, C. Y.; Wang, Y.; Liu, Y. Z.; Shen, C.; Xu, P. F. *J. Org. Chem.* **2012**, *77*, 11307–11312.

(57) Goriya, Y.; Ramana, C. V. *Chem. Commun.* **2013**, *49*, 6376–6378.

(58) Peng, J. B.; Qi, Y.; Ma, A. J.; Tu, Y. Q.; Zhang, F. M.; Wang, S. H.; Zhang, S. Y. *Chem. Asian J.* **2013**, *8*, 883–887.

(59) Aristeo-Dominguez, A.; Melendez-Rodriguez, M.; Castillo, O. R. S.; Contreras-Martinez, Y. M. A.; Suarez-Ramirez, L.; Trejo-Carbajal, N.; Morales-Rios, M. S.; Joseph-Nathan, P. *Heterocycles* **2013**, *87*, 1249–1267.

(60) **Selected reviews:** (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; (b) Negishi, E.-i. *Bull. Chem. Soc. J.* **2007**, *80*, 233–257; (c) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207; (d) Forke, K. K.; Gruner, K. E.; Knott, S.; Auschill, S.; Agarwal, R.; Martin, M.; Boehl, S.; Richter, G.; Tsiavaliaris, R.; Fedorov, D. J.; Manstein, H. O.; Gutzeit, H.-J.; Knoelker, *Pure Appl. Chem.* **2010**, *82*, 1975–1991; (e) Denmark, S. E.; Liu, J. H. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 2978–2986; (f) Fürstner, A. *Israel J. Chem.* **2011**, *51*, 329–345; (g) Djakovitch, L.; Batail, N.; Genelot, M. *Molecules* **2011**, *16*, 5241–5267.

(61) **Total synthesis of isatisine A:** (a) Karadeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1133–1135; (b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830–6841.

(62) Lee, J.; Panek, J. S. *Org. lett.* **2011**, *13*, 502–505.

(63) Zhang, X.; Mu, T.; Zhan, F. X.; Ma, L. J.; Liang, G. X. *Angew. Chem. Int. Ed.* **2011**, *50*, 6164–6166.

(64) Wu, W.; Xiao, M.; Wang, J.; Li, Y.; Xie, Z. *Org. Lett.* **2012**, *14*, 1624–1627.

(65) (a) Denis, J. N.; Mauger, H.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 8515–8518; (b) Chalaye-Mauger, H.; Denis, J. N.; Averbuch-Pouchot, M. T.; Vallee, Y. *Tetrahedron* **2000**, *56*, 791–804; (c) Berini, C.; Minassian, F.; Pelloux-Leon, N.; Vallee, Y. *Tetrahedron Lett.* **2005**, *46*, 8653–8656.

(66) Li, X. L.; Qin, Z. B.; Wang, R.; Chen, H.; Zhang, P. Z. *Tetrahedron* **2011**, *67*, 1792–1798.

(67) **For [In]-Mediated Friedel–Crafts alkylation of indoles** see: (a) Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 1229–1232; (b) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, *46*, 639–641; (c) Yadav, J. S.; Reddy, B. V. S.; Vishnumurthy, P.; Premalatha, K. *Synthesis* **2008**, 719–724; (d) Reddy, B. V. S.; Reddy, M. R.; Madan, C.; Kumar, K. P.; Rao, M. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7507–7511; (e) Ahmed, N.; Babu,

B. V.; Kumar, H. *Synthesis* **2011**, 2471–2477; For a general review see: (f) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982; (g) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199–1222; For the reviews of [In]-metal mediated reactions see: (h) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764; (i) Ghosh, R.; Maiti, S. *J. Mol. Cat. A* **2007**, *264*, 1–8; (j) Yadav, J. S.; Antony, A.; George, J.; Reddy, B. V. S. *Eur. J. Org. Chem.* **2010**, 591–605; (k) Sakai, N.; Konakahara, T. *J. Syn. Org. Chem. J.* **2011**, *69*, 38–47.

(68) **For [In]-Mediated reduction of nitro compounds see:** (a) Moody, C. J.; Pitts, M. R. *synlett* **1998**, 1029; (b) Miyai, T.; Ueba, M.; Baba, A. *synlett* **1999**, 182–184; (c) Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun.* **2000**, *30*, 3745–3754; (d) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. I* **2001**, 955–977; (e) Kim, B. H.; Cheong, J. W.; Han, R.; Jun, Y. M.; Baik, W.; Lee, B. M. *Synth. Commun.* **2001**, *31*, 3577–3586; (f) Lee, J. G.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81–84; (g) Han, R.; Son, K. I.; Ahn, G. H.; Jun, Y. M.; Lee, B. M.; Parkd, Y.; Kim, B. H. *Tetrahedron Lett.* **2006**, *47*, 7295–7299; (h) Sakai, N.; Fujii, K.; Nabeshima, S.; Ikeda, R.; Konakahara, T. *Chem. Commun.* **2010**, *46*, 3173–3175.

(69) **$InCl_3$ reduction of nitrones:** (a) Ilias, M.; Barman, D. C.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **2002**, *43*, 1877–1879; (b) Najahi, E.; Valentin, A.; Fabre, P. L.; Reybier, K.; Nepveu, F. *Eur. J. Med. Chem.* **2014**, *78*, 269–274.

(70) **N–OH reduction:** (a) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773–1776; (b) Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 1209–1212.

(71) CCDC 850037 (**5fb**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam, ac.uk/data_request/cif.

(72) (a) Whistler, R. L., Bemiller, J. N. *J. Org. Chem.* **1961**, *26*, 2886–2892; (b) Whistler, R. L.; BeMiller, J. N. *Methods Carbohydr. Chem.* Academic Press, New York, **1963,** vol 2**,** p. 477 and references cited therein; (c) Trinh, M. C.; Florent, J. C.; Monneret, C. *J. Chem. Soc. Chem. Commun.* **1987**, 615–616; (d) Francisco, C. G.; Freire, R.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **1995**, *36*, 2141–2144.

(73) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978; (b) Krohn, K.; Heins, H.; Wielckensf, K. *J. Med. Chem.* 1992, **35**, 511–517; (c)

Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc. Perkin Trans 1*, 1995, 517–518; (d) Xin, Y. C.; Zhang, Y. M.; Mallet, J. M.; Glaudemans, C. P. J.; Sinay, P. *Eur. J. Org. Chem. 1***999**, 471–476; (e) Aslam, T.; Fuchs, M. G.; Le Formal, G. A.; Wightman, R. H. *Tetrahedron Lett.* **2005**, *46*, 3249–3252.

(74) Brakta, M.; Farr, R. N.; Chaguir, B.; Massiot, G.; Lavaud, C.; W. Anderson, R.; Sinou, D.; Daves, G. D. *J. Org. Chem.* **1993**, *58*, 2992–2998;

(75) Elangovan, A.; Wang, Y. H.; Ho, T. I. *Org. lett.* **2003**, *5*, 1841–1844.

(76) **NO_2–group as spectator group:** (a) Padwa, A.; Krumpe, K. E.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 5595–5603; (b) Woon, E. C. Y.; Dhami, A.; Mahon, M. F.; Threadgill, M. D. *Tetrahedron* **2006**, *62*, 4829–4837; (1) Ramana, C. V.; Mallik, R.; Gonnade, R. G. *Tetrahedron* **2008**, *64*, 219–233.

(77) (a) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569; (b) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372–1375.

(78) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478; (b) Ramana, C. V.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1599–1610; (c) Presser, A.; Hufner, A.; *Monatsh. Chem.* **2004**, *135*, 1015–1022; (d) Kuehnel, E.; Laffan, D. D. R.; Lloyd-Jones, G. C.; del Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 7075–7078.

(79) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873–2875.

(80) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786–6788;

(81) Harrison, D. M. *Tetrahedron Lett.* **1981**, *22*, 2501–2504.

(82) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904–7905.

(83) **Selected reviews/papers on intramolecular nitrone-cycloadditions:** (a) Martin, J. N.; Jones, R. C. F. in "Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products" Padwa, A., Pearson, W. H., Eds.; Wiley: Hoboken, NJ, **2003**; pp 1−81; (b) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298–326; (c) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497–3509; (d) Lebel, N. A.; Balasubramanian, N. *J. Am. Chem. Soc.* **1989**, *111*, 3363–3368; (e) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**,

121, 4900–4901; (f) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113–5123; (g) Smith, C. J.; Holmes, A. B.; Press, N. *J. Chem. Commun.* **2002**, 1214–1215.

(84) Shing, T. K. M.; Fung, W. C.; Wong, C. H. *J. Chem. Soc. Chem. Commun.* **1994**, 449–450.

(85) **Selectivity switch in gold catalysis:** (a) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855–2875; (b) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzic, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 5848–5852; (c) Hashmi, A. S. K. *Pure Appl. Chem.* **2010**, *82*, 1517–1528; (d) Hashmi, A. S. K.; Wang, T.; Shi, S.; Rudolph, M. *J. Org. Chem.* **2012**, *77*, 7761–7767.

(86) (a) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281; (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705; (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

(87) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131–163; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564; (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; **Reviews on Metal catalysis see:** (e) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16; (f) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Top. Organomet. Chem.* **2006**, 259–294.

(88) **For gold catalysis followed by pericyclic reactions** see: (a) Hashmi, A. S. K.; Jaimes, M. C. B.; Schuster, A. M.; Rominger, F. *J. Org. Chem.* **2012**, *77*, 6394–6408; (b) Hashmi, A. S. K.; Littmann, A. *Chem. Asian J.* **2012**, *7*, 1435–1442.

(89) **Selecteed reviews on gold-catalyzed internal redox processes:** (a) Xiao, J.; Li, X. W. *Angew. Chem. Int. Ed.* **2011**, *50*, 7226–7236; (b) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462–1479; (c) Zhang, L. M. *Acc. Chem. Res.* **2014**, *47*, 877–888; (d) Yeom, H. S.; Shin, S. *Acc. Chem. Res.* **2014**, *47*, 966–977.

(90) Jadhav, A. M.; Bhunia, S.; Liao, H. Y.; Liu, R. S. *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771.

(91) **Nitrone as oxidant:** (a) Yeom, H. S.; Lee, J. E.; Shin, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7040–7043; (b) Yeom, H. S.; Lee, Y.; Lee, J. E.; Shin, S. *Org. Biomol.Chem.* **2009**, *7*, 4744–4752; (c) Pati, K.; Liu, R. S. *Chem. Commun.* **2009**, 5233–5235; (d) Chen, D.; Song, G. Y.; Jia, A. Q.; Li, X. W. *J. Org. Chem.* **2011**, *76*, 8488–8494; **N–O as oxidant:** (e) Cui, L.; Peng, Y.; Zhang, L. M. *J. Am. Chem. Soc.* **2009**, *131*, 8394–

8395; (f) Ye, L. W.; Cui, L.; Zhang, G. Z.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259; (g) Ye, L. W.; He, W. M.; Zhang, L. M. *J. Am. Chem. Soc.* **2010**, *132*, 8550–8551.

(92) (a) Zhang, L. M.; Sun, J. W.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346; (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350; (d) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912; (e) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953–965.

(93) CCDC 1012862 (**31bl**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(94) (a) Bhattacharjya, A.; Chattopadhyay, P.; McPhail, A. T.; McPhail, D. R. *J. Chem. Soc. Chem. Commun.* **1990**, 1508–1509; (c) Majumdar, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **1999**, *55*, 12157–12174; (d) Krenske, E. H.; Agopcan, S.; Ayiyente, V.; Houk, K. N.; Johnson, B. A.; Holmes, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 12010–12015.

(95) CCDC 1012861 (**31an**), contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(96) Kumar, C. V. S.; Ramana, C. V. *Org. Lett.* **2014**, *16*, 4766–4769.

(97) (a) Zeng, Y. B.; Li, Q. S.; Hanzlik, R. P.; Aube, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3034–3038; (b) Campbell, J.; Lin, Q.; Geske, G. D.; Blackwell, H. E. *ACS Chem. Biol.* **2009**, *4*, 1051–1059; (c) Borthwick, A. D. *Chem. Rev.* 2012, *112*, 3641–3716.

(98) (a) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.***1982**, *47*, 2663; (b) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503–504.

(99) (a) Katritzky, A. R.; Monro, A. M. *J. Chem. Soc.* **1958**, 1263–1266; (b) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1983**, *24*, 5337–5338; (c) Barton, D. H. R.; Fekih, A.; Lusinchi, X. *Tetrahedron Lett.* **1985**, *26*, 4603–4606; (d) Balicki, R.; Kaczmarek, L.; Malinowski, M. *Syn. Commun.* **1989**, *19*, 897–900; (e) Sarmah, B. K.; Barua, N. C. *Tetrahedron* **1991**, *47*, 8587–8600; (f) Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, *36*, 4881–4882; (g) Baik, W.; Kim, D. I.; Koo, S.; Rhee, J. U.; Shin, S. H.; Kim, B. H. *Tetrahedron Lett.* **1997**, *38*, 845–848; (h)

Somasundaram, N.; Srinivasan, C. *Tetrahedron Lett.* **1998**, *39*, 3547–3550; (i) McAuley, B. J.; Nieuwenhuyzen, M.; Sheldrake, G. N. *Org. Lett.* **2000**, *2*, 1457–1459; (j) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. M. *Tetrahedron Lett.* **2000**, *41*, 2663–2665; (k) Denmark, S. E.; Juhl, M. *Helv. Chim. Acta* **2002**, *85*, 3712–3736; (l) Yoo, B. W.; Choi, A. W.; Kim, D. Y.; Hwang, S. K.; Choi, K. I.; Kim, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 797–798; (m) Cho, Y. S.; Jun, B. K.; Kim, S.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Han, S. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 653–654; (n) Yoo, B. W.; Choi, K. H.; Choi, K. I.; Kim, J. H. *Syn. Commun.* **2003**, *33*, 4185–4189; (o) Han, J. H.; Choi, K. I.; Kim, J. H.; Yoo, B. W. *Syn. Commun.* **2004**, *34*, 3197–3201; (p) Yoo, B. W.; Hwang, S. K.; Kim, D. Y.; Choi, J. W.; Kang, S. O.; Yoo, B. S.; Choi, K. I.; Kim, J. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1633–1634; (q) Kumar, S.; Saini, A.; Sandhu, J. S. *Tetrahedron Lett.* **2005**, *46*, 8737–8739; (r) Park, E. S.; Lee, S. H.; Lee, J. H.; Rhee, H. J.; Yoon, C. M. *Synthesis* **2005**, 3499–3501; (s) Sanz, R.; Escribano, J.; Fernandez, Y.; Aguado, R.; Pedrosa, M. R.; Arnaiz, F. J. *Synlett* **2005**, 1389–1392; (t) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. M. K.; Gupta, M. K. *Tetrahedron Lett.* **2005**, *46*, 8411–8413; (u) Han, J. H.; Choi, K. I.; Kim, J. H.; Yoon, C. M.; Yoo, B. W. *Syn. Commun.* **2006**, *36*, 415–419; (v) Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 395–398; (w) Yoo, B. W.; Choi, J. W.; Yoon, C. M. *Tetrahedron Lett.* **2006**, *47*, 125–126; (x) Singh, S. K.; Reddy, A. S.; Mangle, M.; Ganesh, K. R. *Tetrahedron* **2007**, *63*, 126–130; (y) Yoo, B. W.; Park, M. C. *Syn. Commun.* **2008**, *38*, 1646–1650; (z) Cividino, P.; Dheu-Andries, M. L.; Ou, J.; Milet, A.; Py, S.; Toy, P. H. *Tetrahedron Lett.* **2009**, *50*, 7038–7042; (aa) Yoo, B. W.; Choi, J. W. *Syn. Commun.* **2009**, *39*, 3550–3554; (ab) Caliskan, H.; Zaim, O. *Syn. Commun.* **2010**, *40*, 3078–3083; (ac) Flick, A. C.; Caballero, M. J. A.; Padwa, A. *Tetrahedron* **2010**, *66*, 3643–3650; (ad) Gowda, N. B.; Rao, G. K.; Ramakrishna, R. A. *Tetrahedron Lett.* **2010**, *51*, 5690–5693; (ae) Keith, J. M. *J. Org. Chem.* **2010**, *75*, 2722–2725; (af) Beniazza, R.; Desvergnes, V.; Mehta, G.; Blanchard, N.; Robert, F.; Landais, Y. *J. Org. Chem.* **2011**, *76*, 791–799; (ag) Kokatla, H. P.; Thomson, P. F.; Bae, S.; Doddi, V. R.; Lakshman, M. K. *J. Org. Chem.* **2011**, *76*, 7842–7848; (ah) Yoo, B. W.; Kim, H. M.; Kim, D.; Seok, K. S. *Bull. Korean Chem. Soc.* **2011**, *32*, 2525–2526; (ai) Motiwala, H. F.; Gulgeze, B.; Aube, J. *J. Org. Chem.* **2012**, *77*, 7005–7022; (aj) Chen, Y. L.; Zhang, H. C. *Environ. Sci. Technol.* **2013**, *47*, 11023–11031; (ak) Londregan, A. T.; Piotrowski, D. W.; Xiao, J. *Synlett* **2013**, *24*, 2695–

2700; (al) Ma, R.; Liu, A. H.; Huang, C. B.; Li, X. D.; He, L. N. *Green Chem.* **2013**, *15*, 1274–1279; (am) Yoo, B. W.; Jung, H. I.; Kim, S. H.; Ahn, Y. S.; Choi, J. Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 359–360.

(100) **For Isoxazolidine cleavage see:** (a) Ferrara, M.; Cordero, F. M.; Goti, A.; Brandi, A.; Estieu, K.; Paugam, R.; Ollivier, J.; Salaun, J. *Eur. J. Org. Chem.* **1999**, 2725–2739; (b) Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaun, J.; Brandi, A. *J. Am. Chem. Soc.* **2000**, *122*, 8075–8076; (c) Cordero, F. M.; Vurchio, C.; Brandi, A.; Gandolfi, R. *Eur. J. Org. Chem.* **2011**, 5608–5616.

(101) **For N–O bond cleavage *via* oxidative addition see:** (a) Kitamura, M.; Zaman, S.; Narasaka, K. *Synlett* **2001**, 974–976; (b) Kitamura, M.; Narasaka, K. *Chem. Rec.* **2002**, *2*, 268–277; (c) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505–4519; (d) Parthasarathy, K.; Jeganmohan, M.; Cheng, C. H. *Org. Lett.* **2008**, *10*, 325–328; (e) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909; (f) Too, P. C.; Wang, Y. F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688–5691; (g) Tan, Y. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676–3677; (h) Li, B.; Feng, H. L.; Xu, S. S.; Wang, B. Q. *Chem. Eur. J.* **2011**, *17*, 12573–12577; (i) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353; (j) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457; (k) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551; (l) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736–4740; (m) Zhao, M. N.; Liang, H.; Ren, Z. H.; Guan, Z. H. *Synthesis* **2012**, *44*, 1501–1506; (n) Deb, I.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 4254–4257; (o) Jithunsa, M.; Ueda, M.; Aoi, N.; Sugita, S.; Miyoshi, T.; Miyata, O. *Synlett* **2013**, *24*, 475–478; (p) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328–3331.

(102) (a) Chen, W.; Wilde, R. G.; Seidel, D. *Org. Lett.* 2014, *16*, 730–732; (b) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, *16*, 3556–3559; (c) Qin, Q.; Yu, S. *Org. Lett.* **2014**, *16*, 3504–3507.

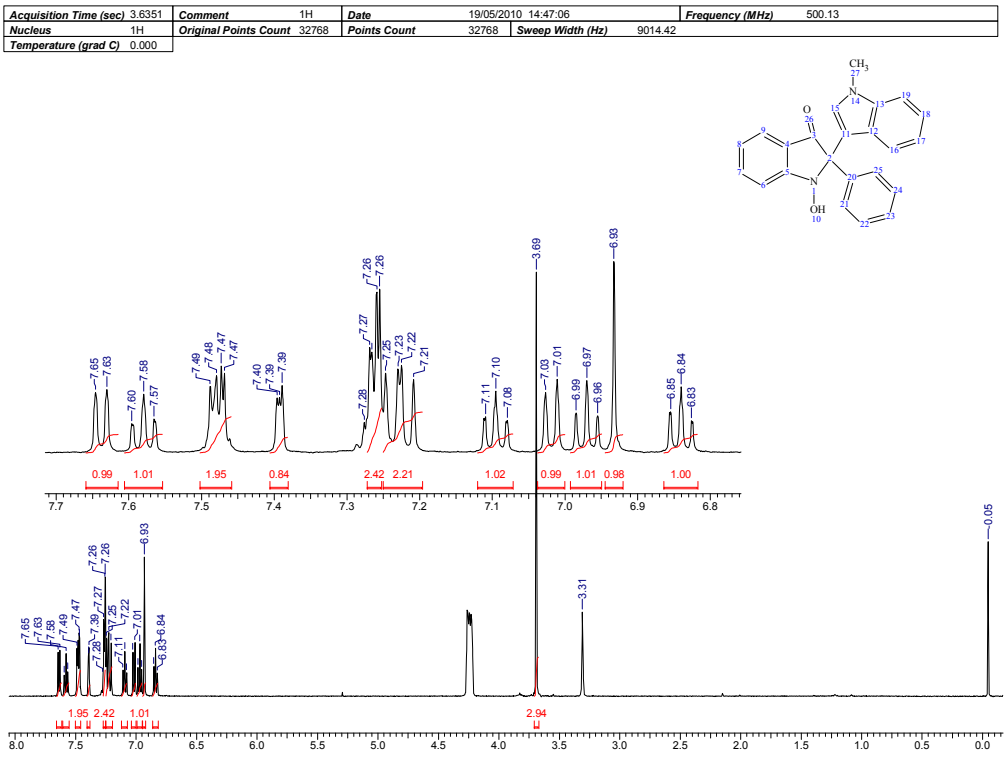
(103) (a) Terai, T.; Nagano, T. *Curr. Opin. Chem. Biol.* **2008**, *12*, 515–521; (b) Matsumoto, S.; Samata, D.; Akazome, M.; Ogura, K. *Tetrahedron Lett.* **2009**, *50*, 111–114; (c) Vendrell, M.; Lee, J. S.; Chang, Y. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 383–389; (d) Lee, J. H.; So, J. H.; Jeon, J. H.; Choi, E. B.; Lee, Y. R.; Chang, Y. T.; Kim, C. H.; Bae, M. A.; Ahn, J. H. *Chem. Commun.* **2011**, *47*, 7500–7502.

(104) **For the leading strategies that address the synthesis of natural product like small molecule libraries see:** (a) C. M. Madsen, M. H. Clausen, *Eur. J. Org. Chem.* **2011**, 3107–3115; (b) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nature Commun.* **2010**, *1*, 80; (c) R. S. Bon, H. Waldmann, *Acc. Chem. Res.* **2010**, *43*, 1103–1114; (d) S. L. Schreiber, *Nature* **2009**, *457*, 153–154; (e) K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2009**, *48*, 3224–3242; (f) T. E. Nielsen, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2008**, *47*, 48–56; (g) R. M. Wilson, S. J. Danishefsky, *Chem. Soc. Rev.* **2007**, *36*, 1207–1226.

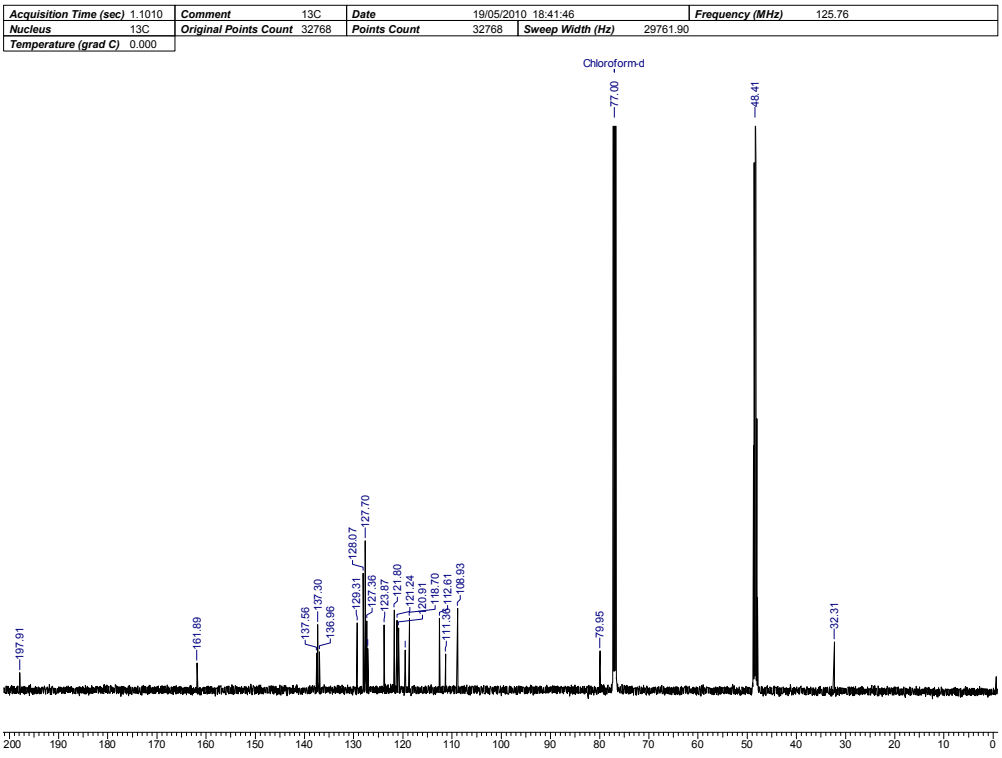
(105) **Medicinally important molecules, pesticides, organic dyes:** (a) Wyrembak, P. N.; Hamilton, A. D. *J. Am. Chem. Soc.* **2009**, *131*, 4566–4567. (b) S. Matsumoto, D. Samata, M. Akazome, K. Ogura, *Tetrahedron. Lett.* **2009**, *50*, 111–114; (c) J. H. Lee, J.-H. So, J. H. Jeon, E. B. Choi, Y.-R. Lee, Y.-T. Chang, C.-H. Kim, M. A. Bae, J. H. Ahn, *Chem. Commun.* **2011**, *47*, 7500–7502.

(106) Yao, C. Z.; Xiao, Z. F.; Liu, J.; Ning, X. S.; Kang, Y. B. *Org. Lett.* **2014**, *16*, 2498–2501.

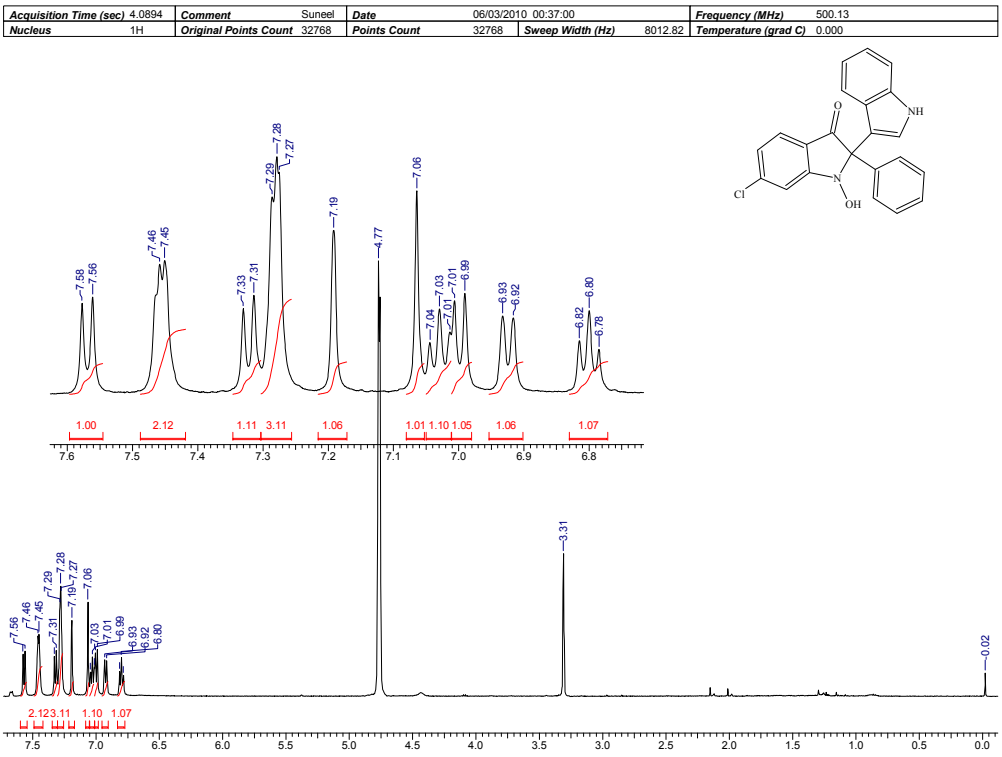
NMR SPECTRA



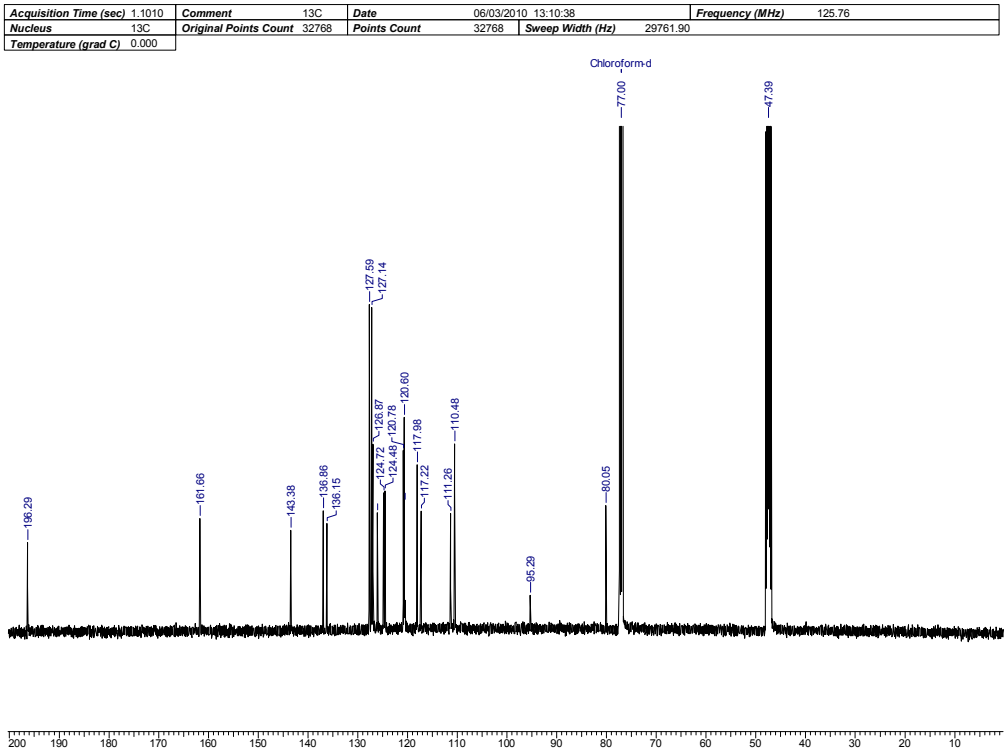
^{1}H NMR Spectrum of 5ab in $CDCl_3$+Methanol-d_4



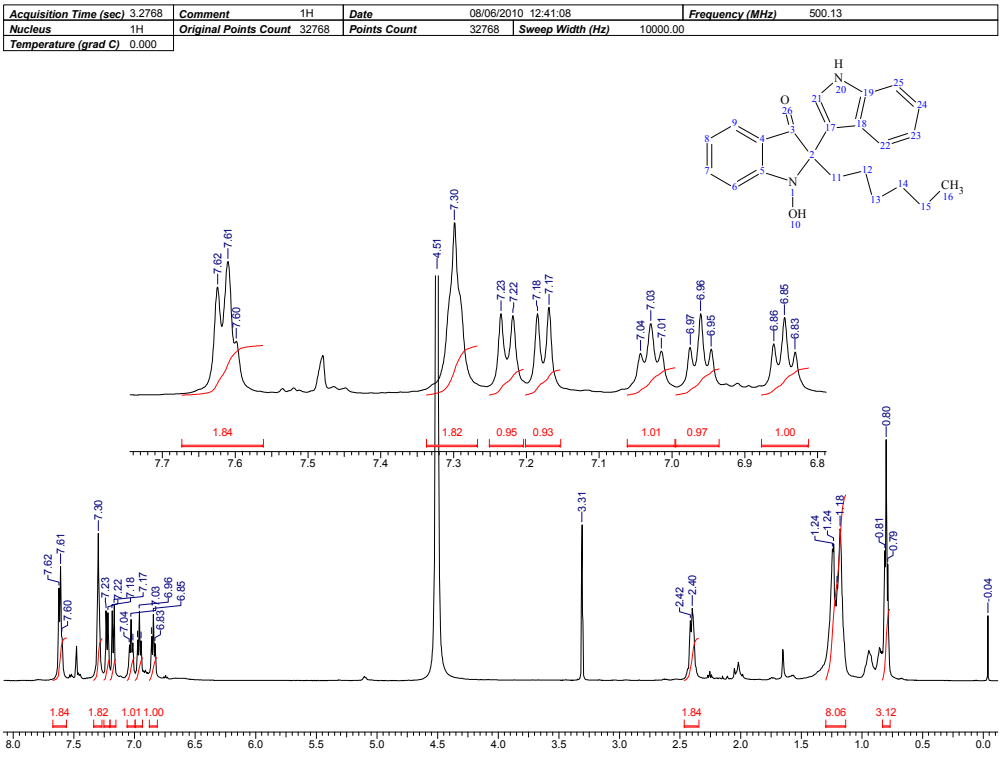
^{13}C NMR Spectrum of 5ab in $CDCl_3$+Methanol-d_4



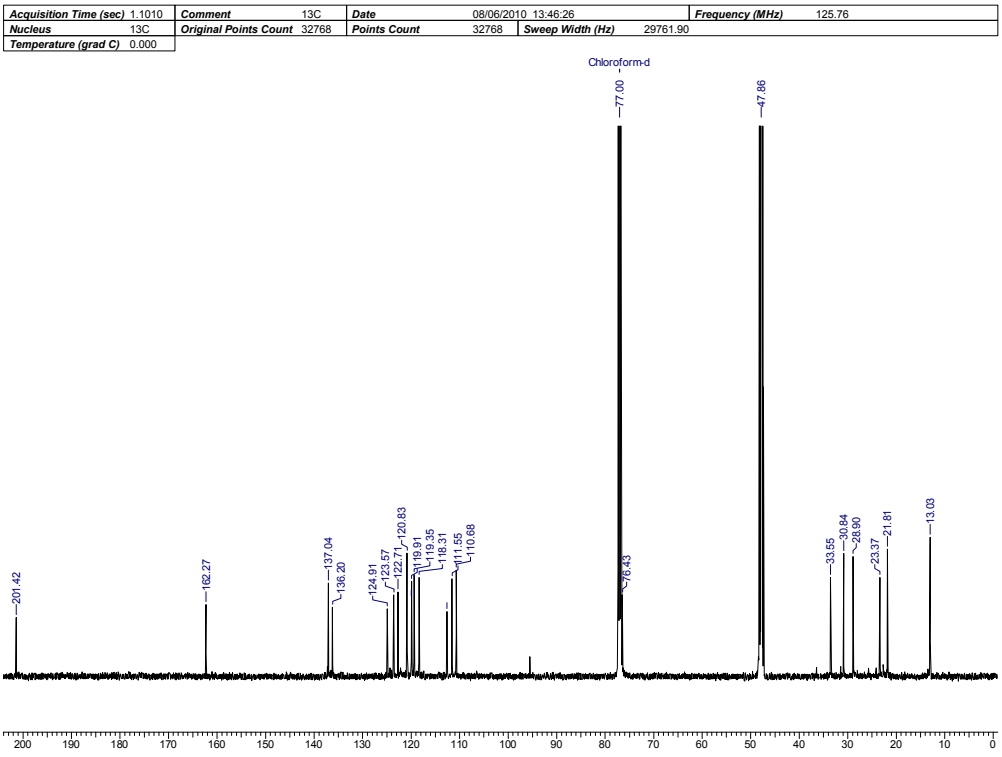
^{1}H NMR Spectrum of 5ca in $CDCl_3$+Methanol-d_4



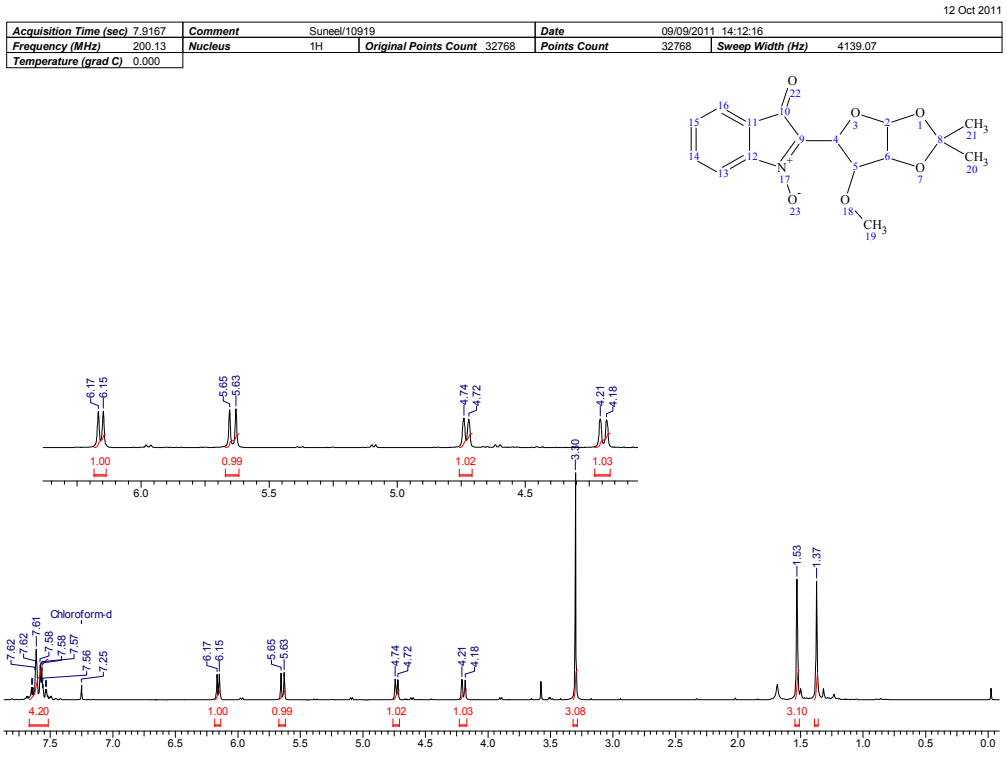
^{13}C NMR Spectrum of 5ca in $CDCl_3$+Methanol-d_4



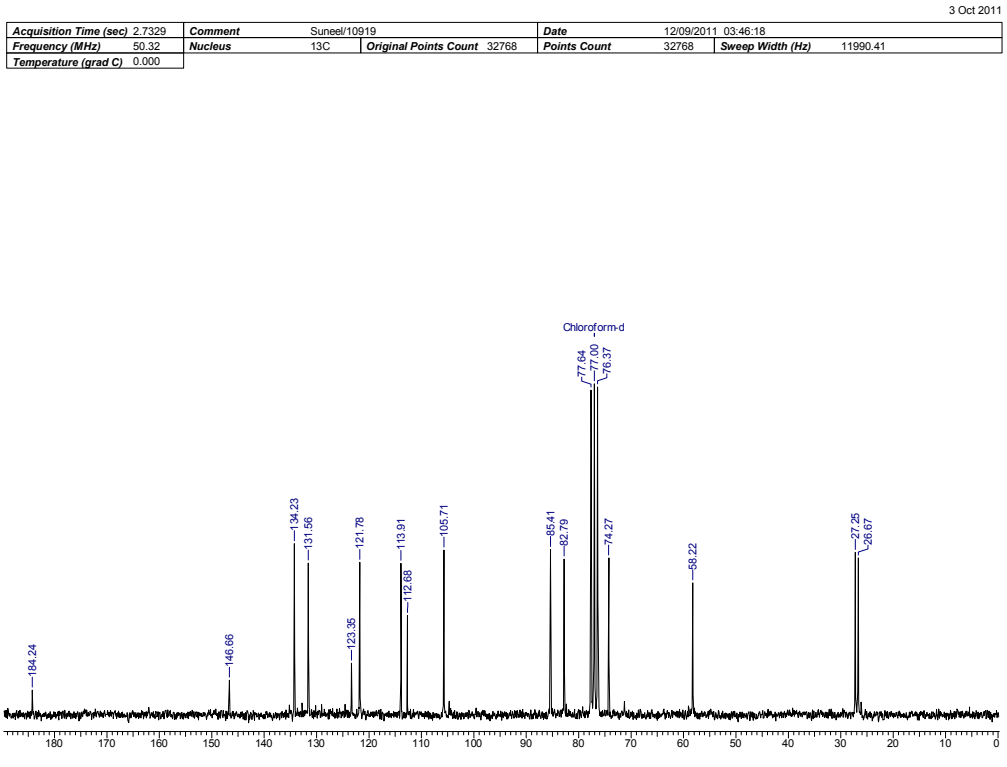
^{1}H NMR Spectrum of 5ea in $CDCl_3$+Methanol-d_4



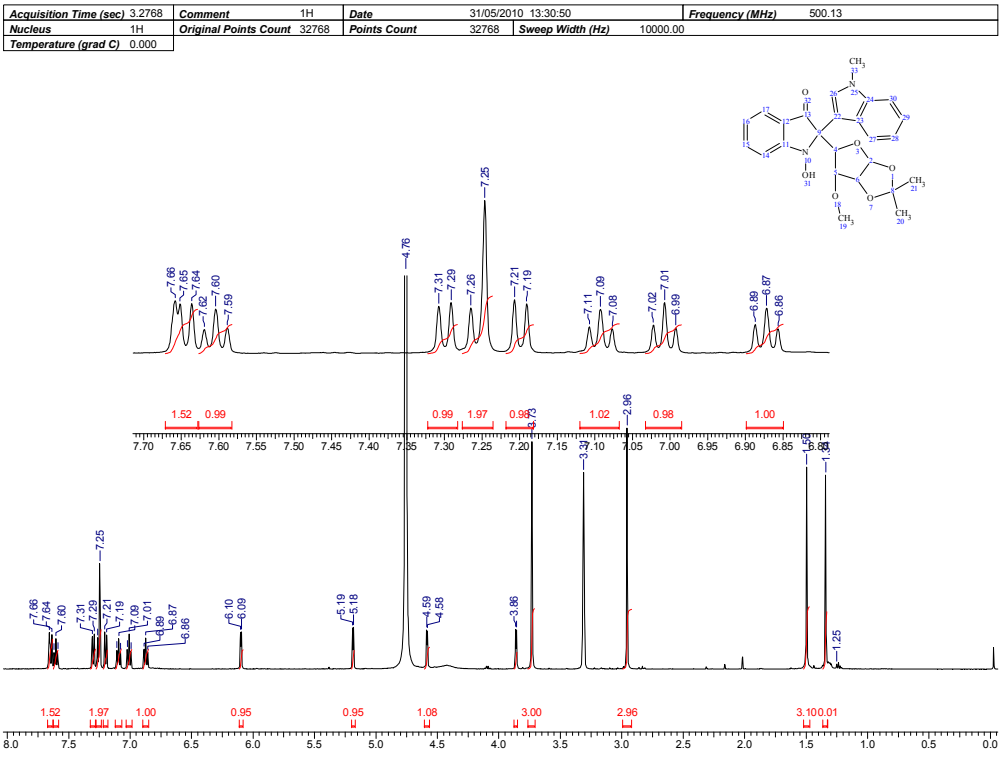
^{13}C NMR Spectrum of 5ea in $CDCl_3$+Methanol-d_4



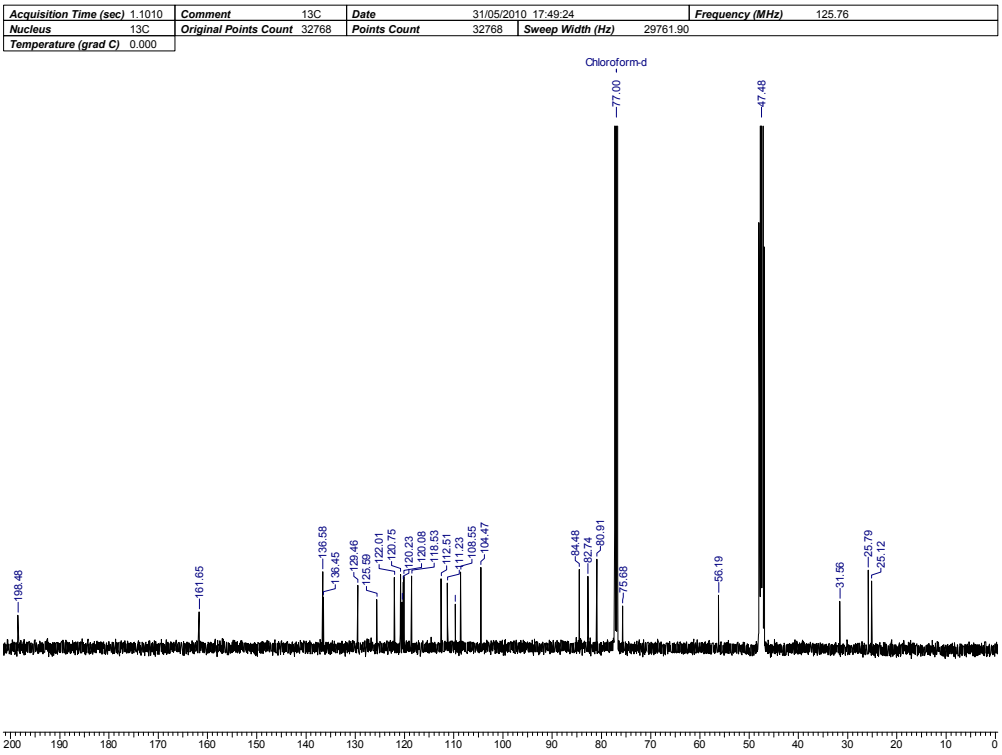
^{1}H NMR Spectrum of 3f in $CDCl_3$



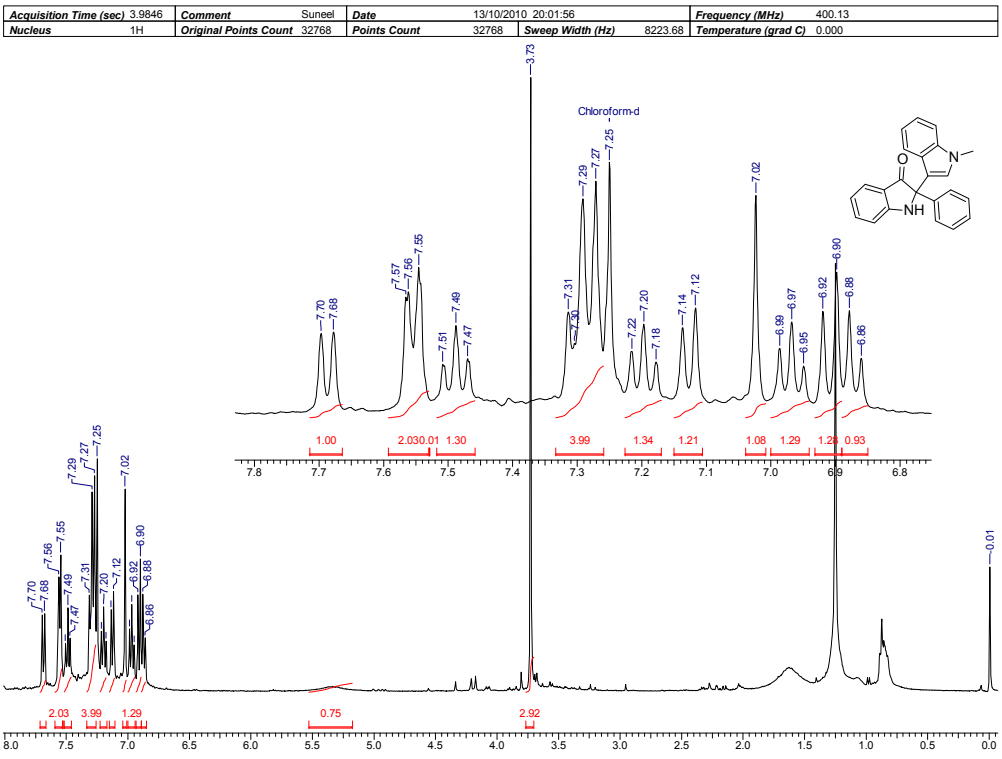
^{13}C NMR Spectrum of 3f in $CDCl_3$



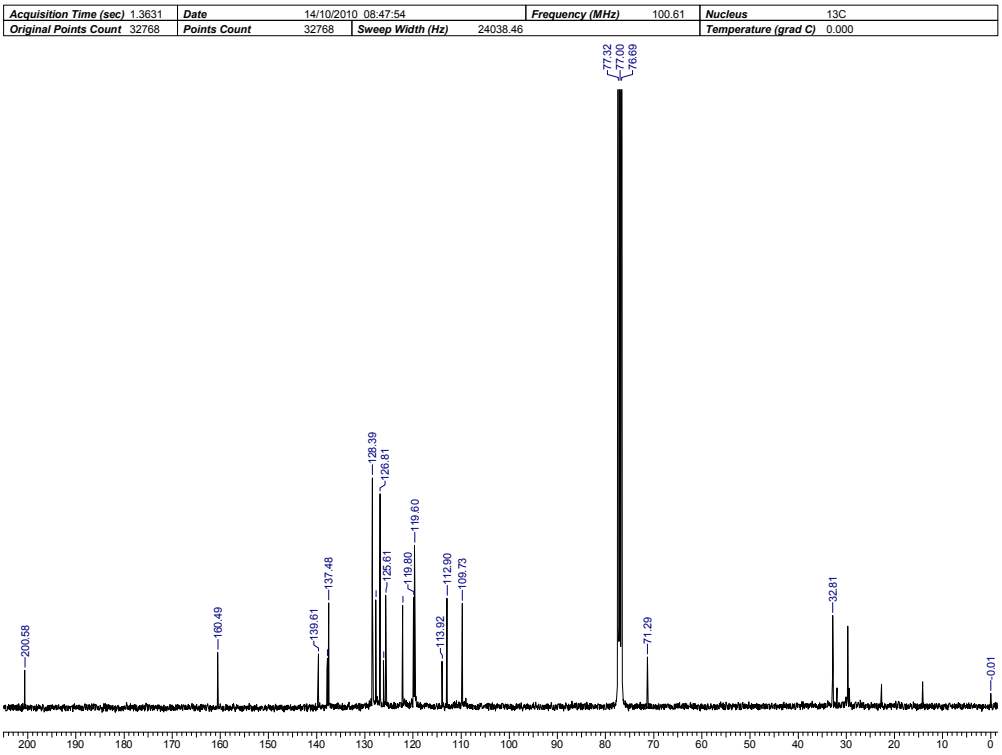
^{1}H NMR Spectrum of 5fb in $CDCl_3$+Methanol-d_4



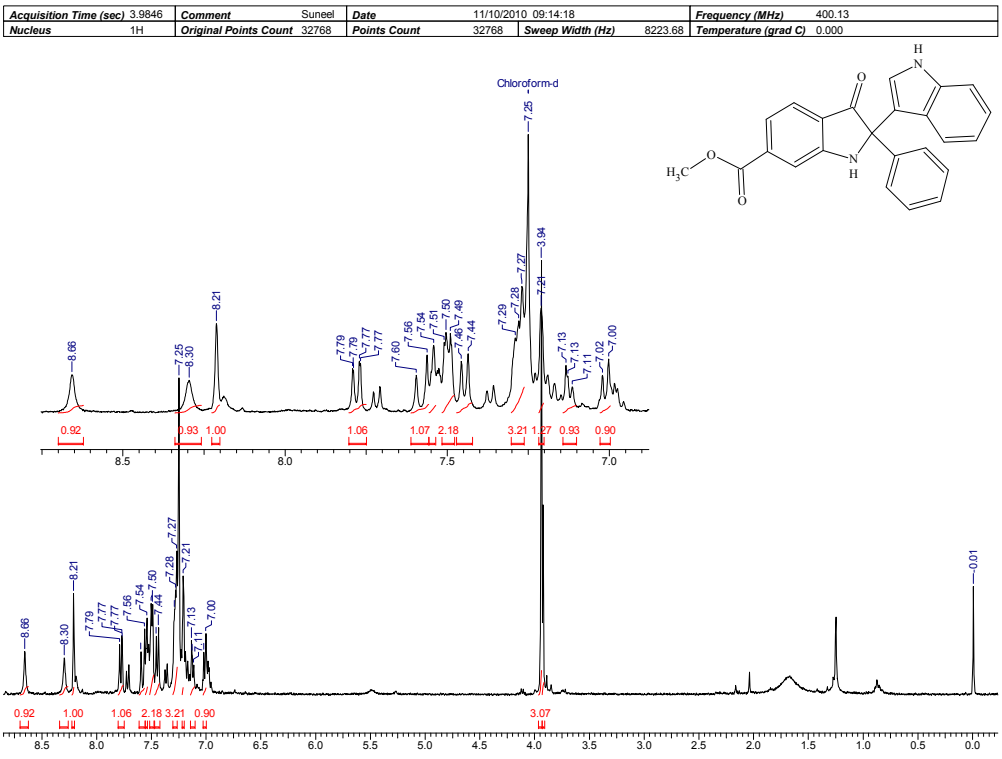
^{13}C NMR Spectrum of 5fb in $CDCl_3$+Methanol-d_4



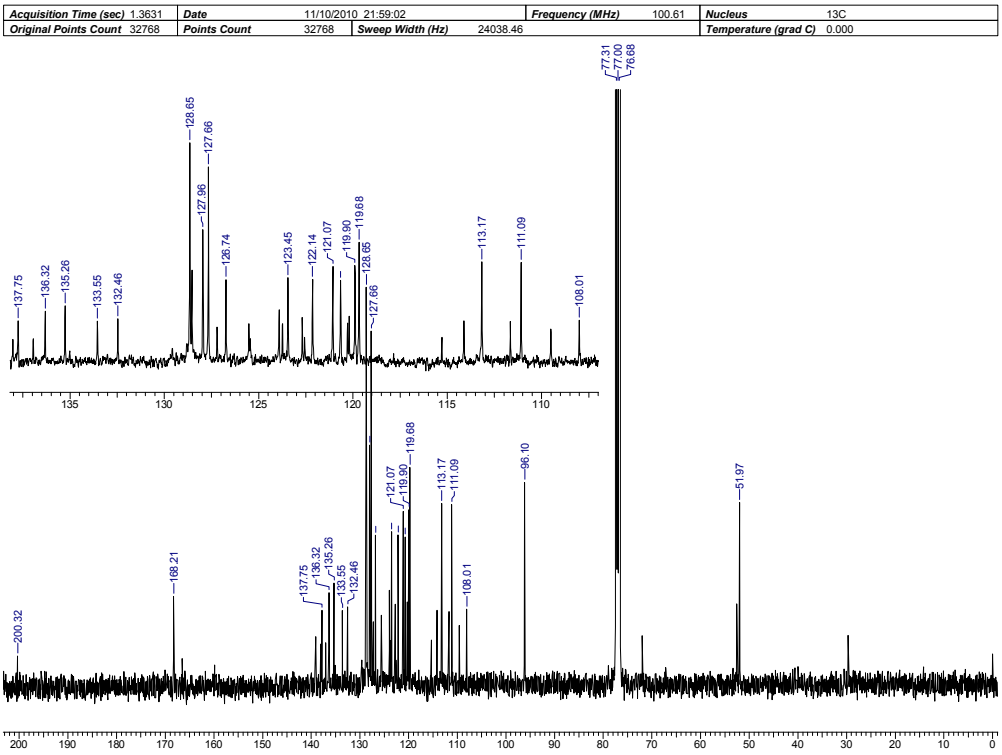
^{1}H NMR Spectrum of 6ab in $CDCl_3$



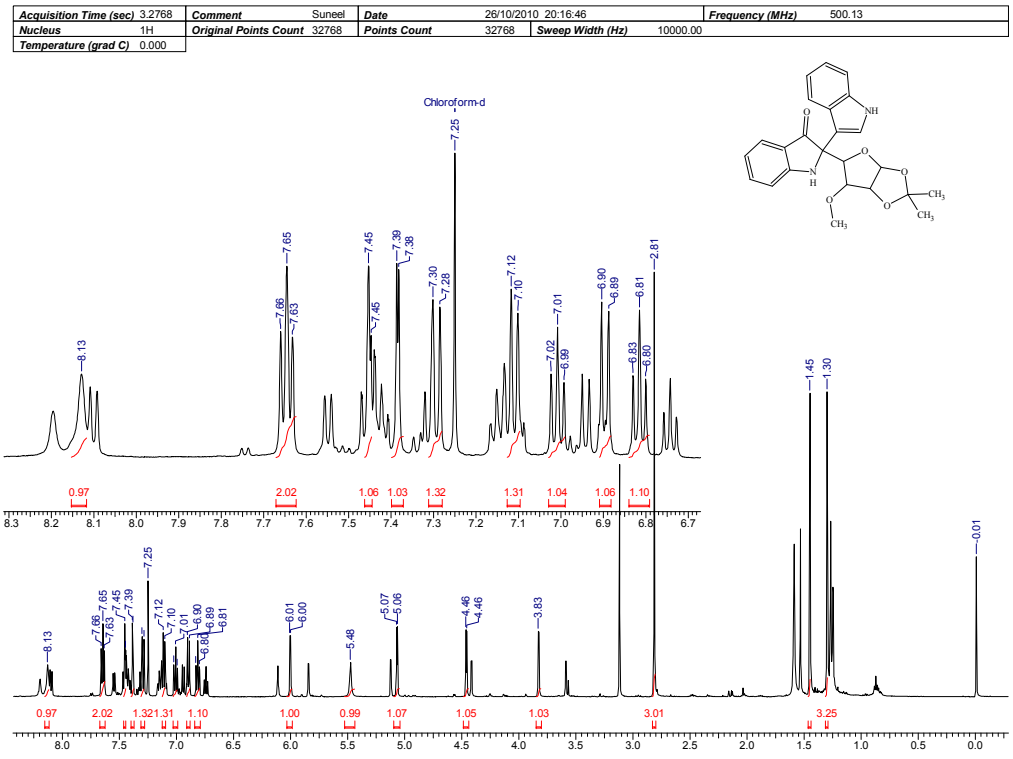
^{13}C NMR Spectrum of 6ab in $CDCl_3$



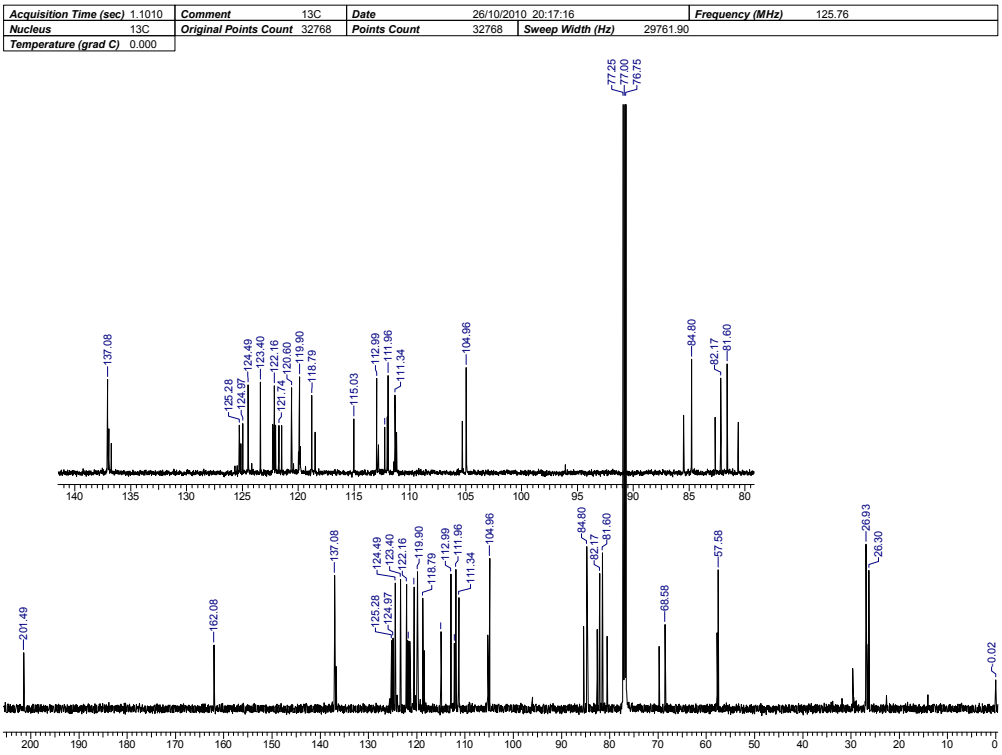
^{1}H NMR Spectrum of 6da+7da in $CDCl_3$



^{13}C NMR Spectrum of 6da+7da in $CDCl_3$

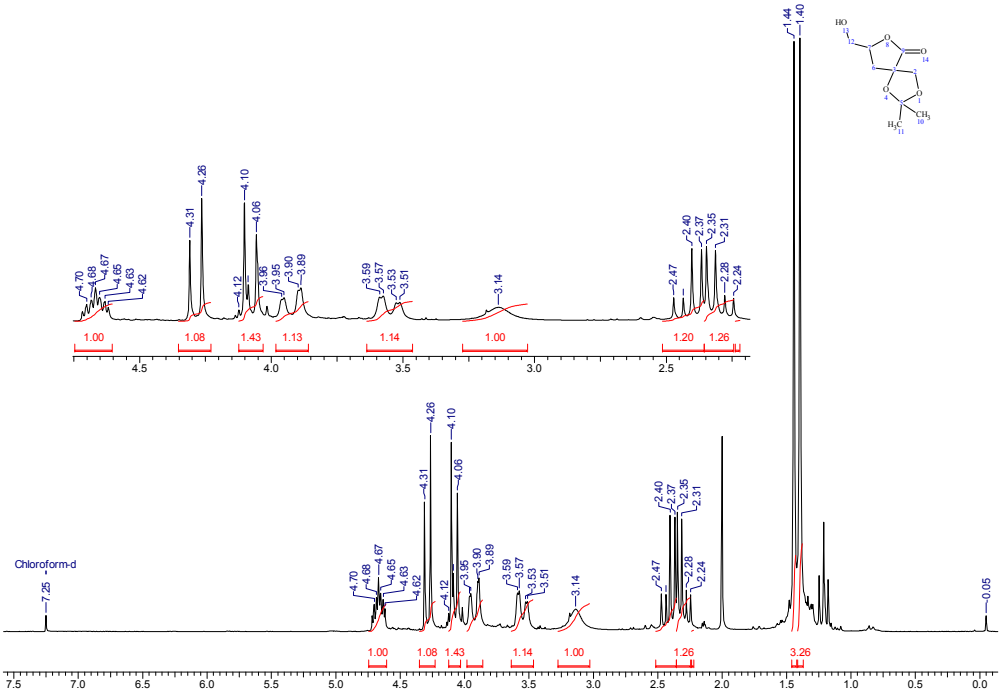


^{1}H NMR Spectrum of 6fa in $CDCl_3$



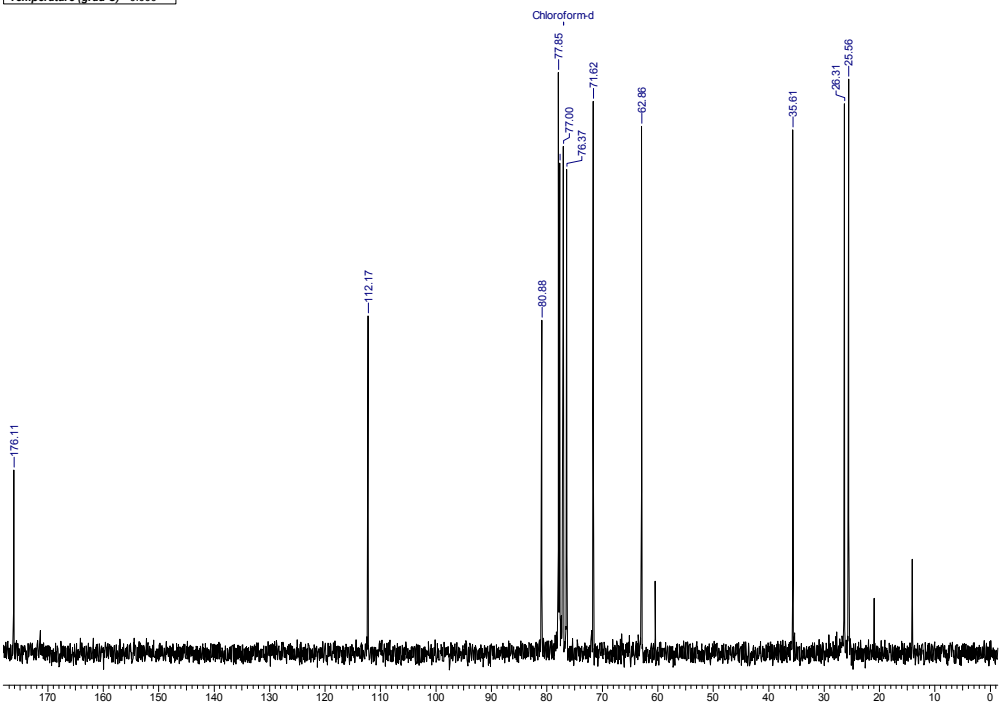
^{13}C NMR Spectrum of 6fa in $CDCl_3$

Acquisition Time (sec)	7.9167	Comment	Suneel	Date	24/02/2010 10:07:52		Frequency (MHz)	200.13
Nucleus	1H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	4139.07	Temperature (grad C)	0.000



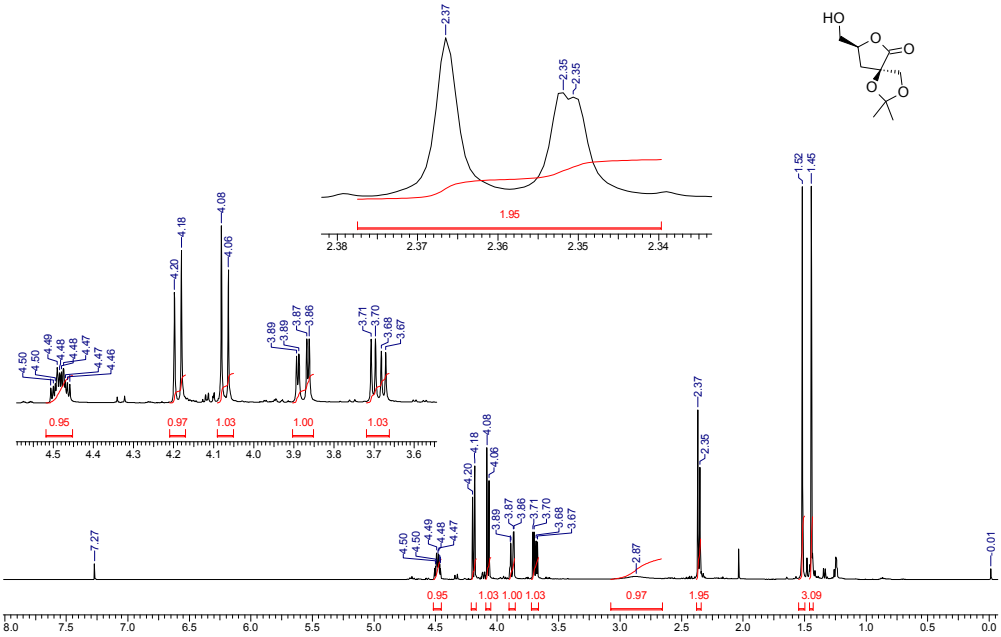
^{1}H NMR Spectrum of 14 in $CDCl_3$

Acquisition Time (sec)	2.7329	Comment	Suneel	Date	01/03/2010 02:52:46		Frequency (MHz)	50.32
Nucleus	13C	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	11990.41	
Temperature (grad C)	0.000							



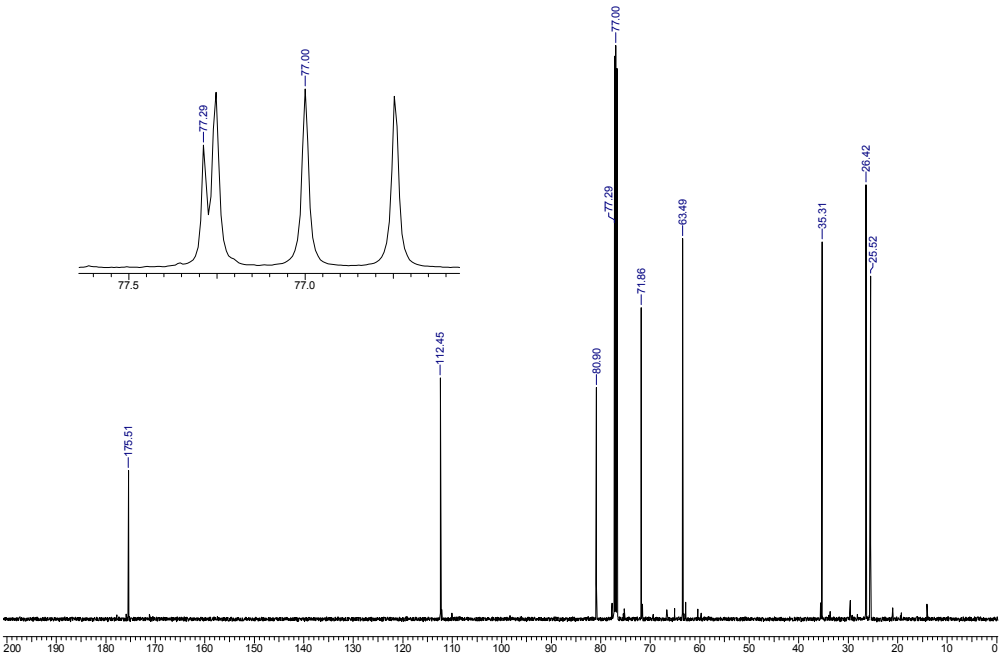
^{13}C NMR Spectrum of 14 in $CDCl_3$

Acquisition Time (sec)	1.6384	*Comment*	Suneel 10919 1H			*Date*	16 Jul 2010 09:30:08
Frequency (MHz)	500.13	*Nucleus*	1H	*Number of Transients*	64	*Original Points Count*	16384
Points Count	32768	*Solvent*	CHLOROFORM-d	*Sweep Width (Hz)*	9999.70	*Temperature (grad C)*	22.200

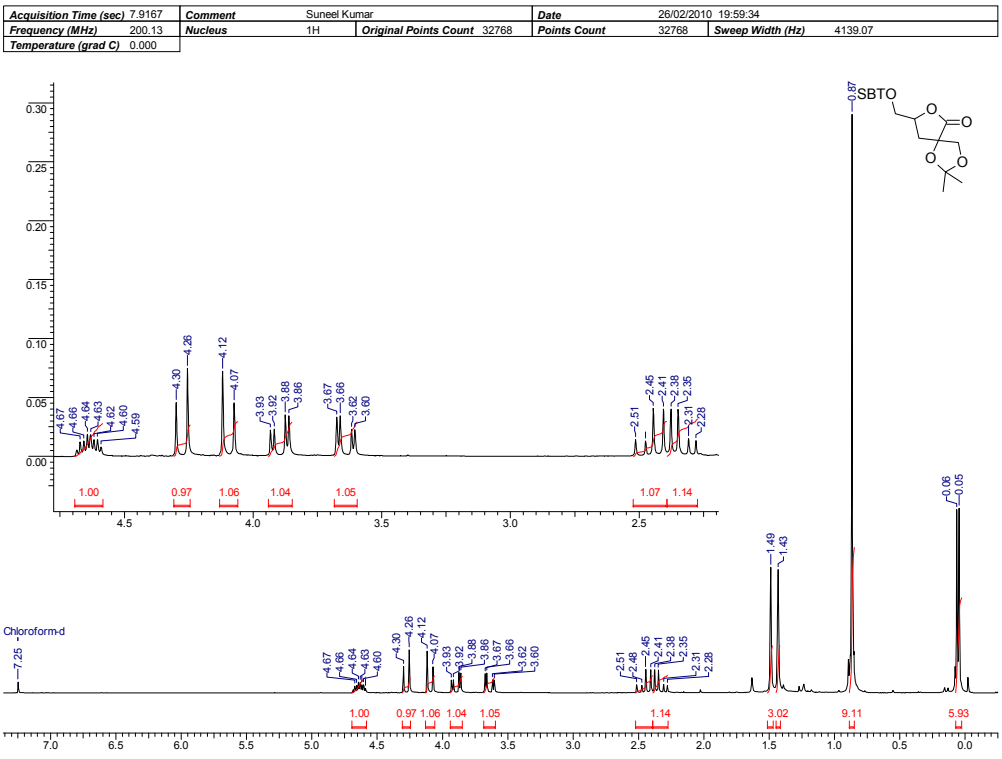


^{1}H NMR Spectrum of 15 in $CDCl_3$

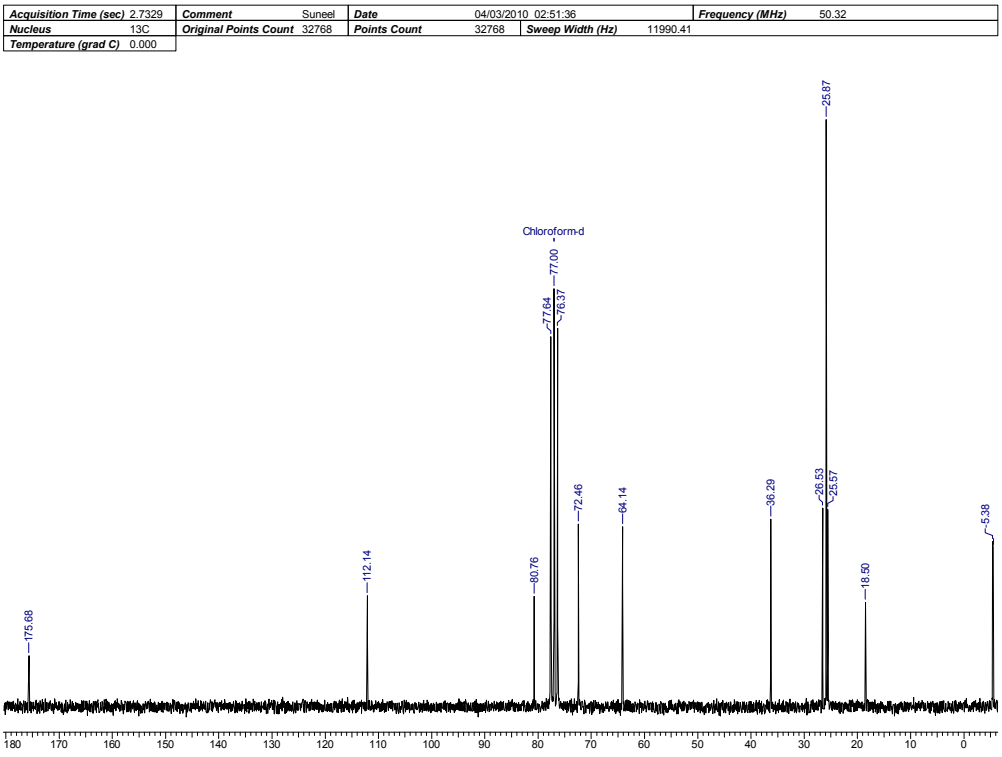
Acquisition Time (sec)	1.1010	*Comment*	13C	*Date*	16 Jul 2010 10:53:20	*Frequency (MHz)*	125.76
Nucleus	13C	*Number of Transients*	930	*Original Points Count*	32768	*Points Count*	32768
Solvent	CHLOROFORM-d	*Sweep Width (Hz)*	29761.00	*Temperature (grad C)*	22.900		



^{13}C NMR Spectrum of 15 in $CDCl_3$

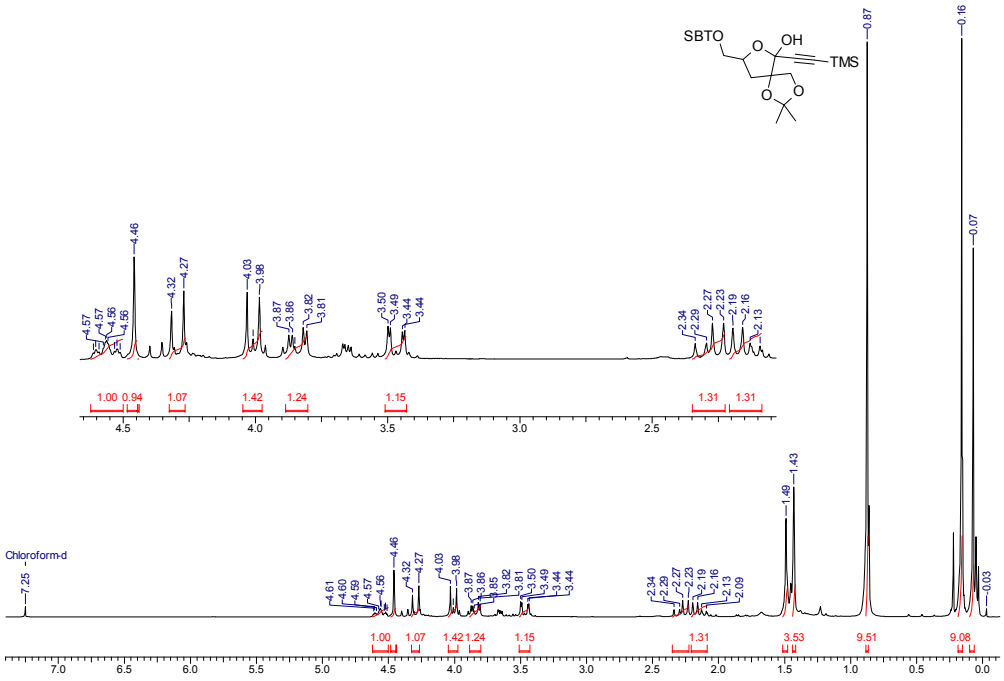


^{1}H NMR Spectrum of 16 in $CDCl_3$



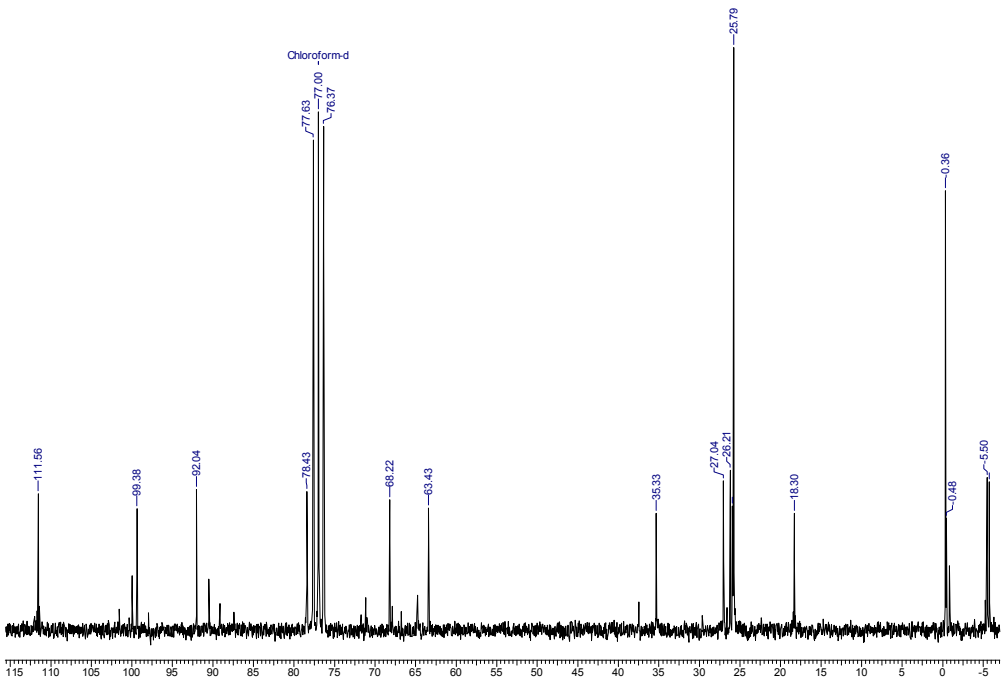
^{13}C NMR Spectrum of 16 in $CDCl_3$

Acquisition Time (sec)	7.9167	Comment	Suneel/10919		Date	28/04/2010 19:30:58	
Frequency (MHz)	200.13	Nucleus	1H	Original Points Count 32768	Points Count	32768	Sweep Width (Hz) 4139.07
Temperature (grad C)	0.000						



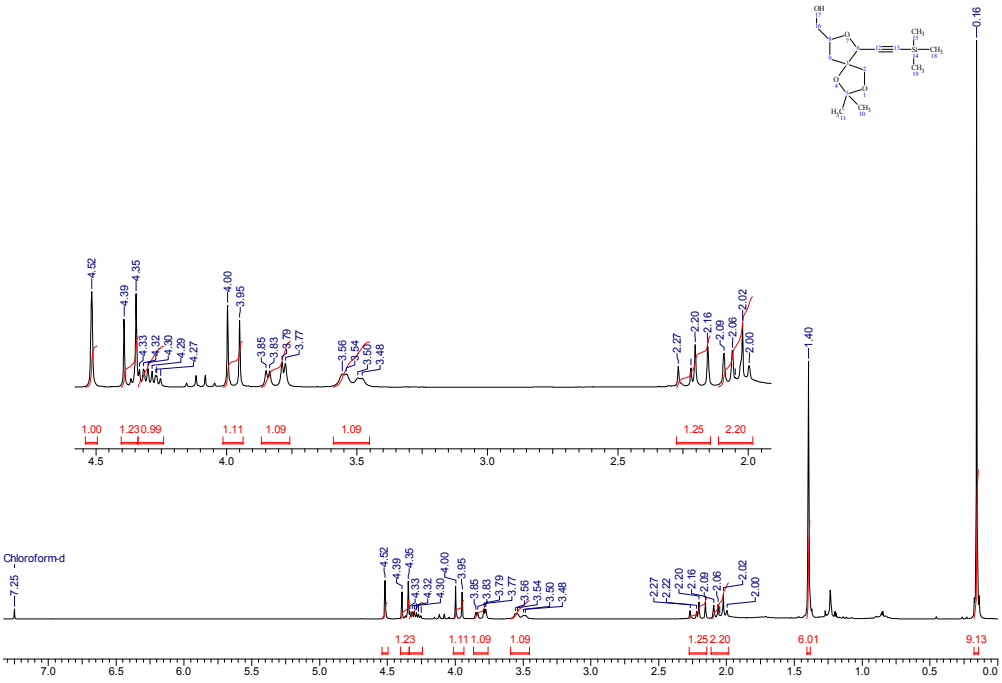
^{1}H NMR Spectrum of 17 in $CDCl_3$

Acquisition Time (sec)	2.7329	Comment	Suneel/10919		Date	02/05/2010 18:40:42	
Frequency (MHz)	50.32	Nucleus	13C	Original Points Count 32768	Points Count	32768	Sweep Width (Hz) 11990.41
Temperature (grad C)	0.000						



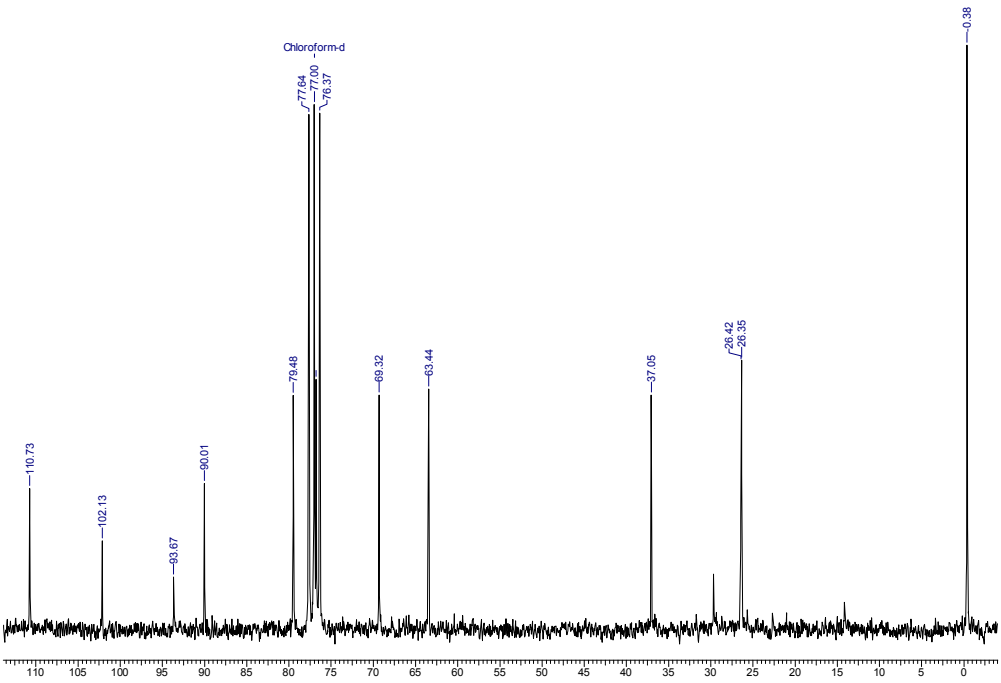
^{13}C NMR Spectrum of 17 in $CDCl_3$

Acquisition Time (sec)	7.9167	Comment	Suneel/10919		Date	18/06/2010 18:07:36	
Frequency (MHz)	200.13	Nucleus	1H	Original Points Count 32768	Points Count	32768	Sweep Width (Hz) 4139.07
Temperature (grad C)	0.000						

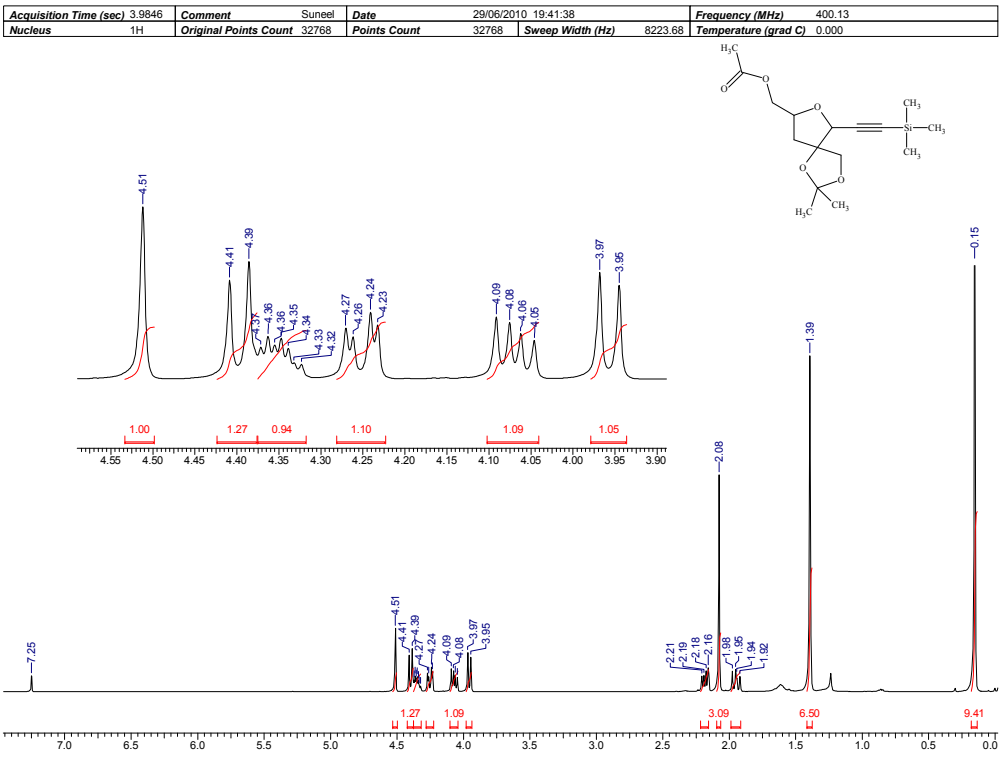


^{1}H NMR Spectrum of 18 in $CDCl_3$

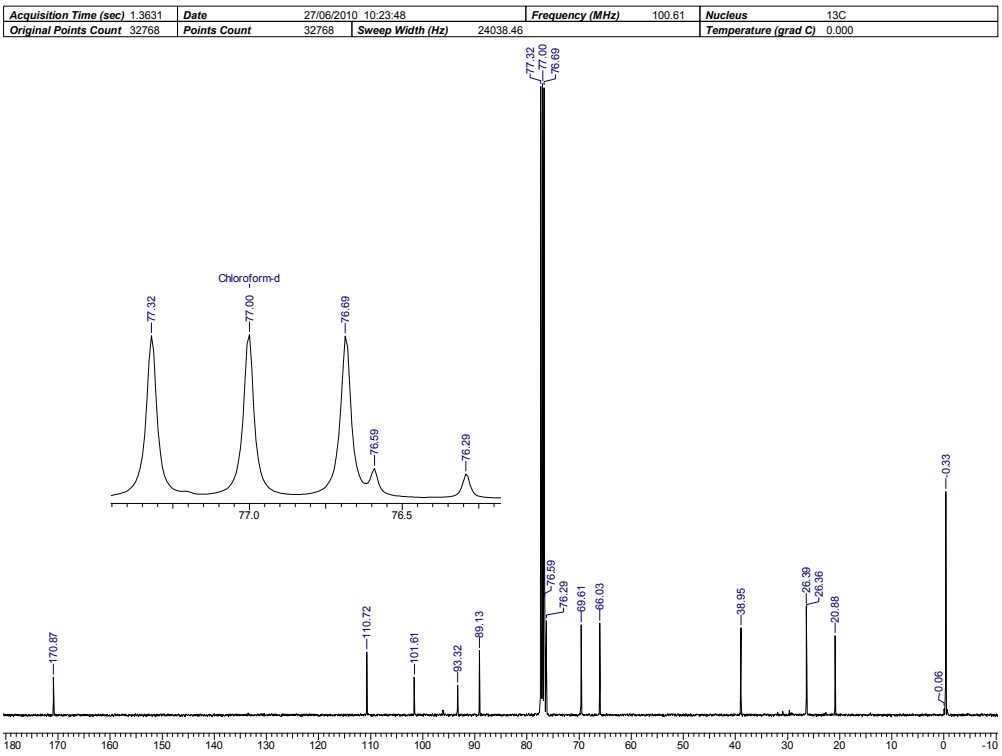
Acquisition Time (sec)	2.7329	Comment	Suneel/10919		Date	24/06/2010 21:07:24	
Frequency (MHz)	50.32	Nucleus	13C	Original Points Count 32768	Points Count	32768	Sweep Width (Hz) 11990.41
Temperature (grad C)	0.000						



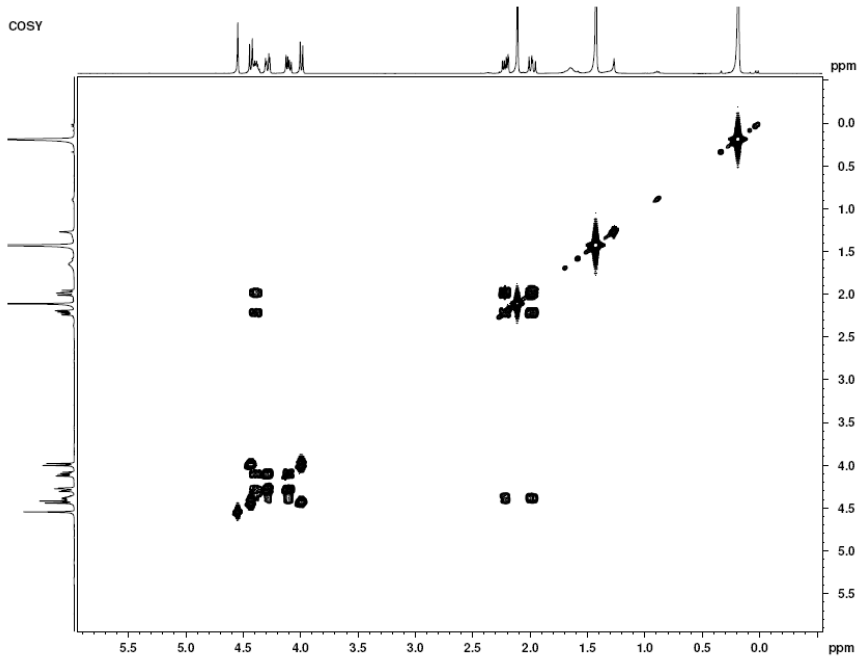
^{13}C NMR Spectrum of 18 in $CDCl_3$



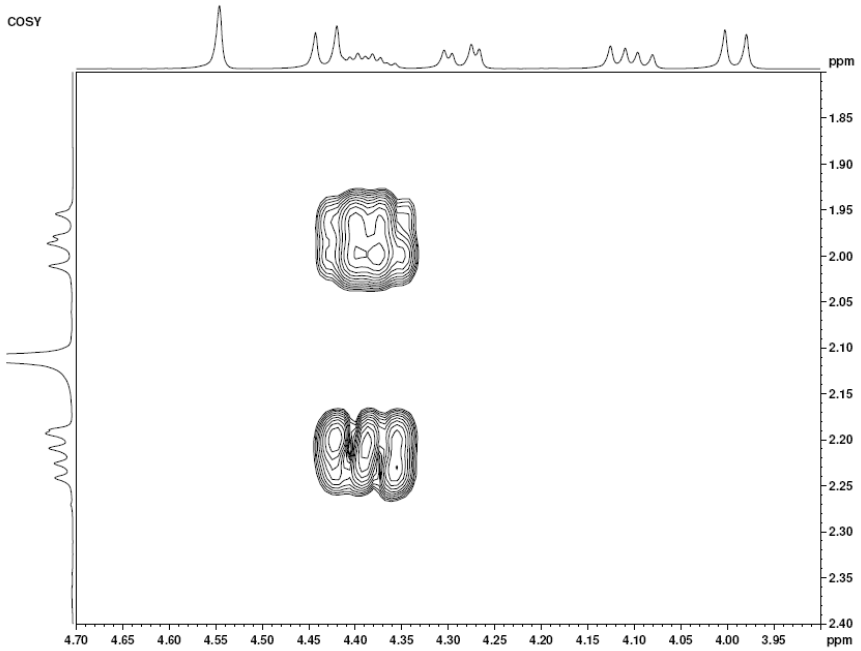
^{1}H NMR Spectrum of 18-Ac in $CDCl_3$



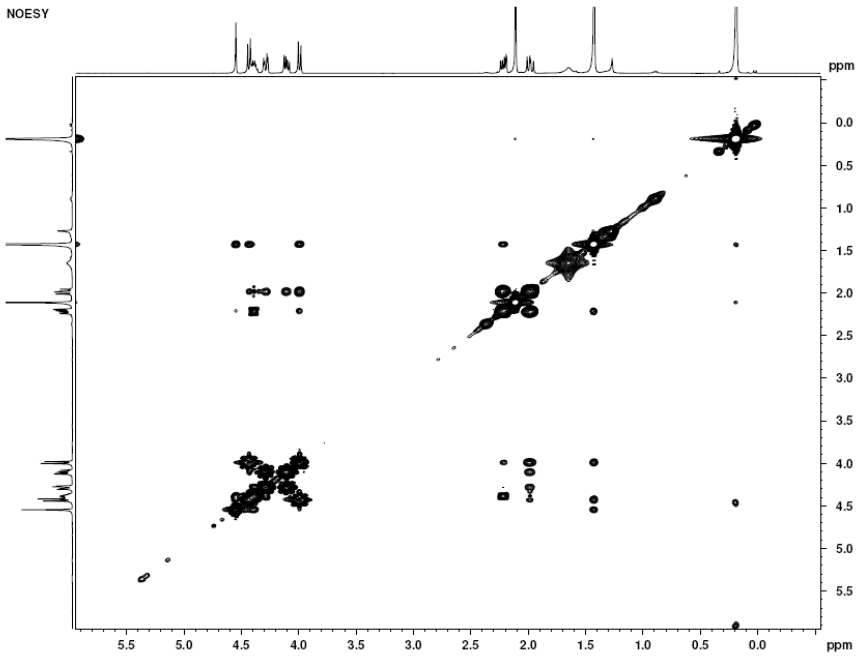
^{13}C NMR Spectrum of 18-Ac in $CDCl_3$



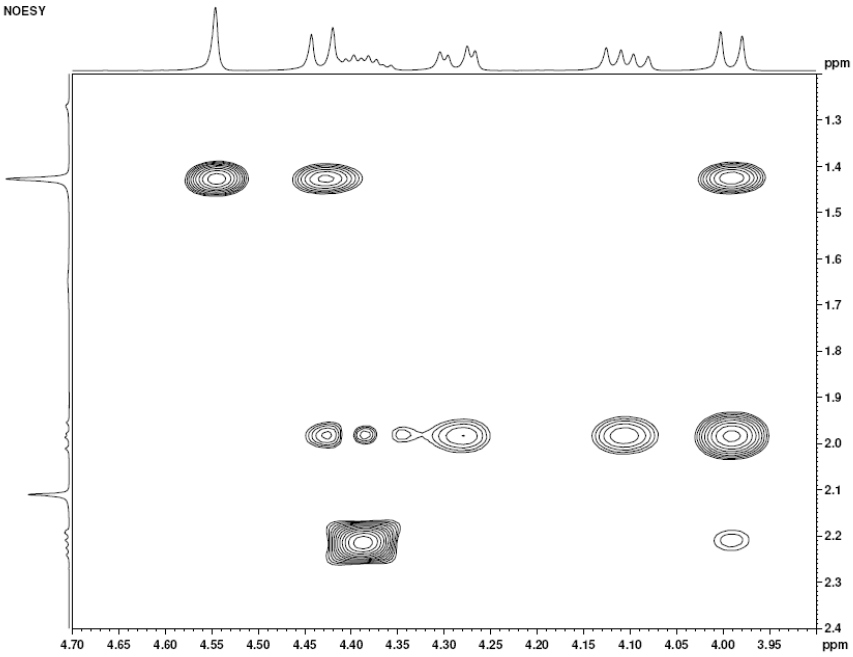
COSY Spectrum of 18-Ac in $CDCl_3$



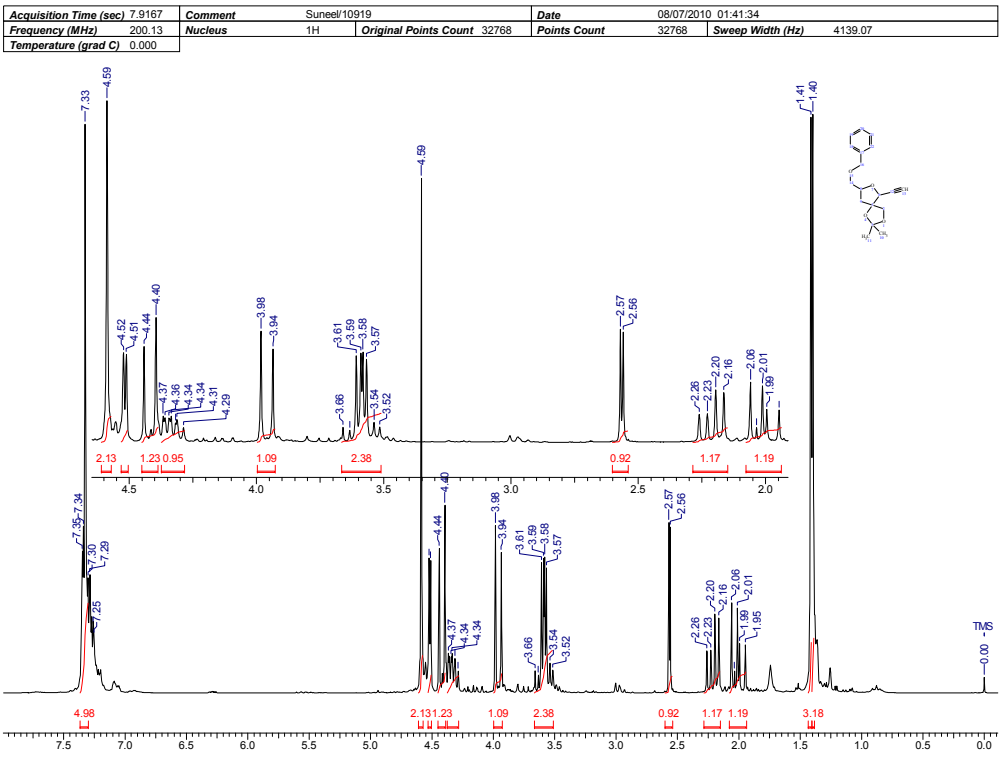
COSY Spectrum of 18-Ac in $CDCl_3$



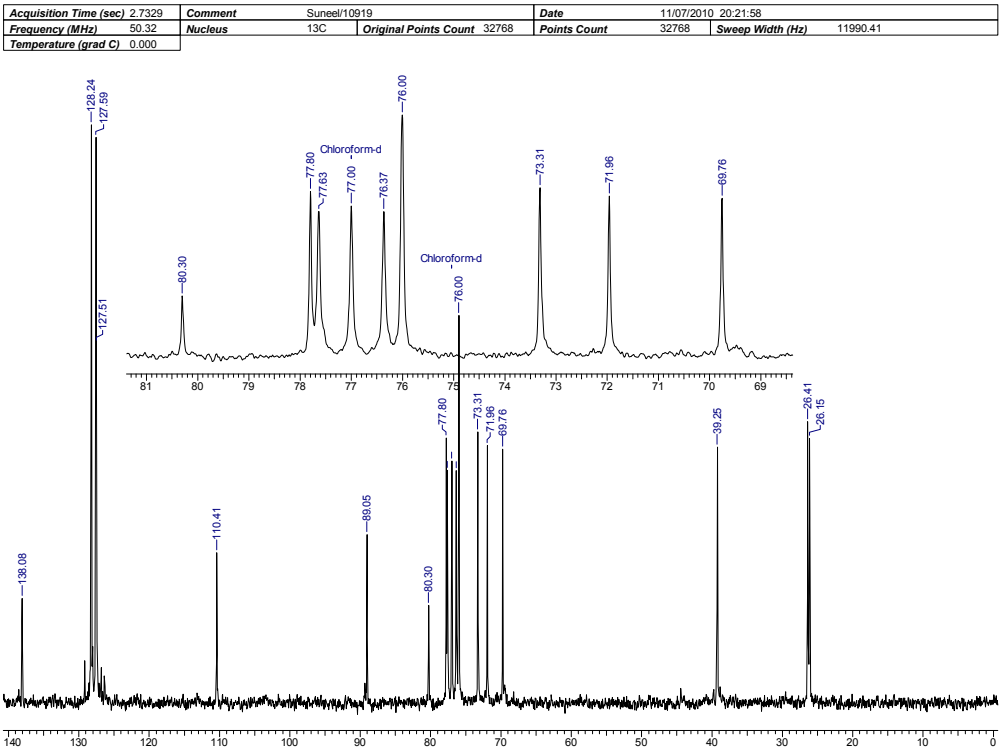
NOESY Spectrum of 18-Ac in $CDCl_3$



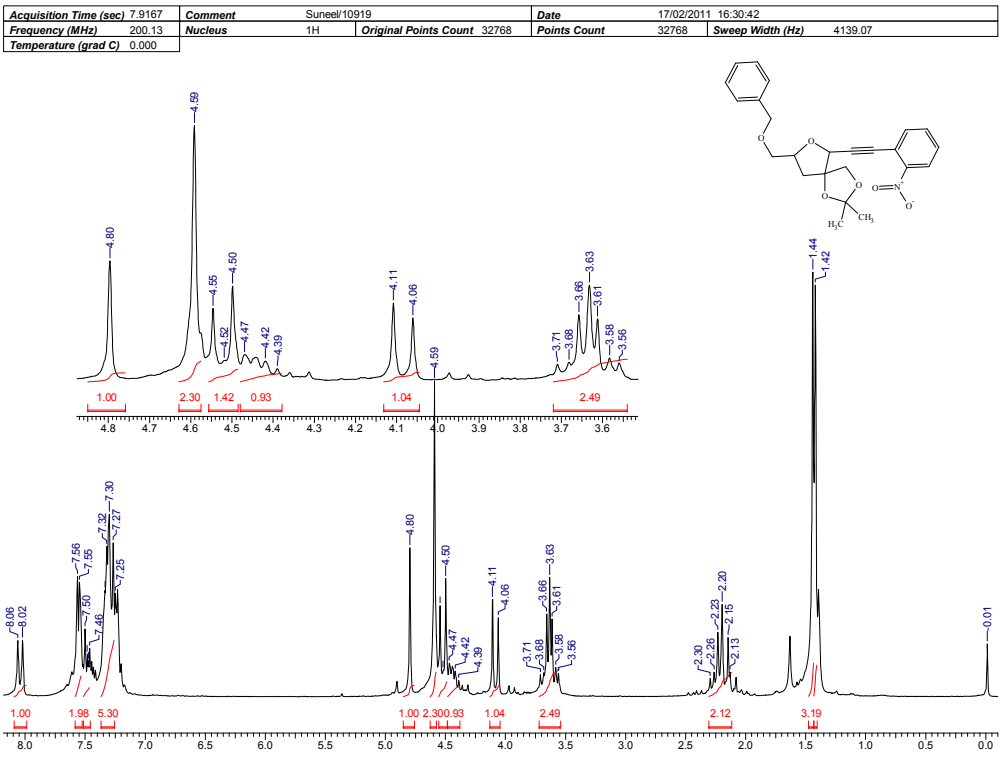
NOESY Spectrum of 18-Ac in $CDCl_3$



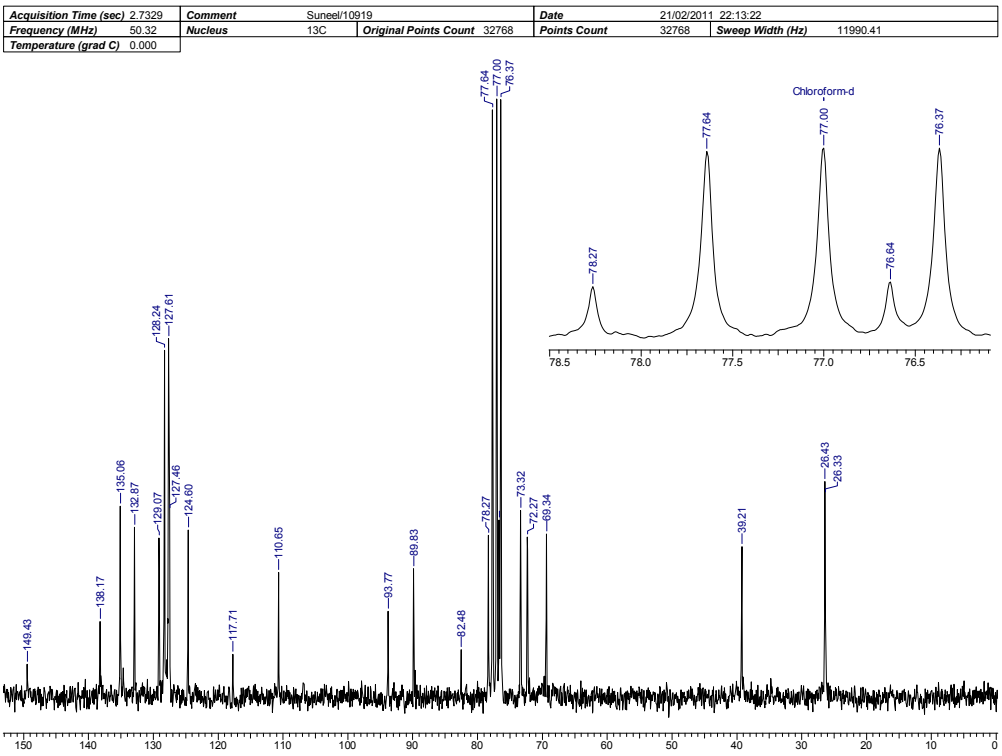
^{1}H NMR Spectrum of 12 in $CDCl_3$



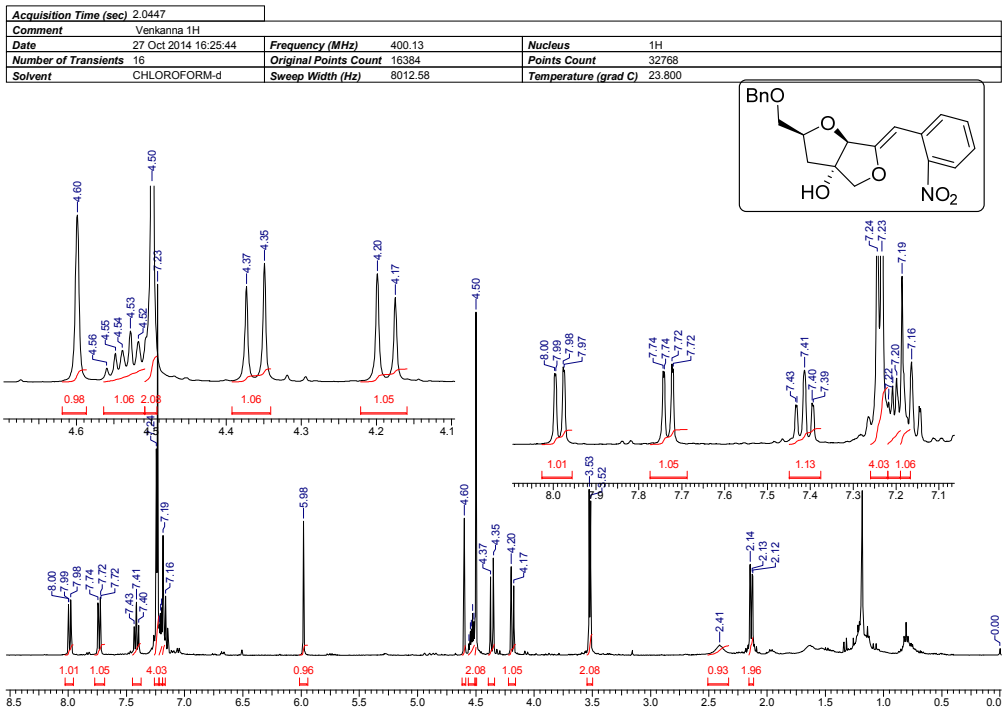
^{13}C NMR Spectrum of 12 in $CDCl_3$



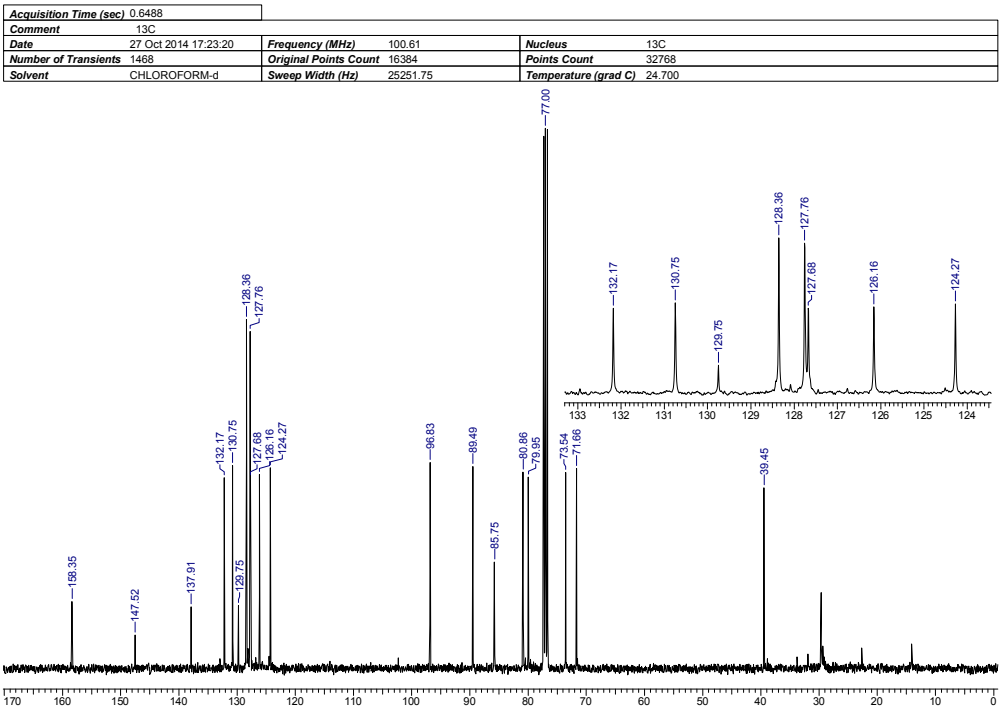
^{1}H NMR Spectrum of 11 in $CDCl_3$



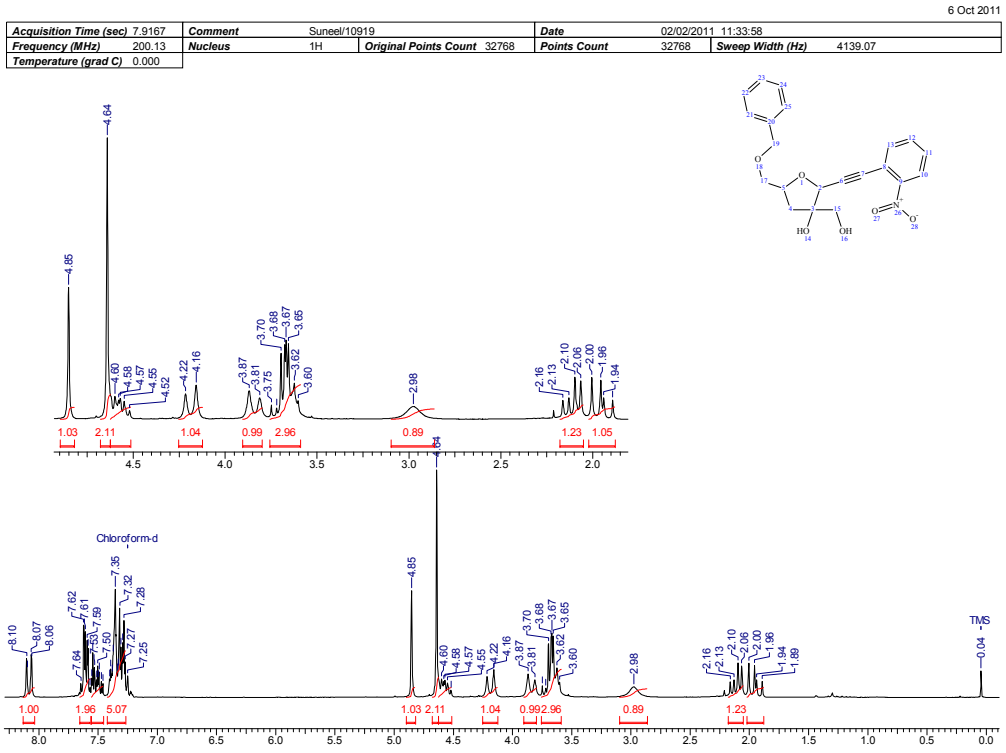
^{13}C NMR Spectrum of 11 in $CDCl_3$



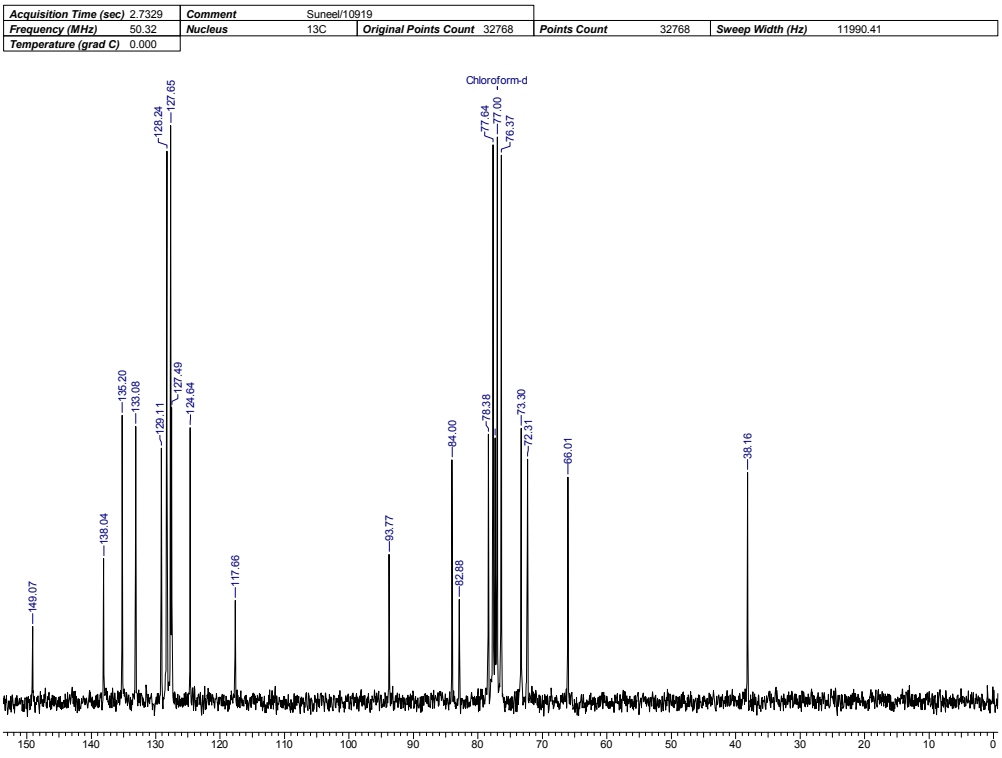
^{1}H NMR Spectrum of 19 in $CDCl_3$



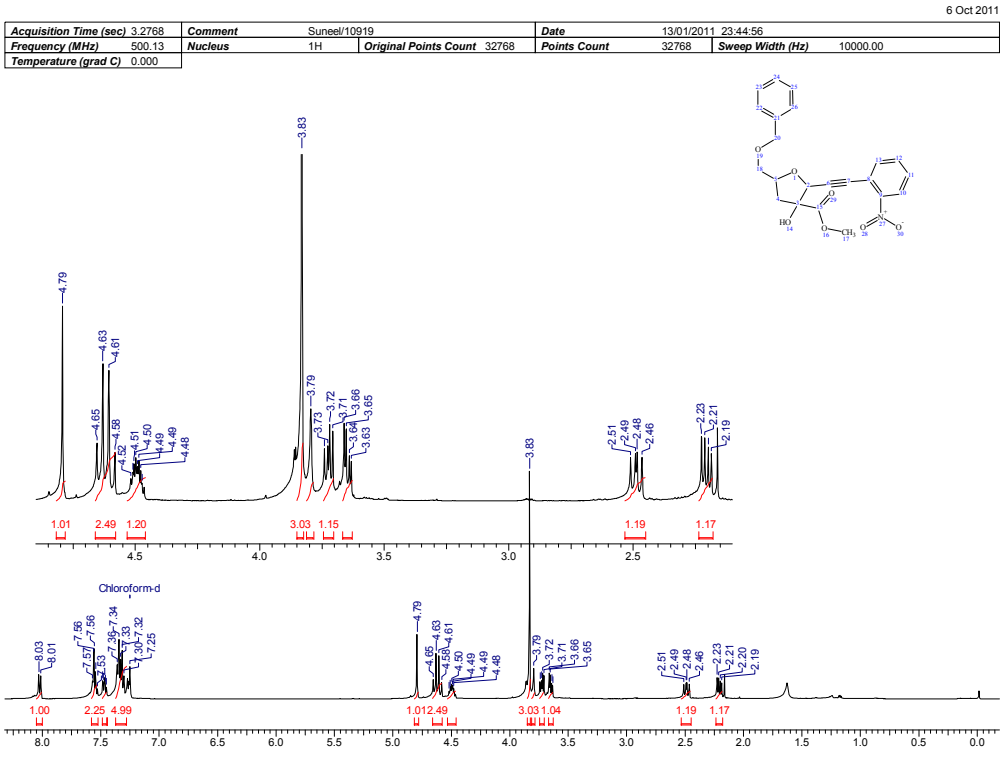
^{13}C NMR Spectrum of 19 in $CDCl_3$



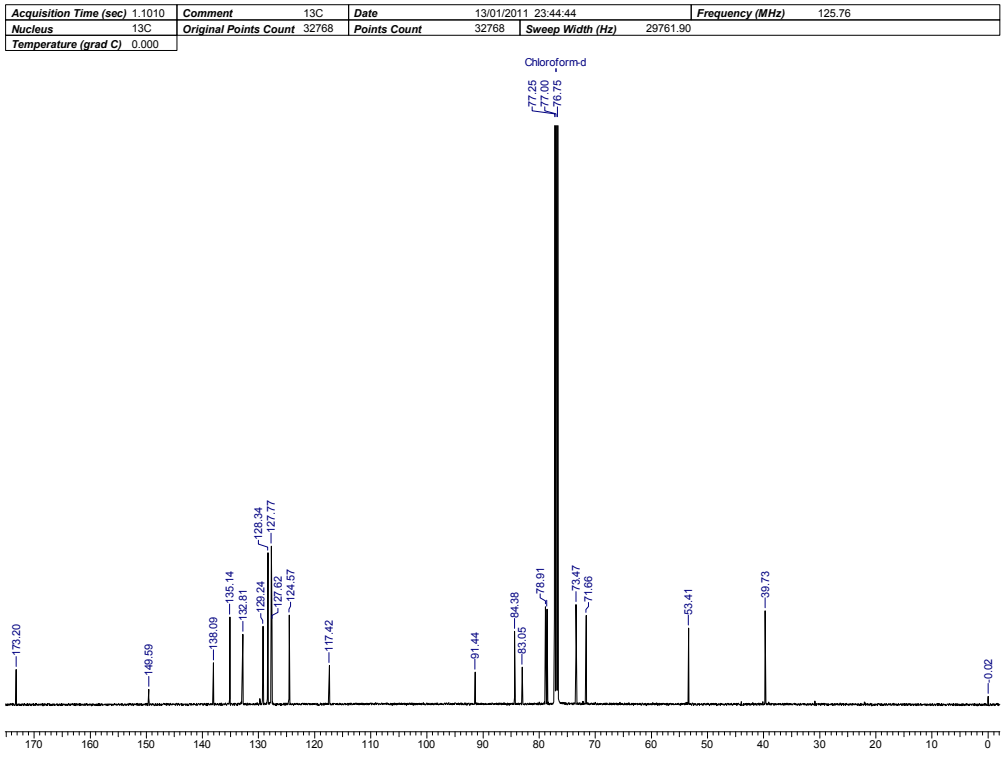
^{1}H NMR Spectrum of 20 in $CDCl_3$



^{13}C NMR Spectrum of 20 in $CDCl_3$

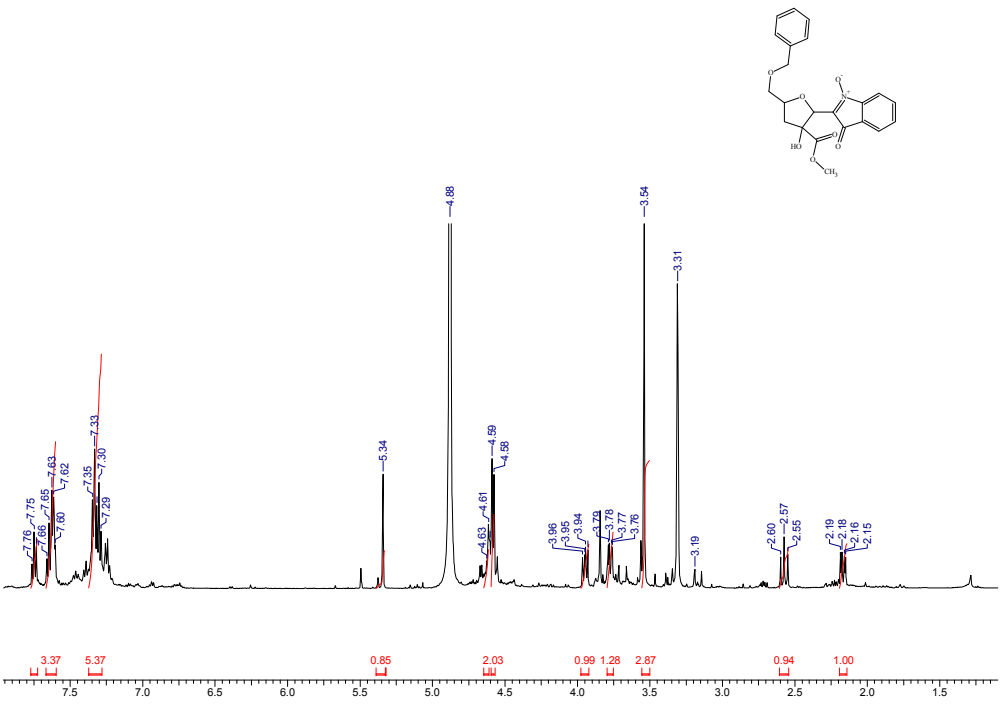


^{1}H NMR Spectrum of 24 in $CDCl_3$



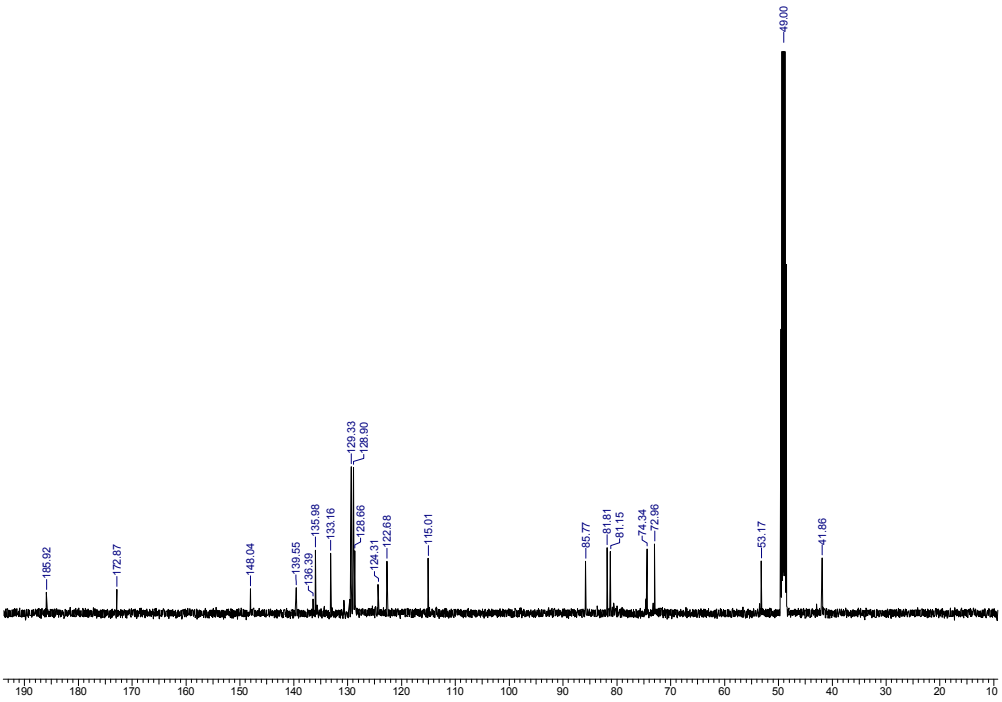
^{13}C NMR Spectrum of 24 in $CDCl_3$

Acquisition Time (sec)	3.2768	Comment	1H	Date	27/05/2011 16:34:26	Frequency (MHz)	500.13
Nucleus	1H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	10000.00
Temperature (grad C)	0.000						

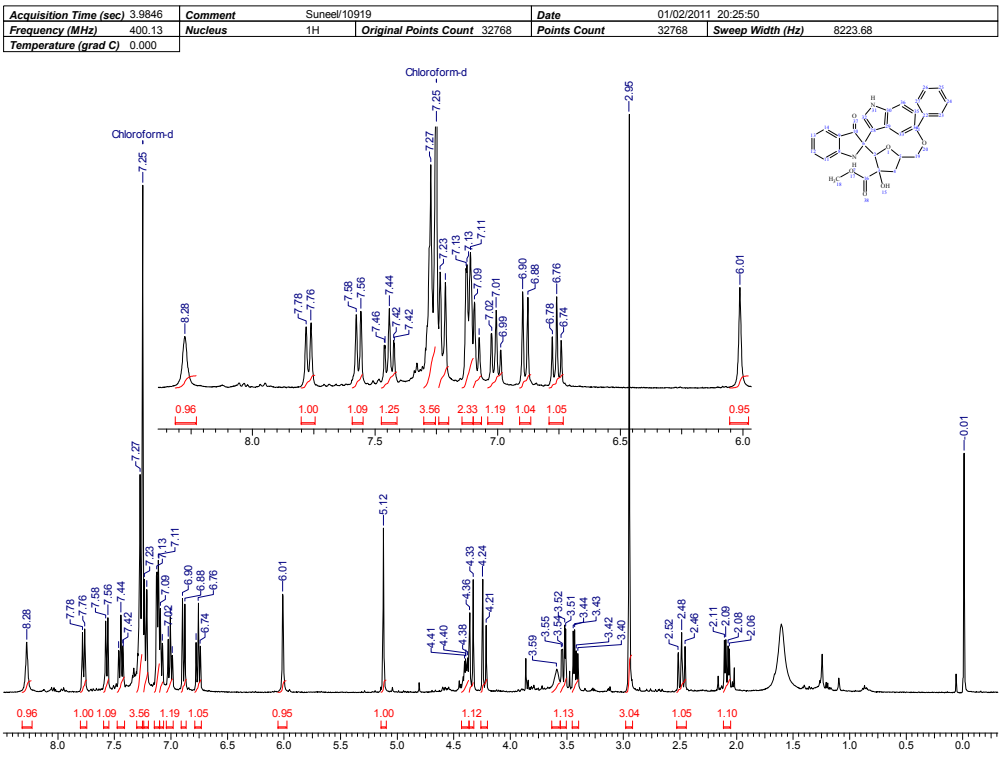


^{1}H NMR Spectrum of 23 in $CDCl_3$

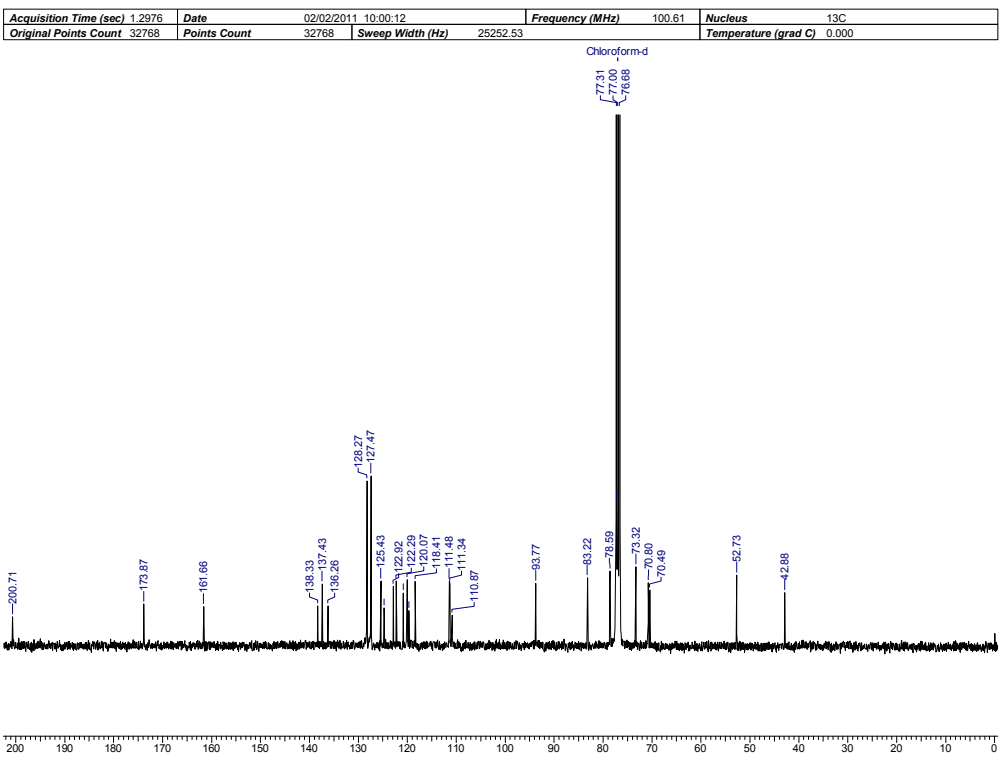
Acquisition Time (sec)	1.1010	Comment	13C	Date	27/05/2011 18:25:02	Frequency (MHz)	125.76
Nucleus	13C	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	29761.90
Temperature (grad C)	0.000						



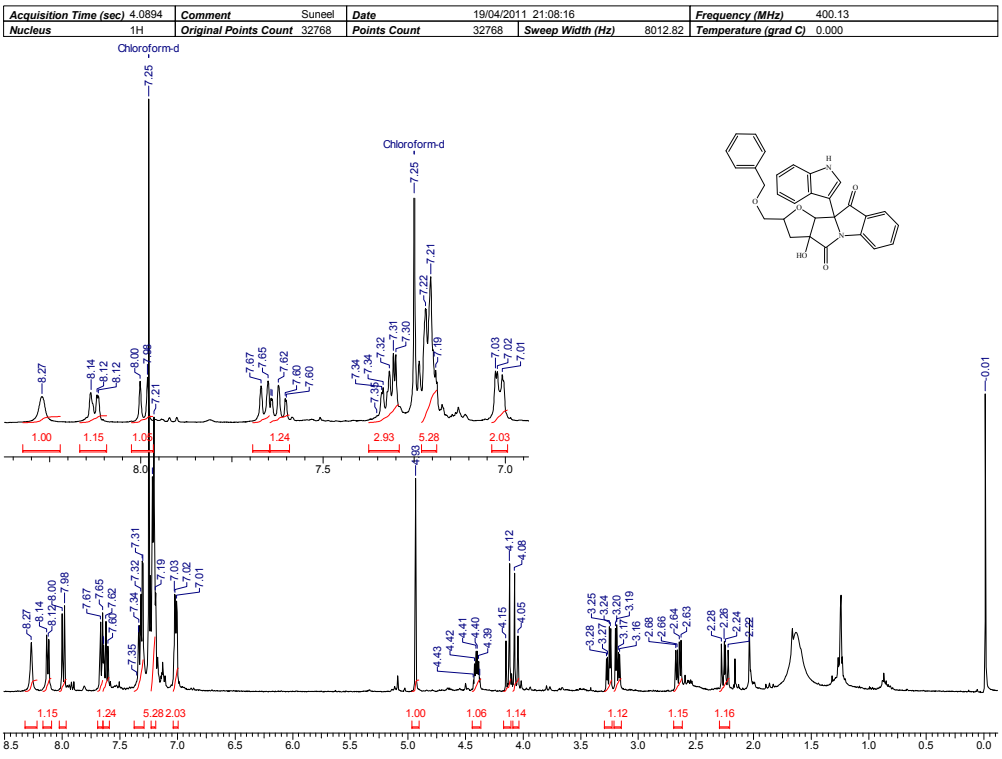
^{13}C NMR Spectrum of 23 in $CDCl_3$



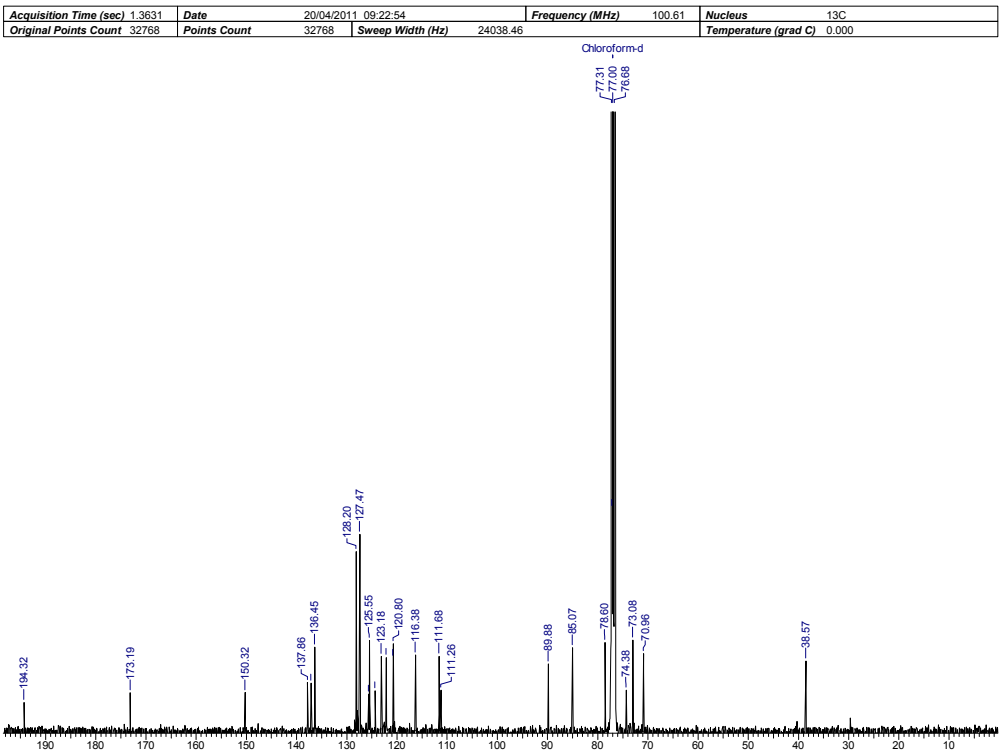
^{1}H NMR Spectrum of 22 in $CDCl_3$



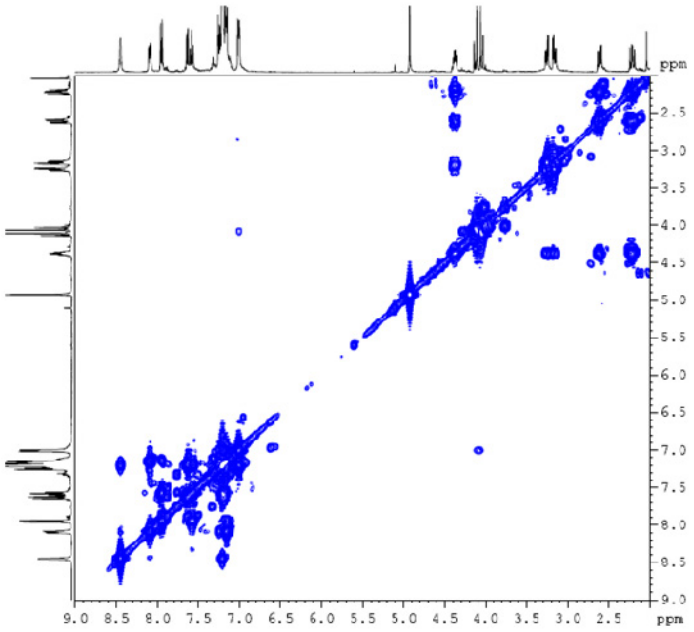
^{13}C NMR Spectrum of 22 in $CDCl_3$



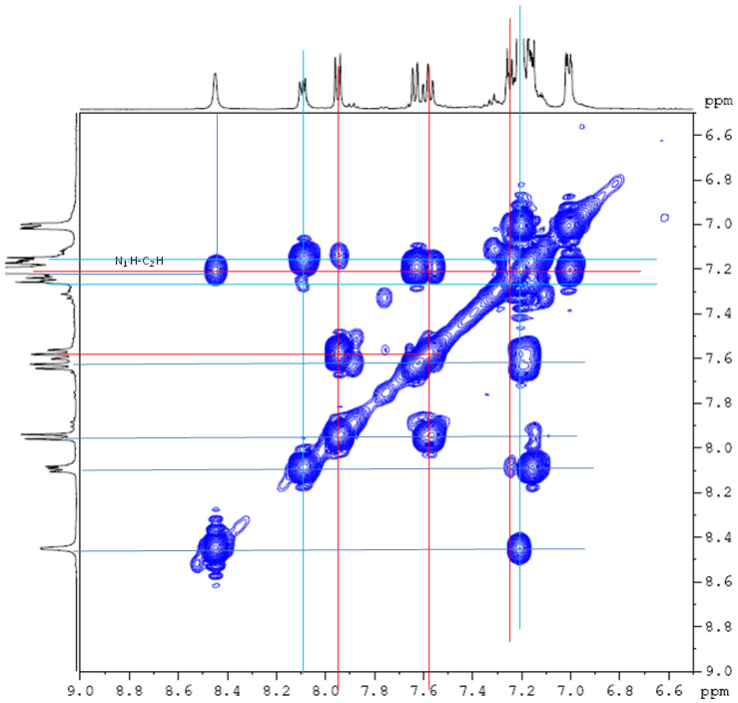
^{1}H NMR Spectrum of 25 in $CDCl_3$



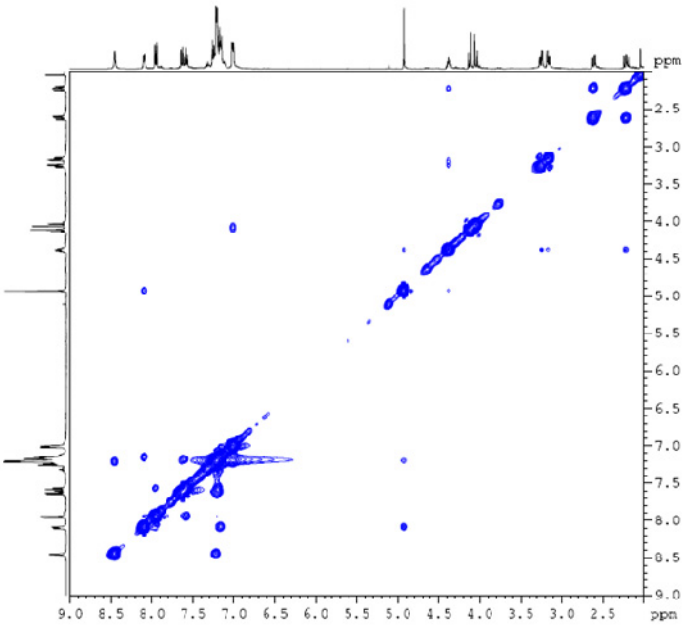
^{13}C NMR Spectrum of 25 in $CDCl_3$



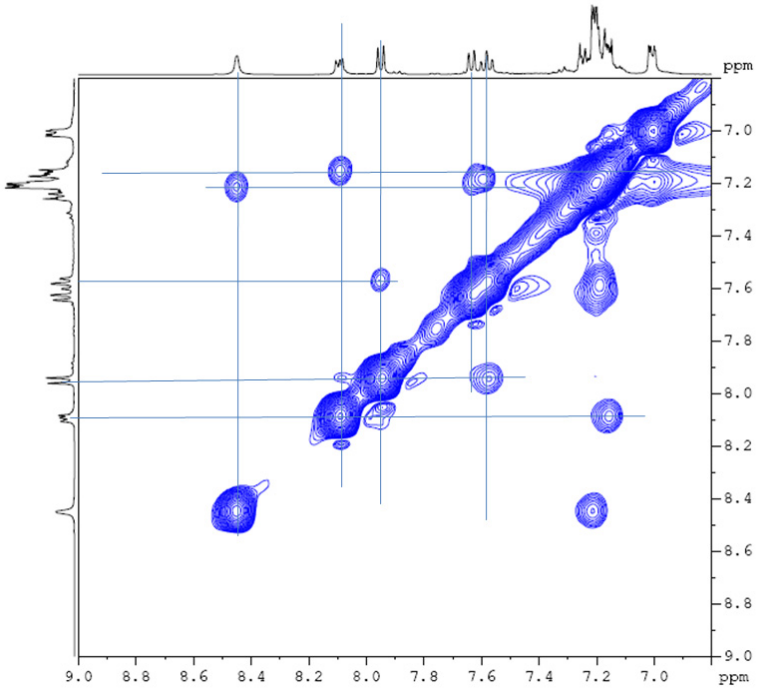
COSY Spectrum of 25 in $CDCl_3$



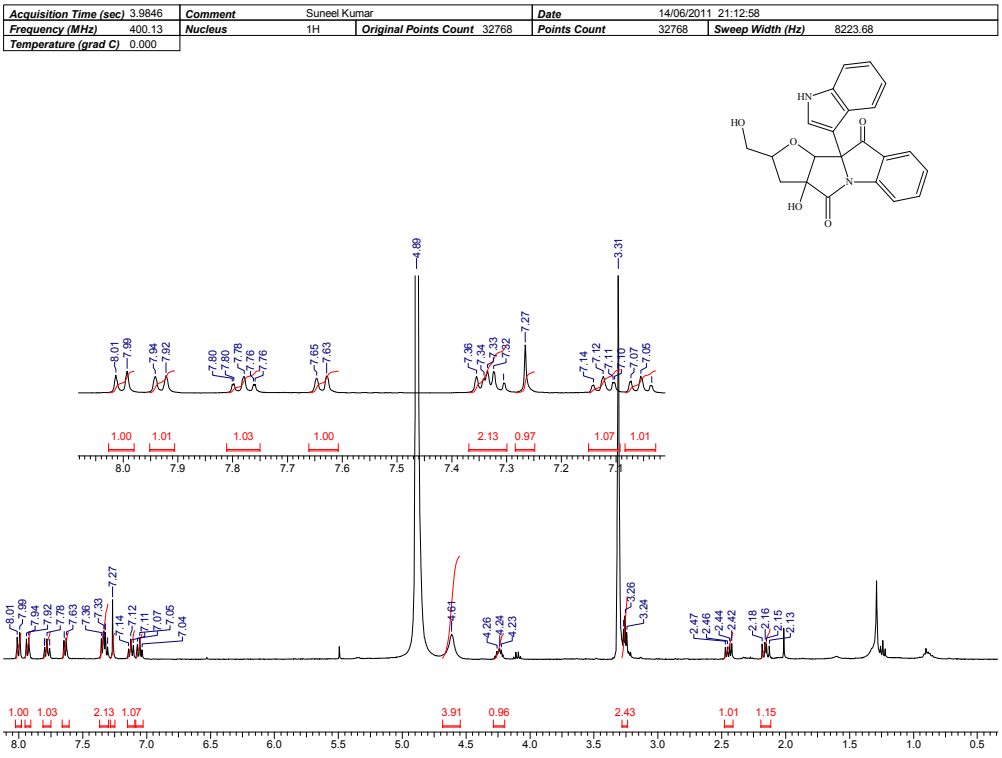
COSY Spectrum of 25 in $CDCl_3$



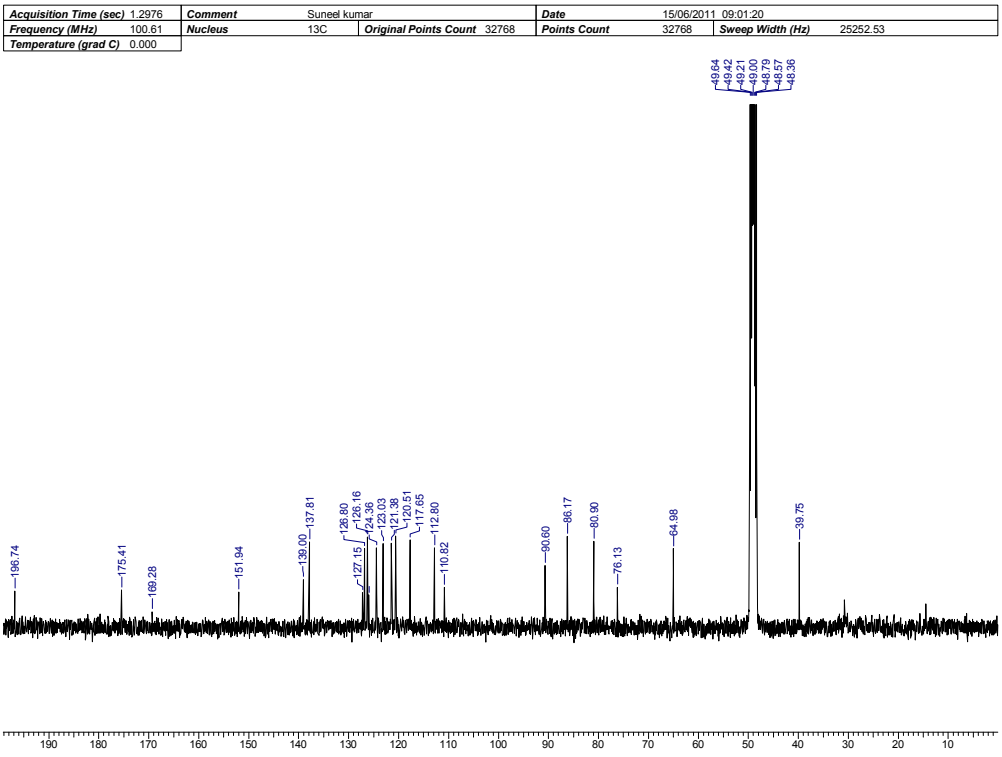
NOESY Spectrum of 25 in $CDCl_3$



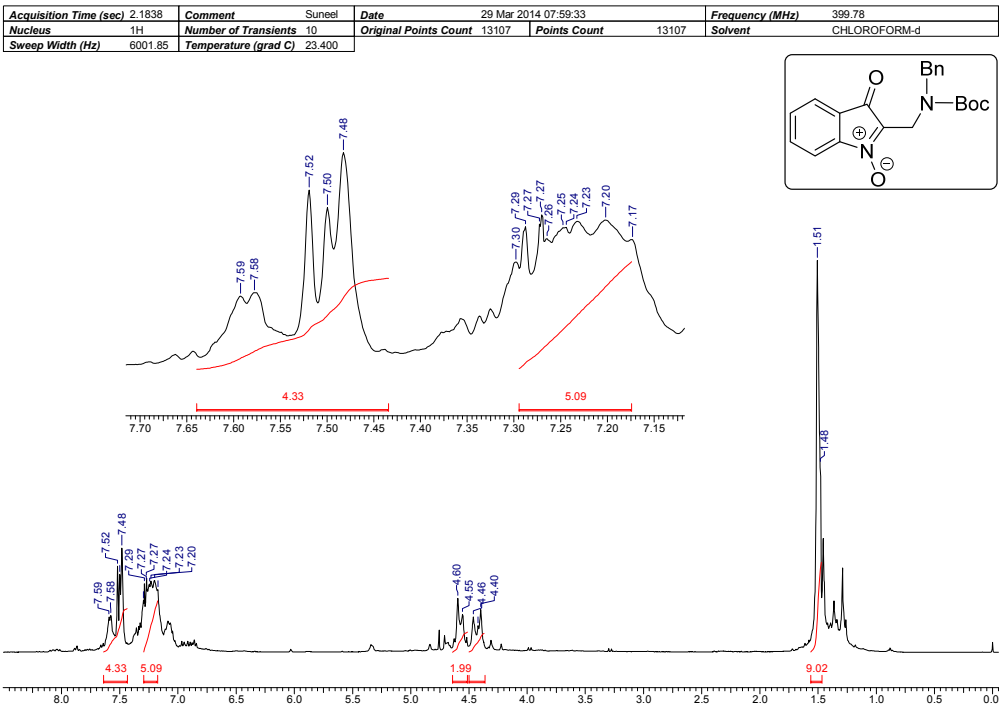
NOESY Spectrum of 25 in $CDCl_3$



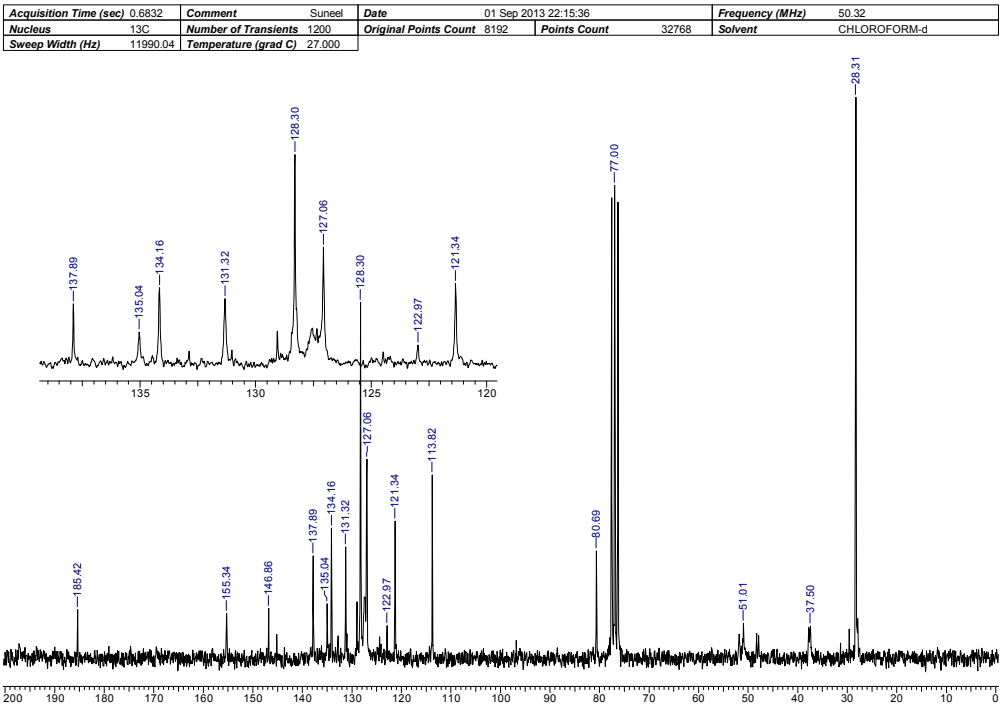
^{1}H NMR Spectrum of 8 in Methanol-d$_4$



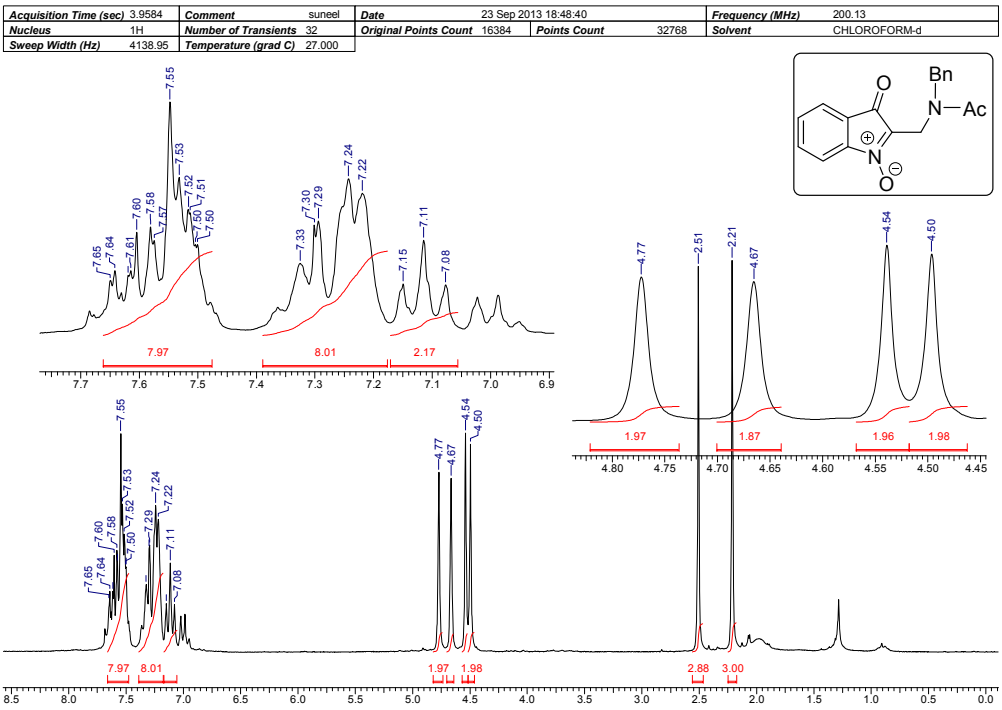
^{13}C NMR Spectrum of 8 in Methanol-d$_4$



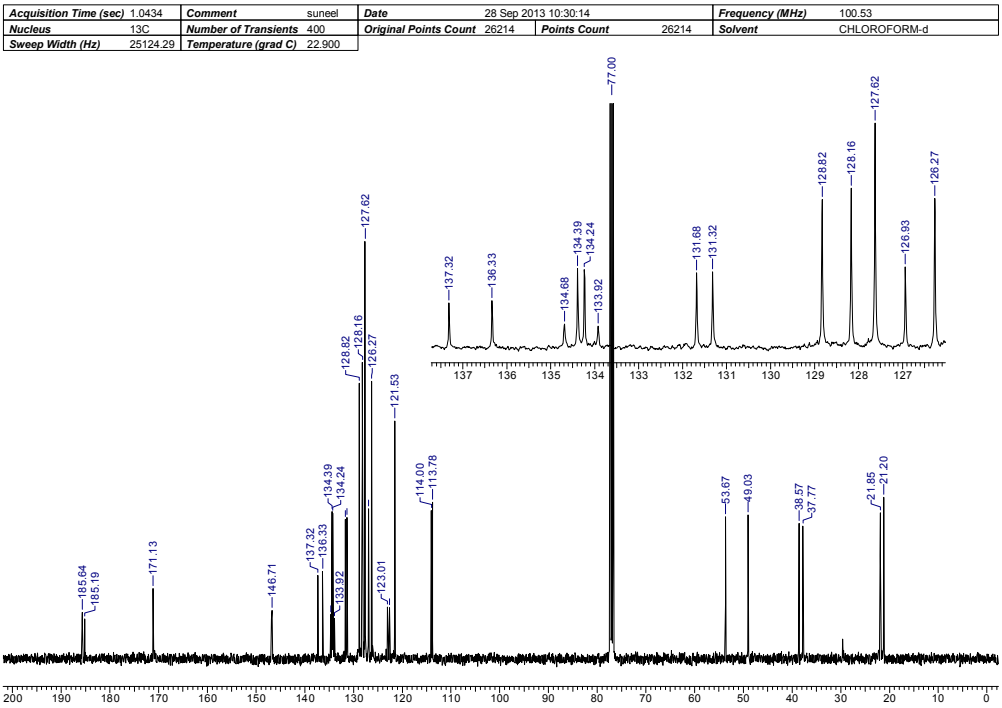
^{1}H NMR Spectrum of 28aa-Boc in $CDCl_3$



^{13}C NMR Spectrum of 28aa-Boc in $CDCl_3$

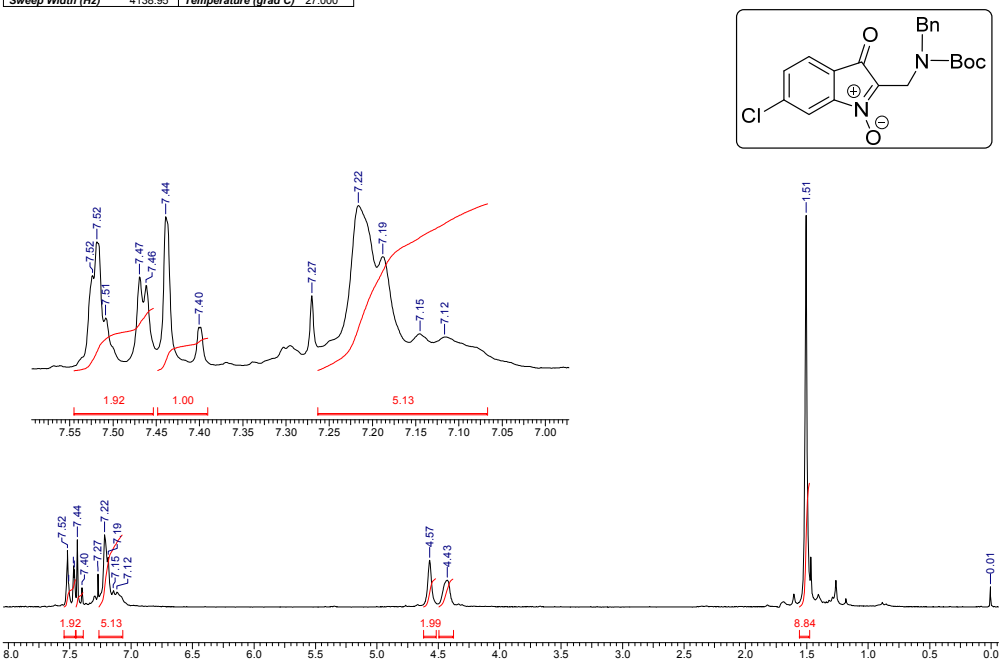


^{1}H NMR Spectrum of 28aa-Ac in $CDCl_3$



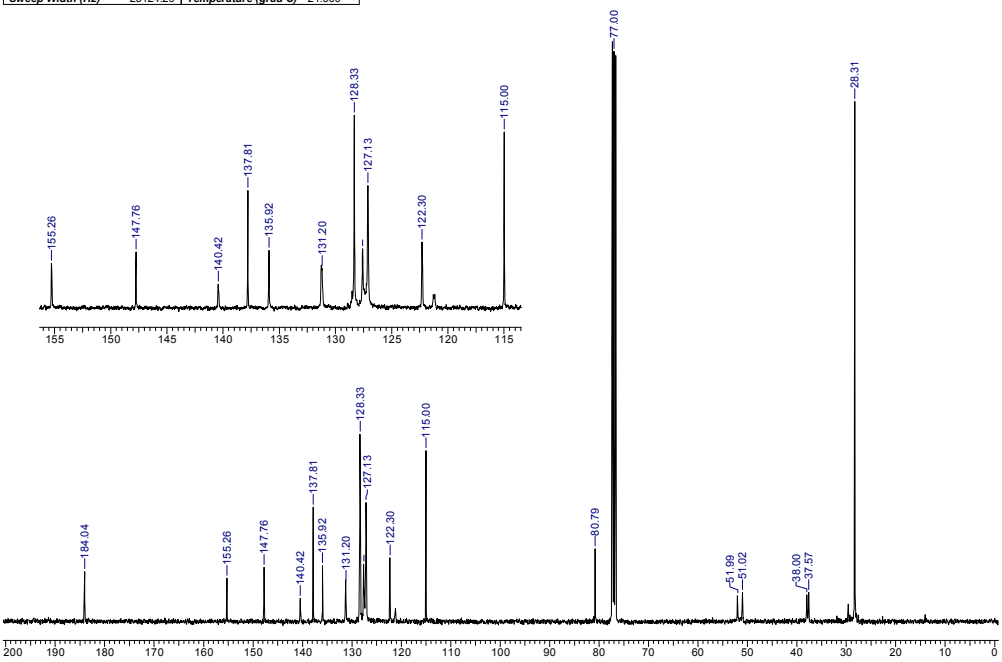
^{13}C NMR Spectrum of 28aa-Ac in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	22 Mar 2014 15:02:32			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						



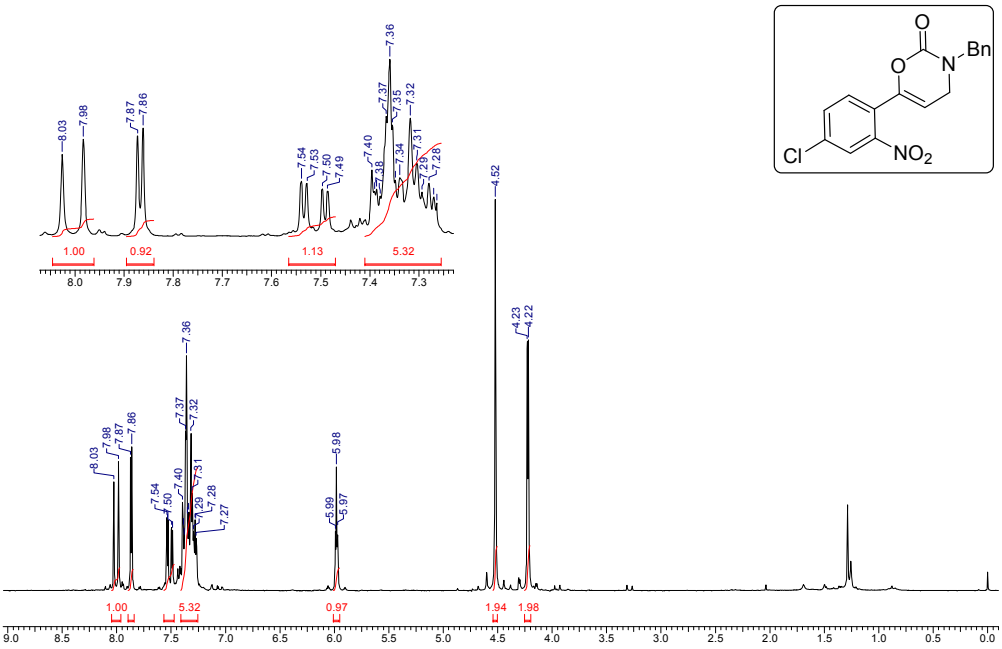
^{1}H NMR Spectrum of 28ca in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	suneel	Date	25 Mar 2014 07:18:53			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	1200	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	21.300						



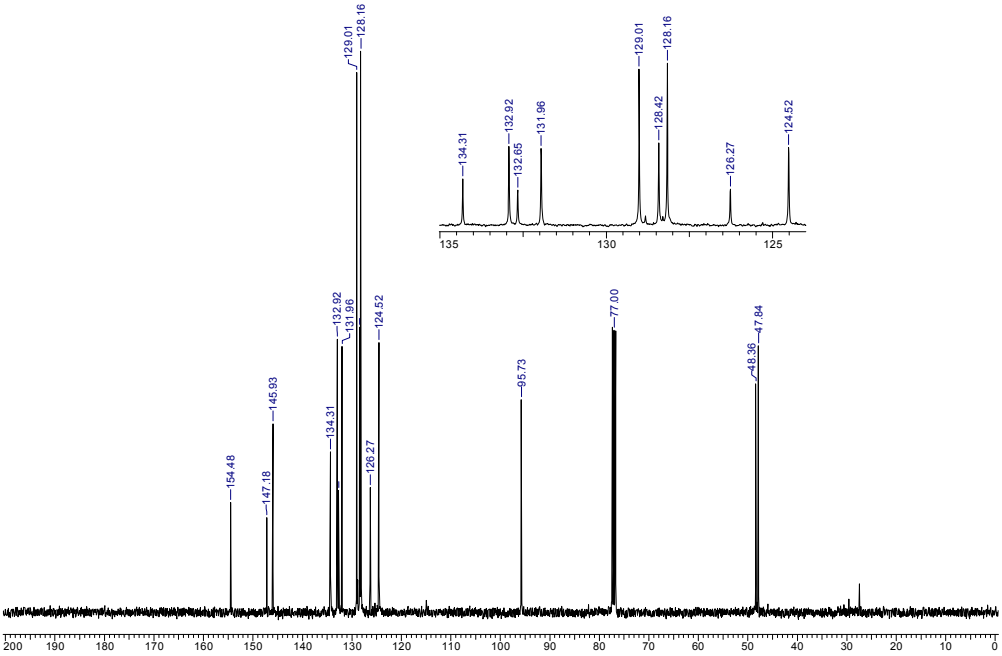
^{13}C NMR Spectrum of 28ca in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	22 Mar 2014 15:11:04			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

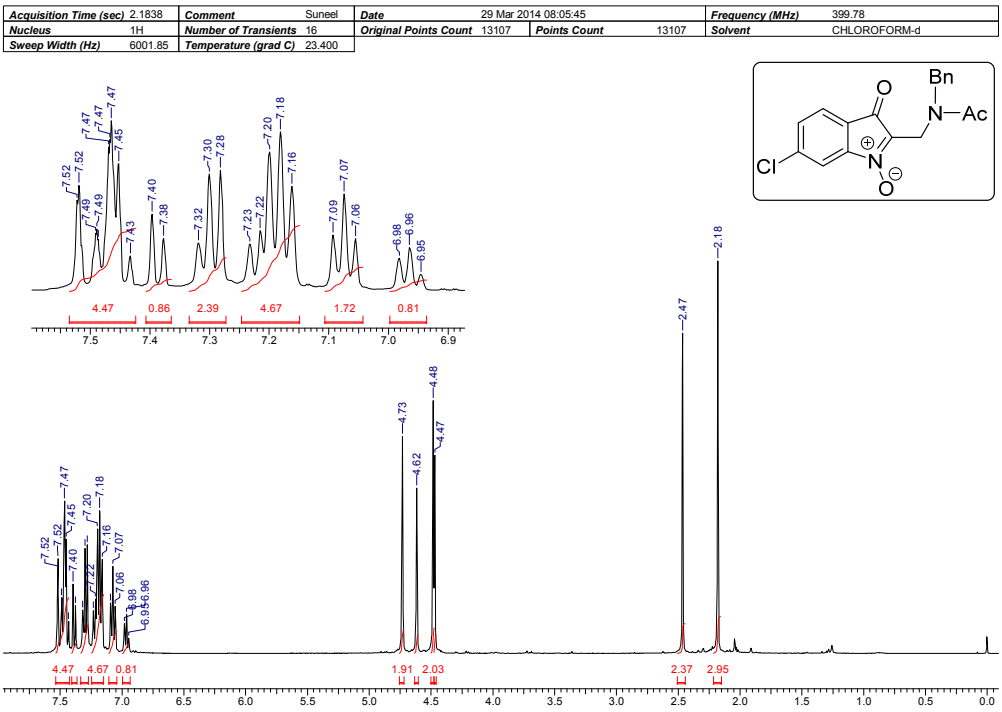


^{1}H NMR Spectrum of 30ca in $CDCl_3$

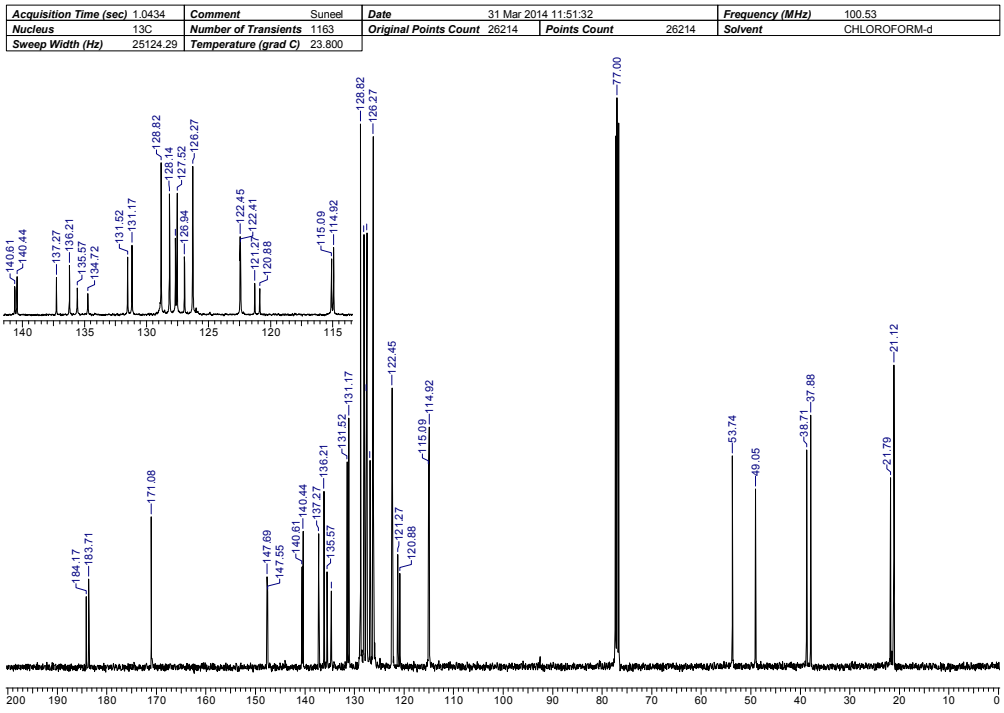
Acquisition Time (sec)	1.0434	Comment	suneel	Date	25 Mar 2014 07:37:47			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	88	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29			Temperature (grad C)	21.300				



^{13}C NMR Spectrum of 30ca in $CDCl_3$

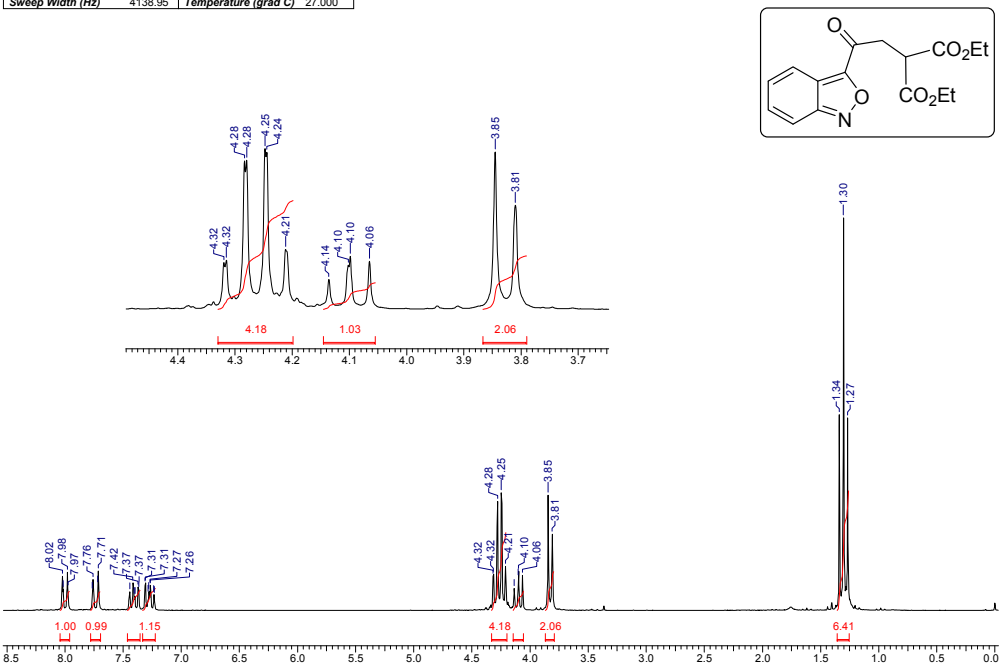


^{1}H NMR Spectrum of 28ca-Ac in $CDCl_3$



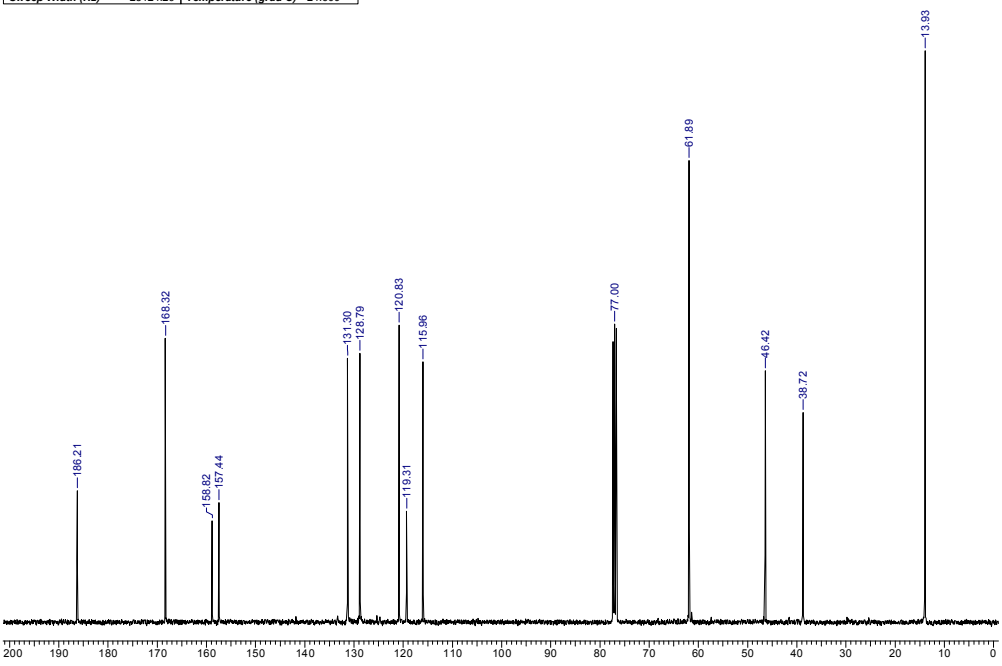
^{13}C NMR Spectrum of 28ca-Ac in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	31 Mar 2014 16:12:56			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

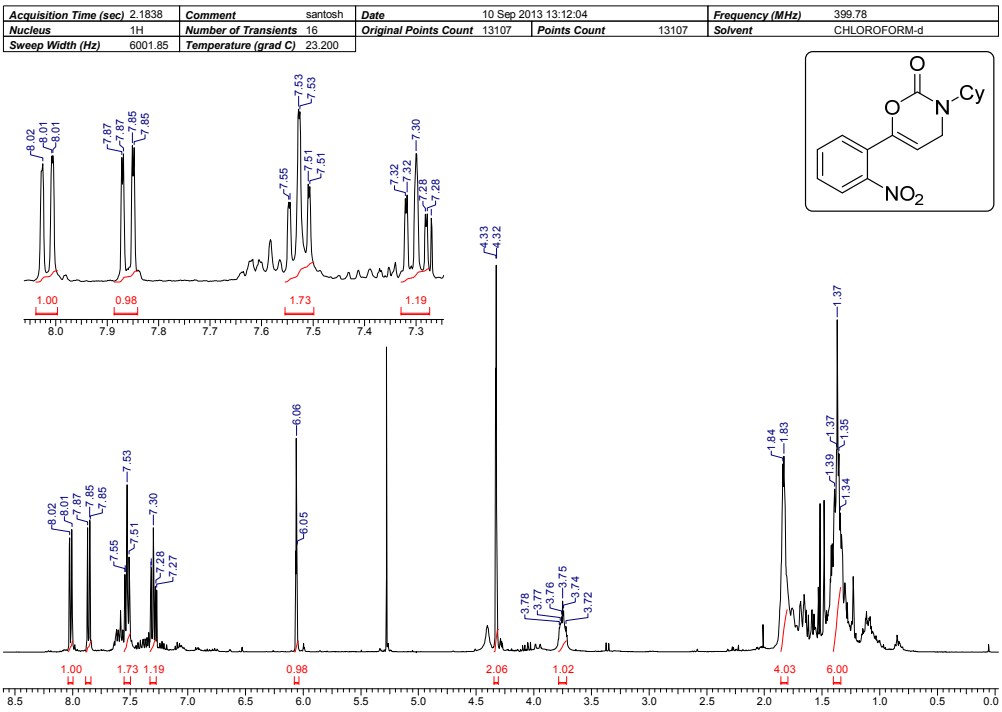


^{1}H NMR Spectrum of 29ac in $CDCl_3$

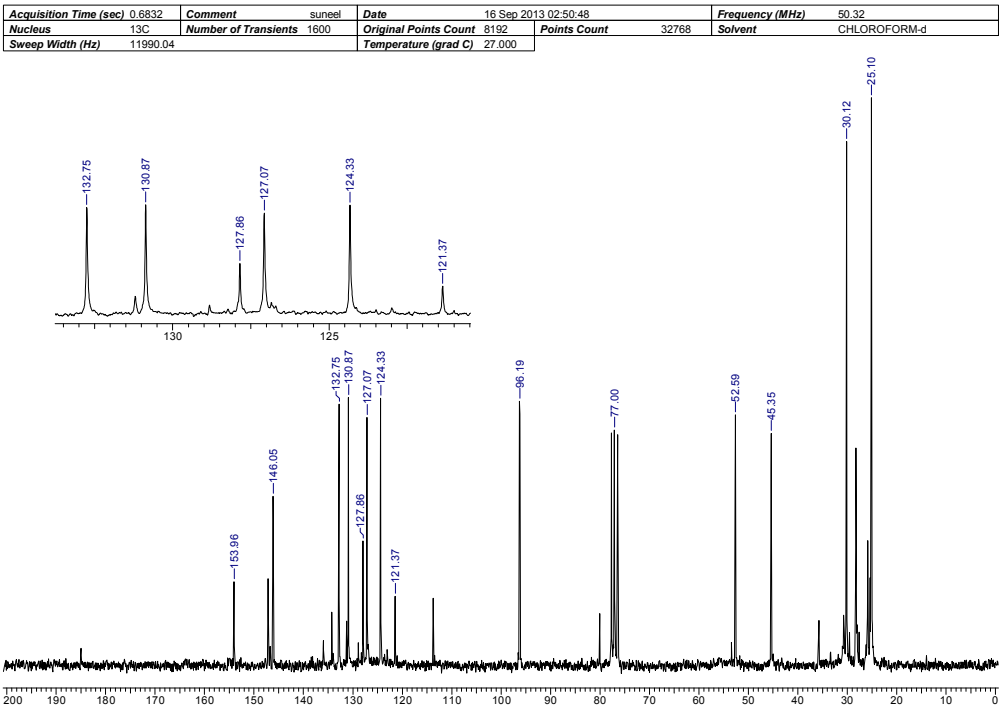
Acquisition Time (sec)	1.0434	Comment	Suneel	Date	05 Apr 2014 00:20:12			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	800	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	21.600						



^{13}C NMR Spectrum of 29ac in $CDCl_3$

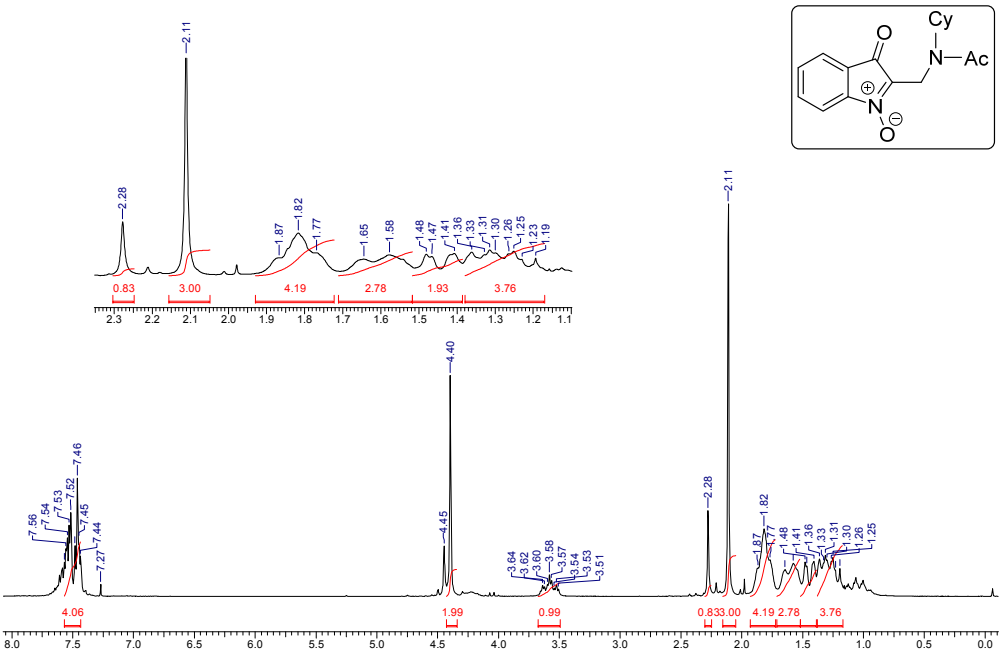


^{1}H NMR Spectrum of 30ad in $CDCl_3$



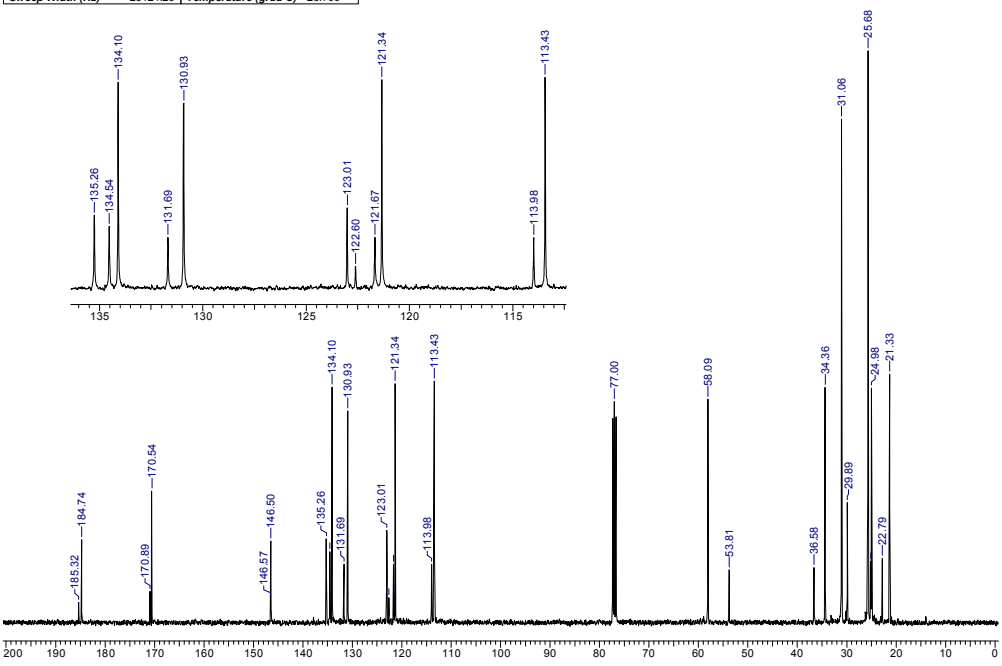
^{13}C NMR Spectrum of 30ad in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	27 Mar 2014 17:14:48	Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000				



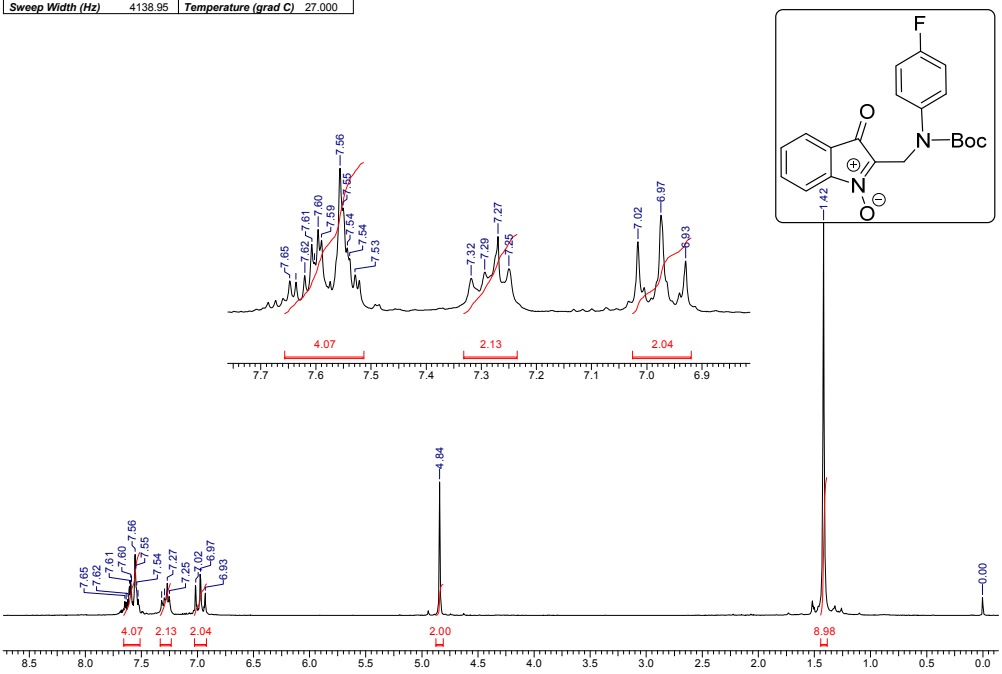
^{1}H NMR Spectrum of 28ad-Ac in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	Suneel	Date	30 Mar 2014 14:39:12	Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	400	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	23.700				



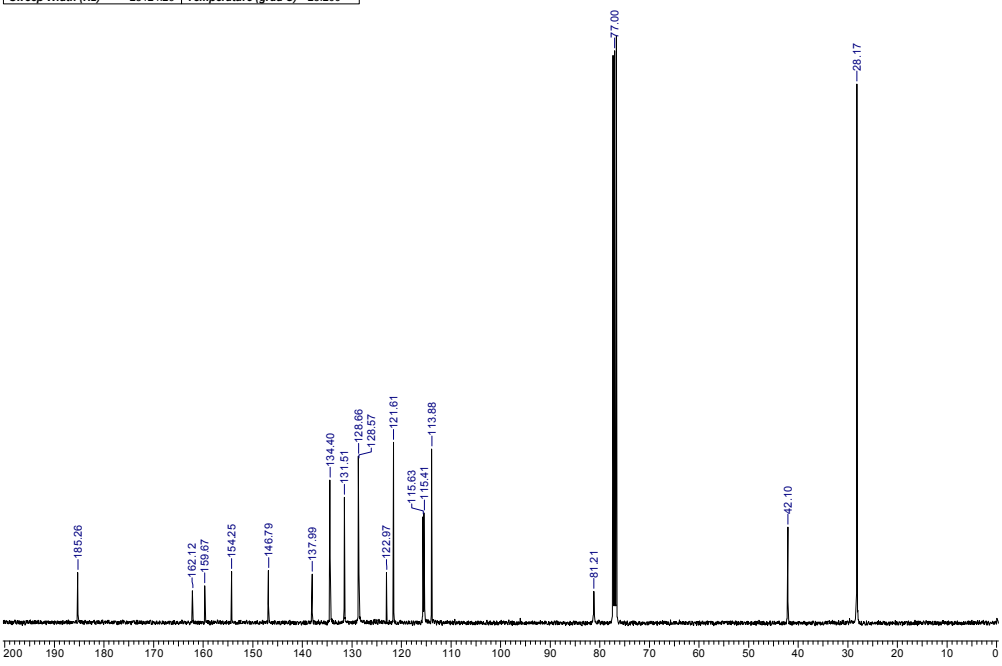
^{13}C NMR Spectrum of 28ad-Ac in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	12 Apr 2014 15:47:20			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

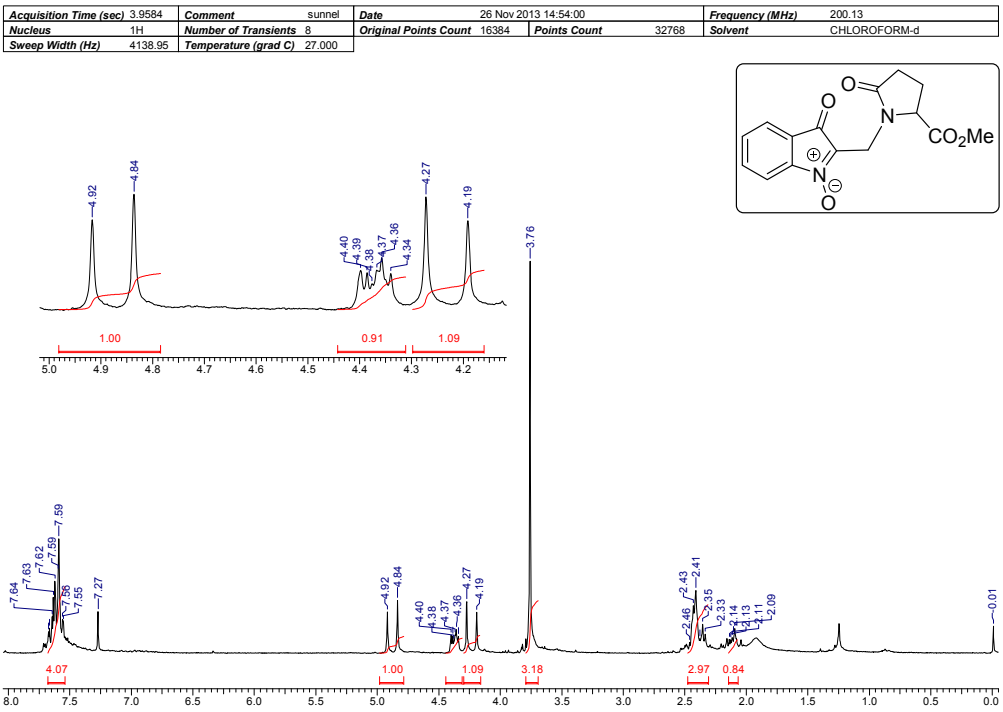


^{1}H NMR Spectrum of 28ag in $CDCl_3$

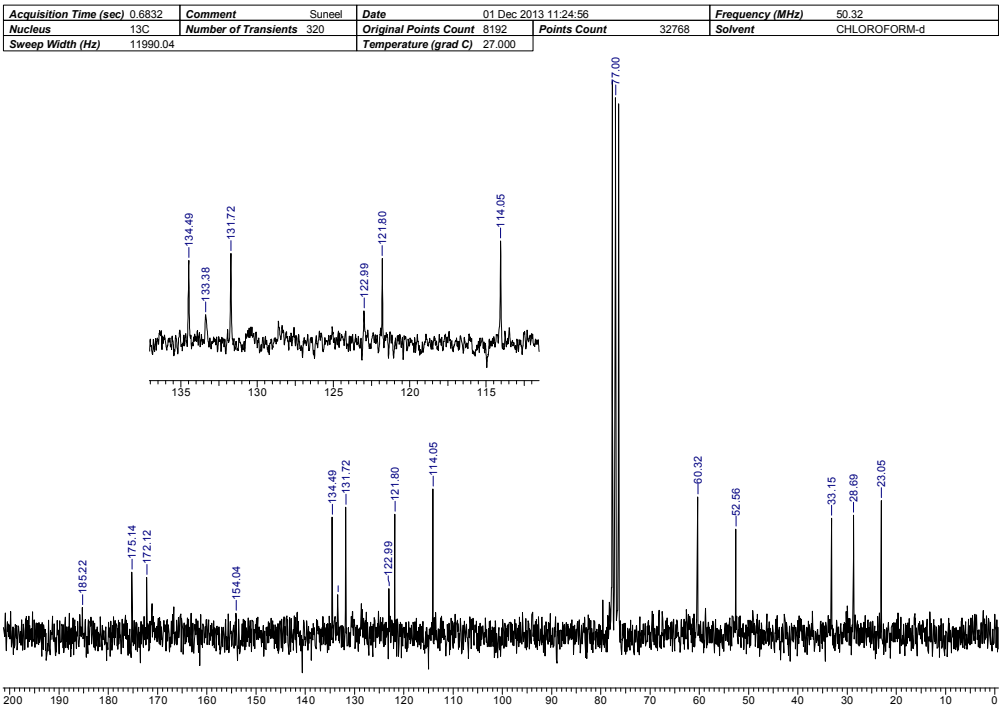
Acquisition Time (sec)	1.0434	Comment	Suneel	Date	15 Apr 2014 05:14:17			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	1200	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	23.200						



^{13}C NMR Spectrum of 28ag in $CDCl_3$

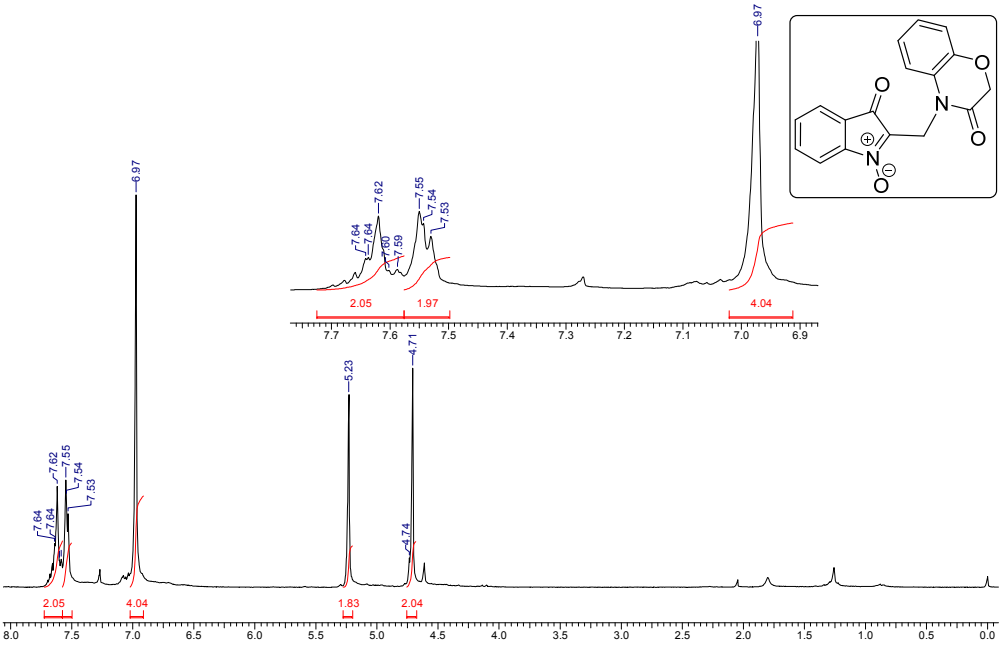


^{1}H NMR Spectrum of 28ai in $CDCl_3$



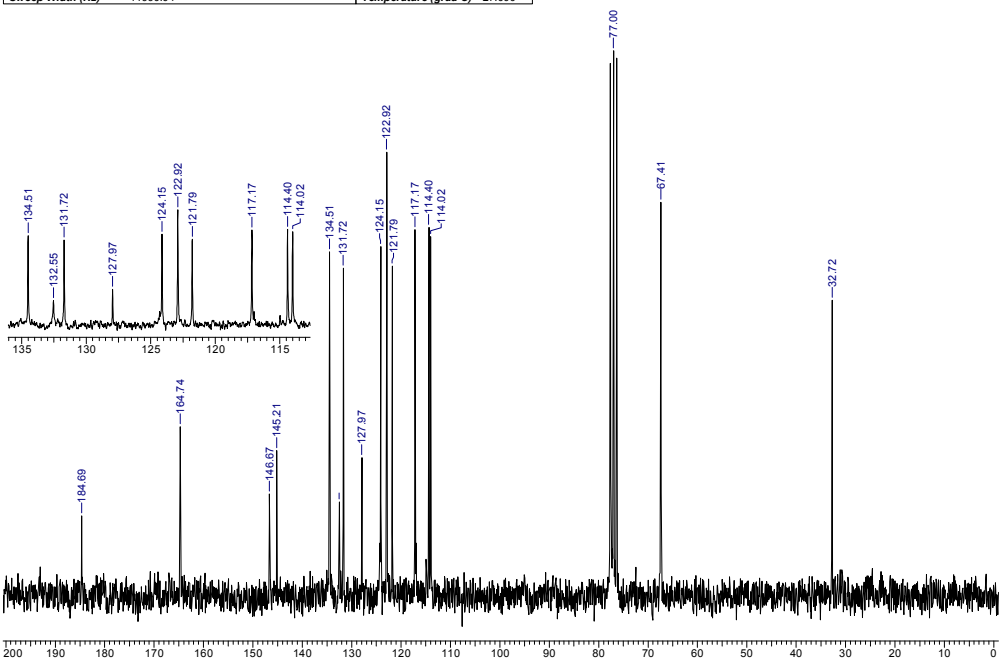
^{13}C NMR Spectrum of 28ai in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	22 Nov 2013 15:26:00	Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000				



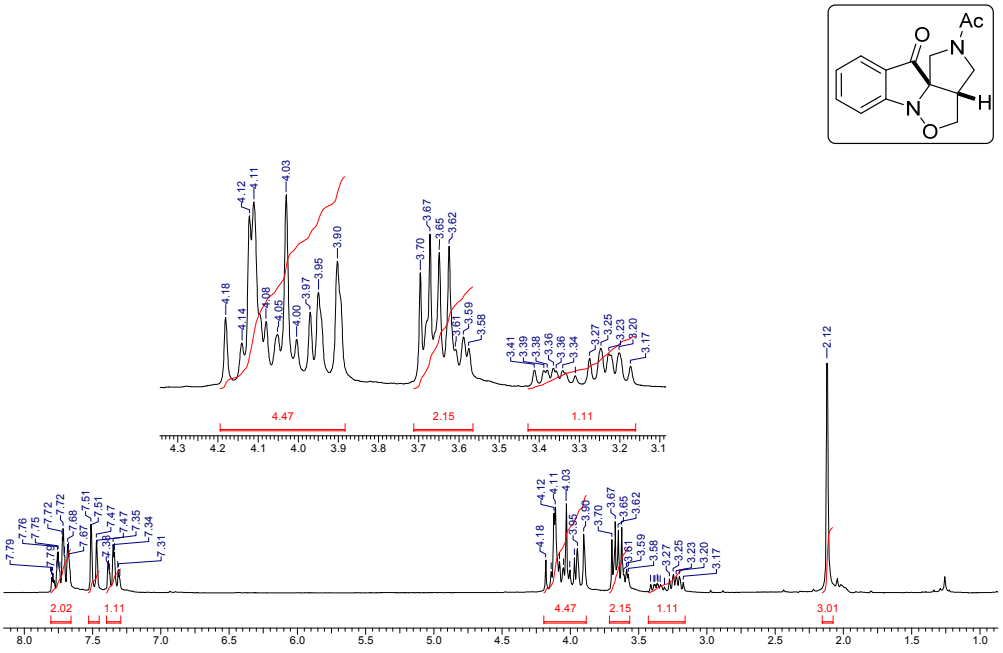
^{1}H NMR Spectrum of 28aj in $CDCl_3$

Acquisition Time (sec)	0.6832	Comment	suneel	Date	30 Nov 2013 06:36:56	Frequency (MHz)	50.32
Nucleus	13C	Number of Transients	400	Original Points Count	8192	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	11990.04			Temperature (grad C)	27.000		



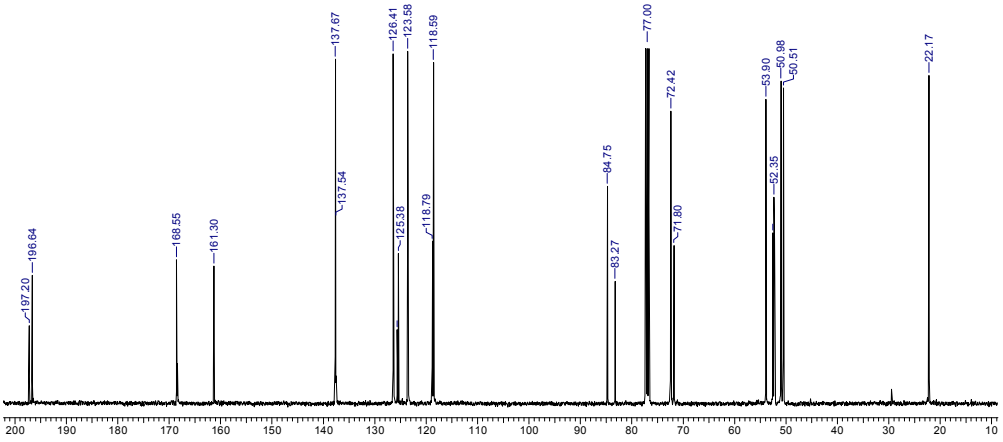
^{13}C NMR Spectrum of 28aj in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	suneel	Date	15 Jan 2014 15:53:44	Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000				



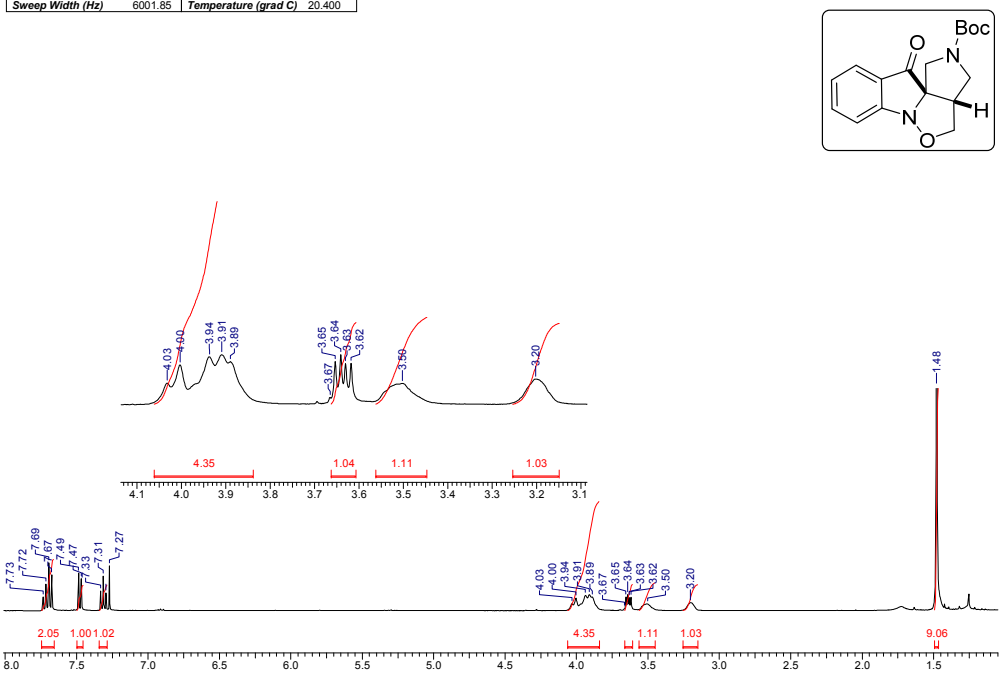
^{1}H NMR Spectrum of 31ak-Ac in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	suneel	Date	17 Jan 2014 05:29:02	Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	800	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	21.600				



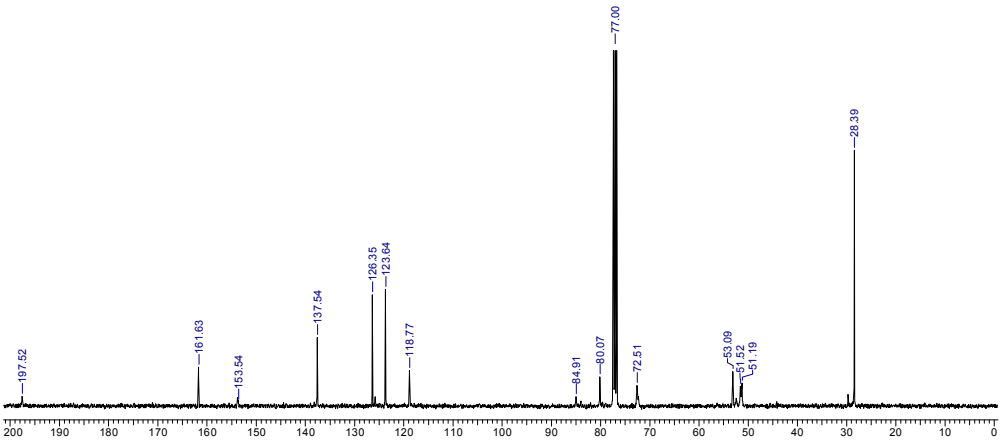
^{13}C NMR Spectrum of 31ak-Ac in $CDCl_3$

Acquisition Time (sec)	2.1838	Comment	suneel	Date	06 Jun 2013 02:32:03			Frequency (MHz)	399.78
Nucleus	1H	Number of Transients	16	Original Points Count	13107	Points Count	13107	Solvent	CHLOROFORM-d
Sweep Width (Hz)	6001.85	Temperature (grad C)	20.400						



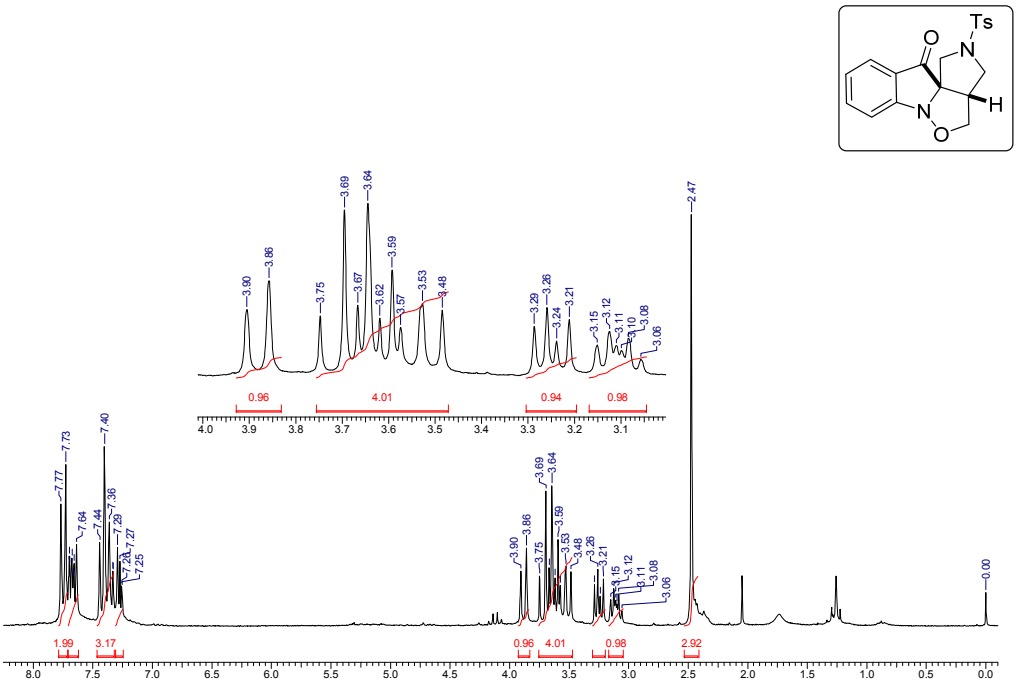
^{1}H NMR Spectrum of 31ak-Boc in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	suneel	Date	09 Jun 2013 16:16:46			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	1200	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	20.900						



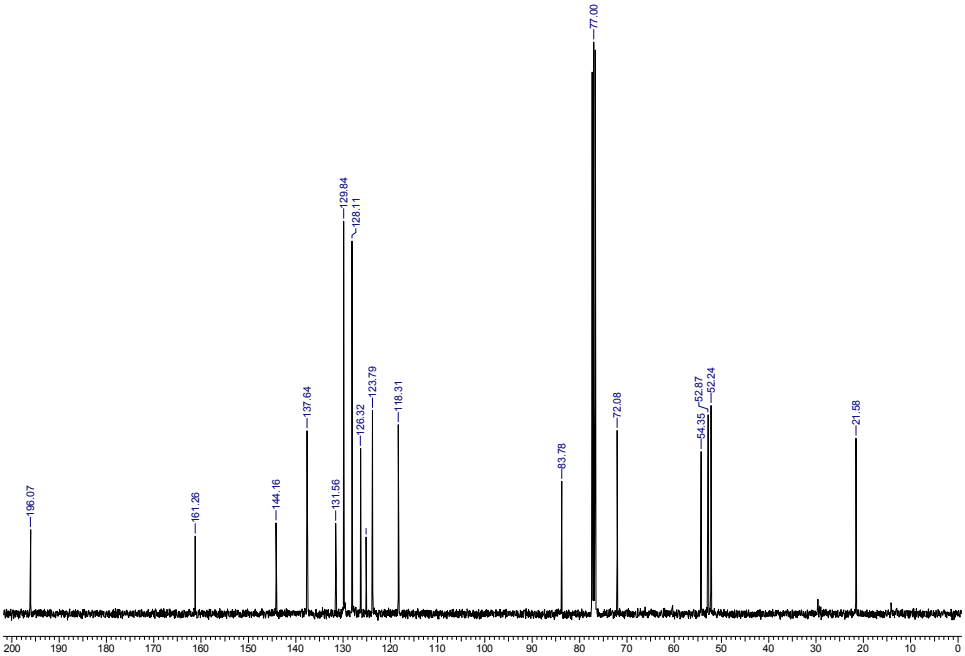
^{13}C NMR Spectrum of 31ak-Boc in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	suneel	Date	20 Jan 2014 19:56:56			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

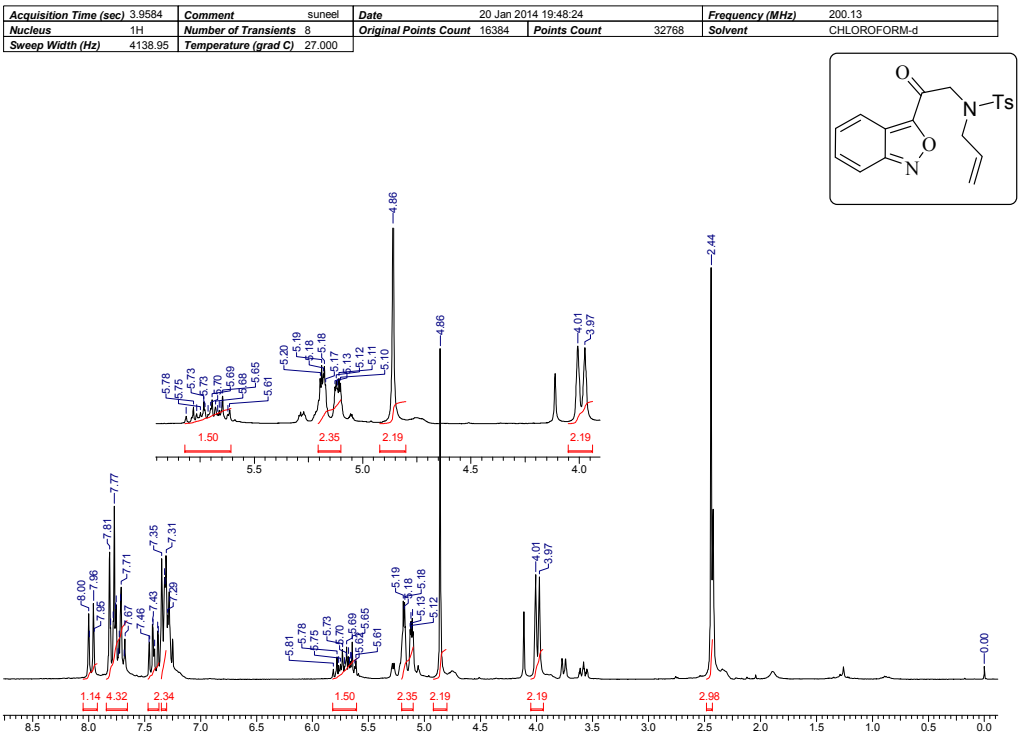


^{1}H NMR Spectrum of 31ak-Ts in $CDCl_3$

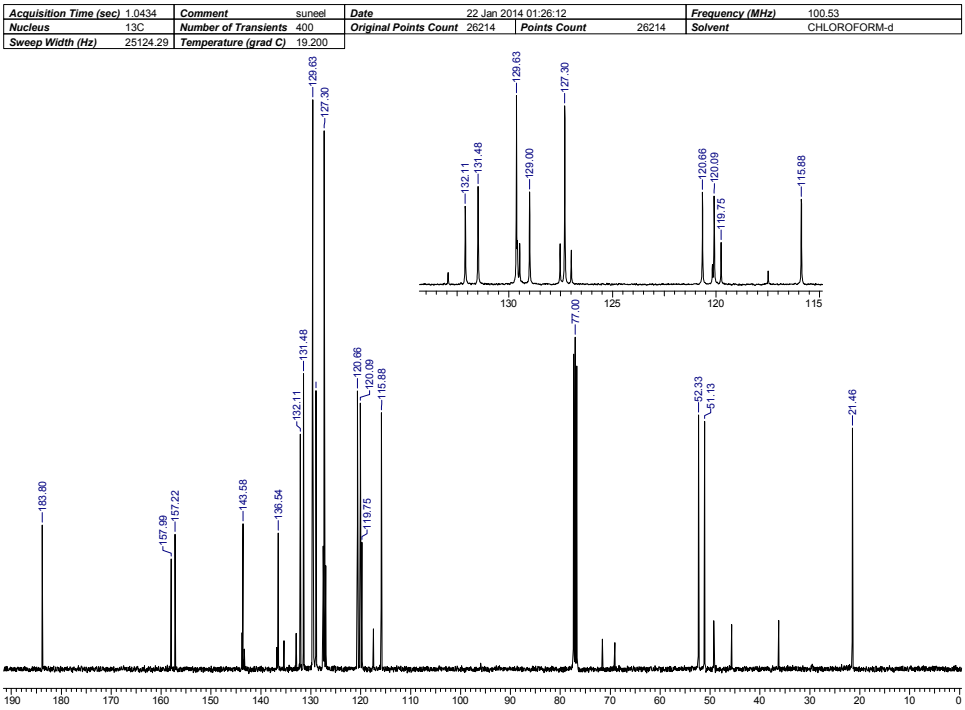
Acquisition Time (sec)	1.0434	Comment	suneel	Date	22 Jan 2014 00:28:53			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	400	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	19.300						



^{13}C NMR Spectrum of 31ak-Ts in $CDCl_3$

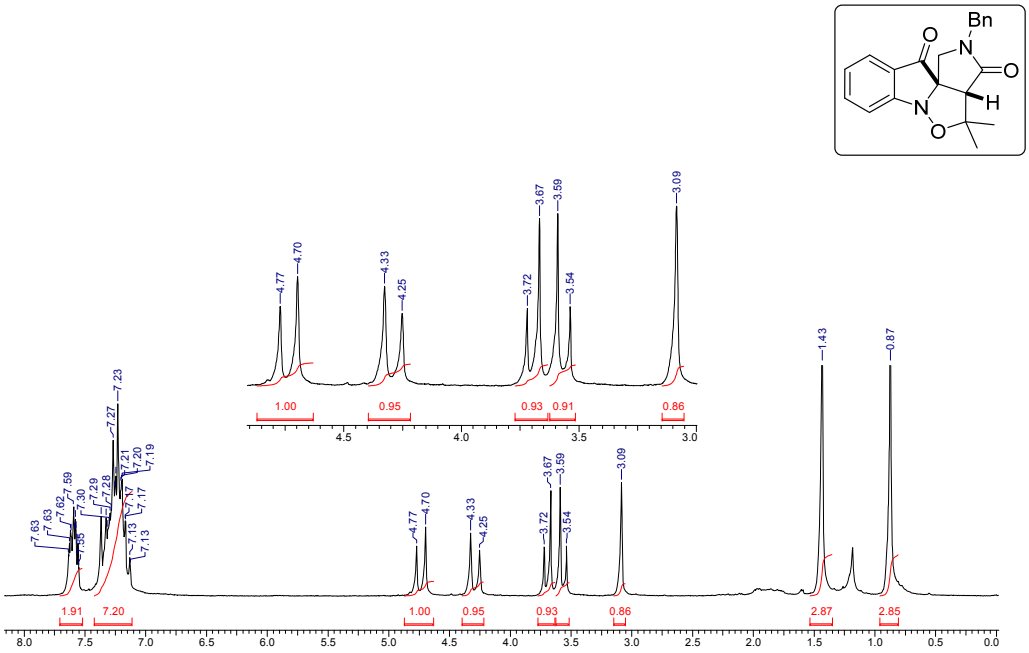


^{1}H NMR Spectrum of 29ak-Ts in $CDCl_3$



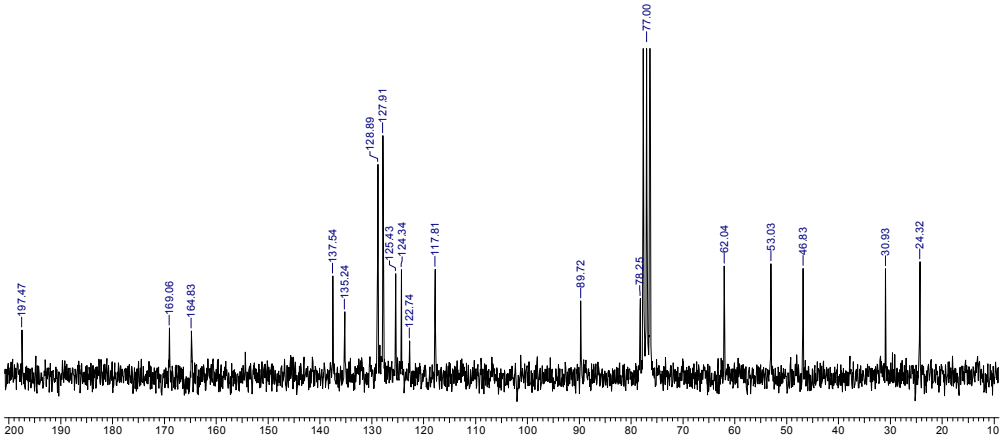
^{13}C NMR Spectrum of 29ak-Ts in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	Santhosh		*Date*	22 Oct 2013 23:02:32	
Frequency (MHz)	200.13	*Nucleus*	1H	*Number of Transients* 32	*Original Points Count*	16384	*Points Count* 32768
Solvent	CHLOROFORM-d			*Sweep Width (Hz)* 4138.95	*Temperature (grad C)*	27.000	



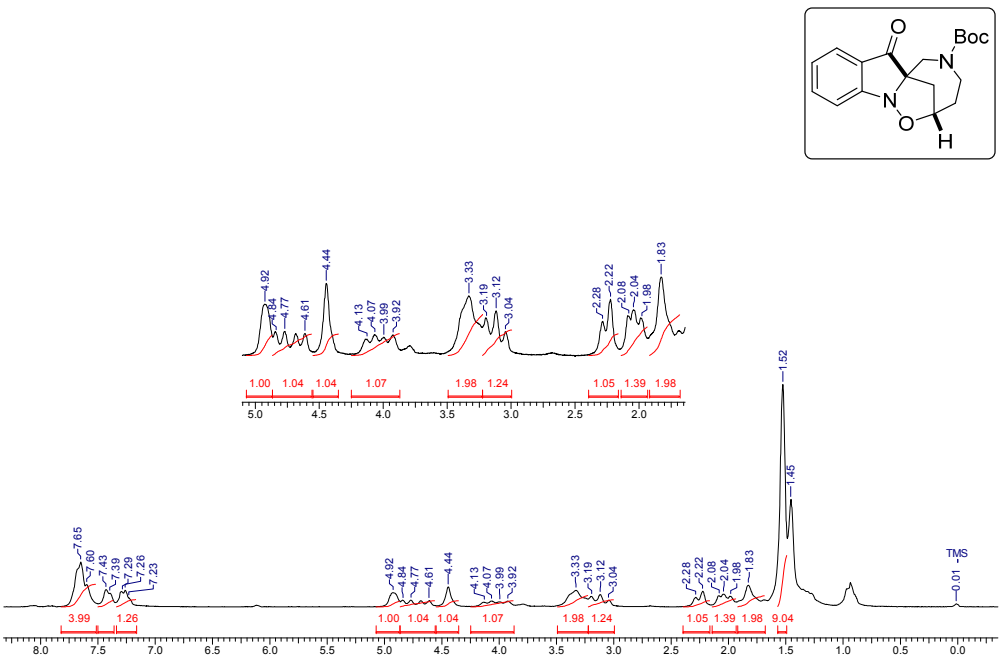
^{1}H NMR Spectrum of 31am in $CDCl_3$

Acquisition Time (sec)	0.6832	*Comment*	suneel	*Date*	29 Oct 2013 09:48:56		*Frequency (MHz)*	50.32	
Nucleus	13C	*Number of Transients*	430	*Original Points Count*	8192	*Points Count* 32768	*Solvent*	CHLOROFORM-d	
Sweep Width (Hz)	11990.04			*Temperature (grad C)*	27.000				



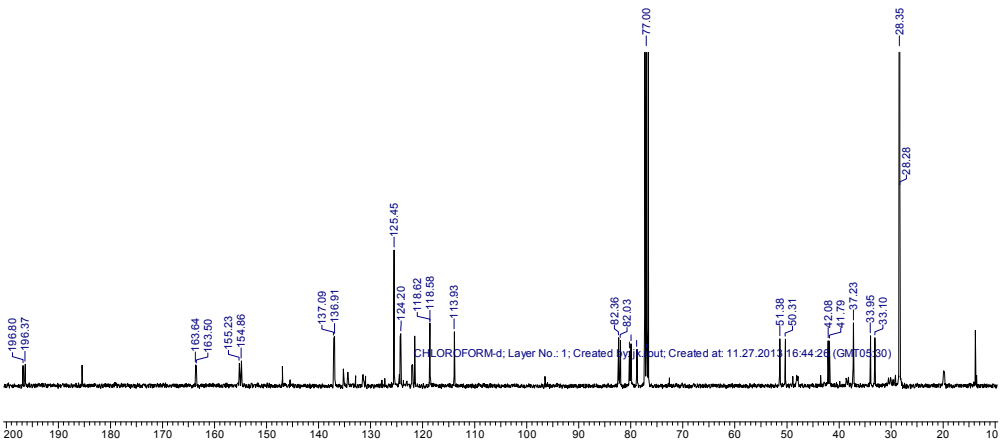
^{13}C NMR Spectrum of 31am in $CDCl_3$

Acquisition Time (sec)	7.9167	Comment	suneel	Date	12/11/2013 02:38:24			Frequency (MHz)	200.13
Nucleus	1H	Original Points Count	32768	Points Count	32768	Sweep Width (Hz)	4139.07	Temperature (grad C)	0.000



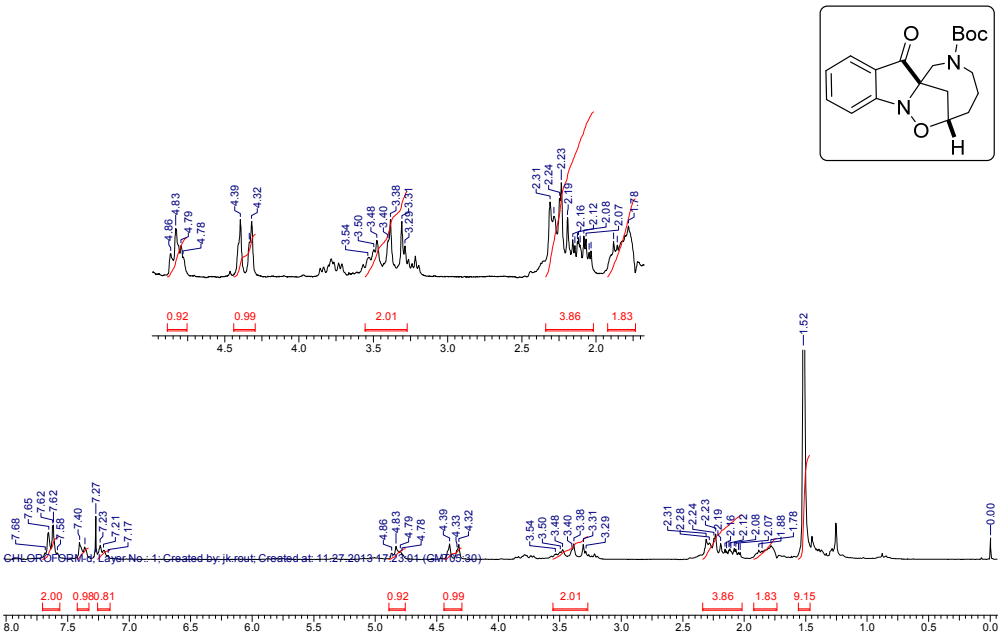
^{1}H NMR Spectrum of 31an in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	suneel	Date	13 Nov 2013 05:10:50			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	600	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	20.300						



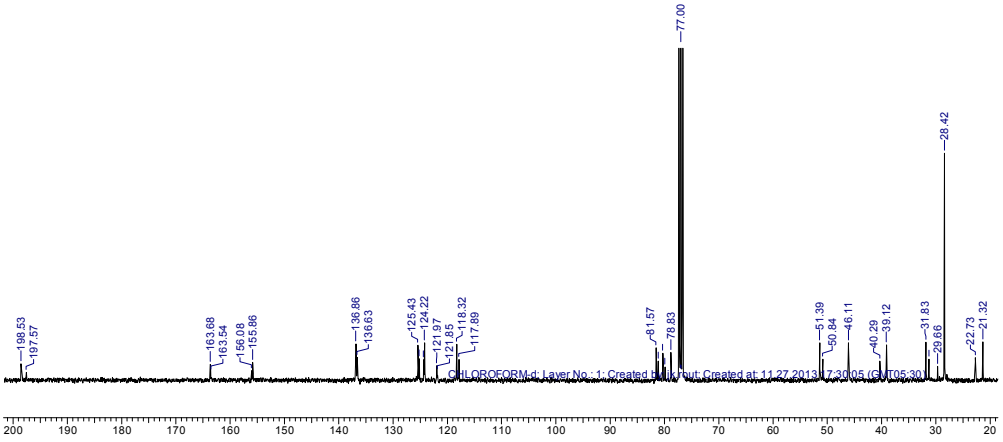
^{13}C NMR Spectrum of 31an in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	suneel	*Date*	14 Aug 2013 03:18:32	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	16	*Original Points Count*	16384	*Points Count* 32768	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000				



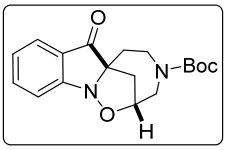
^{1}H NMR Spectrum of 31ao in $CDCl_3$

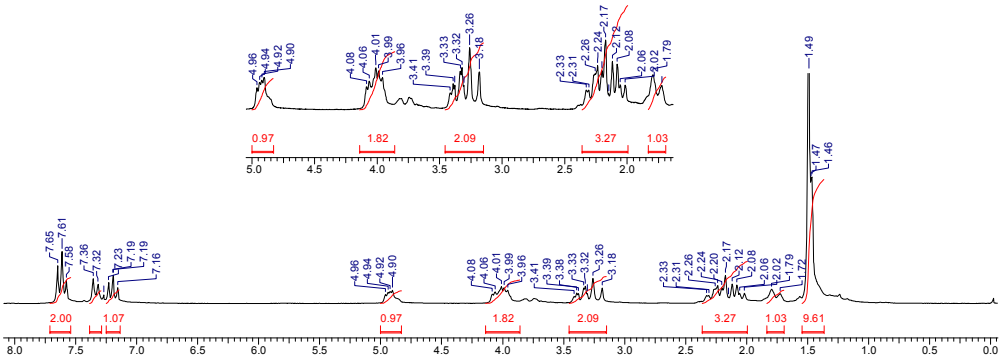
Acquisition Time (sec)	1.0434	*Comment*	Suneel	*Date*	11 Aug 2013 06:28:42	*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	1200	*Original Points Count*	26214	*Points Count* 26214	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	25124.29	*Temperature (grad C)*	21.000				



^{13}C NMR Spectrum of 31ao in $CDCl_3$

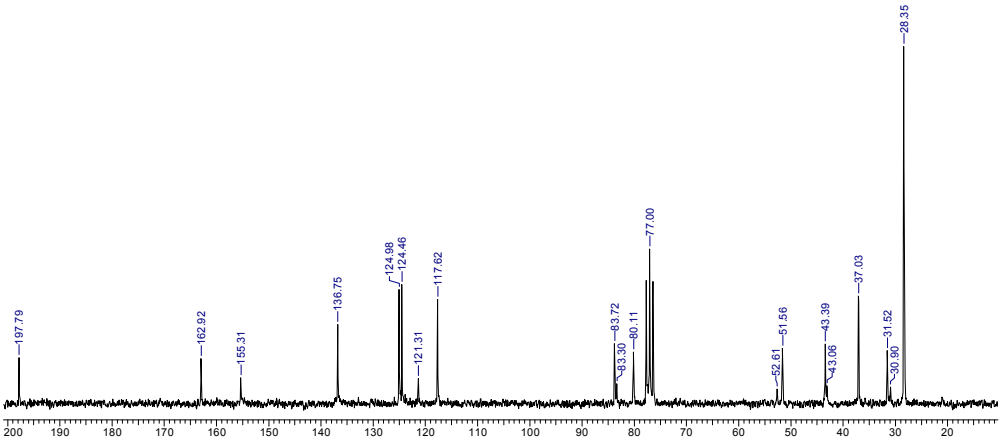
Acquisition Time (sec)	3.9584	*Comment*	suneel	*Date*	12 Nov 2013 02:12:24	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						





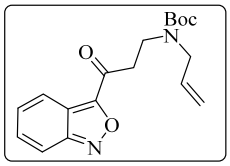
^{1}H NMR Spectrum of 31ap in $CDCl_3$

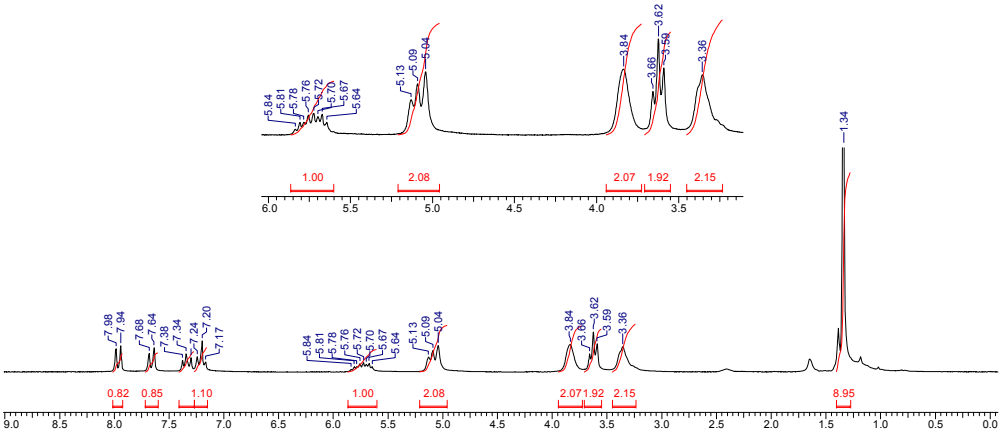
Acquisition Time (sec)	0.6832	*Comment*	Patil	*Date*	13 Nov 2013 07:53:44	*Frequency (MHz)*	50.32
Nucleus	13C	*Number of Transients*	800	*Original Points Count*	8192	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	11990.04			*Temperature (grad C)*	27.000				



^{13}C NMR Spectrum of 31ap in $CDCl_3$

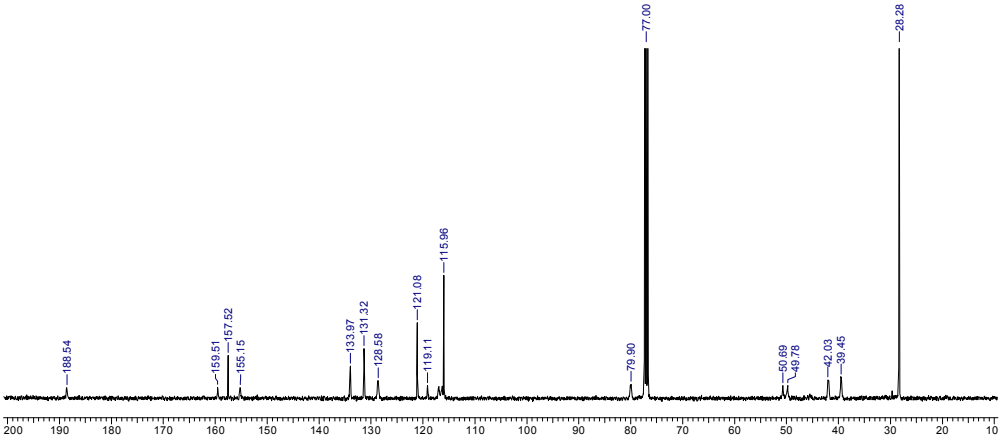
Acquisition Time (sec)	3.9584	Comment	Swami	Date	09 Nov 2013 13:22:16			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	32	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						





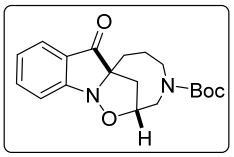
^{1}H NMR Spectrum of 29ap in $CDCl_3$

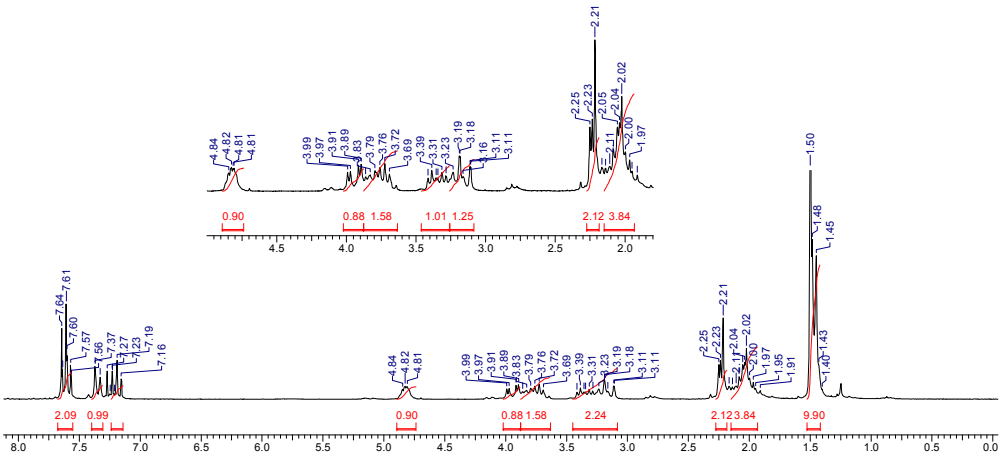
Acquisition Time (sec)	1.0434	Comment	suneel	Date	12 Nov 2013 00:05:52			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	2000	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	21.100						



^{13}C NMR Spectrum of 29ap in $CDCl_3$

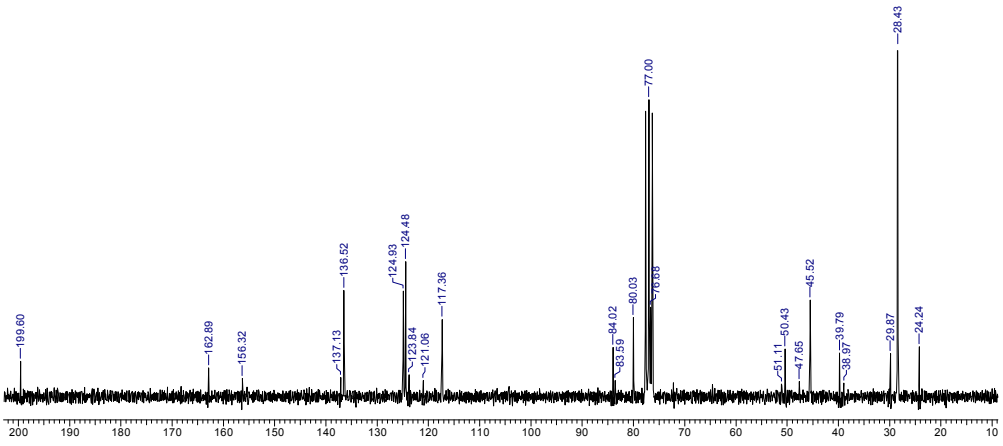
Acquisition Time (sec)	3.9584	*Comment*	suneel	*Date*	23 Oct 2013 16:15:04	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	8	*Original Points Count*	16384	*Points Count* 32768	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000				





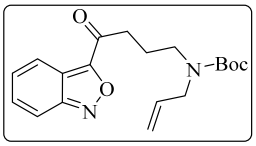
^{1}H NMR Spectrum of 31aq in $CDCl_3$

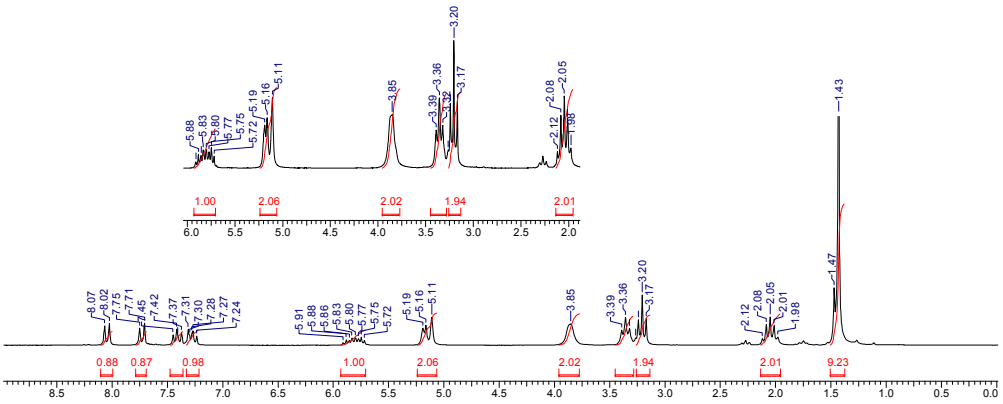
Acquisition Time (sec)	0.6832	*Comment*	Suneel	*Date*	27 Oct 2013 07:58:00	*Frequency (MHz)*	50.32
Nucleus	13C	*Number of Transients*	1000	*Original Points Count*	8192	*Points Count* 32768	*Solvent* CHLOROFORM-d
Sweep Width (Hz)	11990.04			*Temperature (grad C)*	27.000		



^{13}C NMR Spectrum of 31aq in $CDCl_3$

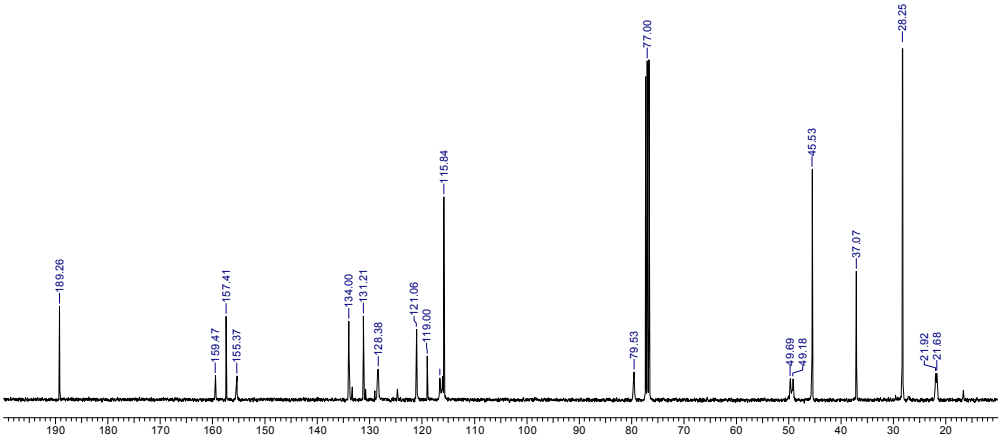
Acquisition Time (sec)	3.9584	Comment	suneel	Date	22 Oct 2013 23:21:44			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	32	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						





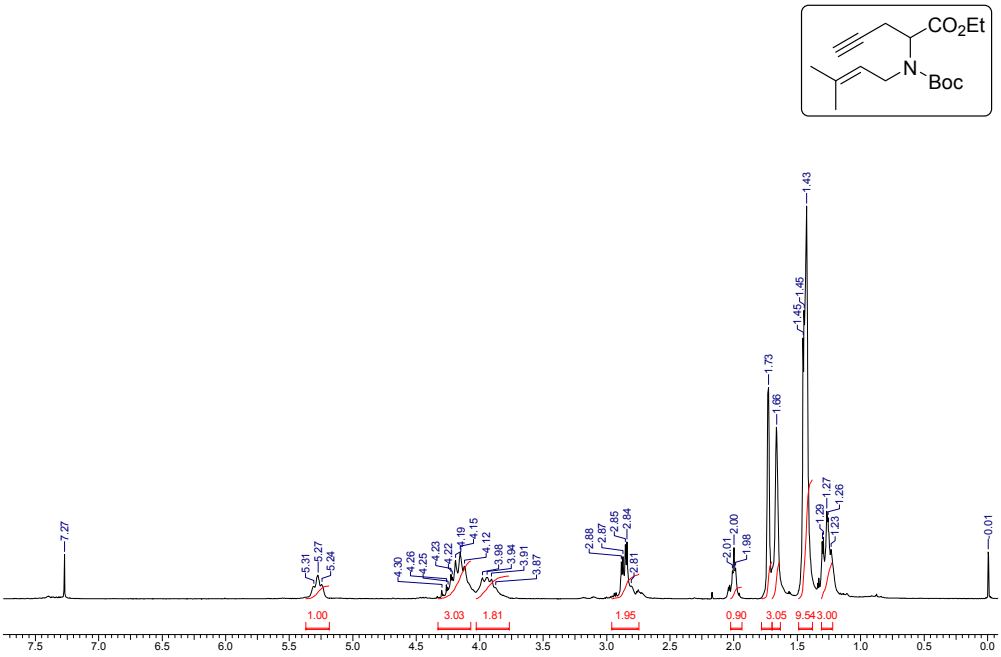
^{1}H NMR Spectrum of 29aq in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	suneel	Date	27 Oct 2013 15:25:08			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	800	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	18.800						



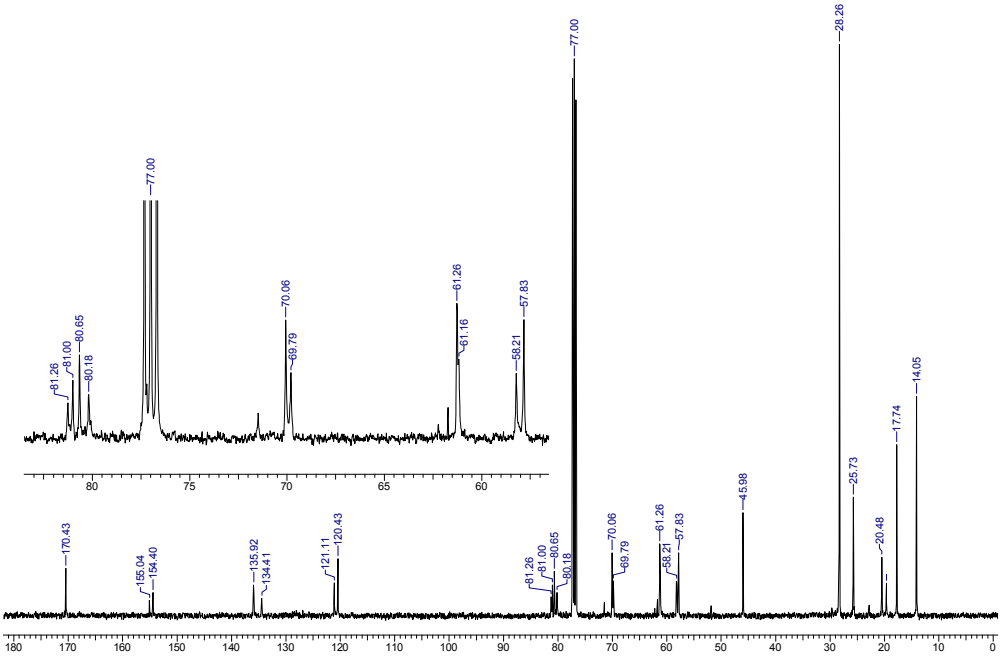
^{13}C NMR Spectrum of 29aq in $CDCl_3$

Acquisition Time (sec)	3.9584	*Comment*	suneel	*Date*	14 Mar 2013 05:35:04	*Frequency (MHz)*	200.13
Nucleus	1H	*Number of Transients*	16	*Original Points Count*	16384	*Points Count*	32768	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	4138.95	*Temperature (grad C)*	27.000						



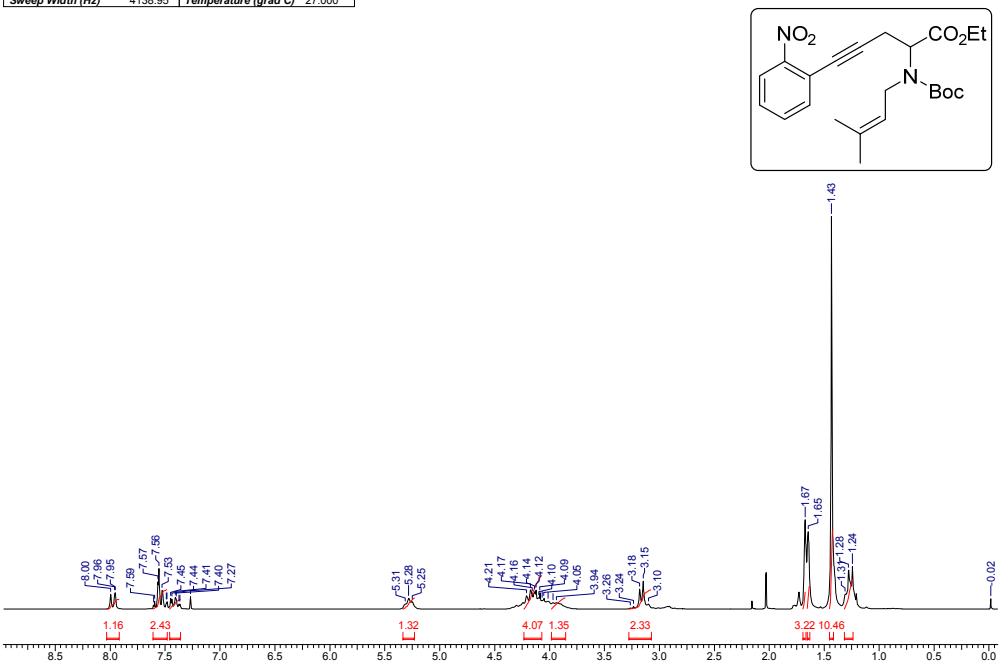
^{1}H NMR Spectrum of 34 in $CDCl_3$

Acquisition Time (sec)	1.0434	*Comment*	suneel	*Date*	17 Mar 2013 12:58:43	*Frequency (MHz)*	100.53
Nucleus	13C	*Number of Transients*	800	*Original Points Count*	26214	*Points Count*	26214	*Solvent*	CHLOROFORM-d
Sweep Width (Hz)	25124.29	*Temperature (grad C)*	19.900						



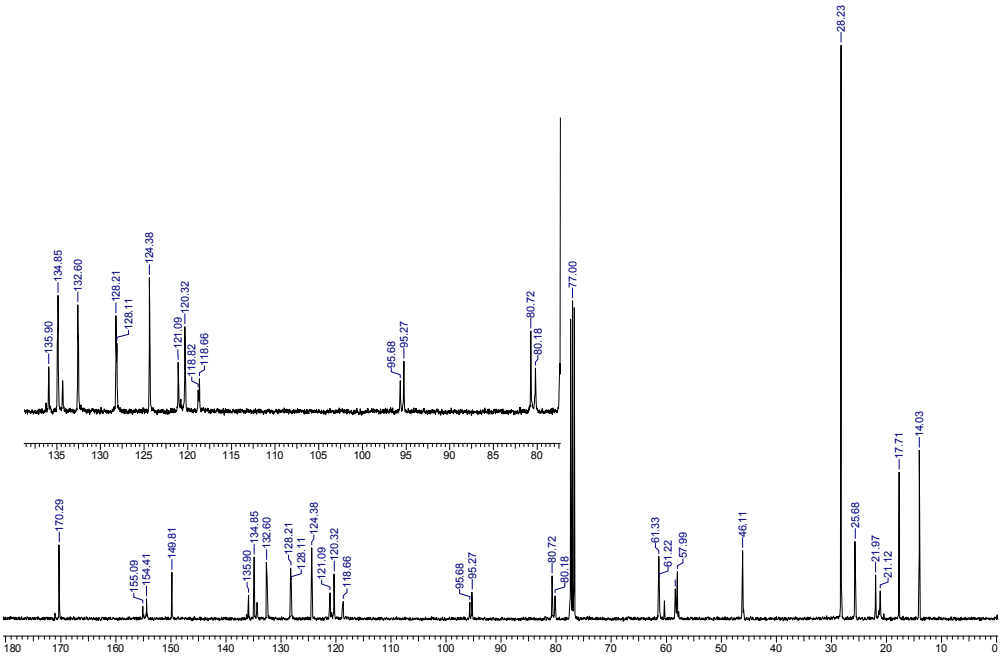
^{13}C NMR Spectrum of 34 in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	suneel	Date	14 Mar 2013 05:24:24			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	16	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

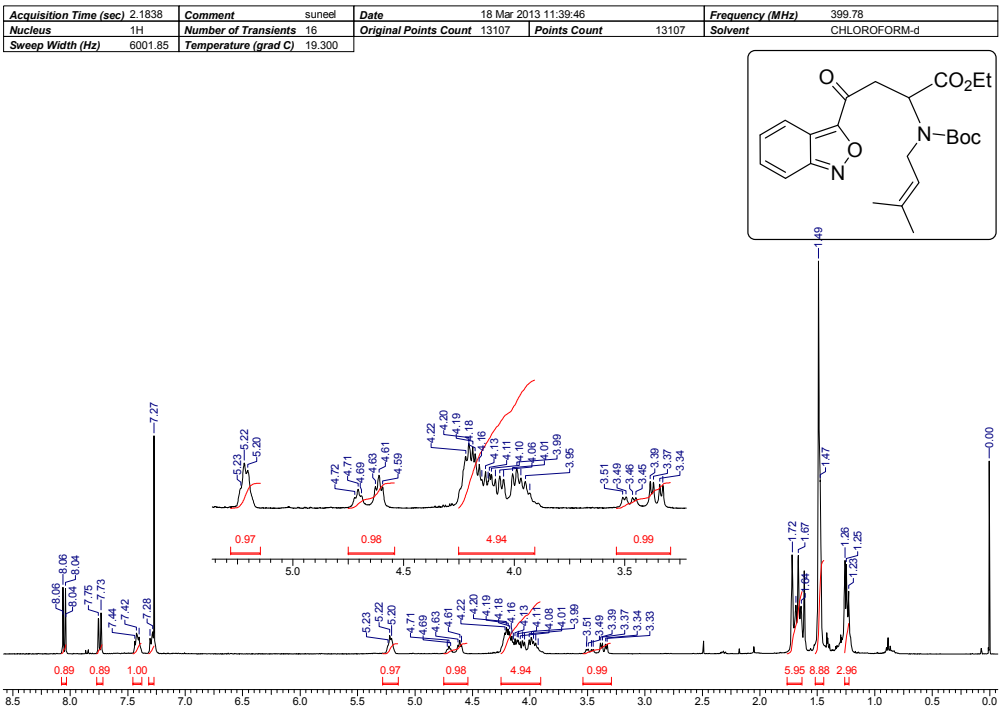


^{1}H NMR Spectrum of 33 in $CDCl_3$

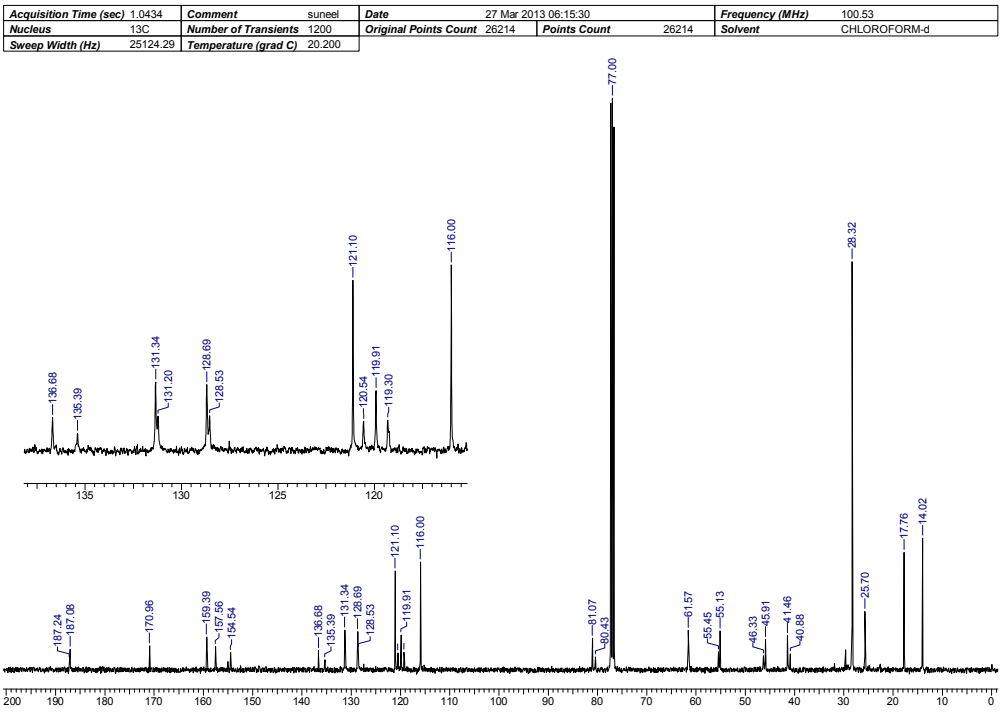
Acquisition Time (sec)	1.0434	Comment	suneel	Date	17 Mar 2013 14:42:05			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	800	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	19.900						



^{13}C NMR Spectrum of 33 in $CDCl_3$

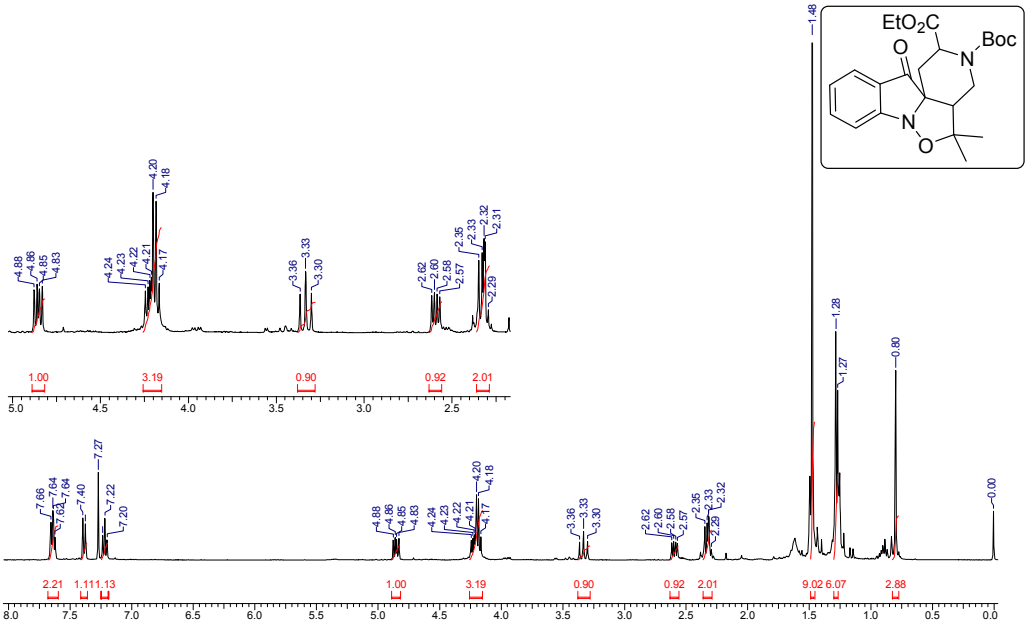


^{1}H NMR Spectrum of 36 in $CDCl_3$



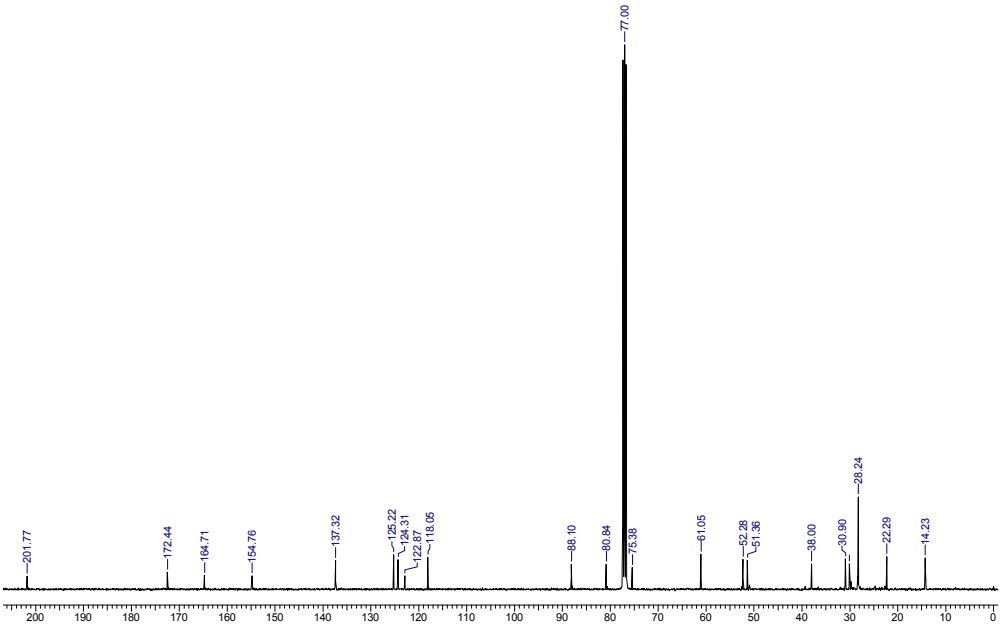
^{13}C NMR Spectrum of 36 in $CDCl_3$

Acquisition Time (sec)	1.9923				
Comment	Suneel 1H				
Date	30 Mar 2013 22:56:08	Frequency (MHz)	400.13	Nucleus	1H
Number of Transients	64	Original Points Count	16384	Points Count	32768
Solvent	CHLOROFORM-d	Sweep Width (Hz)	8223.43	Temperature (grad C)	24.900



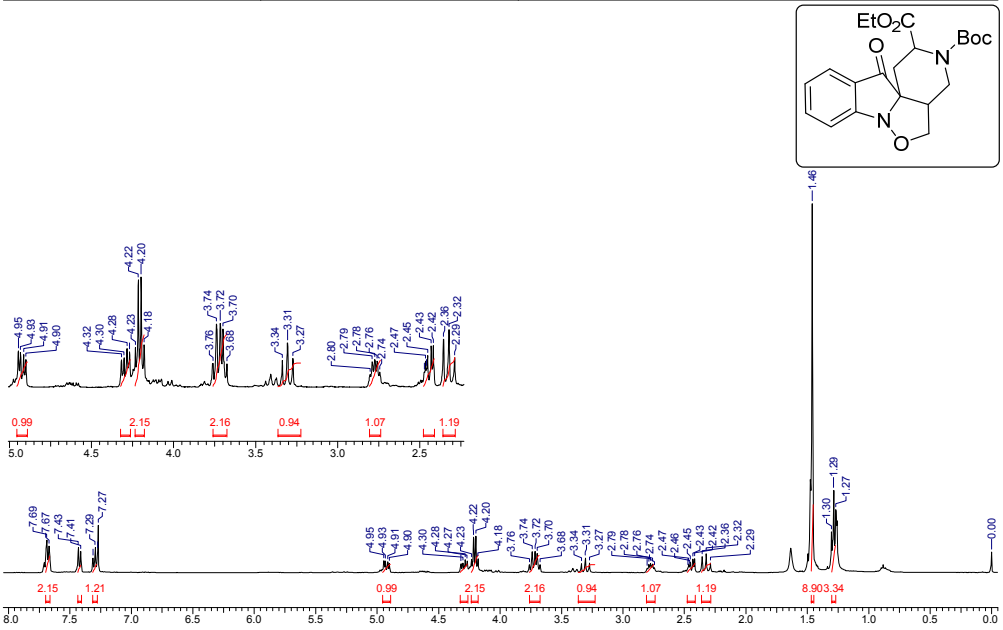
^{1}H NMR Spectrum of 38 in $CDCl_3$

Acquisition Time (sec)	0.6488						
Comment	13C						
Date	31 Mar 2013 07:55:52	Frequency (MHz)	100.61	Nucleus	13C	Number of Transients	6087
Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d	Sweep Width (Hz)	25251.75
Temperature (grad C)	24.900						



^{13}C NMR Spectrum of 38 in $CDCl_3$

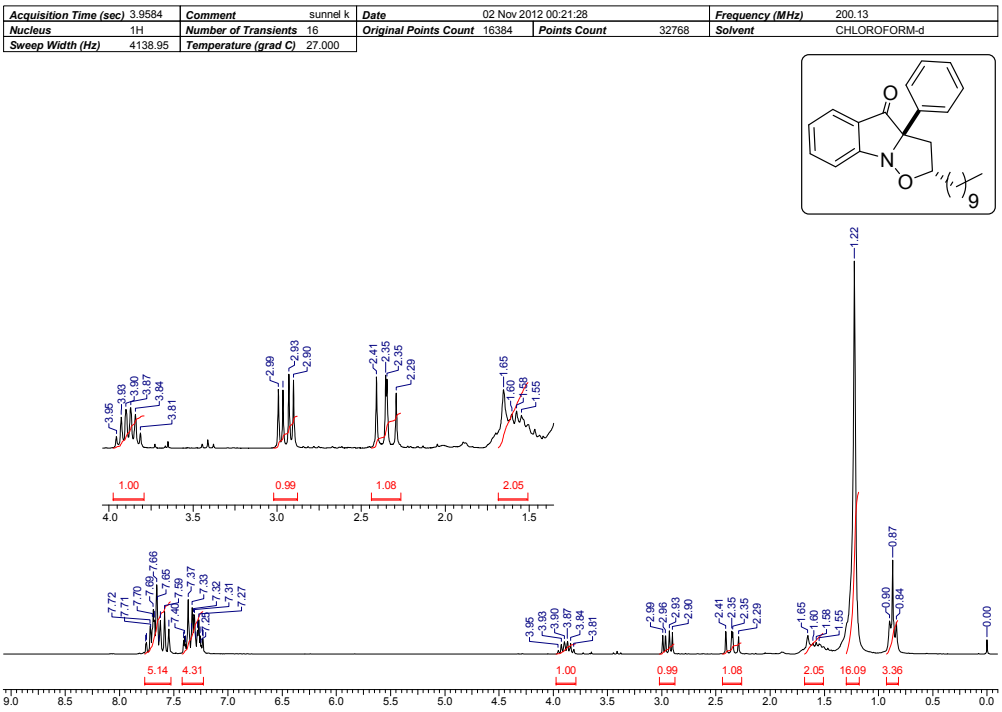
Acquisition Time (sec)	2.0447				
Comment	Santosh 1H				
Date	27 Nov 2013 20:41:44	Frequency (MHz)	400.13	Nucleus	1H
Number of Transients	64	Original Points Count	16384	Points Count	32768
Solvent	CHLOROFORM-d	Sweep Width (Hz)	8012.58	Temperature (grad C)	21.700



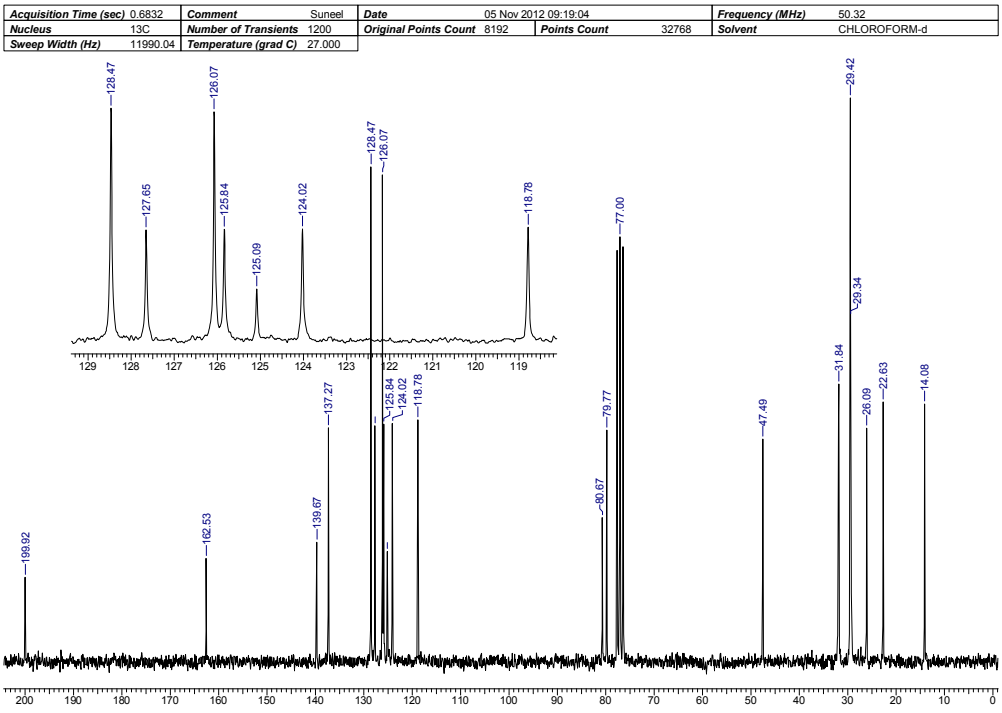
^{1}H NMR Spectrum of 43 in $CDCl_3$

Acquisition Time (sec)	0.6488				
Comment	13C				
Date	27 Nov 2013 21:50:00	Frequency (MHz)	100.61	Nucleus	13C
Number of Transients	1643	Original Points Count	16384	Points Count	32768
Solvent	CHLOROFORM-d	Sweep Width (Hz)	25251.75	Temperature (grad C)	22.000

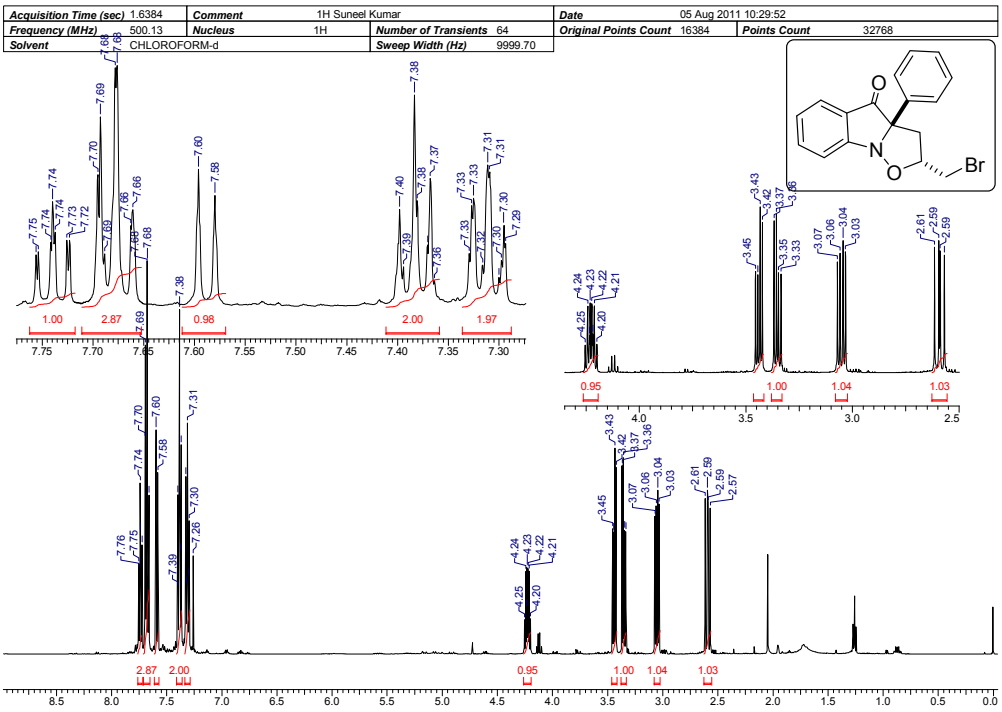
^{13}C NMR Spectrum of 43 in $CDCl_3$



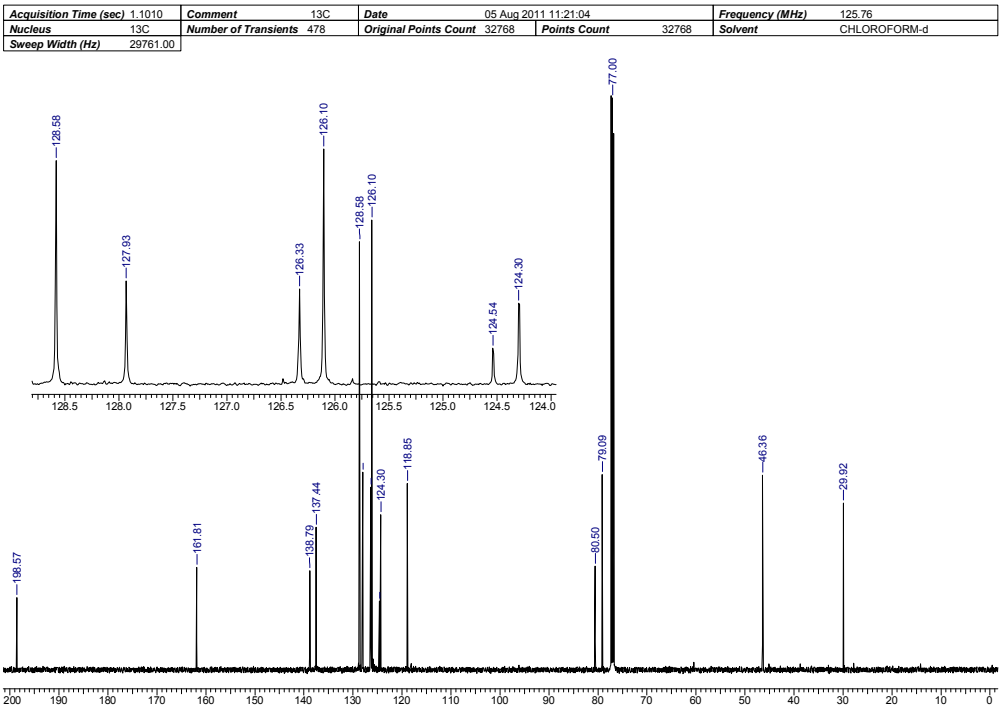
^{1}H NMR Spectrum of 46aa in $CDCl_3$



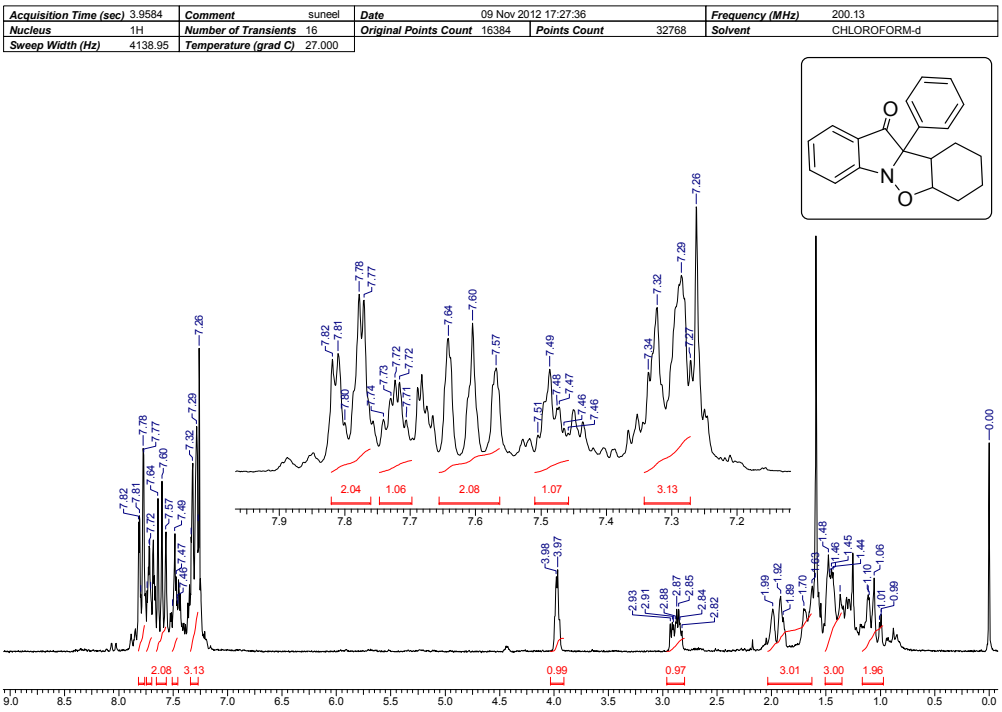
^{13}C NMR Spectrum of 46aa in $CDCl_3$



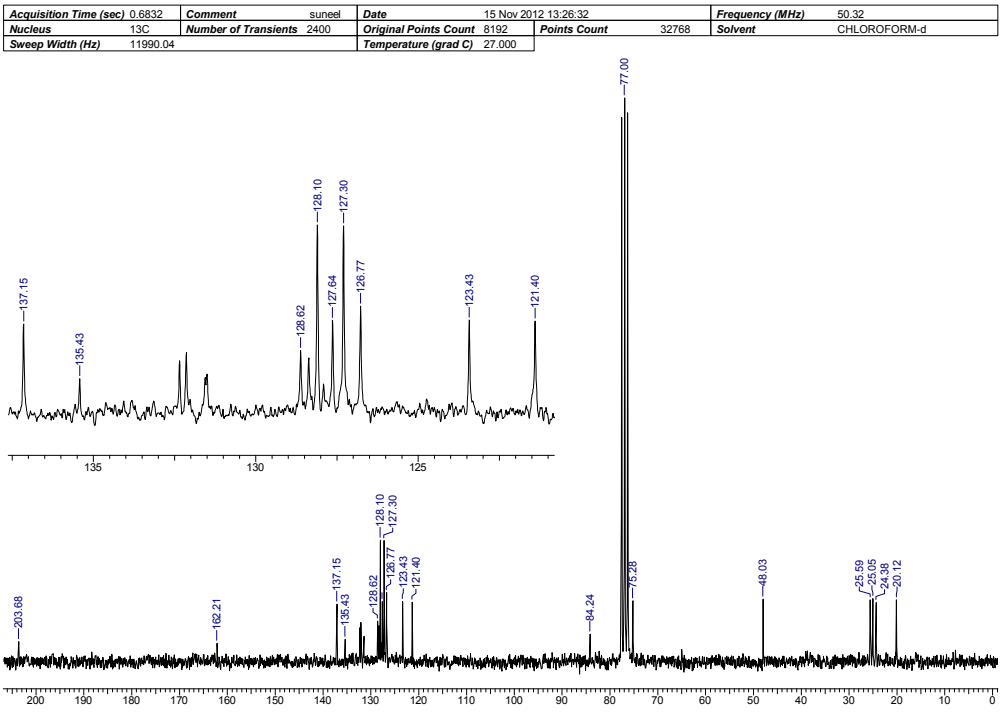
^{1}H NMR Spectrum of 46ac in $CDCl_3$



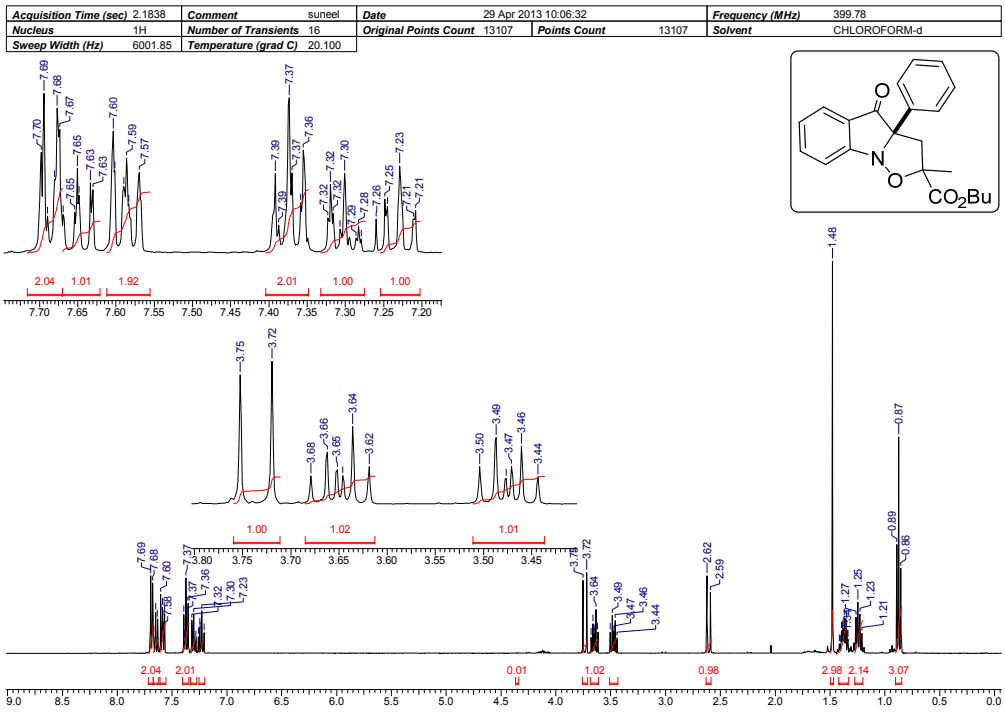
^{13}C NMR Spectrum of 46ac in $CDCl_3$



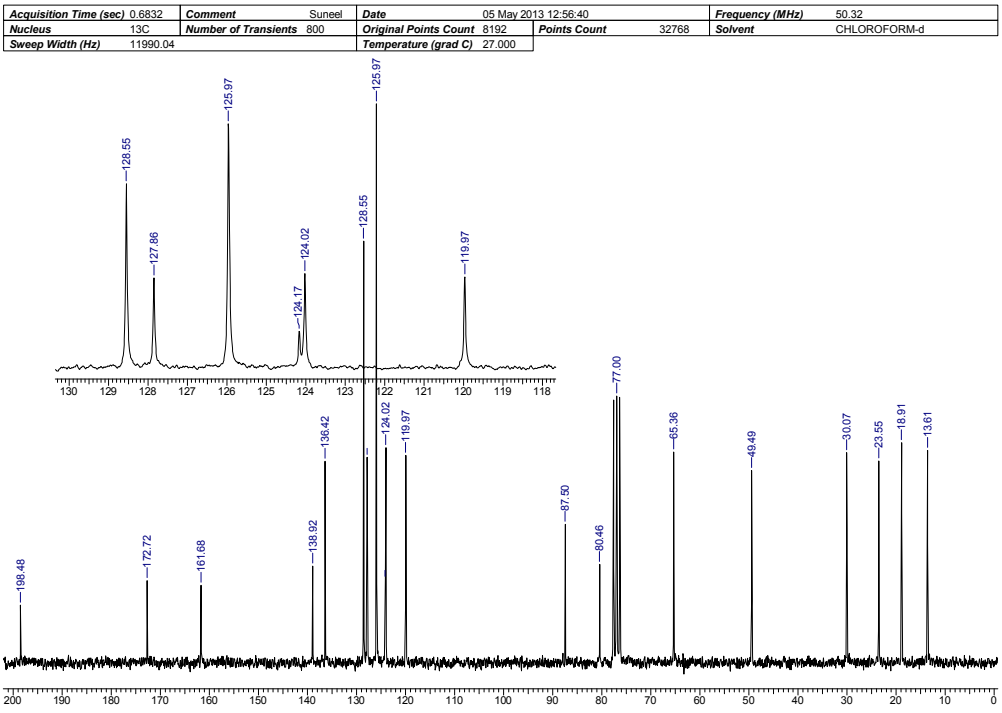
^{1}H NMR Spectrum of 46ae in $CDCl_3$



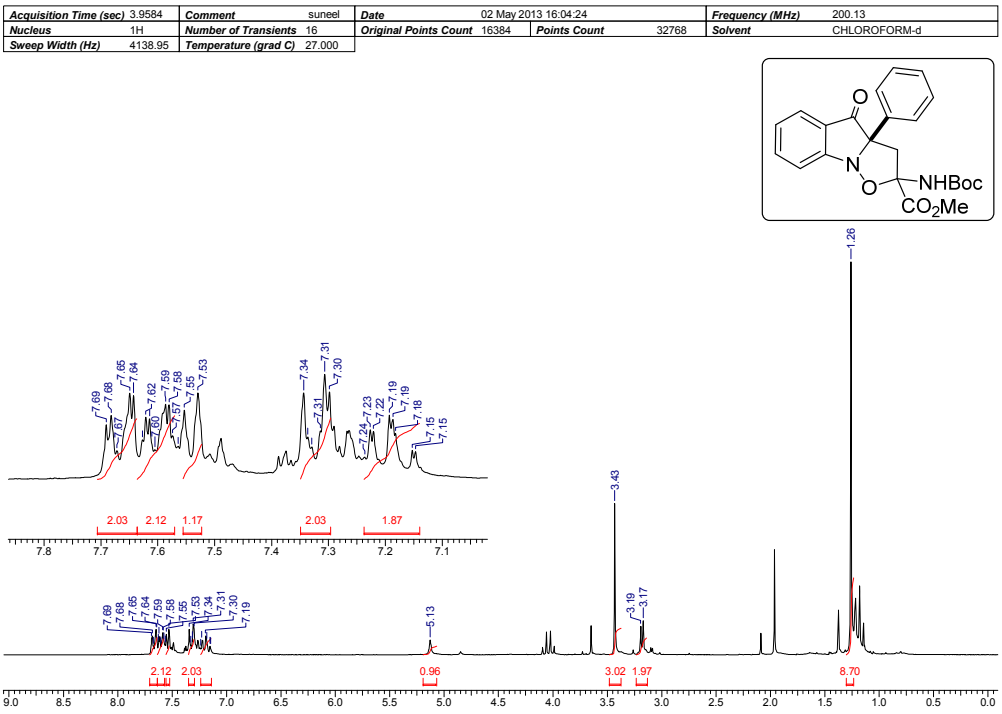
^{13}C NMR Spectrum of 46ae in $CDCl_3$



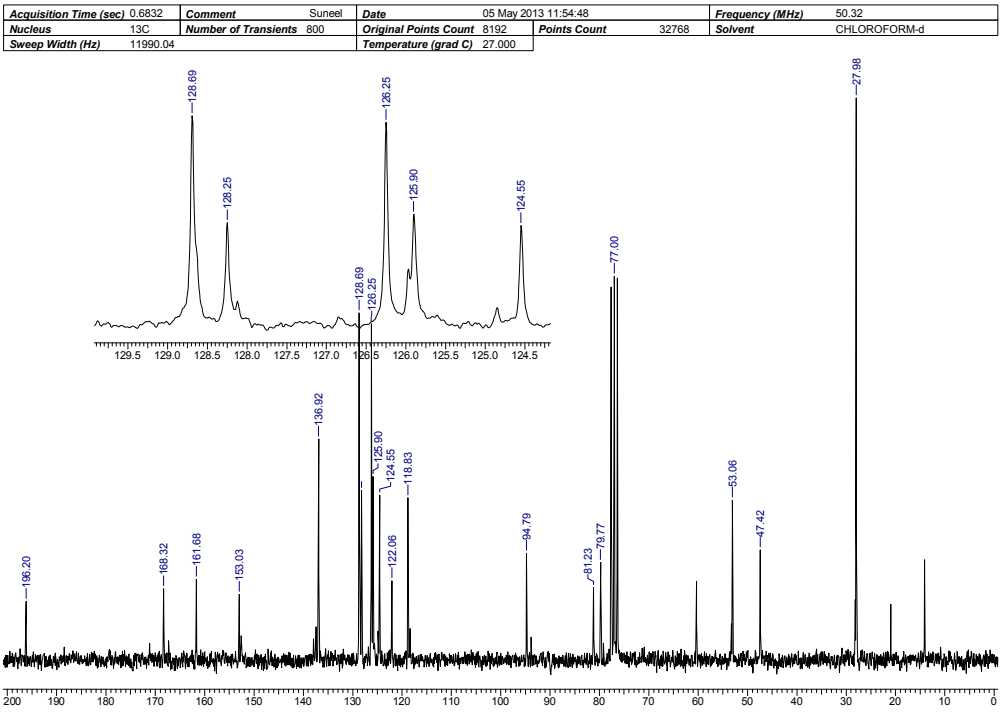
^{1}H NMR Spectrum of 46ag in $CDCl_3$



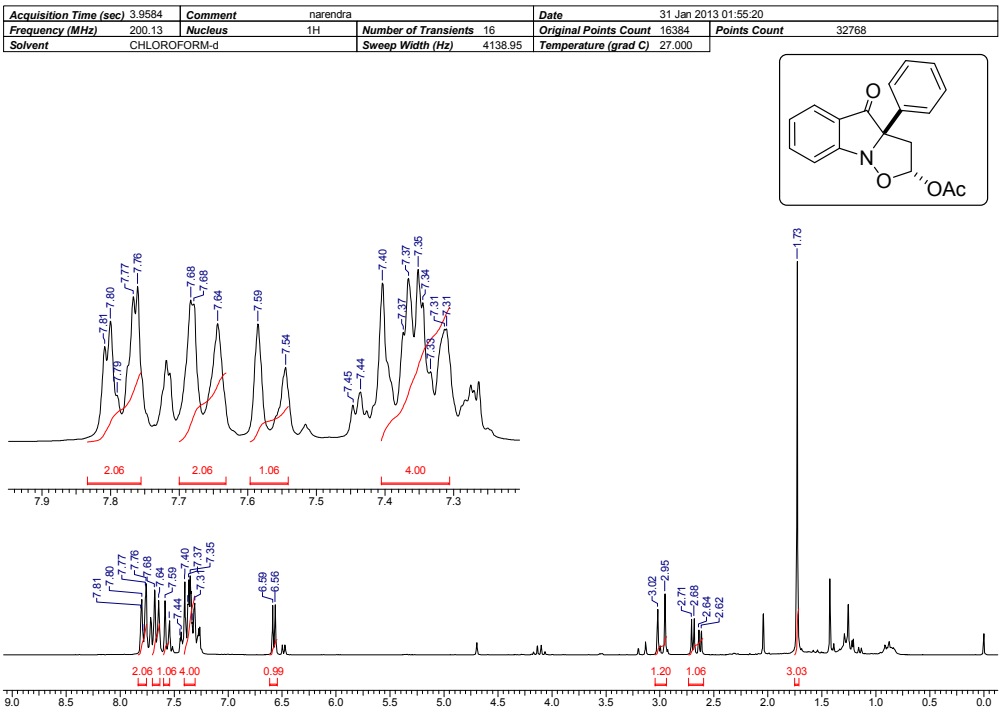
^{13}C NMR Spectrum of 46ag in $CDCl_3$



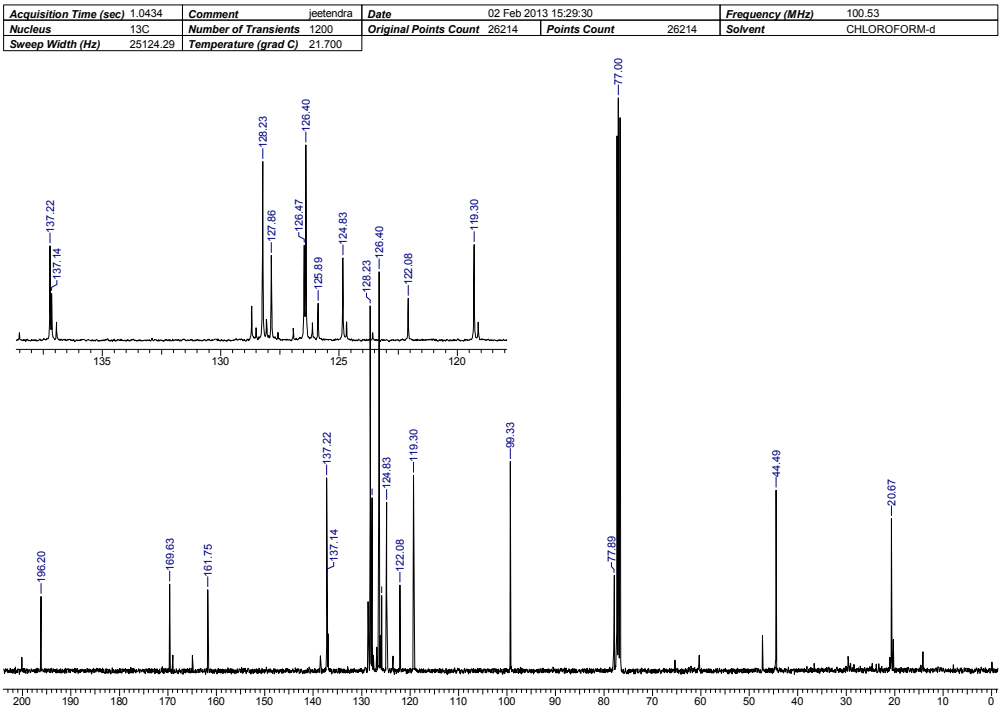
^{1}H NMR Spectrum of 46ah in $CDCl_3$



^{13}C NMR Spectrum of 46ah in $CDCl_3$

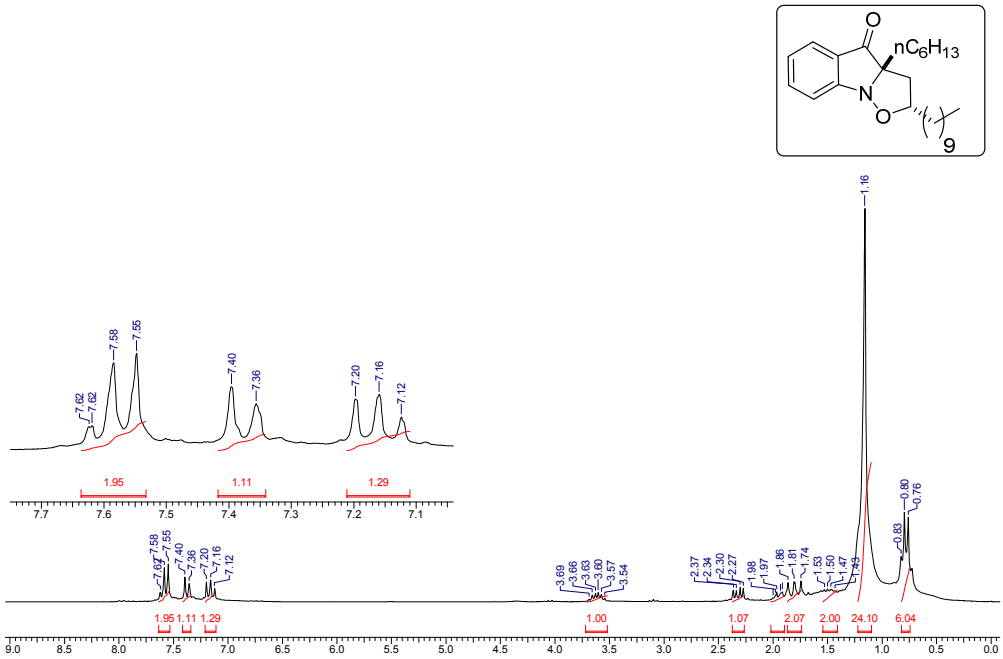


^{1}H NMR Spectrum of 46ai in $CDCl_3$



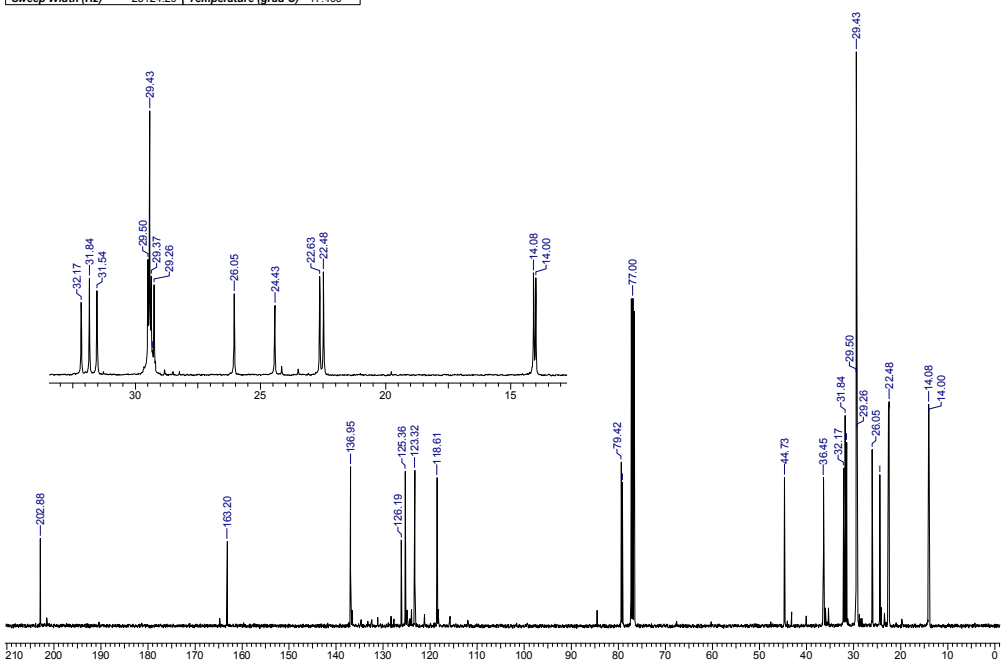
^{13}C NMR Spectrum of 46ai in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	suneel	Date	01 May 2013 02:27:20			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	16	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

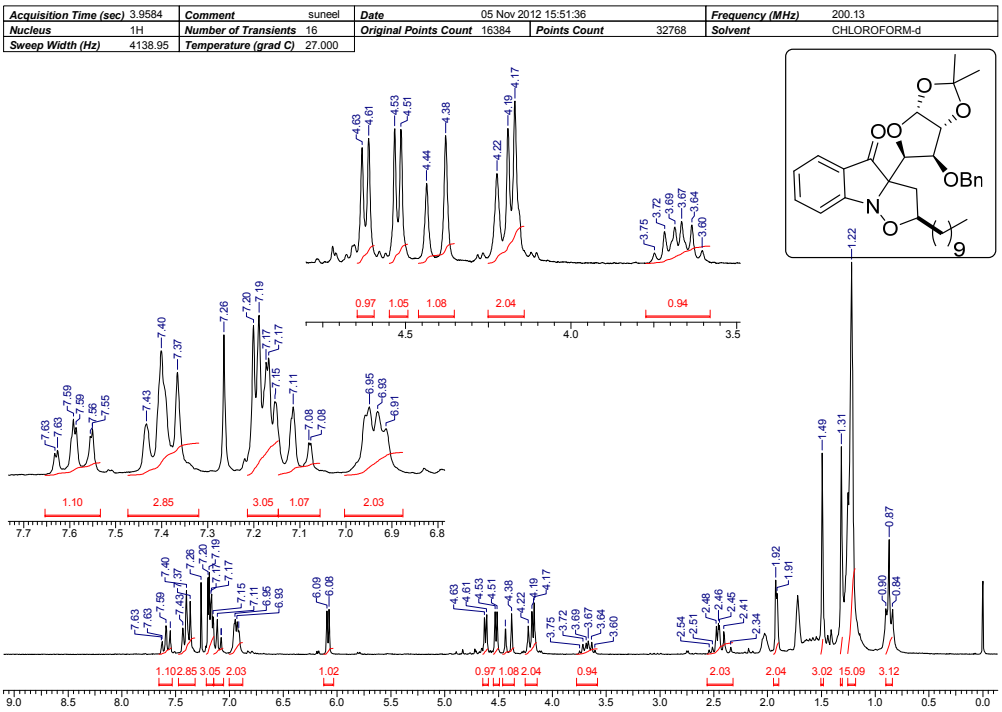


^{1}H NMR Spectrum of 46ea in $CDCl_3$

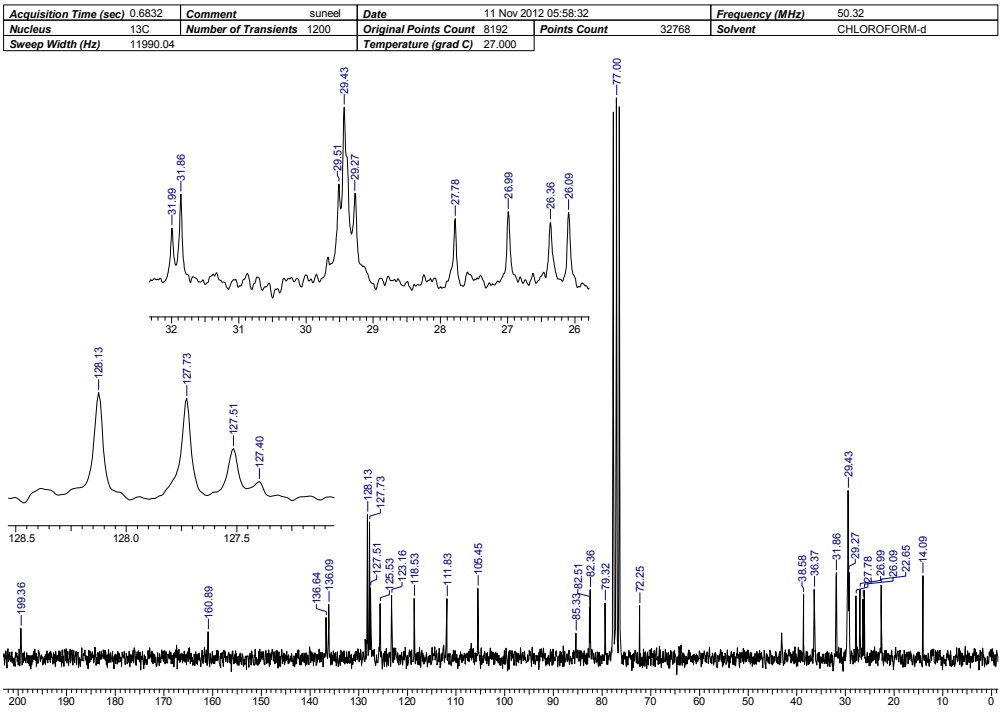
Acquisition Time (sec)	1.0434	Comment	suneel	Date	04 May 2013 09:39:49			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	800	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	17.400						



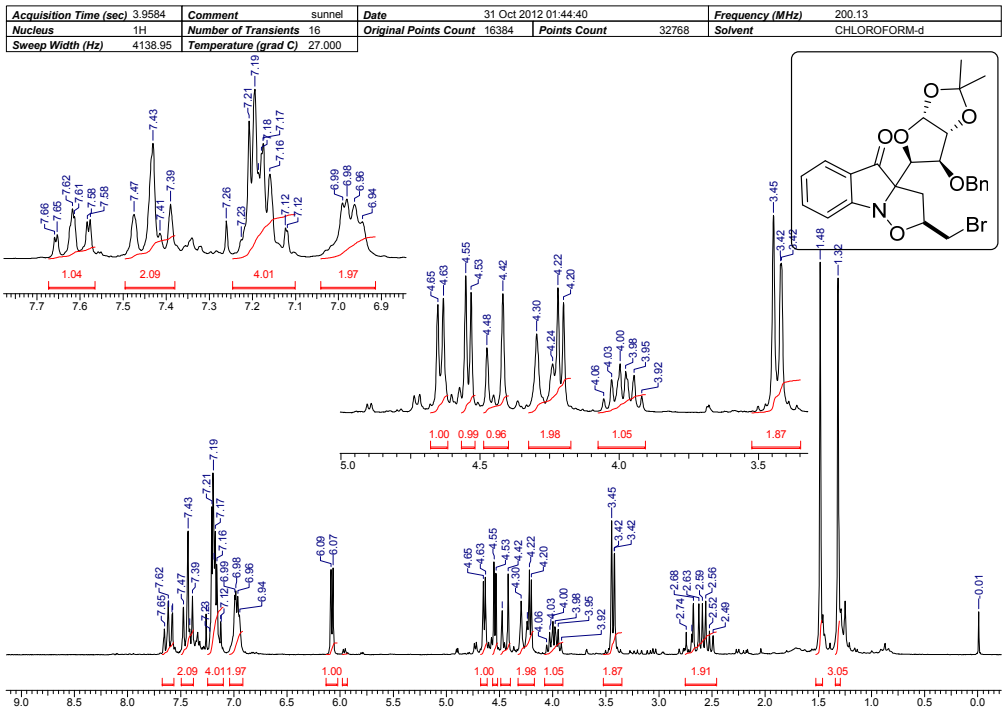
^{13}C NMR Spectrum of 46ea in $CDCl_3$



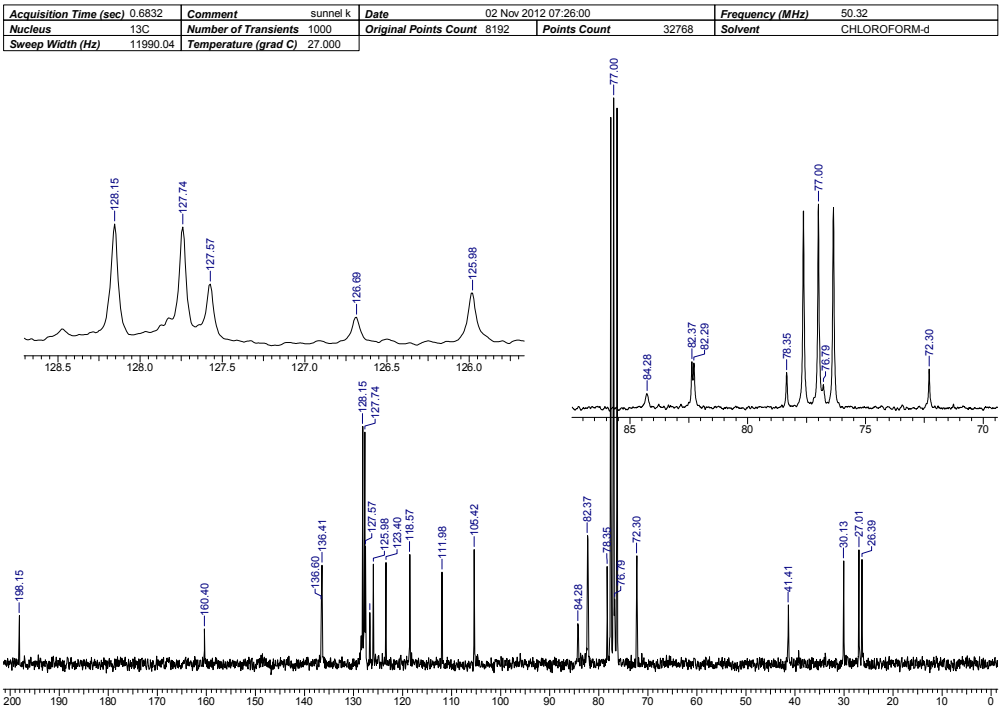
^{1}H NMR Spectrum of 46ga in $CDCl_3$



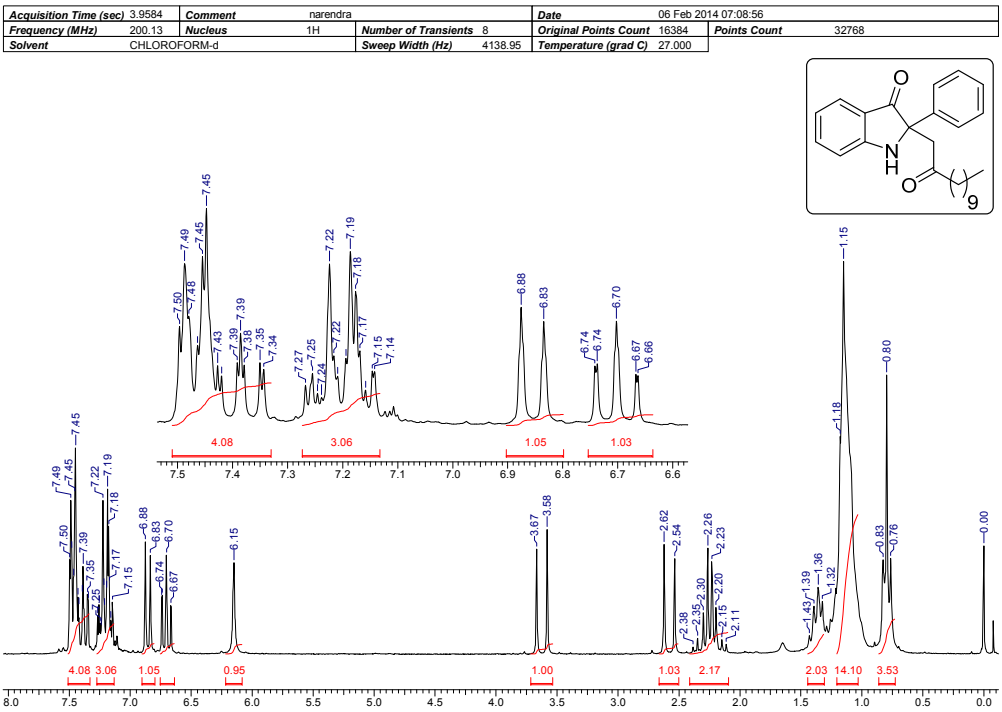
^{13}C NMR Spectrum of 46ga in $CDCl_3$



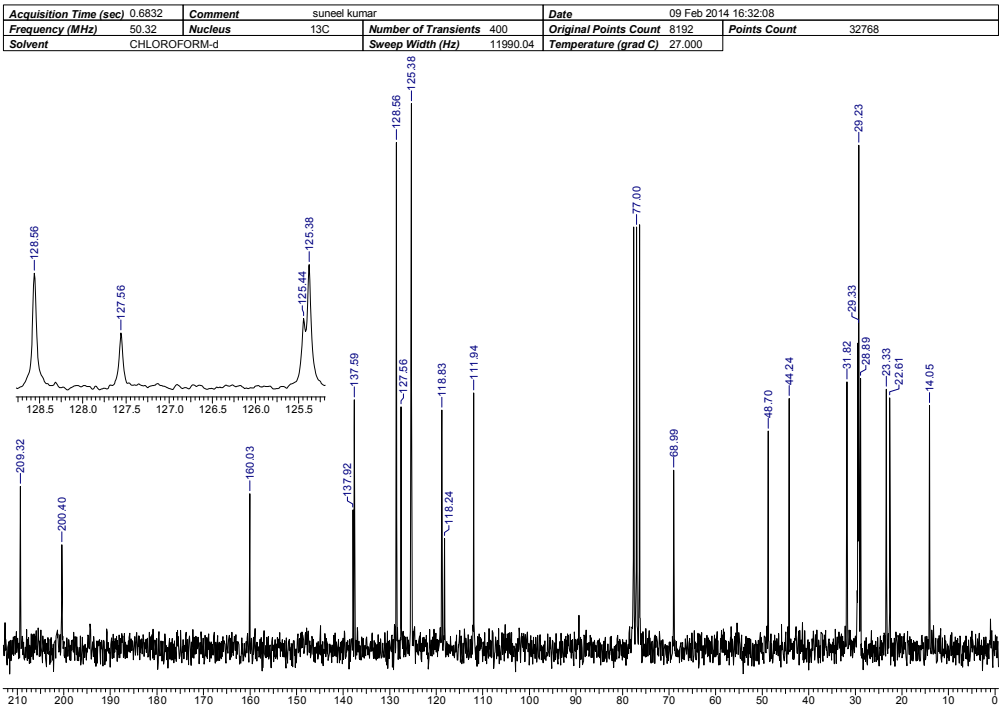
^{1}H NMR Spectrum of 46gc in $CDCl_3$



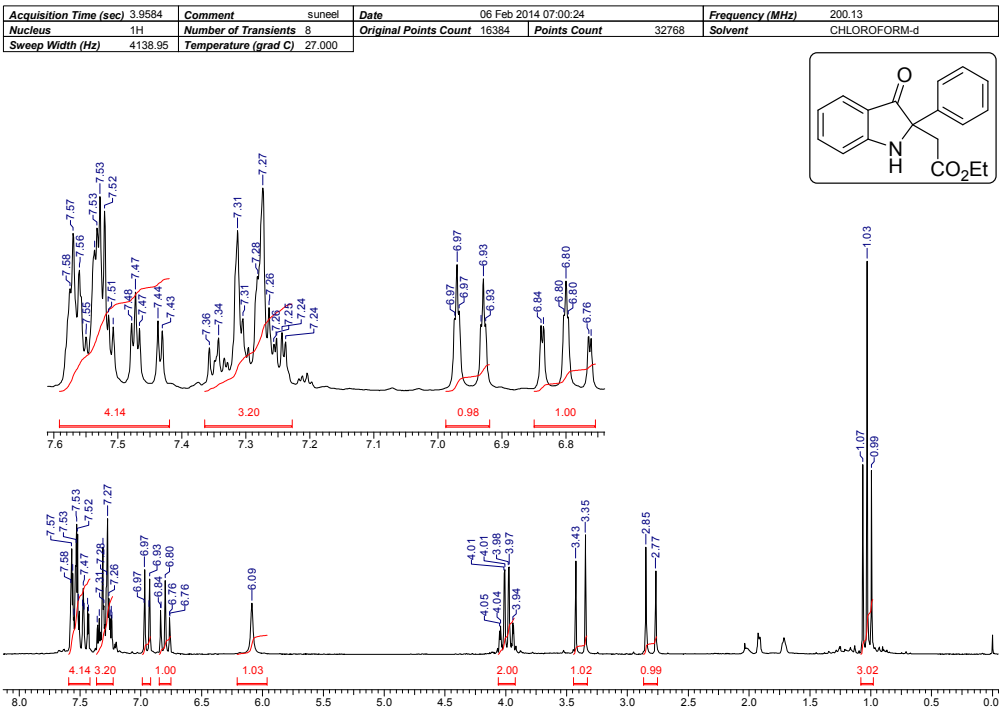
^{13}C NMR Spectrum of 46gc in $CDCl_3$



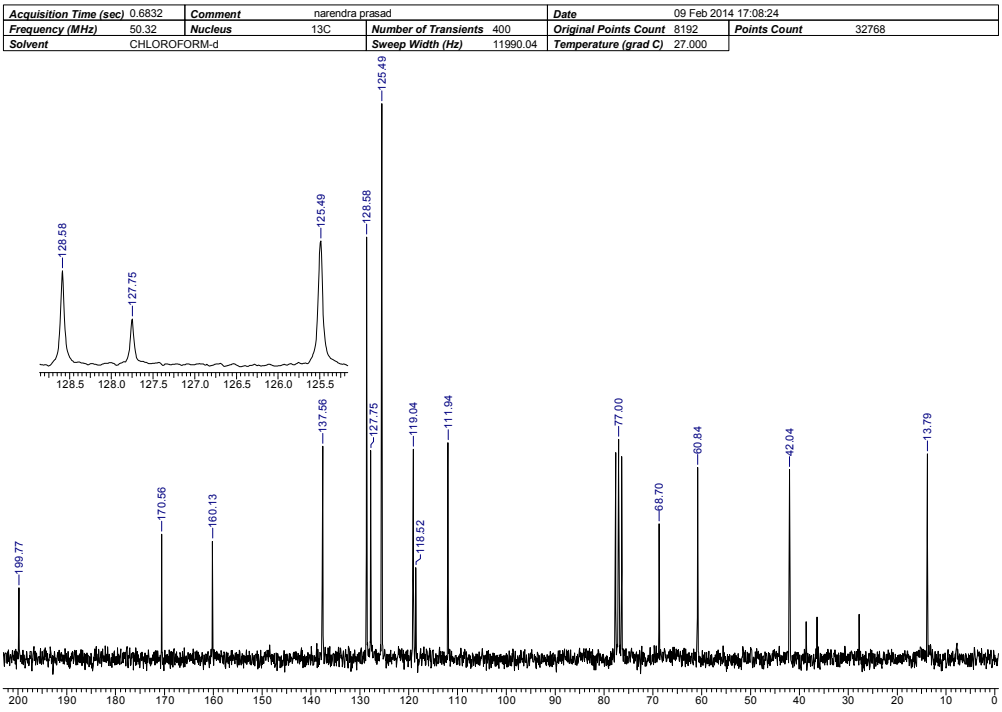
^{1}H NMR Spectrum of 47aa in $CDCl_3$



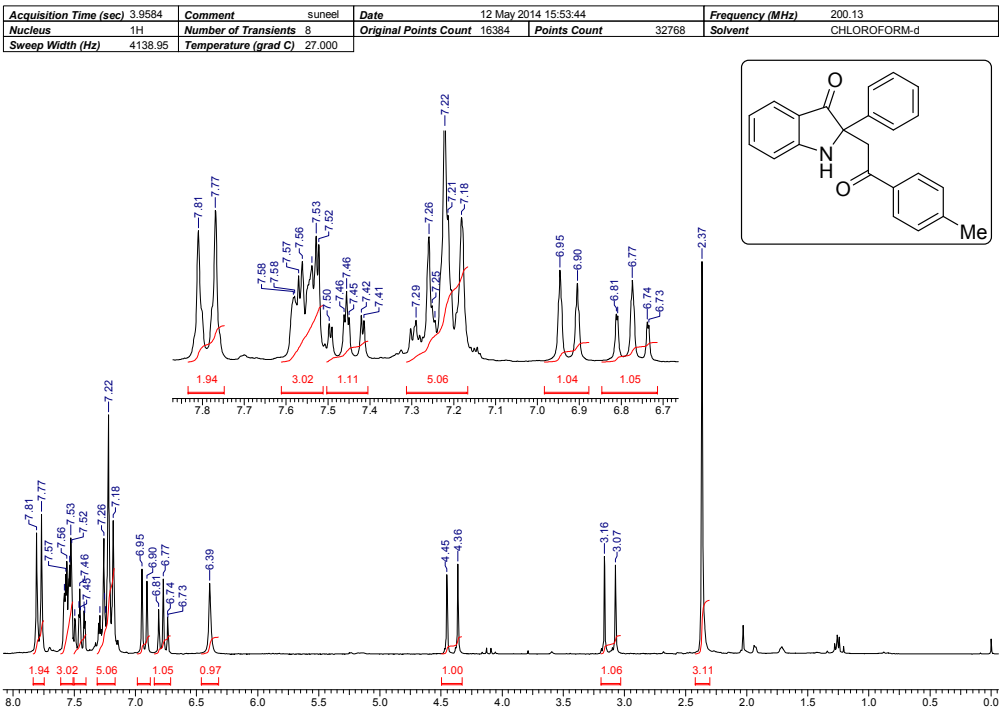
^{13}C NMR Spectrum of 47aa in $CDCl_3$



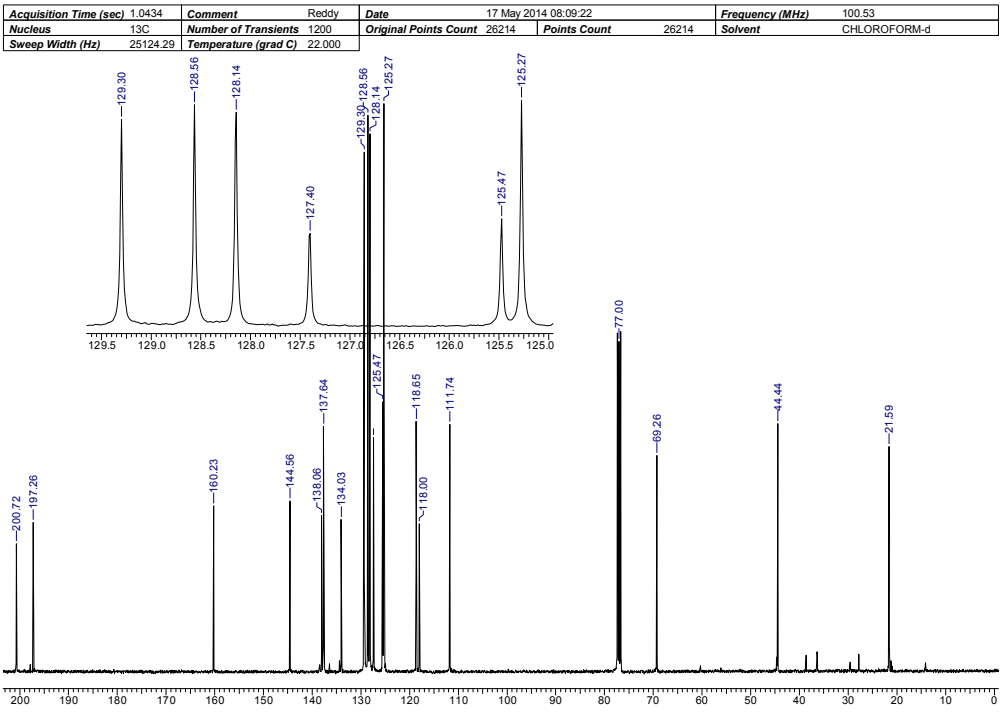
^{1}H NMR Spectrum of 47aj in $CDCl_3$



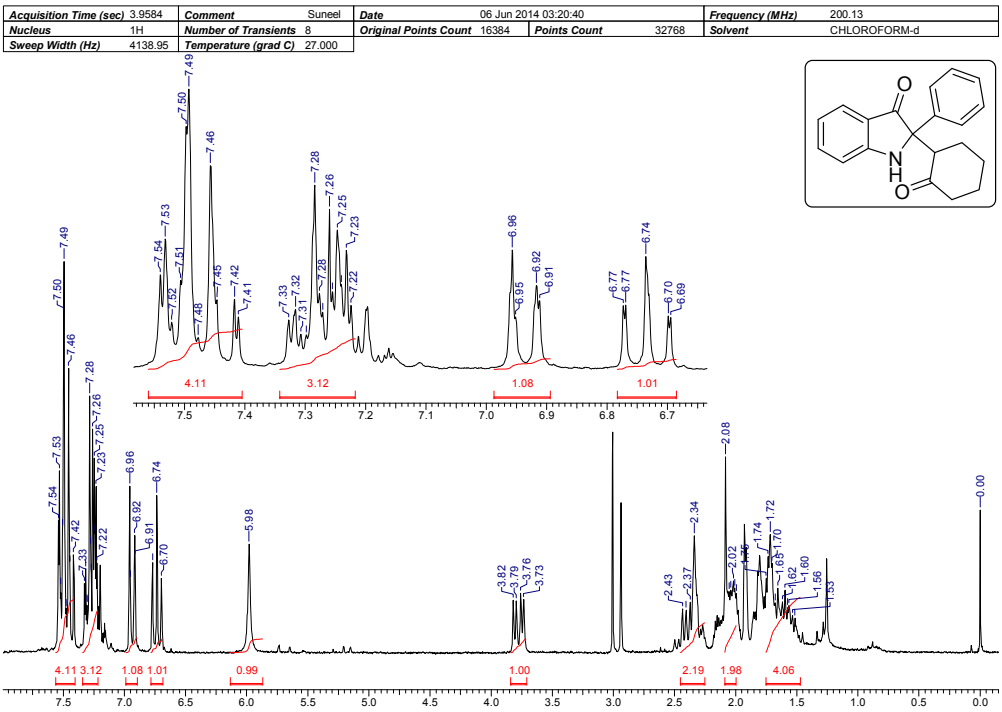
^{13}C NMR Spectrum of 47aj in $CDCl_3$



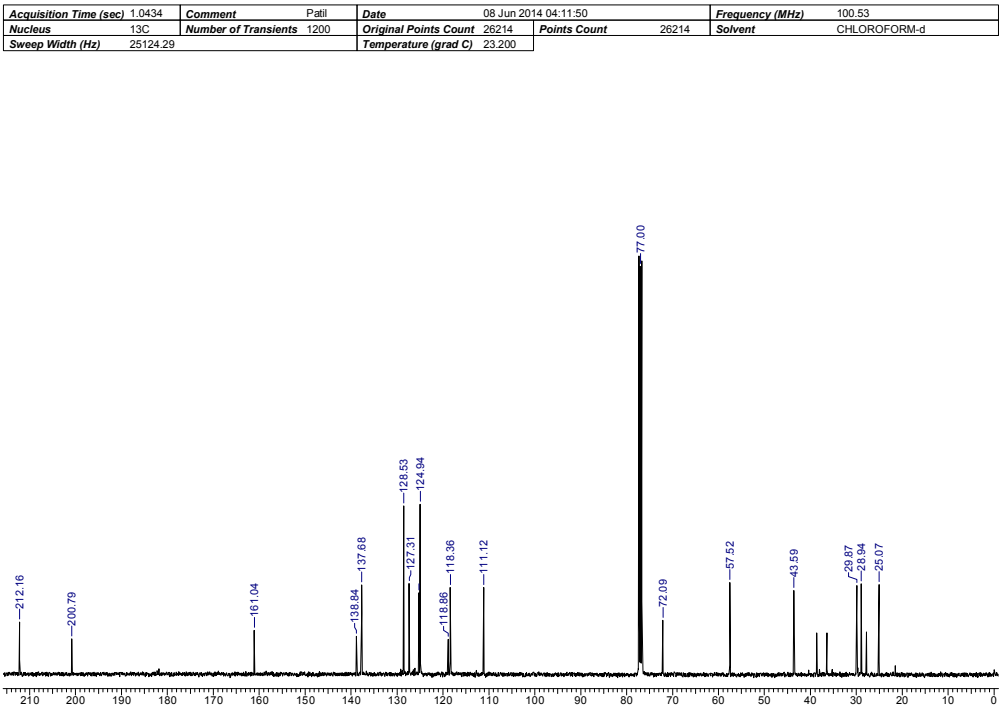
^{1}H NMR Spectrum of 47al in $CDCl_3$



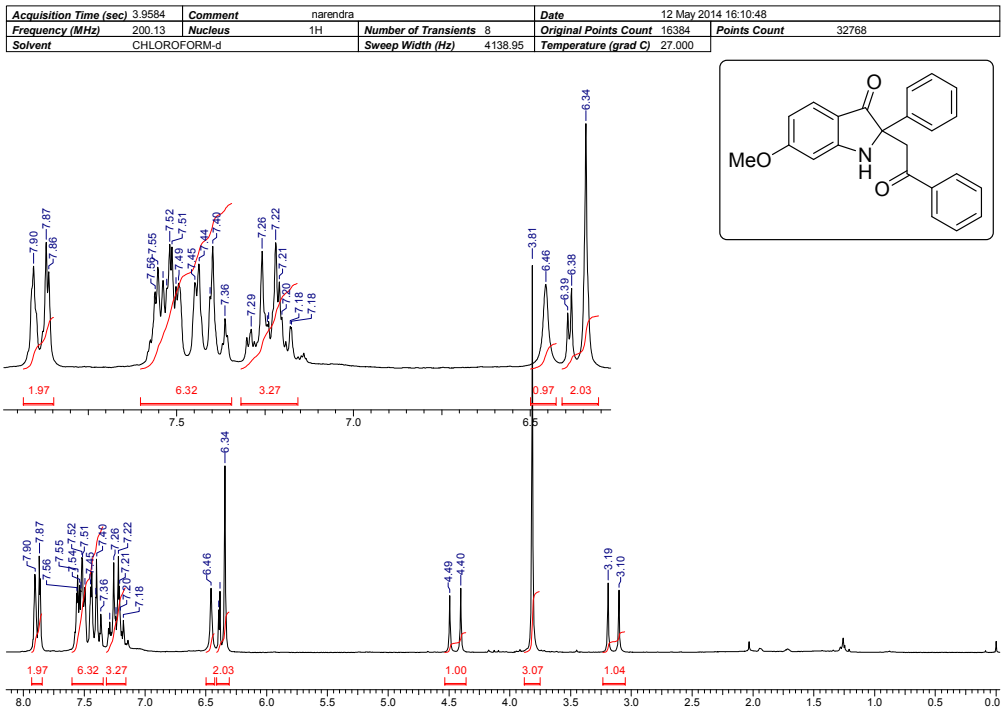
^{13}C NMR Spectrum of 47al in $CDCl_3$



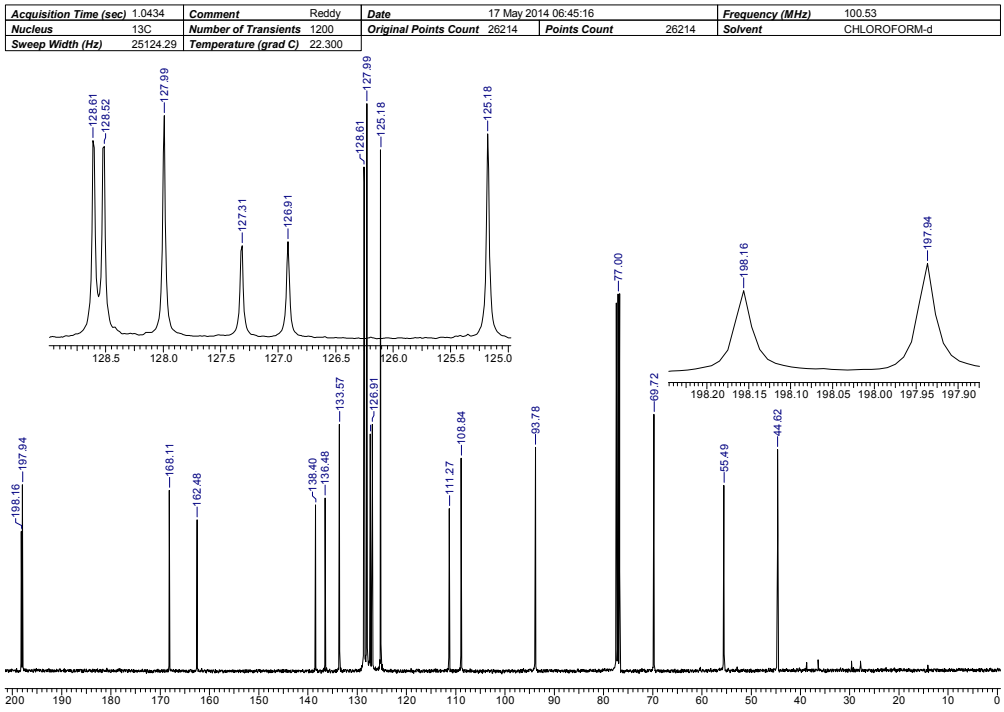
^{1}H NMR Spectrum of 47ae in $CDCl_3$



^{13}C NMR Spectrum of 47ae in $CDCl_3$

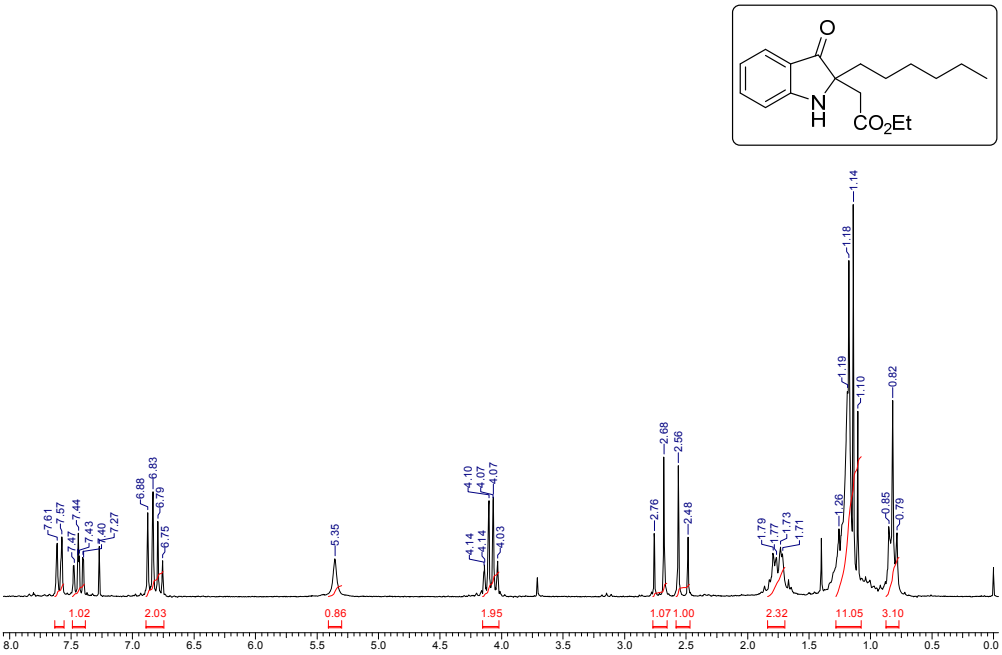


^{1}H NMR Spectrum of 47hb in $CDCl_3$



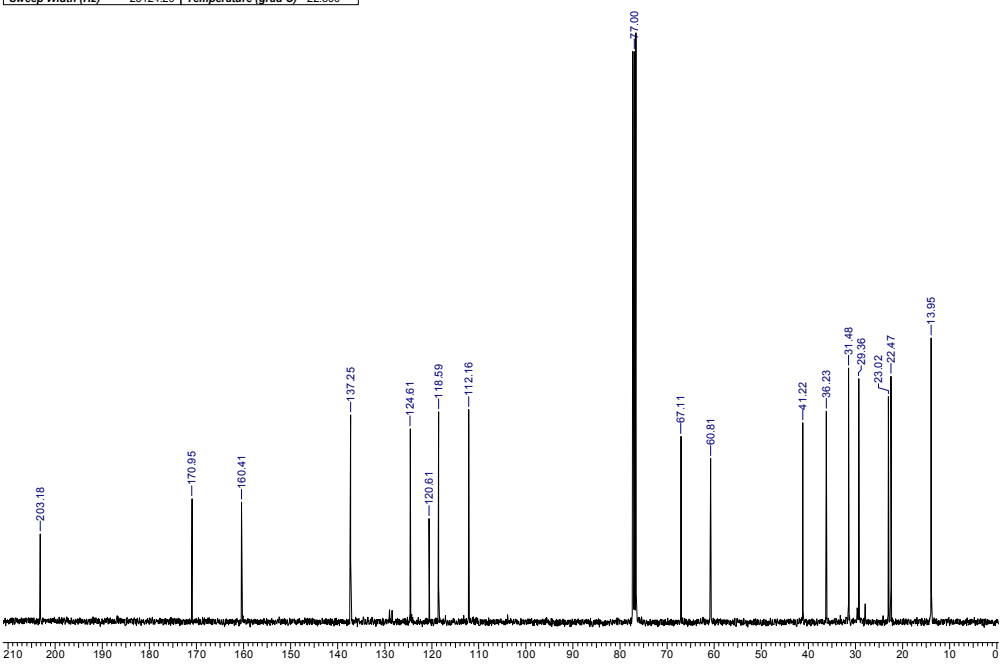
^{13}C NMR Spectrum of 47hb in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Kumar	Date	26 Feb 2014 15:43:04	Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000				



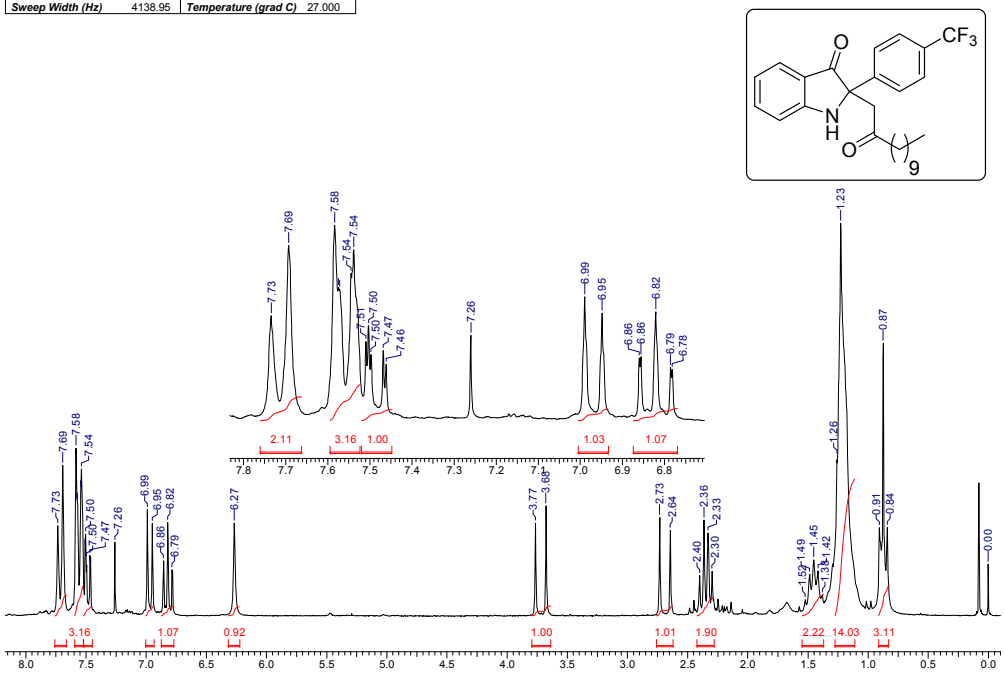
^{1}H NMR Spectrum of 47ej in $CDCl_3$

Acquisition Time (sec)	1.0434	Comment	Suneel	Date	03 Mar 2014 00:41:26	Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	600	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	22.300				



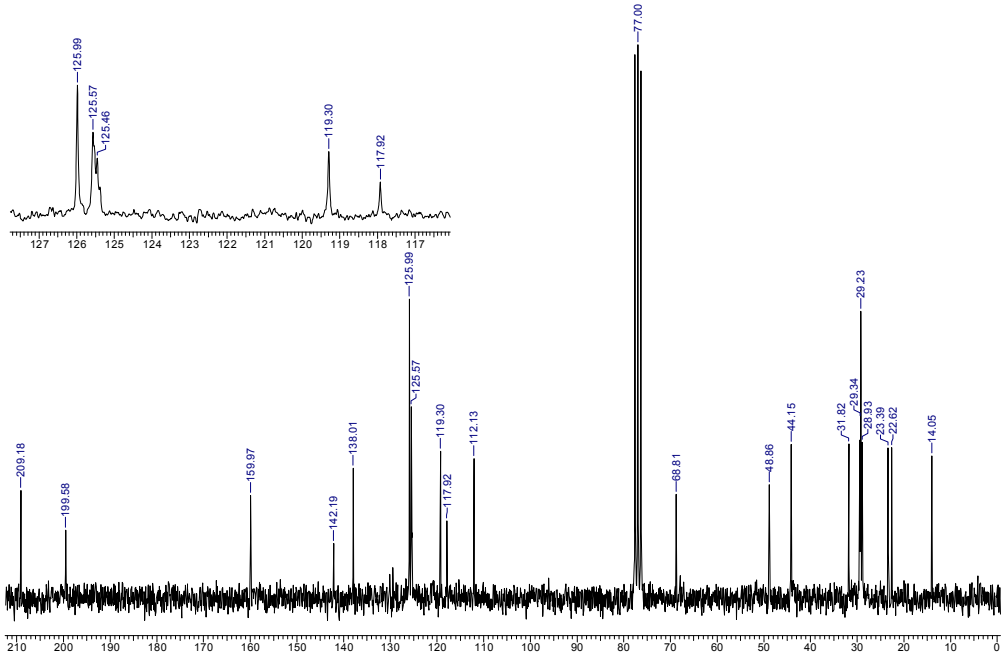
^{13}C NMR Spectrum of 47ej in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	sunnel	Date	26 May 2014 21:50:00			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						



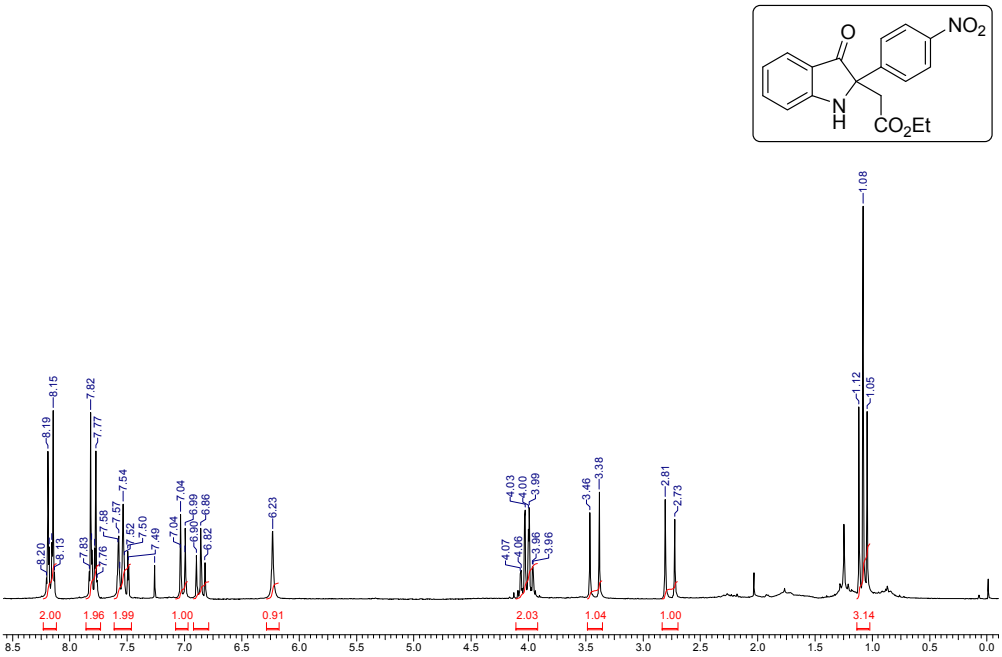
^{1}H NMR Spectrum of 47ka in $CDCl_3$

Acquisition Time (sec)	0.6832	Comment	Suneel	Date	25 May 2014 23:51:36			Frequency (MHz)	50.32
Nucleus	13C	Number of Transients	800	Original Points Count	8192	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	11990.04			Temperature (grad C)	27.000				



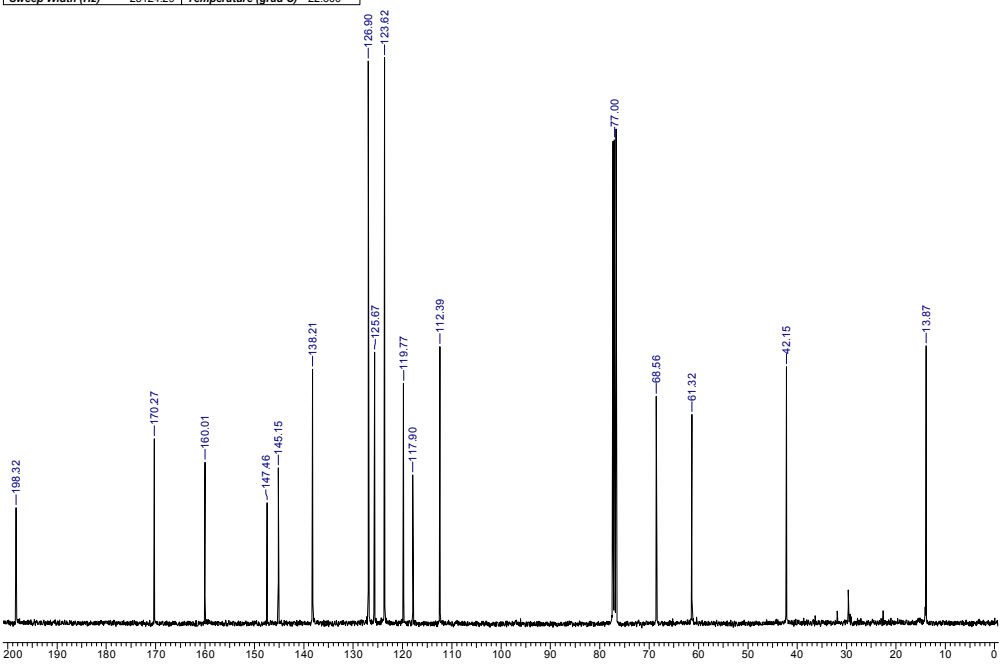
^{13}C NMR Spectrum of 47ka in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	Suneel	Date	27 May 2014 14:58:16			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

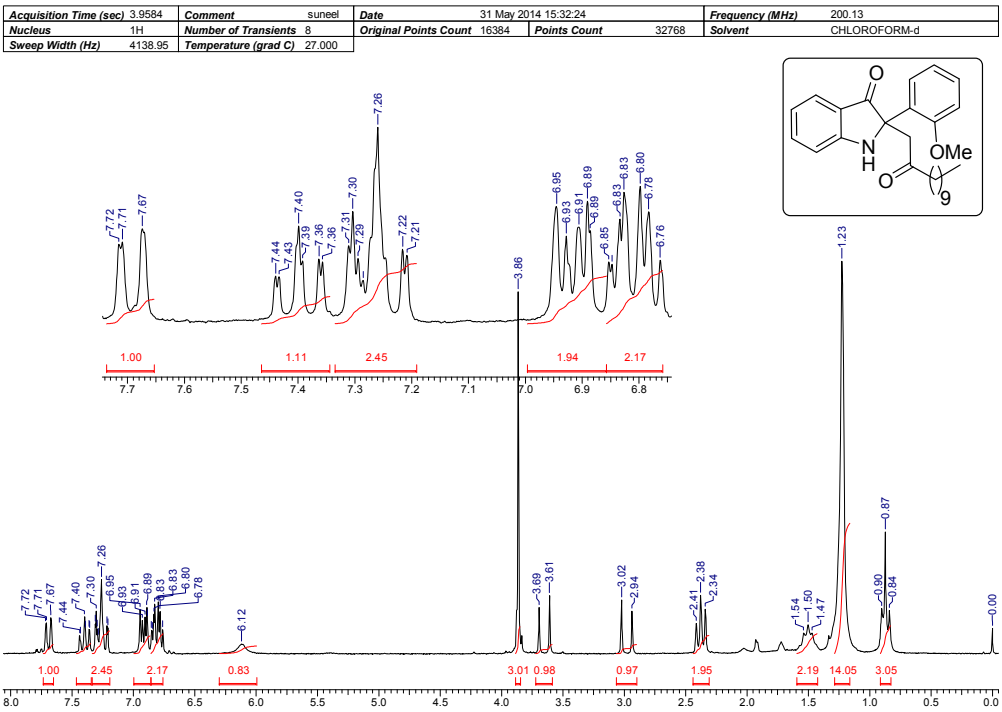


^{1}H NMR Spectrum of 47jj in $CDCl_3$

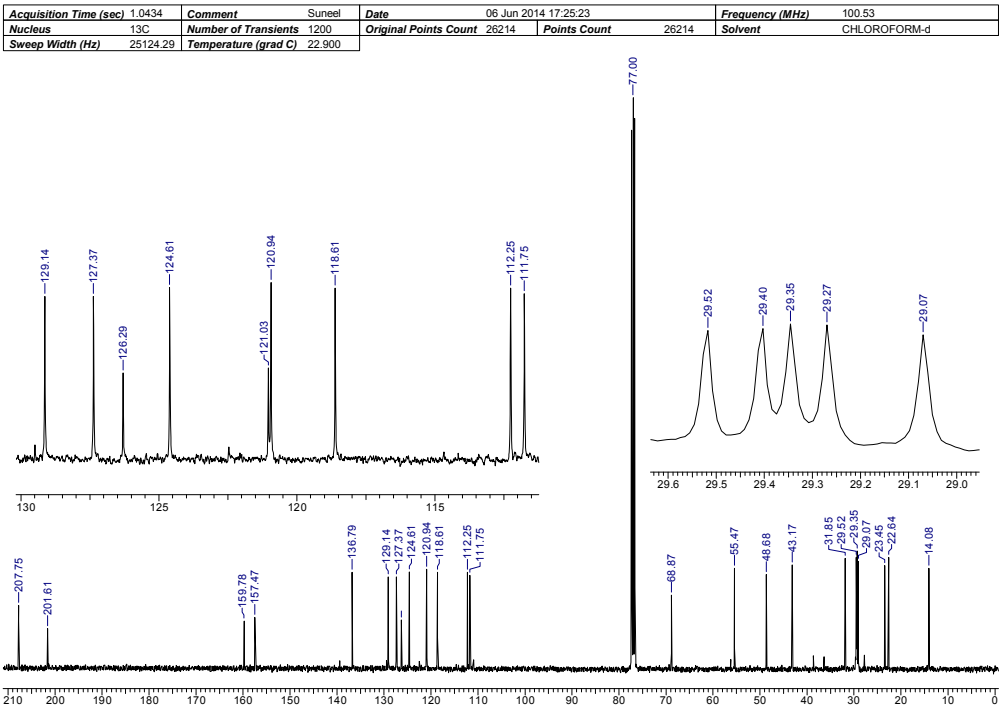
Acquisition Time (sec)	1.0434	Comment	Suneel	Date	28 May 2014 02:02:18			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	1000	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	22.500						



^{13}C NMR Spectrum of 47jj in $CDCl_3$

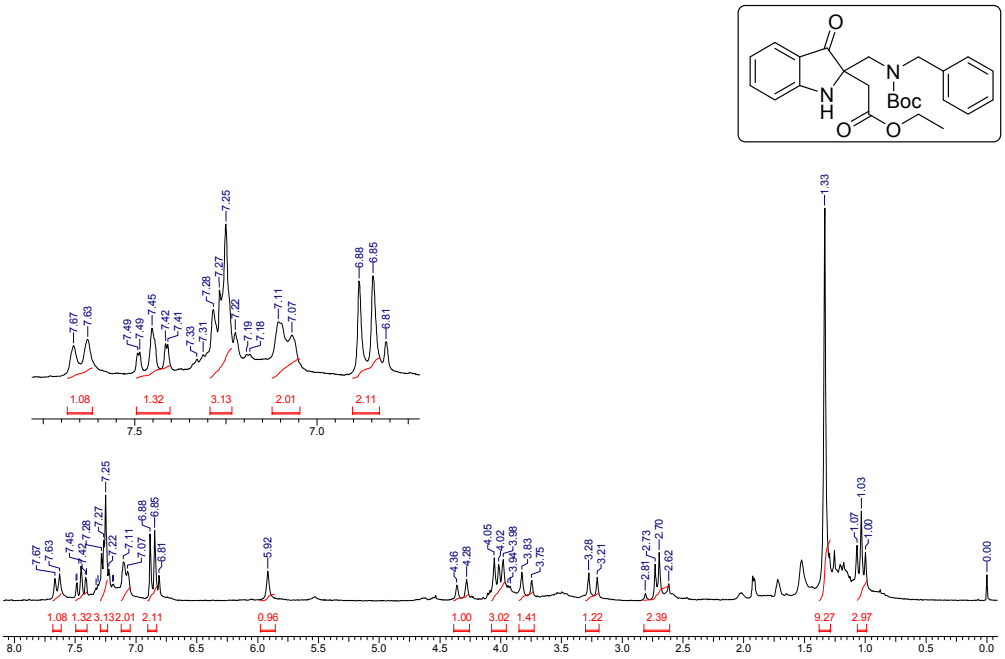


^{1}H NMR Spectrum of 47ma in $CDCl_3$



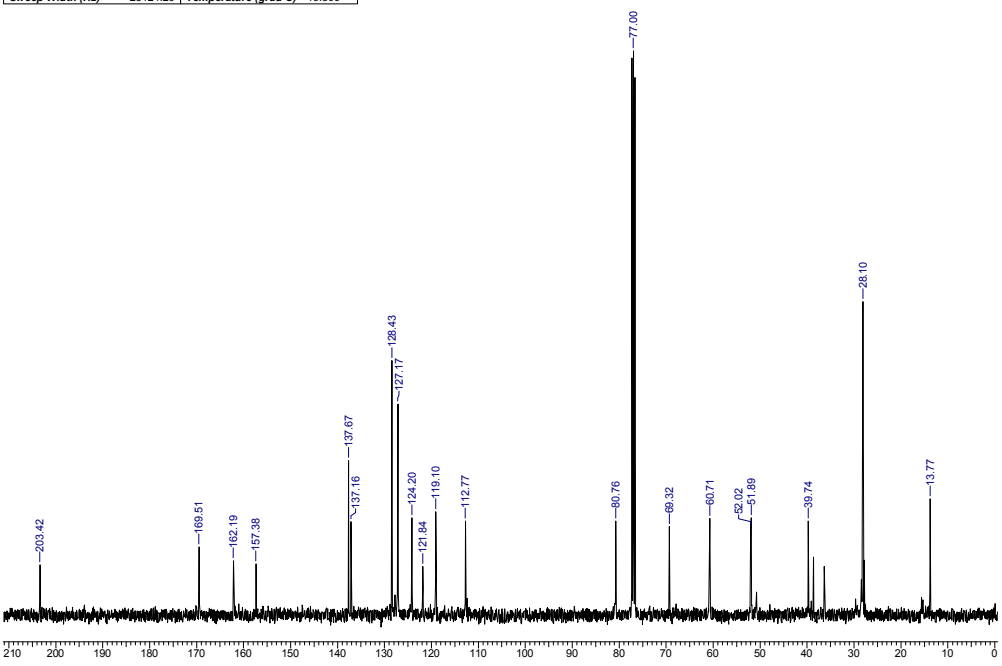
^{13}C NMR Spectrum of 47ma in $CDCl_3$

Acquisition Time (sec)	3.9584	Comment	suneel	Date	20 Jan 2014 19:39:52			Frequency (MHz)	200.13
Nucleus	1H	Number of Transients	8	Original Points Count	16384	Points Count	32768	Solvent	CHLOROFORM-d
Sweep Width (Hz)	4138.95	Temperature (grad C)	27.000						

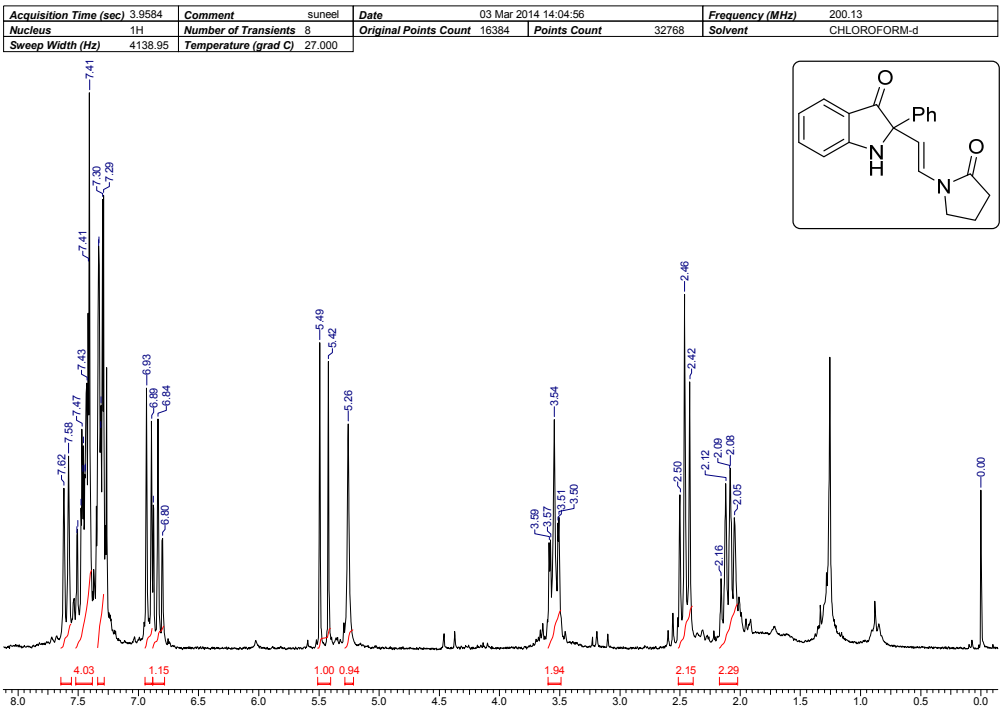


^{1}H NMR Spectrum of 47aaj-Boc in $CDCl_3$

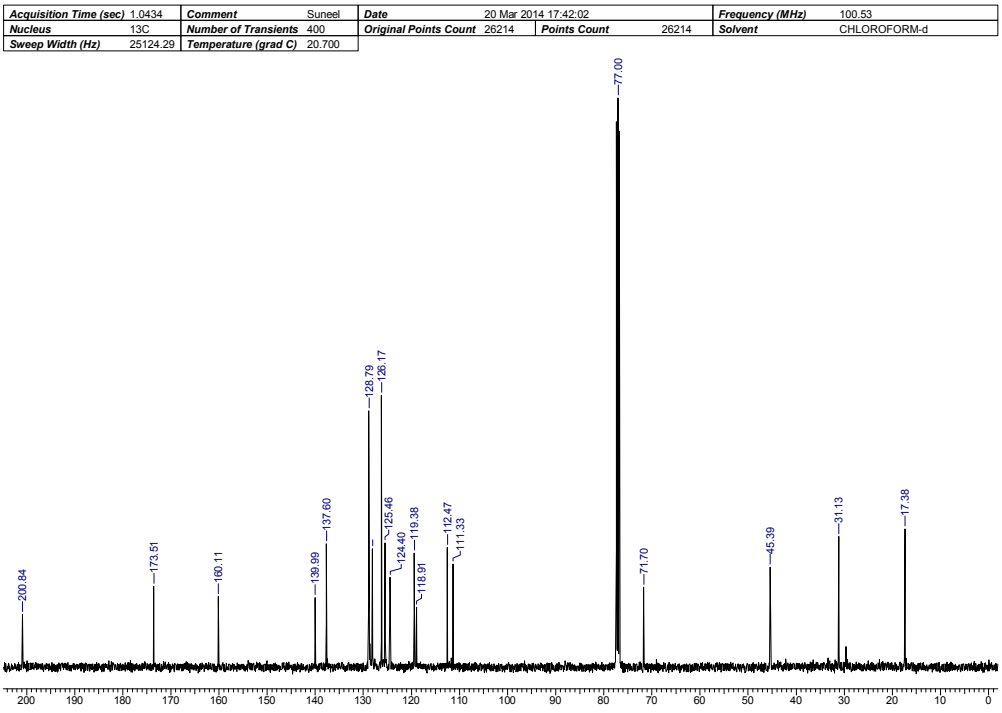
Acquisition Time (sec)	1.0434	Comment	suneel	Date	22 Jan 2014 00:57:37			Frequency (MHz)	100.53
Nucleus	13C	Number of Transients	400	Original Points Count	26214	Points Count	26214	Solvent	CHLOROFORM-d
Sweep Width (Hz)	25124.29	Temperature (grad C)	19.300						



^{13}C NMR Spectrum of 47aaj-Boc in $CDCl_3$



^{1}H NMR Spectrum of 49ap in $CDCl_3$



^{13}C NMR Spectrum of 49ap in $CDCl_3$

LIST OF PUBLICATIONS

- "$InCl_3$-Mediated Addition of Indole to Isatogens: An Expeditious Synthesis of 13-*deoxy*-Isatisine A", **Chepuri V. Suneel Kumar**, V. G. Puranik, and C. V. Ramana*, *Chem. –Eur. J.* **2012**, *18*, 9601 – 9611.
- "Tuning the Regioselectivity of Gold-Catalyzed Internal Nitroalkyne Redox: A Cycloisomerization and [3 + 2]-Cycloaddition Cascade for the Construction of *spiro*-Pseudoindoxyl Skeleton", **Chepuri V. Suneel Kumar** and C. V. Ramana*, *Organic Letters*, **2014**, *16*, 4766-4769.
- "[Ru]-catalyzed Internal Redox Process for Synthesis of 2,2-disubstituted Pseudoindoxyl skeletons", **Chepuri V. Suneel Kumar** and C. V. Ramana*, *"To be communicated"*.

Erratum