An approach toward the total synthesis of biologically active molecules (D_2 receptor agonist quinagolide and antidiabetic drug sitagliptin) & Synthesis of heterocyclic building block and novel triazole methodology

by

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Under the supervision of

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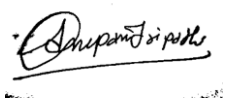
Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*An approach toward the total synthesis of biologically active molecules (D_2 receptor agonist quinagolide and antidiabetic drug sitagliptin) & Synthesis of heterocyclic building block and novel triazole methodology"*, submitted by *Mr. Anupam Tripathi* to the Academy of Scientific and Innovative Research (AcSIR), in partial fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) *etc*., used in the thesis from other source(s), have also been duly cited and acknowledged.



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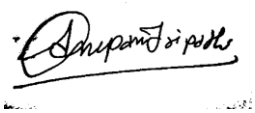
STATEMENTS OF ACADEMIC INTEGRITY

I Mr. Anupam Tripathi, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC15A26009 hereby undertake that, the thesis entitled "An approach toward the total synthesis of biologically active molecules (D_2 receptor agonist quinagolide and antidiabetic drug sitagliptin) & Synthesis of heterocyclic building block and novel triazole methodology" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*



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This dissertation is dedicated to all those people who have always given me the love, trust,

and support to come to this stage of my

life

-To My Family and Teachers-

&

My critic…!

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My emotions are high at this stage while remembering my (Nana and Nani) late. Vibhuti Pathak and late Sushila Pathak, (Bade Pita Ji) late.Vibhuti Tripathi. , I wish to express a great sense of gratitude to Anand, Arvind, Bablu Pinku, Ajith (mamas), Shashi, Sandhya, Anjana, Vandhan, Archna, (Moshi) and my Big B. friend mentor Navendu Pathka who always stood beside me and my family like a strong pillar throughout my life. This journey is an outcome of inspiration, confidence and helps extended by them during the bad time of our family.

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-Anupam Tripathi

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Abbreviations

Units

°C	Degree centigrade
Mg	Milligram
H	Hour
Hz	Hertz
µg	Microgram
mL	Millilitre
min	Minutes
MHz	Megahertz
Mmol	Millimole
Ppm	Parts per million

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
CH_3CN	Acetonitrile
n-BuLi	n-Butyl Lithium
^tBuOH	tert-Butyl alcohol
MOMCl	Chloromethyl Methyl Ether
CCl_4	Carbon tetrachloride
$CDCl_3$	Deuterated Chloroform
CD_3OD	Deuterated Methanol
DBAB	Dibenzyl azodicarboxylate
DMF	N, N'-Dimethylformamide
DMAP	N,N'-Dimethylaminopyridine
DIPEA	N, N-Diisopropylethylamine
Et_2O	Diethyl Ether
$(DHQ)_2PHAL$	1,4-bis(Dihydroquinin-9-O-yl)phthalazine

$(DHQD)_2PHAL$	1,4-bis(Dihydroquinindin-9-O-yl)phthalazine ii
DIAD	Diisopropylazodicarboxylate
DCE	1,2-Dichloroethane
DET	Diethyl Tartrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	N,N' -Dicyclohexylcarbodiimide
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
IBX	Iodoxybenzoic Acid
LAH	Lithium Aluminum Hydride
m-CPBAm-	Chloroperbenzoic Acid
MeOH	Methanol
Me	Methyl
MeI	Methyl Iodide
Ph	Phenyl
PMB	para-Methoxy Benzyl
p-TSA	para-Toluenesulfonic Acid
NaBH4	Sodiumborohydride
NaH	Sodium Hydride
TBAI	Tetra-n-Butylammonium Iodide
TBAF	Tetra-n-Butylammonium Fluoride
TBDMS	tert-ButyldimethylSilyl
TBSCl	tert-ButyldimethylSilyl Chloride
TIPSOTf	TriisopropylsilylTrifluoromethanesulfonate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Ts	Toluenesulfonyl
TMS	Trimethylsilyl

Other Notations

Calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
RCM	Ring Clossing Metathesis
DEPT	DistortionlessEnhancement by Polarization Transfer
Dr	Diastereomeric excess
Ee	Enantiomeric excess
Equiv	Equivalents
ESI	Electrospray ionization Mass spectrometry
HPLC	High Pressure Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Homonuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m/z	Mass-to-charge ratio
M.S	Molecular sieves
Mp	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
rt	Room temperature

General remarks

- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR and 2D NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All hemical shifts are quoted in ppm, relative to TMS and $CHCl_3$ in $CDCl_3$, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}+/- 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as m/z. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- Infrared spectra were scanned on Bruker ALPHA spectrometers with sodium chloride optics and are measured in cm^{-1}
- Optical rotations were measured with a JASCO P-2000 digital polarimeter.
- Melting points were recorded on Buchi M-535, M-560 melting point apparatus and are uncorrected and the temperatures are in centigrade scale.
- All reactions are monitored by Thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde or KMnO4followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. 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.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1. v

- Reactions were carried out in oven-dried glassware under a positive pressure of argon unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.
- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.

AcSIR	**Synopsis of the thesis to be submitted to the Academy of Scientific and Innovative Research for award of the Degree of Doctor of Philosophy in Chemistry**
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Research Supervisor	Dr. S. P. Chavan

1. Introduction:

The synthesis of biologically active marketed drugs and medicinally important natural product synthesis and their synthetic derivatives have played a key role to develop drugs. There are four chapters of the thesis, in which first and second chapter deal with the marketed drug (D_2 receptor agonist (±)-Quinagolide and antidiabetic drug Sitagliptin) synthesis. In that context, indigenous structure attracted the attention of synthetic chemists to the synthesis of these compounds. Formal scalable synthesis of D_2 receptor agonist quinagolide in gram scale is described in first chapter. In second chapter, development of synthetic methodologies for the synthesis of antidiabetic drug sitagliptin is presented. Chapters third and fourth deal with the heterocyclic chemistry. Third chapter includes synthesis of heterocyclic building block (Pulchellalactam and 3-ethyl-4-methyl-3-pyrrolin-2-one) and the fourth chapter describes the development of a new route for synthesis of triazole in a "Green" solvent. All four-chapters describe synthetic challenges faced and development of synthetic routes for biologically active compounds.

2. Statement of problem and objectives:

Total synthesis of quinagolide: Quinagolide[1] is a selective D_2 receptor agonist. Dopamine receptor D_2 also known as D_2R, is a protein present in human body that plays several important roles in the brain and body.

It also helps to reduce the overproduction of a hormone called prolactin.[2] Quinagolide is a marketed drug and its hydrochloride is marketed by Ferring Pharmaceuticals, Switzerland under the trade name NORPROLAC®.

Scalable synthesis of quinagolide was reported by Banziger *et al*[3]. Cost of 30 tablets (75 µg each) of quinagolide is $100. In the reported synthesis using expensive starting material or multiple steps increased the price of quinagolide. More work is needed to make this drug accessible to all and to bring down its cost.

Anti-diabetic drug sitagliptin: Diabetes is establishing itself as a life style disease of the 21st century. Type 2 diabetes (T2D), formerly non-insulin-dependent diabetes,[4,5] accounts for a minimum of 90% of all cases of the disease. Since its launch in 2006 by Merck, sitagliptin phosphate monohydrate, the first DPP-4 (dipeptidyl peptidase 4) inhibitor, has been one of the best-selling orally active and safe agents for the treatment of T2DM (type 2 diabetes mellitus).

In the last decades, a variety of chiral amino acids were made from hemiacetals through catalytic tandem aza-Michael/hemiacetal reaction, using organocatalyst in high yield and enantioselectivity. As part of the efforts of various groups to develop efficient and practical access to stigliptin phosphate monohydrate, many attractive synthetic routes have been reported to make sitagliptin phosphate monohydrate by means of chiral hemiacetal as the key intermediate[6-10].

As evidenced by the foregoing discussion, the total synthesis of sitagliptin has received increasingly growing attention in the beginning of 21st century. The present review is an attempt to showcase the current progress in synthesis and methodology developments. Many research groups across the world are trying to develop cheaper, commercial route for the synthesis of sitagliptin.

Heterocyclic building block for pulchellalactam and 3-ethyl-4-methy-3-pyrrolin-2-one: Recent synthetic studies toward lactam-containing heterocycles for use in biological efforts have been intense. In this total synthesis, the key steps of this approach were focused on the formation of the pulchellalactam and 3-ethyl-4-methy -3-pyrrolin-2-one. The synthesis of pulchellalactam and 3-ethyl-4-methy -3-pyrrolin-2-one began with the condensation of substituted glycine.

A new route for the synthesis of triazole in a "Green" Solvent:

A hugely popular synthetic methodology which enables the chemists to prepare large variety of heterocyclic compounds *via* the Huisgen 1,3-dipolar cycloaddition can be referred as "Click chemistry."[11] Huisgen [3+2] cycloaddition of alkynes and azides under thermal conditions to obtain 1,2,3-triazoles has been widely popular over the period of one century. In particular, 1,2,3-triazole compounds are considered as the one of most important privileged scaffold of all "click" reactions.[12]

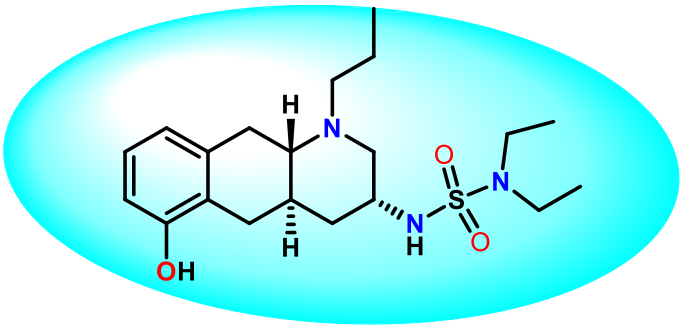
A synthetic route for the direct conversion of arylazides into corresponding trizoles *via* [3+2] Huisgen cycloaddition reaction under basic conditions with readily available reagents is reported. So developed 1,3-dipolar cycloaddition reaction between azide – aldehydes/ketones for the synthesis of substituted 1,2,3-triazoles in good to excellent yields with water as the only solvent. This synthetic methodology has advantages over the previously well-known click reactions like CuAAC, RuAAC, IrAAC and NiAAC etc.

3. <u>Methodology and Results:</u> Each chapter is summarized briefly.

Chapter 1: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide.

Section 1: Introduction and Literature Reports.

Quinagolide is a selective D_2 receptor agonist. Dopamine receptor D_2 also known as D_2R, is a protein present in human body that plays several important roles in the brain and body. Dopaminergic system dysfunction in the central nervous system has been related to brain diseases such as Parkinson's disease, schizophrenia and hyperprolatinemia.



Quinagolide

Figure 1: Structure of quinagolide**.**

Hyperprolactinemia is caused by overproduction of hormone prolactin. Quinagolide is used to reduce the elevated levels of prolactin[8]. Octahydrobenzo[*g*]-quinolines, synthetic analogues of the ergot family structure, are potent dopamine agonists. Quinagolide hydrochloride is marketed under the trade name Norprolac®.

First synthesis was reported in 1985, by Nordmann *et al.* after that Banziger *et al.* gave commercial rute for the synthesis of racemic quinagolide. Few more syntheses reported in the literature are shown below.

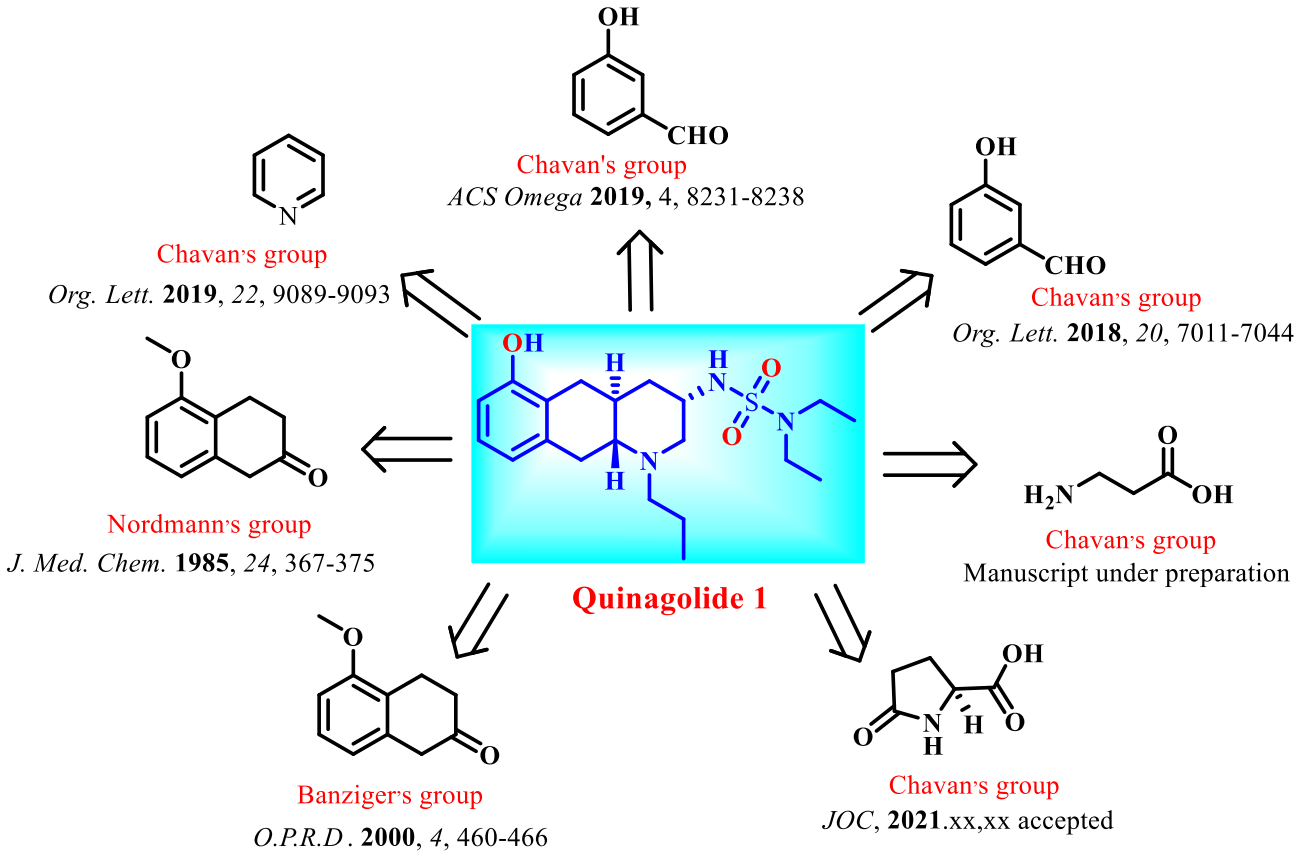
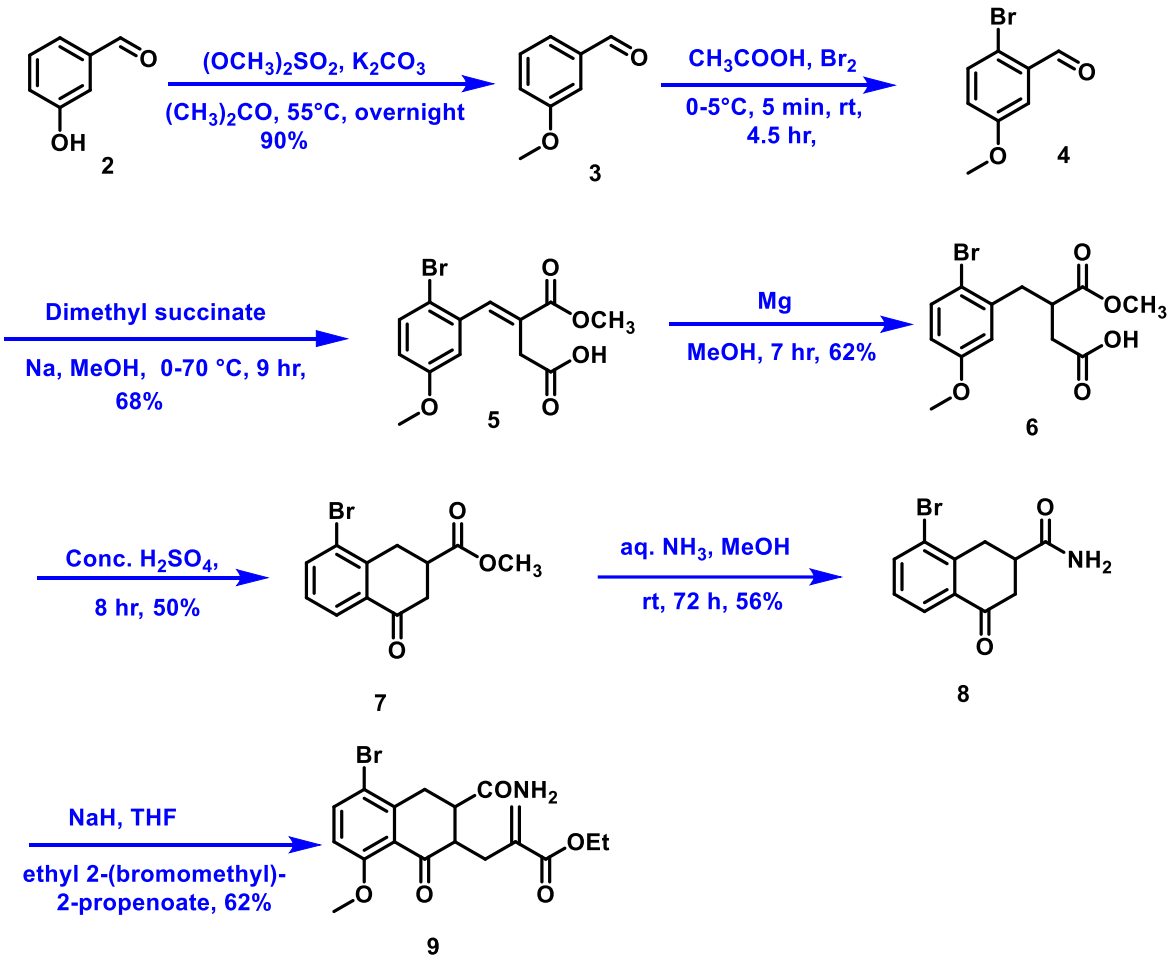


Figure 2: Literature Reports of quinagolide.

Section 2: Synthetic study towards quinagolide by using 3-hydroxybenzaldehyde as a starting material:

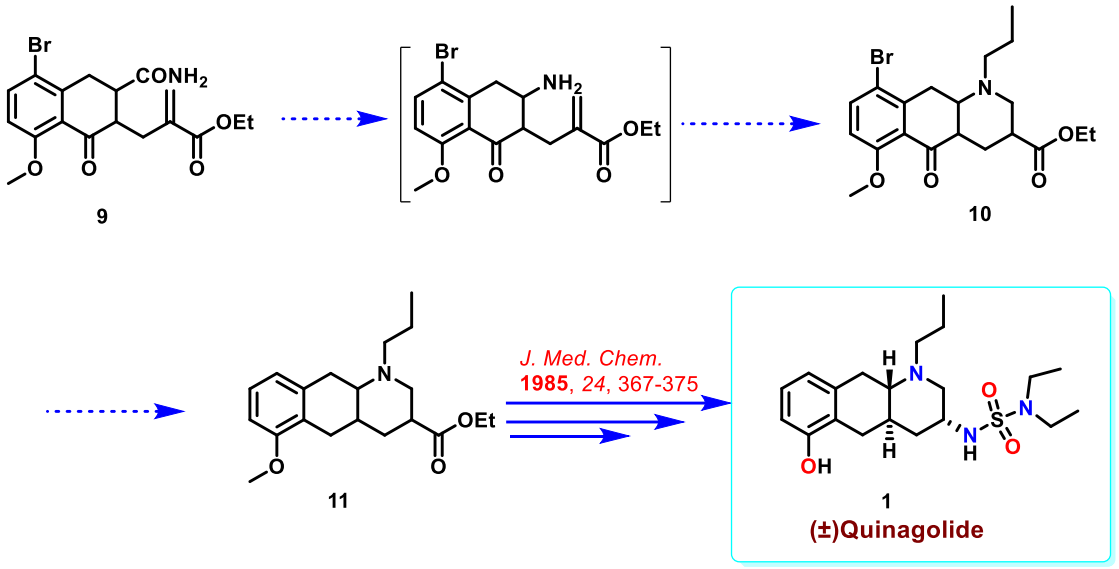
By using simple chemistry and cheap and easily available starting material *viz. meta*-hydroxy benzaldehyde **(2),** the aim was to develop a synthetic methodology for the synthesis of quinagolide.

Scalable steps like bromination and Stobbe condensation, double bond reduction in the presence of aryl halide, amide formation with methanolic ammonia are the key features of this synthesis.



Scheme 1: Synthetic study towards quinagolide**.**

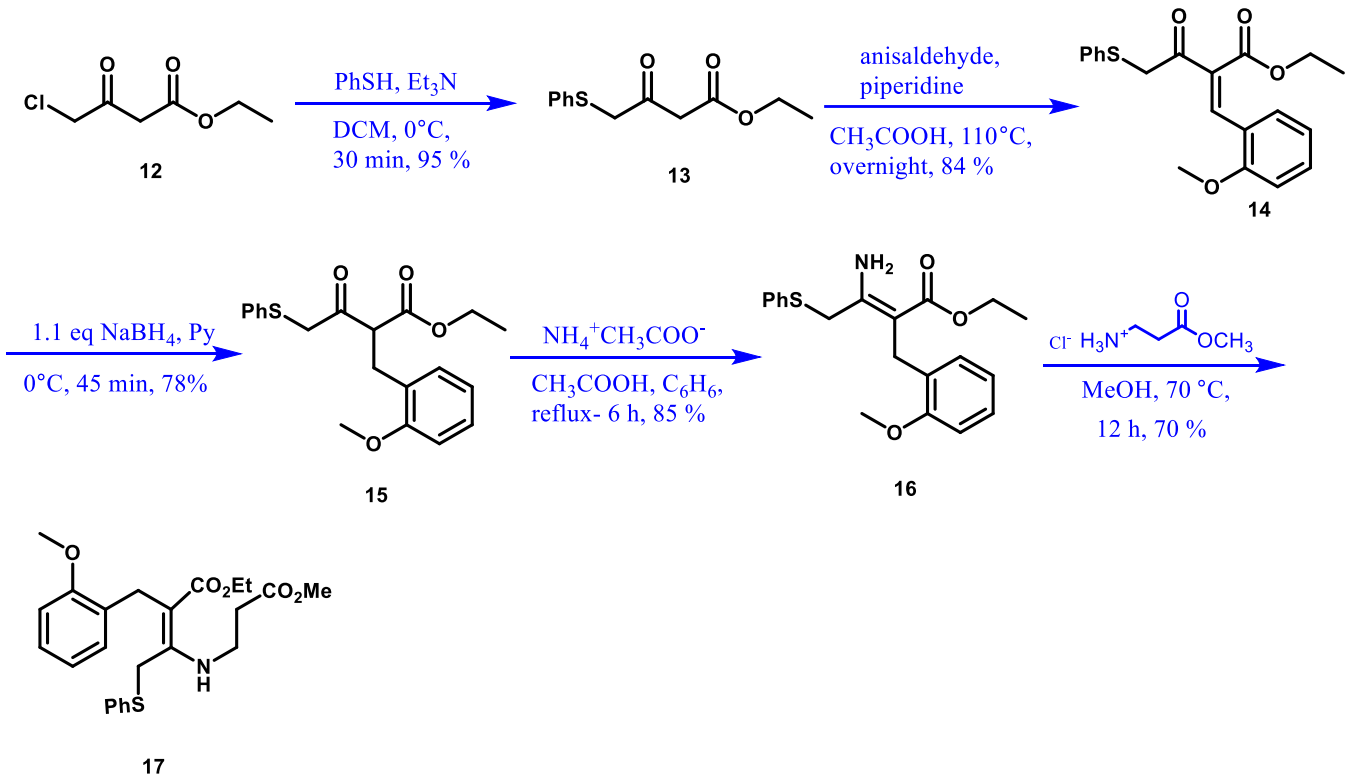
Alkylation reaction of tetralone with ethyl 2-(bromomethyl)-2-propenoate furnished olifin would be subjected to furnish functional group transformation of amide to amine by Hofmann rearrangement followed by cyclization and alkylation to obtain **10**. Tricyclic ring **10** which can be elaborated to quinagolide following routine tranformations.



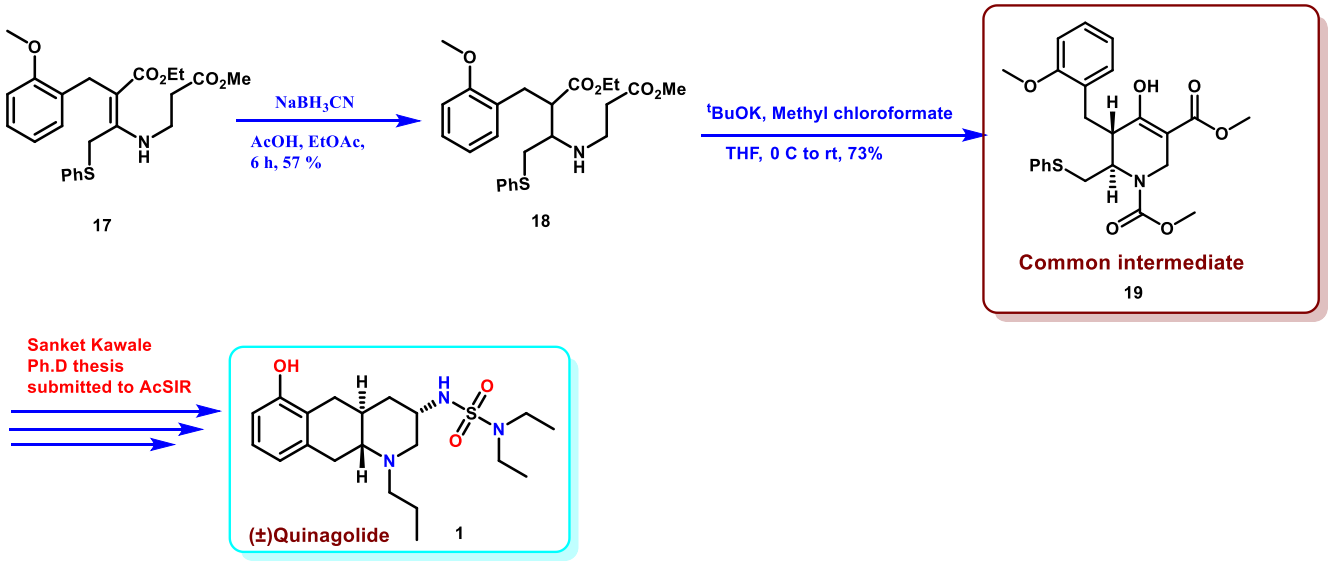
Scheme 2: Synthesis of quinagolide.

Section 3: Studies towards practical synthesis of the (±)-Quinagolide.

This section describes formal and scalable synthesis of quinagolide. An efficient straight forward formal synthesis of quinagolide by using chloro acetoacetate as the starting material has been achieved. Replacement of chloro with thiophenol followed by the treatment with anisaldehyde under Knoevenagel condensation furnished olefin **14**. Furher selective double bond reduction in presence of keto and ester functional groups, with help $NaBH_4$ and pyridine at 0 ^0C afforded compound **15** in good yield. In the next step, regioselectively the compound **15** was converted to β-amino-α,β-unsaturated ester **16**. This amine was replaced by alanine salt. Reduction of the double bond with the $NaCNBH_4$ was carried out and further subjected to cyclisation under basic reaction conditions to furnish pyridine derivative **19**. The compound **19** has been converted to quinagolide by a colleagu from this group and hence this constitutes a formal synthesis of quinagolide.



Scheme 3: Gram scale synthesis of quinagolide.



Scheme 4: Synthesis of common intermediate.

Summary:

Synthesis started with the 3-hydroxybenzaldehyde as a starting material in the first rout. It is a few steps away to achieve to tricyclic core.

Using ethyl 4-chloroacetoacetate, formal synthesis of quinagolide was achieved in good yield.

Chapter 2: Total synthesis of antidiabetic drug sitagliptin.

Section 1: Introduction and Literature Reports.

Diabetes is establishing itself as a life style disease of the 21st century. Type 2 diabetes (T2D), formerly non-insulin-dependent diabetes, accounts for a minimum of 90% of all cases of the disease. Inhibitors of the enzyme DPP-IV(dipeptidyl peptidase 4), are a promising treatment for type II diabetes. Sitagliptin is a potent inhibitor of DPP-IV and since its launch in 2006 by Merck, sitagliptin phosphate monohydrate, the primary DPP-4 inhibitor has been one among the best-selling orally active and safe agents for the treatment of T2DM (type 2 diabetes mellitus) .

Sitagliptin **(1)** a selective, potent DPP-IV inhibitor, is the active ingredient in JANUVIR and JANUMET (a fixed dose combination with the diabetes drug Metformin), both of which have received approval for the treatment of type 2 diabetes by the FDA. Sitagliptin phosphate, also known as Januvir, was touted as a future billion dollar boon for the pharmaceutical industry. On June 26, 2012 Evaluated Pharma revealed its World Preview 2018 projection, giving a nod to Merck's Januvia. With an estimated 10 billion dollars in annual sales, Januvia (Sitagliptin Phosphate) is forecasted to be a top player in the global pharmaceutical market.

A comprehensive set of available literature concerning the sitagliptin is presented. Sitagliptin and its seventeen sister gliptins have been a target for various research groups and as a result of several years of intense research, a number of synthetic schemes have been reported. Some of the important syntheses in each class have been described here.

Sitagliptin was first synthesized by Edmondson *et al*. in 2004[13] and in the first synthetic approach, the synthesis of sitagliptin started with the 2,4,5-trifluorobenzyl bromide and its reaction with Schollkopf reagent[14].

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The first large scale synthesis of sitagliptin started with trifluorophenylacetic acid which was converted to β-keto ester with Meldrum's adduct intermediate.

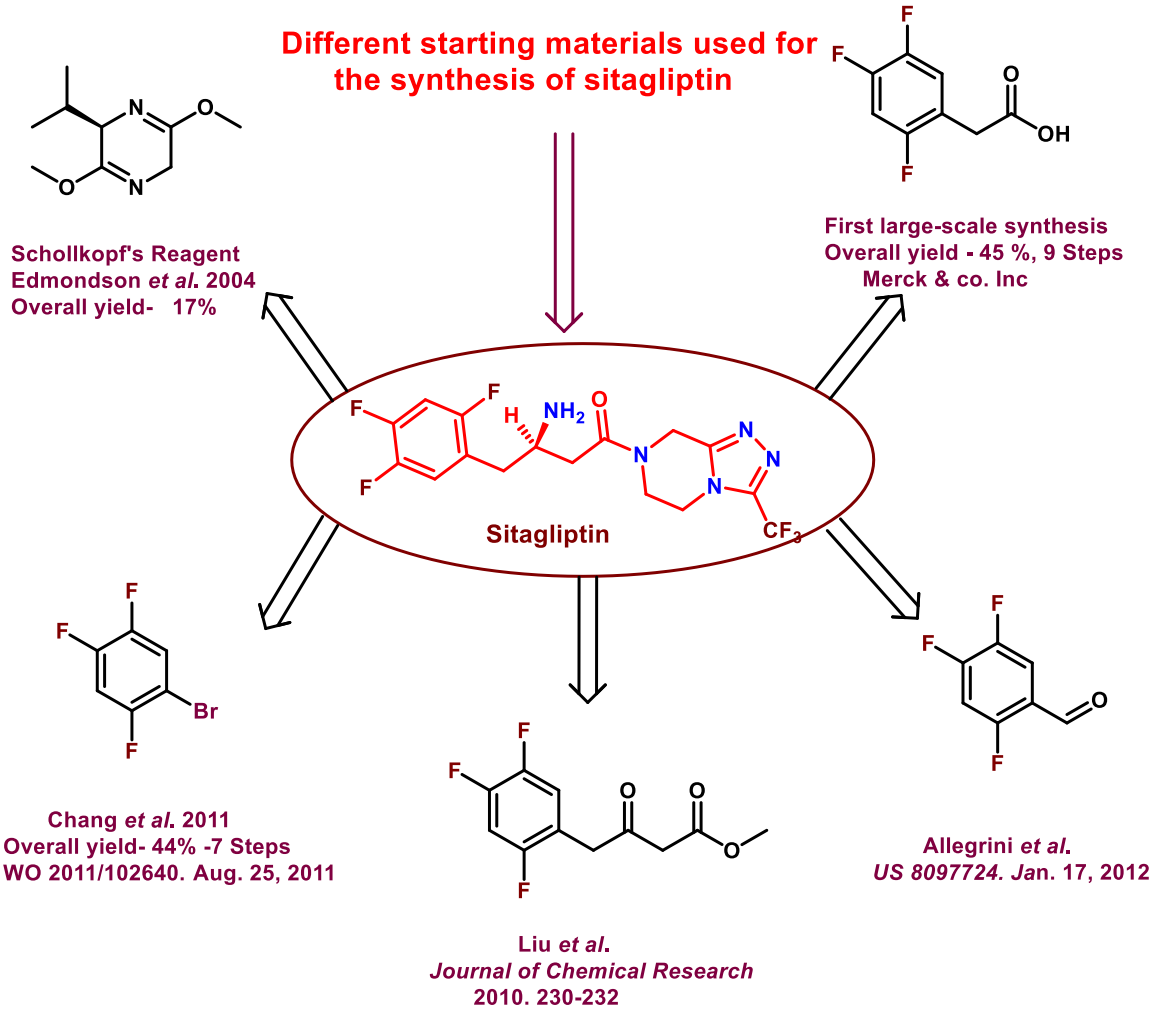


Figure 3: Literature Reports of Sitagliptin.

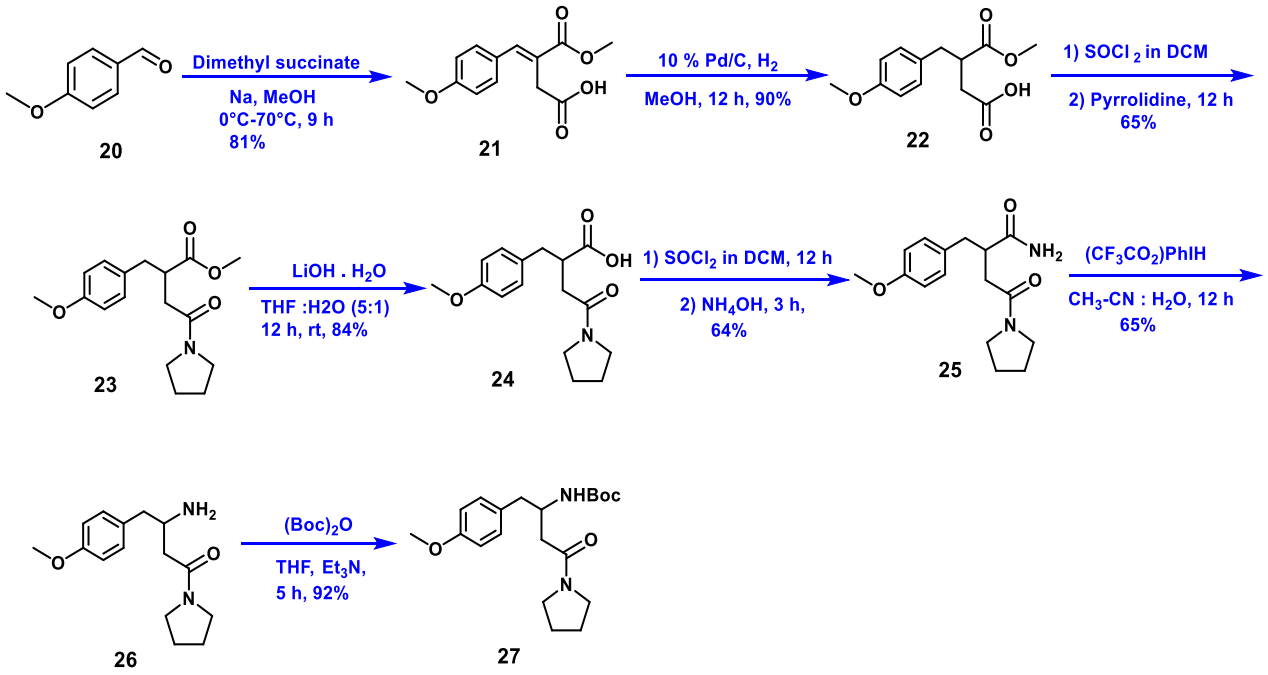
As evidenced by the foregoing discussions, the total synthesis of sitagliptin has received increasingly growing attention in the beginning of 21st century. The present review is an attempt to showcase the current progress in synthesis and methodology developments.Many research groups across the world are trying to develop cheaper, commercial route for the synthesis of sitagliptin.

In year 2019 a paper appeared in E-JOC for the formal synthesis of active moiety. Diabetes patients are increasing day by day all over the world that shows the need to do more research and development in this field.

Section 2: Synthetic studies towards anti-diabetic drug, Sitagliptin.

A) **Model synthesis of sitagliptin results and discussion.**

Synthesis of model compound **27** was achieved from *para*-hydroxy benzaldehyde in 6 steps by using simple scalable chemistry including Stobbe reaction. A $SOCl_2$ mediated C-N coupling reaction performed twice and PIFA reaction for Hofmann rearrangement to convert the amide **25** to amine **26** in 16% overall yield were the key steps of the synthesis.



Scheme 5: Model synthesis of sitagliptin**.**

B) Total synthesis of sitagliptin.

Having performed model study on p-anisaldehyde, the synthesis of the desired molecule sitagliptin was started with 2,4,5-trifluorobenzadehyde. To test the hypothesis for the synthesis of the model synthesis of sitagliptin, amine functional group of sitagliptin was established by using Hofmann rearrangement.

Stobbe condensation on aldehyde followed by selective conversion of acid to amide functional group by conventional method were the key steps.

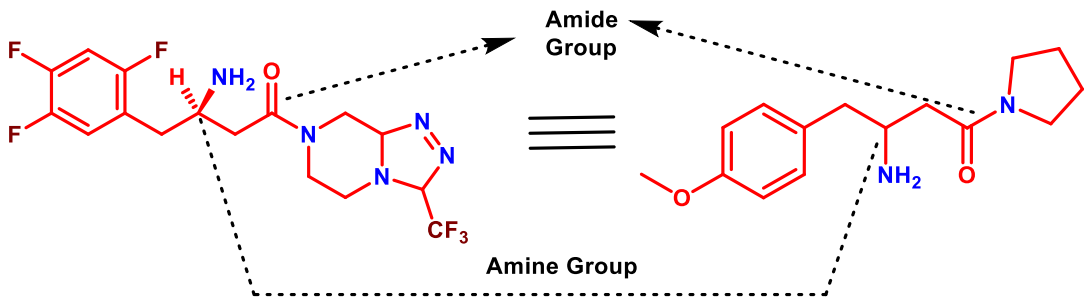
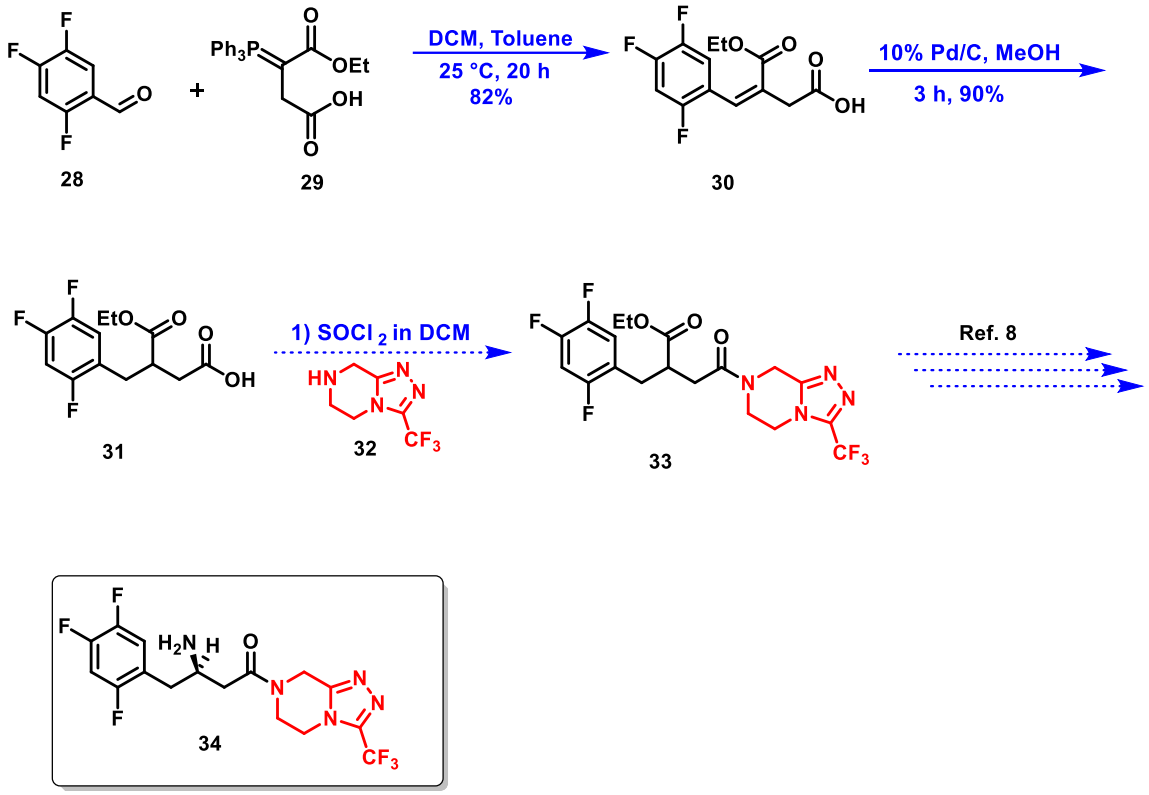


Figure 4: Structural similarity of model synthesis of sitagliptin and sitagliptin.

Synthesis of sitagliptin began by Wittig reaction of aldehyde **28** with **29**. After that all the synthesis is done according to the model synthesis.



Scheme 6: Synthesis of Sitagliptin

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3. Summary:

After completion of model study, sitagliptin synthesis was started with 2,4,5-trifluorobenzaldehyde, a very common starting material for the synthesis of sitagliptin. Two steps were done in this synthesis were in ester 31 was prepared and characterized. After that one paper appeared in *Chem. Asian J.* **2020**, *15*, 1605-1608[15] with same strategy and then this work was stopped here.

Chapter 3: Synthesis of Heterocyclic Building Block Pulchellalactam

Section 1: Introduction and Literature Reports.

Recent synthetic studies towards lactam-containing heterocycles for use in the synthesis of biologically active compounds have been intense. In this total synthesis, the key steps of our approach were focused on the formation of the pulchellalactam. The synthesis of Pulchellalactam began with the condensation of substituted glycine.

A) Introduction and Literature Reports of Pulchellalactam.

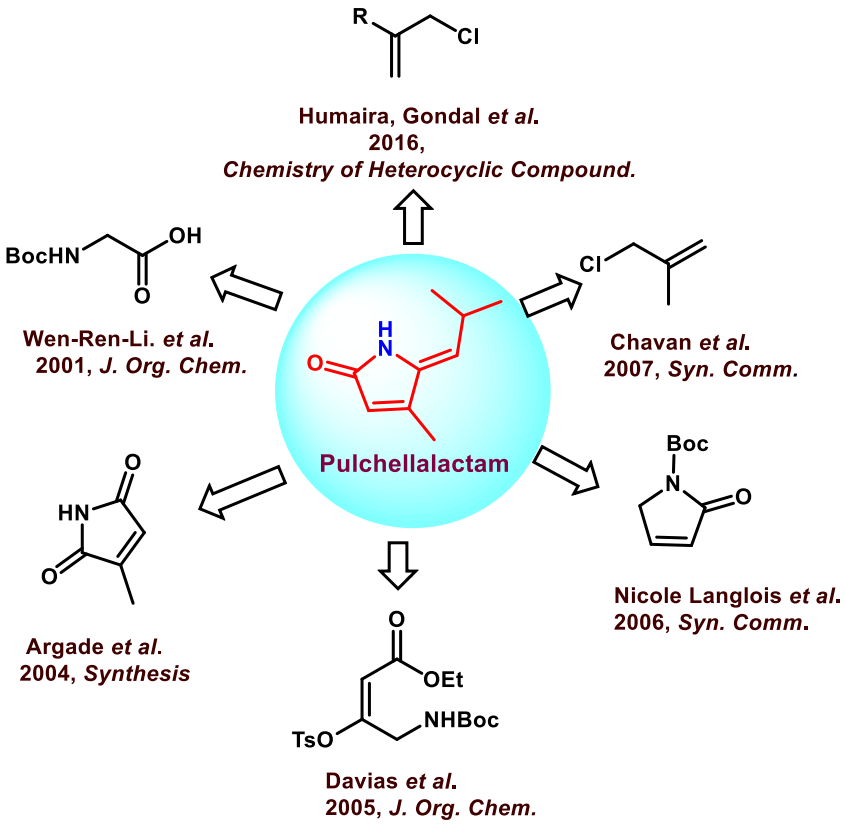


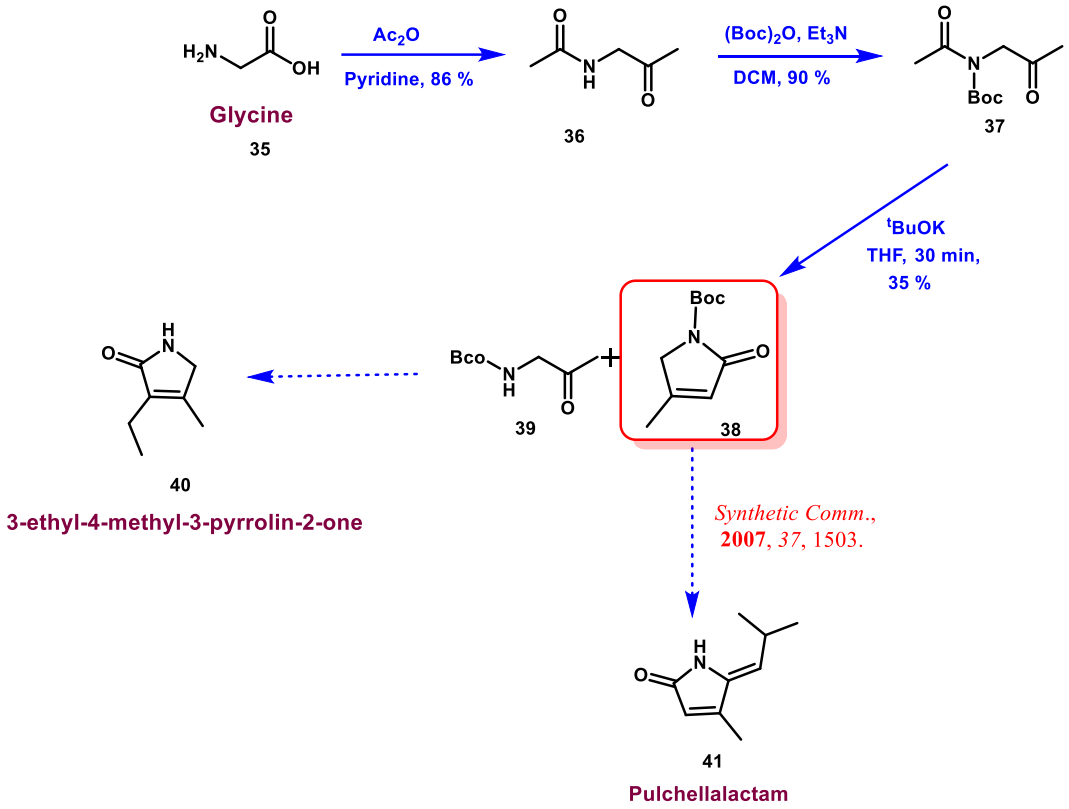
Figure 5: Literature reports of pulchellalactam.

(Z) Pulchellalactam, a pyrrolidinone was isolated in 1997 from the marine fungus *Corollospora pulchella* by Alvi *et al*[16]. Pulchellalactam is a potent CD45 protein tyrosine phosphate (PTP) inhibitor.First total synthesis was reported by **Li *et al*.**[17] in six- steps by using N-Boc-glycine as starting material with 32% overall yield.

Section 2: Synthetic Studies of Heterocyclic Building Block.

As discussed above, heterocyclic building block is a useful intermediate to the synthesis of pulchellalactam and 3-ethyl-4-methyl-3-pyrrolin-2-one medicinally important compound. By

using glycine as starting material and scalable chemistry the strategy was to prepare common intermediates **38** and **39** to be used in the synthesis of compounds **40** and **41**.



Scheme 5: Heterocyclic building block common intermediate of synthesis.

3. <u>Summary:</u>

Heterocyclic building block synthesis started from the glycine as a starting material and the synthesis of key intermediate was accomplished leading to a formal synthesis of pulchellalactam.

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Chapter 4: A New Route for Synthesis of Triazole in a "Green" Solvent.

Section 1: Introduction and Literature Reports.

A hugely popular synthetic methodology which enables the chemist to prepare large variety of heterocyclic compounds *via* the Huisgen 1,3-dipolar cycloaddition is referred as "Click chemistry." Huisgen [3+2] cycloaddition of alkynes and azides under thermal conditions to obtain 1,2,3-triazoles has been widely popular over the period of one century. In particular,

1,2,3-triazole compounds are considered as the one of the most important privileged scaffold of all “click” reactions.

1,4-Disubstituted 1,2,3-triazoles are recognized as an important organic compounds and many of them have found a variety of applications in medicinal field such as, anticancer drugs,

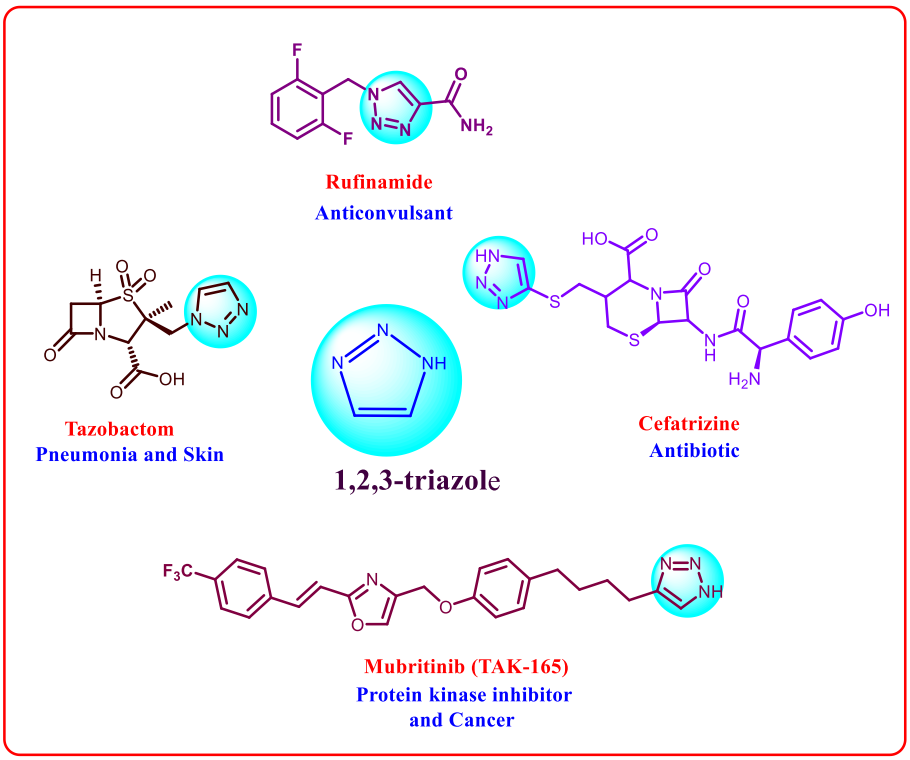


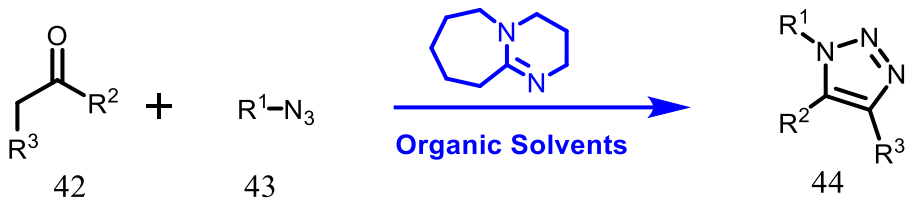
Figure 8. Important triazoles compounde used as a pharmaceuticals.

antifungal agents, antibacterial drugs, antituberculosis drugs, histone deacetylase inhibitors, bioorthogonal probes HIV protease inhibitors, corrosion inhibitors, lubricants, dyes, and photostabilizers and also used as a pharmaceuticals.[3] Thus, development of green and practical approach for triazoles is of significant interest.

It can be noticed that, CuAAC or RuAAC click chemistry reactions containing alkynes substrates which are more expensive than aldehyde derivatives. For example, phenylacetylene and phenylacetaldehyde having commercial price of $76 and only $33 respectively each for 100 mL.Most of the above methods, used either low reactive, costly or non-commercial substrates instead of simple starting materials such as phenylacetaldehyde or arylacetones. Many of them also have the requirement of organic solvents, toxic transition-metal catalysts, loading of stoichiometric amounts of catalysts, tedious workup procedures and inert reaction atmosphere which potentially lead to above reaction conditions inferior. To overcome this

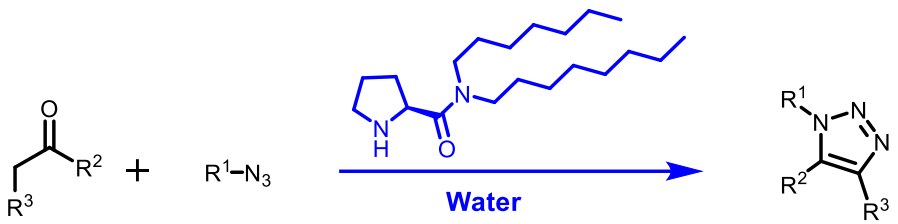
difficulty, herein we present a general metal-free synthetic approach for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles by reaction of arylazides with aldehydes or ketones in water as the only solvent in higher yields.

a) Enolate-mediated click reaction between azide and aldehydes or ketones using organic solvents by Ramacharya (*Angew. Chem*. **2014**, *126*, 10588 –10592)[20].



42 43 44

b) Enamine catalysed click reaction between azide and ketones using water as a solvent by Wang (*Green Chem*., **2013**, *15*, 2384–2388.)[22].



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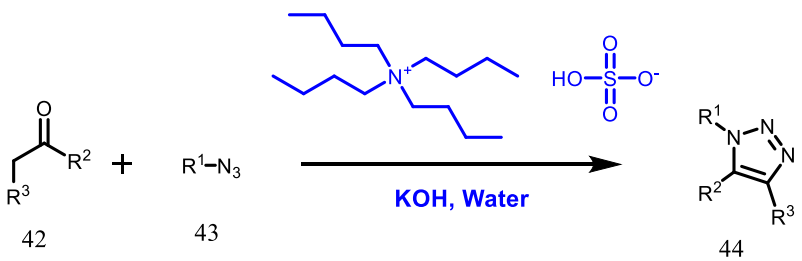
c) Enolate-mediated click reaction between azide and aldehydes or ketones in water as a solvent: present work



42 43 44

Scheme 6: Synthesis of triazoles proceeding *via* [3+2] Huisgen cycloaddition reaction between azide and aldehyde or ketone.

Section 2: Synthesis of triazoles.

Enolate-mediated click reaction between azide and aldehydes or ketones in water as a solvent.

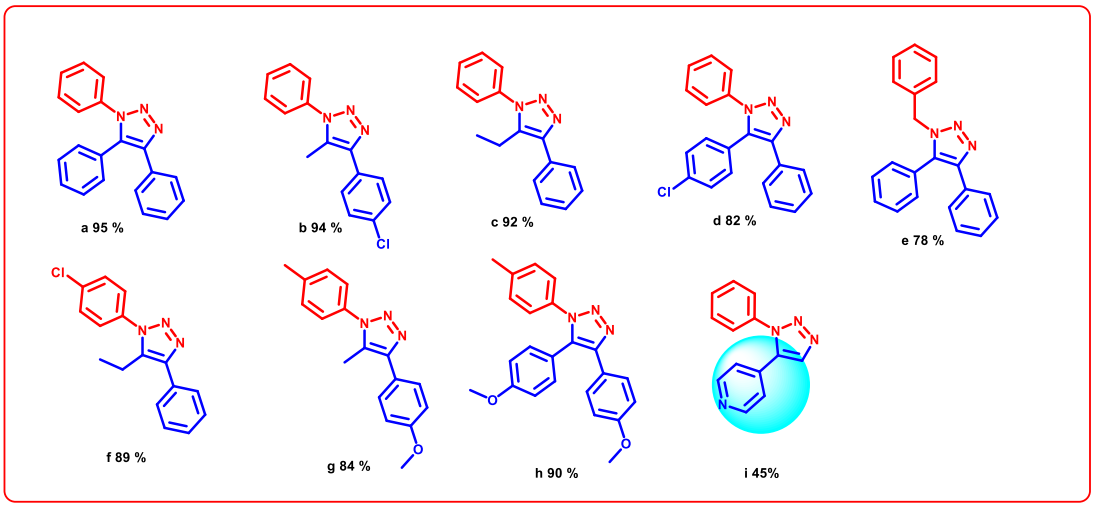
- ✓ **Click Chemistry: Azide-Aldehyde/Ketone**
- ✓ **Excellent Regioselectivity**
- ✓ **High Efficiency**
- ✓ **Aqueous Medium**
- ✓ **Broad Substrate Scop**

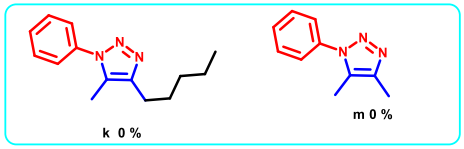
A) Optimization of reaction conditions between arylazide and aldehyde to form triazole.

Entry	**Base (2 equi.)**	**Catalyst (20 mol %)**	**Time (Hour)**	**Temp. ° C**	**Yield (%)[b]**
1	none	none	24	100	0
2	none	TBAHS	24	100	0
3	K_2CO_3	none	24	100	0
4	KOH	K_2CO_3	24	100	10
5	K_2CO_3	TBAHS	24	100	64
6	Na_2CO_3	TBAHS	24	100	61
7	Cs_2CO_3	TBAHS	24	100	69
8	$NaHCO_3$	TBAHS	24	100	25
9	$KHCO_3$	TBAHS	24	100	42
10	KOH	TBAHS	48	RT	21
11	NaOH	TBAHS	24	100	61
12	**KOH**	**TBAHS**	**24**	**100**	**77**
13	KOH	TBAB	24	100	66
14	KOH	TBAI	24	100	62
15[c]	KOH	TBAHS	24	100	45
16[d]	KOH	TBAHS	24	100	75

17	KOH	TBAHS	24	50	48
18[e]	KOH	TBAHS	24	100	70

B) Substrate scope.





3. Summary:

A simple, versatile, greener route for enolate-mediated azide-aldehyde or ketone [3+2]-cycloaddition reaction has been developed which enables the synthesis of important 1,4-disubstituted 1,2,3-triazoles containing a variety of functional groups.

Current protocol is featured with the metal-free conditions with excellent regioselectivity to a library of well decorated 1,2,3-triazoles. This click reaction proceeds with water as the only solvent to furnish noteworthy feature of corresponding triazoles in good to excellent yields.

5. Summary (Overall):

- Synthesis of was quinagolide started with the 3-hydroxybenzaldehyde as a starting material. Successfully to introduce the second ring and few steps away the achieve to tricycle core.
- Using ethyl 4-chloroacetoacetate, a formal synthesis of quinagolide has been achieved in good yields.
- Successfully completed the model study of Sitagliptin with 16% overall yield.

- After compaction of model study, sitagliptin synthesis was started with 2,4,5-trifluorobenzadehyde a very common starting material for the synthesis of sitagliptin. Two steps were done in this synthesis, after that one paper appeared in *Chem. Asian J.* **2020**, *15*, 1605-1608 with the same strategy and then this work had to be stopped here.
- Heterocyclic building block synthesis started from the glycine as a starting material and completed key intermediate synthesis while the formal synthesis of pulchellalactam has been accomplished glimepiride while synthesis of under progress.
- Developed a simple, versatile and green route for enolate-mediated azide-aldehyde or ketone [3+2]-cycloaddition reaction which enables the synthesis of 1,4-disubstituted 1,2,3-triazoles containing a variety of functional groups with excellent regioselectivity using water as the only solvent.

6. Future directions:

The synthetic methodology in the present work can be used for large scale synthesis of quinagolide and by using chiral reduction condition it might give asymmetric synthesis route. Accomplished the formal synthesis of quinagolide which may be converted in gram scale synthesis of quinagolide.Heterocyclic building block synthesis started from the glycine as a starting material and it could be used in different medicinal and natural product syntheses. The methodology used for synthesis of compounds containing trazole moiety in the present work, can be extended further to get combretastatin-inspired triazoles and screened for biological activity.

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7. Publications:

List of Publications:

1. Tripathi, A.; Rode, V. C.; Llop, J.; Chavan, S. P.; Joshi, M. S.;*Tetrahedron Letters* **2019**, *61*, 151662.

Patents: xxx

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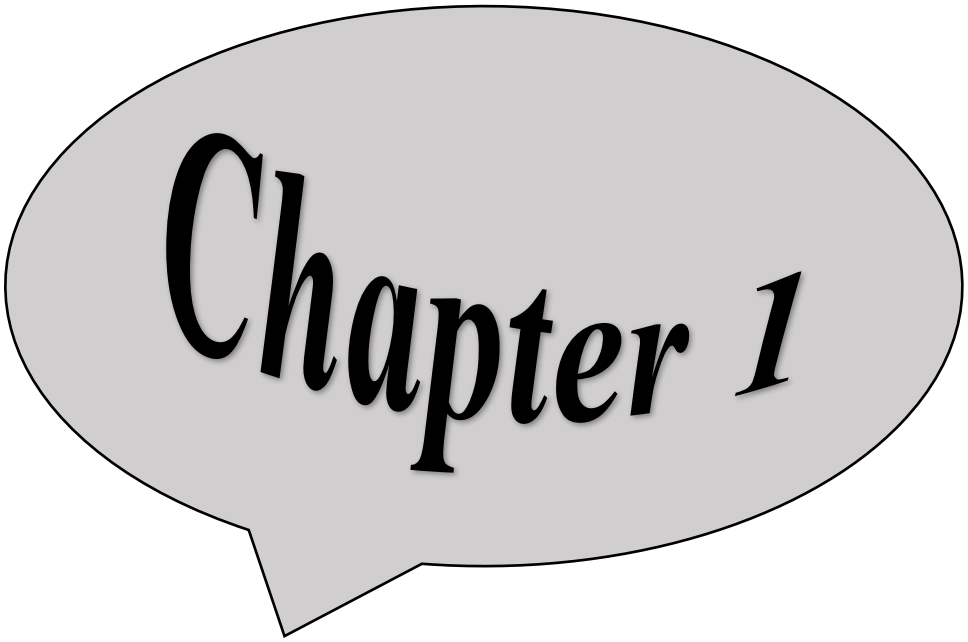
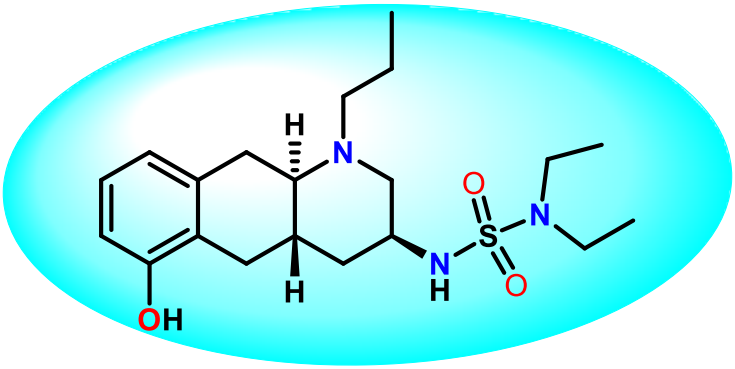


"Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide"

Chapter 1: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide

Chapter-1
Section-1

"Introduction and Literature Review of D_2 Receptor Agonist (±)-Quinagolide"



1.1.1. Introduction:

Ergot alkaloids and their derivatives show a wide spectrum of physiological activities.[1] The ergot alkaloids are mycotoxins produced by several species of fungi in the genus *Claviceps.*[2] The most well-known member of the group is *Claviceps purpurea*, and it has been grown on more than 400 host species but the most common species is *Gramineae* family members e.g. rye and wheat.

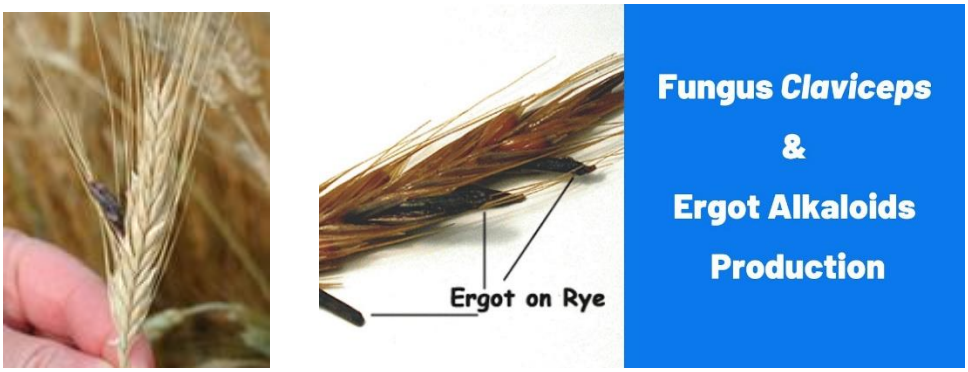


Figure 1: Fungus *Claviceps* and ergot alkaloids natural products.

Structures of Ergot Alkaloids

Ergot alkaloids are nitrogen-containing natural products belonging to indole alkaloids.

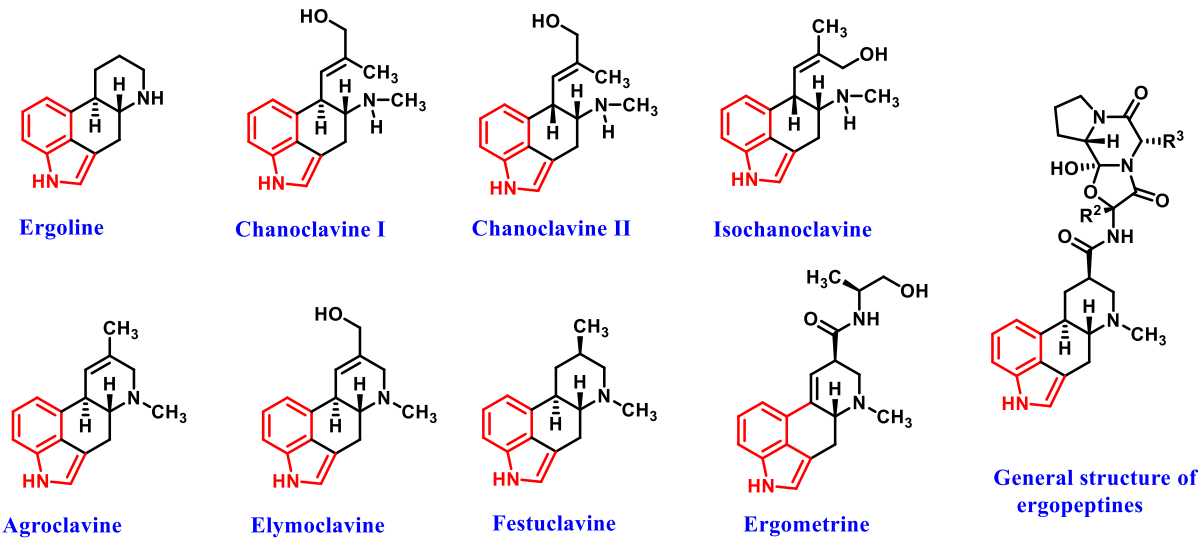


Figure 2: Ergot alkaloids.

Because of their interior structure and medicinal uses[3], they have attracted many organic synthetic groups and biologists as targetsto work on. Many ergot alkaloids and their derivatives are used as a medicine in different roles. Quinagolide[4] is ergot class of alkaloid used for the treatment of hyperprolactinemia[5] that is caused by overproduction of prolactin hormone.

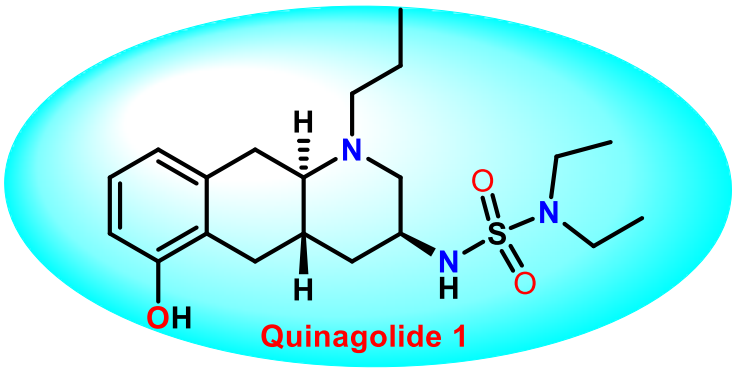


Figure 3: Structure of quinagolide **(1)**.

Prolactin:

Hormones play many important roles in human body,[6] prolactin is one of them. Prolactin is a hormone secreted by the pituitary gland which sits at the bottom of the brain. The hormone prolactin stimulates the breasts to grow and develop and causes milk (lactation) to be made after the baby is born. Biologically prolactin hormone plays many important roles in reproduction,[7] immune response,[8] fats metabolism,[9] osmoregulation,[10] hair shedding[11] and lactation.[12] Prolactin has been found to stimulate the proliferation of oligodendrocytes precursor cells.[13] Production of prolactin is controlled by other hormones called prolactin inhibiting factors (PIFs), such as dopamine.

Hyperprolactinemia:

A prolactinoma is a benign tumor of the pituitary gland, which produces the hormone prolactin and hyperprolactinemia is a condition caused due to elevated prolactin levels in the blood. It is relatively common in women. Hyperprolactinemiaic caused due to certain medications for the treatment of various diseases and physiological reasons along with being pregnant and having strain which are the main factors behind the elevated levels of prolactin.

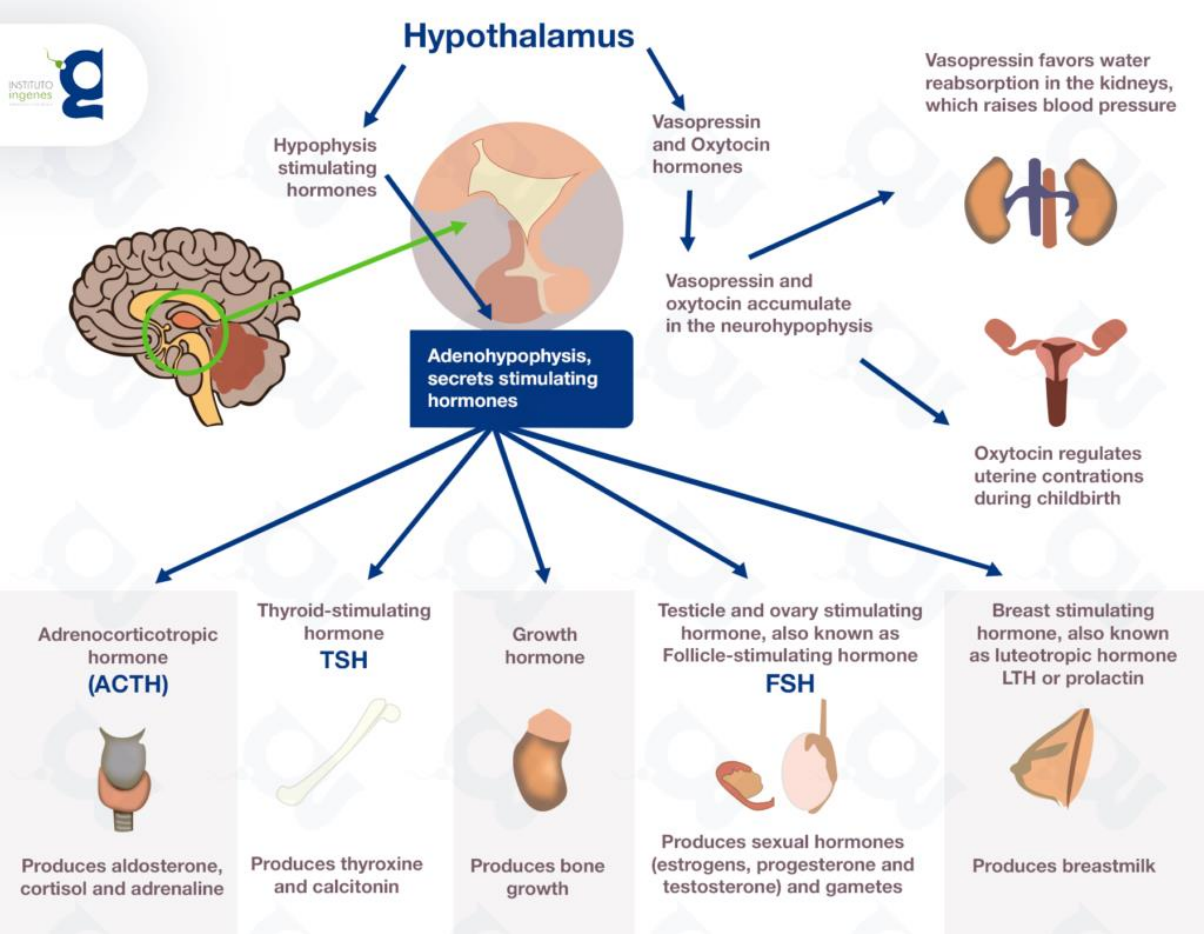


Figure 4: Main symptoms of hyperprolactineomia.

Hyperprolactinemia may also be the result of the disease of other organs such as the liver, kidneys, ovaries, and thyroid. The most common symptoms of hyperprolactinemia are hypogonadism, infertility and erectile dysfunction in male and galactorrhea, and disruptions within the regular menstrual duration in women. Although hyperprolactinemia is not always taken into consideration as life-threatening disease,[14] it causes severe effects on the life of patients and often leads to multiple life-threatening diseases.

Dopamine agonist marketed medicine:

The use of a dopamine agonist drug is observed to be the first choice of therapy for hyperprolactinemia. Dopamine agonist binds to D_2 dopamine receptors on the surface of lactotroph cells inside the anterior pituitary gland which, reduces intracellular cyclic adenosine monophosphate, reduces adenyl cyclase activity, and inhibits prolactin secretion.[15, 16]

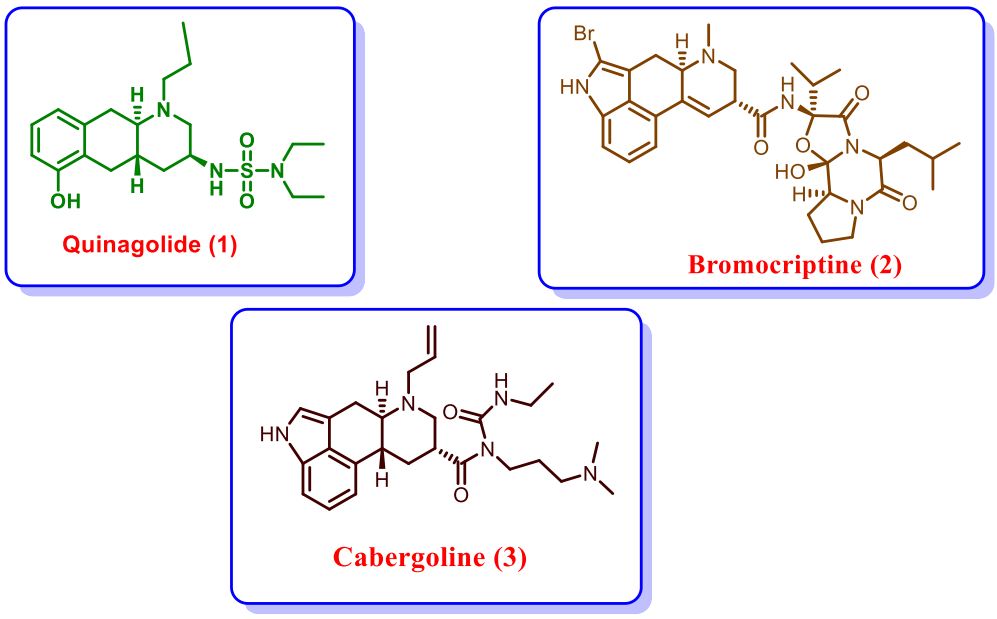


Figure 5: D_2 receptor medicines available in market Quinagolide **(1)**, Bromocriptine **(2)**, Cabergoline **(3)**.

To maintain prolactin hormone and suppress the production, doctors generally prescribe quinagolide **(1)**, bromocriptine **(2)** or cabergoline **(3)**.

Source of Quinagolide:

Ergot alkaloids are well-known for dopaminomimetic activity, like etisulergine (CQ32-084) **(4)**, pergolide (**5)** and apomorphine (**6)** alkaloids are active against dopamine. Nordmann *et al*. were the first to synthesize quinagolide (**1**) by combination of ergot alkaloid and apomorphine alkaloid. In ergoline presence of pyrrolethylamine rigid framework is responsible for the dopaminomimetic pharmacophore.[17, 18] N- Side chain and *trans* ring junction is required for dopaminomimetic bioactivity.

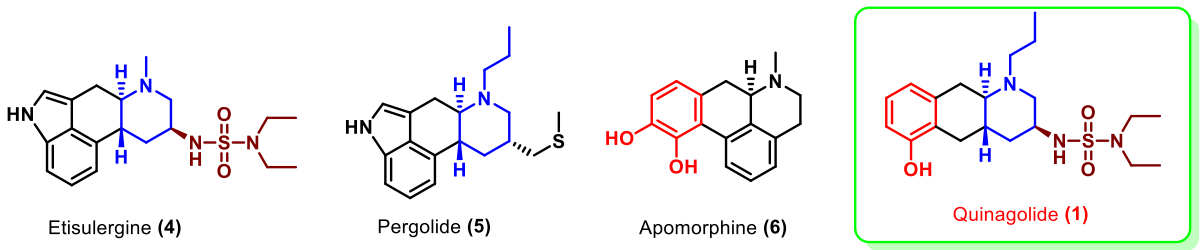


Figure 6: Discovery of quinagolide.

Quinagolide (Norprolac)

Quinagolide exists as a racemate and its relevant clinical activity is mediated predominantly by the (-) enantiomer. It is typically present in the hydrochloride salt form and is marketed as oral tablets under the brand name Norprolac, as a racemate.

Figure 7: Quinagolide oral tablets and Structure.

From the last few decades, increasing efforts have been directed towards the synthesis of new derivatives and partial structures with the primary goal of dissecting out specific dopaminomimetic pharmacopore. Hyperprolactinemia which is responsible for life-threatening diseases is a condition that arises because of the elevated level of prolactin in the blood. Currently, for the treatment of hyperprolactinemia, drugs such as bromocriptine **2**, cabergoline **3** and quinagolide **1** are used as medications. Out of these medications available in the market, bromocriptine and cabergoline have serious side effects whereas quinagolide **1** which is newly introduced by Ferring Pharmaceuticals under the trade name Norprolac is considered as first-line therapy in the treatment of hyperprolactinemia. Quinagolide is developed by combining structural features of ergot and apomorphine alkaloids.

1.1.2. Literature Review:

First synthesis was reported in 1985, by Nordmann *et al.* After that Banziger *et al.* disclosed commercial route for the synthesis of racemic quinagolide. Recently few more syntheses were reported by Chavan *et al.* (this group) and Morandi *et al.* in the literature, shown below in **Figure 8**.

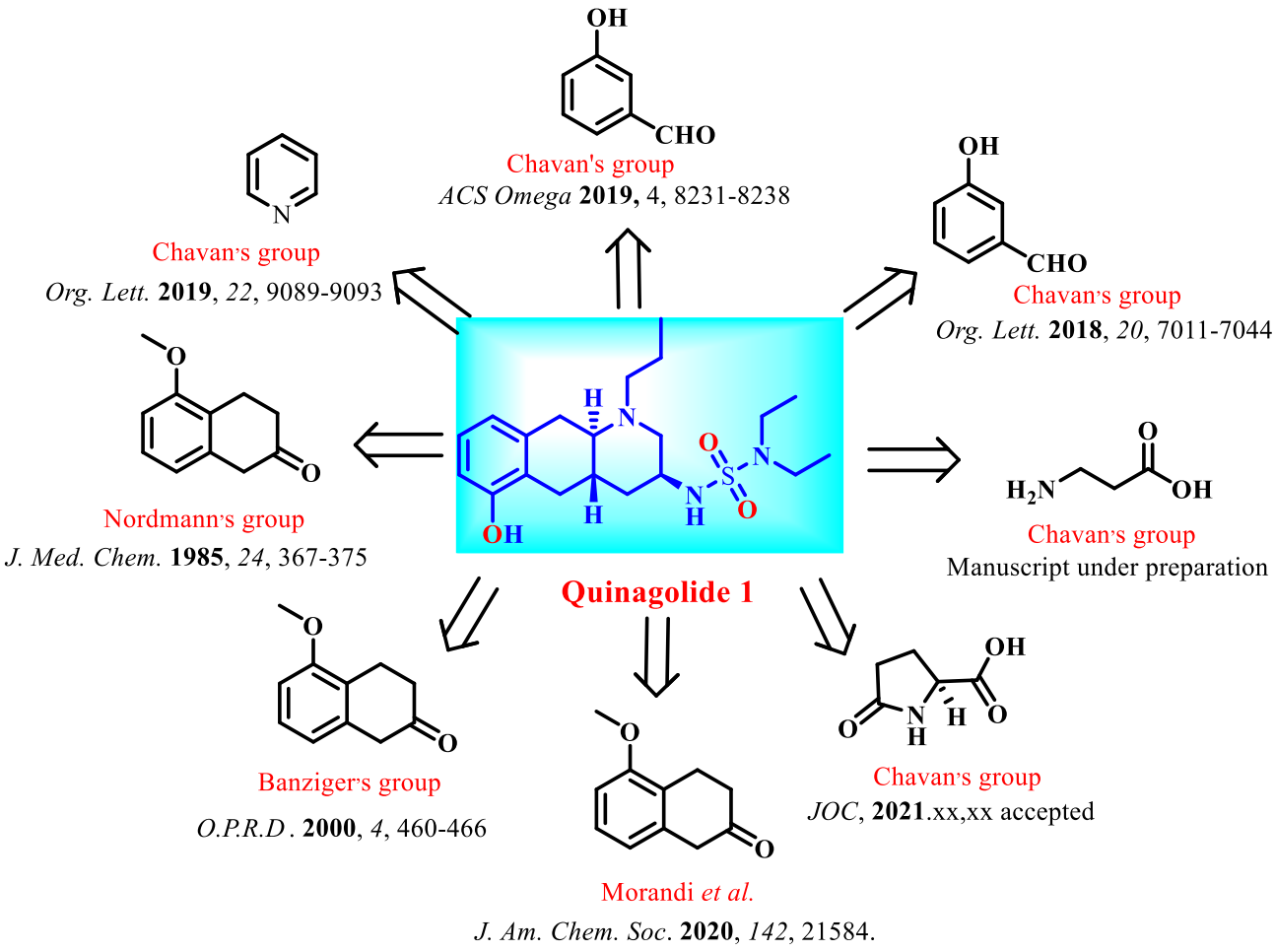
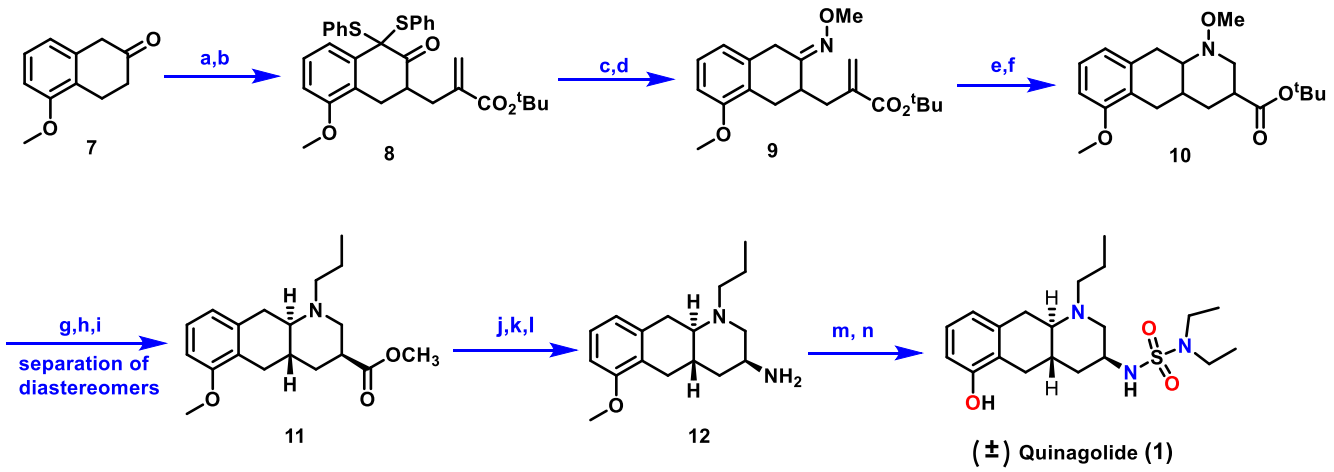


Figure 8: Literature reports of quinagolide.

Nordmann *et al.*, Banziger *et al.*, and Morandi *et al.* used same starting material as shown in **Figure 8** and Chavan *et al.* have explored different and cheap starting materials as compared to reported synthesis. Here a few of these synthetic approaches are discussed in detail.

Nordmann's approach (*J. Med. Chem.* **1985**, *28*, 367-375)[4]

Nordmann *et al.* in year 1985 disclosed a total synthesis of a new dopamine agonist quinagolide by linking the structural features of apomorphine and ergot alkaloids.



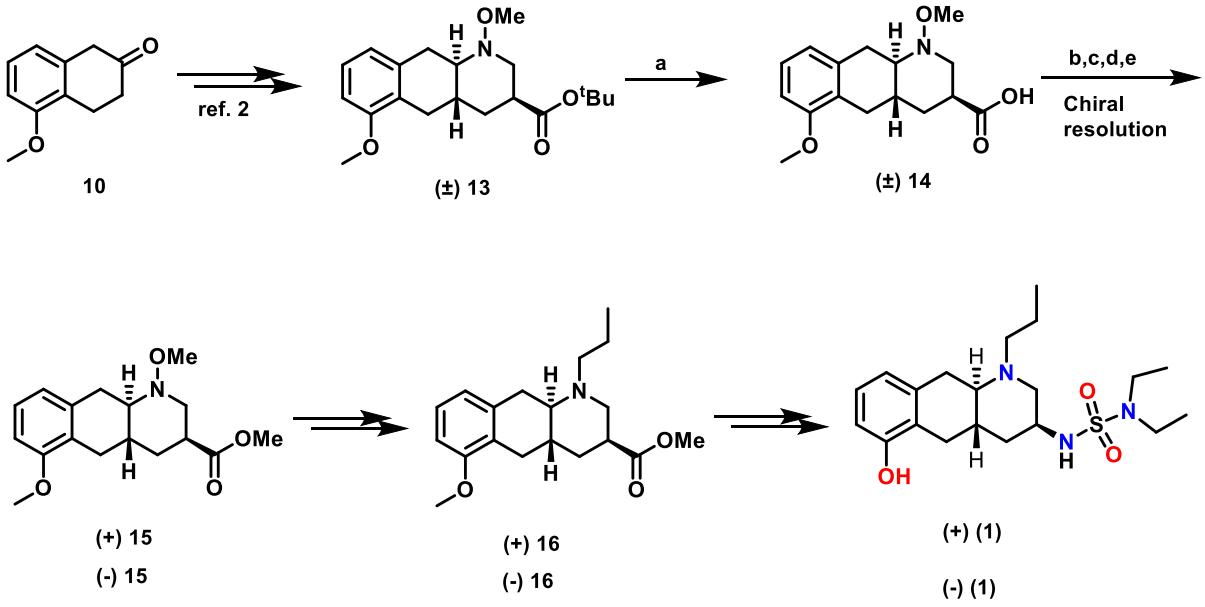
Scheme 1.

Scheme 1: ***Reagents and conditions:*** (a) S-phenyl benzenethiosulfonate, NaOAc, MeOH, rt, 82%; (b) LDA, tert-butyl 2-(bromomethyl)acrylate, Et_2O-THF-HMPT, –78 °C, 66%; (c) Al(Hg), THF-H_2O, 50 °C, 2 h, 71%; (d) H_2NOCH_3.HCl, $Na_2HPO_4.2H_2O$, MeOH, rt, 4 h, 72%; (e) $NaCNBH_3$, MeOH, rt, 12 h; (f) MeOH, rt, 72 h; (g) H_2SO_4, MeOH, reflux, overnight, 92%; (h) Zn, AcOH, H_2O, rt, overnight, 72%; (i) Propanal, H_2, 10% Pd/C, PrOH, rt, overnight, 74%; (j) Hydrazine hydrate, MeOH, 50 °C, 20 h, 80%; (k) NOCl, THF, reflux, 1 h; (l) HCl, THF, reflux, 1 h, 61% (over 2 steps); (m) Et_2NSO_2Cl, $CHCl_3$, 50 °C, overnight, 87%; (n) BBr_3, CH_2Cl_2, –10 °C, 4 h, 89%.

This synthesis was completed in 13 steps, β-tetralone **(7)** was used as a starting material. 5-Methoxy-2-tetralone **(7)** was treated with S-phenyl benzenethiosulfonate and after that alkylation wth *tert*-butyl-2-(bromomethyl)acrylate in basic condition afforded compound **8**. Compound **8** was reacted with Al (Hg) to furnish desulfuratire reduced product and after that keto group was converted to oxime, and the corresponding oxime was reduced by $NaBH_3CN$ to afford diastereoisomeric mixture of tricyclic compound **10**. This diastereoisomeric mixture was purified by column chromatography and the desired diastereomer was subjected to transesterification with MeOH and converted to the methyl ester and this ester was treated with acetic acid and Zn to give cyclic secondary amine which was subsequently hydrogenated in presence of propanal to furnish compound **11**. Compound **11** was converted to hydrazide compound and further this was subjected to Curtius rearrangement and converted to corresponding diamine compound which was treated with diethylsulfamonyl chloride and after that with boron tribromide to give the final product **1**.

Nardman's 2nd approach (*J. Med. Chem*. **1985**, *28*, 1540-1542)[19]

This synthesises was related to chiral resolution of quinagolide and this synthesis was also reported by Nordmann *et al.* in the same year 1985. By using same strategy, racemic mixture of compound (±)**13** a was prepared and that was converted to acid (±)**14** and acid (±)**14** was resolved with D-(+)-α-methylbenzylamine and L-(–)-α-methylbenzylamine. Separated enantiomer was converted to the corresponding (+) **15** and (-) **15** esters with diazomethane. After that following the same reaction sequence that was used in racemic strategy, a (+) or (-) quinagolide was obtained.



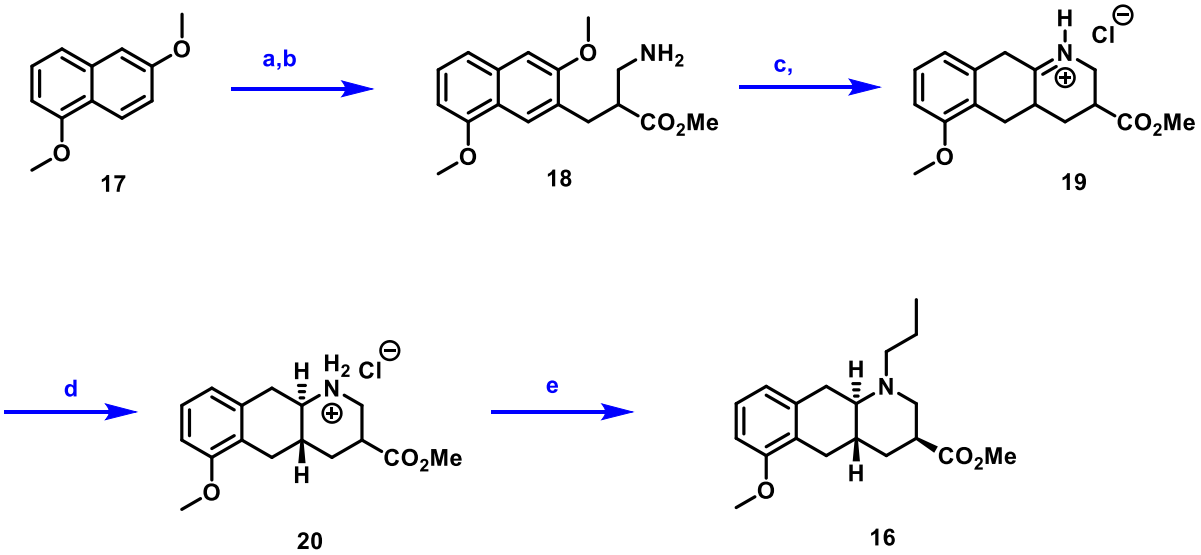
Scheme 2.

Scheme 2: ***Reagents and conditions:*** (a) TFA, rt, 45 min, 90%; (b) D-(+)-α methylbenzylamine CH_2Cl_2-Et_2O, –20 °C, 30%; (c) L-(–)-α-methylbenzylamine, CH_2Cl_2-Et_2O, –20 °C, 28%; (d) 1 N HCl; (e) CH_2N_2, CH_2Cl_2, 98%.

Bänziger's approach (*Org. Process Res. Dev.* **2000**, *4*, 460-466)[20]

Bänziger *et al.* in year 2000, developed a scalable synthetic methodology for the synthesis of quinagolide intermediate **16**. Synthesis began with commercially available 1,6-dimethoxynaphthalene **(17)** which was subjected to *ortho*-lithiation at C-7 position and

alkylated with electrophile ethoxymethylene cyanoacetate to furnish amino acid **18** hydrogenation and after hydrolysis.



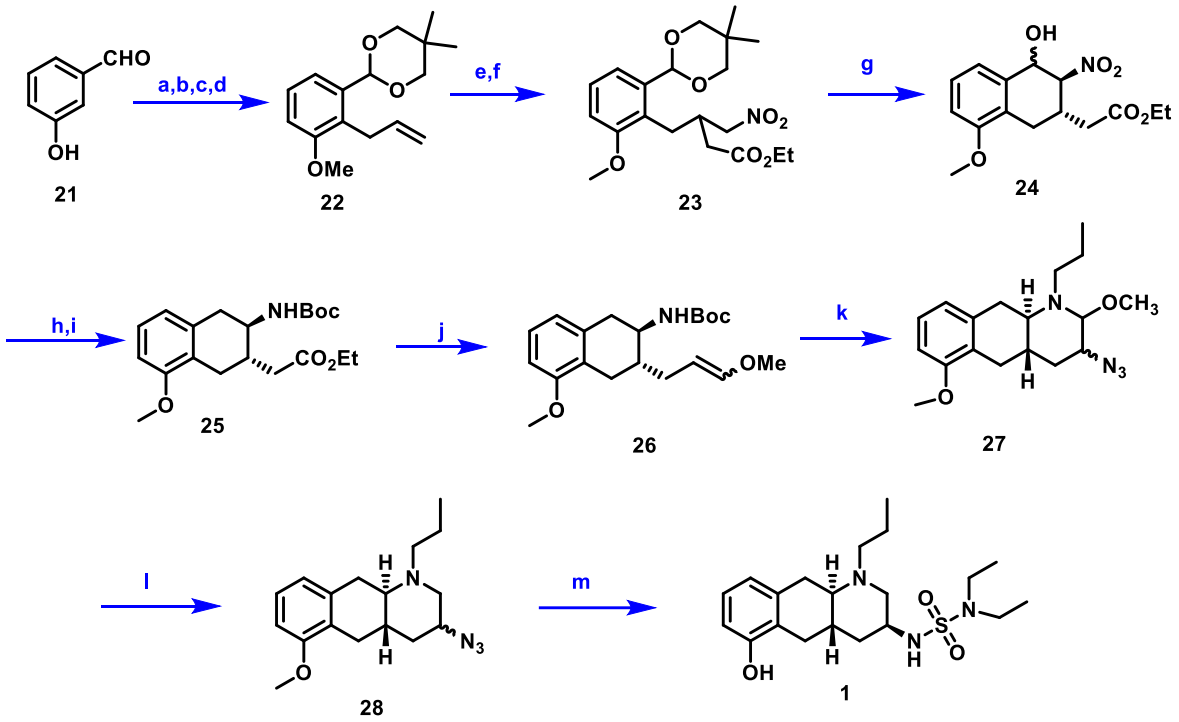
Scheme 3.

Scheme 3: ***Reagents and conditions*****:** a) Hexyllithium, ethoxymethylenecyanoacetate, THF, -70 ^{0}C, 55%; (b) Pt/C, H_2 (10 bar), H_2SO_4, EtOH, 50 ^{0}C then LiOH, H_2O, 83%; (c) Li/NH_3, ^{t}BuOH, THF, -70 ^{0}C then conc. HCl, H_2O, 0 °C 97%: (d) $NaBH_4$, EtOH, 70 °C then conc. H_2SO_4, MeOH, reflux then basic workup then p-TSA, EtOAc, 70 °C, 78%; (e) n-propyliodide, K_2CO_3, DMF, 55 °C then LDA, TMSCl, THF, 40 °C then 15% HCl, 2 h, 85%.

Compound **18** was subjected to Birch reduction and further treated with conc. HCl to afford hydrolyzed product **19**. Iminium compound **19** was converted to amine by using $NaBH_4$ in methanol in presence of H_2SO_4. After that amine was alkylated with propyl iodide to give mixture of diastereomers and finely treated with LDA and TMSCl to afford compound **16** as single diastereomer in 27-29% overall yield in 9 purification steps.

Chavan's approach (*Org. Lett.* **2018**, *20*, 7011-7014)[21]

Chavan *et al.* in year 2018 disclosed a synthesis of quinagolide using ceric ammonium nitrate methodology as key step for azidoalkylation that helped to construct 3-amino piperidone skeleton. Olefin **22** obtained from 3-hydroxybenzaldehyde **21** was dihydroxylated followed by chopping of diol and two-carbon Wittig olefination to give unsaturated ester which on heating in nitromethane in presence of DBU gave Michael addition adduct **23**.



Scheme 4.

Scheme 4: ***Reagents and conditions***: a) allyl bromide, K_2CO_3, EtOH, reflux, 97%; (b) microwave, 800 W, 240 ^{0}C, 45%; (c) Me_2SO_4, K_2CO_3, acetone, reflux, 95%; (d) 2,2-dimethyl-1,3-propanediol, $HC(OEt)_3$, *p*-TSA, CH_2Cl_2, rt, 95%; (e) i) OsO_4, NMO, CH_3CN:H_2O (9:1); ii) $NaIO_4$, acetone:H_2O (3:1), rt, Ph_3PCHCO_2Et, CH_2Cl_2, rt, 72% (over 3 steps); (f) CH_3NO_2, DBU, reflux, 83%; (g) PPTS, acetone:H_2O (4:5), reflux, 82%; (h) H_2, Pd/C, $(Boc)_2O$, Et_3N, EtOAc, 60 psi, 90%; (i) $Pd(OH)_2$, H_2, cat. HCl, MeOH, 60 psi, 83%; (j) i) DIBAL-H, CH_2Cl_2, -78 ^{0}C ii) $CH_3OCH_2PPh_3Cl$, KO*t*-Bu, THF, 0 ^{0}C -rt, *E*/*Z*=80:20, 64% (over 2 steps) ; (k) i) CAN, NaN_3, MeOH, CH_3CN, 0 ^{0}C- rt ii) $NaBH_3CN$, TFA: EtOH (1:9), 0 ^{0}C- rt; iii) *n*-propyl iodide, K_2CO_3, DMF, 50 ^{0}C, 45 % (over 3 steps); (l) PPh_3, H_2O, THF, reflux, 83%; (m) Et_2NSO_2Cl, Et_3N, $CHCl_3$, 50 ^{0}C, 71%; (n) $AlCl_3$, EtSH, CH_2Cl_2, rt, 66%.

The nitroester **23** underwent acetal deprotection by PPTS and Henry reaction in one pot to afford bicyclic compound **24**. Nitro compound **24** was subjected to reduction to afford amine that was converted to corresponding Boc protected amine and further underwent benzylic deoxygenation to give compound **25**. Further, the ester **25** on reduction and MOM-Wittig reaction afforded **26**. It was subjected to ceric ammonium nitrat methodology for azidoalkylation and reduced with $NaBH_3CN$, afforded 3-azido piperidone **28**. Finally, the azide **28** was reduced to amine followed by its protection and demethylation to give quinagolide **1.**

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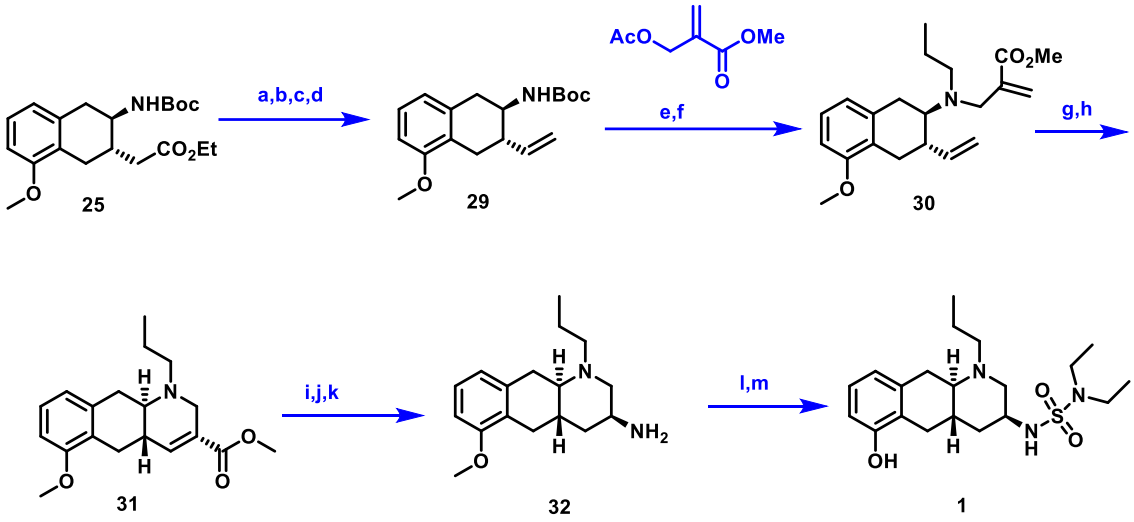
Chavan's approach (*ACS Omega* **2019**, *4*, 8231-8238)[22]

In year 2019 Chavan *et al.* disclosed a synthesis of quinagolide with same starting material, Chavan *et al* by using intermediate **25** that was synthesised as mentioned above and third ring was constructed using ring-closing metathesis with Grubbs' second generation catalyst and PTSA to provide the tricyclic core **31** as shown in Scheme 5.

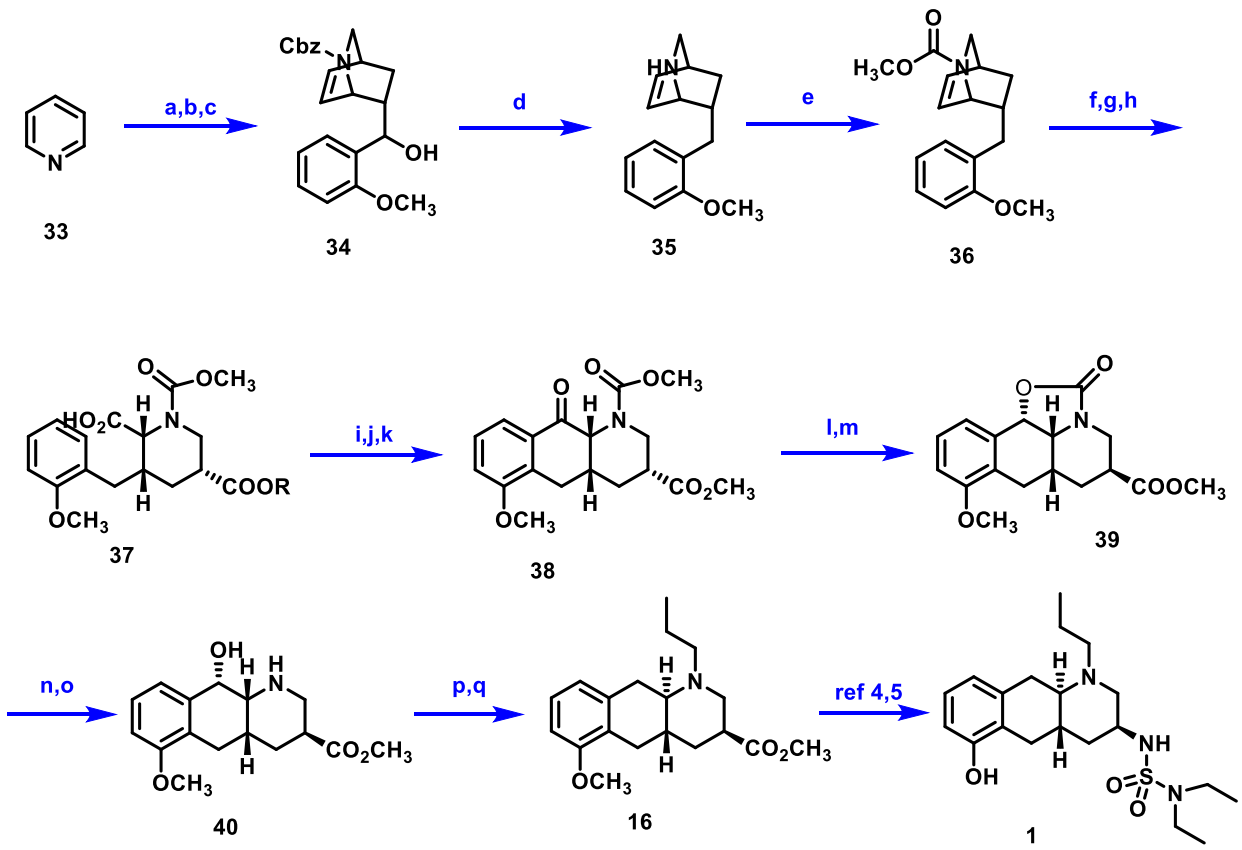


Scheme 5.

Scheme 5: ***Reagents and conditions:*** a) $NaBH_4$, LiCl, THF:EtOH, reflux, 16 h, 68%; (b) $(PhS)_2$, Bu_3P, THF, rt, 24 h, 95% c) $NaIO_4$, MeOH:H_2O, 0 ^{0}C- rt, 12 h, 95% ; (d) $NaHCO_3$, xylene, reflux, 15 h, 98%; (e) i) TFA, CH_2Cl_2, 0 ^{0}C- rt, 5 h, ii) acrylate, CH_2Cl_2, rt, 12 h, 80% (over 2 steps) ; (f) *n*-propyl iodide, K_2CO_3, CH_3CN, reflux, 15 h, 70%; (g) Grubbs' 2nd gen. catalyst, *p*-TSA, toluene, 14 h, 93%; (h) H_2, Pd/C, MeOH, 60 psi, 6 h, 87%; (i) LDA, TMSCl, THF, 40 ^{0}C, 2 h, then H_3O^+, 85%; (j) $CaCl_2$, NH_3, MeOH, 80 ^{0}C (sealed tube), 24 h, 90%; (k) $PhI(CF_3CO_2)$, CH_3CN:H_2O, rt, 12 h, 82%; (l) Diethylsulfamoyl chloride, Et_3N, $CHCl_3$, 50 ^{0}C, 12 h, 71%; (m) $AlCl_3$, EtSH, CH_2Cl_2, rt, 12 h, 66%

Chavan's approach (*Org. Lett.* **2019,** 21 (22), 9089-9093)[23]

Chavan *et al.* in 2019 reported the total first asymmetric synthesis of quinagolide by using pyridine as a starting material (**Scheme 6**).



Scheme 6.

Scheme 6: ***Reagents and conditions*****:** (a) Cbz-Cl, $NaBH_4$, MeOH, -50 °C-0 °C, 2 h; (b) Acrolein CH_3CN-H_2O, 0 °C, 24 h; (c) Grignard reagent from 2-bromoanisole, THF, -30 °C to rt, 2 hr 34% (3 steps); (d) Li, liq NH_3, THF, - 78 °C, 15 min; (e) $ClCO_2CH_3$, Na_2CO_3, CH_2Cl_2, 0 °C to rt, 12 h , 64 % (2 steps); f) OsO_4, NMO, THF-H_2O, rt, 2 days; (g) Silica supported $NaIO_4$, CH_2Cl_2, rt, 1 h; (h) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, t-BuOH, 12 h, 95% (3 steps); (i) $(COCl)_2$, CH_2Cl_2 0 °C to rt, 1 h; (j) $TiCl_4$, CH_2Cl_2, 0 °C, 2 (k) MeOH, -30 °C, to rt, 3 h, 62%; (l) $LiBH_4$, THF, 0 °C to rt, 2 h, 68% ; (m) $NaOCH_3$, MeOH, 0°C to rt, 12 h, 70%; (n) NaOH, EtOH, reflux, 1 h; (o) CH_2N_2, MeOH-Et_2O, 0°C to rt, 1 h, 53 % (2 steps); (p) PTSA, toluene, reflux, 2 h, then $NaBH_3CN$, MeOH; (q) propyl iodide, K_2CO_3, DMF, 50 °C, 2.5 h, 61 % (2 steps).

Pyridine was reduced by sodium borohydride in presence of Cbz-Cl fallowed by Diel-Alder reaction using acrolein and Grignard reaction using 2-bromoanisole to give Cbz protected compound **34** Birch reduction of **34** afforded bicyclic amine **35**. Bicyclic amine was treated with methyl chloroformate to obtain the intermediate **36**. Further dihydroxylation of **36** followed by chopping of diol and Pinnick oxidation gave **37**. Tricyclic core **38** was achieved by conversion of acid **37** into acid chloride followed by $TiCl_4$ mediated Friedel Crafts

cyclization reaction. Reduction of ketone using $LiBH_4$ gave tricyclic carbamate and epimerization of ester using NaOMe afforded carbamate ester **39.** The carbamate **39** was opened under basic condition and esterification with diazomethane gave the amino alcohol **40**. Enamine formation and subsequently reduction with $NaBH_3CN$ and N-alkylation of corresponding amine with propyl iodide afforded ester **16**. The synthesis of quinagolide **1** from the ester **16** is known in literature.

1.1.3. Conclusion

Quinagolide contains a tricyclic ring with three contiguous chiral centres and *trans*-fused 3-aminopiperidine skeleton and has combined structural features of ergot and apomorphine alkaloids and it is used as D_2 receptor agonist for the treatment of hyperprolactinemia. Cost of 30 tablets (75 μg each) of quinagolide is $100 and cost of API is 4.5 lakh US Dollar per Kg (Rs. 3.2 Crore per Kg). The medicinal use of quinagolide and the necessity to make it available in commercial scale at lower price form led to develop a new route for the total synthesis of quinagolide.

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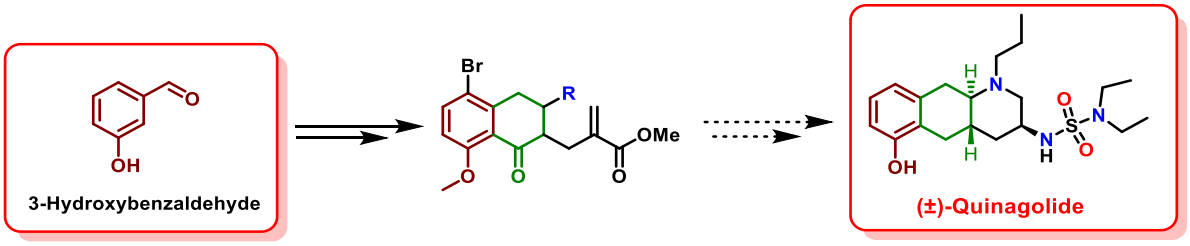
Chapter 1: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide

Chapter-1
Section-2

"Synthetic Study Towards (±)-Quinagolide Using 3-Hydroxybenzaldehyde as Starting Material"



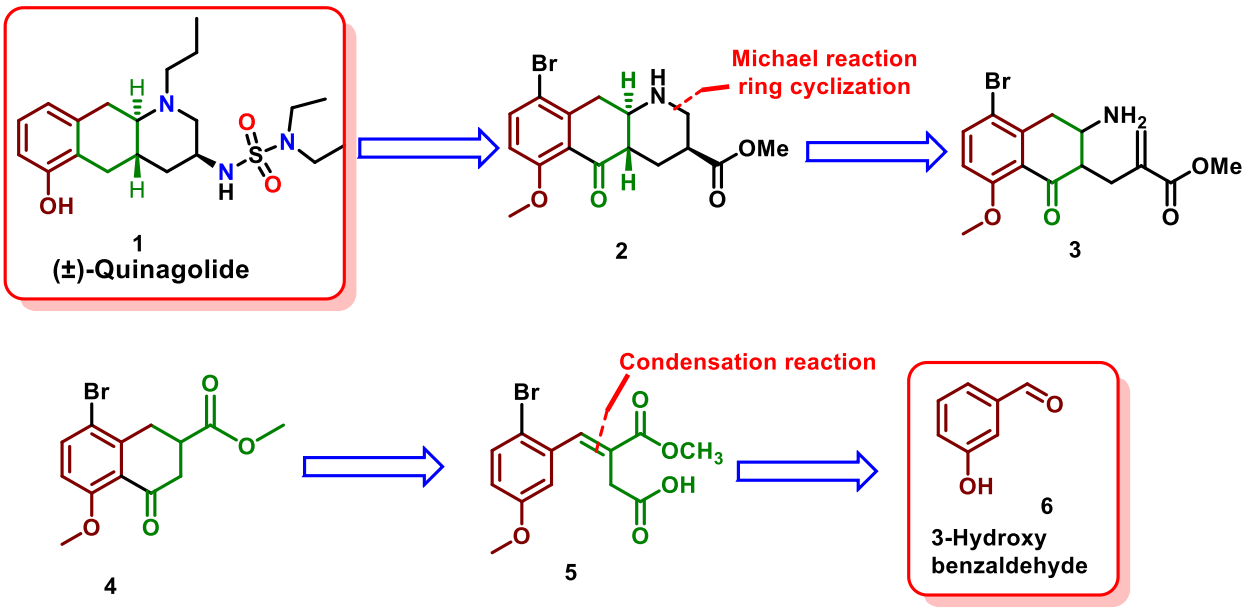
1.2.1. ABSTRACT:

Quinagolide is a selective D_2 receptor agonist. Dopamine receptor D_2 also known as D_2R, is a protein present in the human body that plays several important roles in the brain and body. Dopaminergic system dysfunction in the central nervous system has been related to brain diseases such as Parkinson's disease, schizophrenia, and hyperprolactinemia. Hyperprolactinemia is caused by the overproduction of the hormone prolactin. Quinagolide is used to reduce the elevated levels of prolactin.[1] Quinagolide hydrochloride is marketed under the trade name Norprolac®.

1.2.2. Present Work:

Retrosynthetic analysis:

The retrosynthetic analysis revolves around utilizing starting material used by Chavan *et al.*[2,3](This group) It was thought that quinagolide **1** could be accessed from the same staring material by a different route (**Scheme 1)**.



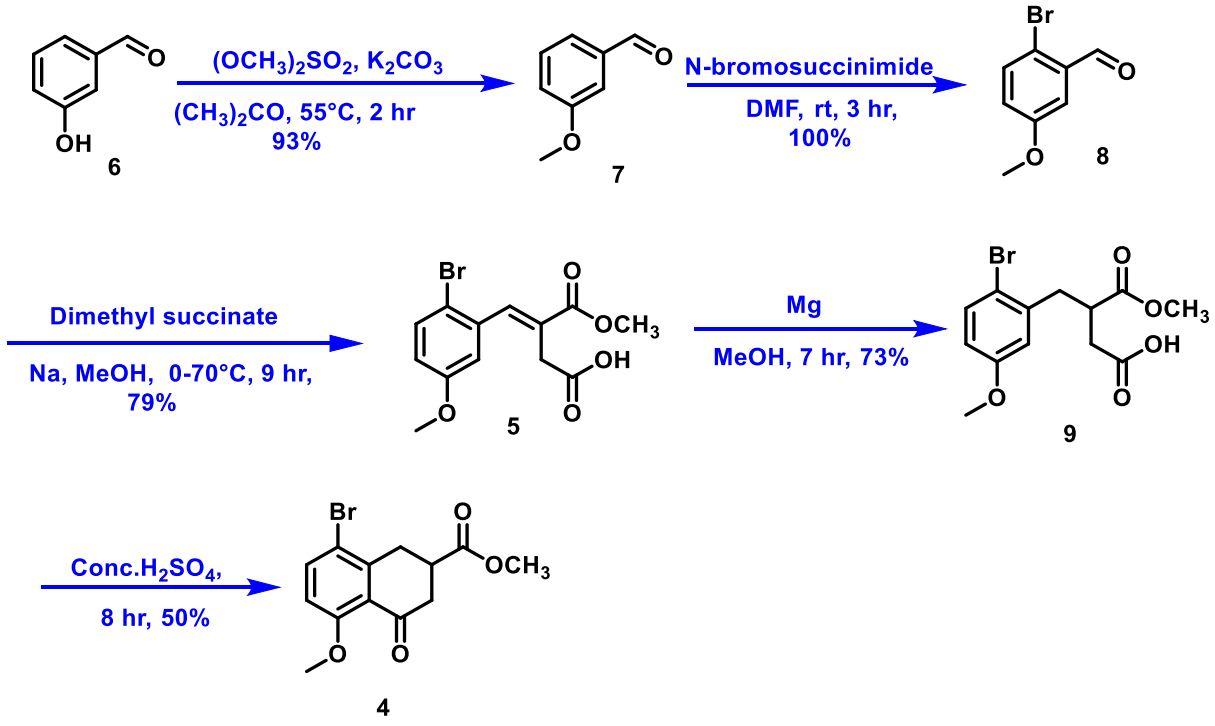
Scheme 1. The retrosynthetic analysis for Quinagolide.

The compound **5** could be accessed from *meta*-hydroxy benzaldehyde by protection, (O-methylation), bromination and Stobbe condensation.[4] Compound **4** could be obtained from

compound **5** in two steps. First reduction[5] of unsaturated acid-ester **5** to corresponding saturated compound followed by acid mediated cyclization reaction. Amino ester **3** could be accessed from compound **4** by SN_2 reaction with ethyl 2-(bromomethyl)-2-propenoate and conversion of acid to amine. When acid is converted to amine, intramolecular Michael addition would lead to the construction of the third ring and the tricyclic core intermediate **2** could be obtained from **3.** Quinagolide **1** could be achieved by functional group interconversion from the tricyclic keto-ester **2.**

1.2.3. Studies towards synthesis of the (±)-Quinagolide, results and discussion:

The synthesis began with the goal of transformation of *meta*-hydroxy benzaldehyde **5** into corresponding acid **9 (Scheme 2)**. First *meta*-hydroxy benzaldehyde was methylated by using dimethyl sulphate, K_2CO_3 in acetone under reflux conditions to afford *meta*-methoxy benzaldehyde **7** in 90% yield. The appearance peak at δ 3.83 (s, 3H) for O-CH_3 in the ^{1}H NMR spectrum and peak at δ 55.6 in the ^{13}C NMR spectrum confirmed the formation of the product **7**.



Scheme 2. Synthesis of bicyclic core of quinagolide.

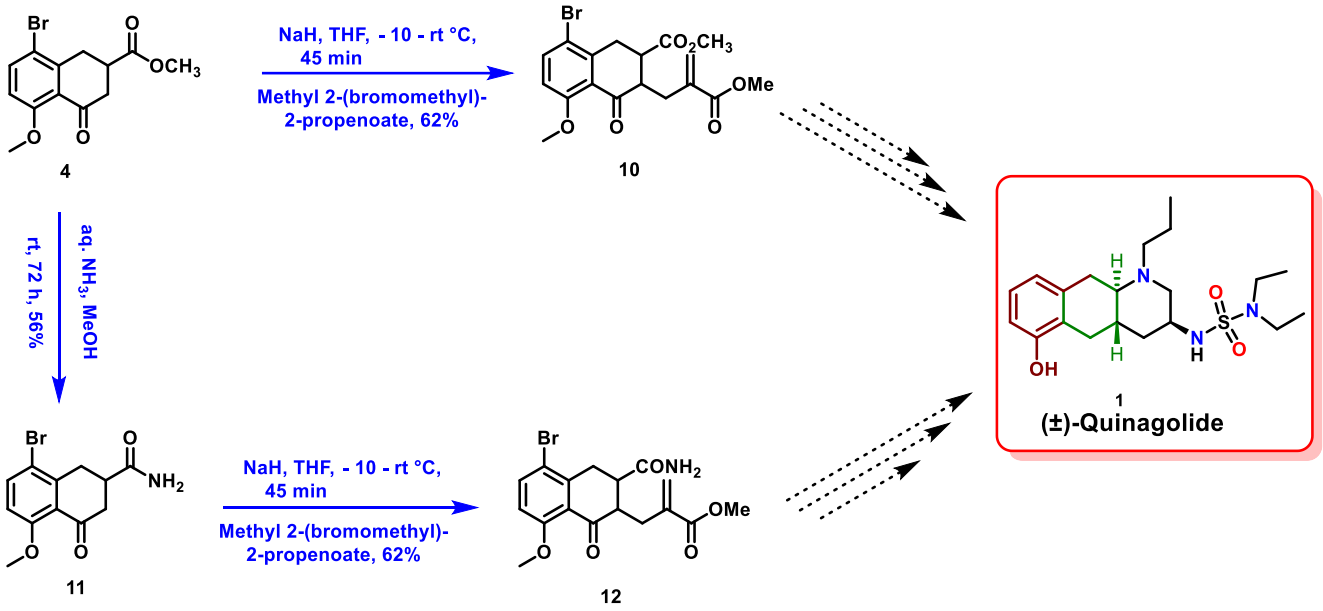
meta-Anisldehyde **7** was treated with N-bromosuccinimide in DMF for 3 h at room temperature to convert it into corresponding brominated derivative **8**. The formation of the product was confirmed by the presence of a signal at 931 cm^{-1} in the IR spectrum corresponding to Ar-Br stretching frequency and disappearance of peak at δ 7.42 - 7.41 (m, 2H) and appearance of peak at δ 7.49 (d, *J* = 8.8 Hz, 1H) in ^{1}H NMR spectrum in aromatic region. HRMS analysis confirmed the formation of the product (HRMS (ESI) m/z calcd for $C_8H_{18}BrO_2$ $[M + H]^+$: 214.9697; found: 214.9602).

In the next step, C-C coupling by the Stobbe condensation reaction in which compound **8** was treated with dimethyl succinate in the presence of *in situ* generated sodium methoxide by using sodium metal and ice cooled methanol under nitrogen atmosphere afforded monoester acid **5** in 79% yield. In the ^{1}H-NMR spectrum of compound **5**, peaks at δ 10.62 (br s, 1H) and 7.86 (s, 1H) corresponding to acid and olefin protons and distinct peaks at δ 3.86 (s, 3H) and 3.63 (s, 3H) for O-C$\underline{H}_3$ protons of ester and aromatic ether and singlet at 3.46 (s, 2H) for -C$\underline{H}_2$ indicated the formation of the product. Also in the ^{13}C-NMR spectrum, peaks at δ 176.7 and 166.8 corresponding to ester and a keto carbonyls were observed.

Then the chemoselective reduction of double bond of acid-ester **5** was achieved by adding to a suspension of magnesium shavings in anhydrous MeOH under inert atmosphere (N_2) and after a 10 minutes of stirring, the reaction vessel was immersed in an ice bath and stirred at 0 °C for 5 h to afford reduced acid-ester **9**. The formation of product **9** was indicated by the disappearance of singlet at δ 7.86 (s, 1H) and 3.46 (s, 2H) for allylic -C$\underline{H}$ and -C$\underline{H}_2$ group and appearance of peaks at δ 3.29 - 3.10 (m, 2H), 2.88 (dd, *J* = 8.4, 13.4 Hz, 1 H) and 2.77 (dd, *J* = 9.2, 17.2 Hz, 1H) but ^{13}C NMR spectrum showed extra peaks. The formation of compound **9** was further confirmed by converting it to corresponding diester derivative. The ^{1}H NMR and ^{13}C NMR spectra of the diester matched well with the assigned structure. The formation of the diester was confirmed by the presence of three singlet peaks at δ 3.74 (s, 3 H) and 3.65 (s, 3H) and 3.62 (s, 3H) for three -OC$\underline{H}_3$ groups and disappearance of singlet at δ 7.86 (s, 1H).

In the next step, acid-ester compound **9** was subjected to cyclisation under acidic condition in which solution of the acid **9** in H_2SO_4 was stirred for 8 hr at 0 °C to rt and then gradually poured on ice. The precipitated solid was collected, washed with water and dried to afford ketone **4** in 50% yield. Formation of bicyclic product **4** was confirmed by peak at δ 194.6 in ^{13}C NMR

spectrum corresponding to newly formed ketone group. HRMS analysis also confirmed its formation (HRMS (ESI) m/z calcd for $C_{13}H_{14}BrO_4$ $[M + H]^+$: 313.0060; found: 313.0070).



Scheme 3. Synthesis of tricyclic skeleton of quinagolide.

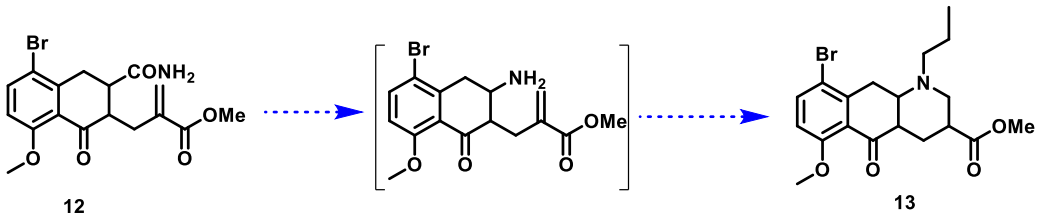
After the successful formation of bicyclic core, the next aim was the formation of tricyclic skeleton for which functionalization of active methylene group adjacent to ketone in compound **4** was required. For that, ketone **4** was subjected for C-alkylation reaction with NaH in THF at -10 °C and methyl 2-(bromomethyl)-2-propenoate was used as electrophile to afford C-alkylated product **10** in 62% yield. The formation of **10** was indicated by ^{1}H NMR spectrum which showed peaks at δ 6.24 (d, *J* = 1.0 Hz, 1H) and 5.63 (d, *J* = 1.1 Hz, 1H) corresponding to C=C$\underline{H}_2$ and three singlet peaks at δ 3.87 (s, 3H) and 3.75 (s, 3H) and 3.67 (s, 3H) for three -OC$\underline{H}_3$ peak at δ 128.4 ppm for =CH_2 and peaks at δ 52.7 and 52.9 ppm for two –OCH_3 carbons confirmed the structure of compound **10**.

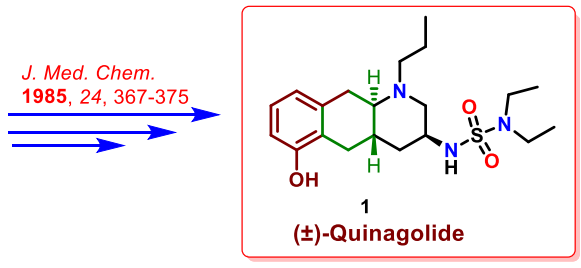
In the alternate approach in this synthetic methodology, ester group in compound **4** was first converted in to amine and after that the active methylene group was C-alkylated. Thus, the compound **4** was treated with aq ammonia, 30% in methanol for 72 hours at room temperature to afford amide **11** in 56% yield. The formation of compound **11** was evident from ^{1}H NMR spectrum which showed the disappearance of peak at δ 3.74 (s, 3H) for ester -OC$\underline{H}_3$ and presence of two peaks at δ 6.60 (br s, 1H) and 6.01 (br s, 1H) for NH_2 protons.

After that the ketone amide compound **11** was subjected for C-alkylation reaction with NaH base in THF at -10 ^{o}C and methyl 2-(bromomethyl)-2-propenoate used as electrophile to afford C-alkylated product **12** in 62% yield. The formation of the product was confirmed by the presence of a bands at 1727 (2 CO) and 1680 cm^{-1} in the IR spectrum corresponding to ketone, ester and amide stretching frequencice respectively. Formation of compound **12** was futher supported by ^{1}H NMR spectrum which showed two singlets at δ 6.23 (s, 1H) and 5.63 (s, 1H) corresponding to C=C$\underline{H}_2$ and appearance of singlet for OCH_3 as well as CH_2 protons. Further confirmation and standardization of this synthetic strategy is under progress.

1.2.4. Conclusion:

In summary, this synthetic strategy started from the 3-hydroxybenzaldehyde and important bicyclic intermediates **10** and **12** were synthesized successfully. It is a few steps away to achieve to tricycle core. Tricyclic core **13** used in the synthesis of quinagolide **1** could be accessed from the key intermediate **12** by using Hofmann rearrangement and after that reported functional group interconversions would give quinagolide **1.**



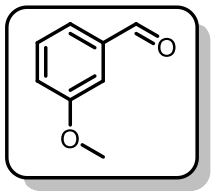


The key steps used in the synthesis were scalable and involved simple chemistry and by using chiral reducing agent for converting compound **5** to compound **9** it can be converted to asymmetric synthesis.

1.2.5. Experimental Section;

1.2.4.1. Experimental Procedures and Characterization Data

3-Methoxybenzaldehyde (7)



3-Hydroxy benzaldehyde **6** (25.0 g, 204.91 mmol), anhydrous potassium carbonate (70 g, 512.29 mmol), and dimethyl sulfate (48.53 mL, 512.29 mol) were heated at reflux with stirring in acetone (500 mL) for ~2 h, and complete consumption of starting material was checked by TLC. After cooling, the solution was filtered and evaporated to dryness under reduced pressure to give to afford the 3-methoxy benzaldehyde **7** in 26 g, 93% yield.

Rf : 0.7 (Ethyl acetate – pet. ether=05:95);

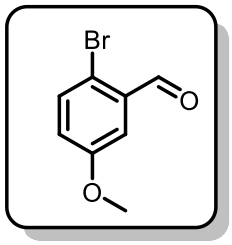
Yield: 93%;

IR ($CHCl_3$): ν_{max} 2955, 2838, 1701, 1592 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.94 (s, 1H), 7.42 - 7.41 (m, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 6.8 Hz, 1H), 3.83 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.3, 160.3, 138.0, 130.2, 123.7, 121.6, 112.3, 55.6.

2-Bromo-5-methoxybenzaldehyde (8)



To a solution of m-anisaldehyde **7** (55.4 g, 410 mmol) in DMF (400 mL) was added a solution of N-bromosuccinimide (124.0 g, 690 mmol) drop wise at room temperature. After the addition, the reaction solution was stirred at room temperature for 12 h, then poured into a mixture of ice and water and stirred for 10 min. The precipitate was collected by filtration and dissolved in ethyl acetate. The resulting solution was washed with water and brine, dried over sodium sulfate and concentrated in vacuum to give compound **8**. Yield 86.7 g, 100%, off-white solid.

Rf : 0.5 (Ethyl acetate – pet. ether=05:95);

Yield: 100%;

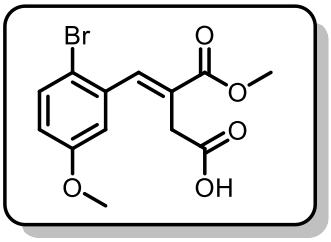
IR ($CHCl_3$): ν_{max} 2870, 1679, 1592, 1470, 931 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.27 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 3.3 Hz, 1H), 7.00 (dd, *J* = 3.2, 8.8 Hz, 1H), 3.82 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 159.1, 134.4, 133.8, 122.9, 117.8, 112.6, 55.6;

HRMS (ESI): m/z calcd for $C_8H_{18}BrO_2$ $[M + H]^+$: 214.9697; found: 214.9602.

4-(2-Bromo-5-methoxyphenyl)-3-(methoxycarbonyl)but-3-enoic acid (5)



Sodium methoxide was generated *in situ* by adding sodium (19.5 g, 0.85 g atom) carefully to ice cooled methanol (500 ml). When sodium was dissolved, dimethyl succinate (166 ml, 1.0 mol) in methanol (50 ml) was added to the solution. 2-Bromo-5-methoxybenzaldehyde **8** (68.1 g, 0.5 mol) in methanol (150 ml) was added dropwise to the solution under an argon atmosphere over 1.5 h under reflux and the reaction mixture was refluxed for 5 h. Methanol was removed under reduced pressure and residue was quenched with conc. HCl, cold water was added to the reaction mixture and the mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with H_2O (80 mL), and extracted with sat. aq. $NaHCO_3$ (3 × 200 mL). The aqueous layer was acidified with conc. HCl, and the mixture was extracted with ethyl acetate (2 × 200 mL) and combined organic layer was washed with brine (200 ml), and dried over anhydrous Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel (pet. ether: ethyl acetate 40:60) to afford the acid ester **5** in 79% yield (83 g).

Rf : 0.3 (Ethyl acetate – pet. ether=60:40);

Yield: 79%;

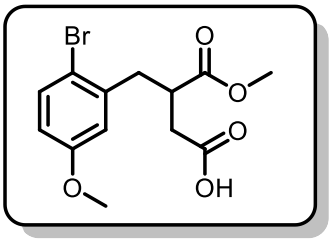
IR ($CHCl_3$): ν_{max} 2932, 1707 (2CO), 1576, 1459, 938 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.62 (br s, 1H), 7.86 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.78 (dd, *J* = 2.9, 8.8 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 3.46 (s, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.7, 166.8, 158.4, 141.5, 135.5, 133.1, 126.5, 116.1, 114.7, 113.7, 55.1, 52.2, 33.3;

HRMS (ESI): m/z calcd for $C_{13}H_{13}BrNaO_5$ $[M + Na]^+$: 350.9824; found: 350.9839.

3-(2-Bromo-5-methoxybenzyl)-4-methoxy-4-oxobutanoic acid (9)



The hemisuccinate **5** (5.2 g, 13.5 mmol) was added to a suspension of magnesium shavings (5.0 g, 208 mmol) in dry methanol (100 ml) under Ar atmosphere. After a few minutes of stirring, the reaction vessel was immersed in an ice bath and stirred at 0 °C for 5 h. The suspension was acidified with hydrochloric acid (6 M) and the remaining solids were

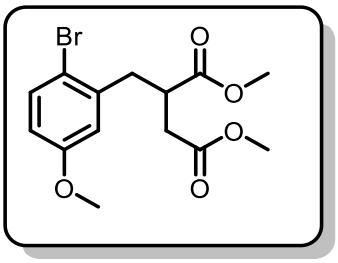
removed by filtration. The filtrate was extracted with dichloromethane (3 × 200 mL), and combined organic layer was washed with brine (200 ml), and dried over anhydrous Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel (Pet. ether: ethyl acetate 40:60) to afford the hemisuccinate **9** (3.8 g, 73%).

Rf : 0.3 (Ethyl acetate – pet. ether=60:40);

Yield: 73%;

IR ($CHCl_3$): ν_{max} 2939, 1697 (2 CO), 1581, 1461, 931 cm^{-1};

Dimethyl 2-(2-bromo-5-methoxybenzyl)succinate



Rf : 0.5 (Ethyl acetate – pet. ether=10:90);

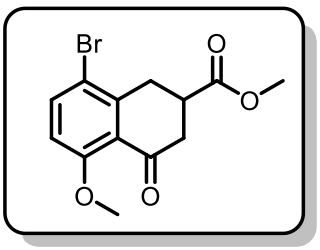
Yield: 80%;

IR ($CHCl_3$): ν_{max} 2932, 1707 (2CO), 1581, 1461, 931 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (dd, *J* = 2.3, 8.7 Hz, 1H), 6.74 - 6.68 (m, 1H), 6.67 - 6.59 (m, 1H), 3.74 (s, 3 H), 3.65 (s, 3H), 3.62 (s, 3H), 3.28 - 3.17 (m, 1H), 3.15 - 3.05 (m, 1H), 2.85 (ddd, *J* = 1.6, 8.4, 13.5 Hz, 1H), 2.70 (ddd, *J* = 1.8, 9.2, 16.7 Hz, 1H), 2.45 (ddd, *J* = 1.5, 4.6, 16.8 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.3, 171.9, 158.7, 138.5, 133.4, 116.6, 114.9, 114.0, 55.3, 51.8, 51.6, 41.2, 37.7, 34.9.

Methyl 8-bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4)



To a solution of acid **9** (13.01 g, 54.6 mmol) in glacial acetic acid (60 mL), cooled at 0 to 5°C, was added dropwise bromine (2.8 mL, 54.2 mmol), stirred for 5 min at this temperature and then for 20 h at room temperature. To the resulting brown solution was added a solution of the sodium bisulfite (5%) till the brown color disappeared and then extracted with chloroform. The combined organic extracts were washed with H_2O (80 mL), and extracted with sat. aq. $NaHCO_3$ (3 × 100 mL). Organic solvent was

removed under reduced pressure. The residue was purified by flash chromatography over silica gel (Pet. ether: ethyl acetate 90:10) to afford the bicyclic compound **4** (28.5 g, 50%).

Rf : 0.8 (Ethyl acetate – pet. ether= 50:50);

Yield: 50%;

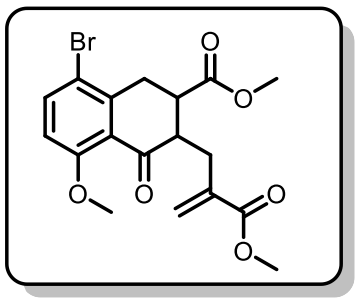
IR ($CHCl_3$): ν_{max} 2927, 1734, 1687, 1568, 815 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3 H), 3.74 (s, 3H), 3.44 - 3.34 (m, 1H), 3.18 - 3.01 (m, 2H), 2.95 - 2.74 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.6, 173.5, 160.0, 142.8, 138.3, 123.6, 115.0, 112.4, 56.6, 52.6, 42.1, 39.3, 33.5, 30.0;

HRMS (ESI): m/z calcd for $C_{13}H_{14}BrO_4$ $[M + H]^+$: 313.0060; found: 313.0070.

Methyl 8-bromo-5-methoxy-3-(2-(methoxycarbonyl)allyl)-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (10)



To a mechanically stirred suspension of sodium hydride (0.022 g of a 50 % oil dispersion, 118.22 mmol, 1.2 eq) in anhydrous THF (6 mL), was added **4** (0.200 g, 0.771 mmol) at – 10 ºC to rt in THF. A solution of methyl 2-(bromomethyl)acrylate (0.176 mL, 0.926 mmol, 1.2 eq) in anhydrous THF was slowly added to reaction mixture at same temperature. After complete consumption of starting material as checked by TLC (~ 6 h), saturated $NaHCO_3$ solution (3 mL) was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure to obtain crude product **10** which was purified by using flash silica gel column chromatography eluting with 20 % ethyl acetate in pet ether as the eluent to furnish pure compound **10** (0.164 g, 62%).

Rf : 0. 5 (Ethyl acetate – pet. ether= 30:70);

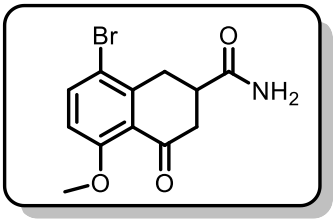
Yield: 62%;

IR ($CHCl_3$): ν_{max} 3606, 3476, 2925, 1724 (3 CO), 1575, 1446, 1278, 959 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 8.9 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 1H), 6.24 (d, *J* = 1.0 Hz, 1H), 5.63 (d, *J* = 1.1 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.30 - 3.09 (m, 3H), 3.03 - 2.90 (m, 2H), 2.50 (ddd, *J* = 0.7, 7.4, 14.6 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.0, 173.6, 167.4, 159.6, 141.6, 138.0, 137.7, 128.0, 123.4, 114.6, 112.4, 56.5, 52.4, 52.3, 48.7, 43.9, 32.2, 32.1.

8-Bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide (11)



To a solution of **4** (0.250 g, 0.803 mmol) in MeOH (5 mL) was added 30% aq ammonia (5 mL) was added dropwise at 0 ˚C and further stirred for 72 hours at room temperature. The organic solvent methanol was concentrated and reaction mixture was allowed to separate in separating funnel, organic layer was separated and aqueous layer was again extracted twice using ethyl acetate (100 mL). The collected organic, layer was dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure to obtain crude product **11** which was purified by using flash silica gel column chromatography eluting with 10 % methanol in dichloromethane as the eluent to furnish pure compound **11** (0.148 g, 62% yield).

Rf : 0. 2 (Ethyl acetate – pet. ether= 60:40);

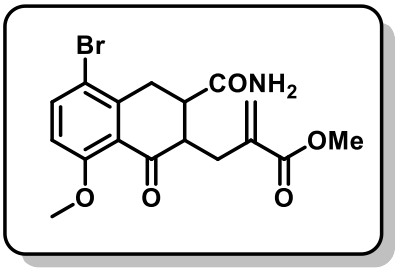
Yield: 62%;

IR ($CHCl_3$): ν_{max} 3843, 3516, 2927, 1734, 1680, 1572, 1453, 1280, 813 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 9.0 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.60 (b s, 1H), 6.01(b s, 1H), 3.90 (s, 3 H), 3.50 - 3.24 (m, 1H), 3.24 - 3.00 (m, 2H), 3.00 - 2.72 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ xxx.

Methyl 2-((5-bromo-3-carbamoyl-8-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)acrylate (12)



To a mechanically stirred suspension of sodium hydride (0.022 g of a 50 % oil dispersion, 0.404 mmol, 1.2 eq) in anhydrous THF (6 mL), was added **4** (0.100 g, 0.366 mmol) in THF at – 10 ºC to rt. A solution of methyl 2-(bromomethyl)acrylate (0.076 mL, 0.463 mmol, 1.2 eq) in anhydrous THF was slowly added to reaction mixture at same temperature. After complete consumption of starting material as checked by TLC (~ 6 h), saturated $NaHCO_3$ solution (3 mL) was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 (3 ×

25 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure to obtain crude product **12** which was purified by using flash silica gel column chromatography eluting with 45 % ethyl acetate in pet ether as the eluent to furnish pure compound **12** (0.030 g, 62% yield).

Rf : 0. 3 (Ethyl acetate – pet. ether= 60:40);

Yield: 62%;

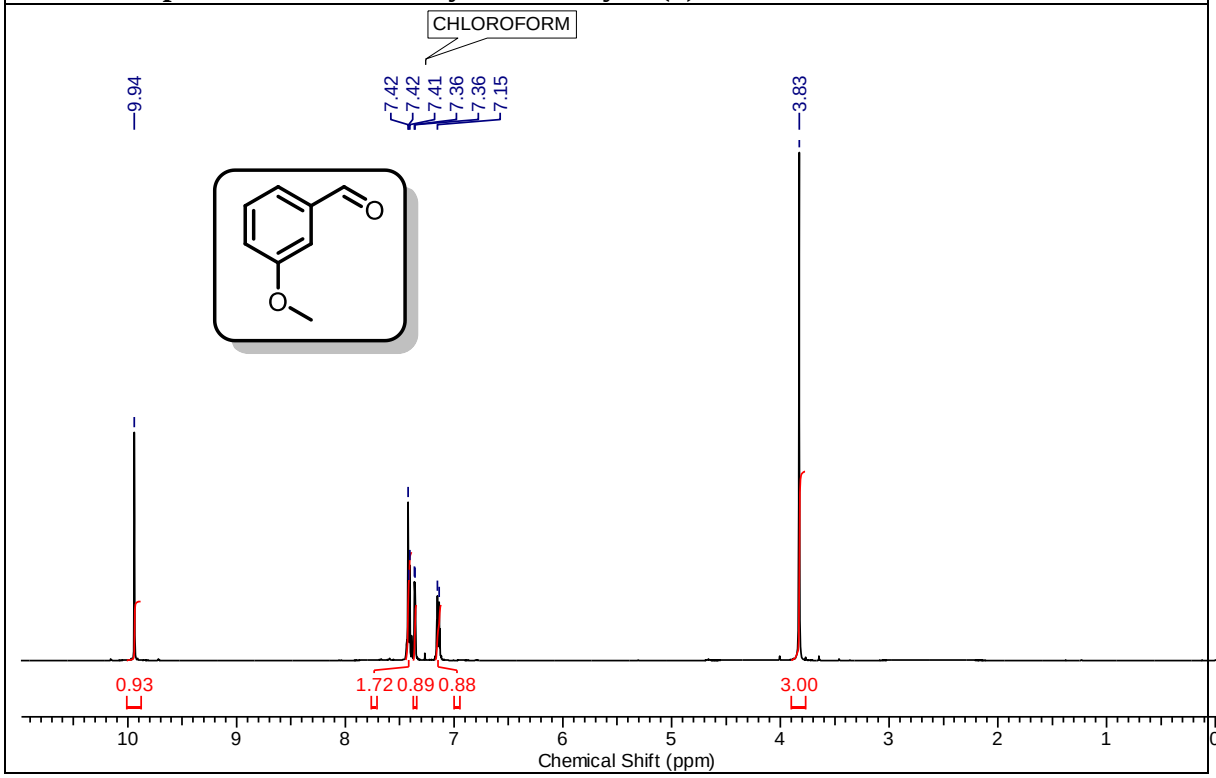
IR ($CHCl_3$): ν_{max}3844, 3760, 3576, 2927, 1727 (2 CO), 1680, 1540, 1440, 1283, 812 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 9.2 Hz, 1H), 6.77 (d, *J* = 9.2 Hz, 1H), 6.23 (s, 1H), 5.63 (s, 1H), 3.91 - 3.84 (m, 3H), 3.75 (s, 2H), 3.69 - 3.64 (m, 3H), 3.34 - 3.06 (m, 3H), 3.02 - 2.87 (m, 2H), 2.49 (dd, *J* = 7.3, 14.7 Hz, 1H)

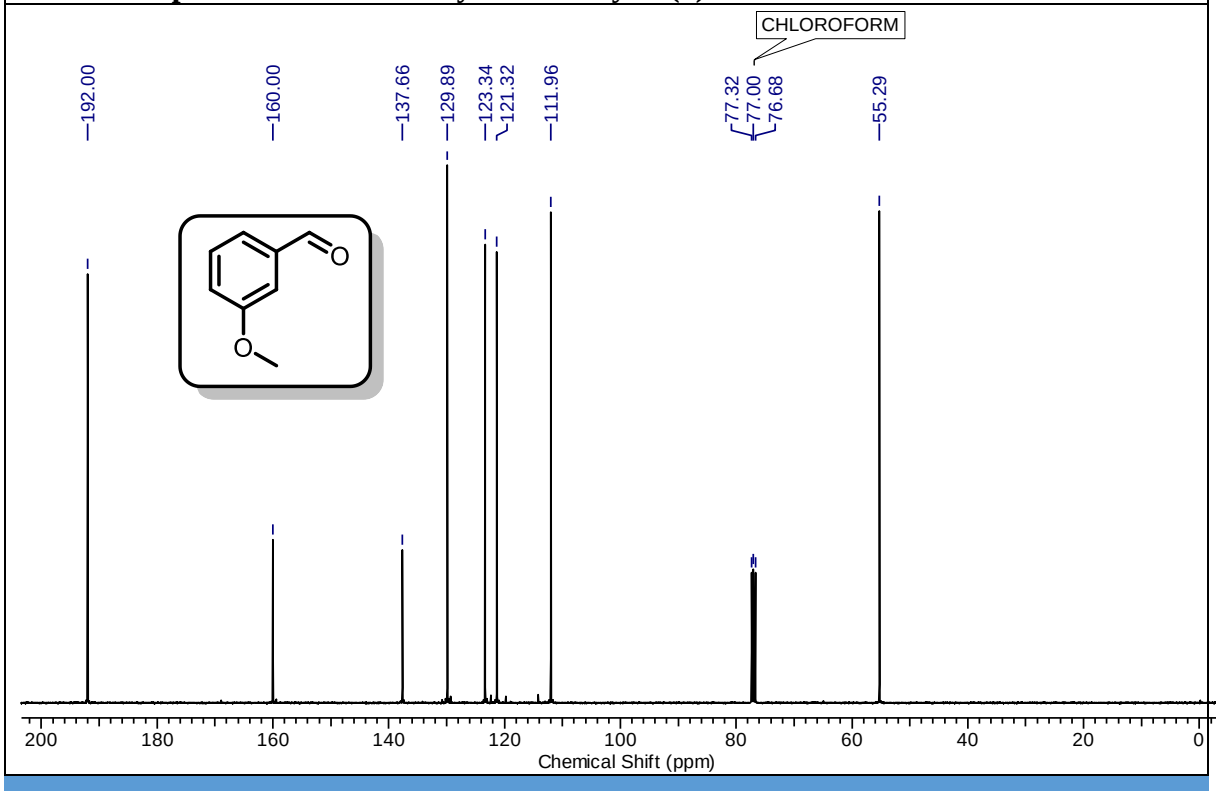
^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.7, 173.3, 167.1, 159.3, 141.3, 137.7, 137.3, 127.6, 123.1, 114.2, 112.0, 56.2, 51.9, 48.3, 43.6, 31.9, 31.7.

1.2.6. Spectral Data

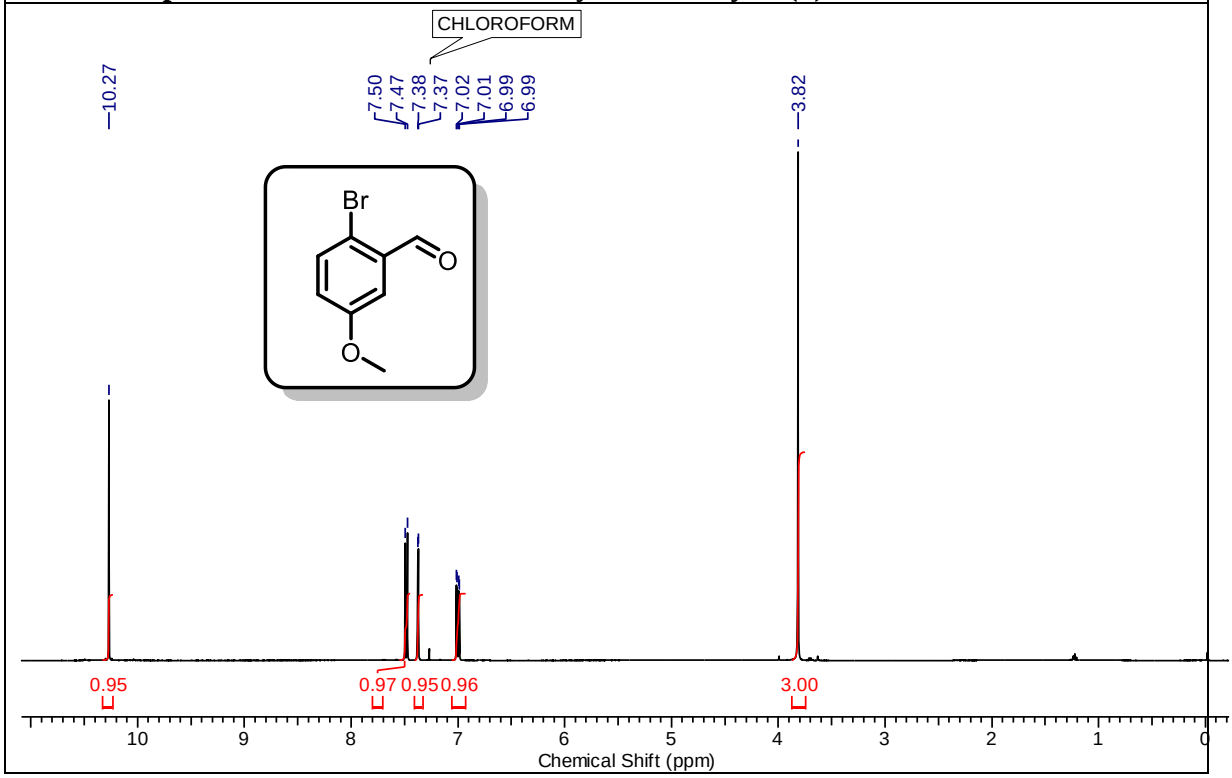
^{1}H-NMR spectrum of 3-methoxybenzaldehyde (7)



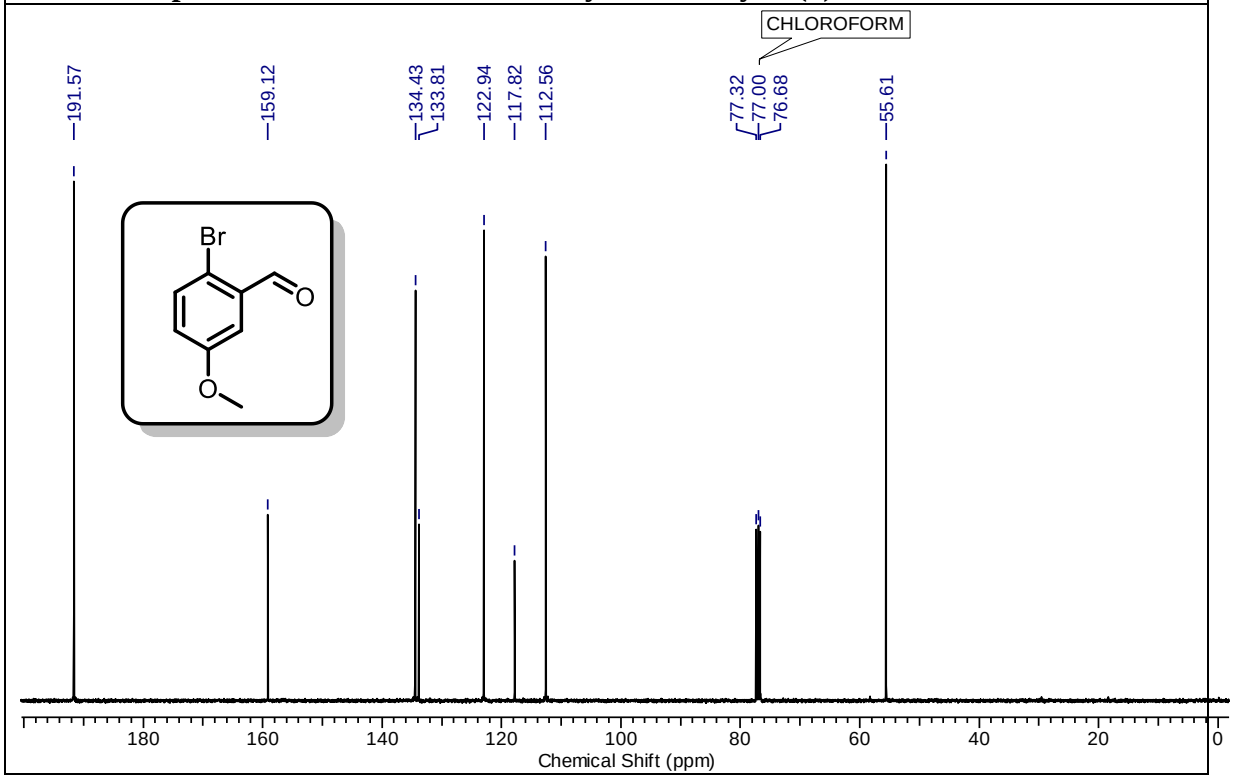
^{13}C-NMR spectrum of 3-methoxybenzaldehyde (7)



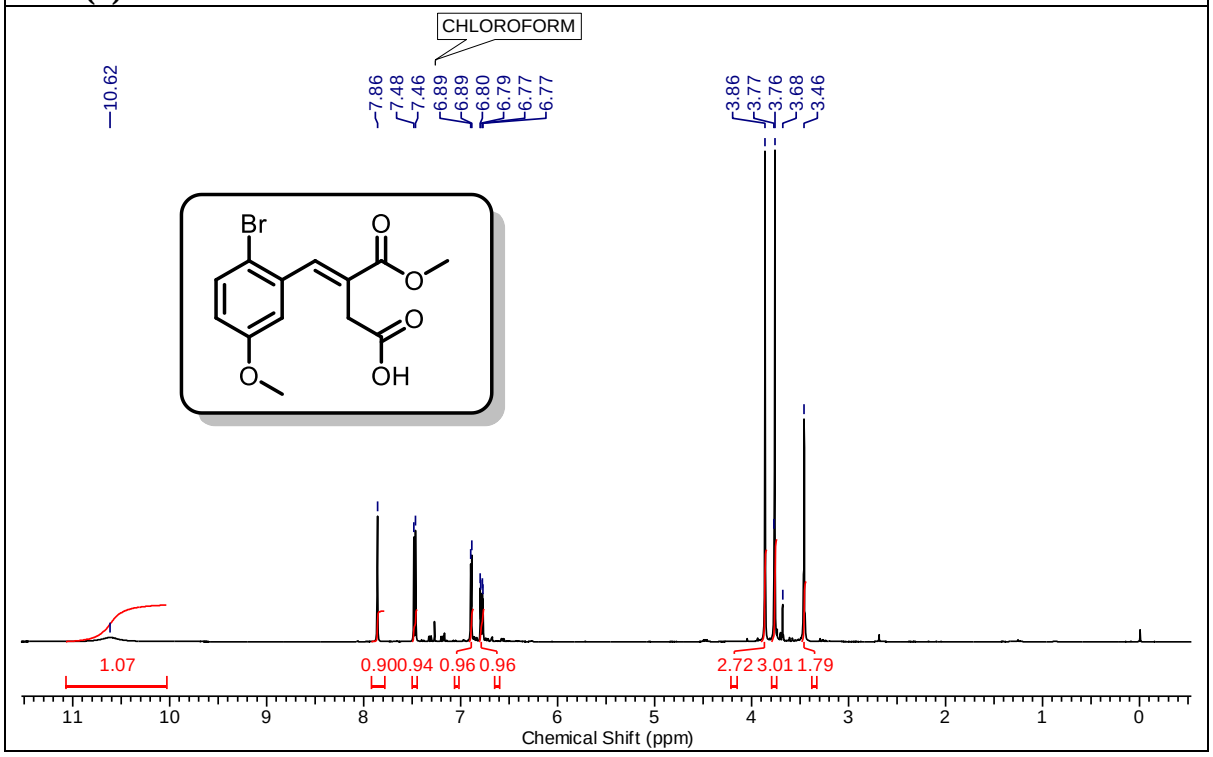
^{1}H-NMR spectrum of 2-bromo-5-methoxybenzaldehyde (8)



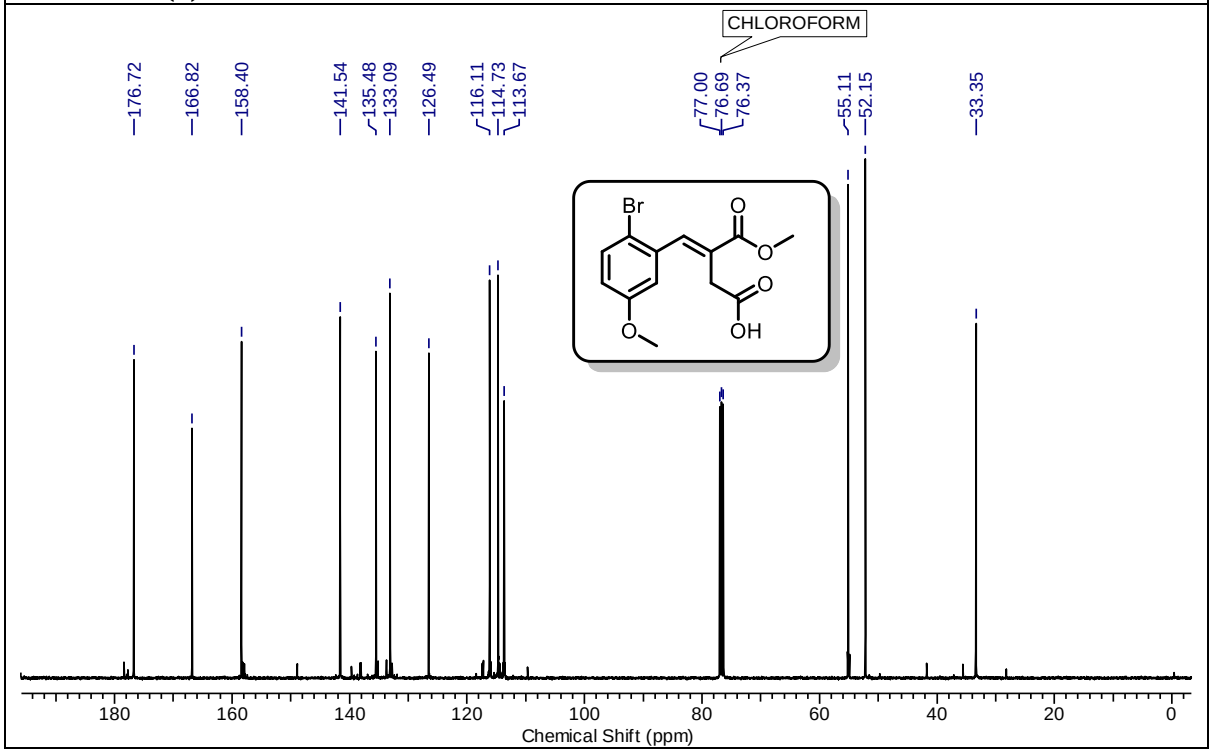
^{13}C-NMR spectrum of 2-bromo-5-methoxybenzaldehyde (8)



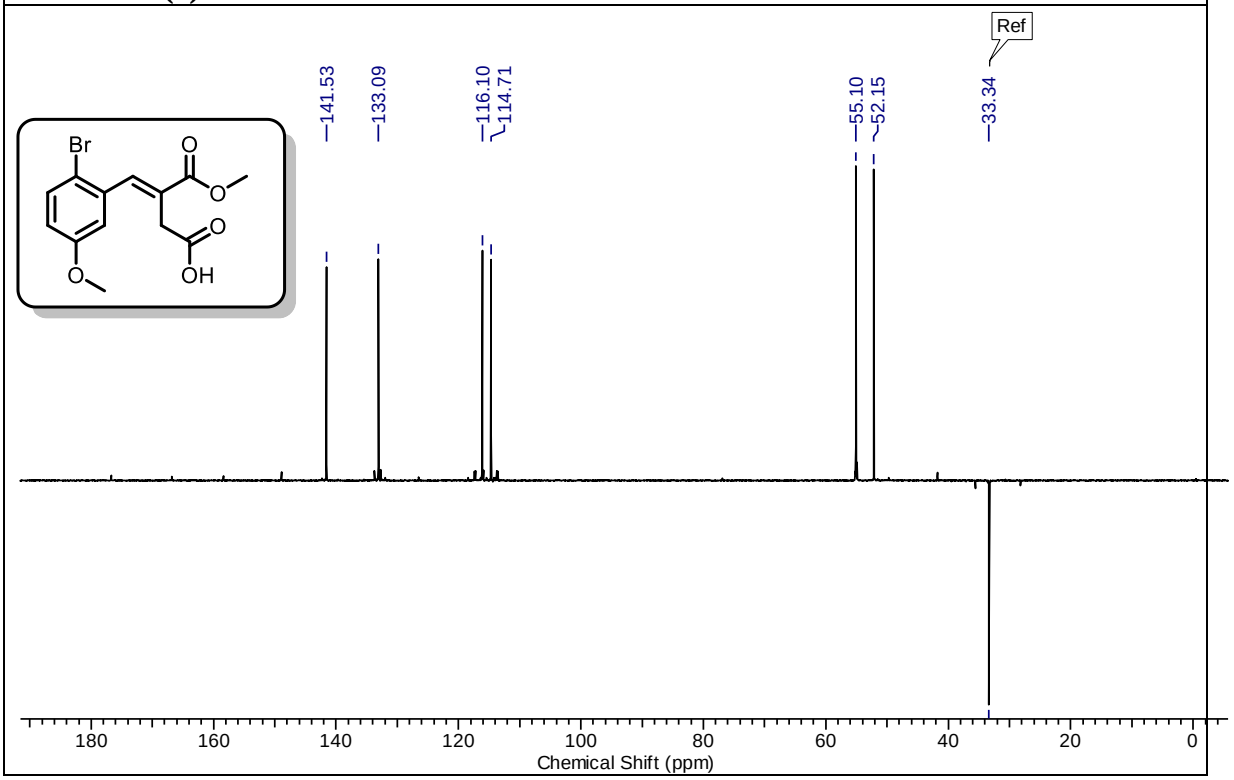
^{1}H-NMR spectrum of 4-(2-bromo-5-methoxyphenyl)-3-(methoxycarbonyl)but-3-enoic acid (5)



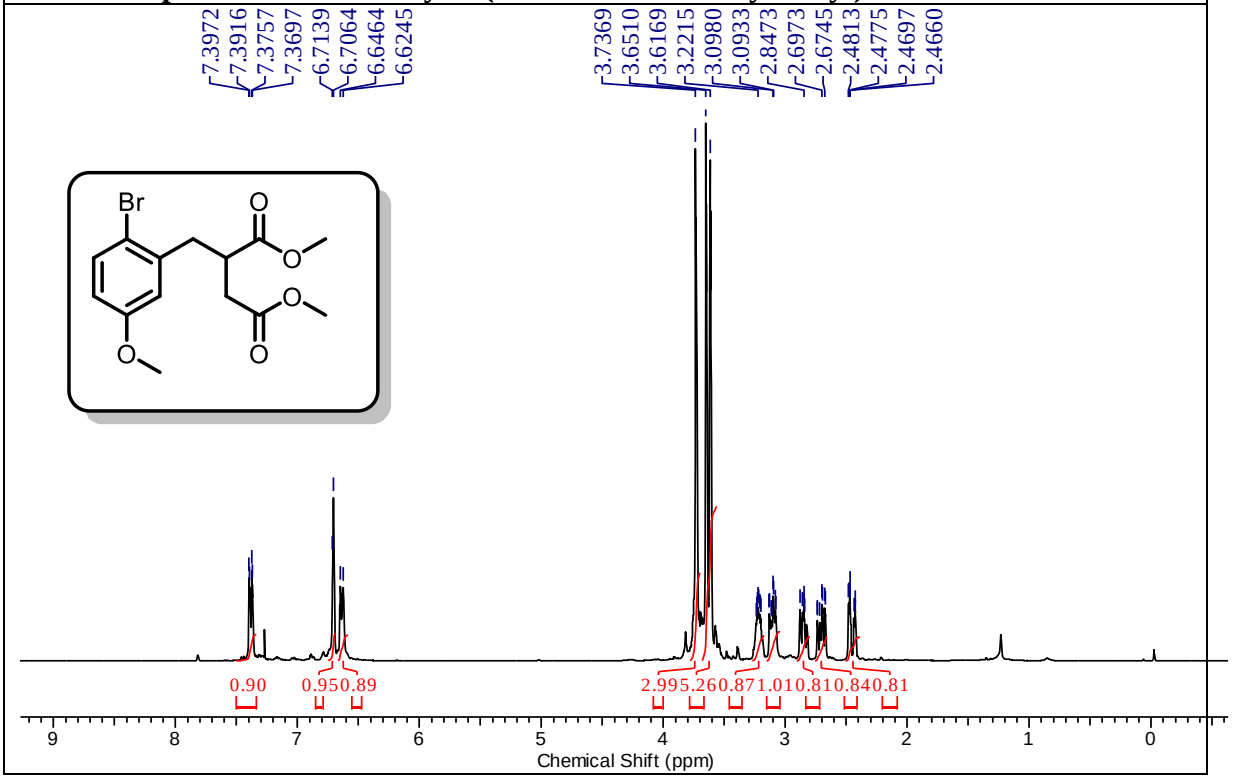
^{13}C-NMR spectrum of 4-(2-bromo-5-methoxyphenyl)-3-(methoxycarbonyl)but-3-enoic acid (5)



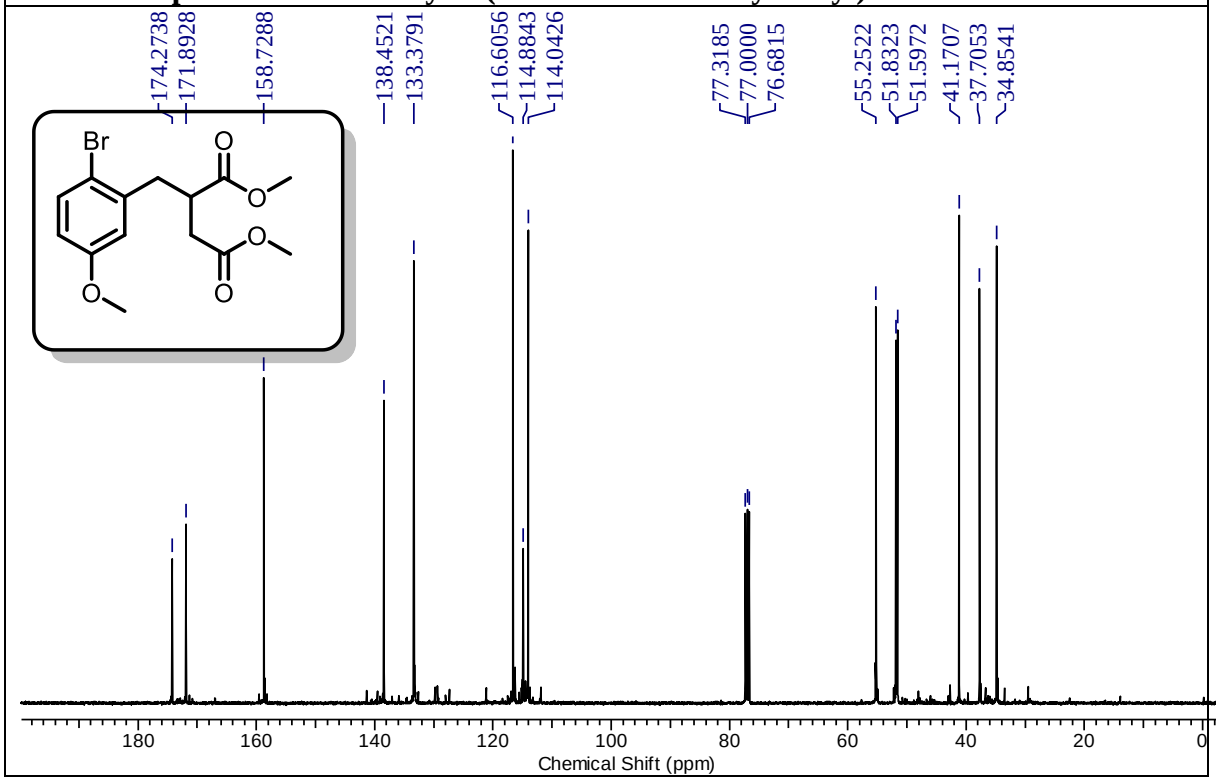
DEPT NMR spectrum of 4-(2-bromo-5-methoxyphenyl)-3-(methoxycarbonyl)but-3-enoic acid (5)



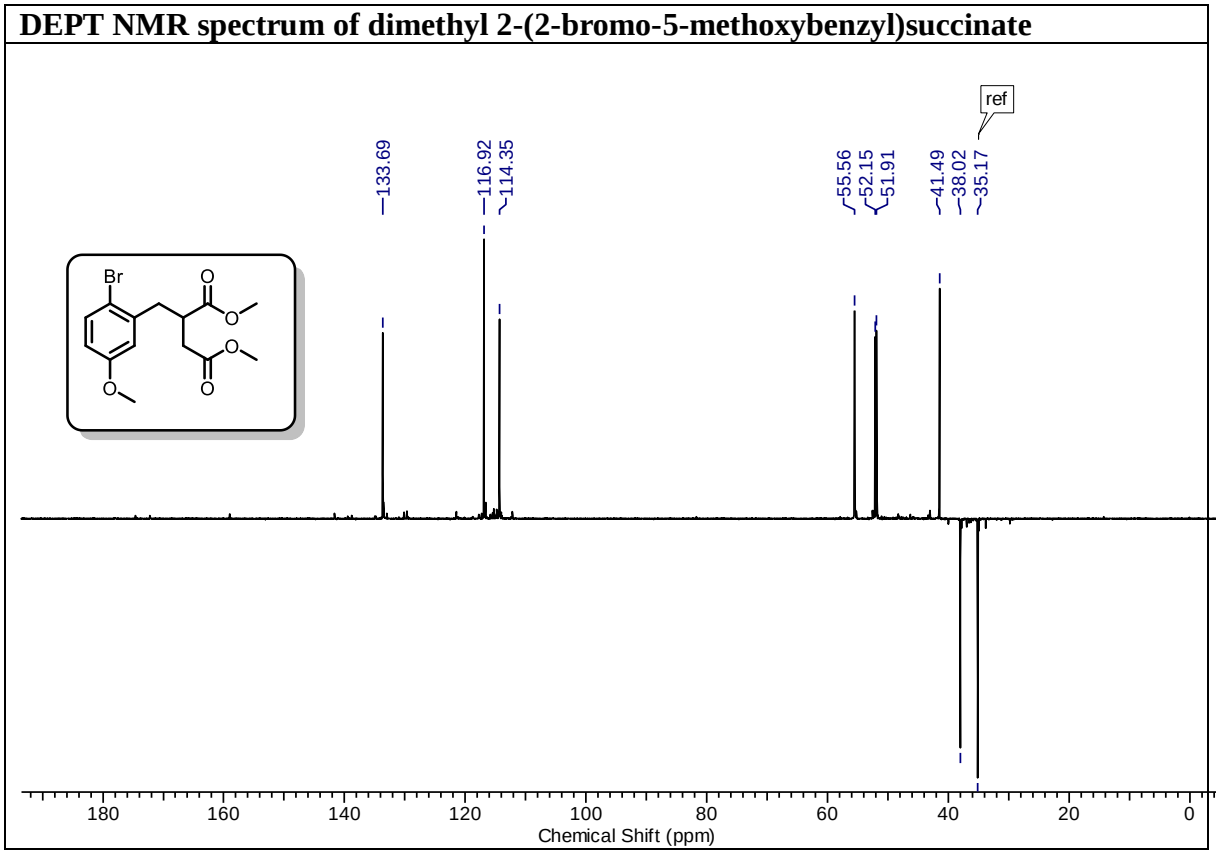
^{1}H-NMR spectrum of dimethyl 2-(2-bromo-5-methoxybenzyl)succinate



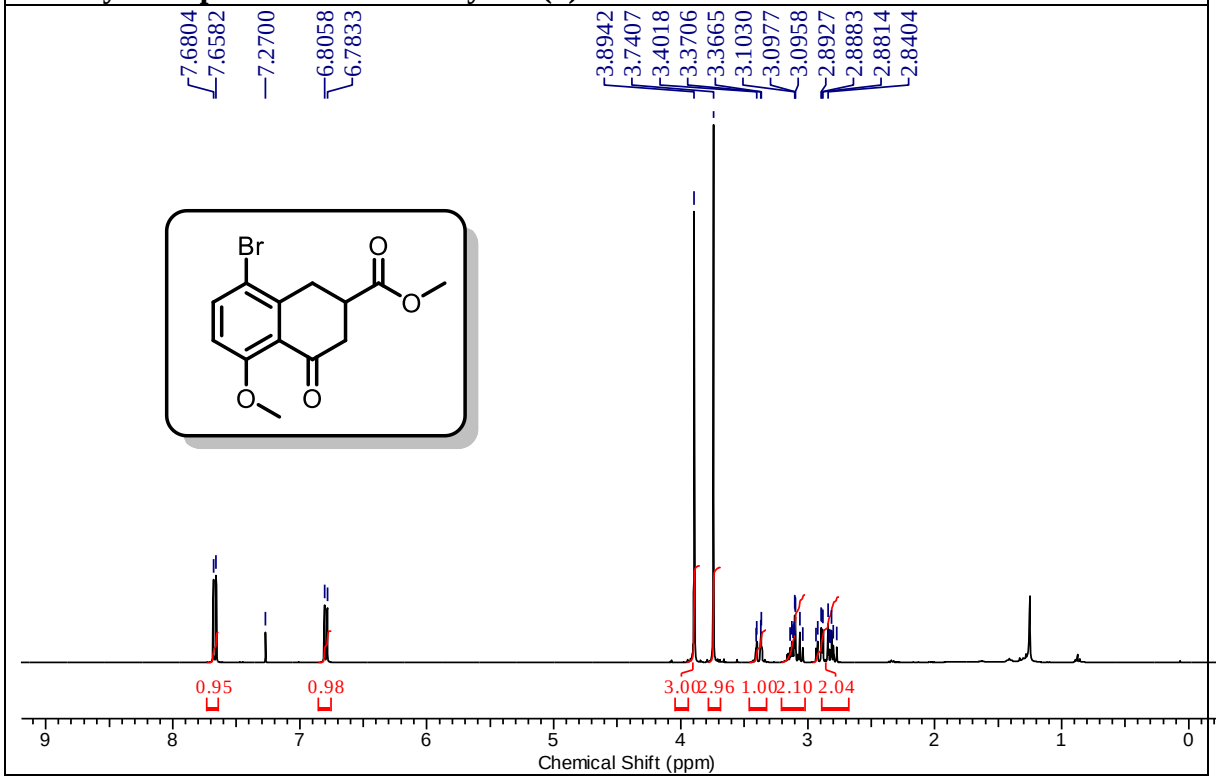
^{13}C-NMR spectrum of dimethyl 2-(2-bromo-5-methoxybenzyl)succinate



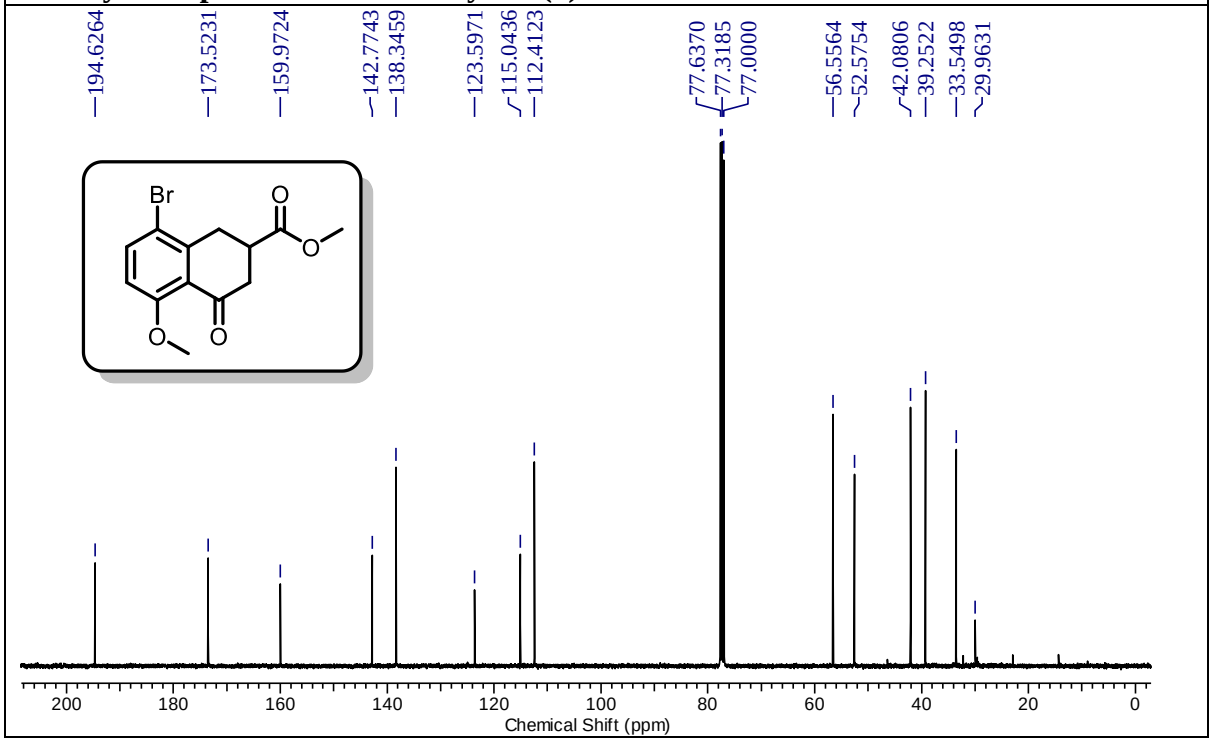
DEPT NMR spectrum of dimethyl 2-(2-bromo-5-methoxybenzyl)succinate



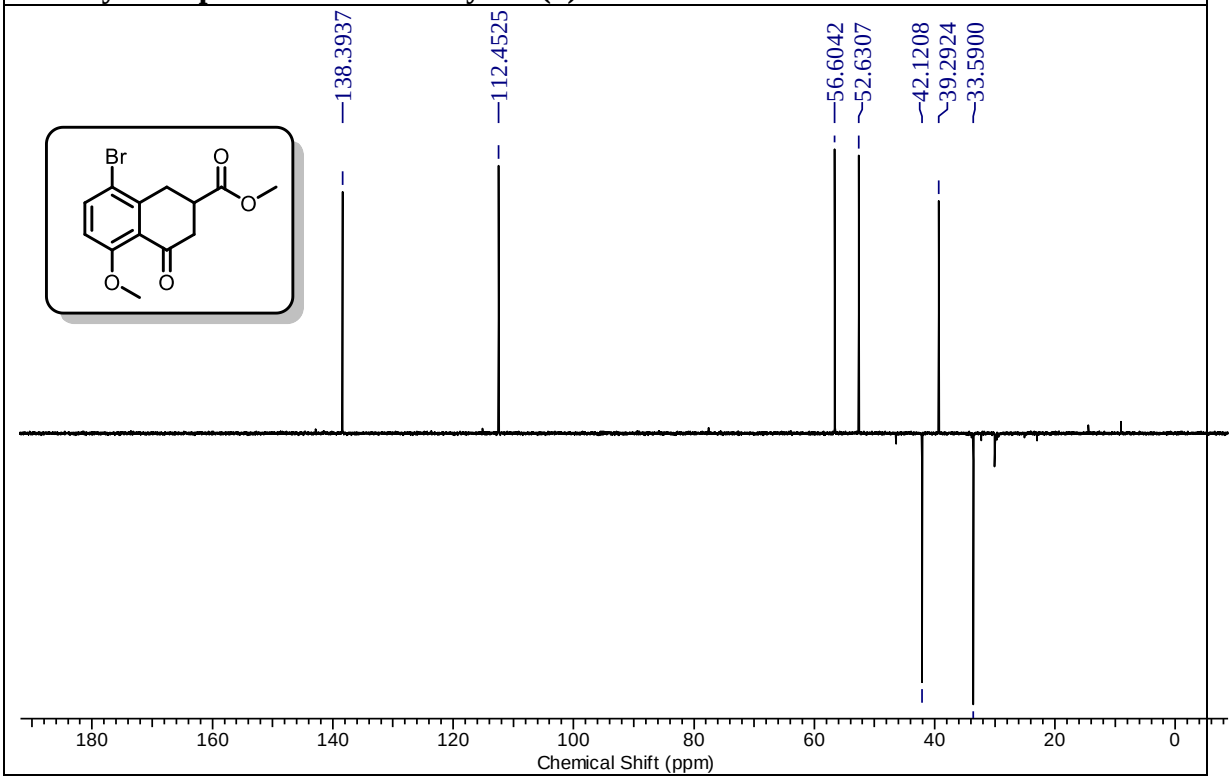
^{1}H-NMR spectrum of methyl 8-bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4)



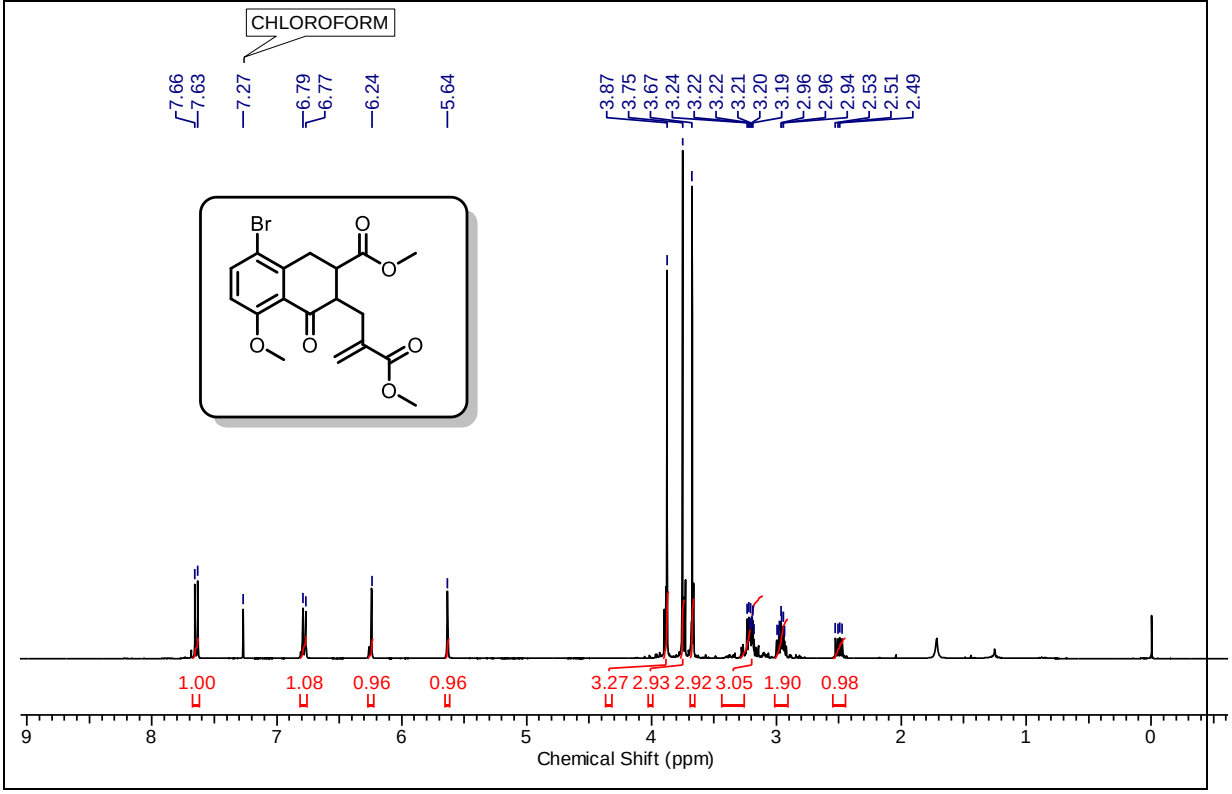
^{13}C-NMR spectrum of methyl 8-bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4)



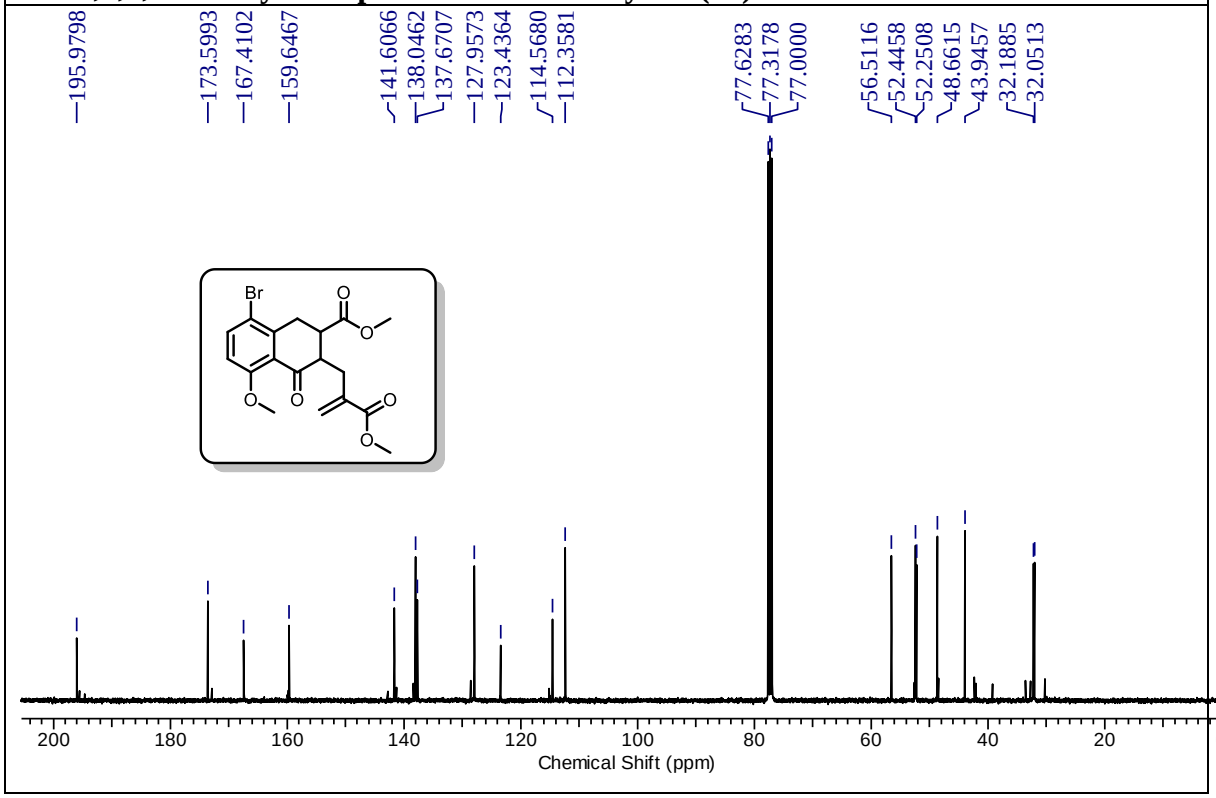
DEPT NMR spectrum of methyl 8-bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4)



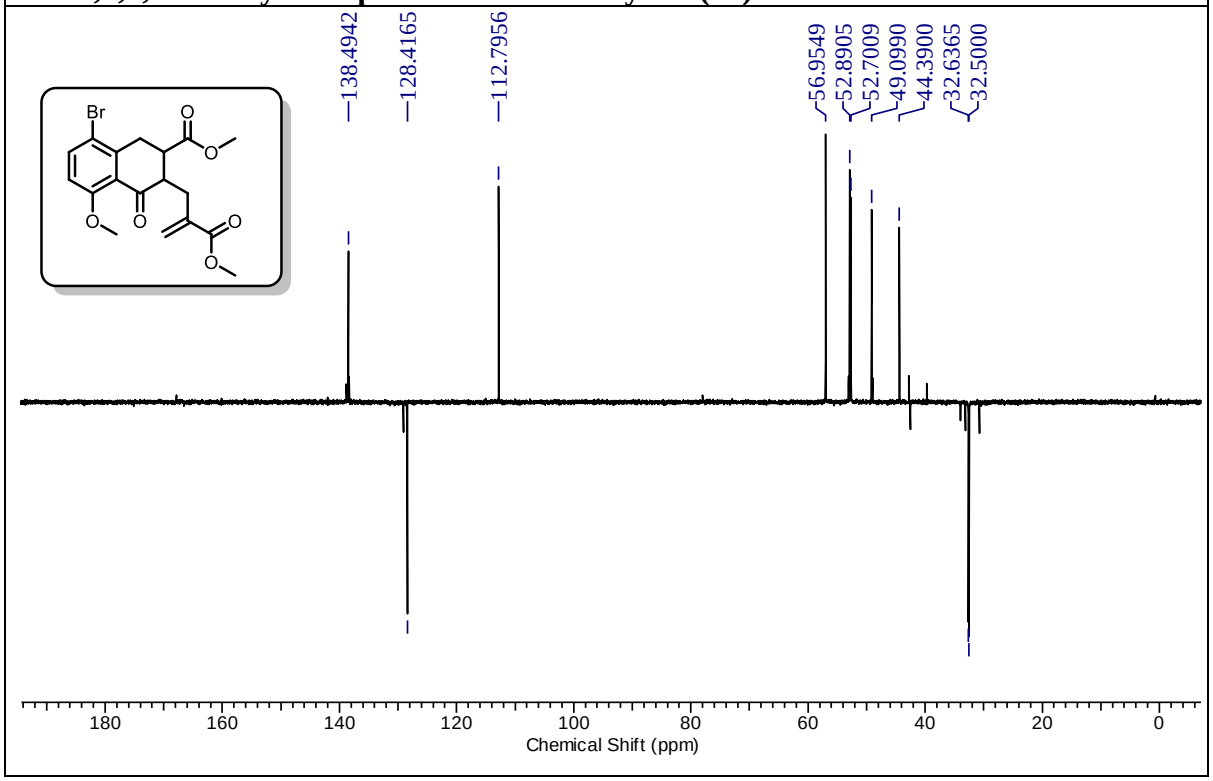
^{1}H-NMR spectrum of methyl 8-bromo-5-methoxy-3-(2-(methoxycarbonyl)allyl)-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (10)



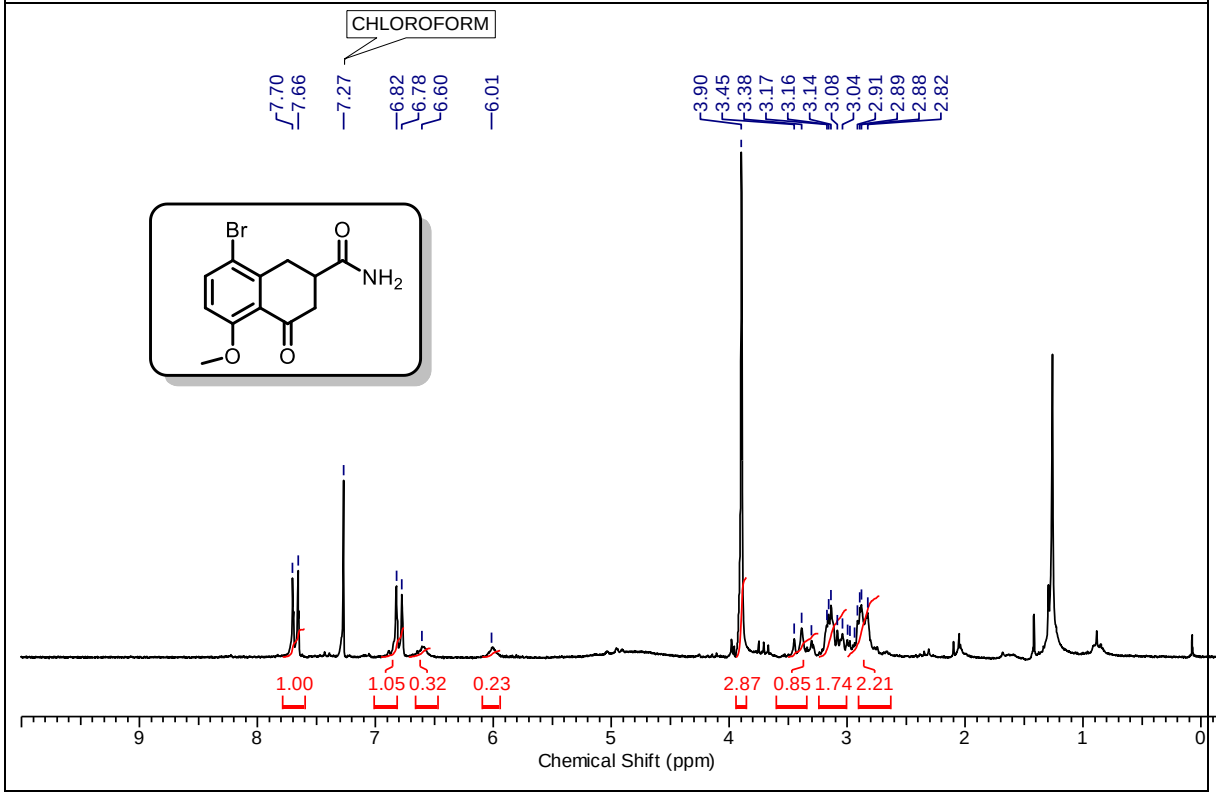
^{13}C-NMR spectrum of methyl 8-bromo-5-methoxy-3-(2-(methoxycarbonyl)allyl)-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (10)



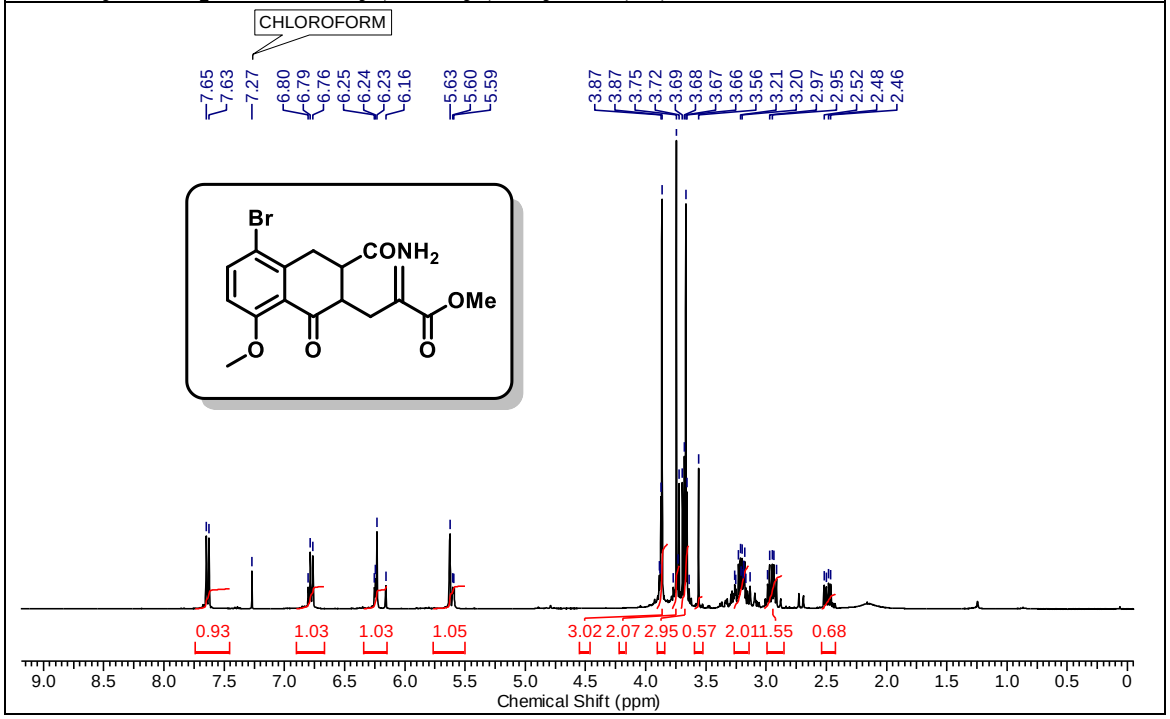
DEPT NMR spectrum of methyl 8-bromo-5-methoxy-3-(2-(methoxycarbonyl)allyl)-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (10)



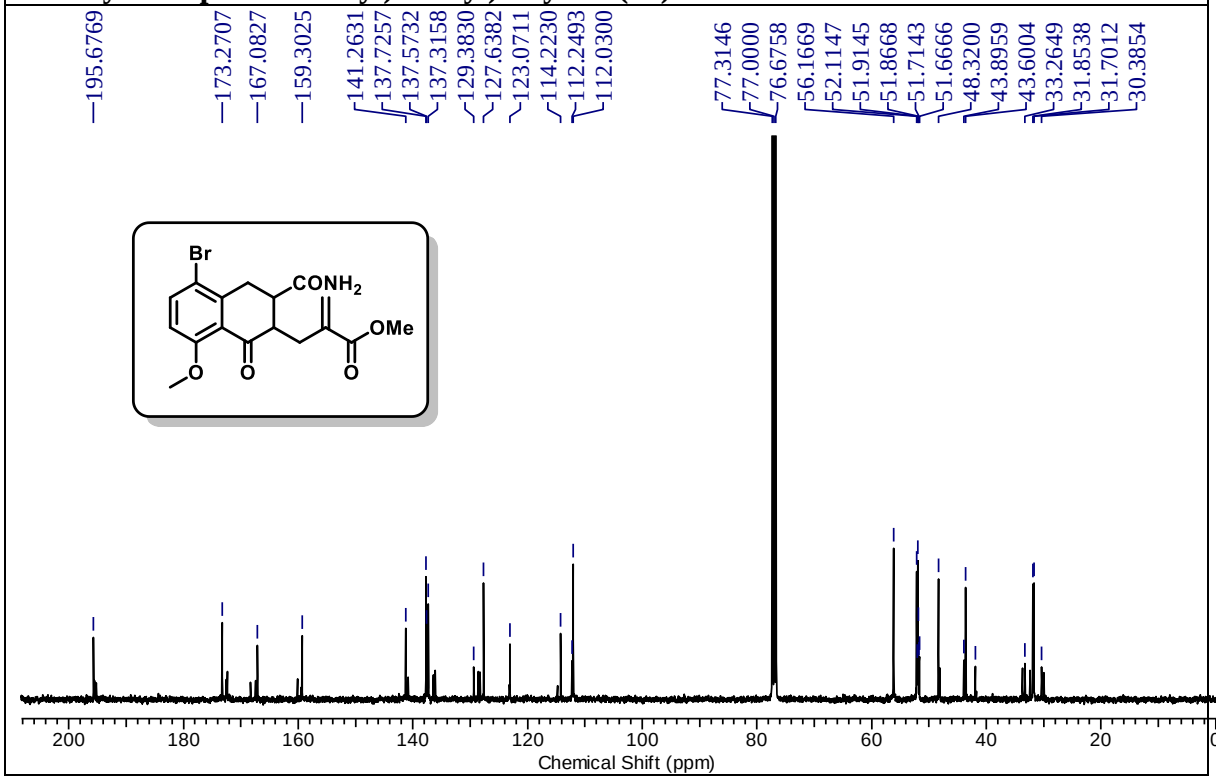
^{1}H-NMR spectrum of 8-bromo-5-methoxy-4-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxamide (11)



^{1}H-NMR spectrum of emthyl 2-((5-bromo-3-carbamoyl-8-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)acrylate (12)



^{13}C-NMR spectrum of ethyl 2-((5-bromo-3-carbamoyl-8-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)acrylate (12)



References:

1. Sarno, A. D.; Landi, M. L.; Marzullo, P; Somma, C. D.; Pivonello, R.; Cerbone, R.; Lombardi, G.; Colao, A. *Clinical Endocrinology*, **2000**, *53*, 53.
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3. Chavan, S. P.; Kadam, A. L.; Kawale, S. A. *ACS omega* **2019**, *4*, 8231.
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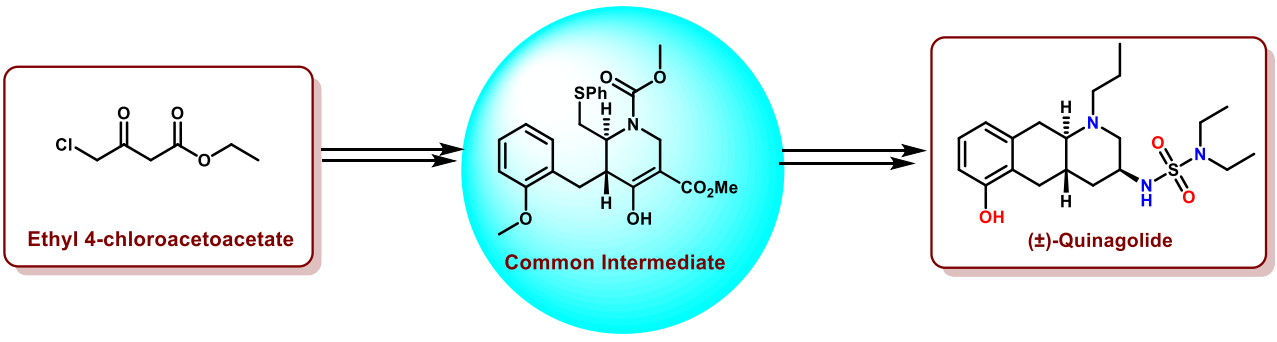
5. Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull*., **2006**, 54, 226.

Chapter 1: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide

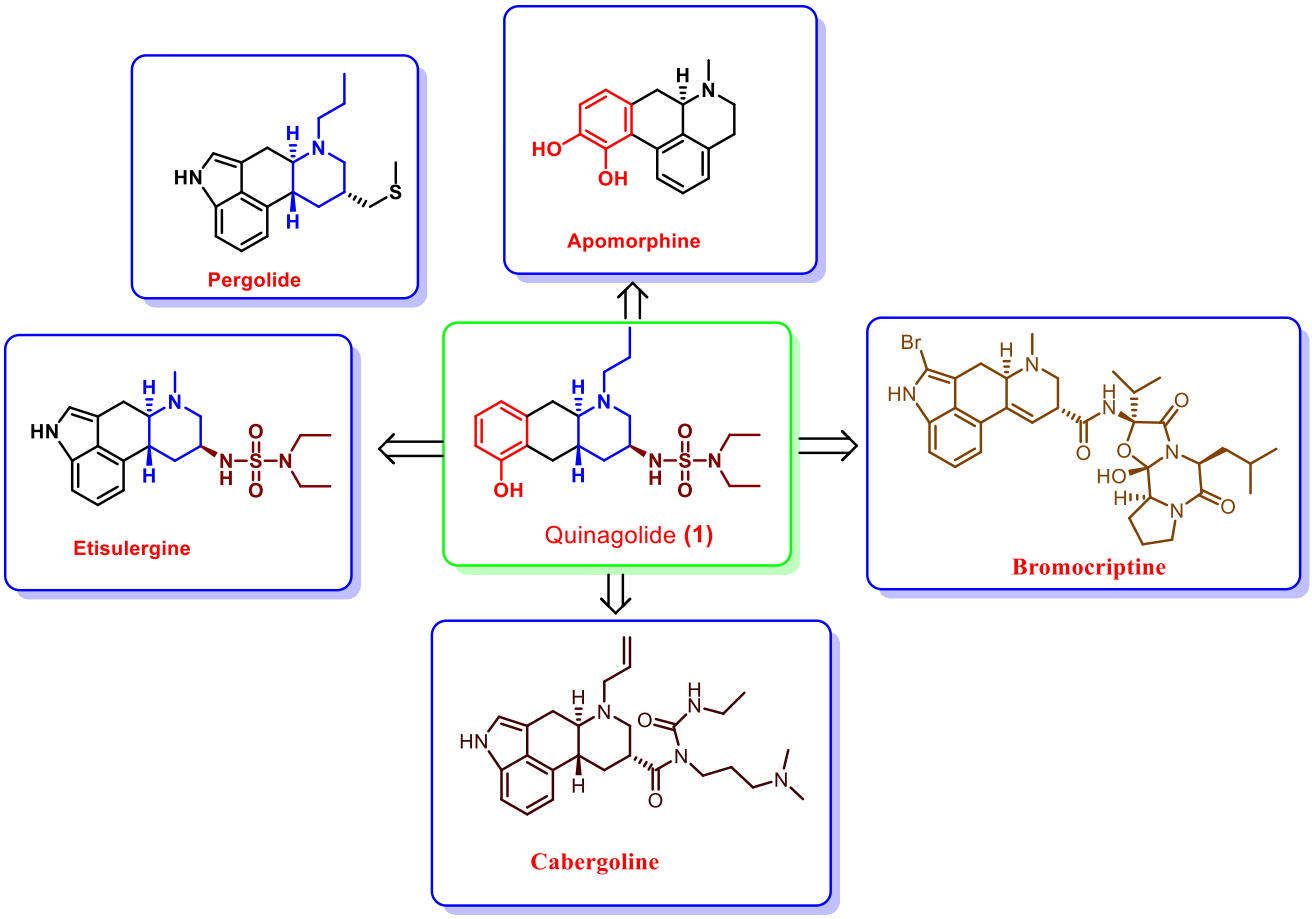
Chapter-1
Section-3

"Studies towards practical synthesis of the (±)-Quinagolide Using 4-chloro ethyl acetoacetate"



1.3.1. Abstract:

Quinagolide is developed by combining structural features of ergot and apomorphine alkaloids. Bänziger *et al.*[2] in year 2000, developed a scalable synthetic methodology for the synthesis of quinagolide intermediate, till date the synthetic chemists have paid a limited attention for its commercial route for the synthesis. The present scheme deals with the scalable and efficient synthetic route for quinagolide intermediate using 4-chloro ethyl acetoacetate as a cheap and commercially available starting material.

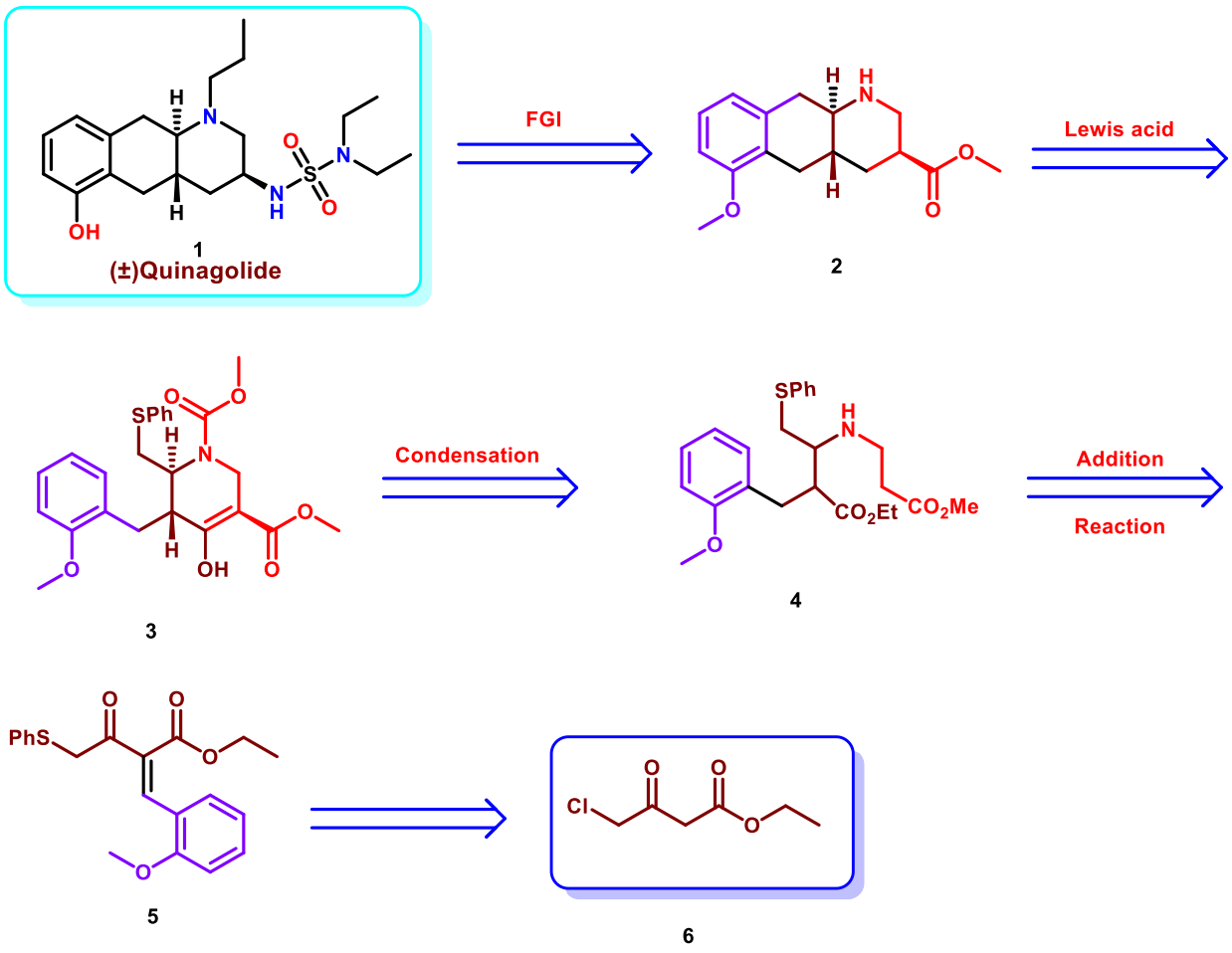


Figer.1 Quinagolide showing combined structural features of ergolines, apomorphine and marketed medicines.

1.3.2. Present Work:

Retrosynthetic analysis:

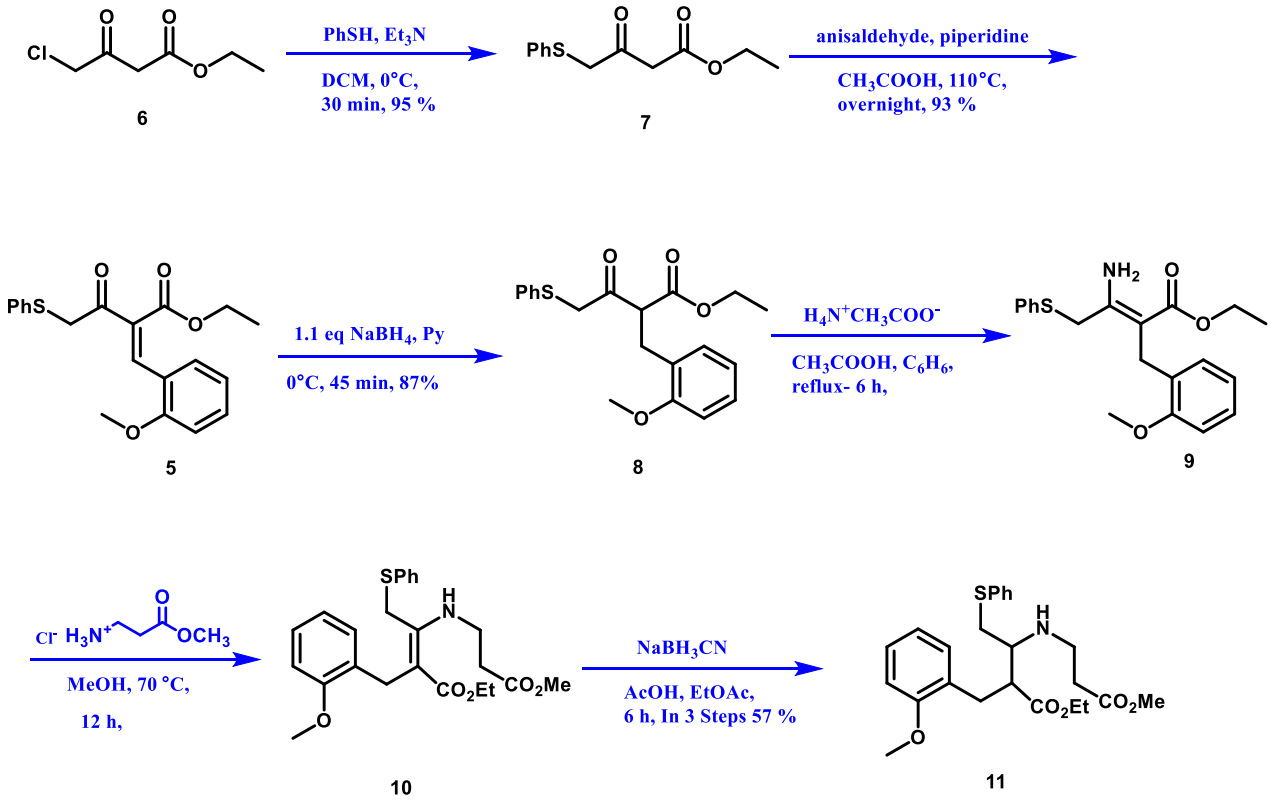
As shown in retrosynthetic plan (**Scheme 1**), tricyclic core of quinagolide **1** could be obtained from pyridine derivative **3** using Lewis acid catalized cyclization and functional group interconversion. Pyridine derivative **3** could be obtained from the diester **4** under basic reaction conditions. Diester **4** could be accessed from α,β-unsaturated dicarbonyl ester **5** by amination followed by Michael addition reaction of methyl acrylate. By using Knoevenagel condensation, 4-chloro ethyl acetoacetate **6** can be converted into α,β-unsaturated dicarbonyl ester **5.**



Scheme 1. Retrosynthetic plan for the synthesis of quinagolide.

1.3.3 Studies towards practical synthesis of the (±)-Quinagolide: results and discussion:

Synthesis of commercial quinagolide intermediate was first reported by Switzerland based companies Ferring pharmaceuticals / Novartis pharma AG in 2000 using tetralone as the starting material. It was thought that quinagolide **1** could be accessed from the 4-chloro ethyl acetoacetate by a different route **(Scheme 2)**. In this formal synthesis of quinagolide **1,** starting material 4-chloro ethyl acetoacetate **6** was stirred with thiophenol and Et_3N for 30 minutes at 0 ^{0}C to obtain ethyl 4-(thioaryloxy) acetoacetate **7** in 83% yield. In ^{1}H NMR spectrum of compound, peaks at δ 7.33 - 7.29 (m, 2H), and 7.28 - 7.21 (m, 2H), and (m, 2H) 7.19 (d, *J* = 7.3 Hz, 1H) corresponding to aromatic portion and also in the ^{13}C-NMR spectrum peaks at δ 133.5, 129.5, 128.6, and 126.5 corresponded to addition of aromatic ring. The HRMS (ESI) showed m/z calcd for $C_{12}H_{14}O_3NaS$ $[M + Na]^+$:261.0551; found: 261.0556 which confirmed the formation of compound **7**.



Scheme 2. Synthesis of diester moiety precursor of common intermediate **2**.

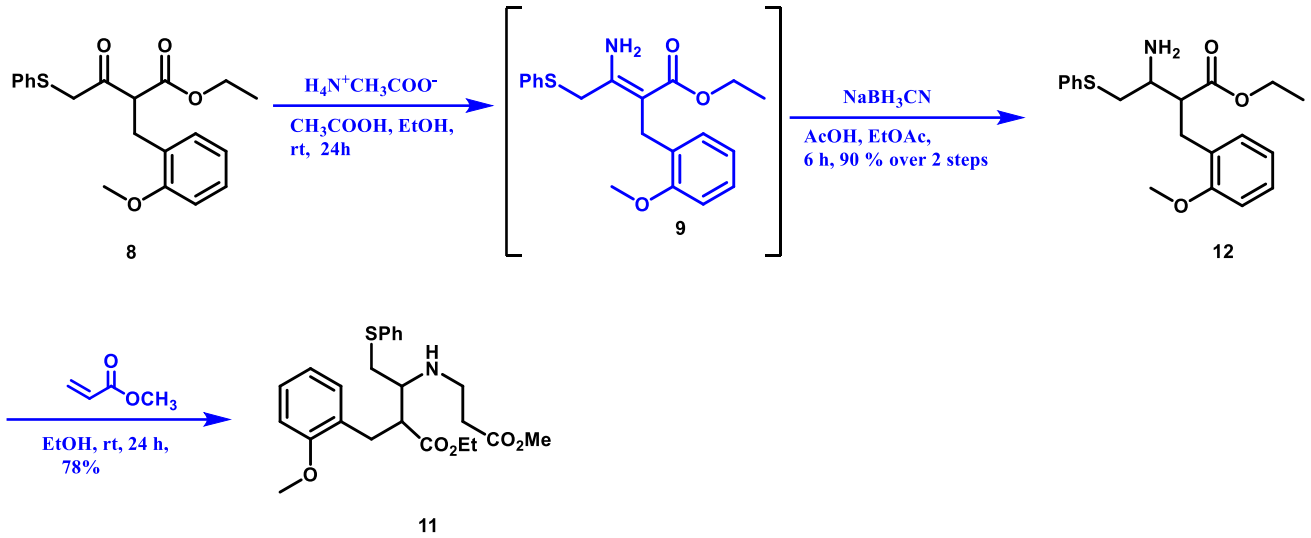
In the next step, compound **7** was treated with anisaldehyde under Knoevenagel condensation reaction condition by using piperidine and cat. amount of acetic acid in anhydrous toluene and the solution was refluxed overnight and the reaction flask was fitted with a Dean-Stark trap which gave 1:2 mixture of olefin isomers in 93% yield. The formation of the product was indicated by the peaks at δ 8.08 (s, 1H) and 8.01 (s, 1H) in ^{1}H NMR Spectrum corresponding to the E/Z mixture, of compound **5**. Due to E/Z mixture, ^{1}H NMR spectrum and ^{13}C-NMR spectrum were complex but they showed all the required peaks. The structure of **5** was further confirmed by HRMS; **(ESI)** m/z calcd for $C_{20}H_{21}O_4S$ $[M + H]^+$: 357.1153; found: 357.1155.

Then the chemoselective reduction of alkene **5** was carried out using $NaBH_4$ and pyridine at ambient temperature to afford compound **8** in 87% yield. The ^{1}H NMR spectrum showed the disappearance of olefinic protons peaks at δ 8.08 (s, 1H) and 8.01 (s, 1H) and presence of peaks at δ 3.79 (d, *J* = 15.38 Hz, 1 H) and 3.73 (d, *J* =15.38, 1H), corresponding to reduced alkene indicated the formation of product **8.** Finally, the formation of **8** was confirmed by its HRMS analysis; m/z calcd for $C_{20}H_{23}O_4S$ $[M + H]^+$: 359.1303; found: 359.1312.

In the next step, the compound **8** was regioselectively converted to β-amino-α,β-unsaturated ester **9** using $NH_4^+CH_3COO^-$ and cat. CH_3COOH under reflux condition in anhydrous benzene solution. The formation of product was indicated by TLC and after work up crude product was used in the next step without further purification.

The compound **9** was treated with alanine salt and amine was replaced by alanine salt by Hoffmann reaction in methanol under reflux for 12 hours and monitored by TLC and after work up the crude product was used in the next step without further purification.

After that, reduction of the double bond was carried out using $NaBH_3CN$ in ethyl acetate and cat. glacial acetic acid at 0^0C to afford compound **11** in 57 % yield over 3 steps . Addition of alanine salt and formation of diester moiety was confirmed by HRMS (ESI) m/z calcd for $C_{24}H_{32}NO_4S$ $[M + H]^+$: 446.1996; found: 446.1996 and in ^{1}H NMR spectrum proton peaks at δ 3.81 (s, 3H) and 3.68 (s, 3H) for two -OC<u>H</u>$_3$ were present in compound. ^{1}H NMR spectrum and ^{13}C-NMR spectrum suggested that compound **11** existed as a mixture of two rotamers.

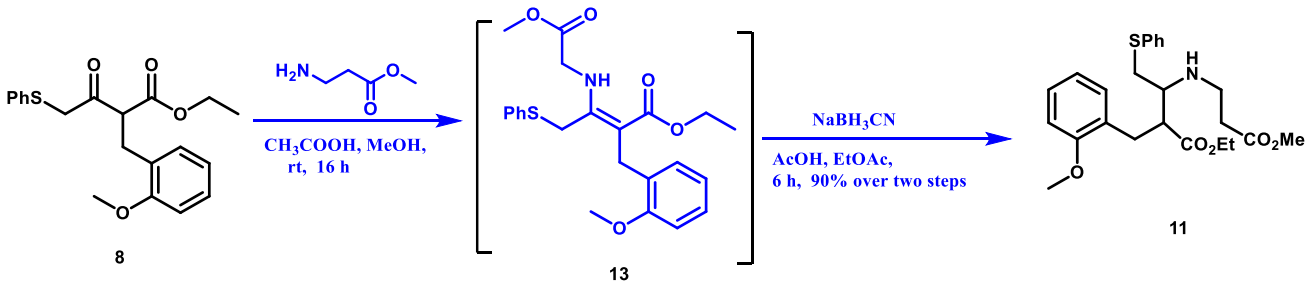


Scheme 3. Synthesis of diester moiety precursor with Michael addition approach.

The above synthetic strategy involving amination reaction with $NH_4^+CH_3COO^-$ and amine replaced by alanine salt using Hoffmann reaction followed by reduction with $NaBH_3CN$ gave only 57 % yield (**Scheme 2**). To improve the yield, the compound **8** was converted regioselectively to β-amino-α,β-unsaturated ester using $NH_4^+CH_3COO^-$ in presence of cat. CH_3COOH at room temperature in ethanol and product formation was monitored by TLC **(Scheme 3**). When the reaction was completed, the crude product **9** was used in the next step without further purification. The enamine reduction was carried out using $NaBH_3CN$ in ethyl acetate and cat. glacial acetic acid cooled to 0^0C to afford compound **12** in 90% yield. The conversion of dicarbonyl compound **8** into β-amino ester **12** was indicated by multiplets present in aliphatic region at δ 3.29 - 3.16 (m, 2 H), 3.09 - 2.92 (m, 2H) and 2.91 - 2.81 (m, 2H) in ^1H NMR. Disappearance of keto carbon peak at δ 199.9 and appearance of peak at δ 55.7 for NH_2-C- in the ^{13}C-NMR spectrum supported the structure which was further confirmed on the basis of its HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_3S$ $[M + H]^+$: 360.1627; found: 360.1628.

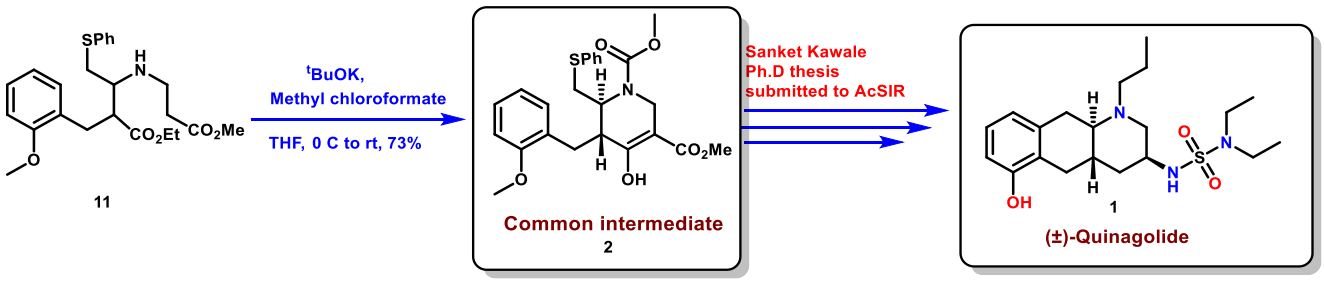
In the next step, β-amino ester **12** was subjected to Michael addition reaction with methyl acrylate at room temperature in ethanol, for 24 hours to obtain the addition product **11** that was characterized as before. The intermediate **11** was prepared in gram scale (5 g) using the strategy given in **Scheme 3**.

In an alternate approach, the dicarbonyl compound **8** was treated with alanine methyl ester in methanol wherein it underwent enamine formation. It was followed by reduction with $NaBH_3CN$ to afford compound **11(Scheme 4)**. Standardization of this synthetic strategy is under progress.



Scheme 4. Synthesis of diester with alanine.

After the successful formation of diester moiety with good yield, the next aim was the preparation of common intermediate **2**. Compound **11** was subjected to cyclisation under basic reaction condition with methyl chloroformate as N-methylcarbamate protecting group to afford the compound **2**. The β-ketoester **2** existed as a mixture of two rotamers in 6:4 ratio. In ^{1}H NMR spectrum, peak at δ 12 indicated enolic proton and presence of peaks at δ 170.9 and 93.8 in ^{13}C-NMR spectrum for alkene carbons suggested the formation of pyridine derivative **2**. It was further confirmed by HRMS analysis (ESI) m/z calcd for $C_{24}H_{28}O_6NS$ $[M + H]^+$:458.1632, found: 458.1629.

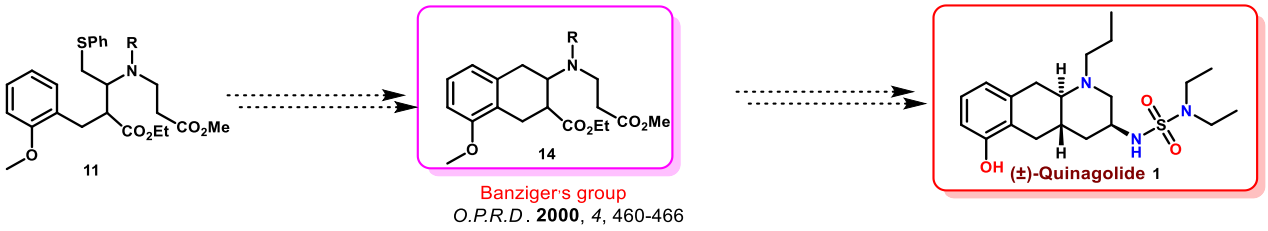


Scheme 5. Synthesis of common intermediate.

Pyridine derivative **2** could be converted to tricyclic core of quinagolide **1** using Lewis acid catalyzed cyclization and functional group interconversion as described in Ph.D thesis of Sanket Kawale submitted to AcSIR. Thus, the present work constitutes the formal synthesis of quinagolide.

1.3.4. Conclusion:

Using ethyl 4-chloroacetoacetate, formal synthesis of quinagolide was achieved in 34% overall yield. Intermediate **11** can be used in the synthesis of common intermediate reported by Bänziger *et al.*[2]

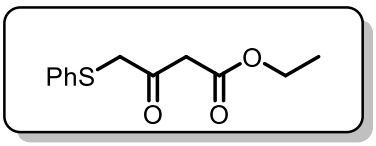


A scalable synthetic methodology for the synthesis of quinagolide intermediate has been developed. The steps involved are simple batch chemistry, commercially readily available inexpensive starting materials, common intermediate was prepared in gram scale.

1.3.5. Experimental Section

Experimental Procedures and Characterization Data

Ethyl 3-oxo-4-(phenylthio)butanoate (7)



A solution of ethyl 4-chloroacetoacetate (26.2 g, 1 eq., 159 mmol), Et_3N (23.3 mL, 1.05 eq., 167 mmol) and PhSH (16.7 mL, 1.025 eq., 163 mmol) in CH_2Cl_2 (320 mL) was stirred at 0 °C for 30 min. The reaction mixture was diluted with EtOAc, washed with 1N NaOH, 1N HCl and the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure to obtain crude product **7** which was purified by using flash silica gel column chromatography eluting with 10 % ethyl acetate in pet. ether as the eluent to furnish pure compound **7** (30.5 g, 80%) as a colourless liquid.

Rf : 0.5 (Ethyl acetate – pet. ether=05:95);

Yield: 80%;

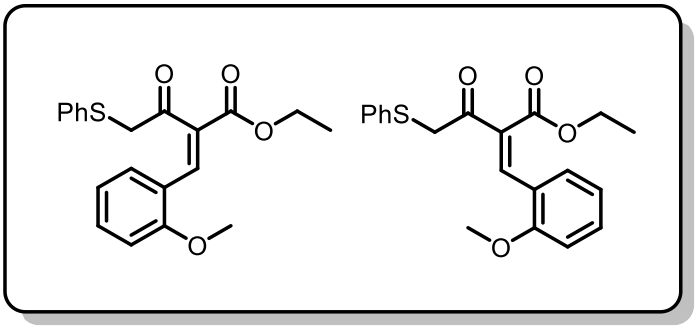
IR ($CHCl_3$): ν_{max} 2937, 1743, 1716, 1439 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 - 7.29 (m, 2H), 7.28 - 7.21 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 4.15 - 4.08 (m, 2H), 3.77 (s, 2H), 3.59 (s, 2H), 1.23 - 1.17 (m, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 166.4, 133.5, 129.5 (2C), 128.6 (2C), 126.5, 60.8, 45.9, 43.3, 13.4;

HRMS (ESI): m/z calcd for $C_{12}H_{14}O_3NaS$ $[M + Na]^+$: 261.0551; found: 261.0556.

Ethyl-2-(2-methoxybenzylidene)-3-oxo-4-(phenylthio)butanoate (5)



To a solution of ethyl 3-oxo-4(phenylthio) butanoate **7** (10 g, 1 eq., 42.01 mmol) in toluene (100 mL) were added anisaldehyde (0.57 mL, 1.5 eq., 63.02 mmol), piperidine (0.415 mL, 0.1 eq., 4.20 mmol) and acetic acid (1.26 mL, 0.5 eq., 21 mmol), successively. The reaction flask was fitted with a Dean-Stark trap and the solution was refluxed overnight. After allowing to cool to room temperature, the reaction mixture was diluted with ethyl acetate and washed once with 1 M

HCl, once with saturated sodium bicarbonate solution and once with brine. The organic phase was dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure. Purification of the crude material *via* column chromatography through silica gel using 95: 5 pet. ether /ethyl acetate as eluent afforded desired product **5** (14.0 g, 93%) as yellow oil, which contained 1:2 mixture of olefin isomers (The geometry of each isomer is not determined).

Rf : 0. 6 (Ethyl acetate – pet. ether=10:90);

Yield: 93%;

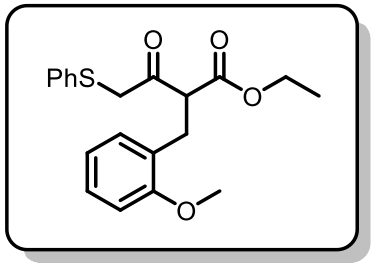
IR ($CHCl_3$): ν_{max} 2979, 1710 (b), 1665, 1607, 1475, 1374 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 8.01 (s, 1H), 7.43 - 7.37 (m, 2H), 7.36 - 7.23 (m, 7H), 7.23 - 7.09 (m, 6H), 6.86 (t, *J* = 8.2 Hz, 3H), 6.78 (s, 2H), 4.27 - 4.18 (m, 4H), 4.08 (s, 2H), 3.92 (s, 2H), 3.82 - 3.77 (m, 6H), 1.30 - 1.11 (m, 6H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 190.6, 167.2, 164.1, 157.6, 157.3, 139.5, 138.8, 134.7, 134.0, 131.8, 131.7, 131.4, 131.2, 130.0, 129.9, 129.2, 129.0, 128.5, 128.4, 126.6, 126.0, 122.0, 121.5, 120.2, 119.9, 110.4, 110.3, 61.0, 60.9, 55.0, 54.9, 44.4, 41.2, 13.6, 13.3;

HRMS (ESI): m/z calcd for $C_{20}H_{21}O_4S$ $[M + H]^+$: 357.1153; found: 357.1155.

Ethyl 2-(2-methoxybenzyl)-3-oxo-4-(phenylthio)butanoate (8)



To a well stirred solution of $NaBH_4$ (0.701 g, 18.53 mmol, 1.1 eq) in pyridine (30 mL) was added compound **5** (6.0 g, 16.853 mmol) dissolved in pyridine (25 mL) at room temperature. The solution was quickly warmed to 50 ^{0}C, at which point it was dipped in water bath. The reaction was allowed to stir at room temperature for a period of 45 min. After complete consumption of starting material as checked by TLC, the reaction mixture was poured into ice cold 2N HCl solution (600 mL) and stirred for 1 h. The solution was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure. Purification of the crude material *via* column chromatography through silica gel afforded the desired product **8** (5.4 g, 91%).

Rf : 0.6 (Ethyl acetate – pet. ether=10:90);

Yield: 91%;

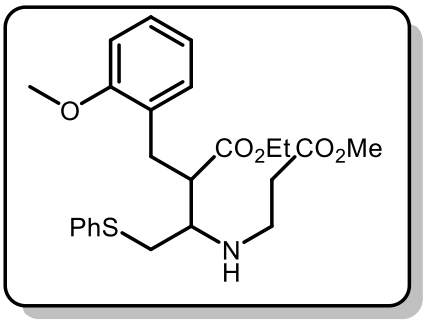
IR ($CHCl_3$): ν_{max} 2925, 1727 (b), 1593, 1467 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 - 7.21 (m, 6H), 7.17 (dd, *J* = 1.7, 7.7 Hz, 1H), 6.92 - 6.84 (m, 2H), 4.43 (t, *J* = 7.4 Hz, 1H), 4.22 - 4.09 (m, 2H), 3.87 (s, 3H), 3.79 (d, *J* = 15.38 Hz, 1 H), 3.73 (d, *J* =15.38, 1H), 3.22 (d, *J* = 2.9 Hz, 1H), 3.20 (d, *J* = 3.3 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.9, 169.3, 157.7, 134.8, 131.5, 130.0 (2C), 129.2 (2C), 128.4, 127.1, 126.2, 120.7, 110.4, 61.6, 55.7, 55.4, 44.4, 30.0, 14.2;

HRMS (ESI): m/z calcd for $C_{20}H_{23}O_4S$ $[M + H]^+$: 359.1303; found: 359.1312.

Ethyl 3-((3-methoxy-3-oxopropyl)amino)-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (11)



a) Ammonium acetate (1.07 g, 5 eq., 13.966 mmol) and 4 drops of CH_3COOH were added to the solution of dicarbonyl compound **8** (1 g, 1 eq., 2.793 mmol) in 15 mL dry benzene. The reaction flask was fitted with a Dean – Stark trap and the solution was refluxed for 8 hours. After allowing to cool to room temperature and work up using ethyl acetate (3× 50 mL) for extraction and water (3×10 mL) for washing the organic layer, the solvent was evaporated under reduced pressure to obtain a pale yellow liquid compound **9** which was used in the next step without further purification.

b) β-Alanine methyl ester hydrochloride (5 eq.) was added to the crude β-amino-α,β-unsaturated ester **9** (1 eq.) in methanol and the reaction mixture was refluxed for 12 h. After evaporating methanol under reduced pressure and work up using ethyl acetate (3×50 mL) for extraction and water (3×5 mL) for washing the EtOAc layer, crude compound **10** obtained was used in the next step without further purification.

c) Crude sample **10** was dissolved in EtOAc, the mixture was cooled to 0^0C and $NaBH_3CN$ (3 eq.) and glacial acetic acid (cat. amount) were added. After 6 hours, the reaction mixture was extracted with 10% Na_2CO_3 (3×15 mL) and the organic phase was dried with Na_2SO_3 and evaporated. Purification of the crude material *via* column chromatography through silica gel afforded desired product **11** (0.690 g, 57% yield) as pale yellow liquid.

Rf : 0.4 (Ethyl acetate – pet. ether=20:80);

Yield: 57%;

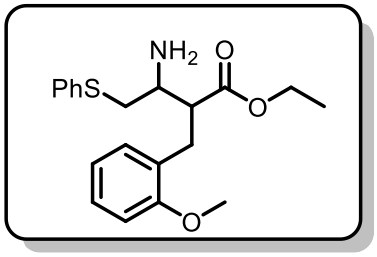
IR ($CHCl_3$): ν_{max} 3729, 3295, 2932, 1702 (b), 1448, 1313 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 - 7.33 (m, 1H), 7.33 - 7.28 (m, 1H), 7.28 - 7.21 (m, 2H), 7.21 - 7.14 (m, 2H), 7.12 - 7.03 (m, 1H), 6.88 - 6.77 (m, 2H), 4.07 - 3.94 (m, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.27 - 3.11 (m, 2H), 3.11 - 2.94 (m, 3H), 2.94 - 2.75 (m, 3H), 2.43 (t, *J* = 6.6 Hz, 2H), 1.88 (br s, 1H), 1.13 - 1.06 (m, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 172.9, 157.4, 136.2, 136.0, 130.8, 130.6, 130.0, 129.7, 128.9, 128.8, 127.6, 127.5, 126.2, 126.1, 120.2, 110.0, 60.2, 58.2, 55.1, 48.0, 47.9, 42.7, 41.8, 36.6, 35.0, 34.9, 29.6, 29.2, 14.0;

HRMS (ESI): m/z calcd for $C_{24}H_{32}NO_4S$ $[M + H]^+$: 446.1996; found: 446.1996.

Ethyl 3-amino-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (12)



a) Ammonium acetate (21.500 g, 10 eq., 279 mmol) and 20 drops of CH_3COOH were added to the solution of dicarbonyl compound **8** (10 g, 1 eq., 27.932 mmol) in methanol at room temperature, and the reaction mixture was stirred for 24 h. Then the solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3× 500 mL) and the organic layer was washed with water (3×100 mL) and dried over Na_2SO_4. Concentration under reduced pressure afforded black coloured crude product **9** which was used in the next step without further purification.

b) Compound **9** was dissolved in EtOAc, the solution was cooled to 0^0C and $NaBH_3CN$ (3 eq.) and glacial acetic acid (2 mL) were added. After 6 hours the reaction mixture was extracted with 10% Na_2CO_3 (3×100 mL) and the organic phase was dried with Na_2SO_3 and evaporated. Purification of the crude material *via* column chromatography through silica gel afforded desired product **12** in 87% yield (8.8 g) as a pale yellow liquid.

Rf : 0.3 (Ethyl acetate – pet. ether=75:25);

Yield: 87%;

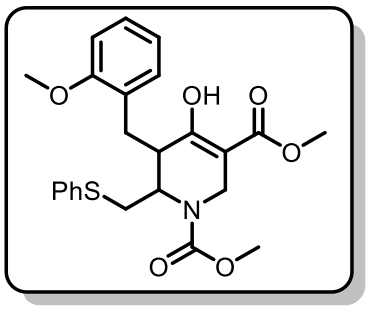
IR ($CHCl_3$): ν_{max} 3653, 2849, 2353, 1710, 1448 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 - 7.33 (m, 1H), 7.33 - 7.24 (m, 3H), 7.23 - 7.16 (m, 2H), 7.05 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.88 - 6.78 (m, 2H), 4.03 (td, *J* = 7.1, 14.1 Hz, 2H), 3.82 (s, 3H), 3.29 - 3.16 (m, 2 H), 3.09 - 2.92 (m, 2H), 2.91 - 2.81 (m, 2H), 2.15 (br s, 3H), 1.10 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 157.4, 135.7, 130.6, 129.9, 129.6 (2C), 128.9, 127.8, 127.1, 126.3, 120.3, 110.1, 60.3, 55.2, 51.8, 50.8, 39.7, 29.2, 14.0;

HRMS (ESI): m/z calcd for $C_{20}H_{26}NO_3S$ $[M + H]^+$: 360.1627; found: 360.1628.

Dimethyl 4-hydroxy-5-(2-methoxybenzyl)-6-((phenylthio)methyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2)



A solution of 0.300 g (1.0 eq., 0.674 mmol) diester **11** in 8 mL of THF was cooled to -10 °C (NaCl/ice bath) and was treated with 0.303 g (4.0 eq., 2.69 mmol) of freshly sublimed ^{t}BuOK. The reaction mixture was stirred at -10 °C for an additional 10 min, a solution of methyl chloroformate (0.127 mL, 1.34 mmol, 2 eq) in anhydrous THF was slowly added to reaction mixture and stirred at RT. After complete consumption of starting material as checked by TLC (~ 6 h), saturated $NaHCO_3$ solution (3 mL) was added to the reaction mixture. The resulting solution was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated on a rotary evaporator under reduced pressure to obtain crude product **2** which was purified by using flash silica gel column chromatography eluting with 10% ethyl acetate in pet. ether as the eluent to furnish pure compound **2** (228 mg, 73%) as a colourless liquid.

Rf : 0.5 (Ethyl acetate – pet. ether=15:85);

Yield: 73%;

IR ($CHCl_3$): ν_{max} 3021, 1694 (br), 1595, 1444, 1216, 778 cm^{-1};

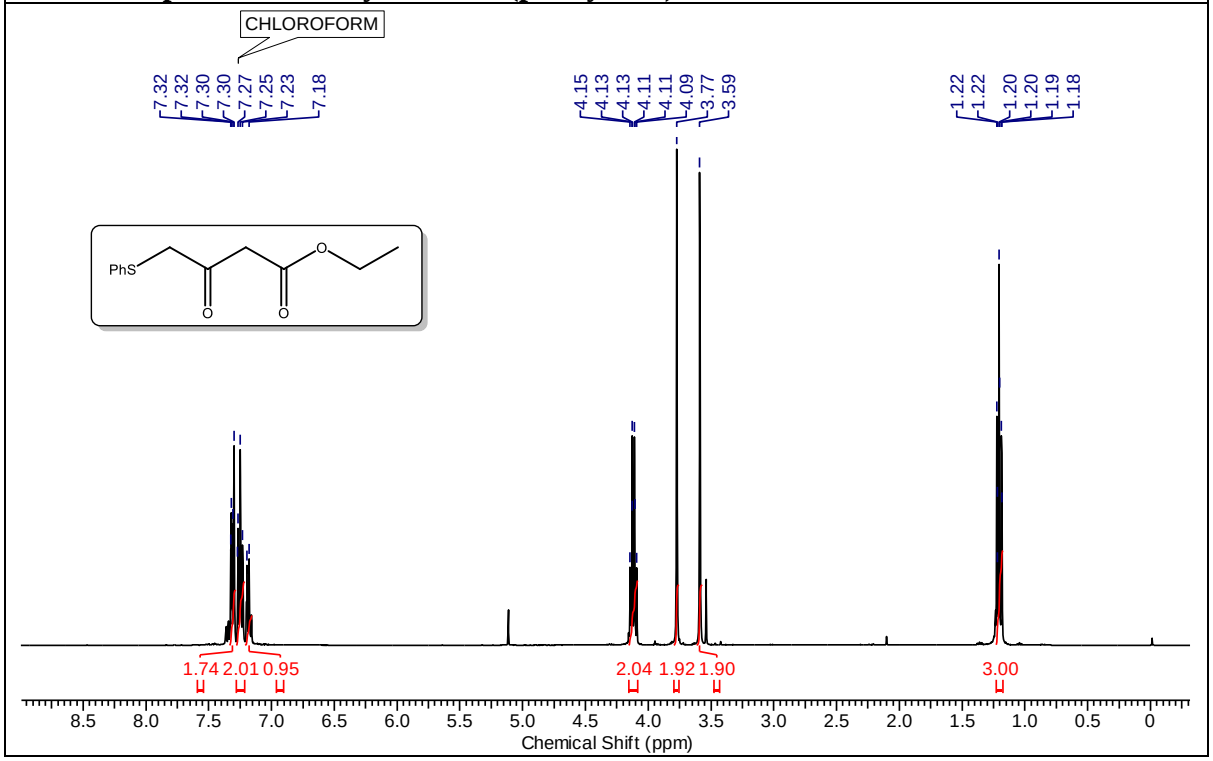
^{1}H NMR ($CDCl_3$, 400 MHz) two rotamers were observed in approximately 6:4 ratio: δ 12.09 - 11.94 (s, 1H), 7.26 - 7.10 (m, 5H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.90 - 6.77 (m, 2H), 4.51 (d, *J* = 16.6 Hz, 1H), 4.18 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.72 - 3.68 (m, 1H), 3.68 - 3.64 (m, 1H), 3.53 (s, 2H), 3.23 - 3.11 (m, 1H), 3.05 - 2.94 (m, 2H), 2.94 - 2.70 (m, 2H), 2.53 (dd, *J* = 10.1, 13.3 Hz, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): two rotamers were observed: δ 171.7, 171.3, 171.1, 171.0, 158.0, 156.7, 135.2, 132.0, 131.7, 130.4, 130.3, 129.1 (2C), 129.0, 128.4(2C), 128.2, 127.0, 126.6, 120.7, 120.5(2C), 110.6, 110.4, 94.1(2C), 55.6, 53.3, 52.7, 52.0, 50.9, 42.3, 42.2, 38.0, 37.9, 36.6, 36.0, 33.6, 33.4;

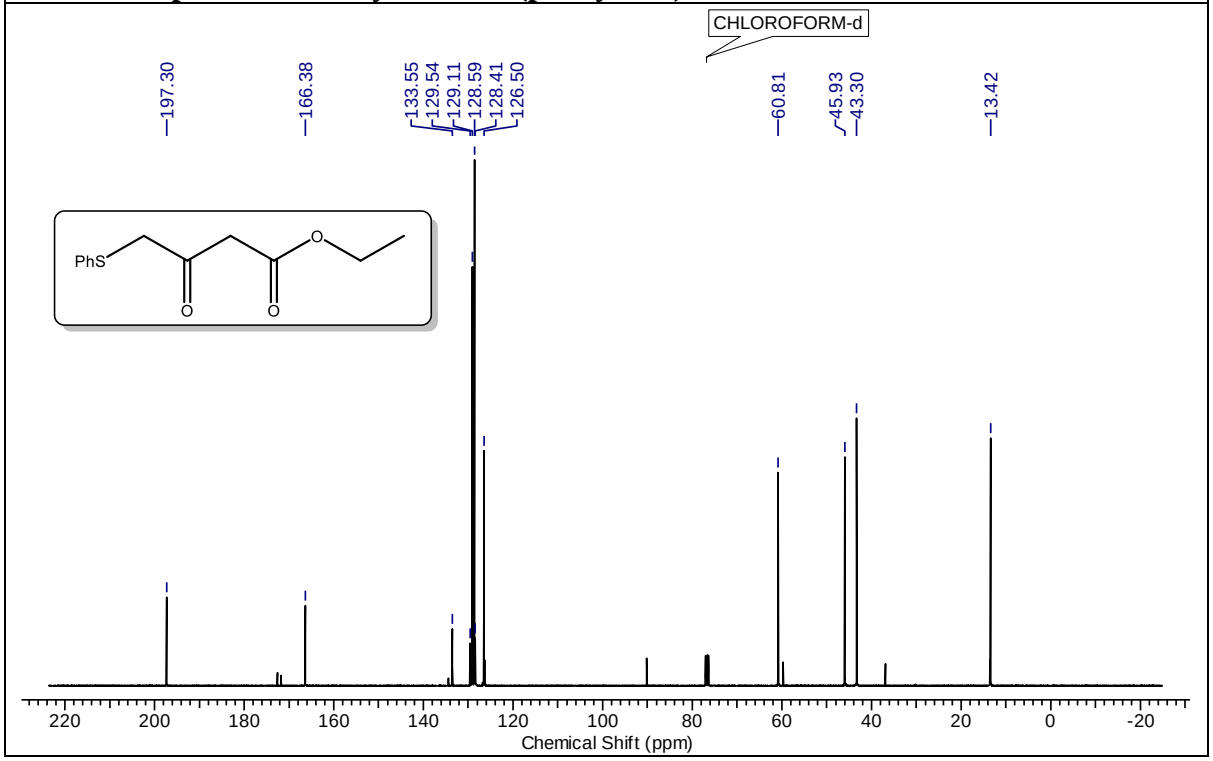
HRMS (ESI): m/z calcd for $C_{24}H_{28}NO_6S$ $[M + H]^+$:458.1632, found: 458.1629.

1.3.6. Spectral Data

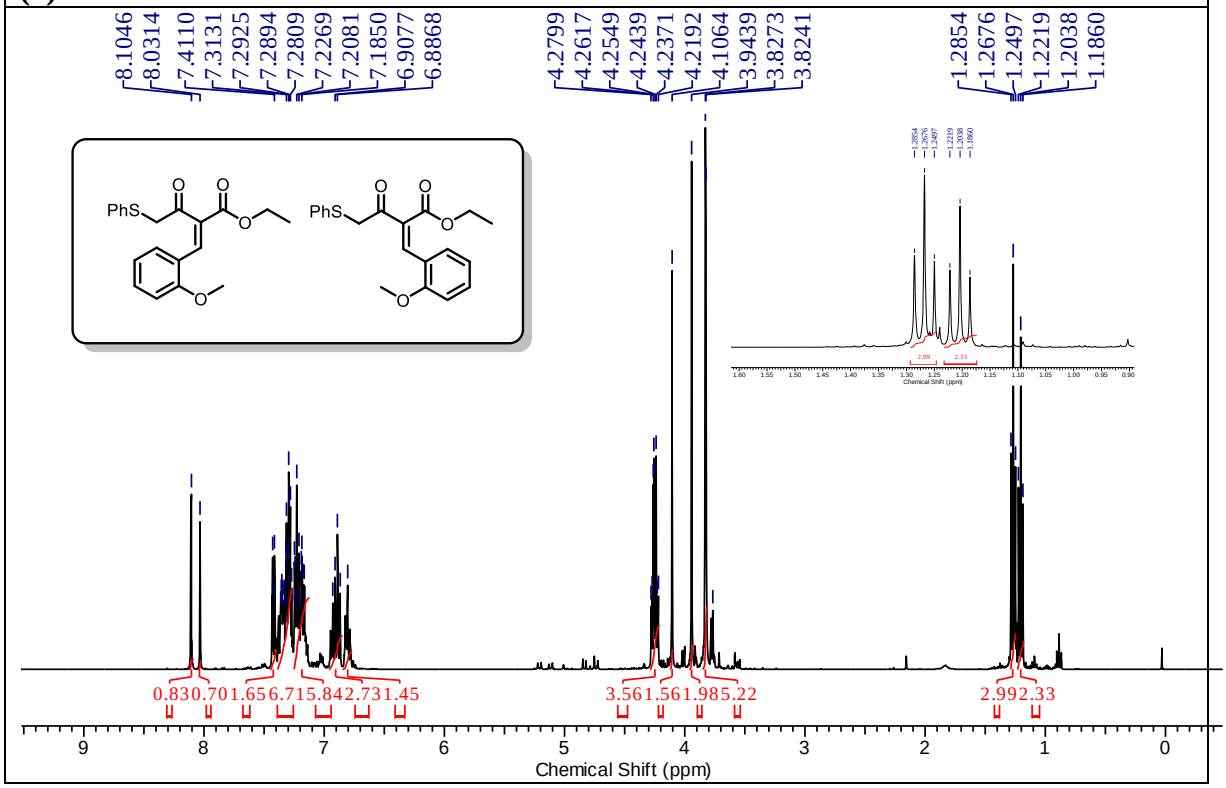
^{1}H-NMR spectrum of ethyl 3-oxo-4-(phenylthio)butanoate



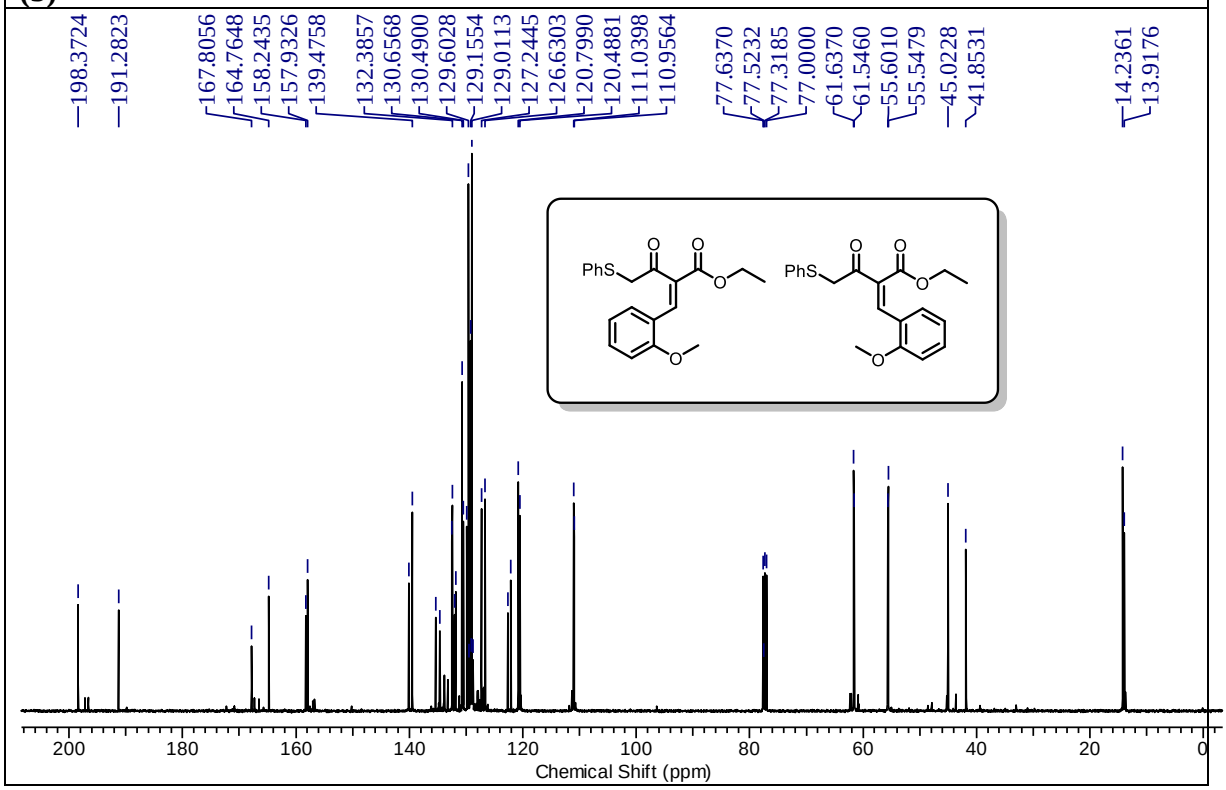
^{13}C-NMR spectrum of ethyl 3-oxo-4-(phenylthio)butanoate



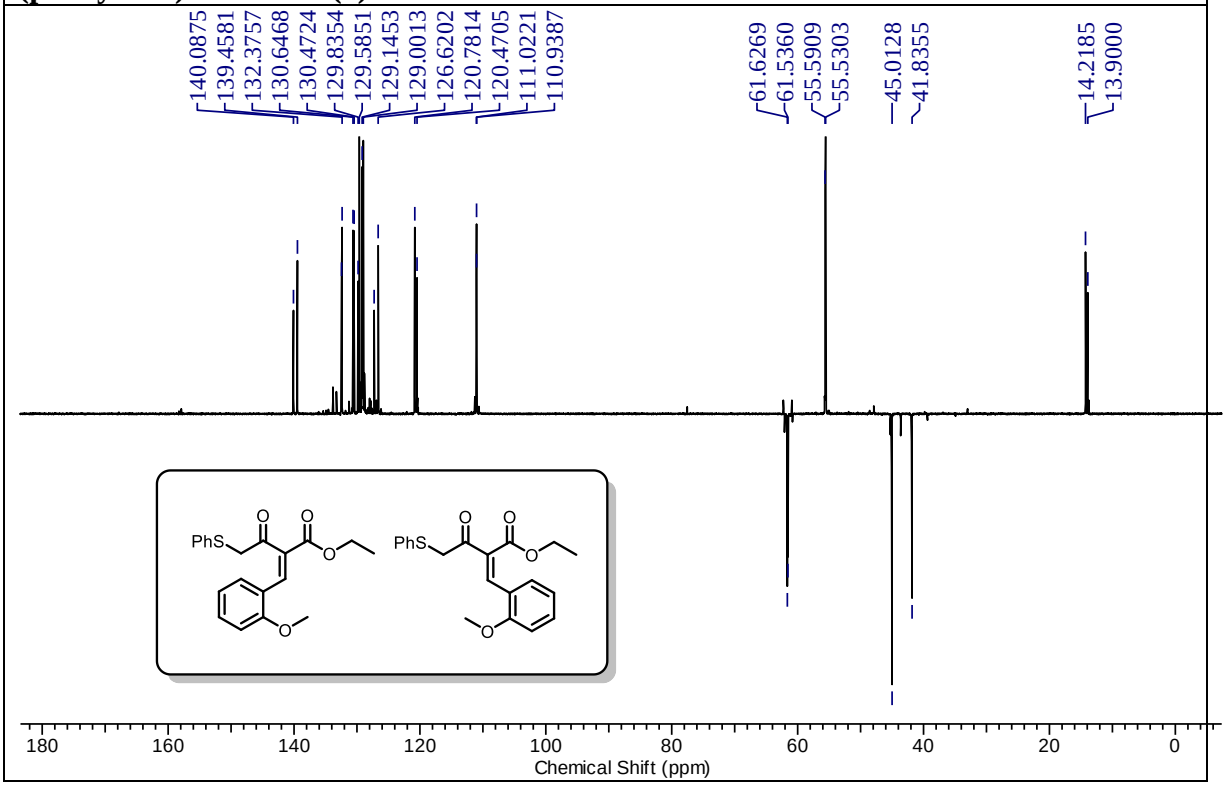
^{1}H-NMR spectrum of ethyl-2-(2-methoxybenzylidene)-3-oxo-4-(phenylthio)butanoate (5)



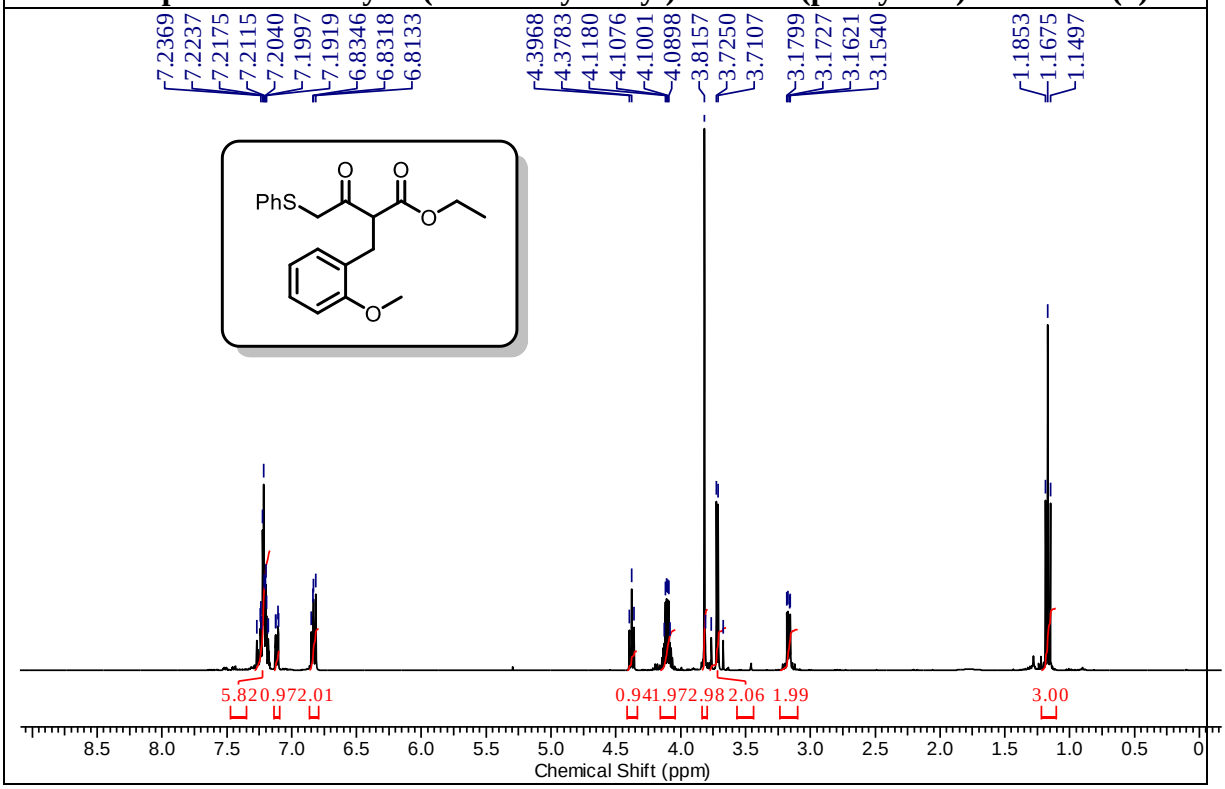
^{13}C-NMR spectrum of ethyl-2-(2-methoxybenzylidene)-3-oxo-4-(phenylthio)butanoate (5)



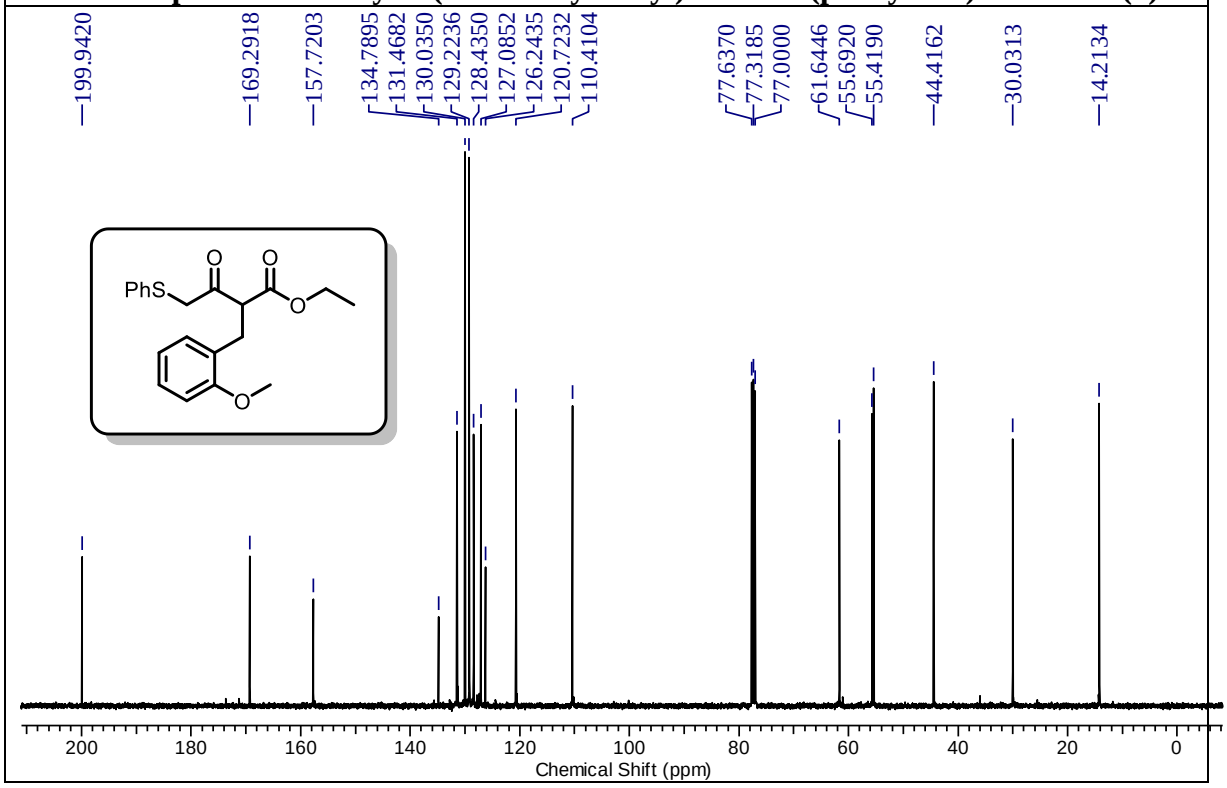
DEPT NMR spectrum of ethyl-2-(2-methoxybenzylidene)-3-oxo-4-(phenylthio)butanoate (5)



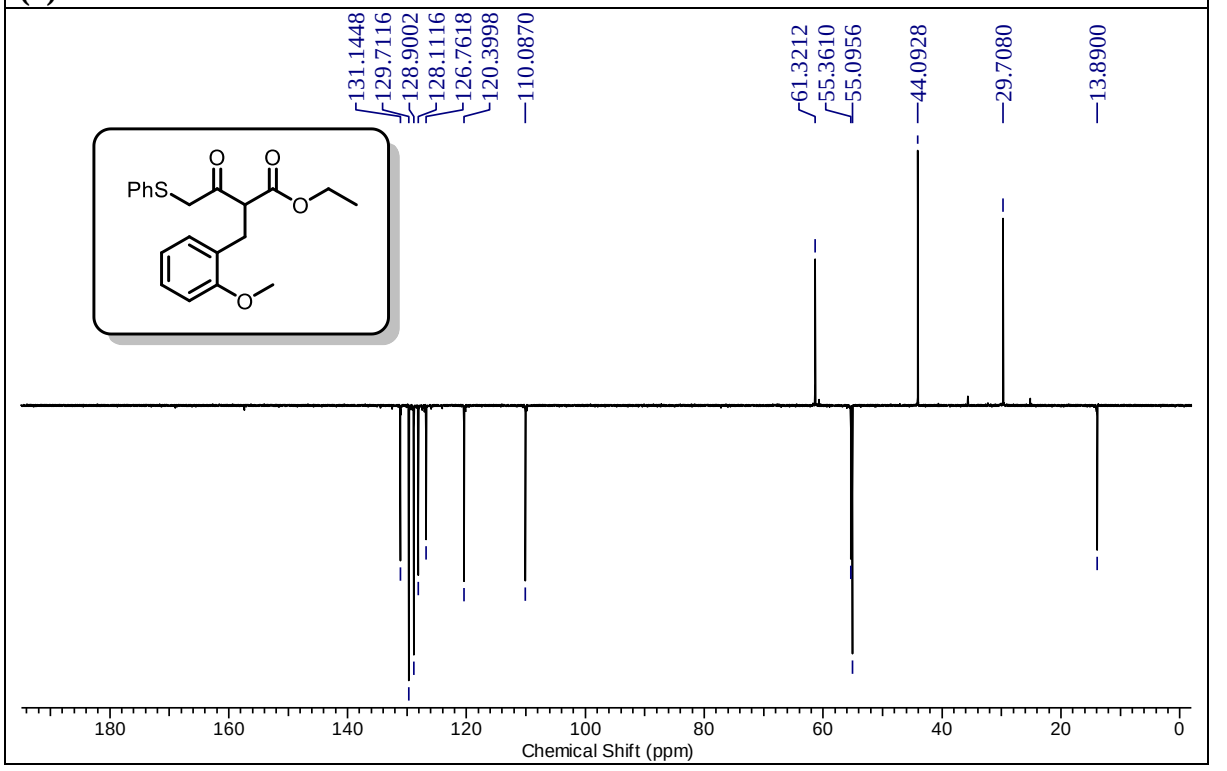
^{1}H-NMR spectrum of ethyl 2-(2-methoxybenzyl)-3-oxo-4-(phenylthio)butanoate (8)



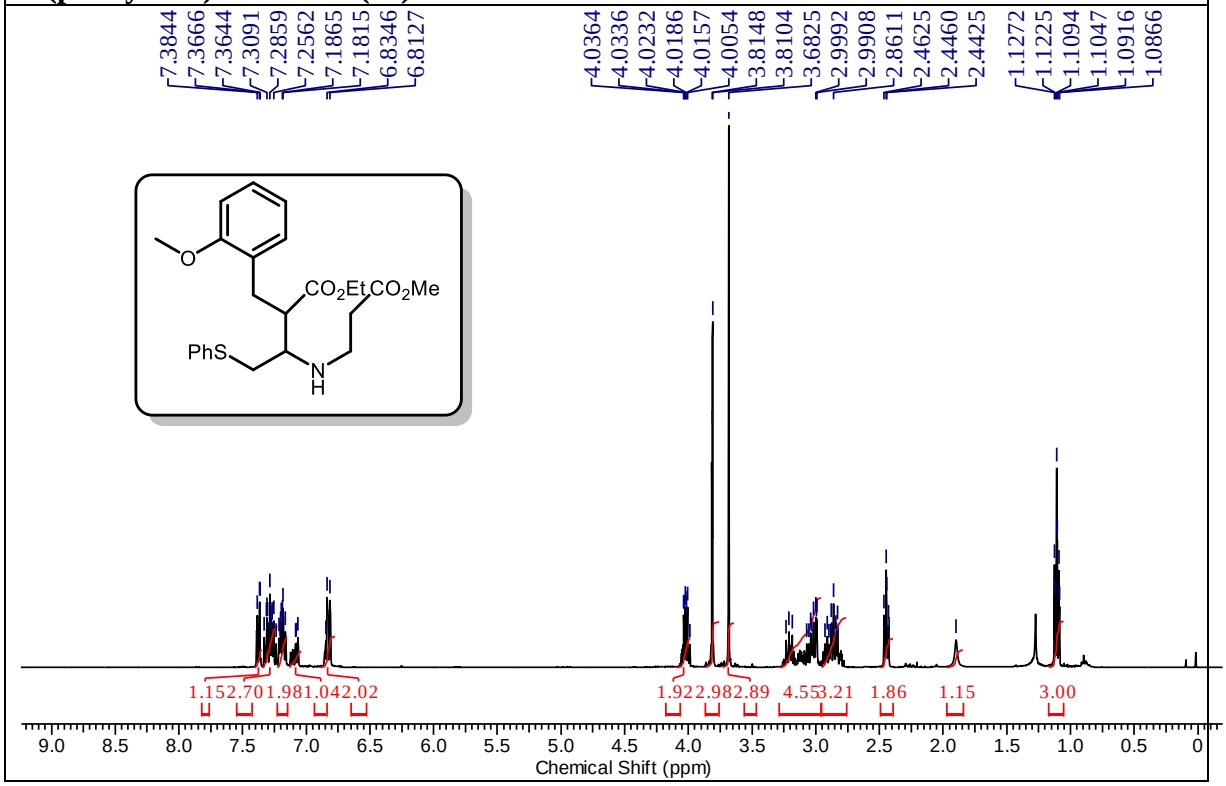
^{13}C-NMR spectrum of ethyl 2-(2-methoxybenzyl)-3-oxo-4-(phenylthio)butanoate (8)



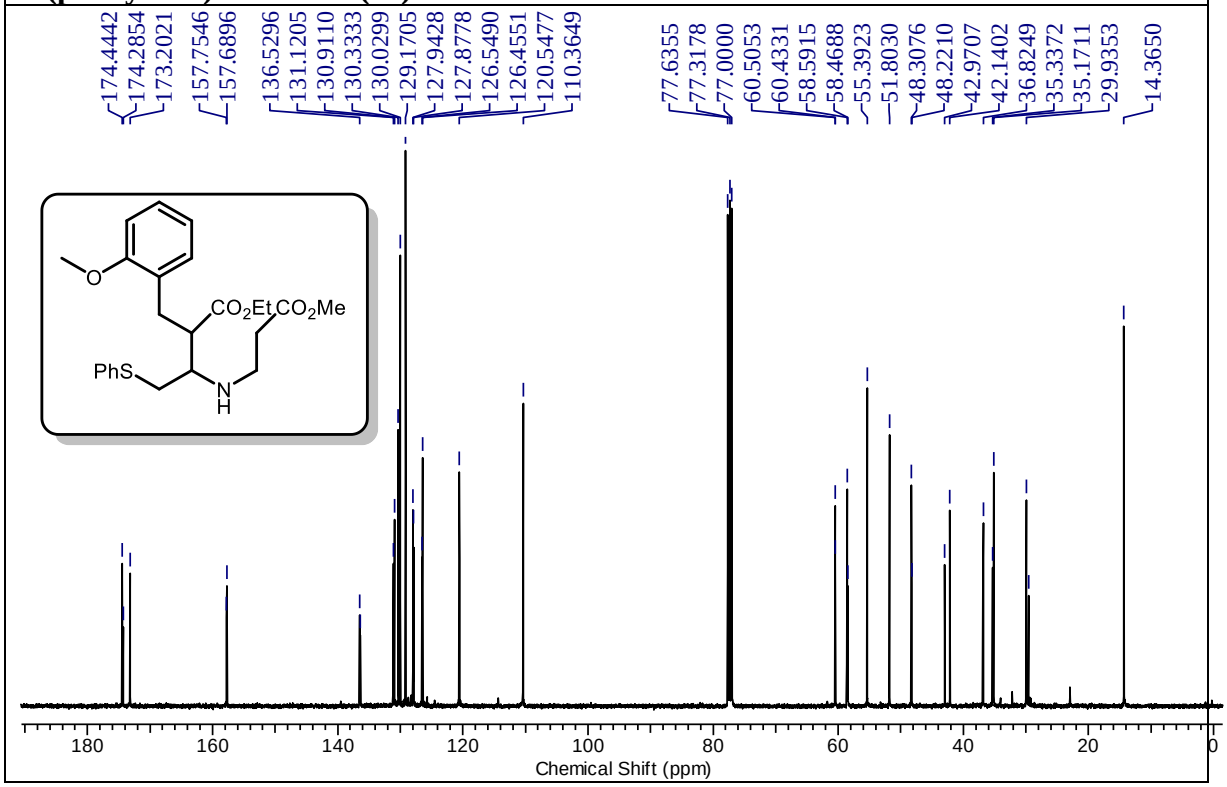
DEPT NMR spectrum of ethyl 2-(2-methoxybenzyl)-3-oxo-4-(phenylthio)butanoate (8)



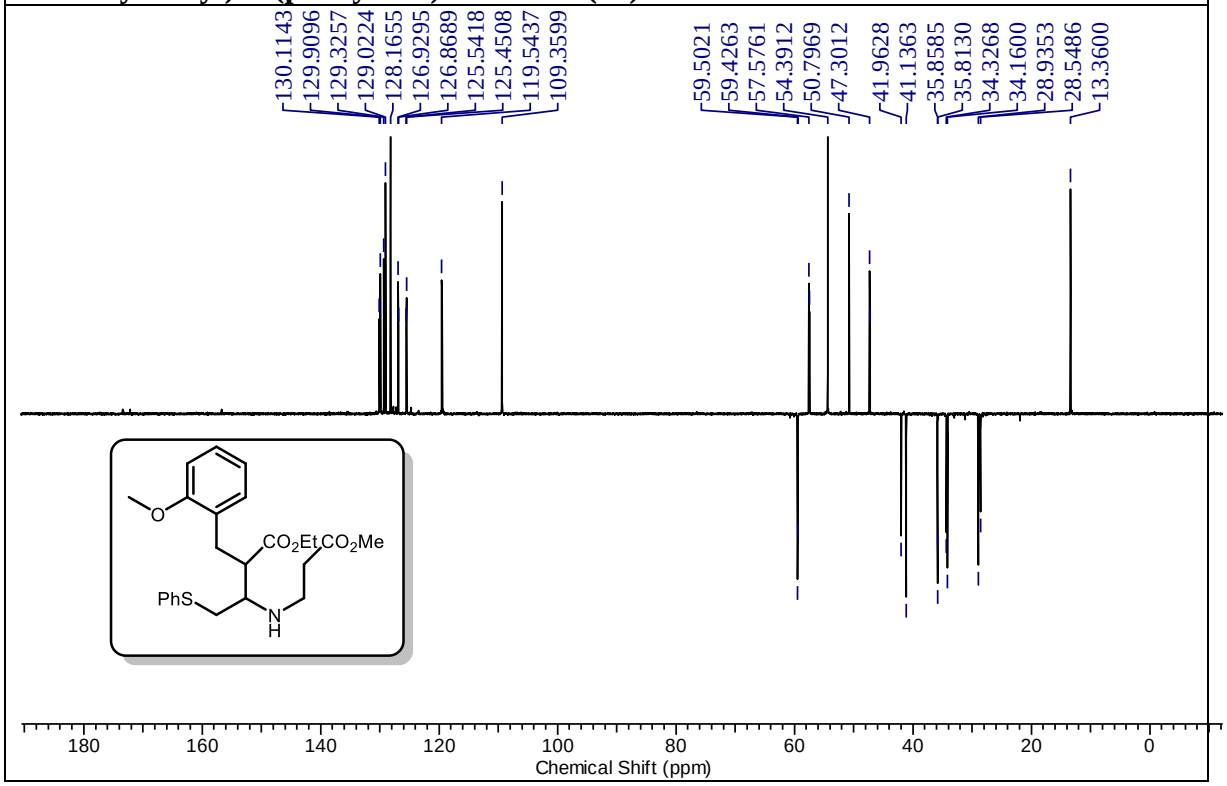
^{1}H-NMR spectrum of ethyl 3-((3-methoxy-3-oxopropyl)amino)-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (11)



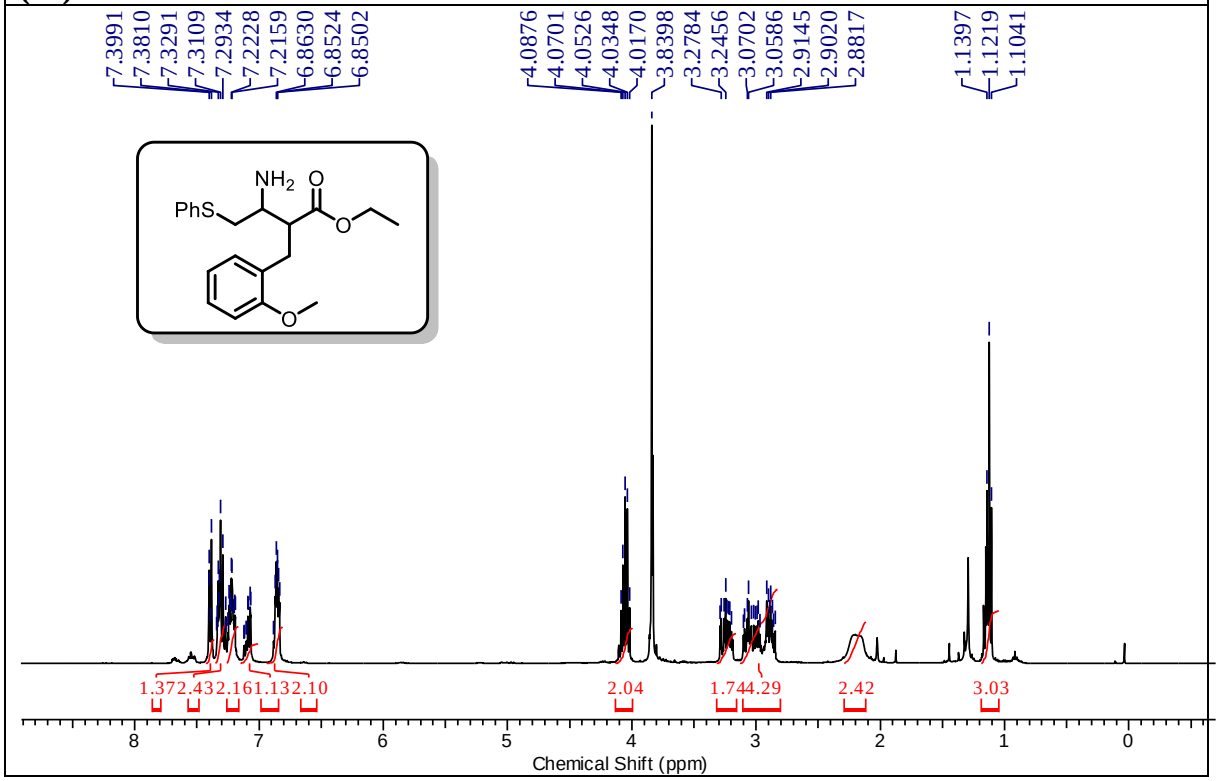
^{13}C-NMR spectrum of ethyl 3-((3-methoxy-3-oxopropyl)amino)-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (11)



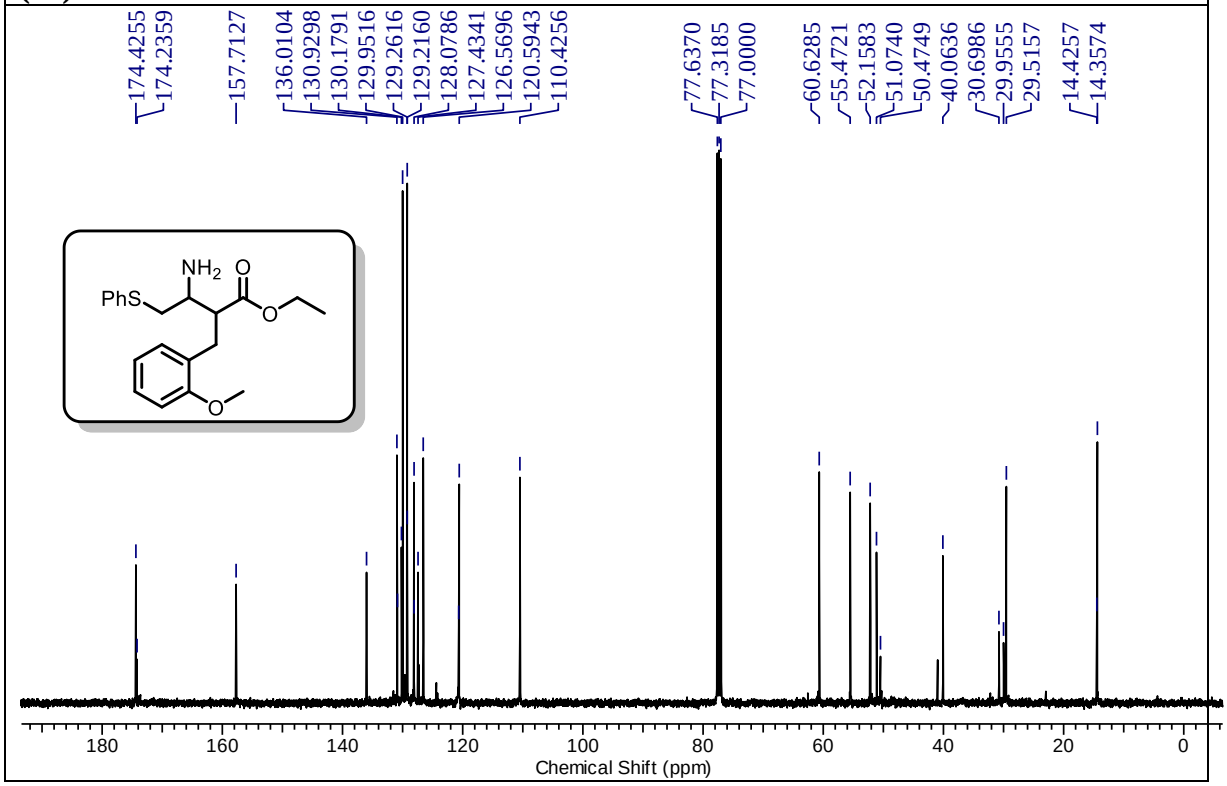
DEPT NMR spectrum of ethyl 3-((3-methoxy-3-oxopropyl)amino)-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (11)



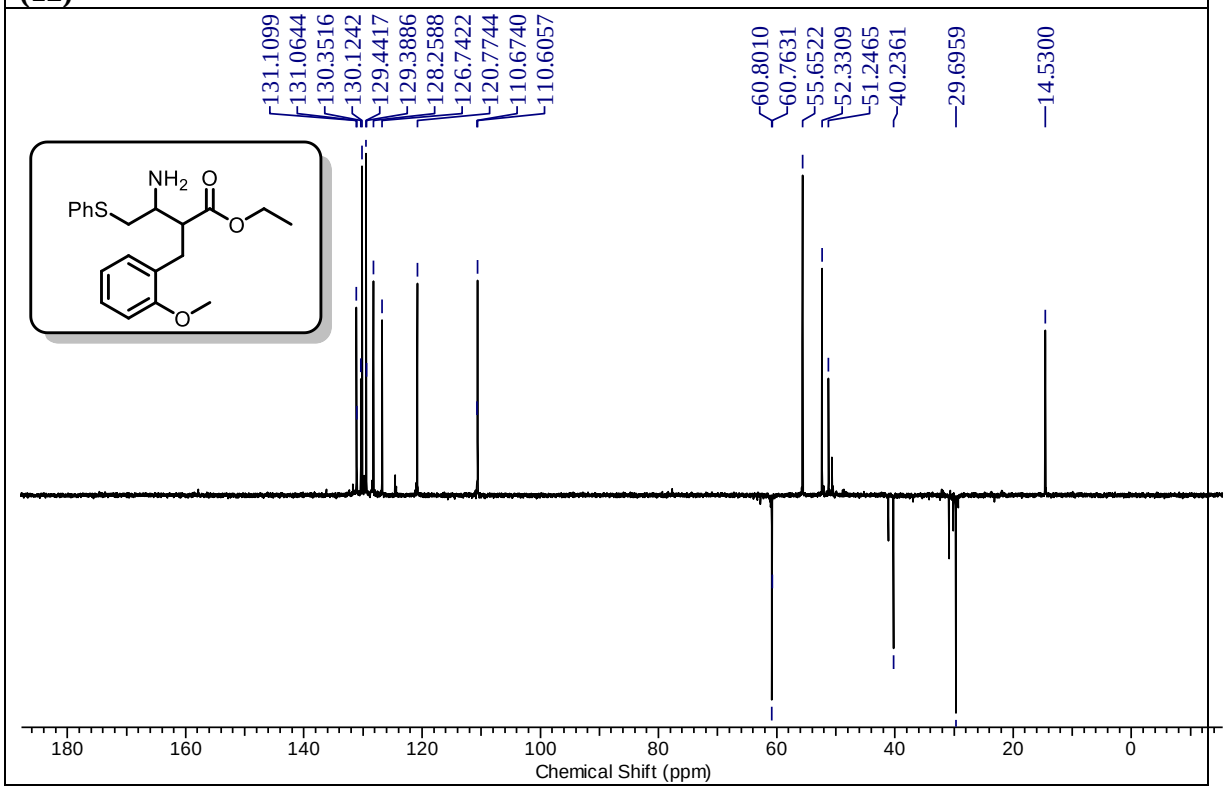
^{1}H-NMR spectrum of Ethyl 3-amino-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (12)



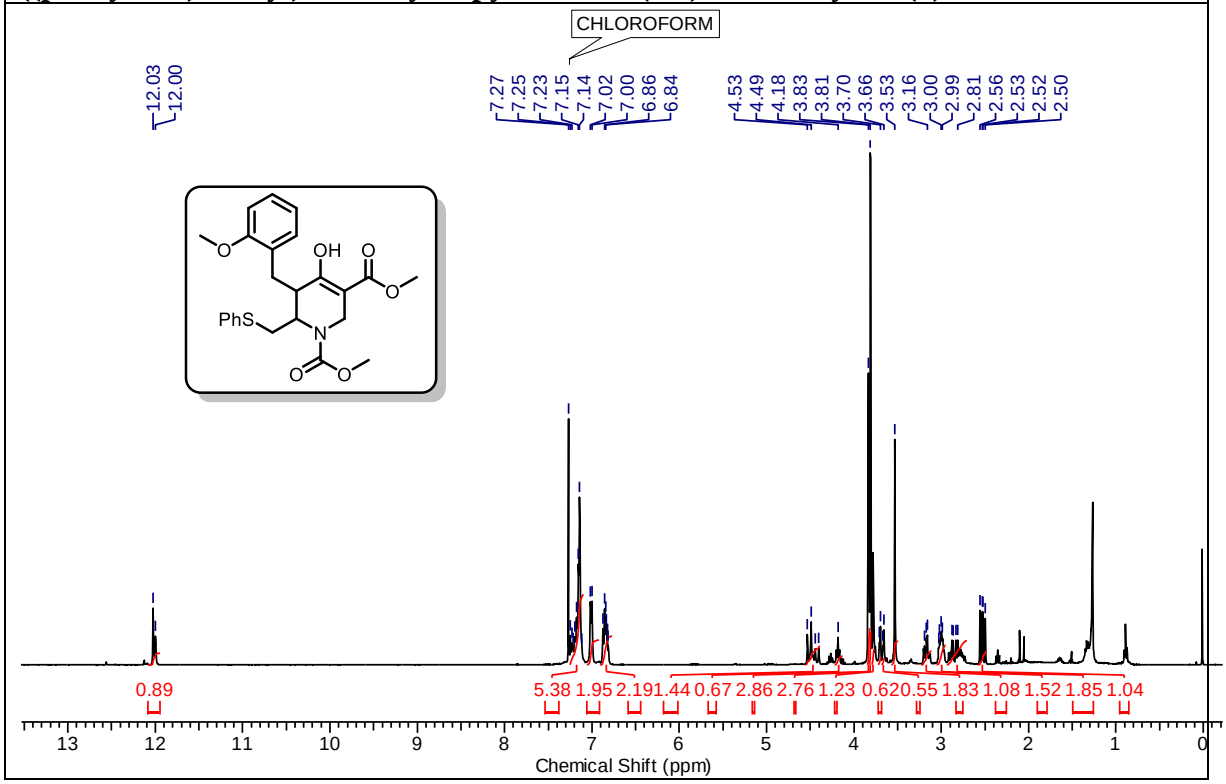
^{13}C-NMR spectrum of Ethyl 3-amino-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (12)



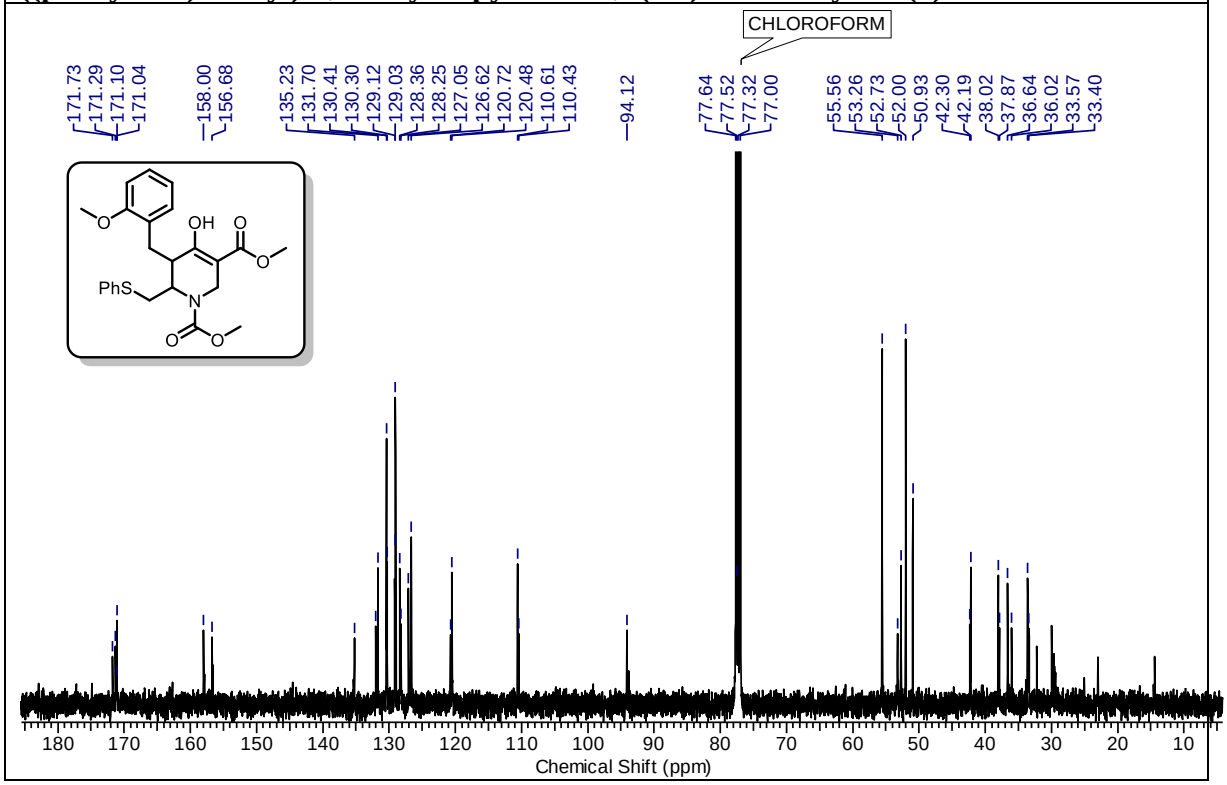
DEPT NMR spectrum of ethyl 3-amino-2-(2-methoxybenzyl)-4-(phenylthio)butanoate (12)



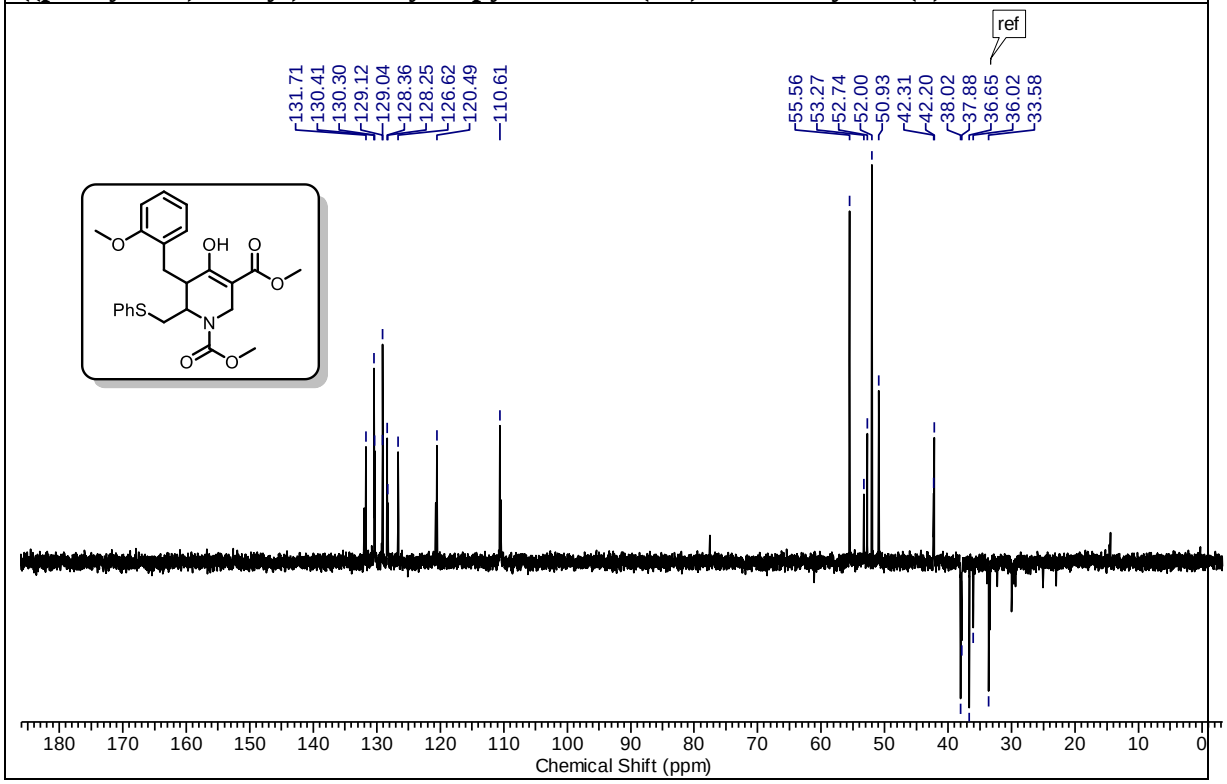
^{1}H-NMR spectrum of dimethyl 4-hydroxy-5-(2-methoxybenzyl)-6-((phenylthio)methyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2)



^{13}C-NMR spectrum of dimethyl 4-hydroxy-5-(2-methoxybenzyl)-6-((phenylthio)methyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2)



DEPT NMR spectrum of Dimethyl 4-hydroxy-5-(2-methoxybenzyl)-6-((phenylthio)methyl)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (2)



References:

1. Nordmann, R.; Petcher, T. J. *J. Med. Chem.* **1985**, *28*, 367.
2. Bänziger, M.; Cercus, J.; Stampfer, W.; Sunay, U. *Organic Process Research & Development* **2000**, *4*, 460
3. Sanket Kawale Ph.D thesis submitted to AcSIR.

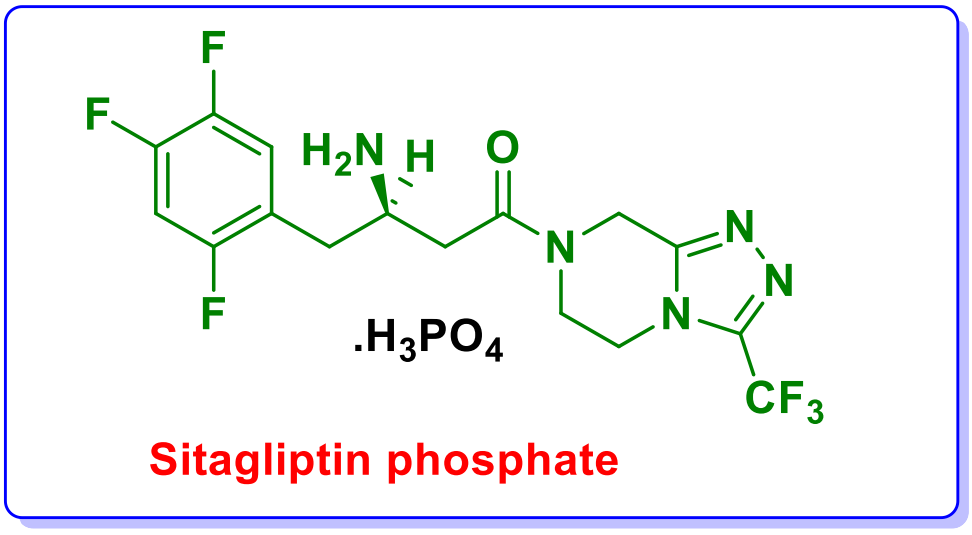
Chapter 2

"Synthesis of antidiabetic drug sitagliptin"

Chapter 2: Total Synthesis of Antidiabetic Drug Sitagliptin

Chapter-2
Section-1

"Introduction and Literature Review of Antidiabetic Drug Sitagliptin"



Sitagliptin phosphate

2.1.1. Introduction:

Diabetes is establishing itself as a heavy infection disease of the 21st century. Type 2 diabetes (T2D), formerly non-insulin-dependent diabetes,[1,2] accounts for a minimum of 90% of all cases of the disease. Inhibitors of the enzyme DPP-IV (dipeptidyl peptidase 4) are a promising treatment for type II diabetes. Sitagliptin **(1)** is a potent inhibitor of DPP-IV and since its launch in 2006 by Merck, sitagliptin phosphate monohydrate,[3-6] the primary DPP-4 inhibitor has been one among the best-selling orally active and safe agents for the treatment of T2DM (type 2 diabetes mellitus).[7]

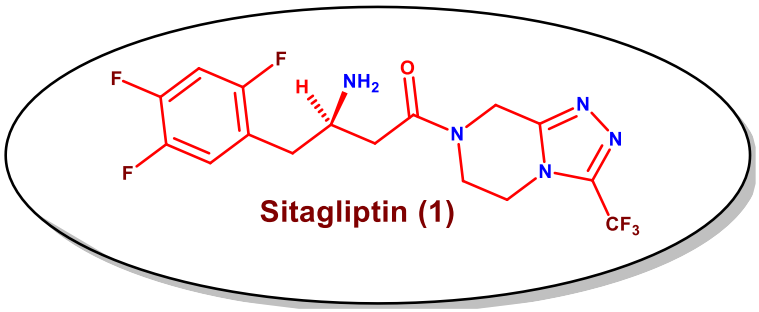


Fig. 1 Sitagliptin.

Diabetes may be multifactorial disease that's classified as chronic hyperglycemia due to defects in insulin secreation, action or both, which end up in abnormalities in carbohydrate, fat and protein metabolism.

WHO published a worldwide report on diabetes in April 2016. It necessitates action to scale back the chance of known risk factors for type 2 diabetes, thereby improving the standard and care of every kind of individuals with diabetes.

The most common is type 2 diabetes, usually in adults, which occurs when the body becomes resistant against insulin or doesn't make enough insulin. Within the past three decades, the prevalence of type 2 diabetes has risen dramatically in countries of all income levels. Type 1 diabetes, once called autoimmune disorder or no insulin-dependent diabetes, could be a chronic condition during which the pancreas produces little or no insulin by itself. For people affected by diabetes, access to affordable treatment including insulin is critical to their survival. There's a globally agreed target to halt the increase in diabetes and obesity by 2025.

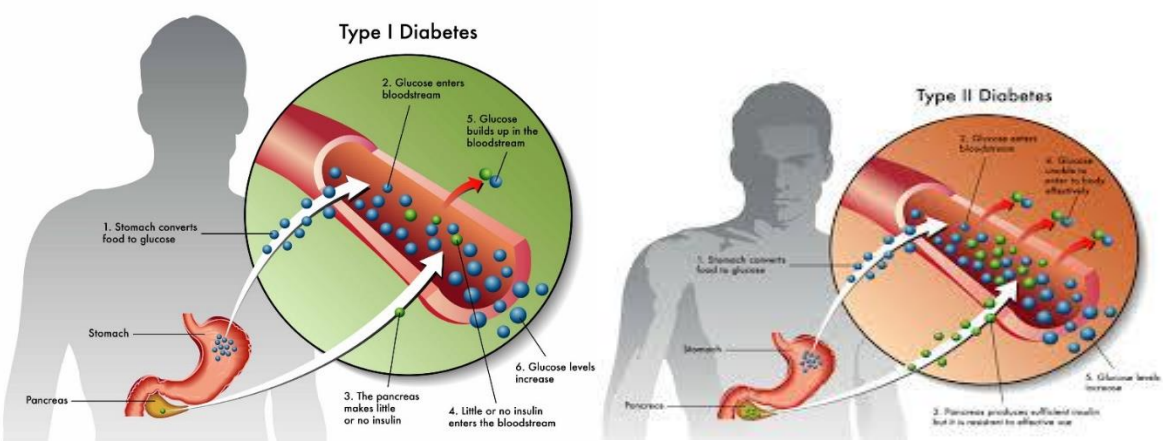


Fig. 2: Difference between Type I and Type II diabetes.

Around 422 million people worldwide have diabetes, particularly in low and middle-income countries and diabetes is directly the reason for death of 1.6 million people every year.

In the previous few decades, there has been a gradual increase in the number of cases and therefore the prevalence of diabetes.

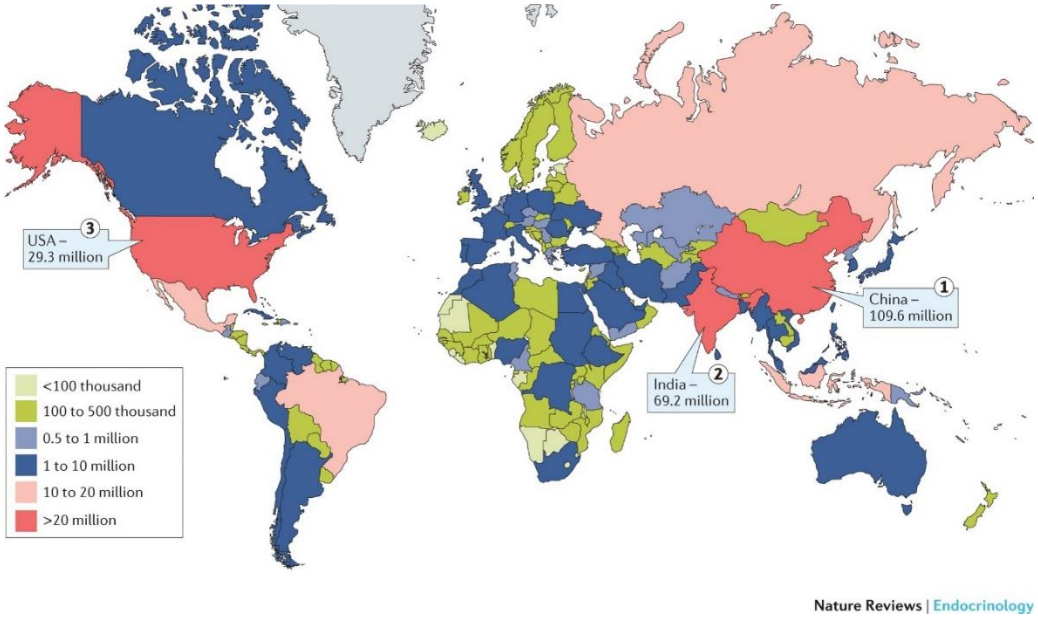


Fig. 3: Worldwide spread statistics.

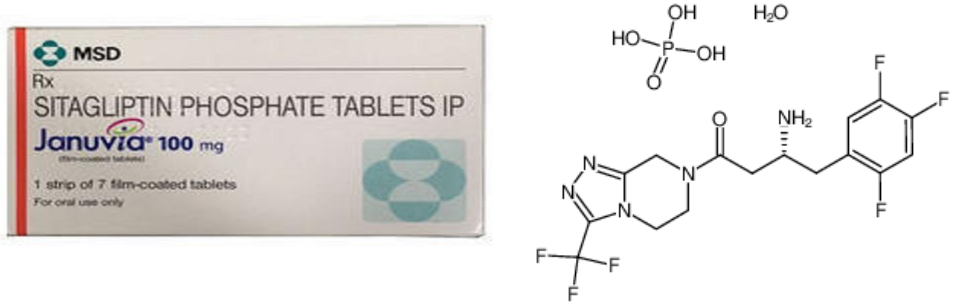


Fig. 4: Sitagliptin marketed drug and structure.

Sitagliptin **(1)** a selective, potent DPP-IV inhibitor, is the active ingredient in JANUVIR and JANUMET (a fixed dose combination with the diabetes agent Metformin), both of which have received approval for the treatment of type 2 diabetes by the FDA[8]. Sitagliptin phosphate, also known as Januvir, was touted as a future billion dollar boon for the pharmaceutical industry. On June 26, 2012 Evaluated Pharma revealed its World Preview 2018 projection, giving a nod to Merck's Januvia. With an estimated 10 billion dollars in annual sales, Januvia (Sitagliptin Phosphate) is forecasted to be a top player in the global pharmaceutical market.

2.1.2. Literature Review:

A comprehensive set of available literature concerning the sitagliptin is presented. Sitagliptin and its seventeen sister gliptins have been a target for various research groups and as a result of several years of intense research, a number of synthetic schemes have been reported. Some of the important syntheses in each class have been described here.

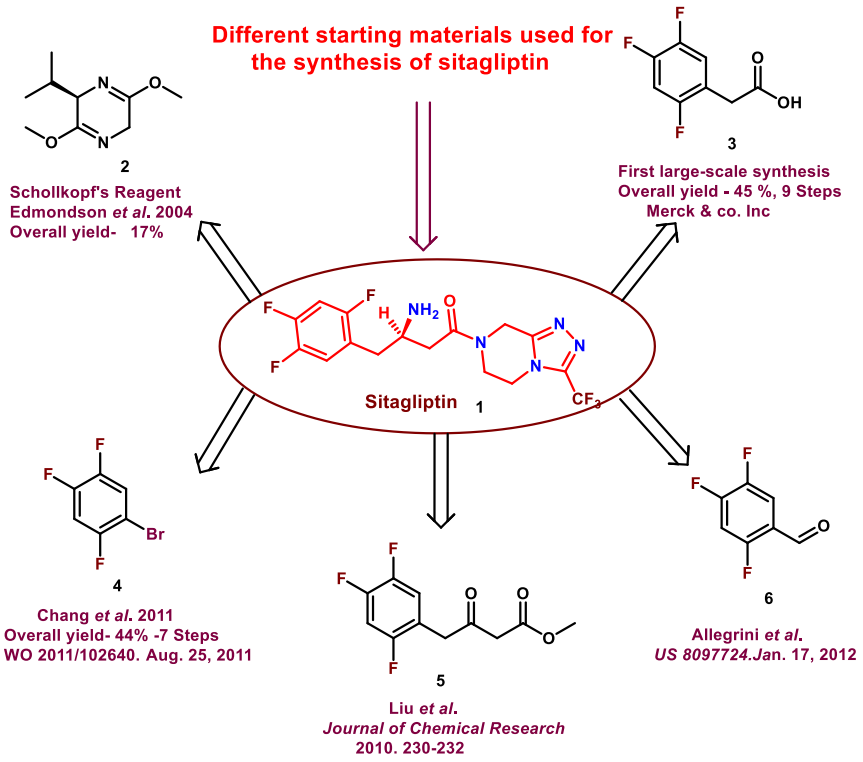


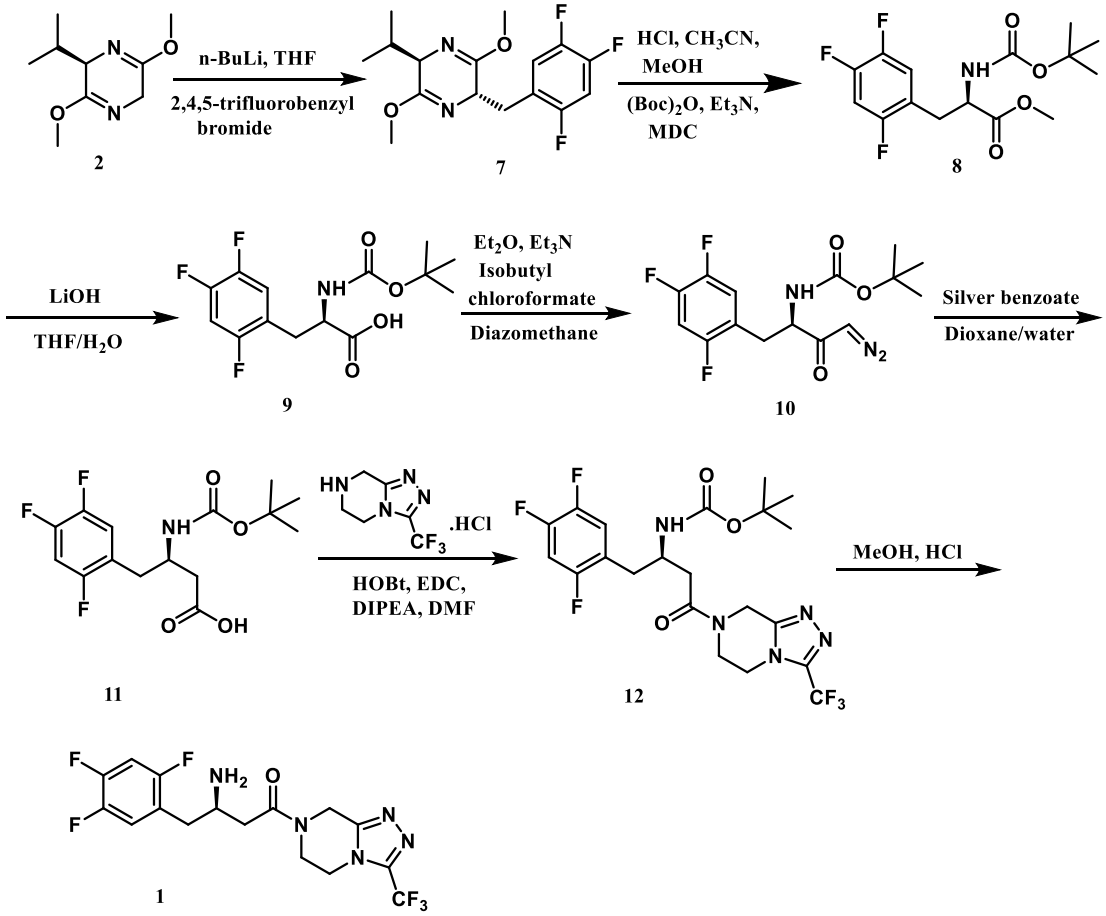
Fig. 6: Total synthesis of sitagliptin by using different starting materials and with different routes.

Synthetic Approaches for Sitagliptin:

Edmondson *et al.* (*US 6699871***, Mar. 02, **2004**, (Assigned to Merck & co., Inc))**[9].

Sitagliptin **(1)** was first synthesized by Edmondson *et al*. in 2004[9] and in the first synthetic approach, the synthesis of sitagliptin was started with the 2,4,5-trifluorobenzyl bromide with Schollkopf reagent[10] **(2)** to afford the compound **7**. By using hydrochloric acid followed by Boc-protection ester **8** was obtained. Amino acid **9** was prepared by hydrolysis. Key step used was treatment with isobutyl chloroformate followed by diazomethane to give diazoketone **10**.

Diazoketone underwent rearrangement and hydrolysis to give β-amino acid. C-N coupling using desired amine moiety followed by Boc-deprotection provided the sitagliptin **(1)** with 17% overall yield (**Scheme 1**).

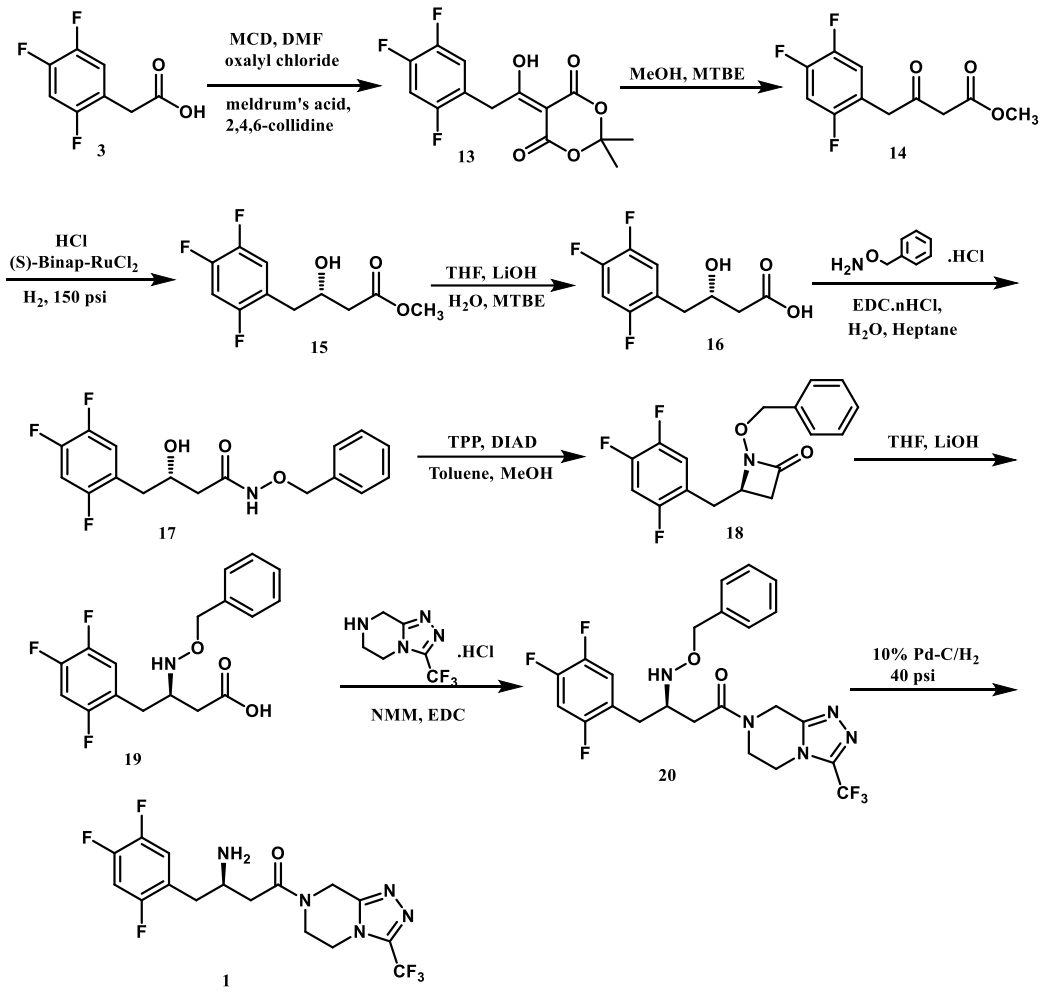


Scheme 1.

R. Angelaud *et al*. (*WO 2004/ 087650*, Oct. 14, **2004**, (Assigned to Merck & co., Inc)) [11].

The first large scale synthesis of sitagliptin started with trifluorophenylacetic acid which was converted to β-keto ester **14** with Meldrum's adduct intermediate. Chiral reduction of β-keto ester was carried out using (S)-Binap.$RuCl_2$-n. triethylamine complex to give β-hydroxy ester **15**. Ester was hydrolysed to give β-hydroxy acid **16**. Hydroxamate **17** was formed by acid-amine coupling by reaction of acid **16** and hydroxylamine hydrochloride by using EDC. Lactam formation was carried out using DIAD and TTP to give **18** with 81% yield. Lactam was the key building block and it was hydrolysed to amino acid **19** with LiOH at room temperature. Desired triazole **20** was prepared by using EDC and NMM as C-N coupling

reagent in 99% yield. The last step was the hydrogenation of compound **20** subjecting it to 10% Pd on carbon to furnish **1** in 99.5 % purity (**Scheme 2**)



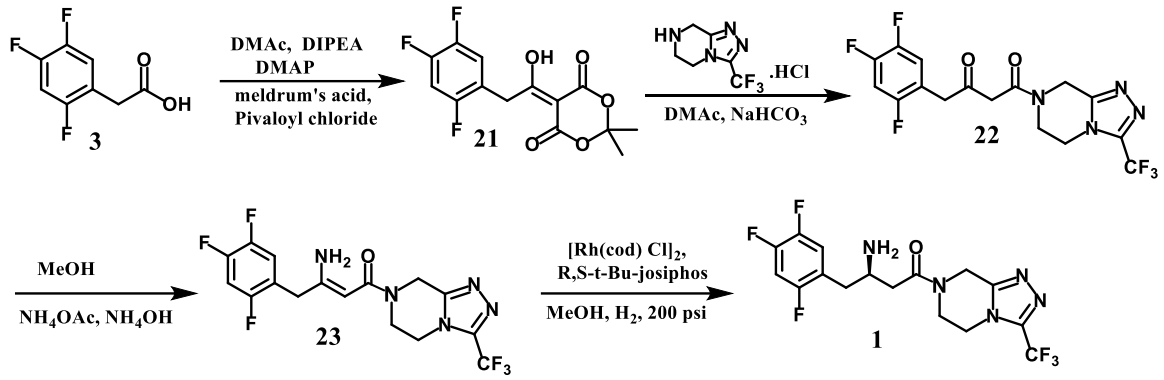
Scheme. 2

This first large-scale synthesis of sitagliptin afforded the desired compound in 45% yield over 9 steps.

Xiao *et al.* (*US 7468459*, Dec. 23, **2008**, (Assigned to Merck & co., Inc)[12].

This approach is highly efficient for a direct preparation of β-keto amide intermediate **22** from acid **3** in which trifluorophenylacetic acid **3** was activated with N,N'-carbonyl di-imidazole reaction condition to give **21** and after that treated with Meldrum's acid to give adduct **22**. Compound **22** was treated with ammonium acetate in methanol to furnish enamine amide **23**. Asymmetric hydrogenation of enamine amide with rhodium complex catalyst in methanol gave **1** in 93% yield and 94% ee. In this synthetic route only three steps required chemical

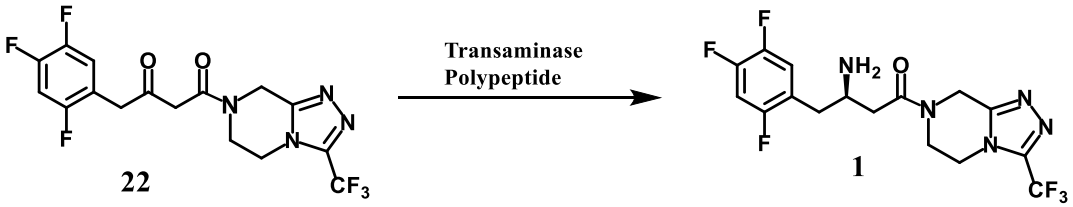
puritfication and overall yield obtained was 63%. This approach is highly efficient (**Scheme 3**).



Scheme 3

Saville *et al.* (*US 2010/0285541,*** Nov. 11, **2010** (assigned to Codexis Inc) [13].

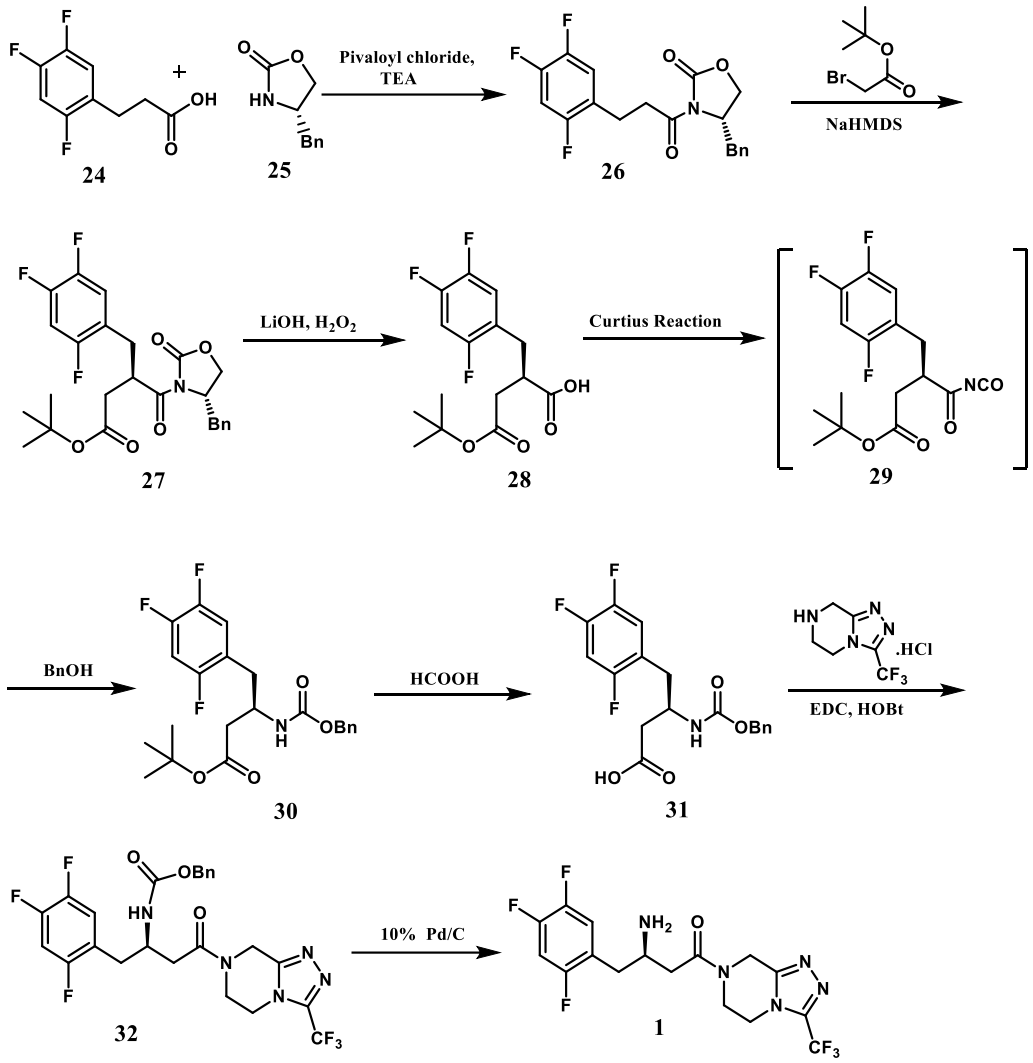
In this method β-keto amide **22** was directly converted to sitagliptin **(1)** in 88-99% yield by using transaminase polypeptides (**Scheme 4**).



Scheme 4

Rasparini *et al.* (WO 2012/150328, Nov. 08, 2012 (Assigned to chemo Iberica, S. A) [14].

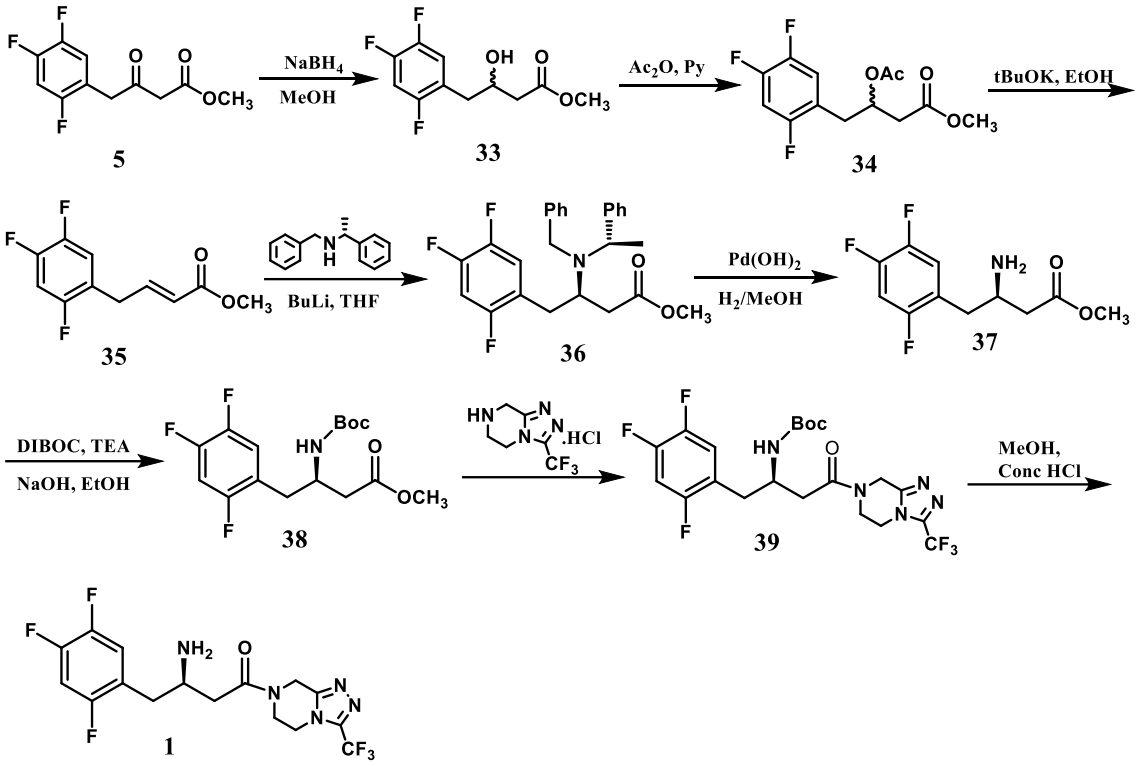
Rasparini *et al.* prepared sitagliptin by using Evans chiral auxiliary methodology. A novel process for the synthesis of sitagliptin was achieved when achiral acid was converted to chiral ester with chiral auxiliary. Important point in this process was an alkylation with an ester of a haloacetic acid followed by Curtius reaction. This multi-step synthesis gave sitagliptin **(1)** in 9% overall yield (**Scheme 5**).



Scheme 5

Liu *et al.* (*Journal of Chemical Research*, **2010**, 230-232.) [15].

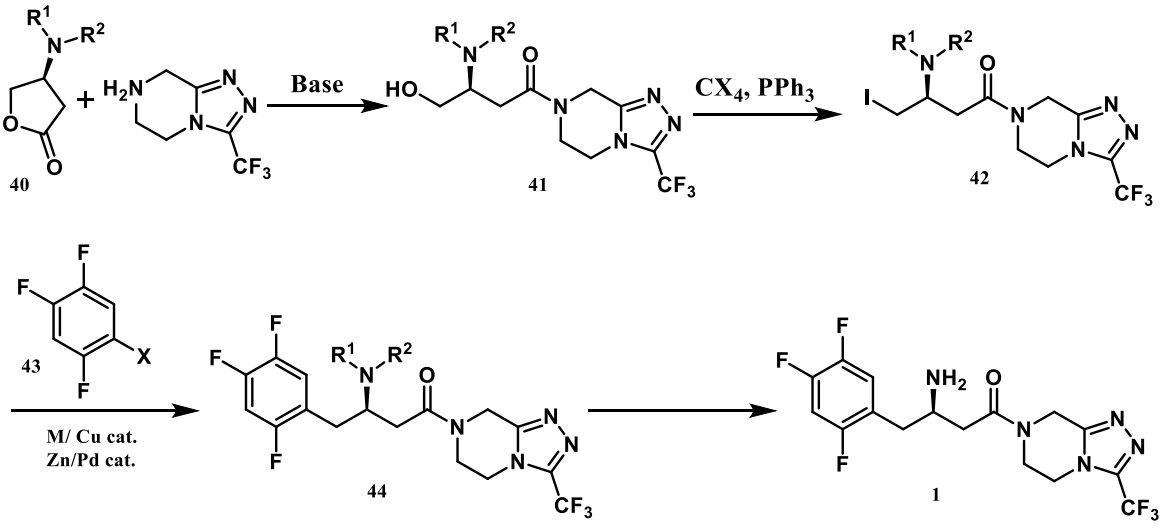
A simple synthesis of the sitagliptin was reported by Liu et al. using Michael addition as the key step. Reduction of β-keto ester followed by treatment with acetic anhydride and then subjecting the resultant acetate to elimination reaction gave acrylate ester **35**. Acrylate ester **35** was subjected to Michael addition as the key reaction followed by multiple steps to give **1** (**Scheme 6**).



Scheme 6

Bartra Sanmarti *et al.* WO 2010/097420, Oct. 02, 2010 (Assigned to Esteve Quimica, S. A) [16].

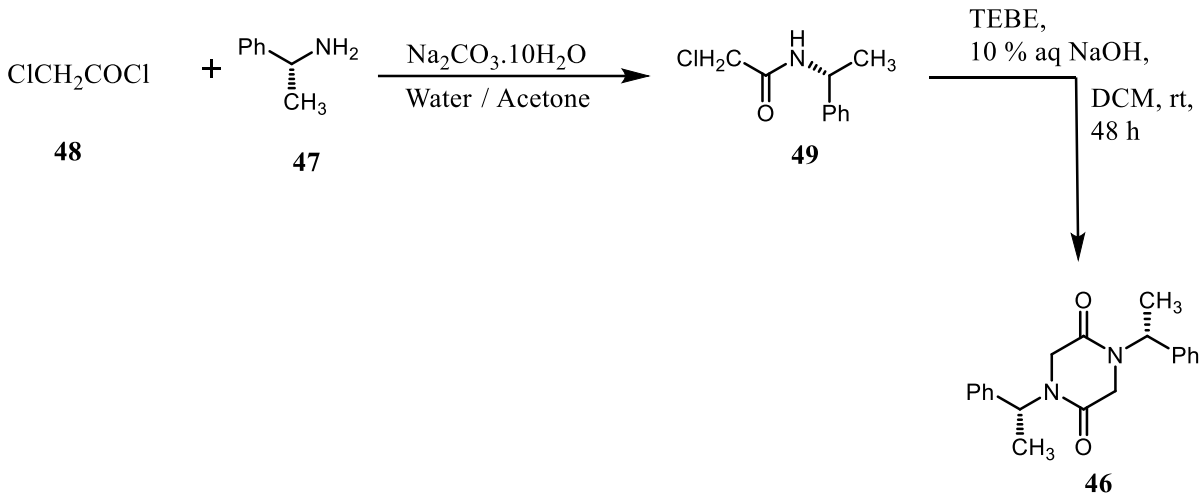
Bartra Sanmarti *et al*. prepared sitagliptin by using C-C coupling reaction between halo-2,4,5-trifluorobenzene **43** and desired triazole moiety **42** and the coupling was carried out *via* the formation of an organocupric or organozinc compound to give **44** wherein R^1 is hydrogen or amino protective group and R^2 is an amino protective group (**Scheme 7**).



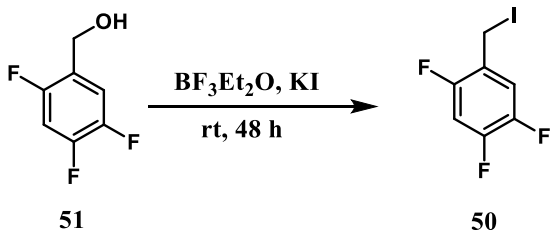
Scheme 7

W. Haq *et al.* (*Tetrahedron: Asymmetry*, **2014**, *25* (13–14), 1026–1030)[17].

In this synthesis, chiral synthon **46** was used which was prepared in two steps by using (R)-phenylethylamine and chloroacetyl chloride **(Scheme 8)** while 2,4,5- trifluorobenzyliodide **50** was the other synthon, prepared from 2,4,5-trifluorobenzyl alcohol using KI and $BF_3.Et_2O$ at rt in 48 % yield **(Scheme 9)**.



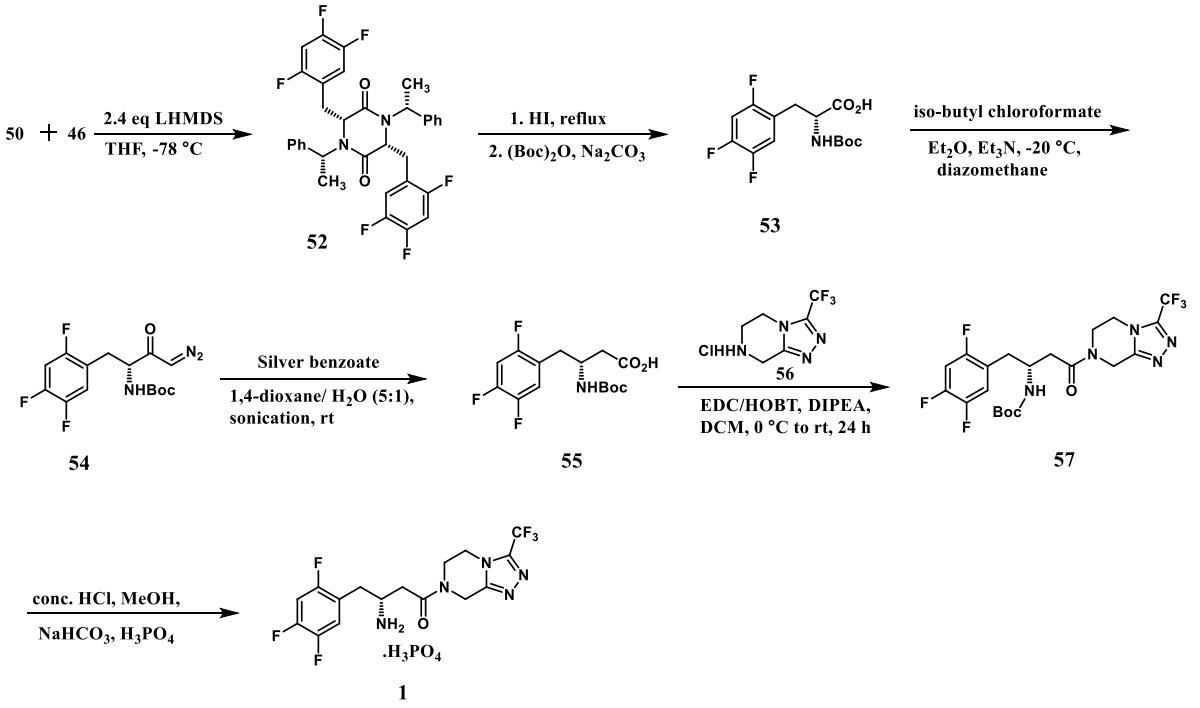
Scheme 8 Synthesis of chiral synthon



Scheme 9 synthesis of iododerivative **50**.

By using chiral synthon **46** and iodo derivative **50** in basic condition (LHMDS), the cis-(3R,6R)-dialkyl derivative **52** was obtained in 73% yield as a single diastereomer. Compound **52** was cleaved by refluxing in 57% HI and subsequently amine group was protected by $(Boc)_2O$ to give **53** in quantitative yield. After that, Arndt-Eistert homologation reaction gave compound **54**. Sonication of diazo ketone **54** using silver benzoate provided β-amino acid **55**

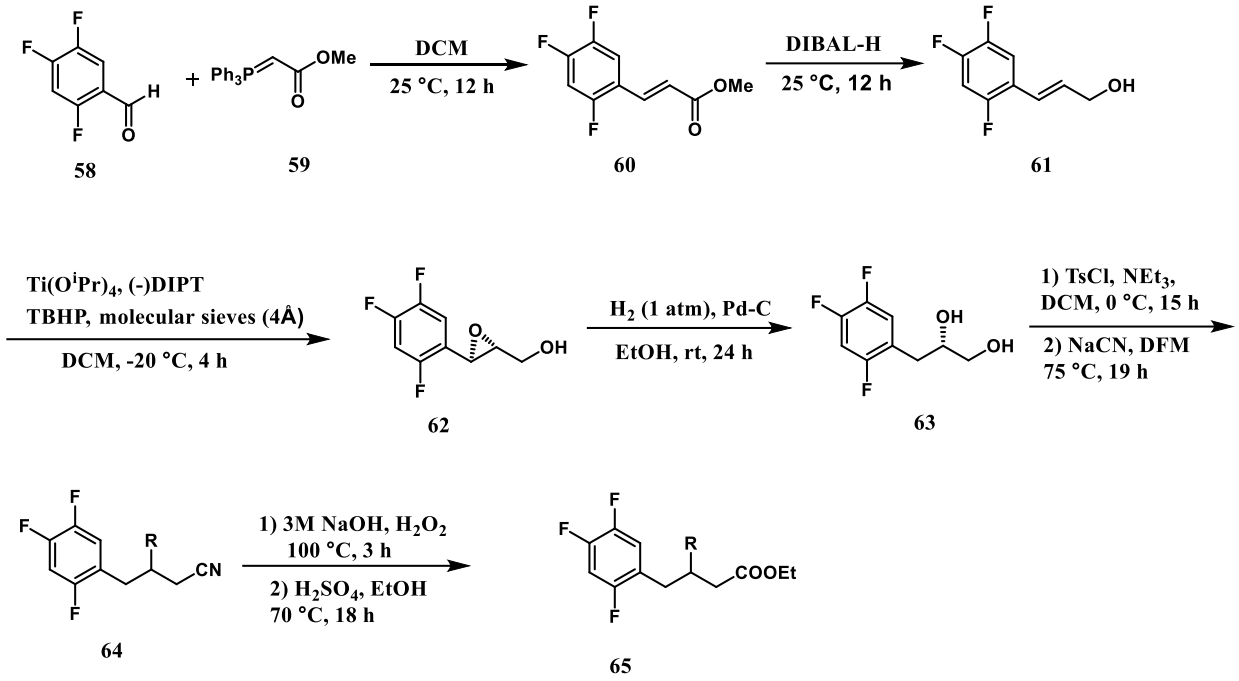
and C-N coupling of **55** with triazolopiperazine **56** using EDC/HOBT afforded **57**. Further deprotection of Boc and treatment with phosphoric acid afforded sitagliptin phosphate **(Scheme 10).**



Scheme 10

Yunus Kara *et al.* (*Synth. Commun*. **2019**, *49*, 852-858)[18].

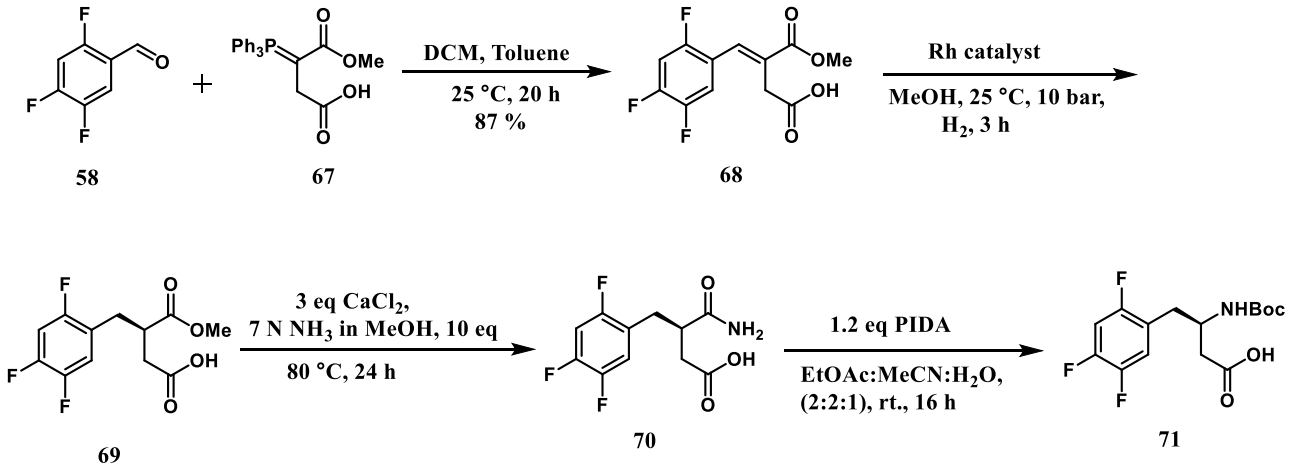
In this synthesis, 2,4,5-trifluorobenzaldehyde **58** was used as a starting material which was converted to α,β-unsaturated ester **60** by using phosphanylidene. Further, ester was reduced with DIBAL-H to give alcohol **61**. Subsequently, Sharpless asymmetric epoxidation protocol was used to afford asymmetric epoxide **62**. Epoxide ring opening by Pd/C catalysed hydrogenation furnished diol **63**. When **63** was in hand, the selective tosylation of primary hydroxyl group was carried out followed by substitution of tosyl group with NaCN to give **64**. The hydrolysis of nitrile group with NaOH afforded the ester **65** as shown in **Scheme 11**.



Scheme 11

Bandichhor *et al.* (*Chem. Asian J.* **2020**, *15*, 1605-1608)[19].

Recently one more synthesis also started from 2,4,5-trifluorobenzaldehyde **58** in which a Wittig reagent **67** prepared from malic anhydride was used . The reaction between this Wittig and aldehyde **58** provided monoester itaconic acid derivative **68**. Use of commercially available ligand DuPhos and Rh catalysed asymmetric hydrogenation afforded the highest conversion (>99%) and enantioselectivity (99%) for the hydrogenated product **69**. Subsequently, ester **69** was converted to amide **70** by using $CaCl_2$ and ammonia in MeOH. Various reaction conditions were tried for Hoffmann rearrangement of **70** and it was found that PIDA gave the best result to obtain the desired acid **71**.



Scheme 12

2.1.3.Conclusion:

As evidenced by the foregoing discussions, the total synthesis of sitagliptin has received increasingly growing attention in the beginning of 21st century. The present review is an attempt to showcase the current progress in synthesis and methodology developments. Many research groups across the world are trying to develop cheaper, commercial route for the synthesis of sitagliptin. Diabetes patients are increasing day by day all over the world that shows the need to do more research and development in this field.

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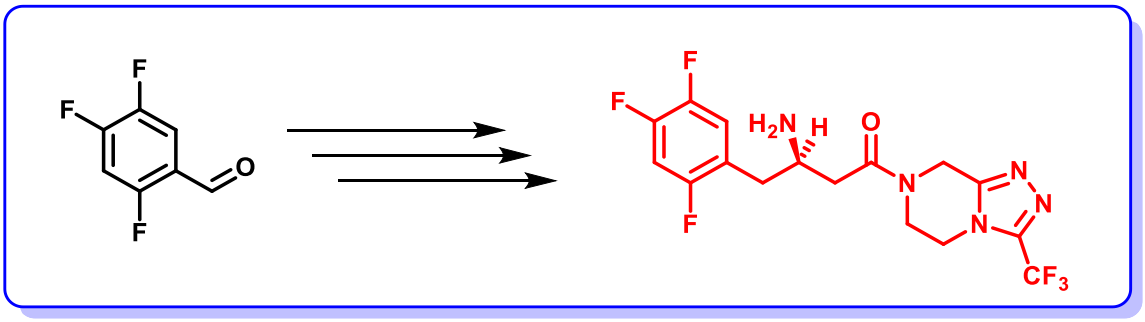
Chapter 2: Total Synthesis of Antidiabetic Drug Sitagliptin

Chapter-2
Section-2

"Synthetic Studies towards Sitagliptin"



2.2.1. ABSTRACT:

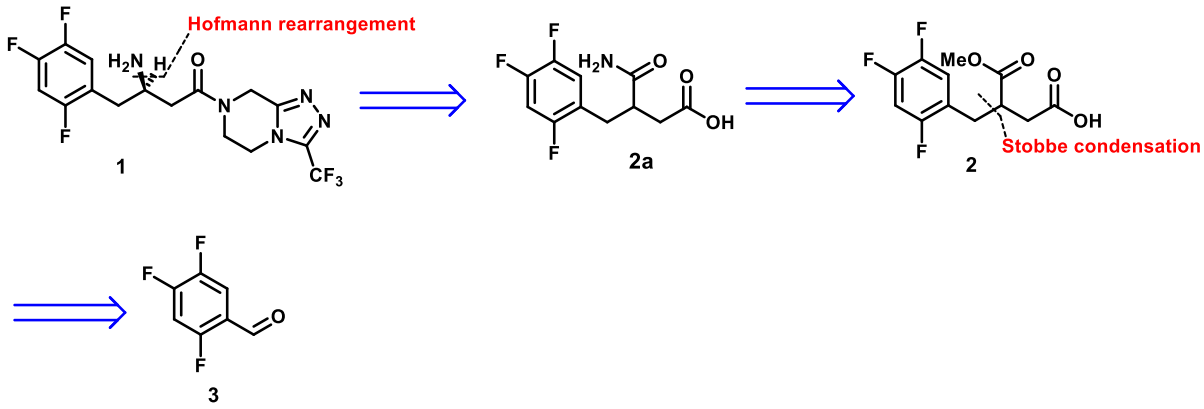
Since its launch in 2006 by Merck, sitagliptin phosphate monohydrate, the first DPP-4 inhibitor, has been one of the best-selling orally active and safe agents for the treatment of T2DM (type 2 diabetes mellitus) [1-2].

Sitagliptin belongs to gliptins family in which there are 17 gliptin compounds, and out of these eight gliptins such as sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, teneligliptin, anagliptin and gemigliptin are under clinical trial for T2DM. There are so many syntheses reported for racemic and chiral sitagliptin.

In the last few decades, a variety of chiral amino acids were made from hemiacetals through catalytic tandem aza-Michael/hemiacetal reaction, using organocatalyst in high yield and enantioselectivity. As part of developing efficient and practical access to sitagliptin phosphate monohydrate, many synthetic routes are reported to make sitagliptin phosphate monohydrate by means of chiral hemiacetal as the key intermediate[3-7].

2.2.2. Present Work:

Retrosynthetic analysis:



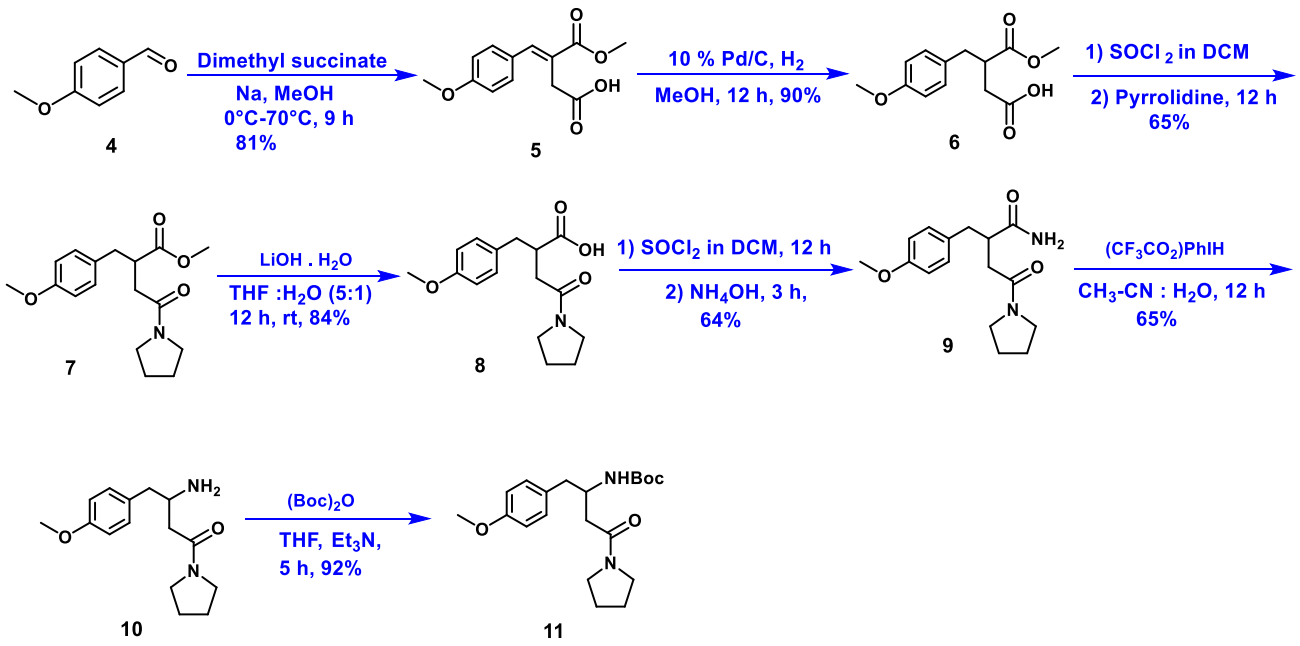
Scheme 1: Retrosynthetic Analysis.

The retrosynthetic analysis for sitagliptin **(1)** is shown in scheme 1. It was thought that amine functionality of sitagliptin could be established by Hofmann rearrangement making use of ester present in intermediate **2**. Conversion of amino acid **2a** to sitagliptin **(1)** is known in the

literature. Compound **2** could be obtained from 2,4,5-trifluorobenzadehyde **(3)** using C-C coupling involving Stobbe condensation. Due to higher price and difficulty in availability of 2,4,5-trifluorobenzaldehyde, it was thought that to first establish synthetic chemistry by using model redaction on *para*-hydroxy benzaldehyde.

2.2.3 Model synthesis of sitagliptin, results and discussion:

Synthesis of model sitagliptin **10** began with the Stobbe condensation using commercially available *para*-hydroxy benzaldehyde as the starting material **(Scheme 2)**. *para*-Hydroxy benzaldehyde **(4)** was treated with dimethyl succinate in the presence of *in situ* generated sodium methoxide by using sodium metal and ice cooled methanol under an nitrogen atmosphere to obtain monoester acid compound **5** in 81% yield. In the ^{1}H-NMR spectrum of compound **5**, peaks at δ 11.32 (br s, 1H), 7.86 (s, 1H), corresponding to acid and olefin protons and distinct peaks at δ 3.80 (s, 3H), 3.82 (s, 3H), for O-C$\underline{H}_3$ protons of ester and aromatic ether and singlet at 3.61 (s, 2H) for -C$\underline{H}_2$ indicated the formation of the product. Also in the ^{13}C-NMR spectrum, peaks at δ 176.89 and 167.72 corresponding to ester and a keto carbonyls were observed.



Scheme. 2 Model synthetic route of sitagliptin.

In the next step, compound **5** when subjected to 10% Pd/C in methanol for 12 hour, underwent hydrogenation to give compound **6**. The formation of product **6** was confirmed by the disappearance of singlet δ 3.61 (s, 2H) for allylic -C<u>H</u>$_2$ group and appearance of peaks at δ 3.01 - 2.93 (m, 1H), 2.76 - 2.61 (m, 2H) and 2.48 - 2.38 (m, 1H) appearance. The peak observed at 275.0890 $[M + Na]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{13}H_{16}O_5$ of compound **6**.

The next aim was the synthesis of amide ester **7** by carrying out the acid-amine coupling reaction. The compound **6** was treated with thionyl chloride and pyrrolidine in CH_2Cl_2 to convert acid to amide compound **7** in 65% yield. Structure of amide was confirmed by ^{1}H-NMR spectrum where peaks at δ 3.49 - 3.33 (m, 4H), 1.97 - 1.74 (m, 4H) were assigned to pyrrolidine ring and the absence of peak at 11.32 (br s, 1H) indicated that the acid was converted to amide.

In the next step, the ester group in **7** was selectively hydrolyzed using 3 eq. of LiOH in THF: H_2O (5:1), for 12 hour at room temperature to provide the acid- amide compound **8** in 84 % yield. Its ^{1}H-NMR showed absence of peak at δ 3.65 (s, 3H), which indicated the hydrolysis of ester. Peak corresponding to -COO<u>H</u>, proton was observed at δ 9.44 (br s, 1H). Also in the ^{13}C-NMR spectrum, peaks were observed at δ 174.9 and 173.5 corresponding to acid and amide carbon. The peak observed at 292.1543 $[M + H]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{16}H_{21}NO_4$ of compound **8**.

For the synthesis of di-amide **9** from acid-amide **8**, it was treated with thionyl chloride and pyrrolidine in CH_2Cl_2. The amidation reaction of monoacid-amide **8** with NH_4OH as a nucleophile proved extremely challenging. Formation of di-amide product **9** was confirmed by absence of peak at δ 9.44 (br s, 1H) and presence of peaks at 6.45 (br s, 1H) 5.74 (br s, 1H) corresponding to amide. Also in the ^{13}C-NMR spectrum, two peak were observed at δ 177.8 and 170.0, corresponding to di-amide. The IR spectrum showed the band at 2925 and 2862 cm^{-1} for ester and amide groups. The peak observed at 291.1703$[M + H]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{16}H_{22}N_2O_3$ of the di-amide.

Amide **9** was treated with 1.5 eq. of [I,I-bis(trifluoroacetoxy) iodo]benzene,in CH_3-CN: H_2O providing 65% yield of the desired amine **10**. Isolation and purification of amine compound was difficult so this amine was treated with Boc-anhydride to afford Boc protected amine

compound **11**. ^{1}H-NMR revealed peak at δ 1.41 (s, 9H) corresponding to Boc protons and δ 5.89 (br s, 1H) corresponding to the –NH-Boc proton. The presence of a peak at δ 28.10 for –$\underline{C}H_3$ (tert-butyl group) in the ^{13}C-NMR spectrum indicated the formation of the product. The IR spectrum showed the 3530 cm^{-1} for N-H stretching frequency of amine band in spectrum. The peak observed at 363.2278 $[M + H]^+$ in the HRMS spectrum further confirmed the molecular formula $C_{20}H_{30}N_2O_4$ of the compound **9**.

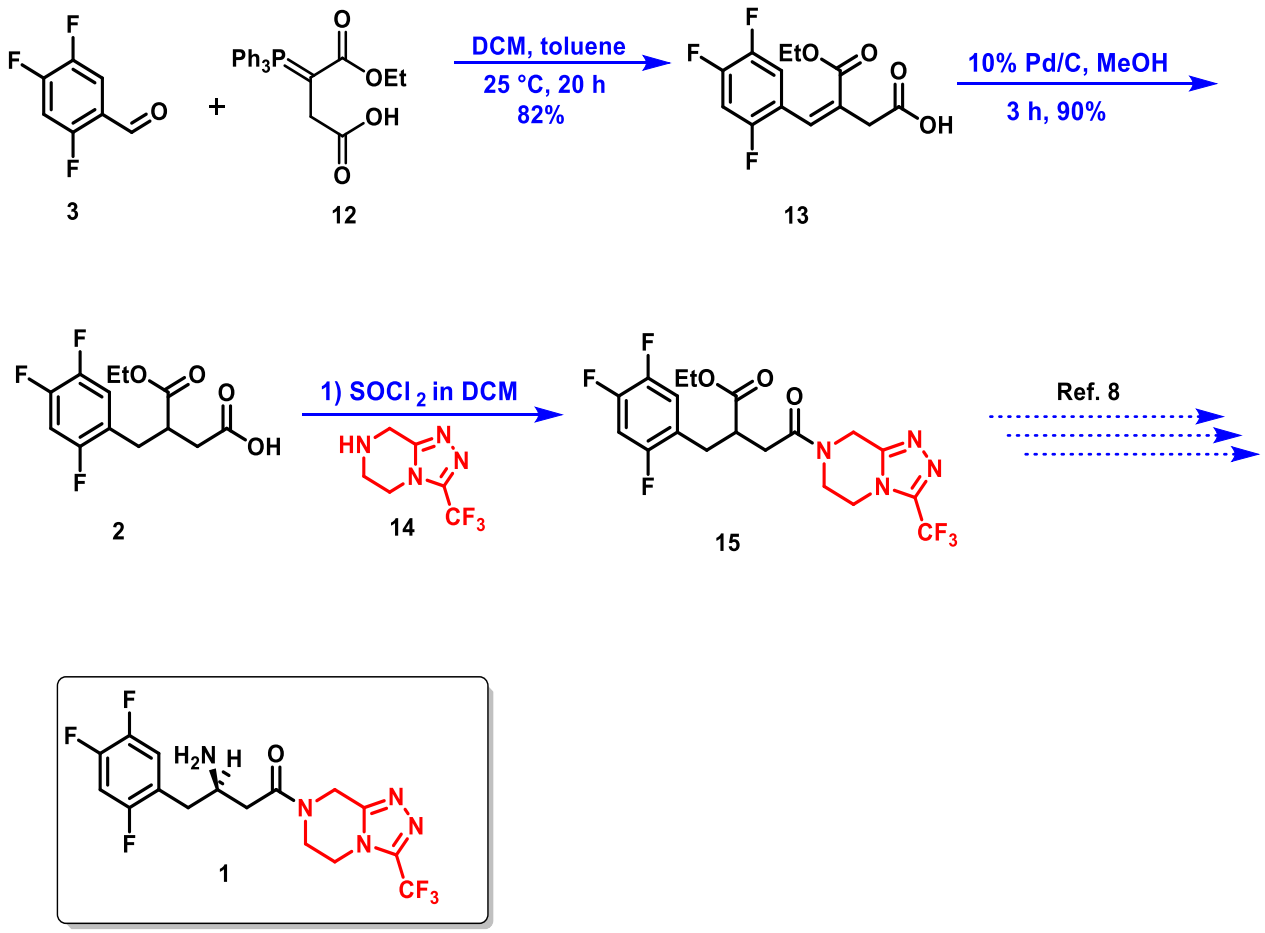
2.2.4. Total synthesis of sitagliptin, results and discussion:

Synthesis of sitagliptin began with the synthesis of Wittig reagent **12**, following a known protocol from malic anhydride **(Scheme 3)**. Ensuing prepared Wittig reagent **12** on reaction with 2,4,5-trifluorobenzadehyde in mixture of DCM and toluene with stirring for 20 h provided monoester itaconic acid derivative **13** in 82% yield. In ^{1}H-NMR spectrum of compound **13** peak at δ 10.86 (br s, 1H) corresponding to acidic proton and distinct peak at δ 4.31 (q, *J* = 7.1 Hz, 2H) for allylic proton -C=C-C$\underline{H}_2$ indicated the formation of the product. Also in the ^{13}C-NMR spectrum, appearance of peaks at δ 176.4 and 166.0 indicated presence of monoester itaconic acid and appearance of acid group bands in IR spectrum at 2986 and 1715 cm^{-1} further confirmed the product formation. The HRMS, spectrum showed a peak at 311.0502 $[M + H]^+$ corresponding to the formula $C_{13}H_{11}F_3O_4$ of the product.

The olefin **13** was then hydrogenated using 10% Pd/C in methanol for 3 hour, underwent double bond reduction. The formation of product **13** was confirmed by the disappearance of singlet δ 3.48 (s, 2 H) for allylic -C$\underline{H}_2$ group and δ 3.09 (m, 1 H), 2.98 (dd, *J* = 6.1, 13.3 Hz, 1 H), 2.84 (dd, *J* = 5.9, 13.3 Hz, 2 H) peak show reduction of double bond. In the ^{13}C-NMR spectrum, δ 41.5, 30.3, 14.1 peak corresponding to aliphatic regain present in the compound and HRMS, which showed a peak at 311.0657corresponding to the formula $C_{13}H_{11}F_3O_4$ $[M + H]^+$ of the product.

The coupling of **2** with triazolopiperazine **14** using $SOCl_2$ afforded **15**. Characterization of compound **7** under progress **(Scheme. 2).**

While this work was in progress, Bandichhor *et al.*[9] reported similar strategy for the synthesis of sitagliptin so the further in work in the present strategy was stopped at this stage.



Scheme 3. Synthetic studies towards sitagliptin.

2.2.5. Conclusion:

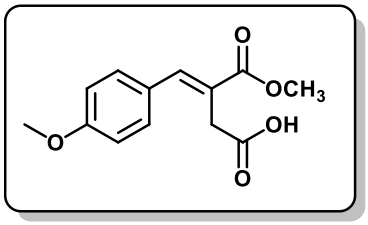
In summary, model strategy for total synthetic of for sitagliptin was established starting from *para*-hydroxy benzaldehyde in 6 steps by using simple scalable chemistry. A $SOCl_2$ catalyzed two time C-N coupling reaction and using PIFA reaction condition for Hofmann rearrangement to convert amide to amine. 16% overall yield.

After compaction of model study, sitagliptin synthesis was started with 2,4,5-trifluorobenzadehyde a very common starting material for the synthesis of sitagliptin. While two steps were established in this synthesis, one paper appeared in literature (*Chem. Asian J.* **2020**, *15*, 1605-1608) with same strategy and then this work had to be stopped at this stage

2.2.6. Experimental Section

Experimental Procedures and Characterization Data

3-(Methoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid (5)



Sodium methoxide was generated by *in situ* adding sodium (19.5 g, 0.85 g atom) carefully to ice cooled methanol (500 ml). When sodium was dissolved, dimethyl succinate (166 ml, 1.0 mol) in methanol (50 ml) was added to the solution. 4-Methoxybenzaldehyde **(4)** (68.1 g, 0.5 mol) in methanol (150 ml) was added dropwise to the solution under an argon atmosphere over 1.5 h under reflux (100 ˚C), and the reaction mixture was refluxed for 5 h. Methanol was removed under reduced pressure and residue was quenched with conc. HCl, cold water was added to the reaction mixture and the mixture was extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with H_2O (80 mL), and extracted with sat. aq. $NaHCO_3$ (3 × 200 mL). The aqueous layer was acidified with conc. HCl, and the mixture was extracted with ethyl acetate (2 × 200 mL) and combined organic layer was washed with brine (200 ml), and dried over anhydrous Na_2SO_4, and filtered. Organic solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel (Pte ether: ethyl acetate 40:60) to afford the acid ester **5** in 28.5 g, 81% yield.

Rf: 0.3 (EtOAc–PE=60:40);

Yield: 81%;

M. p.: 117–120 °C;

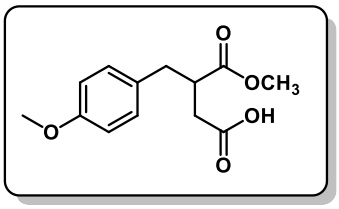
IR ($CHCl_3$): ν_{max} 3008**,** (2CO) 2944, 1705, 1604, 1607, 1511, 1436 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.32 (br s, 1H), 7.86 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 3.61 (s, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.89, 167.72, 159.89, 141.87, 130.47 (2C), 126.59, 122.51, 113.72 (2C), 54.78, 51.82, 33.1;

HRMS (ESI) m/z calcd for $C_{13}H_{15}NaO_5$ $[M + Na]^+$: 273.0733; found: 273.073.

4-Methoxy-3-(4-methoxybenzyl)-4-oxobutanoic acid (6)



To the alkene compound **5** (1 g, 6.94 mmol) in methanol (20 ml), was added catalytic amount of palladium hydroxide (10 mg, 20 % over carbon). The resulting reaction mixture was kept on a under a hydrogen atmosphere for 7 h at room temperature. The Pd-C was filtered off and the filtrate was concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (pet. ether – ethyl acetate 50: 50) to afford colouless oil, 0.900 g, 90 % yield.

Rf: 0.3 (EtOAc–PE=60:40);

Yield: 90%;

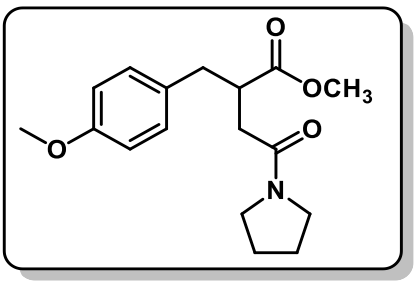
IR ($CHCl_3$): ν_{max} 2951, 2878, (2CO) 1707, 1632, 1510, 1436 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.25 (br. s., 1 H), 7.06 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 3.77 (s, 3 H), 3.65 (s, 3 H), 3.06 (d, J = 5.1 Hz, 1 H), 3.01 - 2.93 (d, 1 H), 2.76 - 2.61 (m, 2 H), 2.48 - 2.38 (m, 1 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.6, 174.6, 158.2, 129.8 (3C), 113.8 (2C), 55.0, 51.8, 42.9, 36.6, 34.7;

HRMS (ESI) m/z calcd for $C_{13}H_{16}NaO_5$ $[M + Na]^+$: 275.0886; found: 275.0890.

Methyl 2-(4-methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanoate (7)



Acid **6** (5 g, 19.841 mmol) was added into DCM (30 mL). Under ice-cooling with stirring, N,N-dimethylformamide (0.1 ml) and thionyl chloride (1.609 mL, 21.825 mmol) were added. Under ice-cooling, the mixture was stirred for 5 minutes and stirred at room temperature for 4 hours. Under water cooling with stirring, pyrrolidine was added dropwise at 0 ˚C and further stirred for 3 hours at room temperature. Reaction mixture was quenched first by using ice followed by careful addition of sat. $NaHCO_3$ solution. Reaction mixture was allowed to separate in separating funnel, organic layer was separated and aqueous layer was again extracted twice using ethyl acetate (100 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to provide sticky dark brown liquid. Purification by flash chromatography (pet ether: ethyl acetate 80:20) furnished 4 g, 65% yield of pure product amide **7** as a colourless dense liquid.

Rf: 0.3 (EtOAc–PE=30:70);

Yield: 65%;

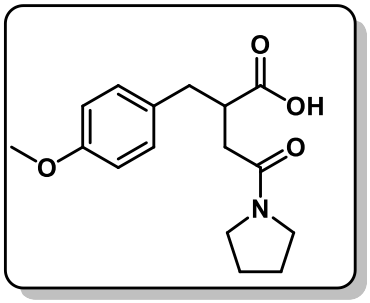
IR ($CHCl_3$): ν_{max} 2948, (2CO) 1732, 1636, 1512, 1441 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, *J* = 8.6 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 3.77 (s, 3 H), 3.65 (s, 3 H), 3.48 - 3.32 (m, 3 H), 3.31 - 3.16 (m, 2 H), 2.96 (dd, *J* = 6.6, 13.7 Hz, 1 H), 2.73 (dd, *J* = 8.3, 13.8 Hz, 1 H), 2.68 - 2.54 (m, 1 H), 2.28 (dd, *J* = 4.8, 16.3 Hz, 1 H), 1.99 - 1.74 (m, 4 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4, 169.0, 157.9, 130.2, 129.5 (2C), 113.5, 113.4, 54.8, 51.4, 46.1, 45.4, 42.8, 36.7, 35.1, 25.6, 24.0;

HRMS (ESI) m/z calcd for $C_{17}H_{24}NO_4$ $[M + H]^+$: 306.1702; found: 306.1700.

2-(4-Methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanoic acid (8)



A solution of LiOH (0.825 g, 19.672 mmol) in water (15 mL) was added to a solution of 2-(4-methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanoic acid (2 g, 6.557 mmol) in THF (60 mL) and the reaction was stirred for 2 hours at room temperature. The mixture was evaporated under reduced pressure, the residue was taken up in water (60 mL) and acidified with 2 M HCl with stirring. The precipitate formed was separated off and dried to provide 1.6 g, 84% yield compound **8**.

Rf: 0.3 (EtOAc–PE=60:40);

Yield: 84%;

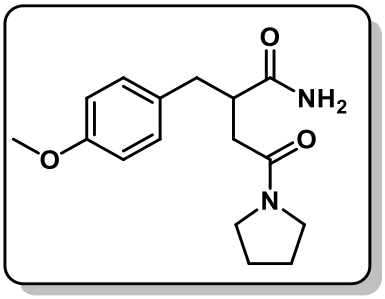
IR ($CHCl_3$): ν_{max} 3825, 3600, 2928, (2CO) 1715, 1617, 1517, 1436 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (br s, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 3.49 - 3.38 (m, 2H), 3.33 (d, *J* = 5.9 Hz, 1H), 3.16 - 3.05 (m, 1H), 2.92 - 2.81 (m, 2H), 2.80 - 2.67 (m, 2H), 2.59 - 2.49 (m, 1H), 1.77 (td, *J* = 6.3, 12.6 Hz, 2H), 1.70 - 1.54 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.9, 173.5, 158.3, 130.5, 129.9 (2C), 113.9, 113.7, 55.2, 46.7, 45.9, 42.1, 37.5, 36.6, 25.7, 24.2;

HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_4$ $[M + H]^+$: 292.1540; found: 292.1543.

2-(4-Methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanamide (9)



Acid **8** (5 g, 19.841 mmol) was added into DCM (30 ml). Under ice-cooling with stirring, N,N-dimethylformamide (0.1 ml) and thionyl chloride (1.609 ml, 21.825 mmol) were also added. Under ice-cooling, the mixture was stirred for 5 minutes and at room temperature stirred for 4 hours. Under water cooling with stirring, aq ammonia, 30% was added dropwise at 0 ˚C and further stirred for 3 hours at room temperature. Reaction mixture was quenched first by using ice followed by careful addition of sat. $NaHCO_3$ solution. Reaction mixture was allowed to separate in separating funnel, organic layer was separated and aqueous layer was again extracted twice using ethyl acetate (100 mL). The collected organic, were dried over anhydrous Na_2SO_4, filtered and concentrated to provide sticky dark brown liquid. Purification by flash chromatography (pet ether: ethyl acetate 70:30) furnished 3.2 g, 64 % of pure amide **9** as a colourless dense liquid.

Rf: 0.3 (EtOAc–PE=40:60);

Yield: 64%;

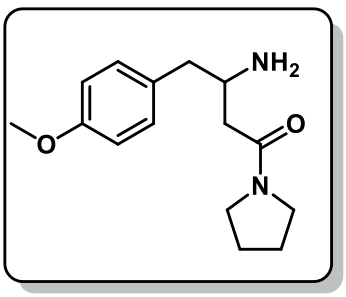
IR ($CHCl_3$): ν_{max} 2925, 2862, (2CO) 1704, 1613, 1507, 1476 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (*J* = 8.5 Hz,, 2 H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.45 (br s, 1 H), 5.74 (br s, 1 H), 3.77 (s, 3 H), 3.49 - 3.33 (m, 2H), 3.32 - 3.04 (m, 3H), 2.96 (dd, *J* = 7.7, 13.7 Hz, 1H), 2.76 - 2.46 (m, 2H), 2.32 (dd, *J* = 3.6, 16.5 Hz, 1H), 1.98 - 1.70 (m, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.8, 170.0, 158.2, 131.0, 130.6 (2C), 113.8 (2C), 55.1, 46.5, 45.7, 43.7, 37.2, 36.5, 25.8, 24.2;

HRMS (ESI) m/z calcd for $C_{16}H_{23}N_2O_3$ $[M + H]^+$: 291.1707; found: 291.1703.

3-Amino-4-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)butan-1-one (10)



A 50 mL, round-bottomed flask was equipped with a magnetic stirring bar and was covered with aluminium foil. To the flask was added a solution of [I,I-bis(trifluoroacetoxy) iodo]benzene (1.1 g, 2.58 mmol) in 6 mL of acetonitrile, and the resulting solution is diluted with (6 mL) of distilled deionized water. 2-(4-Methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanamide (0.500 g, 1.71 mmol) was added; the amide quickly dissolved. Stirring was continued for 4 hr, and the acetonitrile was removed at reduced pressure on a rotary evaporator. The aqueous layer was

extracted using excess ethyl acetate (3 x 50 mL) and the combined organic solvent was dried over anhydrous Na_2SO_4 and filtered. Removal of the organic solvent under reduced pressure furnished a residue. Purification of the residue by flash chromatography over silica gel (DCM: methanol 92:08) afforded 0.296 g, 65% yield amine **10**.

Rf: 0.3 (Methanol–DCM=15:85);

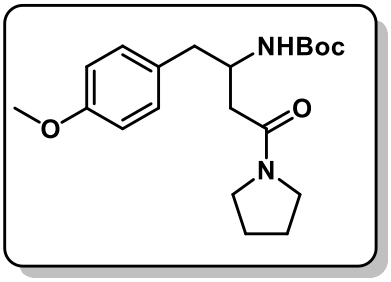
Yield: 65%;

IR ($CHCl_3$): ν_{max} 3461, 2922, 1714, 1614, 1449, 1260 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (dd, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.54 - 3.32 (m, 3H), 3.23 - 3.00 (m, 3H), 3.00 - 2.90 (m, 1H), 2.85 - 2.61 (m, 5H), 1.97 - 1.55 (m, 4 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.8, 158.9, 130.4 (3C), 114.3 (2C), 114.2, 55.6, 47.2, 46.5, 43.7, 37.4, 26.1, 24.4;

***tert*-Butyl (1-(4-methoxyphenyl)-4-oxo-4-(pyrrolidin-1-yl)butan-2-yl)carbamate (11)**



To the amine **10 (**0.100 g, 0.381 mmol) in THF was added triethylamine (0.160 mL, 1.1 mmol) followed by Boc anhydride (0.131 mL, 0.572 mmol) and the reaction mixture was stirred for 5 h. Water (30 mL) was added to reaction mixture and extracted using ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and was filtered. The organic layer was concentrated under reduced pressure and the reaction mass was purified by flash chromatography using silica gel (pet ether- ethyl acetate 90:10) to afford 0.127 g, 92% product **11**.

Rf: 0.3 (Ethyl acetate – pet. ether=60:40);

Yield: 92%;

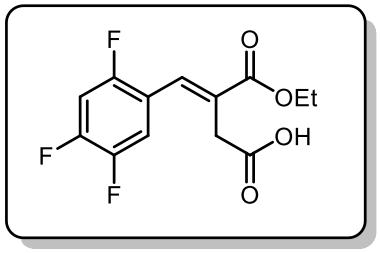
IR ($CHCl_3$): ν_{max} 3733, 3530, 2966, (2CO) 1704, 1627, 1445 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.83 (d, 2H), 5.89 (br s, 1H), 4.13 - 4.01 (m, 1H), 3.79 (s, 3H), 3.56 - 3.39 (m, 2H), 3.25 (td, *J* = 6.5, 10.0 Hz, 1H), 3.19 - 3.10 (m, 1H), 3.06 - 2.93 (m, 1H), 2.82 (dd, *J* = 8.6, 13.6 Hz, 1H), 2.38 (d, *J* = 4.9 Hz, 2H), 1.98 - 1.81 (m, 4H), 1.41 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 157.7, 155.1, 129.8(3C), 113.4(2C), 78.4, 54.9, 49.0, 46.3, 45.2, 38.8, 35.8, 28.1(3C), 25.6, 24.0;

HRMS (ESI) m/z calcd for $C_{20}H_{31}N_2O_4$ $[M + H]^+$: 363.2276; found: 363.2278.

3-(Ethoxycarbonyl)-4-(2,4,5-trifluorophenyl)but-3-enoic acid (13)



To a stirred solution of Wittig reagent **12** (7.120 g, 28.169 mmol) prepared from malic anhydride in toluene (40 mL), a solution of 2,4,5-trifluorobenzadehyde **(3)** (3 ml, . 14.084 mmol) in DCM (15 mL) was added dropwise over 15 min at room temperature under nitrogen atmosphere. The reaction was stirred at room temperature for 16 h. After completion of reaction, the reaction mixture was diluted with EtOAc (60 mL) and extracted with 20% aqueous potassium bicarbonate solution. The organic layer was discarded and aqueous layer was washed with EtOAc (50 mL). The aqueous solution was acidified with 50% aq. HCl at 0 ºC to ~pH 2 and extracted with EtOAc (30 mL × 3). The organic layer was washed with water (50 mL) and brine (30 mL), dried over anhydrous sodium sulphate, filtered and evaporated under vacuum. The residue thus obtained was purified by flash chromatography (pet ether – ethyl acetate 30:70) to afford the compound **13**.4.2g,

Rf : 0.3 (Ethyl acetate – pet ether=60:40);

Yield: 82%;

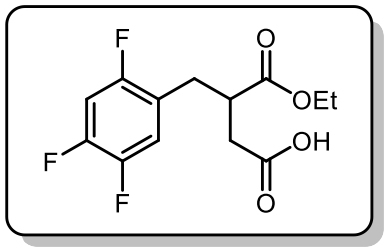
IR ($CHCl_3$): ν_{max} 2986, (2CO) 1715, 1514, 1423, 1159 cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz):δ 10.86 (br. s., 1 H), 7.76 (s, 1 H), 7.24 (dd, *J* = 1.8, 9.9 Hz, 1 H), 7.01 (dd, *J* = 6.6, 9.5 Hz, 1 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 3.48 (s, 2 H), 1.35 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.4, 166.0, 156.5, 148.8, 145.1, 132.8, 128.5, 118.7, 117.3, 105.6, 61.4, 33.4, 13.7;

HRMS (ESI) m/z calcd for $C_{13}H_{11}F_3O_4$ $[M + H]^+$: 311.0505; found: 311.0502.

4-Ethoxy-4-oxo-3-(2,4,5-trifluorobenzyl)butanoic acid (2)



To the alkene compound **13** (1 g, 6.94 mmol) in methanol (20 mL), was added catalyst amount of palladium hydroxide (10 mg, 20 % over carbon). The resulting reaction mixture was kept under a hydrogen atmosphere for 3 h at room temperature at atmospheric pressure. The Pd-C was filtered off and the

filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pet. ether – ethyl acetate 30: 70) afforded colourless oil 0.946 g, 94 % yield.

Rf: 0.3 (Ethyl acetate – pet ether=40:60);

Yield: 94%;

IR ($CHCl_3$): ν_{max} 3066, 2988, 1707, 1638, 1508, 1420 cm^{-1};

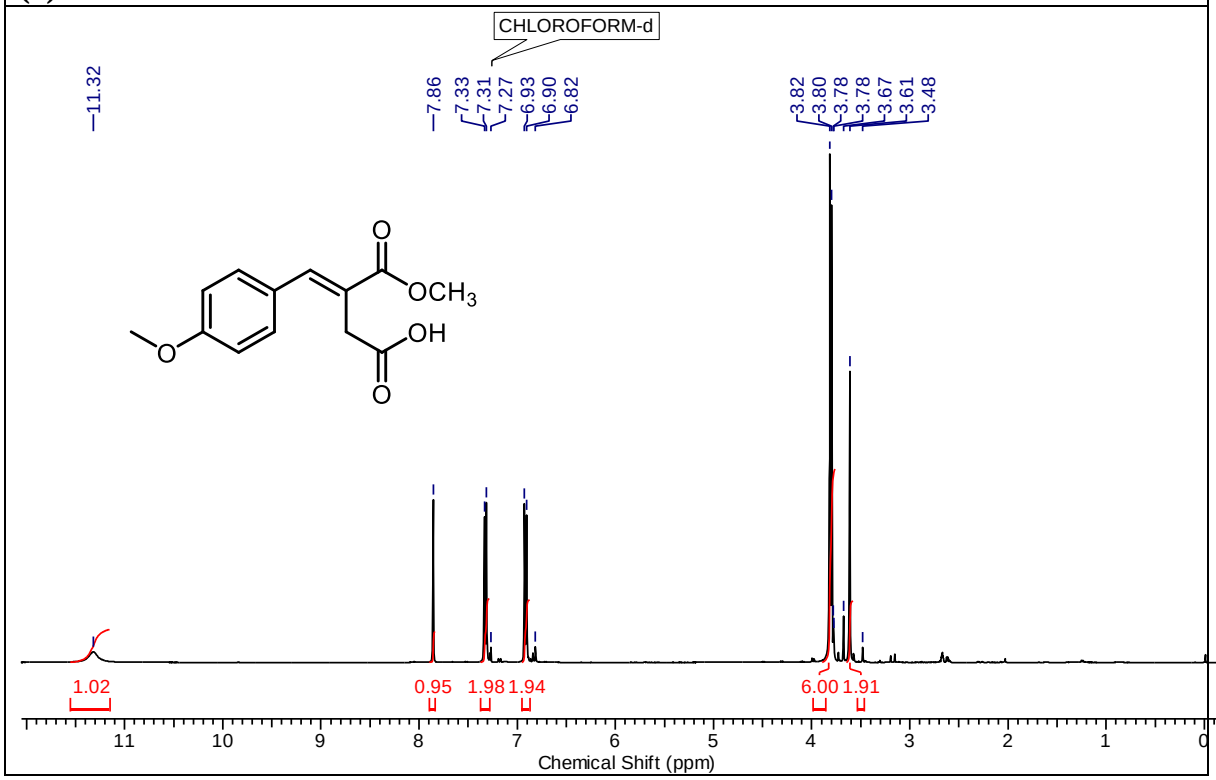
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.45 (br. s., 1 H), 7.08 - 6.97 (m, 1 H), 6.97 - 6.84 (m, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 3.09 (m, 1 H), 2.98 (dd, *J* = 6.1, 13.3 Hz, 1 H), 2.84 (dd, *J* = 5.9, 13.3 Hz, 2 H), 1.19 (t, *J* = 7.1 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 157.4, 154.9, 150.3, 147.9, 145.4, 118.8, 117.5 105.7, 105.5, 105.4, 105.2, 61.1, 41.5, 30.3, 14.1;

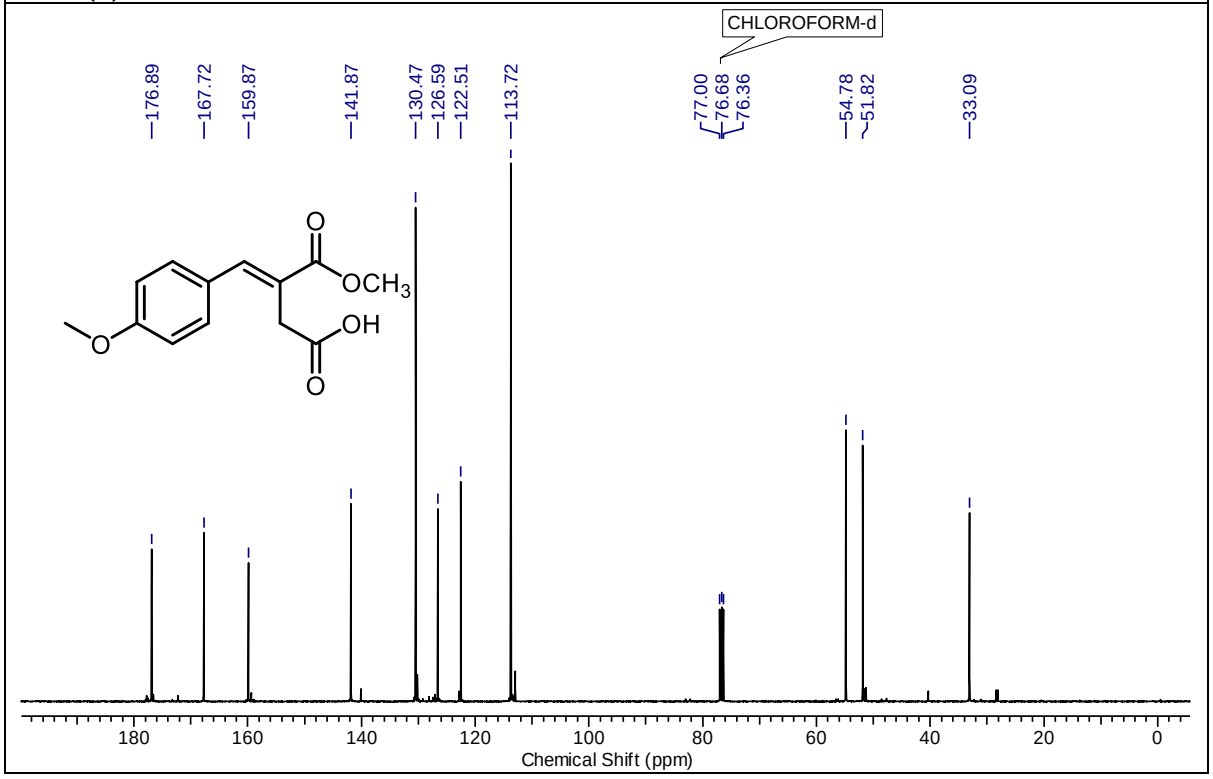
HRMS (ESI) m/z calcd for $C_{13}H_{11}F_3O_4$ $[M + H]^+$: 313.0657; found: 311.0657.

2.2.7. Spectral Data:

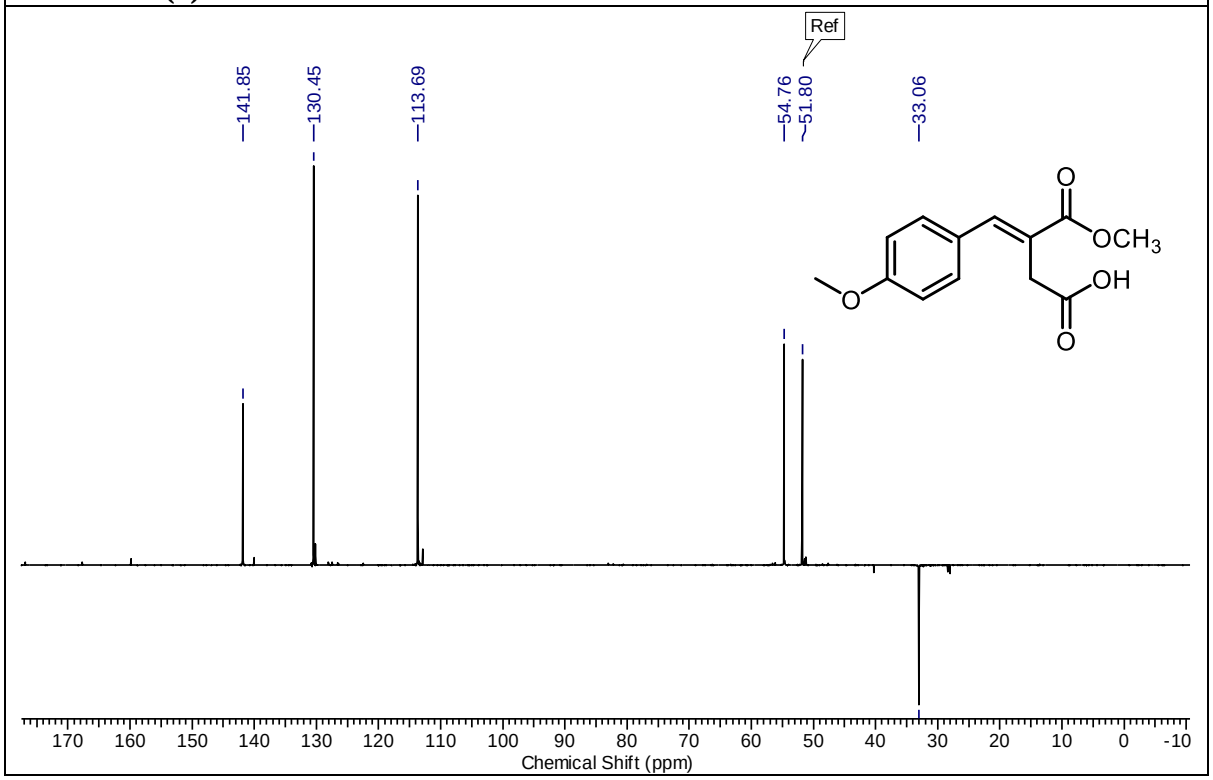
^{1}H-NMR spectrum of (E)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid (5)



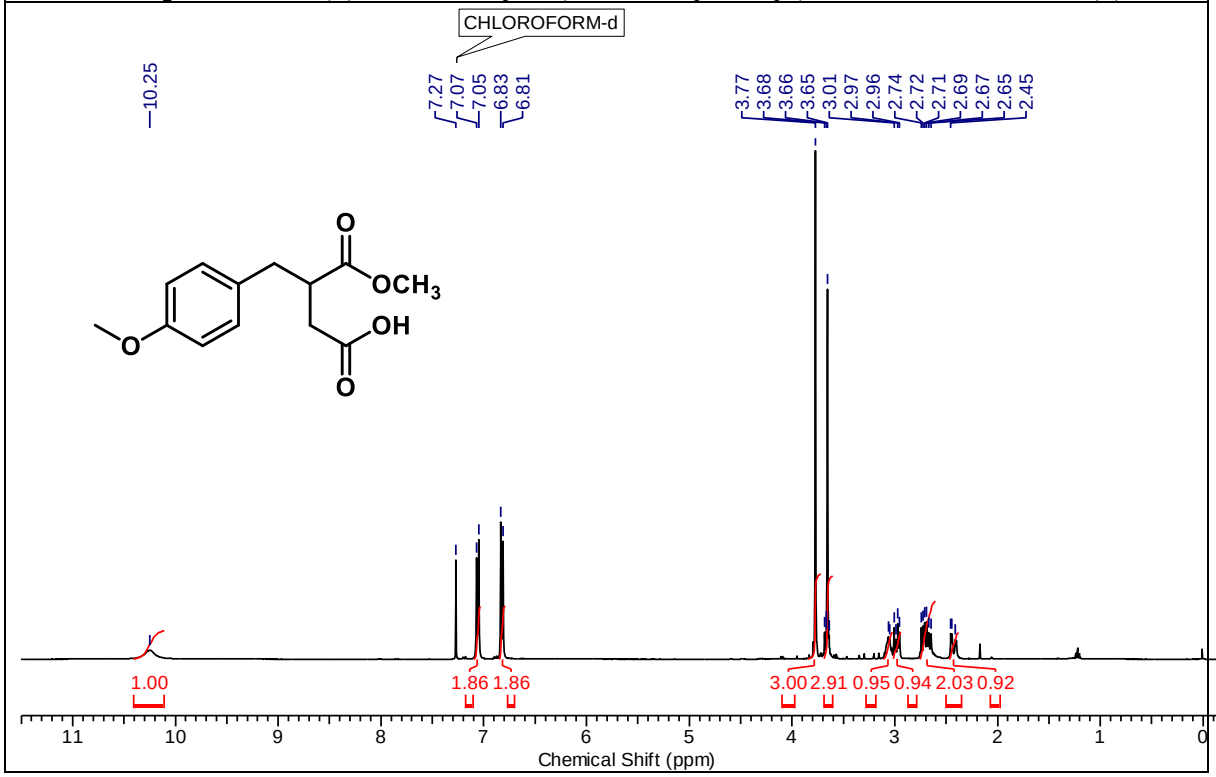
^{13}C-NMR spectrum of (5), (E)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid (5)



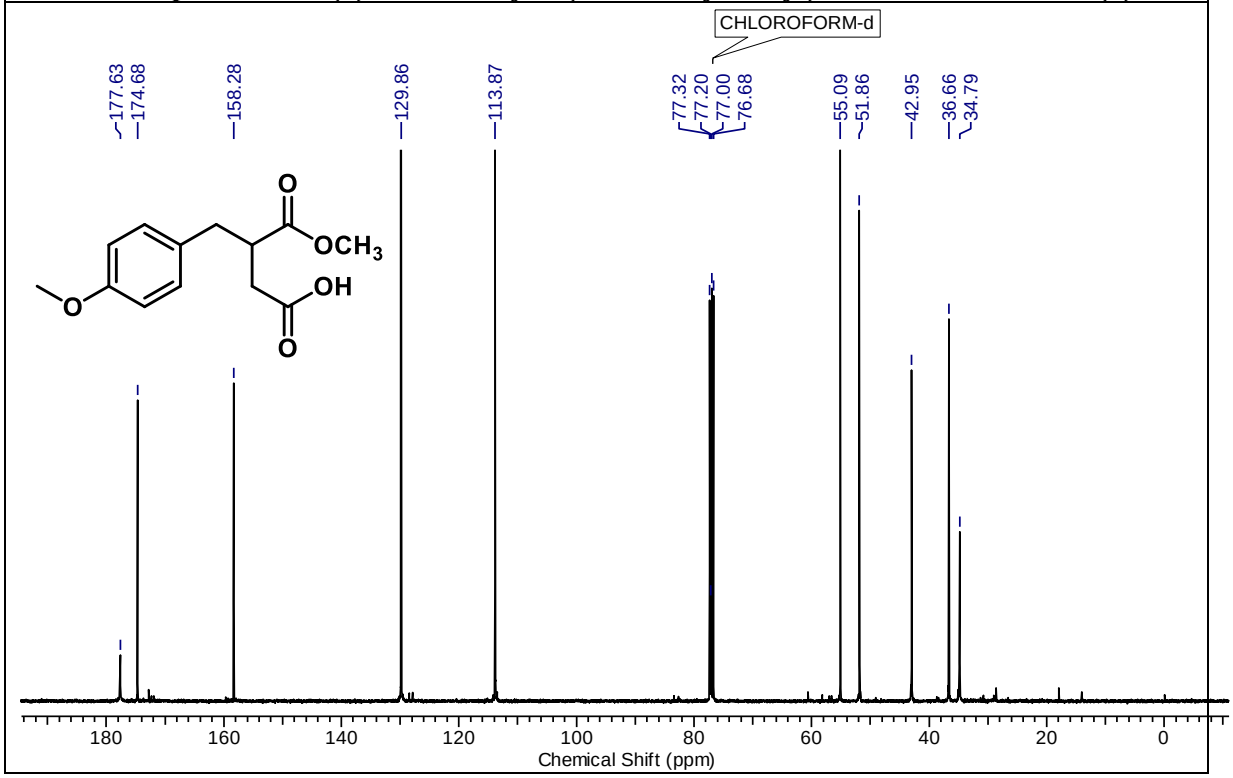
DEPT NMR spectrum of (5), (E)-3-(methoxycarbonyl)-4-(4-methoxyphenyl)but-3-enoic acid (5)



^{1}H-NMR spectrum of (6), 4-methoxy-3-(4-methoxybenzyl)-4-oxobutanoic acid (6)



^{13}C-NMR spectrum of (6), 4-methoxy-3-(4-methoxybenzyl)-4-oxobutanoic acid (6)



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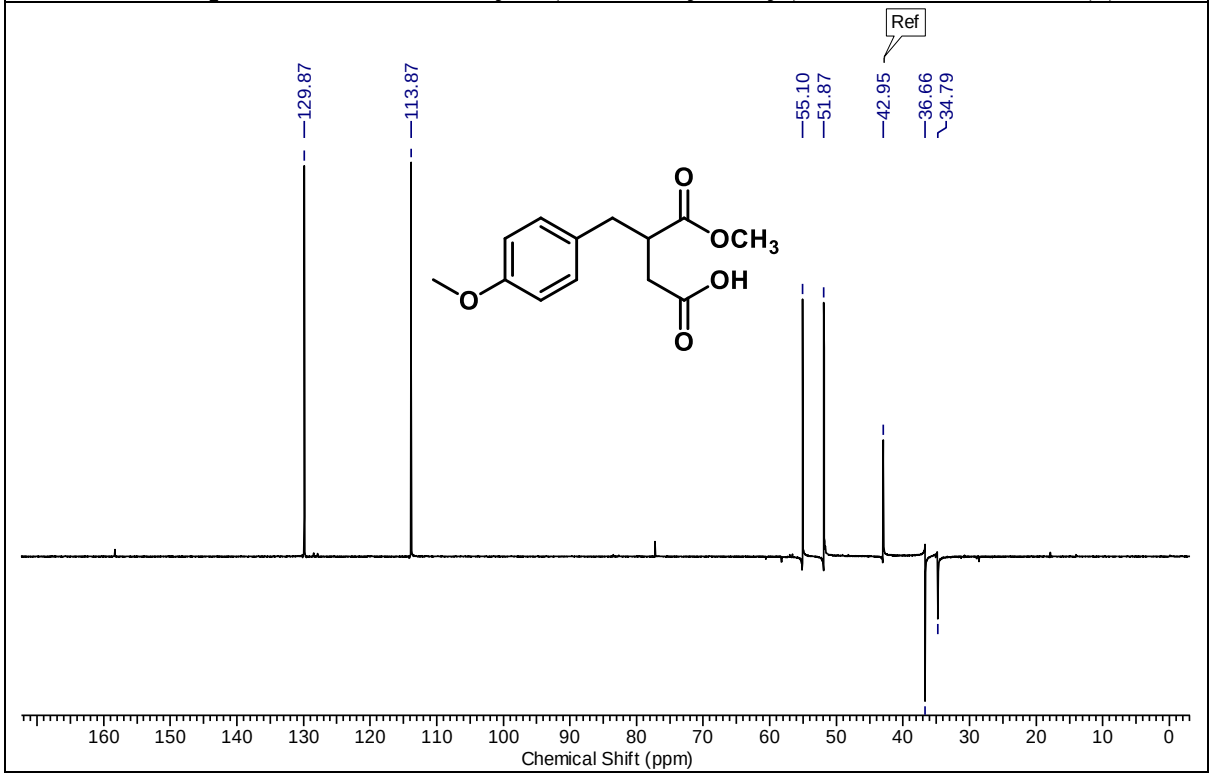
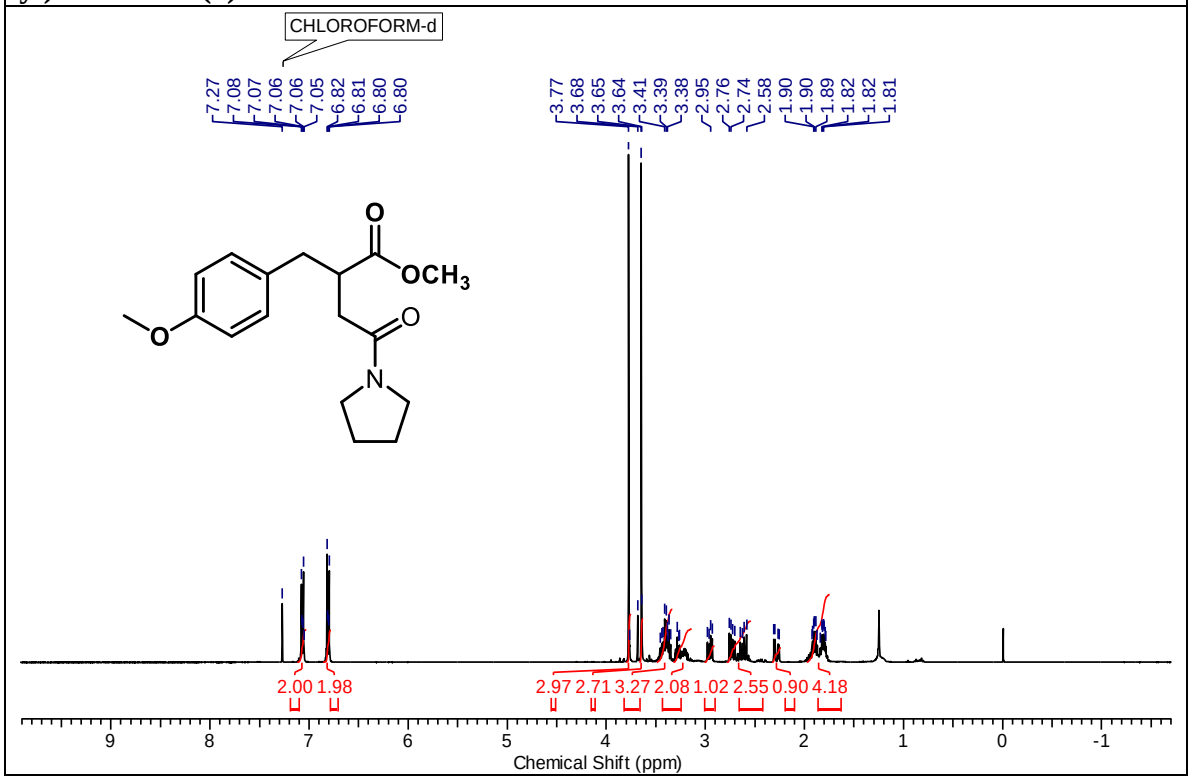


^{1}H-NMR spectrum of methyl 2-(4-methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanoate (7)



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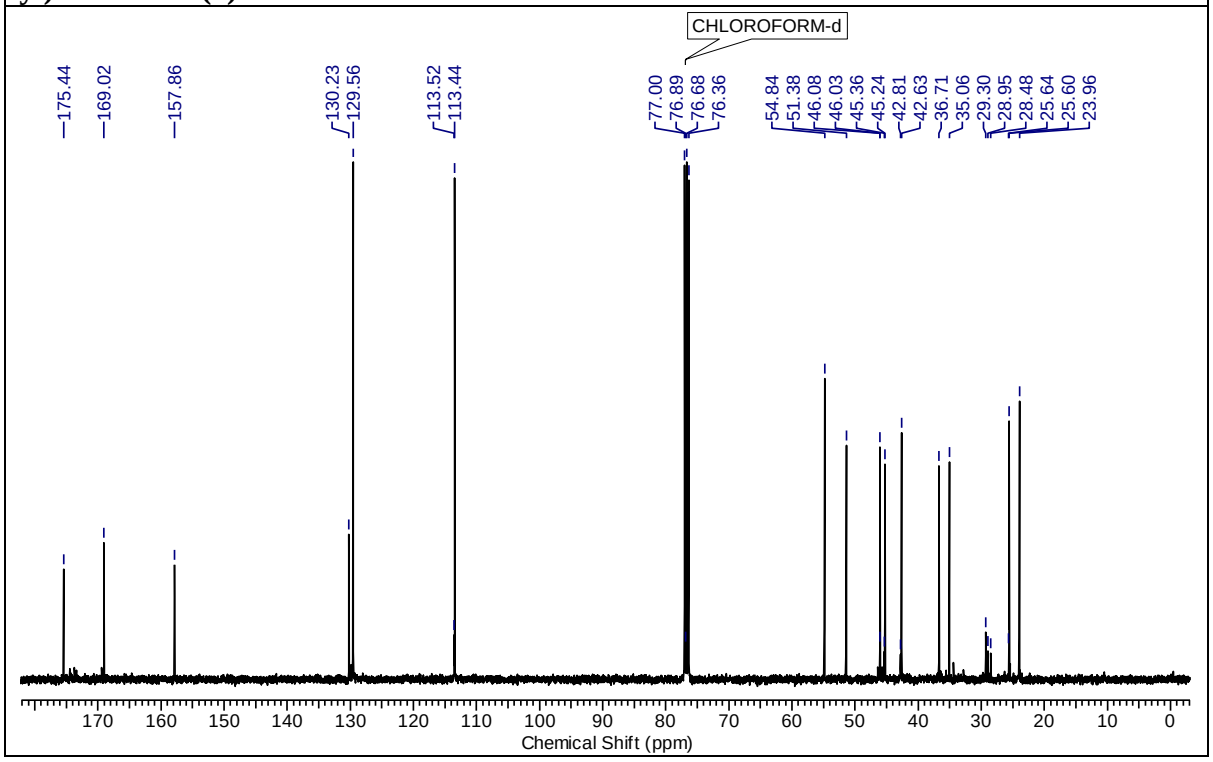

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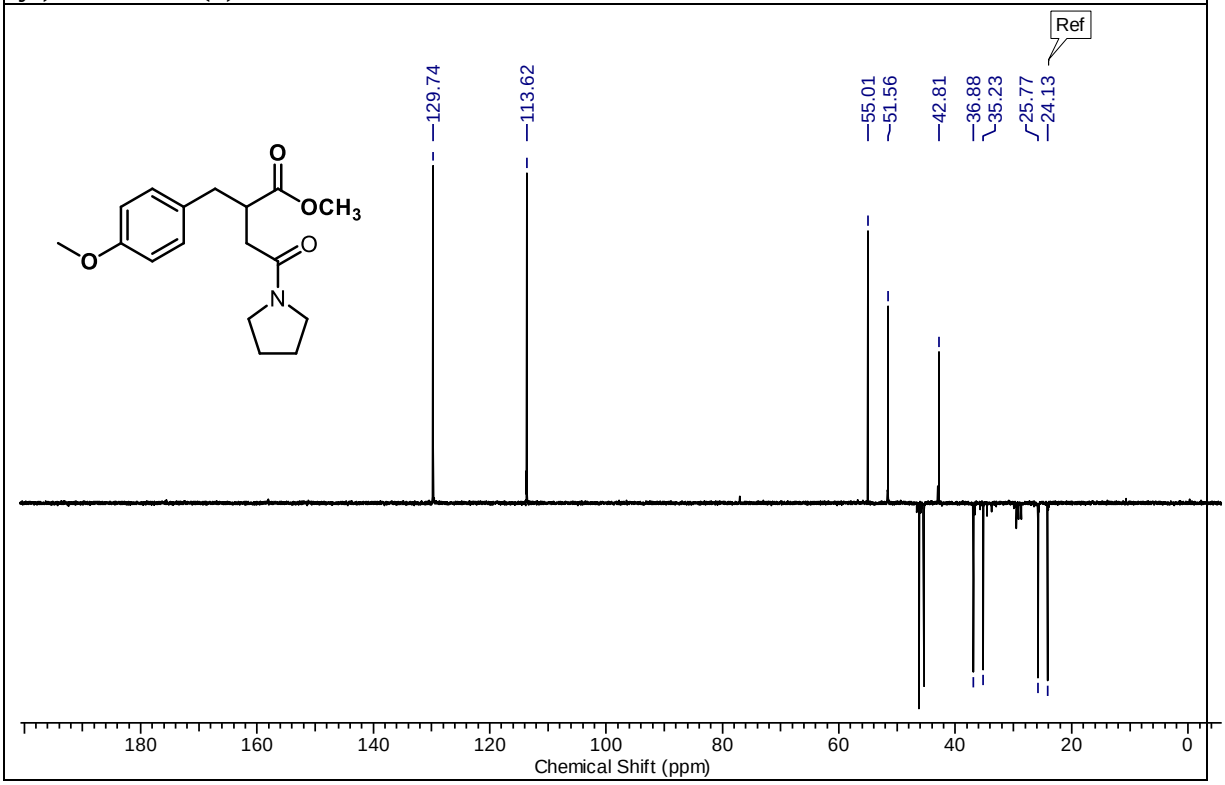

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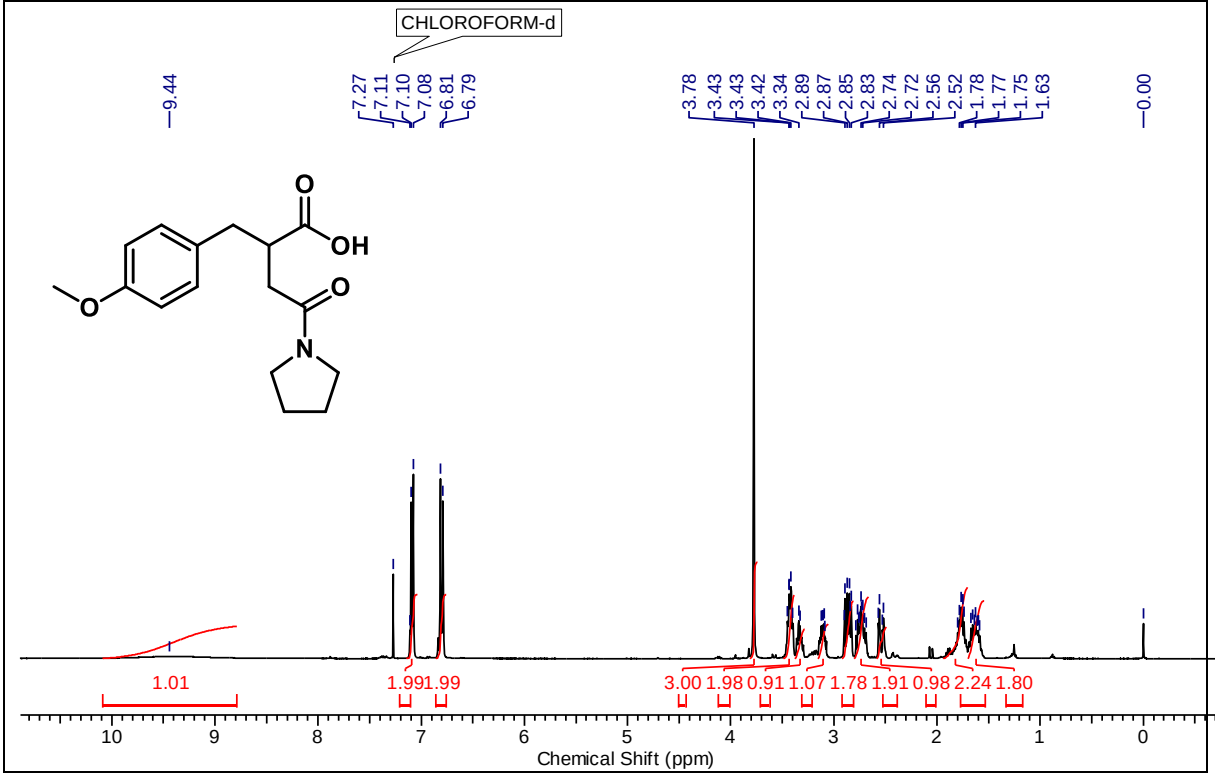

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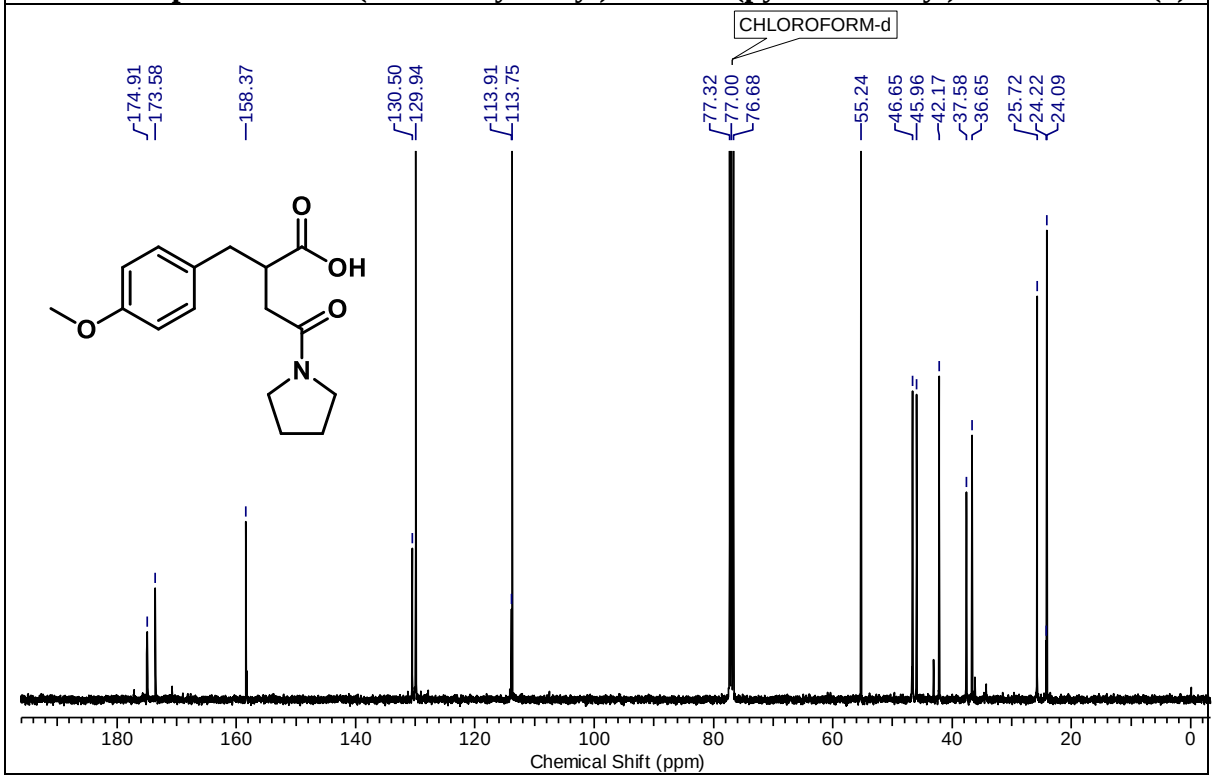
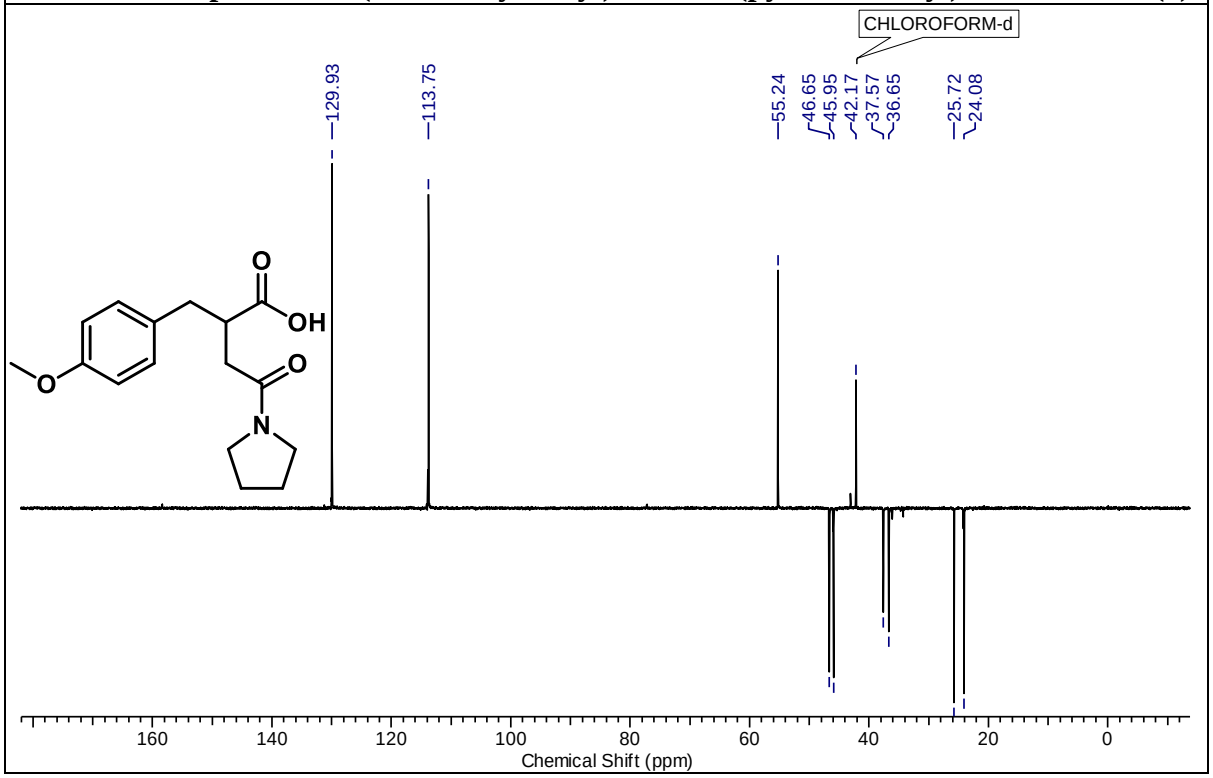


DEPT NMR spectrum 2-(4-methoxybenzyl)-4-oxo-4-(pyrrolidin-1-yl)butanoic acid (8)



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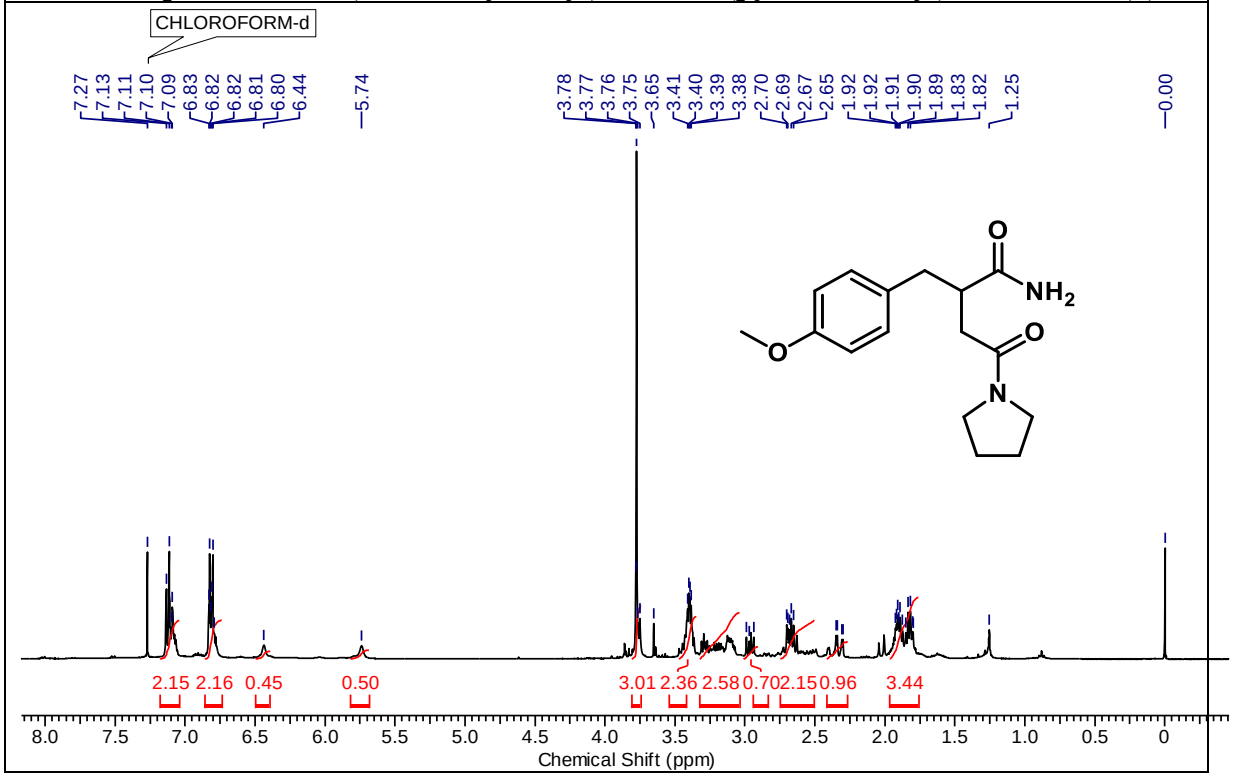

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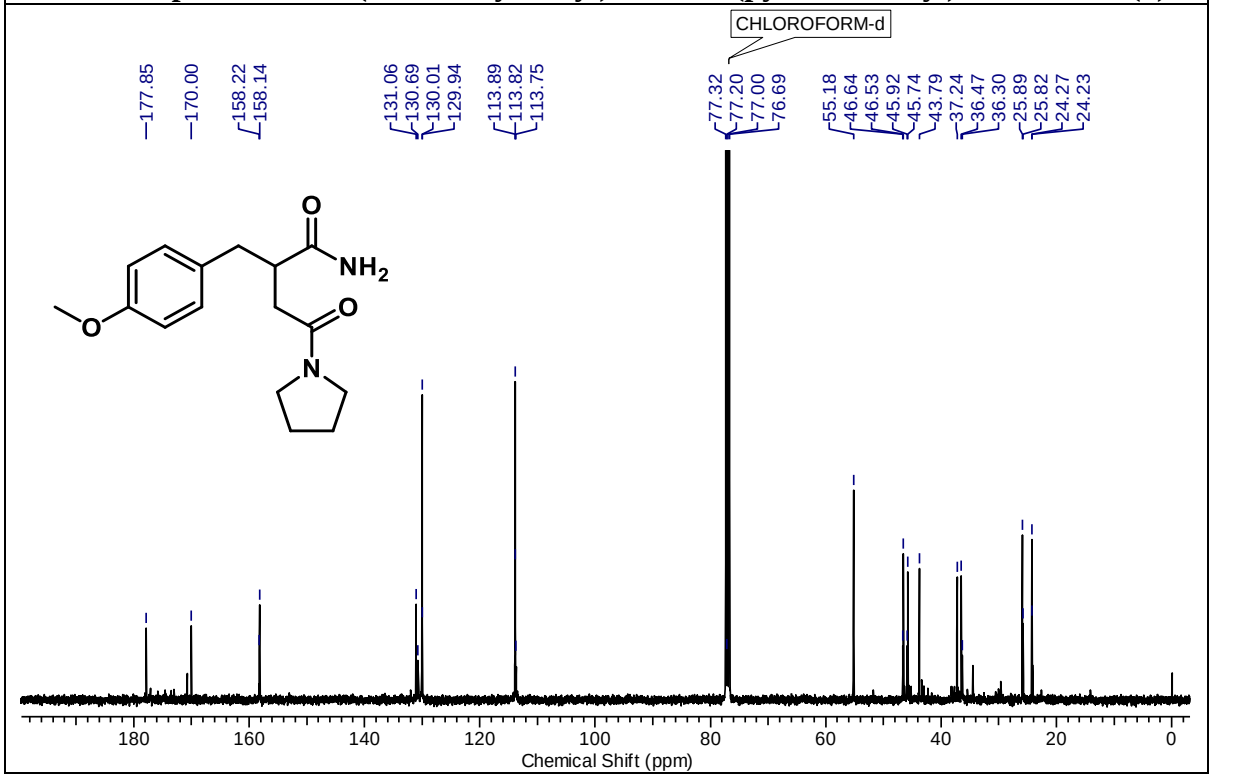

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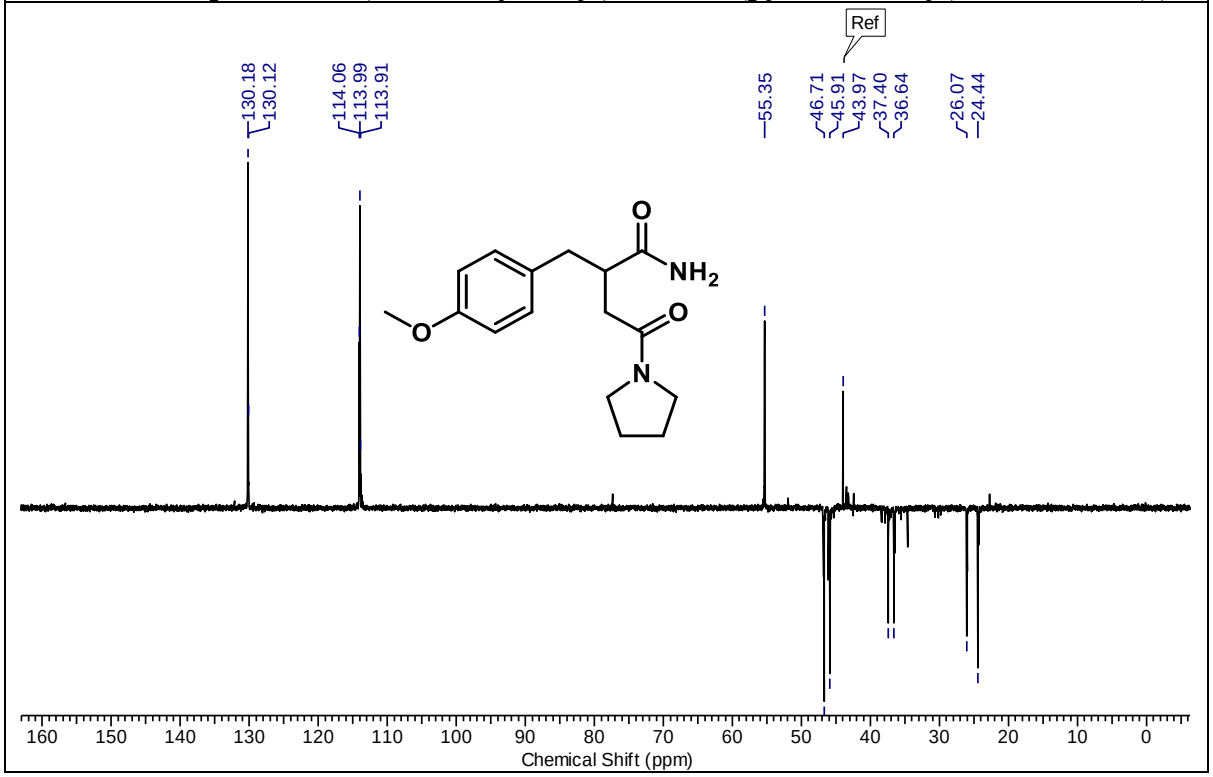
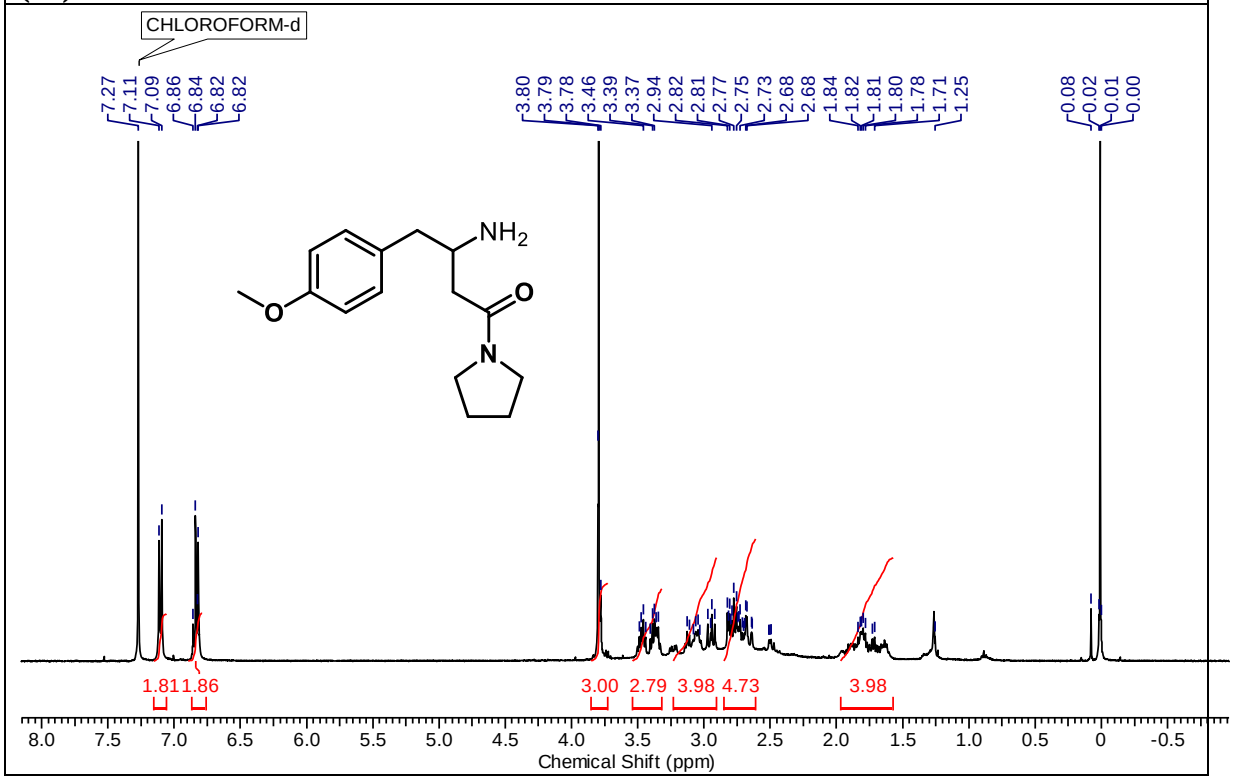


^{1}H-NMR spectrum of 3-amino-4-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)butan-1-one (10)



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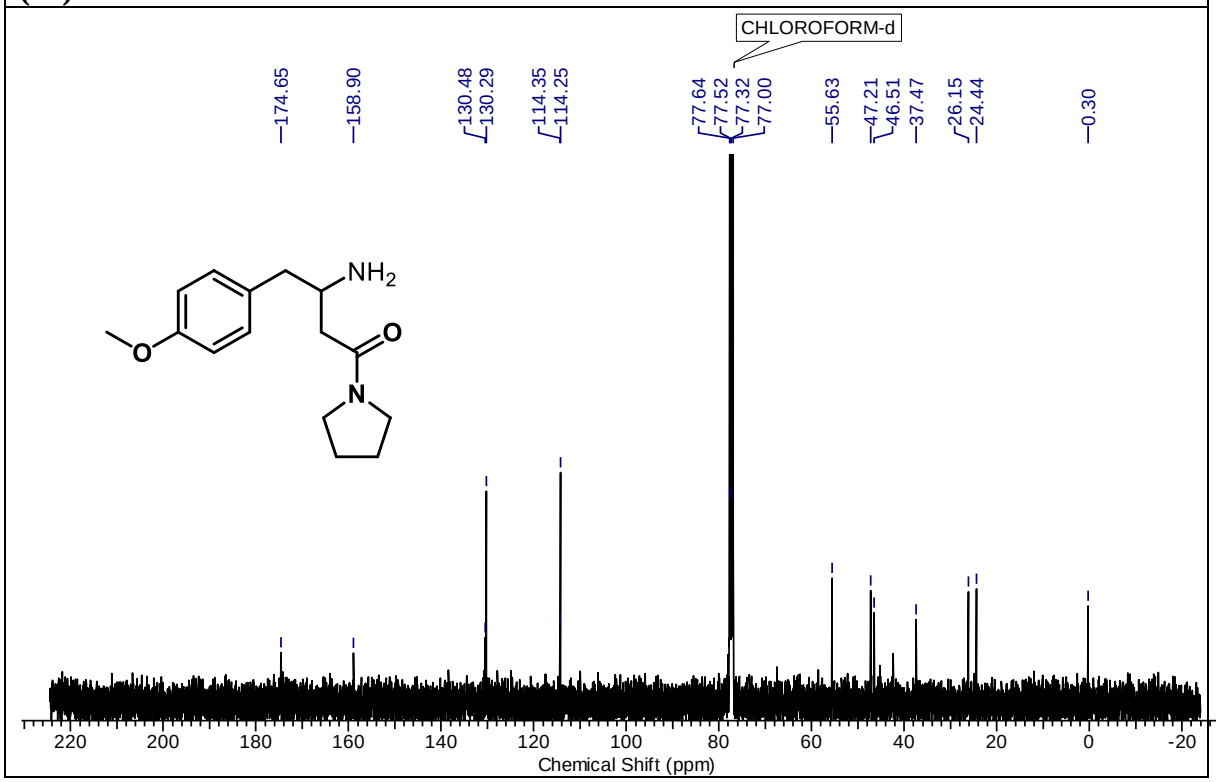
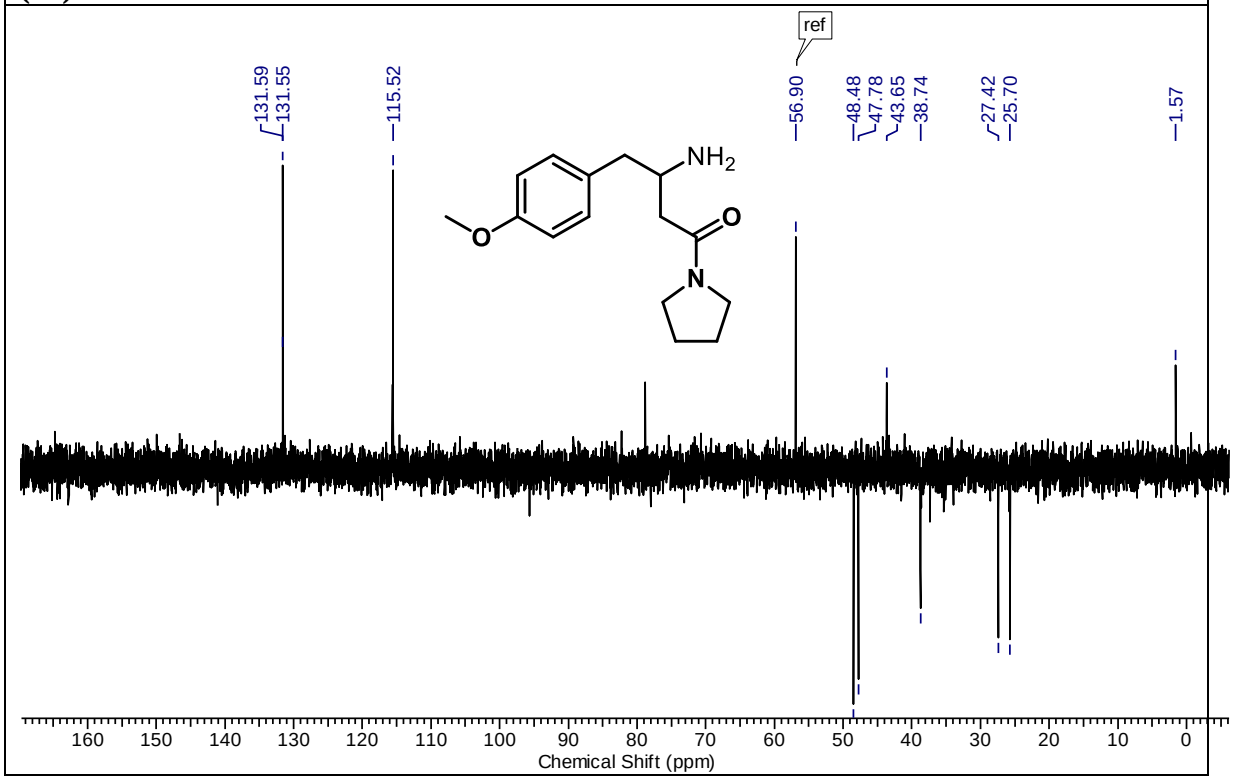
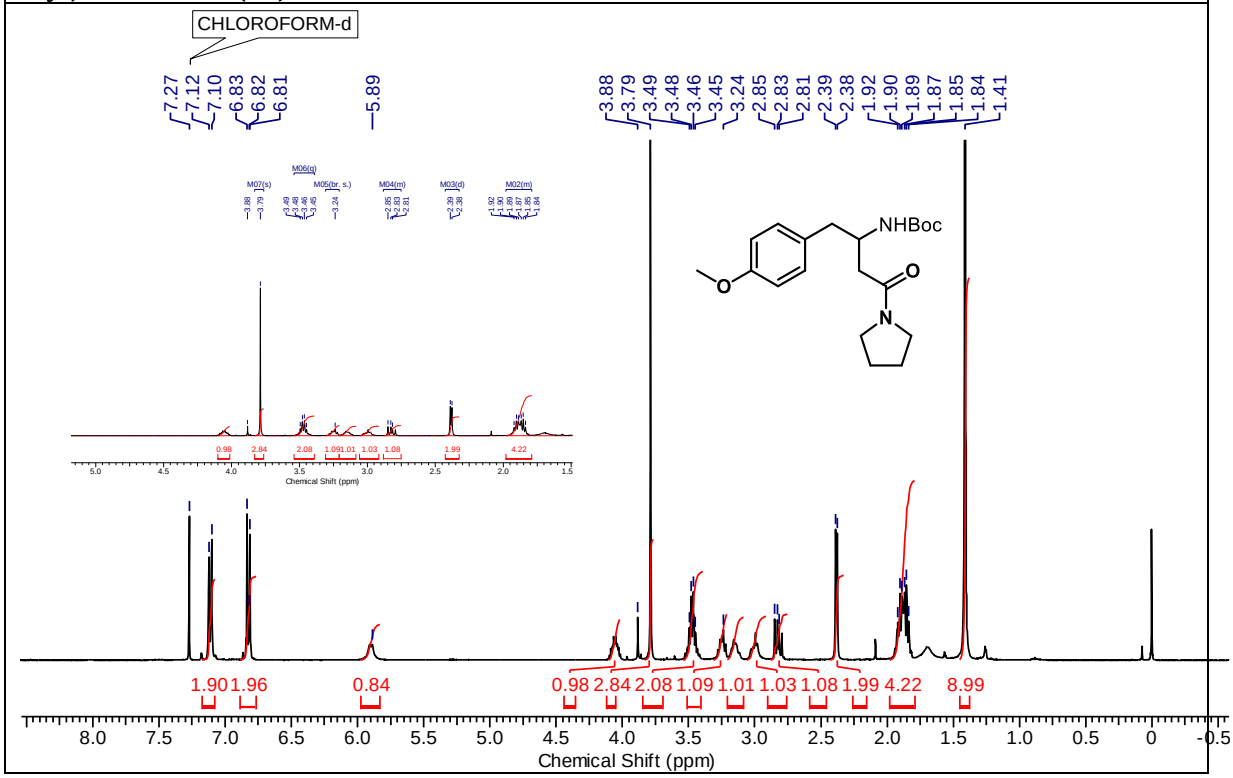


DEPT NMR spectrum 3-amino-4-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)butan-1-one (10)



^{1}H-NMR spectrum of tert-butyl (1-(4-methoxyphenyl)-4-oxo-4-(pyrrolidin-1-yl)butan-2-yl)carbamate (11)



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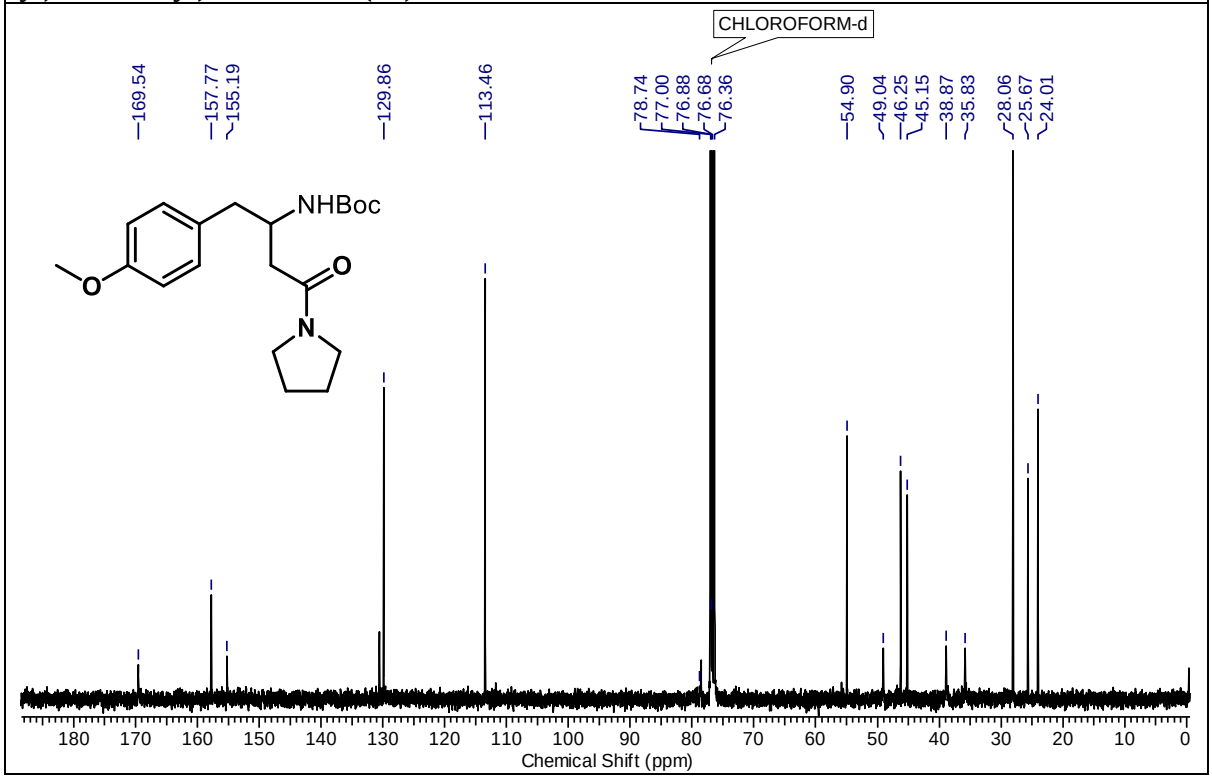
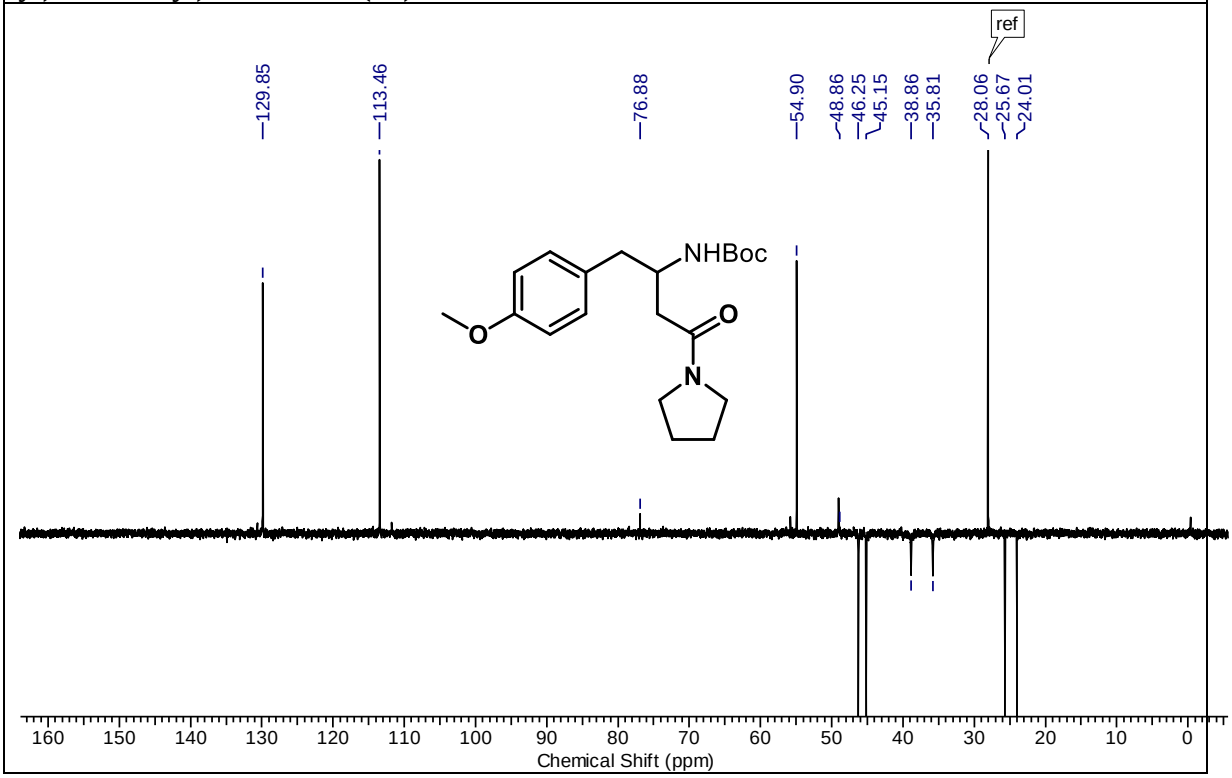


DEPT NMR spectrum tert-butyl (1-(4-methoxyphenyl)-4-oxo-4-(pyrrolidin-1-yl)butan-2-yl)carbamate (11)



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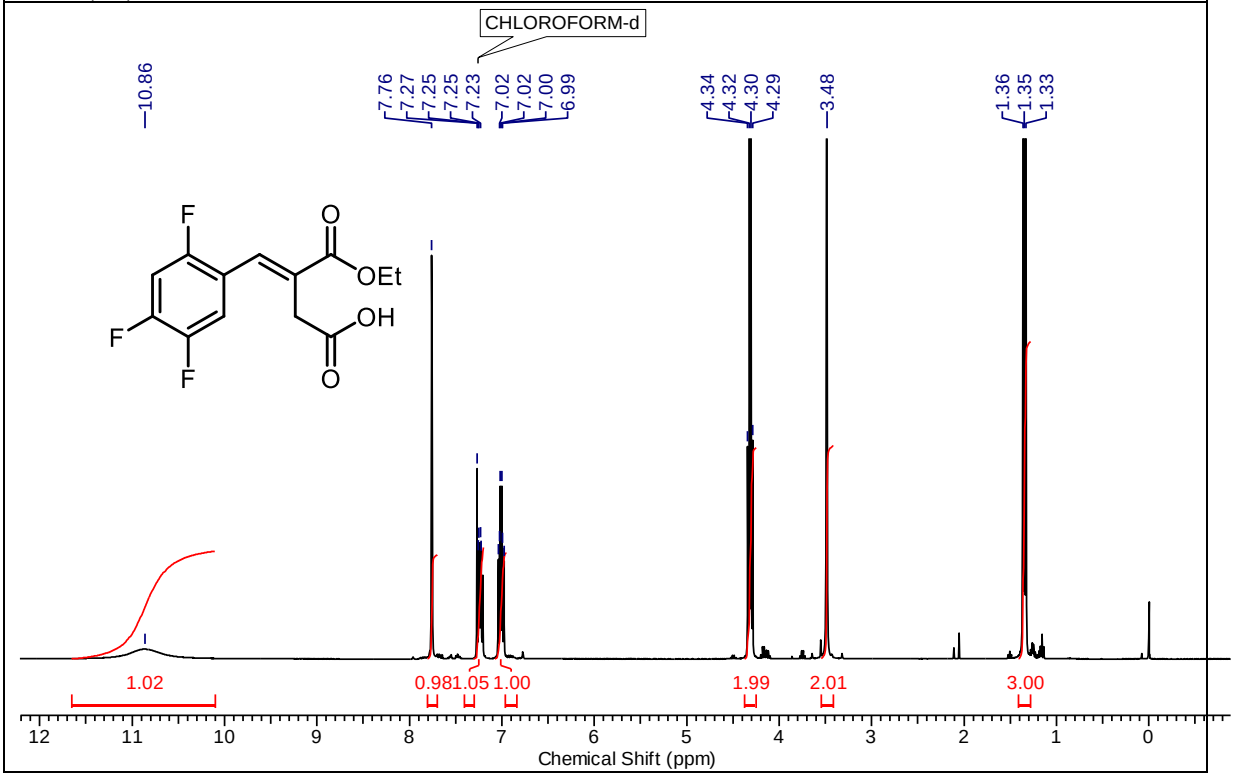

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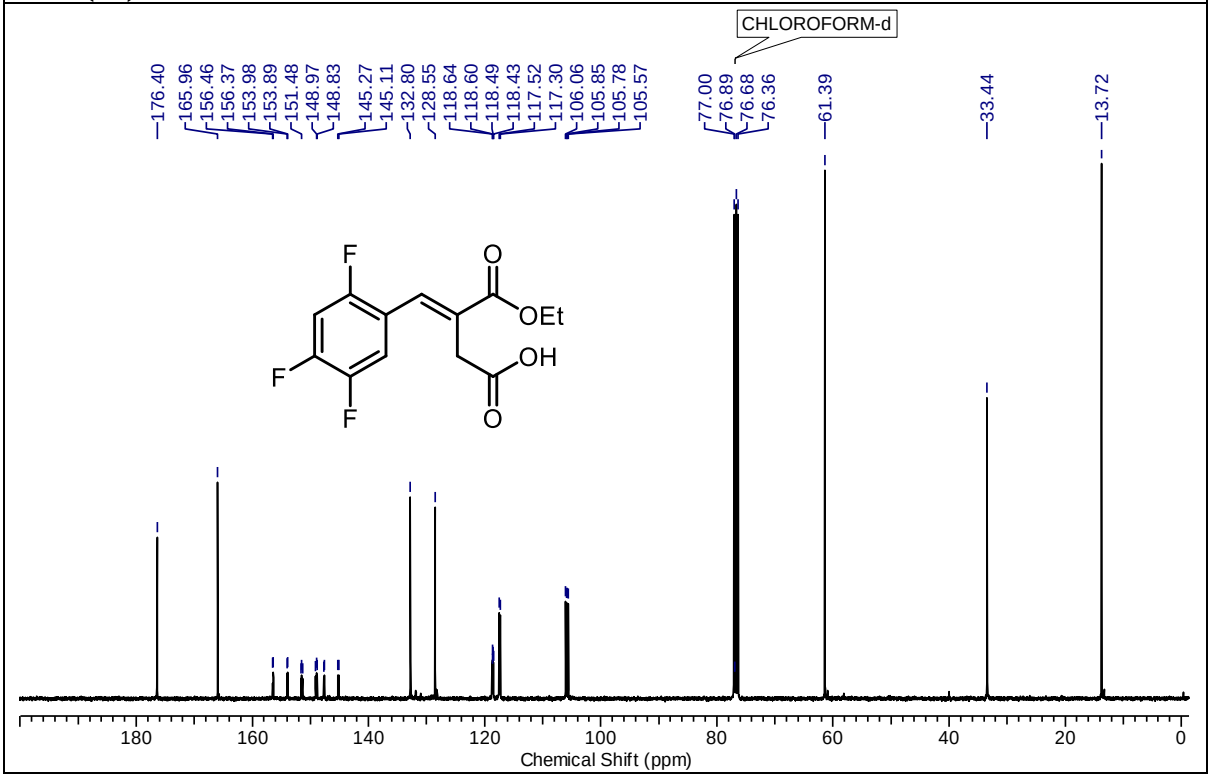

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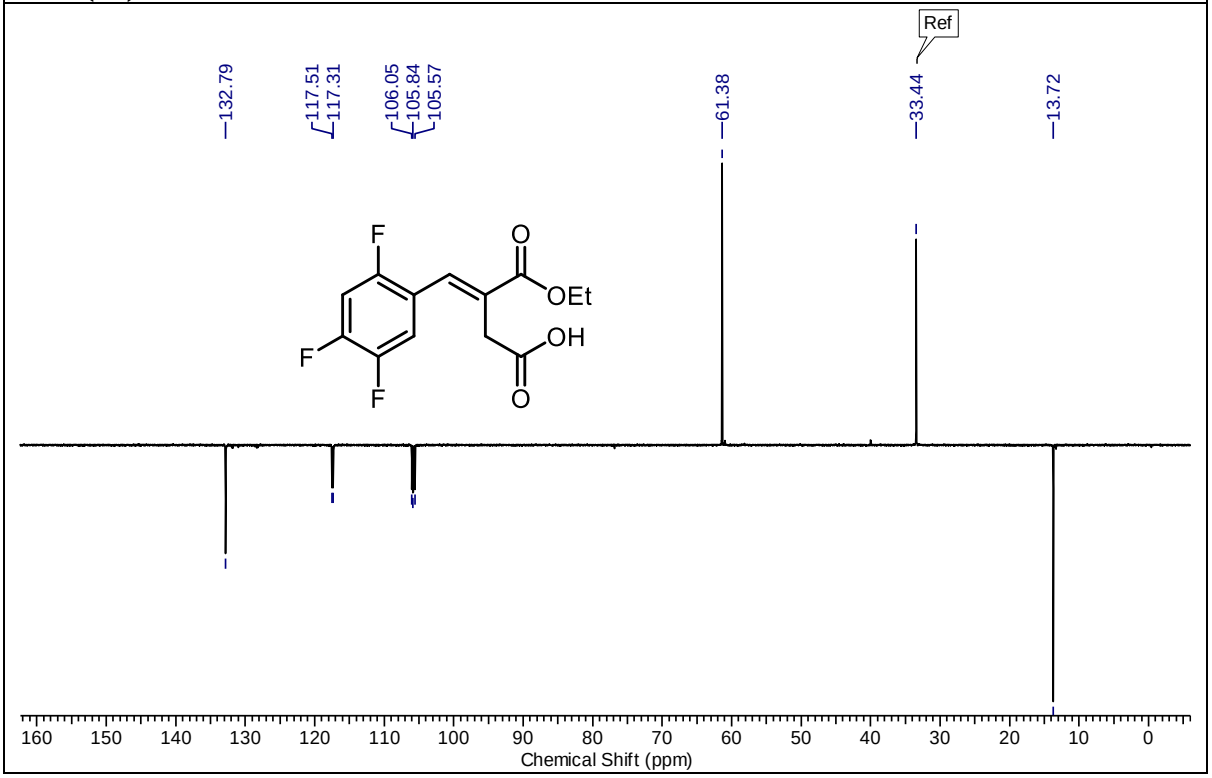

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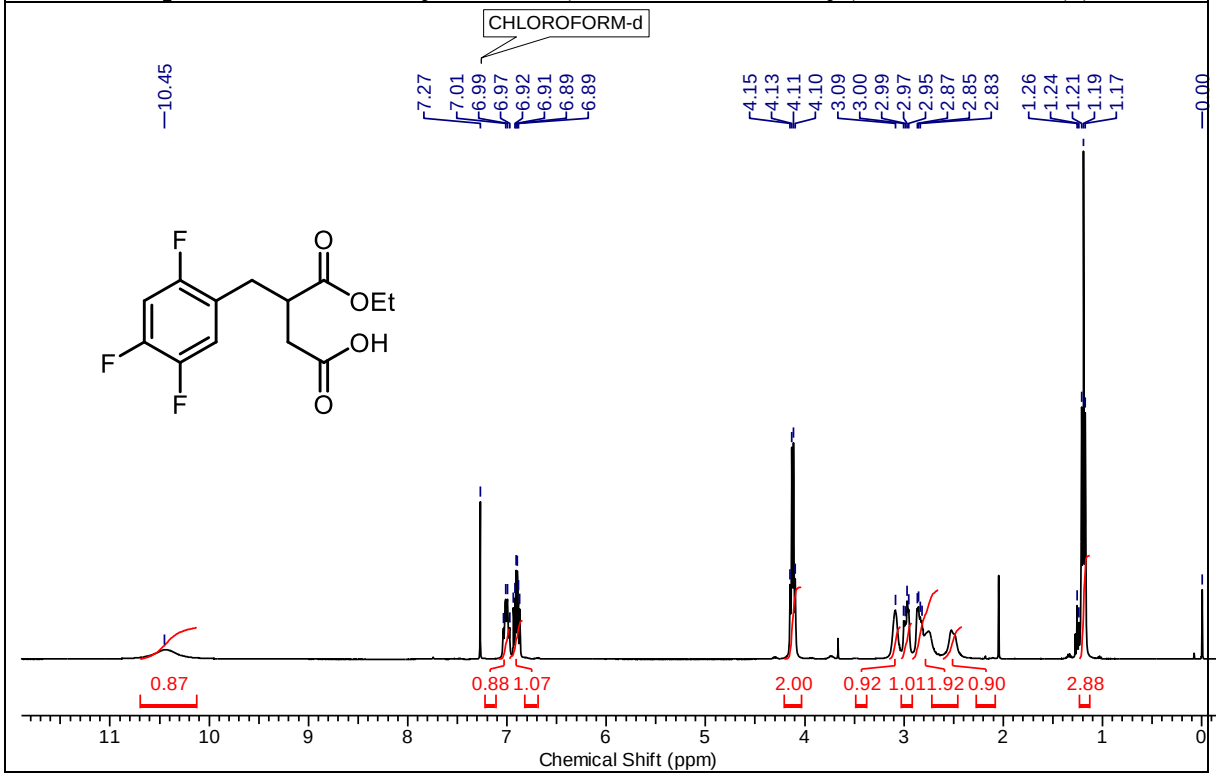

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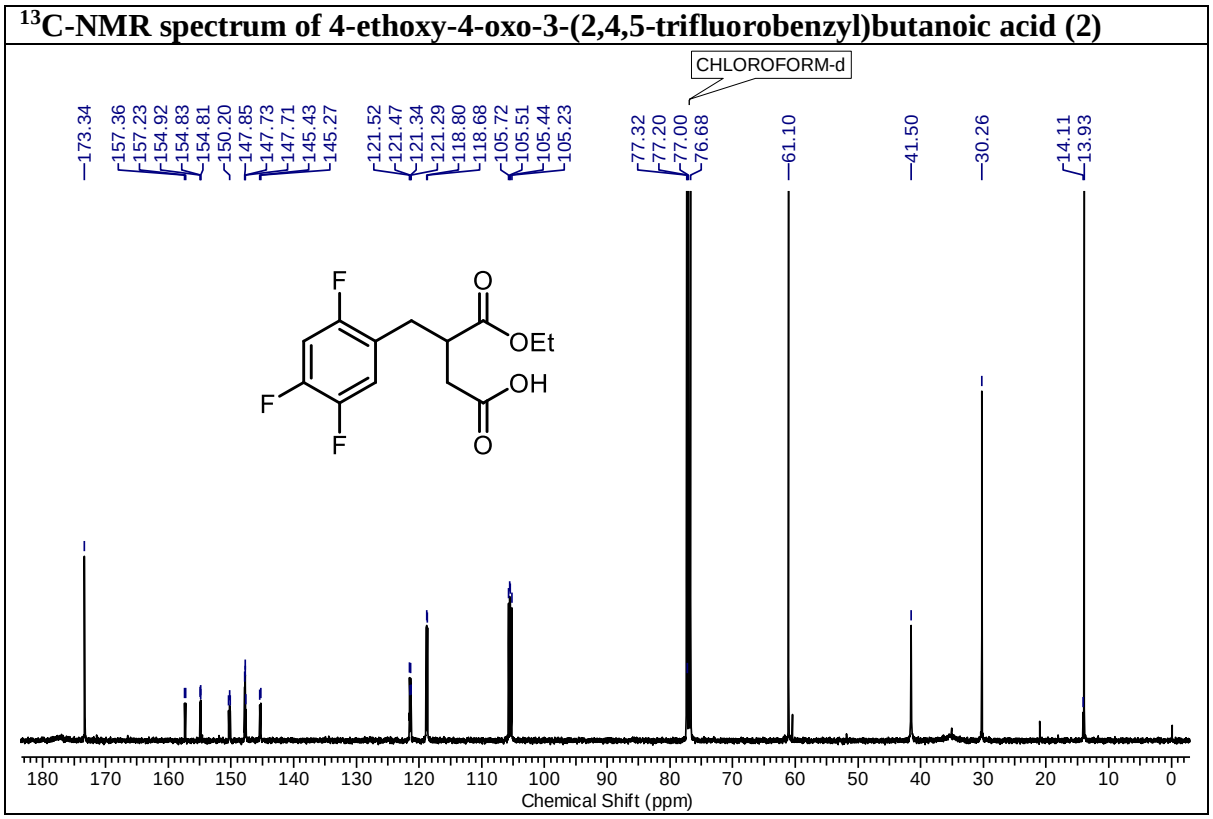

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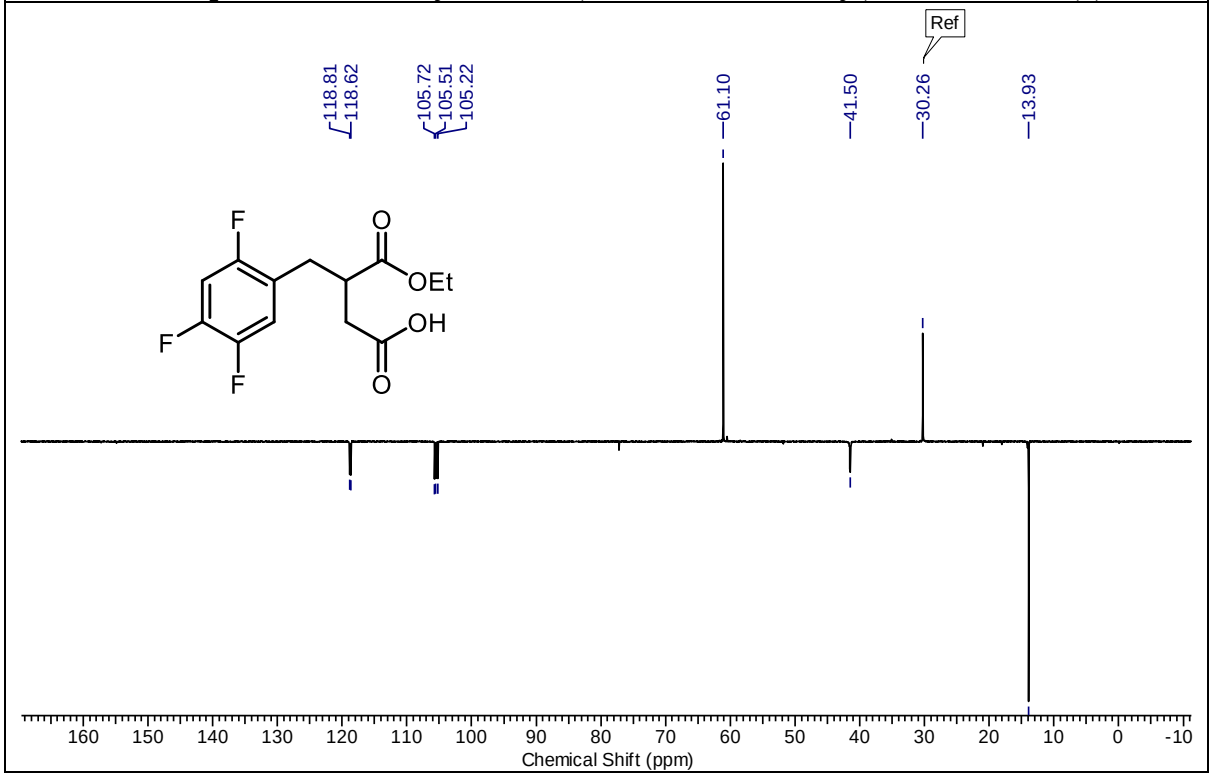

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Chapter 3: Synthesis of Heterocyclic Building Block of Pulchellalactam

"Synthesis of Heterocyclic Building Block of Pulchellalactam"

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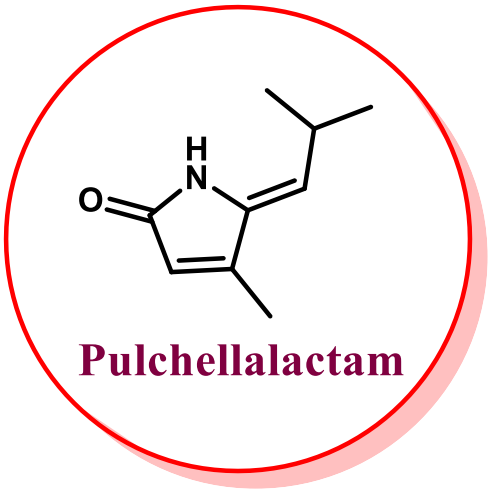
Chapter-3
Section-1

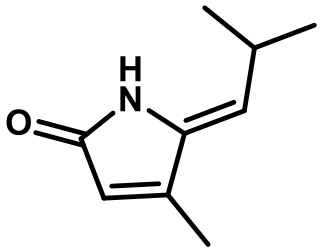
"Introduction and Literature Review of Heterocyclic Building Block of Pulchellalactam"



Pulchellalactam

3.1.1. Introduction:

(Z) Pulchellalactam, a pyrrolidinone was isolated in 1997 from the marine fungus *Corollospora pulchella* by Alvi *et al*[1]. Structurally it contains five-membered α,β- unsaturated lactam that having methyl substituent at β-carbon and a side chain at γ-carbon. Pulchellalactam was extracted from the fungus and it exhibits very potent activity against protein tyrosine phosphatase, (PTP) CD45, B and T cells are activated by this. Tyrosine phosphatase protein has been a target implicated in autoimmune and inti-inflammatory diseases.[2] Pulchellalactam is an important heterocyclic building block that occurs in nature and is synthesized in the laboratory and used for medicinal purposes.



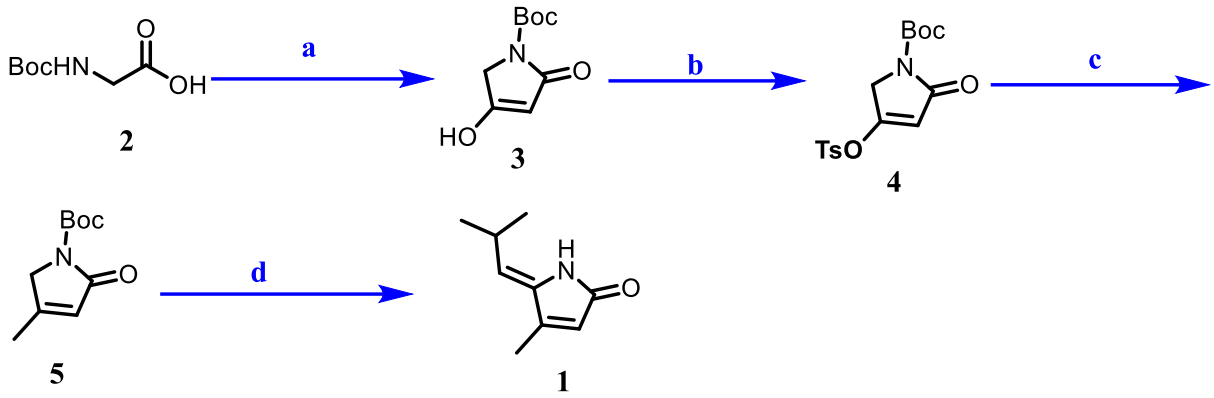
(Z)-Pulchellalactam (1)

Figure 1.

3.1.2. Literature survey

Li's approach[3] (*J. Org.* Chem. **2002**, *67*, 4702)

In the year 2002, Li *et al***.** reported the total synthesis of an important heterocyclic building block (Z)-pulchellalactam which started with the Meldrum's adduct formation of Boc-glycine **2** followed by intamolecular cyclization and decarboxylation to give compound **3**. The free hydroxyl group in **3** was transformed in to corresponding tosyl lactam **4** by using tosyl chloride in CH_2Cl_2 in 93% yield. One-pot Michael addition reaction with Me_2CuLi and elimination of tosylate on **4** furnished lactam **5** in 70% yield. Finally, by using the sodium hydride in THF, isobutyraldehyde was condensed with lactam and while doing workup, the Boc deprotection took place and afforded target molecule (Z)-pulchellalactam (**1)** in 86%. This five-step synthesis gives a 45% overall yield (**Scheme 1).**

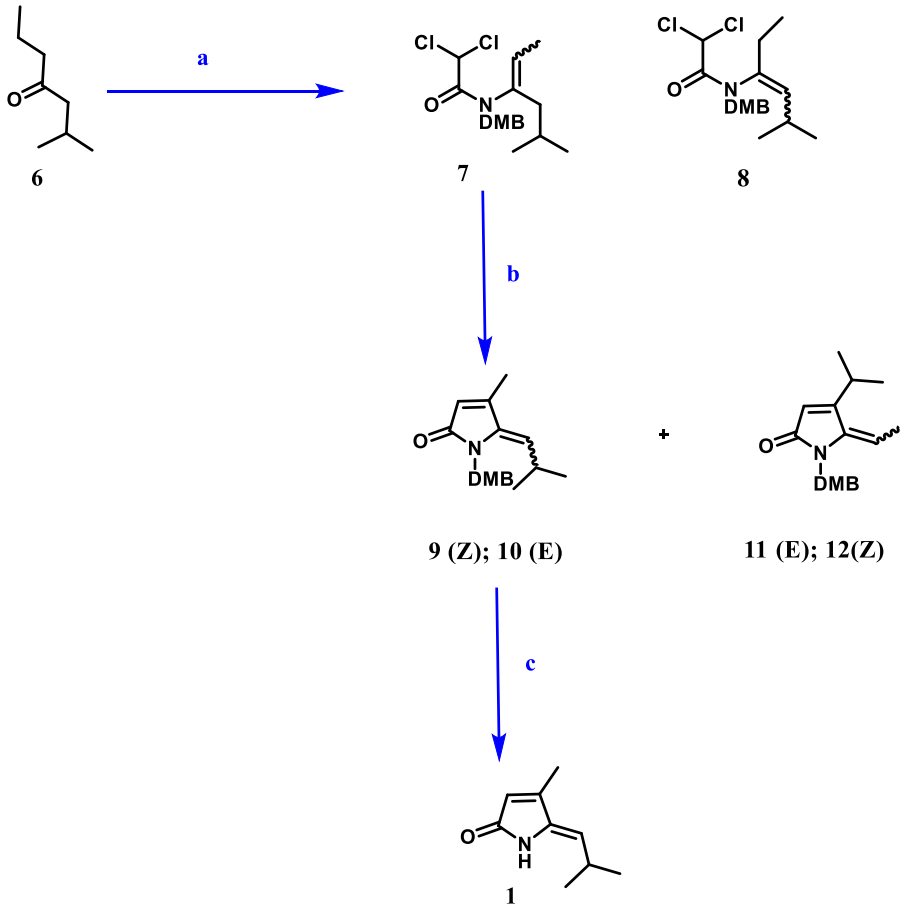


Scheme 1.

Scheme 1. *Reagents and condition:* (a) (i) Meldrum's acid, isopropyl chloroformate, DMAP, CH_2Cl_2, (ii) EtOAc, reflux, 80%. (b) Ts-Cl, DIPEA, CH_2Cl_2, 93%. (c) Me2CuLi, THF, 70%, (d) NaH, isobutyraldehyde, THF, 85%.

Parsons' approach[4] (*Tetrahedron*, **2003**, *59*, 6221)

In the next year (2003), Parsons *et al.* disclosed an efficient and short synthesis of (Z)-pulchellalactam and its (E) isomer. This synthesis started with a reaction of ketone **6** with 2,4-dimethoxybenzylamine and after that treatment of dichloroacetyl chloride provided a 1.5:1 mixture of enamide regioisomers **7** and **8** in 32% yield. Further, this mixture was refluxed with ($RuCl_2$ $(PPh_3)_3$ in dry toluene to give desired dienones **9** and **10** in 32% and 41% yield respectively from enamide **7** while enamide **8** gave isomeric mixture of **11** and **12** in 17% and 14% yield respectively. After that deprotection of Boc proteding group of dienones **9** and **10** with TFA at room temperature afforded desired (Z)-pulchellalactam and (E)-isomer in 66% and 83% yield respectively (**Scheme 2).**

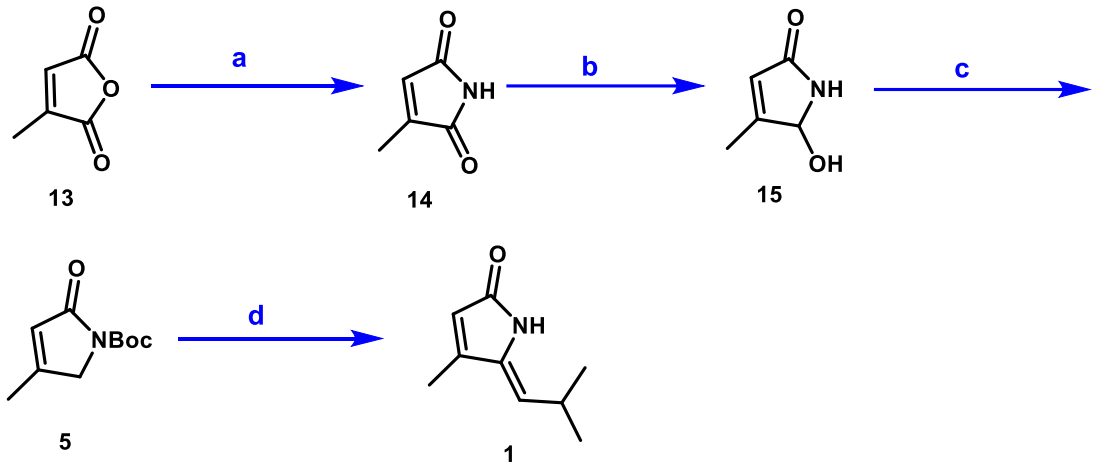


Scheme 2.

Scheme 2. *Reagents and condition*: (a) (i) $PMBNH_2$ (1.0 eq.), dichloroacetyl chloride (1.1 eq.), toluene, reflux, 32%. (b) $RuCl_2$ $(PPh_3)_3$ (0.5 eq.), toluene, reflux, 4 days, 89% mixture of products. (c) TFA, rt, 15 min, 66%.

Takabe's Approach[5] (*Heterocycles*, **2004**, *63*, 1013)

Takabe *et al*. reported the synthesis of pulchellalactam. In this synthetic methodology, citraconic anhydride **13** was treated with HMDS, as an ammonia source, to convert it into citraconimide **14**. Compound **14** was treated with sodium borohydride to give selectively reduced compound **15** in 92% yield. After that deoxygenation reaction employing BF_3.OEt and Et_3SiH and subsequent treatment with Boc-anhydride afforded compound **5** in 91% yield. And finally, by using the LDA in THF, isobutyraldehyde was condensed with lactam and while doing workup the Boc deprotection took place and afforded target molecule (Z)-pulchellalactam (**1)** in 82% yield **(Scheme 3)**.

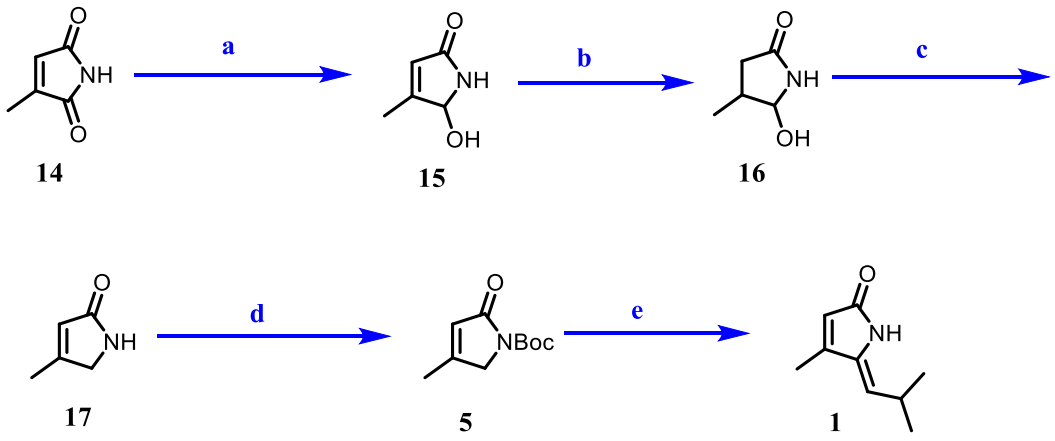


Scheme 3.

Scheme 3. *Reagents and condition:* (a) HMDS, DMF, 100 ºC, 80%. (b) $NaBH_4$, 92%. (c) (i) $BF_3.OEt$, Et_3SiH, CH_2Cl_2,-78 ºC-rt; (ii) $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 91%. (d) LDA, isobutyraldehyde, THF, -78 ºC- 0 ºC, 82%.

Argade's approach[6] (*Synthesis*, **2004**, *10*, 1560)

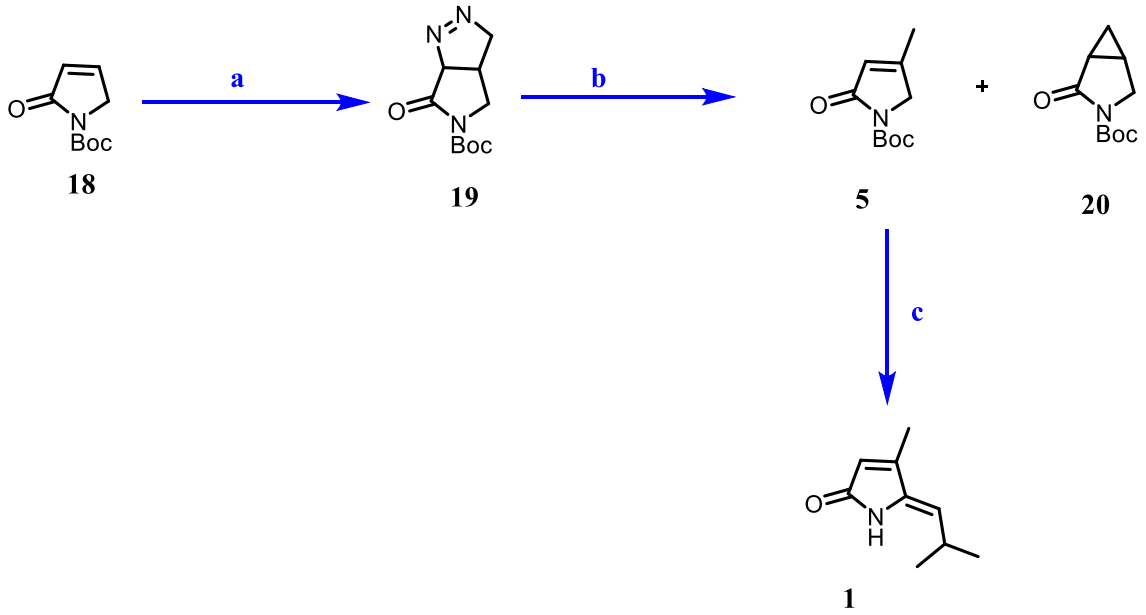
Agrade *et al*. reported a synthesis of **1** wherein they directly used citraconimide (**14)** which was treated with sodium borohydride to afford regioseletive reduction product hydroxylactam **15**. The reduction of double bond was done by using Pd/C under hydrogen to furnish **16**. Next job of dehydration and subsequent isomerisation was performed by using mildly acidic amberlyst resin in acetonitrile to afford α,β- unsaturated lactam **17** in 92% yield. The compound **17** was treated with Boc-anhydride to furnish common intermediate **5**. Finally, the side chain was introduced by aldol condensation with isobutyraldehyde using sodium hydride in THF followed by washing with 10% HCl for deprotection of Boc group to afford (Z)-pulchellalactam (**1)** in 82% yield **(Scheme 4)**.



Scheme 4. *Reagents and condition:* (a) $NaBH_4$ (1.0 eq.), EtOH, -40 °C, 1 h, quantitative (b) Pd/C, H_2, MeOH, rt, 2 h , quantitative. (c) (i) p-TSA (cat), C_6H_6, reflux, 3 h, 25-30%, (ii) AcOH, 80 °C, 1 h, 50-55% (iii) Amberlyst resin, CH_3CN, reflux, 2 h, 92%. (d) $(Boc)_2O$ (1.5 eq.), DMAP, CH_3CN, rt, 3 h, 85%. (e) NaH, THF, isobutyraldehyde, rt, 5 min. 82%.

Langlois's approach[7] (Synthetic *Communications*, **2006**, *36*, 2253)

Langlois and co-worker's in 2006, disclosed a synthesis by using five membered Boc-protected lactam pyrrolinone **18** which underwent reaction with diazomethane in Et_2O at room temperature for overnight to afford pyrazoline **19** in 68% yield.



Scheme 5.

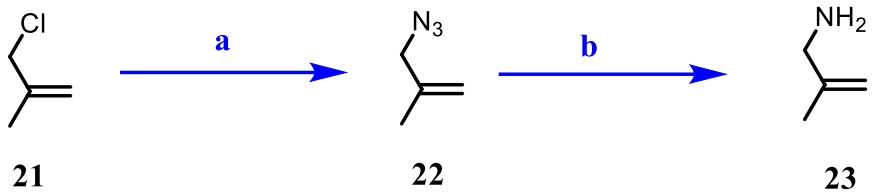
Scheme 5. *Reagents and condition:* (a) CH_2N_2, Et_2O, rt, 14 h, 68%. (b) Toluene, reflux, 8 h, 71%. (c) NaH, isobutyraldehyde, THF, 85%.

The compound **19** was heated in dry toluene for 8 hours wherein it underwent thermolysis to give desired intermediate **5** and cyclopropane **20** in 71% and 9% yield respectively. And finally, condensation reaction with isobutyraldehyde using NaH as the base and Boc deprotection afforded target product (Z)-pulchellalactam (**1)** in 86% yield. This synthesis involved three steps and gave 48% overall yield **(Scheme 5)**.

Chavan's approach[8] (Synthetic *Communications*, **2007**, *37*, 1503)

Chavan *et al*. reported a synthesis of pulchellalactam in year 2007. The synthesis began with nucleophilic substitution on methallyl chloride **21** with NaN_3 to afford corresponding methallyl

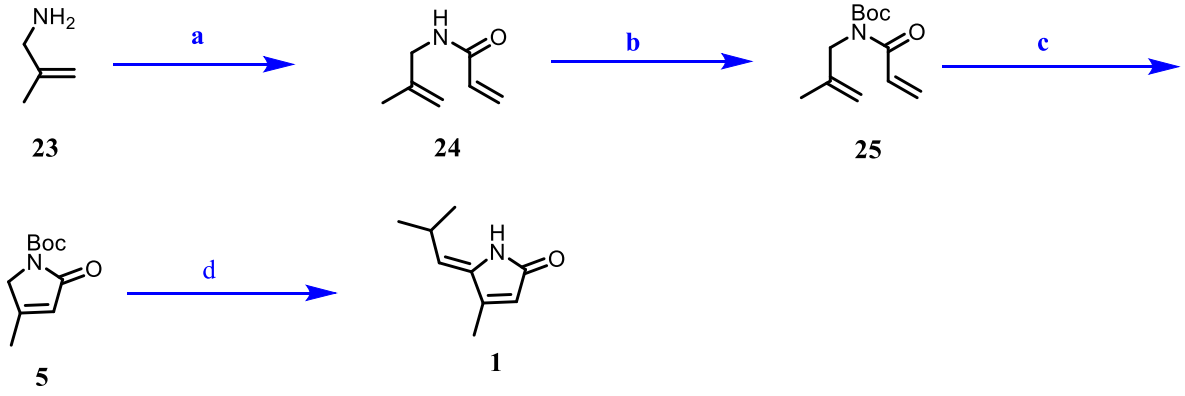
azide **22** which was further reduced by using PPh_3 in Et_2O and catalytic amount of H_2O at ambient temperature to furnish methylallylamine **23 (Scheme 6)**.



Scheme 6. 2-Methylallylamine synthesis.

Scheme 6. *Reagents and condition:* (a) NaN_3 (1.5 eq.), DMSO, 70 °C, 15 h. (b) PPh_3 (1.1 eq.), Et_2O-H_2O, 0 °C-rt, 14 h.

2-Methylallylamine **23** was treated with acryloyl chloride to furnish acrylamide **24**. Boc-protected compound **25** was obtained by treatment with Boc-anhydride and cat. amount of DMAP on **24.** The carbamate **25** was subjected to key step RCM by using Grubbs' catalyst (10 mol %) in dry toluene at 80 °C for overnight to afford the desired lactam **5** in 85% yield. The last job was the aldol condensation of lactam **5** and isobutyraldehyde by using sodium hydride as a base and further treatment with 10% HCl to afford target molecule pulchellalactam (**1**) **(Scheme 7)**.



Scheme 7.

Scheme 7. *Reagents and condition:* (a) acryloyl chloride (1.2 eq.), K_2CO_3 (1.2 eq.), dry DCM, 0 °C, 3 h, 59% over three-steps. (b) Boc-anhydride (1.2 eq.), DMAP (0.1eq.), dry CH_3CN, rt, 3 h, 82%. (c) Grubb's catalyst 2nd generation (5 mol %), dry toluene, 80 °C, 12 h, 85%. (d) NaH (1.5 eq.), isobutyraldehyde (3.0 eq.), THF, rt, 10% HCl, 85%.

3.1.3. Conclusion:

As evidenced by the foregoing discussion, the total synthesis of pulchellalactam started with the different small molecule cheap and commercially available starting materials. It is important building block in many bioactive naturally occurring compounds and medicines. But still this intermediate is not easily available and hence it needs more work to make it easily available for commercial purposes.

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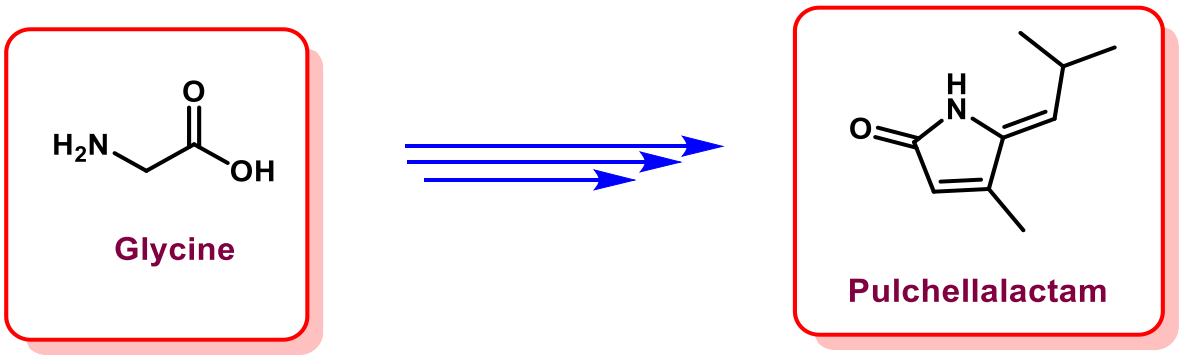
7) Hermet, J. P.; Caubert, V.; Langlois, N. *Synth. Commun*., **2006**, *36*, 2253.
8) Chavan, S. P.; Pathak, A. B.; Dhawane, A. N.; Kalkote, U. R. *Synth. Commun*., **2007**, *37*, 1510.

Chapter 3: Synthesis of Heterocyclic Building Block of Pulchellalactam

Chapter-3
Section-2

"Synthetic Studies of Heterocyclic Building Block"



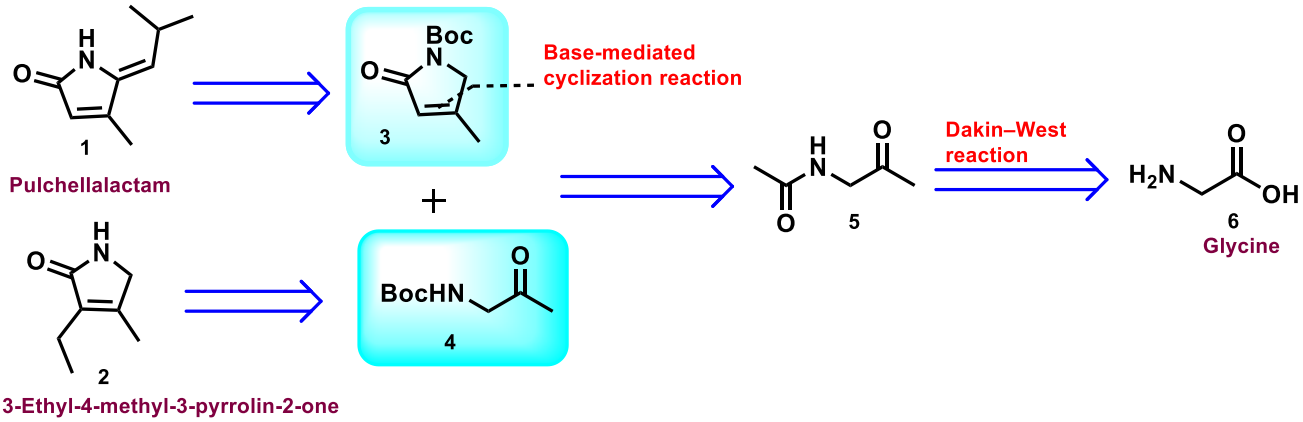
3.2.1. ABSTRACT:

Recent synthetic studies toward lactam-containing heterocycles for use in biological efforts have been intense. In this total synthesis, the key steps were focused on the formation of the pulchellalactam. The synthesis of pulchellalactam began with the substituted glycine.

3.2.2. Present Work:

Retrosynthetic analysis:

Glycine is the common starting material the the synthesis of the Pulchellalactam and 3-ethyl-4-methyl-3-pyrrolin-2-one. This retrosynthesis started with glycine (**6)** to the precursor of **3** and **4** that could be obtained by Dakin-West reaction[1] with glycine and acetic anhydride to afford **5**. Compound **5** could be treated with base-catalyzed cyclization to afford key intermediate **3** and expected side product **4.** Conversion of **3** to **1** is known in literature and compound **4** could be used to synthesize 3-ethyl-4-methy-3-pyrrolin-2-one **(2)** by amide acylation to allow by base-catalyzed cyclization**.**

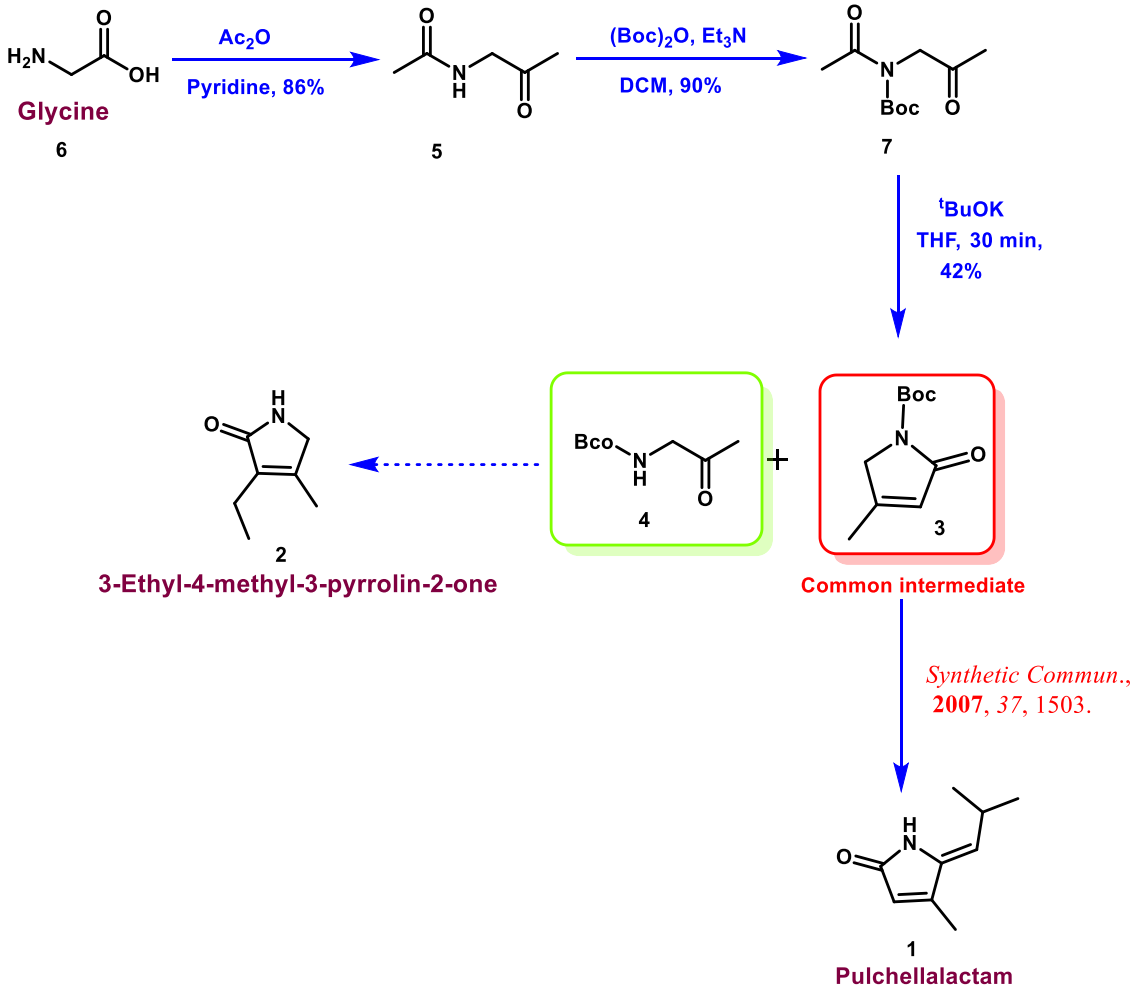


Scheme 1. Retrosynthetic Analysis.

3.2.3. Results and discussion:

A facile and efficient strategy for the synthesis of heterocyclic building blocks started with glycine, by using reported Dakin-West reaction condition glycine was refluxed with 5 eq. of pyridine and acetic anhydride mixture to afford to amide **5** in 86% yield. The structure of **5** was confirmed by spectral analysis. IR spectrum of **5** displayed strong absorption band at 3338 cm-

[1] and 1724 and 1665 cm^{-1} characteristic of H-N and C=O stretching frequency peaks at δ 6.46 (br s, 1H) for N-H proton, δ 4.12 (d, *J* = 4.7 Hz, 2H) and two singlets at δ 2.17 (s, 3H), 2.00 (s, 3H) were seen for two methyl protons in NMR spectrum and peaks appearing at δ 203.7 and 170.9 in ^{13}C NMR spectrum corresponding to keto and amide carbons confirmed the structure.



Scheme 2: Synthesis of heterocyclic building block common intermediate.

The amide **5** was treated with Boc-anhydride using triethylamine as the base in dry CH_2Cl_2 to furnish carbamate **7** in 90% yield. The formation of product **7** was confirmed by the disappearance of singlet δ 6.46 (br s, 1H) for N-H group and appearance of singlet at δ 1.47 for -C(CH_3)$_3$. In the ^{13}C-NMR spectrum, peaks at δ 151.9 and 27.5 (3C) were seen corresponding to carbamate protection.

The carbamate **7** was subjected to base-catalyzed cyclization with different bases like NaOH, K_2CO_3, NaH etc and the best result was obtained with ^{t}BuOK to give 42% cyclized product **3** and carbmate protected β-keto amine **4**.

The structure of **3** was ascertained by spectroscopic methods. The ^{1}H-NMR spectrum revealed peak at δ 5.85 (s, 1H) C=C<u>H</u> indicating presence of alkene presence and absence of peaks at δ 2.52 (s, 3H) and 2.14 (s, 3H) and presence of peak at δ 2.09 (s, 3H) showing that only one methyl group was present and in ^{13}C-NMR spectrum absence of peak at δ 201.4 and presence of peaks at δ149.8 and δ 123.2 corresponding to olefinic quaternary and methine carbon, indicated the formation of a common intermediate **3** known in the literature.[2]

The β-keto amine **4** was characterized by ^{1}H-NMR spectroscopy. The peak at δ 5.22 (br s, 1H) for N-<u>H</u> and 4.03 (d, *J* = 4.6 Hz, 2H) for C<u>H$_2$</u> and 2.18 (s, 3H) indicating presence of only one methyl group and δ 203.3 in ^{13}C-NMR spectrum corresponding to keto carbon indicated the hydrolyzed product carbamate protected β-keto amine **4**.

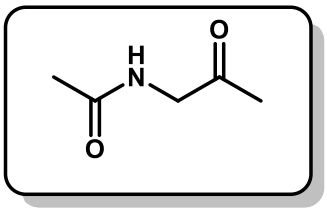
3.2.4 Conclusion:

In summary, heterocyclic building block synthesis started from the glycine as a starting material and the key steps used in the synthesis were conversion of amino acid to the corresponding β-keto amide by Dakin-West reaction, base-mediated cyclization reaction to synthesize the of key intermediate accomplishing the formal synthesis of pulchellalactam.

3.2.5. Experimental Section

3.3.4.1. Experimental Procedures and Characterization Data

N-(2-Oxopropyl)acetamide (5)



A mixture of 81.5 g. (6 eq., 0.79 moles) of pyridine, 64.35 g. (6 eq., 0.79 moles) of acetic anhydride and 10.0 g. (0.133 mole) of vacuum-dried alanine was heated with stirring on the steam bath for 6 hours. The excess pyridine, acetic anhydride, and the acetic acid, were removed at reduced pressure. The residue was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate- petroleum ether (80:20) as a solvent system to deliver the amide **5** in 13.3 g, 86% yield.

Rf: 0.2 (Ethyl acetate – pet. ether=80:20);

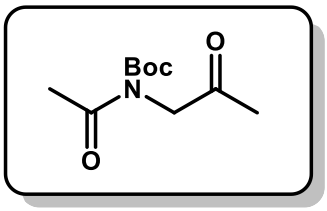
Yield: 86%;

IR ($CHCl_3$): ν_{max} 3338, 2922, 1724, 1665 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.46 (br s, 1H), 4.12 (d, *J* = 4.7 Hz, 2H), 2.17 (s, 3H), 2.00 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.7, 170.9, 50.4, 27.8, 23.3.

***tert*-Butyl acetyl(2-oxopropyl)carbamate (7)**



A solution of 10.0 g (1.0 eq., 0.0869 moles) of amide **5** in 80 mL of CH_2Cl_2 was treated successively with 12.77 mL (2.0 eq., 0.173 moles) of Et_3N, 19.95 g (1.0 eq., 0.086. moles,) of $(Boc)_2O$, and 9.75 g (1.0 eq., 0.086 moles) of DMAP. The reaction was then stirred at room temperature for 1 h before being concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate- petroleum ether (10:90) as a solvent system to deliver the amide **7** in 16.3 g, 90 % yield.

Rf: 0.6 (Ethyl acetate – pet. ether=15:85);

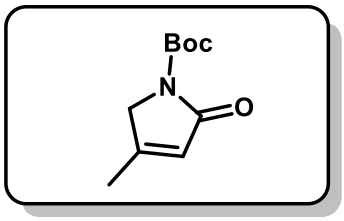
Yield: 90%;

IR ($CHCl_3$): ν_{max} 2980, 1733, 1692 (br), 1342 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.50 (s, 2H), 2.52 (s, 3H), 2.14 (s, 3H), 1.47 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.4, 172.4, 151.9, 83.3, 52.7, 27.5 (3C), 26.4, 25.9.

***tert*-Butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (3)**



A solution of 0.300 g (1.0 eq., 1.395 mmol) of carbamic amide **7** in 8 mL of THF was cooled to -10 °C (NaCl/ice bath) and was treated with 0.313 g (2.0 eq., 2.79 mmol) of freshly sublimed ^{t}BuOK. The reaction mixture was stirred at -10 °C for an additional 20 min, poured into 10 mL of ice-cold H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and the residue obtained was purified by flash column chromatography (SiO_2) eluting with the mixture of ethyl acetate- pet. ether (30:70) as eluent to furnish cyclized product 0.116 gm. **3** in 42% and keto amide 0.147 g, **4** in 50% yield.

Rf: 0.2 (Ethyl acetate – pet. ether=30:70);

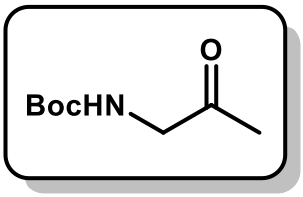
Yield: 42%;

IR ($CHCl_3$): ν_{max} 3392, 2975, 1704 (2CO), 1509, 1365 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.85 (s, 1H), 4.20 (s, 2H), 2.09 (s, 3H), 1.54 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.9, 158.3, 149.8, 123.2, 82.9, 54.6, 28.4, 15.8.

***tert*-Butyl (2-oxopropyl)carbamate (4)**



Rf: 0.3 (Ethyl acetate – pet. ether=30:70);

Yield: 47%;

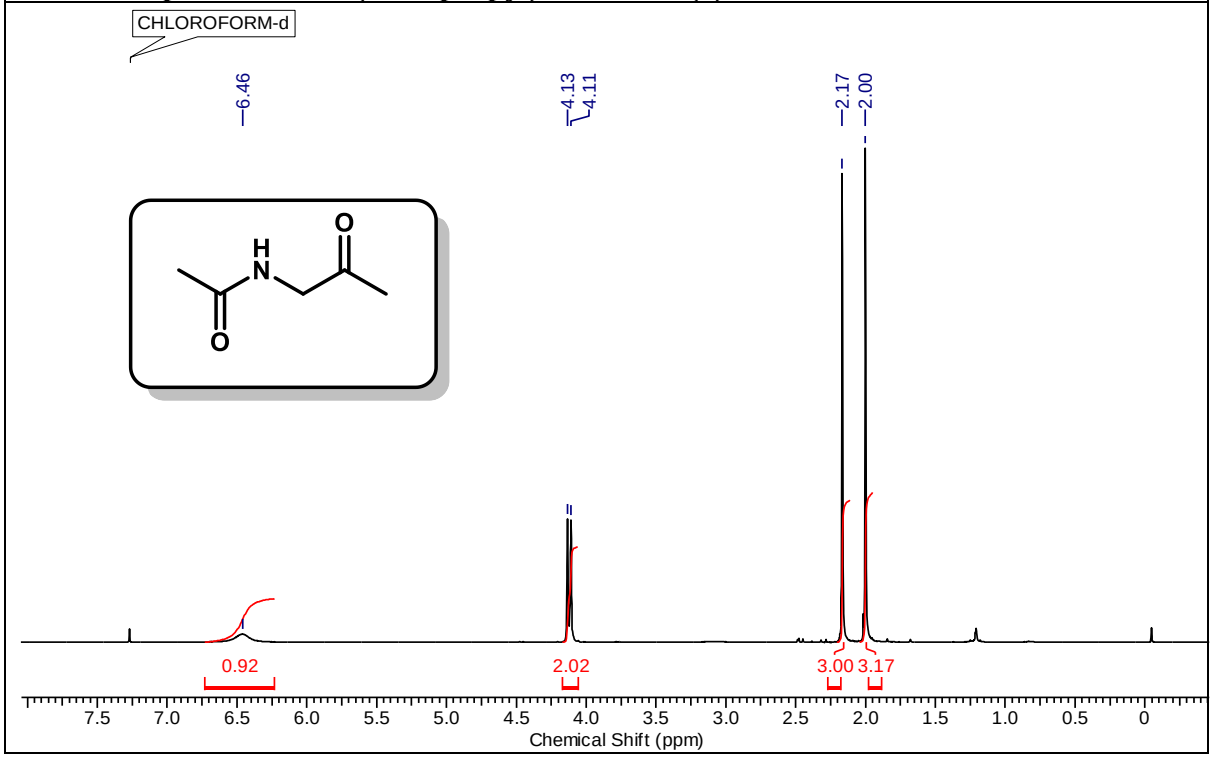
IR ($CHCl_3$): ν_{max} cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.22 (br s, 1H), 4.03 (d, *J* = 4.6 Hz, 2H), 2.18 (s, 3H), 1.45 (s, 9H);

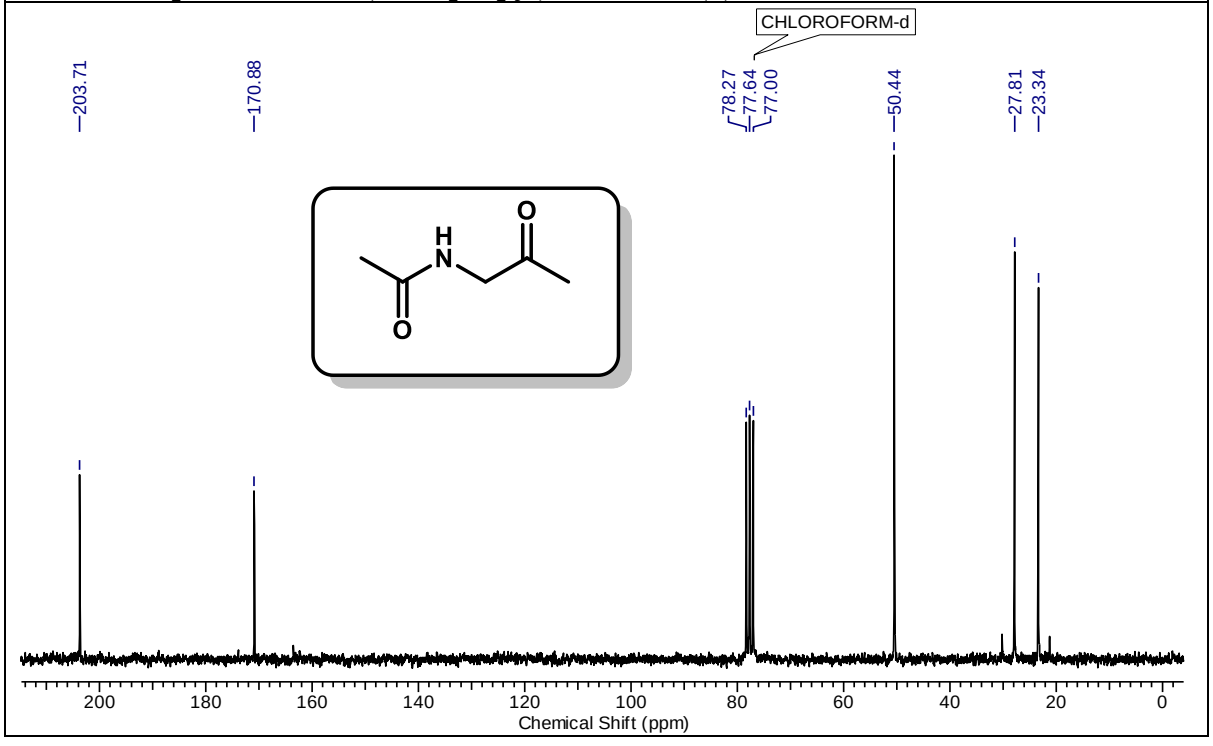
^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.3, 155.6, 79.9, 50.9, 28.3, 27.1.

3.2.6. Spectral Data

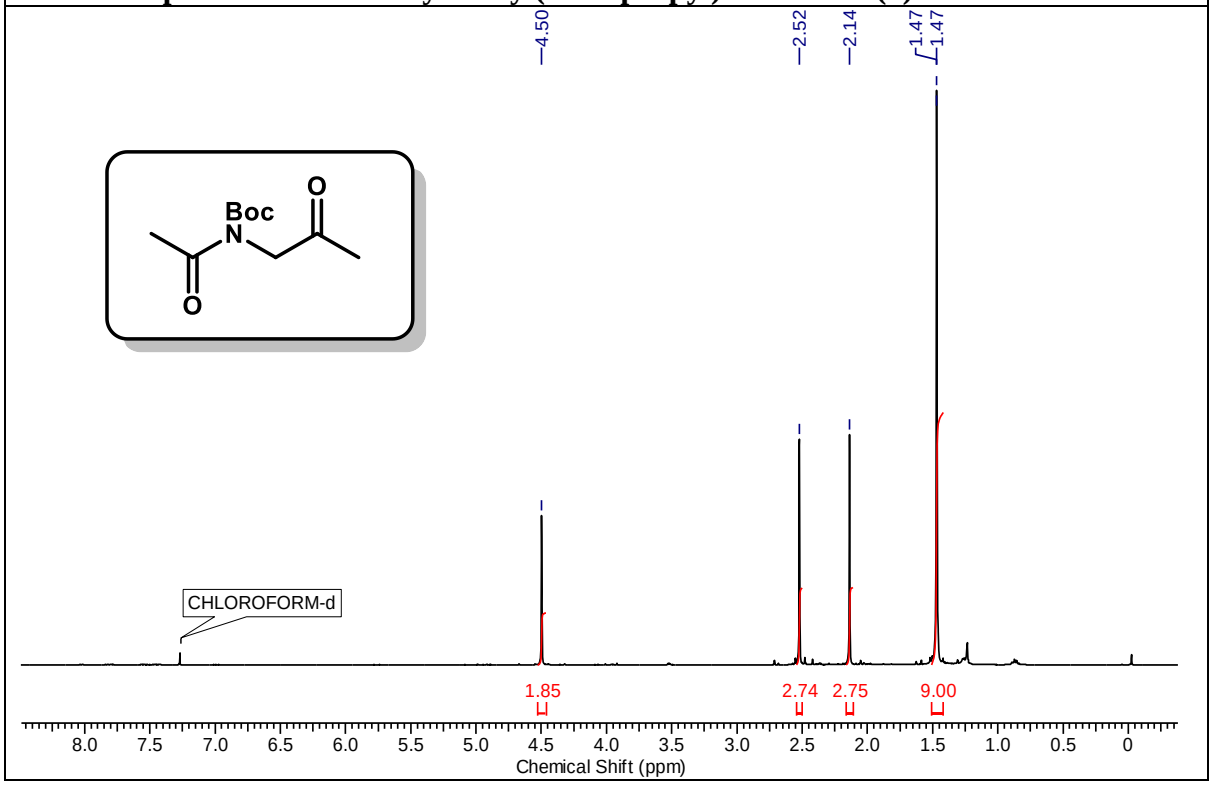
^{1}H-NMR spectrum of N-(2-oxopropyl)acetamide (5)



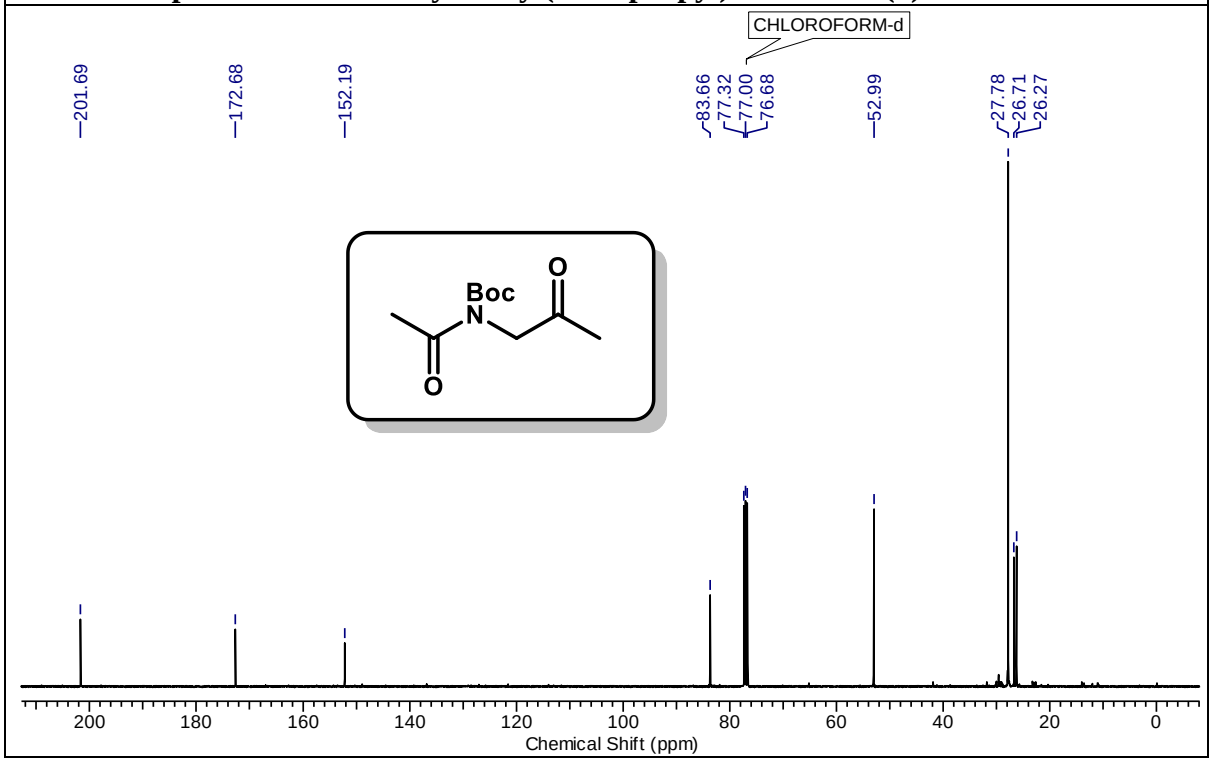
^{13}C-NMR spectrum of N-(2-oxopropyl)acetamide (5)



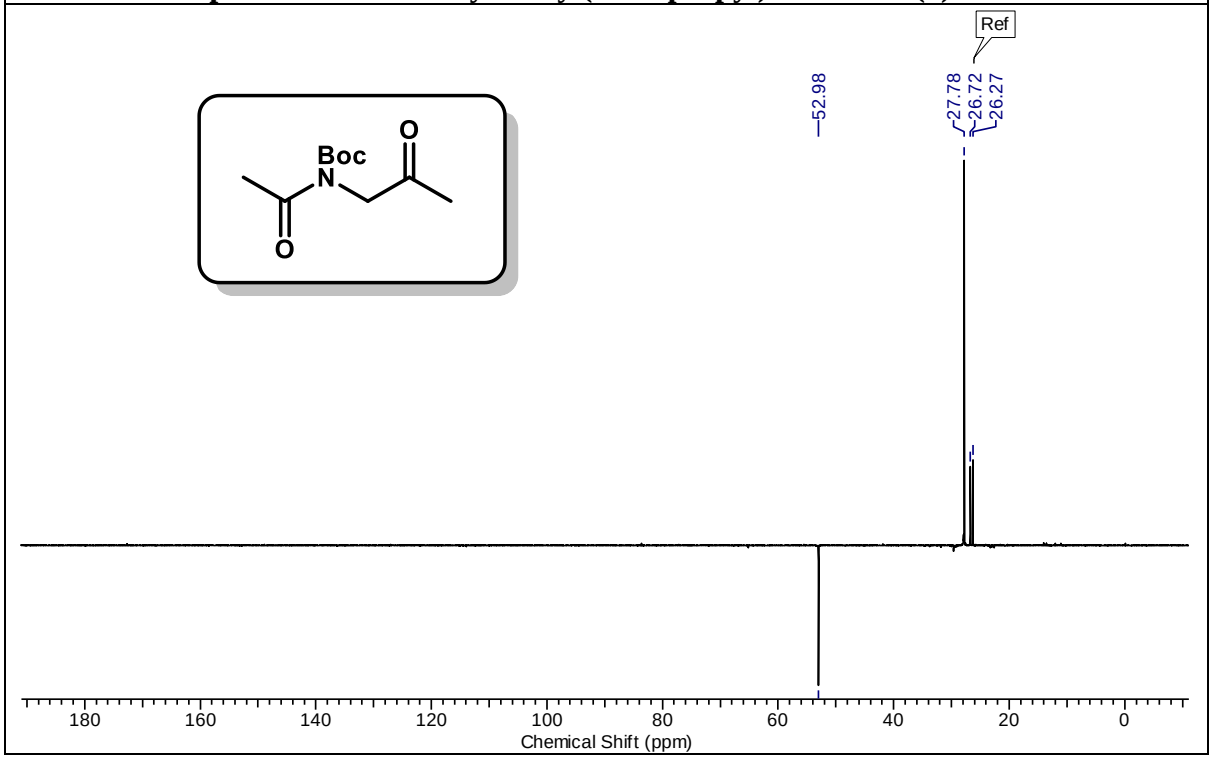
^{1}H-NMR spectrum of *tert*-butyl acetyl(2-oxopropyl)carbamate (7)



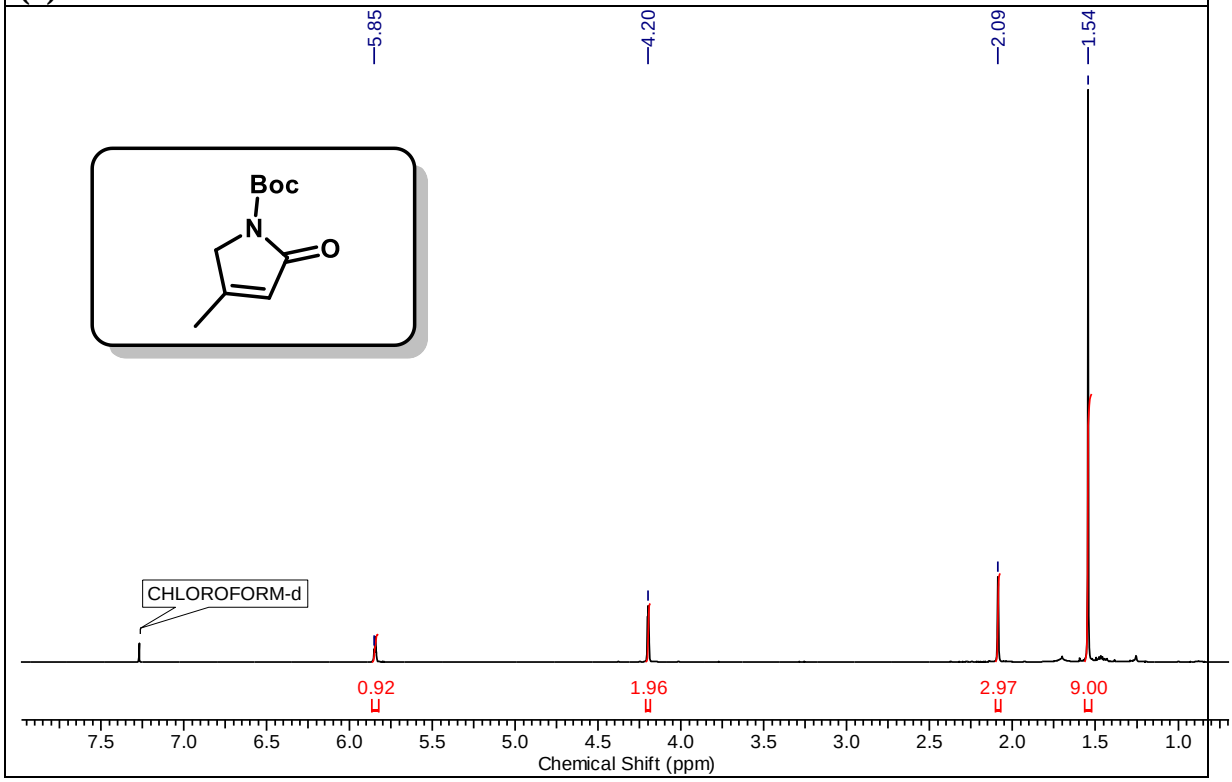
^{13}C-NMR spectrum of *tert*-butyl acetyl(2-oxopropyl)carbamate (7)



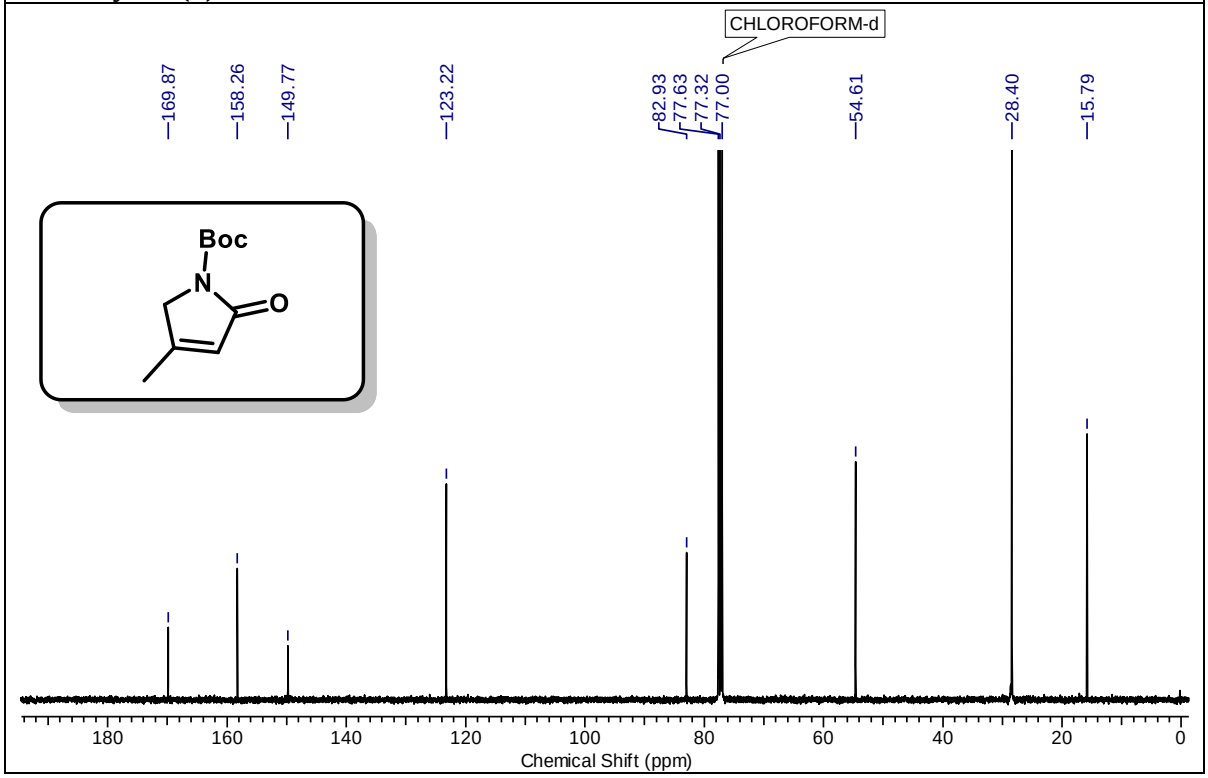
DEPT NMR spectrum of *tert*-butyl acetyl(2-oxopropyl)carbamate(7)



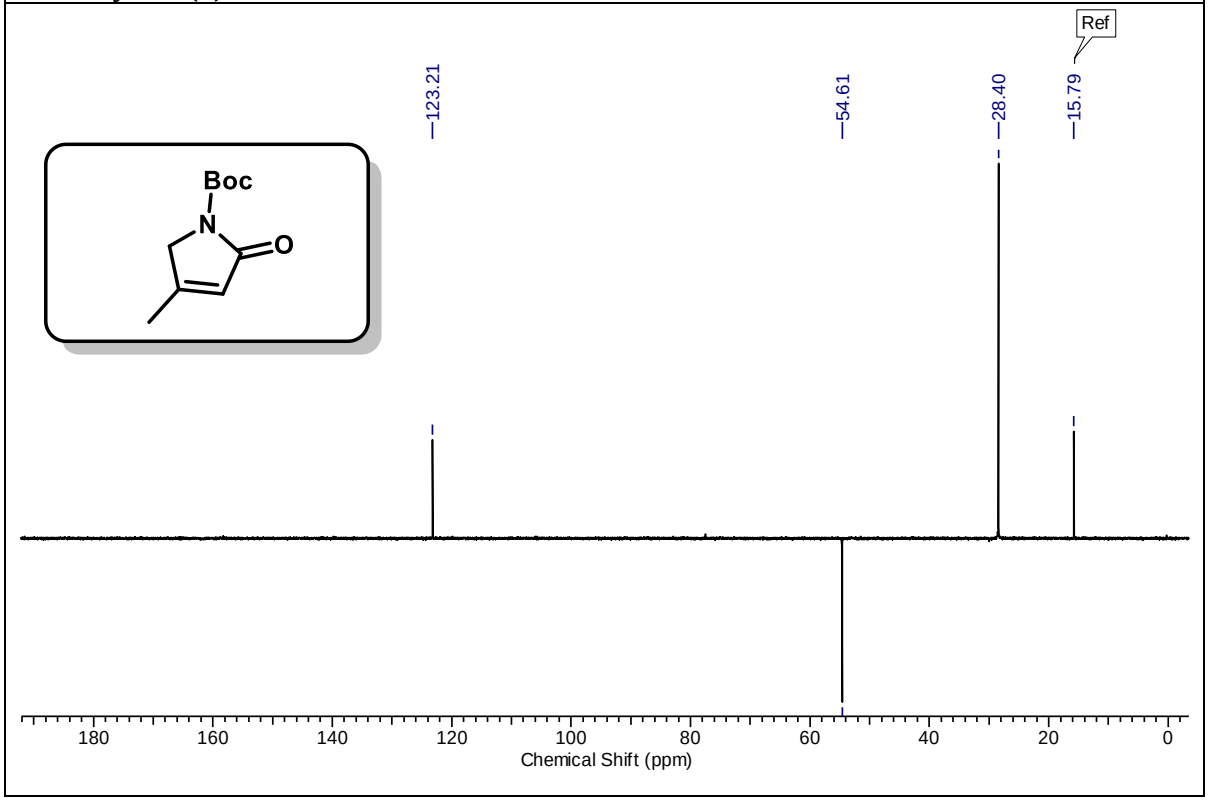
^{1}H-NMR spectrum of *tert*-butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (3)



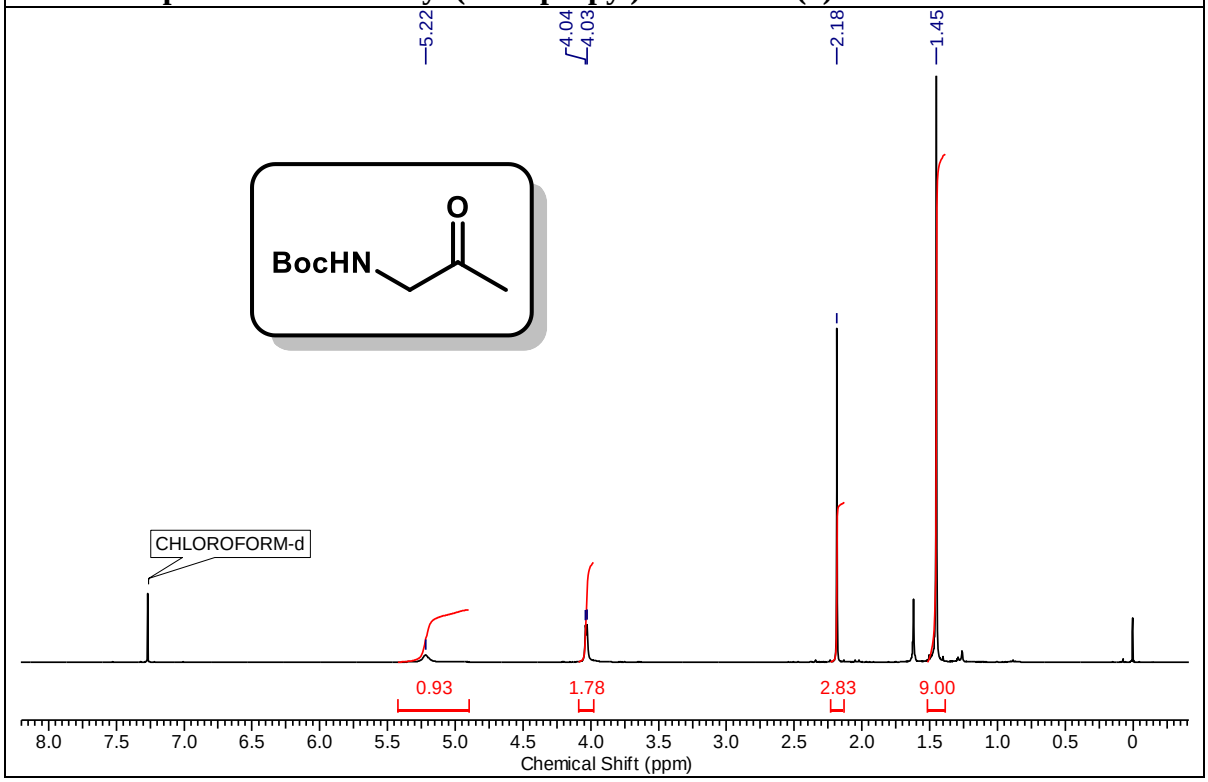
^{13}C-NMR spectrum of *tert*-butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate(3)



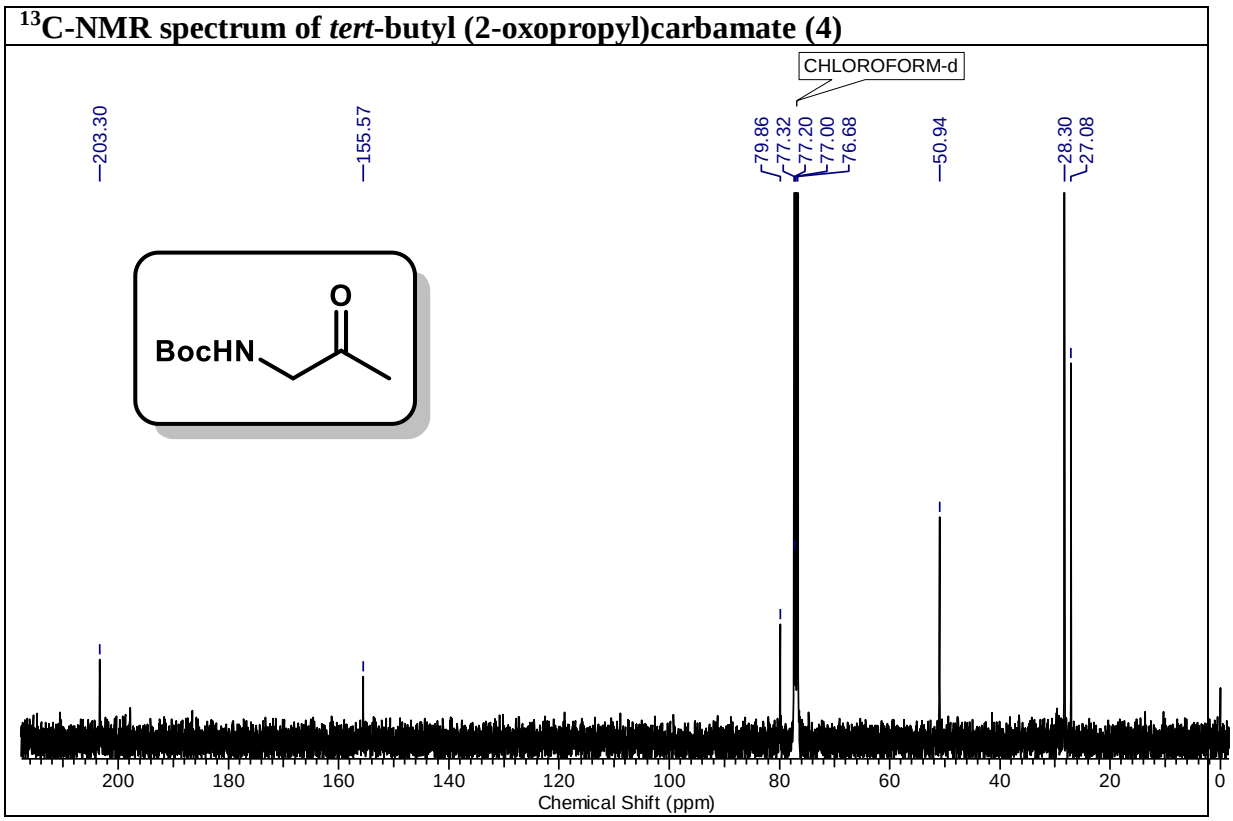
DEPT NMR spectrum of *tert*-Butyl 4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (3)



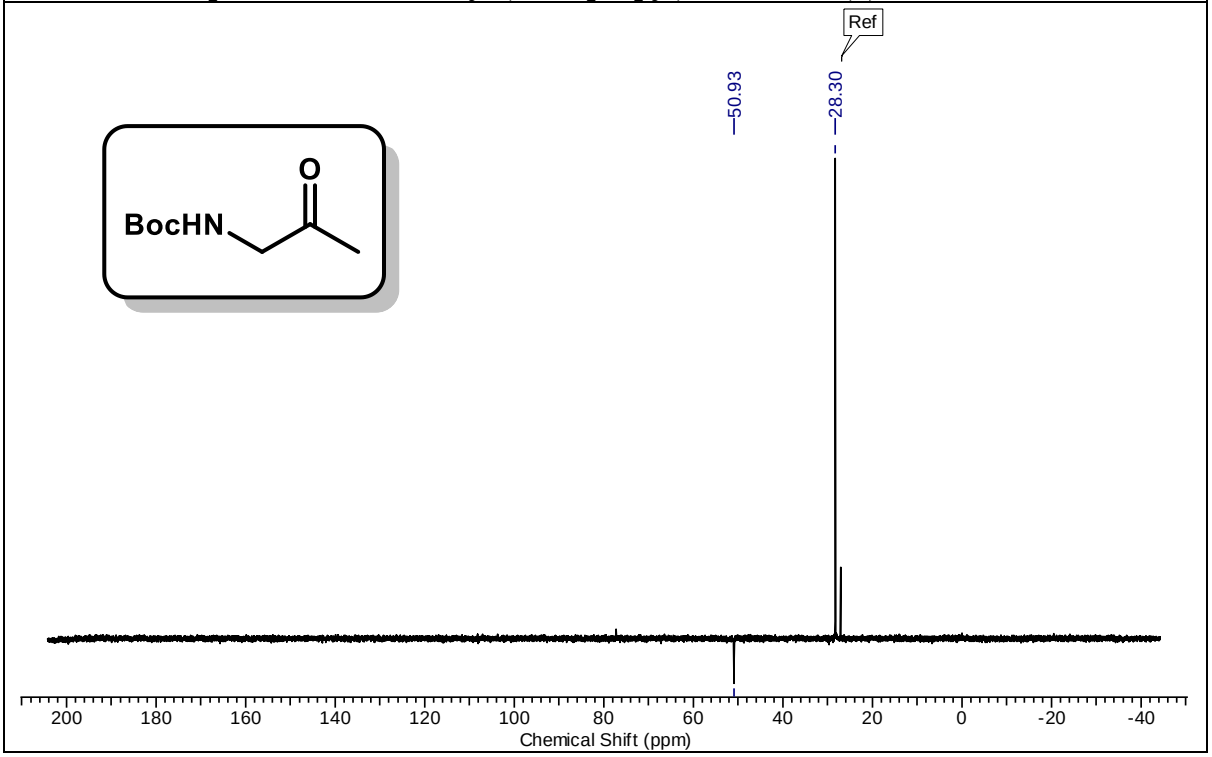
^{1}H-NMR spectrum of *tert*-butyl (2-oxopropyl)carbamate (4)



^{13}C-NMR spectrum of *tert*-butyl (2-oxopropyl)carbamate (4)



DEPT NMR spectrum of *tert*-butyl (2-oxopropyl)carbamate (4)



References:

1. a) Dakin.; West. *J. Biol. Chem.*, **1928**, *78* (91), 757 b) Wiley, R. H.; Borum, O. H. *Organic Syntheses*, **1953**, *33*, 1963.

2. Chavan, S. P.: Pathak, A. B.; Dhawane, A. N.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 1510.

"A New Route Synthesis of Triazole in a "Green" Solvent"

4.1 Abstract:

A synthetic route for the direct conversion of arylazides into the corresponding trizoles via phase transfer catalyst-assisted [3+2] cycloaddition reaction under basic conditions in aqueous medium is reported. This synthetic methodology, which offers high yields and excellent regioselectivity for varieties of triazoles at 100 °C for 24 hr- 48 hr and this 'greener' synthesis constitutes an alternative to the previously reported well established click reactions

Figure 1. A new synthetic route for triazoles compound.

4.2 Introduction:

A hugely popular synthetic methodology which enables the chemist to prepare large variety of heterocyclic compounds *via* the Huisgen 1,3-dipolar cycloaddition can be referred as "Click chemistry." [1] Huisgen [3+2] cycloaddition of alkynes and azides under thermal conditions to obtain 1,2,3-triazoles has been widely popular over the period of one century. In particular, 1,2,3-triazole compounds are considered as the one of the most important privileged scaffold of all "click" reactions.[2]

1,4-Disubstituted 1,2,3-triazoles are recognized as an significant organic compounds in which many of them found variety of applications in medicinal field such as, anticancer, fungal bacterial , antituberculosis drugs, histone deacetylase inhibitors, bioorthogonal probes HIV protease inhibitors, corrosion inhibitors, lubricants, dyes, and photostabilizers and also used as a pharmaceuticals.[3] Thus, development of green and practical approach of triazoles is of significant interest.

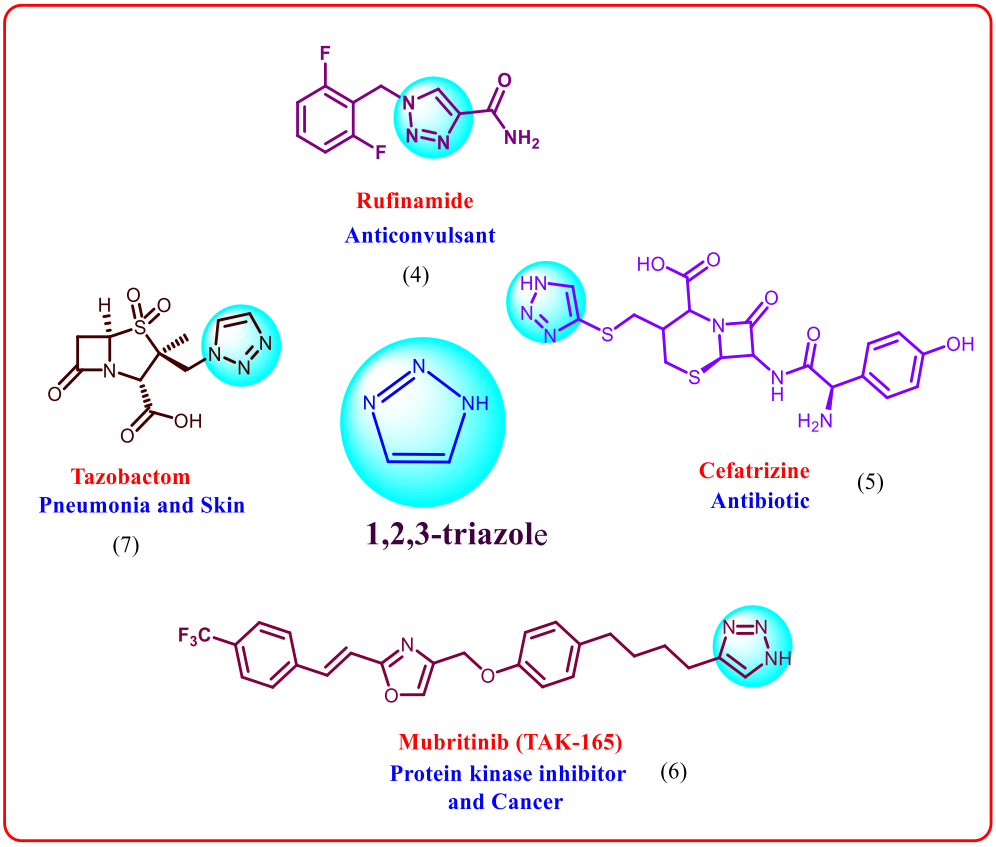


Figure 2. Important triazoles compounde used as a pharmaceuticals.

1,4 -disubstituted 1,2,3-triazoles regioselective synthesis is gaining huge attention in the last two decades due to excellent work carried out by Meldal and Sharpless groups in copper catalysed azide-alkyne [3+2] cycloaddition (CuAAC) reactions.[4] However, it can be obtained by (RuAAC) reactions.[5] Very recently nickel-catalyzed azide−alkyne cycloaddition (NiAAC)[6] to furnish 1,5 -disubstituted 1,2,3-triazoles in water has been developed.

It is worth noting that, 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles have been vastly used in medicinal chemistry (**Figure 1**, I & II) However, 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles synthesis have been less explored in the past by regioselective and thus, it was of interest to prepare these kind of compounds. According to reported methods, an alternative method which includes reaction of metal acetylides (metal=Li, Mg, Zn and Te) with organic azides and its subsequent *in situ* reaction with various electrophiles led to form metalated triazoles involve reverse selectivity and high reactivity.[7] Other synthetic approaches for the synthesis of triazoles involve palladium- or copper-catalyzed reactions [8] and reactions in presence of arylboronic

acid or potassium aryltrifluoroborates [9] and reaction of aryl azides with active methylenes or symmetrical ketones at higher temperatures.[10]

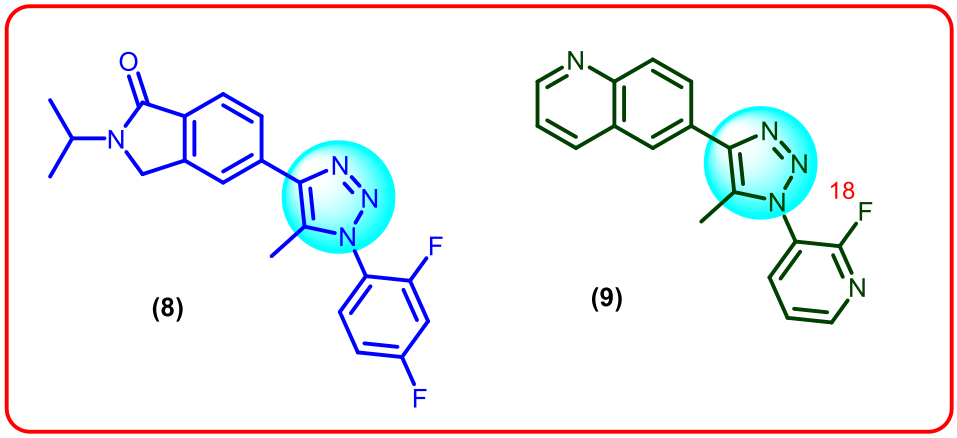


Figure 3. Important triazoles 8) mgluR1 antagonist and I. 9) PET ligand for imaging mGluR1.

Furthermore, water is used as a green as well as environmental friendly solvent as compared with organic solvents for chemical reactions. Nowadays, many successful examples of catalytic reactions using metal that can be smoothly performed under aqueous conditions.[11]

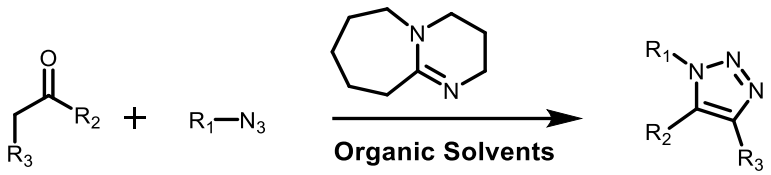
Organocatalytic azide-aldehyde[12] and azide-ketone [13] using [3+2] cycloaddition to furnish 1,4 -disubstituted 1,2,3-triazoles has been successfully reported by Ramacharya. **(Scheme 1a).** In addition, 1,2,3-triazoles were synthesized by reaction of unactivated ketones with azide was developed by Bressy.[14] Unfortunately, both the above methods have been limited to organic solvents such as DMSO and CH_2Cl_2 respectively. However, development of enamine catalysed azide-ketone organic transformation to yield 1,2,3-triazoles under aqueous conditions by Wang.[15] **(Scheme 1b)** Despite having aqueous conditions, this method in presence of organocatalyst containing long aliphatic chain. Herein, out interest to address the issue of aqueous phase for click chemistry reaction.

It can be noticed that, CuAAC or RuAAC click chemistry reactions containing alkynes substrates which are more expensive than aldehyde derivatives. For example, phenylacetylene and phenylacetaldehyde having commercial price of $76 and only $33 respectively each for 100 mL (Aldrich). Most of the above methods, either used low reactive, costly or non-commercial substrates instead of simple starting materials such as phenylacetaldhyde or arylacetones. Many of them also indeed involved requirement of organic solvents, toxic

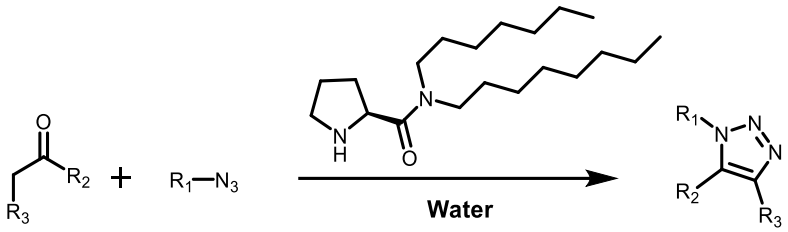
transition-metal catalysts, loading stoichiometric amounts of catalysts, tedious workup procedures and inert reaction atmosphere which are less attractive and lead above reaction conditions inferior.

To overcome this difficulty, herein we present a general metal-free synthetic approach for the regioselective synthesis of 1,4 -disubstituted 1,2,3-triazoles by reaction of arylazides with aldehydes or ketones in water as the only solvent in higher yields is presented.

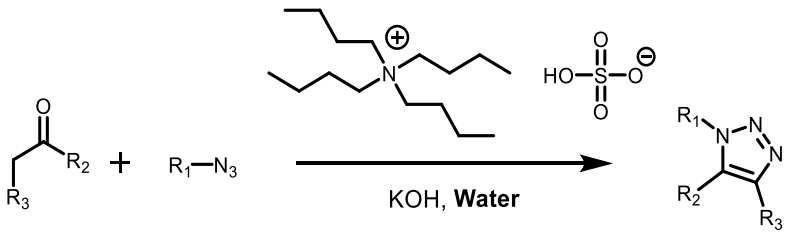
a) Enolate-mediated click reaction between azide and aldehydes or ketones using organic solvents by Ramacharya (*Angew. Chem.* **2014**, *126*, 10588 –10592)



b) Enamine catalysed click reaction between azide and ketones using water as a solvent by Wang (*Green Chem.*, **2013**, *15*, 2384–2388.)



c) Enolate-mediated click reaction between azide and aldehydes or ketones in water as a solvent: present work



Scheme 1. Synthesis of triazoles proceeding *via* [3+2] Huisgen cycloaddition reaction between azide and aldehyde or ketone.

4.3 Results and Discussions:

Initially, efforts were made in optimizing the click reaction for the model reaction between phenyl azide and phenyl acetaldehyde by varying base and catalysts in water under various reaction conditions. In our first attempts, formation of desired triazole was not observed under neat thermal conditions in water. (Entry 1, Table 1) Unfortunately, similar results were recorded in absence of either any of the catalyst or base. (Entries 2-3, Table 1) Trace amount of corresponding triazole was observed in presence of alkali. (KOH+ K_2CO_3) (Entry 4, Table 1) Literature study reveals that phase transfer catalyst such as TBAHS under basic conditions in water have been used for transition metal free reactions of amides with peroxides.[16] Therefore, It was decided to try phase transfer catalyst in order to sustain the reaction mixture in aqueous medium. Interestingly, moderate yields of 64% and 61%, 69% were obtained for the formation of triazole in presence of TBAHS as a catalyst and with potassium carbonate, sodium carbonate and cesium carbonate as a base respectively (Entries 5-7, Table 1) Furthermore, TBAHS as a catalyst and in presence of weak bases such as sodium bicarbonate and potassium bicarbonate afforded poor yields of 25% and 42% respectively. (Entries 8-9, Table 1) Surprisingly, by using same catalyst in presence of KOH as a base at room temperature, only 21% for the formation of desired triazole was observed even after prolonged time of 48 hours. (Entry 10, Table 1) 61% of yield was obtained for triazole by using NaOH as a base under similar catalytic conditions at 100 °C. (Entry 11, Table 1) Pleasingly, 77% of isolated yield was achieved in presence of KOH as a base and TBAHS as a catalyst in water as only solvent at 100 °C after 24 hours. (Entry 12, Table 1) This value is significantly higher than that achieved in presence of alternative catalysts such as TBAB and TBAI under similar reaction conditions 66% and 62% respectively. (Entries 13-14, Table 1)

Upon lowering both the catalyst to 10 mol% and base (0.21 mmol) poor yield 45% was obtained. (Entry 15, Table 1,) There was no major improvement in reaction rate after increasing the catalyst loading as well as base amount. (Entry 16, Table 1, 75%) However, decreasing the temperature to 50 °C caused a rapid loss in the chemical yield to 48%. (Entry 17, Table 1) It can be noticed that, the appropriate amount of water (1.0mL) was also found to be a critical

factor for this synthetic approach as 70% of chemical yield was obtained in presence of less volume of water. (Entry 18, Table 1)

Finally, it was possible successful obtain the synthesis of exclusively 1,4-disubstituted 1,2,3-triazoles for the reaction involving phenyl azide (0.21 mmol) and phenyl acetaldehyde (0.21 mmol) in presence of TBAHS as a catalyst (0.042 mmol) and potassium hydroxide (0.42 mmol) as a base in water as a solvent at 100 °C for 24 hours. This is the best optimized reaction conditions in hand for this protocol to obtain maximum yield of 77% for triazole. (Table 1)

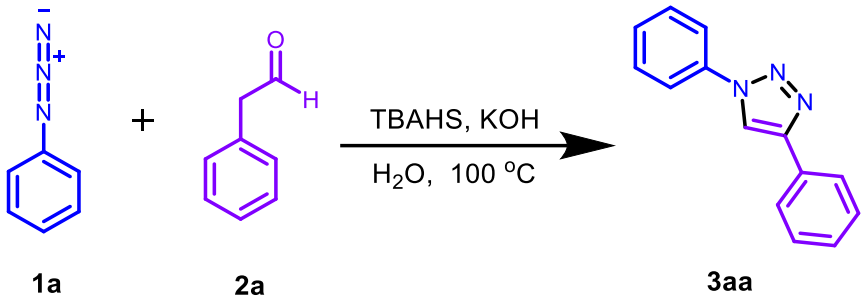


Table 1: Optimization of reaction conditions between arylazide and aldehyde to form triazole. [a]

Entry	Base (2 equi.)	Catalyst (20 mol %)	Time (Hour)	Temp. ° C	Yield (%)[b]
1	none	none	24	100	0
2	none	TBAHS	24	100	0
3	K_2CO_3	none	24	100	0
4	KOH	K_2CO_3	24	100	10
5	K_2CO_3	TBAHS	24	100	64
6	Na_2CO_3	TBAHS	24	100	61
7	Cs_2CO_3	TBAHS	24	100	69
8	$NaHCO_3$	TBAHS	24	100	25
9	$KHCO_3$	TBAHS	24	100	42
10	KOH	TBAHS	48	RT	21
11	NaOH	TBAHS	24	100	61
12	**KOH**	**TBAHS**	**24**	**100**	**77**
13	KOH	TBAB	24	100	66
14	KOH	TBAI	24	100	62
15[c]	KOH	TBAHS	24	100	45
16[d]	KOH	TBAHS	24	100	75
17	KOH	TBAHS	24	50	48
18[e]	KOH	TBAHS	24	100	70

[a] All reactions were carried out with **1a** (0.21 mmol), **2a** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL). [b] Isolated yields after column chromatography. [c] catalyst- 10 mol% and KOH- 0.21 mmol [d] catalyst- 30 mol% and KOH- 0.63 mmol [e] Water- 0.5 mL [f] TBAHS = Tetrabutyl ammonium hydrogen sulfate, TBAB = Tetrabutylammonium bromide, TBAI = Tetrabutylammonium iodide.

With optimized reaction conditions in hand a variety of carbonyl compounds were reacted with phenyl azide in order to achieve the synthesis of desired triazoles. Interestingly, hydocinnamaldehyde despite of containing extra methylene group showed 59% yield for the formation of corresponding triazole after prolonged reaction time of 48 hours. (Entry 2, Table 2) In addition, reaction was monitored in presence of simple aliphatic aldehydes to investigate the electronic and acidic nature of the alpha methylene groups of aldehydes **2**. Surprisingly, the formations of desired triazoles were not observed from the reaction between aliphatic aldehydes and phenyl azide under optimized reaction conditions. (Entries 3 and 4, Table 2) Aliphatic aldehydes (2 c-d, Table 2) having less acidic alpha-methylene groups as compared with aromatic aldehydes (2 a-b, Table 2) and hence lack of possibility to form enolate intermediate to produce triazole. Unfortunately, reaction was also unsuccessful in case of aliphatic esters with phenyl azide under similar reaction conditions. (Entries 5 and 6, Table 2 Later, the reactivity of ketones were also and thus explored reaction was performed between ketones and phenylazide to obtain the corresponding of triazoles. Pleasingly, treatment of phenyl azide with 2-phenylacetophenone and 4-chloro phenylacetone afforded corresponding triazoles in excellent yields 99% and 98% respectively. (Entries 7 and 8, Table 2) Acidity of a compound is directly related to the stability of its conjugate base. In case of ketones, enolate ion is resonance stabilised. On the other hand, esters also containing conjugate base which is resonance stabilized but here the negative charge of the conjugate base is stabilized by the same exact oxygen atom whose lone pair is involved in resonance. Hence, here the resonance is not that effective and thus the conjugate base of ketone is more stable and leads to a more acidic compound.

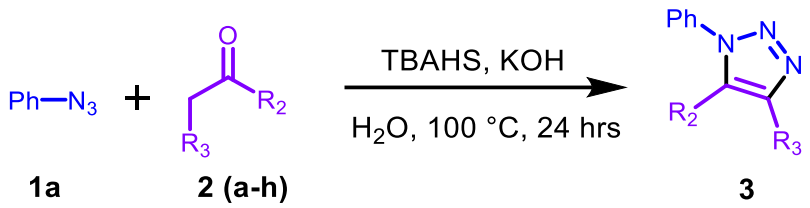
After getting these encouraging results, the scope of arylazides **1 (a-e)** with ketones **2** was explored in order to study the generality as well as potential of this approach for further synthetic exploitation. Table 3 clearly showed that the noteworthy cycloaddition reactions were performed well and without being affecting by the electronic nature of the substituents on the aromatic rings. Fascinatingly, a variety of arylazides (1a-e) including electron withdrawing groups such as chloro, bromo at para position (3cg-3dm, Table 3), electron-donating groups like methyl group at para position (3eg-3em, Table 3), or electron-neutral (3ag-3ao, Table 3) groups on the aromatic ring delivering the corresponding products of triazoles in good to excellent yields. Notably, benzyl azide 1b was also suitable for this system to afford the desired

triazoles in good to high yields, regardless of an additional methylene group between phenyl ring and azido moiety. (3bg-3bj, Table 3)

In view of these above results, a variety investigated of ketones **2 (g-o)** with arylazides **1** in (3+2) cycloaddition reaction at 100 °C were. Interestingly, among the various examined aromatic substituted ketones, all produce the triazolees in well to excellent yields. In a similar manner to azides, electronic nature of the substituentwas also tested. Stimulatingly, phenylacetone having electron withdrawing groups such as chloro at para and trifluoromethyl group at *meta* position affords to desired triazoles in 98% and 85% respectively. (3ah and 3al, Table 3) In addition, in case of phenylacetone having electron donating group such as methoxy group at para position afforded desired triazole product in 82% yield. (3am, Table 3) Interestingly, aromatic ketone having electron donating group such as methoxy group even after incorporating both sides of the phenyl ring at para positions did not affect the reaction rate and which delivers corresponding triazoles in good to excellent yields. (3ak, 3ck and 3dk, Table 3, 81%, 97%, 84%) pleasingly, 1-Phenyl-2-butanone also showed similar results leading to corresponding triazoles in excellent yields (3ai and 3ci, Table 3, 99%, 92%) The best yield was obtained with 2-phenylacetophenone, which afforded the desired triazole in 99% isolated yield (3ag, Table 3) However, when alkyl ketones namely 2-butanone and 2- octanone were employed in this process, as expected the reaction did not proceed to yield the desired triazole to produce 0% product (3ao and 3ap, Table 3). As aliphatic ketones containing less acidic alpha-methylene groups in comparison with aromatic ketones and thus there is less probability to form enolate ion as an intermediate for subsequent (3+2) cycloaddition reaction to yield triazoles. The results in Table 3 demonstrate the broad scope of this synthetic approach covering a structurally diverse group of aryl azides (2g–o) and aromatic ketones (1a-e).

It is worth mentioning that, yields obtained for many of the products **3** were excellent especially taking in to account in water as an only solvent. In fact, twenty-six different compounds of triazoles were prepared by this synthetic route and out of which fourteen compounds are novel compounds. (See the Supporting Information S1).

Table 2: Scope of carbonyl compounds with arylazide to form triazole. [a]

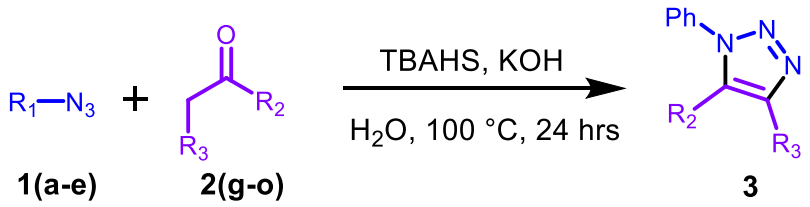


1a **2 (a-h)** **3**

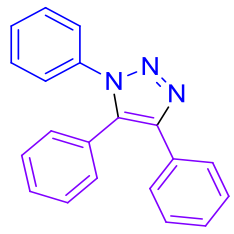
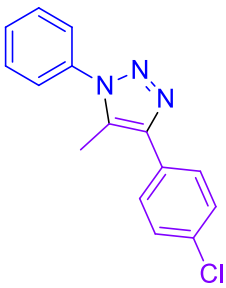
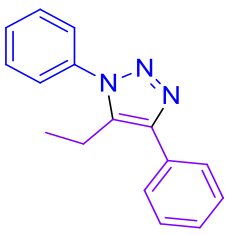
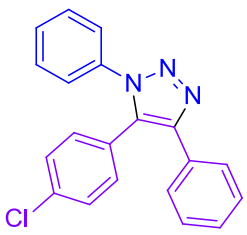
Entry	Substrate 2 (R_3)	Substrate 2 (R_2)	Product	Yield (%)[b]
1	Ph	H	3aa	77
2[c]	$PhCH_2$	H	3ab	59
3	$MeCH_2CH_2$	H	3ac	0
4	$MeCH_2CH_2CH_2$	H	3ad	0
5	MeCO	OCH_2CH_3	3ae	0
6	MeCO	OCH_3	3af	0
7	**Ph**	**Ph**	**3ag**	**99**
8	4-ClC_6H_4	CH_3	3ah	98

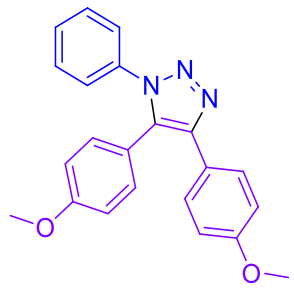
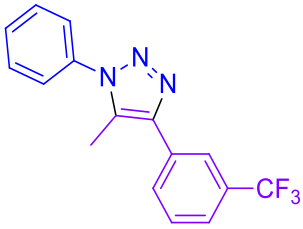
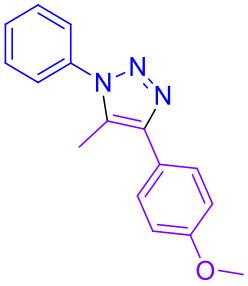
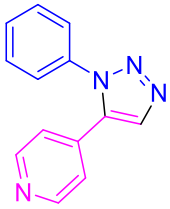
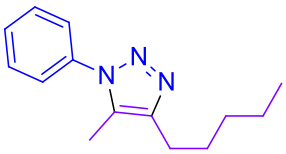
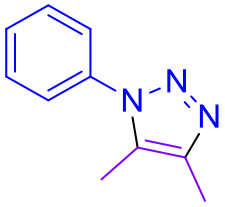
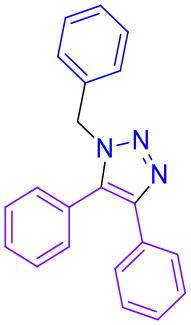
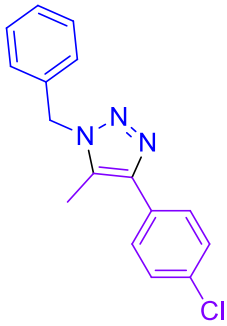
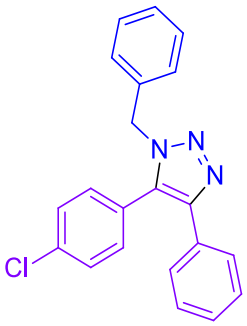
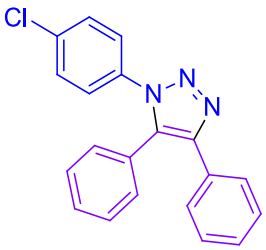
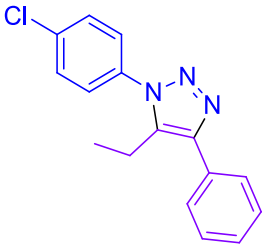
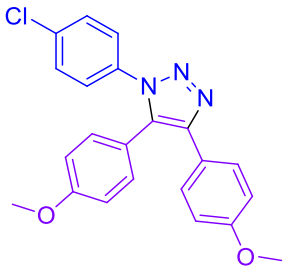
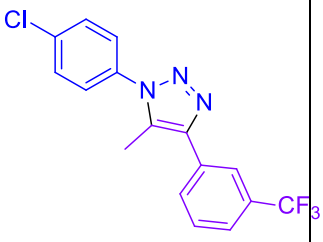
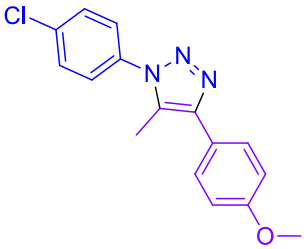
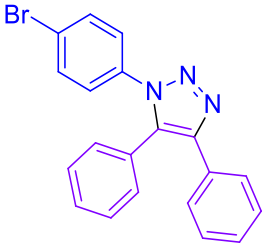
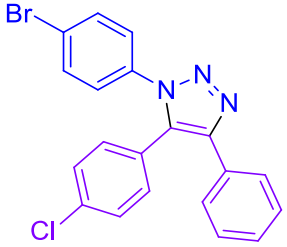
[a] All reactions were carried out with **1a** (0.21 mmol), **2a** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL) and was stirred at 100 °C for 24 hr. [b] Isolated yields after column chromatography. [c] Reaction time: 48 hr.

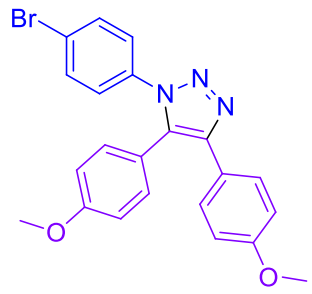
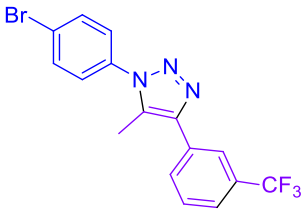
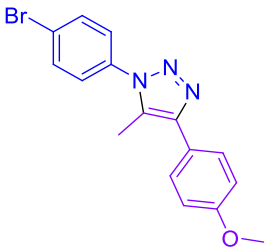
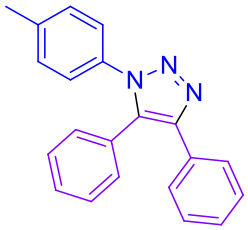
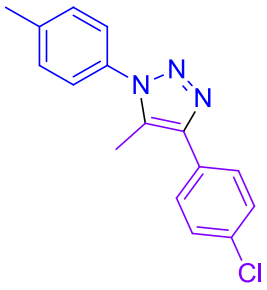
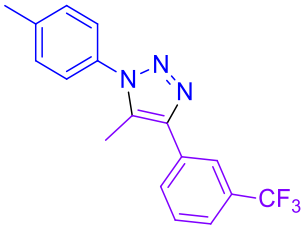
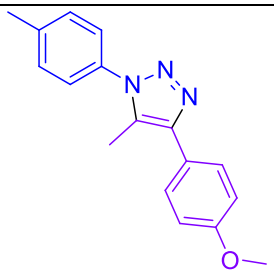
Table 3: Substrate scope. [a]



1(a-e) **2(g-o)** **3**

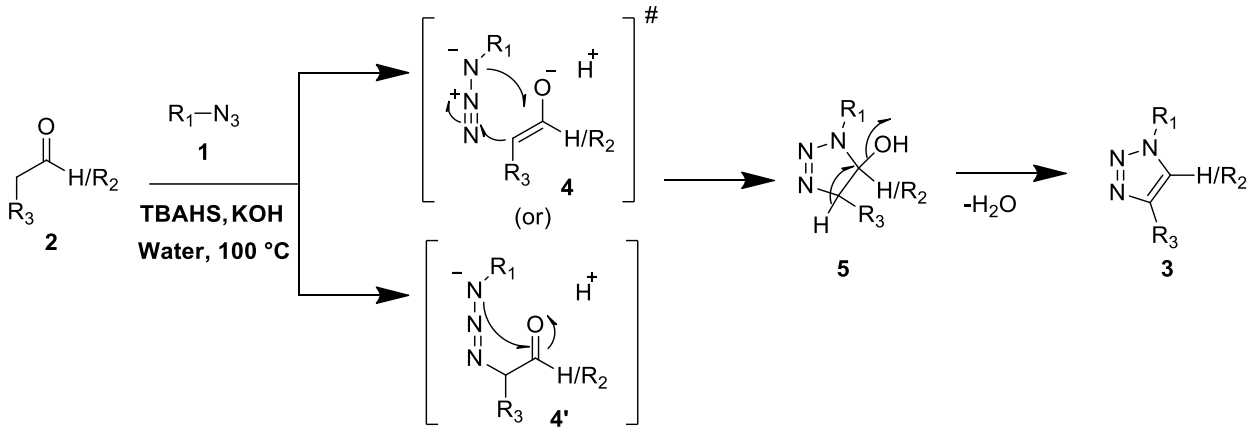
 **3ag,** 99 %	 **3ah,** 98 %	 **3ai,** 99 %	 **3aj,** 87 %

 **3ak,** 81 %	 **3al,** 85 %	 **3am,** 82 %	 **3an,** 43 %
 **3ao,** 0**%**	 **3ap,** 0 %	 **3bg,** 78 %	 **3bh,** 81 %
 **3bj,** 92 %	 **3cg,** 74 %	 **3ci,** 92 %	 **3ck,** 97 %
 **3cl,** 84 %	 **3cm,** 88 %	 **3dg,** 94 %	 **3dj,** 91 %

 **3dk,** 84 %	 **3dl,** 98 %	 **3dm,** 98 %	 **3eg,** 78 %
 **3eh,** 87 %	 **3el,** 90 %	 **3em,** 96 %	

[a] All reactions were carried out with **1a** (0.21 mmol), **2a** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL) and was stirred at 100 °C for 24 hr.

The possible intermediates to the synthesis of triazole 3 from 1 and 2 (either with aldehyde or ketone) by using phase transfer catalyst such as TBAHS under basic conditions with KOH in water as a solvent is illustrated in **Scheme 2**. The reaction of phase transfer catalyst with phenylacetaldehyde/ phenylacetones **2** under basic conditions bring about the formation of enolate ion intermediate **4** or **4'**, which subsequently affords the 1,2,3-triazolines adduct **5** *via* concerted or stepwise [3+2] cycloaddition amination–cyclization reaction [8,9]. Furthermore, adduct **5** can be converted into the corresponding 1,2,3-triazole **3** by loss of water. In other words, dehydration reaction at ambient reaction conditions leads to form desired triazole **3**. It can be noticed that, TBAHS acts as a phase transfer catalyst in aqueous medium which potentially leads to generate enolate ion as an intermediate under basic conditions. Reported method suggested that phase transfer mediated cycloaddition reaction process under TBAHS in KOH. [17]



Scheme 2. Plausible reaction mechanism for the (3+2) cycloaddition reaction between azide and aldeyde or ketone.

4.4 Conclusions:

In conclusion, the simple, useful, greener route developed for enolate-mediated azide-aldehyde or ketone [3+2]-cycloaddition reaction has been which enables the synthesis of important 1,4-disubstituted 1,2,3-triazoles containing variety of functional groups. The current method is featured with metal-free conditions with excellent regioselectivity to a library of well decorated 1,2,3-triazoles. A noteworthy feature of this click reaction is that it procees with water as the only solvent to furnish corresponding triazoles in good to excellent yields. Further work is in progress in laboratory for this newly developed method to other types of reactions and will be presented shortly.

4.5. Experimental Section

4.5.1. General methods and materials

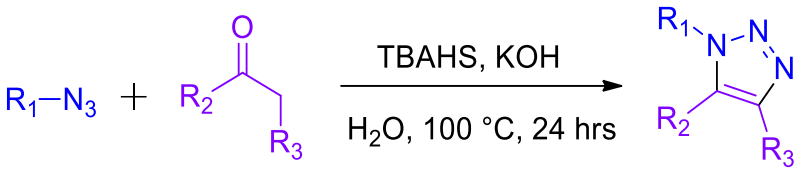
Azidobenzene solution ~0.5 M in tert-butyl methyl ether (95%), Benzyl bromide (reagent grade, 98%), Sodium azide (Reagaent Plus, 99%), 1-Azido-4-chlorobenzene solution ~0.5 M in tert-butyl methyl ether (95%), 1-Azido-4-bromobenzene solution ~0.5 M in tert-butyl methyl ether (95%), 4-Azidotoluene solution ~0.5 M in tert-butyl methyl ether (95%), Phenylacetaldehyde (90%), Hydrocinnamaldehyde (95%), Pentanal (97%), Hexanal (98%), Ethyl acetoacetate (99%), Methyl acetoacetate (Reagaent Plus, 99%), 2-Phenylacetophenone (97%), 1-Phenyl-2-butanone (98%), 4′-Chloro-2-phenylacetophenone (97%), Desoxyanisoin (98%), 3-(Trifluoromethyl)phenylacetone (97%), 4-Methoxyphenylacetone (97%), 2-Butanone ACS reagent, 99%), 2-Octanone (98%), Tetra-n-butylammonium hydrogen sulfate,

Tetrabutylammonium bromide (Reagaent Plus, 99%), Tetrabutylammonium iodide (99%), Sodium hydroxide (98%), Potassium hydroxide, Sodium carbonate anhydrous, potassiumcarbonate (99%), Cesium carbonate (Reagaent Plus, 99%), Sodium bicarbonate (ACS reagent, 99%), Potassium bicarbonate (ACS reagent, 99%), Sodium chloride (99%), Pentane (anhydrous, 99%), Hexane (anhydrous, 95%) and dimethyl sulfoxide (anhydrous, 99.9%) were purchased from Sigma-Aldrich and used without further purification. 4-Chlorophenylacetone is purchased from SynQuest laboratories. Petroleum ether and Ethyl acetate used for column purification purpose after distillation. Ultrapure water (Type I water, ISO 3696) was obtained from a Milli-Qs purification system (Merck Millipore).

General: All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus *via* rubber septa. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel. The ^{1}H NMR spectra were recorded on 200, 400, and 500 MHz NMR spectrometers using solvent residue signal as an internal standard [^{1}H NMR: $CDCl_3$ (7.27); ^{13}C NMR: $CDCl_3$ (77.00). The ^{13}C NMR spectra were recorded on 200 NMR (50 MHz), 400 NMR (100 MHz), and 500 NMR (125 MHz) spectrometers. HRMS (ESI) were taken on an Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. Column chromatographic separations were carried out on silica gel (60–120 mesh and 230–400 mesh).

4.5.2. General procedure for the synthesis: In an ordinary glass tube equipped with a magnetic stirring bar, to aldehydes or ketones (0.21 mmol, 1 equiv.), TBAHS (14 mg, 0.042 mmol, 20 mol %) and potassium hydroxide (23 mg, 0.42 mmol, 2 equiv.) were added successively in Milli-Q water (1.0 mL) at room temperature. Finally, corresponding arylazide (0.21 mmol, 1 equiv.) was added to above reaction mixture. This reaction mixture was stirred at room temperature for 2 minutes which was subsequently heated for 24 hours to 48 hours at 100 °C. The reaction progress was monitored by TLC and after consumption of starting aldehyde/ketone, reaction mixture was cooled to room temperature. The crude reaction mixture was extracted with ethyl acetate (3 x 7 mL). These combined mixtures of organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. Pure product **3** was obtained by column chromatography (silica gel, mixture of petroleum ether/ethyl acetate).

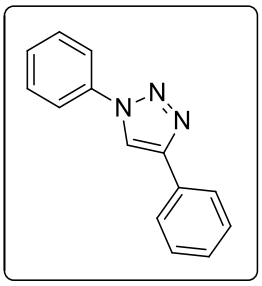
Characterization of the product was performed using ^{1}H- and ^{13}C-NMR and Mass spectrometry. Characterization data of all known triazoles were compared to literature.[2,3,4,5]



27 examples Yield: 43-95%

4.6. NMR Spectral Data:

1, 4-Diphenyl-1*H*-1, 2, 3-triazole (3aa)



Yield: 77 %

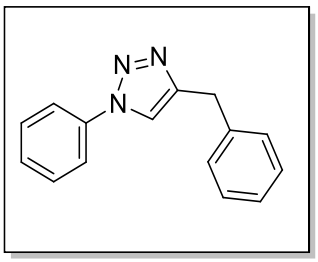
IR($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.21 (s, 1H), 7.94 (td, *J* = 8.4, 1.2 Hz, 2H), 7.81 (br d, *J* = 8.4 Hz, 2H), 7.57 (tt, *J* = 7.2, 2.0 Hz, 2H), 7.54-7.47 (m, 3H), 7.38 (tt, *J* = 7.2, 2.0 Hz, 1H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.4, 137.0, 130.2, 129.8, 128.9, 128.8, 128.4, 125.8, 120.5, 117.6;

HRMS m/z calculated for $C_{14}H_{11}N_3H$ ($M + H^+$): 222.1026 Found: 222.1023.

4-Benzyl-1-phenyl-1*H*-1,2,3-triazole (3ab):



Yield: 59 %

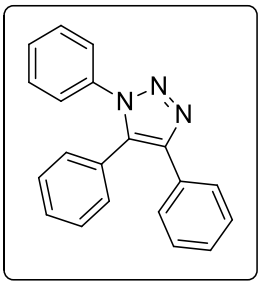
IR ($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) 7.70 (d, *J* = 7.6 Hz, 2H), 7.61 (br s, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.34-7.33 (m, 4H), 7.27-7.25 (m, 1H), 4.19 (s, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.5, 138.8, 137.1, 129.6, 128.8, 128.6, 128.5, 126.6, 120.4, 119.7, 32.3;

HRMS m/z calculated for $C_{15}H_{13}N_3H$ (M + H^+): 236.1182 Found: 236.1178.

1,4,5-Triphenyl-1*H*-1,2,3-triazole (3ag):



Yield: 99 %;

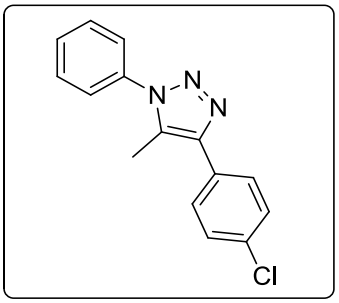
IR ($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ7.61 (dd, J = 8.0, 2.0 Hz, 2H), 7.40-7.38 (m, 6H), 7.37-7.33 (m, 5H), 7.31 (d, J = 6.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.8, 136.5, 133.7, 130.1, 130.2, 129.3, 129.1, 129.0, 128.9, 128.5, 127.9, 127.7, 127.3, 125.1;

HRMS m/z calculated for $C_{20}H_{15}N_3H$ (M + H^+): 298.1339 Found: 298.1334.

4-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-1, 2, 3-triazole (3ah):



Yield: 98 %;

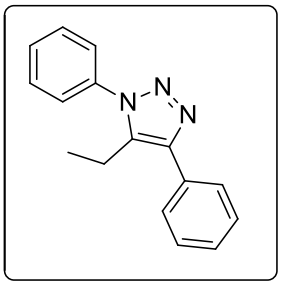
IR ($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.67 (br d, J = 8.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 2.39 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.5, 135.9, 133.4, 129.6, 129.4, 129.2, 128.6, 128.0, 124.9, 9.9;

HRMS m/z calculated for $C_{15}H_{12}ClN_3H$ (M + H^+): 270.0793 Found: 270.0790

Data for 5-Ethyl-1,4-diphenyl-1*H*-1,2,3-triazole (3ai):



Yield: 99%**;**

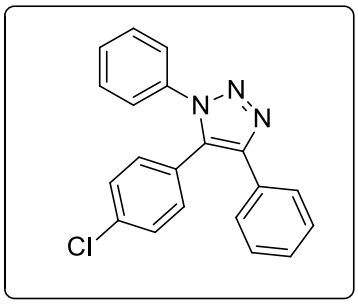
IR ($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80 (d, J = 7.6 Hz, 2H), 7.58-7.57 (m, 3H), 7.51-7.47 (m, 4H), 7.39 (t, J = 7.6 Hz, 1H), 2.94 (q, J = 7.6 Hz, 2H), 1.10 (t, J = 7.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.1, 136.5, 135.5, 131.4, 129.7, 129.5, 128.7, 127.8, 127.2, 125.8, 16.7, 13.2;

HRMS m/z calculated for $C_{16}H_{15}N_3H$ ($M + H^+$): 250.1339 Found: 250.1335.

5-(4-chlorophenyl)-1,4-diphenyl-1*H*-1,2,3-triazole (3aj):



Yield: 87%:

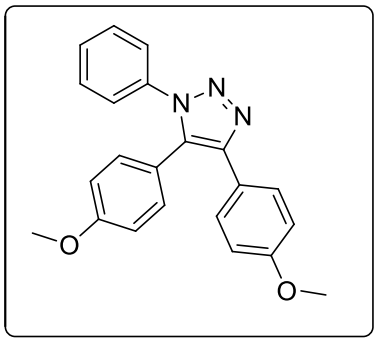
IR ($CHCl_3$): V_{max} 3600, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.54-7.52 (m, 2H), 7.39-7.37 (m, 3H), 7.31-7.28 (m, 7H), 7.11-7.10 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 145.0, 136.2, 135.6, 132.5, 131.4, 130.5, 129.4, 129.3, 129.2, 128.6, 128.1, 127.4, 126.1, 125.2;

HRMS m/z calculated for $C_{20}H_{14}ClN_3H$ ($M + H^+$): 332.0949 Found: 332.0944.

4,5-bis(4-methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazole (3ak):



Yield: 81%;

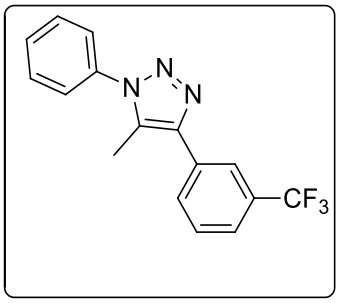
IR ($CHCl_3$): V_{max} 3600, 2955, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56-7.54 (m, 2H), 7.40-7.39 (m, 2H), 7.38-7.36 (m, 1H), 7.33-7.30 (m, 2H), 7.10-7.08(m, 2H), 6.89- 6.86 (m, 4H), 3.83 (s, 6H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.8, 158.9, 144.1, 136.4, 132.5, 131.1, 128.8, 128.4, 128.2, 124.8, 123.2, 119.4, 114.2, 113.6, 54.9;

HRMS m/z calculated for $C_{22}H_{19}N_3O_2H$ ($M + H^+$): 358.1550 Found: 358.1544.

5-methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3al):



Yield: 85%**;**

IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 1330 cm^{-1};

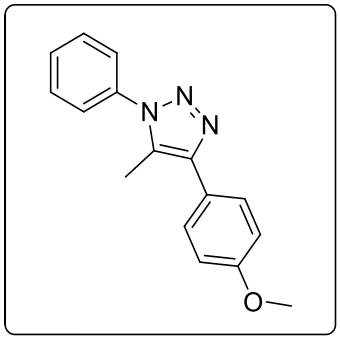
^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07 (s, 1 H), 7.98 (dd, *J*=4.17, 1.77 Hz, 1 H), 7.63 -7.57 (m, 3 H), 7.56 -7.48 (m, 4 H), 2.51 (s, 3 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.5, 136.0, 132.2, 130.2, 129.7, 129.6, 127.0, 125.2, 124.4, 124.3, 123.8, 10.2;

^{19}F NMR ($CDCl_3$, 400 MHz) δ -62.68 (S);

HRMS m/z calculated for $C_{16}H_{12}F_3N_3H$ ($M + H^+$): 304.1054 Found: 304.1049.

4-(4-methoxyphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole (3am):



Yield: 82%;

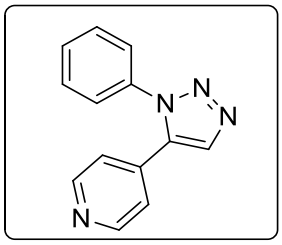
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.71 (td, J = 9.0, 2.5 Hz, 2H), 7.54-7.51 (m, 2H), 7.51-7.49 (m, 3H), 7.02 (td, J = 9.0, 2.5 Hz, 2H), 3.85 (s, 3H), 2.44 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.5, 144.9, 136.6, 129.7, 129.3, 128.7, 128.4, 125.4, 124.2, 114.4, 55.5, 10.4;

HRMS m/z calculated for C16H15N3OH (M + H^+): 266.1288 Found: 266.1286

4-(1-phenyl-1*H*-1,2,3-triazol-5-yl)pyridine (3an):



Yield: 46%;

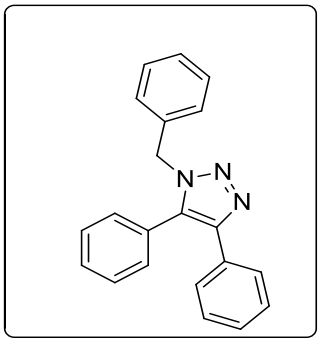
IR ($CHCl_3$): V_{max} 3600, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.54 (s, 2H), 7.92 (s, 1H), 7.45-7.41 (m, 3H), 7.27-7.24 (m, 2H), 7.08-7.07 (m, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.4, 136.3, 135.5, 135.4, 134.5, 130.3, 130.1, 125.6, 122.9;

HRMS m/z calculated for $C_{16}H_{15}N_3OH$ (M+ H^+): 223.0977 Found: 223.0978.

1-benzyl-4,5-diphenyl-1*H*-1,2,3-triazole (3bg):



Yield: 78%

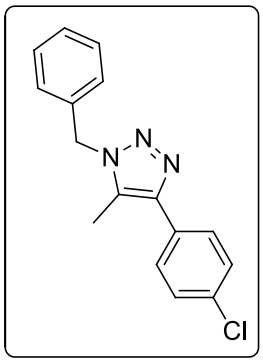
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ7.45-7.43 (m, 2H), 7.35-7.34 (m, 1H), 7.32-7.30 (m, 2H), 7.17-7.13 (m, 6H), 7.08-7.07 (m, 2H), 7.06-7.05 (m, 2H), 5.32 (s, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.8, 135.6, 134.5, 131.1, 130.3, 129.3, 129.1, 129.0, 128.9, 128.7, 128, 4, 127.9, 127.7, 127.0, 126.7, 52.3;

HRMS m/z calculated for $C_{21}H_{17}N_3H$ ($M + H^+$): 312.1495 Found: 312.1489.

1-benzyl-4-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole (3bh):



Yield: 81 %;

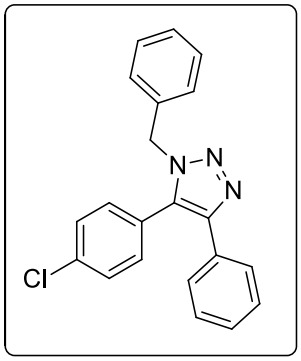
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.61-7.57 (m, 2H), 7.39-7.35 (m, 3H), 7.34-7.31 (m, 2H), 7.30-7.29 (m, 2H), 5.51 (s, 2H,), 2.28 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.9, 134.5, 133.2, 130.0, 129.0, 128.8, 128.2, 127.1, 52.0, 9.1;

HRMS m/z calculated for $C_{16}H_{14}ClN_3H$ ($M + H^+$): 284.0944 Found: 284.0945.

1-benzyl-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3bj):



Yield: 92 %;

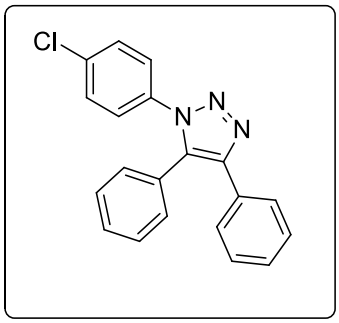
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.54−7.50 (m, 2H), 7.40− 7.35 (m, 2H), 7.27−7.23 (m, 6H), 7.07−7.04 (m, 2H), 7.03−6.99 (m, 2H), 5.39 (s, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.7, 135.9, 135.1, 132.6, 131.4, 130.5, 129.4, 128.7, 128.5, 128.2, 127.8, 127.3, 126.7, 126.2, 117, 52.1

HRMS m/z calculated for $C_{21}H_{16}ClN_3H$ ($M + H^+$): 346.1106 Found: 346.1108.

1-(4-chlorophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3cg):



Yield: 74 %;

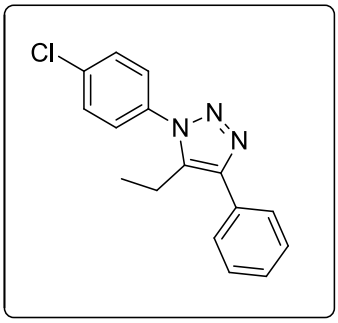
IR ($CHCl_3$): V_{max} 3600, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.44-7.39 (m, 3H), 7.36-7.29 (m, 5H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 8.0, 1.2 Hz, 2H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.6, 134.7, 134.6, 133.4, 130.2, 130.1, 129.8, 129.0, 128.9, 128.2, 128.0, 127.4, 127.0, 125.9;

HRMS m/z calculated for C20H14ClN3H ($M + H^+$): 332.0949 Found: 332.0946.

1-(4-chlorophenyl)-5-ethyl-4-phenyl-1*H*-1,2,3-triazole (3ci):



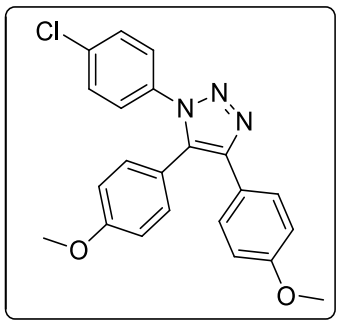
Yield: 92 %;

IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.77 (d, *J*=7.63 Hz, 2 H) 7.57 (d, *J*=8.01 Hz, 2 H) 7.47 - 7.45 (m, 4 H) 7.42 - 7.40 (m, 1 H) 2.91 (q, *J*=7.25 Hz, 2 H) 1.09 (t, *J*=7.44 Hz, 3 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.7, 136.1, 135.8, 134.2, 131.5, 130.0, 129.0, 127.5, 127.2, 16.9, 13.5; **HRMS m/z** calculated for C16H14ClN3H ($M + H^+$): 284.0949 Found: 284.0950.

1-(4-chlorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3ck):



Yield: 97 %;

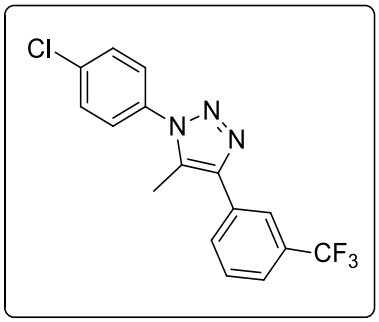
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) 7.45 (dq, *J*=6.85, 1.87 Hz, 2 H) 7.27 - 7.17 (m, 4 H) 7.02 - 6.98 (m, 2 H) 6.80 - 6.73 (tt, *J*=8.63, 1.85 Hz, 4 H) 3.73 (s, 6 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.9, 159.9, 145.2, 135.8, 135.3, 134.0, 132.0, 129.9, 129.1, 126.8, 123.9, 119.9, 115.2, 114.5, 55.9;

HRMS m/z calculated for $C_{22}H_{18}ClN3O_2H$ ($M + H^+$): 392.1160 Found: 392.1161.

1-(4-chlorophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3cl):



Yield: 84 %;
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 1330, 750 cm^{-1};

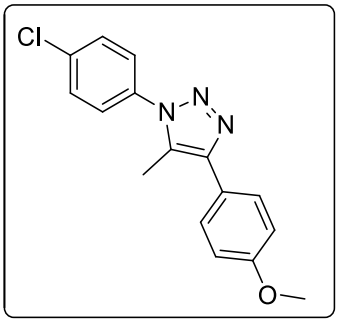
^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 1H), 7.94 (t, *J* = 1.5 Hz, 1H), 7.74 – 7.60 (m, 3H), 7.43 – 7.27 (m, 3H), 2.51 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.4, 135.7, 133.5, 133.3, 132.8, 132.4, 130.9, 129.9, 127.3, 124.7, 124.4, 10.8 (s);

^{19}F NMR ($CDCl_3$, 400 MHz) δ -62.71 (S);

HRMS m/z calculated for $C_{16}H_{11}ClF3N_3H$ (M + H^+): 338.0594 Found: 338.0.

1-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3cm):



Yield: 88 %**;**

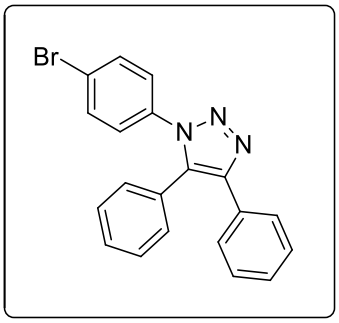
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 750 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.70 - 7.65 (m, 2 H), 7.52 - 7.43 (m, 4 H), 7.03 - 6.99 (m, 2 H) 3.85 (s, 3 H) 2.45 (s, 3 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.8, 134.4, 134.3, 129.1, 127.9, 125.7, 123.1, 113.6, 54.7, 9.6;

HRMS m/z calculated for $C_{16}H_{14}ClN3OH$ (M + H^+): 300.0898 Found: 300.0898.

1-(4-bromophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3dg):



Yield: 94 %;

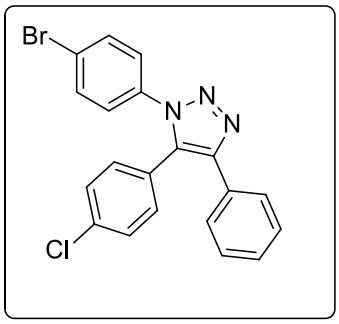
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 1330, 720 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.69 (dd, J = 7.6, 2.4 Hz, 2H), 7.60 (br d, J = 8.8 Hz, 2H), 7.49-7.40 (m, 3H), 7.39-7.30 (m, 3H), 7.29- 7.27 (m, 4H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.7, 135.2, 133.4, 132.0, 130.4, 130.2, 129.8, 129.2, 128.2, 128.0, 127.3, 127.0, 126.1, 122.6;

HRMS m/z calculated for $C_{20}H_{14}BrN3H$ ($M + H^+$): 376.0444 Found: 376.0444.

1-(4-bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3dj):



Yield: 91 %;

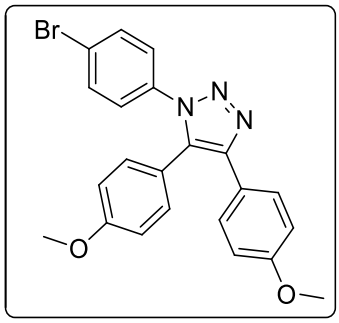
IR ($CHCl_3$): Vmax 3600, 2850, 1650-2000, 1330, 750, 720 cm-1;

^{1}H NMR (CDCl3, 200 MHz) δ 7.57 - 7.55 (m, 4 H), 7.37 - 7.36 (m, 2 H), 7.35 - 7.33 (m, 3 H), 7.20 - 7.14 (m, 4 H);

^{13}C NMR (CDCl3, 50 MHz) δ 144.9, 135.6, 135.5, 132.2, 131.1, 130.5, 129.4, 128.3, 128.0, 127.1, 126.2, 125.5, 122.9;

HRMS m/z calculated for C20H13BrClN3H (M + H+): 411.9955 Found: 411.0087.

1-(4-bromophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3dk):



Yield: 84 %;

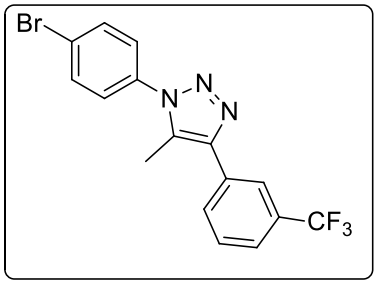
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 720 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56- 7.52 (m, 4 H), 7.27- 7.17 (m, 2H), 7.18 - 7.09 (m, 2 H) 6.93 - 6.84 (m, 4 H) 3.85 (s, 6 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.3, 159.4, 144.6, 135.7, 132.3, 131.4, 128.5, 126.4, 123.2, 122.7, 119.3, 114.7, 113.9, 55.3;

HRMS m/z calculated for $C_{22}H_{18}BrN3O_2H$ ($M + H^+$): 436.0655 Found: 436.0656.

1-(4-bromophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3dl):



Yield: 98 %;

IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 1330, 720 cm^{-1};

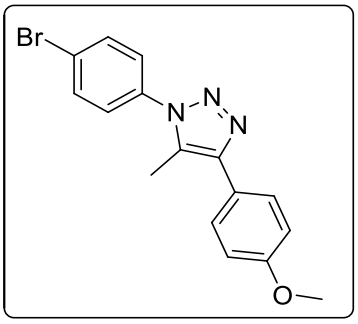
^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 1H), 7.96 (t, *J* = 1.5 Hz, 1H), 7.64 – 7.56 (m, 3H), 7.55- 7.48 (m, 3H), 2.51 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.7, 135.8, 135.6, 132.0, 131.5, 130.2, 129.9, 129.3, 126.4, 124.6, 124.5, 123.9, 123.8, 121.3, 10.2;

^{19}F NMR ($CDCl_3$, 400 MHz) δ -62.69 (S);

HRMS m/z calculated for $C_{16}H_{11}BrF_3N3H$ ($M + H^+$): 382.0161 Found: 382.0158.

1-(4-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3dm):



Yield: 98 %;

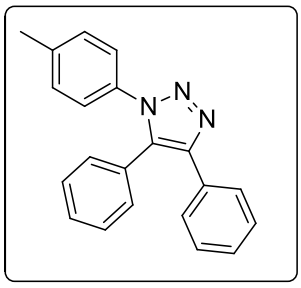
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 720 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.71 - 7.65 (m, 4 H) 7.41 - 7.37 (m, 2 H) 7.03 – 6.99 (m, 2 H) 3.85 (s, 3 H) 2.45 (s, 3 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.0, 145.6, 136.0, 133.3, 129.1, 127.2, 124.2, 117.2, 114.8, 55.9, 10.8;

HRMS m/z calculated for $C_{16}H_{14}BrN3OH$ ($M + H^+$): 344.0393 Found: 344.0393

4,5-diphenyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eg):



Yield: 78 %;

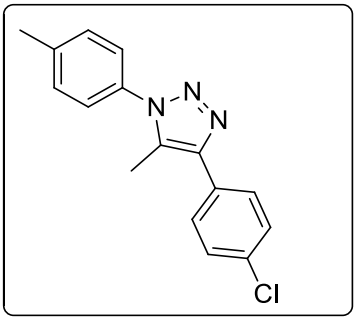
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.62 (td, J = 8.5, 2.0 Hz, 2H), 7.39 (tt, J = 7.0, 1.5 Hz, 1H), 7.37 (tt, J = 7.0, 1.5 Hz, 2H), 7.33-7.28 (m, 3H), 7.21 (td, J = 7.0, 1.5 Hz, 2H), 7.20-7.17 (m, 4H), 2.35 (s, 3H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.6, 139.0, 134.0, 133.7, 130.8, 130.1, 129.6, 129.2, 128.9, 128.4, 127.7, 127.6, 127.3, 124.9, 21.1;

HRMS m/z calculated for $C_{21}H_{17}N3H$ ($M + H^+$): 312.1495 Found: 312.1494.

4-(4-chlorophenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eh):



Yield: 87 %;

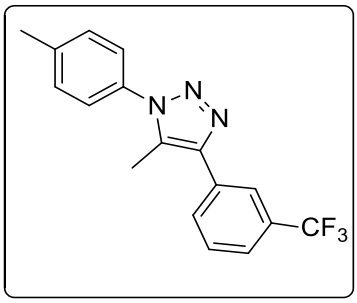
IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 720 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.96 (s, 1 H), 7.86 (dd, *J*=4.02, 1.82 Hz, 1 H), 7.52 - 7.49 (m, 2 H), 7.27- 7.25 (m, 4 H), 2.38 (m, 6 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.3, 139.9, 133.6, 132.4, 131.7, 131.2, 130.1, 129.2, 126.8, 125.1, 124.3, 124.2, 123.8, 123.7, 121.3, 21.2, 10.1;

HRMS m/z calculated for $C_{16}H_{14}ClN3H$ ($M + H^+$): 284.0949 Found: 284.0948.

5-methyl-1-(p-tolyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3el):



Yield: 90 %;

IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000, 1330 cm^{-1};

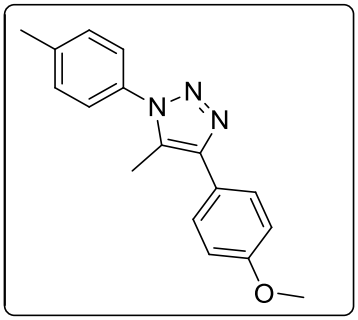
^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65 (s, 1 H), 7.60 (t, *J* = 1.5 Hz, 1H), 7.37 - 7.31 (m, 3 H), 7.30 - 7.25 (m, 3 H) 2.36 (s, 6 H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.6, 139.8, 133.7, 133.6, 130.1, 128.9, 128.3, 125.1, 21.2, 10.2;

^{19}F NMR ($CDCl_3$, 400 MHz) δ -62.69 (S);

HRMS m/z calculated for $C_{17}H_{14}F_3N3H$ ($M + H^+$): 318.1213 Found: 318.1213.

4-(4-methoxyphenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3em):



Yield: 96 %;

IR ($CHCl_3$): V_{max} 3600, 2850, 1650-2000 cm^{-1};

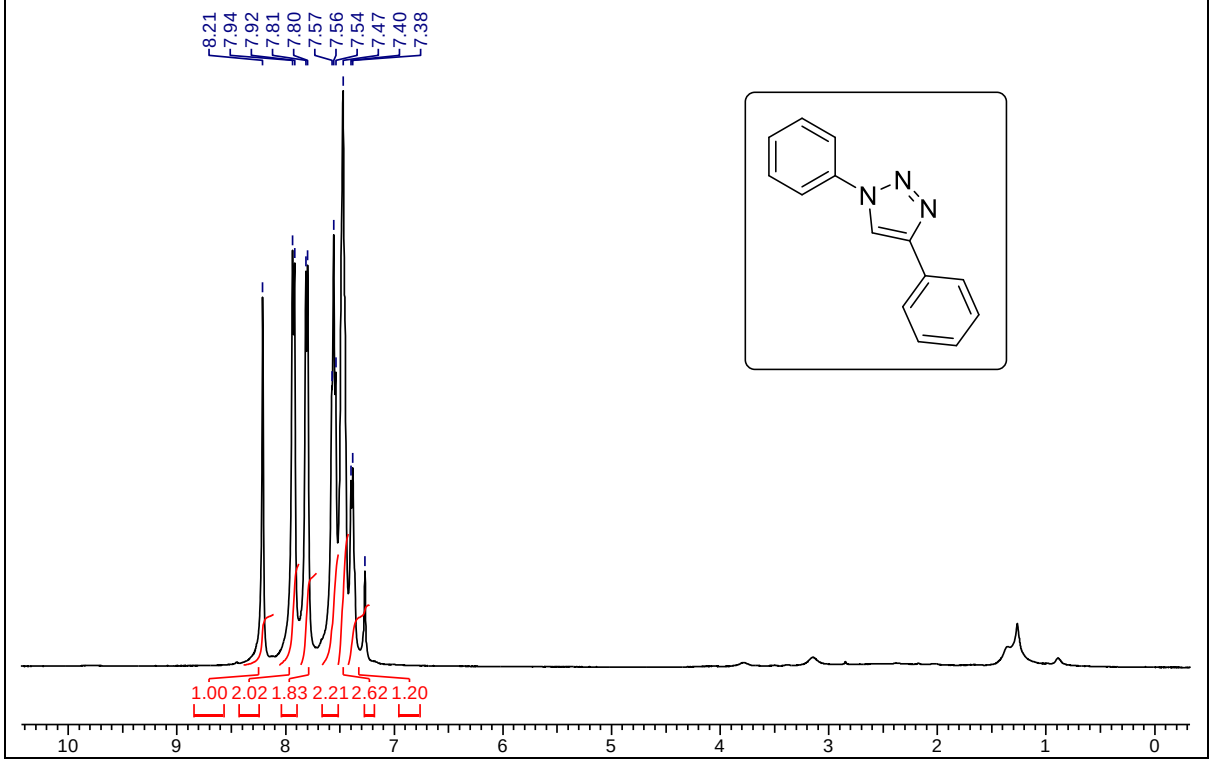
^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66 - 7.59 (m, 2 H), 7.31 - 7.27 (m, 4 H), 6.97 - 6.90 (m, 2 H), 3.76 (m, 3 H), 2.36 (m, 6 H):

^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.8, 145.1, 140.1, 134.5, 130.6, 129.6, 129.0, 125.6, 124.7, 114.7, 55.8, 21.8, 10.7;

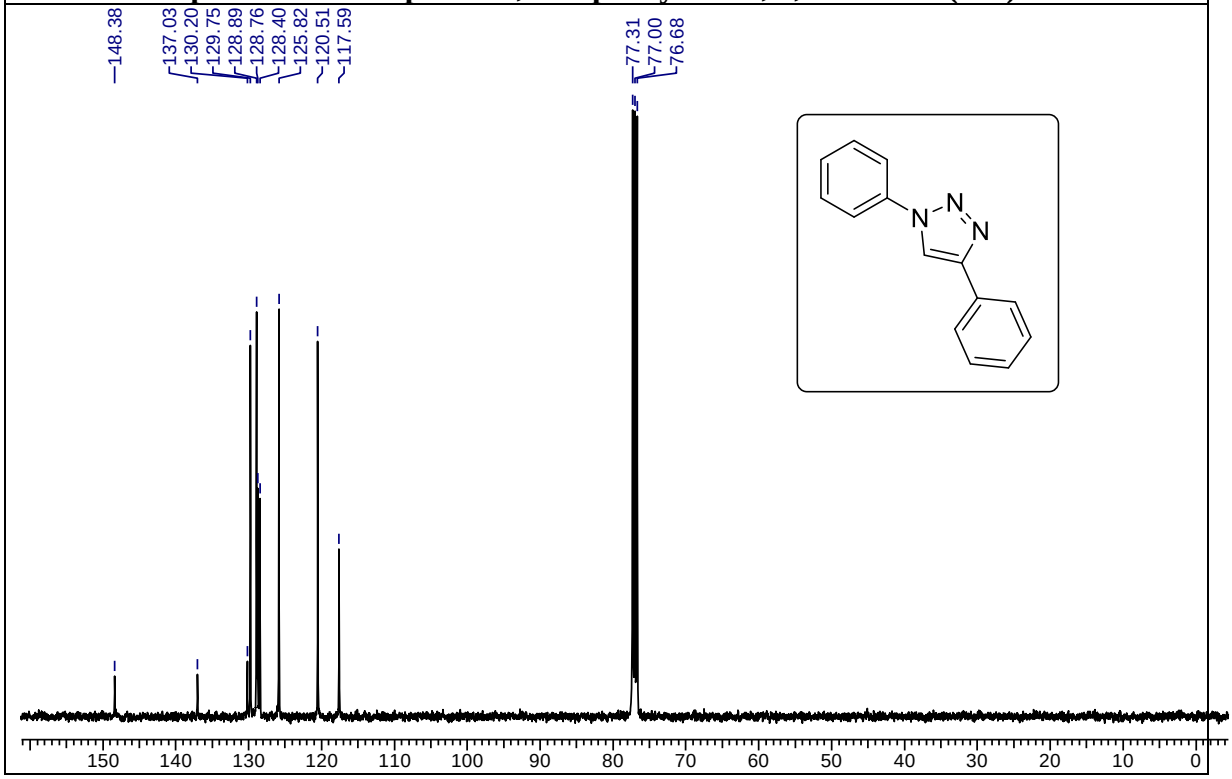
HRMS m/z calculated for $C_{17}H_{17}N3OH$ ($M + H^+$): 280.1444 Found: 280.1444.

4.1.4.5 Images for ^{1}H and ^{13}C NMR Spectral Data:

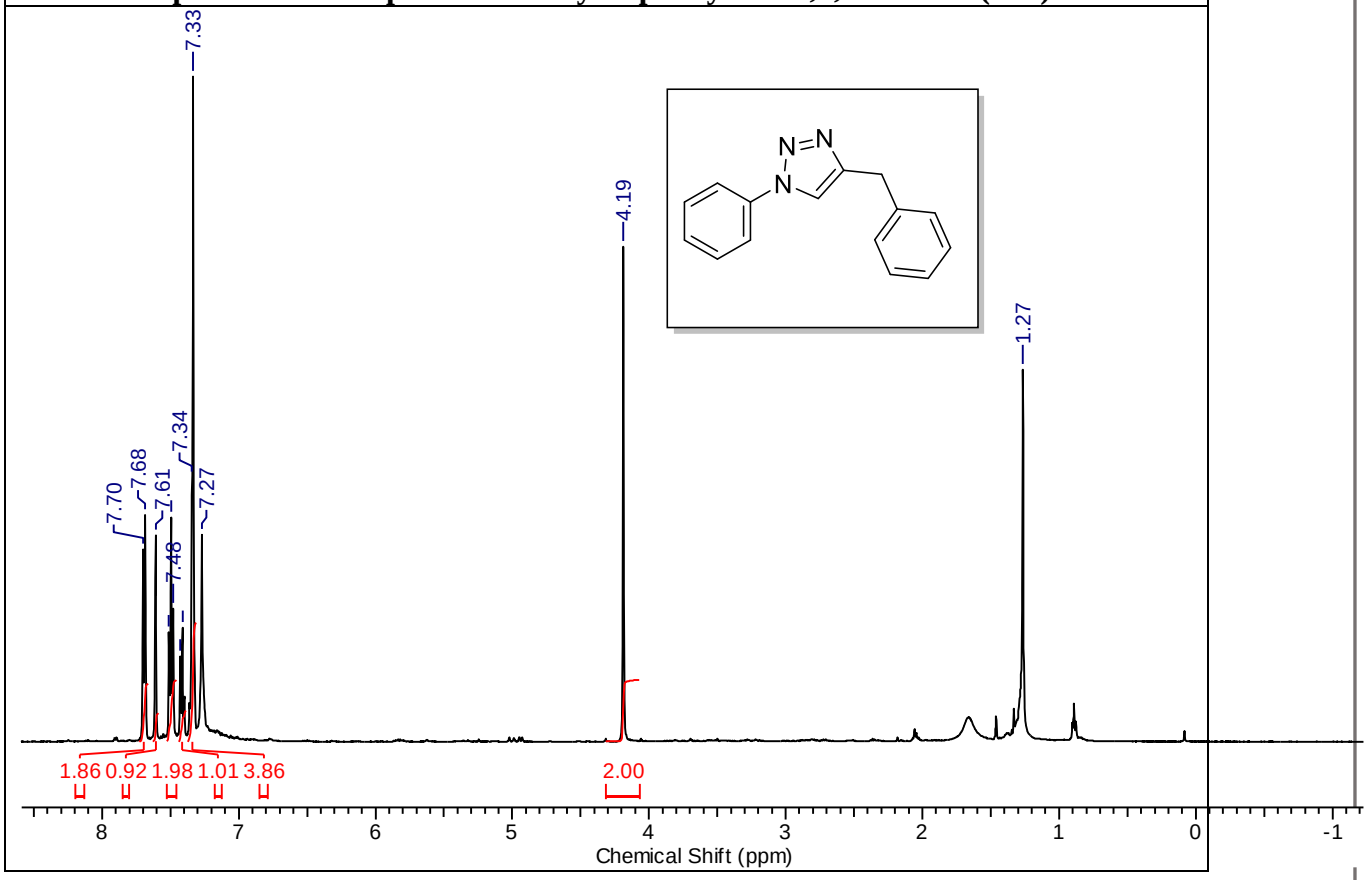
^{1}H-NMR spectrum of compound 1, 4-Diphenyl-1*H*-1, 2, 3-triazole (3aa)



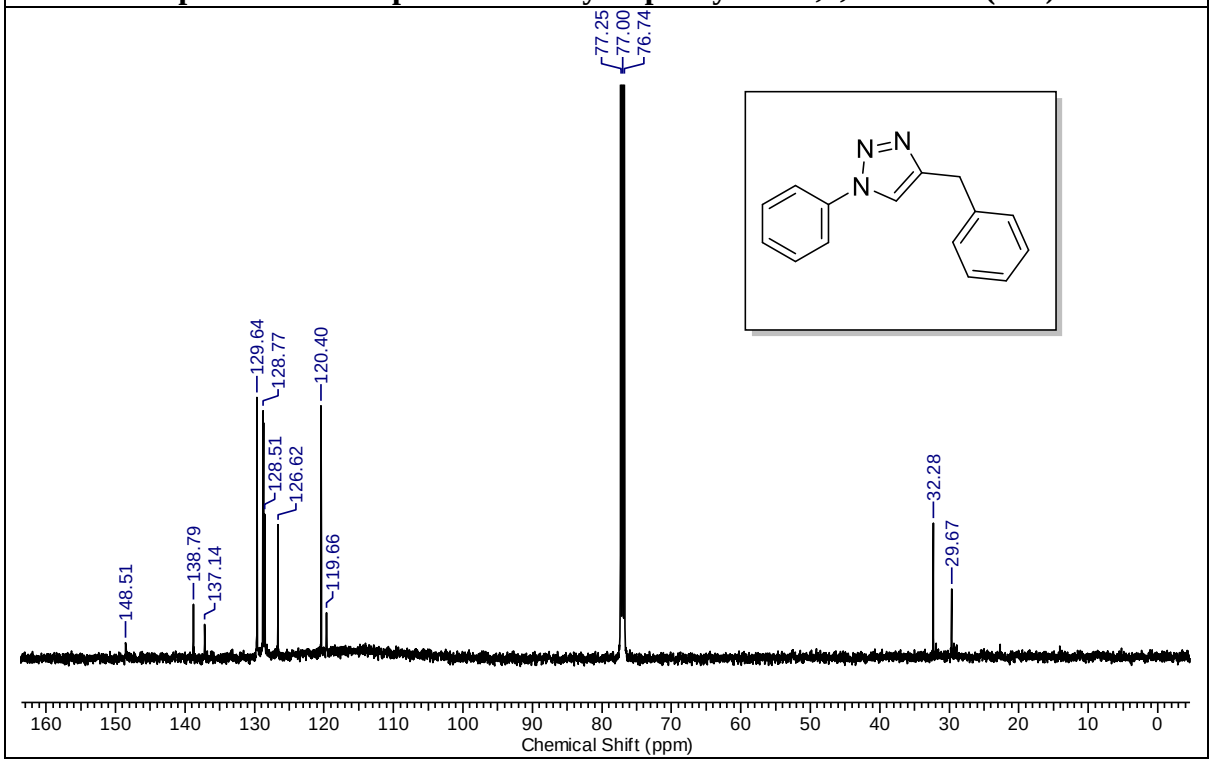
^{13}C-NMR spectrum of compound 1, 4-Diphenyl-1*H*-1, 2, 3-triazole (3aa)



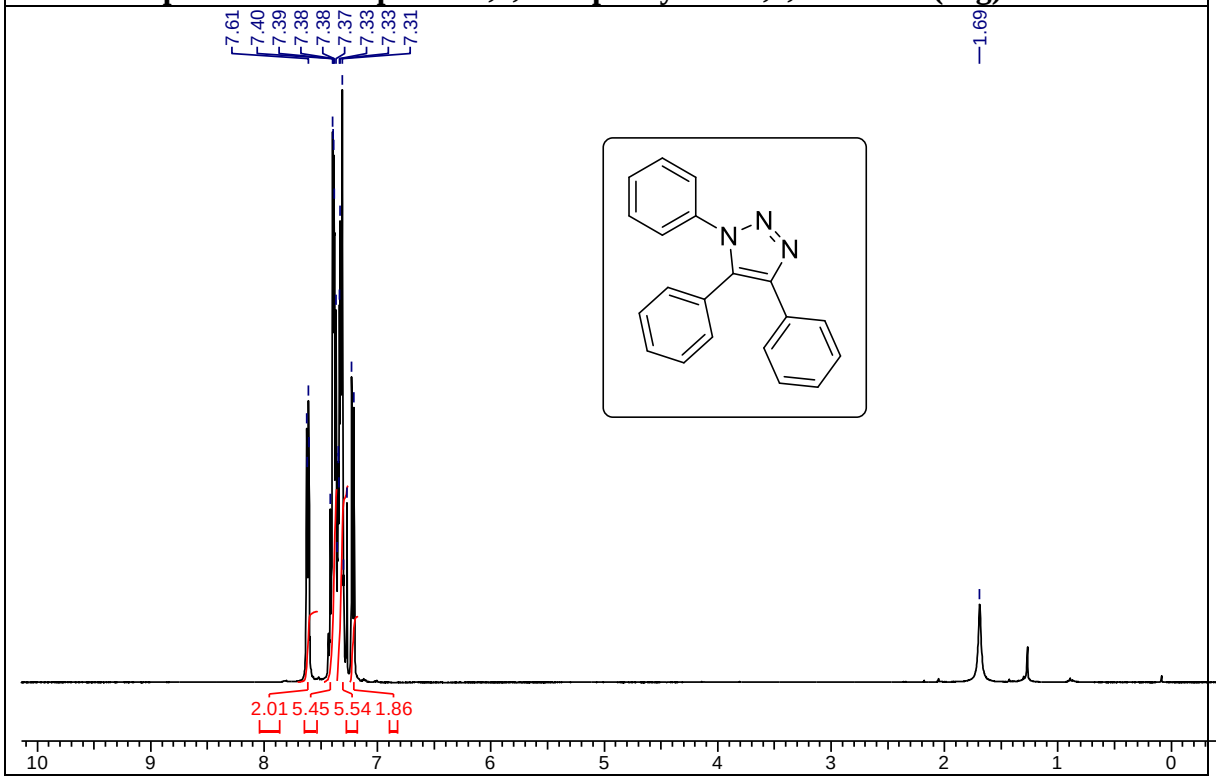
^{1}H-NMR spectrum of compound 4-Benzyl-1-phenyl-1*H*-1,2,3-triazole (3ab)



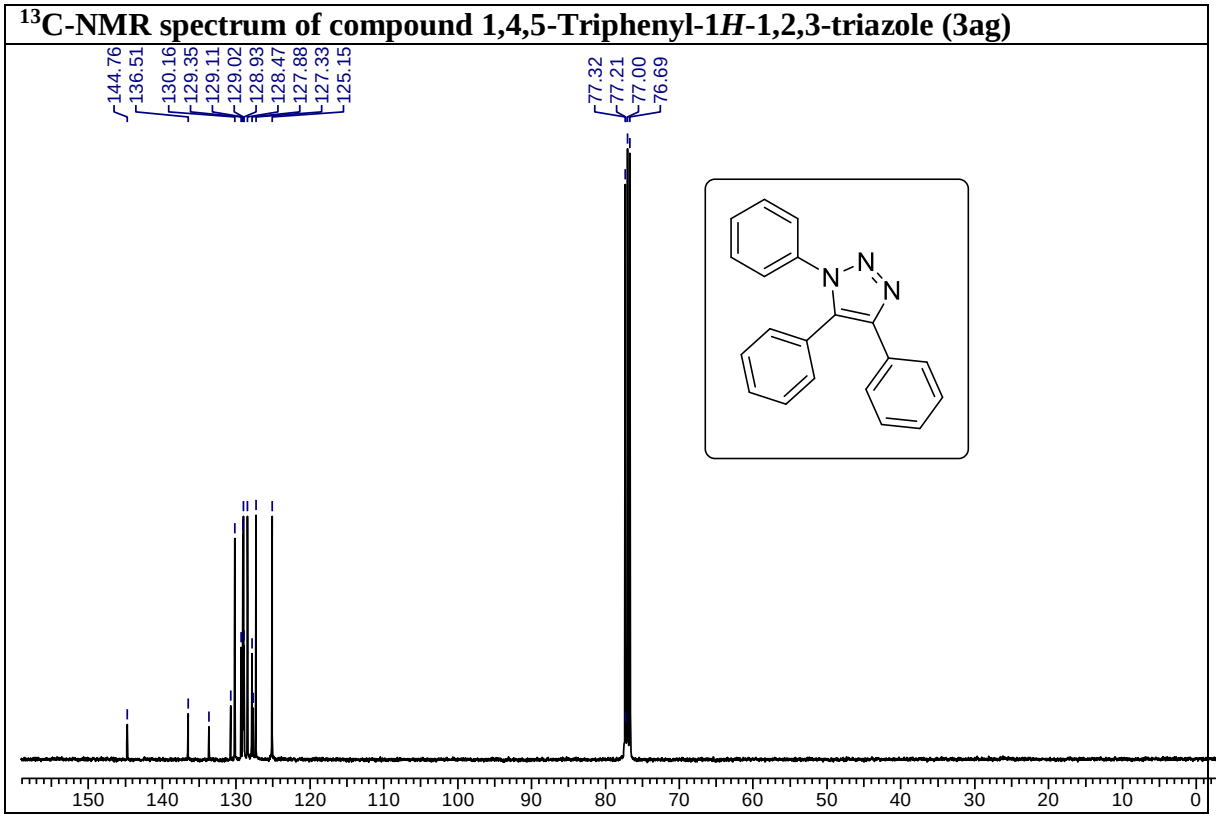
^{13}C-NMR spectrum of compound 4-Benzyl-1-phenyl-1*H*-1,2,3-triazole (3ab)



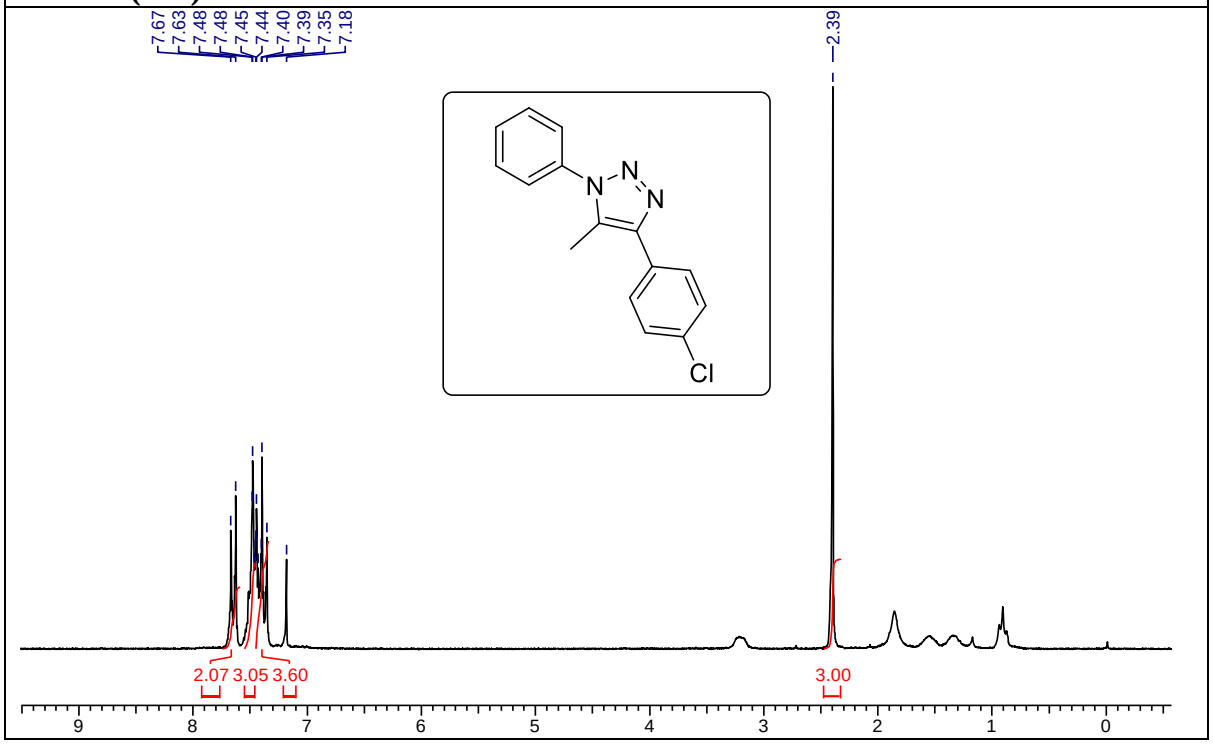
^{1}H-NMR spectrum of compound 1,4,5-Triphenyl-1*H*-1,2,3-triazole (3ag)



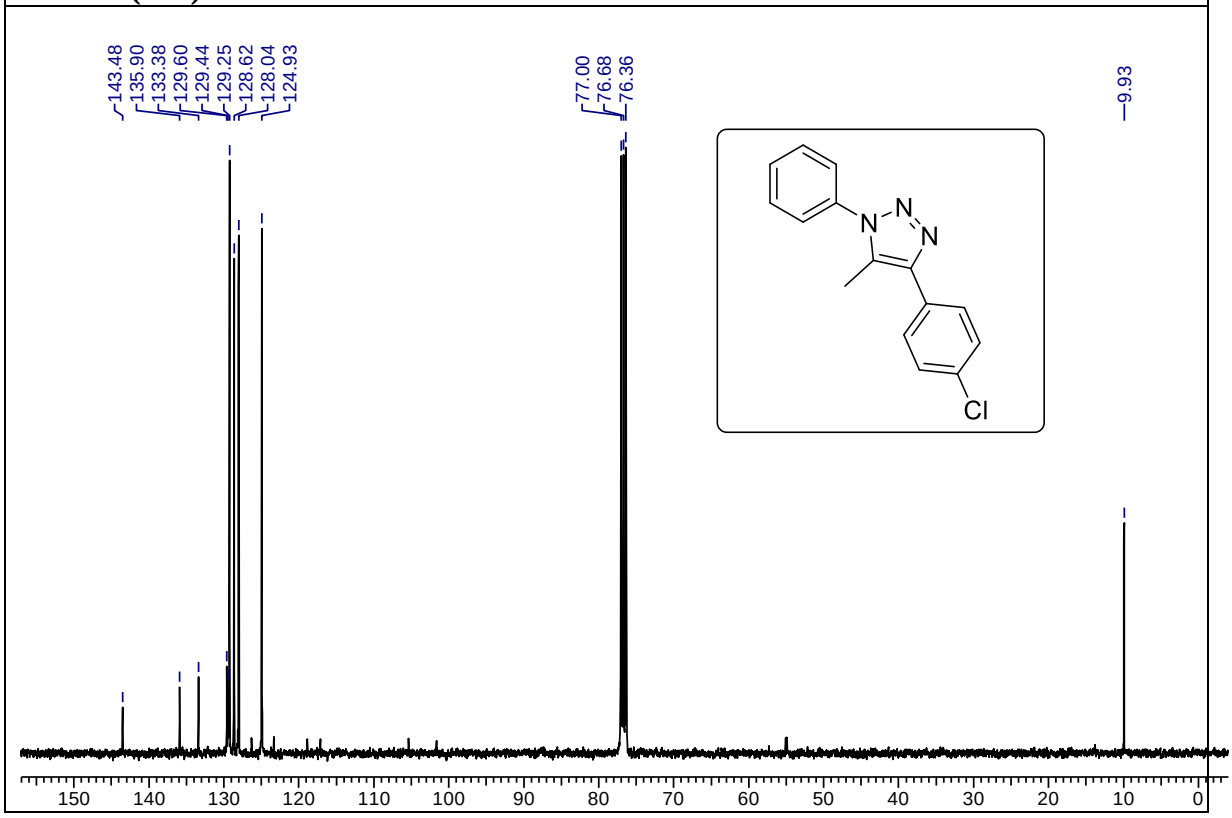
^{13}C-NMR spectrum of compound 1,4,5-Triphenyl-1*H*-1,2,3-triazole (3ag)



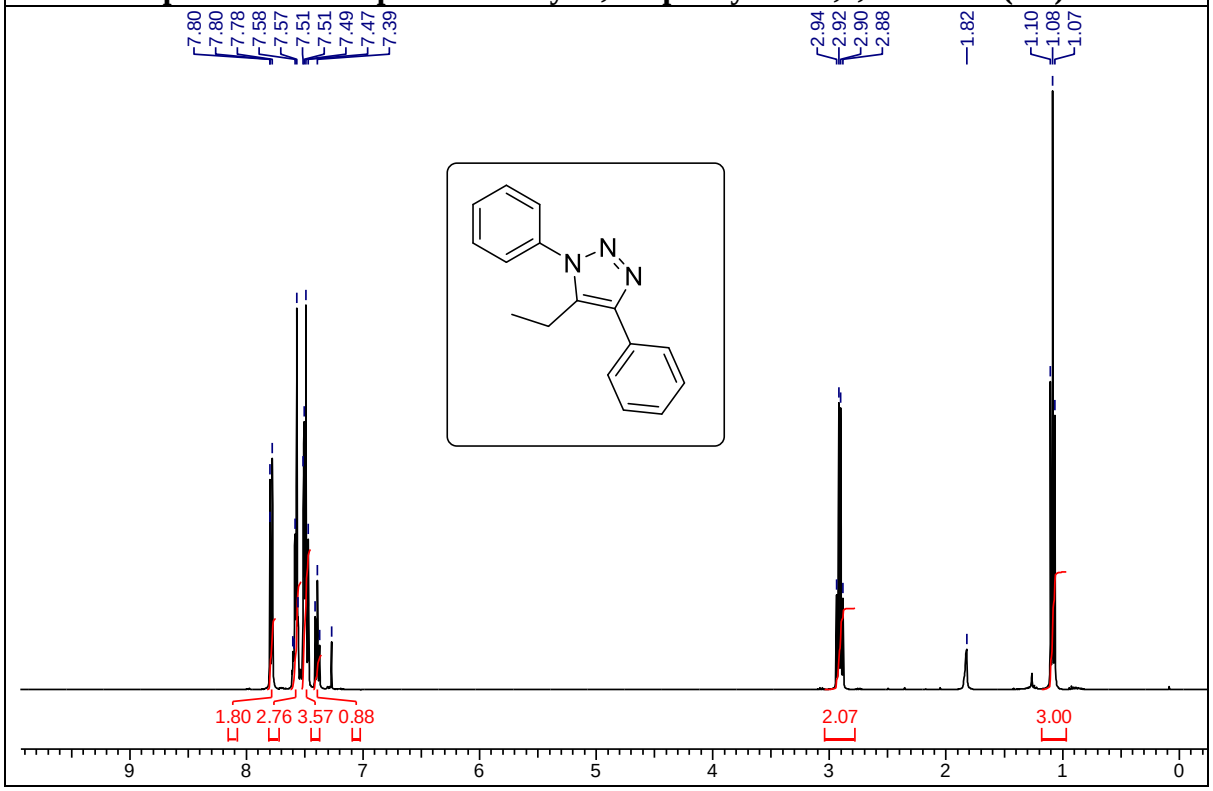
^{1}H-NMR spectrum of compound 4-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-1, 2, 3-triazole (3ah)



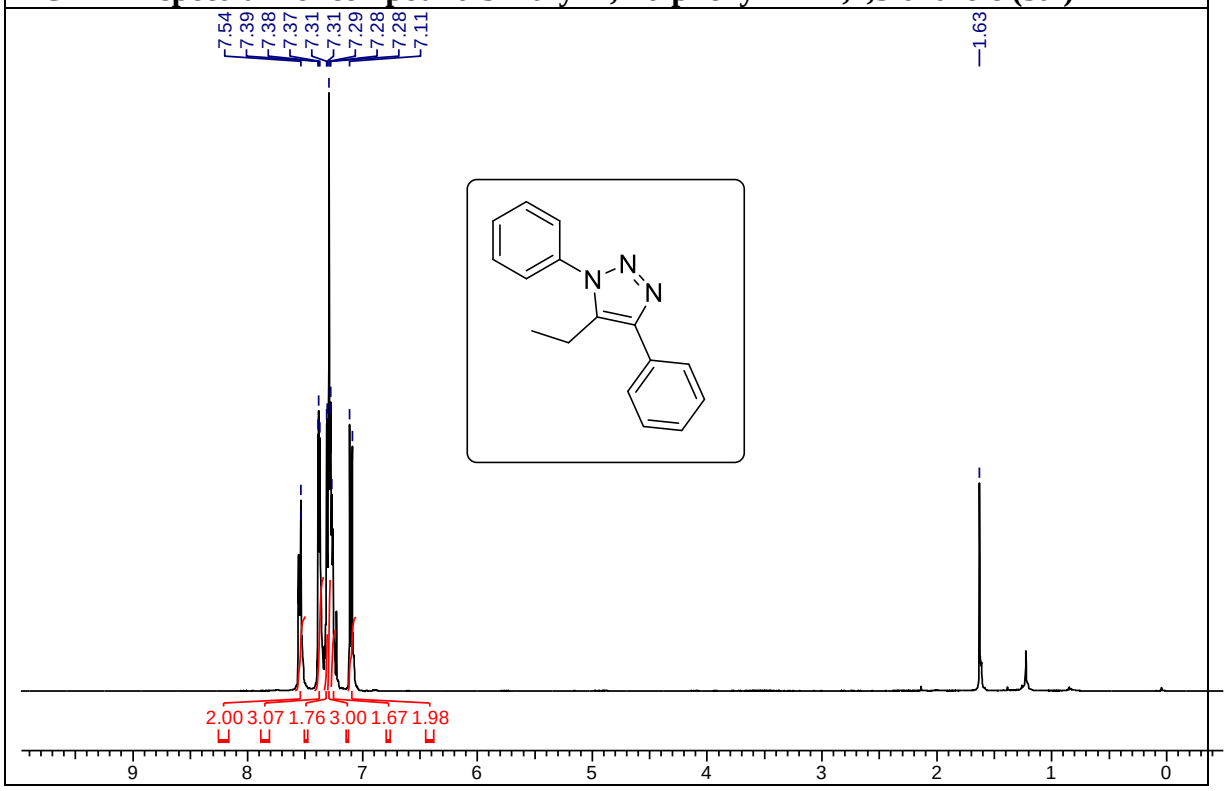
^{13}C-NMR spectrum of compound 4-(4-Chlorophenyl)-5-methyl-1-phenyl-1*H*-1, 2, 3-triazole (3ah)



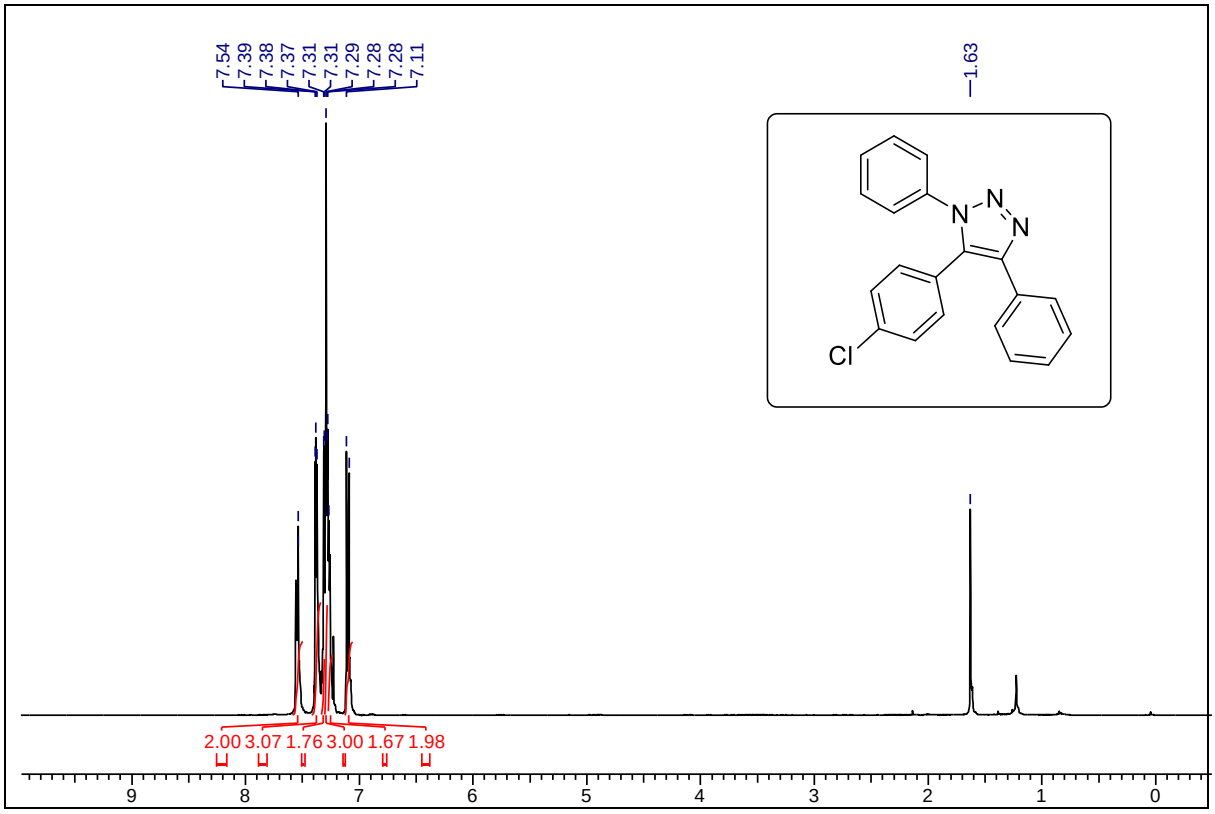
^{1}H-NMR spectrum of compound 5-Ethyl-1,4-diphenyl-1*H*-1,2,3-triazole (3ai)



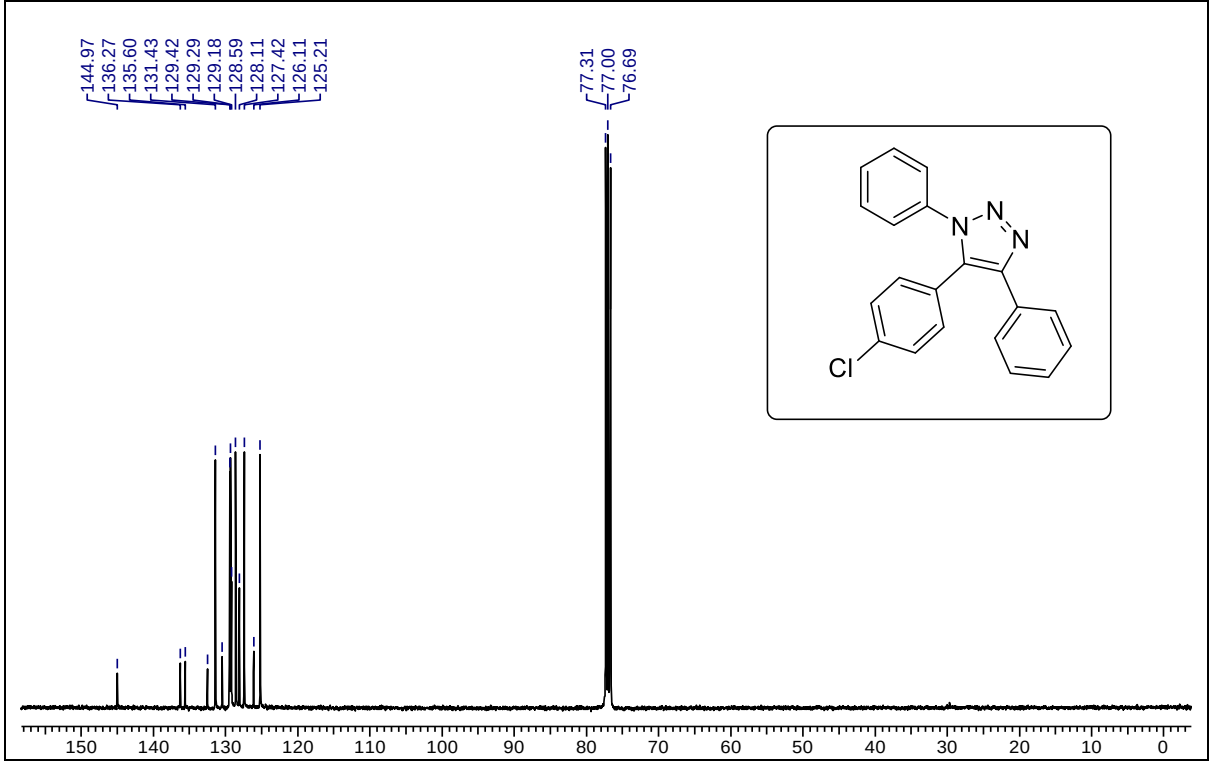
^{13}C-NMR spectrum of compound 5-Ethyl-1,4-diphenyl-1*H*-1,2,3-triazole (3ai)



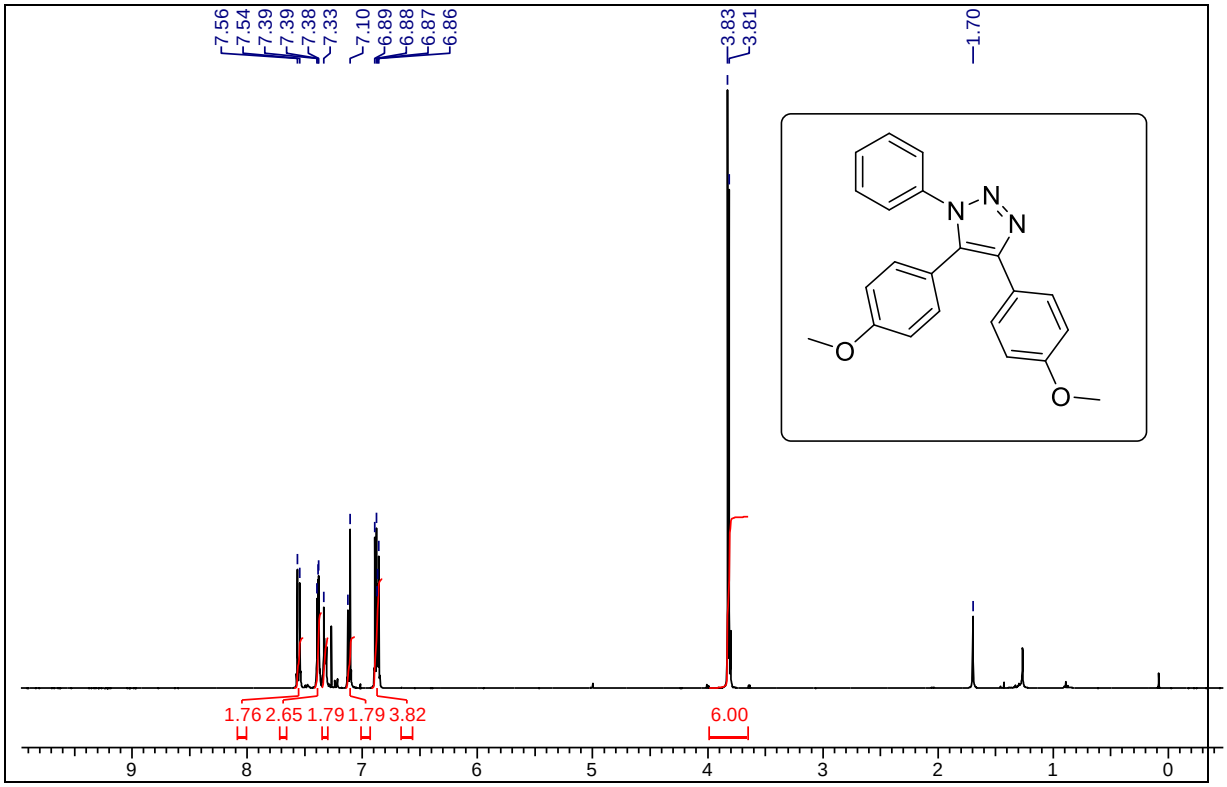
^{1}H-NMR spectrum of compound 5-(4-chlorophenyl)-1,4-diphenyl-1*H*-1,2,3-triazole (3aj)



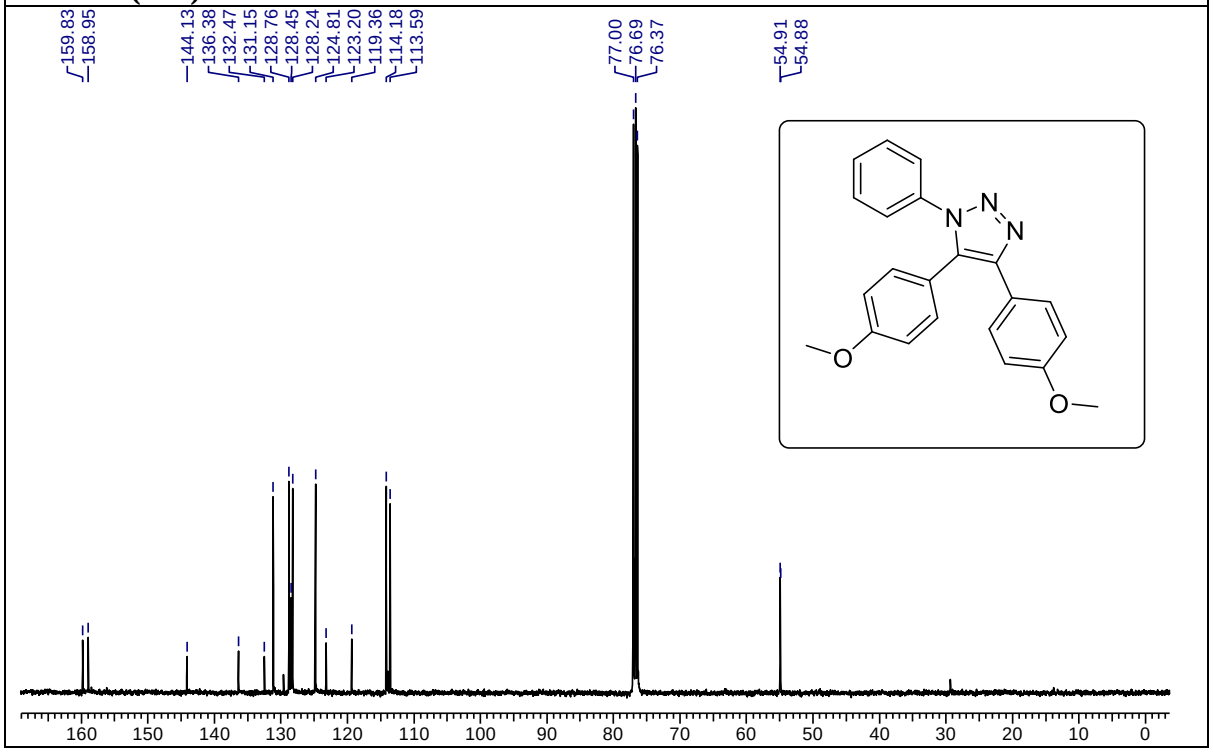
^{13}C-NMR spectrum of compound 5-(4-chlorophenyl)-1,4-diphenyl-1*H*-1,2,3-triazole (3aj)



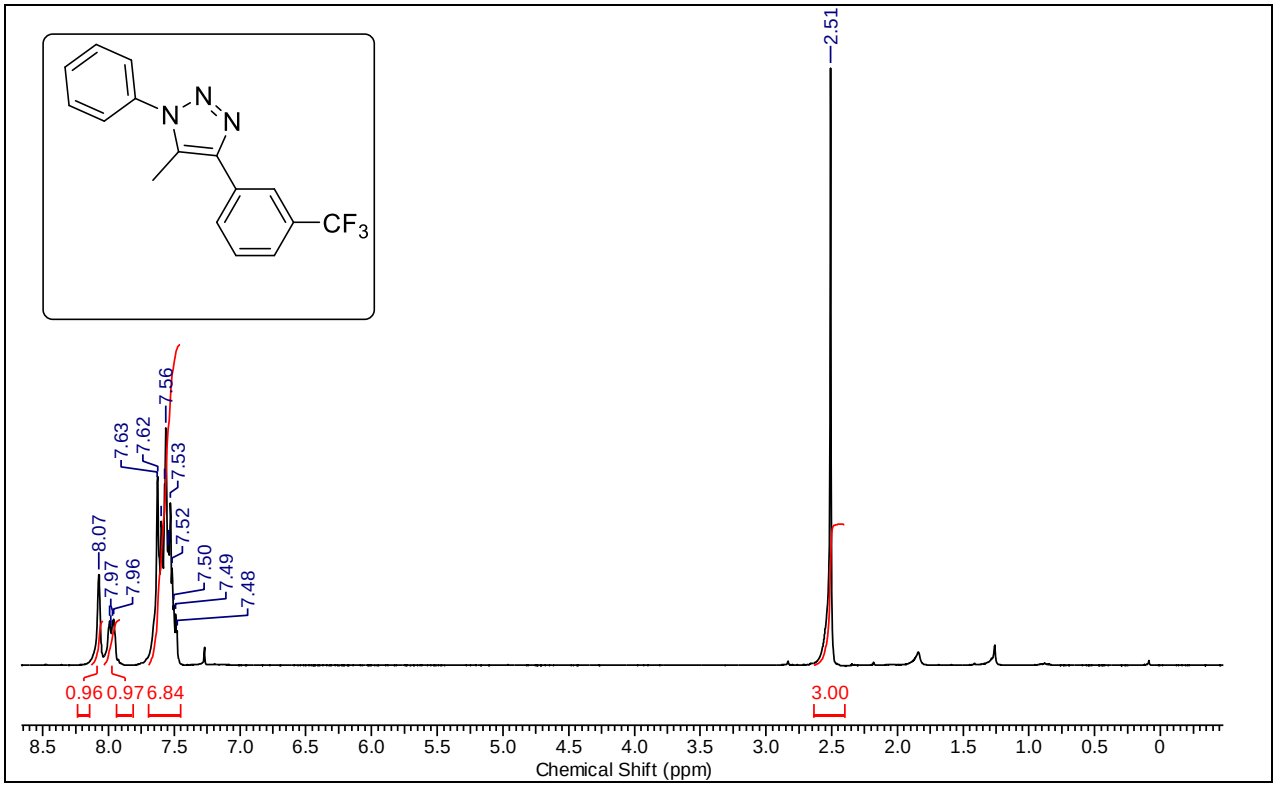
^{1}H-NMR spectrum of compound 4,5-bis(4-methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazole (3ak)



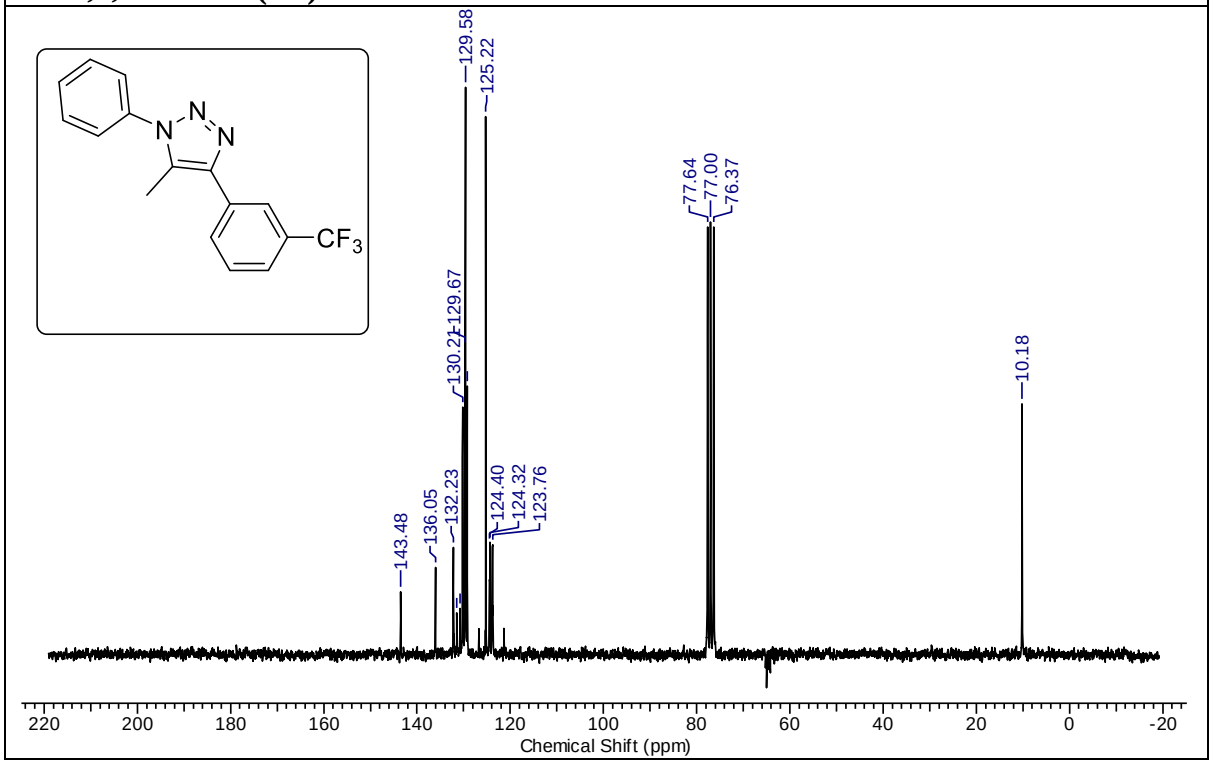
^{13}C-NMR spectrum of compound 4,5-bis(4-methoxyphenyl)-1-phenyl-1*H*-1,2,3-triazole (3ak)



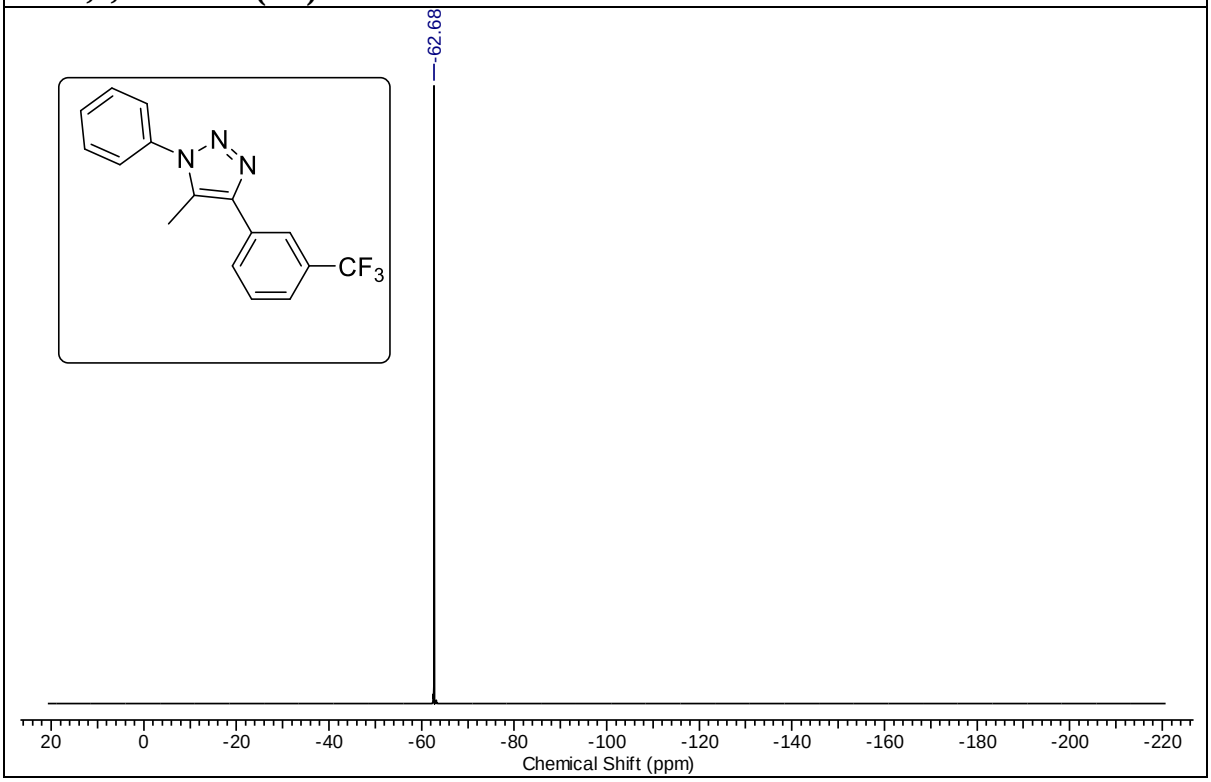
^{1}H-NMR spectrum of compound 5-methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3al)



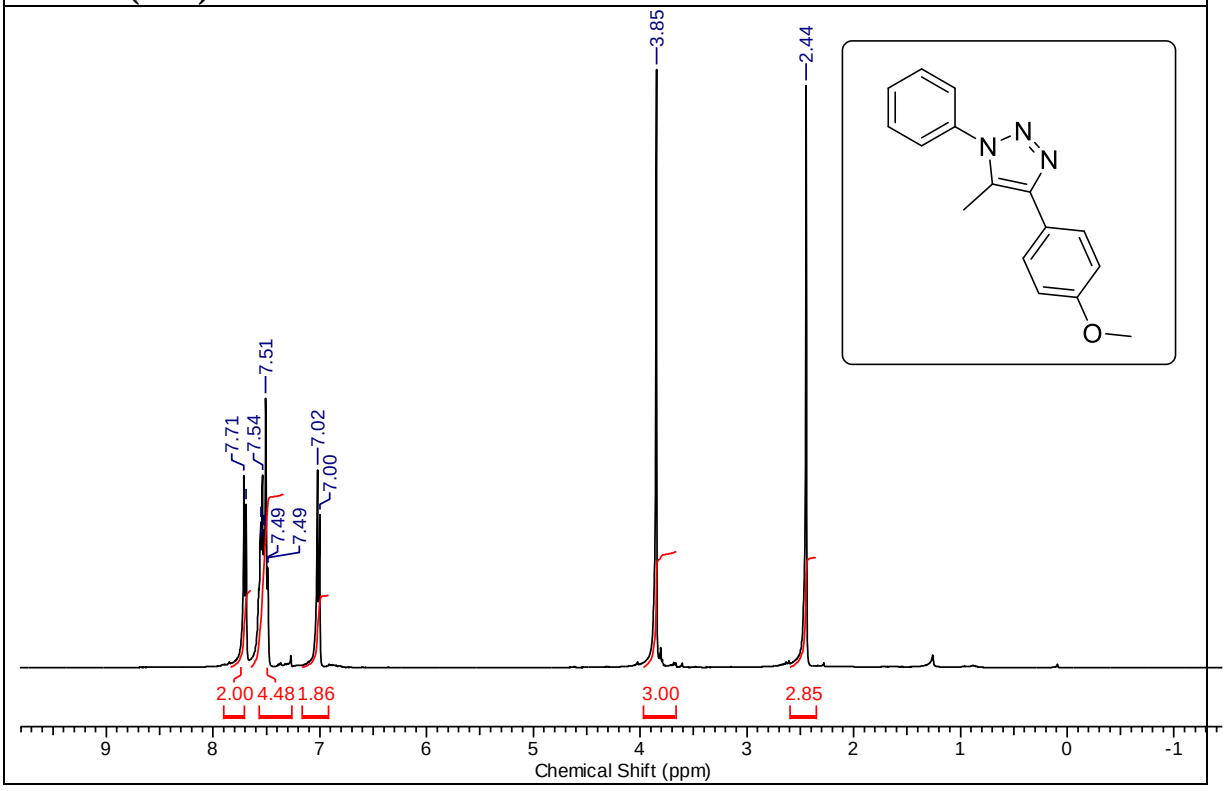
^{13}C-NMR spectrum of compound5-methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3al)



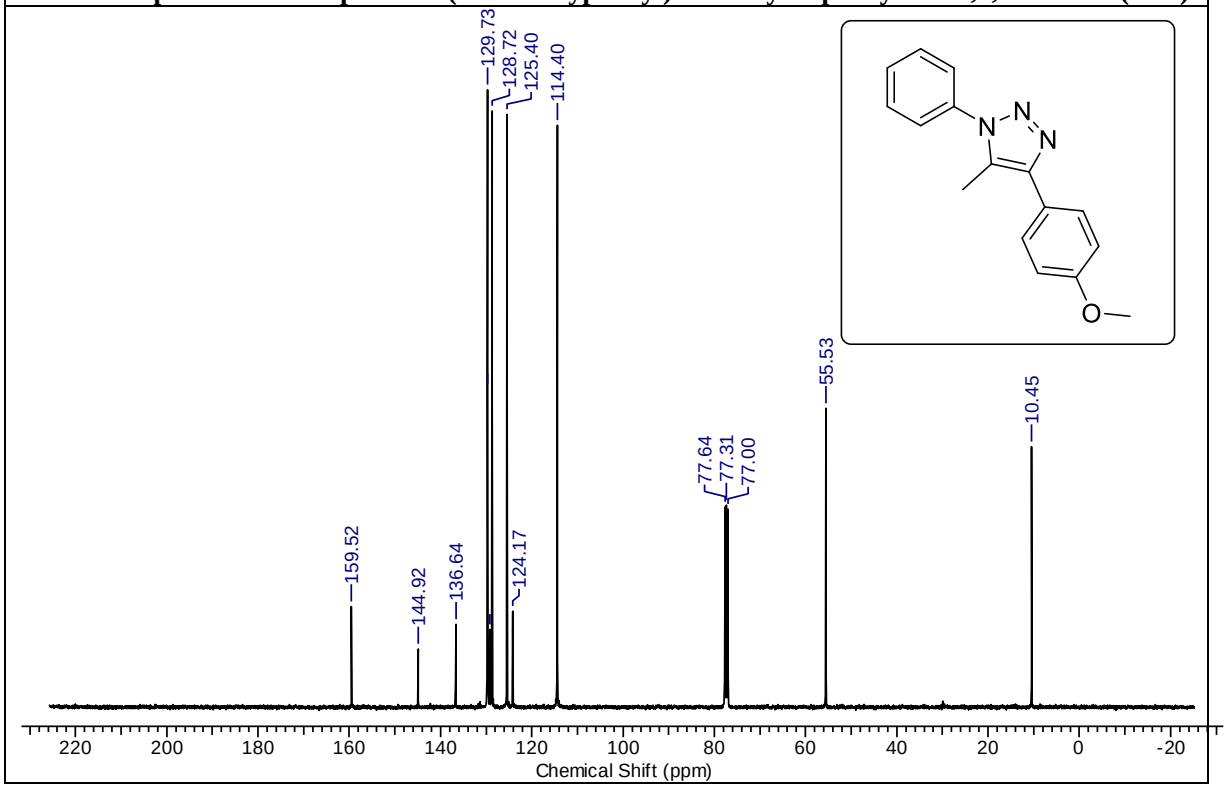
F^{19}- NMR spectrum of compound5-methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (3al)



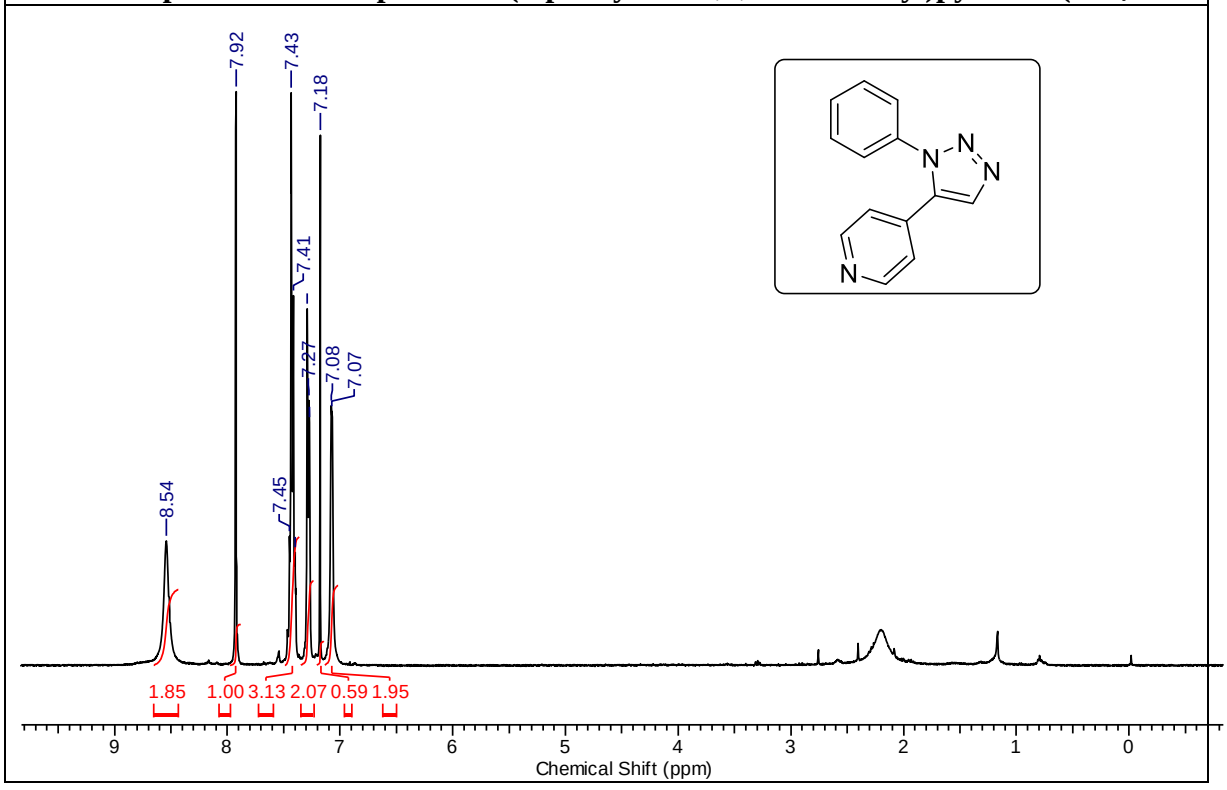
^{1}H-NMR spectrum of compound 4-(4-methoxyphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole (3am)



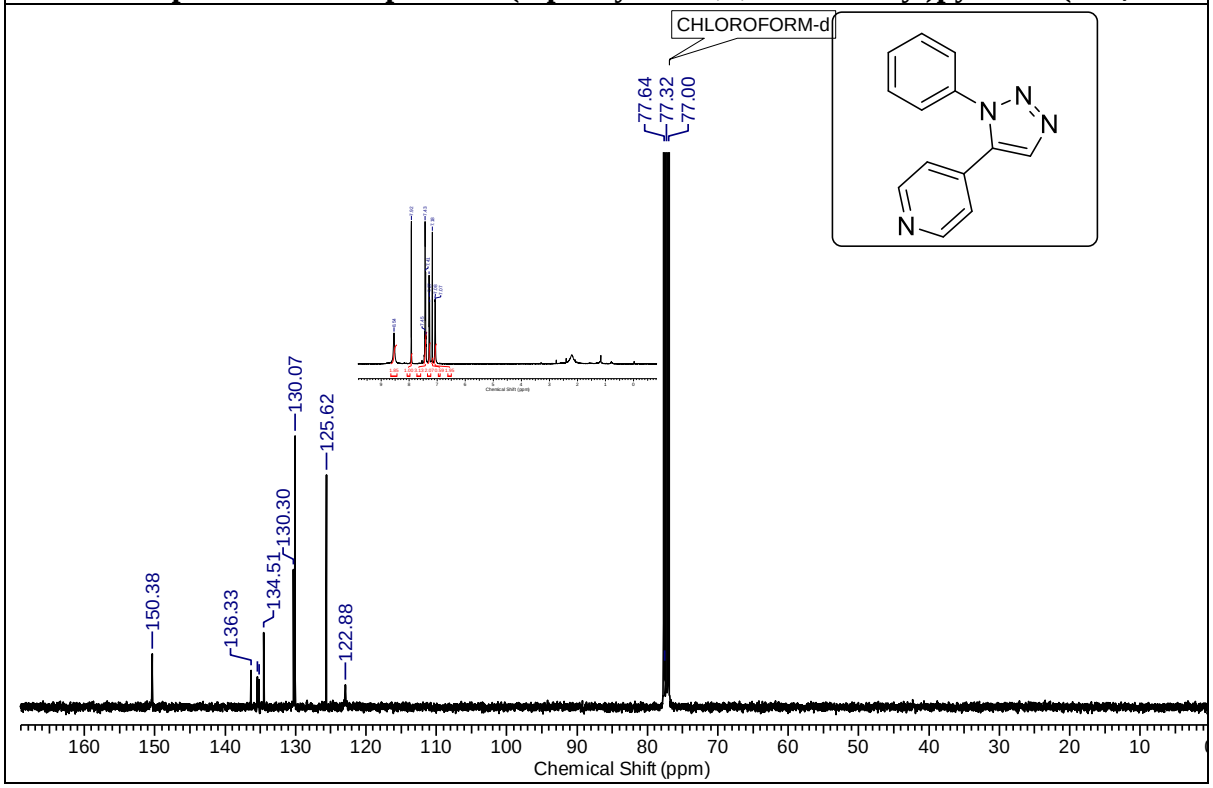
^{13}C-NMR spectrum of compound 4-(4-methoxyphenyl)-5-methyl-1-phenyl-1*H*-1,2,3-triazole (3am)



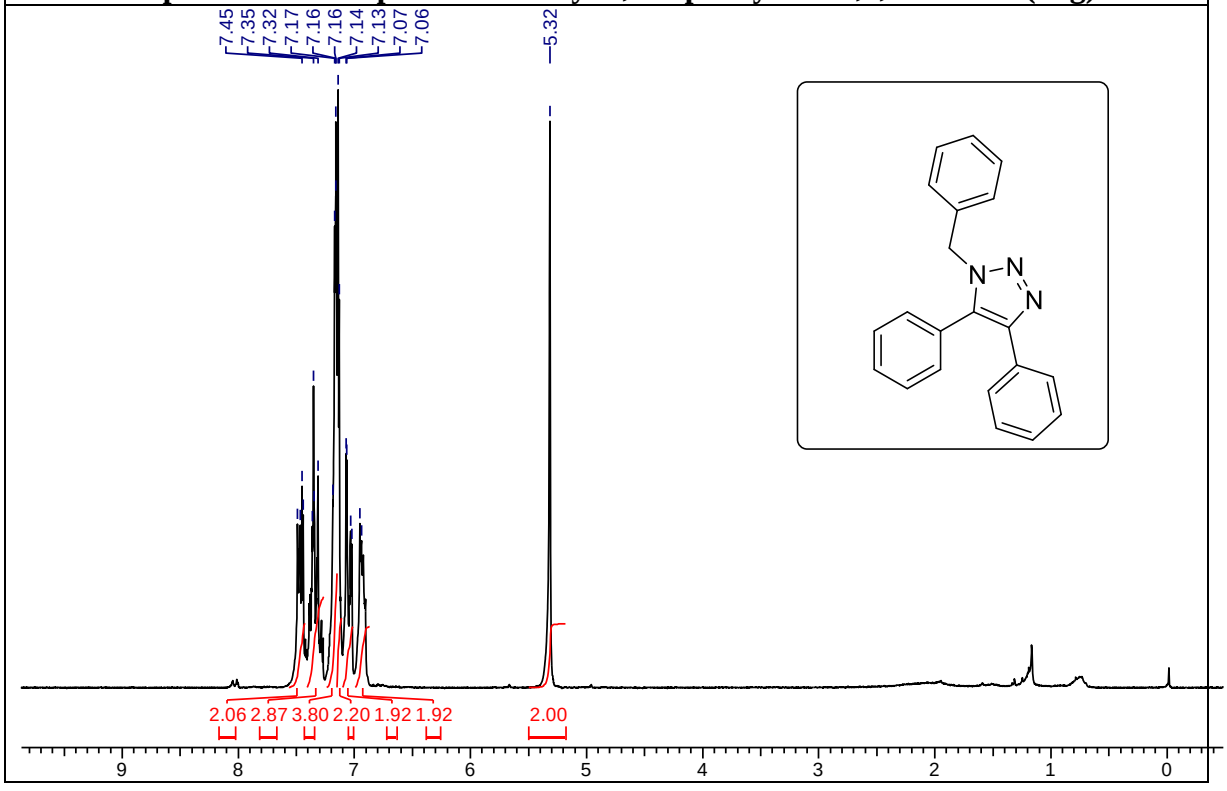
^{1}H-NMR spectrum of compound 4-(1-phenyl-1*H*-1,2,3-triazol-5-yl)pyridine (3an)



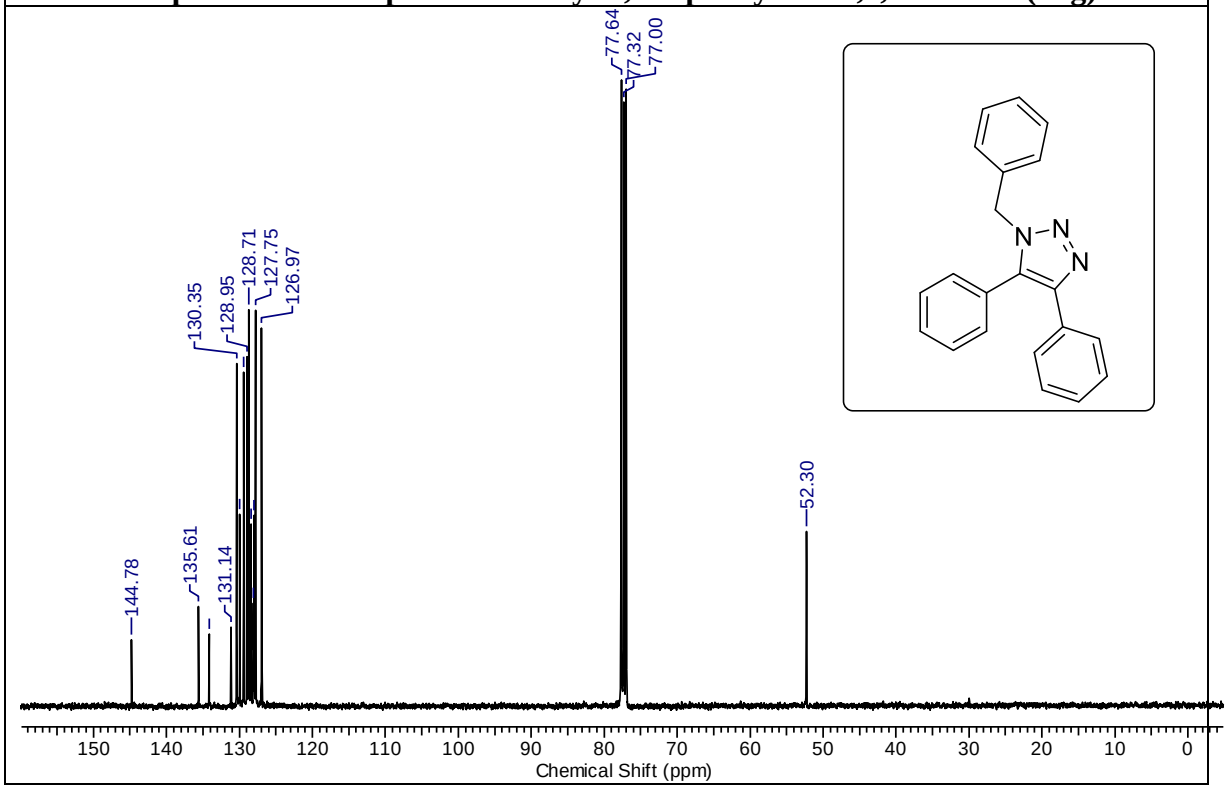
^{13}C-NMR spectrum of compound 4-(1-phenyl-1*H*-1,2,3-triazol-5-yl)pyridine (3an)



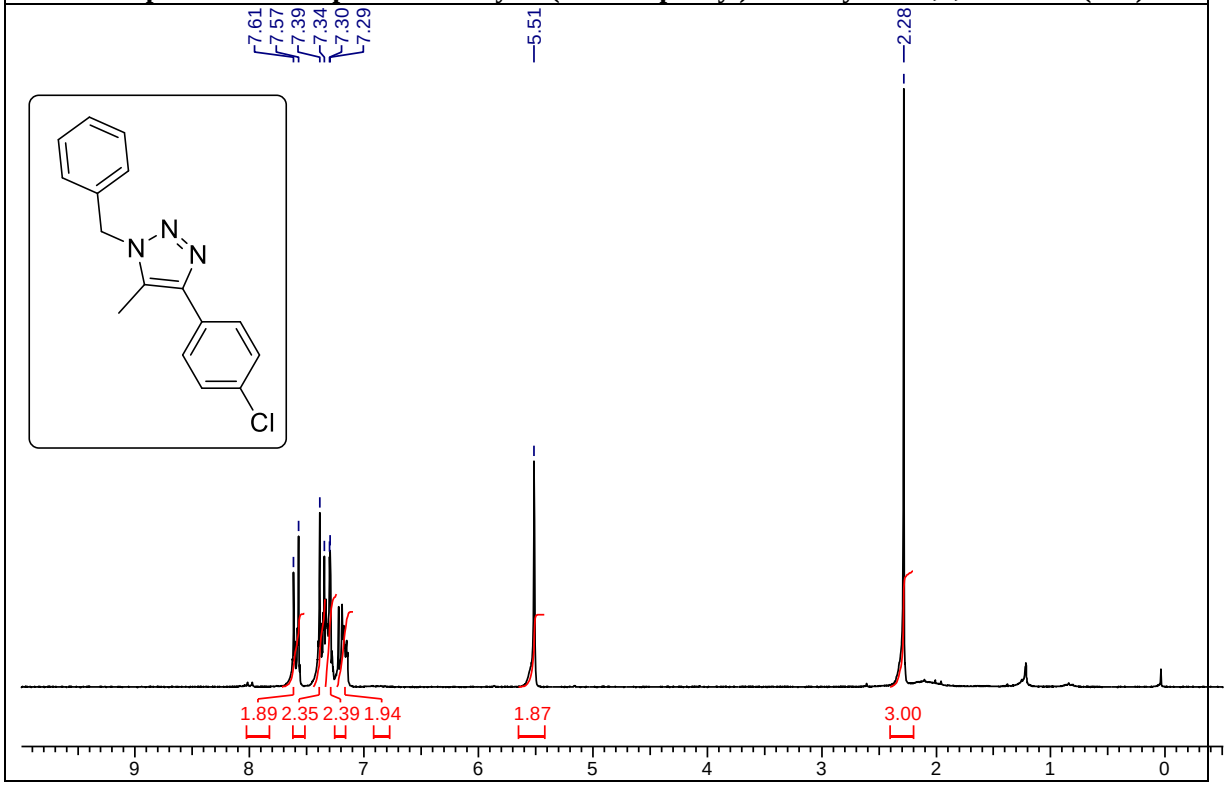
^{1}H-NMR spectrum of compound 1-benzyl-4,5-diphenyl-1*H*-1,2,3-triazole (3bg)



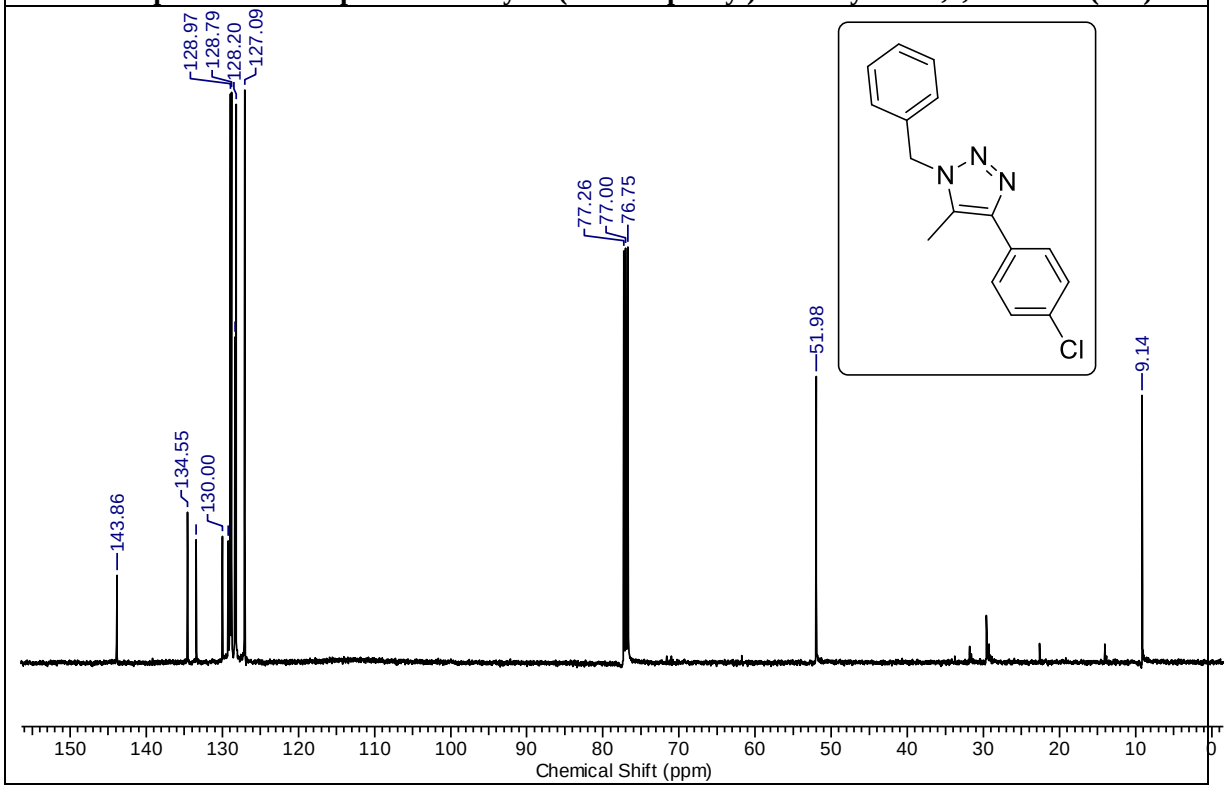
^{13}C-NMR spectrum of compound 1-benzyl-4,5-diphenyl-1*H*-1,2,3-triazole (3bg)



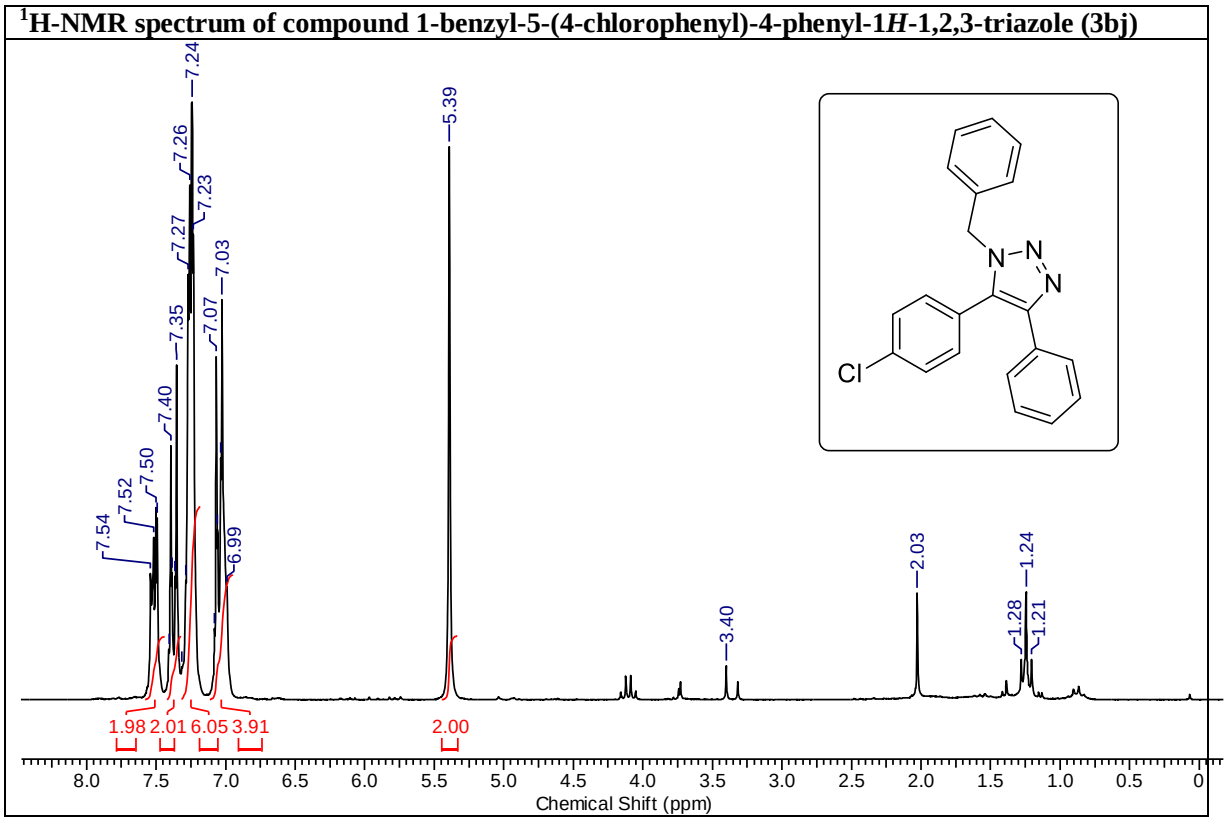
^{1}H-NMR spectrum of compound 1-benzyl-4-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole (3bh)



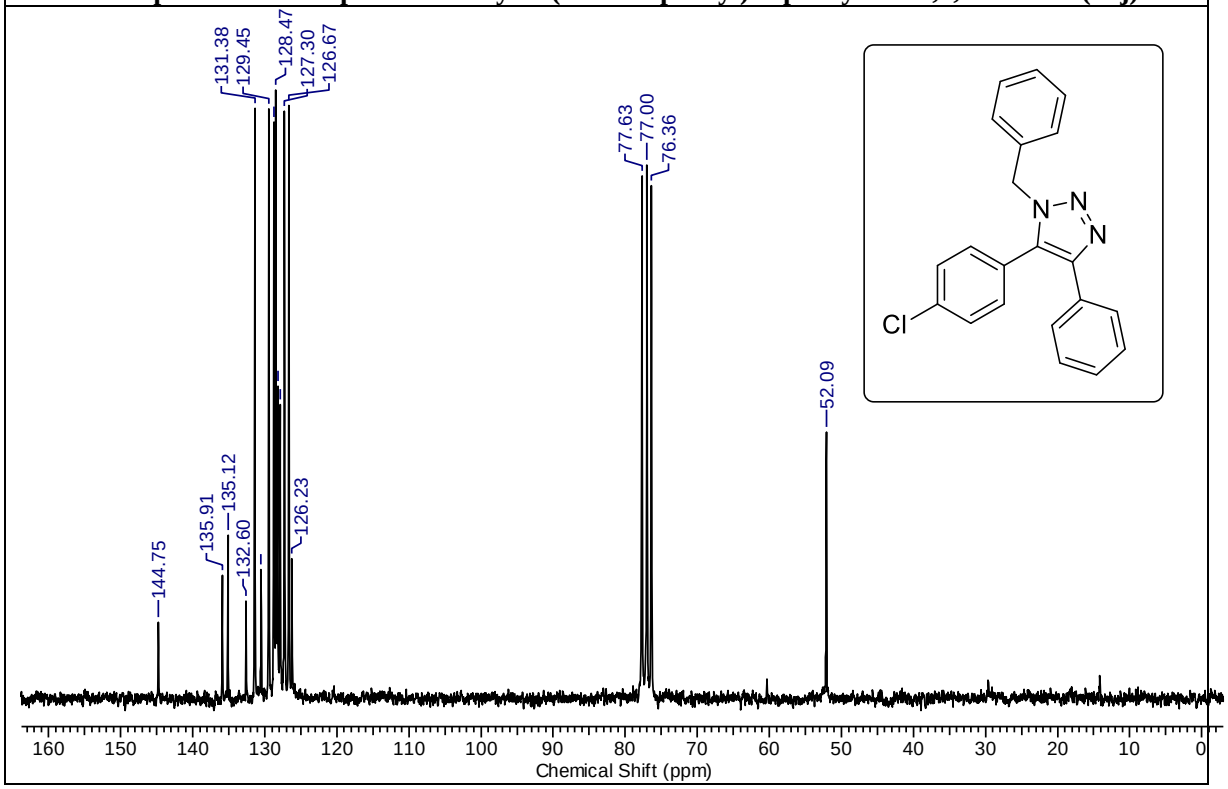
^{13}C-NMR spectrum of compound 1-benzyl-4-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole (3bh)



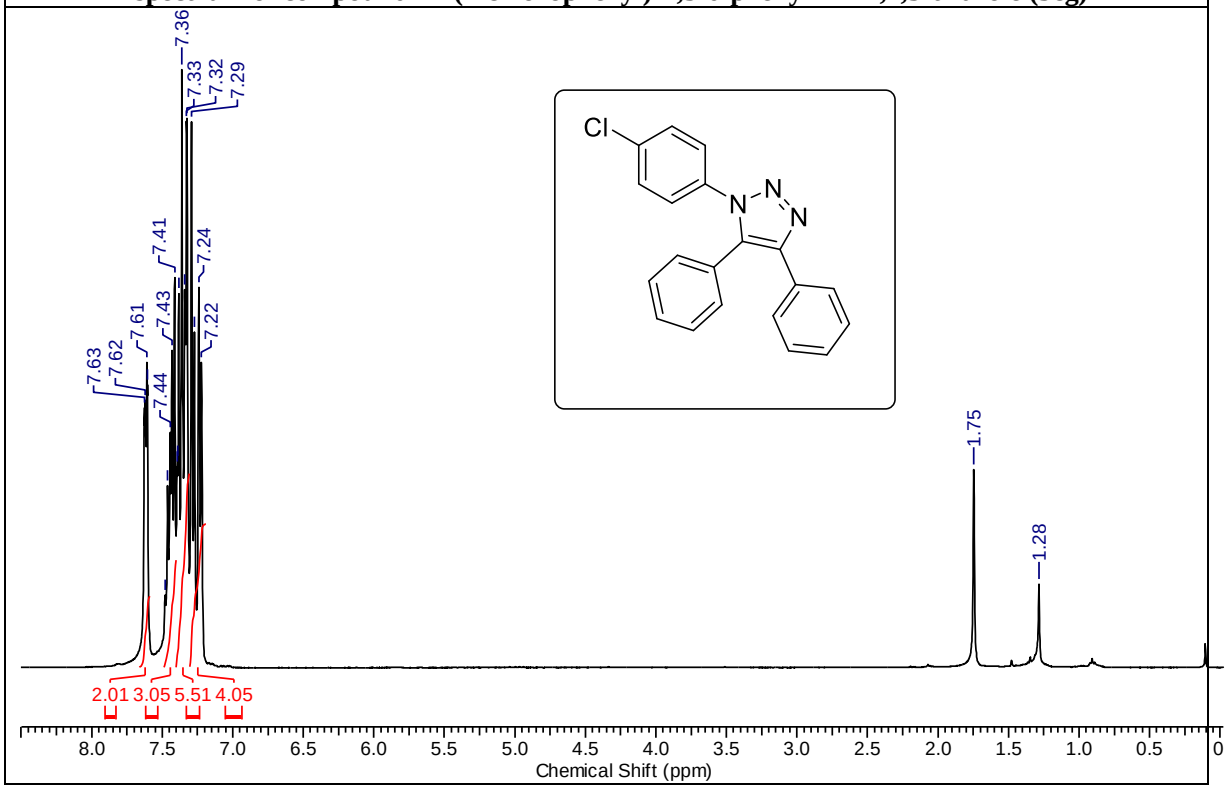
^{1}H-NMR spectrum of compound 1-benzyl-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3bj)



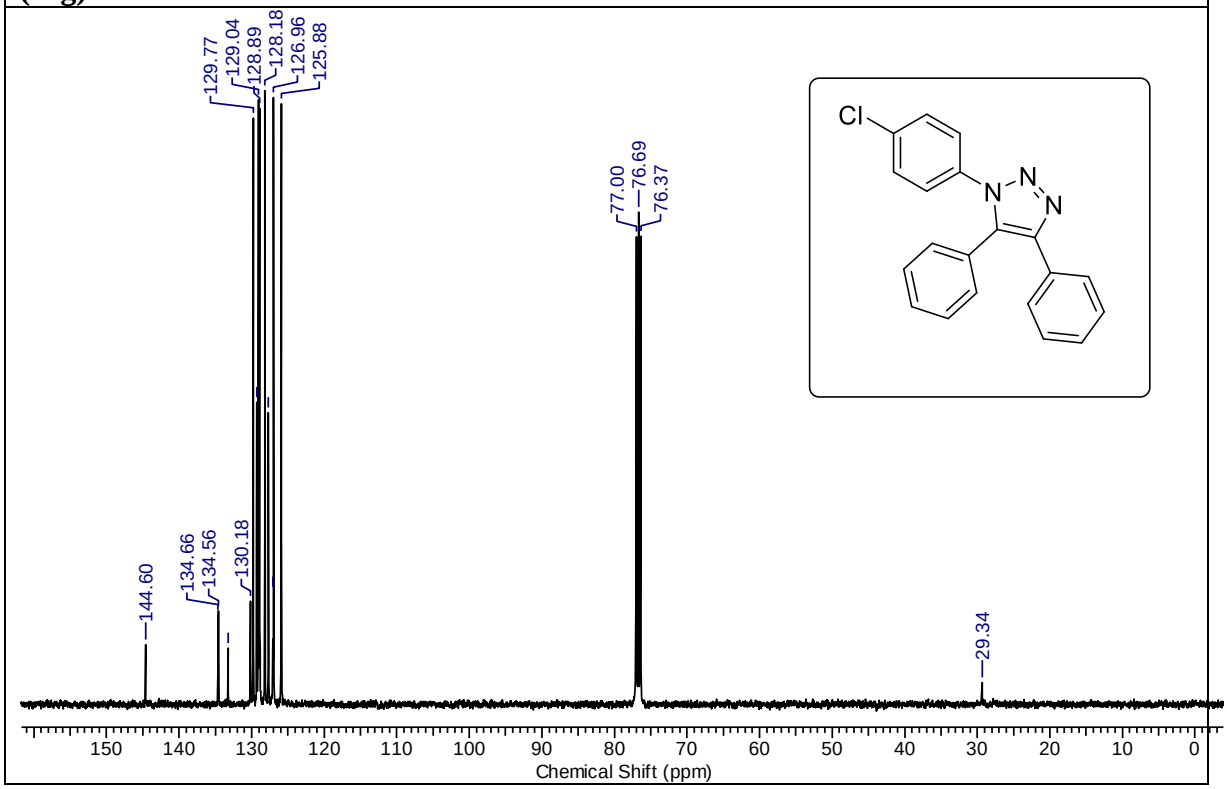
^{13}C-NMR spectrum of compound1-benzyl-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3bj)



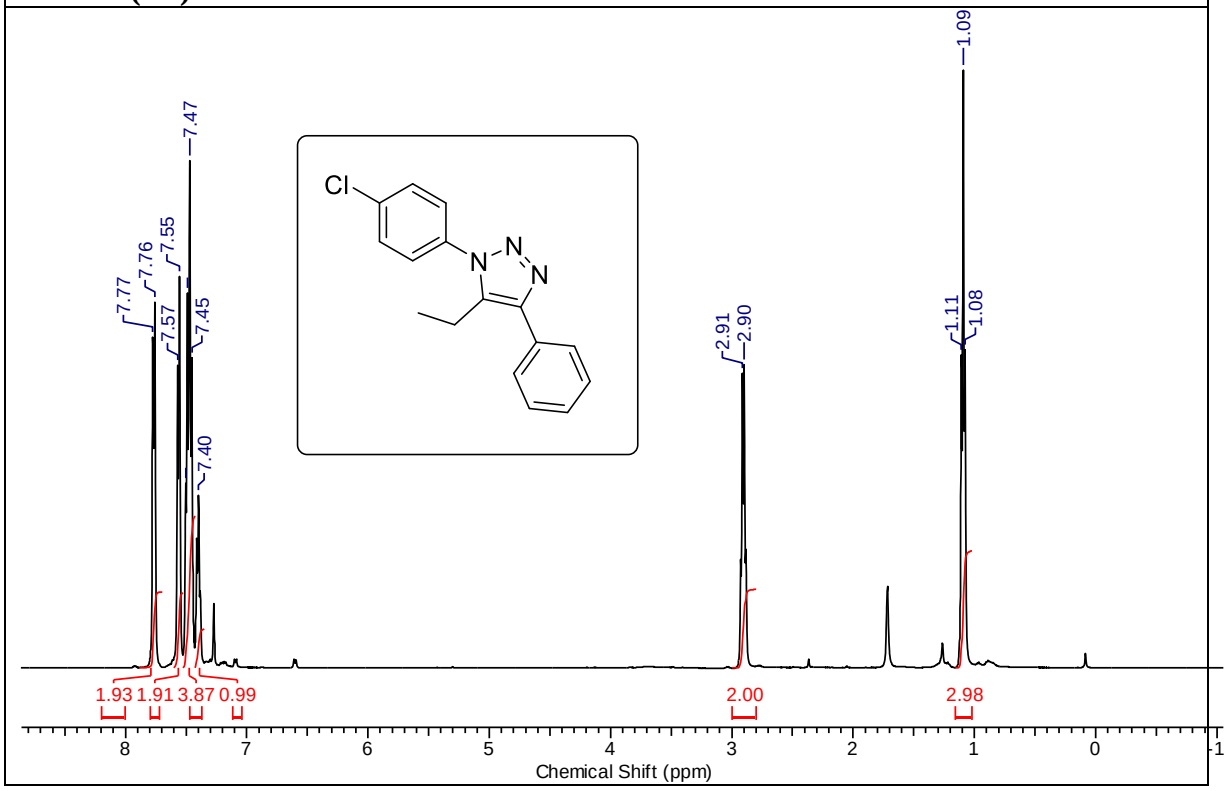
^{1}H-NMR spectrum of compound 1-(4-chlorophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3cg)



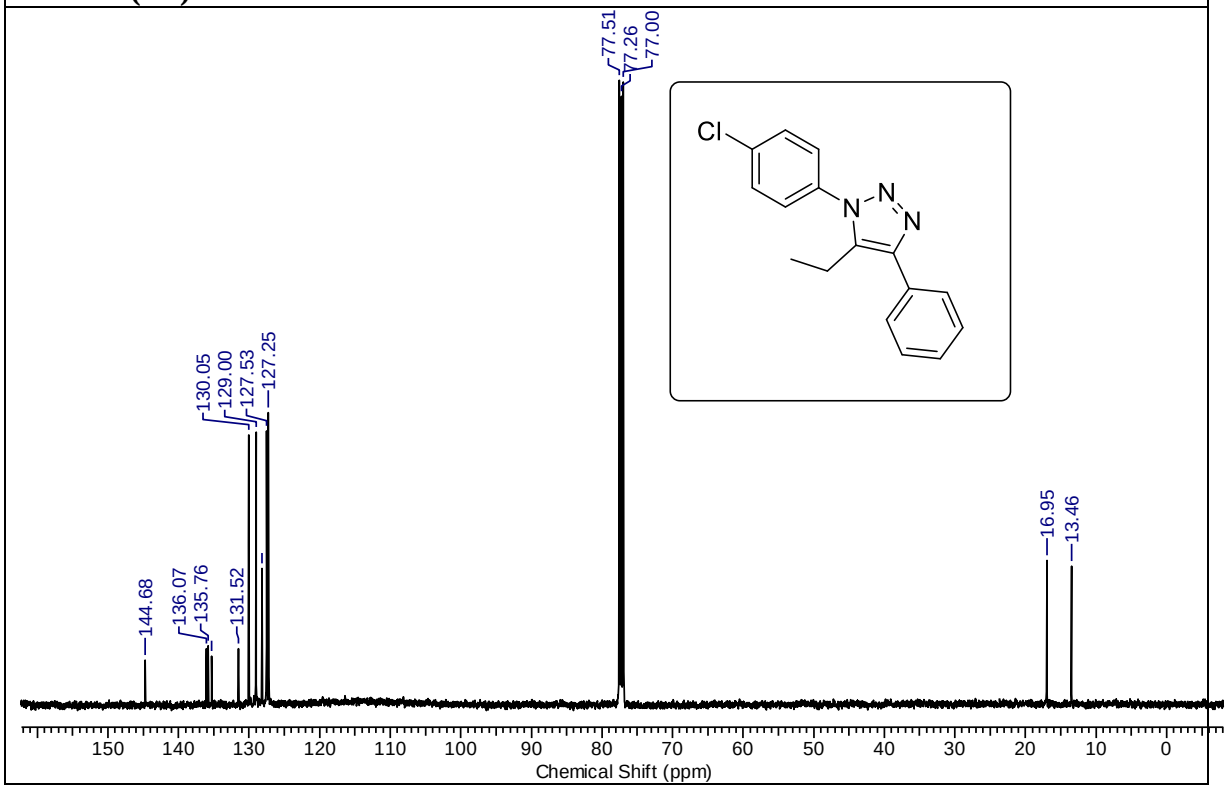
^{13}C-NMR spectrum of compound 1-(4-chlorophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3cg)



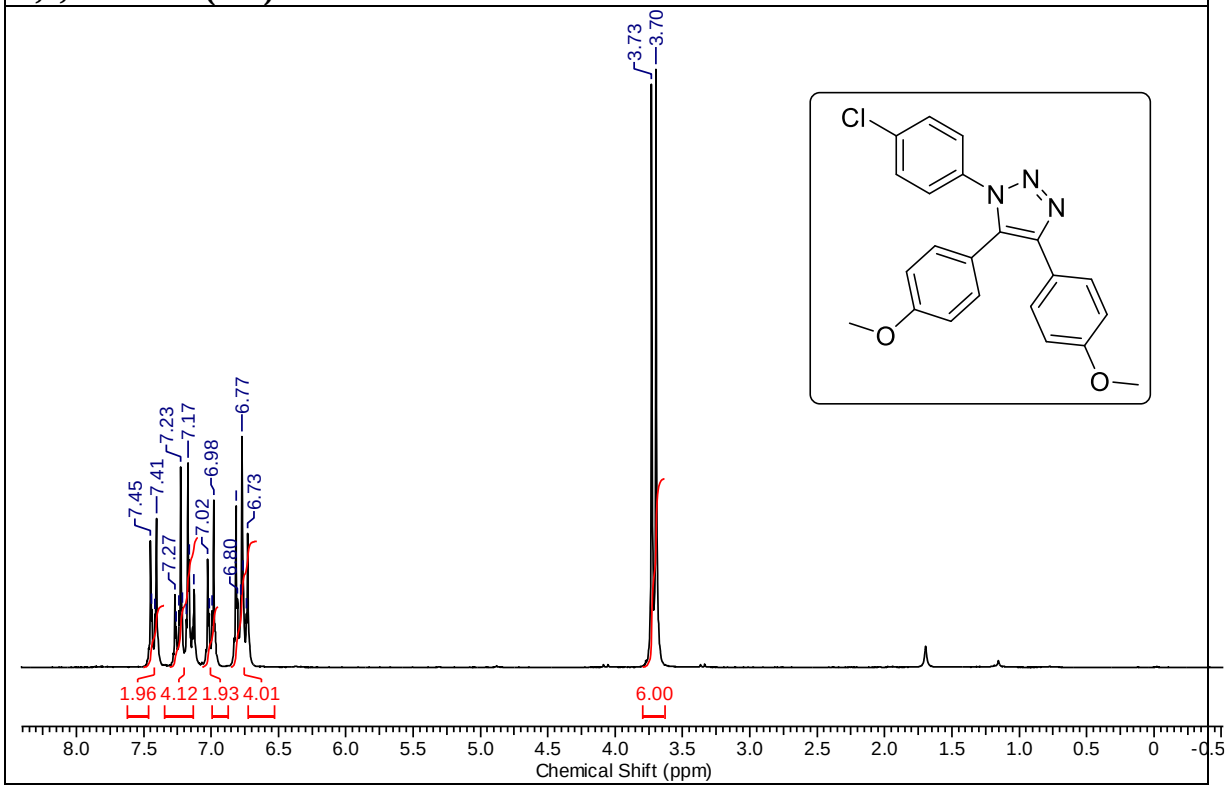
^{1}H-NMR spectrum of compound 1-(4-chlorophenyl)-5-ethyl-4-phenyl-1*H*-1,2,3-triazole (3ci)



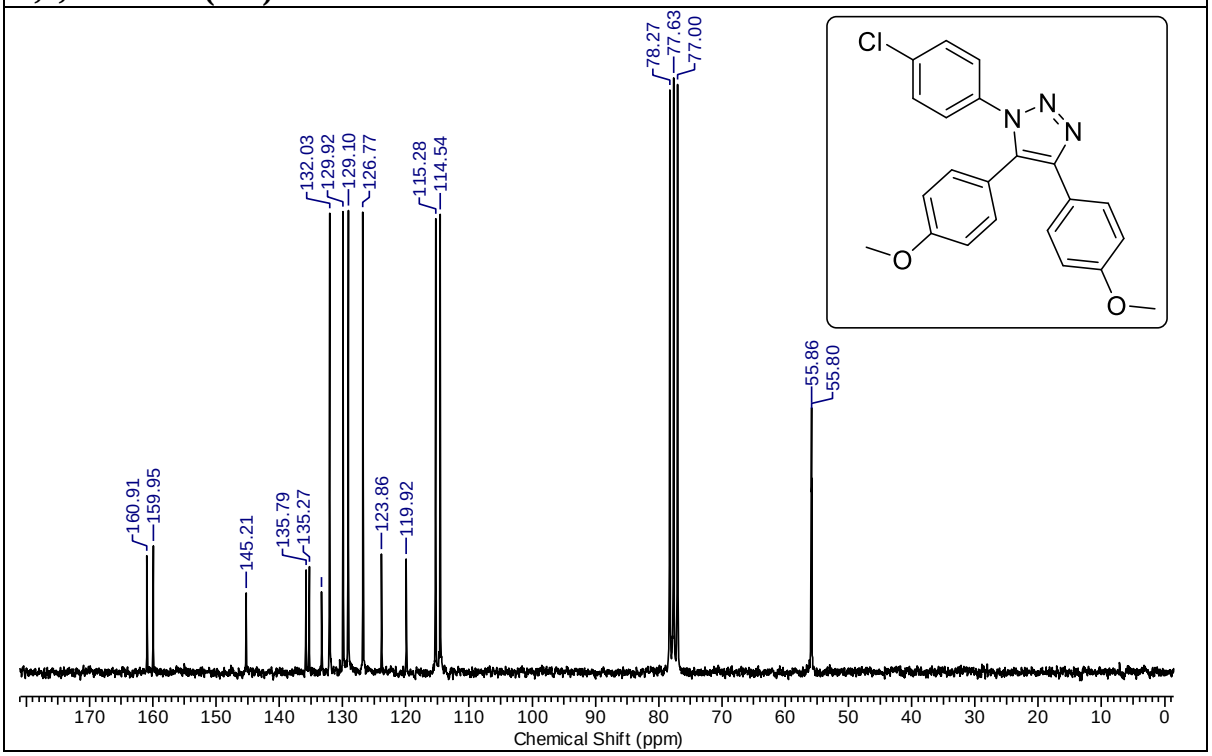
^{13}C-NMR spectrum of compound 1-(4-chlorophenyl)-5-ethyl-4-phenyl-1*H*-1,2,3-triazole (3ci)



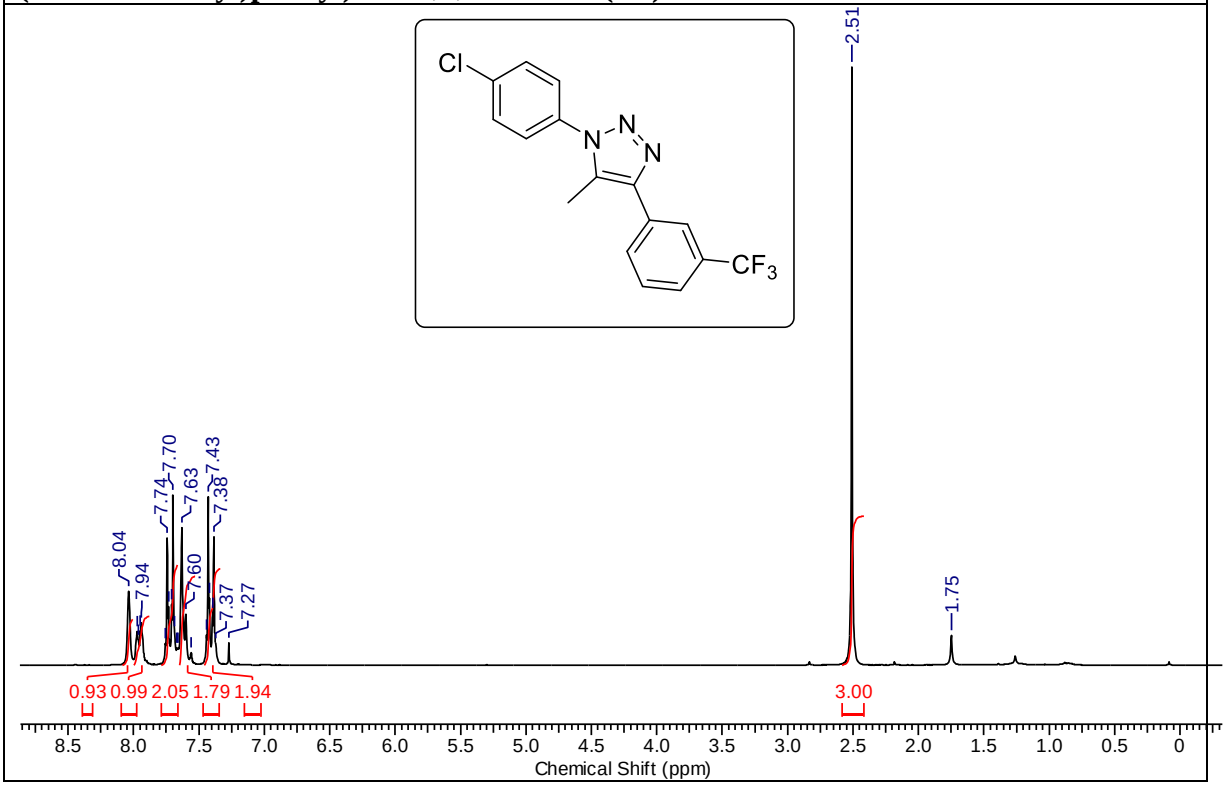
^{1}H-NMR spectrum of compound 1-(4-chlorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3ck)



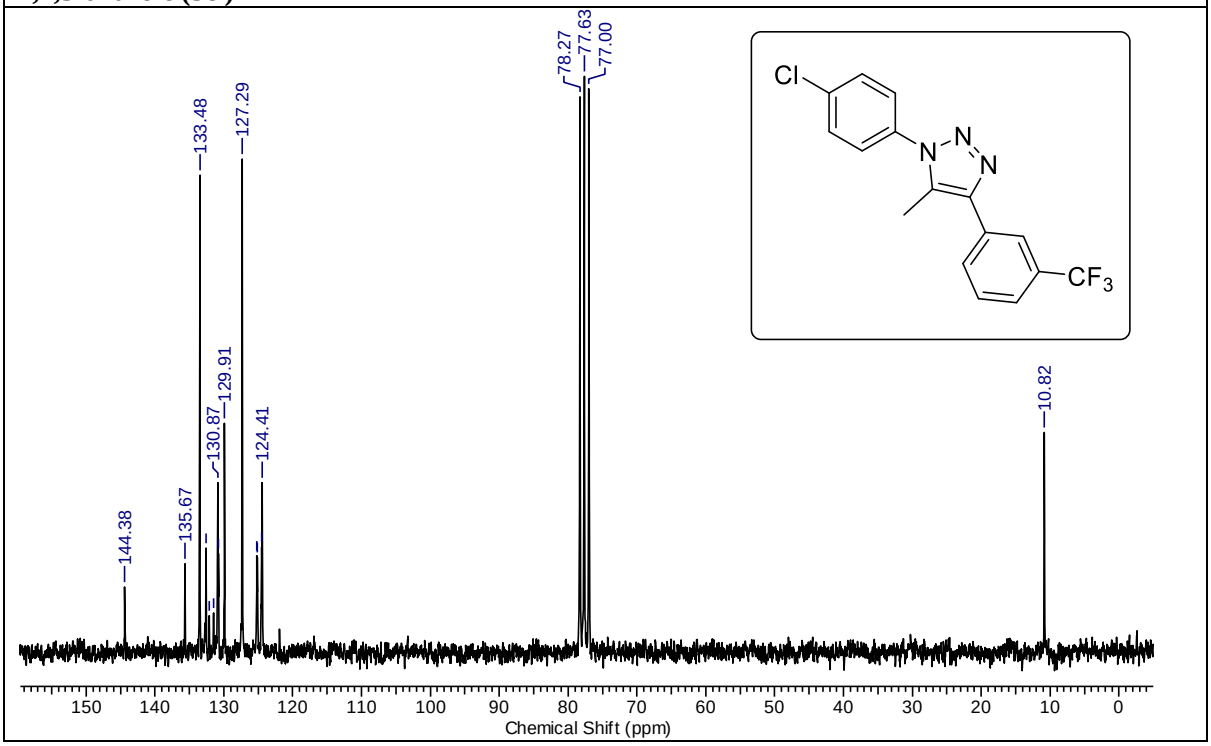
^{13}C-NMR spectrum of compound 1-(4-chlorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3ck)



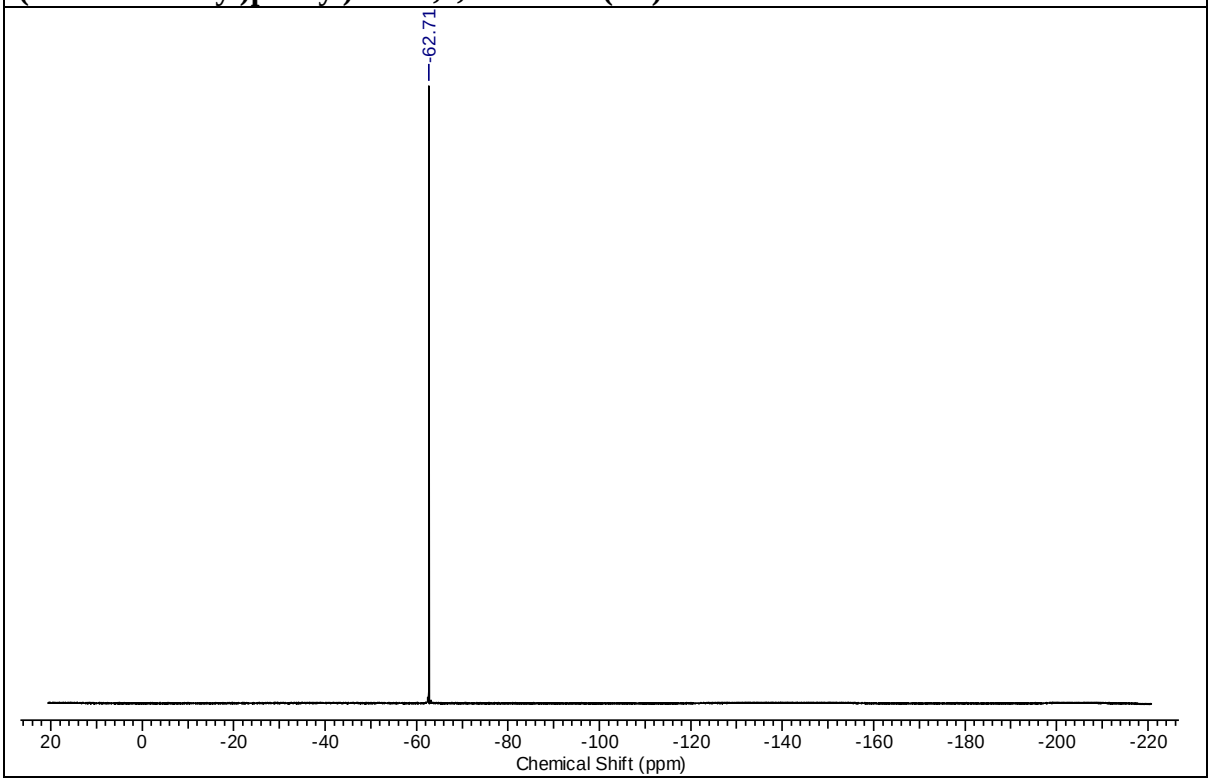
^{1}H-NMR spectrum of compound 1-(4-chlorophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3cl):



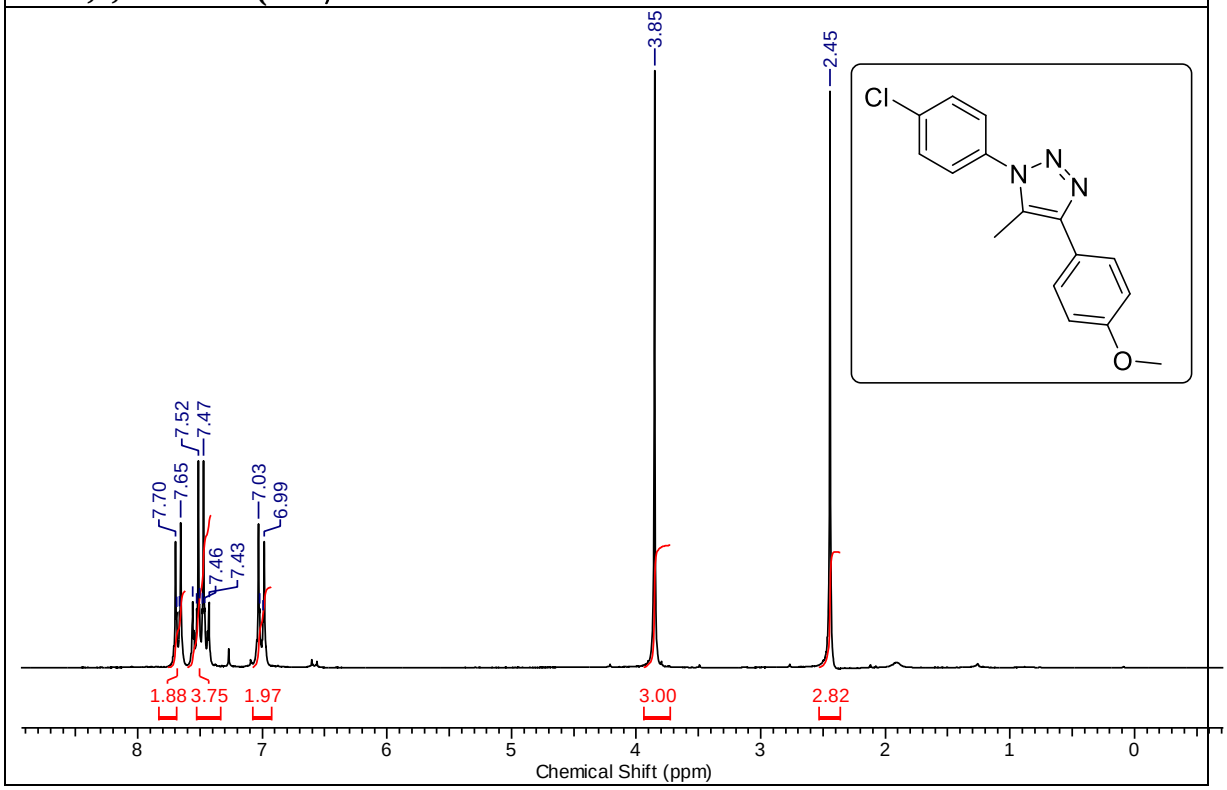
^{13}C-NMR spectrum of compound1-(4-chlorophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3cl)



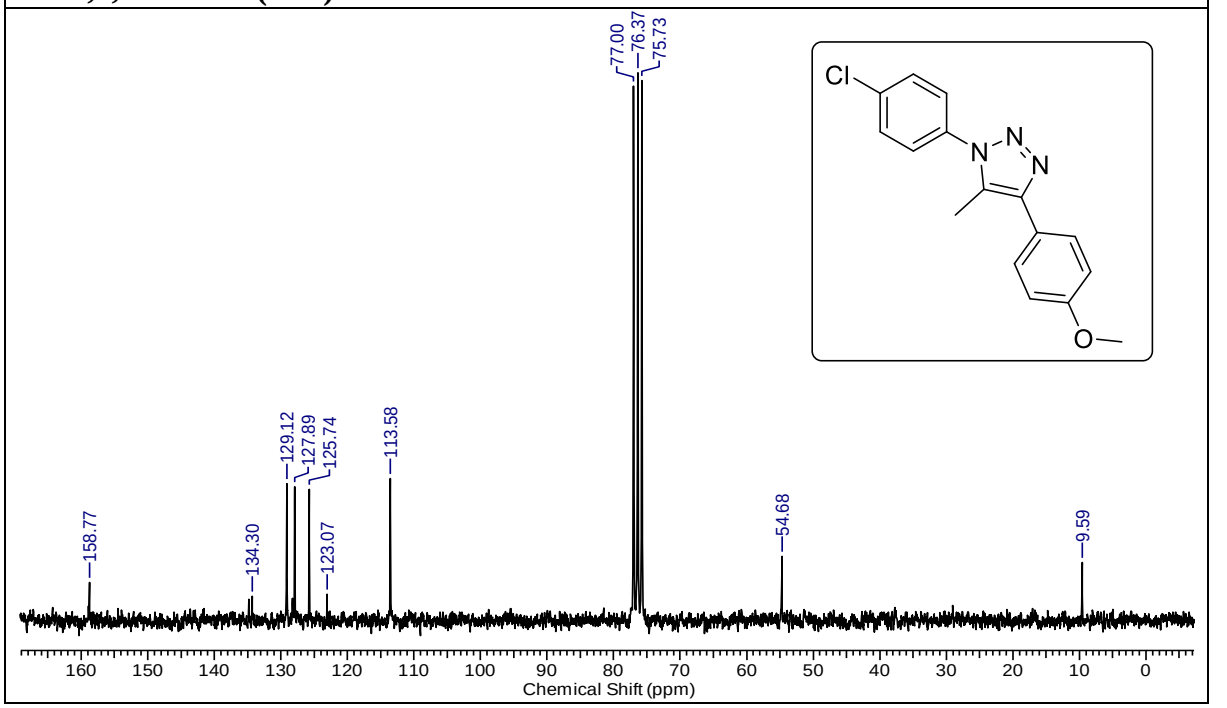
F^{19}- NMR spectrum of compound1-(4-chlorophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3cl)



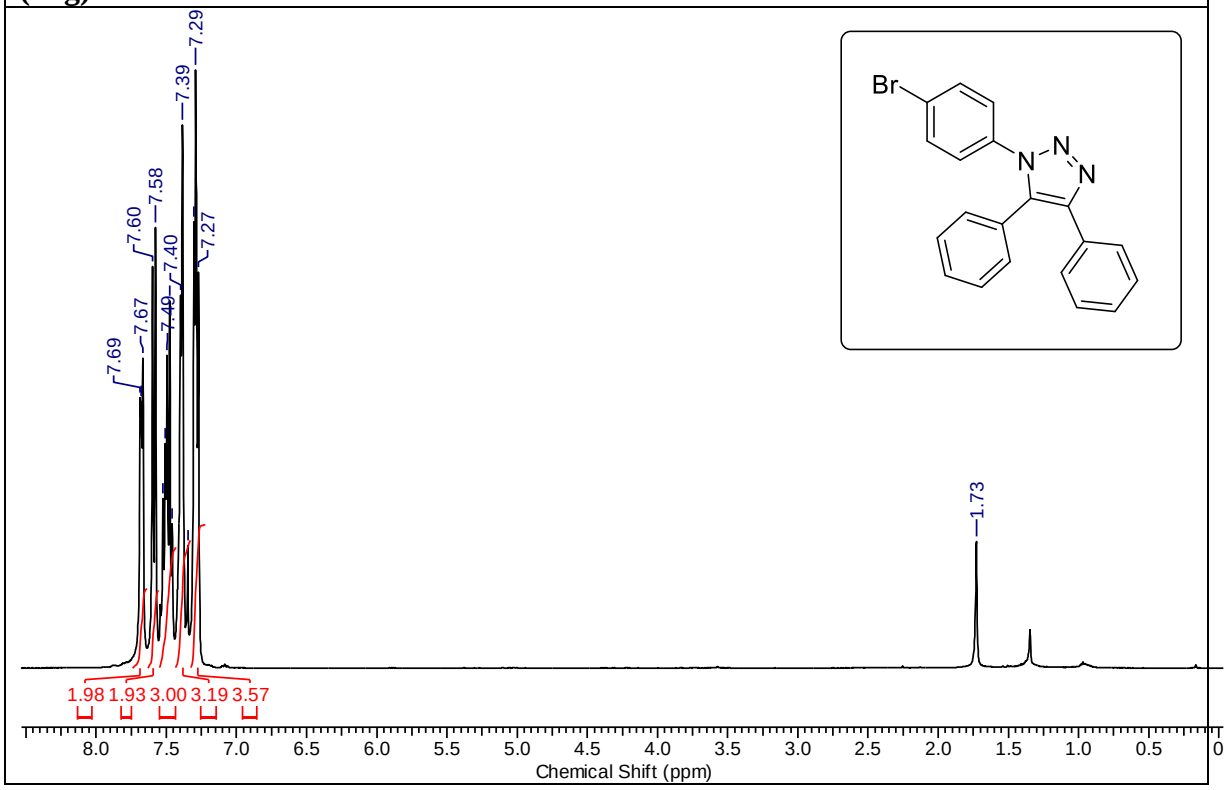
^{1}H-NMR spectrum of compound 1-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3cm)



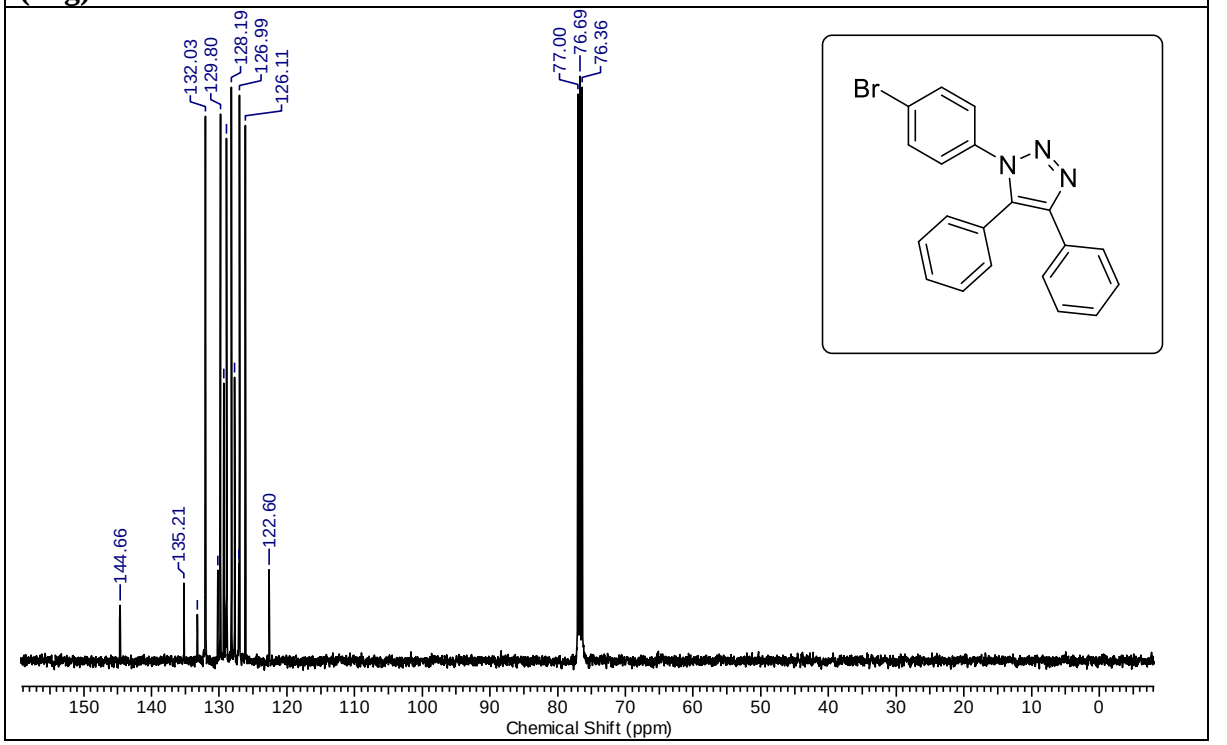
^{13}C-NMR spectrum of compound 1-(4-chlorophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3cm)



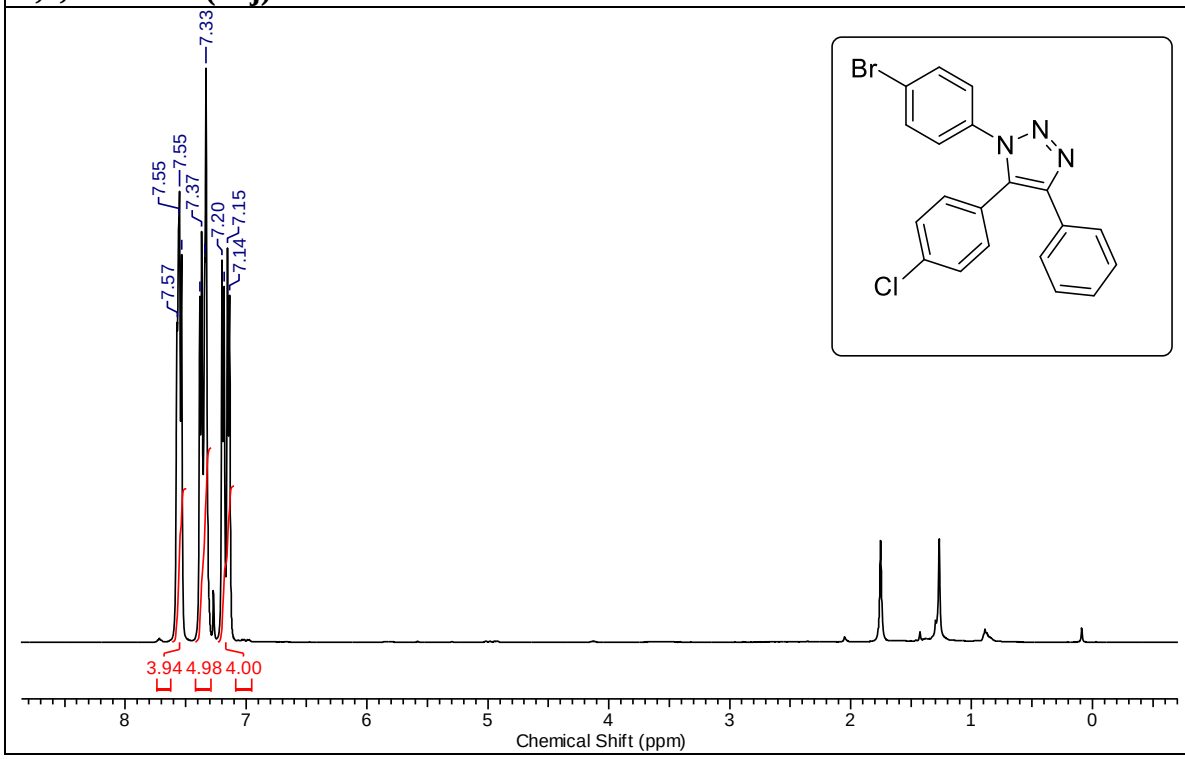
^{1}H-NMR spectrum of compound 1-(4-bromophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3dg)



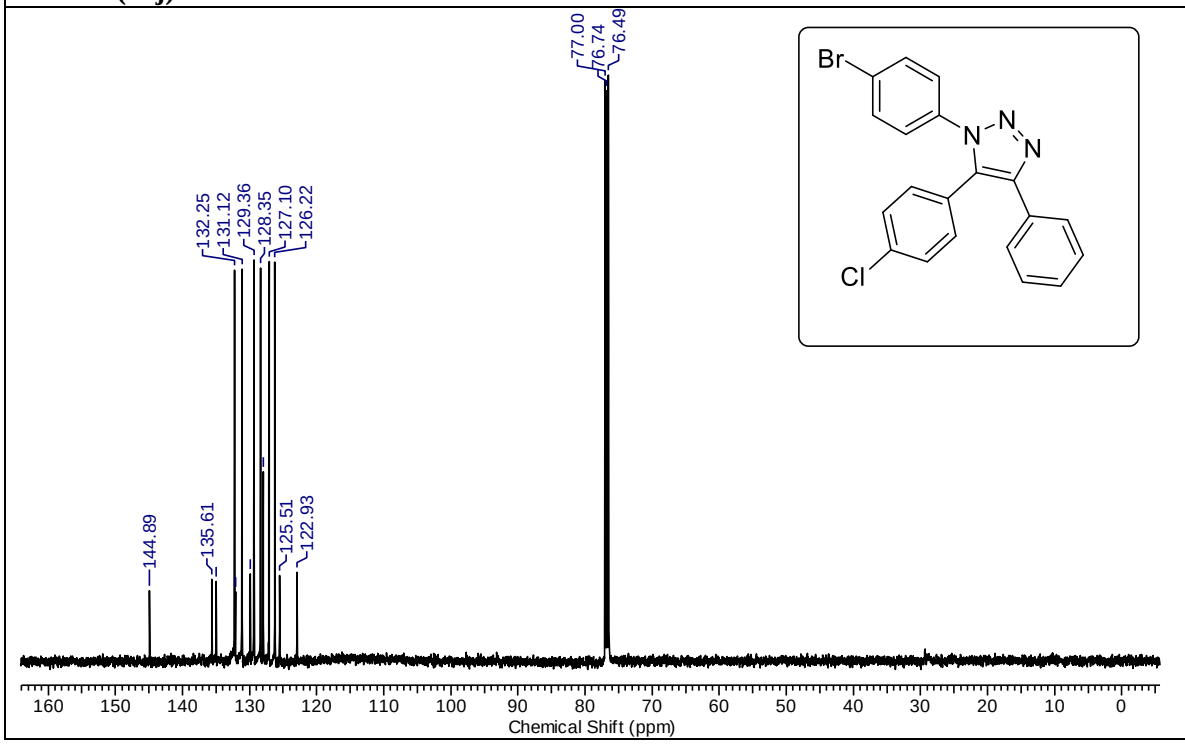
^{13}C-NMR spectrum of compound 1-(4-bromophenyl)-4,5-diphenyl-1*H*-1,2,3-triazole (3dg)



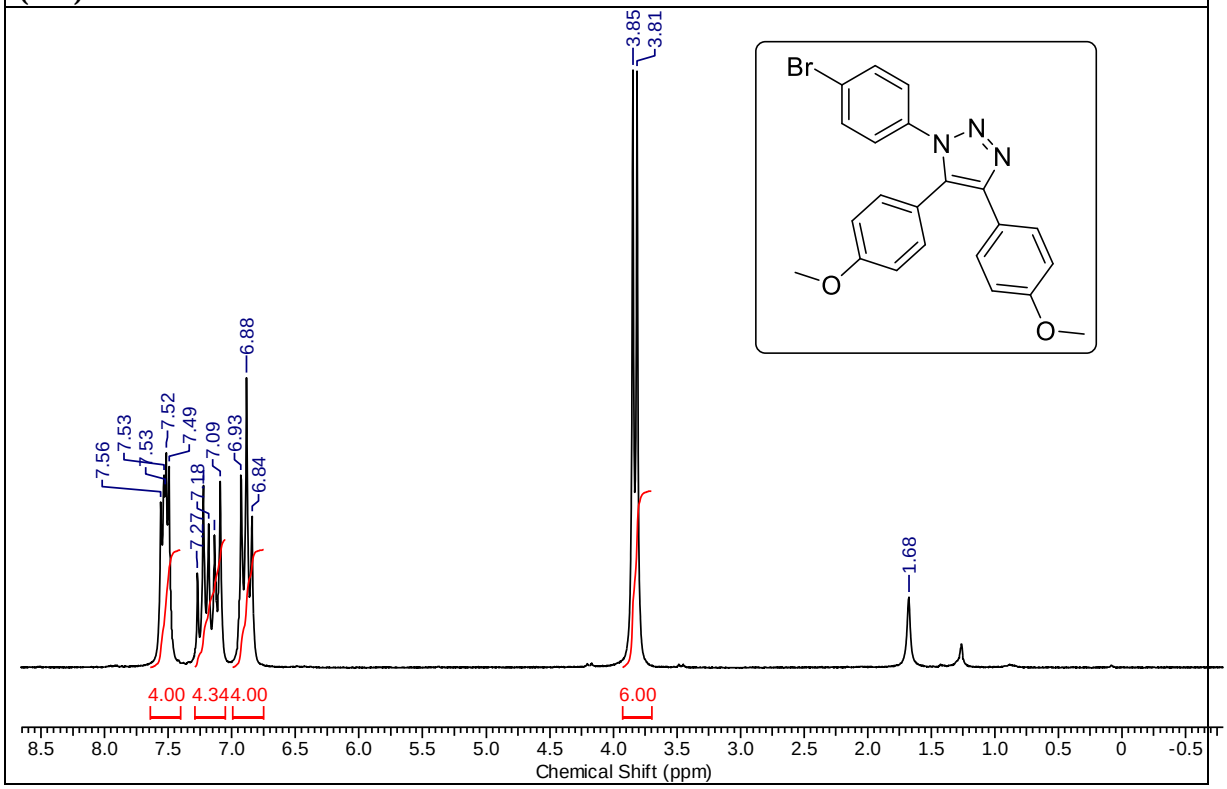
^{1}H-NMR spectrum of compound 1-(4-bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3dj)



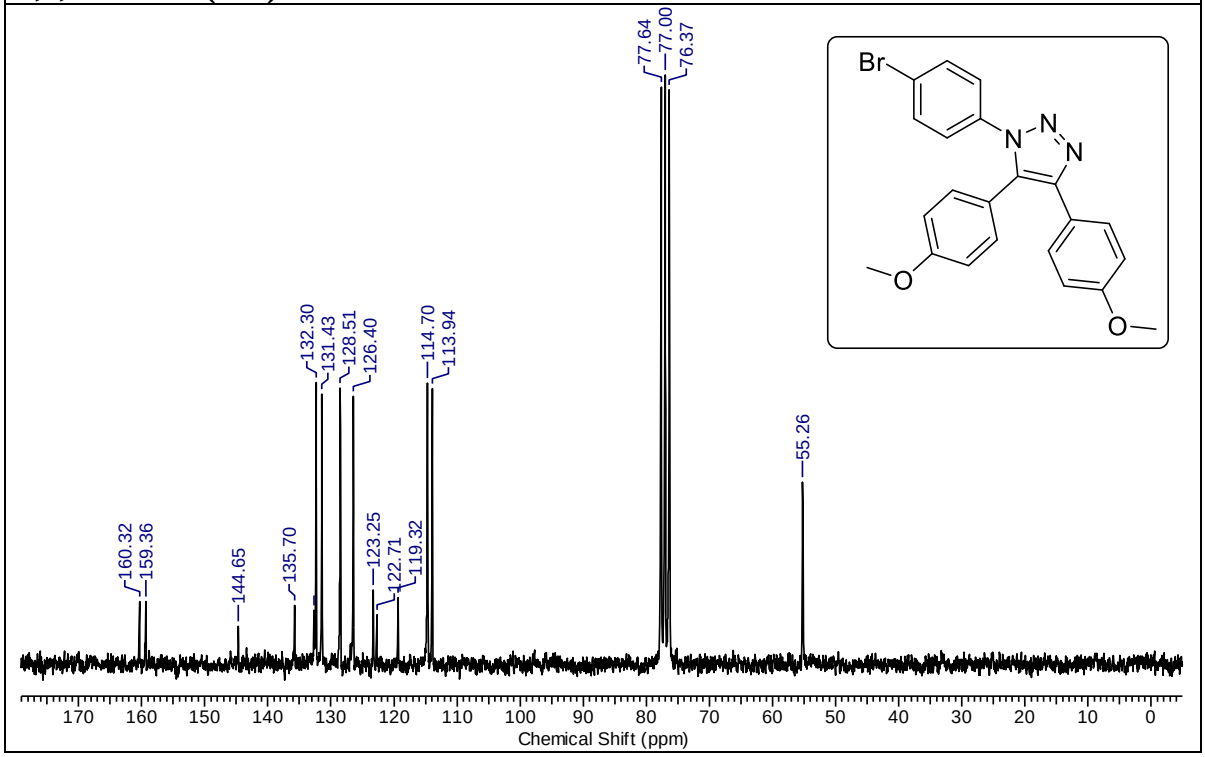
^{13}C-NMR spectrum of compound1-(4-bromophenyl)-5-(4-chlorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3dj)



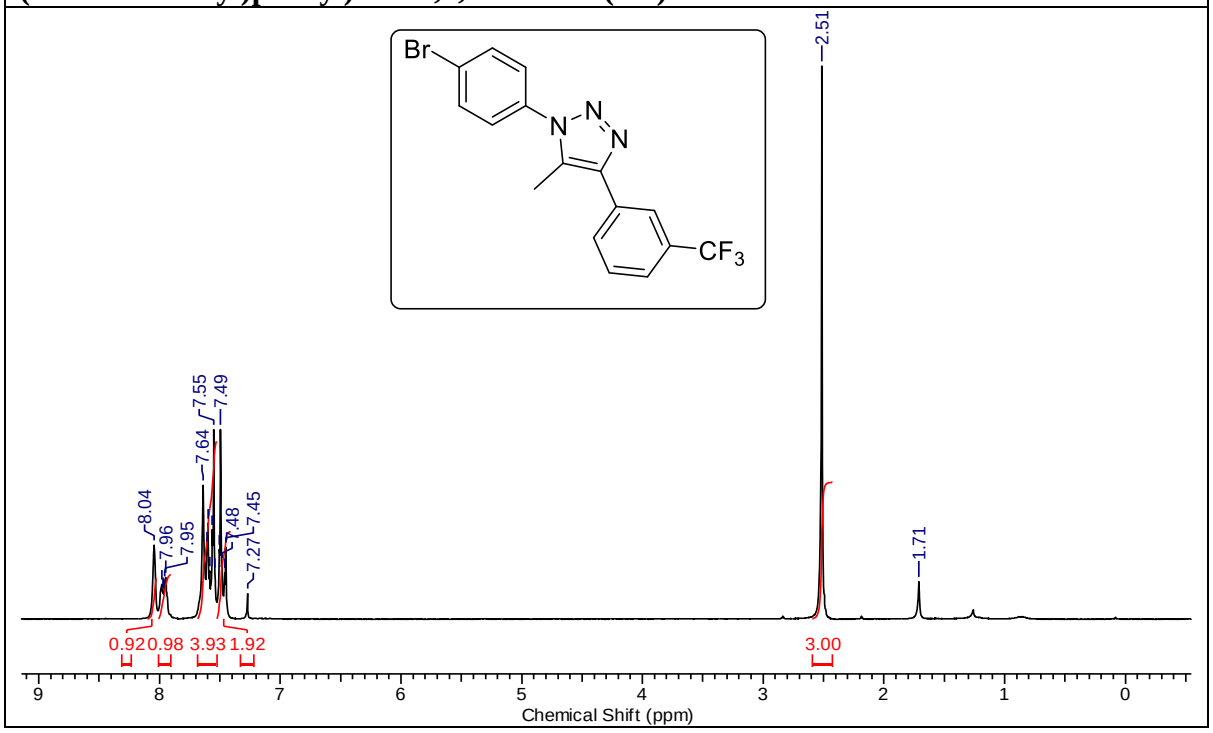
^{1}H-NMR spectrum of compound 1-(4-bromophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3dk)



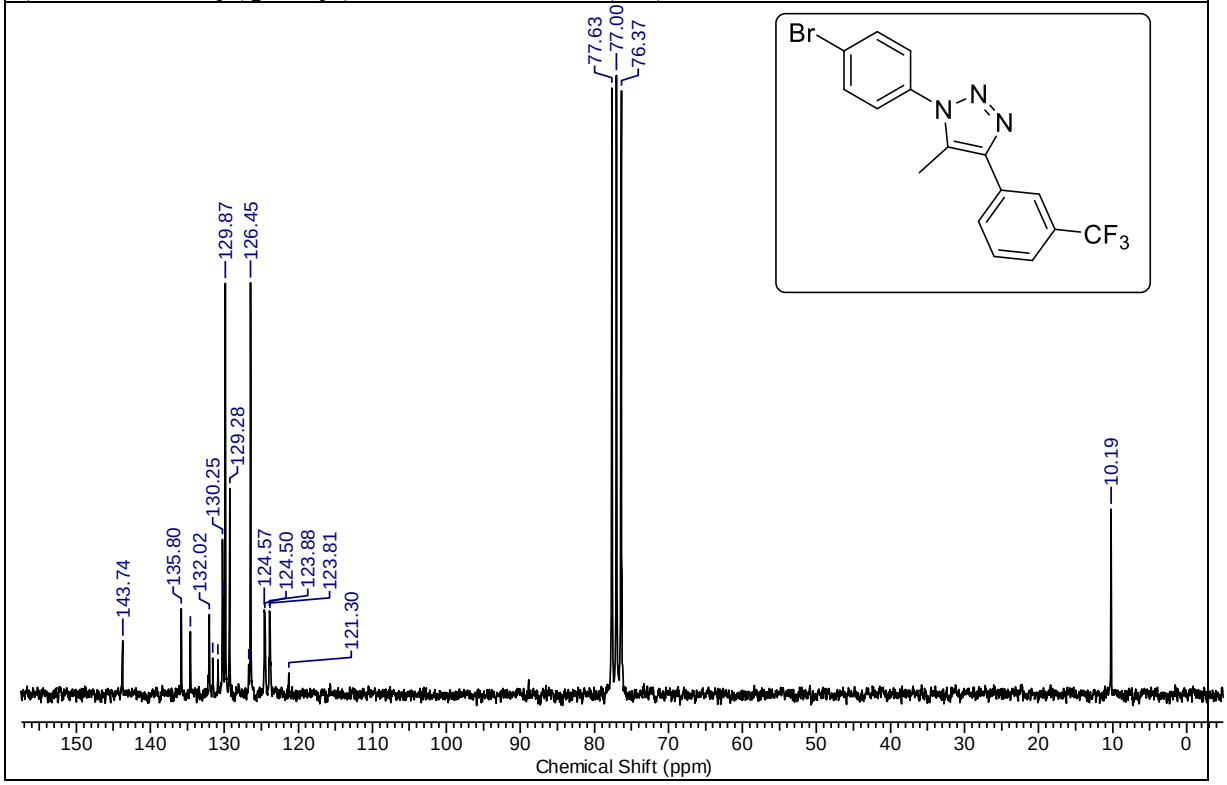
^{13}C-NMR spectrum of compound 1-(4-bromophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-1,2,3-triazole (3dk)



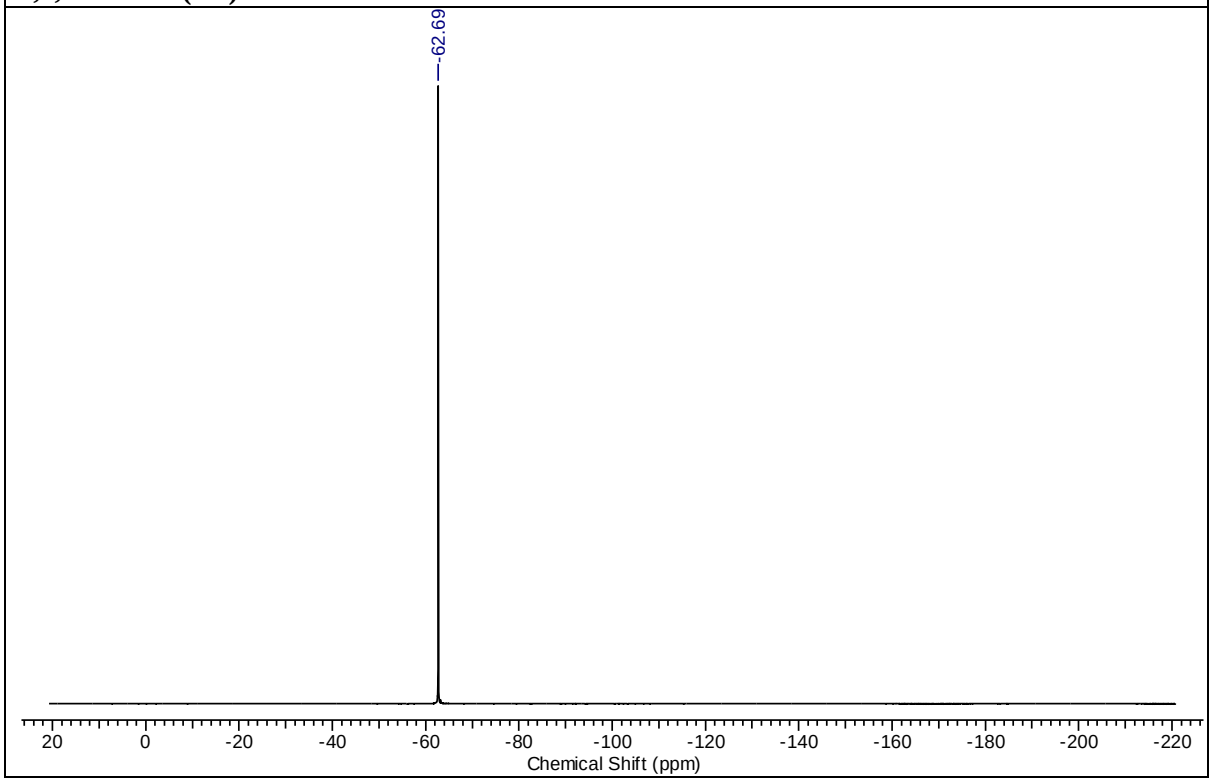
^{1}H-NMR spectrum of compound 1-(4-bromophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3dl)



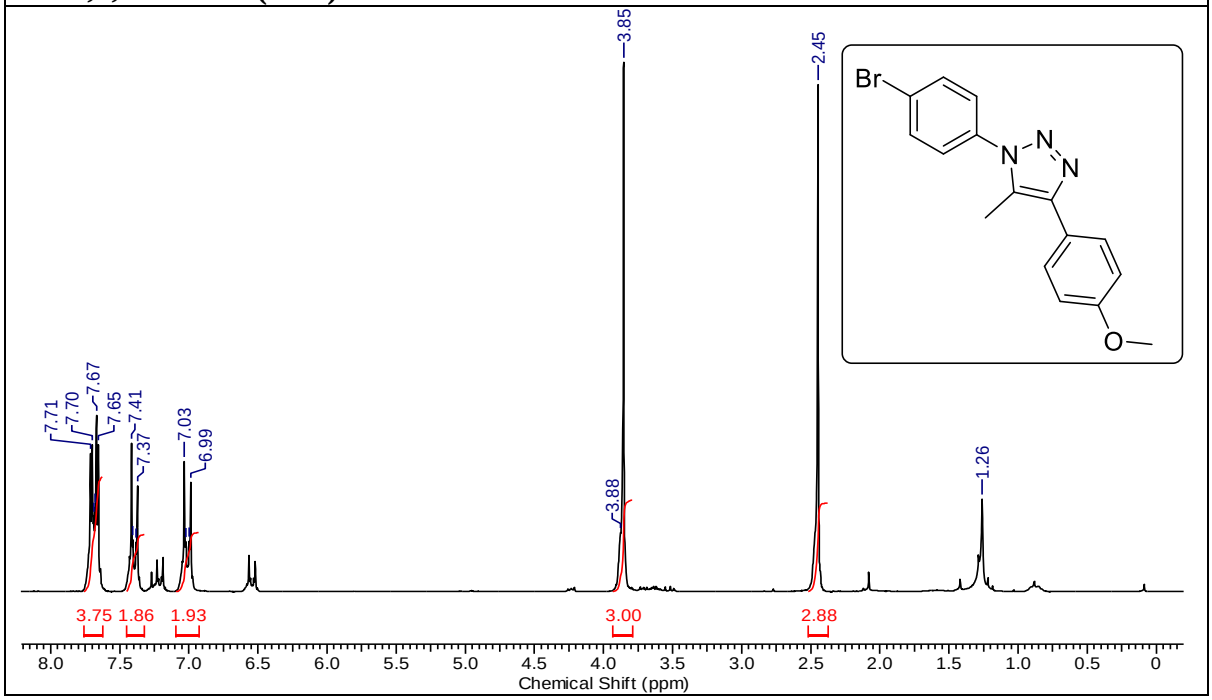
^{13}C-NMR spectrum of compound1-(4-bromophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3dl)



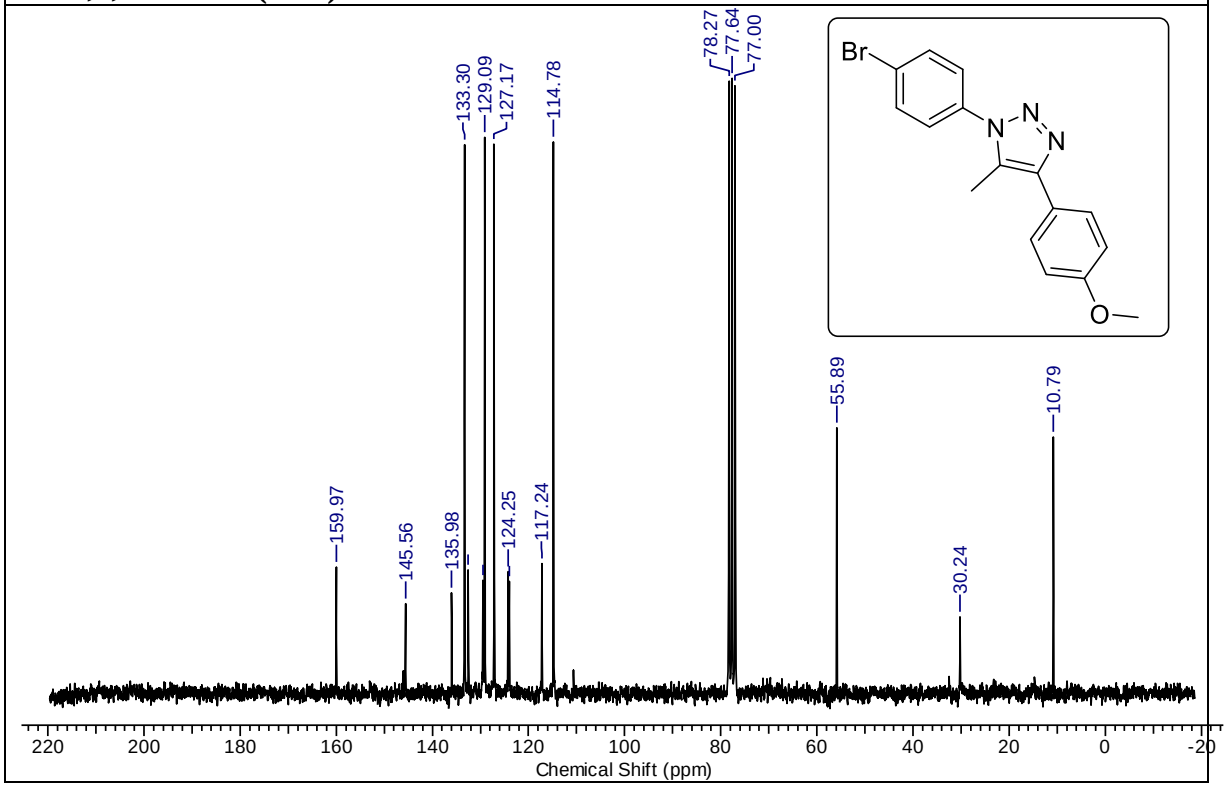
F^{19}- NMR spectrum of compound1-(4-bromophenyl)-5-methyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3dl)



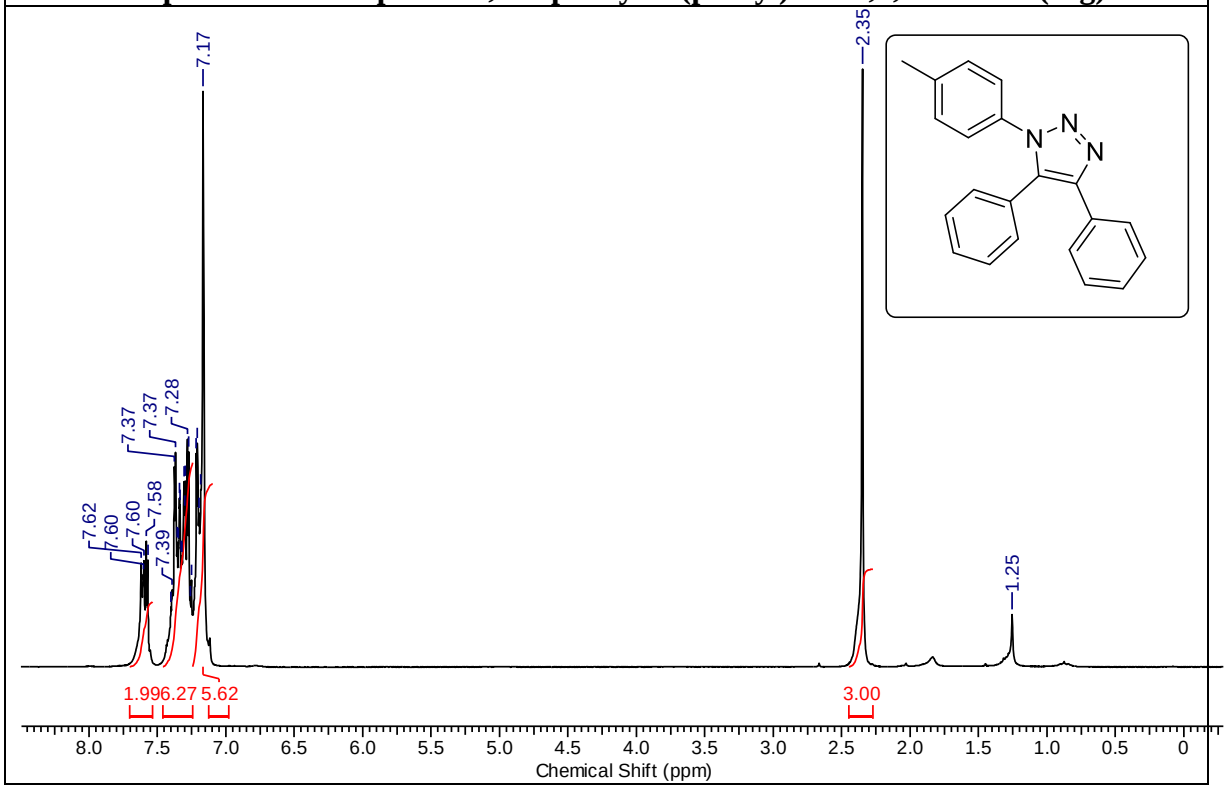
^{1}H-NMR spectrum of compound 1-(4-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3dm)



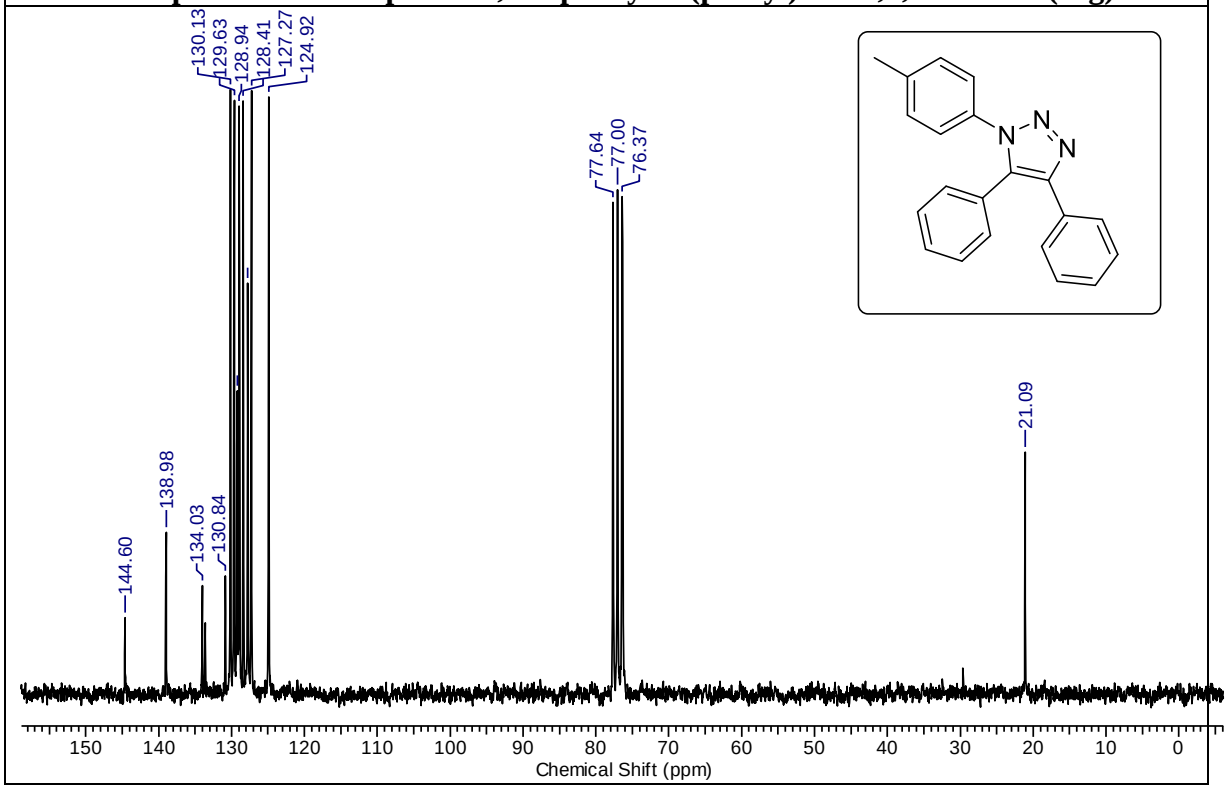
^{13}C-NMR spectrum of compound 1-(4-bromophenyl)-4-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole (3dm)



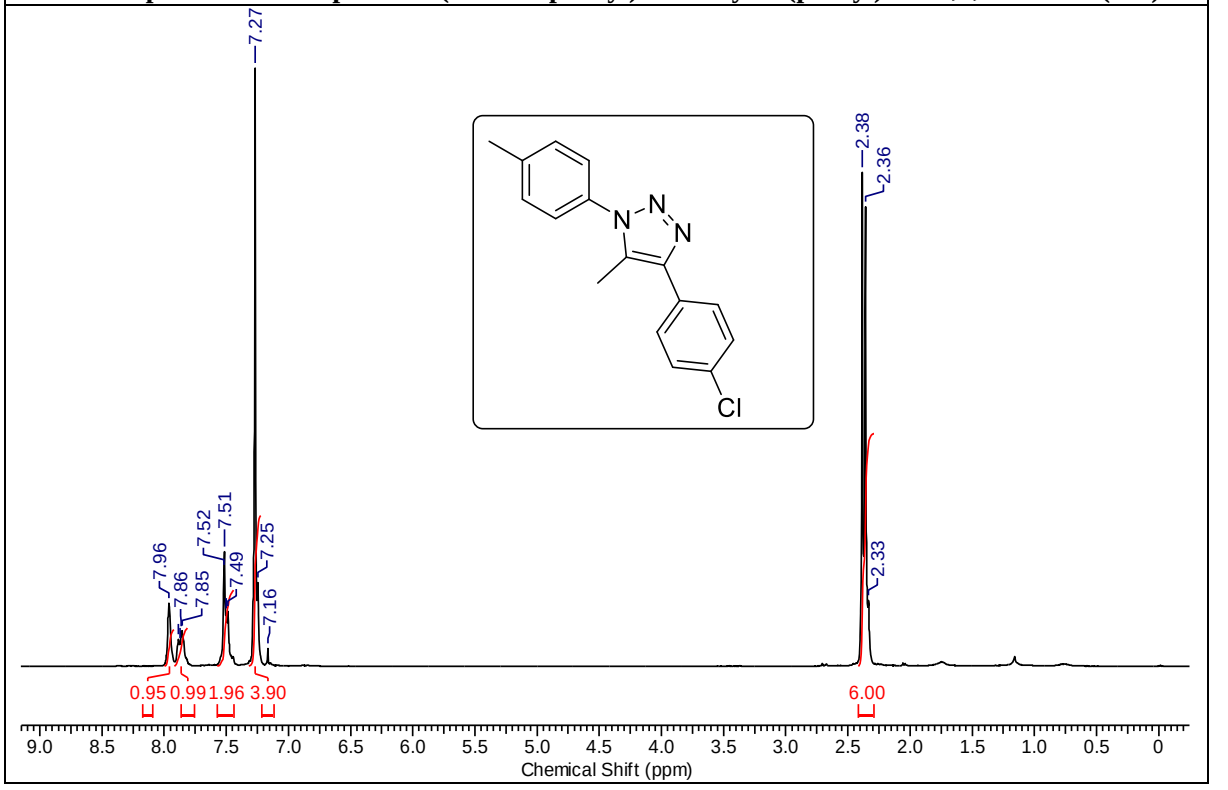
^{1}H-NMR spectrum of compound 4,5-diphenyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eg)



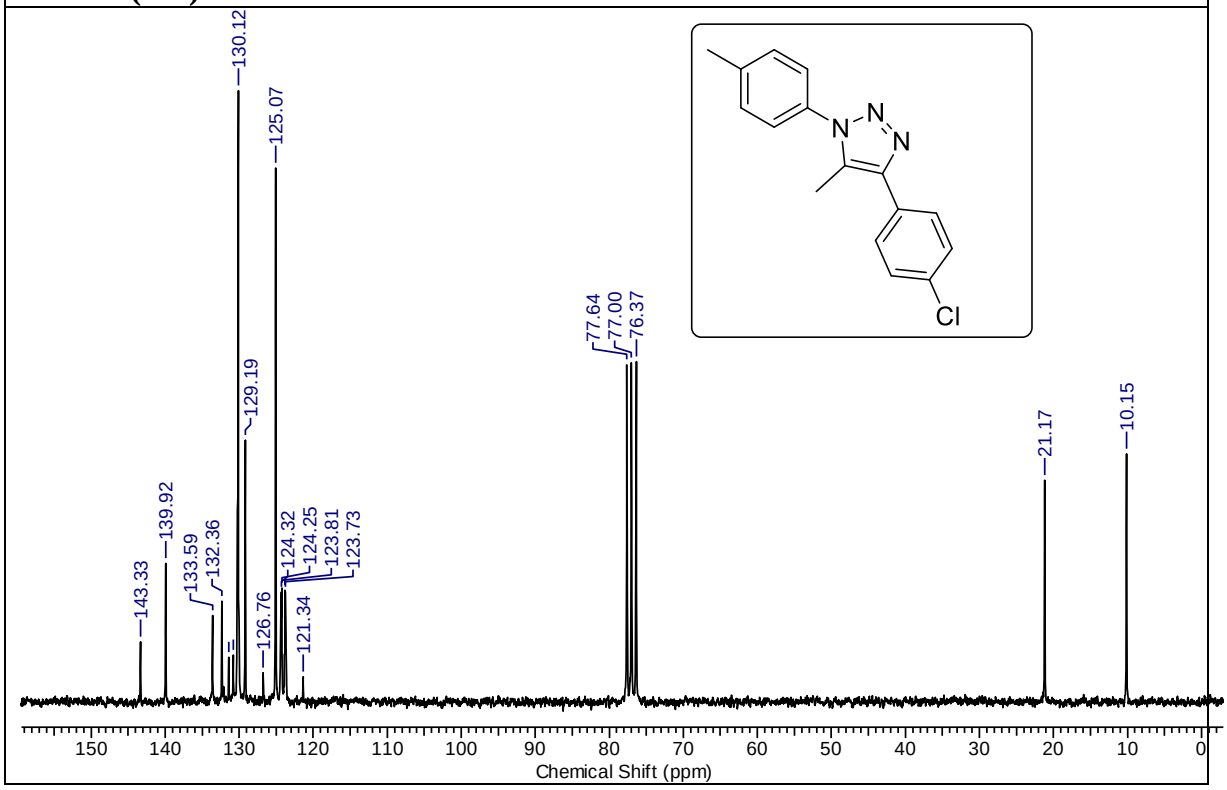
^{13}C-NMR spectrum of compound 4,5-diphenyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eg)



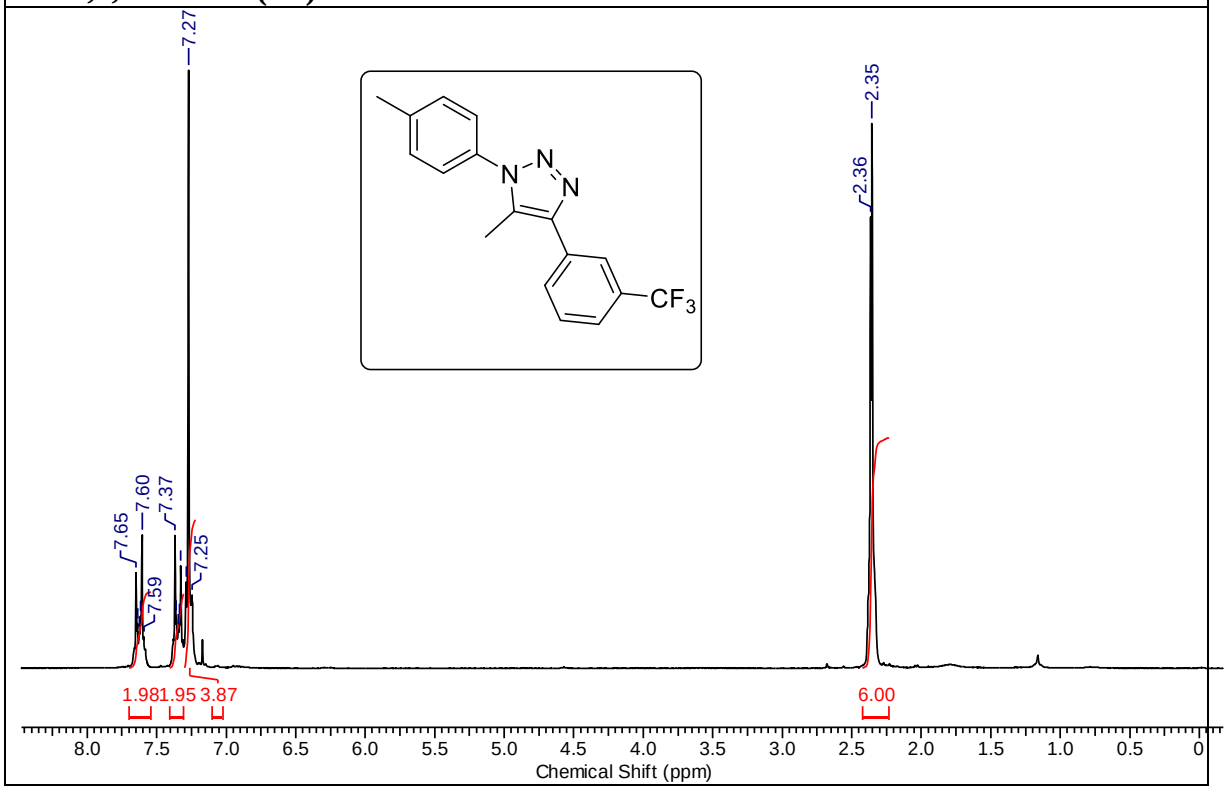
^{1}H-NMR spectrum of compound 4-(4-chlorophenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eh)



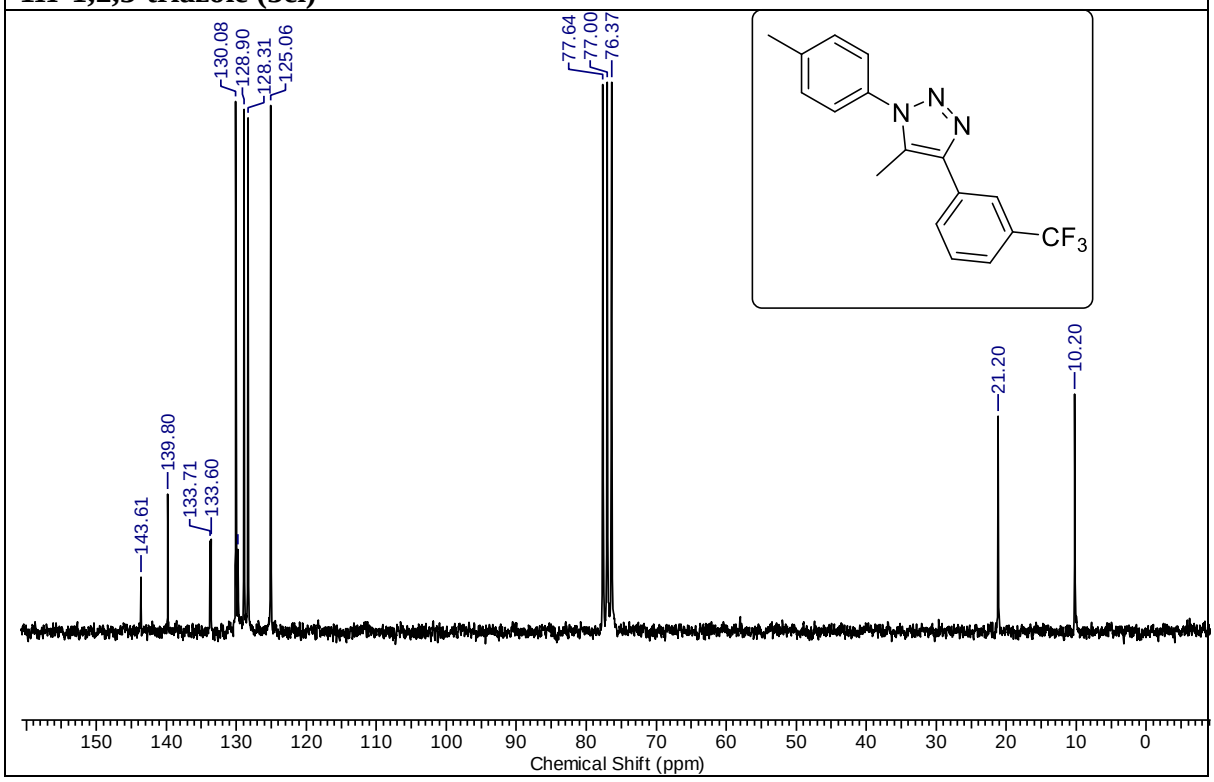
^{13}C-NMR spectrum of compound 4-(4-chlorophenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3eh)



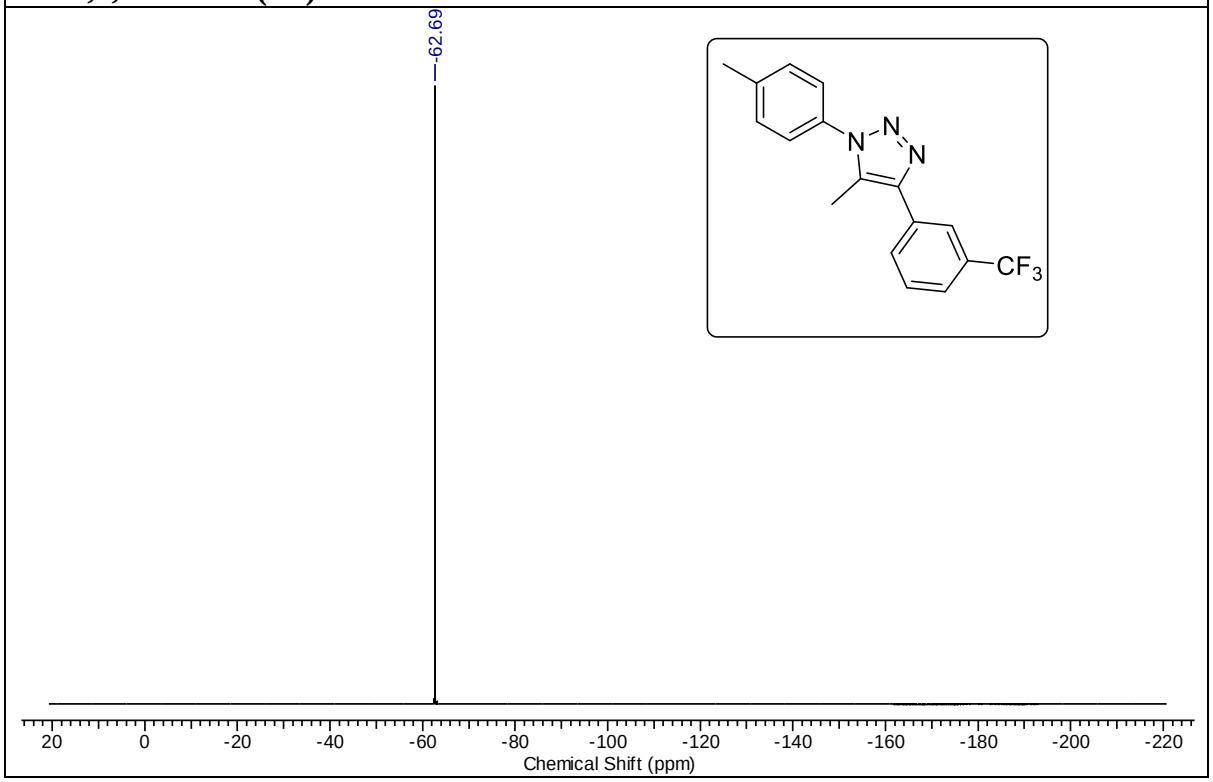
^{1}H-NMR spectrum of compound 5-methyl-1-(p-tolyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3el)



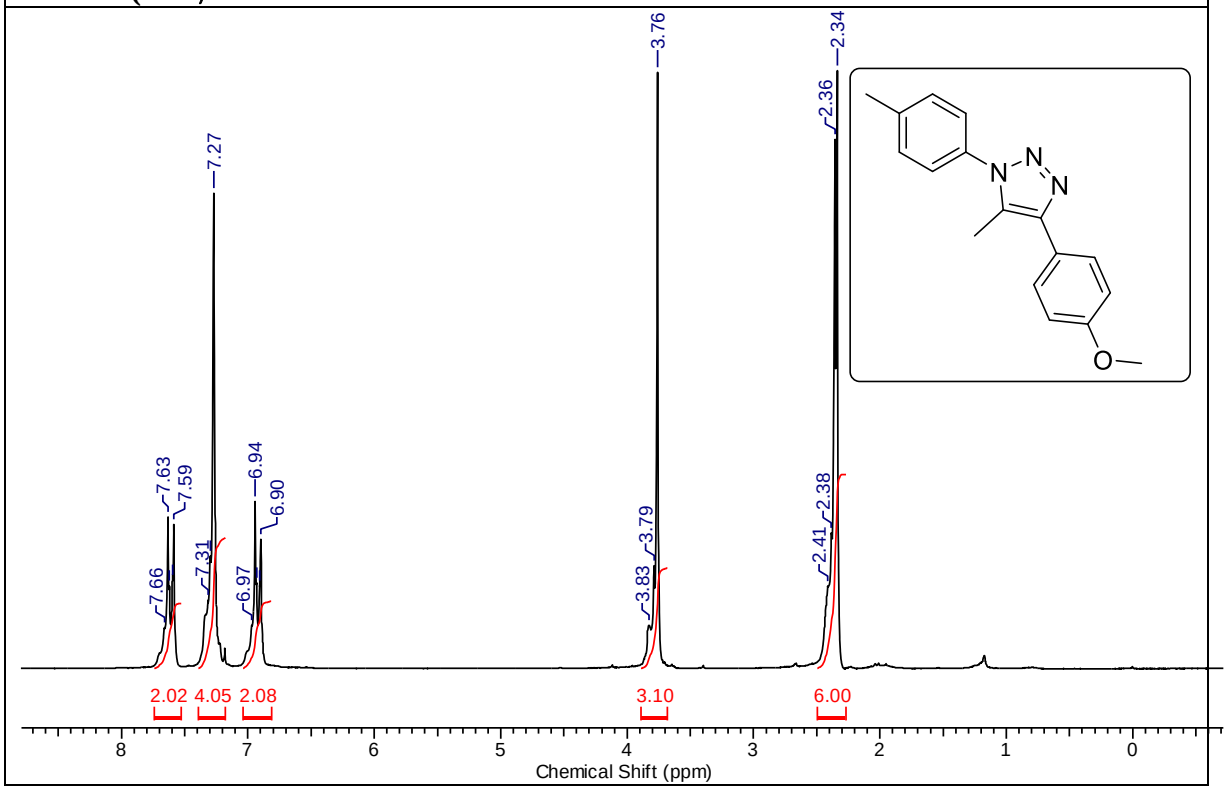
^{13}C-NMR spectrum of compound 5-methyl-1-(p-tolyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3el)



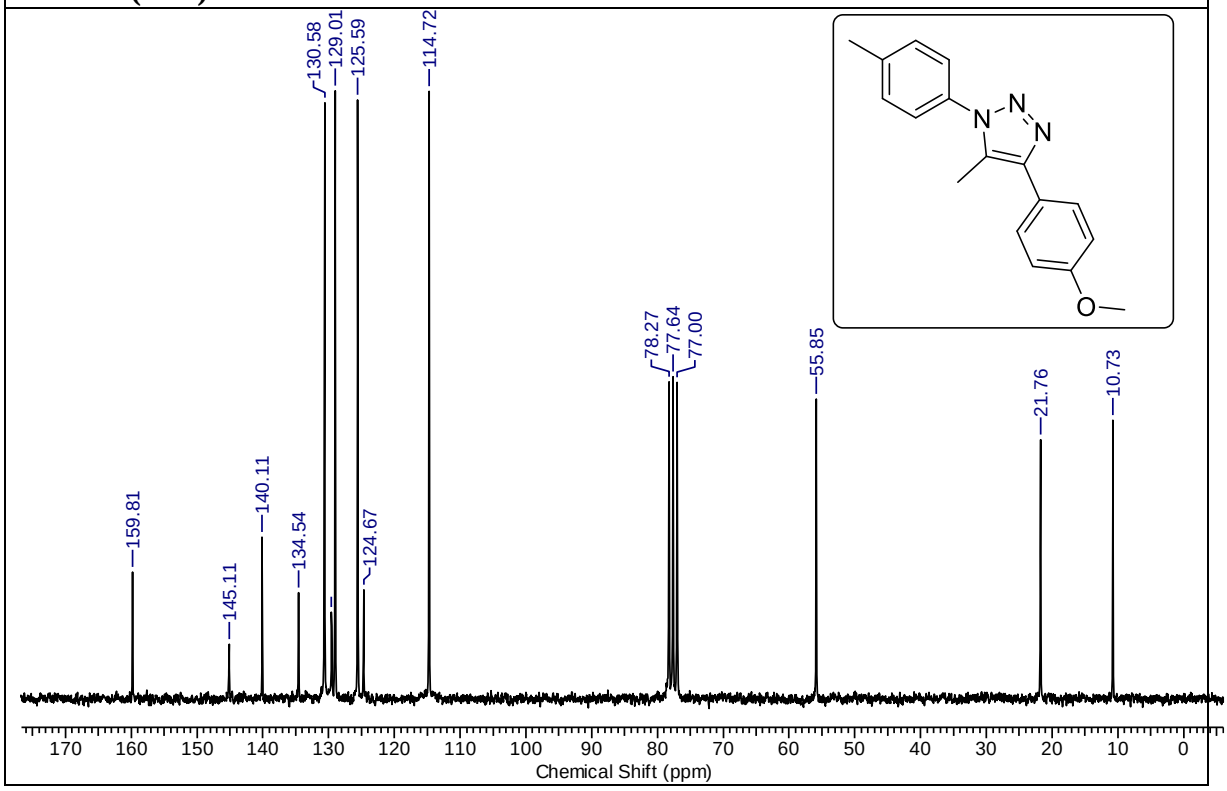
F^{19}- NMR spectrum of compound 5-methyl-1-(p-tolyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3el)



^{1}H-NMR spectrum of compound 4-(4-methoxyphenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3em)



^{13}C-NMR spectrum of compound 4-(4-methoxyphenyl)-5-methyl-1-(p-tolyl)-1*H*-1,2,3-triazole (3em)



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1. a) Lutz, J.-F. *Angew. Chem*. **2007**, *119*, 1036; *Angew. Chem. Int. Ed.* **2007**, *46*,; b). Agard, N. J.; Prescher,J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 11196.
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ABSTRACT

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Title of the thesis: An approach toward the total synthesis of biologically active molecules (D_2 receptor agonist quinagolide and antidiabetic drug sitagliptin) & Synthesis of heterocyclic building block and novel triazole methodology

The synthesis of biologically active marketed drugs and medicinally important natural product synthesis and their synthetic derivatives have played a key role to develop drugs. There are four chapters of the thesis, in which first and second chapter deal with the marketed drug (D_2 receptor agonist (±)-Quinagolide and antidiabetic drug Sitagliptin) synthesis. In that context, indigenous structure attracted the attention of synthetic chemists to the synthesis of these compounds. Formal scalable synthesis of D_2 receptor agonist quinagolide in gram scale is described in first chapter. In second chapter, development of synthetic methodologies for the synthesis of antidiabetic drug sitagliptin is presented. Chapters third and fourth deal with the heterocyclic chemistry. Third chapter includes synthesis of heterocyclic building block Pulchellalactam and the fourth chapter describes the development of a new route for synthesis of triazole in a "Green" solvent. All four-chapters describe synthetic challenges faced and development of synthetic routes for biologically active compounds.

List of Publications Emanating from the Thesis Work

1. Tripathi, Anupam.; Rode, V.; Chandrashekhar.; Llop, Jordi.; Chavan, S. P.; Joshi, M. Sameer. *Tetrahedron Letters* **2019**,*61*, 151662

List of Posters Presented with Details

1. National Science Day Poster presentation at CSIR-National Chemical Laboratory, Pune (February 26-27, **2020**):

   Title: An enolate-mediated regioselective synthesis of 1,2,3-triazoles via Huisgen (3+2) cycloaddition reactions of azides with aldehydes or Ketones in aqueous phase.

   Abstract: A synthetic route for the direct conversion of arylazides into the corresponding trizoles via phase transfer catalyst-assisted [3+2] Huisgen cycloaddition reaction under basic conditions in aqueous medium is reported. This synthetic methodology, which offers high yields and excellent regioselectivity, has advantages over previously reported, well established click reactions.

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An enolate-mediated regioselective synthesis of 1,2,3-triazoles via azide-aldehydes or ketones [3+2]-cycloaddition reactions in aqueous phase

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ABSTRACT

A synthetic route for the direct conversion of arylazides into the corresponding trizoles via phase transfer catalyst-assisted [3+2] cycloaddition reaction under basic conditions in aqueous medium is reported. This synthetic methodology, which offers high yields and excellent regioselectivity for varieties of triazoles at 100 °C for 24 h–48 h and this 'greener' synthesis constitutes an alternative to the previously reported well established click reactions.

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Click chemistry involving Huisgen [3+2] cycloaddition of alkynes and azides under thermal conditions to obtain 1,2,3-triazoles has been widely used for more than a century [1,2], and has been extensively applied to the preparation of 1,4- and 1,5-disubstituted 1,2,3-triazoles, which find application in a broad range of industrial and societal sectors [3]. Early works to achieve regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles was carried out by Meldal and Sharpless' groups using copper catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) reactions [4], while regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles can be carried out by ruthenium-catalyzed azide alkyne cycloaddition (RuAAC) reactions [5]. Very recently, nickel-catalyzed azide-alkyne cycloaddition (NiAAC) to yield 1,5-disubstituted 1,2,3-triazoles in aqueous media has been described [6].

Among triazoles, 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles have shown promise in the pharmaceutical sector. However, the development of regioselective synthetic procedures for their preparation has not been thoroughly explored. One alternative involves the reaction of metal acetylide (metal = Li, Mg, Zn or Te) with an organic azide and its subsequent *in situ* reaction with an electrophile to form a metalated triazole with reverse selectivity and high reactivity [7]. Palladium- or copper-catalyzed reactions [8], in the presence of arylboronic acid or aryltrifluoroborates [9], and reaction of aryl azides with active methylenes or symmetrical ketones at high temperature have also been described [10]. Of note, most of the above mentioned methods employ costly or non-commercial substrates instead of using simple starting materials such as phenylacetaldhyde or arylacetones.

Organocatalytic azide-aldehyde [11] and azide-ketone [13a,14] reactions using [3+2] cycloaddition to furnish 1,4-disubstituted 1,2,3-triazoles have been reported. However, their application is limited to organic solvents. Previous attempts to conduct the reaction in aqueous media show limited scope (i.e. simple ketones such as cyclohexanone), and require the use of organocatalysts with long aliphatic chains [12a]. The outcome becomes more dramatic when translated to cycloaddition reactions involving azides and aldehydes. For example, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted azide-aldehyde reaction results in less than 5% yields in water (Scheme 1a) [11]. Still, the use of water as the solvent as reported by Yeung et al. [12a] would be highly desirable to achieve environmental-friendly, easy to scale up synthetic routes. Recently, we have described the preparation of ^{13}N-labelled azides [15], triazoles [16], and tetrazoles [17] under catalytic conditions. In continuation of our work, we here present a azide-aldehydes or ketones [3+2]-cycloaddition reactions for the synthesis of triazoles in water as a green solvent (Scheme 1b).

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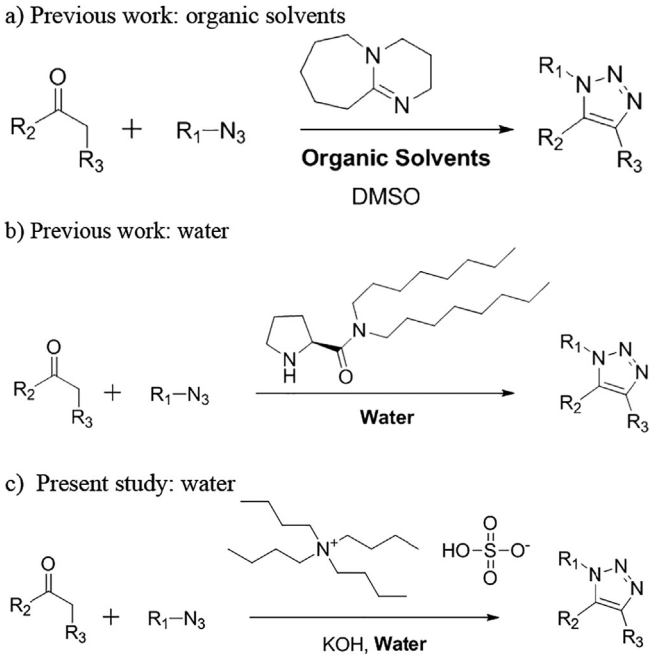


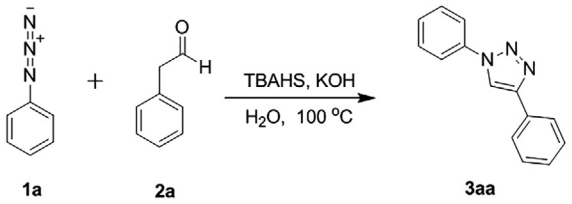
Scheme 1. (a) Reaction reported in previous work [11]. When R_1 = R_3 = Ph and R_2 = H, yield = 5% in water; (b) similar kind of work in water [12a] and (c) reaction reported in this work, When R_1 = R_3 = Ph and R_2 = H, yield = 77% and When R_2 = Ph, yield = 95%.

Initially, the reaction between phenyl azide and phenyl acetaldehyde was assayed as a model reaction using different bases, catalysts and reaction conditions, and using water as the only solvent. In the absence of catalyst, the formation of the desired triazole was not observed (Table 1, entries 1 and 3), and identical results were obtained when only TBAHS was added as the catalyst (Table 1, entry 2). Simultaneous addition of KOH and K_2CO_3 resulted in the formation of the corresponding triazole in trace amount (Table 1, entry 4).

Previous works have shown that phase transfer catalyst (PTC) such as TBAHS can be used under aqueous basic conditions to achieve metal-free reactions of amides with peroxides [18]. Therefore, we decided to explore the suitability of this catalyst to achieve the desired triazole. In the presence of TBAHS, moderate yields (64%, 61% and 69%) were obtained when potassium, sodium and caesium carbonates, respectively, were used as the base, and the reaction was conducted at 100 °C for 24 h (Table 1, Entries 5–7). These values decreased to 25% and 42% when sodium and potassium bicarbonates were used respectively (Table 1, Entries 8 and 9). The addition of a stronger base such as NaOH resulted in yields equivalent to those obtained with carbonates (61%; Table 1, entry 10), although this value increased to 77% when KOH was used (Table 1, entry 11). The use of alternative catalysts including tetrabutylammonium bromide (TBAB) and tetrabutylammonium iodide (TBAI) resulted in slightly lower yields (66% and 62%, respectively; Table 1, Entries 12 and 13).

The effect of the concentrations of the catalyst and the base was also investigated. While lowering the concentrations of catalyst

Table 1
Optimization of reaction between arylazide and aldehyde.[a]



1a 2a 3aa

Entry	Base[b]	Catalyst[c]	t/h	T/°C	Yield(%)[d]
1	None	none	24	100	0
2	None	TBAHS	24	100	0
3	K_2CO_3	none	24	100	0
4	KOH	K_2CO_3	24	100	10
5	K_2CO_3	TBAHS	24	100	64
6	Na_2CO_3	TBAHS	24	100	61
7	Cs_2CO_3	TBAHS	24	100	69
8	$NaHCO_3$	TBAHS	24	100	25
9	$KHCO_3$	TBAHS	24	100	42
10	NaOH	TBAHS	24	100	61
11	KOH	TBAHS	24	100	77
12	KOH	TBAB	24	100	66
13	KOH	TBAI	24	100	62
14[e]	KOH	TBAHS	24	100	45
15[f]	KOH	TBAHS	24	100	75
16	KOH	TBAHS	24	50	48
17	KOH	TBAHS	48	RT	21

[a] All reactions were carried out with 1a (0.21 mmol), 2a (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL).
[b] 0.42 nmol.
[c] 0.042 nmol.
[d] Isolated yields after column chromatography.
[e] Catalyst- 10 mol% and KOH- 0.21 mmol.
[f] Catalyst- 30 mol%; TBAHS: Tetrabutyl ammonium hydrogen sulfate; TBAB: Tetrabutylammonium bromide; TBAI: Tetrabutylammonium iodide.

and base to 10 mol% and 0.21 mmol, respectively, resulted in moderately lower yields (45%; Table 1, entry 14), an increase in the amount of both the base and the catalyst did not positively affect the yield (Table 1, entry 15). Later, the effect of the temperature was also explored. Our results clearly show that lower reaction temperatures dramatically decrease reaction yields (Table 1, entries 16 and 17).

We next explored the substrate scope of our reaction by reacting a variety of carbonyl compounds with phenyl azide (Table 2). Aliphatic aldehydes did not yield the desired triazoles under our experimental conditions (Table 2, entries 3 and 4), probably due to the lower acidic character of the alpha methylene groups, which hampers the formation of the enolate intermediate. However, the formation of the product was achieved when hydrocinnamaldehyde was used, in spite of the presence of one additional methylene group (59%, Table 2, entry 2). The reaction was also unsuccessful in the case of aliphatic esters (Table 2, entries 5 and 6). Finally, we explored the reactivity of ketones and almost quantitative yields were obtained (Table 2, entries 7 and 8). As in the case of esters, the enolate ion is resonance-stabilised in ketones. However, the negative charge of the conjugate base of the ester is stabilized by the same oxygen atom whose lone pair is involved in the resonance, resulting in a lower effectiveness. Overall, this results in a higher stability of the conjugate base of the ketone, leading to the formation of a more acidic compound which favours the formation of the triazole.

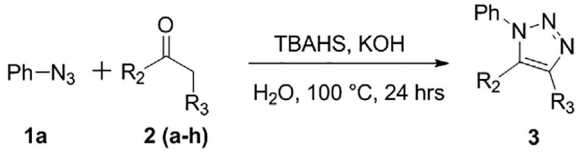
Encouraged by these results, we investigated the reactivity of different ketones (Table 3, 2g-2n) with different arylazides (Table 3, 1a-1e). Cycloaddition reactions proceeded smoothly, irrespective of the electronic properties of the substituents on the aromatic rings. The presence of both electron withdrawing groups such as chloro and bromo at the *p*- position (Table 3, 3cg-3dm), electron-donating groups like methyl moieties at the *p*-position (Table 3, 3eg-3em), or electron-neutral groups (Table 3, 3ag-3an) on the phenyl azide yielded the corresponding triazoles in very good yields. Notably, high yields were also obtained with benzyl azide (Table 3, 3bg-3bj).

The effect of substituents on the ketone was also explored. When substituted phenyl acetones were used, good yields were obtained irrespective of the substituents on the aromatic rings. The presence of electron withdrawing groups such as chloro and trifluoromethyl at the *p*-and *m*-positions, resulted in 94% and 75% yields, respectively (Table 3, 3ah and 3al). Similar results were obtained with electron donating groups such as methoxy at the *p*-position of the phenyl rings (Table 3, 3am, 3cm, 3dm and 3em) In addition, aromatic ketones containing two methoxy groups also did not affect the reaction rate and which delivers corresponding triazoles in higher yields. (3ak, 3ck and 3dk). 1-Phenyl-2-butanone also resulted in excellent yields (Table 3, 3ai and 3ci). Pleasingly, the best yield was obtained with 2-Phenylacetophenone, which afforded the desired triazole in 95% isolated yield (Table 3, 3ag). However, 4-acetyl pyridine having low reactivity since lack of extra methylene group next to carbonyl group which afforded corresponding triazole only in 43% yield (Table 3, 3an). As expected, alkyl ketones, namely 2-butanone and 2- octanone, did not yield the formation of the triazole (Table 4, 3ao and 3ap), due to the low acidic character of alpha-methylene groups in comparison with aromatic ketones, which hampers the formation of the enolate ion for the subsequent [3+2] cycloaddition reaction. Also reaction was unsuccessful, when it is performed in presence of sulfonylazides (Table 4, 3fg). The results in Table 3 demonstrate the broad scope of this synthetic approach covering a structurally diverse group of aryl azides 1(a-e) and aromatic ketones 2(g–n). It is worth mentioning that, the high yields are even more impressive considering that water was the only solvent. Overall, our methodology has proven robust and demonstrated by the preparation of twenty-seven different triazoles, fourteen of them reported for the first time.

The exact reaction mechanism remains to be explored. However, we hypothesize that the reaction of phase transfer catalyst (PTC) with aldehyde/ketone **2** under basic conditions, forms the enolate ion intermediate **4** or **4′**, which subsequently reacts with R_1-N_3 (**1**) rapidly to yield the 1,2,3-triazoline adduct **5** *via* concerted or stepwise [3+2] cycloaddition amination-cyclization reaction.[11,13a] Adduct **5** then yields the corresponding 1,2,3-triazole **3** by loss of a water molecule (dehydration) (Scheme 2).

In conclusion, we have developed a simple, versatile, and green route for enolate-mediated azide-aldehyde or ketone [3+2]-cycloaddition reaction which enables the synthesis of 1,4-disubstituted 1,2,3-triazoles containing a variety of functional groups with excellent regioselectivity using water as the only solvent. This water-compatible and phase transfer catalyst (PTC)-assisted cat-

Table 2
Scope of carbonyl compounds.[a]

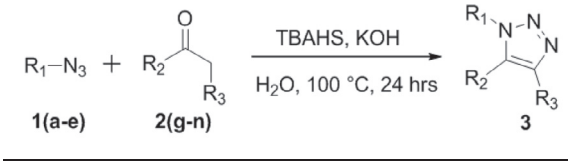


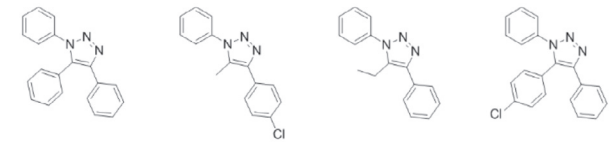
1a **2 (a-h)** **3**

Entry	Substrate 2		Carbonyl compd	Product	Yield (%)[b]
	R_3	R_2			
1	Ph	H	2a	3aa	77
2[c]	$PhCH_2$	H	2b	3ab	59
3	$Me(CH_2)_2$	H	2c	3ac	0
4	$Me(CH_2)_3$	H	2d	3ad	0
5	MeCO	OCH_2CH_3	2e	3ae	0
6	MeCO	OCH_3	2f	3af	0
7	Ph	Ph	2 g	3ag	95
8	4-ClC_6H_4	CH_3	2 h	3ah	94

[a] All reactions were carried out with 1a (0.21 mmol), 2 (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (1.0 mL) at 100 °C for 24 h.
[b] Isolated yields after column chromatography.
[c] Reaction time: 48 h.

Table 3
Substrate scope.[a]

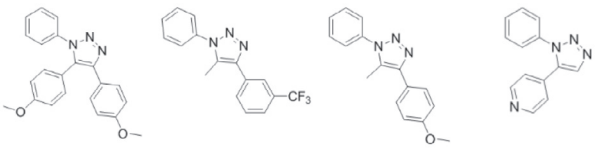



3ag, 95%

3ah, 94%

3ai, 92%

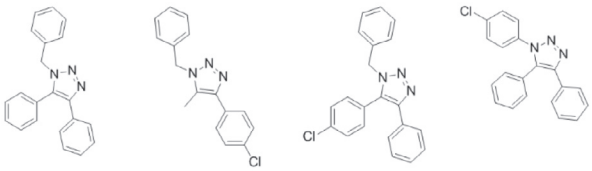
3aj, 82%


3ak, 79%

3al, 75%

3am, 82%

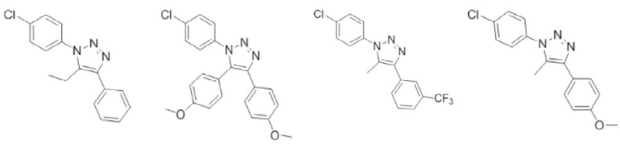
3an, 43%


3bg, 78%

3bh, 81%

3bj, 90%

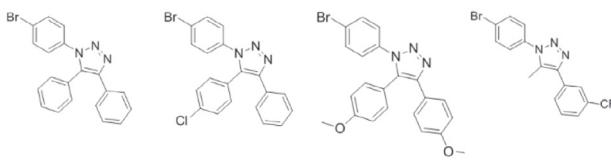
3cg, 79%


3ci, 89%

3ck, 90%

3cl, 82%

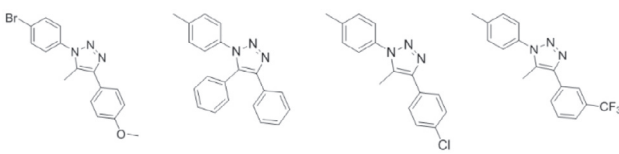
3cm, 87%


3dg, 88%

3dj, 91%

3dk, 81%

3dl, 89%


3dm, 91%

3eg, 77%

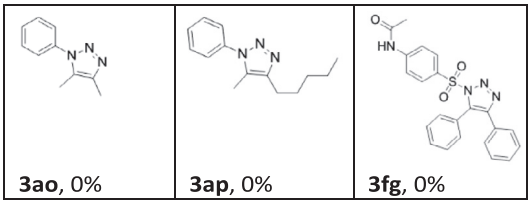
3eh, 87%

3el, 90%


3em, 84%

[a] All reactions were carried out with **1** (0.21 mmol), **2** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (100 °C, 24 h).

Table 4
Substrate that doesn't work.[a]


3ao, 0%

3ap, 0%

3fg, 0%

[a] All reactions were carried out with **1** (0.21 mmol), **2** (0.21 mmol) in presence of TBAHS (0.042 mmol) and KOH (0.42 mmol) in water (100 °C, 24 h).

alytic synthetic approach described here provides a stepping stone towards a greener organic synthesis in pharmaceutical industries.

Experimental

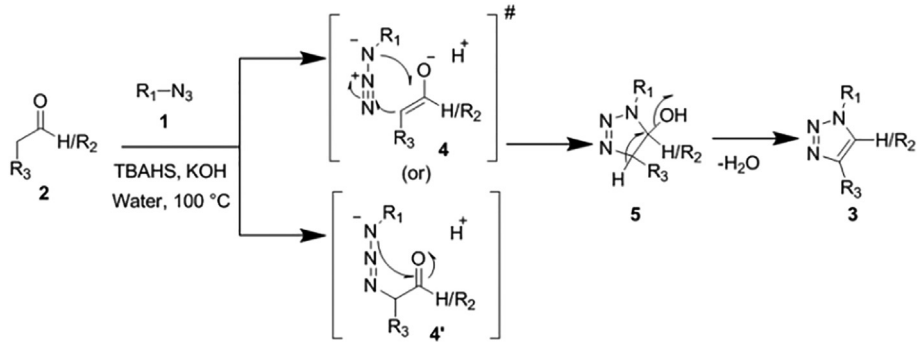
1,4-Diphenyl-1H-1,2,3-triazole (3aa): typical procedure

In an ordinary glass tube equipped with a magnetic stirring bar, to phenylacetaldehyde (25.2 mg, 0.21 mmol, 1 equiv.), TBAHS (14 mg, 0.042 mmol, 20 mol %) and potassium hydroxide (23 mg, 0.42 mmol, 2 equiv.) were added successively in Milli-Q water (1.0 mL) at room temperature. Finally, corresponding phenylazide (25 mg, 0.21 mmol, 1 equiv.) was added to above reaction mixture. This reaction mixture was stirred at room temperature for 2 min which was subsequently heated for 24 h at 100 °C. The reaction progress was monitored by TLC and after consumption of starting aldehyde, reaction mixture was cooled to room temperature. The crude reaction mixture was extracted with ethyl acetate (3 × 7 mL). These combined mixtures of organic layers were dried over sodium sulfate, filtered and concentrated. Pure product **3aa** was obtained by column chromatography (silica gel, mixture of ethyl acetate/petroleum ether) and was isolated as a white solid. 35 mg, 77% yield. 1,4,5-Triphenyl-1H-1,2,3-triazole (3ag): Typical procedure

In an ordinary glass tube equipped with a magnetic stirring bar, to 2-Phenylacetophenone (41.2 mg, 0.21 mmol, 1 equiv.), TBAHS (14 mg, 0.042 mmol, 20 mol %) and potassium hydroxide (23 mg, 0.42 mmol, 2 equiv.) were added successively in Milli-Q water (1.0 mL) at room temperature. Finally, corresponding phenylazide (25 mg, 0.21 mmol, 1 equiv.) was added to above reaction mixture. This reaction mixture was stirred at room temperature for 2 min which was subsequently heated for 24 h at 100 °C. The reaction progress was monitored by TLC and after consumption of starting ketone, reaction mixture was cooled to room temperature. The crude reaction mixture was extracted with ethyl acetate (3 × 7 mL). These combined mixtures of organic layers were dried over sodium sulfate, filtered and concentrated. Pure product **3ag** was obtained by column chromatography (silica gel, mixture of ethyl acetate/petroleum ether) and was isolated as a white solid. 59 mg, 95% yield. This particular reaction was also reproducible in tap water.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Scheme 2. Plausible reaction mechanism.

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Appendix A. Supplementary data

Supplementary data (characterization details of 1,2,3-triazoles by 1H and 13C NMR) to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151662.

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