“Synthesis of small molecule PIP3 antagonists as potential anticancer agents and Metal-catalyzed C-H oxidation of cyclotriveratrylene derivatives”

A THESIS
SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

TO

SAVITRIBAI PHULE PUNE UNIVERSITY

BY

B. Senthilkumar

Dr. C. V. Ramana

(Research Guide)

ORGANIC CHEMISTRY DIVISION

CSIR-NATIONAL CHEMICAL LABORATORY

PUNE–411008

February–2015

DECLARATION

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

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CERTIFICATE

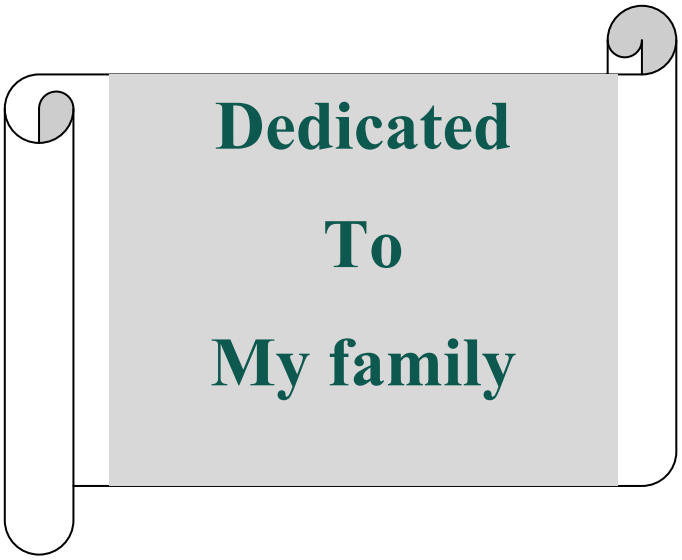
The research work presented in thesis entitled "**Synthesis of small molecule PIP3 antagonists as potential anticancer agents and Metal-catalyzed C-H oxidation of cyclotriveratrylene derivatives.**" has been carried out under my supervision and is a bonafide work of **Mr. B. Senthilkumar** This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune – 411008.

February– 2015

Dr. C. V. Ramana

(Research Guide)


Dedicated
To
My family

Acknowledgements

It gives me great pleasure in expressing my gratitude to all those people who have supported and encouraged me throughout my journey. First and foremost, I must acknowledge and thank god for blessing and guiding me throughout my journey.

I express my profound sense of reverence to my adviser, **Dr. C. V. Ramana** for his valuable guidance, scholarly inputs and constant encouragement; without his guidance and encouragement, none of this would have been possible. It is really great opportunity to do my doctoral programme under his guidance and I shall always remain beholden to him.

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Atul, Ravindra, Dinesh, Narendra, Srinu, Sridhar, Ajay, Tejas, Venkat, Anand, Anuradha, Janhavi and Sravani. I also thankful to Mr. Vasudevan for his valuable help during my research work.

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I must express my very profound gratitude to my beloved parents Mr. Beeran, Ms. Indhrani, providing me with unfailing support and continuous encouragement throughout my life. This accomplishment would not have been possible without them. In continuation, I also thankful to my younger brothers Mr. B. Sivakumar and B. Rajkumar for their supports.

Last, but certainly not least, I must acknowledge with tremendous and deep thanks to my wife Ms. Uma Baburao and my son Aathithiya balaji. They form backbone and origin of my happiness. Their love and support without any complaint or regret has enabled me to complete my research work peacefully. She took every responsibility and suffered all the bitterness to take care of my son. I owe my every achievement to both of them.

Finally, I thank Dr. S. Sivaram (Former director) and Dr. Saurav Pal, Director, CSIR-NCL, Pune for providing the infrastructural facilities to complete my work successfully.

B. Senthilkumar

DEFINATIONS AND ABREVIATIONS

Ac	–	Acetyl
Ac_2O	–	Acetic anhydride
AcOH	–	Acetic acid
ATP	–	Adenosine tri phosphate
Bu	–	Butyl
BuOH	–	Butyl alcohol
Cat.	–	Catalytic/catalyst
CH_3CN	–	Acetonitrile
CHV	–	Cyclo hexa veratrylene
Conc.	–	Concentrated
DCM	–	Dichloromethane
DM	–	Di methyl
DMF	–	*N,N*-Dimethylformamide
DMSO	–	Dimethyl sulfoxide
Et	–	Ethyl
EtOAc	–	Ethyl acetate
Et_3N	–	Tri ethyl amine
HRMS	–	High Resolution Mass Spectroscopy
Liq.	–	Liquid
Me	–	Methyl
NMR	–	Nuclear Magnetic Resonance
Pd	–	Palladium
PEG	–	Poly ethylene glycol
Pet.	–	Petrolium

Py	–	Pyridine
p-TSA	–	*para*-Toluenesulfonic acid
Ph	–	Phenyl
rt	–	Room temperature
SAR	–	Structure activity relationship
THF	–	Tetrahydrofuran
TPP	–	Triphenylphosphine

Abbreviations used for NMR spectral informations:

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

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz) and DRX–125 MHz spectrometer.
- Mass spectroscopy was carried out on Thermo Finngan (single Quadrupole) LC/MS ESI and High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and also EI Mass spectra were recorded on MSI-Autoconcept spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- Some reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All sample melting points were recorded on Buchi B-540 melting point apparatus.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

Abstract

Research Student	: B. Senthilkumar
Research Guide	: Dr. C. V. Ramana
Title of Thesis	: **Synthesis of small molecule PIP3 antagonists as potential anticancer agents and metal-catalyzed C-H oxidation of cyclotriveratrylene derivatives**
Registration Number	: PGS/Ph.D/2786. Dated 11.08.2012 (Title change: PGS/2366. Dated 02.07.2014)
Date of registration	: 18.10.2011
Place of Work	: Division of Organic Chemistry *CSIR* – National Chemical Laboratory, Pune (INDIA)

The thesis entitled **"Synthesis of small molecule PIP3 antagonists as potential anticancer agents and metal-catalyzed C-H oxidation of cyclotriveratrylene derivatives"** is divided into two chapters. The first chapter reveals the synthesis of acylthiourea, 1,2,4-triazole and imidazo-1,2,4-triazole derivatives and their evaluation as potential anticancer agents. In chapter 2, the inner-rim C–H oxidation of CTV has been explored employing palladium-catalyzed benzylic oxidation and an interesting array of CTV derivatives have been obtained by simple changes in the solvent/conditions employed.

Chapter-1: Synthesis of small molecule PIP3 antagonist PITENIN–1 analogues and their evaluation as potential anticancer agents.

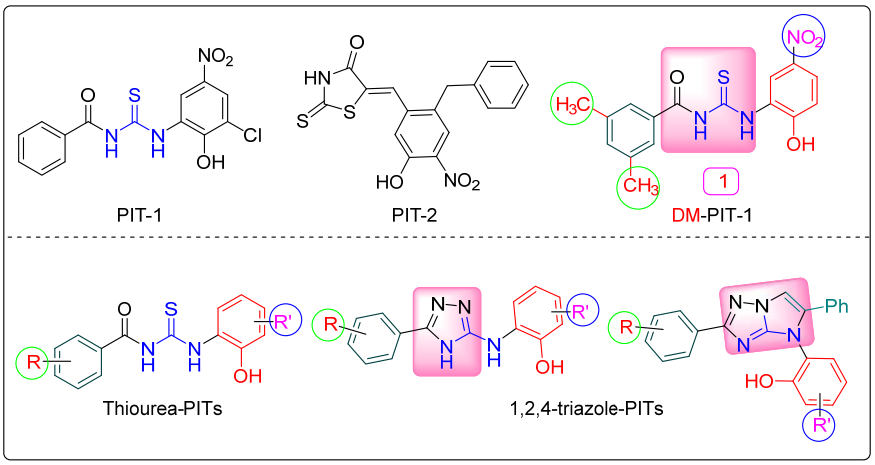
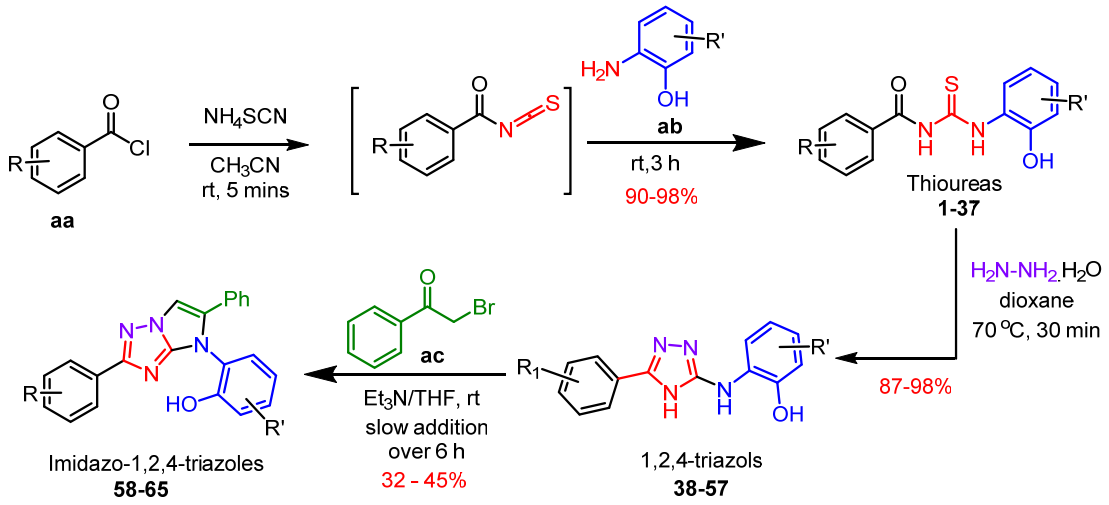


Figure 1: Structures of PITENINS and newly designed small molecule antagonists of PIP3 around them

Abstract

PITENINS (Fig. 1) are a class of small molecules which inhibit phospoinositide 3-kinase (PI3K or PI3-kinase). PI3K plays a critical role in many cellular pathways and is known to play an important role in tumorigenesis. Considering some of the drawbacks with these PITENINS (activity and low stability for DMPIT-1 the $T_{1/2}$<2 min in mouse liver microsomal stability assay *in vitro*, the present investigations have been undertaken as a means of improving the activity and the pharmaceutical features of this new class. As a first step, we explored the possibility of replacing the susceptible methyl group from benzoyl unit with (CF_3 and OMe) and also identified the alternative to the NO_2 group (Figure 1). Given the objective of understanding the SAR around the acylthioureas, especially in the direction of having a good number of samples, we developed a simple one-pot protocol for their synthesis that expedited the synthesis of a focused library of thioureas (**1-37**). The optimized reaction conditions involve the treatment of three different aroyl chlorides - i. 3,5-dimethyl-; 3,5-bis(trifluoromethyl)- and 3,5-dimethoxybenzoyl chloride (**aa)** with ammonium thiocyanate and corresponding different substituted *o*-aminophenols (**ab)**. All these synthesized molecules have been screened for their anticancer activity against the human ovarian carcinoma A2780 cell line.

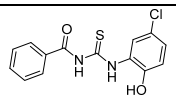
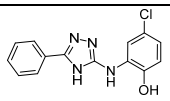
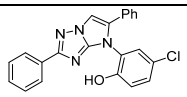
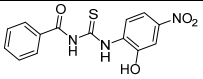
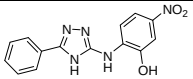
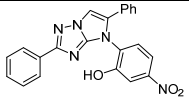
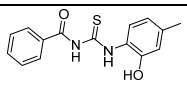
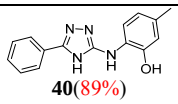
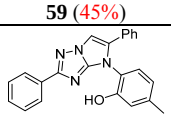
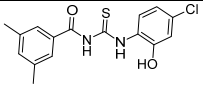
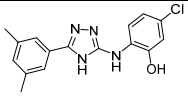
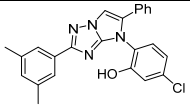
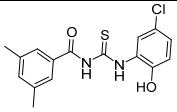
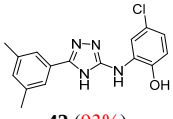
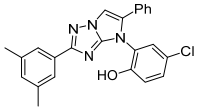
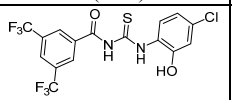
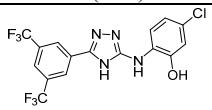
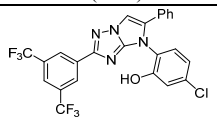
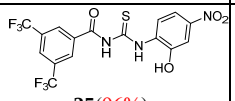
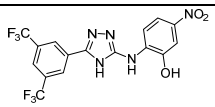
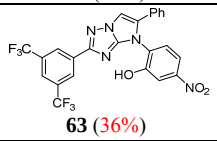
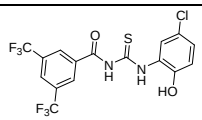
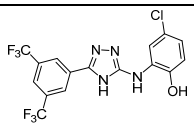
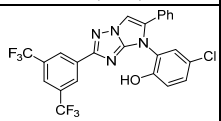


Scheme 1: *Synthesis of acylthioureas, 1,2,4-triazoles and Imidazo-1,2,4-triazoles*

In these thiourea-PITs series, first, we found that substitution of methyl groups with trifluoromethyls resulted in increased activity, e.g. **5** vs **24** vs **2** and **25** vs **3**. Second, the nitrogroup, which represents a potential metabolic liability and a general toxicophore, can be

replaced with chlorine, e.g. **24** vs **25**. Third, the *meta*- or *para*-position of chlorine is preferred (**24** and **27**). Furthermore, some increase in cytotoxicity in combination with TRAIL was retained with analogues, albeit the differences were less than for DM-PIT-1. This may indicate additional modes of toxicity of the drug alone, which will need to be explored in the future. Our data further showed that combination of CF_3 groups in the R^1position and the Cl in the R^4 position in **24** leads to maximal antitumor effect.

Table 1. Anticancer activity data of synthesized compounds

Entry	Thioureas 1 EC_{50}(μM)			1,2,4-Triazoles 2 EC_{50}(μM)			Imidazo-1,2,4-Triazoles 3 EC_{50}(μM)		
	Compounds (Yield)	Alone	With TRAIL	Compounds (Yield)	Alone	With TRAIL	Compounds (Yield)	Alone	With TRAIL
1	 **2** (90%)	35.6	20.6	 **38** (92%)	35.1	12.8	 **58** (36%)	46.8	33.5
2	 **3** (96%)	28.8	11.3	 **39** (96%)	58.3	26.6	 **59** (45%)	>100	>100
3	 **4** (93%)	>100	>100	 **40**(89%)	>100	>100	 **60** (39%)	>50	>50
4	 **5** (93%)	22.7	11.8	 **41** (96%)	54.4	34.7	 **64** (35%)	>50	>50
5	 **6** (92%)	32.1	21.5	 **42** (93%)	27.2	16.9	 **65**(32%)	>100	34.7
6	 **24** (95%)	6.8	4.0	 **47** (89%)	>100	>100	 **61** (38%)	71.1	5.8
7	 **25**(96%)	14.8	8.4	 **49** (91%)	60.5	39.1	 **63** (36%)	>50	>50
8	 **27** (94%)	12.9	10.9	 **48** (87%)	13.8	5.9	 **62** (40%)	13.2	3.9

Having the preliminary SAR information of a large set of acylthiourea derivatives, we next proceeded for the synthesis of the corresponding 3-amino-1,2,4-triazoles (**Triazole-PITs**) by replacing the susceptible acylthiourea unit with a 1,2,4-triazole structural motif as its stable bioisostere. The 3,5-disubstituted-1,2,4-triazole derivatives have been synthesized from 1,2,4,-triazole derivatives by using the hydrazine hydrate in 1,4-dioxane at 70°C for 0.5 h to afford 1,2,4-triazoles **38**–**57** (Scheme 1). The substitution of thiourea with triazole provides an improvement in pharmacological properties as it eliminates a metabolically labile thio group and a Michael's acceptor in thiourea. While 1,2,4-triazoles generally displayed reduced anti-tumor activity compared to corresponding thioureas, the nitro (NO_2), and the Cl in R^3 position in **48** provided a reasonable level of activity, comparable to that displayed by the corresponding thiourea analog series **27**.

As a part of replacing the acylthiourea unit completely, we proceeded further to synthesize the imidazo-[1,2,4]triazole derivatives. The imidazo-[1,2,4]triazole derivatives **58–65** (Triazole-PITs) have been prepared from the corresponding amino-1,2,4-triazole by the treatment with 2-bromoacetophenone. The compound **62** with Cl again in R^3 position has shown reasonable activity alone and the TRIAL. Other compounds **61** and **64** showed less activity when employed alone, but the activity showed excellent improvements with TRIAL. In this entry, only the combination of the CF_3 groups in the R^1position shows good activity. As indicated in the Table 1, generally compounds belonging to the dimethoxy series are less active when compared to the unsubstituted or substituted either with methyl or trifluormethyl and the Cl in R^3 position is important for retaining activity of the series.

Chapter-II: Metal-catalyzed C-H oxidation of cyclotriveratrylene derivatives.

Cyclotriveratrylene (CTV) is a supramolecular scaffold with applications in host-guest chemistry, drug delivery and liquid crystals. In this part of the thesis, is described our efforts towards the inner rim functionalization of cyclotriveratrylene (CTV) by palladium catalyzed benzylic C-H oxidation and the synthesis of variously oxidized CTV derivatives.The investigations in this direction were commenced by selecting the three known CTV analogues **66**, **68** and **69** (Figure 2) as the substrates, which were prepared by following the established procedures.

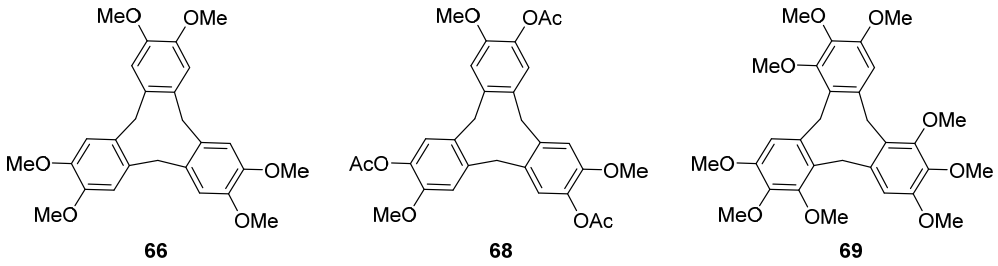
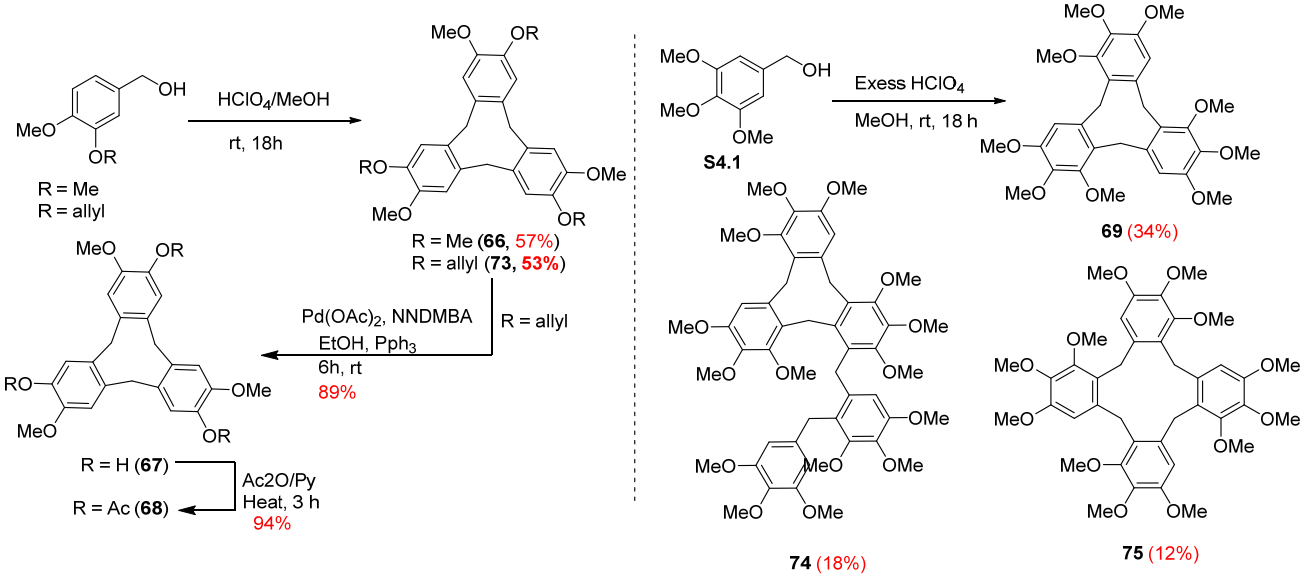


Figure 2: *Selected CTV analogues for the C-H activation studies*

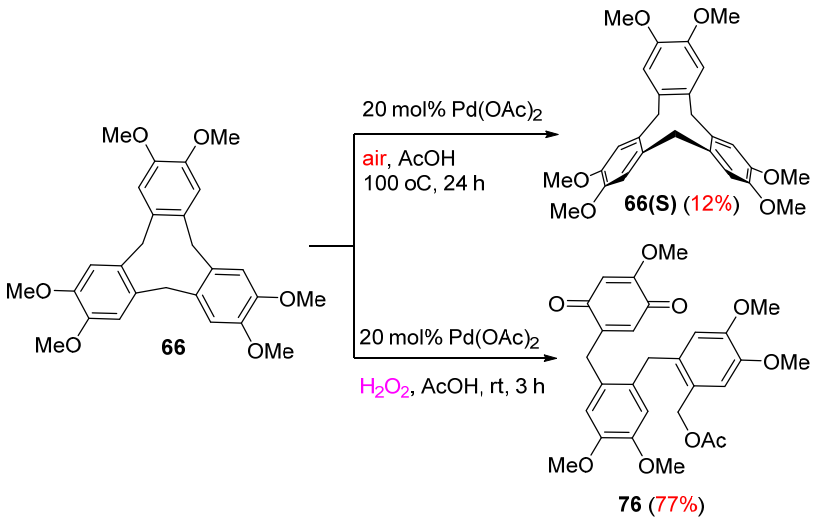
The trimerization of veratryl alcoholby using 65% perchloric acid at rt gave the cyclotriveratrylene **66** in 57% yield (Scheme 2). Cyclotriveratrylene **68** has been synthesized from allyl-protected vanilyl alcohol using the same procedure and the resultingtris-(*O*-allyl)-cyclotriveratrylene **73** has been subjected for de-allylation with $Pd(OAc)_2$, NNDMBA and triphenylphosphine to afford the tri-hydroxy cyclotriveratrylene CTV **67** in 89% yield Finally, the acetylation of **67** with acetic anhydride in pyridine afforded the C_3-tris-(O-acetyl)-cyclotriveratrylene **68** (C_3-functionalized CTV) in good yield.



Scheme 2: *Synthesis of cyclotriveratrylene(CTV) derivatives **66, 68** and **69.***

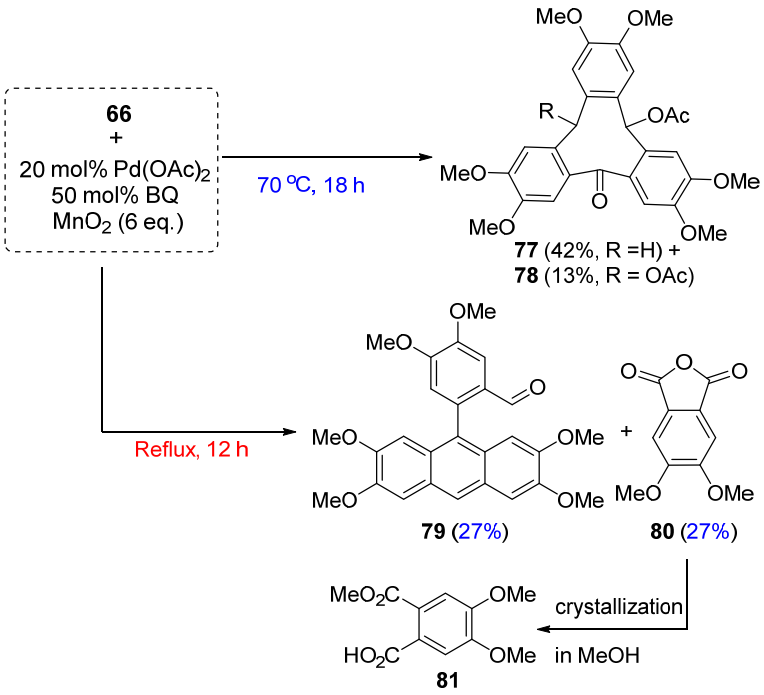
Next, the cyclotriveratrylene **69** was prepared by the trimerization of 3,4,5-trimethoxybenzyl alcohol (**S4.1**) by using excess of 65% perchloric acid which gave trimer **69** along with its benzylated product **74** and the tetramer **75**.

Next, we proceeded for the oxidation of these CTV derivatives employing Pd-catalyzed benzylic C–H oxidations. Our first experiments in this direction started with the aerial oxidation of CTV **66** which was carried out by employing 20 mol% of palladium acetate as catalyst in acetic acid. The reaction was sluggish and a part of the CTV was converted to the corresponding saddle conformer **66(S)** in 12% yield (Scheme 3). As the aerial benzylic oxidation of CTV **66** was found to be unsuccessful, we next examined the possibility of hydrogen peroxide as a co-oxidant, which gave exclusively one product **76** the structure of which has been established as quinone resulting from theoxidation of the phenyl ring followed by the cleavage of the methylene unit connected to it. Various other catalysts such as $Cu(OAc)_2$, $Ni(OAc)_2$, $CuCl_2$and $FeCl_2$ have been examined for the control of the oxidation albeit without any success.



Scheme 3: *Pd-Catalyzed C-H oxidation of CTV* ***66*** *employing* O_2 *or* H_2O_2

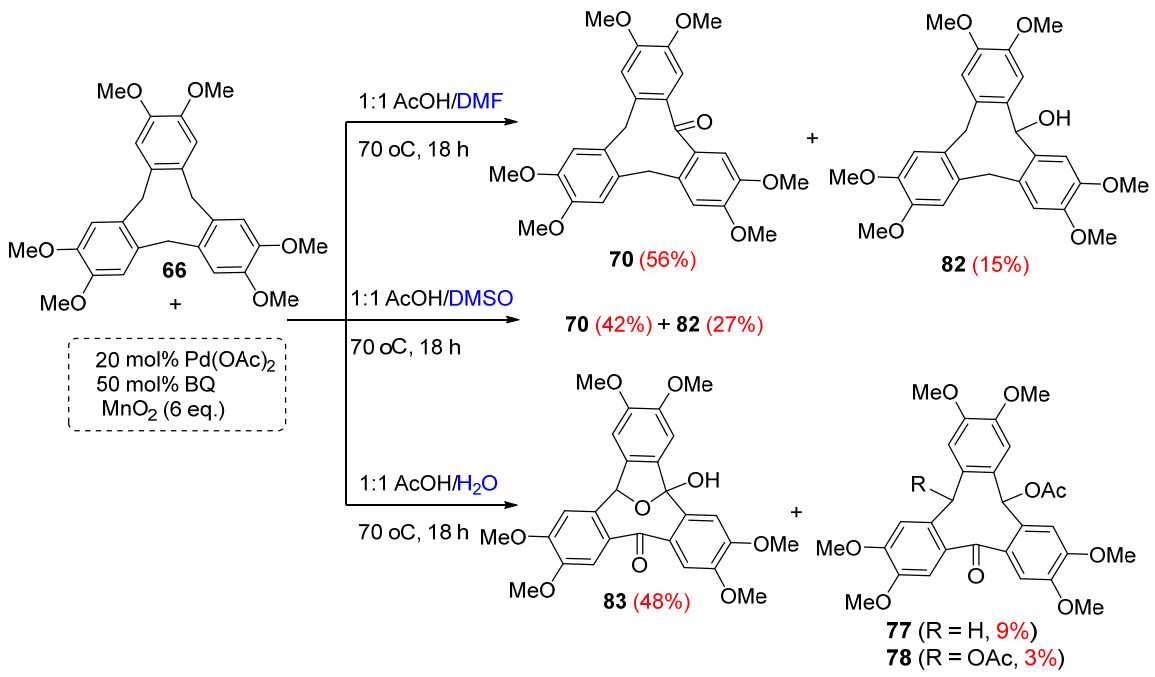
Next, the Pd-catalyzed benzylic C–H oxidation of CTV **66** was examined by employing benzoquinone as an additive and MnO_2 as a co-oxidant in acetic acid (Scheme 4). Under these conditions the CTV **66** was seen to completely disappeared and two new products, 10-acetoxy cyclotriveratrylene-5-one (**77**) and 10,15-diacetoxy cyclotriveratrylene-5-one **(78**) have been isolated. The spectral data indicated a crown conformation for **77** and a saddle conformation for compound **78** (Figure 5).



Scheme 4: *Pd-Catalyzed C-H oxidation of CTV **66** using MnO_2*

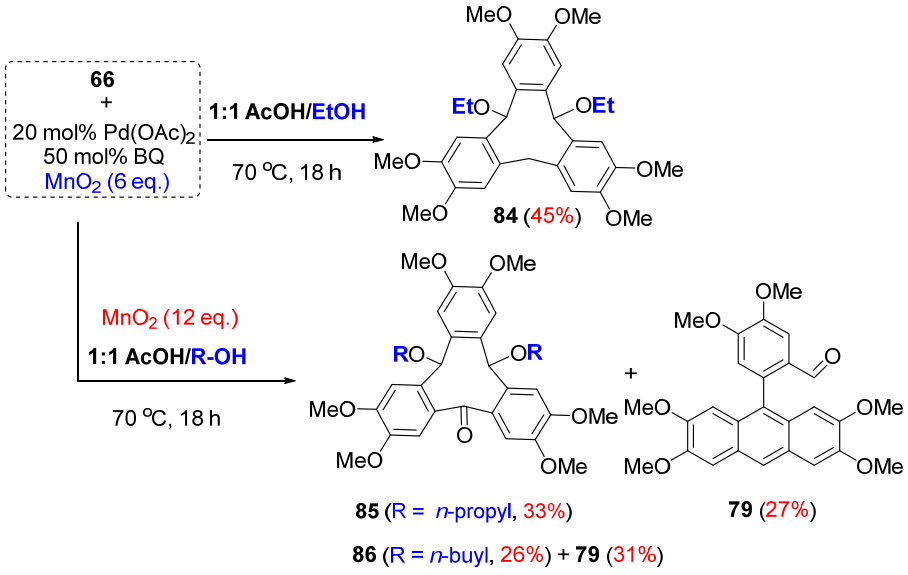
When the same reaction was examined at reflux temperature, 2'-(9-anthracenyl)benzaldehyde **(79**) and 3,4-dimethoxyphthalic anhydride (**80)** were isolated. The single crystal X-ray analysis of crystals resulting from the recrystallization of **80** in methanol revealed that **80** was converted to its half methyl ester **81** (Figure 7) during the crystallization.

Next, we examined the benzylic C-H oxidation of **66** with the BQ-MnO_2 system in combination with other solvents along with AcOH. As shown in Scheme 5, when employed a 1:1 AcOH-DMF was employed it as solvent, gave mainly two products, which have been characterized as cyclotriveratrylene-5-one (**70**) and cyclotriveratrylene-5-ol (**82**). Changing the solvent from DMF to DMSO also resulted in the isolation of these two products, although the proportion of the alcohol **82** was seen to increase. The NMR analysis of both **70** and **82** revealed crown conformations for both these products.



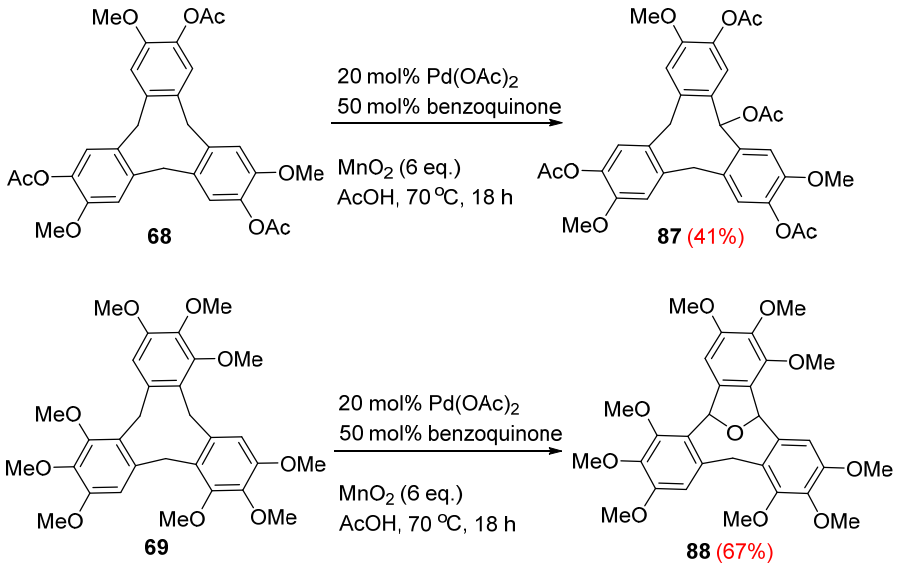
Scheme 5: *Solvent dependent Pd-Catalyzed C-H oxidation of CTV* ***66***

When the oxidation of **66** was conducted under similar conditions except that a 1:1 AcOH and water was used as a solvent system, the reaction mixture gave completely different products – a new cyclized compound **83** was obtained along with the two other previously characterized compounds **77** and **78** as the minor products.



Scheme 6: *Pd-Catalyzed C-H oxidation of CTV* ***66*** *in protic solvents*

Next examined was the C–H oxidation of **66** in AcOH-ethanol (1:1) which resulted mainly in the isolation of the 5,10-diethoxycyclotriveratrylene (**84**) in 45% yield. The ^{1}H NMR data of compound **84** revealed that it exists as a stable crown conformer. Then, the solvent was changed from ethanol to *n*-propanol, and were used **12** equivalents of MnO_2 Interestingly, 10,15-dipropoxy-cyclotriveratrylene-5-one **85** was obtained along with the anthracenylbenzaldehyde **79**. Similarly, when *n*-butanol was employed as a co-solvent gave 10,15-dibutoxy-cyclotriveratrylene-5-one **86** in 26% yield and anthracenylbenzaldehyde **79** in 31% yield.



Scheme 7: *C-H oxidation of CTV analogue **68** and **69***

Next, the Pd-catalyzed oxidation of other CTV analogues **68** and **69** has been examined in acetic acid alone. The reaction was incomplete and gave mainly 5-acetyloxy-CTV **87** in 41% yield (Scheme 7). A stable crown conformerfor the compound **87** has been indicated by NMR analysis. On the other hand, the C–H oxidation of **69** gave the furan derivative **88** as the main product in 67% yield and the structure has been confirmed by single crystal X-ray structure analyses

As described earlier, we isolated a novel anthracene aldehyde **79** as one of the product when the oxidation of CTV **66** was conducted with Pd/BQ/MnO_2 in acetic acid at reflux. The isolation of this product indicates an acid catalyzed trans-annular rearrangement of the partially oxidized CTV derivative. To probe in this direction, the previously synthesized mono- and di-

acetoxy CTV-monoketone derivatives **77** and **78** respectively have been treated with *p*-TSA in methanol at rt. Under these conditions, the monoacetate **77** gave the anthracene aldehyde **79** whereas the diacetate **78** gave **89** resulting from the reduction of the carbonyl and cyclization. Further, when **77** was treated with NaH in THF the known anthone spiral lactone **72** was isolated in 81% yield. Thus these acid/based promoted reactions of **77** and 78 reveal that these CTV derivatives can undergo oxidation/reduction quite easily.

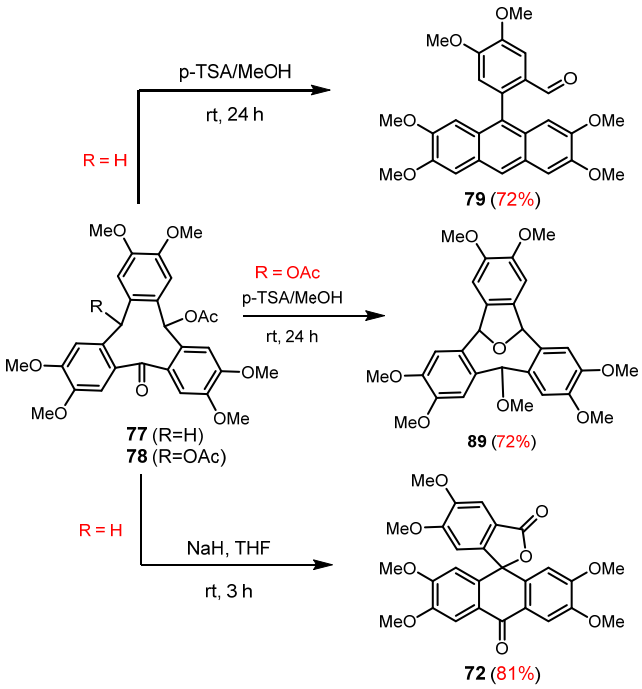


Figure 6: *Acid-/base-mediated rearrangement of **77** and **78***

To conclude, the Pd-catalyzed C-H oxidation of the CTV has been examined with different co-oxidants under different conditions. An interesting array of CTV derivatives have been synthesized with a simple change in the conditions. Some of the oxidations are selective resulting in CTV derivatives with interesting structural features. The acid/base catalyzed trans-annular rearrangement of the partially oxidized CTV derivatives reveal that these compounds readily undergo oxidation or reduction depending upon the conditions employed.

1.1.1 Over View of Cancer

Cancer is a deadly disease, which is known for uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue through invasion or by implantation into distant sites by metastasis.[1] According to the GLOBOCAN 2012 worldwide survey report, in 2012 there were 32.6 million people (over the age of 15 years) alive who were diagnosed with a cancer (2007-2012). In 2012, about 14.1 million new cancer cases have been reported and around 8.2 million cancer-related deaths.[2] This was quite alarming when compared with the 2008 statistics (12.7 million cancer cases and 7.6 million cancer-related deaths). It was estimated that the number will increase to 19.3 million new cancer cases per year by 2025, because of the increase of the aged population. Very importantly, 56.8% of all cancers and 64.9% cancer deaths in 2012 occurred in the poor and developing countries. According to a WHO report, nearly seven lakh Indians die of cancer every year, while over 10 lakh are newly diagnosed with some form of the disease. Thus, there is an urgent need for cancer control today through the development of effective and affordable drugs for less developed countries.

1.1.2. Treatment

There are 200 different types of cancer diseases known till date, affecting various parts of the body which are all unique in their causes and symptoms.[3] Cancer treatment is usually a combination of a number of different modalities. Most common types of cancer treatment are:

- Surgery
- Chemotherapy
- Radiation therapy
- Targeted therapy
    - Antibody therapy
    - Small molecule inhibitors
- Immunotherapy
- Hyperthermia
- Stem cell transplant and laser treatment

The severe side-effects caused by some of the early cancer treatment methods such as chemo-, surgery, and radiation sometimes give a feeling that cancer treatment is worse than cancer. Once the treatment begins, people often begin to feel quite sick. Targeted therapy is another option, which has a significant impact in the treatment of some types of cancer, and is currently a very active research area.[4] For targeted therapy, which became available from the late

1990s, most conventional anticancer drugs have been designed with deoxyribonucleic acid (DNA) synthesis as their target. Most targeted therapies are either small-molecule drugs or monoclonal antibodies.[5]Most monoclonal antibodies cannot penetrate the cell's plasma membrane and are directed against targets that are outside cells or on the cell surface. The past two decades has witnessed antibody-based therapy for cancer.[6]

Small molecule inhibitors are one of the active research areas in targeted therapy in the present scenario. Small-molecule drugs are typically able to diffuse into cells and can act on targets that are found inside the cell.[7] The newly introduced drugs have shifted the targets from the direct synthesis of DNA to basic function, which is responsible for tumor formation.[8] One such target, the protein kinase family, has become increasingly important over the past 20 years, with approximately 30 distinct kinase enzymes being targeted by drugs under development for clinical trials. Kinases, which are part of the larger family of phosphotransferases are critical in cellular functions such as metabolism, cell signaling, protein regulation, cellular transport, secretory processes, and myriad other cellular pathways. Kinase is a type of enzyme that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific substrates. The deregulation of kinase activity affects the signals that promote or regulate the cell cycle, growth factors and their receptors, signal transduction pathways and thus has emerged as a major mechanism by which cancer cells evade normal physiological constraints on growth and survival, leading to tumorigenesis. Thus, the kinase signaling pathway is an important potential target for inhibition.

Two examples of small molecule anticancer kinase inhibitors in the clinic are Gleevec (Imatinib), which is approved for the treatment of chronic myeloid leukaemia[9] and gastrointestinal stromal tumours, and Iressa (gefitinib) which is approved for the treatment of non-small-cell lung cancer.[10] These drugs were designed to inhibit receptor tyrosine kinases that are associated with development and progression of the tumor. Targeted molecular therapies, such as the receptor tyrosine kinase inhibitors, have shown greater tolerance than traditional non-specific chemotherapeutic drugs towards normal tissues, presenting, a larger therapeutic window.

This approach seems applicable to certain classes of intracellular signalling proteins and pathways that possess heavily mutated hotspots. Three major signalling pathways that have been identified as playing important roles in cancer include the mitogen-activated protein kinase (MAPk)/Ras, the protein kinase C (PKC) and the PI3K/AKT signaling cascade. The PI3K/AKT

signaling pathway plays a vital role in the cellular functions and the deregulation or disruption of this pathway causes tumorigenesis.[11]

1.1.3 Phosphatidylinositol 3-kinases (PI3Ks)

Cancer is characterized by uncontrolled cell growth and the division of abnormal cells. Cancer can be caused by a variety of factors and each tumor is unique, even those of the same tissue type. Despite tumor heterogeneity, there are several hallmarks of cancer that have been shown to be important drivers of malignancy (Figure F1).[12] Each of these hallmarks results from a perturbation of normal cellular pathways. The phosphoinositide 3-kinase (PI3K) signaling pathway has been shown to be involved with several of these traits.[13] Repairing normal function of this pathway has been shown to result in cellular apoptosis and tumor inhibition.[14]

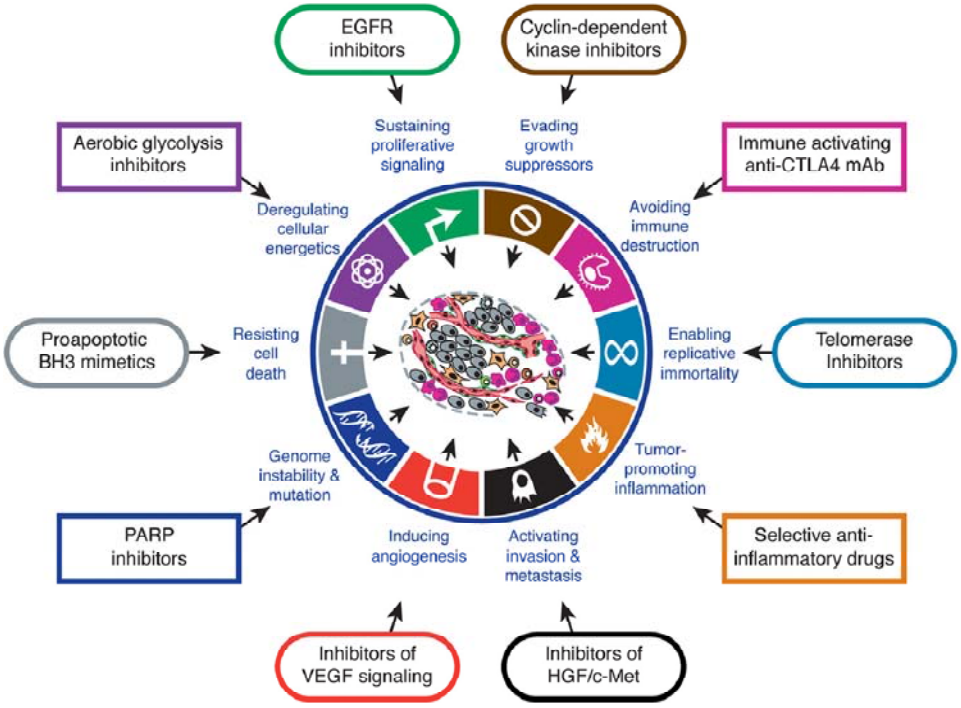


Figure 1: *The 10 hallmarks of cancer and the treatments associated with each*[12]

Phosphatidylinositol 3-kinases (PI3Ks) belong to an enzyme family of vitally important regulators for intracellular signaling pathways. PI3Ks catalyze the phosphorylation of phosphatidylinositol at the 3′-position of the inositol ring producing secondary messenger lipids which control cellular activities including cell survival, growth and proliferation. A large

proportion of cell-surface receptors, are linked to tyrosine kinases activate PI3Ks.[15] Dysregulation of the PI3K pathway has been implicated in many human diseases. Hyper activation of this pathway is known to play an important role in tumorigenesis, whereas the deficiencies in the PI3K pathway contribute to the development of type II diabetes. Therefore, this pathway offers promising targets for the development of drugs to combat this disease.[13,16]

The PI3K family is divided into three different classes: Class I, Class II, and Class III, based on their primary structure, mode of regulation, substrate specificity, tissue distribution and function within the cell.[17,18] The class I PI3Ks are responsible for the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). Class I PI3Ks (α, β, and γ) are recruited to the plasma membrane in response to growth factor and hormone stimulation to mediate the phosphorylation of lipid phosphatidylinositol-4,5-bisphosphate (PIP2), generating PIP3, which orchestrates multiple downstream intracellular signaling events. PIP3 signaling is terminated by the phosphatase PTEN, which dephosphorylates PIP3. Genetic alterations targeting PTEN are among the most frequent mutations in human cancers, indicating a critical role of uncontrolled signaling through PIP3 in tumorigenesis and metastasis.[19] This conclusion is reinforced by transgenic studies establishing that loss of PTEN leads to tumorigenesis.

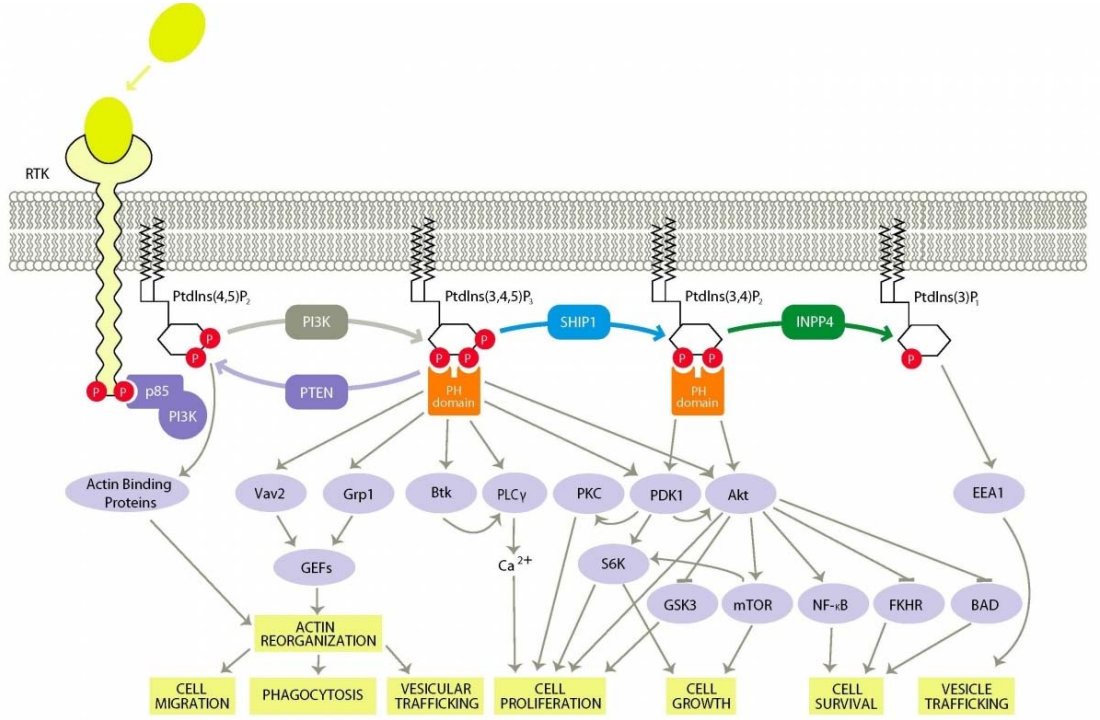


Figure 2: *The PI3K signalling pathway*[20]

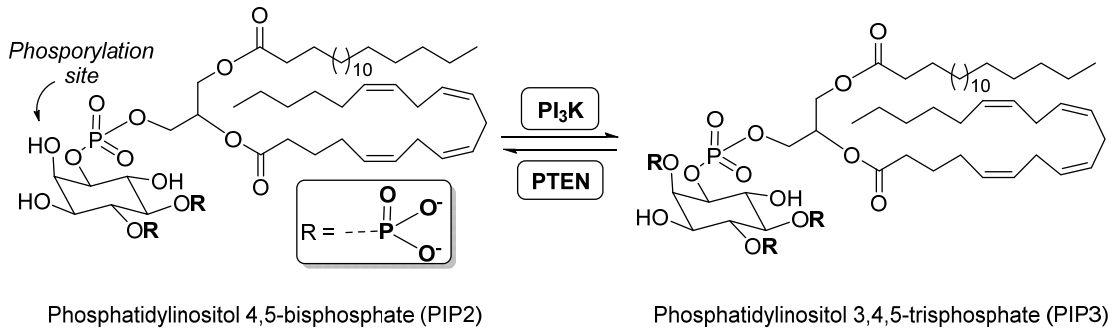


Figure 3: *Phosphate transfer reaction canalized by Class I PI3K isoforms*

PIP3 controls a complex cellular signaling network regulating cell growth, proliferation, and survival. The PIP3 target proteins are located in the cytosol of unstimulated cells and are recruited to the membrane through pleckstrin-homology (PH) domain-mediated binding to newly formed PIP3. Membrane translocation and activation of the PIP3 target proteins initiate a variety of local responses, including assembly of signaling complexes and priming of protein kinase cascades.[13, 16] PIP3 regulates an array of PH domain-containing proteins,[21] such as serine-threonine kinases Akt and PDK1, GRP1, a GDP/GTP exchange factor of ADP ribosylating factor, and protein tyrosine kinases of the Bruton's tyrosine kinase (Btk) and Tec families.[22, 23] This diversity in PIP3 signaling makes it one of the most important second messengers downstream from growth factor and oncogene signals. A particularly important example of PIP3-dependent activation is that of serine-threonine kinase Akt. It is achieved both through the binding of the Akt PH domain to PIP3 and membrane translocation of another target of PIP3, PDK1, which phosphorylates and activates Akt. The Akt family plays a fundamental role in cell survival, growth, and energy metabolism.[24]

Although lipid–protein interactions mediate PI3K signaling and are frequently deregulated in cancer, most therapeutic strategies targeting the PI3K pathway have focused on inhibitors for downstream targets, including PDK1[25] and Akt.[26] Phospholipid–protein interactions have not been as actively targeted, even though lipid molecules are among the most important classes of second messengers. This is surprising considering that they represent "prototypic" small molecule–protein interactions usually involving well-defined binding sites.[27] Conceptually, protein–lipid interactions may be more readily targetable compared with protein–protein interactions, which frequently involve interactions of extended flat protein surfaces that are difficult to disrupt by small molecules.

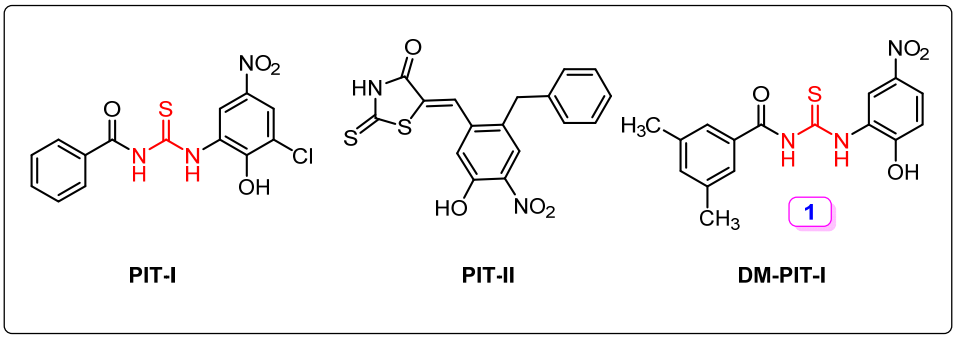


Figure 4: *Small molecule antagonists of PIP3*

There are many approaches focused on targeting enzymatic activities in the PI3K network. We have recently described a new approach aimed at targeting a universal central step in PI3K signal transduction, i.e. binding of PIP3 to PH domains of effector proteins.[28] In particular, we have developed two selective new classes of small molecule nonphosphoinositide PIP3 inhibitors, termed PITenins (PITs), PIT-1 (N-((3-chloro-2-hydroxy-5-nitrophenyl)carbamothioyl)benzamide,) and PIT-2 ((Z)-5-(2-benzyl-5-hydroxy-4-nitrobenzylidene)-2-thioxothiazolidin-4-one,).[14,29] Surprisingly, these two structurally dissimilar molecules displayed very similar antitumor activities, including induction of apoptosis and metabolic stress and inhibition of cell migration and invasion. Particularly, both PIT-1 and PIT-2 displayed synergistic toxicity with TRAIL in human glioblastoma U87MG cells. These activities have been linked to the inhibition of Akt signaling and actin remodeling by ARF6, two pathways regulated by PI3K. These *in vitro* activities of PITs translated into the significant inhibition of tumor growth and lung metastasis formation in 4T1 and B16-F10 syngeneic xenograft models by the dimethyl analog of PIT-1.

Despite the promising initial results, PITs have displayed some obvious limitations, including high micromolar activity. This means that the particular compound required more quantity and as well as multiple non-drug-like features. In particular, nitrophenyl and thiourea moieties of PIT-1 described potential toxicity concerns and metabolic liabilities. The initial analysis of the PIT-1 series revealed surprisingly specific SAR for a micromolar compound suggesting several changes to the molecule, leading to some increase in activity and changes in targeting different PH domains. In particular, the addition of two methyl groups to the phenyl ring in PIT-1 (DM-PIT-1, Figure F1.4) resulted in some increase in activity and improved incorporation into long-circulating PEG-PE micelles for *in vivo* delivery.[14,30] DM-PIT-1

displayed $T_{1/2}$<2 min in mouse liver microsomal stability assay *in vitro*. Due to these limitations, the present inventions were undertaken to explore and seek to improve activity and pharmaceutical features of this new class of anti-cancer lead molecule. Our first concern was to replace the nitro (NO_2) group with different functional groups and subsequently remove the susceptible acylthiourea unit with a stable bioisostere. In this context, we have devided the whole exercise into two parts. First, SAR studies have been considered around the DM-PIT to identify promising acylthiourea derivatives and identify the suitable replacement for the nitro group. The next consideration was the chemical modification of identified acylthioureas into corresponding amino-1,2,4-triazoles and finally the corresponding imidazotriazoles. Given this overall objective, in the following section is described the details of some of the earlier reports on biological studies dealing with the small molecules that carry any of these three types of structural units.

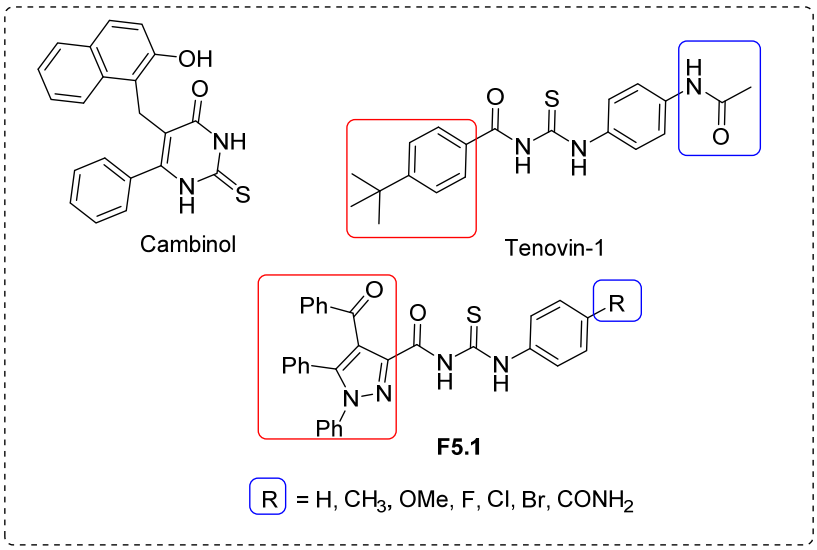


Figure 5: *Some representative bioactive acyl thioureas*

The acyl thiourea compounds Cambinol and Tenovin-1 (Figure5) are small molecule inhibitors of the NAD^+ dependent family of protein de-acetylases known as the sirtuins. There is considerable interest in the inhibitors of this enzyme family due to possible applications in both cancer and neurodegenerative disease therapy.[31,33] Koca and co-workers have employed to improve the anticancer activity by replacing the aryl units with a pyrazolyl unit. A series of novel pyrazolylacylthioureas (Figure6) were synthesized by the addition of various aromatic amines to

4-benzoyl-1,5-diphenyl-1H-pyrazole-3-carbonyl isothiocyanate. The anticancer potential of compounds of the derived pyrazolylacyl thioureas were evaluated on human leukemia, colon, and liver cancer cell lines.[34]

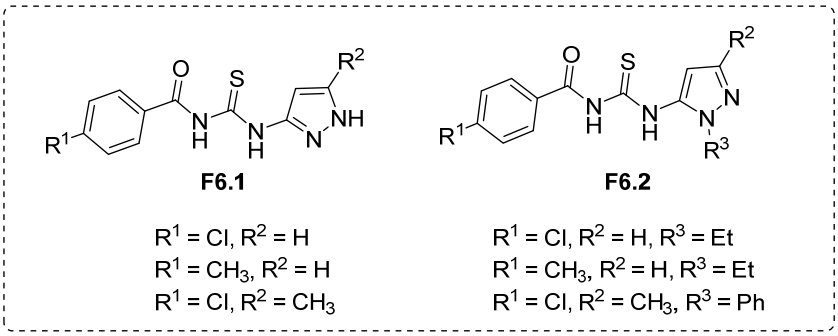


Figure 6: *Structure of pyrzolylacyl thioureas evaluated as protein kinases inhibitors*

One similar lines, Nitulescu and co-workers have designed the pyrazolethiourea derivatives and synthesized as potential protein kinase inhibitors with the view to developing specific antitumor therapies. All these pyrazole thiourea compounds resulted in with a lower cytotoxicity against the *brine shrimp lethality* bioassay. The 3-aminopyrazole derivatives **F6.1** of R^1group seems to have little influence on the toxic effect, whereas for the 5-aminopyrazole **F6.2** series, the 4-chlorobenzoyl derivatives (LC_{50}=3.05–4.68µmol/L) were found to benearly 2–3 times more toxic than the corresponding 4-methylbenzoyl derivatives (LC_{50}=4.61–11.09µmol/L). Next, the 4-methylbenzoyl derivative (IC_{50}= 9.82 µmol/L) has a better cytotoxic effect than the corresponding 4-chlorobenzoyl derivative (IC_{50}= 9.82 µmol/L), compared to the *Artemia* assay.[35]

Subsequently, Zvarych and co-workers have synthesized the 1,2,4-triazole derivatives of 9,10-anthraquinone **F7.2** by the replacement of acylthiourea from N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracene-1-yl)-thiourea derivatives **F7.1** (Figure 7).[36] The 1,2,4-triazole compounds have been predicted to have typical pharmacological activity, which include: mucomembranous protection, antineoplastic (anticancer) activity, angiogenesis inhibition, 3-hydroxybenzoate 6-monooxygenase inhibition, protine kinase inhibition, pterin deaminase inhibition andantiarthritic behavior. The screened experimental data using the computer online PASS program provided the basis for predicting a potent anticancer activity of 1,2,4-triazole derivatives of 9,10-anthraquinone.

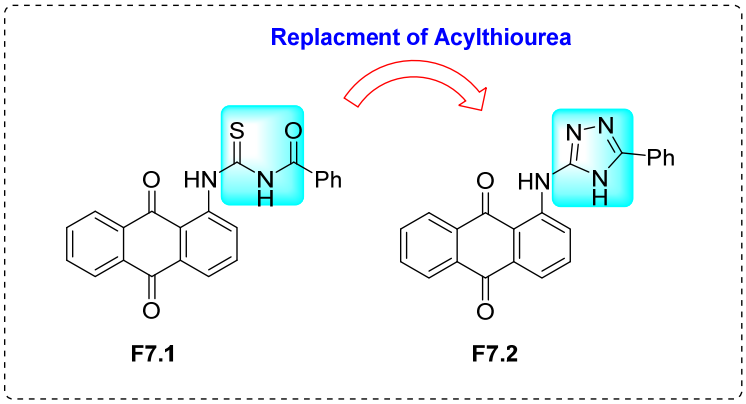


Figure 7: *Anthraquinone containing thiourea derivatives predicted with multiple biological activities*

1.1.4 Anticancer activity of 1,2,4-triazole derivatives

The 1,2,4-triazole nucleus is one of the important structural units that has been frequently used in anticancer drug development studies. For example, the Schiff base of an amino-1,2,4-triazole bearing 2,4-dichlorophenoxy group **F8.1a** was found to be active against thirty-one cancer cell lines with potent in *vitro* activity at concentrations less than 20 µM.[37] The compound **F8.1b** was found to be active against six cancer cell lines at the concentrations less than 20µM.

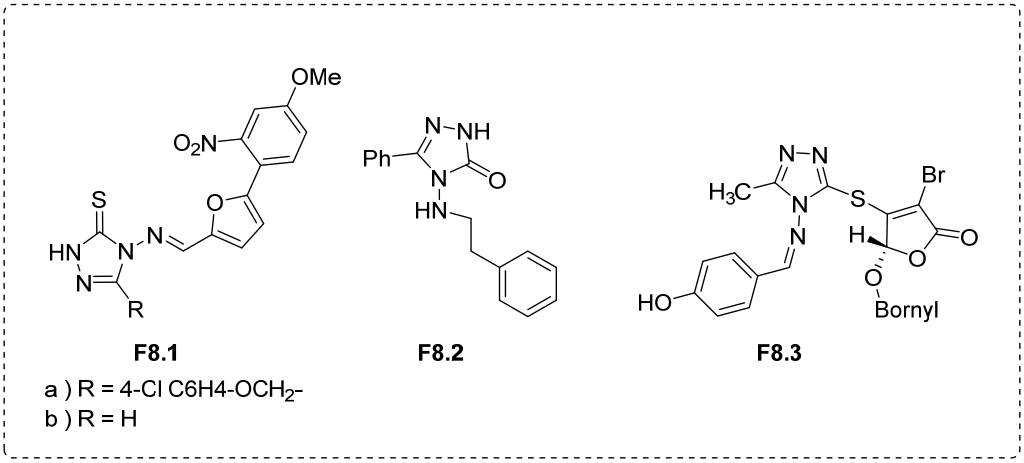


Figure 8: *Structure of 4-amino-1,2,4-triazole derivatives*

The compounds containing phenylethylamino groups at position 4 of the 1,2,4-triazole moieties **F8.2** have been reported to possess excellent *in vitro* antitumor activity against three tumor cell lines. It has been reported that the antitumor property appears to be as a result of the

conversion of the dihydro analogue of 4-amino-1*H*-1,2,4-triazole into dihydro 4-alkylidenamino or dihydro 4-alkylamino-1H-1,2,4-triazole.[38] Li and co-workers reported potent anticancer activities exhibited by new chiral 1,2,4-triazole derivatives towards Hela's cervical cancer cell lines using the MTT assay.[39] The compound **F8.3** (Figure 8) showed the best inhibitory activity with an IC_{50}=1.8 µM.

Flefel and co-workers reported the synthesis of some 1,2,4-triazolopyrazole (**F9.1**, **F9.2**) derivatives and evaluated their anticancer activities against breast carcinoma (MCF7) and cervix carcinoma (HELA) human cell lines compared with Doxorubicin positive control. The compounds showed good activity against both types of carcinoma cell lines than that obtained by doxorubicin (Figure9).[40]

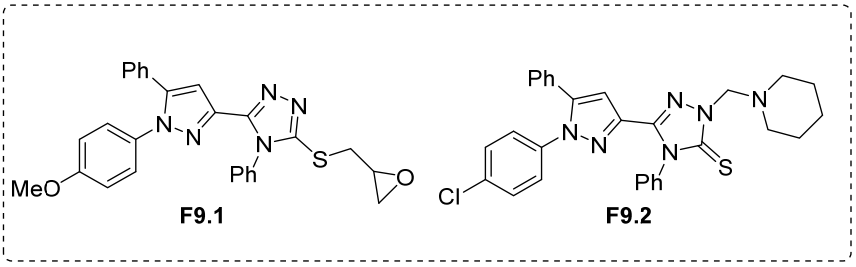


Figure 9: *Structure of 1,2,4-triazolopyrazole derivatives*

Hou and co-workers documented the synthesis and screening of a series of 1,2,4-triazole derivatives containing 1,4-benzodioxolan for their anti-proliferative activity against HEPG2, HELA, SW1116 and BGC823 cell lines.[41] Compound **F10.1** (Figure 10) showed the best potent inhibitory activity against HEPG2 cells with IC_{50}=0.81µM and inhibited the activity of MeAP2 with IC_{50}=0.93µM. The SAR studies indicated that compounds with electron withdrawing groups on the aryl ring showed superior activity than those compounds having electron donating groups. Kalluraya and co-workers have reported the synthesis of 1,2,4-triazolothiazole **F10.2** derivatives by conventional and microwave irradiation methods (Figure10). The compounds were screened for their anticancer activity against cancer cell lines HT29 (human adenocarcinoma), K292 (human kidney cancer) and MDA231 (human breast cancer) by using the MTT assay. The 1,2,4-triazolothiazole compounds exhibited significant activity comparable to 5-Flurouracil.[42]

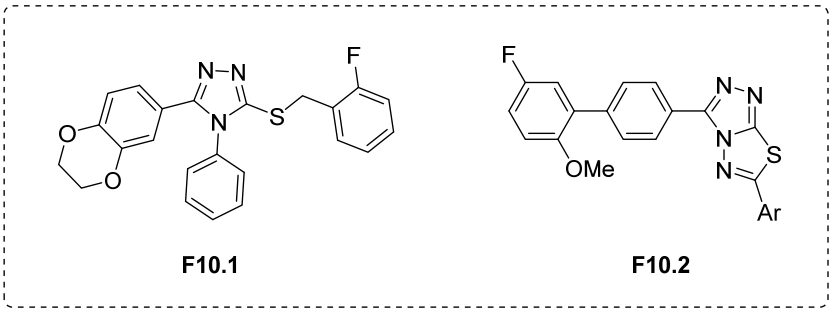
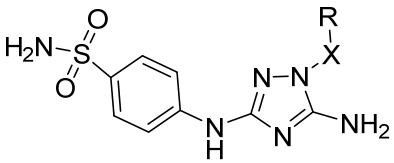


Figure 10: *Structure of 3,4,5-trisubsitituted triazole and 1,2,4-triazolothiazole*

Lin and co-workers documented the synthesis of a series of novel1-acyl-1*H*-[1,2,4]triazole-3,5-diamine **F11.1** analogues (Figure11) and revealed them as potent, selective, and presumably ATP-competitive cyclin dependent kinase (CDK) inhibitors. Some of these compounds inhibited the *in vitro* growth of various human cancer cells including melanoma, colon, prostate, ovarian, and breast cancer cells.[43]



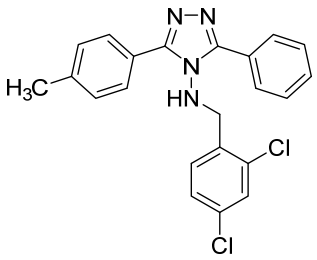
F11.1

X = C=O, C=S, CH_2, SO_2

R = C_6H_5, (2,6-F_2)C_6H_3, (2,6-F_2-3-Me)C_6H_2, (2,3,6-F_3)C_6H_2, 2-thienyl, (3-Me)$_2$-thienyl, NH(2,6-F_2)C_6H_3, etc.

Figure 11: *Structure of 1-acyl 3,5-diaminotriazole evaluated as* CDK *inhibitors*

Bekircan and co-workerssynthesized the 3-phenyl-5-(*p*-tolyl)-4-(2,4-dichlorobenzylamino)-4H-1,2,4-triazole **F12.1** and evaluated the same for anticancer activity. Compound showed higher anticancer activity in the preliminary test with the 3 human cancer cell lines of breast cancer (MCF7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) and exhibited the remarkable anticancer potential against 60 human cancer cell lines.[44]

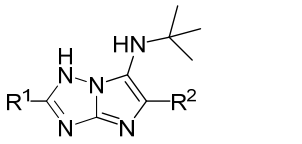


F12.1

Figure 12: *Structure of 3,4,5-trisubsitituted triazole evaluated for anticancer activity*

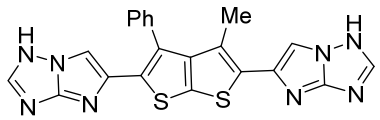
1.1.5 Imidazo-[1,2,4]-triazoles

The organic fused heterocyclic compound of Imidazo-[1,2,4] triazole derivatives have been widely reported in the mainstream as well as in the patent literature because of their potential biological properties. Huang and co-workers reported an efficient and multicomponent method for the synthesis of imidazo[1,2-b]-1,2,4-triazoles **F13.1** (Figure13) and revealed that they showed good cytotoxic activities at10^{-4}M concentration in the inhibition of tumor cell growth as evaluated by the MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) method.[45]

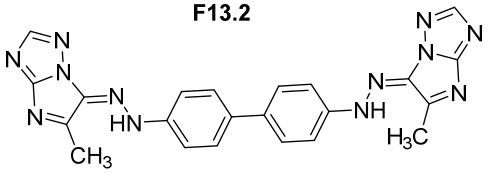


F13.1

a) R^1 = H, R^2 = 4-$Me_2NC_6H_4$
b) R^1 = 4-ClC_6H_4, R^2 = Ph
c) R^1 = 4-ClC_6H_4, R^2 = 4-ClC_6H_4
d) R^1 = 4-ClC_6H_4, R^2 = 3-ClC_6H_4



F13.2



F13.3

Figure 13: Structure of imidazo-1,2,4-triazole analogues

Mabkhot and co-workers have been designed and synthesized the bi-heterocyclic ring compound containing the sulphur atom of bis(1H-imidazo[1,2-b][1,2,4]triazole)-3-methyl-4-phenylthieno[2,3-b]thiophene **F13.2**.[46] Compound **F13.2** was evaluated for anti-cancer activity against PC-3 cell lines, *in vitro* antioxidant potential and β-glucuronidase and α-glucosidase

inhibitory activities. Farghaly and co-workers documented the synthesis of bis-azole compound **F13.3** with an IC_{50}= 23.4µg/ml against human liver cancer cell line (HEPG-2, using MTT assay).[47]

The above brief information about the various 1,2,4-triazoles and their fused analogues reveal that these scaffolds are have potential in developing new anti-cancer hits. Having identified PIT-1 and DMPIT-1 as starting hits in the area of PIP3 inhibitors and considering their drawbacks such as poor bioavailability and toxic functional groups such as nitro and labile units such as acylthioureas, we have been interested in exploring the possible replacement of the acyl thiourea unit in a step-wise manner with a 1,24-triazole and finally with a imidao-triazole unit. In the following section will be described the SAR around the initially identified PIT-1 derivatives, then their chemical transformation to amino-1,2,4-triazoles and finally the conversion of some representative amino-1,2,4-triazoles into imidazo-triazoles along with the anti-cancer screening of all the synthesized compounds.

Over activation of the phosphoinositide 3-kinase (PI3K) signalling pathway has been shown to be a common phenomenon in several cancers.[13] Repairing the normal function of this pathway has been shown to result in cellular apoptosis and tumor inhibition. We have recently documented an unique approach aimed at targeting the binding of PIP3 to PH domains of effector proteins - a universal central step in PI3K signal transduction.[14] A random screening of a chemical library has resulted in the identification of two structurally dissimilar small molecule antagonists of PIP3, termed PIT-1 and PIT-2 (Figure 1) displaying very similar activities in cancer cells, including induction of apoptosis and metabolic stress and inhibition of cell migration and invasion. Furthermore, both PIT-1 and PIT-2 displayed synergistic toxicity with TRAIL in human glioblastoma U87MG cells. These activities have been linked to the inhibition of Akt signaling and act in remodeling by ARF6, two pathways regulated by PI3K.[14,30] Further studies in this direction have led to identification of DM-PIT-1 with some increase in activity and improved incorporation into long-circulating PEG-PE micelles for *in vivo* delivery.[3,5]

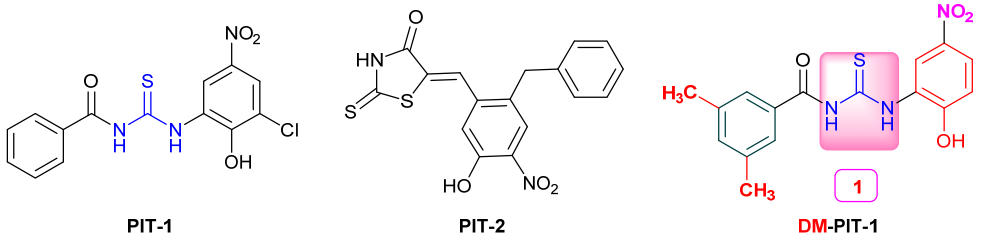


Figure 14: *Structures of the two classes (PIT-1 and PIT-2) of inhibitors of phopshotidylinositol-3 kinase (PI3K) signaling pathway, termed PITENINs (PITs)*

Despite the promising initial results, DM-PIT-1 displayed $T_{1/2}$<2 min in mouse liver microsomal stability assay *in vitro*. Due to these limitations, the present inventions were undertaken to explore and seek the improvement in activity and pharmaceutical features of this new class of anti-cancer lead molecule. Our first concern was to replace the nitro (NO_2) group with different functional groups and subsequently remove the susceptible acylthiourea unit with a stable bioisostere. In this context, we have devised the whole exercise in to two parts. First, QSAR studies were done around the DM-PIT to identify promising acylthiourea derivatives and identify the suitable replacement for the nitro group. Next, the chemical modification of identified acylthioureas into the corresponding amino-1,2,4-triazoles and finally to the corresponding

imidazotriazoles were done. Another aspect of this program was about replacing the thiourea with a 1,2,3-triazole as a bio isostere that has been dealt separately by another colleague of our group.

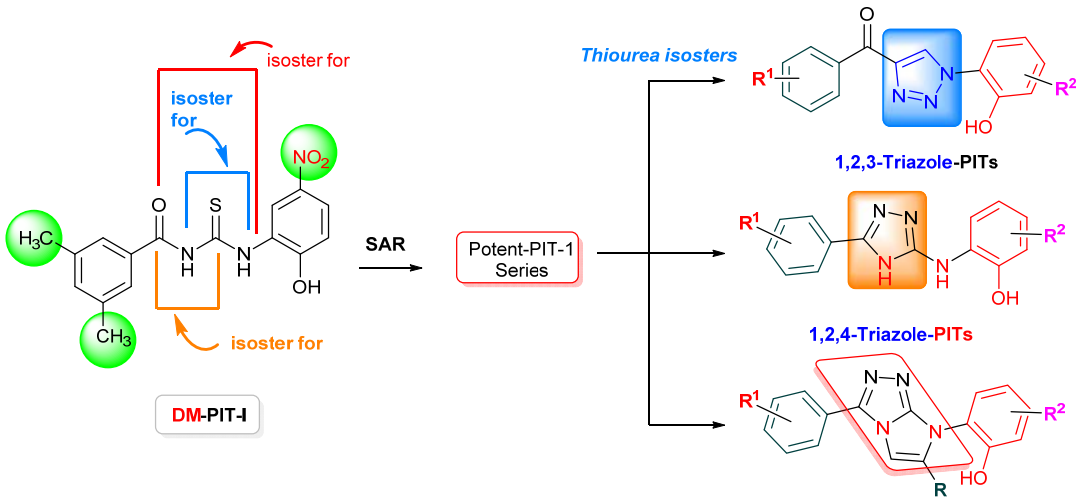


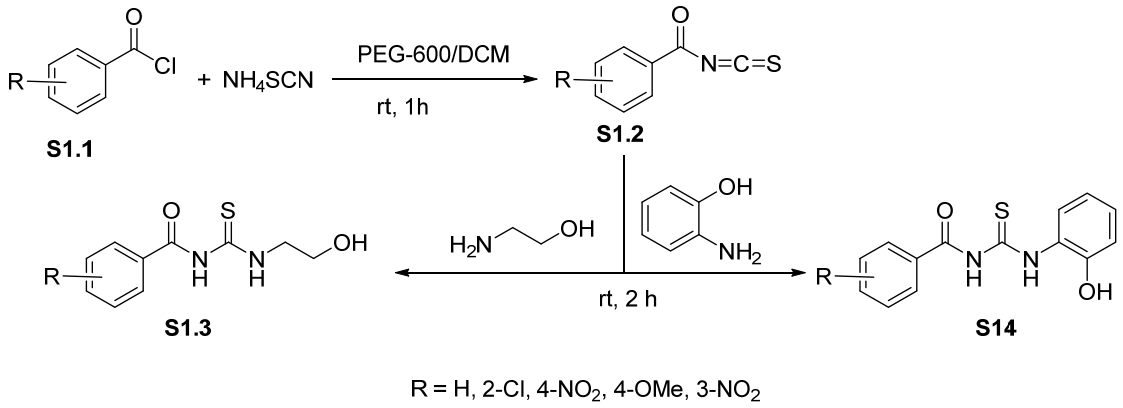
Figure 15: *Structure of DM-PIT-1 and project SAR around it and intended replacement of functional unitis of acyclthiourea unit with identified heterocyclic bioisoeres.*

1.2.1 Synthesis of Acylthioureas and SAR

The thiourea derivatives display a wide spectrum of biological activities such as antimicrobial, antifungal, antimalarial, antitubercular, anticancer, and anti-HIV.[48] In addition, the aroylthioureas have found applications in metal complexation and molecular electronics. In addition, the thiourea functional unit is an excellent handle for the introduction of a variety of heterocyclic scaffolds such as 1,3-thiazole,[49] 1,2,4-thiadiazolidine,[50] 1H-1,2,4-triazole,[51] tetrazole,[52] 1,2,4-oxathiazole[53] etc. There are several methods reported in literature for their synthesis of acylthioureas. In general, the synthesis was carried out in two steps – the preparation of acylthiocynate and its subsequent reaction with an amine. The second step seems to be a straightforward reaction, needing no special conditions, however, in many of the reports; the reactions are carried out at reflux temperatures. The following are some of the recent examples on the acylthioureas synthesis.

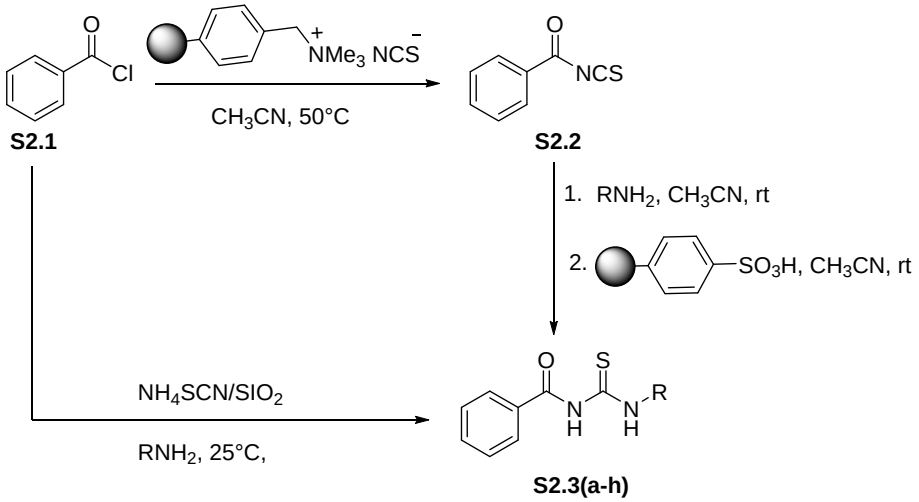
In 1998, Zhang's group reported a convenient high yielding method for the preparation of N-aroyl-N'-hydroxyethyl **S1.3** and N-aroyl-N'-hydroxyethyl hydroxyl phenyl thiourea **S1.4**

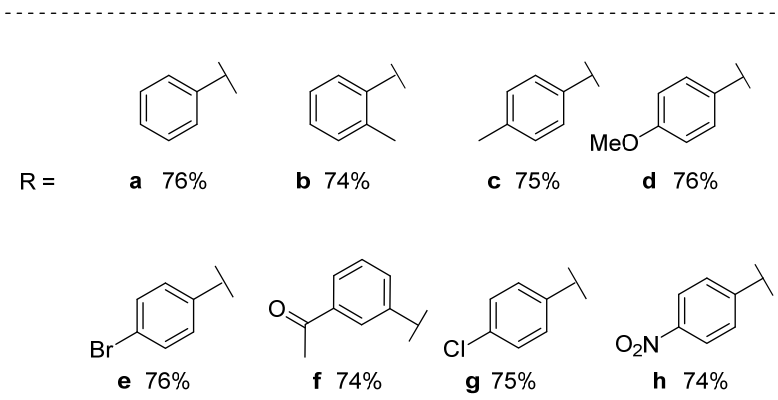
derivatives under solid-liquid phase transfer catalysis conditions employing 3% PEG-600 as the catalyst (Scheme S1).[54]



Scheme 1: *Synthesis of thioureas under phase transfer catalyst*

In 2003,Yang and co-workers[55] reported a clean synthesis of an array of N-benzoyl-N'-arylthioureas using polymer-supported reagents with benzoylchloride to obtain benzoyl isothiocyanate **S2.2**, which on further reaction with the corresponding amines using Amberlyst 732 afforded thiourea derivatives **S2.3** (Scheme 2). Next, in 2005, Kodomari's groups revealed a one-pot synthesis of N-substituted-N'-benzoyl thiourea under solvent-free conditions. The benzoyl isothiocyanate **S2.2** is formed by the reaction of benzoyl chloride **S2.1** with silica gel supported ammonium thiocyanate (NH_4SCN/SiO_2).[51] The benzoyl isothiocyanate reacted with an amine to afford the N-substituted-N'-benzoyl thiourea **S2.3a-h** (Scheme 2).





Scheme 2: *Synthesis of benzoyl thioureas under polymer and slilica gel supported reagents.*

In 2004, Zhang group reported an efficient method for the synthesis of the benzoyl thiourea compounds employing microwave irradiation.[56] The effect of microwave irradiation power, reaction times and phase transfer catalysis on the reaction has been studied in details. Another alternative methods have been used to prepare 1-benzoylthiourea synthesis **F16.1** (Fig. 16), comprising of the condensation of acetyl thiourea and substituted benzoyl chloride.[57]

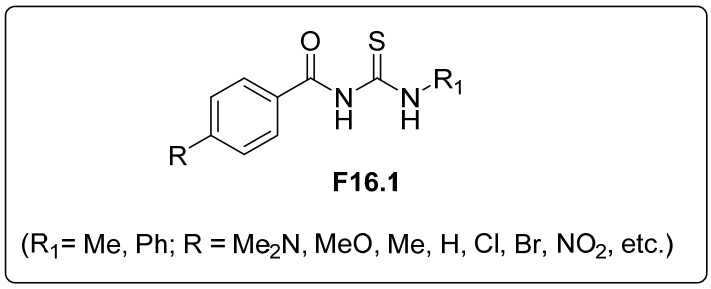


Figure 16: *Thiourea derivatives under microwave irradiation*

1.2.2 Present work

The initial objective of the present work was to optimize the anti cancer activity of the initially identified structural scaffold of the PIT1, and to explore the SAR analysis. Next, we intended to replace the susceptible methyl group from benzoyl unit with (CF_3 and OMe) and also identify the alternative to the nitro the NO_2 group (Figure 17). Given the objective of understanding the SAR around the acylthioureas, especially in the direction of having a good number of samples, we have intended to develop a simple one-pot protocol for their synthesis that can expedite the synthesis of a focused library of thioureas. The optimized reaction conditions

involve the treatment of aroylchloride with ammonium thiocyanate in acetonitrile and later of the addition of the aniline. Both the steps are operational at rt. We employed three different aroyl chlorides - i. 3,5-dimethyl-; 3,5-bis(trifluoromethyl)- and 3,5-dimethoxybenzoyl chloride **aa** and synthesized the corresponding series employing a good number of different substituted *o*-aminophenols **ab** (Scheme 3).

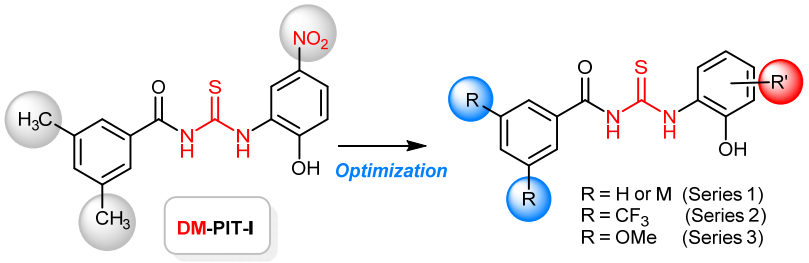
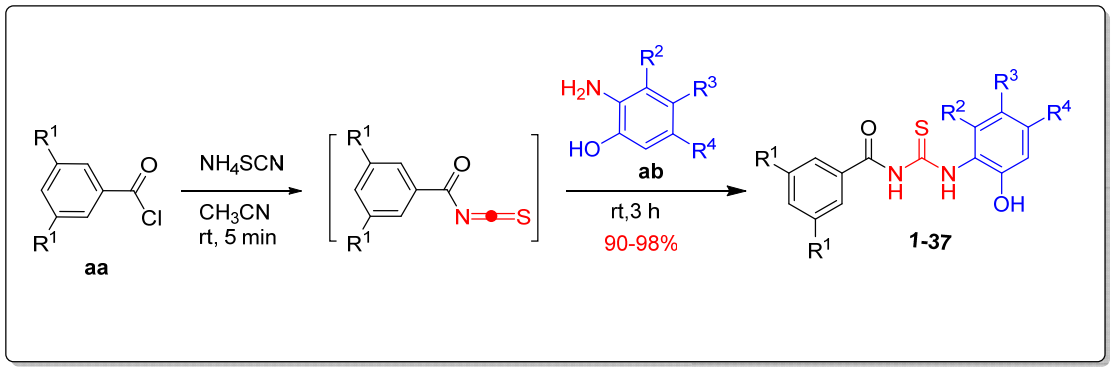


Figure 17: *Three series of thiourea-PITs planned for the SAR studies*



Scheme 3: *Synthesis of thiourea derivatives*

Synthesis and SAR Analysis of PIT- and DM-PIT Thioureas Series 1:

Given the objective of understanding the SAR around the acylthioureas especially in the direction of having a good number of samples, we have intended to develop a simple one-pot protocol for their synthesis that can expedite the synthesis of a focused library of thioureas. Having this as a first objective, the possibility combining both the steps has been explored in various solvents. To this end, acetonitrile was found to be the solvent of choice. The optimized reaction conditions involve the treatment of aroylchloride with ammonium thiocyanate in acetonitrile and later of the addition of the aniline both the steps being operational at rt. We employed two different aroyl chlorides - i. benzoyl and ii. 3,5-dimethyl-; and synthesized the

corresponding series employing a good number of substituted *o*-aminophenols (Table 1). The target compounds were obtained in 82-96% good yields. All the synthesized compounds **1**–**23** were characterized completely with the help of ^{1}H, ^{13}C NMR, IR and HRMS data. For example, in the ^{1}H NMR spectra of the compound **2**, the characteristic acyl thiourea N–H protons resonated at δ 9.68 and 12.85 ppm as broad singlets. In the ^{13}C NMR spectra, the carbons associated with the amide carbon (C=O) and thioamide (C=S) appeared respectively at δ 166.7 and 176.4 ppm. The presence of N-H and carbonyl groups were also evident from the IR spectrum, where the absorption was observed at 3362 cm^{-1}. In the HRMS, the exact mass of the compound for $C_{14}H_{11}N_3O_4SNa$ $[M+Na]^+$ was calculated to be 340.0362 and it was found to be 340.0357. All these synthesized PIT-1 and DM-PIT molecules have been screened for their anticancer activity against the human ovarian carcinoma A2780 cell line and the results are provided in Figure18.

The anticancer activity has been evaluated on human ovarian carcinoma A2780 cell line as described in Cell viability experiments were performed in A2780 cells as previously described.[58] Briefly, cells were treated with a range of compound concentrations (100 – 1.3μM) in white, clear bottom 96 well plates. Compounds were added alone or in combination with recombinant TRAIL (1 μg/ml), and expressed and purified from *E.coli*. Cell viability was determined 24 hr later using Cell TIter-Glo assay (Promega). TRAIL alone did not show significant toxicity towards A2780 cells under these conditions (not shown) as had been previously described by us for U87MG glioblastoma cells[17]. Curve fitting to the obtained EC_{50} was performed using the GraphPad Prism software.

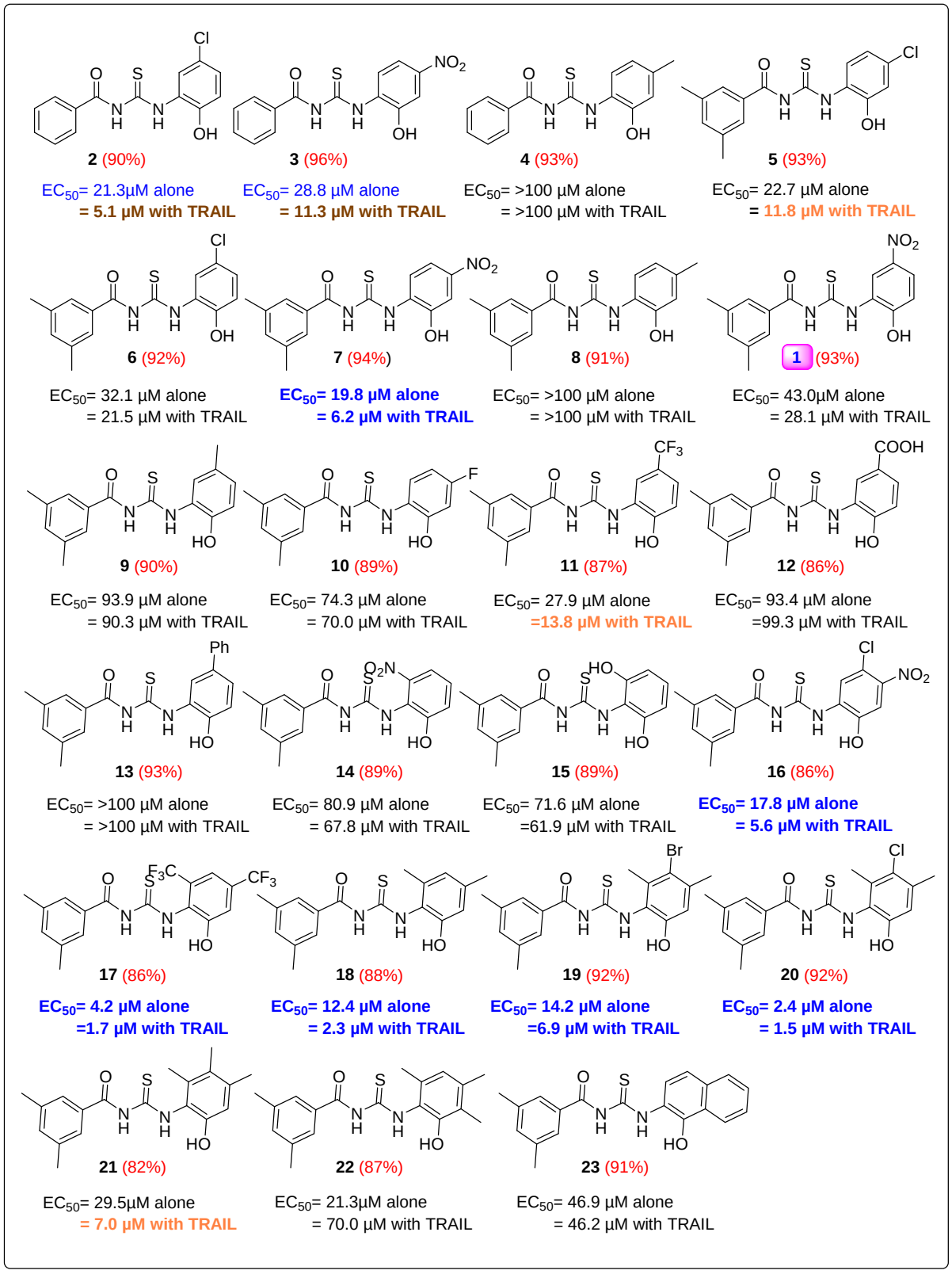


Figure 18: *Structure and anticancer activity data of thiourea-PITs series**1–23***

Notably, our initial SAR suggested that addition of methyl groups to the positions R_1 led to an increase in cytotoxicity of the resulting DM-PIT-1 molecule towards U87MG cells. In addition in our previous work, we showed that DM-PIT-1 synergizes with an anti-cancer cytokine TRAIL[7] to further promote cancer cell death. In the current work, we continued the DM-PIT-1 thiourea series with different functional groups of aminophenol. In these series, the initial screening of benzoyl thioureas **2** and **3** showed improved activity when used alone, and excellent improvement upon combination of TRAIL. However, compound **4** doesn't show any significant activity in A2780 cells. Next, coming to 3,5-dimethybenzoyl thioureas (DM-PIT-1) series (Figure18), the compounds **7**, **16**, **18**, **19** and **20** have shown excellent activity in A2780 human ovarian cancer cells when used alone and with TRAIL, which is more promising and excellent activity when compared with that of the DM-PIT-1. The compounds **5**, **6**, **1**, **11**, **21**, **22** and **23** showed some improved activity when used alone and with TRAIL. However, the compound **21** showed better improvement as EC_{50} 7.0 µM with the combination of TRAIL. Next, the compounds **8**, **9**, **12**, **13**, **14** and **15** showed limited and reduced anticancer activity in A2780 cells. In this series, the compounds **17** and **20** are the more promising molecules showing the best anticancer activity as EC_{50} 4.2 and 2.4 µM when used alone, EC_{50} 1.7 and 1.5 µM with the combination of TRAIL in A2780 human ovarian cancer cells.

Synthesis and SAR analysis of designed 3, 5-bis (trifluoromethyl) benzoyl thioureas

We have intended to incorporate the CF_3 group on the benzoyl unit, differing in the functional groups on the aminophenol. The 3, 5-bis (trifluoromethyl) benzoyl thioureas have been synthesized from 3, 5-bis (trifluoromethyl)benzoyl chloride with ammonium thiocyanatein acetonitrile and added corresponding aminophenols (scheme 1.1). The target compounds were obtained in 92-96% good yields (Fig. 19).

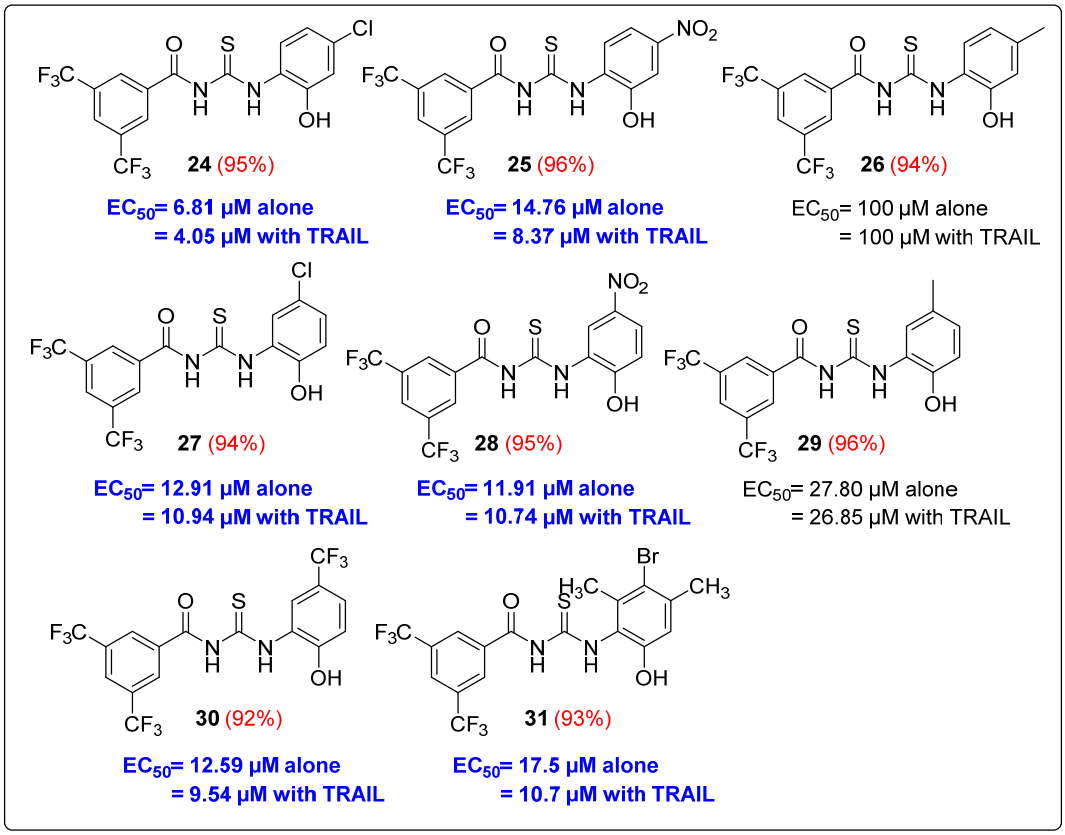


Figure 19: *Structure and anticancer activity data of thiourea-PITs series**24–31***

Next, the anticancer activity of the 3,5-bis(trifluoromethyl) benzoyl thioureas series has been examined against A2780 human ovarian cancer cells. The compounds **24**, **25**, **27**, **28**, **30** and **31** showed excellent activity when used alone and also better improvement with when combained with TRAIL (Fig. 19). The compound **29** showed reasonable activity, however the compound **26** showed no improvement in the activity. In these series, first, we found that substitution of methyl groups with trifluoromethyls resulted in increased activity. Second, nitrogroup, which represents a potential metabolic liability and a general toxicophore, can be replaced with chlorine, e.g. **24** vs **25**. Third, the *meta*- or *para*-position of chlorine is preferred (**24** and **27**). Furthermore, some increase in cytotoxicity in combination with TRAIL was retained with analogues, albeit the differences were less than for DM-PIT-1. This may indicate additional modes of toxicity of drug alone, which needs to be explored in the future. Our data further showed that the combination of CF_3 groups in the R_1 position and Cl in the R_4 position in **24** led to maximal antitumor effect.

Synthesis and SAR analysis of designed 3,5-dimethoxybenzoyl thioureas

Next, we moved to the replacement of the CH3 group on the benzoyl unit with -OMe group (3 and 5 position) and differing in the functional groups on the aminophenol. The 3,5-dimethoxybenzoyl thioureas have been synthesized from 3,5-dimethoxybenzoylchloride with ammonium thiocyanate in acetonitrile and added corresponding aminophenols (scheme 3). The target compounds (**32**–**37**) were obtained in 92–98% yields (Fig. 20). The screening of this series of compounds against A2780 human ovarian cancer cells revealed that only, the CF_3 (R^3) substituted compound **36** has showed good activity as EC_{50} 14.7 when used alone and EC_{50} 6.3µM with the combination of TRAIL. The compound **32**, **33**, **34** and **35** showed a reasonable improved activity. However, the compound **37** has showed no anticancer activity in A2780 human ovarian cancer cell lines.

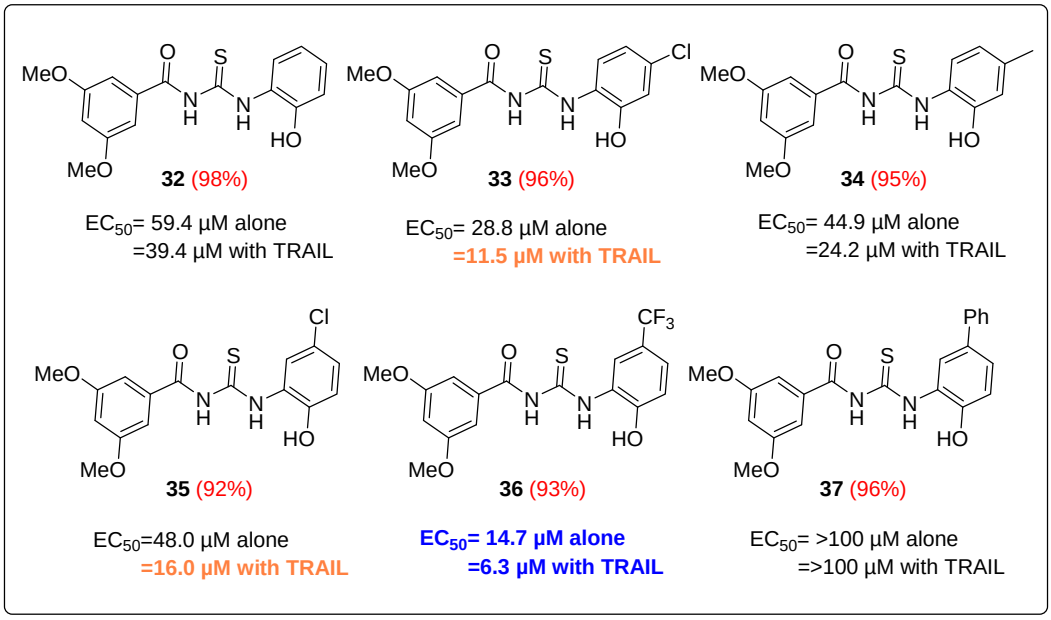


Figure 20: *Structure and anticancer activity data of thiourea-PITs series**32–37***

1.2.3 1,2,4-triazoles

Triazoles are heterocyclic compounds containing three nitrogen atoms in a five-membered cyclic structure. There are different structural and positional isomers of triazoles. Triazoles are the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazoles exist in different isomeric forms, having enormous synthetic and biological importance.

Among the isomers of triazoles, during the last decade, the 1,2,3- triazoles have seen lot of attention because of the introduction of Cu-catalyzed azide-alkyne cycloaddition.[59] One the other hand, the 1,2,4-triazole unit is one of the well sought out structural units by medicinal chemists and there are several commercial drugs containing the same. 1,2,4-Triazoles have two proton transfer tautomer forms as shown in Figure 21,1,2,4-triazoles, for the most part, subsist as 1*H*-1,2,4-triazole tautomeric form **a.** The other possible 4*H*-1,2,4-triazole form **b** does not exist both in solid state or in solution. The amino-substituted 1,2,4-triazoles were electronically preferred in the 1*H* form.[60] In general, the 1,2,4-triazoles are soluble both in acidic and basic media due to salt formation by protonation and deprotonation respectively. There are several approaches available for the synthesis of 1,2,4-triazoles.

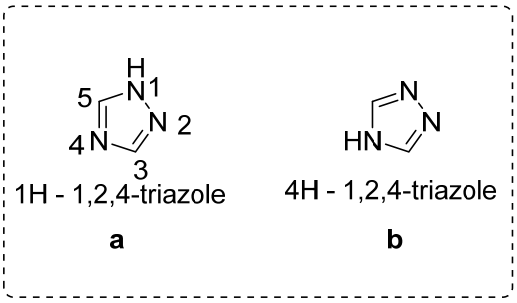
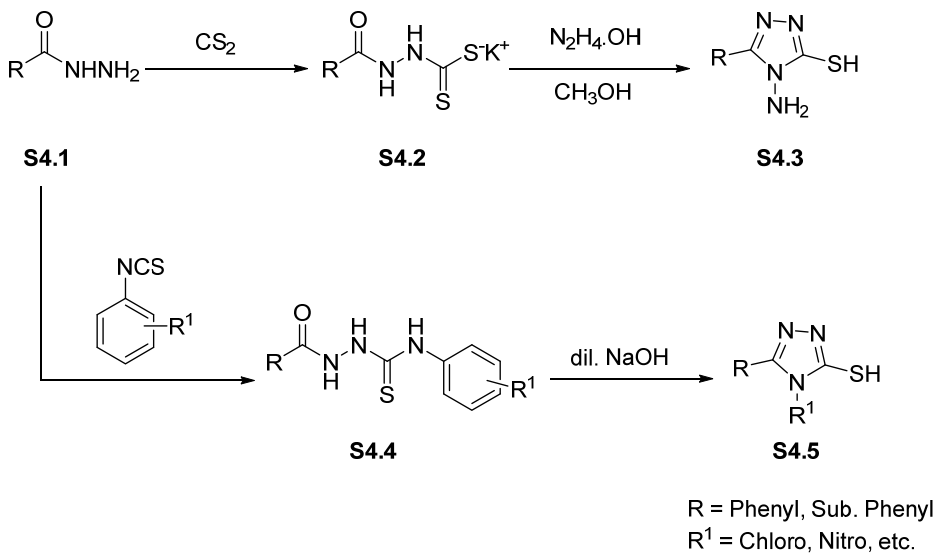


Figure 21: Tautomerism in 1,2,4-triazoles

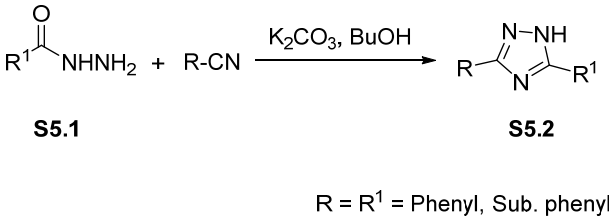
Synthesis of 1,2,4-triazoles

There are various synthetic routes adapted for the synthesis of 1,2,4-triazole nuclei. Some of the methods have been discussed here. Cansiz and co-workers[61] reported that the reaction of carbohydrazides **S4.1** with CS_2 in ethanolic potassium hydroxide gave the dithiocarbazate **S4.2**, which upon treatment with hydrazine hydrate resulted in 4-amino-5-aryl-4*H*-1,2,4-triazole-3-thiol **S4.3** (Scheme S1.3). The cyclodehydration of the thio semicarbazides **S4.4** in basic medium leads to the formation of 1,2,4-triazoles **S4.5**. Next, Maity and co-workers reported the same 4-amino-5-mercapto 3-(substituted)-1,2,4-triazole derivatives **S4.5** and revealed their anticancer activity on EAC bearing mice.[62]



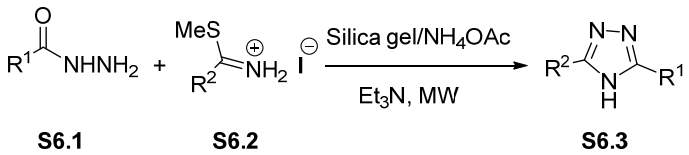
Scheme 4: *Synthesis of 3-mercapto-1,2,4-triazoles*

A convenient and efficient one-step base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles **S5.2** has been reported by Yeung's group.[63] The method is claimed to be a general one and tolerable for a wide range of functional groups (Scheme 5).



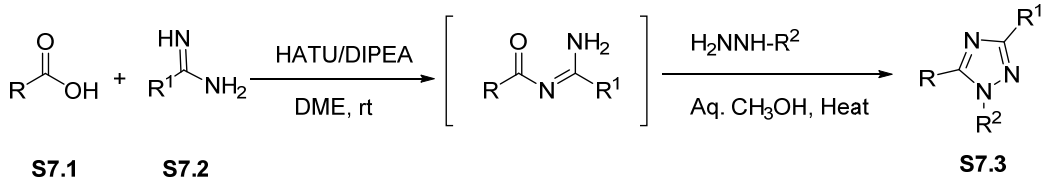
Scheme 5: *Base-catalyzed synthesis of 3,5-disubstituted-1,2,4-triazoles*

Rostamizadeh and co-workers reported the sold-phase synthesis of 1,2,4-triazoles.[64] A three-component condensation of acylhydrazines **S6.1** in the presence of S-methyl isothioamide hydroiodide **S6.2**, silica gel, and ammonium acetate under microwave irradiation of 900 W power afforded 1,2,4-triazole derivatives **S6.3** (Scheme 6). Silica gel has been used as a solid acidic catalyst.



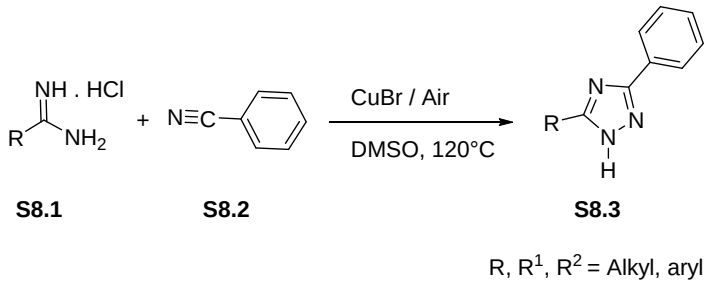
Scheme 6: *Synthesis of 1, 2, 4-triazoles using silica gel*

Castanedo and co-workers documented a highly regioselective one-pot process for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles **S7.3**. The reported method involves the condensation of carboxylic acid **S7.1**, primary amidine **S7.2**, and mono substituted hydrazine in one pot employing HATU (2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexa fluorophosphate) as the peptide coupling reagent (Scheme 7). This synthesis allows greater flexibility for the functional groups at the 5-position.[65]



Scheme 7: *Synthesis of 1,3,5-trisubstituted 1,2,4-triazoles*

A copper-catalyzed coupling of amidines **S8.2** and nitriles **S8.3** *via* sequential N–C and N–N oxidative coupling reactions has been reported by Ueda's group.[66] A wide range of functional groups are tolerated (Scheme 8). This is based on the well-known ability of transition metals to activate nitriles.



Scheme 8: *Synthesis of 1,2,4-triazole derivatives using copper catalyst*

1.2.4 Present work

Having synthesized a large set of acylthiourea derivatives and with preliminary SAR information, we next proceeded for the synthesis of the corresponding 3-amino-1,2,4-triazoles, with the objective of replacing the susceptible thiourea unit with a 1,2,4-triazole structural motif as its stable bioisostere.[67] As mentioned previously, the 1,2,4-triazole unit has been identified as the bioequivalent surrogate for the amide bond. This concept has been well exploited for the development of potential anticancer agents as well as for developing non-nucleoside reverse transcriptase inhibitors. With this anticipation of the best antitumor activity with the 3,5-disubstituted-1,2,4-triazole derivatives (**Triazole-PITs**), we proceeded further by selecting specific acylthioureas from the three series that we have synthesized and screened.

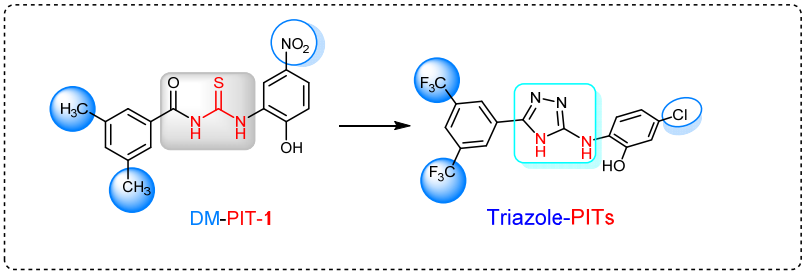
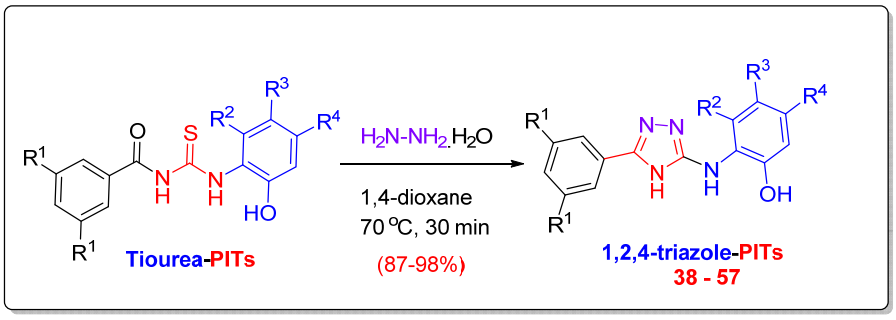


Figure 22: *1,2,4-triazole-PITs for the SAR studies*

Synthesis of 1,2,4-triazole derivatives

The synthesis of 1,2,4,-triazole derivatives from the corresponding N-aryl-N'-benzoylthioureas (thiourea-PITs)has been carried out by using hydrazine hydrate in 1,4-dioxane at70°C for 0.5 h to afford **38**–**57** in 87–98% yields (Scheme 9).



Scheme 9: *Synthesis of amino-1,2,4-triazole derivatives*

All synthesized 1,2,4-triazole have been completely characterized with help of ^{1}H, ^{13}C NMR, IR and HRMS data. For example, in the ^{1}H NMR spectrum of the compounds **41**, the 3,5-dimethylsubstituted phenyl ring aromatic protons appeared at δ 7.04 and 7.62 as two singlets integrating for 3 protons. At the other end, the (R_4) Cl substituted phenyl ring of R^3 proton appeared at δ 6.81 (*J*=2.3, 8.5 Hz) as a doublet of doublet; the R_2 proton appeared at δ 6.90 (*J*=2.3 Hz) as a doublet; and the proton *ortho* to the hydroxyl group appeared at δ 7.92 (*J*=8.7 Hz) as a doublet. The N–H protons resonated at δ 8.68 and 10.02 ppm as broad singlets. In the ^{13}C NMR spectra of **41**, the carbons of the C=N have appeared at δ 159.9 and 161.9 ppm. The presence of N–H groups was also evident from the IR spectrum, where the absorption was observed at 3390 cm^{-1}. In the HRMS, the exact mass of the compound showed, as calculated, for (MH^+) $C_{16}H_{16}N_4OCl$: 315.1007and it was found to be 315.1007.All these synthesized amino-1,2,4-triazole (triazole-PITs) molecules have been screened for their anticancer activity against the human ovarian carcinoma A2780 cell line.

Anticancer activity of 1,2,4-triazole derivatives

First, we started the course of SAR analysis, the compounds **38–40** having a simple phenyl (R^1=H) substituted at the C-3 position on triazole and at the other end, different functional groups on the aminophenol unit (Fig. 1.6). These three compounds **38–40** have showed a reasonable activity when used alone and with the combination of TRAIL. However, the compound **39** has showed improved activity as EC_{50} 12.8μM with the combination of TRAIL. Next, the replacement of the phenyl ring with the 3,5-dimethyl substituted phenyl ring at the C-3 position on the triazole units **41**–**46** have been synthesized and were taken forward for screening against A2780 cells. The compound **43** has good improved activity as EC_{50} 15.24μM when used alone and EC_{50} 12.17μM with the combination of TRAIL. The compounds **41**, **42** and **44** showed moderate activity when employed alone and improved activity when applied in combination to TRAIL. However, the other compounds **45** and **46** were found to be ineffective upto EC_{50}>100μM when used alone but while using the TRAIL combination, the compound **46** has showed better activity as EC_{50} 19.82μM in human ovarian carcinoma A2780 cells.

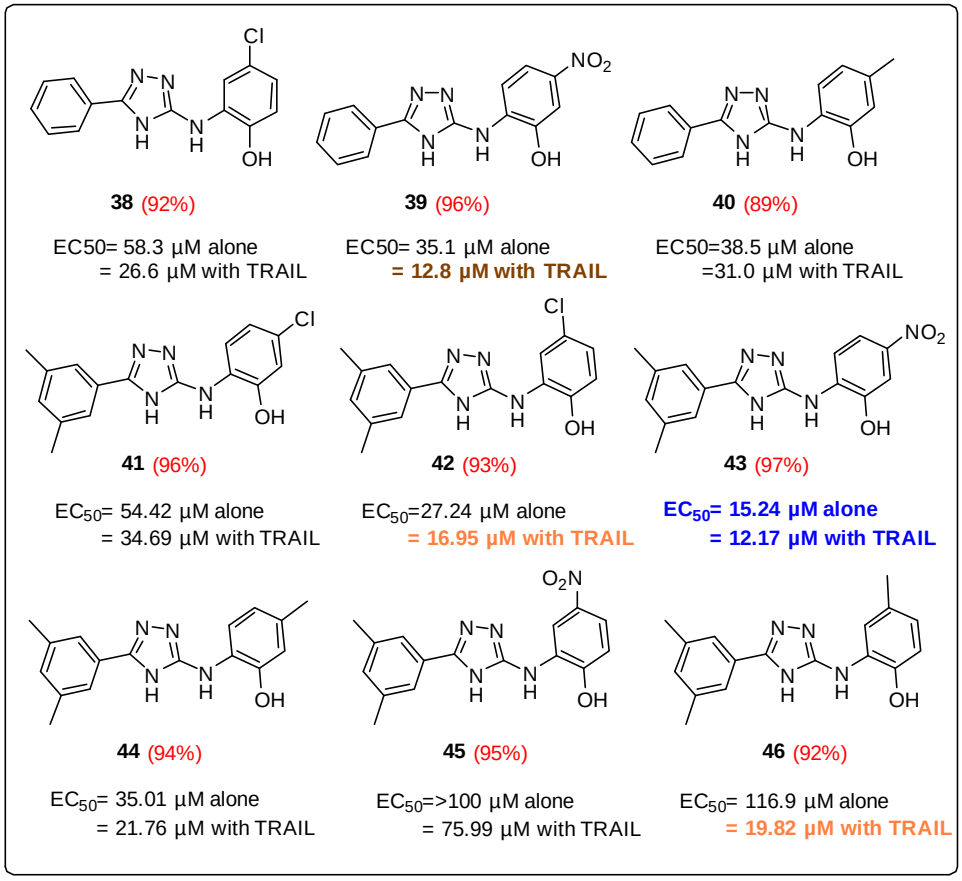


Figure 23: *Structure and anticancer activity data of 1,2,4-triazol-PITs series **38–46***

Next, we intended to incorporate the CF_3 (R^1) group in the phenyl ring at the C-3 position on the triazoles unit. Very interestingly, all the endeavours indicated that the addition of the CF_3 group at the C3 and C5 (R^1) positions on the phenyl ring, with a chloro group at the R^3position on aminophenol unit **48** has showed excellent improvement as EC_{50} 13.8µM when used alone and EC_{50} 5.9µM with the combination of TRAIL (Figure 24). The compounds **47**, **50** and **51** were found to be ineffective in human ovarian carcinoma A2780 cells. The compound **49** has shown a comparable activity with DM-PIT-1with in regard to anticancer activity.

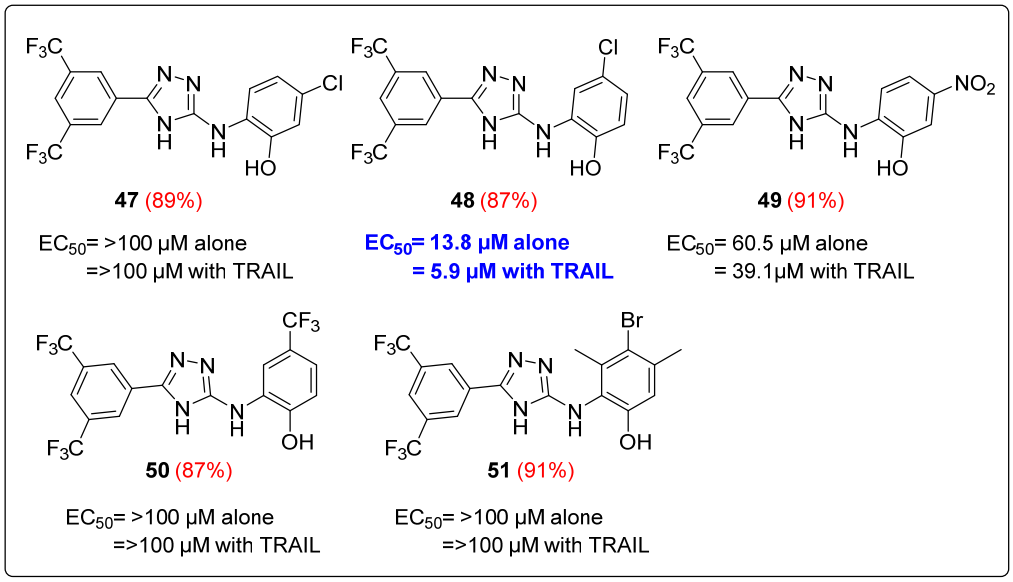


Figure 24: *Structure and anticancer activity data of 1,2,4-triazol-PITs series* ***47–51***

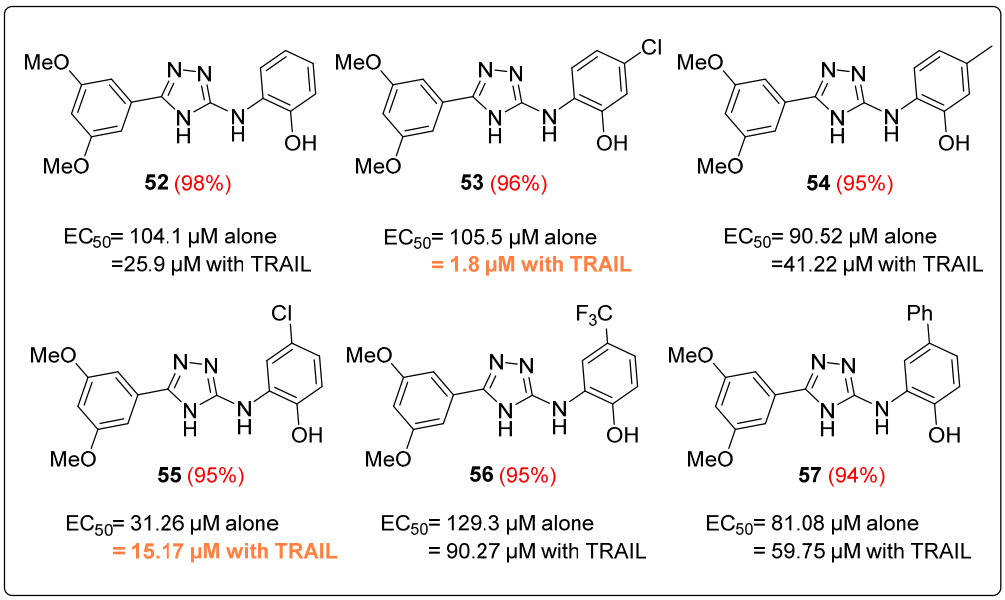


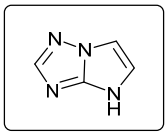
Figure 25: *Structure and anticancer activity data of 1,2,4-triazol-PITs series* ***52–57***

Next, we examined the anticancer activity of the next series of compounds **52**–**57** where the two CF3 groups on the phenylring at the C-3 position oftriazole unit have been replaced with the –OMe groups. In this series, the chloro (Cl) substituted compound **55** has shown reasonable activity as EC_{50} 31.26µM when used alone and EC_{50} 15.17µM with the combination of TRAIL. However, the other compounds **52**, **53**, **54**, **56** and **57** were ineffective when used alone and

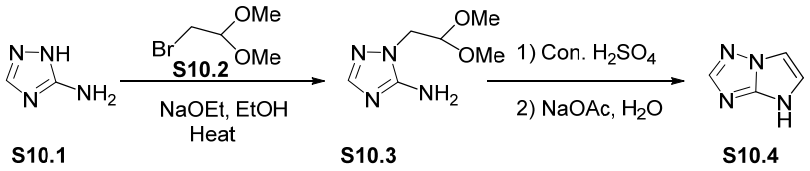
showed reasonable improvement with TRAIL. The compound **53** has shown excellent improvement (EC_{50} 1.8µM) only in combination with TRAIL.

1.2.5 Imidazo-1,2,4-triazoles

The chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their ease of synthesis and biological importance. The imidazo-1,2,4-triazoles, contain two rings imidazole and triazole – fused together, and the imidazo-[1,2,4] triazole derivatives have been widely reported in the mainstream as well as in the patent literature with potential antimicrobial, anti-fungicidal and anticancer activities.[68]

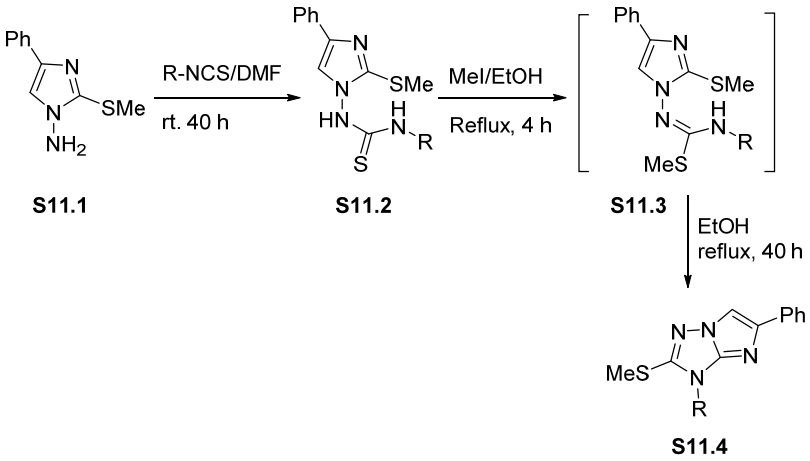


Faure and co-workers have reported the synthesis of imidazo-[1,2,4]triazole **S10.4** from the reaction of 3-amino-l,2,4-triazole **S10.1** and bromoacetaldehyde dimethyl acetal **S10.2** with base catalyzed alkylation followed by acid catalyzed cyclization (Scheme 10).[69]



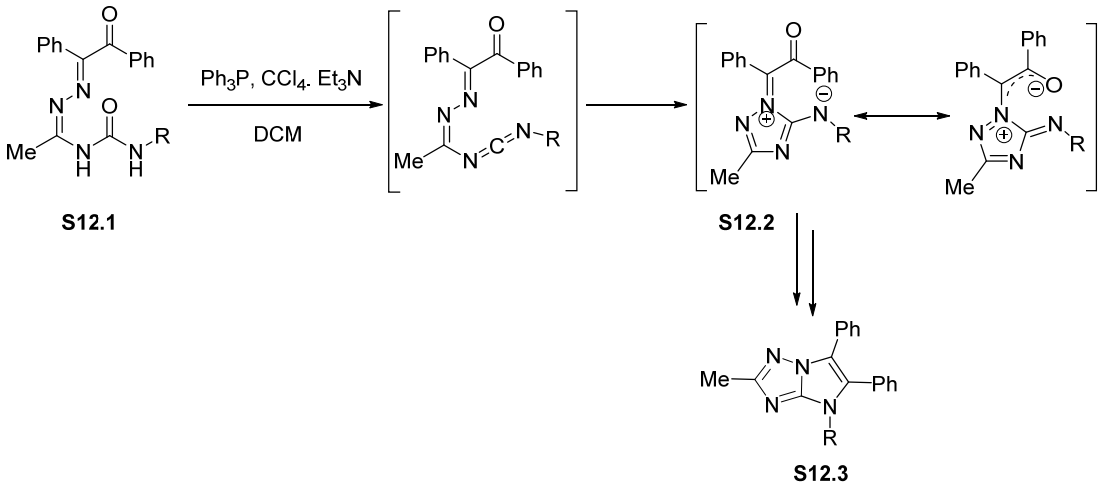
Scheme 10: *Synthesis of imidazo-1,2,4-triazole from 1,2,4-triazole moiety*

Molina's group reported the synthesis of imidazo-1,2,4-triazoles **S11.4** by condensing the 1-amino-2-methylthioimidazole **S11.1** with isothiocyanates to give (*N*-heteroaryl)-thioureas **S11.2**, which, upon S-methylation to **S11.3** followed by heating, afforded the desired imidazo-1,2,4-triazoles (Scheme 11).[70]



Scheme 11: *Synthesis of imidazo-1,2,4-triazoles*

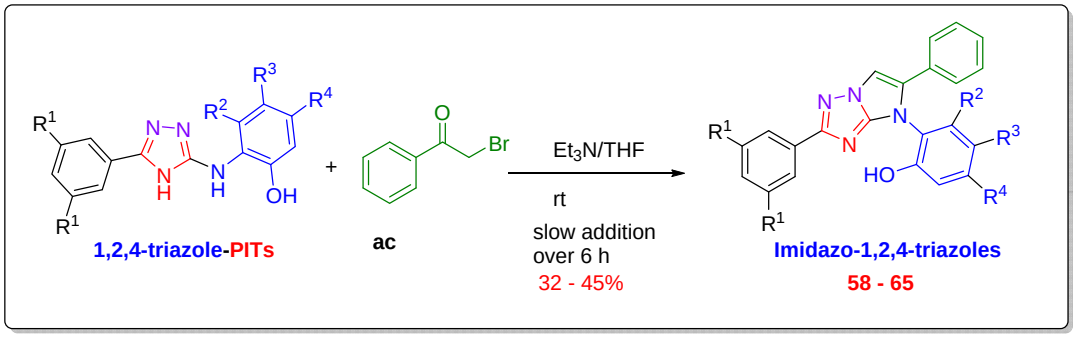
Lee and co-workers reported an efficient route in which both the rings of the bicyclic fused ring of imidazo-1,2,4-triazole **S12.3** derivatives have been forged in one-step presumably *via* the intermediate of the amino triazoles **S12.2** (Scheme 12).[71]



Scheme 12: *Synthesis of imidazo-1,2,4-triazoles via. bicyclic ring closure*

1.2.6 Present work

As a part of replacing the susceptible acylthiourea unit and considering the poor results with the simple amino-[1,2,4]-triazole series, we proceeded further to synthesise the imidazo-[1,2,4]triazole derivatives. After exploring various options, the optimum conditions for the synthesis of imidazo-triazoles have been identified (Scheme 13). The general procedure for their preparation involves the treatment of a solution of amino-1,2,4-triazole derivative (Triazole-PITs) and triethylamine (Et_3N) in THF with 2-bromoacetophenone **ac** (slowly added over 6 h at room temperature) to afford imidazo-1,2,4-triazoles (**58**–**65**). The compounds were confirmed with the help of ^1H, ^{13}C NMR, IR and HRMS data. All these synthesized molecules have been screened for their anticancer activity against the human ovarian carcinoma A2780 cell lines and the results are provided in Figure 26.



Scheme 13: *Synthesis of Imidazo-1,2,4-triazole derivatives*

Coming to the imidazo-1,2,4-triazole series with different substituted (R_1=H,CF_3,Me) aryl groups for activity, the compound **62** with Cl again in R^3 position has shown good activity(higher than that of the **DM-PIT-1**)as EC_{50} 13.19µM when used alone and EC_{50} 3.9µM with the combination of TRAIL. Other compounds **61** and **64**showed less activity using alone, but the activity was seen to show excellent improvements with TRIAL. In this entry, only the combination of CF_3 groups in the R^1 position shows good activity. As indicated in the Figure 1.9, generally compounds belonging to the dimethoxy series are less active when compared to the unsubstituted or substituted either with methyl or trifluormethyl, and Cl in the R^3 position is important for retaining the activity of the series.

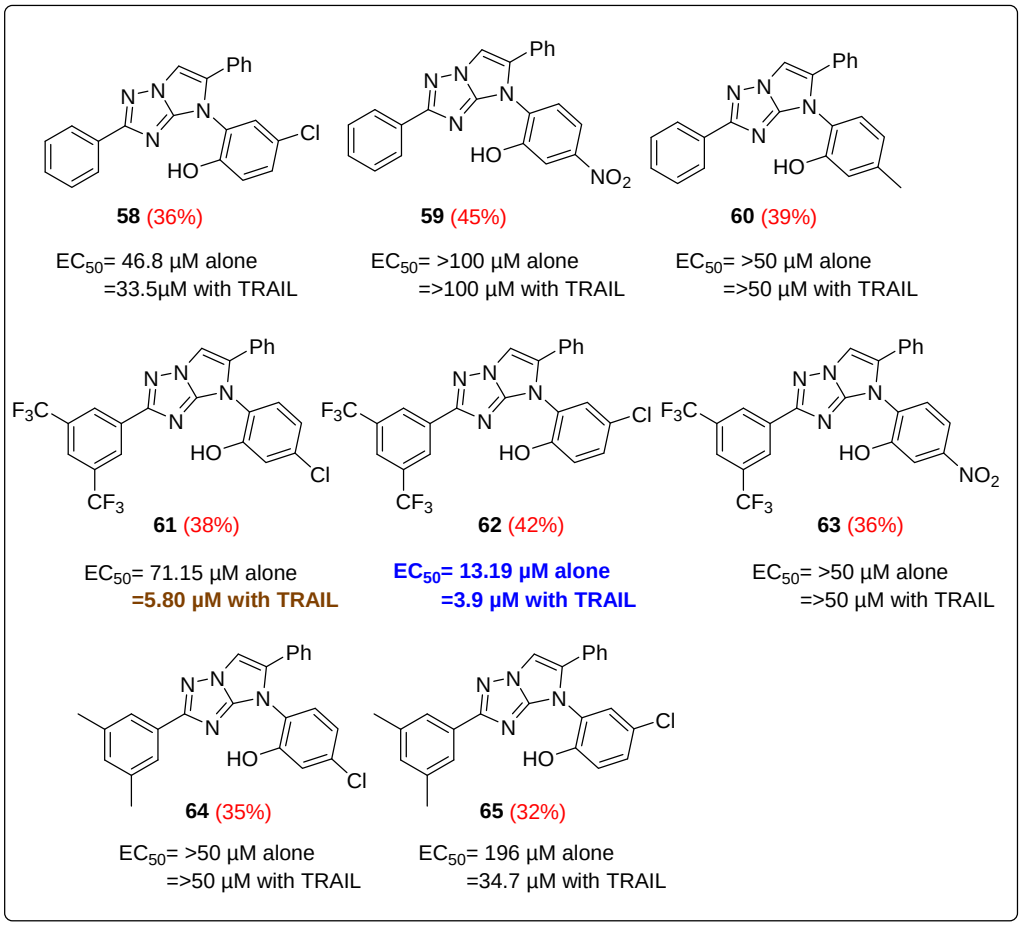


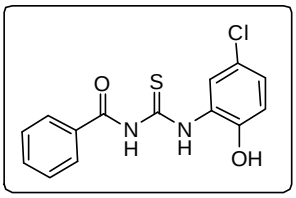
Figure 26: *Structure and anticancer activity data of imidazo-1,2,4-triazol-PITs* ***58–65***

To conclude, a simple scheme for the synthesis of three different types of compounds has been executed with the synthesis of a good number of compounds in each series. Out of the two new series that have been synthesized in view of replacing the thiourea unit, only the screening results with the imidazotraizole series are encouraging. The compounds of this series showed moderately improved activity alone and excellent improvement upon combination of TRIAL, when compared with the parent DM-PIT-1. Further investigations on the synthesis of some more new derivatives in the series of imidazotriazoles are required before proceeding for their animal studies as well as pharmaco kinetic data. Work in this direction is currently under progress.

1.3.1 General Procedure I: Preparation of Thiourea derivatives (1)

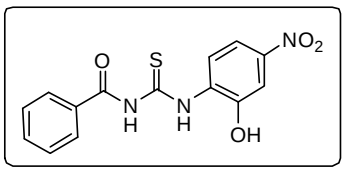
To a solution of ammonium thiocyanate (108 mg, 1.4 mmol) in 20 mL of acetonitrile, benzoyl chloride (100 mg, 0.71 mmol) was added dropwise, the mixture was stirred for 5 minutes to form white precipitate of isothiocyanate, and then a solution of corresponding amine (0.71 mmol) in acetonitrile (5 mL) was added slowly. The reaction mixture was stirred at rt for 24 h. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography with Pet. ether/EtOAc (9:1) as eluent to give thiourea derivative.

N-((5-chloro-2-hydroxyphenyl)carbamothioyl)benzamide (2):



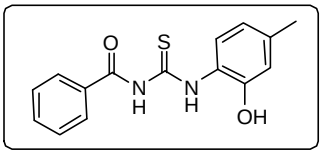
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (196 mg, 90%). M. P.: 215–216 °C; IR ($CHCl_3$): ν 3458, 3021, 1724, 1674, 1538, 1496, 1348, 1278, 1139, 761cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 6.76-6.90 (m, 2H), 7.34-7.53 (m, 3H), 7.82 (d, *J* = 7.7 Hz, 2H), 8.64 (d, *J* = 2.2, 8.97 Hz, 1H), 9.68 (s, 2H), 12.85 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 115.3, 121.5, 122.0, 125.0, 126.4, 127.4 (2C), 127.9 (2C), 131.2, 132.5, 146.8, 166.7, 176.4 ppm; HRMS ESI calcd for (MH^+) $C_{14}H_{12}N_2O_2ClS$ 307.0303, found 307.0298.

N-((2-hydroxy-4-nitrophenyl)carbamothioyl)benzamide (3):



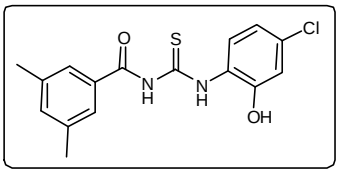
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (216 mg, 96%). M. P.: 223–224 °C; IR ($CHCl_3$): ν 3362, 3025, 1734, 1667, 1542, 1492, 1139, 921 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 7.22–7.37 (m, 3H), 7.47 (dd, *J* = 1.3, 9.3 Hz, 1H), 7.57 (d, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 8.90 (d, *J* = 9.3 Hz, 1H), 10.27 (s, 1H), 10.72 (s, 1H), 13.13 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 109.3, 114.0, 120.9, 128.3 (2C), 128.4 (2C), 131.7, 132.7, 133.1, 144.1, 148.6, 167.7, 177.8 ppm; HRMS ESI calcd for (MH^+) $C_{14}H_{12}N_3O_4S$ 318.0543, found 318.0538, calcd for $[M+Na]^+$ $C_{14}H_{11}N_3O_4SNa$ 340.0362, found 340.0357.

N-((2-hydroxy-4-methylphenyl)carbamothioyl)benzamide (4): Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as



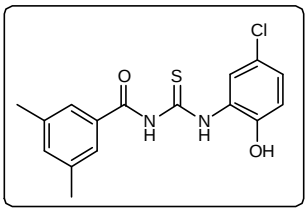
yellow solid (189 mg, 93%). M. P.: 218–219 °C; IR ($CHCl_3$): ν 3402, 3021, 1734, 1674, 1542, 1496, 1278, 1139 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 7.21–7.37 (m, 3H), 7.47 (dd, *J* = 1.3, 9.3 Hz, 1H), 7.56 (d, *J* = 1.3 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 8.90 (d, *J* = 9.3 Hz, 1H), 10.27 (s, 1H), 10.72 (s, 1H), 13.13 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+ DMSO-d_6, 50 MHz): δ 20.08, 114.8, 123.0, 125.0, 126.5, 127.4 (2C), 128.0 (2C), 131.3, 132.5, 146.1, 166.6, 176.4 ppm; HRMS ESI calcd for (MH^+) $C_{15}H_{15}N_2O_2S$ 287.0849, found 287.0845, calcd for $[M+Na]^+$ $C_{15}H_{14}N_2O_2SNa$ 309.0668, found 309.0663.

N-(4-chloro-2-hydroxyphenylcarbamothioyl)-3,5-dimethylbenzamide (5):



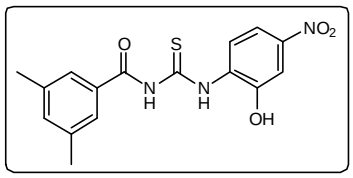
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (184 mg, 93%). M. P.: 210–211 °C; IR ($CHCl_3$): ν 3412, 3025, 3246, 1655, 1601, 1536, 11460, 1105 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.37 (s, 6H), 7.04 (d, *J* = 8.95 Hz, 1H), 7.23 (s, 1H), 7.51 (s, 2H), 7.95 (dd, *J* = 2.75, 8.95 Hz, 1H), 9.67 (s, 1H), 9.82 (d, *J* = 2.75 Hz, 1H), 13.11 (s,1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ19.4, 113.4, 116.5, 122.3, 123.7, 124.7 (2C), 128.5, 130.3, 133.0 , 136.3 (2C), 148.4, 166.7, 176.0 ppm; HRMS ESI calcd for (M^+) $C_{16}H_{15}N_2O_2ClS$ 334.0537, found 334.0797.

N-(5-chloro-2-hydroxyphenylcarbamothioyl)-3,5-dimethylbenzamide (6):



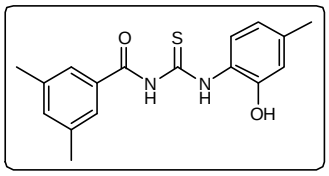
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (182 mg, 92%). M.P.: 220 °C; IR ($CHCl_3$): ν 3442, 3248, 1657, 1601, 1533, 1377, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.36 (s, 6H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.97 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.22 (s, 1H), 7.52 (s, 2H), 8.78 (d, *J* = 2.4 Hz, 1H), 9.85 (s, 1H), 13.00 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50 MHz): δ19.7, 114.6, 120.8, 121.0, 124.2, 124.8 (2C), 126.0, 130.5, 133.3, 136.6 (2C), 146.2, 166.8, 176.1 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_2O_2ClS$ 335.0612, found 335.0616, calcd for $[M+Na]^+$ $C_{16}H_{16}N_2O_2ClSNa$ 357.0434, found 357.0435.

N-(2-hydroxy-4-nitrophenylcarbamothioyl)-3,5-dimethylbenzamide (7):



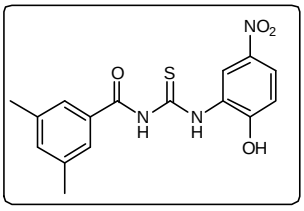
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (191 mg, 94%). M. P.: 235.8 °C; IR ($CHCl_3$): ν3368, 3323, 2503, 1595, 1564, 1521, 1462, 1376, 1337 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.35 (s, 6H), 7.22 (s, 1H), 7.50 (s, 2H), 7.72 (dd, *J* = 2.5, 9.0 Hz, 1H), 7.82 (d, *J* = 2.5 Hz, 1H), 9.12 (d, *J* = 9.0 Hz, 1H), 9.69 (s, 1H), 13.30 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 21.0 (2C), 109.4, 114.8, 121.1, 125.49 (2C), 131.3, 132.4, 135.4, 138.9 (2C), 144.6, 148.5, 167.3, 177.1 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_3O_4S$ 346.0855, found 346.0856, calcd for $[M+Na]^+C_{16}H_{15}N_3O_4SNa$ 368.0675, found 368.0675.

N-(2-hydroxy-4-methylphenylcarbamothioyl)-3,5-dimethylbenzamide (8):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (171 mg, 93%). M. P.: 199.9 °C; IR ($CHCl_3$): ν3472, 3402, 1655, 1596, 1551, 1459, 1360, 1213, 1107 cm^{-1}; ^1H NMR ($CDCl_3$+Methanol-d_4, 200 MHz): δ 2.31 (s, 3H), 2.42 (s, 6H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.78 (s, 1H), 7.28 (s, 1H), 7.57 (s, 2H), 8.26 (d, *J* = 8.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$+Methanol-d_4, 50 MHz): δ 20.9 (2C), 29.5, 116.9, 120.3, 123.0, 123.7, 125.3 (2C), 131.5, 135.1 (2C), 137.8, 138.7, 148.8, 167.6, 176.9 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_2O_2S$ 315.1161, found 315.1162, calcd for $[M+Na]^+$ $C_{17}H_{18}N_2O_2SNa$ 337.0981, found 337.0981.

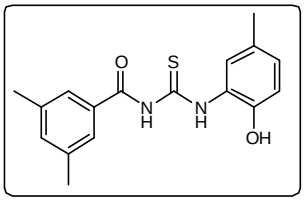
N-(2-hydroxy-5-nitrophenylcarbamothioyl)-3,5-dimethylbenzamide (1):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (186 mg, 91%). M. P.: 204.7 °C; IR ($CHCl_3$): ν 3368, 3291, 2506, 1637, 1598, 1560, 1520, 1459, 1377, 1350, 1105 cm^{-1}; ^1H NMR ($CDCl_3$ + 2 drops DMSO-d_6, 200 MHz): δ 2.43 (s, 6H), 7.03 (d, *J* = 9.0 Hz, 1H), 7.30 (s, 1H), 7.50 (s, 1H), 7.59 (s, 2H), 8.04 (dd, *J* = 2.6, 9.0 Hz, 1H), 9.87 (d, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ20.8 (2C), 114.0, 118.2, 122.3, 125.3 (2C), 126.1, 131.3, 135.1 (2C), 138.7, 139.3, 154.6, 167.5,

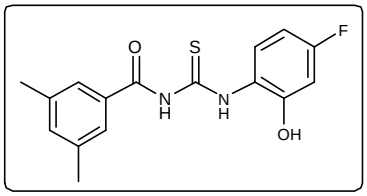
177.2 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_3O_4S$ 346.0855, found 346.0856, calcd for $[M+Na]^+$ $C_{16}H_{15}N_3O_4SNa$ 368.0675, found 368.0675.

N-(2-hydroxy-5-methylphenylcarbamothioyl)-3,5-dimethylbenzamide (9):



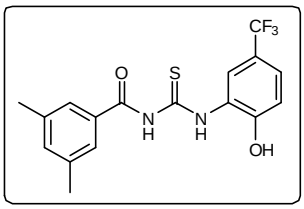
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (168 mg, 90%). M. P.: 219.1 °C; IR ($CHCl_3$): ν3409, 1659, 1599, 1565, 1460, 1375, 1218, 1101 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.29 (s, 3H), 2.39 (s, 6H), 6.86 (s, 2H), 7.24 (s, 1H), 7.60 (s, 2H), 8.39 (d, J = 10.7 Hz, 1H), 9.59 (s, 1H), 10.46 (s, 1H), 12.92 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ19.6 (2C), 19.9, 114.1, 122.5, 124.7, 124.8, 125.8 (2C), 126.5, 130.8, 133.6 (2C), 137.0, 145.6, 166.7, 176.1 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_2O_2S$ 315.1160, found 315.1162, calcd for $[M+Na]^+$ $C_{17}H_{18}N_2O_2SNa$ 337.0981, found 337.0981.

N-(4-fluoro-2-hydroxyphenylcarbamothioyl)-3,5-dimethylbenzamide (10):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (149 mg, 89%). M. P.: 160.1 °C; IR ($CHCl_3$): ν 3228, 1615, 1598, 1521, 1466, 1376, 1255, 1017, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 6H), 6.74 (ddd, *J* = 2.8, 7.8, 10.5 Hz, 1H), 6.84 (dd, *J* = 2.8, 9.6 Hz, 1H), 7.29 (s, 1H), 7.32 (dd, *J* = 6.0, 8.9 Hz, 1H), 7.48 (s, 2H), 9.17 (s, 1H), 12.56 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 50 MHz): δ 20.7 (2C), 102.3, 104.6, 122.6, 126.3 (2C), 131.9, 134.9, 137.7 (2C), 150.8, 159.0, 160.9, 168.4, 178.1 ppm; ESI-MS (*m/z*): 341.3 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{15}FN_2O_2S$: C, 60.36; H, 4.75; F, 5.97; N, 8.80 Found: C, 60.30; H, 4.70; F, 5.92; N, 8.76.

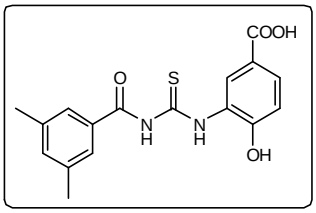
N-(2-hydroxy-5-(trifluoromethyl)phenylcarbamothioyl)-3,5-dimethylbenzamide (11):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (168 mg, 87%). M. P.: 208.6 °C; IR ($CHCl_3$): ν 3425, 3392, 1740, 1652, 1567, 1374, 1233, 1144 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.40 (s, 6H), 7.08 (d, *J* = 8.34 Hz, 1H), 7.26 (s, 1H), 7.30 (dd, *J* = 2.27, 8.59 Hz, 1H), 7.61 (s,

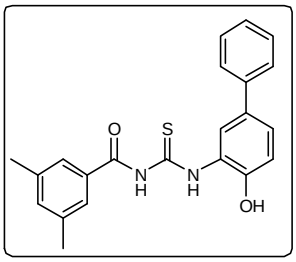
2H), 9.15 (d, *J* = 1.76, Hz, 1H), 10.47 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 20.2 (2C), 114.2, 118.9, 119.5, 122.2, 125.0 (2C), 125.6, 126.2, 130.9, 133.9, 137.3 (2C), 150.8, 167.0, 176.7 ppm; ESI-MS (*m/z*): 391.4 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{15}F_3N_2O_2S$: C, 55.43; H, 4.10; N, 7.60 Found: C, 55.38; H, 4.07; N, 7.56

3-(3-(3,5-dimethylbenzoyl)thioureido)-4-hydroxybenzoic acid (12):



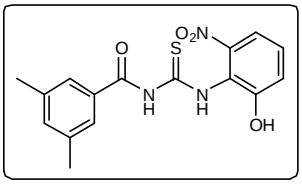
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (156 mg, 86%). M. P.: 265.0 °C; IR ($CHCl_3$): ν 3431, 3287, 2671, 1885, 1696. 1657, 1598, 1509, 1460, 1344, 1275, 1217, 1149 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.36 (s, 6H), 7.03 (d, *J* = 8.5 Hz, 1H), 7.30 (s, 1H), 7.64 (s, 2H), 7.61 (dd, *J* = 2.0, 8.5 Hz, 1H), 9.25 (d, *J* = 2.0 Hz, 1H), 11.15 (br s, 1H), 11.42 (s, 1H), 12.59 (br s, 1H), 13.06 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 50 MHz): δ 20.7 (2C), 114.8, 120.9, 124.6, 125.9 (2C), 126.3, 128.3, 131.8, 134.5, 137.8 (2C), 153.0, 167.0, 168.4, 177.9 ppm; ESI-MS (*m/z*): 373.4 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13 Found: C, 59.34; H, 4.72; N, 8.17.

N-(4-hydroxybiphenyl-3-ylcarbamothioyl)-3,5-dimethylbenzamide (13):



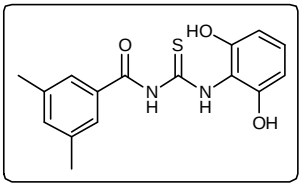
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (184 mg, 93%). M. P.: 117.6 °C; IR ($CHCl_3$): ν 3492, 3378, 2923, 1725, 1667, 1610, 1554, 1460, 1377, 1336, 1230, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.42 (s, 6H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.30 (s, 1H), 7.36–7.40 (m, 1H), 7.43–7.48 (m,2H), 7.50–7.60 (m,5H), 7.69 (d, *J* = 2.3 Hz, 1H), 9.22 (br s, 1H), 12.76 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.3 (2C), 116.4, 123.6, 125.1 (2C), 126.5 (2C), 127.7 (2C), 129.3 (2C), 133.6, 134.0, 134.5, 135.1, 136.5, 138.8 (2C), 144.6, 165.9, 177.8 ppm; ESI-MS (*m/z*): 399.5 $[M+Na]^+$; Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35; N, 7.44 Found: C, 70.24; H, 5.38; N, 7.40.

N-(2-hydroxy-6-nitrophenylcarbamothioyl)-3,5-dimethylbenzamide (14): Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was



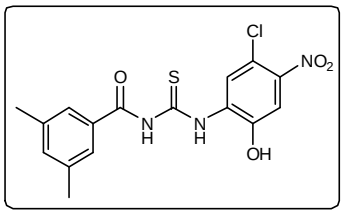
determined as yellow solid (162 mg, 89%). M. P.: 233.5 °C; IR ($CHCl_3$): ν 3483, 3384, 3286, 1675, 1521, 1463, 1376, 1160, 1107 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.36 (s, 6H), 6.49 (dd, *J* = 7.6, 8.8 Hz, 1H), 6.92 (dd, *J* = 1.3, 7.6 Hz, 1H), 7.32 (s, 1H), 7.42 (d, *J* = 7.6, 8.0 Hz, 1H), 7.65 (s, 2H), 10.74 (s,1H), 11.73 (s,1H), 12.25 (s,1H) ppm; ^{13}C NMR (DMSO-d_6, 50 MHz): δ 20.9, 21.0, 114.7, 115.5, 117.2, 126.5 (2C), 126.66, 137.4, 138.0 (2C), 146.5, 147.3, 154.2, 168.9, 181.4 ppm; ESI-MS (*m/z*): 368.2 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{15}N_3O_4S$: C, 55.64; H, 4.38; N, 12.17 Found: C, 55.60; H, 4.33; N, 12.13.

N-(2,6-dihydroxyphenylcarbamothioyl)-3,5-dimethylbenzamide (15):



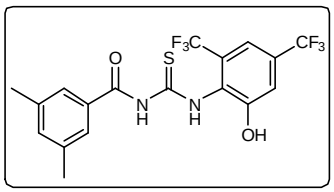
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (148 mg, 89%). M. P.: 207.2–209.1 °C; IR ($CHCl_3$): ν 3440, 3185, 2853, 1737, 1682, 1608, 1509, 1465, 1376, 1148, 1009 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.39 (s, 6H), 6.49 (d, *J* = 8.2 Hz, 2H), 7.99 (t, *J* = 8.2 Hz, 1H), 7.24 (s, 1H), 7.61 (s, 2H), 8.87 (s, 2H), 10.86 (br s, 1H), 12.25 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+ DMSO-d_6, 50 MHz): δ19.9 (2C), 107.1, 113.3, 125.0 (2C), 127.2, 130.8, 133.6, 137.0 (2C), 151.5, 167.4, 178.4 ppm; ESI-MS (*m/z*): 339.2 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85 Found: C, 60.69; H, 5.06; N, 8.81.

N-(5-chloro-2-hydroxy-4-nitrophenylcarbamothioyl)-3,5-dimethylbenzamide (16):



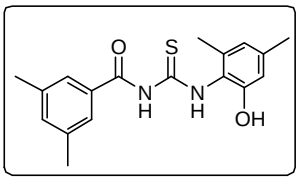
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (172 mg, 86%). M. P.: 249.7 °C; IR ($CHCl_3$): ν 3342, 1653, 1590, 1558, 1377, 1325, 1105 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.40 (s, 6H), 7.26 (s, 1H), 7.60 (s, 2H), 7.63 (s, 1H), 9.40 (s, 1H), 10.47 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 20.6 (2C), 111.0, 116.1, 122.4, 125.3 (2C), 130.9, 131.1, 134.6, 138.0 (2C), 142.4, 146.7, 167.3, 177.2 ppm; ESI-MS (*m/z*): 402.6 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{14}ClN_3O_4S$: C, 50.60; H, 3.72; N, 11.06 Found: C, 50.55; H, 3.68; N, 11.00.

N-(2-hydroxy-4,6-bis(trifluoromethyl)phenylcarbamothioyl)-3,5-dimethylbenzamide (17):



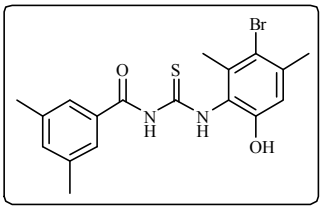
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (197 mg, 86%). M. P.: 167.5 °C; IR ($CHCl_3$): ν 3388, 2853, 1680, 1604, 1459, 1376, 1279, 1214, 1127, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 6H), 6.85 (s, 1H), 7.32 (s, 1H), 7.52 (s, 2H), 7.61 (s, 2H), 9.32 (br s, 1H), 12.84 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1 (2C), 116.1, 121.5, 124.2, 125.5 (2C), 126.7, 127.3, 130.5, 131.3, 131.6, 136.1, 139.3 (2C), 152.6, 167.9, 179.3 ppm; ESI-MS (*m/z*): 459.1 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{14}F_6N_2O_2S$: C, 49.54; H, 3.23; N, 6.42 Found: C, 49.49; H, 3.19; N, 6.39.

N-(2-hydroxy-4,6-dimethylphenylcarbamothioyl)-3,5-dimethylbenzamide (18):



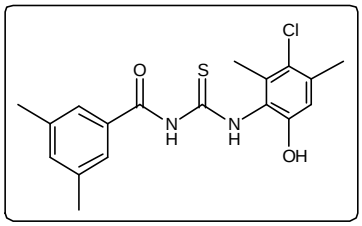
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (152 mg, 88%). M. P.: 170.2 °C; IR ($CHCl_3$): ν 3376, 3138, 1798, 1739, 1665, 1590, 1519, 1463, 1377, 1340, 1208, 1146 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz): δ 2.14 (s, 3H), 2.20 (s, 3H), 2.35 (s, 6H), 6.54 (d, *J* = 5.6 Hz, 2H), 7.29 (s, 1H), 7.63 (s, 2H), 9.37 (s, 1H), 11.41 (s, 1H), 11.78 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 50 MHz): δ17.9 (2C), 20.7, 20.8, 114.2, 121.3, 121.9, 126.3 (2C), 132.0, 134.4, 136.1, 137.4, 137.7 (2C), 152.2, 168.5, 181.2 ppm; ESI-MS (*m/z*): 351.4 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53 Found: C, 65.79; H, 6.09; N, 8.49.

N-(3-bromo-6-hydroxy-2,4-dimethylphenylcarbamothioyl)-3,5-dimethylbenzamide (19):



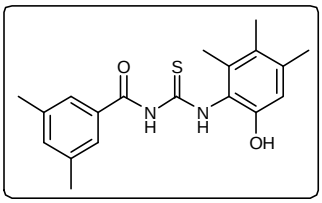
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (184 mg, 92%). M. P.: 164.6–166.0 °C; IR ($CHCl_3$): ν 3325, 1679, 1605, 1515, 1403, 1211, 1157, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (s, 9H), 2.44 (s, 3H), 6.92 (s, 1H), 7.30 (s, 1H), 7.50 (s, 2H), 9.26 (s, 1H), 12.31 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ19.5 (2C), 21.2, 24.1, 119.2, 123.6, 125.4 (2C), 131.0, 134.0, 135.9, 139.3 (2C), 139.7, 149.6, 167.9, 178.7 ppm; ESI-MS (*m/z*): 429.2 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{19}BrN_2O_2S$: C, 53.08; H, 4.70; N, 6.88 Found: C, 53.11; H, 4.73; N, 6.93.

N-(3-chloro-6-hydroxy-2,4-dimethylphenylcarbamothioyl)-3,5-dimethylbenzamide (20):



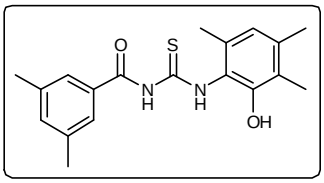
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (176 mg, 92%). M. P.: 185.7 °C; IR ($CHCl_3$): ν 3322, 1681, 1528, 1460, 1377, 1296, 1164, 1051, 720 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.37 (s, 3H), 2.39 (s, 3H), 2.42 (s, 6H), 6.23 (br s, 1H), 6.89 (s, 1H), 7.30 (s, 1H), 7.50 (s, 2H), 9.22 (s, 1H), 12.32 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ16.2 (2C), 20.9, 21.2, 118.7, 123.5, 125.4 (2C), 127.0, 130.9, 132.4, 135.7, 137.5 (2C), 139.1, 148.9, 167.9, 179.1 ppm; ESI-MS (*m/z*): 385.8 $[M+Na]^+$; Anal. Calcd for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28; Cl, 9.77; N, 7.72; Found: C, 59.63; H, 5.32; Cl, 9.80; N, 7.70.

N-(6-hydroxy-2,3,4-trimethylphenylcarbamothioyl)-3,5-dimethylbenzamide (21):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (147 mg, 82%). M. P.: 201.6–203 °C; IR ($CHCl_3$): ν 3339, 1667, 1596, 1532, 1463, 1377, 1156 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 2.06 (s, 6H), 2.18 (s, 3H), 2.35 (s, 6H), 6.58 (s, 1H), 7.29 (s, 1H), 7.63 (s, 2H), 9.11 (s, 1H), 12.40 (s, 1H), 11.82 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ15.0 (2C), 15.1, 20.4, 20.7, 114.8, 122.3, 124.9, 126.3 (2C), 132.0, 134.3, 134.4, 135.8, 137.7 (2C), 149.6, 168.5, 181.3 ppm; ESI-MS (*m/z*): 365.2 $[M+Na]^+$; Anal. Calcd for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.48; N, 8.18 Found: C, 66.68; H, 6.52; N, 8.20.

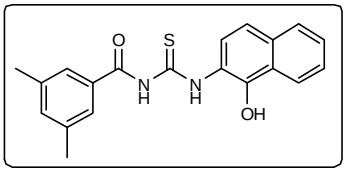
N-(2-hydroxy-3,4,6-trimethylphenylcarbamothioyl)-3,5-dimethylbenzamide (22):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (157 mg, 87%). M. P.: 130.6–131.4 °C; IR ($CHCl_3$): ν 3318, 2728, 1673, 1604, 1519, 1462, 1377, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.22 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 2.41 (s, 6H), 6.24 (br s, 1H), 6.72 (s, 1H), 7.29 (s, 1H), 7.50 (s, 2H), 9.19 (s, 1H), 12.25 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.0 (2C), 17.9, 19.9,

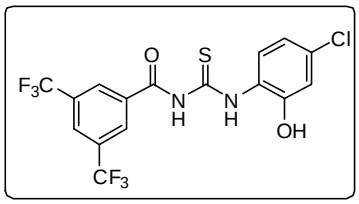
21.1, 122.6, 124.1, 124.4, 125.3 (2C), 130.1, 131.1, 135.5, 137.7 (2C), 139.0, 148.5, 167.8, 178.6 ppm; ESI-MS (*m/z*): 365.5 $[M+Na]^+$; Anal. Calcd for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.48; N, 8.18 Found: C, 66.59; H, 6.43; N, 8.13.

N-(1-hydroxynaphthalen-2-ylcarbamothioyl)-3,5-dimethylbenzamide (23):



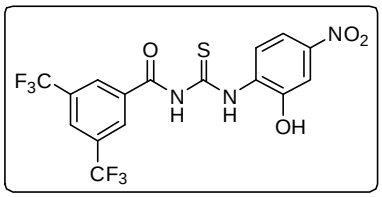
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (173 mg, 94%). M. P.: 169.6 °C; IR ($CHCl_3$): ν 3317, 2726, 1741, 1666, 1601, 1527, 1463, 1377, 1214, 1137 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.42 (s, 6H), 7.18 (br s, 1H), 7.29 (m, 1H), 7.49–7.56 (m, 51H), 7.79–7.84 (m, 1H), 8.41–8.45 (s, 2H), 9.24 (s, 1H), 12.79 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 21.1 (2C), 120.3, 121.4, 123.2, 125.1(2C), 126.0, 126.2, 127.1, 128.6, 132.8, 134.2, 138.7 (2C), 144.5, 167.6, 177.2 ppm; ESI-MS (*m/z*): 373.6 $[M+Na]^+$; Anal. Calcd for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99 Found: C, 68.59; H, 5.23; N, 8.04.

N-(4-chloro-2-hydroxyphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (24):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (151 mg, 95%). M. P.: 156 °C; IR ($CHCl_3$): ν 3546, 3362, 3020, 1672, 1601, 1562, 1541, 1421, 1278, 1128, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.02 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 8.18 (s, 1H), 8.35 (s, 2H), 9.34 (s, 1H), 12.40 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 115.5 118.6, 119.9, 123.8, 124.7 (2C), 125.8, 129.1 (2C), 131.1 (2C), 131.8, 134.2, 149.7, 165.1, 177.1 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_2O_2ClF_6S$ 443.0056, found 443.0050.

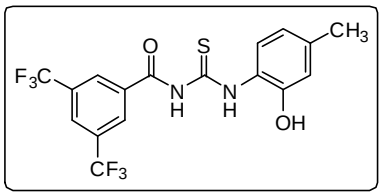
N-(2-hydroxy-4-nitrophenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (25):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (156 mg, 96%). M. P.: 187 °C; IR ($CHCl_3$): ν 3309, 3020, 1661, 1555, 1456, 1280, 1215, 1146, 756 cm^{-1}; ^1H NMR

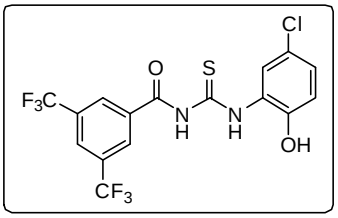
($CDCl_3$+DMSO-d_6, 200 MHz): δ 7.77 (dd, *J* = 2.55, 9.07 Hz, 1H), 7.86 (d, *J* = 2.5, Hz, 1H), 8.08 (s, 1H), 8.65 (s, 2H), 9.20 (d, *J* = 9.07 Hz, 1H), 10.91 (s, 1H), 12.09(s, 1H), 13.33 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6 , 50 MHz): δ 109.2 (s) 113.9(s), 120.70 (s), 125.6 (t, 2C), 129.1 (d, 2C), 130.7 (s), 131.4 (s), 132.2 (s, 2C), 133.8 (s), 144.0 (s), 148.3 (s), 165.0 (s), 177.4 (s) ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_3O_4F_6S$ 454.0291, found 454.0291.

N-(2-hydroxy-4-methylphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (26):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (139 mg, 91%). M. P.: 149 °C; IR ($CHCl_3$): ν 3588, 3362, 3020, 2926, 1685, 1604, 1560, 1542, 1457, 1351, 1279, 1215, 1141, 756, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.35 (s, 3H), 6.85 (dd, *J* = 1.1, 8.0 Hz, 1H), 6.89 (d, *J* = 1.1 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 8.37 (s, 2H), 9.41 (s, 1H), 12.34 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 20.2, 115.1, 118.4, 122.4, 122.5, 124.8 (2C), 128.6 (2C), 130.1, 130.7, 133.7, 135.8, 148.1, 164.4, 176.2 ppm; HRMS EI calcd for (M^+) $C_{17}H_{12}N_2O_2F_6S$ 422.0524, found 422.0521.

N-(5-chloro-2-hydroxyphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (27):

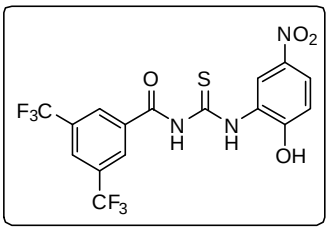


Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (149 mg, 94%). M. P.: 169 °C; IR ($CHCl_3$): ν 3362, 3020, 1734, 1674, 1542, 1496, 1278, 1185, 1139, 761, cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6, 400 MHz): δ 6.79 (d, *J* = 8.6 Hz, 1H), 6.88 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.91 (s, 1H), 8.46 (s, 2H), 8.66 (d, *J* = 2.4 Hz, 1H), 9.71 (s, 1H), 11.58 (s, 1H), 12.83 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 119.5, 121.1, 123.8, 124.5 (2C), 125.8, 127.2, 128.2 (2C), 128.5 (2C), 133.1, 133.5, 147.7, 164.8, 177.0 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_2O_2ClF_6S$ 443.0050, found 443.0053.

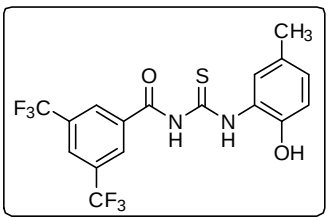
N-(2-hydroxy-5-nitrophenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (28):

Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (148 mg, 90%). M. P.: 132 °C; IR ($CHCl_3$): ν 3503, 3020, 2400,

1700, 1602, 1542, 1474, 1216, 770, 669 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 7.09 (d, *J* = 8.97 Hz, 1H), 8.00 (dd, *J* = 2.74, 8.97 Hz, 1H), 8.08 (s, 1H), 8.64 (s, 2H), 9.89 (d, *J* = 2.76 Hz, 1H), 11.25 (s, 1H), 11.92 (s, 1H), 13.14 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 114.38, 118.11, 122.10, 125.31, 125.8 (t, 2C), 126.11, 129.2 (d, 2C), 131.07, 131.75, 134.05, 139.13, 154.62, 165.26, 177.55 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_3O_4F_6S$ 454.0291, found 454.0290.

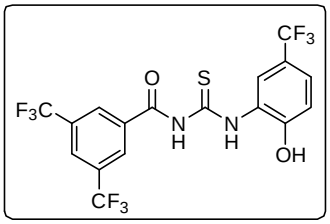


N-(2-hydroxy-5-methylphenylcarbamothioyl)-3,5-bis(trifluoromethyl)benzamide (29):



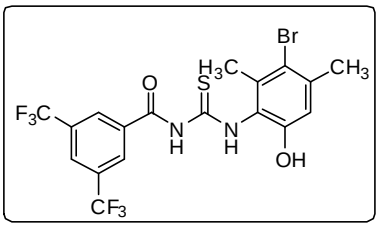
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (136 mg, 89%). M. P.: 149 °C; IR ($CHCl_3$): ν 3588, 3362, 3020, 2926, 1685, 1604, 1560, 1542, 1457, 1351, 1279, 1215, 1141, 756, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.32 (s, 3H), 6.19 (s, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 7.07 (dd, *J* = 1.7, 8.3 Hz, 1H), 7.36 (d, *J* = 1.7 Hz, 1H), 8.15 (s, 1H), 8.37 (s, 2H), 9.54 (s, 1H), 12.38 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.5, 119.2, 125.1, 125.2 (2C), 127.19 (2C), 128.0, 129.8 (2C), 131.3, 132.6, 133.3, 133.7, 147.0, 164.6, 176.9 ppm; HRMS EI calcd for (M^+) $C_{17}H_{12}N_2O_2F_6S$ 422.0524, found 422.0518.

N-(2-hydroxy-5-(trifluromethyl)phenylcarbamothioyl)-3,5-bis(trifluoromethyl) benzamide (30):



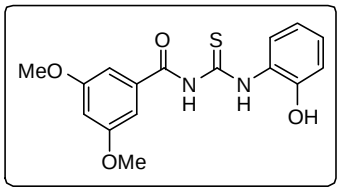
Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (158 mg, 92%). M. P.: 176 °C; IR ($CHCl_3$): ν 3402, 3021, 1682, 1615, 1514, 1332, 1280, 1216, 1149, 1084123, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.63 (br s, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.54 (dd, *J* = 2.1, 8.6 Hz, 1H), 8.10 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 8.38 (s, 2H), 9.41 (s, 1H), 12.54 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 113.2, 123.3, 123.7, 123.9 (2C), 124.0, 126.8, 127.2 (2), 127.5, 131.4 (2C), 134.1, 148.6, 165.9, 177.8 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{10}N_2O_2F_9S$ 477.0314, found 477.0314.

N-(3-bromo-6-hydroxy-2,4-dimethylphenylcarbamothioyl)-3,5bis(trifluoromethyl) benzamide (31): Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.4), The title compound was determined as yellow solid (172 mg, 93%). M. P.: 167 °C; IR ($CHCl_3$): ν 3403, 3020, 1686, 1580, 1542, 1523, 1458, 1379, 1280, 1216, 1188, 1148, 909, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.40 (s, 3H), 2.43 (s, 3H), 6.14 (br s, 1H), 6.88 (s, 1H), 8.17 (s, 1H), 8.40 (s, 2H), 9.68 (s, 1H), 11.99 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.4, 24.1, 118.5 (2C), 122.9, 127.2 (2C), 128.1 (2C), 132.7, 133.5, 134.5, 140.1, 149.5, 164.8, 178.8 ppm; HRMS ESI calcd for (MH^+) $C_{18}H_{14}N_2O_2{}^{81}BrF_6S$ 516.9838, found 516.9838, calcd for $[M+Na]^+$ $C_{18}H_{13}N_2O_2{}^{81}BrF_6SNa$ 538.9658, found 538.9657.



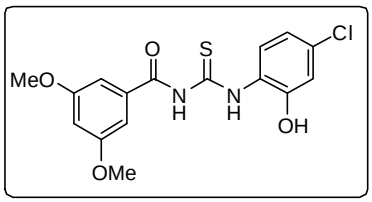
N-(2-hydroxyphenylcarbamothioyl)-3,5-dimethoxybenzamide (32):

Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (163 mg, 98%). M. P.: 156 °C; IR ($CHCl_3$): ν3422, 3020, 1651, 1589, 1553, 1523, 1461, 1361, 1218, 1205, 1138, 1051, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 6H), 6.71 (t, J = 2.3 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 7.04 (d, *J* = 1.2, 8.0 Hz, 1H), 7.10 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.31 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.47 (dd, *J* = 1.0, 8.0 Hz, 1H), 9.14 (s, 1H), 12.59 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.7 (2C), 105.4 (2C), 105.8, 119.7, 121.7, 125.0, 125.8, 128.9, 133.3, 149.5, 161.3 (2C), 167.2, 167.2, 177.4 ppm; HRMS ESI calcd for $[M+Na]^+$ $C_{16}H_{16}N_2O_4SNa$ 355.0728, found 355.0723.



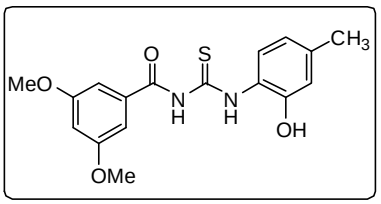
N-(4-chloro-2-hydroxyphenylcarbamothioyl)-3,5-dimethoxybenzamide (33):

Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (175 mg, 96%). M. P.: 170 °C; IR ($CHCl_3$): ν 3391, 3020, 1657, 1592, 1555, 1534, 1456, 1370, 1218, 1207, 1159, 1066, 770 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 3.86 (s, 6H), 6.68 (t, J = 2.3 Hz, 1H), 6.86 (dd, *J* = 2.3,8.7 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 2.3 Hz, 2H), 8.53 (d, *J* = 8.7 Hz, 1H), 9.64 (s, 1H), 12.84 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 55.4 (2C), 105.4 (2C),



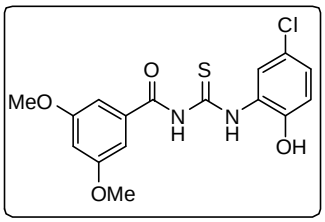
106.9, 115.5, 118.6, 123.7, 124.7, 131.0, 133.7, 149.6, 160.7 (2C), 166.6, 176.7 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_2O_4ClS$ 367.0519, found 367.0514, calcd for $[M+Na]^+C_{16}H_{15}N_2O_4ClSNa$ 389.0333, found 389.0333.

N-(2-hydroxy-4-methylphenylcarbamothioyl)-3,5-dimethoxybenzamide (34):



Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (163 mg, 95%). M. P.: 155 °C; IR ($CHCl_3$): ν 3422, 3020, 1670, 1603, 1542, 1524, 1498, 1371, 1216, 1161, 1065, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34 (s, 3H), 3.85 (s, 6H), 6.70 (t, *J* = 2.3 Hz, 1H), 6.83 (dd, *J* = 1.3, 8.0 Hz, 1H), 6.91 (d, *J* = 1.3 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 1H), 9.13 (s, 1H), 12.49 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.0, 55.6 (2C), 105.3 (2C), 105.4, 117.4, 120.3, 123.2, 123.6, 133.8, 137.7, 149.0, 160.9 (2C), 166.7, 176.7 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_2O_4S$ 347.1060, found 347.1060, calcd for $[M+Na]^+$ $C_{17}H_{18}N_2O_4SNa$ 369.0880, found 369.0879.

N-(5-chloro-2-hydroxyphenylcarbamothioyl)-3,5-dimethoxybenzamide (35):

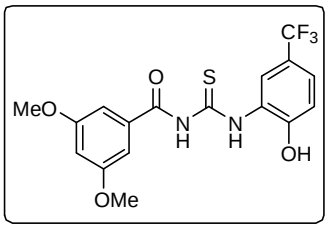


Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (174 mg, 95%). M. P.: 196 °C; IR ($CHCl_3$): ν 3407, 3020, 1661, 1598, 1561, 1526, 1496, 1371, 1215, 1159, 1065, 757 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 3.86 (s, 6H), 6.68 (t, *J* = 2.3 Hz, 1H) 6.94 (d, *J* = 8.7 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 2H), 7.07 (d, *J* = 2.3 Hz,1H), 8.70 (d, *J* = 2.3 Hz, 1H), 9.48 (s, 1H), 12.90 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ 55.4 (2C), 105.3, 105.5 (2C), 115.9, 122.1, 125.7, 126.9, 133.6, 147.3, 160.6 (2C), 166.7, 176.7 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_2O_4ClS$ 367.0519, found 367.0514, calcd for $[M+Na]^+$ $C_{16}H_{15}N_2O_4ClSNa$ 389.0334, found 389.0333.

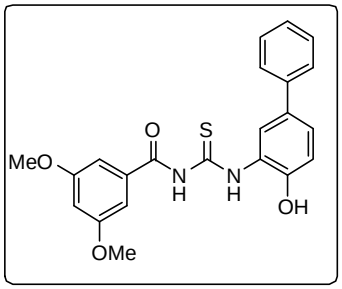
N-(2-hydroxy-5-(trifluromethyl)phenylcarbamothioyl)-3,5-dimethoxybenzamide (36):

Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (192 mg, 96%). M. P.: 173 °C; IR ($CHCl_3$): ν 3412, 3394, 3019,

2840, 1675, 1595, 1556, 1514, 1358, 1306, 1207, 1159, 1065, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 6H), 6.70 (t, *J* = 2.3, 1H), 7.0 (d, *J* = 2.2 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.36 (d, *J* = 1.9 Hz, 1H), 9.23 (s, 1H), 12.80 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5 (2C), 105.2, 105.4 (2C), 115.4, 120.1, 123.5, 123.6, 126.2, 133.7, 151.6, 160.9 (2C), 166.6, 176.9 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{16}N_2O_4F_3S$ 401.0777, found 401.0777, calcd for $[M+Na]^+C_{17}H_{15}N_2O_4F_3SNa$ 423.0597, found 423.0597.



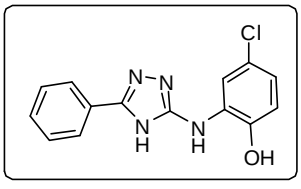
N-((4-hydroxy-[1,1'-biphenyl]-3-yl)carbamothioyl)-3,5-dimethoxybenzamide (37): Isolated by column chromatography (pet.ether/ethyl acetate = 9:1, R_f = 0.3), The title compound was determined as yellow solid (183 mg, 92%). M. P.: 171 °C; IR ($CHCl_3$): ν 3412, 3394, 3019, 2840, 1675, 1595, 1556, 1514, 1358, 1306, 1207, 1159, 1065, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 6H), 6.71 (t, J = 2.3 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.32-7.58 (m, 6H), 7.73 (d, *J* = 2.1 Hz, 1H), 9.18 (s, 1H), 12.69 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.7 (2C), 105.4 (2C), 105.8, 120.0, 123.5, 126.0, 126.8, 127.1, 127.5 (2C), 128.8 (2C), 133.3, 134.8, 148.9, 161.3 (2C), 167.3, 177.4 ppm; HRMS ESI calcd for (MH^+) $C_{22}H_{21}N_2O_4S$ 409.1216, found 409.1217, calcd for $[M+Na]^+$ $C_{22}H_{20}N_2O_4SNa$ 431.1036, found 431.1036.



1.3.2 General Procedure II: preparation of 1,2,4-Triazole derivatives (2)

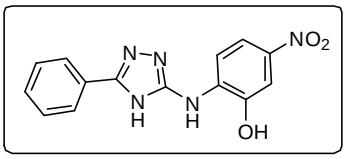
To a solution of thiourea (150 mg, 0.49 mmol) in 1, 4-dioxane (20 mL), hydrazine hydrate (1.96 mmol) was added dropwise and the reaction mixture was heated at 70°C for 0.5 h. Solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography with Pet. Ether/EtOAc (1:1) as eluent to give 1,2,4-triazole.

4-chloro-2-((5-phenyl-4H-1,2,4-triazol-3-yl)amino)phenol (38): Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (129 mg, 92%). M. P.: 218–219 °C; IR (Neat): ν 3384, 3191, 3073, 1639, 1571,



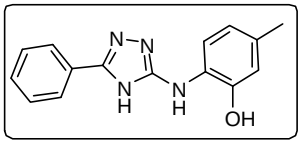
1434, 1275, 1198, 1131, 914 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 6.45–6.70 (m, 3H), 6.84 (d, *J* = 2.3 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 2H), 7.49 (s, 1H), 7.76 (dd, *J* = 1.8, 7.7 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 8.41 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 115.0, 115.7, 119.8, 123.7, 125.9 (2C), 128.6 (2C), 129.4, 130.6, 143.3, 153.1, 157.3 ppm; HRMS ESI calcd for (MH^+) $C_{14}H_{12}N_4OCl$ 287.0694, found 287.0694.

5-nitro-2-((5-phenyl-4H-1,2,4-triazol-3-yl)amino)phenol (39):



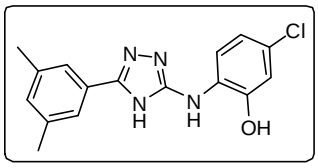
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (134 mg, 96%). M. P.: 252–254 °C; IR (Neat): ν 3402, 3098, 1639, 1607, 1571, 1434, 1275, 1198, 1131, 914 cm^{-1}; ^1H NMR ($CDCl_3$ +DMSO-d_6, 200 MHz): δ 7.42–7.53 (m, 3H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.79 (dd, *J* = 2.3, 9.0 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 108.5, 109.1, 111.4, 116.7, 117.9, 125.9 (2C), 128.2, 128.5 (2C), 139.5, 143.9, 153.3, 157.9 ppm; HRMS ESI calcd for (MH^+) $C_{14}H_{12}N_5O_3$ 298.0935, found 298.0933.

5-methyl-2-((5-phenyl-4H-1,2,4-triazol-3-yl)amino)phenol (40):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (123 mg, 89%). M. P.: 230–231°C; IR (Neat): ν 3401, 3207, 3072, 1639, 1607, 1556, 1434, 1275, 1192, 1131, 914 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.29 (s, 3H), 6.62 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.38–7.47 (m, 3H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.72 (s, 1H), 8.0-8.05 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 20.9, 114.7, 117.5, 121.1, 125.9, (2C), 128.4 (2C), 128.7, 129.0, 129.1, 142.6, 156.1, 157.3 ppm; HRMS ESI calcd for (MH^+) $C_{15}H_{15}N_4O$ 267.1240, found 267.1240.

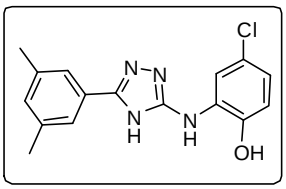
5-chloro-2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (41):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (148 mg, 96%). M. P.: 257 °C; IR (Neat): ν 3390, 3253, 3013, 1607, 1571, 1419, 1107, 831 cm^{-1}; ^1H NMR ($CDCl_3$+DMS-d_6, 200 MHz): δ 2.36

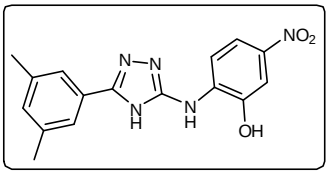
(s, 6H), 6.73 (br s,1H), 6.81 (dd, *J* = 2.3, 8.7 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 7.04 (s, 1H), 7.62 (s, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 8.68 (s, 1H), 10.02 (s,1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ21.0 (2C), 115.4, 116.1, 117.6, 119.4, 123.7 (2C), 126.3, 128.2 , 131.0, 138.0 (2C), 145.8, 159.9, 161.9 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_4OCl$ 315.1007, found 315.1007.

4-chloro-2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (42):



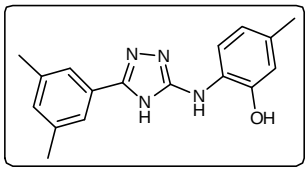
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (143 mg, 93%). M. P.: 254 °C; IR (Neat): ν 3408, 3248, 2993, 1601, 1567, 1377, 1152, 789 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMS-d_6, 200 MHz): δ 2.36 (s, 6H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.80 (dd, *J* = 1.6, 8.6 Hz, 1H), 7.04 (s, 1H), 7.60 (s, 2H), 7.74 (s, 1H), 8.11 (d, *J* = 1.6 Hz, 1H). 8.46 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6,125 MHz): δ21.1 (2C), 115.3, 116.3, 117.8, 119.8, 121.4, 123.8 (2C), 124.0, 127.7, 131.3, 138.1 (2C), 143.6, 157.4, 159.9 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_4OCl$ 315.1008, found 315.1007.

2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)-5-nitrophenol (43):



The Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (91mg, 97%). M. P.: 126 °C; IR (Neat): ν 3398, 3319, 2986, 2503, 1563, 1524, 1462, 1376, 1332, 1084, 903 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMS-d_6, 200 MHz): δ 2.39 (s, 6H), 7.08 (s, 1H), 7.14 (s, 1H), 7.48 (s, 1H), 7.65 (s, 2H), 7.75 (d, *J* = 2.7 Hz, 1H), 7.84 (dd, *J* = 2.7, 8.9 Hz, 1H), 8.38 (d, *J* = 8.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ21.0 (2C), 108.6, 113.6, 116.9, 123.8 (2C), 125.3, 131.3, 132.4, 132.9, 138.1 (2C), 143.9, 158.2, 160.2 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_5O_3$326.1248, found 326.1248.

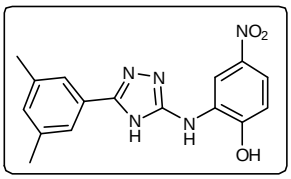
2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)-5-methylphenol (44):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (88 mg, 94%). M. P.: 202 °C; IR (Neat): ν 3412, 3302, 1655, 1551, 1459,

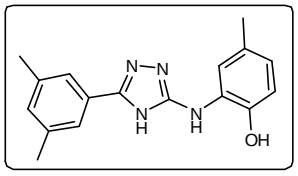
1361, 1214, 1105 cm^{-1}; ^1H NMR ($CDCl_3$+DMS-d_6, 200 MHz): δ 2.27 (s, 3H), 2.36 (s, 6H), 6.67 (dd, *J* = 1.3, 8.0 Hz, 1H), 6.78 (d, *J* = 1.3 Hz, 1H), 7.04 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 2H), 10.71 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ21.1 (2C), 20.6, 109.1, 115.2, 116.7, 117.7, 120.3, 123.8 (2C), 126.7, 130.9, 137.9 (2C), 145.3, 156.4, 157.6 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_4O$ 295.1553, found 295.1553.

2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)-4-nitrophenol (45):



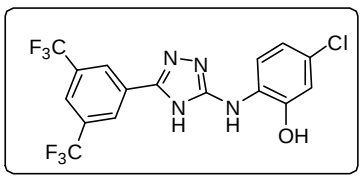
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (89 mg, 95%). M. P.: 261°C; IR (Neat): ν 3368, 3291, 2996, 2526, 1637, 1560, 1520, 1459, 1377, 1350, 1105, 813 cm^{-1}; ^1H NMR ($CDCl_3$+DMS-d_6, 200 MHz): δ 2.37 (s, 6H), 6.92 (d, *J* = 8.8 Hz, 1H), 7.06 (s, 1H), 7.60 (s, 2H), 7.70 (dd, *J* = 2.7, 8.8 Hz, 1H), 9.21 (d, *J* = 2.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz) : δ20.9 (2C), 112.8, 116.2, 123.6 (2C), 124.5, 128.4, 130.2, 134.0, 138.0(2C), 140.4, 150.5, 159.7, 161.4 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_5O_3$ 326.1248, found 326.1248, calcd for $[M+Na]^+C_{16}H_{15}N_5O_3Na$ 348.1064, found 348.1067.

2-((5-(3,5-dimethylphenyl)-4H-1,2,4-triazol-3-yl)amino)-4-methylphenol (46):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (86 mg, 92%). M. P.: 161°C; IR (Neat): ν 3409, 3308, 2998, 1659, 1565, 1462, 1218, 1101 cm^{-1}; ^1H NMR ($CDCl_3$ +DMS-d_6, 200 MHz): δ 2.28 (s, 3H), 2.35 (s, 6H), 6.62 (dd, *J* = 1.3, 8.0 Hz, 1H), 8.81 (d, *J* = 8.0 Hz, 1H), 7.03 (s, 1H), 7.41 (s, 1H), 7.63 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ20.8, 21.1 (2C), 115.9, 118.3, 121.8, 123.8 (2C), 124.7, 129.1, 131.0, 133.0, 138.0 (2C), 143.1, 156.1, 160.1 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_4O$ 295.1553, found 295.1553.

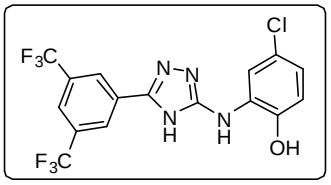
2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-5-chlorophenol (47):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.4), The title compound was determined as yellow solid (128 mg, 89%). M. P.: 124 °C; IR (Neat): ν 3421, 3215, 3021, 1645,

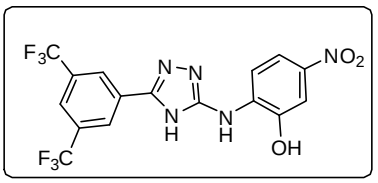
1613, 1572, 1434, 1275, 1189, 1129, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ6.82 (dd, *J* = 2.3, 8.5 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.97 (s, 1H), 8.48 (s, 2H), 8.51 (s, 1H), 8.86 (s, 1H) ppm;^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 116.7, 119.2, 124.2 (2C), 124.9, 125.5, 126.1, 127.7 (2C), 130.8, 131.5 (2C), 134.8, 150.8, 162.3, 164.1 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_4OClF_6$ 423.0446, found 423.0442.

2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-4-chlorophenol (48):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.4), The title compound was determined as yellow solid (125 mg, 87%). M. P.: 126–127 °C; IR (Neat): ν 3421, 3121, 3021, 1645, 1614, 1571, 1451, 1273, 1189, 1131, 915 cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 6.82 (dd, *J* = 1.9, 8.5 Hz, 1H), 7.0 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 7.84 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 2H), 10.02 (s, 1H) ppm;^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ 117.9, 120.2, 120.3, 123.5, 124.8 (2C), 126.1, 127.5, 128.6 (2C), 131.0, 131.6 (2C), 136.0, 162.2, 162.7 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_4OClF_6$ 423.0442, found 423.0444.

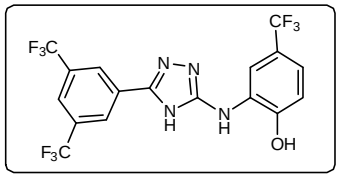
2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-5-nitrophenol (49):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.4), The title compound was determined as yellow solid (131 mg, 91%). M. P.: 121°C; IR (Neat): ν 3409, 3290, 3020,1621, 1586, 1557, 1497, 1322, 1278, 1122, 901, 811cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 7.79 (d, *J* = 2.5, Hz, 1H), 7.88 (s, 1H), 7.95 (dd, *J* = 2.5, 9.0 Hz, 1H), 8.49 (d, *J* = 9.0 Hz, 1H), 8.59 (s, 2H), 8.80 (s, 1H), 10.12 (s, 1H), 10.36 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6 , 50 MHz): δ 113.4, 116.8, 124.3, 125.9 (2C), 127.7, 128.2 (2C), 131.1, 131.4 (2C), 134.8, 135.2, 150.2, 161.0, 164.3 ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{10}N_5O_3F_6$ 434.0682, found 434.0682, calcd for $[M+Na]^+$ $C_{16}H_9N_5O_3F_6Na$ 456.0501, found 456.0502.

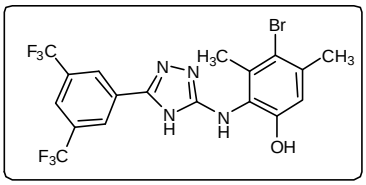
2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-4-(trifluoromethyl)phenol (50): Isolated by column chromatography (pet.ether/ethyl acetate =

1:1, R_f = 0.4), The title compound was determined as yellow solid (83mg, 87%). M. P.: 116 °C; IR (Neat): ν 3404, 3321, 3019, 1615, 1514, 1280, 1216, 1149, 1084, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.44 (br s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 1.4, 8.4 Hz, 1H), 7.31 (d, *J* = 1.4 Hz, 1H), 8.46 (s, 2H), 8.57 (s, 1H), 10.02 (s, 1H), 11.59 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz): δ108.4, 114.2, 120.1, 124.3 (3C), 125.8 (2C), 127.7 (2C), 131.0, 134.7 , 147.4 , 150.1, 164.5 , 170.8 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{10}N_4OF_9$ 457.0707, found 457.0705, calcd for $[M+Na]^+$ $C_{17}H_9N_4OF_9Na$ 479.0521, found 479.0525.



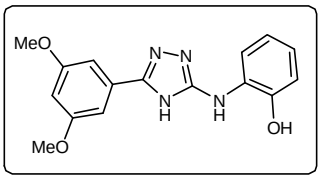
2-((5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazol-3-yl)amino)-4-bromo-3,5-dimethylphenol (51):

Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.4), The title compound was determined as yellow solid (88 mg, 91%). M. P.: 114 °C; IR (Neat): ν3403, 3298, 3020, 1686, 1580, 1542, 1458, 1379, 1280, 1216, 1188,909, 660cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.46 (s, 3H), 2.51 (s, 3H), 6.23 (br s, 1H), 6.05 (s, 1H), 8.05 (s, 1H), 8.26 (s, 2H), 8.41 (s, 1H), 9.34 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.4, 24.1, 118.5, 119.3, 122.9, 127.2 (2C), 128.1 (2C), 132.7, 133.5, 134.5, 140.1, 149.5, 164.8, 178.8 ppm; HRMS ESI calcd for (MH^+) $C_{18}H_{13}N_4OBrF_6$ 495.0251, found 495.0250, calcd for $[M+Na]^+$ $C_{18}H_{13}N_4OBrF_6Na$ 517.0073, found 517.0069.



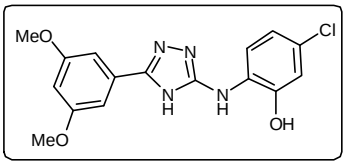
2-((5-(3,5-dimethoxyphenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (52):

Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (92 mg, 98%). M. P.: 184 °C; IR (Neat): ν 3411, 3301, 3026, 1676, 1589, 1554, 1522, 1463, 1361, 1218, 1138, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.84 (s, 6H), 6.71 (t, J = 2.2 Hz, 1H), 6.58 (br s, 1H), 6.81- 6.88 (m, 2H), 6.92 (dd, *J* = 1.8, 7.4 Hz, 1H), 7.22 (d, *J* = 2.2 Hz, 2H), 7.75 (s, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 10.89 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.2 (2C), 101.7, 103.8 (2C), 105.5, 108.6, 115.9, 117.6, 119.9, 120.7, 121.4, 129.0, 145.3, 160.6 (2C) ppm; HRMS ESI calcd for (MH^+)



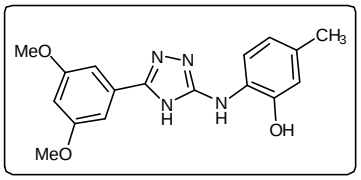
$C_{16}H_{17}N_4O_3$ 313.1295, found 313.1295, calcd for $[M+Na]^+C_{16}H_{16}N_4O_3Na$ 335.1109, found 335.1115.

5-chloro-2-((5-(3,5-dimethoxyphenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (53):



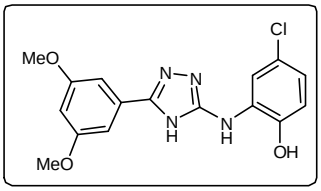
Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (91mg, 96%). M. P.: 224 °C; IR (Neat): ν3391, 3305, 3023, 1659,1555, 1534, 1456, 1370, 1207, 1159, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.85 (s, 6H), 6.19 (br s, 1H), 6.51 (t, J = 2.3 Hz, 1H), 6.83 (dd, *J* = 2.3,8.5 Hz, 1H), 6.90 (d, *J* = 2.3 Hz, 1H), 7.21 (d, *J* = 2.3 Hz, 2H), 7.65 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ 55.2 (2C), 101.7, 103.8 (2C), 109.2, 115.2, 116.1, 117.3, 119.4,123.7, 124.8, 128.1, 145.6, 160.7 (2C) ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_4O_3Cl$ 347.0905, found 347.0905, calcd for $[M+Na]^+$ $C_{16}H_{15}N_4O_3ClNa$ 369.0718, found 369.0725.

2-((5-(3,5-dimethoxyphenyl)-4H-1,2,4-triazol-3-yl)amino)-5-methylphenol (54):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (92 mg, 96%). M. P.: 181°C; IR (Neat): ν 3422, 3302, 3020, 1603, 1542, 1524, 1498, 1216, 1161, 1065, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 2.25 (s, 3H), 3.83 (s, 6H), 6.49 (t, *J* = 2.2 Hz, 1H), 6.66 (dd, *J* = 1.3, 8.0 Hz, 1H), 6.77 (d, *J* = 1.3 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 9.14 (s, 1H), 12.49 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.57, 55.2 (2C), 101.7, 103.8 (2C), 109.1, 115.3, 116.9, 117.9, 120.3, 124.3, 126.4, 131.4, 145.4, 160.7 (2C) ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{19}N_4O_3$ 327.1452, found 327.1452, calcd for $[M+Na]^+C_{17}H_{18}N_4O_3Na$ 349.1269, found 349.1271.

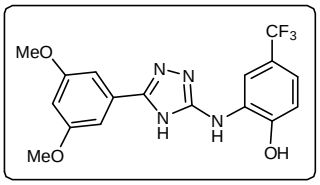
4-chloro-2-((5-(3,5-dimethoxyphenyl)-4H-1,2,4-triazol-3-yl)amino)phenol (55):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (90mg, 95%). M. P.: 227°C; IR (Neat): ν 3407, 3316, 3016, 1665,1561,1496, 1371, 1215, 1159, 1065, 757 cm^{-1}; ^1H NMR

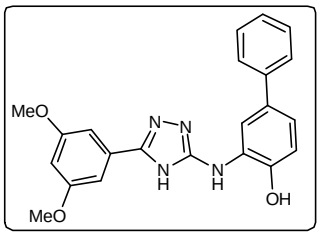
($CDCl_3$+DMSO-d_6, 200 MHz): δ 3.86 (s, 6H), 6.51 (t, *J* = 2.3 Hz, 1H) 6.70 (dd, *J* = 2.3, 8.7 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 1.8 Hz,1H), 8.20 (d, *J* = 2.3 Hz, 1H), 9.53 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$+DMS-d_6, 50 MHz): δ 55.2 (2C), 101.7, 103.8 (2C), 109.5, 115.0, 115.7, 119.3, 124.0, 130.4, 132.5, 143.1, 154.4, 160.7 (2C) ppm; HRMS ESI calcd for (MH^+) $C_{16}H_{16}N_4O_3Cl$ 347.0906, found 347.0905, calcd for $[M+Na]^+C_{16}H_{15}N_4O_3ClNa$ 369.0721, found 369.0725.

N-(2-hydroxy-5-(trifluromethyl)phenylcarbamothioyl)-3,5-dimethoxybenzamide (56):



Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (91 mg, 95%). M. P.: 251°C; IR (Neat): ν 3412, 3387, 3019, 2840, 1675, 1557, 1514, 1358, 1306, 1207, 1159, 1065, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 6H), 6.70 (t, *J* = 2.3, 1H), 7.0 (d, *J* = 2.2 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.36 (d, *J* = 1.9 Hz, 1H), 9.23 (s, 1H), 12.79 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5 (2C), 105.2, 105.4 (2C), 115.4, 120.0, 120.1, 123.5, 123.6, 126.2, 133.7, 151.6, 160.9 (2C), 166.6, 176.9 ppm; HRMS ESI calcd for (MH^+) $C_{17}H_{16}N_4O_3F_3$ 381.1169, found 381.1169.

N-((4-hydroxy-[1,1'-biphenyl]-3-yl)carbamothioyl)-3,5-dimethoxybenzamide (57):

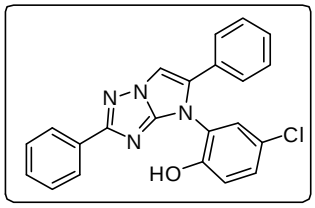


Isolated by column chromatography (pet.ether/ethyl acetate = 1:1, R_f = 0.3), The title compound was determined as yellow solid (90 mg, 94%). M. P.: 187°C; IR (Neat): ν 3412, 3391, 3032, 1698, 1559, 1514, 1467, 1304, 1220, 1159, 1065, 879, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.86 (s, 6H), 6.71 (t, J = 2.3 Hz, 1H), 6.94 (d, *J* = 2.2 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.32-7.58 (m, 6H), 7.73 (d, *J* = 2.1 Hz, 1H), 9.8 (s, 1H), 12.69 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.7 (2C), 105.4 (2C), 105.8, 120.0, 123.5, 126.0, 126.8, 127.1, 127.5, 128.8 (2C), 133.3, 134.8, 148.9, 161.3 (2C), 167.3, 177.4 ppm; HRMS ESI calcd for (MH^+) $C_{22}H_{21}N_4O_3$ 389.1608, found 389.1608, calcd for $[M+Na]^+$ $C_{22}H_{20}N_4O_3Na$ 411.1425, found 411.1428.

1.3.3 General Procedure III: preparation of Imidazo-[1,2,4]-Triazole derivatives (3)

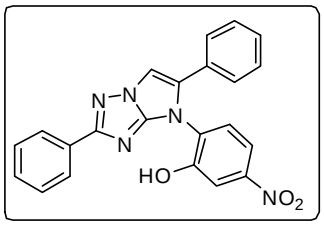
To a solution of 1,2,4-triazole (100 mg, 0.35 mmol) in THF (5 mL) containing triethylamine (0.8 mmol) and then a solution 2-bromoacetophenone (0.128 g, 1 mmol) in THF (2 mL) was added by slow addition. The reaction mixture was stirred at rt for 6 h. After completion of the reaction, solvent was evaporated and admixed with ethyl acetate (20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a silica gel column (20% EtOAc/Pet.Ether) as eluent to give Imidazo-[1,2,4]-triazole.

4-chloro-2-(2,5-diphenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)phenol (58):



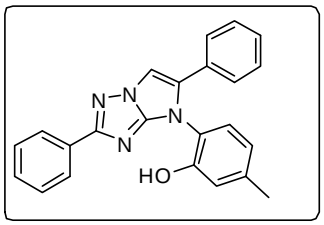
Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (48 mg, 36%). M. P.: 153–154°C; IR (Neat): ν 3408, 3248, 2993, 1608, 1567, 1477, 1162, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.19 (t, J = 2.9 Hz, 3H), 7.23–7.27 (m, 4H), 7.39–7.43 (m, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 118.9, 120.7, 122.5, 127.2 (2C), 127.5 (2C), 127.9, 128.2, 128.6 (2C), 128.9 (2C), 129.3, 130.9, 131.9, 132.8, 133.1, 137.3, 147.0, 147.8, 159.8 ppm; ESI MS calcd for (MH^+) $C_{22}H_{15}N_4OCl$ 387.1013, found 387.10.

2-(2,5-diphenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)-5-nitrophenol (59):



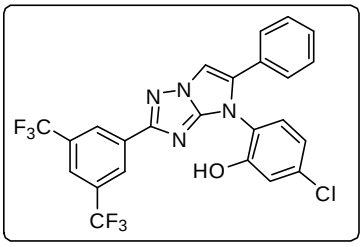
Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (47 mg, 45%). M. P.: 195-196°C; IR (Neat): ν 3403, 3290, 3020, 1621, 1497, 1278, 1152, 901, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.18-7.21 (m, 3H), 7.23–7.27 (m, 4H), 7.39-7.41 (m, 1H), 7.54 (t, J = 7.5 Hz, 2H), 7.62-7.65 (m, 1H), 7.70 (d, J = 1.4 Hz, 1H), 7.72 (d, J = 1.4 Hz, 1H), 7.75 (s, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 114.7, 117.8, 125.7, 126.7, 128.8 (2C), 128.9 (2C), 129.2, 129.4 (2C), 129.5 (2C), 131.7, 133.9, 134.1, 134.7, 138.1, 146.3, 147.0, 147.4, 158.8 ppm; ESI MS calcd for (MH^+) $C_{22}H_{16}N_5O_3$ 398.1253, found 398.11.

2-(2,5-diphenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)-5-methylphenol (60):



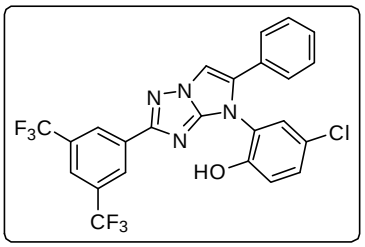
Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (50 mg, 39%). M. P.: 147–148°C; IR (Neat): ν 3248, 2993, 1605, 1517, 1377, 1152 cm^{-1}; ^1H NMR (Acetone-d_6, 200 MHz): δ 2.29 (s, 3H), 6.77 (dd, *J* = 1.9, 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.28–7.59 (m, 8H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.76 (s, 1H), 7.90 (t, *J* = 1.6 Hz, 1H), 7.94 (t, *J* = 1.6 Hz, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 21.2, 116.3, 123.7, 124.2, 126.7 (2C), 127.0 (2C), 128.6, 128.9, 129.3 (2C), 129.4 (2C), 131.7, 133.9, 134.1, 134.7, 138.1, 139.7, 147.0, 147.4, 158.8 ppm; HRMS ESI calcd for (MH^+) $C_{23}H_{19}N_4O$ 367.1553, found 367.1548.

2-(2-(3,5-bis(trifluoromethyl)phenyl)-5-phenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)-5-chlorophenol (61):



Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (47 mg, 38%). M. P.: 115–116°C; IR (Neat): ν 3405, 3192, 3082, 1612, 1576, 1438, 1275, 1198, 914 cm^{-1}; ^1H NMR (Acetone-d_6, 200 MHz): δ 6.91 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 2.3, 4.7 Hz, 1H), 7.28–7.47 (m, 3H), 7.80 (s, 1H), 7.90–7.95 (m, 2H), 8.01 (s, 1H), 8.16 (d, *J* = 8.5, 2.0 Hz, 1H), 8.24 (s, 2H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 119.1 (2C), 120.3, 120.6, 122.3 (2C), 126.0 (3C), 126.6, 126.7, 128.8 (3C), 129.3, 129.4, 129.7, 131.2, 134.8, 148.0, 148.3, 159.8 ppm; ESI MS calcd for (MH^+) $C_{24}H_{14}N_4OClF_6$ 523.0760, found 532.1, calcd for $[M+Na]^+$ $C_{24}H_{13}N_4OClF_6Na$ 545.0580, found 545.0.

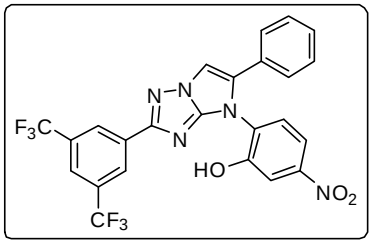
2-(2-(3,5-bis(trifluoromethyl)phenyl)-5-phenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)-4-chlorophenol (62):



Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (49 mg, 40%). M. P.: 118–119°C; IR (Neat): 3405, 3184, 3091, 1623, 1576, 1452, 1275, 1182, 875 cm^{-1}; ^1H NMR (Acetone-d_6, 200 MHz): δ 6.91 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 0.7 Hz, 1H), 7.33–

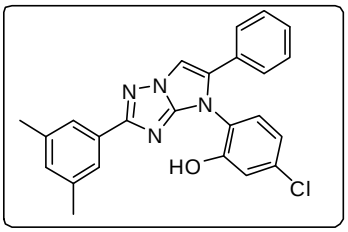
7.49 (m, 3H), 7.78 (s, 1H), 7.93–7.98 (m, 2H), 8.07 (s, 1H), 8.37 (s, 2H), 8.47 (dd, *J* = 0.7, 2.0 Hz, 1H), 9.04 (br s, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 117.2, 119.1, 122.4, 123.1, 124.9 (2C), 126.6 (3C), 127.8, 128.6, 129.5 (3C), 130.3, 131.5 (2C), 133.0, 135.5, 145.3, 146.1, 158.2 ppm; ESI MS calcd for $[M+Na]^+$ $C_{24}H_{13}N_4OClF_6Na$ 545.0580, found 545.07.

2-(2-(3,5-bis(trifluoromethyl)phenyl)-5-phenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)-5-nitrophenol (63): Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (44 mg, 36%). M. P.: 128–129°C; IR (Neat): ν 3406, 3237, 2993, 1609, 1567, 1377, 1162, 915 cm^{-1}; ^{1}H NMR (Acetone-d_6, 200 MHz): δ 7.23 (d, *J* = 1.7 Hz, 1H), 7.23 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.63–7.71 (m, 3H), 7.76 (s, 1H), 7.99 (s, 1H), 8.19 (d, *J* = 1.5 Hz, 1H), 8.22-8.24 (m, 2H), 8.30 (s, 2H), 8.58 (br s, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 116.6, 120.3, 120.6, 122.4, 123.3, 124.9 (2C), 126.6, (3C), 127.3, 129.4 (3C), 130.9 (2C), 131.8, 132.0, 136.6, 147.3, 148.0, 149.3, 159.6 ppm; ESI MS calcd for $[M+Na]^+$ $C_{24}H_{13}N_5O_3F_6Na$ 556.0820, found 556.09.

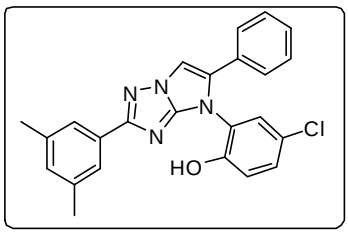


5-chloro-2-(2-(3,5-dimethylphenyl)-5-phenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)phenol (64):

Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title compound was determined as yellow solid (46 mg, 35%). M. P.: 142–143°C; IR (Neat): ν 3396, 3241, 3028, 1607, 1571, 1459, 1180, 828 cm^{-1}; ^{1}H NMR (Acetone-d_6, 200 MHz): δ 2.42 (s, 6H), 7.09 (dd, *J* = 2.3, 8.6 Hz, 1H), 7.27 (s, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.59–7.68 (m, 3H), 7.75 (s, 2H), 7.80 (s, 1H), 8.11–8.16 (m, 2H), 8.49 (d, *J* = 8.6 Hz, 1H), 9.52 (s, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): δ 21.2, 21.3, 117.6, 120.4, 122.2, 124.7, 127.4 (2C), 127.8, 128.7 (2C), 129.0, 129.7, 131.0, 134.7 (2C), 136.3, 138.6, 139.1 (2C), 148.0, 150.1, 160.7 ppm; HRMS ESI calcd for (MH^+) $C_{24}H_{20}N_4OCl$ 415.1320, found 415.1312.



4-chloro-2-(2-(3,5-dimethylphenyl)-5-phenyl-4H-imidazo[1,2-b][1,2,4]triazol-4-yl)phenol (65): Isolated by column chromatography (pet.ether/ethyl acetate = 7:3, R_f = 0.4), The title



compound was determined as yellow solid (43 mg, 32%). M. P.: 148–149°C; IR (Neat): ν 3408, 3394, 3249, 3027, 1614, 1557, 1457, 1167, 811 cm^{-1}; ^{1}H NMR (Acetone-d_6, 200 MHz): δ 2.42 (s, 6H), 7.10 (dd, *J* = 2.6, 8.6 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.29 (s, 1H), 7.58-7.71 (m, 3H), 7.76 (s, 2H), 7.81 (s, 1H), 8.08-8.13 (m, 2H), 8.60 (d, *J* = 8.6 Hz, 1H), 9.63 (s, 1H) ppm; ^{13}C NMR (Acetone-d_6, 50 MHz): 21.2, 21.3, 118.0, 119.6, 122.9, 25.9, 126.3, 126.8 (2C), 127.4, 128.7, 129.7 (2C), 130.2, 131.0, 132.1, 134.6 (2C), 139.1 (2C), 144.7, 146.0, 158.4 ppm; HRMS ESI calcd for (MH^+) $C_{24}H_{20}N_4OCl$ 415.1320, found 415.1313.

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2.1 Introduction

The art of organic synthesis encompasses an enormous range of activities in which the synthesis of molecules with desired properties has its own unique features and challenges. The crown ethers are one of the simple and classical symmetric molecules that led to a huge breakthrough that changed the course of the scientific world. Though the discovery of crown ethers was serendipitous, however, their initial isolation was due to the meticulous experimental skills of Charles Pedersen at DuPont, who isolated the first crown ether as a 0.4 percent impurity. Subsequent contributions from the Cram and Lehn groups have added more sophistication to the concept of crown ethers that subsequently led to the evolution of supramolecular chemistry. Supramolecular chemistry deals with the non-covalent molecular association due to the weaker and reversible attractive forces such as intermolecular forces, electrostatic or hydrogen bonding. Subsequently, the study of non-covalent interactions has become an important component even in understanding many biological processes from cell structure to vision that rely on these forces for structure and function. Biological systems are often the inspiration for supramolecular research.

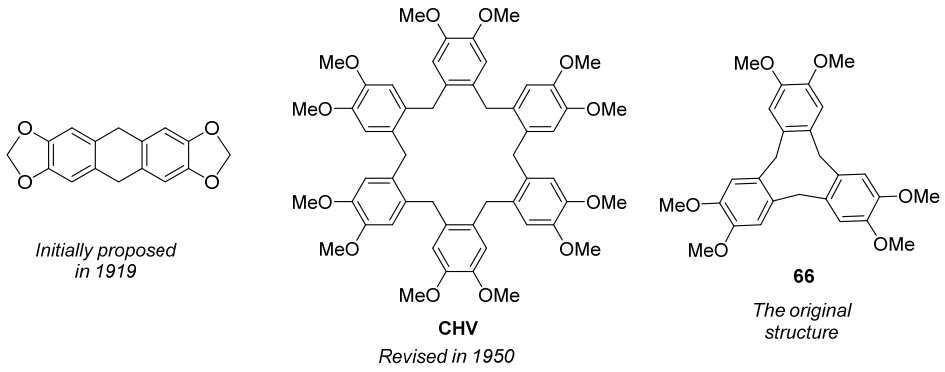
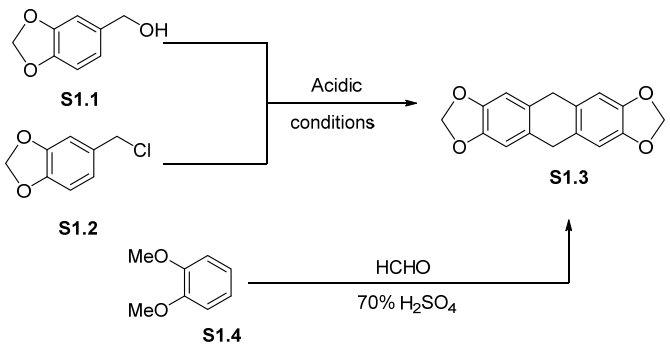


Figure 1. Proposed dimeric and hexameric structures of CTV along with the original trimeric structure **66**

Another important class of molecules needs a mention in this context is that of are cyclotriveratrylenes (CTV). The story of the CTV **66** is exactly opposite to that of the crown ethers. Despite the fact that it has been made almost a century back especially as the major component of several different approaches, almost for the first four decades, its potential could not be realized because of the wrongly assigned constitution/structure.

Arthur Ewins was the first one to synthesize CTV. In 1909,[1] Ewins documented that the reaction of homopiperonyl alcohol **S1.1** or its chloride **S1.2** under a variety of acidic conditions led a crystalline compound that he thought was a 2,3,6,7-tetramethylene-9,10-dihydroanthracene **S1.3** structure (Scheme 1). In 1915,[2] Gertrude Robinson reported that when homoveratryl alcohol **S1.2** was condensed in the presence of sulfuric acid in glacial acetic acid mixture, the same dimeric (2,3,6,7-tetramethoxy-9,10-dihydroanthracene) was obtained. It has also been revealed that an identical product could be obtained also by the acid-catalyzed condensation of veratrole (1,2-dimethoxy benzene) **S1.4** with formaldehyde (Scheme1).



Scheme 1: Synthesis of 2,3,6,7-tetramethylene-9,10-dihydroanthracene

The Ewin and Robinson publications were broadly accepted until 1950. In 1950, Italian chemists[3] proposed that the condensation product between veratrole and formaldehyde under acidic conditions was a cyclic hexamer (CHV) containing six units of veratrole (Figure 1).[4-6]After a decade, Lindsey established that the condensation product was actually not a cyclic dimer or a cyclic hexamer,[4,5] but a cyclic trimer (m.p. 234^{o}C) which, for convenience, was called *cyclotriveratrylene (CTV)* **66**. The establishment of the structure **66** was based on chemical evidence, molecular weight determination, ultraviolet, infrared, and nuclear magnetic resonance spectroscopy (NMR) measurements. It was later supported by the independent work of Erdtman and his co-workers,[7] Miller and Gesner,[6] and Goldup *et al.*[8] based on molecular weight measurements, mass, NMR and X-ray diffraction studies, which clearly showed a trimeric crown-shaped structure of cyclotriveratrylene (CTV).[9]

The trimeric structure of CTV was characterized with a crown-like conformation with a possibility of two enantiomeric forms if the two methoxy groups are dissimilar. In the ^{1}H NMR spectrum of CTV, the methylene hydrogens have been noticed separately as an AB quartet at δ 3.45 (quasi-equatorial) and 4.70 (quasi-axial) J=14 Hz, Δν 1.25 ppm. This revealed that the linker groups were asymmetric and that the two methylene protons were not magnetically equivalent.[7] In addition, even when recorded at 150°C (in $CDBr_3$), the AB quartet remained unchanged.[10] This suggested the rigidity of the crown conformation. This crow-like shape of CTV features a pyramidal shape shallow molecular cavity. The aromatic rings form the three sides of the pyramid and the methylene hydrogens lying close together at the apex. This pyramidal shape with a shallow cavity has led to the identifying of CTV as acting as a host-molecule.[11] One of the early examples reported in this context are the co-crystals of CTV with both benzene and water, the benzene being incorporated into the cavity and the water hydrogen-bonding to the methoxy groups.

Another surprising structural aspect of CTV has been documented in this century. The rigidity of the crown conformer of CTV has been taken granted until recently. However, in 2004, it has been shown that the rapid quenching with ice of a hot solution or melts of CTV compounds led to the isolation of another minor compound along with starting the CTV.[12] This new compound was found to be identical in all other aspects except that its 1H NMR spectrum was drastically different from that of the original CTV – the methylene bridge hydrogens resonated as a sharp singlet at δ 3.89 ppm and the aromatic protons also appeared as a singlet at δ 6.83 ppm [in case of 1, CH_2 as AB doublet at δ 3.55 and 4.77 ppm and aromatic-H as singlet at δ 7.36]. Further NMR studies have revealed that the saddle form is much more flexible than the crown with a half-life of the inter conversion being about a day in chloroform solution. In polar solvents the crown form appears even more rapidly. However, the solid samples of the saddle form are found to stable for months at room temperature.

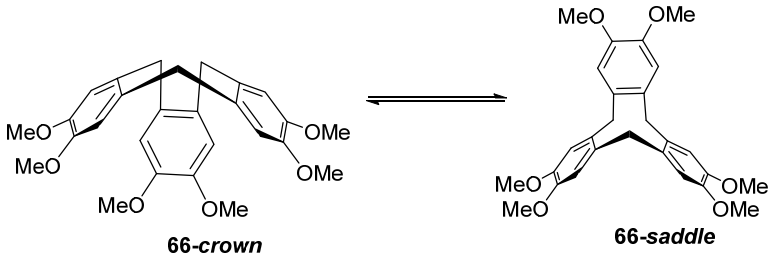


Figure2: Cyclotriveratrylene (CTV) crown and saddle conformations

2.1.1 Synthesis of cyclotriveratrylene (CTV):

Some of the procedures documented so far for the synthesis of CTV **66** have been listed in Table 1.[5,9,13] In the majority of the cases, along with CTV, the tetramer trivially called as cyclotetraveratrylene–CTTV,[13a] and also small amounts of other higher order cyclic oligomers were found to be formed as side products.

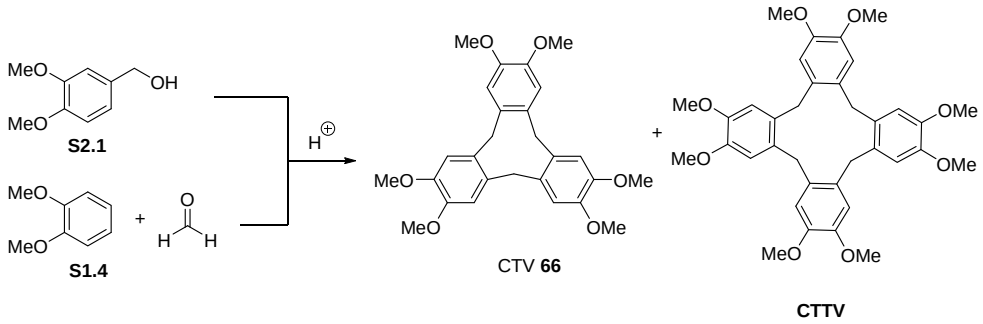


Table 1: *Selected synthesis procedures for preparation of CTV* ***66***

Starting Material	Acid	Solvent	Temp.(°C)	CTV	CTTV
S1.4 + aq.HCHO	70% H_2SO_4	none	25	70	-
S1.4 + aq.HCHO	70% H_2SO_4	none	0	21	-
S1.4 + aq.HCHO	70% H_2SO_4	none	0	68	16
S1.4 + aq.HCHO	60% H_2SO_4	none	25	70	-
S1.4 + p-HCHO	Con. HCl	none	25	45	-
S2.1	H_2SO_4	Acetic acid	90	68	16
S2.1	H_2SO_4	Acetic acid	warm	87	-
S2.1	60% H_2SO_4	None	25	35	-
S1.4or**S2.1**	HCl	1,4-Dioxane	rt	70	-

Scheme 2: Synthesis of CTV **66** and the side product cyclotetraveratrylene CTTV

Apart from the parent CTV having the symmetrically substituted two methoxy groups, efforts have been made to synthesize CTV derivatives with an unsymmetrical substitution pattern. One of the reasons for these efforts was to accommodate the functional units on the pyramidal structure which can in effect facilitate the binding of the guest molecules. The routinely followed acid catalyzed trimerization is useful in the synthesis of these unsymmetrical CTV derivatives. However, they sometimes required the potentially tedious synthesis of the appropriate benzyl alcohol.

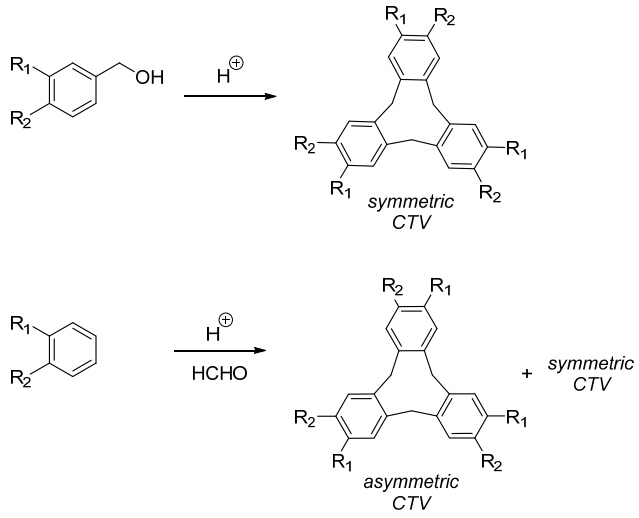


Table 2: *Some reported functional groups for CTV synthesis via benzyl alcohol.*

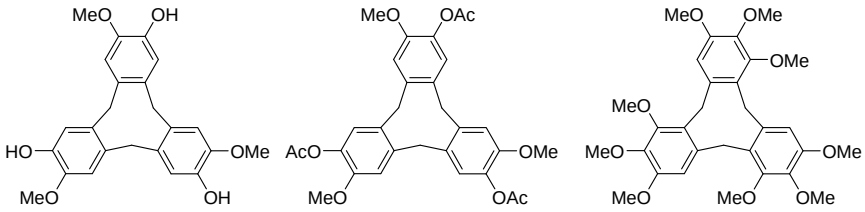
Entry	**R_1**	**R_2**	Yield (%)
1	OCH_3	OCH_3	70
2	OH	OCH_3	0
3	OCH_2CH_3	OCH_3	51
4	OCH_2COOH	OCH_3	45
5	OCH_3	OCH_2CH_3	42
6	$OCH_2CH_2OCH_2COOH$	OCH_3	40
7	$OCH_2CH{=}CH_2$	OCH_3	55
8	$OCH_2CH{=}CH_2$	OCH_2CH_3	15
9	Br	OCH_3	25-40
10	OCH_3	Br	0
11	H	OCH_3	6.5
12	$NHCOCH_3$	OCH_3	97

Scheme 3: *Synthesizing CTVs through benzyl alcohol route or through the arene/carbon source route.*

As shown in the following scheme, treatment of an appropriately 1,2-disubstituted arene, with formaldehyde and a strong acid results in a mixture of C_3 and the C_1 symmetric CTVs when $R_1 \neq R_2$.The functional group tolerance of the condensation reaction dictates that R_2 (which is present *meta* to the reactive benzylic methylene unit, must be electron donating (e.g. alkoxy) while R_1 (present *para* to the benzylic carbon) can simply be a place holding group, and ultimately results in low yields. Some notable functional groups that have been explored in the literature following the benzylic alcohol route can be seen in Table 2.[2,11,14] However, on several

instances, the modification of the R_1 or R_2 groups after the cyclization step to introduce desired chemical functionality seems to be more practical.

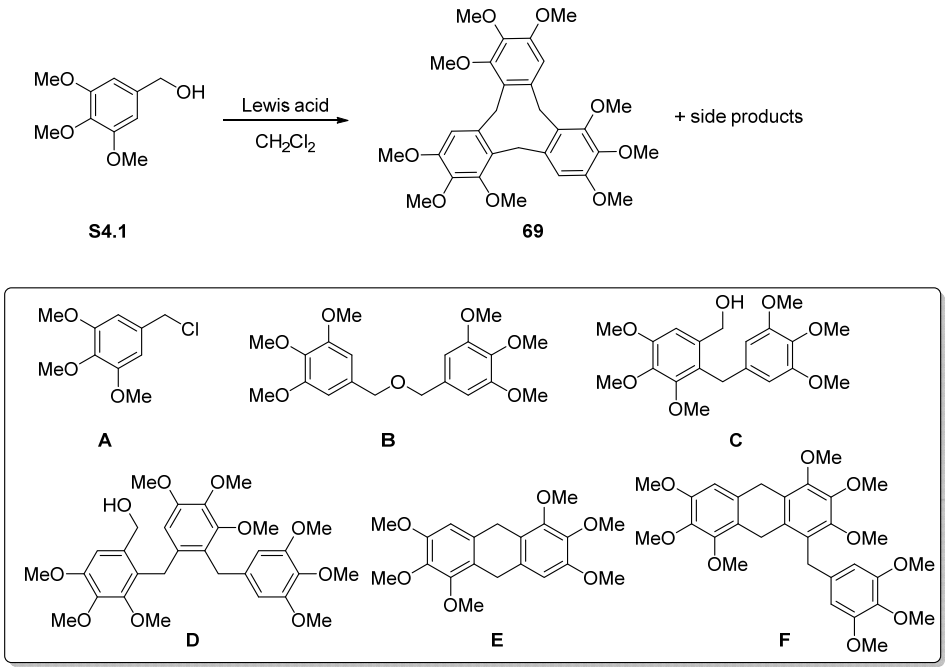
Apart from the parent CTV, amongst the other simple CTV derivatives synthesized are the CTVs **67** – **69**. The BBr_3 or the acid mediated hydrolysis of **66** has been used to prepare the CTV **67**.[14a,15] The synthesis of CTV **68**[14b] involves a multistep procedure which will be detailed in the next part. On the other hand, CTV **69** has been prepared by several groups and interestingly the formation of several other side products depending upon the conditions employed has been noticed.



CTV **67** CTV **68** CTV **69**

Figure 3: *The structures of the simple CTV derivatives*

For example, Zhang and co-workers reported the synthesis of racemic hexamethoxy substituted cycltroveratrylene **69** (Scheme4) via trimerization of 3,4,5-trimethoxybenzyl alcohol catalyzed by Lewis acids such as $AlCl_3$, $ZnCl_2$, $FeCl_3$ and $SnCl_4$ in chlorinated solvents. Along with CTV **69**, the side products A – D have been obtained in substantial amounts. The best results were obtained with $SnCl_4$ as catalyst in dichloromethane giving **69** in 54% yield.[16] Later, Miranda and Salmón have shown that the same alcohol when subjected for microwave heating in the presence of Tonsil Actisil FF (TAFF, a commercial bentonite clay) without any solvent **69** was obtained as the major product and the compounds E and F were obtained as the minor products.



Scheme 4: *The trimerization of 3,4,5-trimetoxy benzyl alcohol & various side products obtained*

2.1.2 Functionalization of Cyclotriveratrylene (CTV):

As it has been mentioned earlier, the parent CTV **66** has been shown to encapsulate the simple molecules such as benzene, ethanol and water. This has prompted the synthesis of various functionalized CTV derivatives for a wide range of applications. CTV and its congeners have been endowed as precursors to cryptophanes/cavitands,[17] and as components in coordination and self-assembled supramolecular networks.[18] For example, CTV and its derivatives have been extensively studied for their binding with molecules like C60 and anionic C70 dimers,[19] lanthanides and the xenon.[20] Thus, the manipulation of functional and structure/conformational aspects of the CTV holds great promises as increasing number of applications for this class of molecules are being continuously reported. The functionalization of CTV can be carried out either at aromatic rings in the "outer-rim" or at the methylene bridges in the "inner-rim or apex", which are complementary to each other. The outer-rim functionalization is important in modulating the host-guest properties of the CTV. Whereas, the apex functionalization which is challenging, has been thought to be a handle for tuning the conformational aspects of CTV.

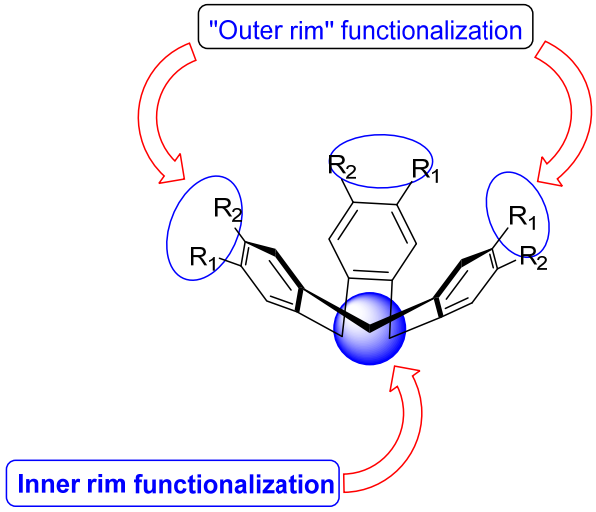


Figure 4: *Functionalization of CTV derivatives*

2.1.3 Cyclotriveratrylene "Outer-rim" functionalization

During the last three decades, cyclotriveratrylene outer-rim functionalization has been executed for wide range of applications. Their ability to host xenon has led to the development of functionalized CTV derivatives for biomedical applications such as biological delivery of fullerenes and MRI-based diagnostic techniques.[21] The crown-type conformation exhibited by CTVs allows them to form inclusion complexes with a variety of guests. For example, Mendoza and co-workers have reported a series of CTV-based macrocycles **F5.1**, which formed dimeric hydrogen-bonded capsules in certain organic solvents.[22] These capsules demonstrated high affinity and selectivity for C70 over C60 (Figure 5). Moreover, the capsules could be disrupted by polar solvents such as tetrahydrofuran (THF) which release the bound guests. By utilizing this property, C70 was obtained in a purity of 97% from the fullerene mixture.[22]

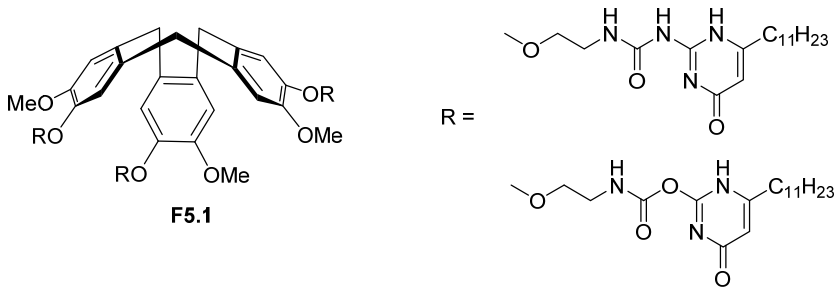
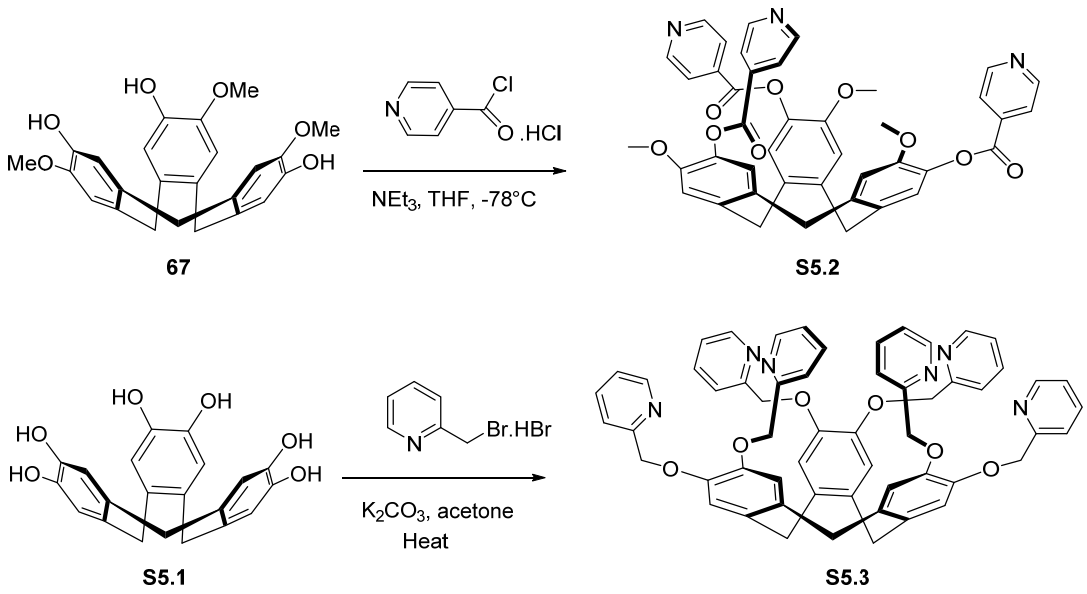


Figure 5: *Outer-rim functionalized CTV host analogue*

Hardie and co-worker reported the outer ring functionalization of CTV with pyridyl functional groups and revealed their application as multifunctional ligands in coordination networks.[23] Ligand **S5.2** was prepared by reaction of the trihydroxy derivative of CTV **67**, the cyclotriguaiacylene (CTG, **67**),[15] with isonicotinoyl chloride hydrochloride to obtain the tri-substituted CTV ligand **S5.2** (Scheme 5). The hydrogen bonded network structures and coordination networks formed by the CTV **S5.2** represent an elegant example where the solid state structure of the building blocks is echoed in the resulting supramolecular assembly. The 2-D sheets are further stabilized by π-π stacking interactions between pyridyl donors of alternate 1-D coordination polymers.

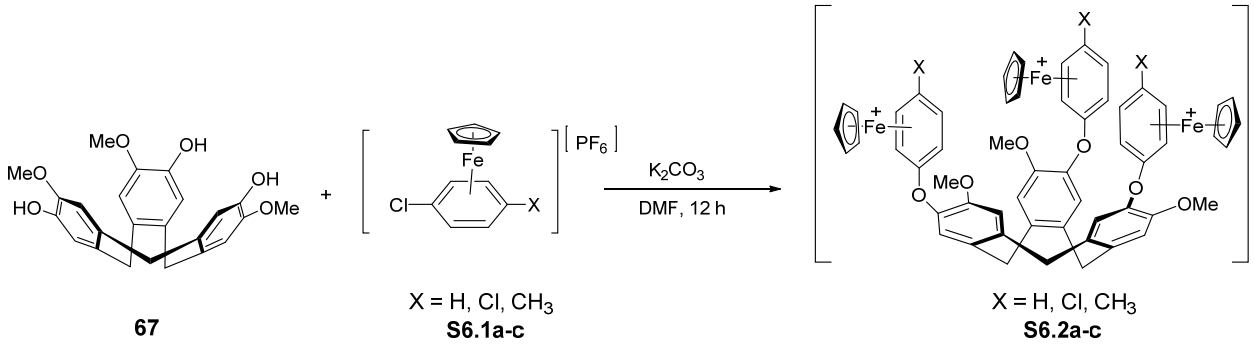


Scheme 5: *Synthesis of tri- and hexa-substituted CTV ligands*

The hexa-substituted ligand **S5.3** can be accessed *via* the demethylated CTV analogue cyclotricatechylene **S5.1**.[24] The hexa-substituted ligand hexakis(2-pyridylmethyl)-cyclotriveratrylene **S5.3** forms a clathrate inclusion complex with water. Within this complex, the host molecules form an aligned self-stacking motif with one host fitting into the bowl of the next host to form an infinite pillar of host molecules.

Atwood reported $[CpFe(arene)]^+$-based CTV derivatives deep-cavity anion hosts **S6.1a-c** whose upper rim charge pre organization allows the binding of anions exclusively within the host cavity, and without the use of hydrogen bonding residues.[25] Racemic cyclotriveratrylene-based hosts **S6.1a-c** were synthesized as their $[PF6]^-$ salts by S_NAr substitution of the respective

[CpFe(chloroarene)][PF6] **S6.2a–c** complex with *rac*-cyclotriguaiacylene (CTG)[15] **67** in DMF containing excess K_2CO_3 (Scheme 6).[26]



Scheme 6: *CTV tri-functionalized deep cavity [CpFe(arene)]$^+$-based hosts* ***S6.2***

CTV based cryptophanes (molecular cages) have been synthesized by Rousseau and co-workers.[27] The connection of two cyclotriveratrylene units has been carried through formylidene bridging (Figure 6). The resulting cryptophanes exhibited outstanding xenon encapsulation. The cavity size, which directly depends on the length of the molecular bridge, dramatically affects both the affinity for xenon and the rate of in and out exchange of xenon. The majority of the CTV based biosensors constructed are mainly from **F6.2**. Although cryptophane **F6.1** displayed the highest affinity for xenon in both organic solvents[28] and water,[29] it has never been used for the synthesis of biosensors.

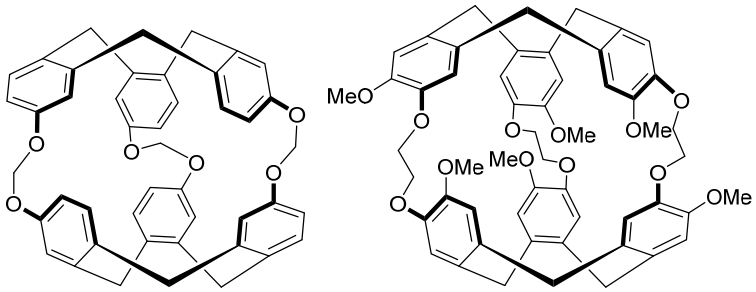


Figure 6: *Structure of cryptophane-111* ***F6.1*** *and cryptophanes A(222)* ***F6.2***

Pines and coworkers[30] reported the Xe encapsulation approach to bio-sensing by conjugating the CTV derived cryptophane with the biotin ligand employing a peptide based solubilizing chain as a tether. The resulting cryptophane demonstrated a ^{129}Xe NMR signal response to the binding of the sensor by avidin in aqueous solution (Figure 7).

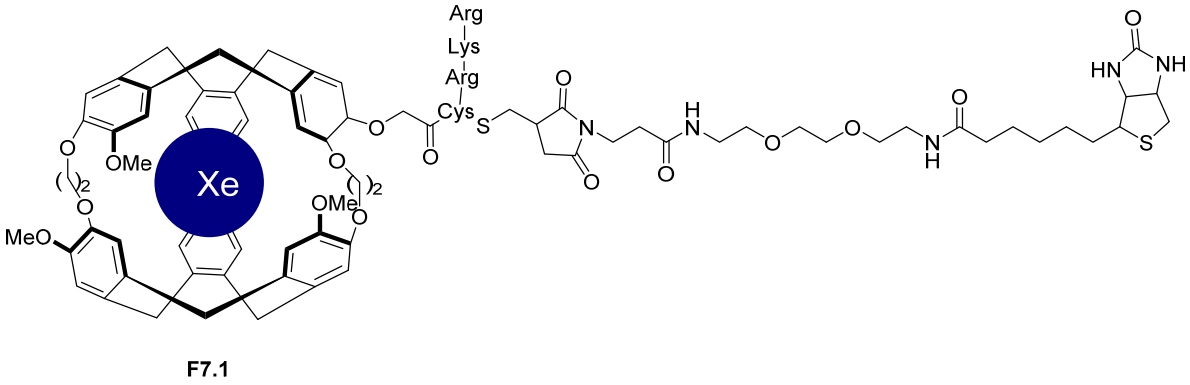
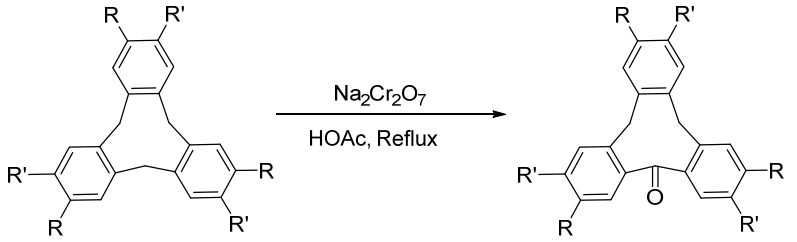


Figure 7: *The structure of the biosensor molecule as a ^{129}Xe NMR based biosensor.*

2.1.4 Cyclotriveratrylene "Inner-rim" functionalization

The oxidation of the CTV methylene bridges is one of the simple means for inner-rim functionalization that has been explored by several groups. One of the early reports for the oxidation of CTV **66** (Scheme 7) was reported with sodium dichromate to obtain themonoketone **70**[4,5,10,31] and **S7.2**.[32] Stevens and co-workers have assigned a flexible 'saddle' conformation (Fig. 8) for this monoketone **70**. This conformation is evidenced by the ^{1}H NMR spectrum (in pyridine), which shows the methylene protons as a sharp singlet at δ 5.95, as would be expected for a rapidly inverting molecule.



Scheme 7: *C-H oxidation of cyclotriveratrylene (CTV)*

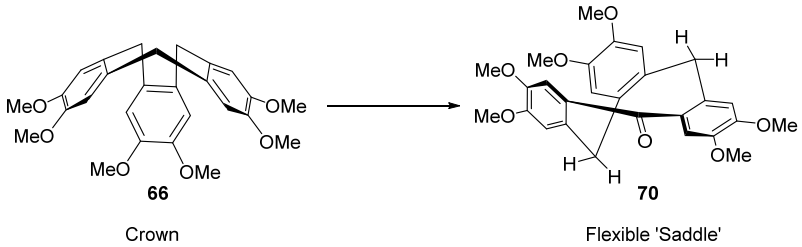
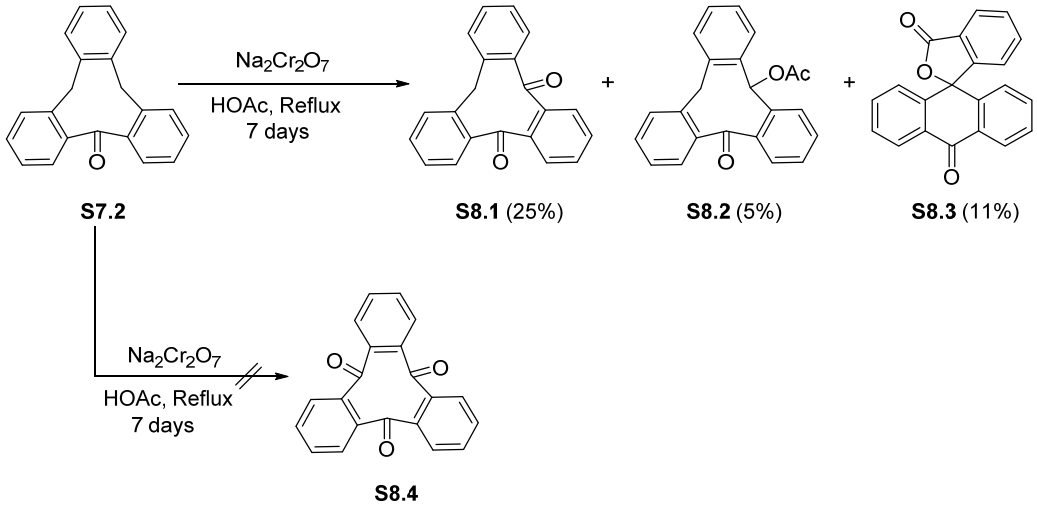


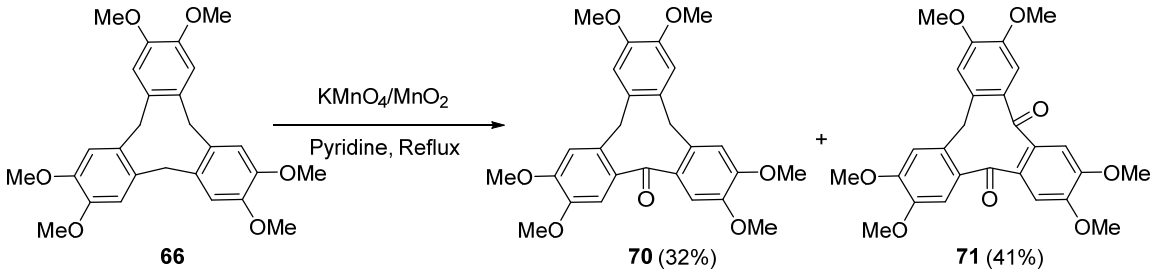
Figure 8: *Conformation structure of CTV* ***66*** *and CTV-monoketone* ***70***

Later, Yamato and co-workers have reported that the further oxidation of CTV–monoketone **S7.2** furnished the diketone **S8.1** in 25% yield along with a lactone **S8.3** (Scheme 8)[33] having a 10-benzoyloxy-9-anthrone unit in 11% yield, formed possibly as a result of the transannular rearrangement of triketone **S8.4** due to the release of strain on changing the tribenzocyclonone skeleton to an anthrone. Furthermore, compound **S8.2** was also isolated in lower yield. The CTV-diketone **S8.1** was also found to exist in a flexible 'saddle' conformation.



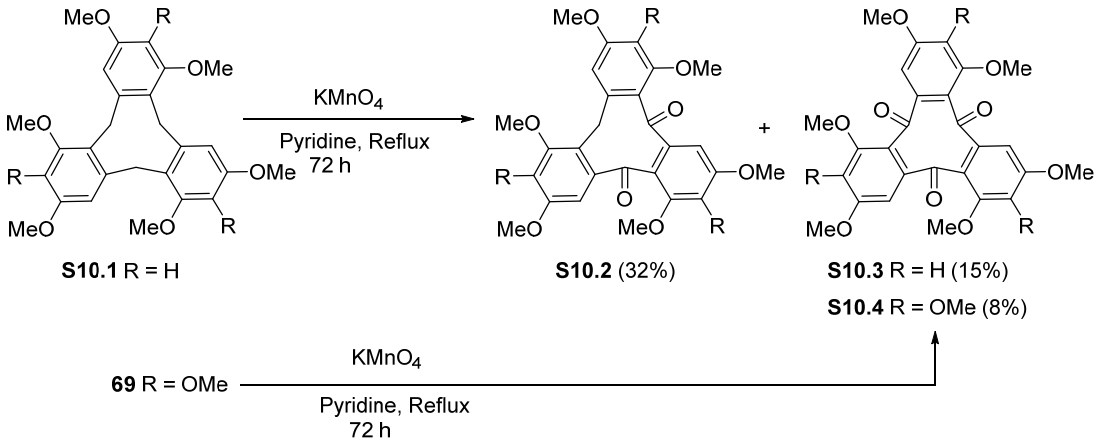
Scheme 8: *C-H oxidation of cyclotriveratrylene (CTV)* ***S7.2***

Recently, Becker and co-workers reported that the oxidation of CTV **66** (Scheme 9) by using potassium permanganate and activated MnO_2 results in a mixture CTV diketone **71** and CTV monoketone **70** in comparable amounts (41% diketone and 32% monoketone). Higher temperatures could be utilized to enable all CTV to be converted to CTV diketone.[34]



Scheme 9: *Synthesis of CTV mono-**70** and diketone **71***

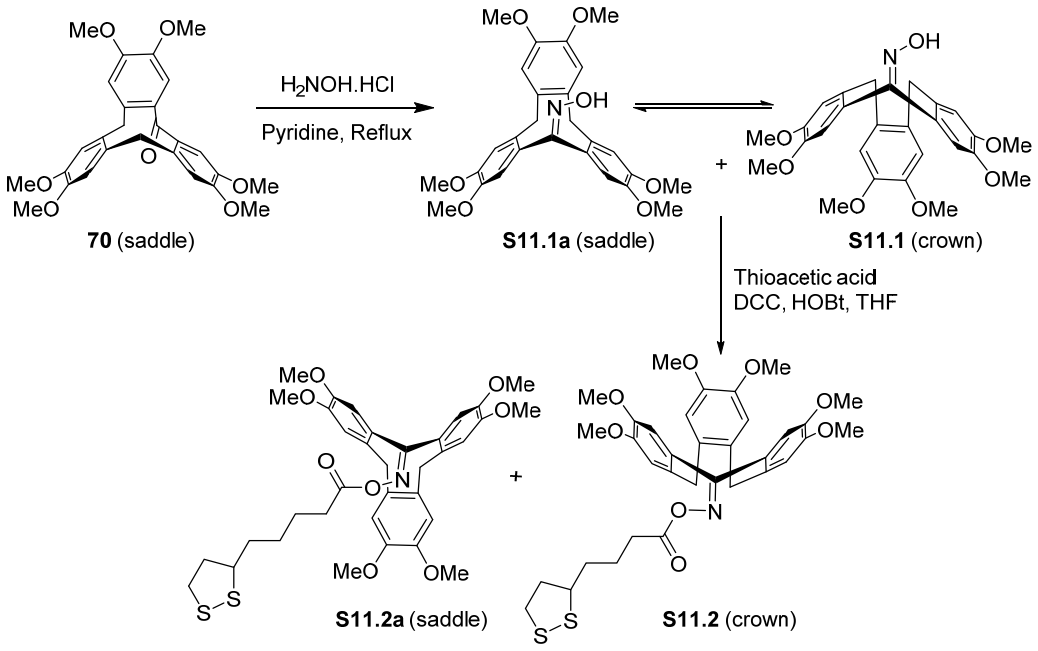
Apart from the above mentioned reports on oxidation of CTV **66**, there has been a continuous effort to synthesize its triketone. However, in most of the instances, it was the trans-annular product that has been isolated. Snyder and co-workers recently documented the first CTV triketone derivative by employing modified CTVs **S10.1** and **69**. The oxidation of CTV **S10.1** with $KMnO_4$ gave the CTV-diketone **S10.2** and triketone **S10.3**. As indicated (Scheme 10), the diketone **S10.2** is the favored product of this process. The starting material is recovered in small amounts and no trace of monoketone was observed. X-ray crystallography revealed that **S10.2** and **S10.3** possess a saddle-like conformation. Similarly, the hexamethoxy cyclotriveratrylene **69** has been also oxidized to the corresponding triketonetriketone **S10.4** in 8% yield by using the same oxidation protocol. This prediction for oxidation without rearrangement proved correct with triketone.[35]



Scheme 10: *Synthesis of CTV di- **S10.2**, triketone **S10.3** and **S10.4***

With regard to the use of inner-rim modified CTVs in host guest chemistry, the reports are scarce. Becker has recently documented the exploitation of an oxime functional group

placed on the apex of the CTV to anchor it to a solid surface so that the concave bowl receptor pointed away from the surface, enabling CTV to function as a surface-bound host molecule. The monoketone **70** was converted to the corresponding CTV-oxime **S11.1** which was found to exist as an equilibrium mixture of the crown and the saddle conformers.[36] The CTV oxime was coupled to *(±)-α*-lipoic acid affording a conformational mixture of CTV–lipoic-acid derivatives **S11.2** in 52% yield (Scheme 11).



Scheme 11: *Synthesis of the apex-modofied dithiol CTV-oxime* ***S11.2***

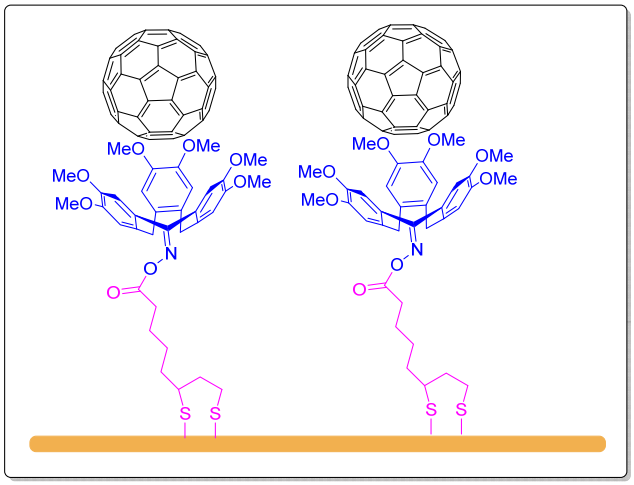
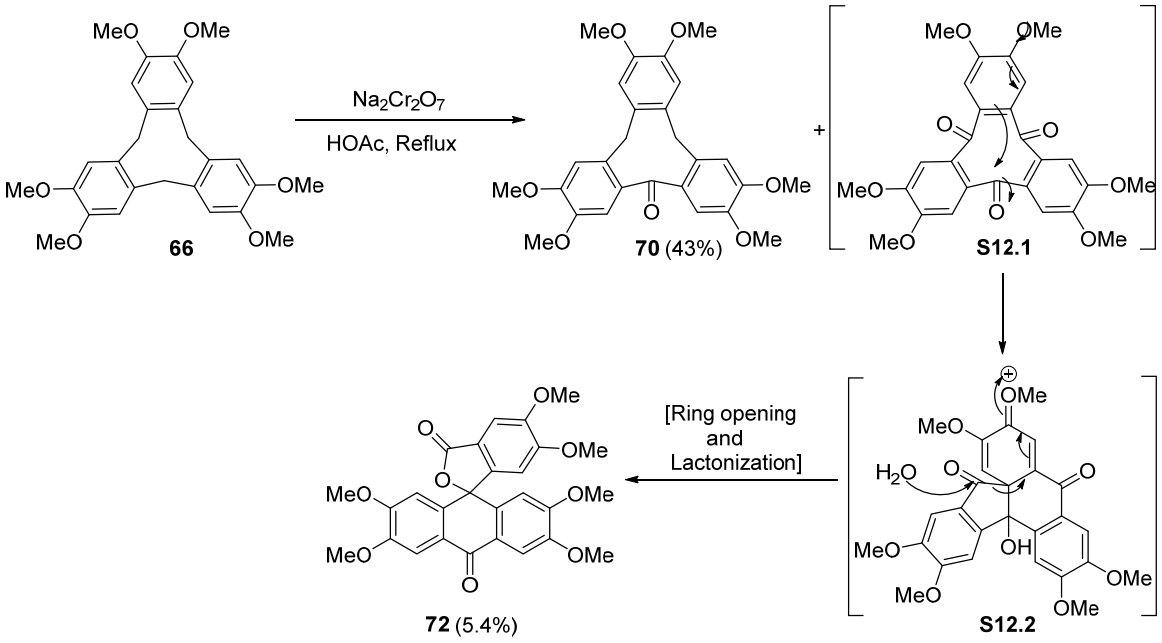


Figure 9: *Becker proposed C60 binding to the apex-modified, surface-bound CTV.*

The S–S bond in the dithiolane of **S11.2** has been cleaved and then the resulting dithiol was used to cap the gold surface, [37] thus making the bowl of CTV to face away from the surface (Fig. 9).

2.1.5 Transannular rearrangement of CTV analogue

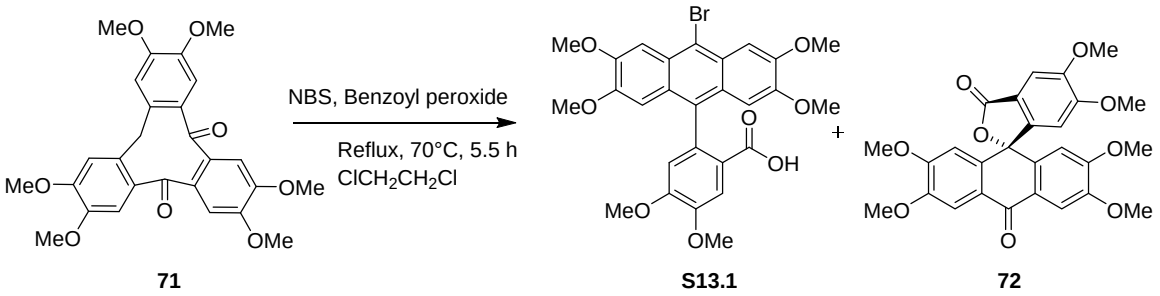
Cookson and co-workers reported in 1968 that the oxidation of cyclotriveratrylene with chromic acid could afford its corresponding monoketone **70** and a small amount of symmetric triketone **S12.1**.[10] However, the Baldwin group refuted this claim later that same year,[38] proving that spirocycle **72**, not the triketone **S12.1**, was the obtained fully oxidized product (Scheme 12). It appears that the triketone **S12.1** is, in fact, an intermediate in the production of lactone, since the transannular cyclization product **S12.1** obtained directly from the triketone could readily open to yield the hydroxyl-acid **S12.2**, and the lactonization then yields the rearrangement product of 2,3,5',6,6',7-hexamethoxy-3'H,10H-spiro[anthracene-9,1'-isobenzofuran]-3',10-dione **72**.



Scheme 12: *Transannular rearramgement of CTV-triketone **S12.1***

Recently, Becker reported the oxidative bromination of the CTV diketone **71** resulting in a mixture of 10-bromo-9-phenyl anthracene derivative **S13.1** along with the lactone **72** as a side product (Scheme 13).[39] A similar type of transannular rearrangement catalyzed by the liberated

acid after the bromination reaction (HBr) has been proposed for the formation of these products.[40]



71 **S13.1** **72**

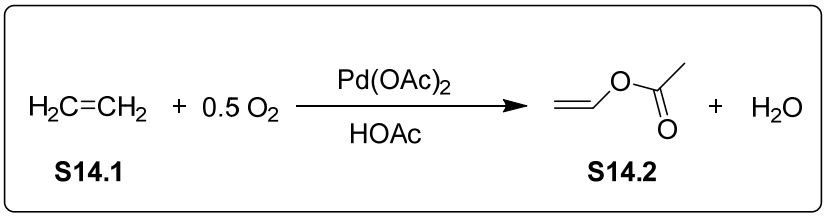
Scheme 13: *Bromination followed by transannular rearrangement of CTV diketone* ***71***

To conclude this part, the oxidation of the CTV has been extensively studied by employing chromium and permanganate based reagents. As mentioned above, the CTV monoketone **70** is the commonly isolated product and sometimes the diketone is also isolated. The further chemistry of this oxidized CTV derivatives has not been explored, May be because of the lack of reliable procedures for the oxidation. Given the availability of the active methylene groups in CTV that can be functionalized easily *via* their C–H activation, we wondered about the possibility of the catalytic benzylic oxidation of CTV employing metal complexes, with a particular interest on the Pd-based C–H oxidation.

2.1.6 Palladium Catalyzed C–H Oxidations

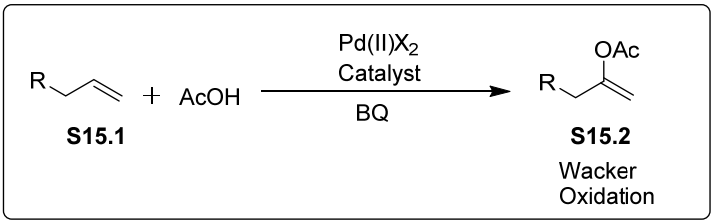
The addition of oxygen to organic molecules, in general, has been traditionally employed olefins as the suitable handles. For example, epoxidation, dihydroxylation and Wacker oxidation are the important oxidative transformations of olefins that have been extensively studied by employing all possible types of reagents/reactions.[41] For a long time, the addition of oxygen across the C–H bonds has been well sought and the important contributions in this area are emerging only recently. The palladium catalyzed C–H acetoxylation is one of the early reactions that has been studied in this context. For example, the acetoxylation of ethylene and acetic acid to produce vinyl acetate studied by Moiseev during the 1960s is one of the early industrial successes in this regard.[42] Later, this acetoxylation reaction has been extended to allyl, benzyl and aryl hydrogen oxidations. Apart from this, the directed SP^3 C–H acetoxylation of methyl groups has been the topic of research in recent times. However, considering the focus of

the next part of this chapter, the discussion of the earlier work will be mainly restricted to the selected examples that dealt with the direct acetoxylations.



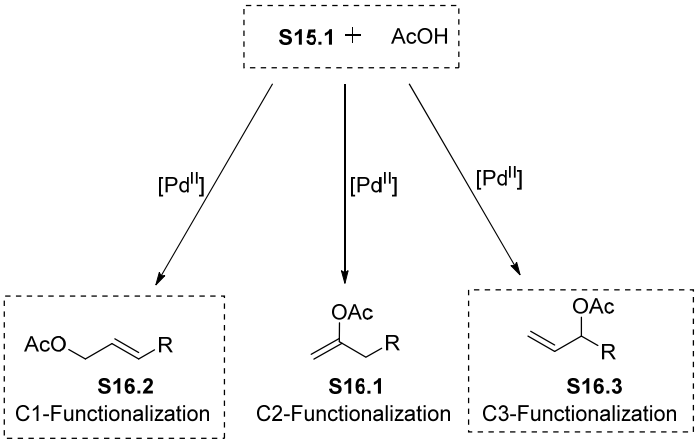
Scheme 14: *Palladium catalyzed acetoxylation of ethylene*

In 1973, Trost and Fullerton showed that the non-functionalized alkenes could undergo allylic acetoxylation employing stoichiometric amounts of Pd^{II}.[43] While this discovery had important mechanistic implications, it was of little practical use and is not cost-effective. The catalytic version requires reaction conditions that support the Pd^{II}-mediated electrophilic C–H cleavage, the nucleophilic attack and the re-oxidation of Pd^{0} to Pd^{II}. One of the difficulties with these steps is the formation of Wacker-type products (Scheme 15).[44]



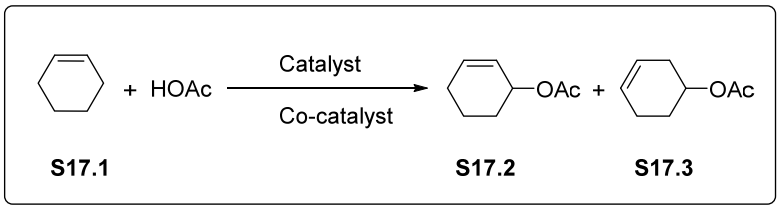
Scheme 15: *The formation of the product **S15.2** from Wacker oxidation*

The subsequent study of this reaction with higher olefins revealed that, in addition to C-2 acetoxylation, allylic acetoxylation occurs to generate products with the acetoxy group at the C-1 and C-3 positions (Scheme 16).[42,45]



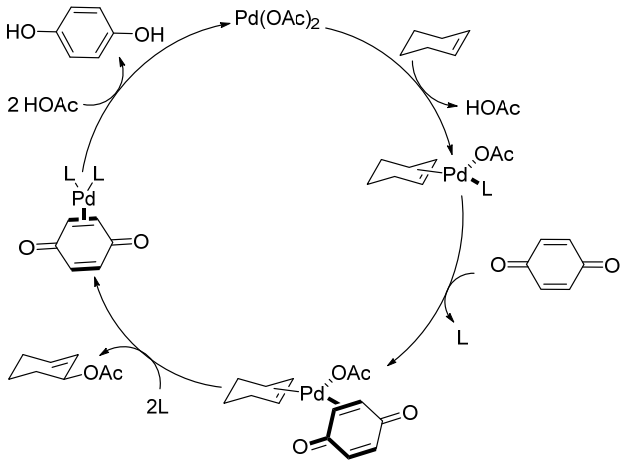
Scheme 16: *Possible outcomes of the palladium-catalyzed oxidative acetoxylation of alkenes*

In subsequent years, Akermark and Bäckvall developed multicomponent catalytic systems that use benzoquinone (BQ) as co-catalyst with more environmentally benign terminal oxidants, including O_2 and H_2O_2, to carry out selective alkene acetoxylation.[46]



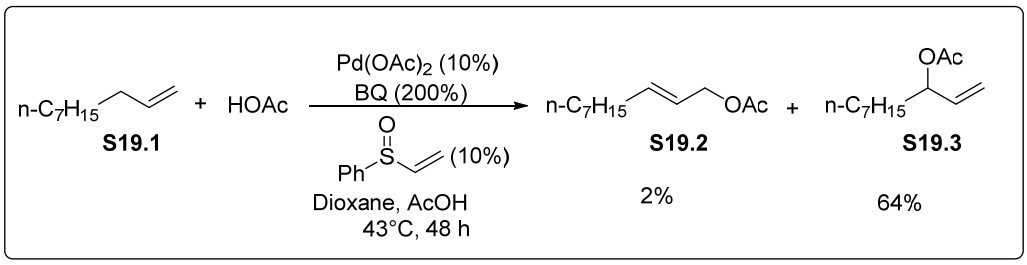
Scheme 17: *Palladium catalyzed acetoxylation of cyclohexene*

The proposed mechanism for the allylic acetoxylation of cyclohexene is illustrated in Scheme 18. Pd^{II}-mediated activation of the allylic C–H bond generates a π-allyl-Pd^{II} intermediate. The coordination of BQ to the Pd^{II} center promotes nucleophilic attack by acetate on the coordinated allyl ligand, which yields cyclohexenyl acetate and a Pd^{0}–BQ complex. The latter species reacts with two equivalents of acetic acid to complete the cycle, forming $Pd(OAc)_2$ and hydroquinone. The HQ product can be recycled to BQ if a suitable co-catalyst and/or stoichiometric oxidant are present in the reaction. This mechanism reveals that BQ is more than a re-oxidant for the Pd-catalyst. Mechanistic studies reveal that BQ is required to promote nucleophilic attack on the π-allyl fragment.[47]



Scheme 18: *Proposed mechanism for the allylic acetoxylation of cyclohexene* ***S17.2***

During the last decade, White and coworkers have documented the breakthrough in this area by introducing sulphoxide based ligands in the Pd-catalyzed allylic acetoxylation (Scheme 19). The vinyl sulfoxide ligand has promoted the catalytic system for the mild, chemo- (n-C_7H_{15}- versus internal olefins), and highly regioselective C-H oxidation of n-C_7H_{15}-olefins **S19.1** to furnish allylic alkyl **S19.2** and aryl esters by generating presumably a highly electrophilic/cationic palladium species *in situ*, thus facilitating the C–H bond cleavages to form a π-allyl palladium complex (II).[48]

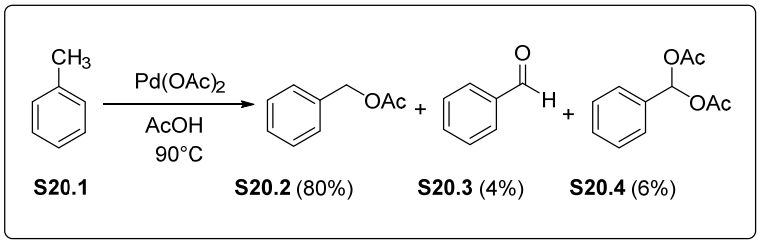


Scheme 19: *Solvent dependent condition allylic acetoxylation of* ***S19.1***.

2.1.7 Palladium Catalyzed Benzylic C–H acetoxylation

Unlike with the acetoxylation, the reports on the Pd-catalyzed benzylic oxidations are limited. The early reports on the benzylic C–H acetoxylation have been documented by Bryant and Davidson groups employing stoichiometric amounts of $Pd(OAc)_2$ in acetic acid.[49] In 1968, Bushweller reported the Pd-catalyzed benzylic C–H oxidation of toluene in AcOH (Scheme 20),

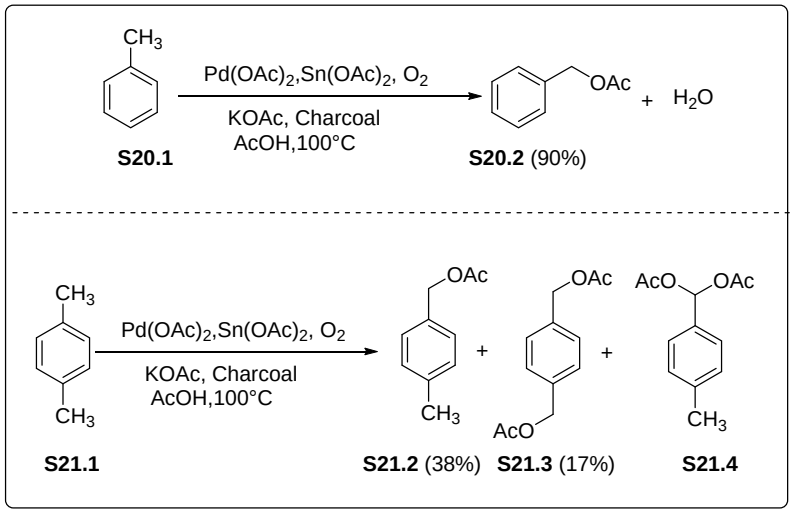
The reaction achieved an excellent yield of the corresponding benzyl acetate **S20.2** with minor yields of benzaldehyde and benzylidinediacetate, which exhibits the generally observed that sensitivity to electronic effect with electron-donating groups effects the benzyl acetate.[50]



Scheme 20: *Palladium-catalyzed benzylic C-H oxidation of toluene* ***S20.1***.

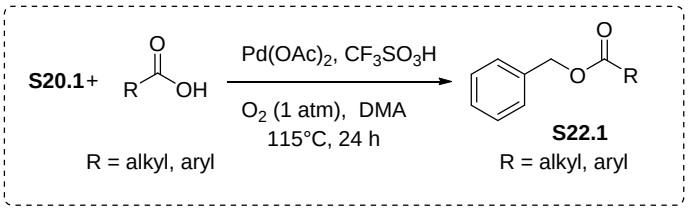
In the preceding year, Bryant *et al.* had established and found that the addition of charcoal and tin(II) salts to reaction mixtures containing Pd^{II} and potassium acetates was particularly effective for the benzylic acetoxylation of toluene.[51] The reaction proceeded at 100°C under oxygen at atmospheric pressure (Scheme 21), giving benzyl acetate **S20.2** with 90% selectivity. No explanation regarding the roles of either tin or charcoal was advanced. The oxygen served to reoxidize of Pd(0) to Pd(II), although neither the particular role of oxygen nor the precise nature of the catalytically active palladium entity was addressed.

In the subsequent report in 1969, the same group documented Pd-catalyzed oxidation of *p*-xylene leading to *p*-xylyl acetate **S21.2** and the *p*-xylylenediacetate **S21.3** along with the minor amounts of *p*-methylbenzylidene diacetate **S21.4**.[52]



Scheme 21: *Benzylic C-H acetoxylation of tolune* ***S20.1*** *and p-xylene* ***S21.1***

In 2013, Zhang *et al* reported the direct benzylation of carboxylic acids using toluene *via* palladium–catalyzed C–H functionaliztion under 1 atm of oxygen (Scheme 22).[80] This reaction demonstrated good functional group tolerance and high yields, providing a facile, atom-economic, and efficient method for the synthesis of benzyl esters. A plausible mechanism was proposed, as shown in Figure 10. The catalytic cycle starts with Pd^{II}-mediated C–H cleavage to form the benzyl Pd^{II} species **A**. The benzylation products may result from nucleophilic attack on the benzylic carbon by benzoate (Path I). Alternatively, **A** may undergo ligand exchange to afford benzyl Pd^{II}-carboxylate **B**, and subsequent reductive elimination yields the benzylation product **C** (Path II).[53]



Scheme 22: *Benzylation of carboxylic acid with toluene* ***S20.1***

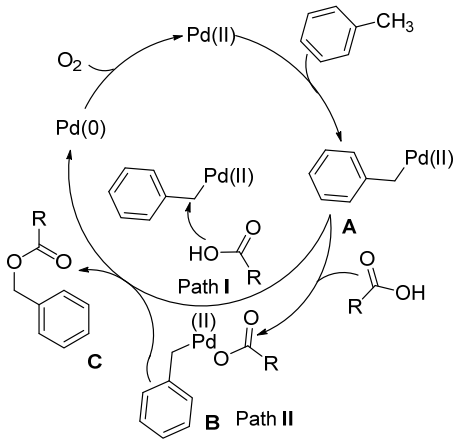


Figure 10: *Proposed mechanism for the Pd-catalyzed benzylation of carboxylic acids.*

From the above brief introduction about the applications of CTV and reports on its oxidation employing highly toxic reagents and considering diverse conditions for Pd-catalyzed C–H oxidation, it is a quite puzzling that CTV missed the attention of researchers working in this area. In the following section will be presented the work that has been carried out to uncover this puzzle.

2.2. Present work

Cyclotriveratrylene (CTV) is an interesting macrocyclic molecule characterized with a crown-like structure having a shallow molecular cavity and a pyramidal shape with the aromatic rings forming the three sides of the pyramid and the methylene hydrogens lying close together at the apex.[5,7,9] The manipulation of functional and structure/conformational aspects of the CTV holds great promises as increasing number of applications for this class of molecules are being continuously reported. As described in the previous section, the functionalization of CTV can be carried out either at the aromatic rings "outer-rim" or at the methylene bridges "inner-rim or apex" which are complementary to each other. The outer-rim functionalization is an important in modulating the host-guest properties of the CTV. Whereas, the apex functionalization, which is challenging, has been thought to be a handle for tuning the conformational aspects of CTV. The oxidation of the methylene bridges of the CTV is one of the simple means for inner-rim functionalization that has been explored by several groups.[10.33,34] Reports for the reliable preparation of the mono- and diketones of the CTV are documented and the corresponding triketone is known to undergo trans-annular rearrangement.[38,39,54] In general, these oxidations are carried out under harsh conditions employing the chromium and permanganate based oxidants in solvents such as conc. H_2SO_4 or pyridine. Given the importance of the functionalized CTV derivatives and the challenges associated with the inner-rim functionalization, we sought to explore the possibility of metal-catalyzed controlled C–H oxidation of the CTV especially those employing the Pd-complexes. As mentioned in the previous section, while the Pd-catalyzed allylic acetoxylation which is very popular,[47,55] the Pd-catalyzed benzylic oxidations are scarcely reported.[49-54]

The application of transition metal-catalyzed C–H oxidation in organic synthesis has received increasing attention in the recent years. Since their high oxidation-potential, the reports on the catalytic oxidation of allylic and benzylic methylene groups are well documented, employing a wide range of metal complexes. Coming to the catalytic C-H oxidation with Pd-complexes, there is a constant interest on the allylic acetoxylation during the last two decades. However, the reports on the benzylic oxidations are scarcely reported, although it was known much earlier for the catalytic allylic acetoxylation. A close examination of the methods reported for benzylic oxidations shows that, unlike with the commonly used

oxidants, with the palladium oxidation, there is a scope for controlling the oxidation. Considering this, we have pursued our investigations on the oxidation of the CTV with the Pd-complexes to develop methods for variously oxidized CTV derivatives. The following three known CTV analogues **66**, **68** and **69** (Figure 1) have been selected as the substrates and were prepared by following the established procedures.[15a]

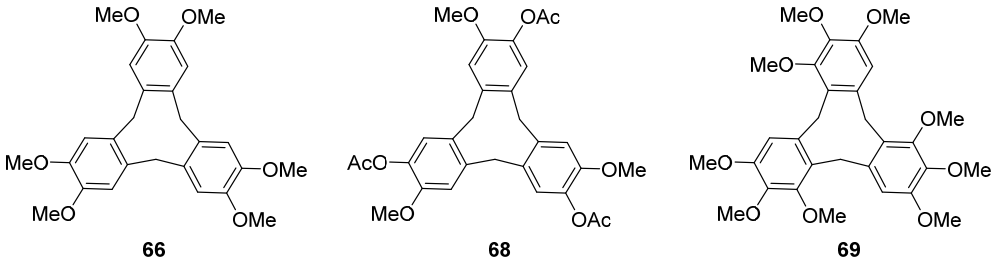
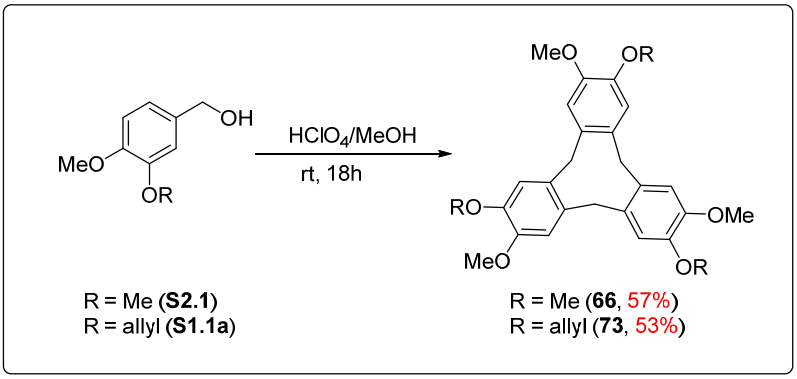


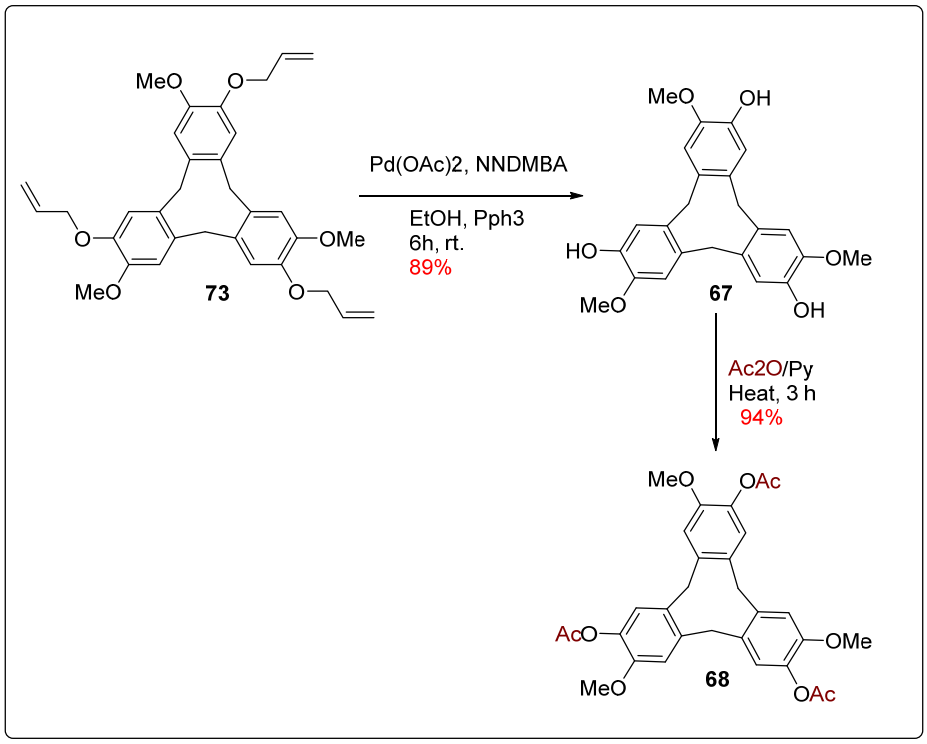
Figure 1: *Selected CTV analogues for the C-H activation studies*

2.2.1 Synthesis of Cyclotriveratrylene (CTV) Derivatives.

The trimerization of veratryl alcohol by using 65% perchloric acid in methanol for 18 h at room temperature gave the cyclotriveratrylene **66** in 57% yield (Scheme 1). Cyclotriveratrylene **68** has been synthesized from allyl-protected vanilyl alcohol using the same procedure and the resulting tris-(*O*-allyl)-cyclotriveratrylene **73** was subjected for de-allylation with $Pd(OAc)_2$, NNDMBA[56] and triphenylphosphine in ethanol at room temperature for 6h to afford the tri-hydroxy cyclotriveratrylene CTV **67** in 89% yield (Scheme 2). Finally, the acetylation of **67** with acetic anhydride in pyridine at 100°C afforded the C_3-tris-(O-acetyl)-cyclotriveratrylene **68** (C_3-functionalized CTV) in good yield.

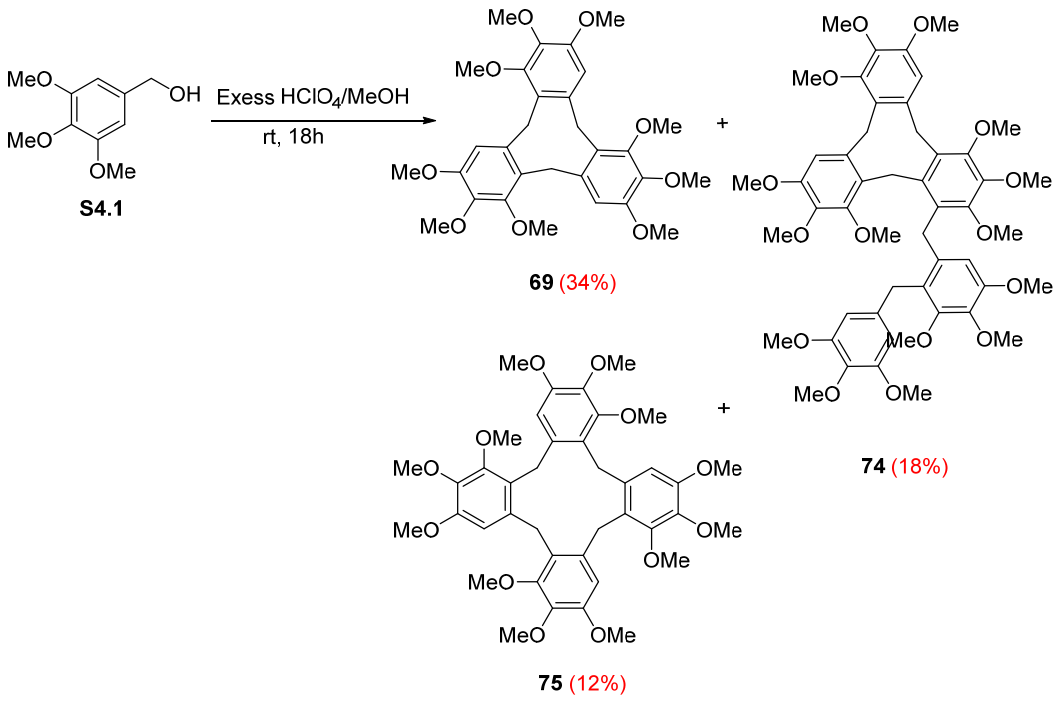


Scheme 1: *Synthesis of cyclotriveratrylene (CTV) derivatives **66** and **73***



Scheme 2: *Synthesis of cyclotriveratrylene(CTV) derivatives **68***

Next, the trimerization of 3,4,5-trimethoxybenzyl alcohol (**S4.1**) by using excess of 65% perchloric acid in methanol for 18 h at rt gave trimer **69** in 34% yield along with benzylated trimer **74** in 18% yield and the tetramer of **75** in 12% yield (Scheme 3). In the ^{1}H NMR spectrum of CTV **69**, two AB doublets at δ 4.03 and 4.43 (J = 13.6 Hz) for the two methylene protons and the remaining one methylene (CH_2) proton at δ 3.94 as singlet have appeared. This indicated a crown conformation for CTV **69**. In addition, the methoxy (OMe) protons appeared as six singlets (δ 3.69 – 3.98) and the aromatic protons occur as two singlets (δ 6.58 and 7.24). On the other hand,, in case of the ^{1}H NMR spectrum of trimer **74**, the methylene protons appeared as broadened singlets (δ 3.98 and 4.07) indicating a saddle conformation and this was further substantiated by the single crystal *X*-ray structure analysis (Figure 2). In the ^{1}H NMR spectrum of tetramer **75**, the methylene protons appeared at δ 4.04, 4.06 and 4.10 as singlets and the aromatic protons appeared at δ 6.18, 6.51 and 6.58 also as singlets. The NMR analysis of tetramer **75** indicated the possibility of either a saddle or a boat conformation for this compound.



Scheme 3: *Synthesis of cyclotriveratrylene(CTV) derivatives* ***69, 74*** *and tetramer* ***75****.*

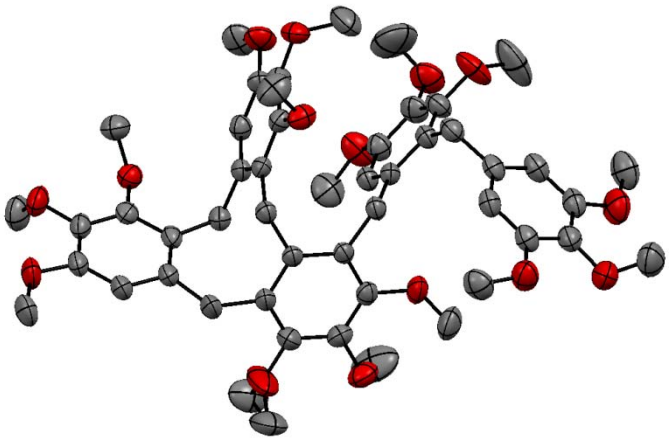


Figure 2: *Molecular structure of compound* ***74***

Having the three different CTV derivatives in hand we moved to examine their Pd-catalyzed benzylic C–H oxidations. Coming to the Pd-catalyzed benzylic oxidations, one of the earliest reports by Bryant and co-workers employed air as the oxidant for the conversion of xylene to the xylene diacetate.[52] Hydrogen peroxide is another oxidant that has been widely employed in the Pd-catalyzed oxidations.[57] A combination of benzoquinone along with MnO_2

as the co-oxidant has been employed in the Pd-catalyzed allylic oxidations. Considering all these reports, we have intended to proceed for the oxidation of **66** under all the possible conditions and examine the outcome.

Our initial experiments in this direction started with the oxidation of CTV **66** employing oxygen as reported by Bryant for toluene. As shown in Scheme 4, the aerial oxidation of CTV was carried out employing 20 mol% of palladium acetate as catalyst in acetic acid.[49] The reaction was sluggish and the CTV seems to be converting into another product **66(S)** as indicated by a clear separation of **66** and **66(S)** TLC. However, there was no progress in the reaction even after prolonged heating for 3 d. The reaction was seen to have stopped at this stage and the new product **66(S)** (obtained in 12% yield, 80% of **66** was recovered) has been separated by silica gel chromatography and characterized by spectral data analysis.

Scheme 4: *Pd–Catalyzed aerial oxidation of CTV **66***

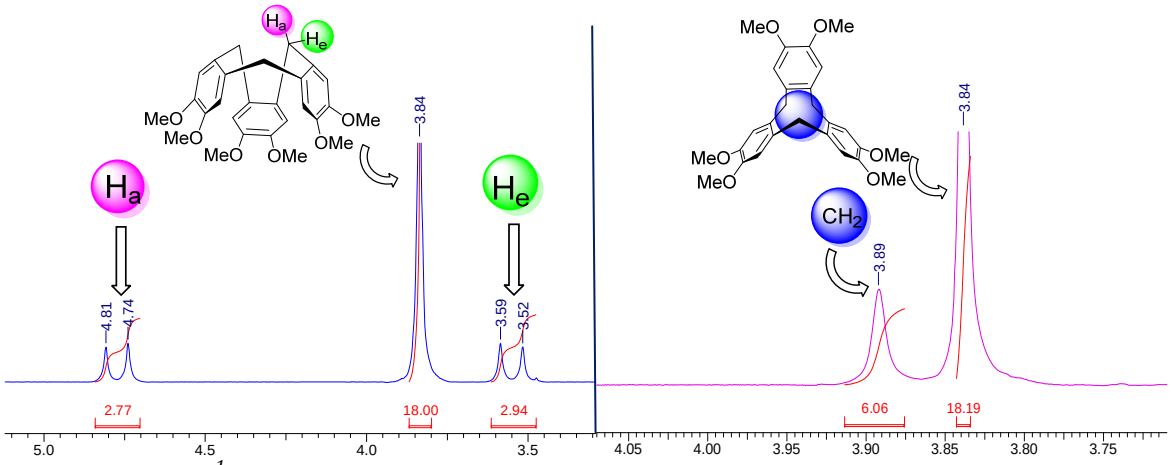
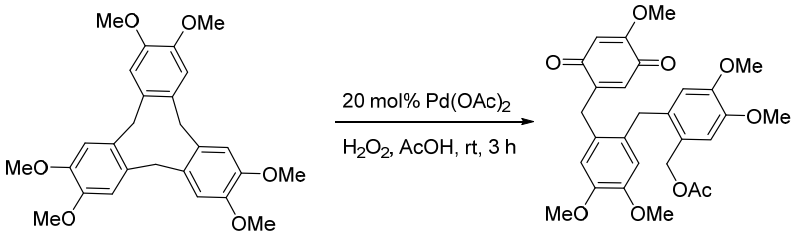


Figure 3: *^{1}H NMR spectrum of **66** CTV (crown) and **66(S)** CTV (Saddle**b**)*

Initial analysis of the constitution of newly formed **66(S)** by LCMS revealed that its mass is exactly the same as the starting **66,** revealing that it maybe the conformational isomer of **66**. In the ^{1}H NMR spectrum of compound **66(S)** (Figure 3), it has been found that all the

three methylene bridge hydrogens are intact and resonated collectively as a sharp singlet at δ 3.89 ppm. In addition, all the three aromatic protons also appeared collectively as a singlet at δ 6.83 ppm [in case of **66**, CH_2 as AB doublet at δ 3.55 and 4.77 ppm and aromatic C–H as singlet at δ 7.36].[15a]



66 **76** (77%)

Table 1.Catalyst screening for the H_2O_2 oxidations

Entry	Catalyst	Solvents	Time/h	Yield %
1	$Pd(OAc)_2$	AcOH	3	77
2	$Cu(OAc)_2$	AcOH	3	58
3	$Ni(OAc)_2$	AcOH	3	50
4	$CuCl_2$	AcOH	6	23
5	$FeCl_2$	AcOH	6	18
6	$Pd(OAc)_2$	CH_3CN	8	-
7	$Cu(OAc)_2$	CH_3CN	8	-
8	$Ni(OAc)_2$	CH_3CN	8	-

Scheme 5: *Oxidation of CTV 66 employing H_2O_2 as co-oxidant*

As the aerial benzylic oxidation of CTV **66** was found to be unsuccessful, next we examined hydrogen peroxide as a co-oxidant. The reaction was carried out at rt by employing 20 mol% of $Pd(OAc)_2$ and 10 equivalents of aq. hydrogen peroxide in acetic acid as a solvent at rt. Interestingly, the starting CTV **66** disappeared within 3 h and provided exclusively one product **76** in 77% yield. In the ^1H NMR spectrum of **76**, there are three sets of methylene (CH_2) protons seen separately at δ 3.67 (d, J = 1.8 Hz), at δ 3.87 ppm (singlet) and at δ5.86 (d, J = 2.7 Hz) and there was a methyl CH_3 that resonated at δ 1.58 ppm as a singlet. This indicated that the one of the methylene unit was separated from the aryl ring and oxidized to form the quinine derivative, the quinone moiety C–H protons appearing at δ 5.86 (d, J = 1.8 Hz). The structure of quinine **76** was also confirmed by single crystal X-ray structure analysis (Figure 4).

Considering the mild conditions when H_2O_2 was employed as a co-oxidant, to control over that oxidation, various other catalysts such as $Cu(OAc)_2$, $Ni(OAc)_2$, $CuCl_2$and $FeCl_2$[58] have been examined. However, as shown in Table 1, in all the cases, the quinine **76** was isolated as the only product with varying yields.

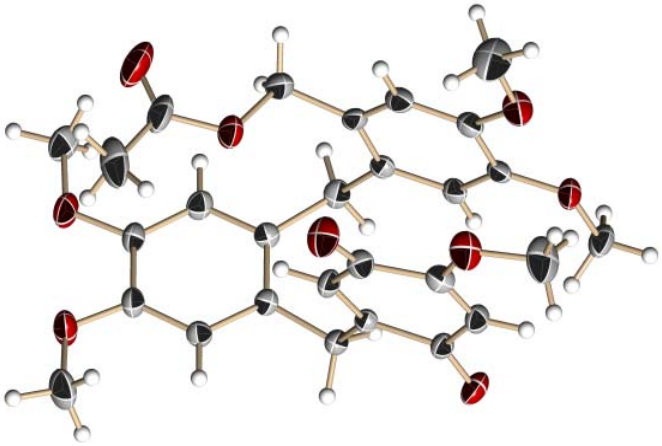
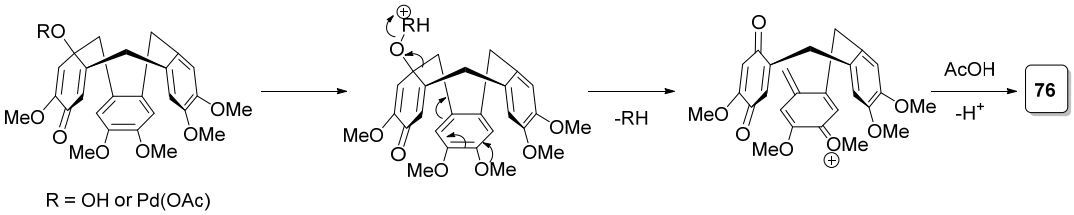


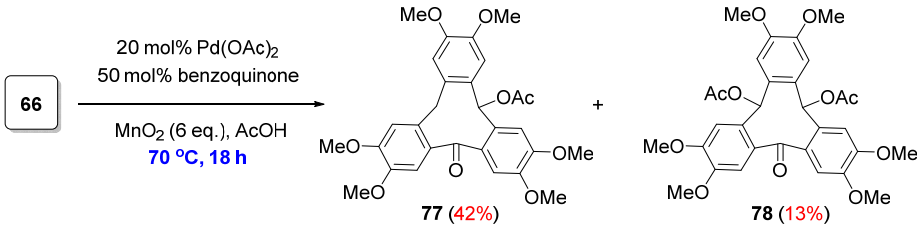
Figure 4: *Molecular structure of compound* ***76***

The formation of the quinone **76** reveals that nuclear hydroxylation (at the more electron rich ring carbon) is preferred over benzylic oxidation in the presence of hydrogen peroxide (Scheme 5).[59] There exist two possibilities for the fragmentation of the resulting bridge-head alcohol; either *via* the acid catalyzed cleavage-rearrangement reaction of the corresponding hydroperoxide[60] or a mechanism operating through a Pd-mediated oxidative fragmentation[61] of the *tert*-alcohol. The stabilization of the released benzylic carbocation through the participation of a *p*-methoxy group along with the release of the steric strain might be playing an important role during these cleavage-rearrangement reactions. Detailed mechanistic studies are required to delineate the role of the Pd-catalyst and its exact mode of action.



Scheme 5: *Possible for Pd-H_2O_2 mediated oxidation of CTV* ***66***

Next, the Pd-catalyzed benzylic C–H oxidation of CTV **66** was examined by employing benzoquinone as an additive and MnO_2 as a co-oxidant in acetic acid. The conditions employed involve the heating of a solution of CTV and $Pd(OAc)_2$ (20 mol%), benzoquinone (0.5 eq.), and MnO_2 (6 eq.) in acetic acid at 70°C. The complete disappearance of CTV was noticed after 18 h and two new products of **77** and **78** were isolated (Scheme 6).



Scheme 6: *Pd–Catalyzed C-H oxidation of CTV **66** using MnO_2 at 70°C*

The structure of the major compound **77** has been confirmed as 10-acetoxy cyclotriveratrylene-5-one (42% yield) and that of **78** as 10,15-diacetoxy cyclotriveratrylene-5-one (13% yield). In the ^{1}H NMR spectrum of **77,** the acetoxy (CH_3) methyl protons were seen to resonate at δ 2.07 ppm as singlet, the benzylic methylene protons were displayed at δ3.45 and 4.00 (J =15.2 Hz) as two AB doublets, the acetoxylated benzylic C–H proton resonated at δ 6.51 as singlet and the aromatic protons were seen to resonate as six singlets. In the ^{13}C NMR spectrum of **77**, the acetoxycarbonyl carbon resonated at δ 169.0 ppm and the benzylic carbonyl carbon appeared at δ 192.7 ppm. This indicated a crown conformation for compound **77**. Coming to **78**, in the ^{1}H NMR spectrum, the two acetoxy (CH_3) methyl protons were seen to resonate at δ 2.08 ppm as singlet, the benzylic acetoxylated C–H protons were shifted to δ 6.59 ppm as singlet and the aromatic protons were seen at δ 6.59, 7.25, and 7.53 ppm as three singlets. In the ^{13}C NMR spectrum of **78**, the two acetoxy carbonyl carbon resonated at δ 168.8 ppm as singlet and the benzylic carbonyl carbon appeared at δ 191.2 ppm. This spectral data indicated a saddle conformation for compound **78**. The saddle conformation of **78** has been further confirmed by its single crystal *X*-ray structure analysis (Figure 5).

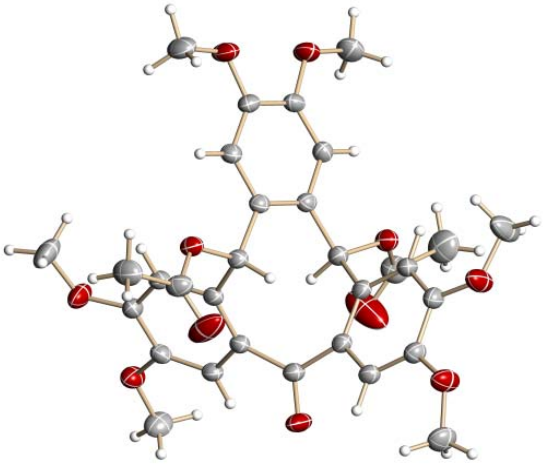
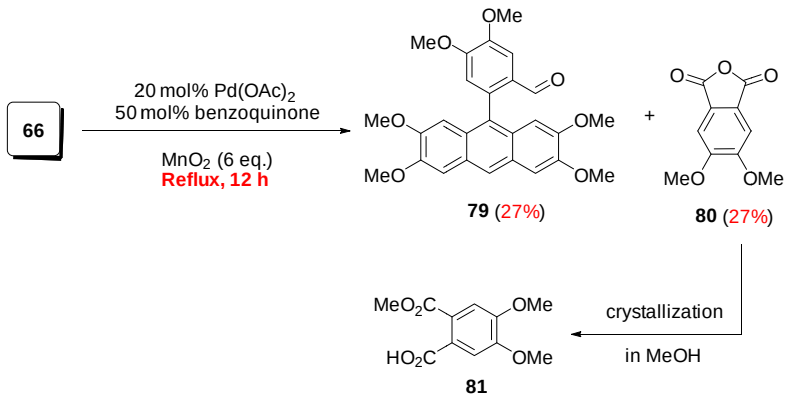


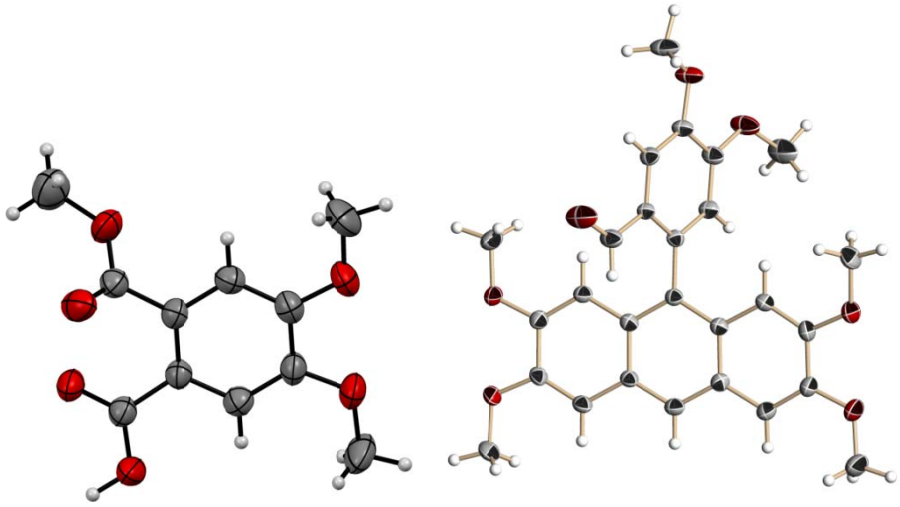
Figure 5: *Molecular structure of compound **78***

Next, we examined the same reaction at reflux temperature and employed all reagents in the same molar proportions as described above (Scheme 7). Quite interestingly, two new products **79** and **80** that are different from **77/78** were isolated. Compound **79** provided complete unsymmetrical spectra whereas the spectrum of **80** was highly symmetric with only two signals in the ^{1}H NMR, which has displayed at δ 4.03 ppm for methoxy protons and 7.36 ppm for aromatic protons and no protons corresponding to the methylene groups noticed. The ^{13}C NMR spectra of **80** displayed only five signals. The single crystal X-ray analysis of crystals resulting from recrystallization of **80** in methanol revealed that **80** is 3,4-dimethoxyphthalic anhydride that was converted to its half methyl ester **81** (Figure 7) during crystallization.[61]

The structure of compound **79** has been assigned as 2'-(9-anthracenyl)benzaldehyde with the help of ^{1}H, ^{13}C NMR and HRMS spectral as well as by single crystal X-ray analysis (Figure 6). For example, in the^{1}H NHR spectrum of **79**, all methoxy protons appeared at δ 3.73–4.09 ppm as four singlets. Furthermore, five separate singlets signals corresponding to aromatic protons and a singlet at δ 9.22 ppm corresponding to the aldehyde were seen. In the ^{13}C NMR spectrum of **79**, the aldehyde carbonyl carbon was appeared at δ 191.1ppm. The formation of aldehyde **79** reveals that it may result from the trans-annular rearrangement of partially oxidized CTV. Further experiments to probe in these directions will be described later.



Scheme 7: *Pd–Catalyzed C-H oxidation of CTV* ***66*** *using* MnO_2 *with reflux*

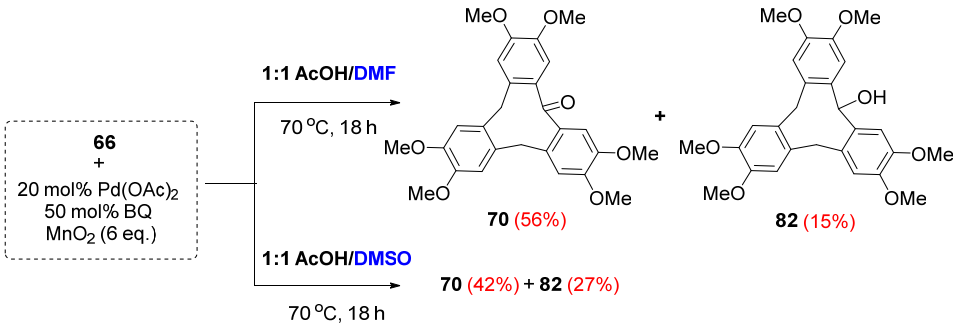


(a) (b)

Figure 6: *Molecular structures of compounds****79*** *&* ***80***

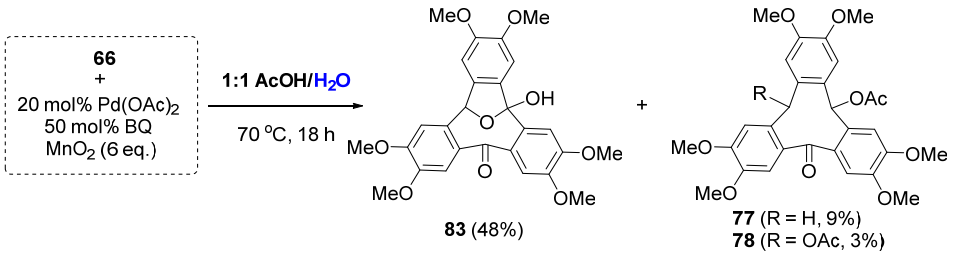
Having met with exhaustive oxidation at reflux, we next examined the oxidation of **66** with the BQ-MnO_2 system in combination with other solvents along with AcOH. As shown in Scheme 8, when employing a 1:1 AcOH-DMF as the solvent at 70 °C for 18 h, the reaction gave mainly two products that have been characterized as known compounds cyclotriveratrylene-5-one (**70**, 56% yield) and cyclotriveratrylene-5-ol (**82**, 15% yield). The spectral data of compounds **70** and **82** was in agreement with the data reported earlier in the literature.

For example, in the ^{1}H NMR spectrum of compound **70**, the two methylene protons appeared at δ 3.62 and 4.88 ppm as two doublets with a coupling constant *J* = 14.0 Hz, the methoxy (OMe) protons displayed at δ 3.84 and 3.86 ppm as singlets and the aromatic protons were seen to resonate as three singlets. In the ^{13}C NMR spectrum of **70**, the benzylic methylene carbons were displayed at δ 36.9 ppm as singlet and the carbonyl carbon resonated at δ194.0 ppm. Next with regard to the ^{1}H NMR spectrum of compound **82**, the two benzylic methylene protons appeared at δ 3.57 and 4.77 ppm as two doublets with a coupling constant *J* = 14.0 Hz, the benzylic C–H proton resonated as a singlet at down field δ 6.99 ppm, the hydroxyl (OH) proton was seen to resonate as a singlet at δ 7.0 ppm and the aromatic protons appeared as three singlets. In the ^{13}C NMR spectrum of **82**, the benzylic methylene carbons resonated at δ 35.7 ppm as singlet and the benzylic C-H carbon appeared at δ 67.0 ppm. The NMR analysis of both **70** and **82** revealed that they had crown conformations.



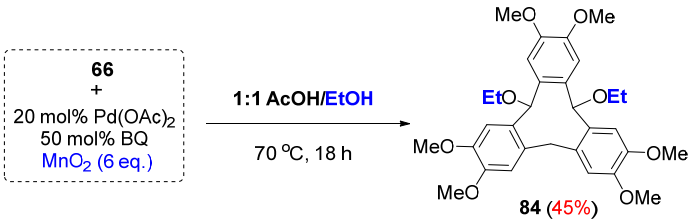
Scheme 8: *Catalytic oxidation of CTV 66 employing Pd/BQ/MnO_2 in DMF or DMSO*

Increasing the temperature or prolonging the reaction for longer periods led to the isolation of the same products in diminished yields. Next, we examined the oxidation of the CTV using the same reagents combination and replaced the solvent from DMF to DMSO. As shown in Scheme 8, in DMF too, the same two products **70** and the formation of aldehyde **79** reveals that it may result from the trans-annular rearrangement of partially oxidized CTV, which was isolated, albeit the proportion of the alcohol **82** was seen to increase. When the oxidation of **66** was conducted under similar conditions except that a 1:1 AcOH and water was used as a solvent system (Scheme 9), the reaction mixture gave completely different products – a new compound **83** was obtained in 48% yield along with the two other previously characterized compound **77** (9%) and **78** (3%), which were seen to be the minor products.



Scheme 9: *Catalytic oxidation of CTV **66** employing Pd/BQ/MnO_2 in H_2O*

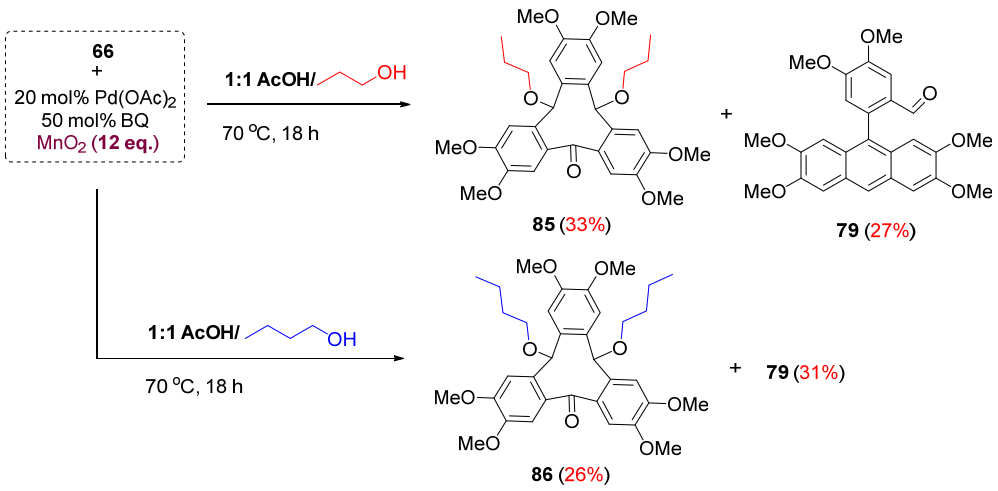
The structure of compound of **83** has been established with the help of ^{1}H and ^{13}C NMR, HR MS and IR spectral analysis. In the ^{1}H NMR spectrum of compound **83**, five signals corresponding to the methoxy groups were seen to resonate as at δ 3.61–4.0 ppm and six separate singlets were seen for the aromatic protons. There is only one benzylic C–H proton that appeared at down field δ 6.0 ppm. In the ^{13}C NMR spectrum of **83**, the methoxy carbons were seen to resonate as three singlets at δ 55.9, 56.0 and 56.1 ppm, the benzylic tertiary C–H carbon was displayed at δ 60.4 ppm, the benzylic quaternary carbon was resonated at δ 87.1 ppm and the carbonyl carbon was seen to resonate δ 181.8 ppm. In the HRMS, the exact mass of the compound as calculated for $C_{27}H_{26}O_9Na^+$ $[M+Na]^+$ was 517.1469 and it was experimentally found to be 517.1465.



Scheme 10: *Pd-Catalyzede oxidation of CTV **66** using ethanol solvent*

Next, we examined the oxidation of **66** (Scheme 10) in AcOH-ethanol (1:1). The reaction was incomplete (65% conversion) and provided mainly the 5,10-diethoxy cyclotriveratrylene (**84**) in 45% yield. In the ^{1}H NMR spectrum of compound **84**, the methyl (CH_3) protons of ethoxy group resonated at δ 1.31 ppm as triplet of triplet with a coupling constant J = 7.0, 7.0 Hz and methylene (CH_2) protons appearing as a multiplet at 3.58–3.62 ppm. The benzylic methylene (CH_2) proton was appeared at δ 3.58 and 4.78 ppm as two

doublets with a coupling constant J = 13.8 Hz, the two benzylic (C-H) protons appeared as a singlet at δ 6.45 ppm and the aromatic protons were seen to resonate as three signals at 6.78, 6.82 and 7.16 ppm. In the ^{13}C NMR spectrum, the methyl (CH_3) carbon of ethoxy groups resonated at δ15.3, 15.4 ppm as doublet, δ 35.8 ppm for the benzylic methylene carbon and the benzylic C–H carbons were appeared at δ 73.0 ppm. The ^{1}H NMR data of compound **84** revealed that it exists as a stable crown conformer. In the HRMS, the exact mass of the compound showed as calculated for $C_{31}H_{38}O_8Na^+$ $[M+Na]^+$ was 561.2459 and it was found to be 561.2449.

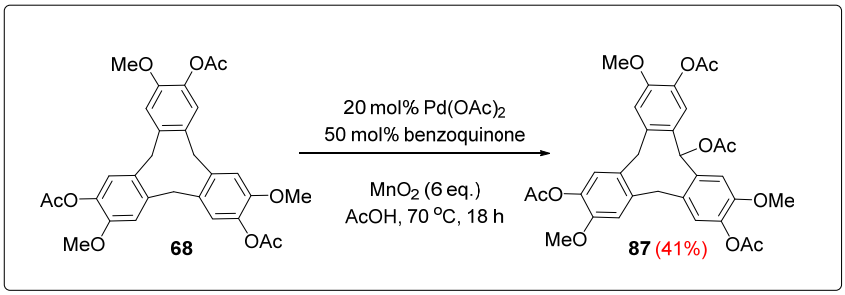


Scheme 11: *Pd-Catalyzede oxidation of CTV **66** using protic solvents*

Next, the solvent was changed from ethanol to *n*-propanol, and used **12** equivalents of MnO_2 were used and heated the reaction mixture was heated at 70°C for 18 h. Interestingly, 10,15-dipropoxy-cyclotriveratrylene-5-one (**85**, 33% yield) was obtained along with the anthracenylbenzaldehyde **79** in 27% yield (Scheme 11). Compound **85** was identified with the help of ^{1}H, ^{13}C NMR and HRMS spectral data analysis. For example, in the ^{1}H NMR spectrum of compound **85**, the methyl (CH_3) protons of the propyloxy group were resonated at δ 0.84 ppm as triplet with a coupling constant J = 7.4 Hz, the methylene (CH_3-CH_2) protons of propyloxy groups were appeared as quartet at 1.47 (J = 6.8Hz) ppm and the other methylene (CH_2-O) was resonated as multiplet at δ 2.97–3.16 ppm. The methoxy protons were seen to appear as three signals at δ 3.81, 3.95 and 3.98 ppm, the benzylic C–H protons appeared as singlet at δ 5.39 ppm and aromatic protons displayed as three signals. In the ^{13}C NMR

spectrum of compound **85**, the methyl (CH_3) carbons of propyloxy groups were resonated at δ 10.7 ppm as singlet, δ 22.8 for the methylene (CH_2-CH_2) carbons, δ 69.7 for the methylene (CH_2-O) carbons, the benzylic C–H carbons appeared at δ 73.1 ppm and the benzylic carbonyl carbon resonated at δ 192.6 ppm. In the HRMS, the exact mass of the compound calculated for $C_{33}H_{40}O_9Na^+$ $[M+Na]^+$ was 603.2565 and it was found to be 603.3557.

A similar result was observed when *n*-butanol was employed as a co-solvent gave 10,15-dibutoxy-cyclotriveratrylene-5-one **86** in 26% yield and anthracenylbenzaldehyde**79** in 31% yield. The spectral of data of **86** was comparable with that of **85**. For example, in the ^1H NMR spectrum of **86**, the terminal methyl CH_3 of butyloxy group resonated at δ 0.83 ppm as triplet with a coupling constant J = 7.0 Hz, the methylene (CH_2-CH_2) protons of butyloxy groups were appeared as multiplet at 1.23-1.48 ppm and the other methylene (CH_2-O) carbon was resonated as multiplet at δ 3.0–3.17 ppm andthe benzylic C–H protons were appeared as singlet at δ 5.38 ppm. In the ^{13}C NMR spectrum, all the carbons appeared at the expected positions. Finally, in the HRMS, the exact mass of the compound showed as calculated for $C_{35}H_{44}O_9Na^+$ $[M+Na]^+$ was 631.2878 and it was found to be 631.2874.

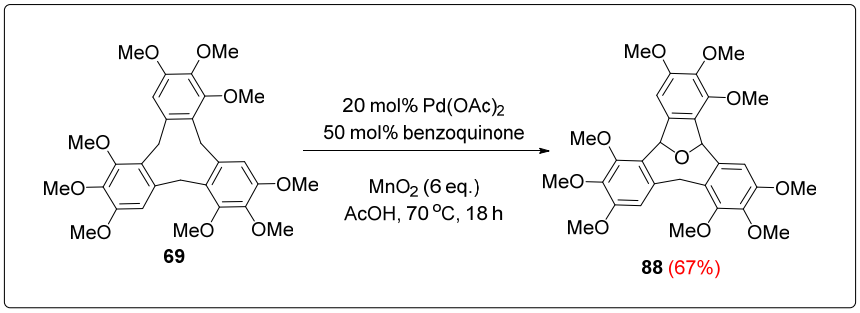


Scheme 12: *C-H oxidation of CTV analogue **68***

Next, the Pd-catalyzed oxidation of other CTV analogues **68** and **69** has been examined in acetic acid alone. The C–H oxidation of **68** (Scheme 12) was incomplete and gave mainly 5-acetyloxy-CTV **87** in 41% yield and the starting compound **68** was recovered in 55% yield. Compound **87** has been confirmed by ^1H, ^{13}C NMR data analysis. In the ^1H NMR spectrum of **87**, the methyl group of the aryl-acetyloxy group was resonated at δ 2.03 ppm as singlet and one of the benzylic-acetyloxy group resonated as singlet at δ 2.15 ppm. The methoxy protons appeared as two singlets at δ 3.79 and 3.81ppm and the benzylic methylene protons were seen to resonate as two AB doublets at 3.64 and 4.82 (J = 13.8 Hz) ppm and the benzylic C–H

proton appeared as singlet at δ 6.82 ppm and the aromatic protons were displayed as six singlets. In the ^{13}C NMR spectrum of **87**, the methyl carbon of aryl-acetyloxy group resonated at δ20.6, 21.2 ppm for the benzylic-acetyloxy carbon as singlet. The benzylic methylene carbons were displayed at δ 35.8 ppm, and the benzylic C–H carbon resonated at 68.2 ppm as singlet. The NMR analysis revealed that the compound **87** exists as a stable crown conformer. In the HRMS, the exact mass of the compound calculated for $C_{32}H_{32}O_{11}Na^+$ $[M+Na]^+$ was 615.1837 and it was found to be 615.1832.

On the other hand (Scheme 13), the C–H oxidation of **69** gave the furan derivative **88** as the main product (67% yield). The structure of the compound **88** was established with the help of the spectral and analytical data. For example, in the ^1H NMR spectrum of compound **88**, the benzylic methylene (CH_2) protons appeared at δ 2.98 and 3.72 ppm as two doublets with a coupling constant J = 14.0 Hz, the two benylic (C-H) protons appeared at δ 6.19 and 6.46 ppm as two separate singlets and the aromatic protons were resonated as three singlets at δ 6.76, 6.79 and 6.85 ppm. In the ^{13}C NMR spectrum, the benzylic methylene carbon seen to resonate at δ 27.5 ppm, the benzylic C–H carbon was appeared at δ 62.2 ppm. The structure of compound **88** has been confirmed by single crystal X-ray structure analyses (Figure 8).



Scheme 13: *C-H oxidation of CTV analogue **69***

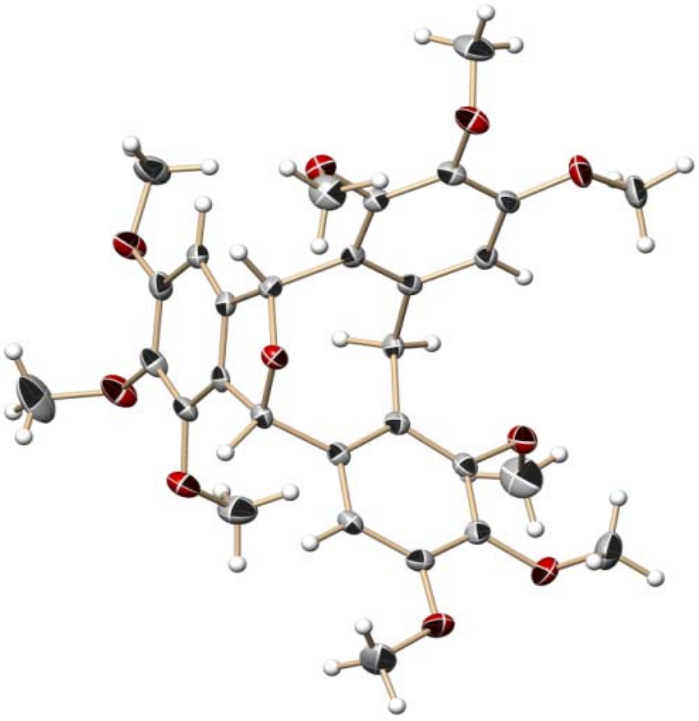
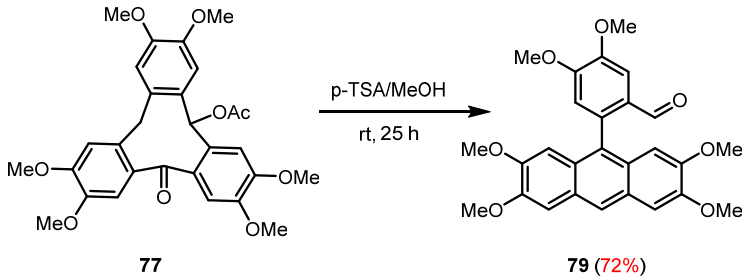


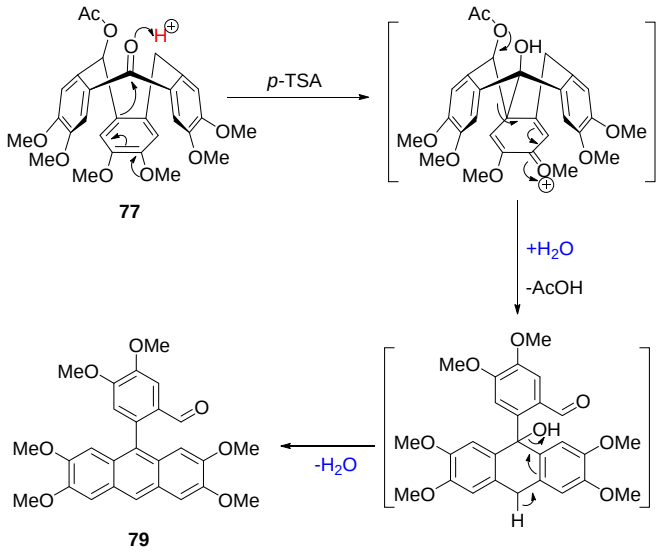
Figure 8: *Molecular structure of compounds* ***88***

2.2.3. Acid or base catalyzed rearrangements

As described earlier, when the oxidation of CTV with Pd/BQ/MnO2 combination was carried out in acetic acid alone at reflux, we isolated a novel anthracene aldehyde **79** as one of the product. We presumed that it might be arising from the acid catalyzed trans-annular rearrangement of partially oxidized CTV derivatives. Having an easy access for the differently synthesized and differently oxidized CTV derivatives **77** and **78** in hand, we next examined their trans-annular rearrangements to unravel the origin of anthracene aldehyde **79**. Surprisingly, the acid catalyzed rearrangement of 10-acetoxycyclotriveratrylene-5-one (**77**) with *p*-toluenesulfonic acid (*p*-TSA) in methanol at room temperature for 24 h gave the same anthracenealdehyde **79** as the main product (72% yield) (Scheme 14). With this observation in mind, we extended the following mechanism for the trans-annular rearrangement of **77** (Scheme 15). The acid catalyzed Friedel-Crafts type electrophilic attack by an aromatic ring on the trans-annular carbonyl group in **77** leads to the corresponding arenium ion intermediate. Rearomatization through a C-C bond cleavage to generate an aldehyde, from which a molecule of water is eliminated, gave the anthracenealdehyde derivative **79**.

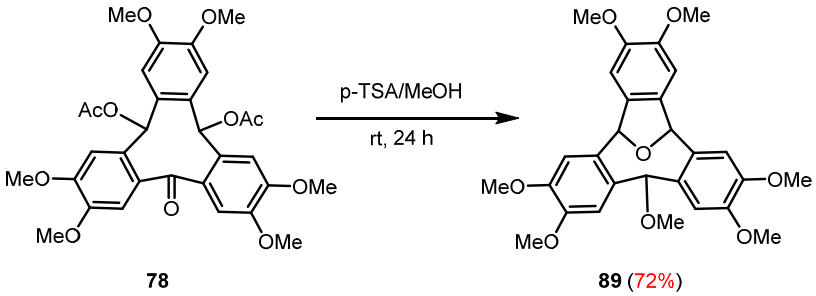


Scheme 14: *Acid or base catalyzed rearrangement of CTV-monoacetoxylketone**77**.*



Scheme 15: *transannular rearrangement of ketoacetate**77***

Next, we performed acid catalyzed cyclization of 15-diacetoxy cyclotriveratrylene-5-one (**78**) with *p*-toluenesulfonic acid (*p*-TSA) in methanol at room temperature for 24 h (Scheme 16). The rearrangement of **78** proceeded smoothly and provided exclusively the cyclized compound **89** in excellent yield. The structure of compound **89** has been established with the help of ^{1}H, ^{13}C NMR, HRMS and single crystal X-ray structure analysis (Figure 9). In the ^{1}H NMR of **89**, the benzylic methoxy (OMe) protons appeared as a singlet at δ 2.94 ppm, the benzylic methoxy group C-H proton appeared at δ 4.73 ppm, the benzylic C–H protons of cyclised benzofuran occured as singlet at δ 6.09 ppm and the aromatic protons were resonated as three singlets at δ 6.78, 6,92 and 7.23 ppm. In the 13C NMR spectrum, the benzylic methoxy carbon appeared at δ 57.2 ppm, δ 73.9 ppm for methoxy substituted benzylic C-H carbon, and the furan cyclised C–H carbon resonated at δ 88.2 ppm.



78 **89** (72%)

Scheme 16: *Acid catalyzed cyclization of diacetate**78***

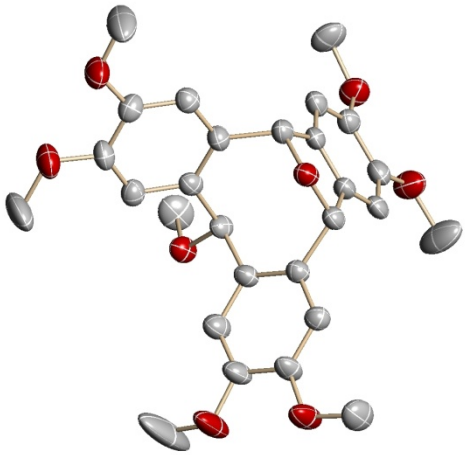
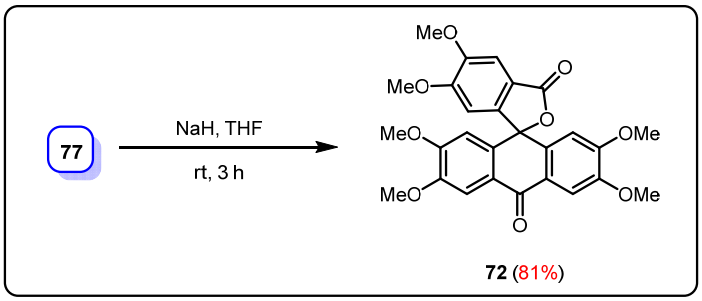


Figure 9: *Molecular structure of compound **89***

Next, when **77** was treated with sodium hydride (NaH) in THF at room temperature for 3h, it gave mainly the known 10-benzoyloxy-9-anthrone (**72,** 80% yield) in excellent yields (Scheme 17). The structure of compound **72** has been confirmed by comparing its spectral data with the data reported earlier and also by a single crystal X-ray structure analysis (Fig. 10). The compound **72** has been isolated earlier during the oxidation of CTV with permanganate or chromate solutions and it was proposed that **72** resulted from the acid catalyzed trans-annular rearrangement of intermediate CTV-trione. The formation of the compound **72** from the over oxidation of the acetoxyketone **78** with NaH and that of the benzofuran **89** from the compound **77** with a net carbonyl reduction reveals that these CTV derivatives can undergo oxidation or reduction quite easily.



Scheme 17: *Trans-annular rearrangement of ketoacetate* ***77***

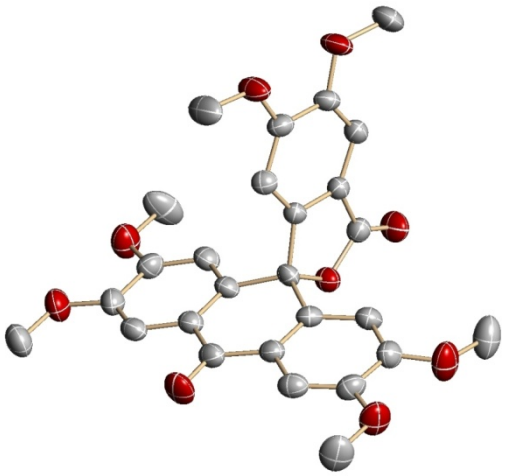
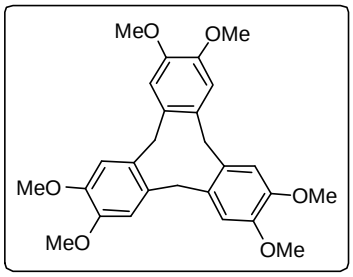


Figure 10: *Molecular structure of compound* ***72***

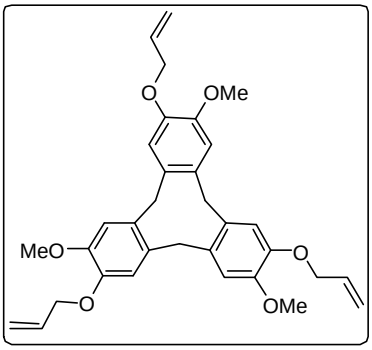
To conclude, the Pd-catalyzed C–H oxidation of the CTV has been examined with different co-oxidants under different conditions. An interesting array of CTV derivatives have been synthesized with a simple change in the conditions. Some of the oxidations are selective resulting in CTV derivatives with interesting structural features. The acid/base catalyzed trans-annular rearrangement of the partially oxidized CTV derivatives reveal that these compounds readily undergo oxidation or reduction depending upon the conditions employed.

2.3.1. General Procedure for synthesis of Cyclotriveratrylene CTV (A)

A solution of veratryl alcohol (10 g, 0.59 mol) in 150 mL methanol, cooled in an ice bath and magnetically stirred, was added dropwise 30 mL of 65% perchloric acid, and the resulting pink solution was stirred under nitrogen at room temperature for 18 h The solvent was evaporated and the residue was dissolved in ethylacetate (200 mL), water (100 mL) and the organic phase was thoroughly washed with water until neutral. The ethyl acetate solution was dried over sodium sulfate and evaporated under vacuum, and the residue was purified by column chromatography using ethylacetate-petroleum ether (4:6, R*f* = 0.4) to give cyclotriveratrylene CTV **66 (**5.1g, 57%) as white solid. Mp. 234 °C, ^{1}H NMR (200 MHz, CDCl3): δ 3.55 (d, *J* = 13.8 Hz, 3H), 3.84 (s, 18H), 4.77 (d, J = 13.8 Hz, 3H), 6.83 (s, 6H) ppm; ^{13}C NMR (50 MHz, CDCl3): δ 36.3, 55.9, 112.9, 131.7, 147.5 ppm; HRMS (EI) Calculated for $C_{27}H_{30}O_6$ (M^+) 450.2042, found 450.2040.

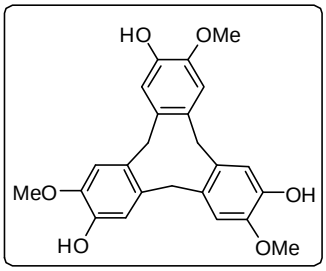


Tris-(O-allyl)-cyclotriveratrylene (73): The general procedure **A** was followed. Phenol-protected vanillyl alcohol **S1.1a** (10g, 0.52 mol) and 30 mL of 65% perchloric acid. The product was purified by column chromatography using ethylacetate-petroleum ether (3:7, R*f* = 0.4) to give **73** (5g, 55%) as white solid. Mp. 174–175, ^{1}H NMR (200 MHz, CDCl3): δ 3.51 (d, *J* = 13.8 Hz, 3H), 3.84 (s, 9H), 4.57-4.61 (m, 6H), 4.74 (d, *J* = 13.8 Hz, 3H), 5.21-5.28 (m, 6H), 5.97-6.16 (m, 3H), 6.79 (s, 3H), 6.85 (s, 3H) ppm; ^{13}C NMR (50 MHz, CDCl3): δ 36.5 (3C), 56.0 (3C), 70.1 (3C), 113.4 (3C), 115.4 (3C), 117.5 (3C), 131.6 (2C), 132.2 (2C), 133.7 (4C), 146.6 (2C), 148.1(2C) ppm; HRMS (ESI) Calculated for $C_{33}H_{36}O_6Na^+$ $[M+Na]^+$: 551.6342, found 551.6340.

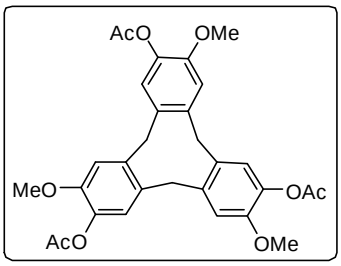


Tri-hydroxy cyclotriveratrylene (67): A solution of 1,3-Dimethyl barbituric acid (4.5g, 28.5mmol), $Pd(OAc)_2$ (106mg, 0.47mmol) and triphenylphosphine (1.2g, 4.7mmol) in 100 mL of ethanol, in a 250 mL of round-bottomed flask, stirred about 5-10 mints at rt. The solution colour became orange, after dissortion of all the ingredients in ethanol. CTV **66** (5g, 9.5mmol) in 15 mL THF was added, after 10 mints the colour of solution gradually changed from orange

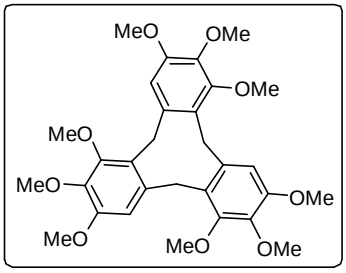
to strong orange or blood colour. The reaction mixture stirred for 3h at rt. The mixture was filtrated with celite layer, the celite layer was washed successively with 100 mL of $CHCl_3$/EtOAc (1:1). After evaporation of the solvent, the product was purified by column chromatography using chloroform-ethylacetate (9:1, R*f* = 0.4) to give **67** as a brown solid (3.4g, 89%), Mp. 308-309°C dec. ^{1}H NMR (200 MHz, Acetone d^6): δ 3.49 (d, *J* = 13.8 Hz, 3H), 3.80 (s, 9H), 4.73 (d, *J* = 13.8 Hz, 3H), 6.94 (s, 2H), 7.0 (s, 2H), 7.24 (s, 2H) ppm; ^{13}C NMR (50 MHz, Acetone d^6): δ 36.4 (3C), 56.5 (3C), 114.2 (3C), 117.1(3C), 131.9 (3C), 133.8 (3C), 145.8 (3C), 146.8 (3C) ppm; HRMS (ESI) Calculated for $C_{24}H_{24}O_6Na^+$ $[M+Na]^+$: 431.1465, found 431.1463.



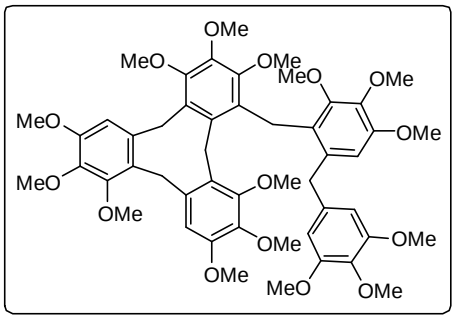
Tris-(O-acetyl)-cyclotriveratrylene (68): A solution of tri-hydroxy cyclotriveratrylene **67** (3g, 7.3 mmol), acetic anhydride (4.5 mL, 44 mmol) and then pyridine (1.1 mL, 14.6 mmol) were added. The resultant solution was heated at 100°C for 3 h. Water was added to the reaction mixture, and ethyl acetate was then added. The organic layer was washed with 1 N HCl, a saturated sodium hydrogen carbonate aqueous solution, and saturated brine, and was dried with anhydrous sodium sulfate. The organic layer was filtered, and concentrated under reduced pressure to give pure compound **68** (3.68 g, 94% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.17 (s, 9H), 3.59 (d, *J* = 13.8 Hz, 3H), 3.81 (s, 9H), 4.73 (d, *J* = 13.8 Hz, 3H), 6.87(s, 3H), 7.01(s, 3H)ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.7(s, 3C), 36.3(s, 3C), 56.1(s, 3C), 114.0(s, 3C), 123.9(s, 3C), 131.3(s, 3C), 137.89(s, 3C), 138.3(s, 3C), 149.6(s, 3C), 169.1ppm; HRMS (ESI) Calculated for $C_{30}H_{30}O_9Na^+$ $[M+Na]^+$: 557.1778, found 557.1779.



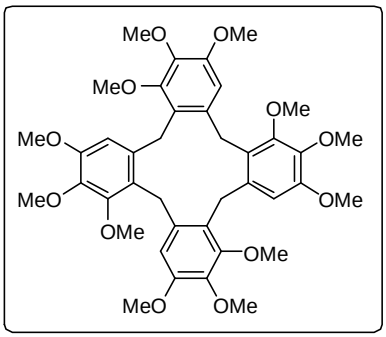
Cyclotriveratrylene CTV (69): The general procedure **A** was followed. 3,4,5-trimethoxy benzyl alcohol (**S4.1**) (10g, 50.5 mmol) Excess 45 mL of 65% perchloric acid. The crude product was purified by column chromatography using ethylacetate-pet.ether (4:6, R*f* = 0.4–0.3) to give trimer CTV **69** (3.18g, 34%) along with aryl-substituted trimer CTV **74** (1.14g, 12%) and cyclotetraveratrylene CTTV **75** (1.7g, 18%) as white solids.



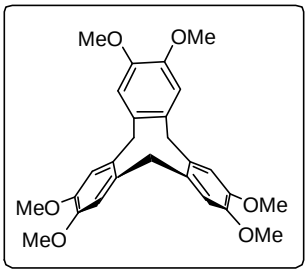
Characterization data of CTV (69): Mp. 200-202, ^{1}H NMR (200 MHz, CDCl3): δ 3.69 (s, 3H), 3.78 (s, 6H), 3.80 (s, 6H), 3.82 (s, 3H), 3.84 (s, 3H), 3.94 (s, 2H), 3.98 (s, 6H), 4.03 (d, *J* = 13.7 Hz, 2H), 4.43 (d, *J* = 13.7 Hz, 2H), 6.58 (s, 1H), 7.24 (s, 2H) ppm; ^{13}C NMR (50 MHz, CDCl3): δ 29.8 (2C), 31.2, 55.6 (2C), 55.7, 60.4 (2C), 60.5 (3C), 60.7, 109.9, 110.2 (2C), 124.9, 125.4 (3C), 134.9, 136.1 (3C), 140.3, 140.6, 151.4 (4C) ppm; HRMS (ESI) Calculated for $C_{30}H_{36}O_9Na^+$ $[M+Na]^+$: 563..2252, found 563.2241.



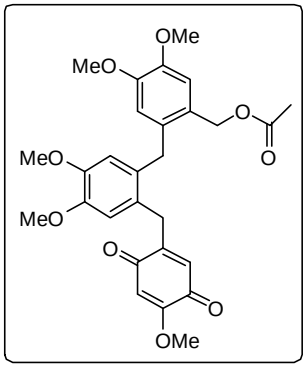
Characterization data of CTV (74): Mp. 115°C, ^{1}H NMR (200 MHz, CDCl3): δ 3.36 (s, 3H), 3.45 (s, 3H), 3.49 (s,3H), 3.65 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.74 (s, 3H), 3.76 (s, 6H), 3.77 (s,3H), 3.78 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 3.89 (s, 2H), 3.98 (s, 4H), 4.06 (s, 4H), 5.60 (s, 1H), 6.41 (s, 2H), 6.50(s, 1H), 6.54 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl3): δ 29.2, 29.6, 30.5, 30.8, 31.7, 55.1, 55.6, 55.7, 55.9 (2C), 60.2, 60.4, 60.5 (2C), 60.6 (2C), 60.7 (2C), 60.9, 61.1, 105.1 (2C), 106.5, 109.6, 110.1, 123.7, 124.5, 124.6, 128.0, 129.2, 134.4, 134.7, 134.9, 135.4, 135.8, 137.0 (2C), 139.6, 140.2, 140.4, 150.0, 151.1 (2C), 151.3 (2C), 151.5 (2C), 151.7, 153.0 (2C) ppm; HRMS (ESI) Calculated for $C_{50}H_{60}O_{15}Na^+$ $[M+Na]^+$: 923.3824, found 923.3811.



Characterization data of cyclotetraveratrylene CTTV (75): Mp. 76-78°C, ^{1}H NMR (200 MHz, CDCl3): δ 3.62 (s, 3H), 3.63 (s, 3H), 3.66 (s,6H), 3.72 (s, 3H), 3.73 (s, 3H), 3.75 (s, 6H), 3.77 (s, 3H), 3.83 (s, 6H), 3.89 (s,3H), 3.99 (s, 2H), 4.04 (s, 2H), 4.06 (s, 2H), 4.10 (s, 2H), 6.18 (s, 2H), 6.51 (s, 1H), 6.58 (s, 1H) ppm; ^{13}C NMR (50 MHz, CDCl3): δ 28.3, 29.2, 31.6, 32.1, 55.6, 55.7(2C), 55.8, 60.3, 60.5(2C), 60.6, 60.7, 60.8, 61.0, 104.9, 109.8, 110.4, 124.5, 125.0, 128.2, 129.0, 134.3, 134.7, 135.5, 137.1, 1140.2, 140.4, 150.2, 151.2, 151.3, 151.4, 151.5, 152.6 ppm; HRMS (ESI) Calculated for $C_{40}H_{48}O_{12}Na^+$ $[M+Na]^+$: 743.3038, found 743.3027.



Cyclotriveratrylene-Saddle Conformer (66(S)): A solution of cyclotriveratrylene (**66)** (200 mg, 0.4 mmol), $Pd(OAc)_2$ (20 mg, 0.08 mmol) and potassium acetate (42 mg, 0.22 mmol) in 20 mL of acetic acid was stirred at 100 °C for 24 h, while air was blown over its surface. After 24 h, the reaction mixture was cooled and filtrated over the Celite pad. The filtrate was diluted with an equal volume of water and extracted with EtOAc (2 x 20 ml). The combined extract was washed successively with a saturated $NaHCO_3$ solution, water, and brine, dried (Na_2SO4) and evaporated under reduced pressure. The crude was purified by column chromatography (ethyl acetate-petroleum ether (4:6, R*f* = 0.3) to obtain starting CTV **66** (160 mg, 80%) and **66(S)** (22 mg, 12%) as a white solid. Mp. 219-220°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.84 (s, 18H), 3.89 (s, 6H), 6.62 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.5, 56.0, 113.2, 131.8, 147.7 ppm; HRMS (ESI) Calculated for $C_{27}H_{31}O_6$ $[M+H]^+$: 451.2115, found 451.2103.

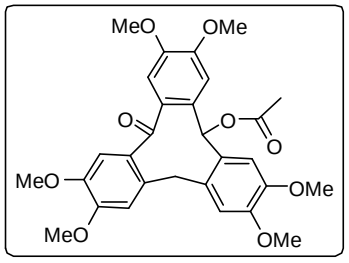


Pd-catalyzed Oxidation of CTV 66 in AcOH with H_2O_2 at rt (76): A solution of CTV **66** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol) in acetic acid (10 mL) was treated slowly with 30% aqueous H_2O_2 (0.2 ml, 2 mmol,) and stirred at rt for 3 h. The excess peroxide was quenched with MnO_2 and the reaction mixture was filtered over Celite pad and the Celite pad was washed successively with 35 mL of EtOAc and 25 mL of water. The organic layer was separated and the aqueous layer was extracted three times with 15 mL of EtOAc. The combined organic layer was washed successively with water, aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by column chromatography using ethyl acetate-petroleum ether (3:7, R*f* = 0.4) to afford quinone **76** (86 mg, 77%) as an orange solid. Mp. 120–121°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.58 (s, 3H), 3.67 (d, *J* = 1.8 Hz, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.88 (s, 2H), 4.93 (s, 2H), 5.86 (d, *J* = 2.7Hz, 2H), 6.47 (s, 1H), 6.62 (s, 2H), 6.75 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.8, 32.4, 36.3, 55.7, 55.8, 55.9, 56.0, 56.2, 64.2, 107.3, 113.4, 113.7, 113.9, 114.2, 126.1, 126.5, 130.6, 130.9, 131.9, 147.1, 147.7, 148.0, 148.8, 148.8, 158.4, 170.8, 182.0, 187.4 ppm; FTIR ($CHCl_3$): ν 3435 (br), 3020, 1736, 1651, 1605, 1517, 1216, 1021 cm-1; HRMS (ESI) Calculated for $C_{28}H_{30}O_9Na^+$ $[M+Na]^+$: 533.1782, found 533.1782.

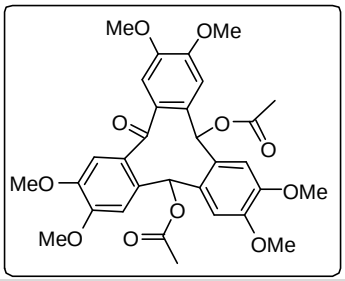
2.3.2. General Procedure for C–H Oxidation with MnO_2 and BQ (B): In a 250-mL round-bottomed, were placed CTV **66** (2.22 mmol), $Pd(OAc)_2$ (0.4 mmol), benzoquinone (1.1 mmol) and 100 mL of acetic acid and heated to 70 °C To this manganese dioxide (13.3 mmol) was added and the reaction mixture was stirred at 70 °C for 18h. The reaction mixture was cooled and diluted with 50 mL of EtOAc and stirred for 10 min. The content was filtrated over Celite pad and the Celite pad was washed successively with 50 mL of EtOAc and 100 mL of water. The organic phase was separated and washed successively with water, 2N NaOH, brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by column chromatography using a mixture of ethyl acetate-petroleum ether as eluent to give corresponding products.

Pd-catalyzed Oxidation of CTV 66 in AcOH at 70 °C:

The general procedure **B** was followed. **66** (1 g, 2.22 mmol), $Pd(OAc)_2$ (100 mg, 0.4 mmol), benzoquinone (120 mg, 1.1 mmol) and MnO_2 (1.2 g, 13.3 mmol). The product was purified by column chromatography using ethyl acetate-petroleum ether (4:6, R*f* = 0.3) as the eluent to give 10-acetoxycyclotriveratrylene-5-one **77** (490 mg, 42%) and 10,15-diacetoxycyclotriveratrylene-5-one **78** (165 mg, 13%) as white solids.



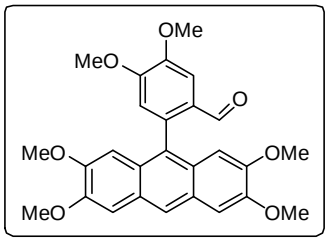
***Characterization data of 77*:** Mp. 182–183 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07 (s, 3H), 3.45 (d, *J* = 15.2 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 3.96 (s, 6H), 3.98 (s, 3H), 4.00 (d, *J* = 15.2 Hz, 1H), 6.51 (s, 1H), 6.56 (s, 1H), 6.79 (s, 1H), 7.11 (s, 1H), 7.24 (s, 1H), 7.40 (s, 1H), 7.56 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.0, 37.5, 55.8, 55.9, 56.0, 56.1, 56.1, 56.2, 68.6, 107.8, 109.5, 110.7, 111.8, 112.6, 114.2, 131.1, 131.3, 131.8, 132.7, 133.2, 147.6, 147.9, 148.1, 148.8, 152.6, 152.8, 169.0, 192.7 ppm; FTIR ($CHCl_3$): ν 3402 (br), 1597, 1511, 1264, 1218, 1020, 768 cm-1; HRMS (ESI) Calculated for $C_{29}H_{30}O_9Na^+$ $[M+Na]^+$: 545.1782, found 545.1784.



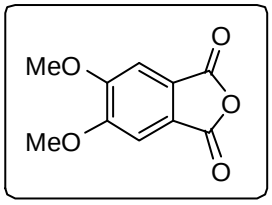
Characterization data of 78: Mp. 190–191°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 6H), 3.81 (s, 6H), 3.97 (s, 6H), 3.98 (s, 6H), 6.59 (s, 2H), 6.95 (s, 2H), 7.26 (s, 2H), 7.53 (s, 2H) ppm; 13C NMR (50 MHz, $CDCl_3$): δ 21.0, 55.9 (2C), 56.1 (2C), 56.2 (2C),

68.3, 107.6 (2C), 109.4 (2C), 111. (2C), 129.9 (2c), 131.0 (2C), 133.2 (2C), 147.9 (2C), 149.1 (2C), 153.0 (2C), 168.8, 191.2ppm; FTIR ($CHCl_3$): ν 3414 (br), 3016, 1602, 1514, 1267, 1216, 1094, 1021, 757 cm-1; HRMS (ESI) Calculated for $C_{31}H_{32}O_{11}Na^+$ $[M+Na]^+$: 603.1837, found 603.1838.

Pd-catalyzed Oxidation of CTV 66 in AcOH at reflux: The general procedure **B** was followed **-66** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), benzoquinone (12 mg, 0.1 mmol) and MnO_2 (114 mg, 1.3 mmol), the mixture was refluxed for 12 h. After usual workup, the crude was purified by column chromatography using ethyl acetate-petroleum ether (3:7, R*f* = 0.4) as the eluent to give 2'-(9-anthracenyl)benzaldehyde **79** (41 mg, 44%) and 3,4-dimethoxyphthalic anhydride **80** (14 mg, 15%) as yellow solid.



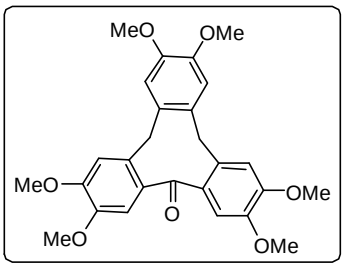
***Characterization data of* 79:** Mp. 126 °C, ^1H NMR (200 MHz, $CDCl_3$): δ 3.73 (s, 6H), 3.92 (s, 3H), 4.05 (s, 6H), 4.09 (s, 3H), 6.59 (s, 2H), 6.89 (s, 1H), 7.21 (s, 2H), 7.71 (s, 1H), 8.17 (s, 1H), 9.22 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.7 (2C), 55.9, 56.0, 56.1, 56.4, 103.1 (2C), 105.0 (2C), 108.3, 113.1, 113.8, 123.2, 127.0 (2C), 128.6, 131.7, 138.6, 147.7, 149.0, 149.3 (2C), 149.9 (2C), 154.2, 191.11ppm; FTIR ($CHCl_3$): ν 3432 (br), 3020, 2930, 1596, 1509, 1490, 1434, 1267, 1216, 1149, 1095, 1014cm-1; HRMS (ESI) Calculated for $C_{27}H_{26}O_7Na^+$ $[M+Na]^+$: 485.1571, found: 485.1566.



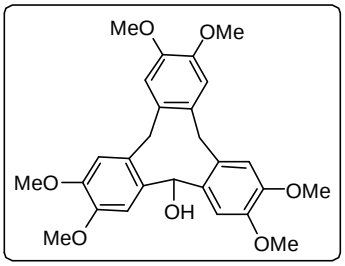
***Characterization data of* 80:** MP. 167.168 °C, (400 MHz, $CDCl_3$): δ 4.04 (s, 6H), 7.36 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.9 (2C), 106.1(2C), 124.9 (2C), 155.8 (2C), 163.1(2C) ppm; HRMS (ESI) Calculated for $C_{10}H_8O_5Na^+$ $[M+Na]^+$: 231.0264, found: 231.0262.

Pd-catalyzed Oxidation of CTV 66 in AcOH-DMF (1:1):

The general procedure **B** was followed. **66** (200 mg, 0.4 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), benzoquinone (24 mg, 0.2 mmol) and MnO_2 (230 mg, 2.6 mmol) in 30 mL of acetic acid and DMF (1:1). After usual workup, the resulting crude was purified by column chromatography (ethyl acetate-petroleum ether 4:6) as the eluent to give cyclotriveratrylene-5-one **70** (115 mg, 56%) and cyclotriveratrylene-5-ol **82** (31 mg, 15%) as yellow solids

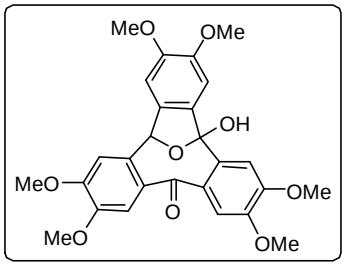


Characterization data of 70: Mp. 197–198 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.62 (d, *J* = 14.0 Hz, 2H), 3.84 (s, 12H), 3.86 (s, 6H), 3.88 (d, *J* = 14.0 Hz, 2H), 6.80 (s, 2H), 6.81 (s, 2H), 7.07 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.9 (2C), 55.8 (2C), 55.9 (2C), 56.1 (2C), 111.4 (2C), 112.6 (2C), 114.2 (2C), 131.9 (2C), 132.7 (2C), 132.9 (2C), 147.4 (2C), 147.8 (2C), 152.5 (2C), 194.0 ppm; HRMS (ESI) Calculated for $C_{27}H_{29}O_7$ [M+H]+: 465.1908, found 465.1909, HRMS (ESI) Calculated for $C_{27}H_{28}O_7Na$+ $[M+Na]^+$: 487.1727, found 487.1725.



Characterization data of 82: Mp. 144–145 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.57 (d, *J* = 14.0 Hz, 2H), 3.83 (s, 6H), 3.84 (s, 6H), 3.87 (s, 6H), 4.77 (d, *J* = 14.0 Hz, 2H), 6.77 (s, 2H), 6.80 (s, 2H), 6.99 (s, 1H), 7.28 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.7 (2C), 55.8 (2C), 55.9 (2C), 56.0 (2C), 67.1, 107.9 (2C), 112.3 (2C), 113.1 (2C), 129.7 (2C), 131.3 (2C), 134.3 (2C), 147.8 (2C), 148.1 (2C), 148.2 (2C) ppm; HRMS (ESI) Calculated for $C_{27}H_{29}O_6$ $[M-H_2O]^+$: 449.1959, found 449.1956.

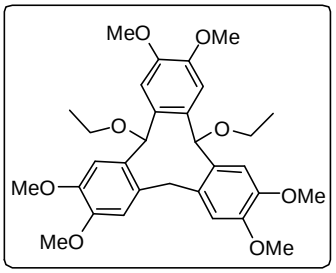
Pd-catalyzed Oxidation of CTV 66 in AcOH-H_2O (1:1): The general procedure **B** was followed. **66** (200 mg, 0.4 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), benzoquinone (24 mg, 0.2 mmol) and MnO_2 (229 mg, 2.6 mmol) in 30 mL of acetic acid and water (1:1). After usual workup, the crude was purified by column chromatography using ethyl acetate - petroleum ether (1:1, R*f* = 0.3) as the eluent to give hemi-acetal **83** (106 mg, 48%) with **77** (21 mg, 9%) and **78** (9 mg, 3%).



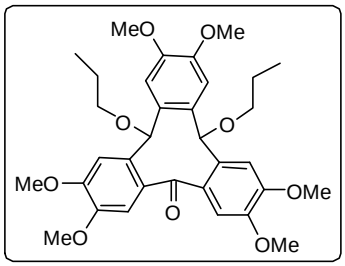
Characterization data of 83: yellow solid, Mp. 156–157 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.61 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.00 (s, 6H), 6.00 (s, 1H), 6.60 (s, 1H), 6.97 (s, 1H), 7.10 (s, 1H), 7.41 (s, 1H), 7.75 (s, 1H), 7.77 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.9 (2C), 56.0 (2C), 56.1 (2C), 60.4, 87.1, 102.0, 103.3, 105.0, 107.9, 108.2, 110.6, 123.4, 124.0, 128.0,

138.7, 139.8, 140.0, 149.1 (2C), 149.7, 151.3, 153.5, 153.6, 181.8 ppm; FTIR ($CHCl_3$): ν 3432 (br), 3020, 1598, 1508, 1465, 1421, 1292, 1292, 1117, 1019 cm-1; HRMS (ESI) Calculated for $C_{27}H_{26}O_9Na^+$ $[M+Na]^+$: 517.1469, found 517.1465.

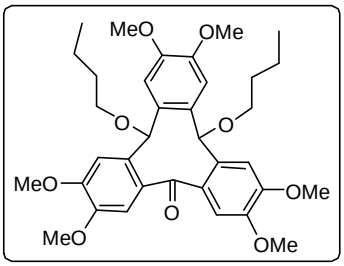
Pd-catalyzed Oxidation of CTV 66 in AcOH-EtOH (1:1): The general procedure **B** was followed. **66** (100 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), benzoquinone (12 mg, 0.1 mmol) and MnO_2 (114 mg, 1.3 mmol) in 20 mL of acetic acid and ethanol (1:1). After usual workup, the crude was purified by column chromatography using ethyl acetate - petroleum ether (3:7, R*f* = 0.3) as the eluent to give CTV **66** (35 mg) and 5,10-diethoxycyclotriveratrylene **84** as yellow solid (53 mg, 45%), Mp. 97-98 °C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31 (tt, *J* = 7.0, 7.0 Hz, 6H), 3.58 (d, *J* = 13.8Hz, 1H), 3.58-3.62 (m, 4H), 3.84 (s,9H), 3.85 (s, 9H), 4.78 (d, *J* = 13.8Hz, 1H), 6.45 (s, 2H), 6.78 (s, 2H), 6.82 (s, 2H), 7.26 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.3 (2C), 35.7, 55.8 (4C), 55.9 (2C), 64.1 (2C), 73.0 (2), 107.3, 107.9, 108.2, 112.3, 113.0, 113.1, 129.6, 130.1, 131.3 (2C), 133.0, 134.5, 147.6, 147.7, 148.0, 148.1, 148.2ppm; HRMS (ESI) Calculated for $C_{31}H_{38}O_8Na^+$ $[M+Na]^+$: 561.2459, found: 561.2449.



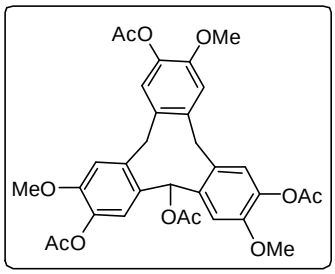
Pd-catalyzed Oxidation of CTV 66 in AcOH-*n*Propanol (1:1) with 12 eq. MnO_2: The general procedure **B** was followed. **66** (200 mg, 0.4 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), benzoquinone (24 mg, 0.2 mmol) and with 12 eq. of MnO_2 (418 mg, 4.8 mmol) in 30 mL of acetic acid and propanol (1:1). After usual workup, the crude was purified by column chromatography using ethyl acetate-petroleum ether (2:8, R*f* = 0.4) as the eluent to give **79** (50 mg, 27%) and 10,15-dipropoxy-cyclotriveratrylene-5-one **85** (77mg, 33%) as yellow solid. Mp. 170–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, *J* = 7.4 Hz, 6H), 1.47 (q, *J*= 6.8 Hz, 4H), 2.97- 3.16 (m, 4H), 3.81 (s, 6H), 3.95 (s, 6H), 3.98 (s, 6H), 5.39 (s, 2H), 6.73 (s, 2H), 7.41 (s, 2H), 7.49 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.7, 22.8 (2C), 55.9 (2C), 56.0 (2C), 56.1 (2C), 69.7 (2C), 73.1 (2C), 107.8 (2C), 109.6 (2C), 110.0 (2C), 132.3 (2C), 133.9 (2C), 134.5 (2C), 147.4 (2C), 148.6 (2C), 153.3 (2C), 192.7ppm; HRMS (ESI) Calculated for $C_{33}H_{40}O_9Na^+$ $[M+Na]^+$: 603.2565, found 603.2557.



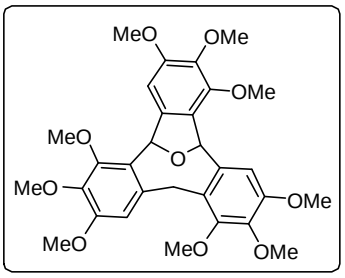
Pd-catalyzed Oxidation of CTV 66 in AcOH-*n*Butanol (1:1) with 12 eq. MnO_2: The general procedure **B** was followed. **66** (200mg, 0.4 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), benzoquinone (24 mg, 0.2 mmol) and MnO_2 (418mg, 4.8 mmol) in 30 mL of acetic acid and butanol (1:1).The product was purified by column chromatography using ethyl acetate-petroleum ether (2:8, R*f* = 0.4) as the eluent to give **79** (58 mg, 31%) and 10,15-dibutoxy-cyclotriveratrylene-5-one **86** (64 mg, 26%) as yellow solid. Mp. 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, *J*= 7.0 Hz, 6H), 1.23-1.48 (m, 8H), 3.0-3.17 (m,4H), 3.80 (s. 6H), 3.94 (s, 6H), 3.97 (s, 6H), 5.38 (s, 2H), 6.72 (s, 2H), 7.41 (s, 2H), 7.47 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (2C), 19.4 (2C), 31.6 (2C), 55.9 (2C), 56.0 (2C), 56.1 (2C), 67.8 (2C), 73.1 (2C), 107.9 (2C), 109.5 (2C), 110.0 (2C), 132.3 (2C), 133.9 (2C), 134.5 (2C), 147.4 (2C), 148.6 (2C), 153.3 (2C), 192.7 ppm; HRMS (ESI) Calculated for $C_{35}H_{44}O_9Na^+$ $[M+Na]^+$: 631.2878, found 631.2874.



Pd-catalyzed Oxidation of CTV 68 in AcOH at 70 °C: The general procedure **B** was followed. **68** (100 mg, 0.19 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol), benzoquinone (10 mg, 0.09 mmol) and MnO_2 (98 mg, 1.14 mmol) in 20 mL of acetic acid. The product was purified by column chromatography using ethyl acetate-petroleum ether (4:6, R*f* = 0.3) as the eluent to give starting compound **68** (32 mg) and 5-acetyloxy-CTV **87** as a yellow solid (46 mg, 41%). Mp.101–103 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 9H), 2.16 (s,3H), 3.64 (d, *J* = 13.8 Hz, 2H), 3.79 (s, 6H), 3.81 (s, 3H), 4.82 (d, *J* = 13.8 Hz, 2H), 6.82 (s, 1H), 6.84 (s, 1H), 6.98 (s, 1H), 6.99 (s, 1H), 7.10 (s, 1H), 7.24 (s, 1H), 7.89 (s, 1H)ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6 (3C), 21.2, 35.8 (2C), 56.0, 56.1, 56.1, 68.2, 109.6, 113.3, 114.1, 119.6, 123.6, 124.1, 129.9, 130.7, 130.9, 136.3, 137.2, 137.8, 138.4, 138.8, 139.2, 149.8, 150.1, 150.4, 168.7, 168.8, 169.0, 169.6 ppm; HRMS (ESI) Calculated for $C_{32}H_{32}O_{11}Na^+$ $[M+Na]^+$: 615.1837, found: 615.1832.



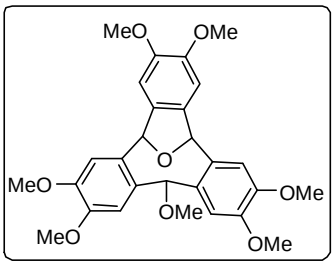
Pd-catalyzed Oxidation of CTV 69 in AcOH at 70 °C: The general procedure **B** was followed. **69** (200 mg, 0.37 mmol), $Pd(OAc)_2$ (17 mg, 0.07 mmol), benzoquinone (20mg, 0.18 mmol) and MnO_2 (192 mg, 2.22 mmol) in 30 mL of acetic acid. The product was purified by column chromatography using ethyl acetate-petroleum ether (3:7, R*f* = 0.4) as the eluent to give



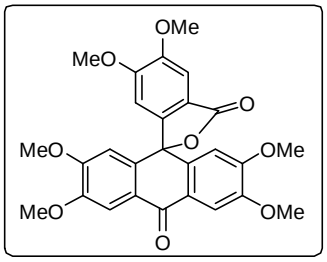
furan derivative **88** as a yellow solid (138 mg, 67%), Mp. 98–99 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.98 (d, *J* = 14.0 Hz, 1H), 3.56 (s, 3H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 6H), 3.88 (s, 3H), 3.89 (s, 3H), 3.95 (s, 3H), 6.19 (s, 1H), 6.46 (s, 1H), 6.76 (s, 1H), 6.79 (s, 1H), 6.85 (s, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 55.8, 56.0, 56.2, 60.4, 60.6, 60.8, 61.1 (2C), 62.2, 79.6, 87.6, 99.6, 109.7, 112.4, 125.9, 126.1, 127.2, 136.6, 136.9, 137.9, 140.0, 141.8, 141.9, 147.1, 151.1, 152.1, 152.4, 152.7, 155.1 ppm; HRMS (ESI) Calculated for $C_{30}H_{34}O_{10}Na^{+}$ $[M+Na]^{+}$: 577.2044, found: 577.2036.

2.3.3. General Procedure for Acid catalyzed rearrangements of 77 and 78 (C): A solution of compound **77** (100 mg, 0.19 mmol) in 25 mL methanol and added catalytic amound of *p*-toluensulfonic acid (*p*-TsOH), the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was dissolved in ethylacetate (25 mL), water (20 mL) and the organic layer extracted twice. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethylacetate – petroleum ether (4:6, R*f* = 0.4) to give 2'-(9-anthracenyl)benzaldehyde **79** (72%) as a yellow solid.

15-Methoxy-5,10-epoxy-cyclotriveratrylene (89): The general procedure **C** was followed. **78** (50 mg, 0.09 mmol), catalytic amound of *p*-toluensulfonic acid (*p*-TsOH). The crude product was purified by column chromatography using ethylacetate – petroleum ether (4:6, R*f* = 0.4) to give **89** (72%) as a yellow solid. Mp. 169 °C; ^{1}H NMR (200 MHz, CDCl3): δ 2.94 (s, 3H), 3.88 (s, 6H), 3.90 (s, 12H), 4.73 (s, 1H), 6.09 (s, 2H), 6.78 (s, 2H), 6.92 (s, 2H), 7.23 (s, 2H), ^{13}C NMR (50 MHz, CDCl3): δ 56.0 (2C), 56.1 (2C), 56.2 (2C), 57.2, 73.9 (2C), 88.2, 103.6 (2C), 108.9 (2C), 114.3 (2C), 131.8 (2C), 132.3 (2C), 135.1 (2C), 146.88 (2C), 148. 9 (2C), 150.2 (2C) ppm; HRMS (EI) Calculated for $C_{28}H_{30}O_8$ (M^{+}) 494.1941, found 494.1882.



Base catalyzed rearrangements of 77: A solution of compound **77** (50 mg, 0.09 mmol) in 10 mL THF and added NaH (4 mg, 0.18) the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in ethylacetate (20 mL), water



(15 mL) and the organic layer extracted twice. The organic layer was then dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product was purified by column chromatography using ethylacetate–petroleum ether (3:7, R*f* = 0.4) to give 10-benzoyloxy-9-anthrone **72** (80%) as a white solid. Mp. 256 °C; ^{1}H NMR (200 MHz, CDCl3): δ 3.72 (s, 3H), 3.81 (s, 6H), 3.98 (s, 3H), 4.02 (s, 6H), 6.19 (s, 1H), 6.48 (s, 2H), 7.38 (s, 1H), 7.81 (s, 2H), ^{13}C NMR (50 MHz, CDCl3): δ 55.9, 56.0, 56.2, 56.2, 56.4, 56.5, 93.2, 107.2 (2C), 108.8 (2C), 109.3, 115.4, 117.3, 124.3 (2C), 134.2 (2C), 149.0, 150.0 (2C), 151.1, 153.8 (2C), 155.9, 171.0, 184.1 ppm; HRMS (ESI) Calculated for $C_{27}H_{24}O_9Na^+$ $[M+Na]^+$: 515.4692, found: 515.4691.

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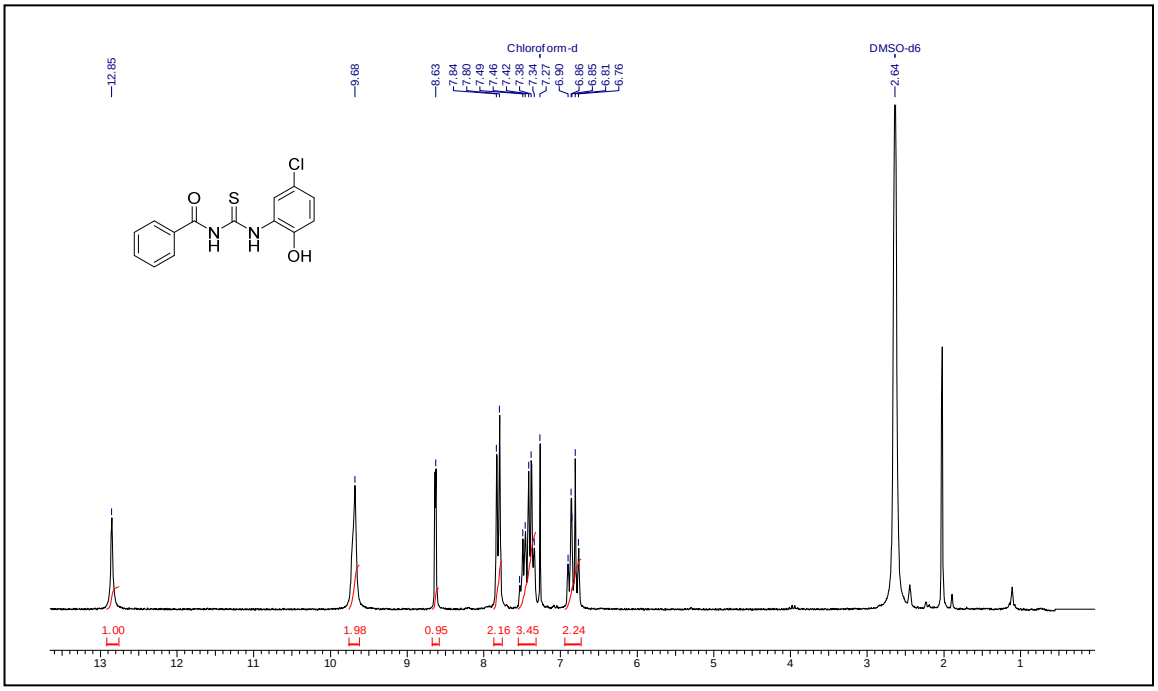
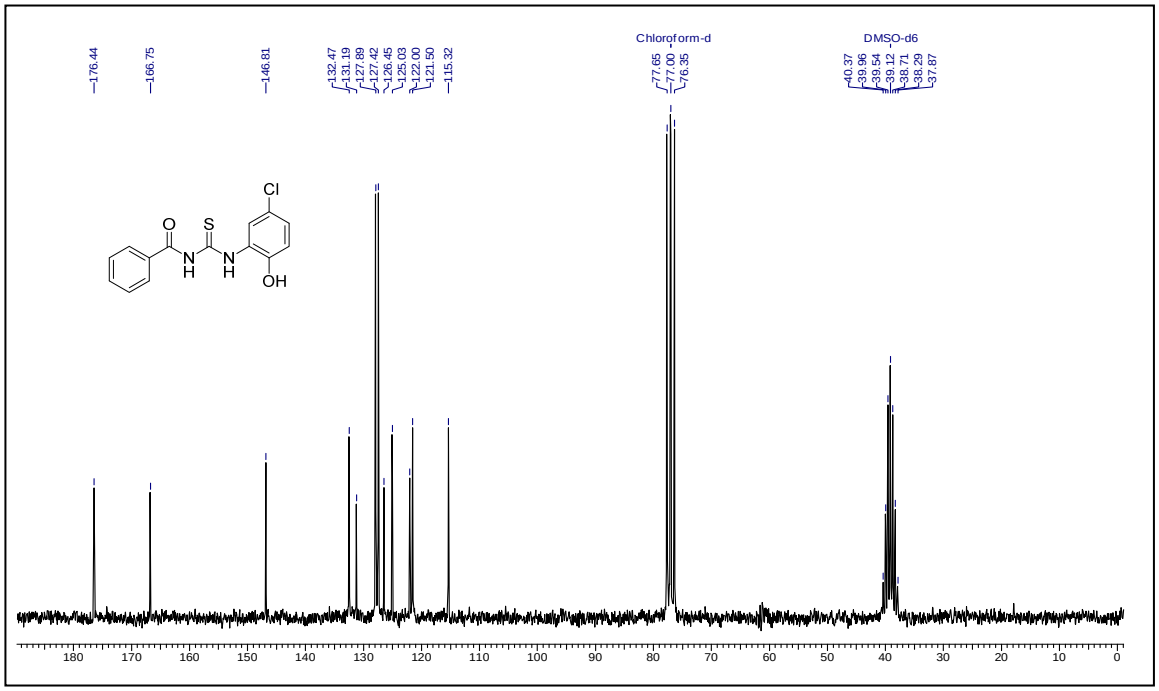
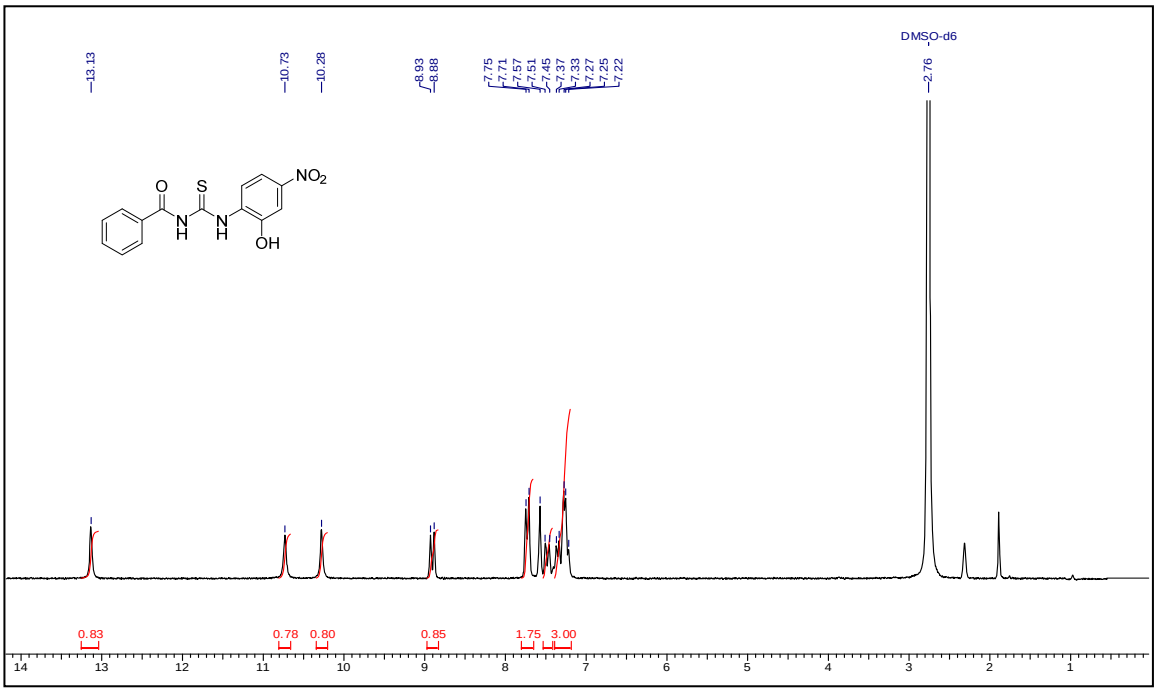


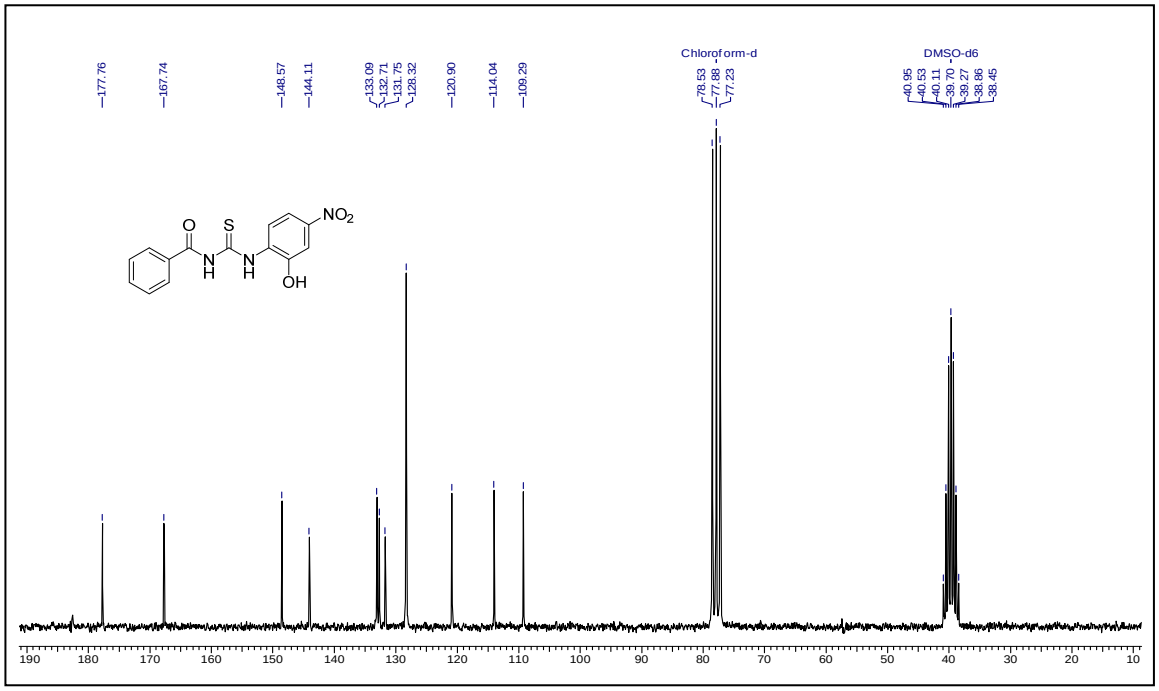
^{1}H NMR Spectrum of **2** in $CDCl_3$+ DMSO-d_6 (200 MHz)



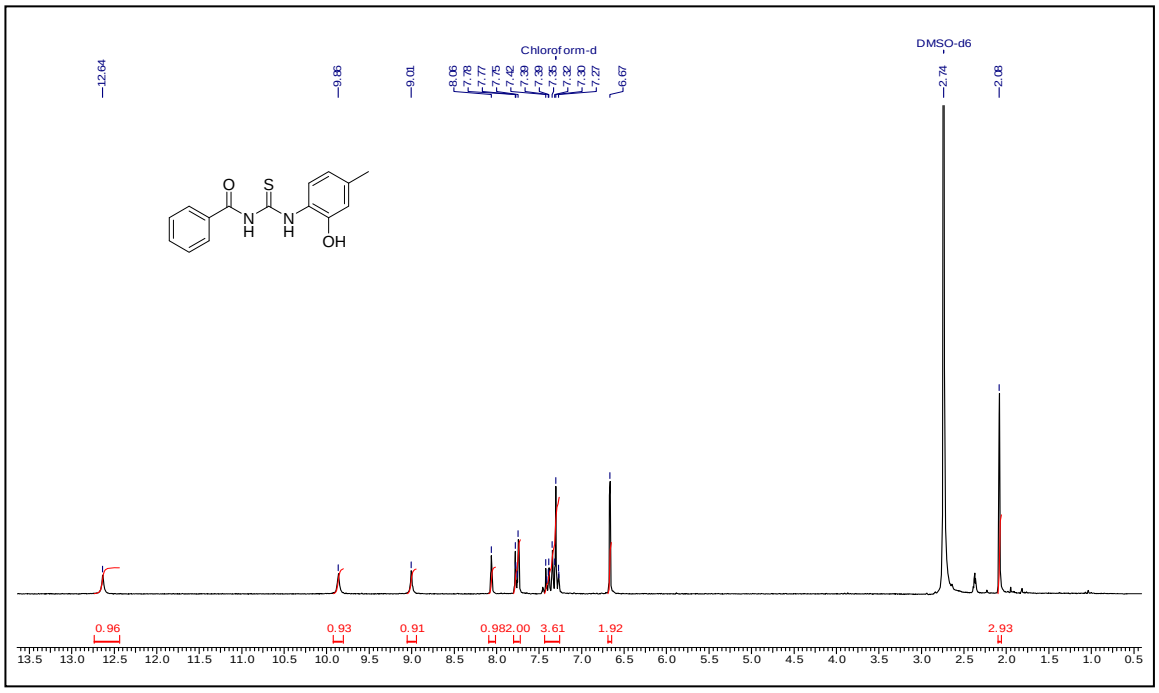
^{13}C NMR Spectrum of **2** in $CDCl_3$+ DMSO-d_6 (50 MHz)



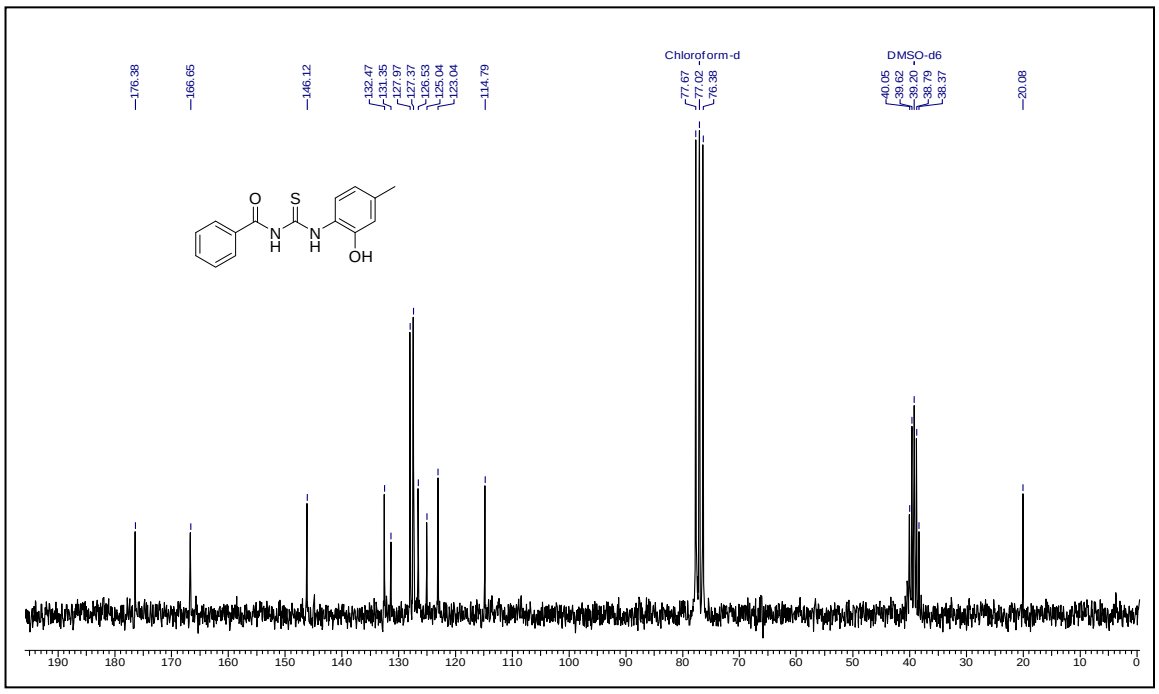
^{1}H NMR Spectrum of **3** in $CDCl_3$+DMSO-d_6 (200 MHz)



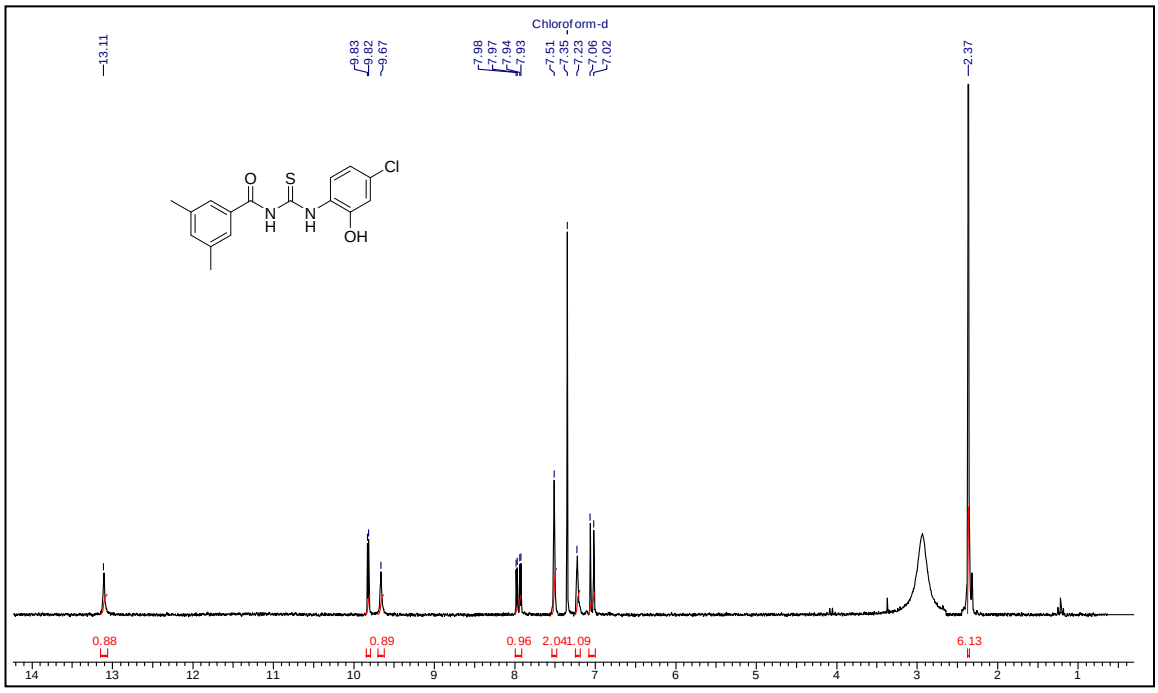
^{13}C NMR Spectrum of **3** in $CDCl_3$+ DMSO-d_6 (50 MHz)



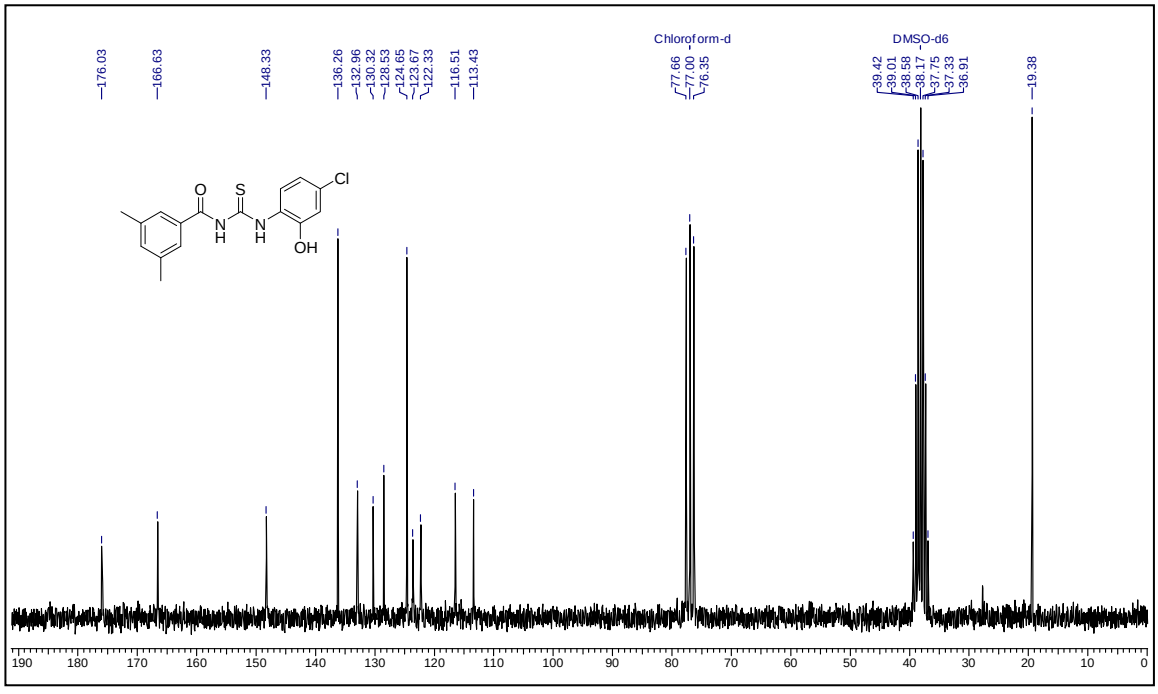
^{1}H NMR Spectrum of **4** in $CDCl_3$+ DMSO-d_6 (200 MHz)



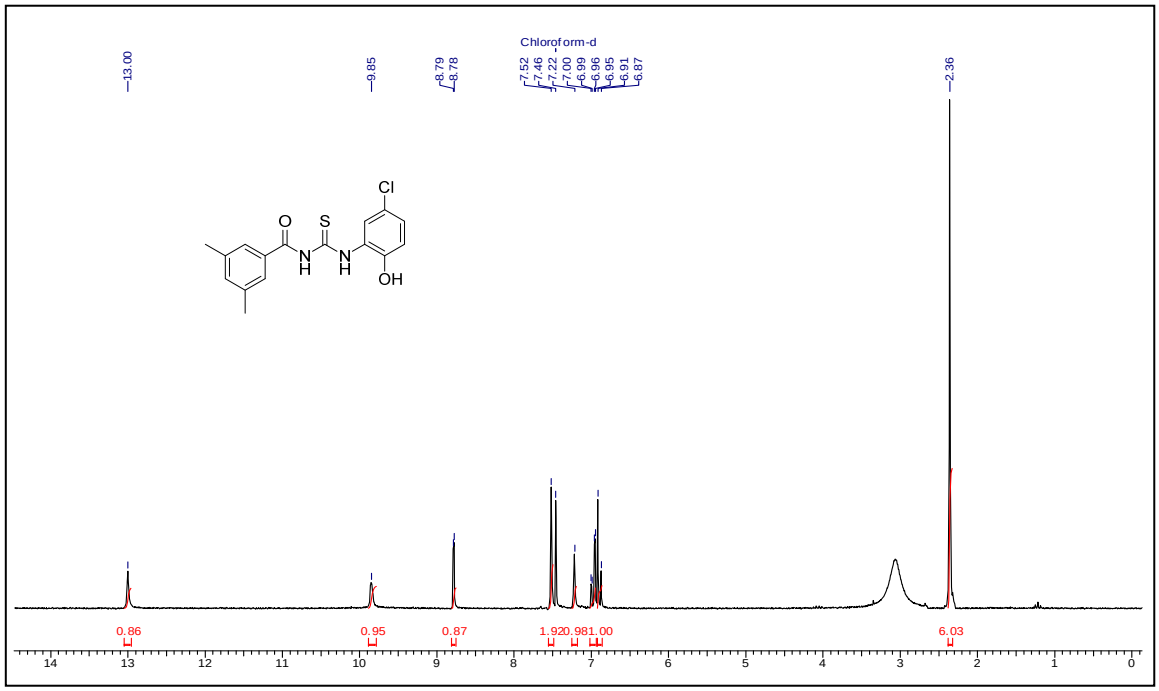
^{13}C NMR Spectrum of **4** in $CDCl_3$+ DMSO-d_6 (50 MHz)



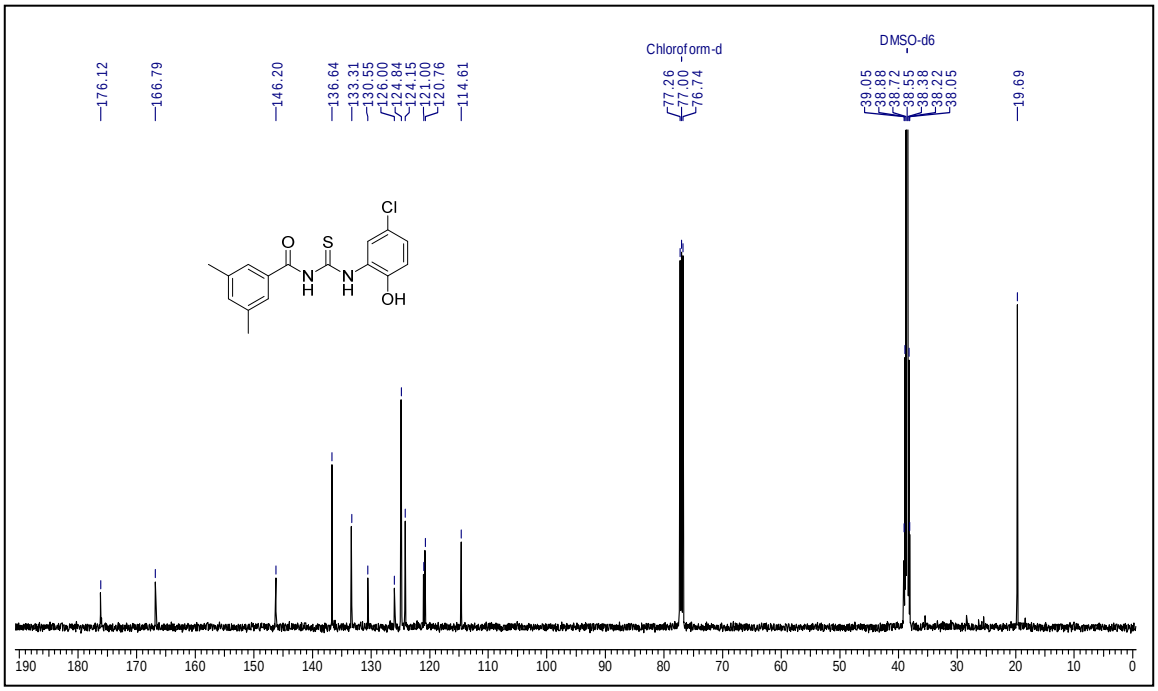
^{1}H NMR Spectrum of **5** in $CDCl_3$+DMSO-d_6 (200 MHz)



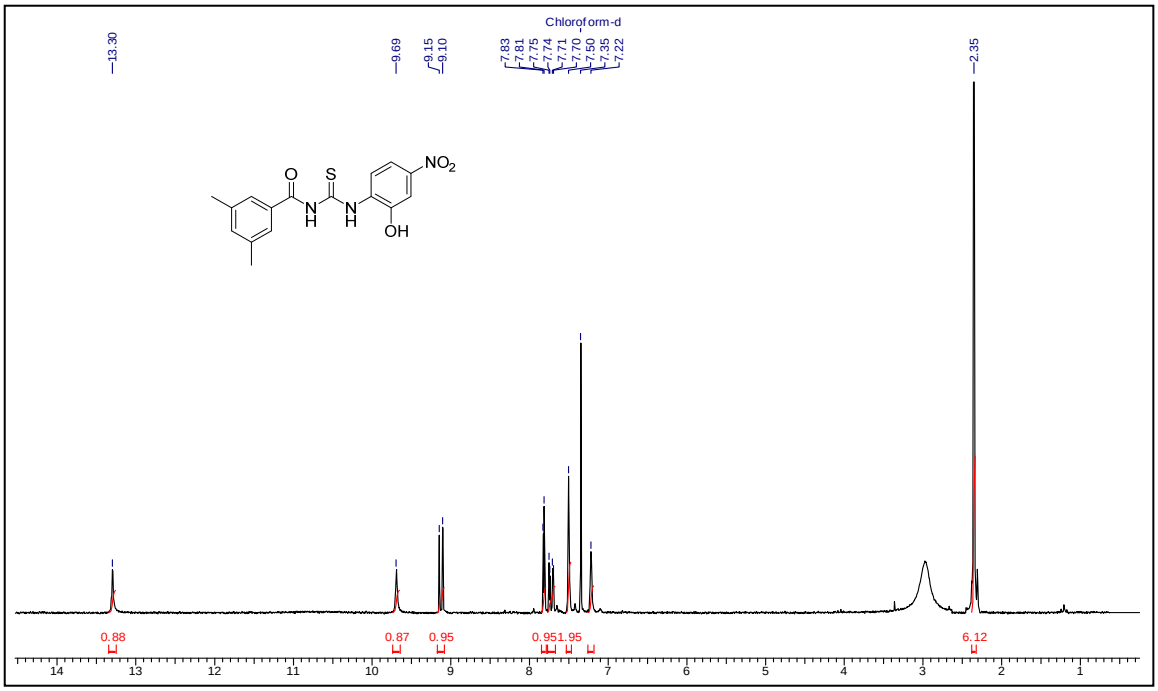
^{13}C NMR Spectrum of **5** in $CDCl_3$+ DMSO-d_6 (50 MHz)



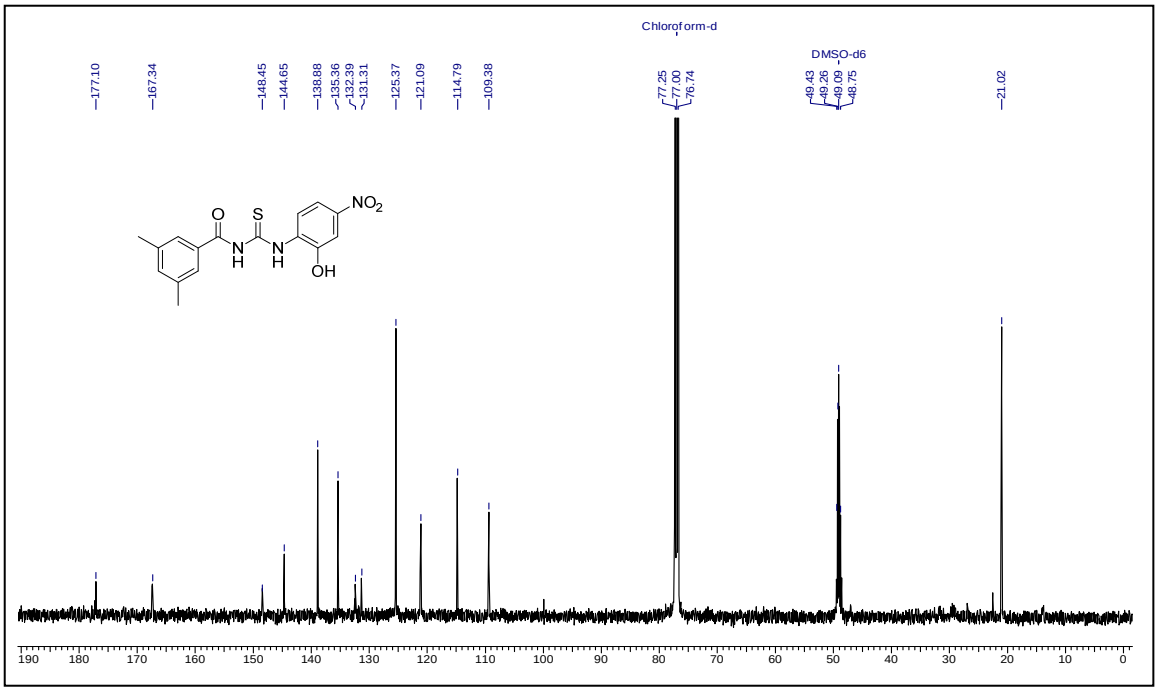
^{1}H NMR Spectrum of **6** in $CDCl_3$+DMSO-d_6 (200 MHz)



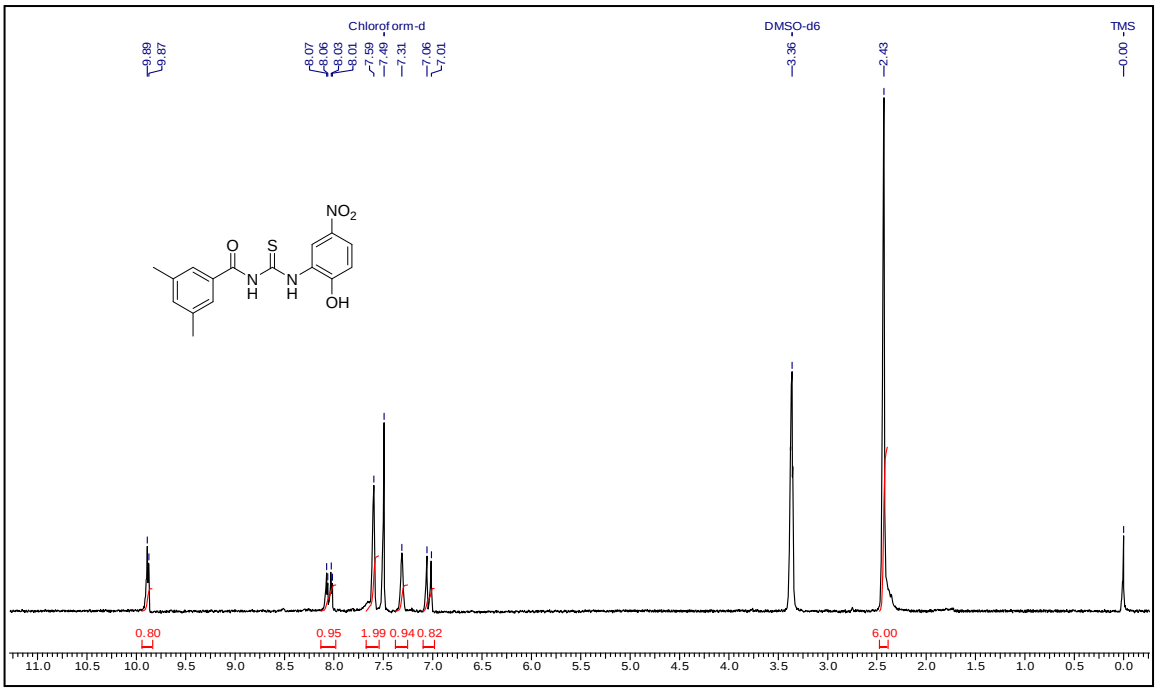
^{13}C NMR Spectrum of **6** in $CDCl_3$+ DMSO-d_6 (50 MHz)



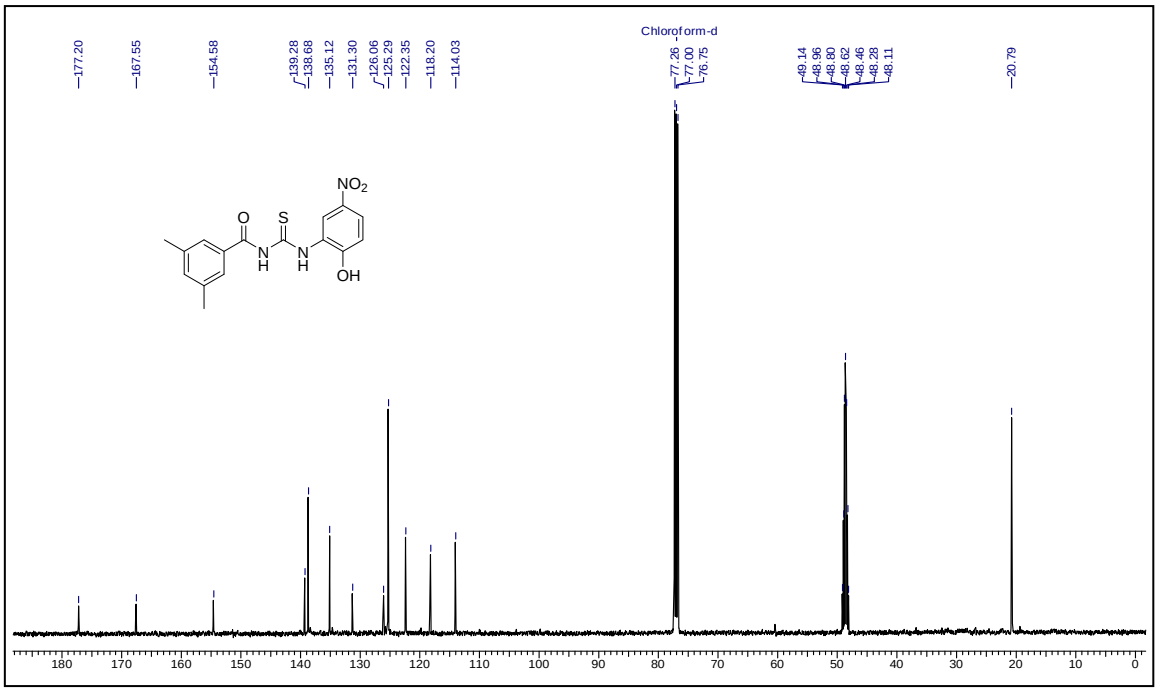
^{1}H NMR Spectrum of **7** in $CDCl_3$+ DMSO-d_6 (200 MHz)



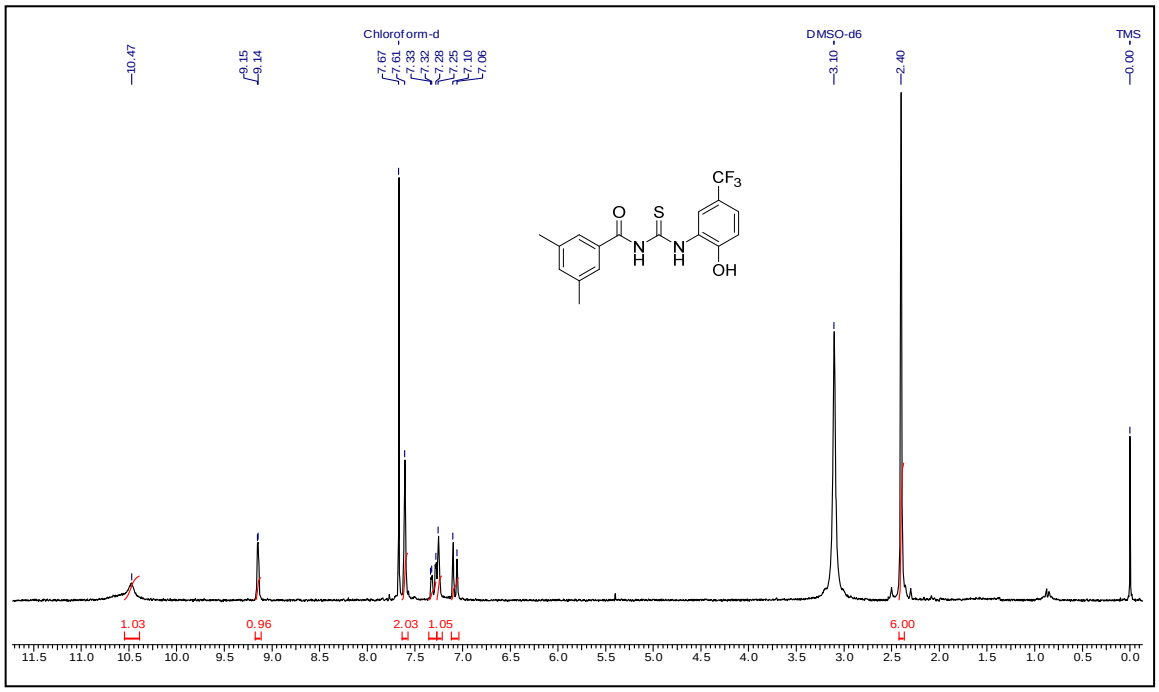
^{13}C NMR Spectrum of **7** in $CDCl_3$+ DMSO-d_6 (50 MHz)



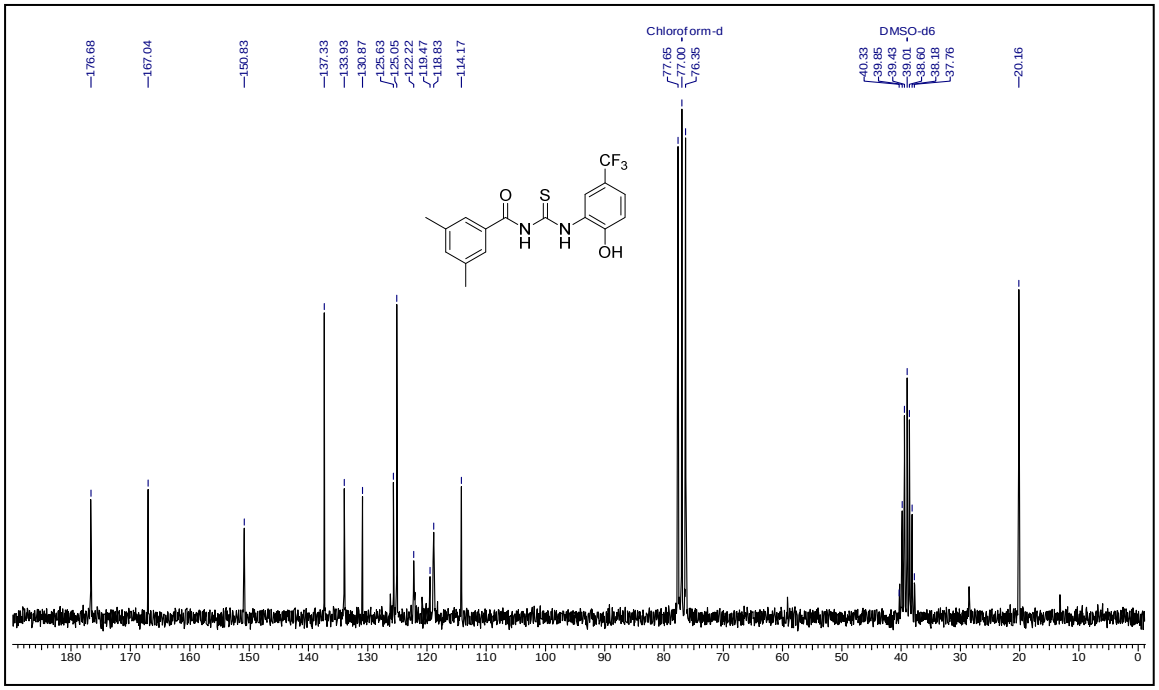
^{1}H NMR Spectrum of **1** in $CDCl_3$+ DMSO-d_6 (200 MHz)



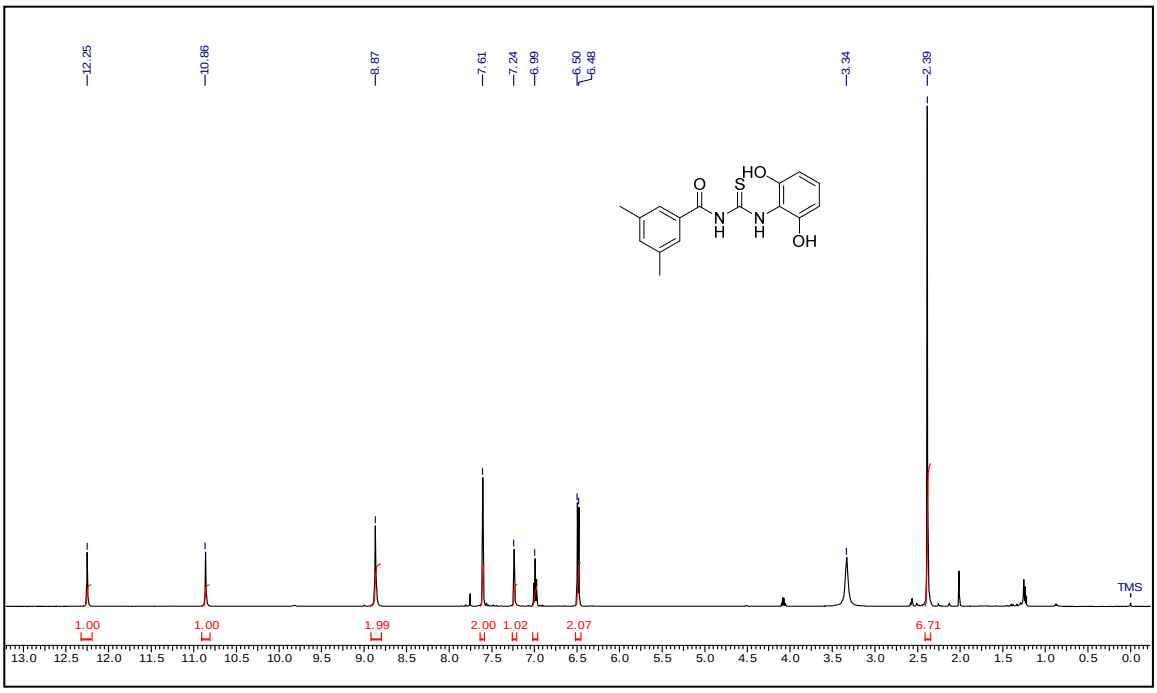
^{13}C NMR Spectrum of **1** in $CDCl_3$+ DMSO-d_6 (50 MHz)



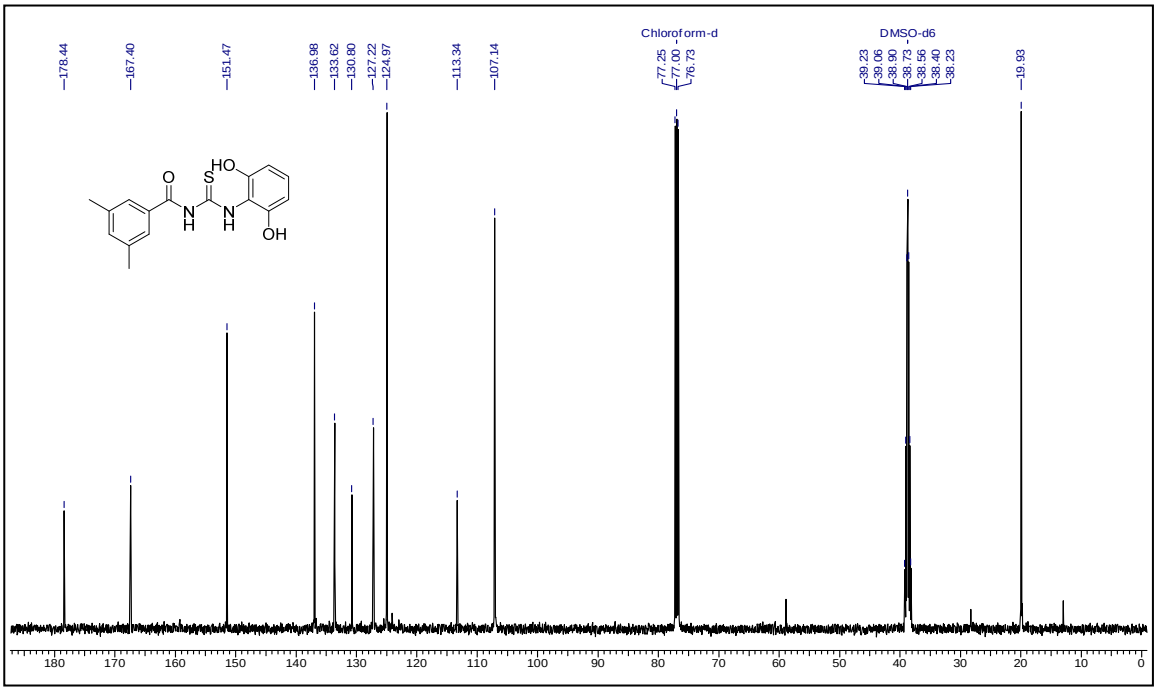
^{1}H NMR Spectrum of **11** in $CDCl_3$+ DMSO-d_6 (200 MHz)



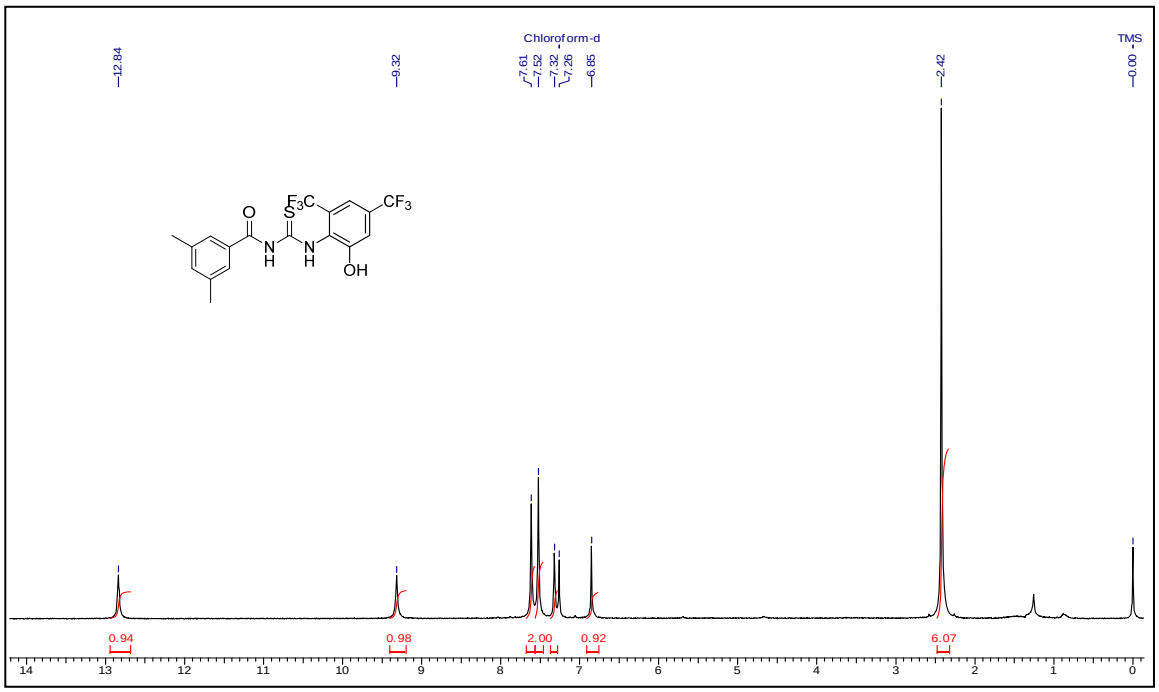
^{13}C NMR Spectrum of **11** in $CDCl_3$+ DMSO-d_6 (50 MHz)



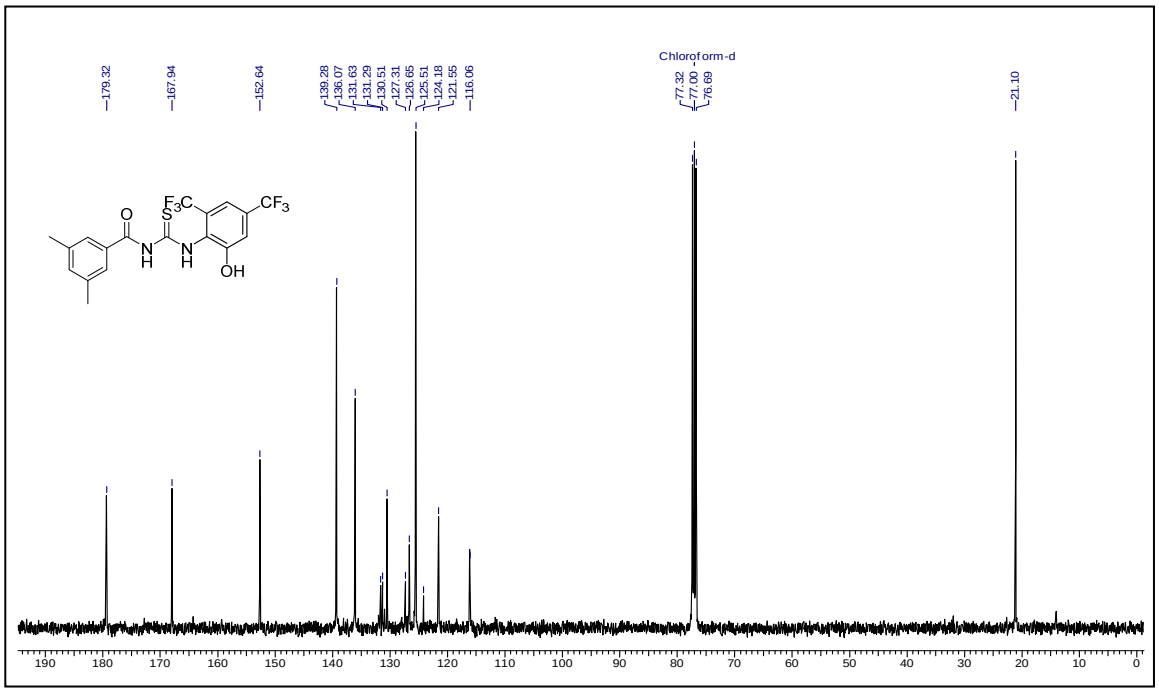
^{1}H NMR Spectrum of **15** in $CDCl_3$+ DMSO-d_6 (500 MHz)



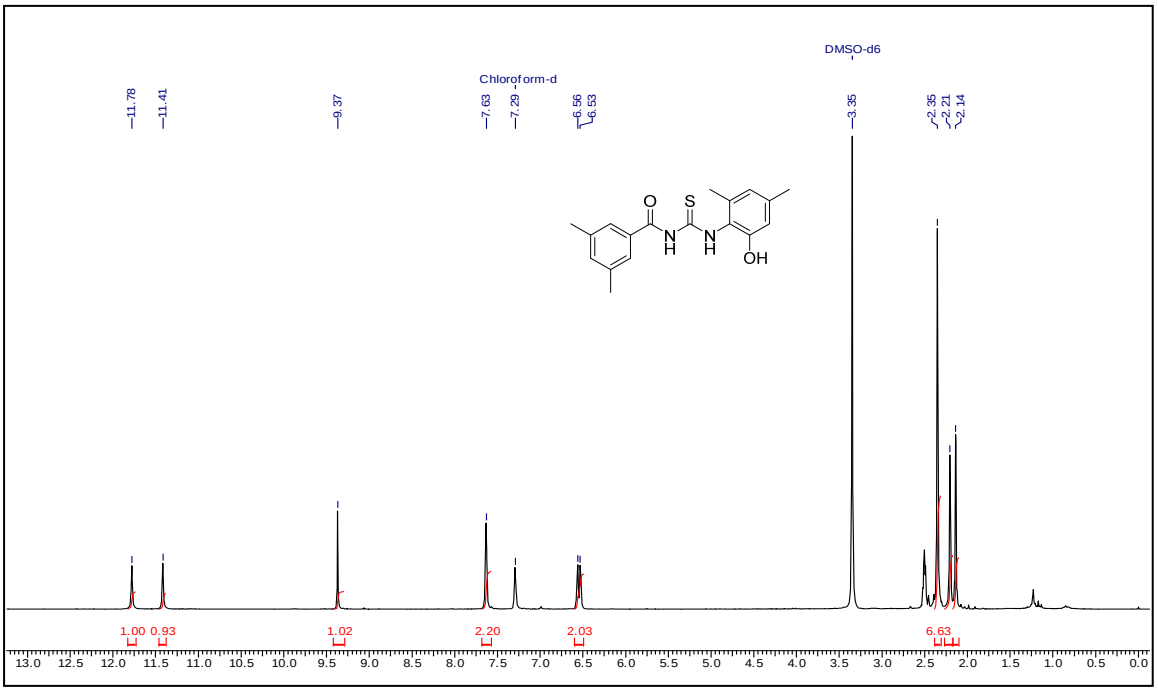
^{13}C NMR Spectrum of **15** in $CDCl_3$+ DMSO-d_6 (125 MHz)



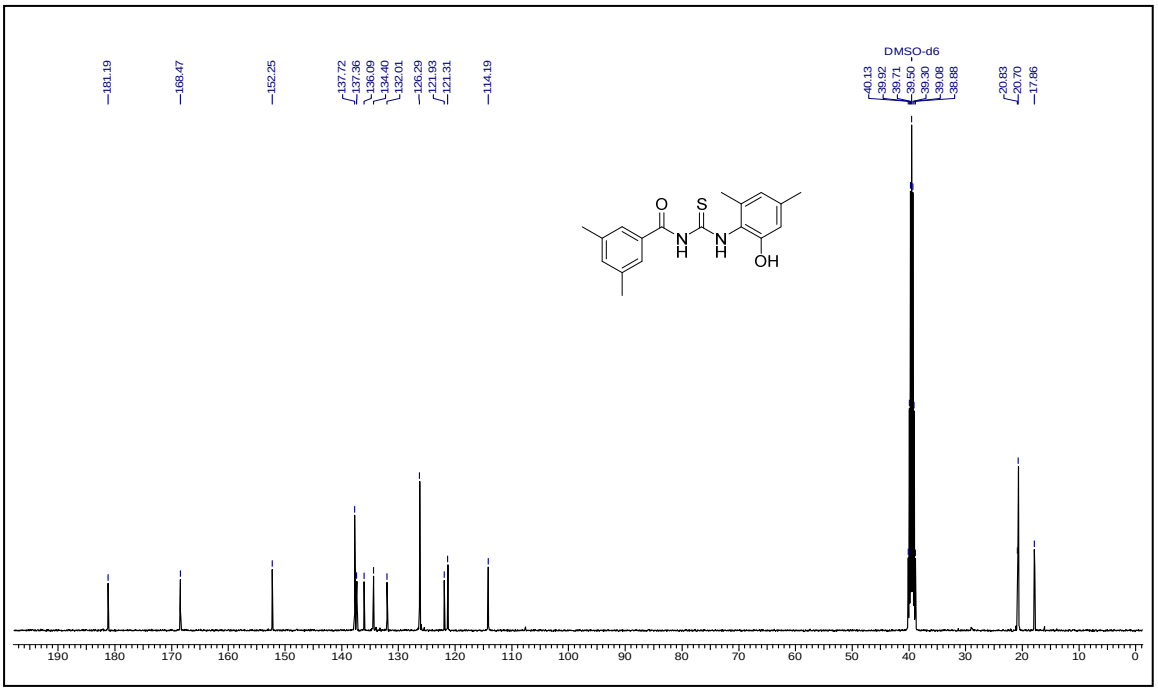
^{1}H NMR Spectrum of **17** in $CDCl_3$ (400 MHz)



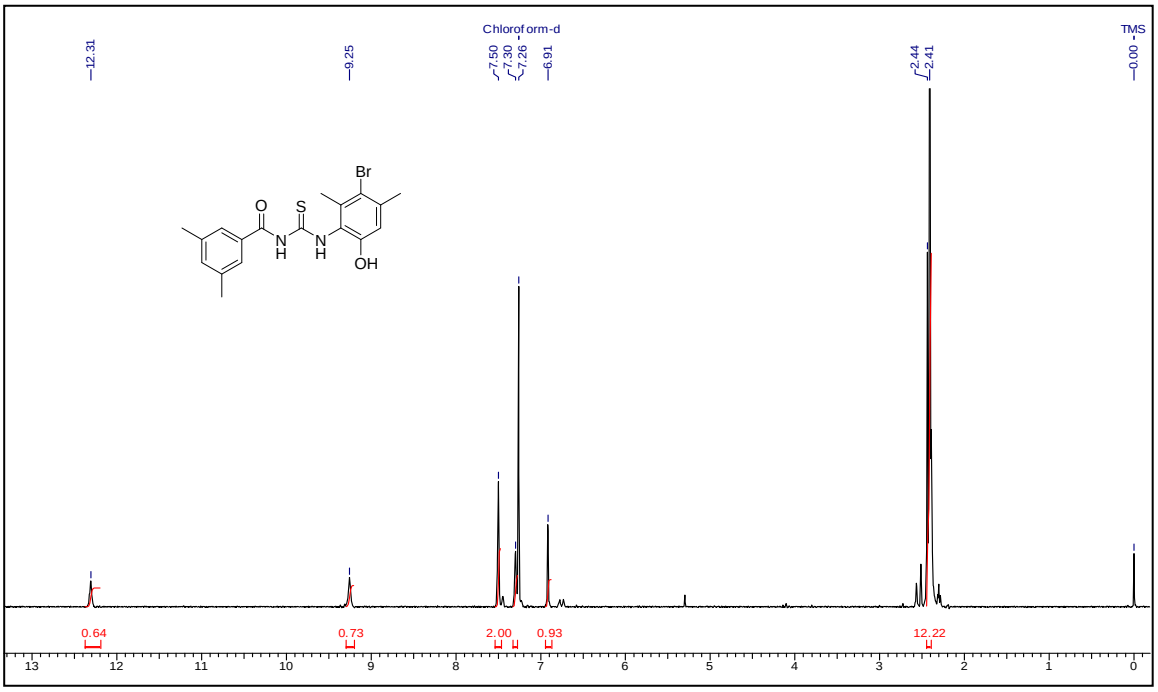
^{13}C NMR Spectrum of **17** in $CDCl_3$ (100 MHz)



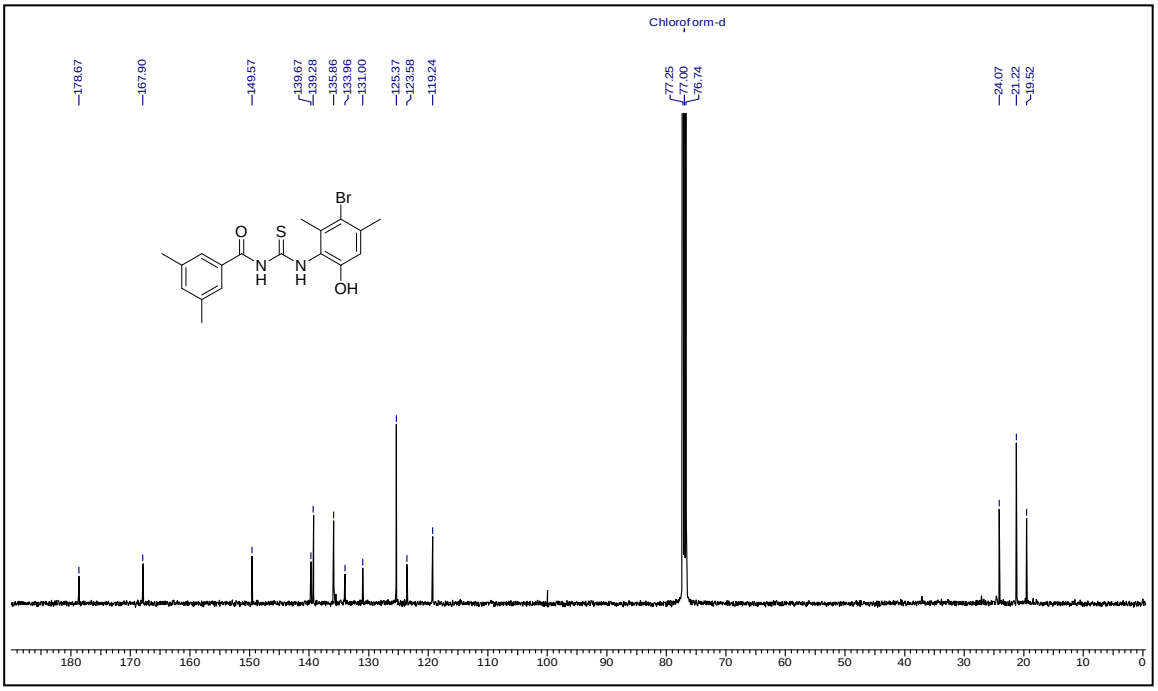
^{1}H NMR Spectrum of **18** in $CDCl_3$+ DMSO-d_6 (200 MHz)



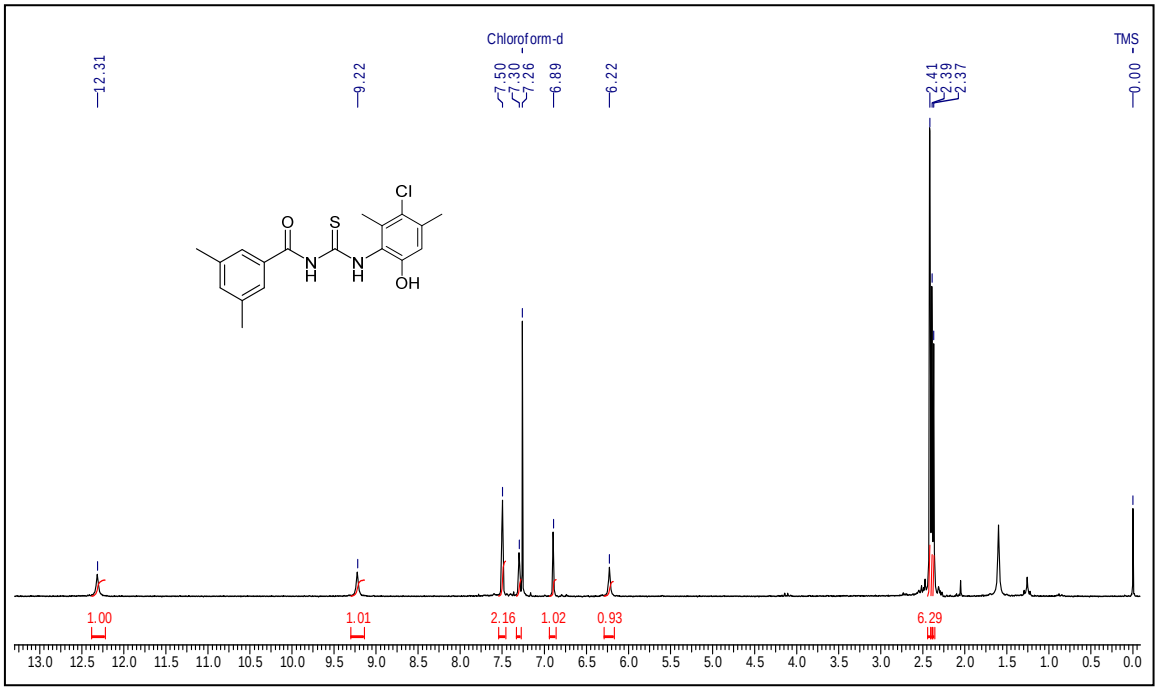
^{13}C NMR Spectrum of **18** in $CDCl_3$+ DMSO-d_6 (50 MHz)



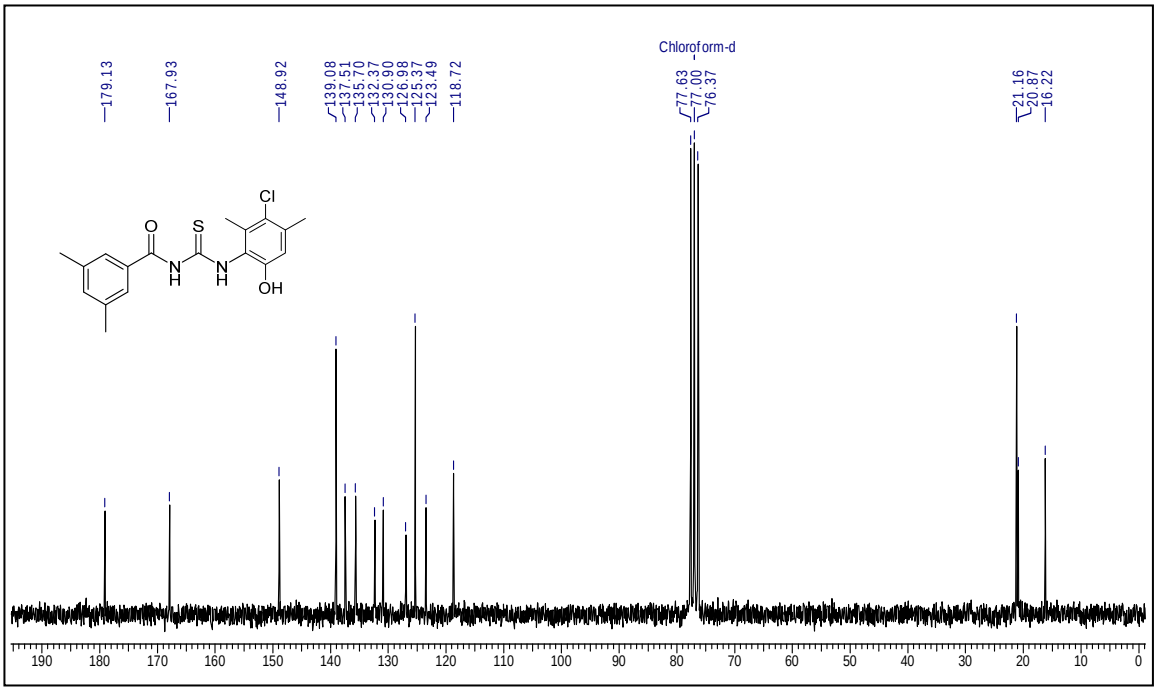
^{1}H NMR Spectrum of **19** in $CDCl_3$ (200 MHz)



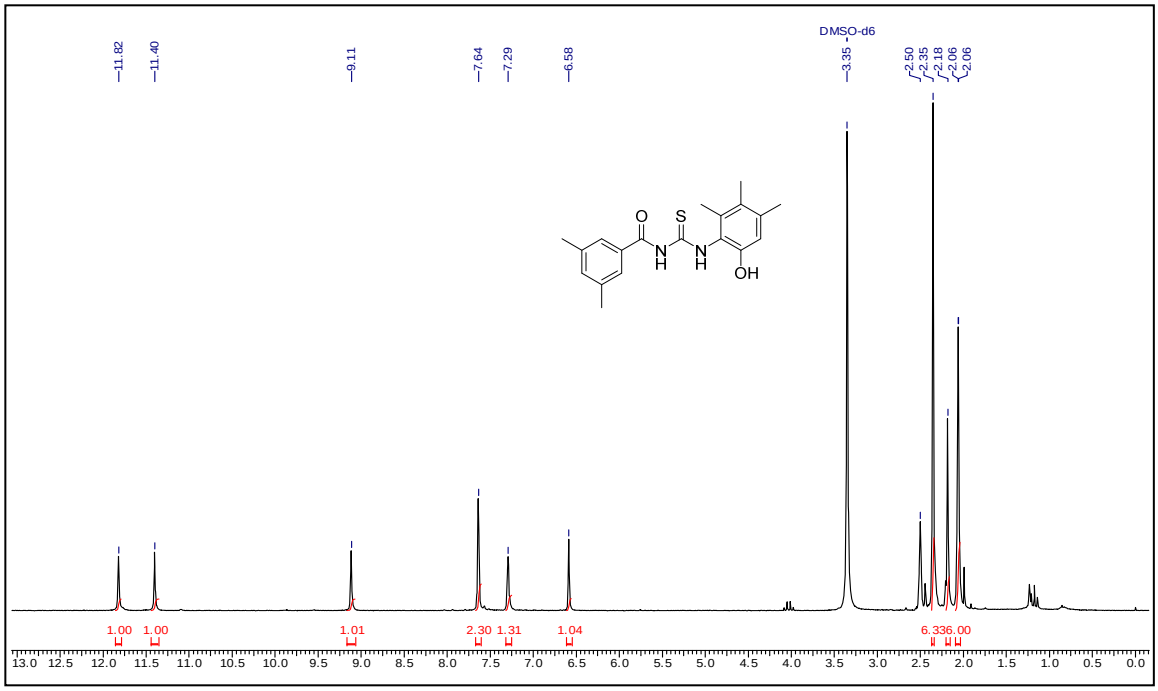
^{13}C NMR Spectrum of **19** in $CDCl_3$ (50 MHz)



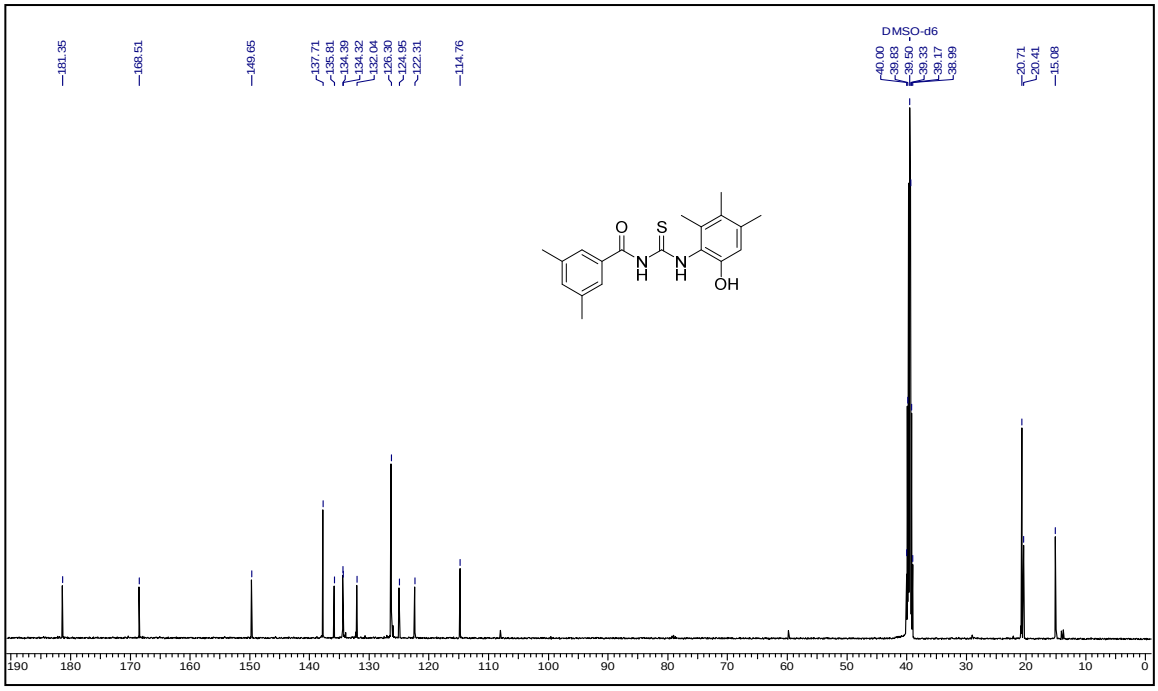
^{1}H NMR Spectrum of **20** in $CDCl_3$ (200 MHz)



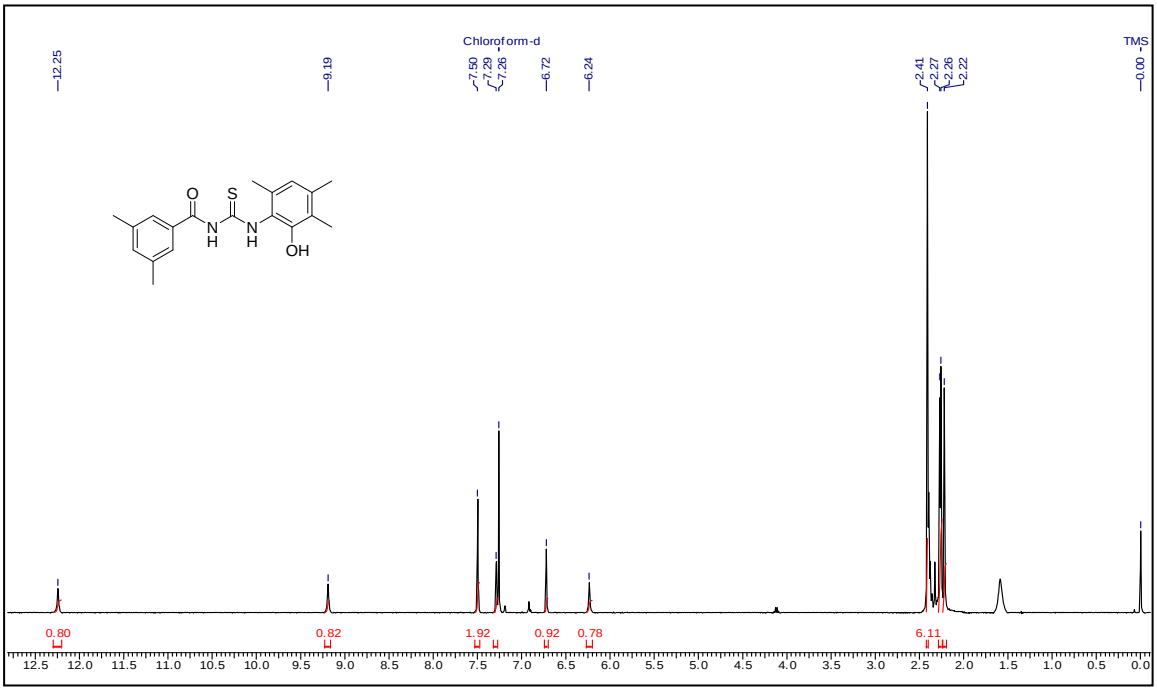
^{13}C NMR Spectrum of **20** in $CDCl_3$ (50 MHz)



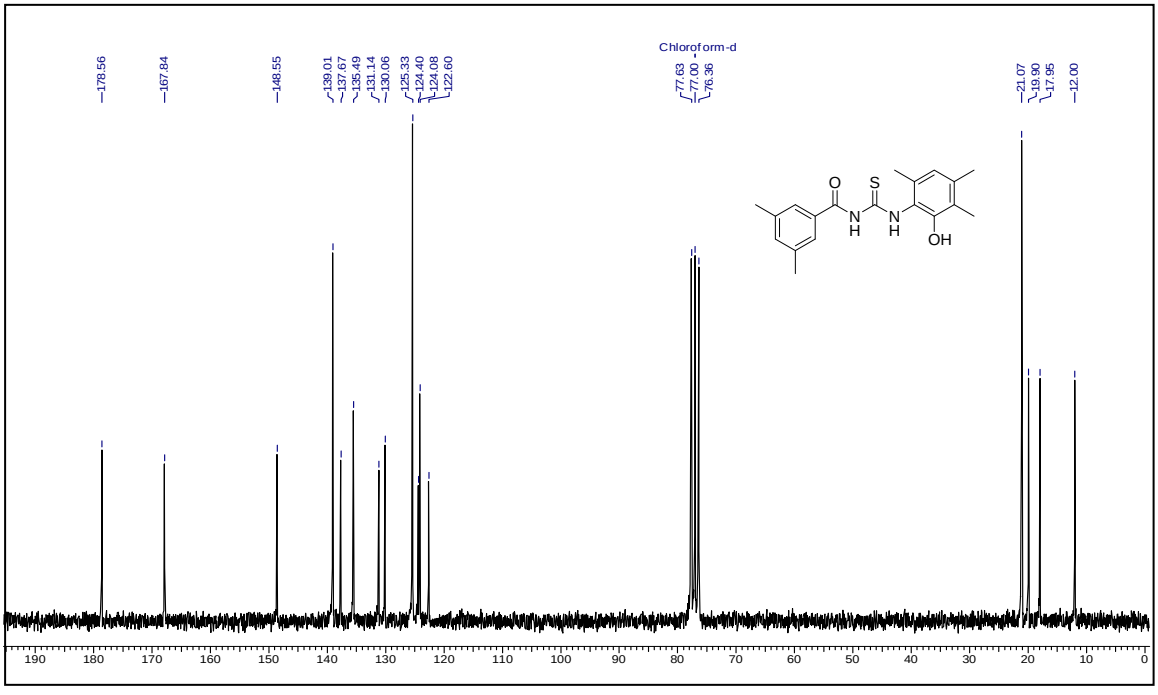
^{1}H NMR Spectrum of **21** in DMSO-d_6 (500 MHz)



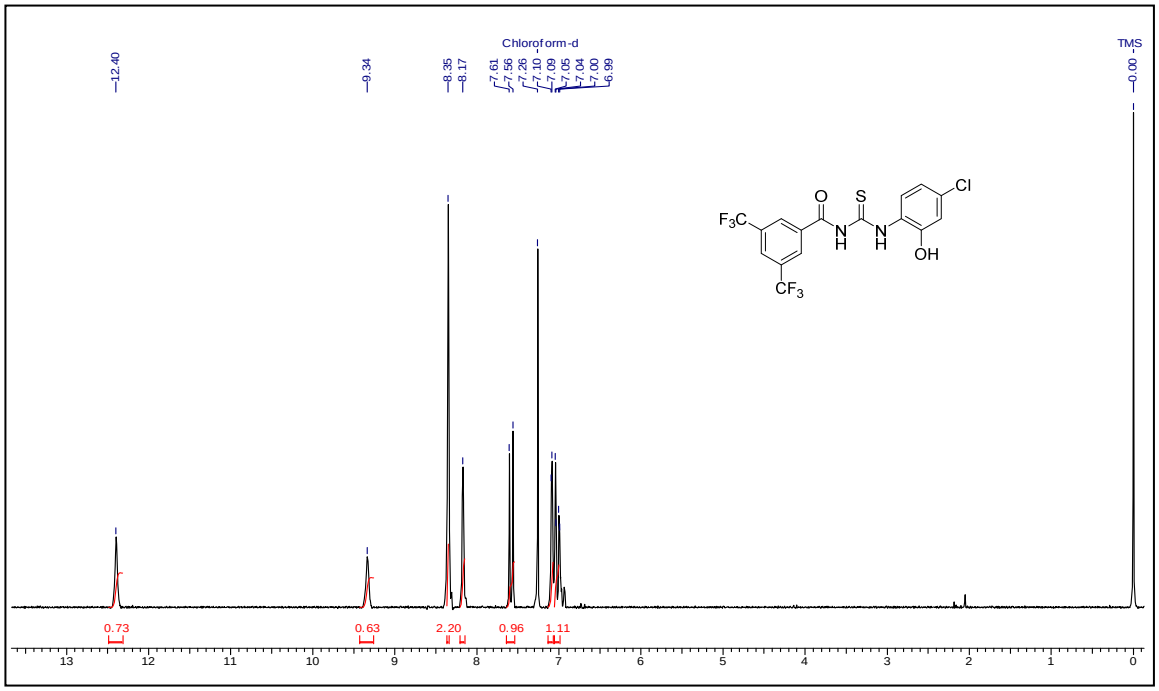
^{13}C NMR Spectrum of **21** in DMSO-d_6 (125 MHz)



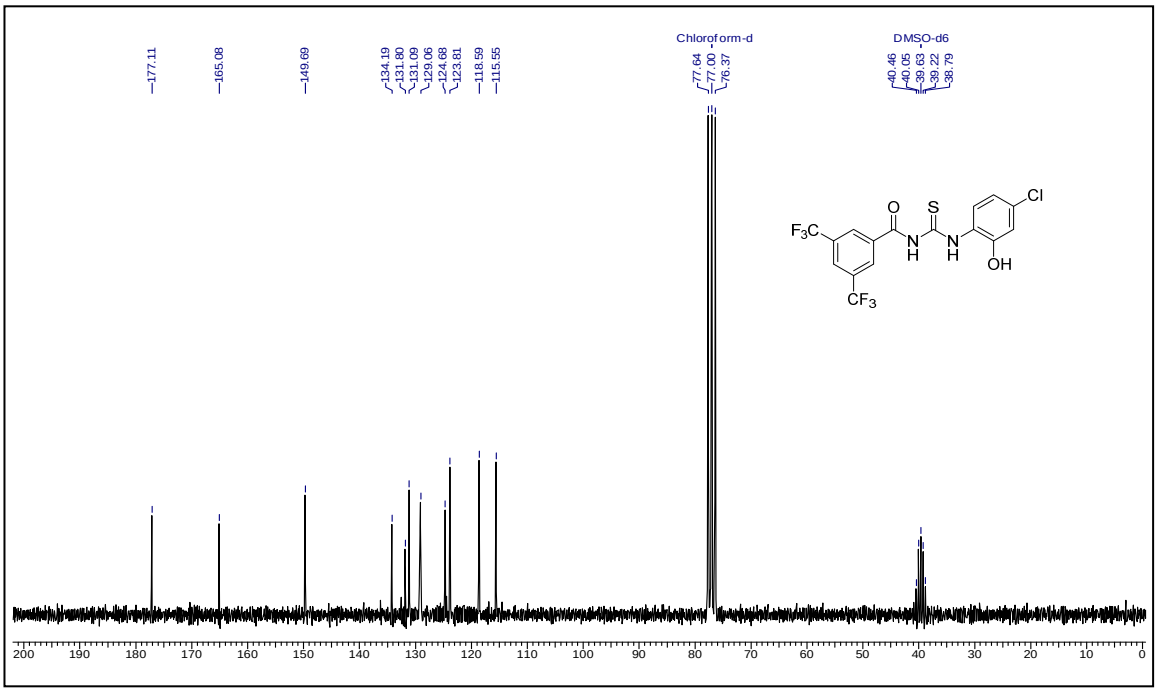
^{1}H NMR Spectrum of **22** in $CDCl_3$ (200 MHz)



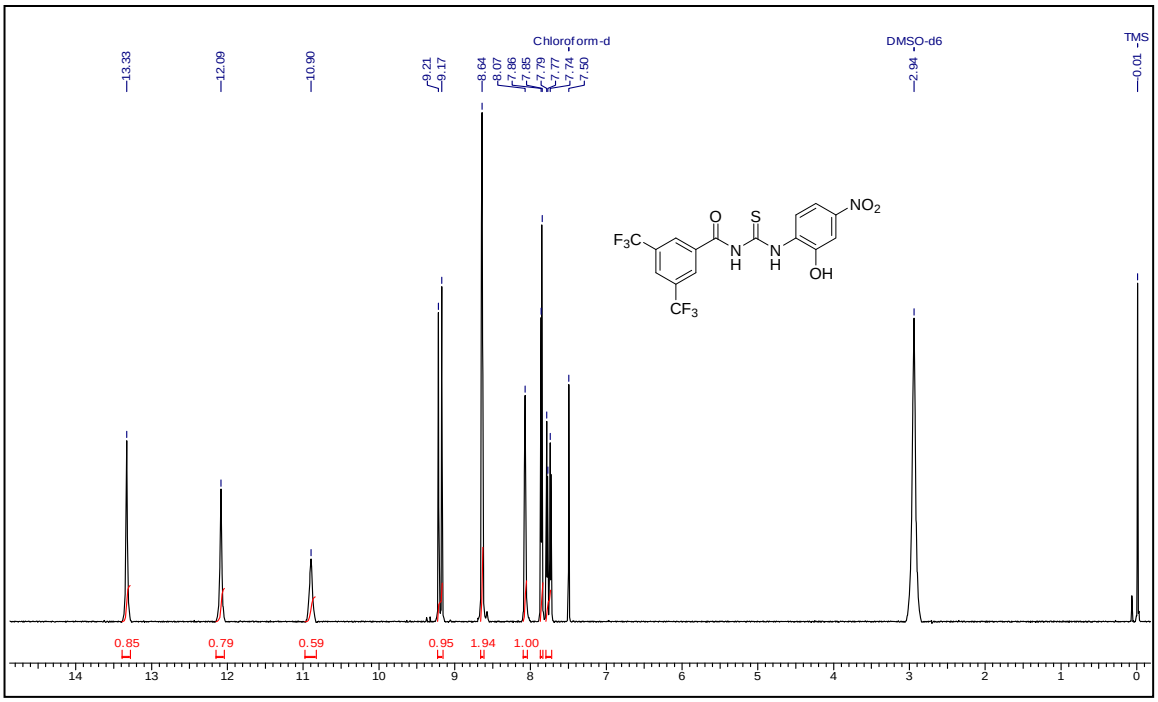
^{13}C NMR Spectrum of **22** in $CDCl_3$ (50 MHz)



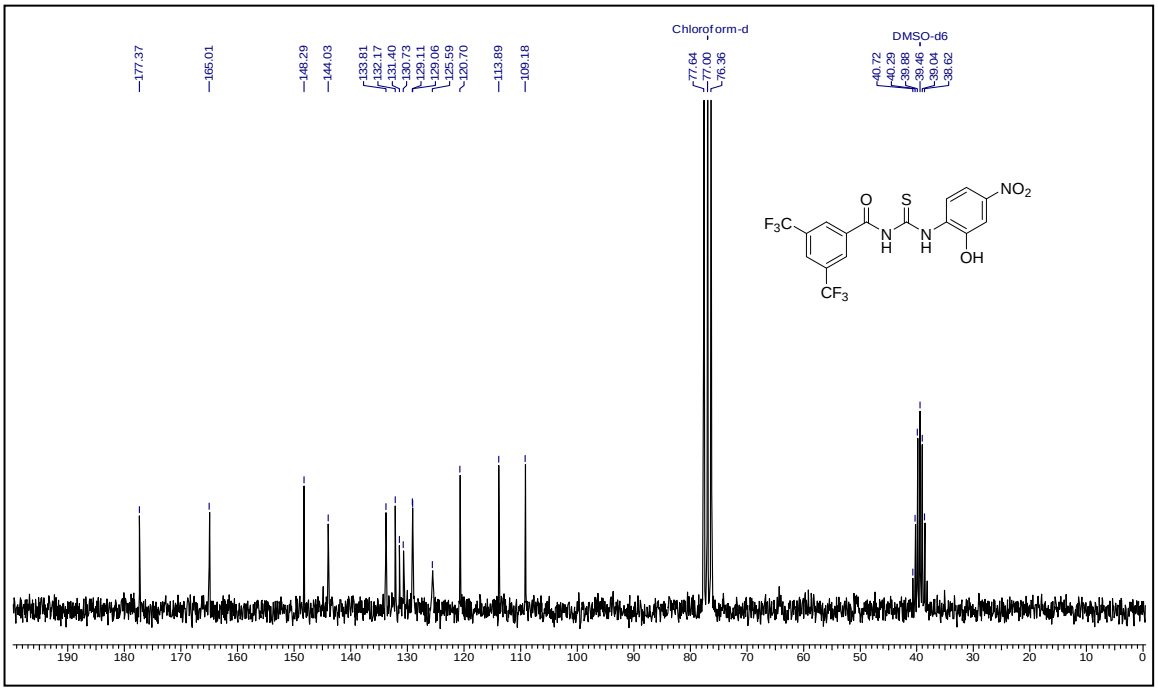
^{1}H NMR Spectrum of **24** in $CDCl_3$ (200 MHz)



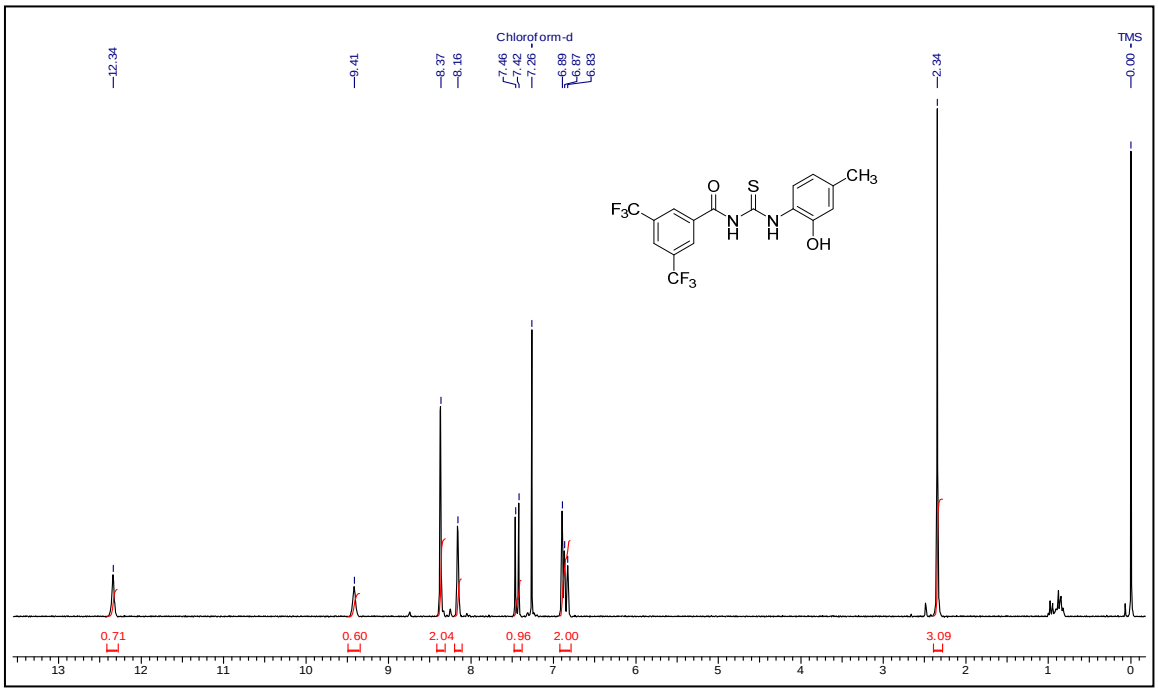
^{13}C NMR Spectrum of **24** in $CDCl_3$+DMSO-d_6 (50 MHz)



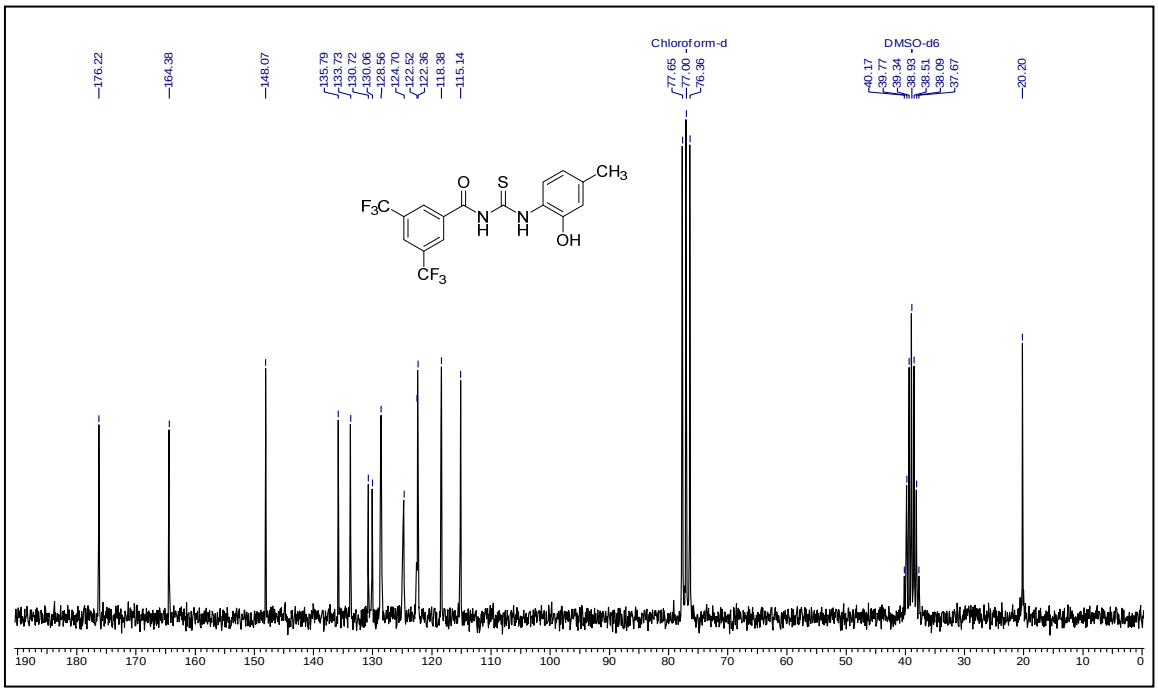
^{1}H NMR Spectrum of **25** in $CDCl_3$+DMSO-d_6 (200 MHz)



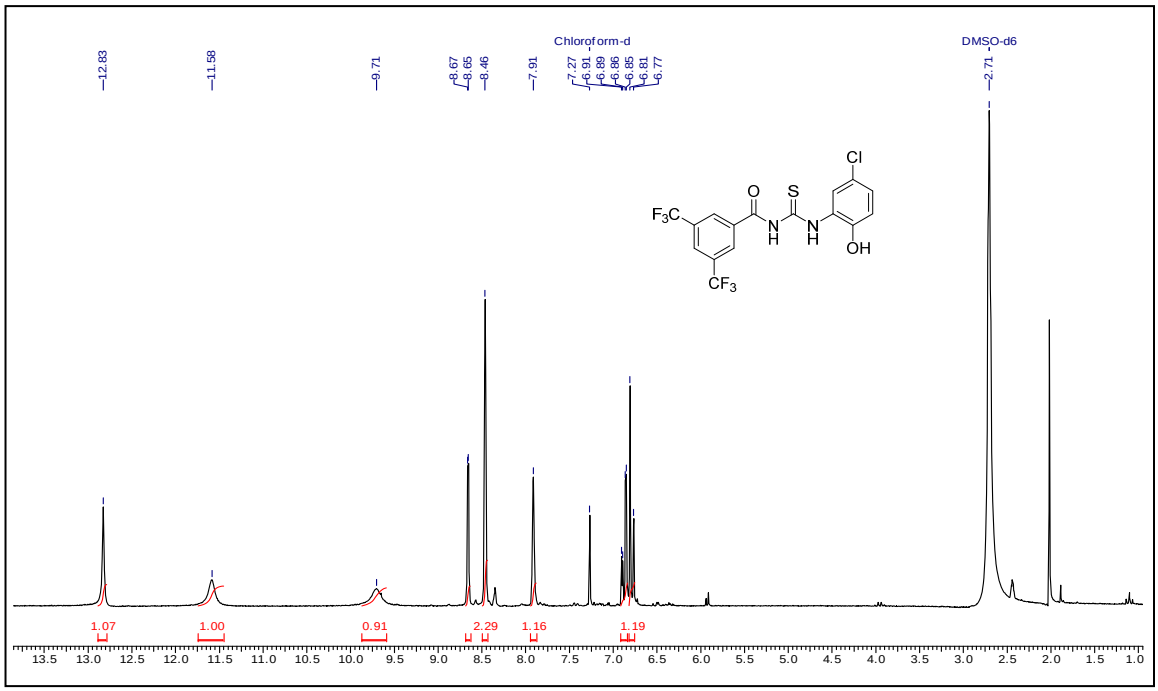
^{13}C NMR Spectrum of **25** in $CDCl_3$+DMSO-d_6 (50 MHz)



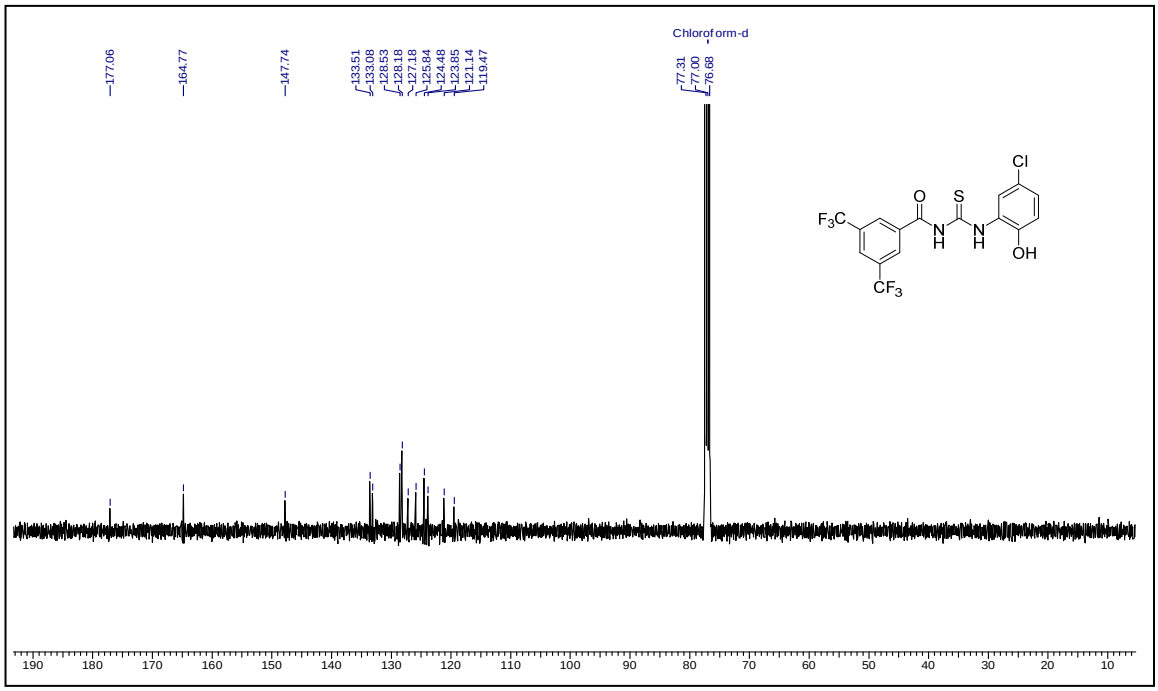
^{1}H NMR Spectrum of **26** in $CDCl_3$ (200 MHz)



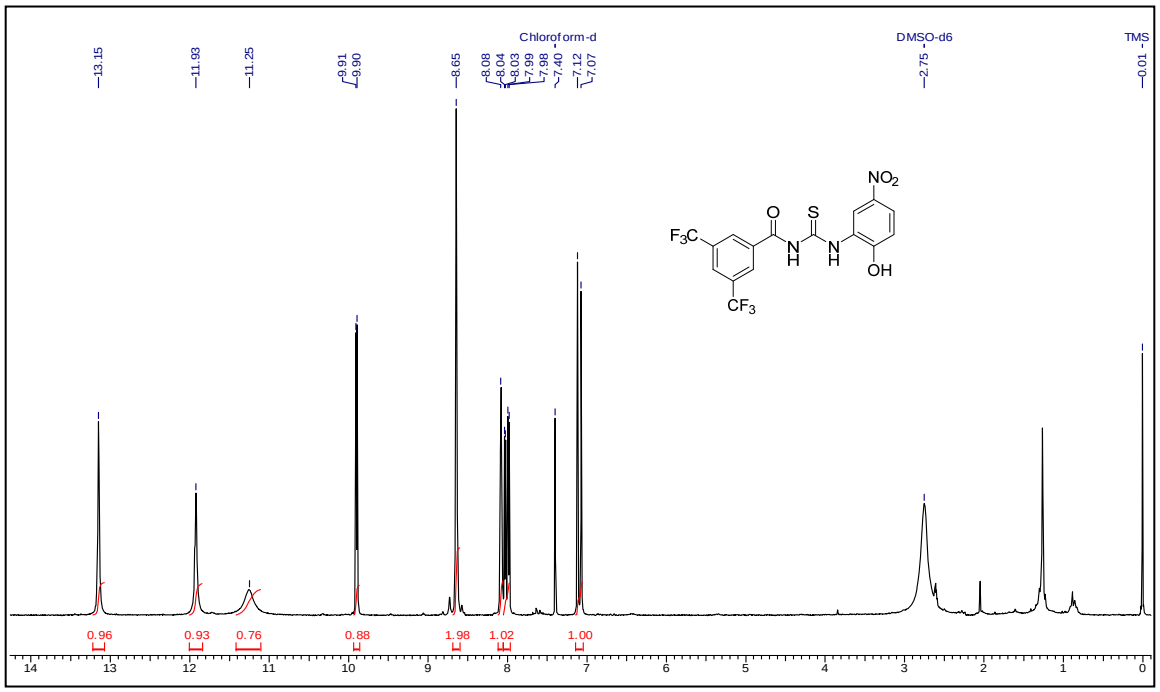
^{13}C NMR Spectrum of **26** in $CDCl_3$+DMSO-d_6 (50 MHz)



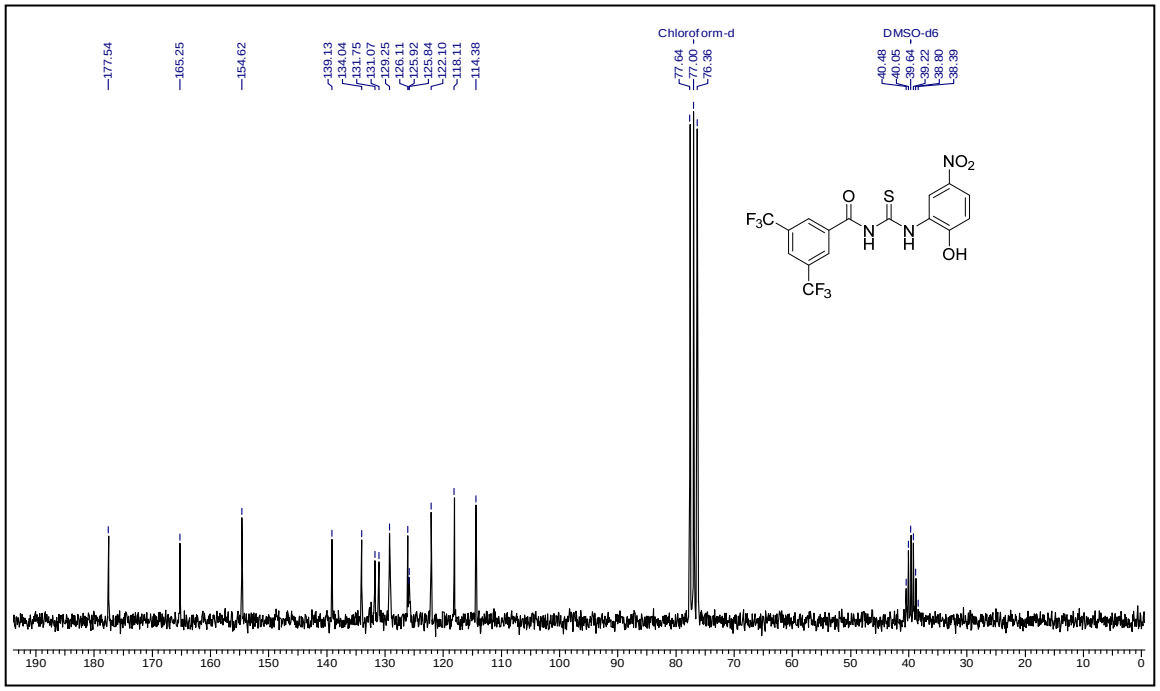
^{1}H NMR Spectrum of **27** in $CDCl_3$+DMSO-d_6 (400 MHz)



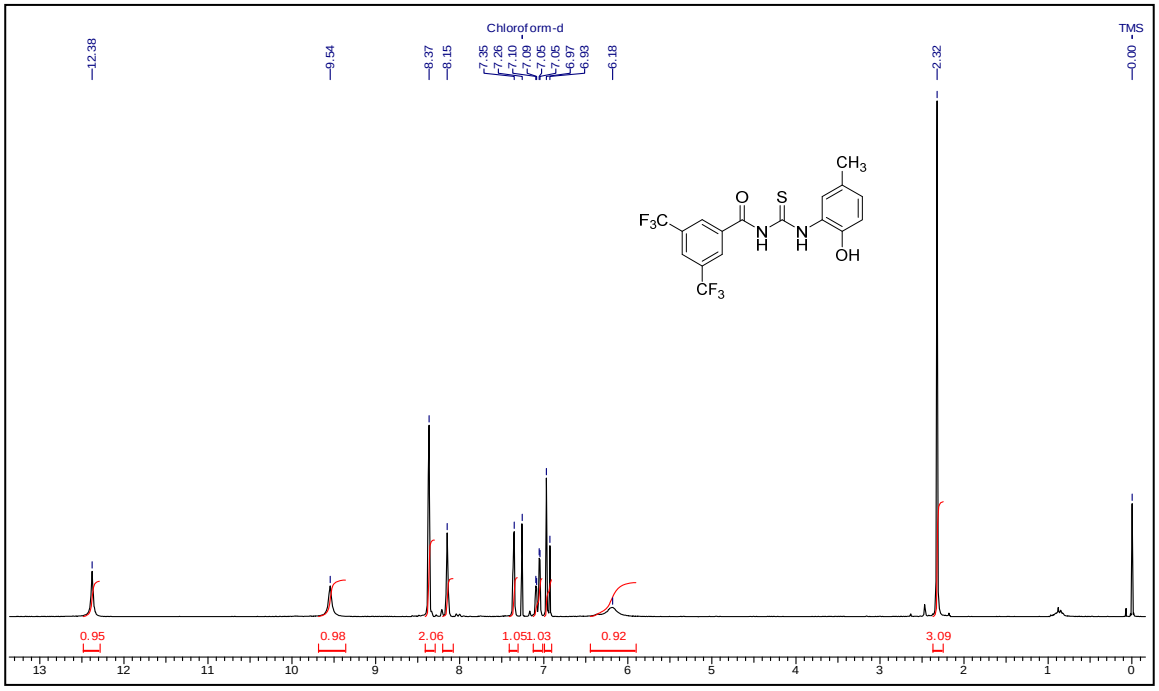
^{13}C NMR Spectrum of **27** in $CDCl_3$ (100 MHz)



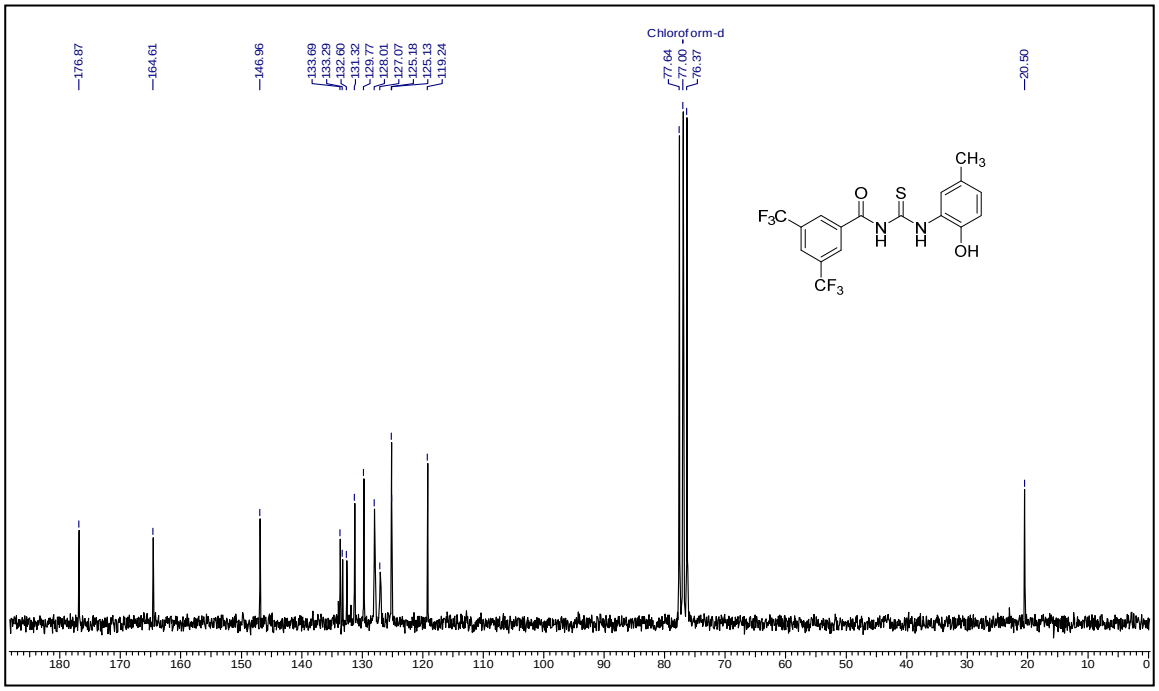
^{1}H NMR Spectrum of **28** in $CDCl_3$+DMSO-d_6 (200 MHz)



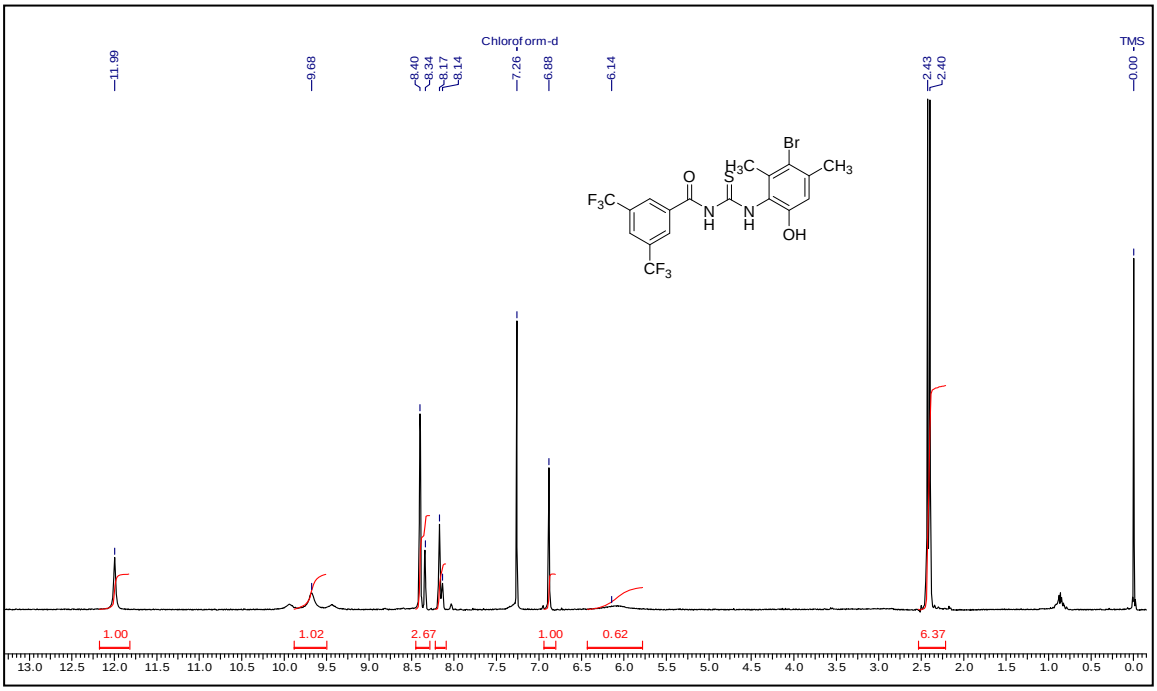
^{13}C NMR Spectrum of **28** in $CDCl_3$+DMSO-d_6 (50 MHz)



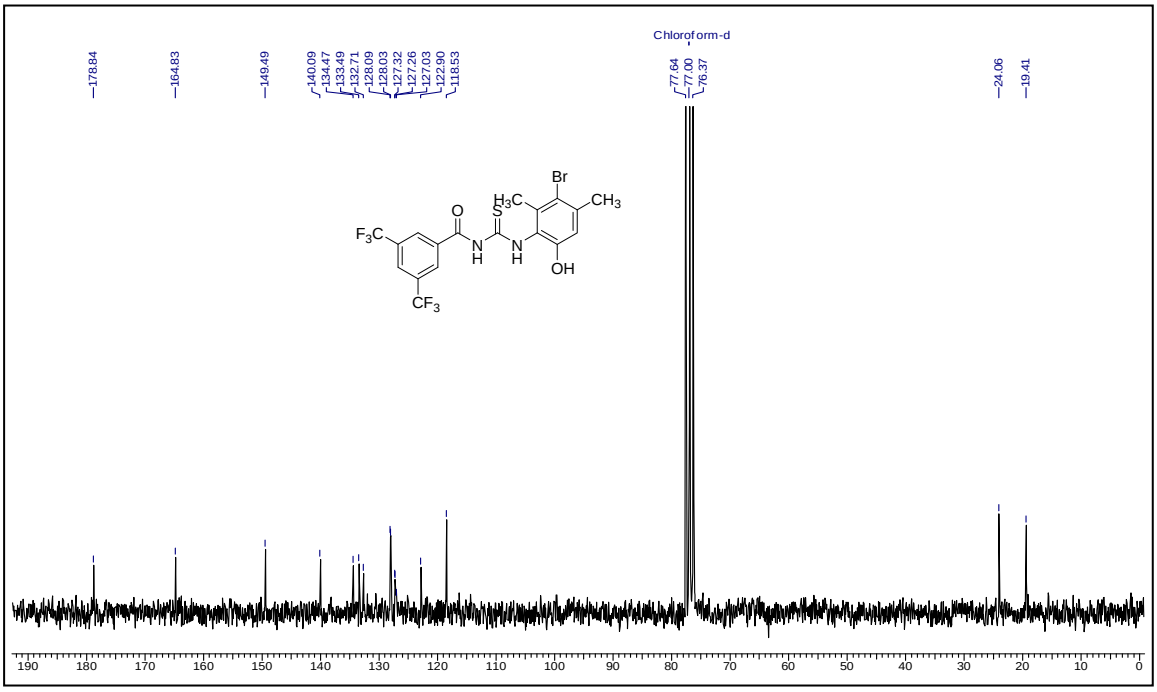
^{1}H NMR Spectrum of **29** in $CDCl_3$ (200 MHz)



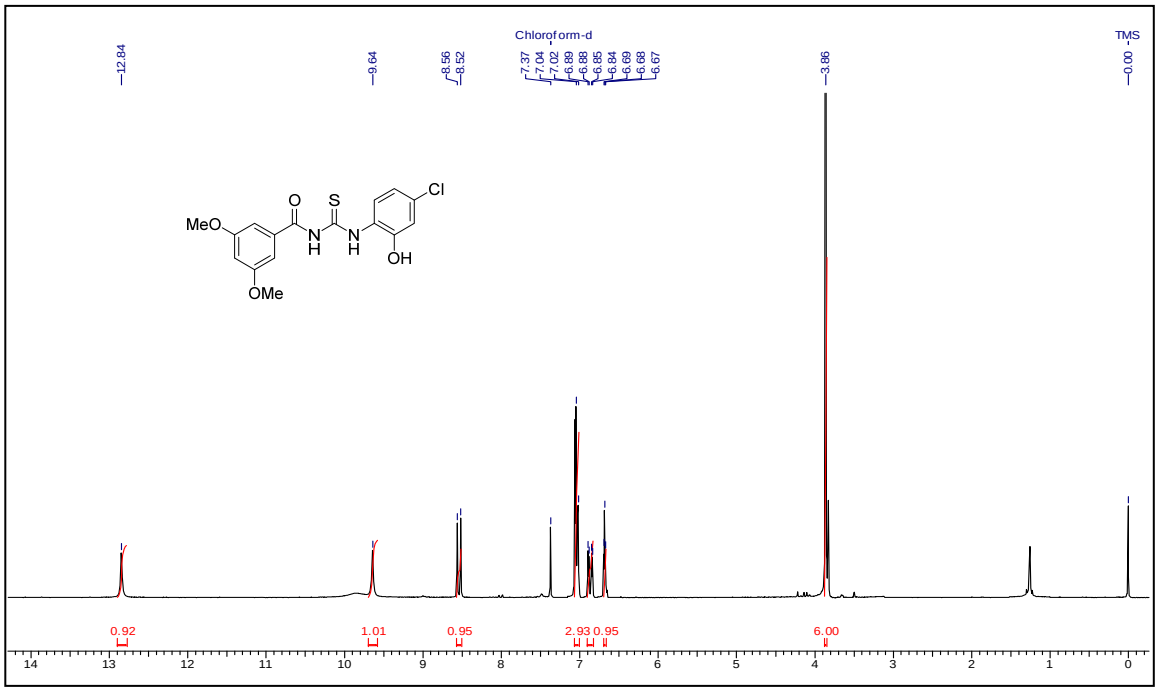
^{13}C NMR Spectrum of **29** in $CDCl_3$ (50 MHz)



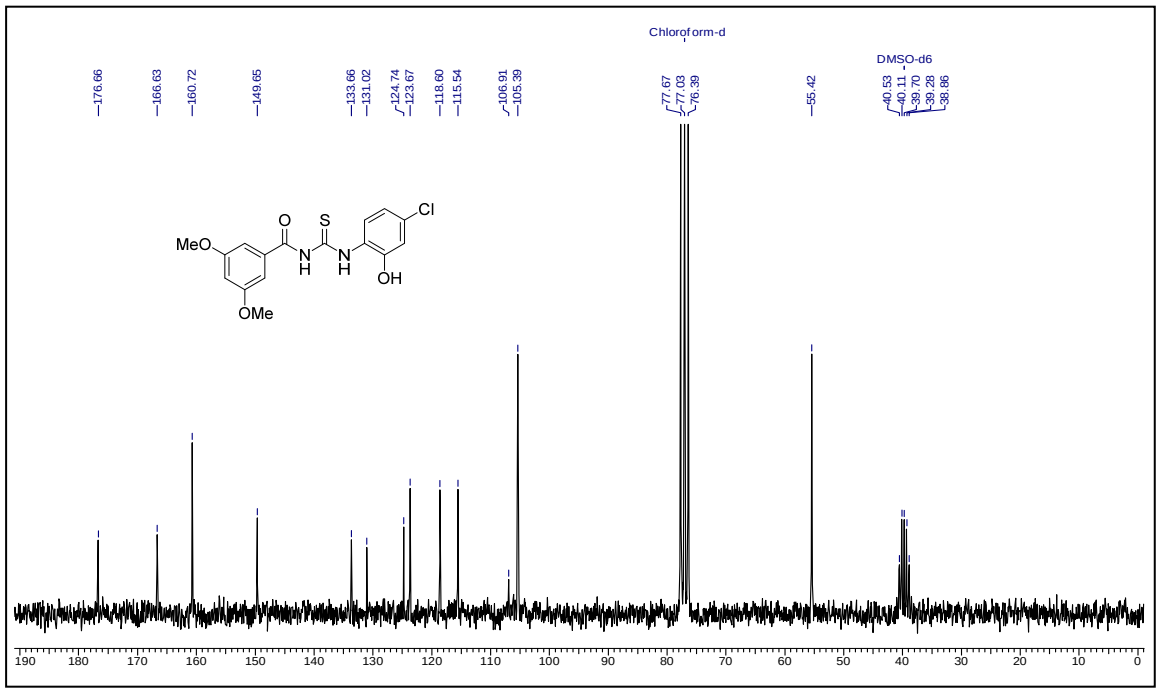
^{1}H NMR Spectrum of **31** in $CDCl_3$ (200 MHz)



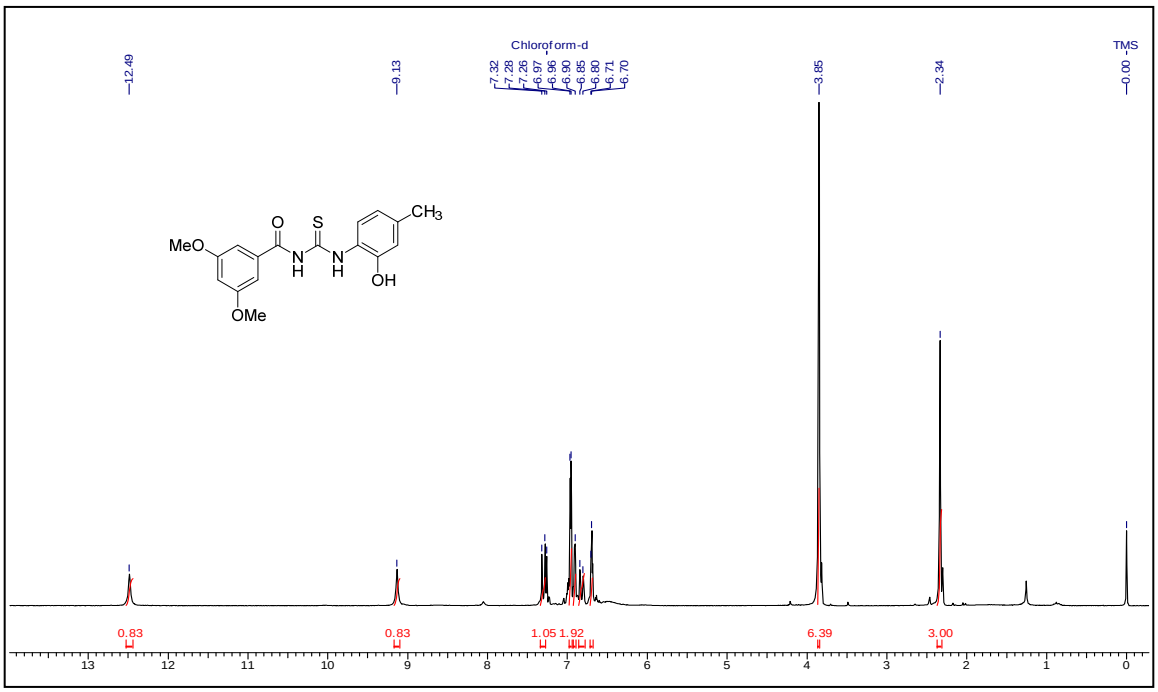
^{13}C NMR Spectrum of **31** in $CDCl_3$ (50 MHz)



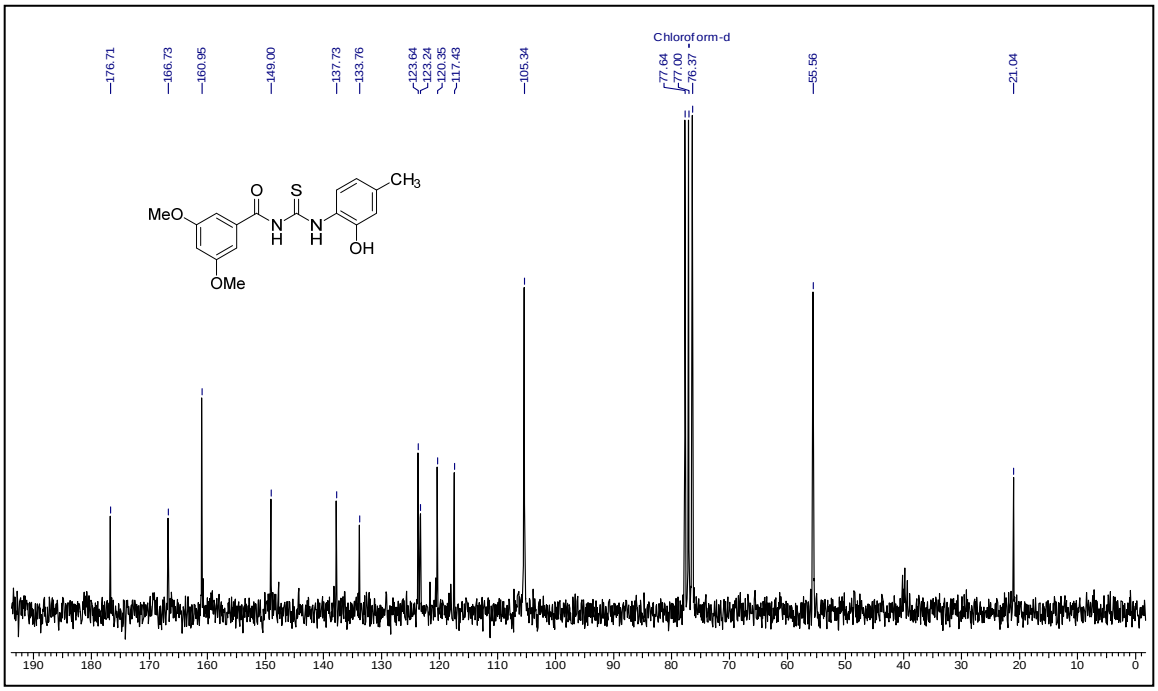
^{1}H NMR Spectrum of **33** in $CDCl_3$ (200 MHz)



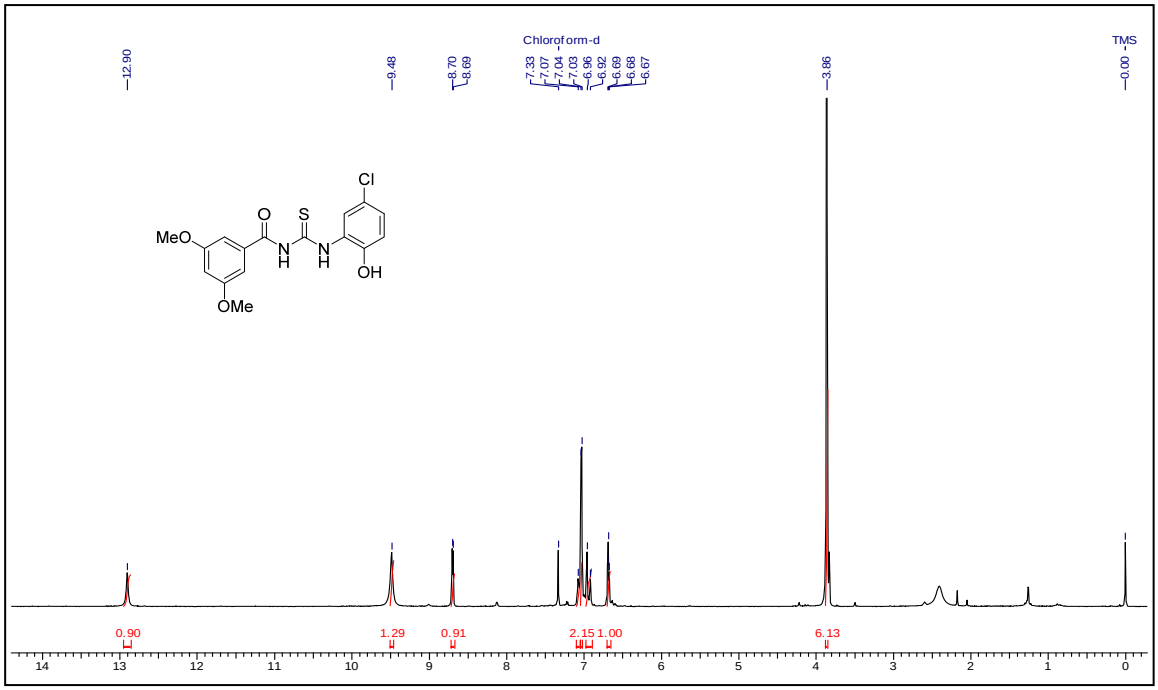
^{13}C NMR Spectrum of **33** in $CDCl_3$+DMSO-d_6 (50 MHz)



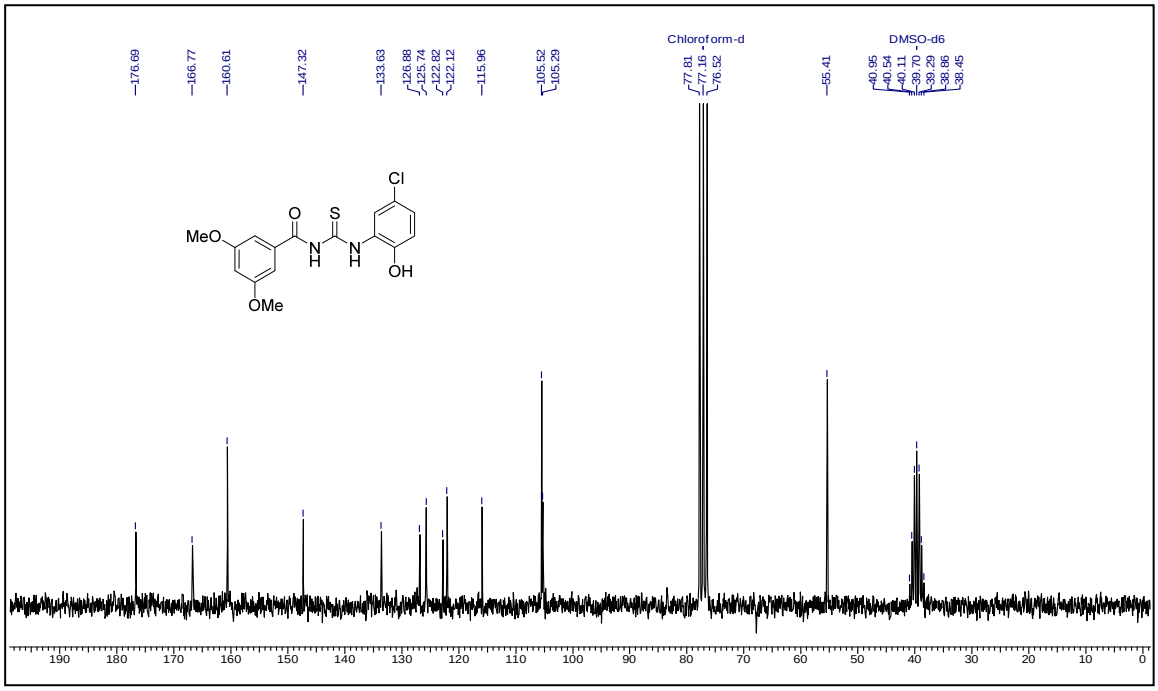
^{1}H NMR Spectrum of **34** in $CDCl_3$ (200 MHz)



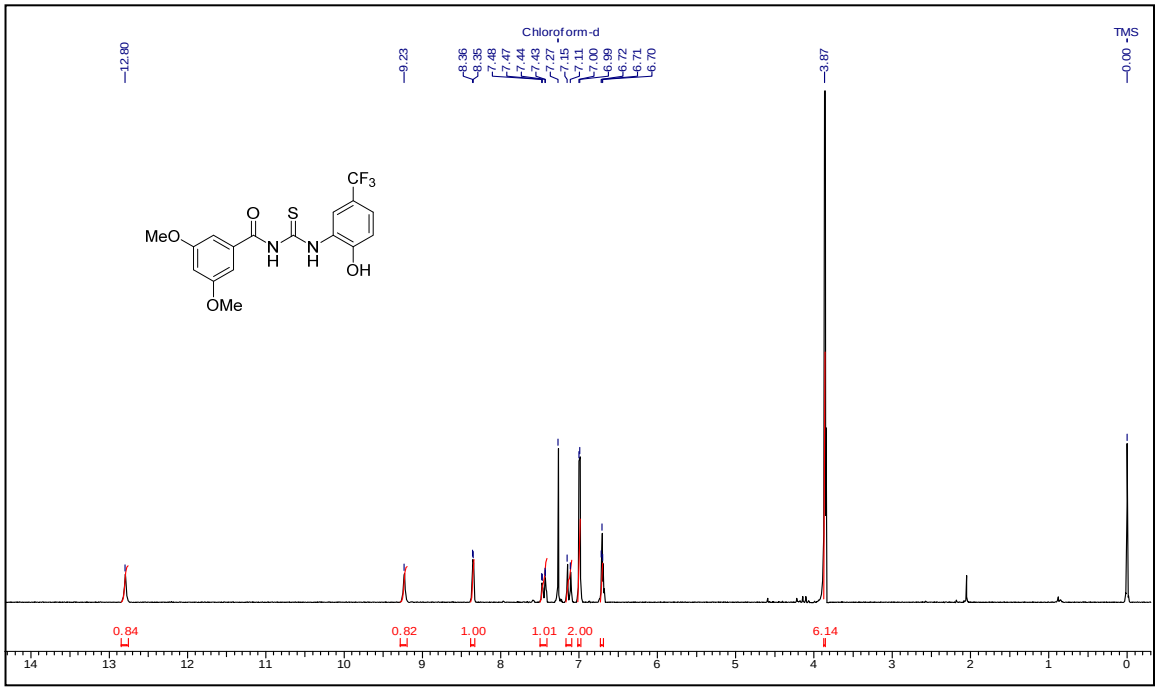
^{13}C NMR Spectrum of **34** in $CDCl_3$ (50 MHz)



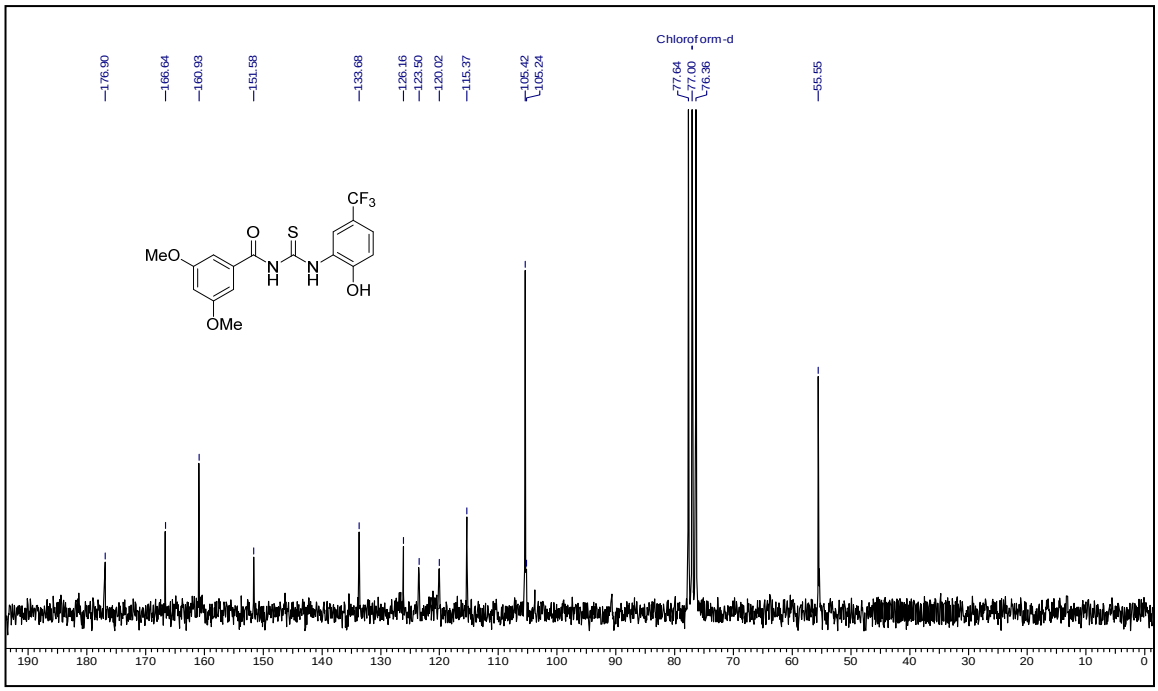
^{1}H NMR Spectrum of **35** in $CDCl_3$ (200 MHz)



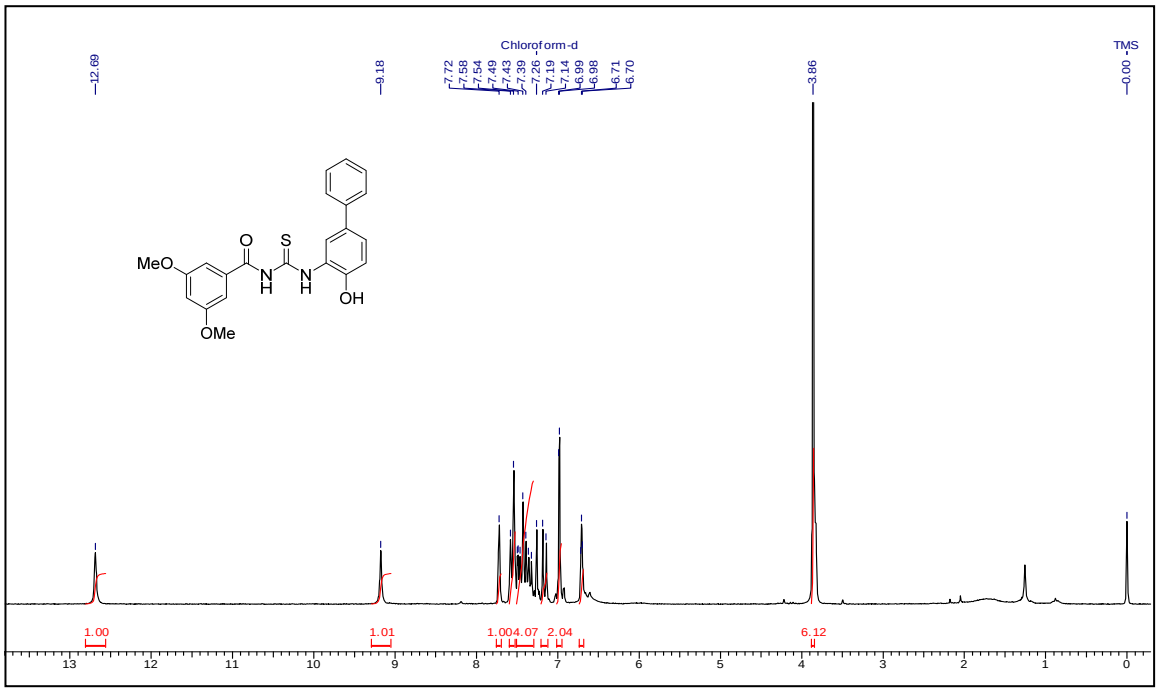
^{13}C NMR Spectrum of **35** in $CDCl_3$+DMSO-d_6 (50 MHz)



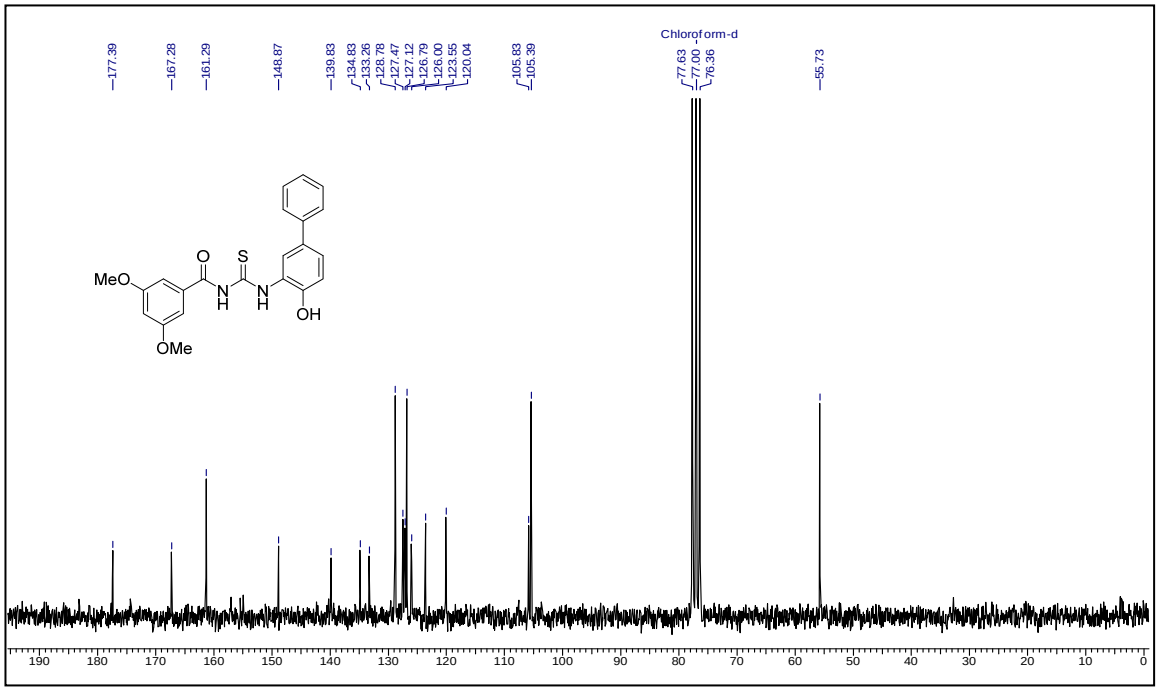
^{1}H NMR Spectrum of **36** in $CDCl_3$ (200 MHz)



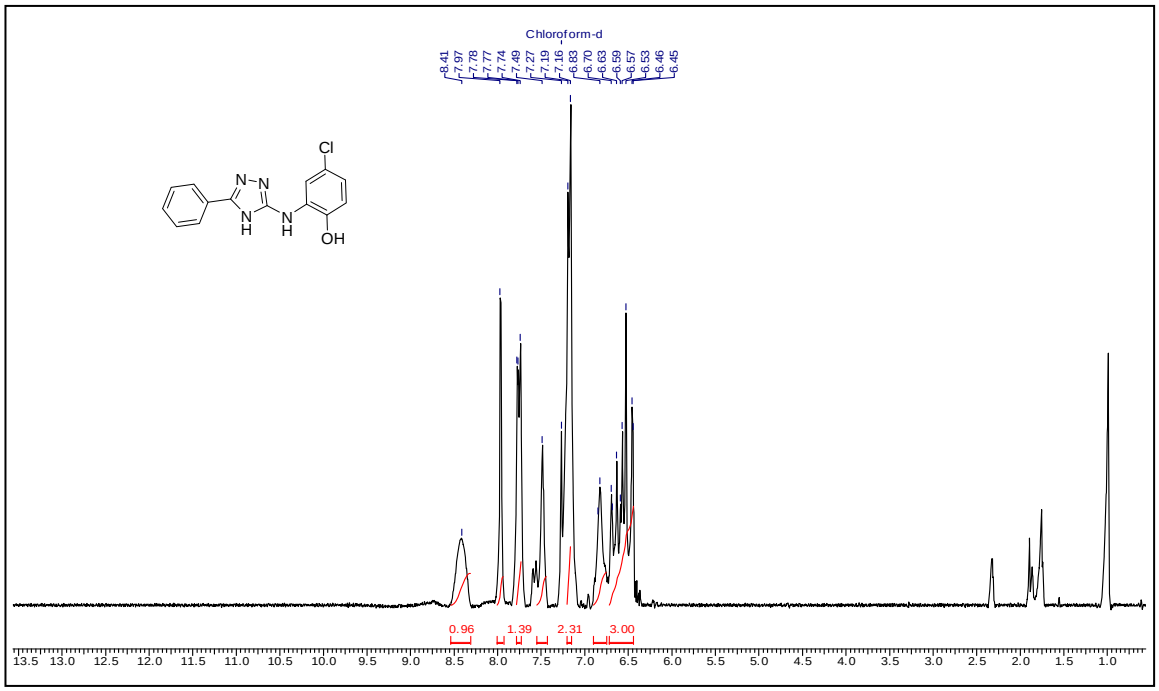
^{13}C NMR Spectrum of **36** in $CDCl_3$ (50 MHz)



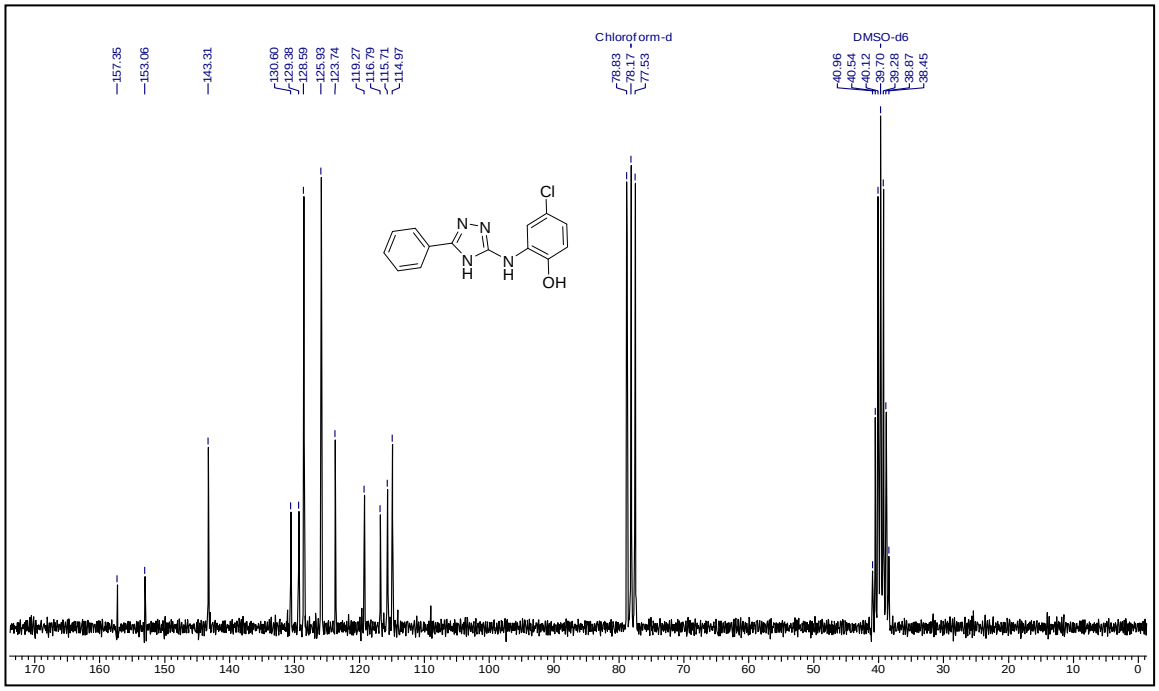
^{1}H NMR Spectrum of **37** in $CDCl_3$ (200 MHz)



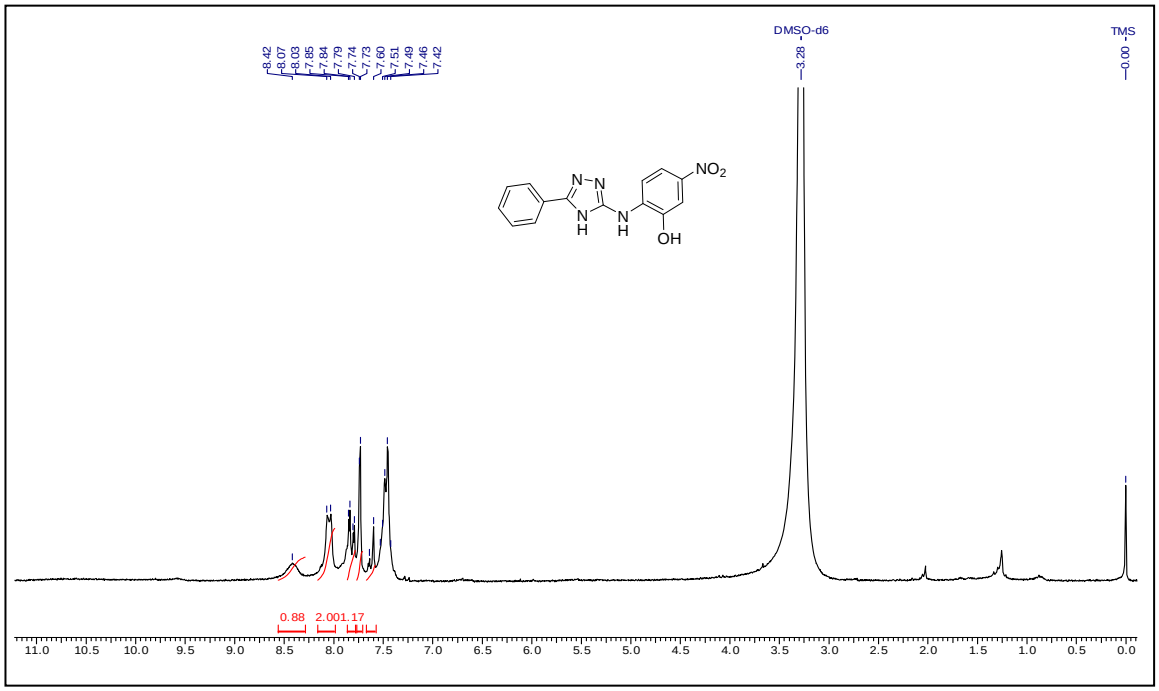
^{13}C NMR Spectrum of **37** in $CDCl_3$ (50 MHz)



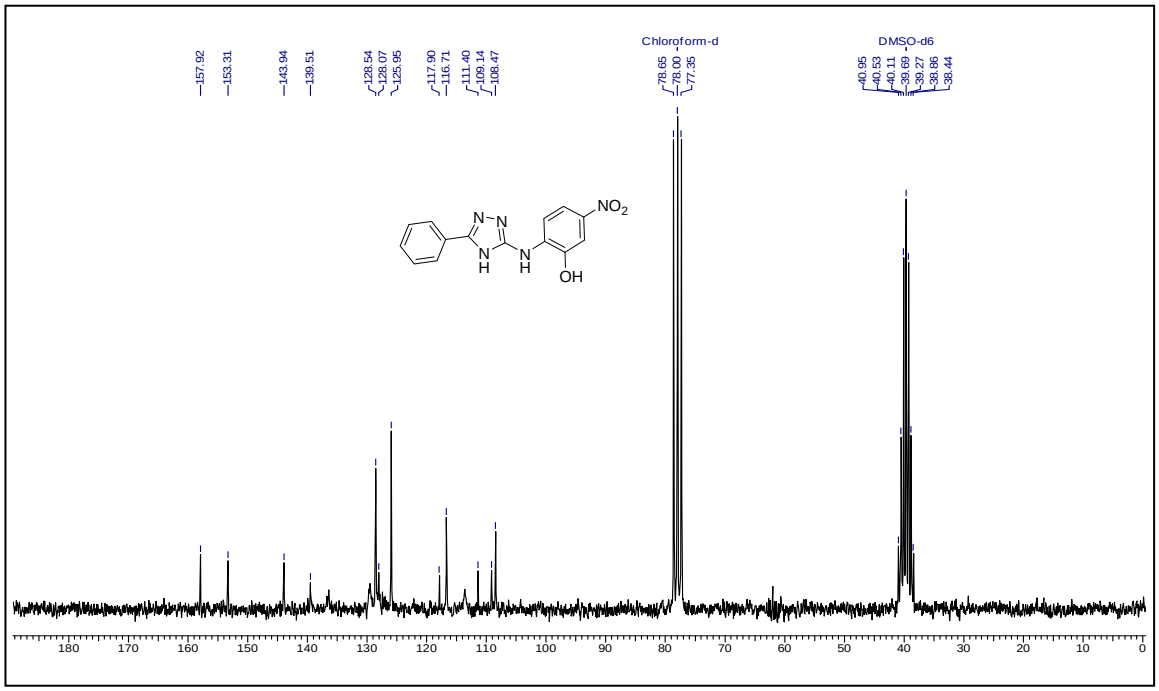
^{1}H NMR Spectrum of **38** in $CDCl_3$+DMSO-d_6 (200 MHz)



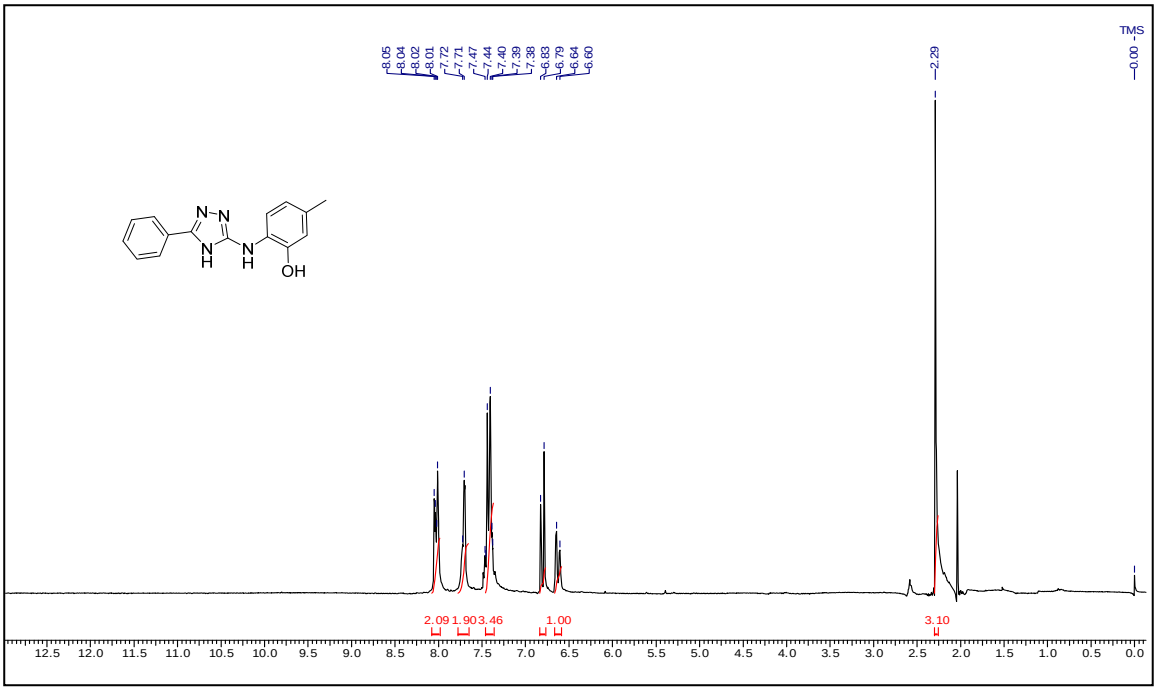
^{13}C NMR Spectrum of **38** in $CDCl_3$+DMSO-d_6 (50 MHz)



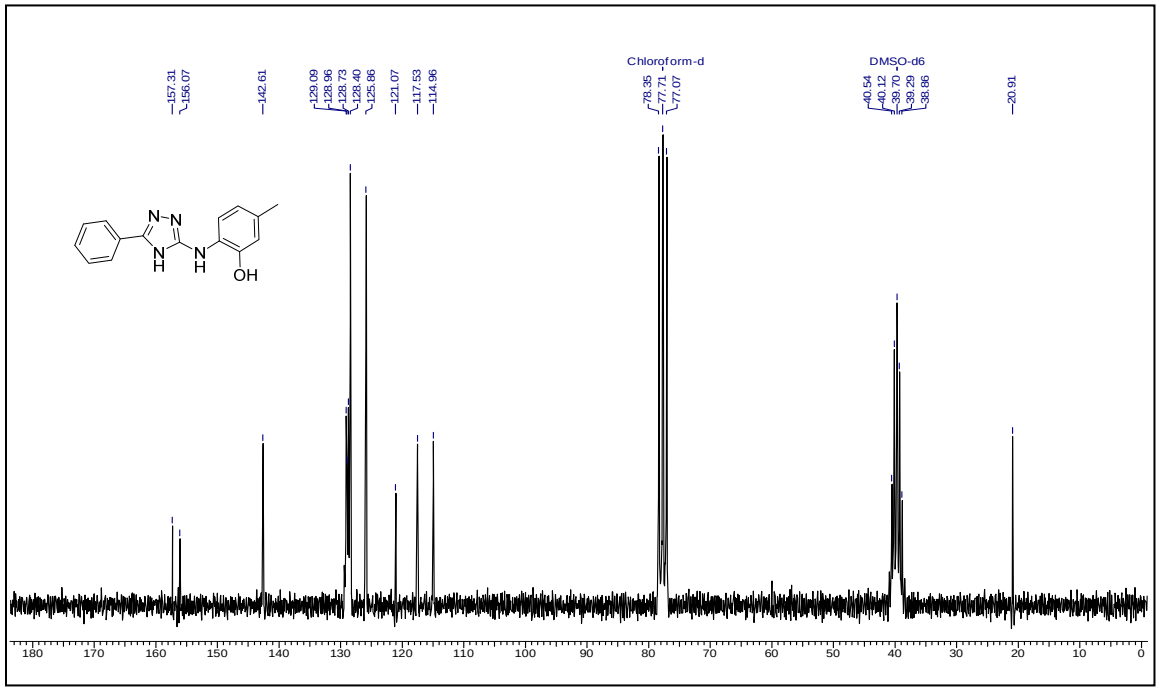
^{1}H NMR Spectrum of **39** in $CDCl_3$+DMSO-d_6 (200 MHz)



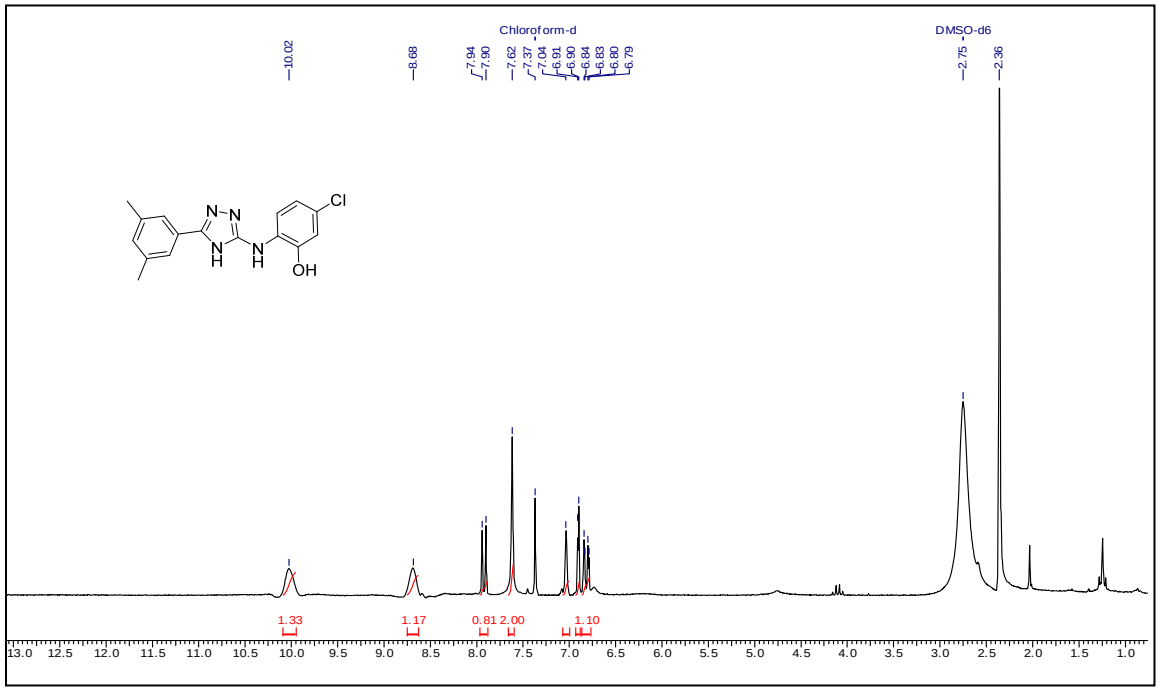
^{13}C NMR Spectrum of **39** in $CDCl_3$+DMSO-d_6 (50 MHz)



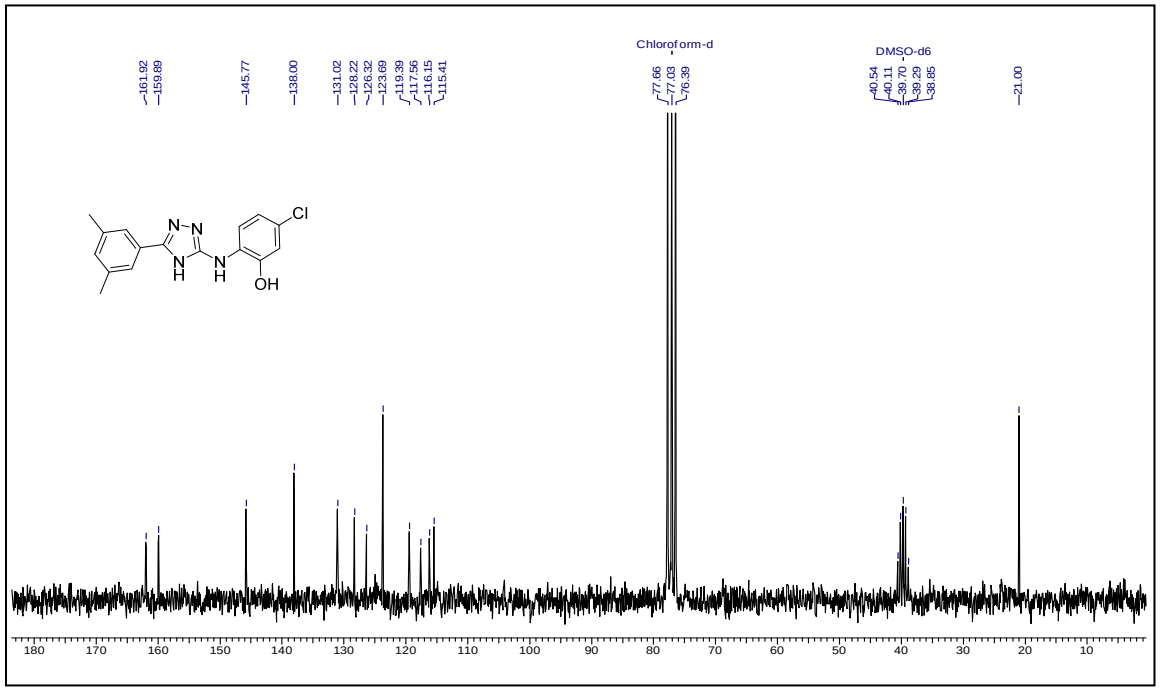
^{1}H NMR Spectrum of **40** in $CDCl_3$+DMSO-d_6 (200 MHz)



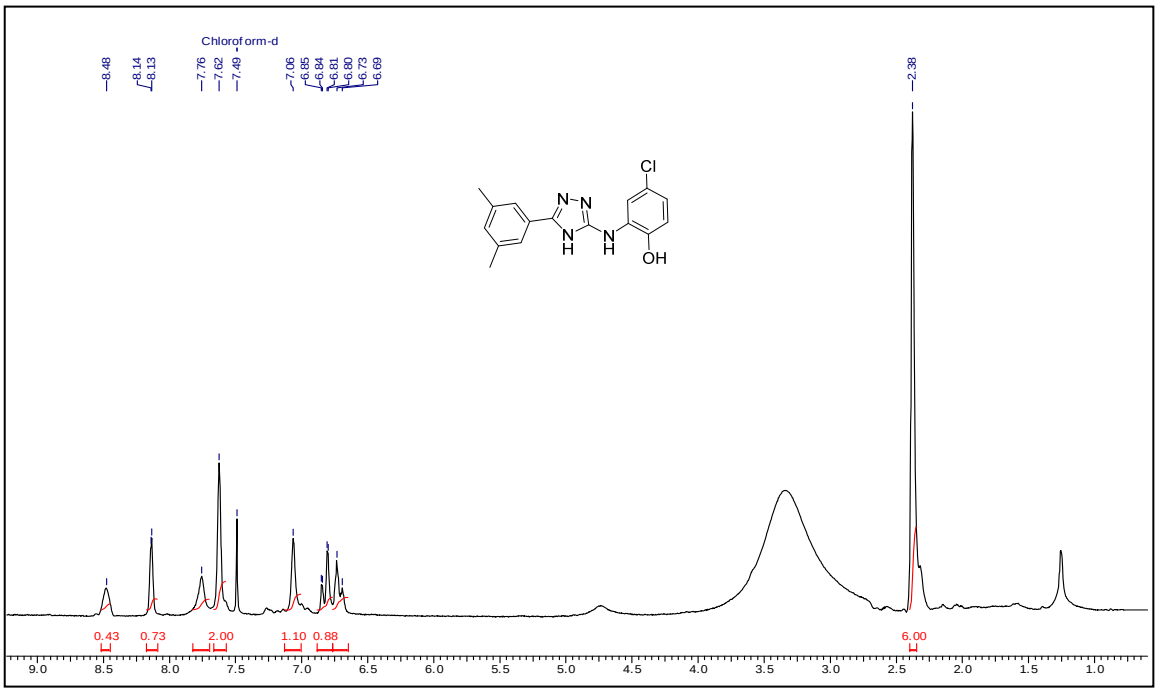
^{13}C NMR Spectrum of **40** in $CDCl_3$+DMSO-d_6 (50 MHz)



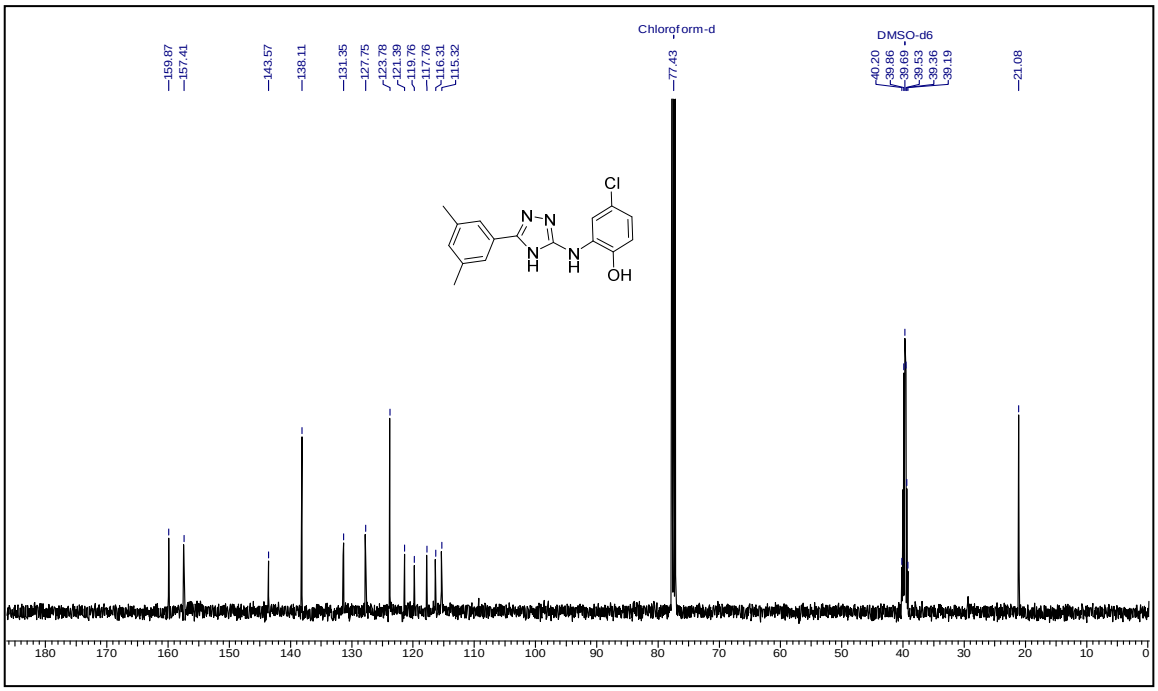
^{1}H NMR Spectrum of **41** in $CDCl_3$+DMSO-d_6 (200 MHz)



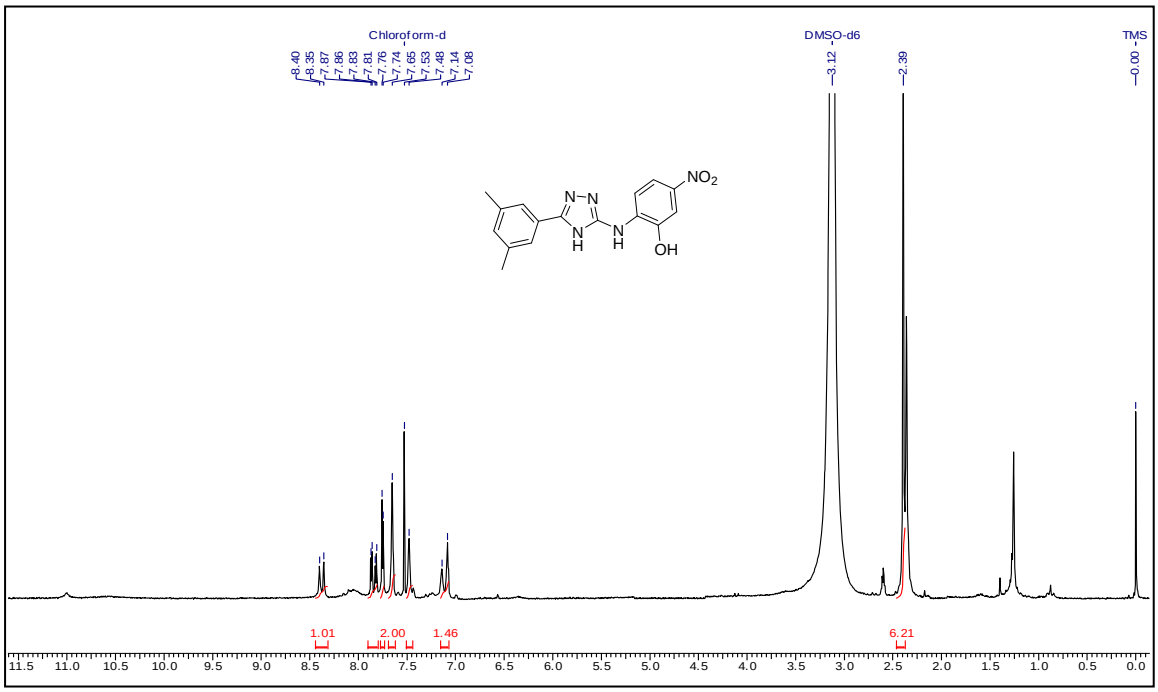
^{13}C NMR Spectrum of **41** in $CDCl_3$+DMSO-d_6 (50 MHz)



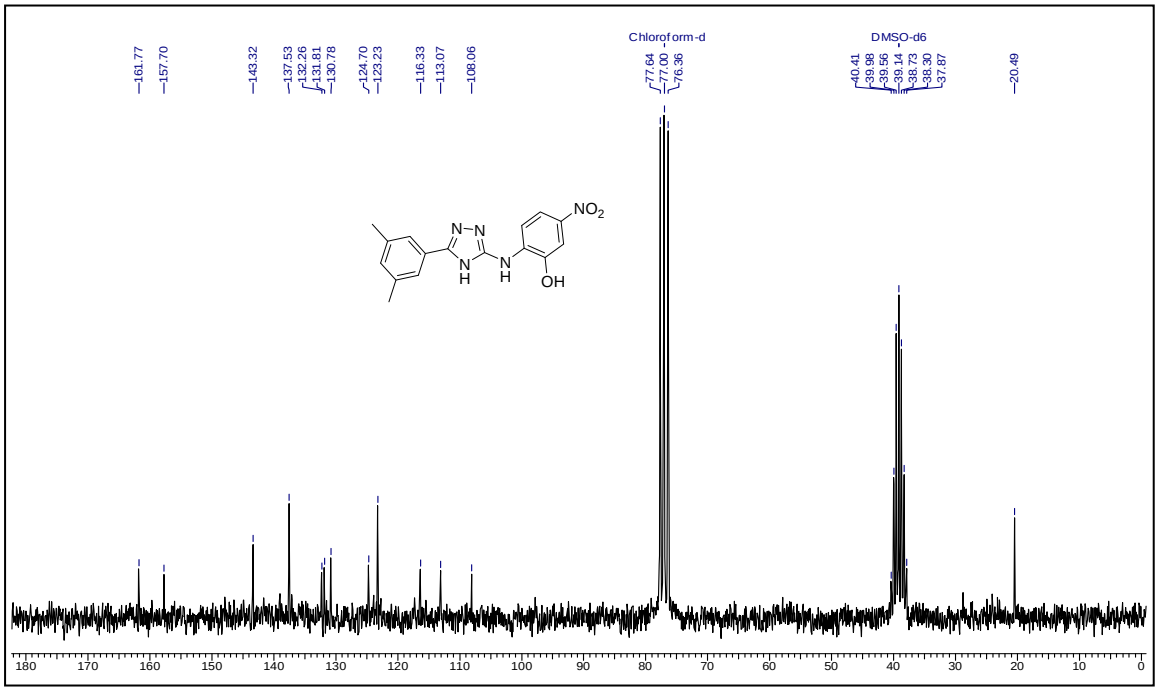
^{1}H NMR Spectrum of **42** in $CDCl_3$+DMSO-d_6 (200 MHz)



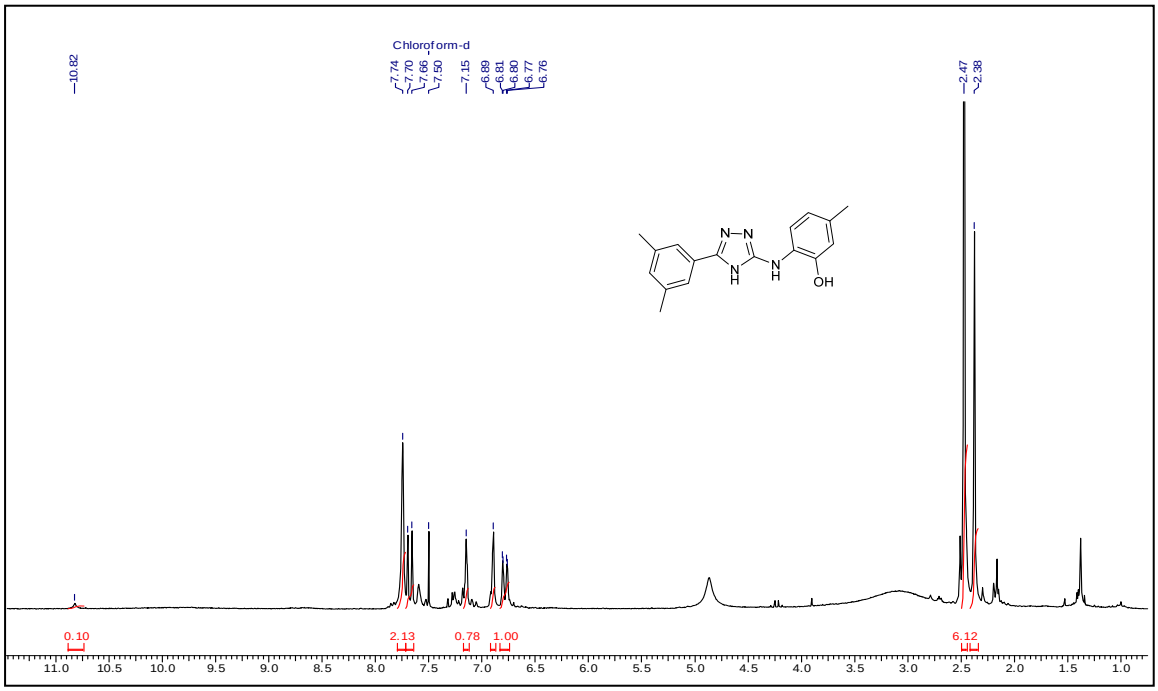
^{13}C NMR Spectrum of **42** in $CDCl_3$+DMSO-d_6 (50 MHz)



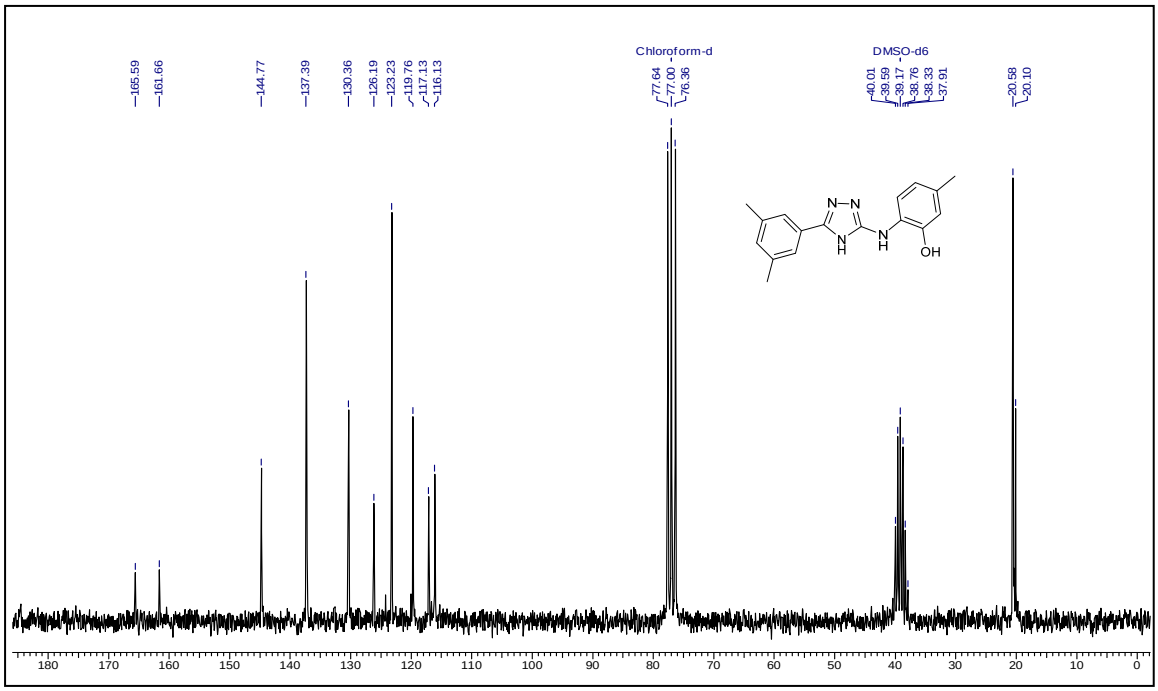
^{1}H NMR Spectrum of **43** in $CDCl_3$+DMSO-d_6 (200 MHz)



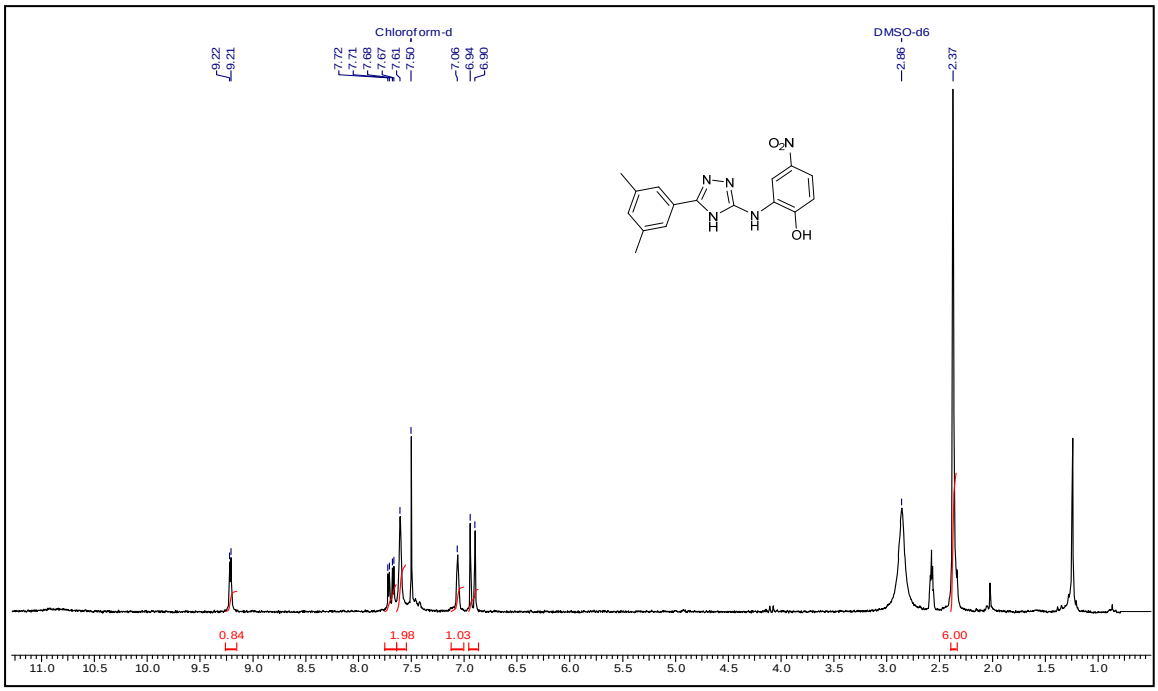
^{13}C NMR Spectrum of **43** in $CDCl_3$+DMSO-d_6 (50 MHz)



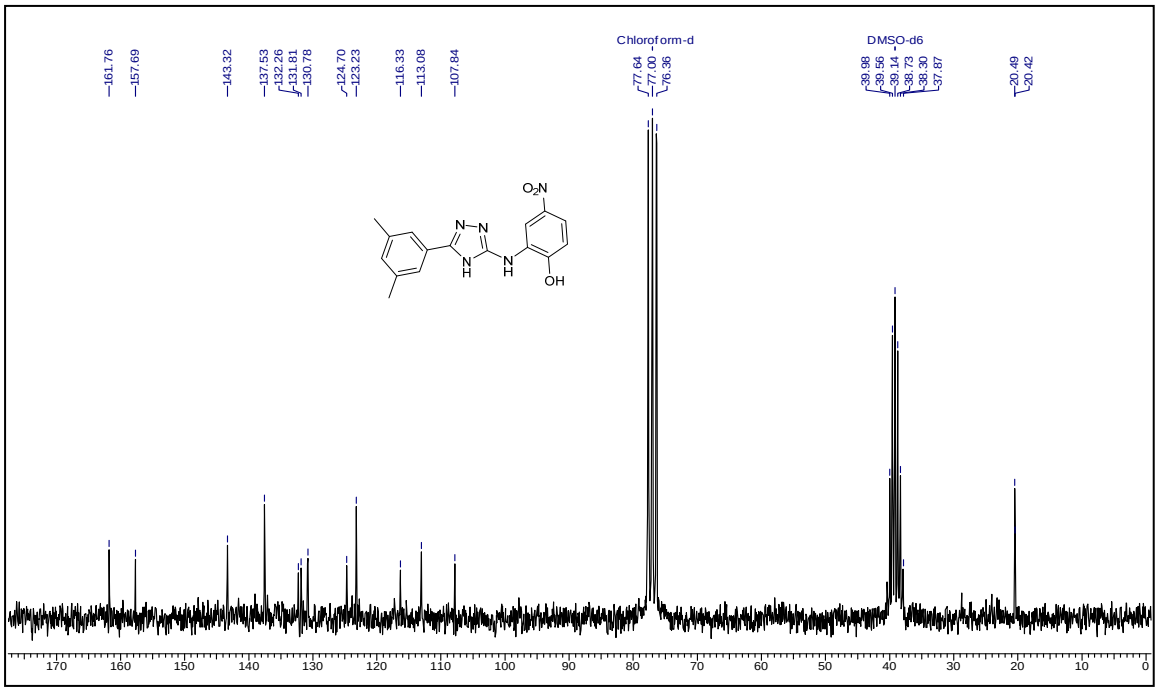
^{1}H NMR Spectrum of **44** in $CDCl_3$+DMSO-d_6 (200 MHz)



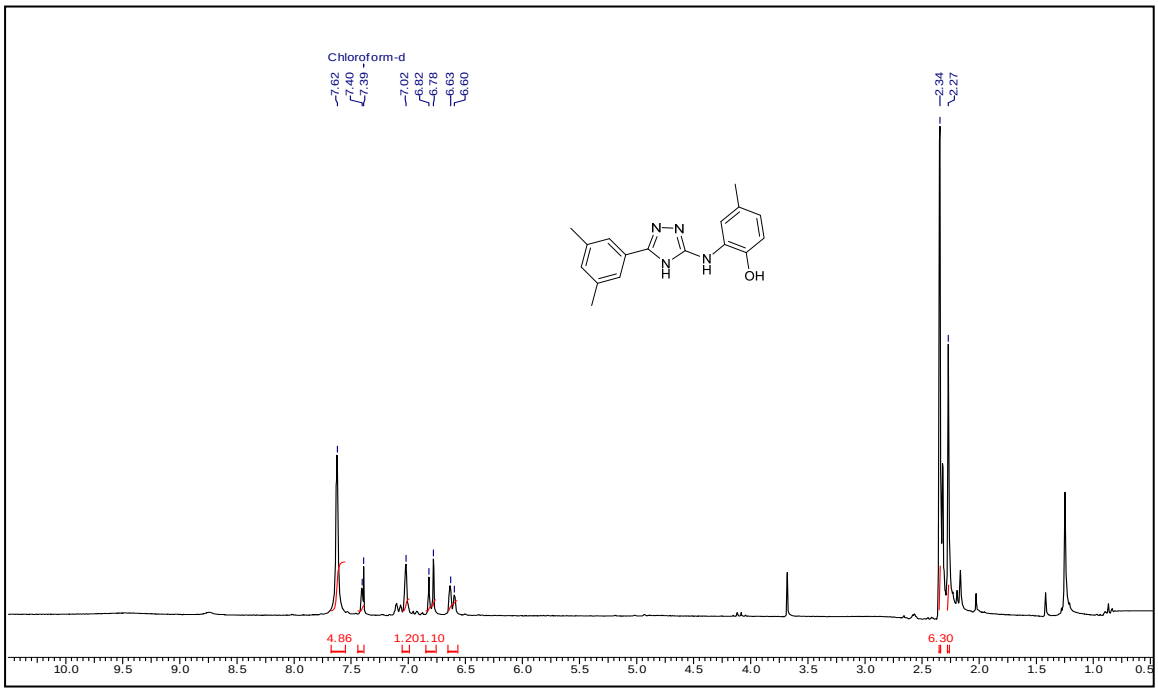
^{13}C NMR Spectrum of **44** in $CDCl_3$+DMSO-d_6 (50 MHz)



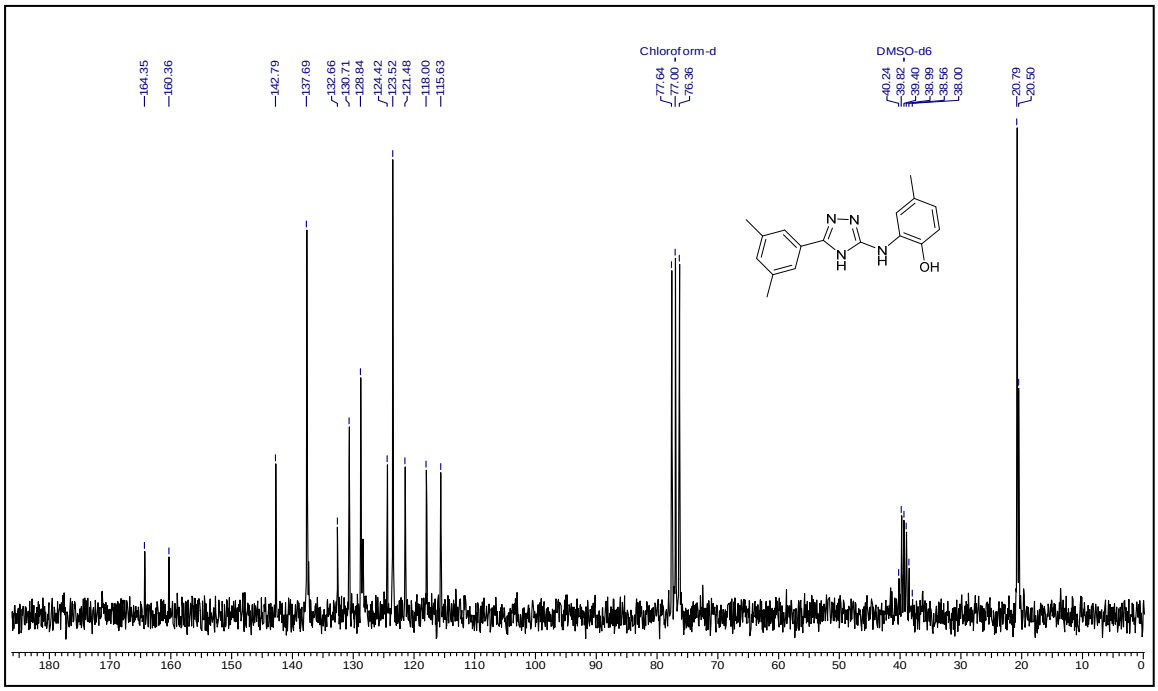
^{1}H NMR Spectrum of **45** in $CDCl_3$+DMSO-d_6 (200 MHz)



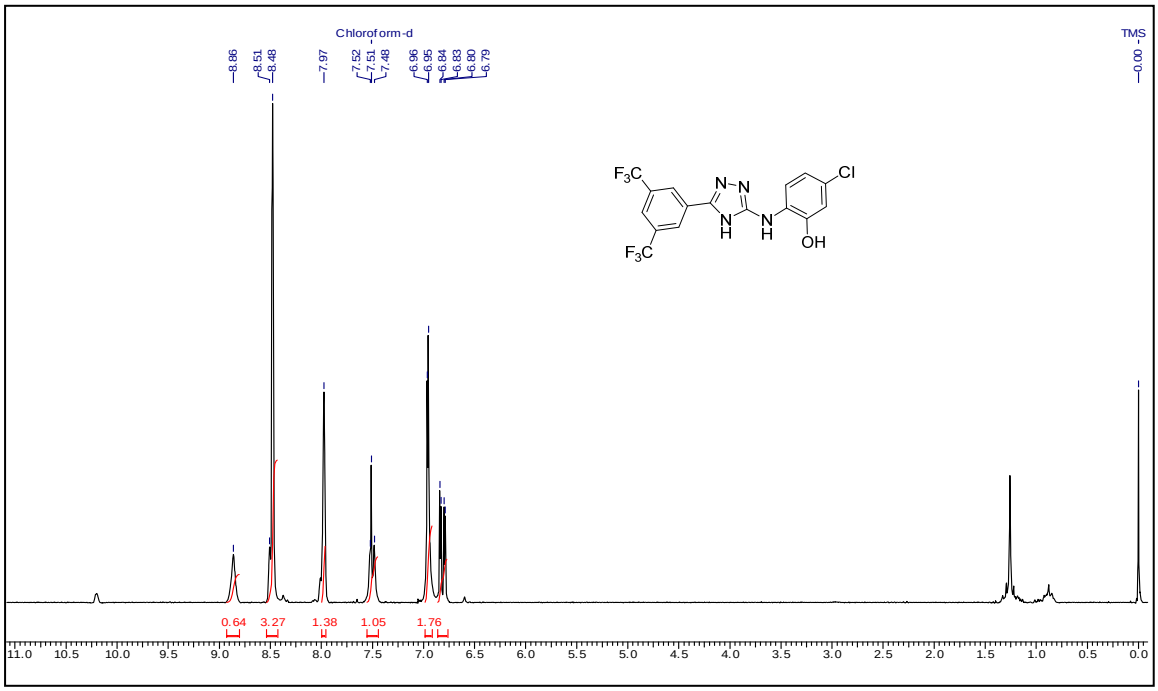
^{13}C NMR Spectrum of **45** in $CDCl_3$+DMSO-d_6 (50 MHz)



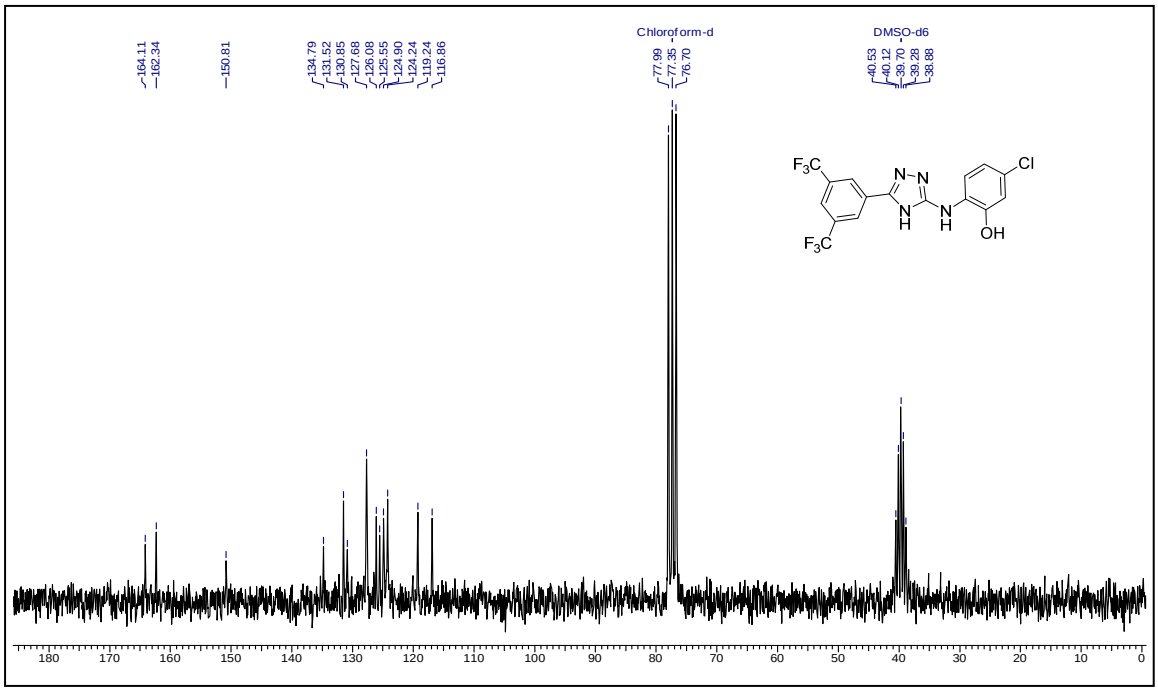
^{1}H NMR Spectrum of **46** in $CDCl_3$+DMSO-d_6 (200 MHz)



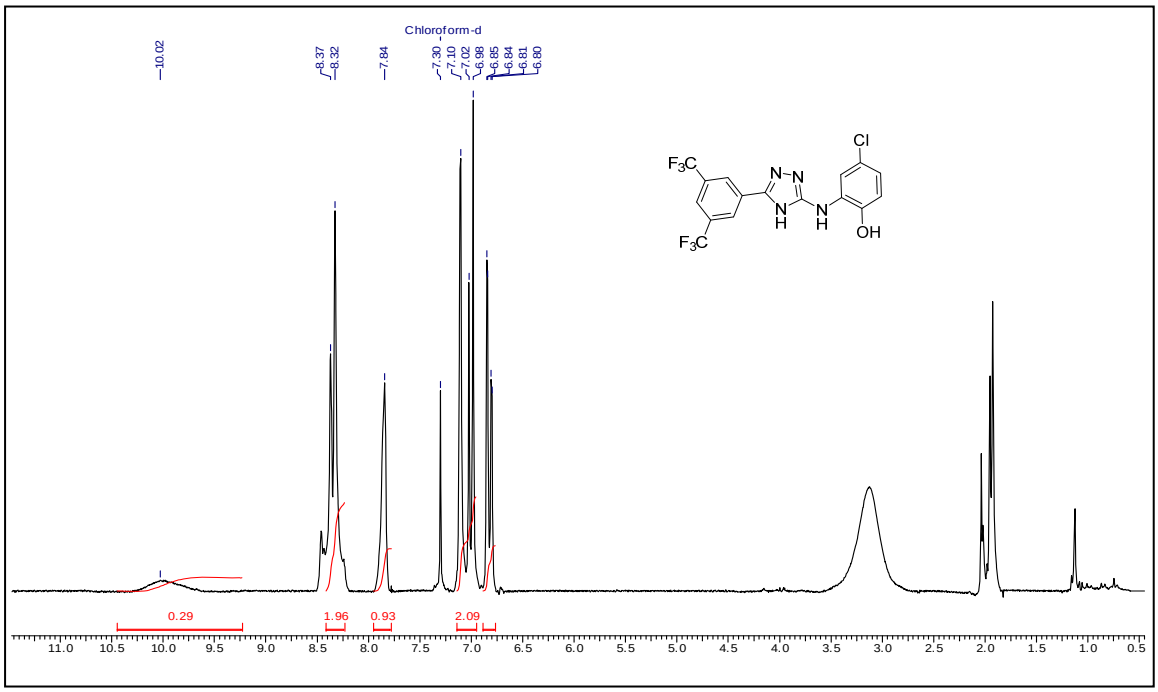
^{13}C NMR Spectrum of **46** in $CDCl_3$+DMSO-d_6 (50 MHz)



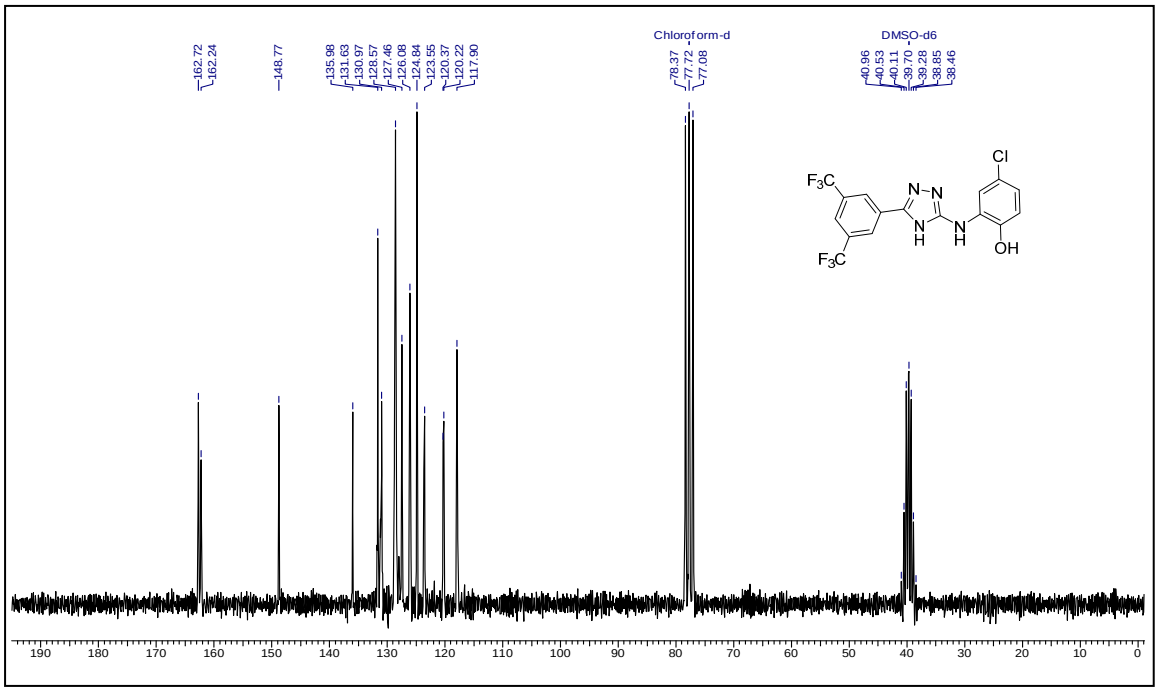
^{1}H NMR Spectrum of **47** in $CDCl_3$ (200 MHz)



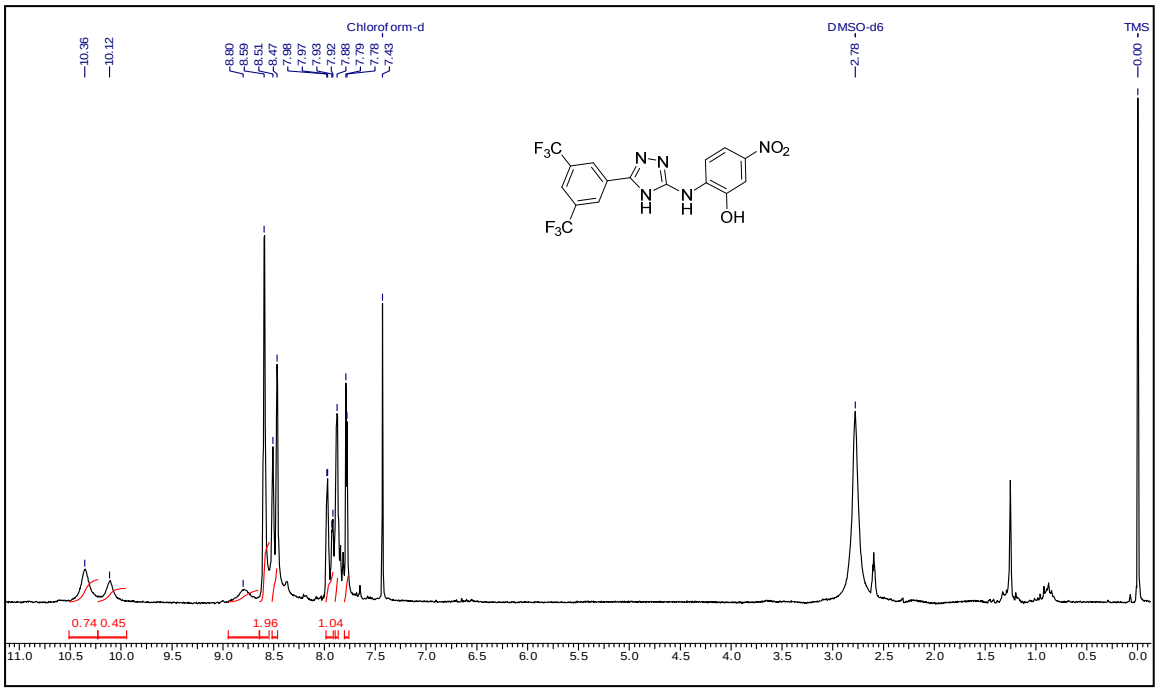
^{13}C NMR Spectrum of **47** in $CDCl_3$+DMSO-d_6 (50 MHz)



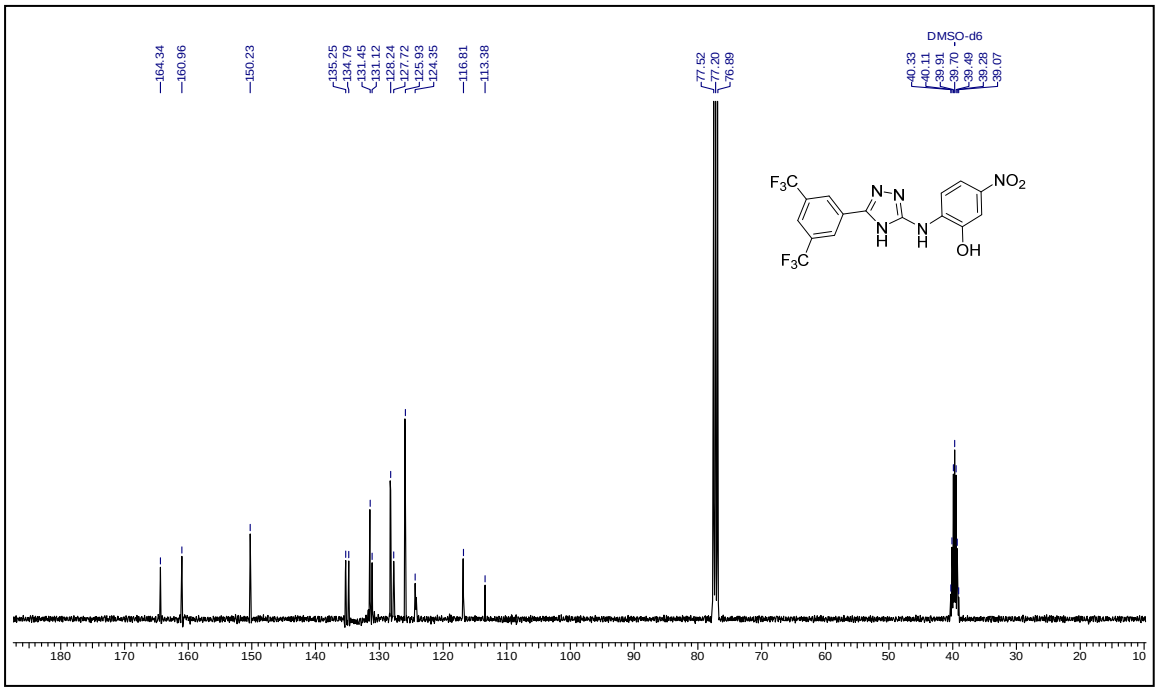
^{1}H NMR Spectrum of **48** in $CDCl_3$+DMSO-d_6 (200 MHz)



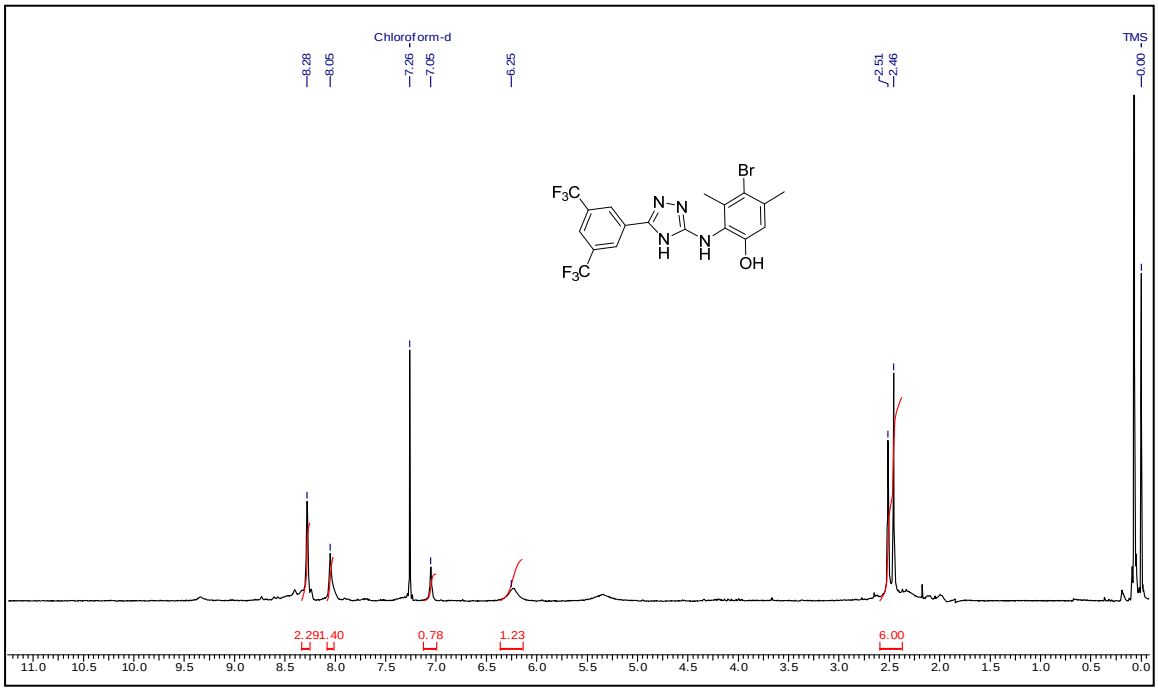
^{13}C NMR Spectrum of **48** in $CDCl_3$+DMSO-d_6 (50 MHz)



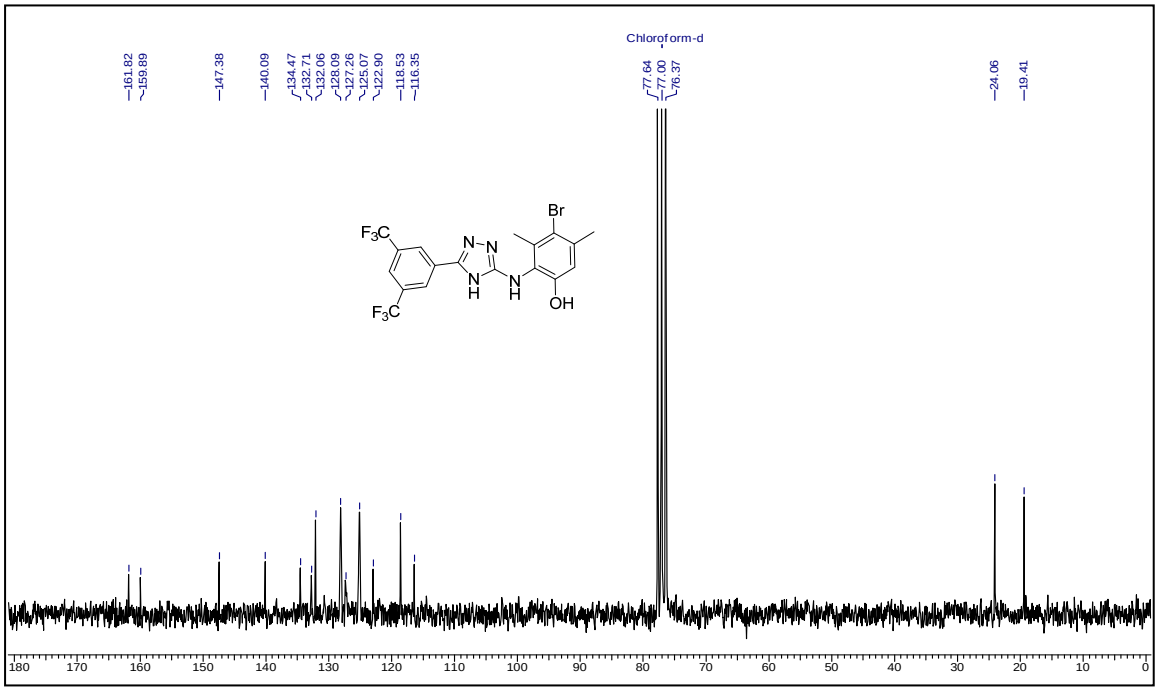
^{1}H NMR Spectrum of **49** in $CDCl_3$+DMSO-d_6 (200 MHz)



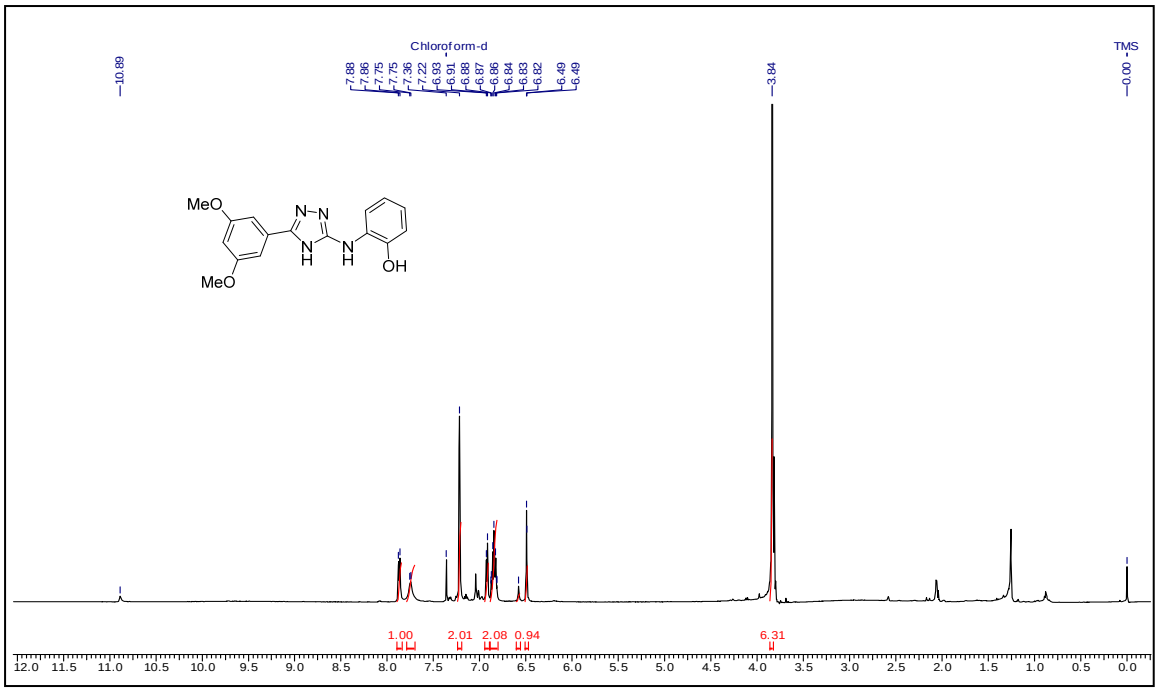
^{13}C NMR Spectrum of **49** in $CDCl_3$+DMSO-d_6 (50 MHz)



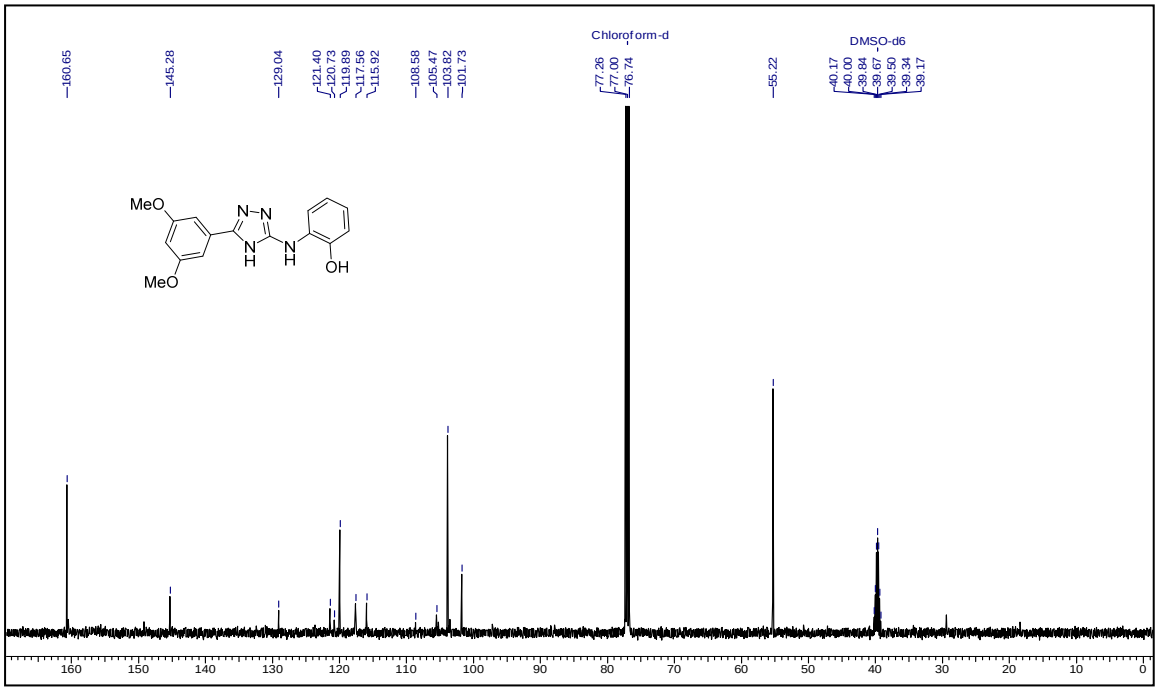
^{1}H NMR Spectrum of **51** in $CDCl_3$ (200 MHz)



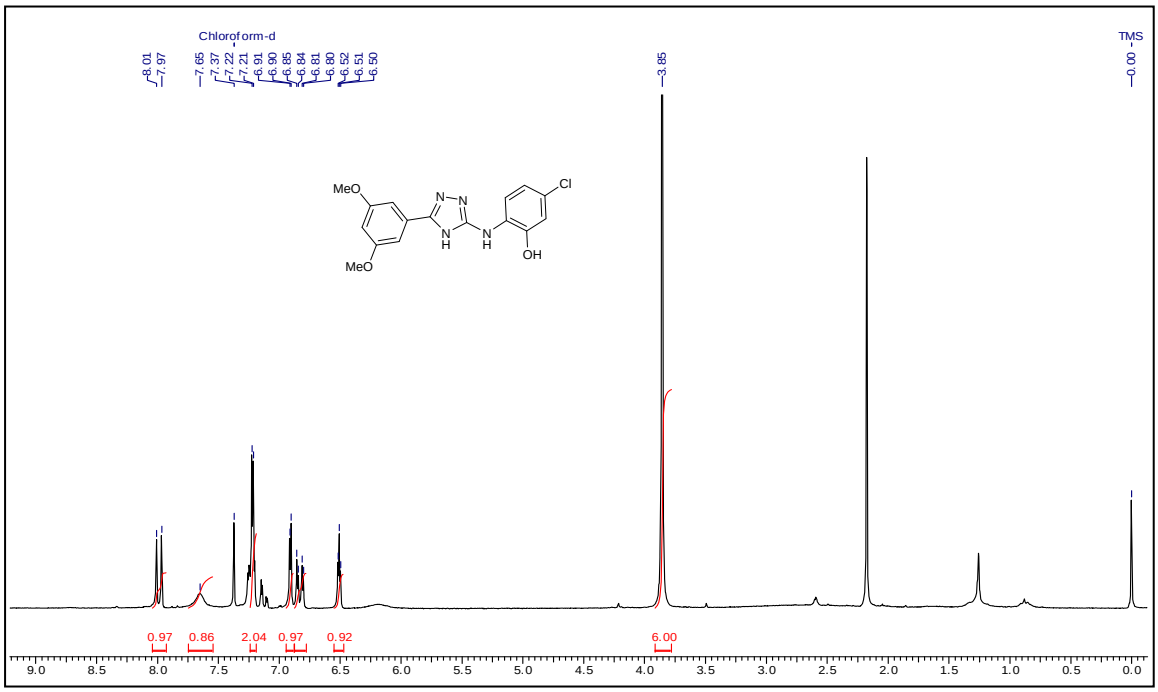
^{13}C NMR Spectrum of **51** in $CDCl_3$ (50 MHz)



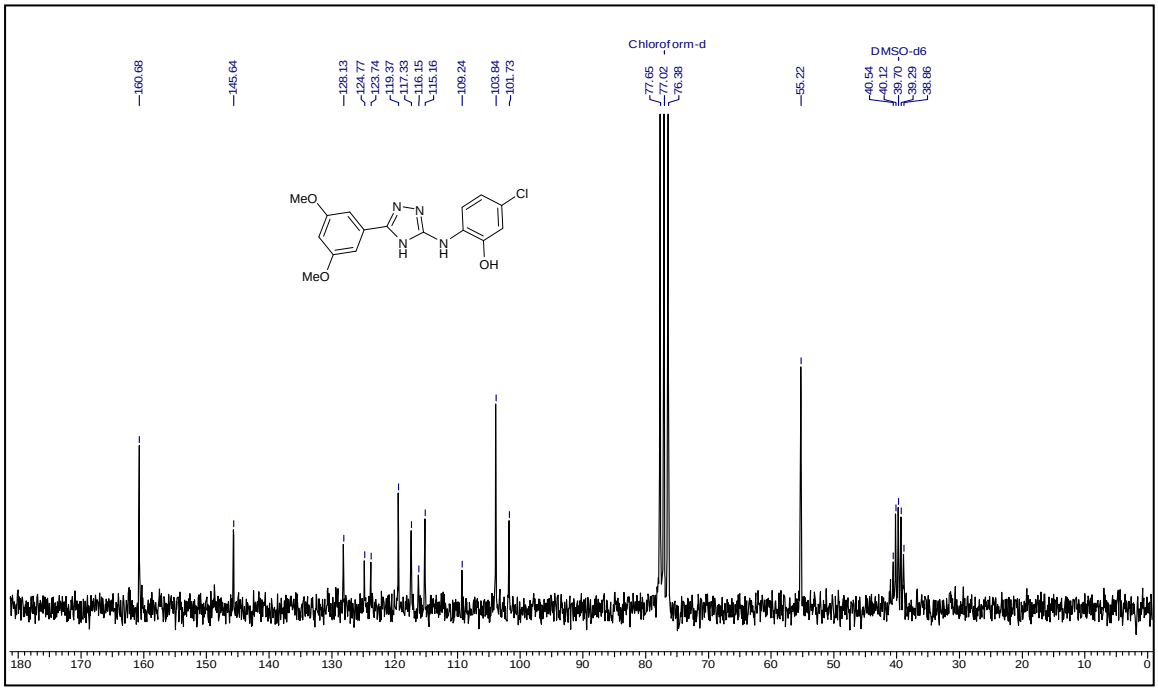
^{1}H NMR Spectrum of **52** in $CDCl_3$+DMSO-d_6 (500 MHz)



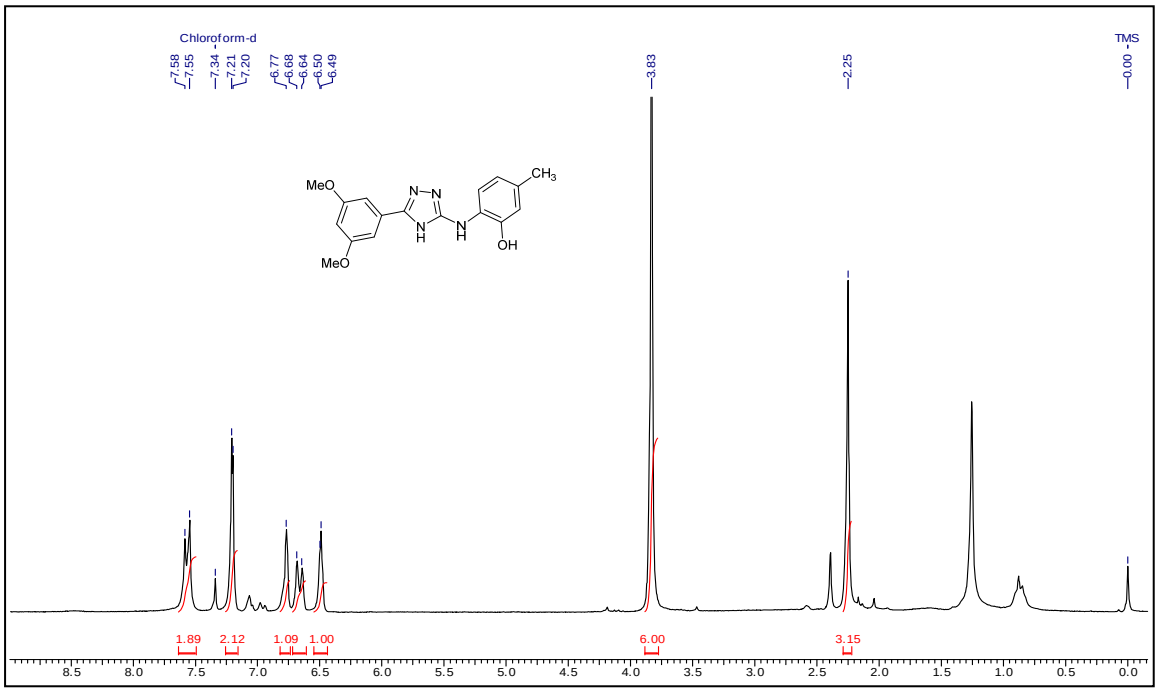
^{13}C NMR Spectrum of **52** in $CDCl_3$+DMSO-d_6 (125 MHz)



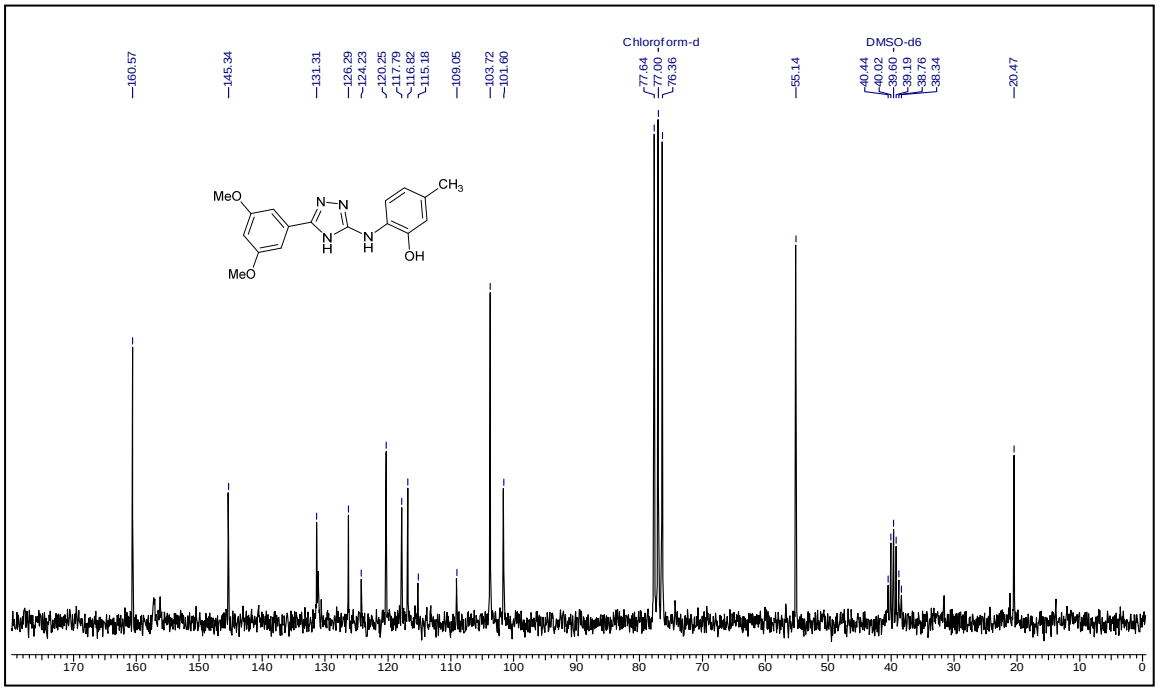
^{1}H NMR Spectrum of **53** in $CDCl_3$+DMSO-d_6 (200 MHz)



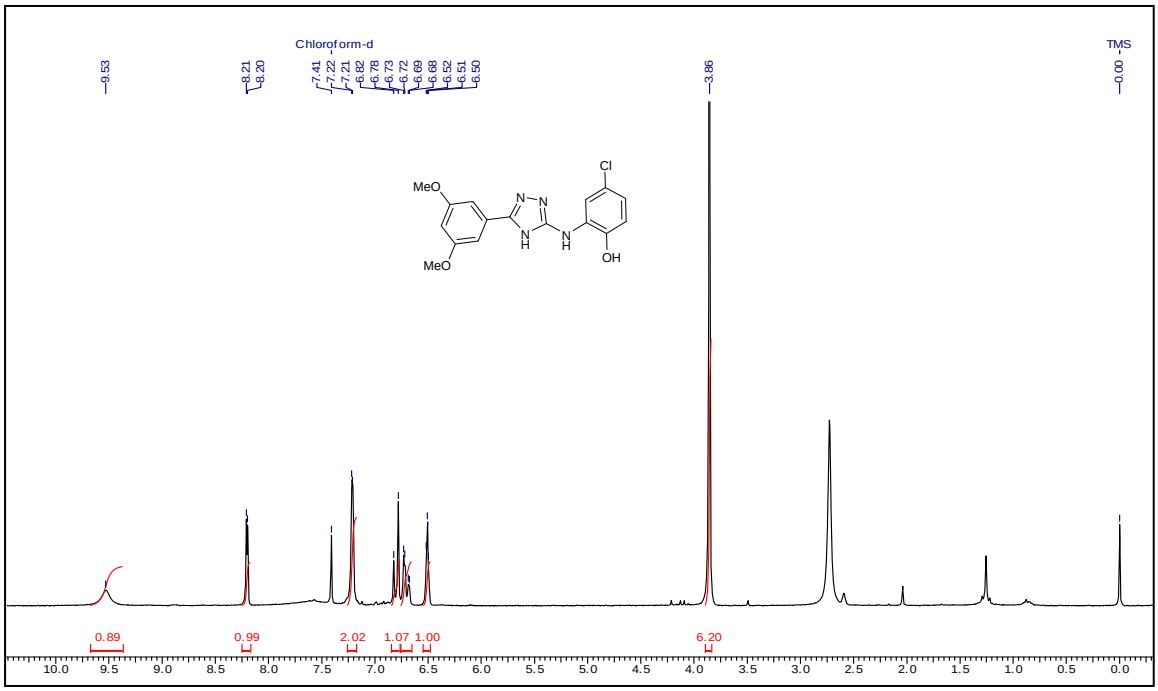
^{13}C NMR Spectrum of **53** in $CDCl_3$+DMSO-d_6 (50 MHz)



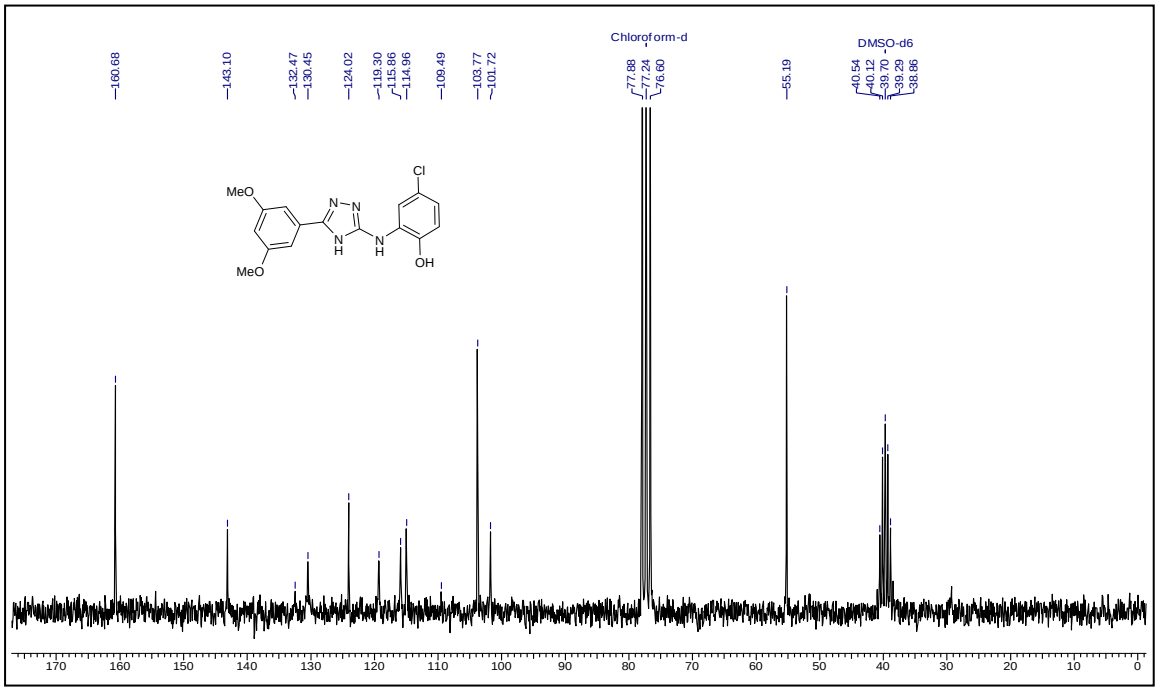
^{1}H NMR Spectrum of **54** in $CDCl_3$+DMSO-d_6 (200 MHz)



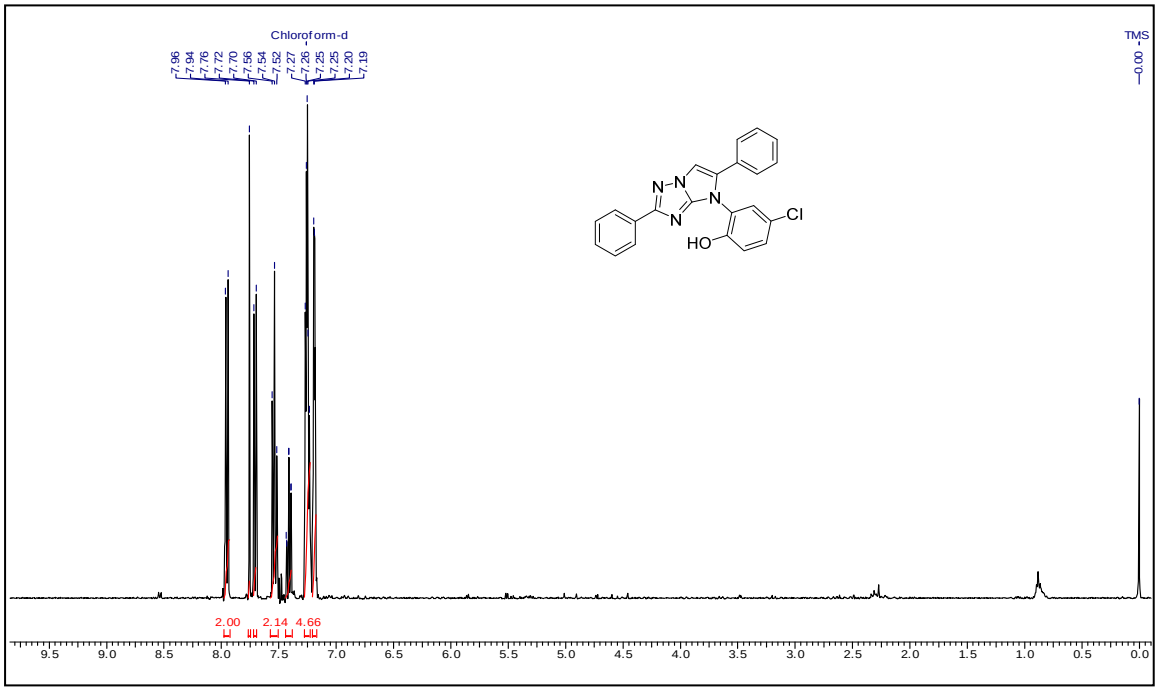
^{13}C NMR Spectrum of **54** in $CDCl_3$+DMSO-d_6 (50 MHz)



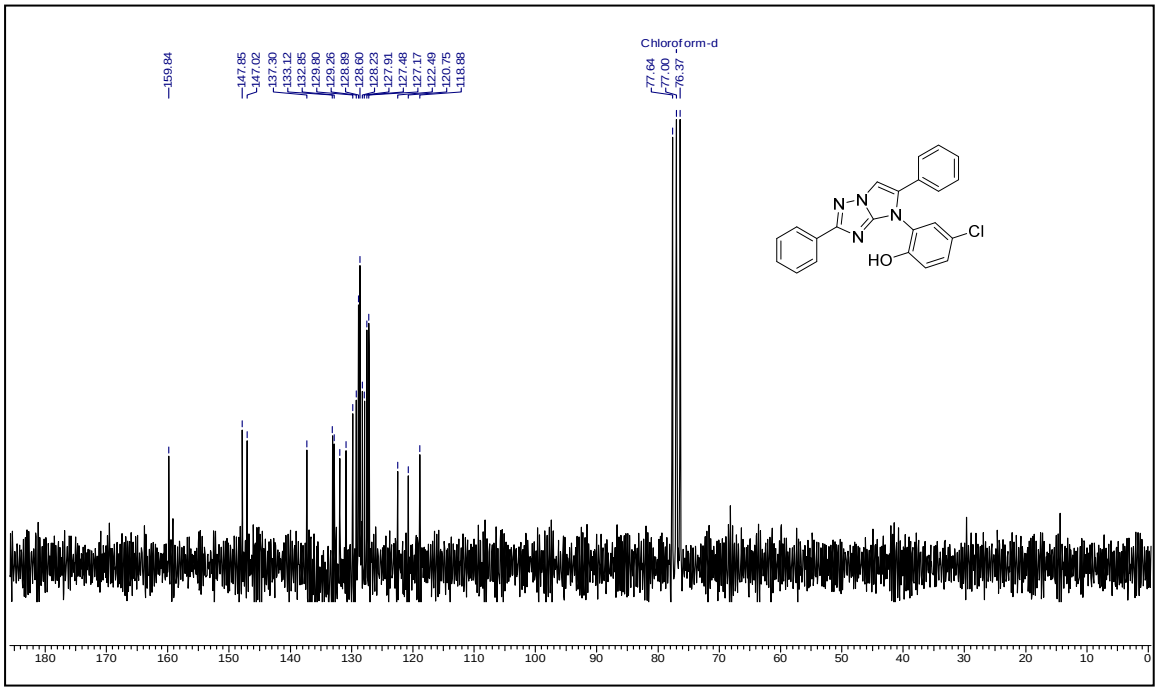
^{1}H NMR Spectrum of **55** in $CDCl_3$+DMSO-d_6 (200 MHz)



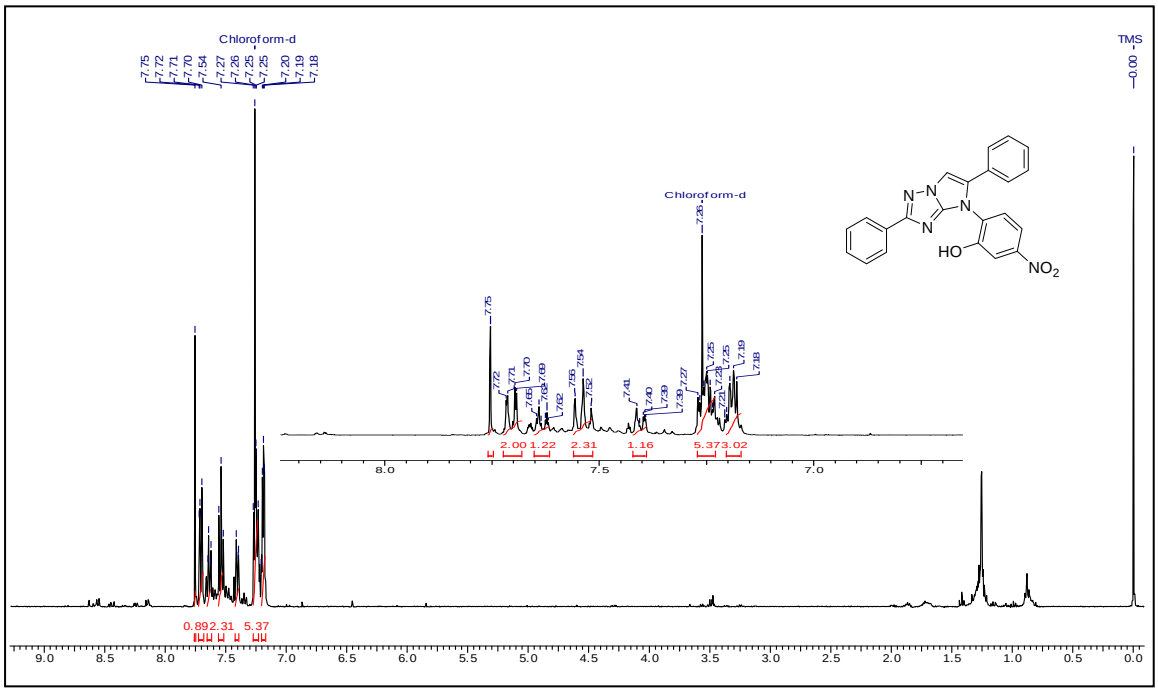
^{13}C NMR Spectrum of **55** in $CDCl_3$+DMSO-d_6 (50 MHz)



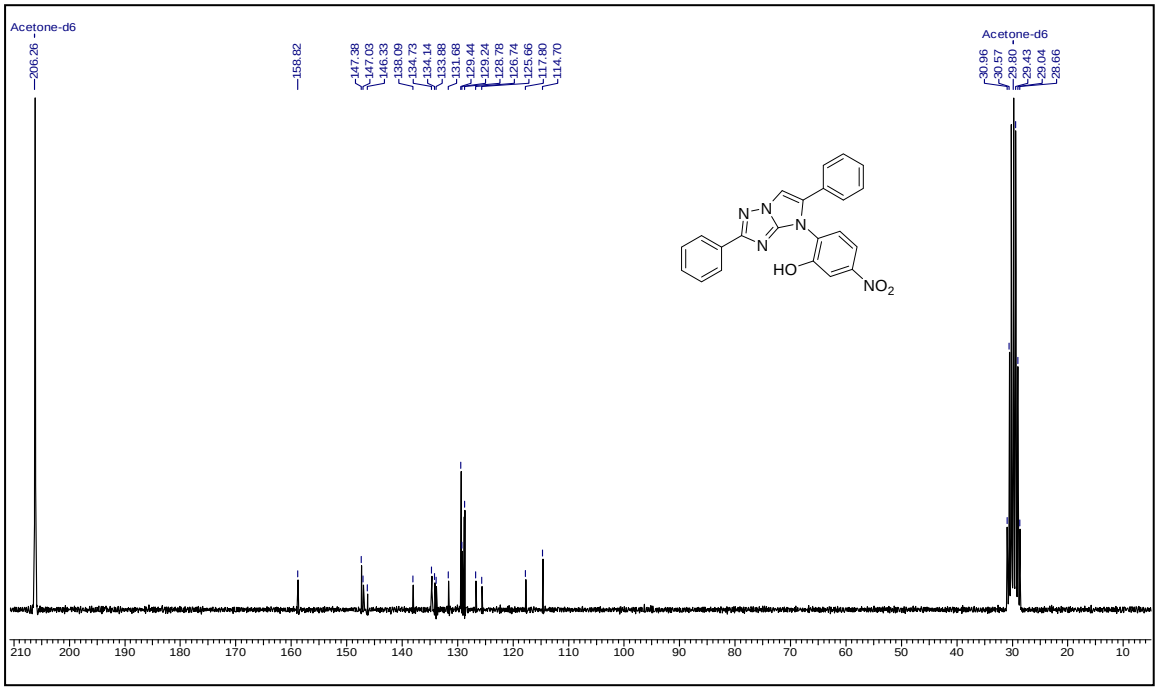
^{1}H NMR Spectrum of **58** in $CDCl_3$ (200 MHz)



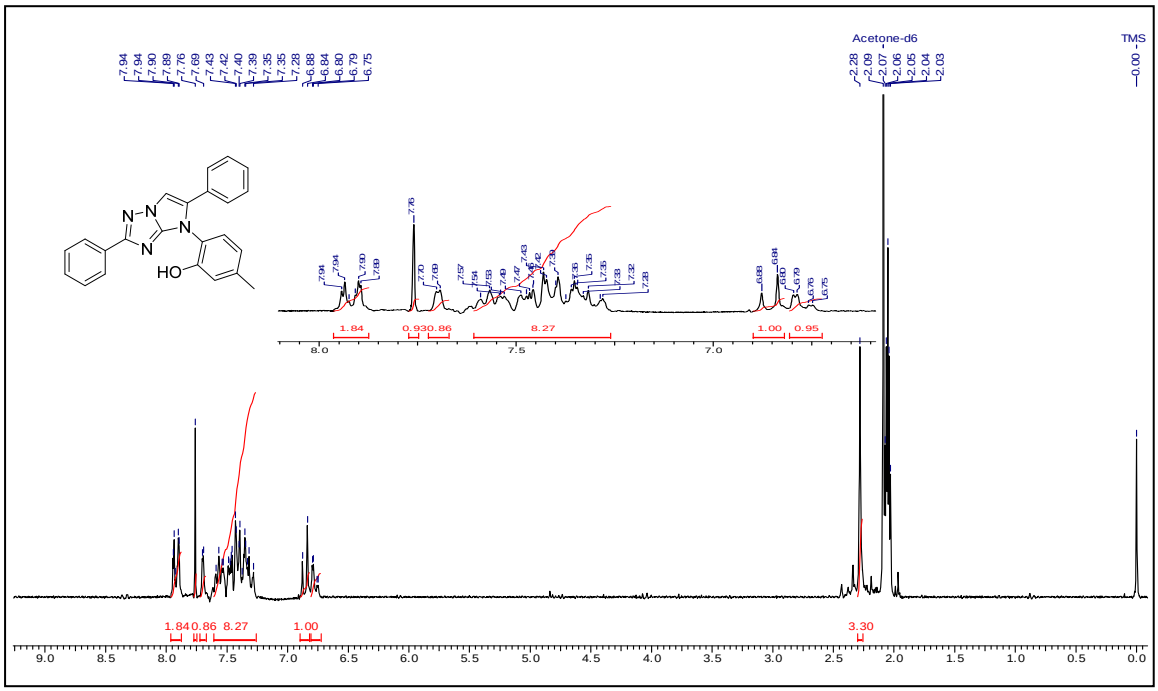
^{13}C NMR Spectrum of **58** in $CDCl_3$ (50 MHz)



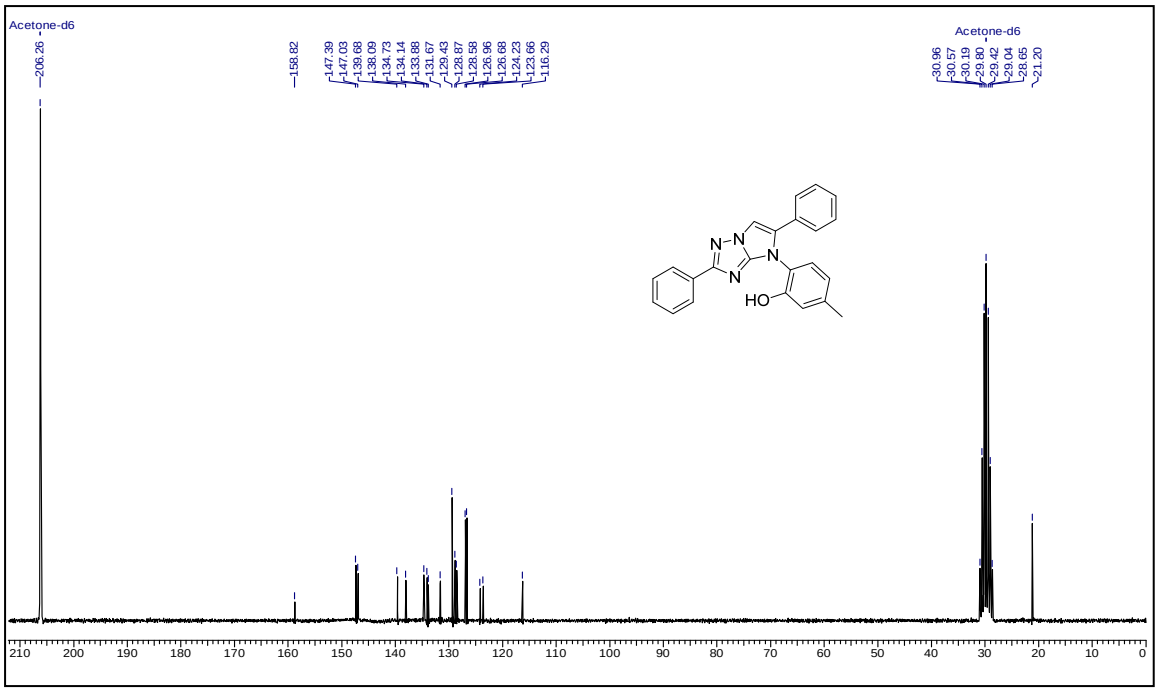
^{1}H NMR Spectrum of **59** in $CDCl_3$ (200 MHz)



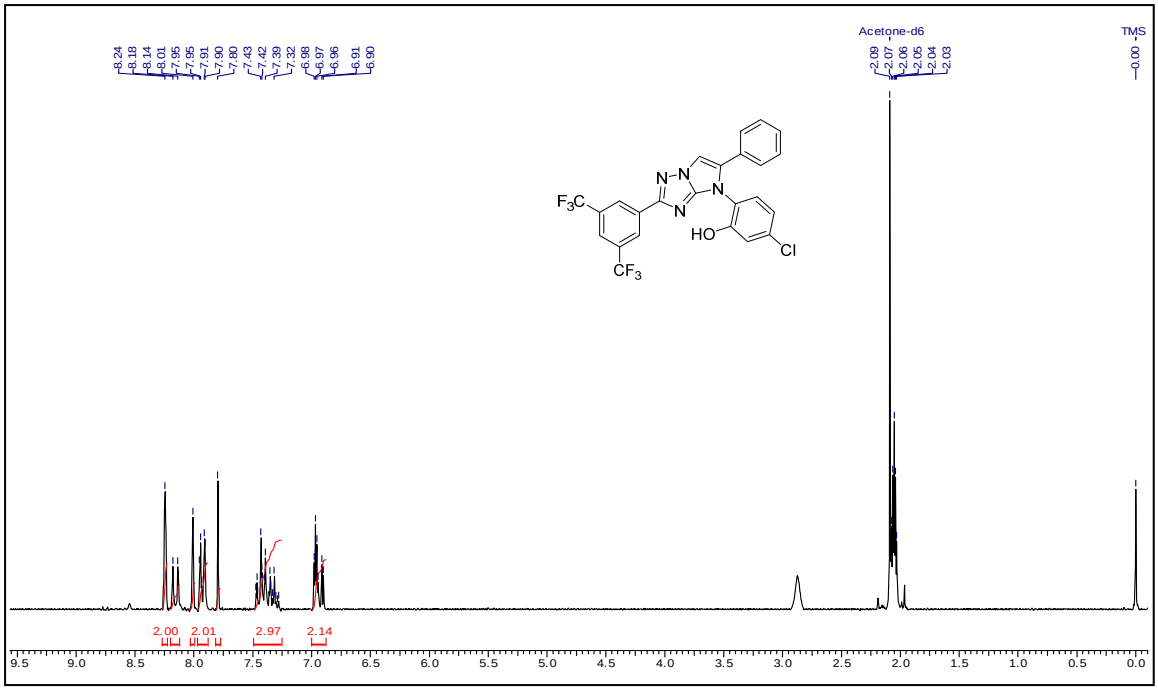
^{13}C NMR Spectrum of **59** in Acetone-d_6 (50 MHz)



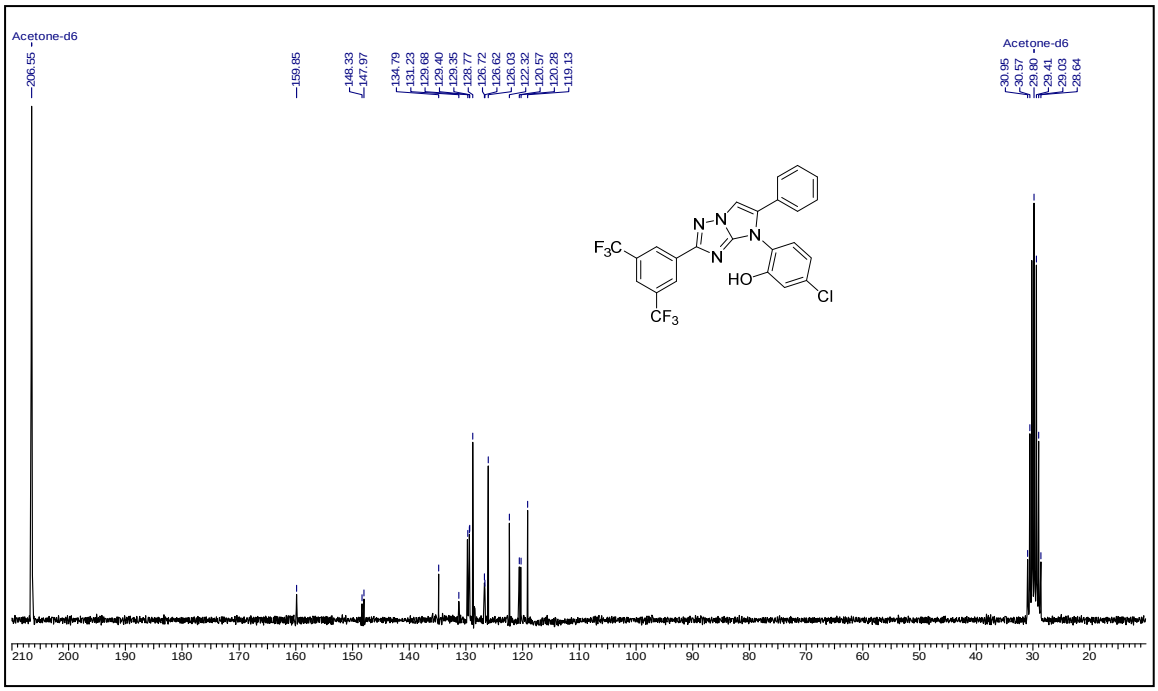
^{1}H NMR Spectrum of **60** in Acetone-d_6 (200 MHz)



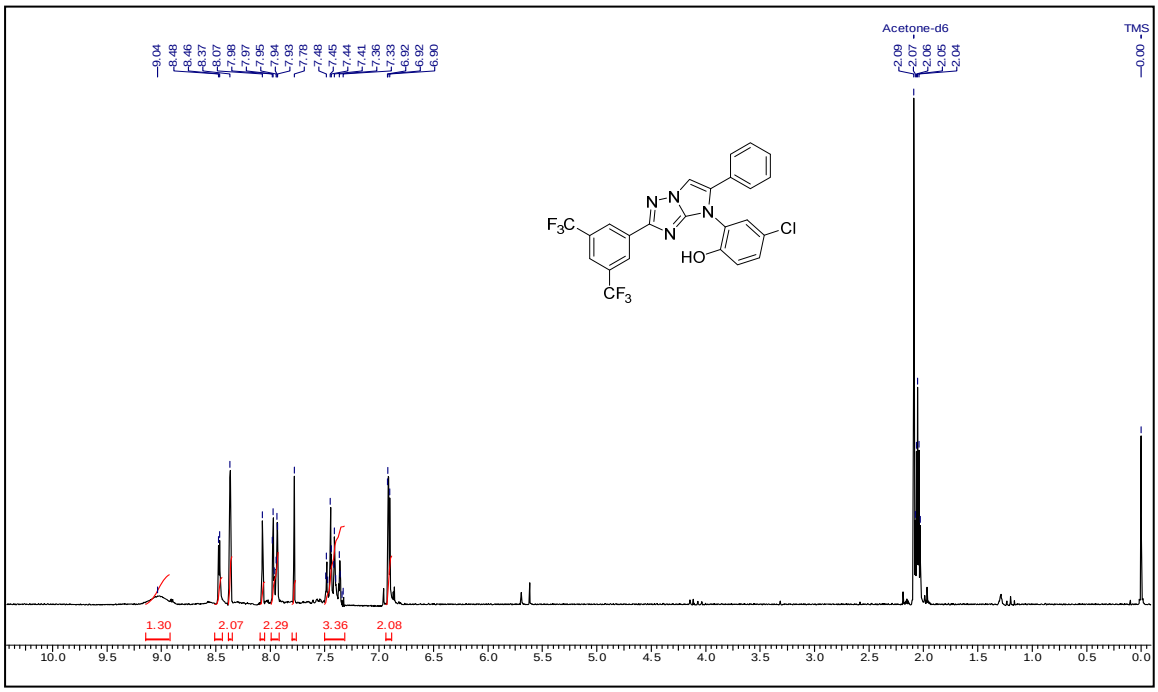
^{13}C NMR Spectrum of **60** in Acetone-d_6 (50 MHz)



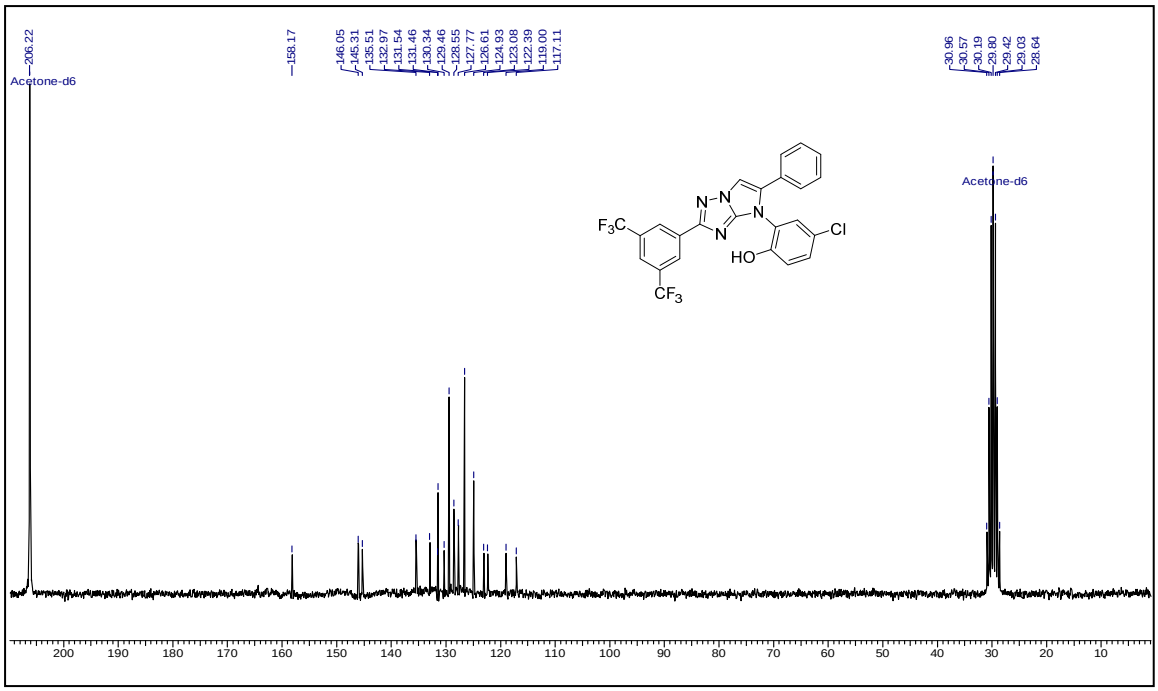
^{1}H NMR Spectrum of **61** in Acetone-d_6 (200 MHz)



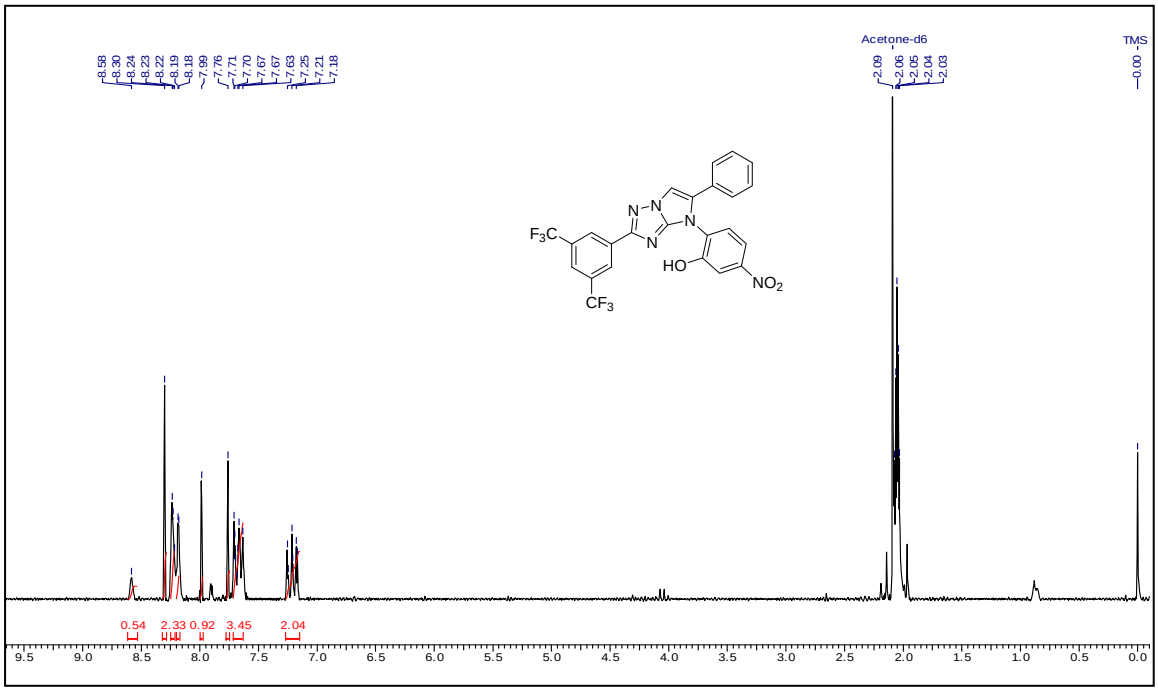
^{13}C NMR Spectrum of **61** in Acetone-d_6 (50 MHz)



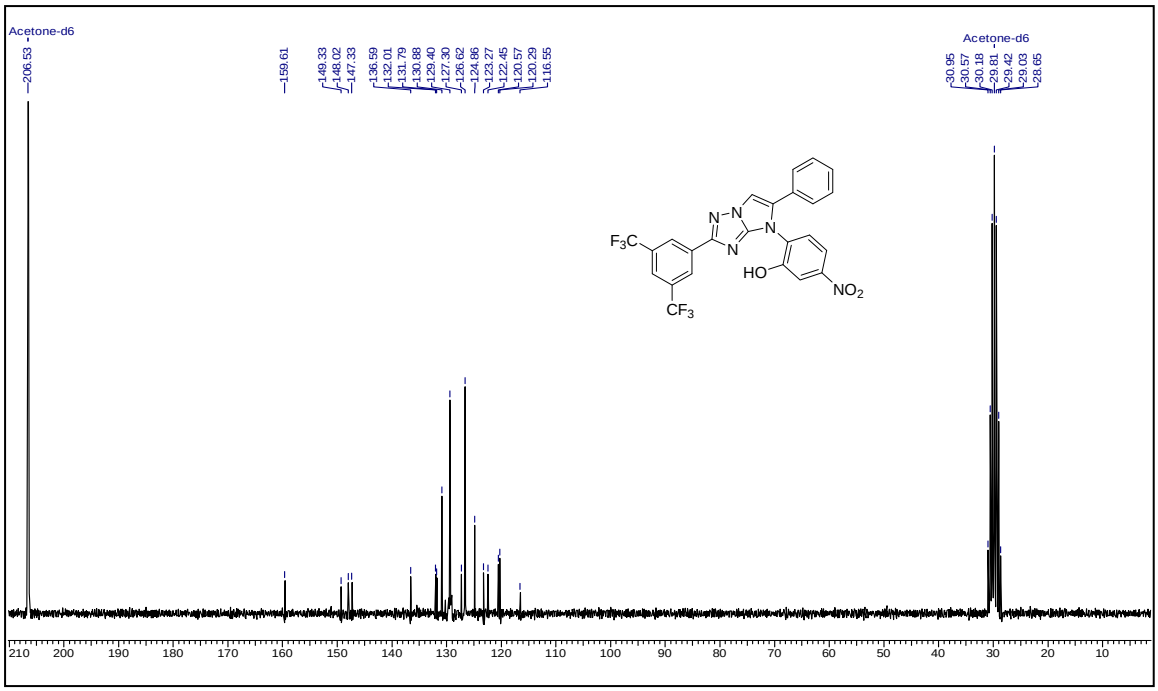
^{1}H NMR Spectrum of **62** in Acetone-d_6 (200 MHz)



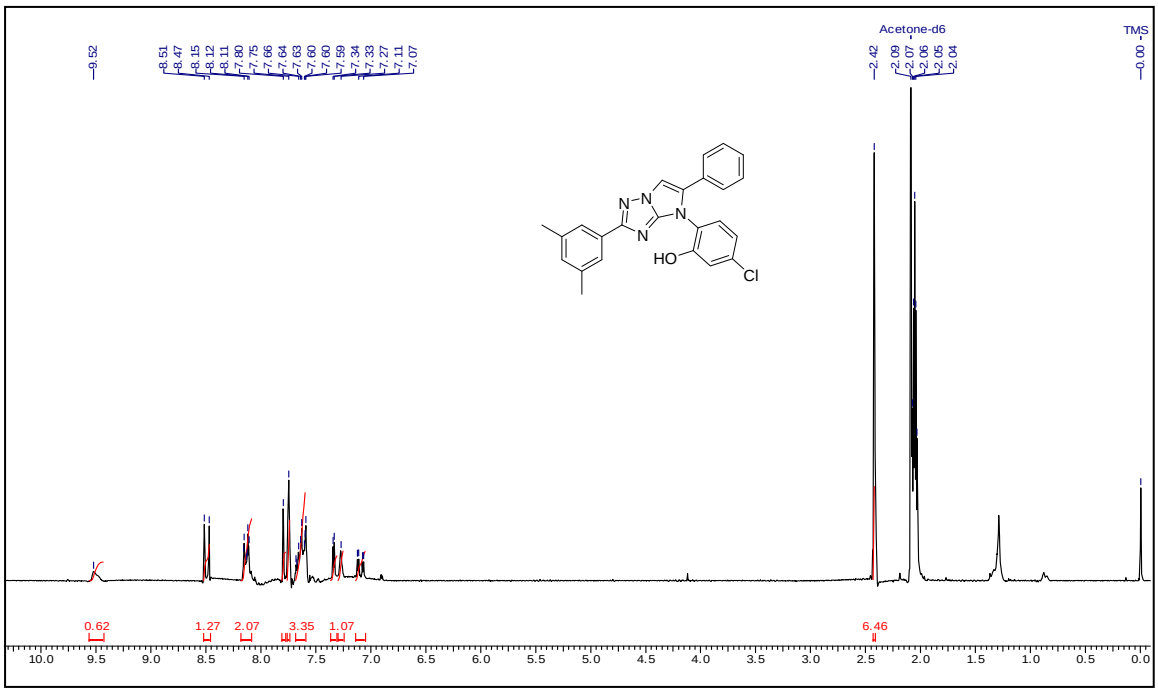
^{13}C NMR Spectrum of **62** in Acetone-d_6 (50 MHz)



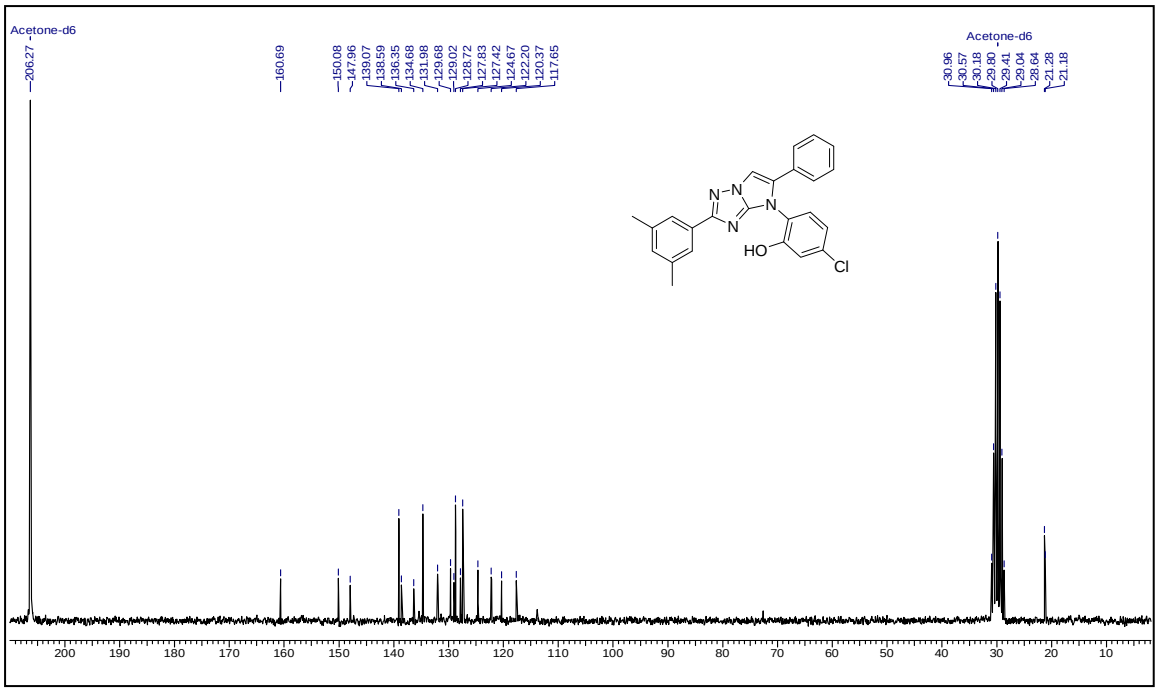
^{1}H NMR Spectrum of **63** in Acetone-d_6 (200 MHz)



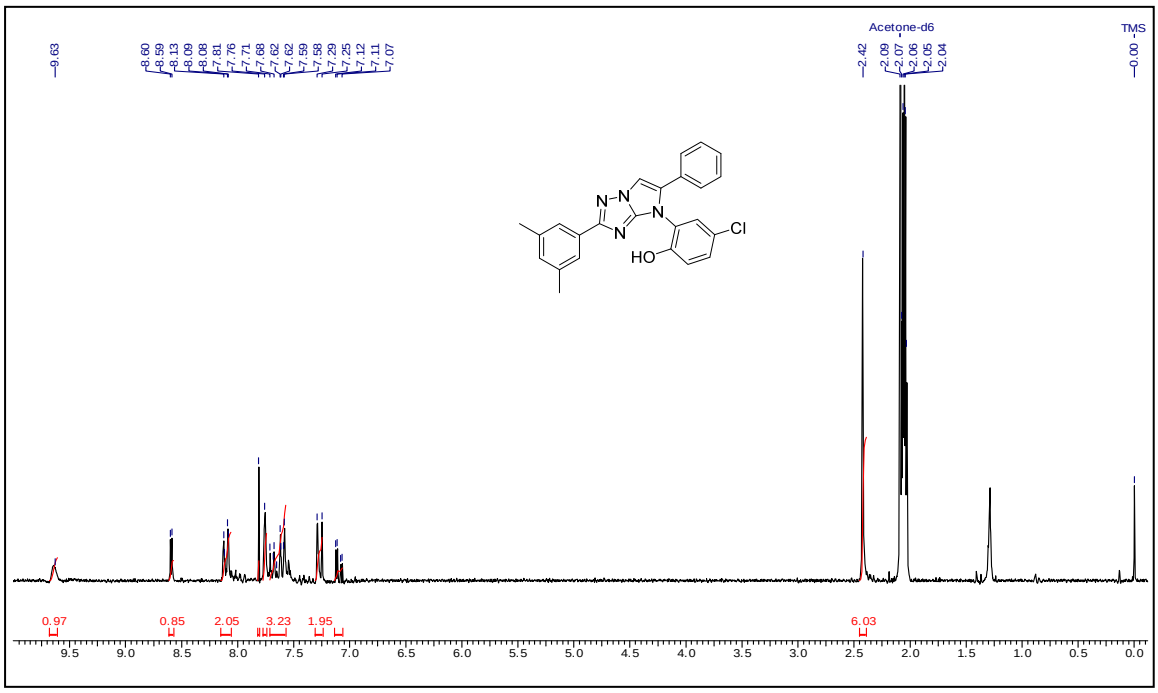
^{13}C NMR Spectrum of **63** in Acetone-d_6 (50 MHz)



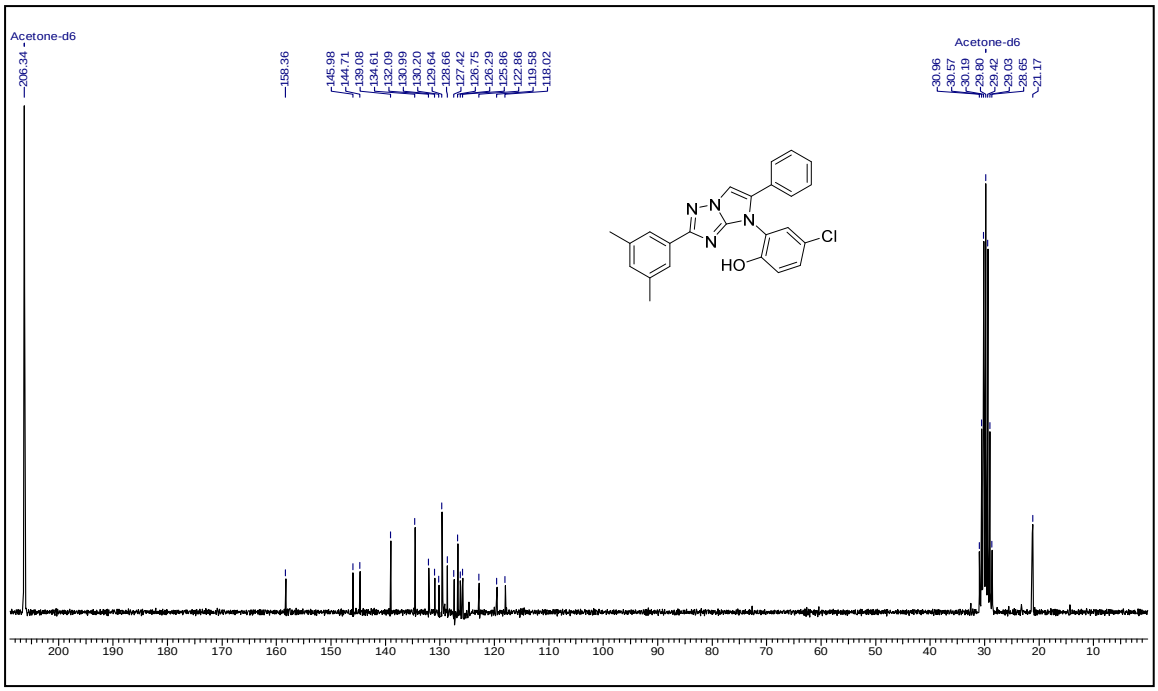
^{1}H NMR Spectrum of **64** in Acetone-d_6 (200 MHz)



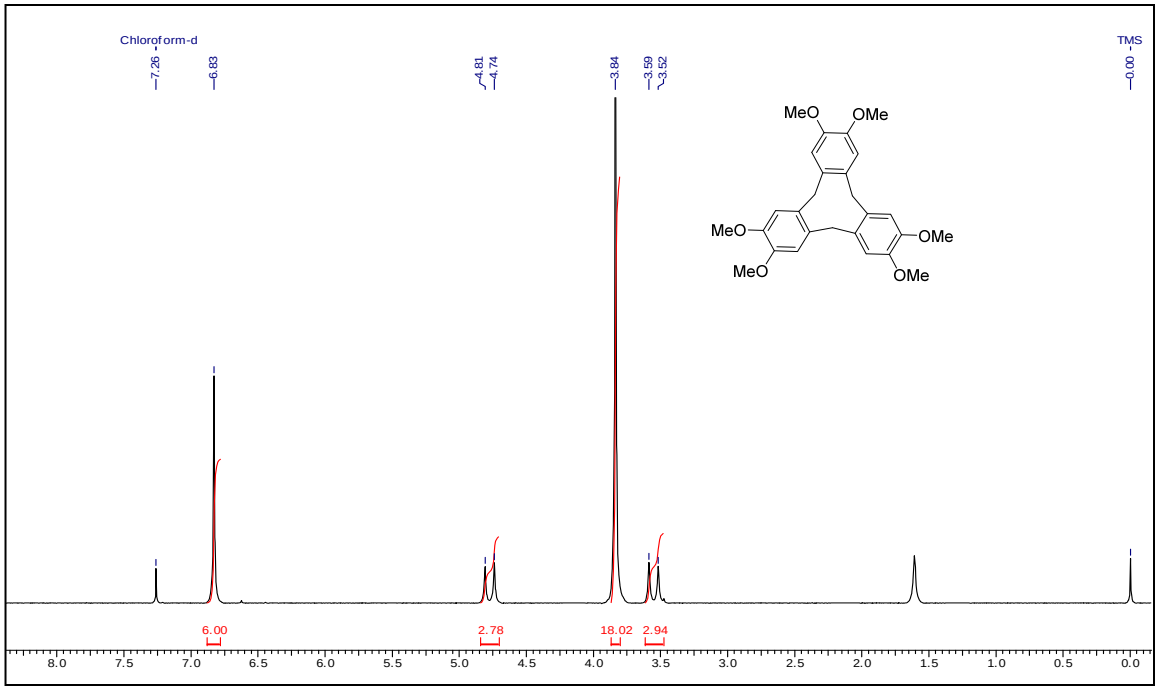
^{13}C NMR Spectrum of **64** in Acetone-d_6 (50 MHz)



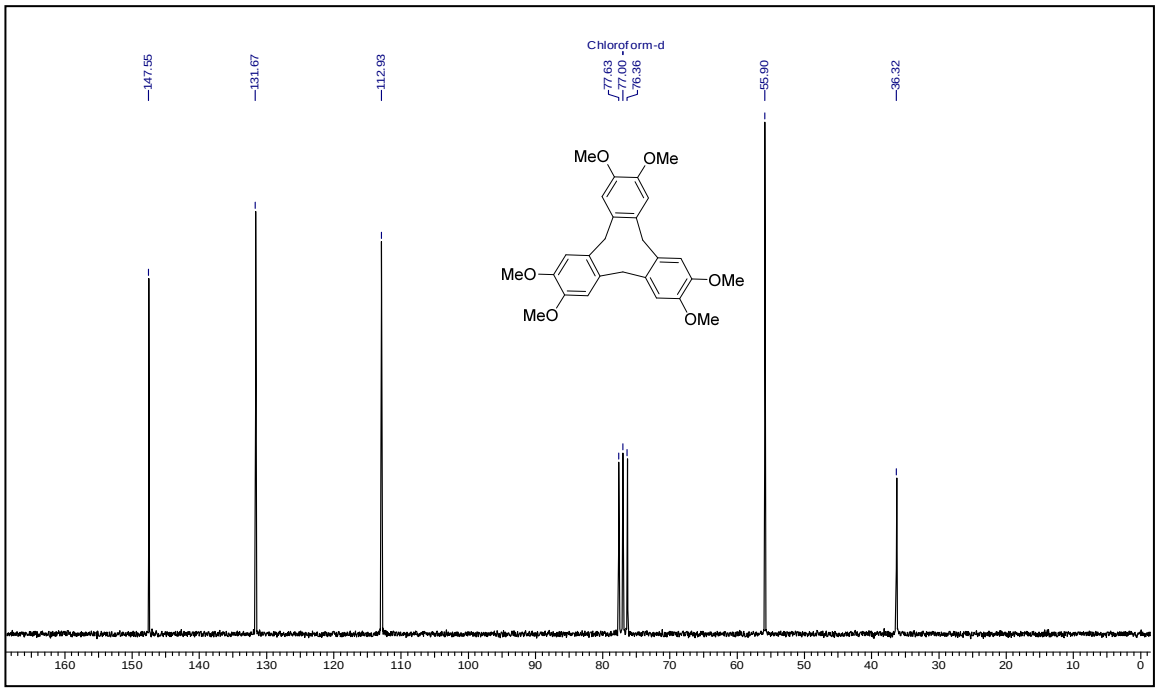
^{1}H NMR Spectrum of **65** in Acetone-d_6 (200 MHz)



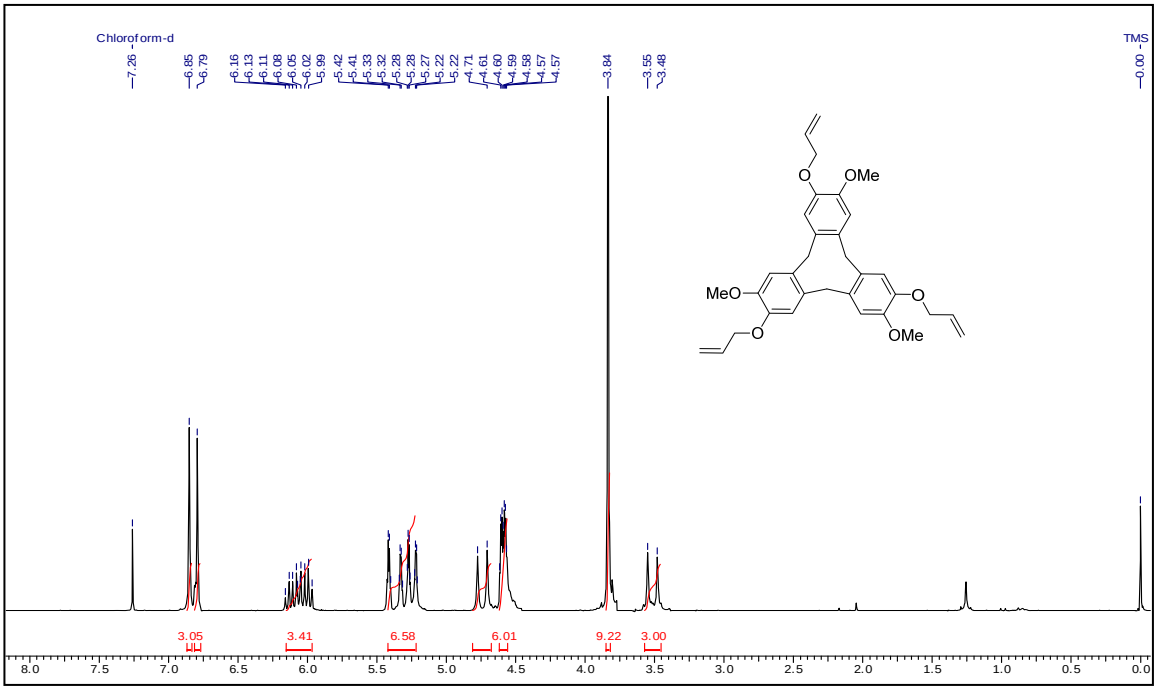
^{13}C NMR Spectrum of **65** in Acetone-d_6 (50 MHz)



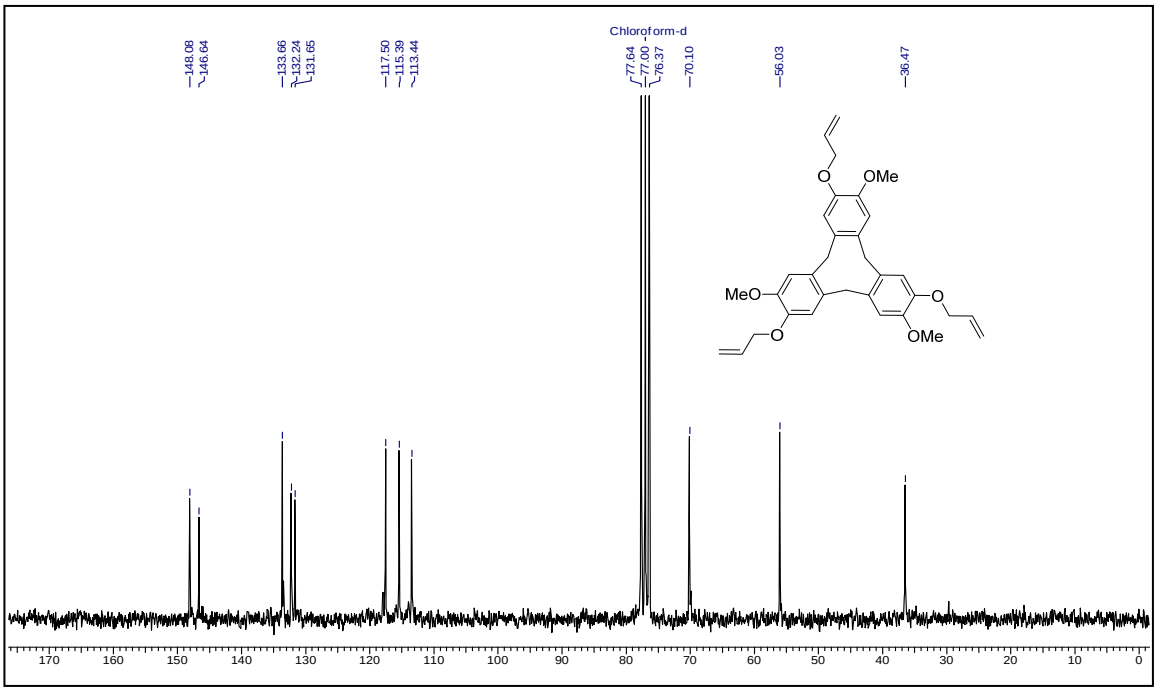
^{1}H NMR Spectrum of **66** in $CDCl_3$ (200 MHz)



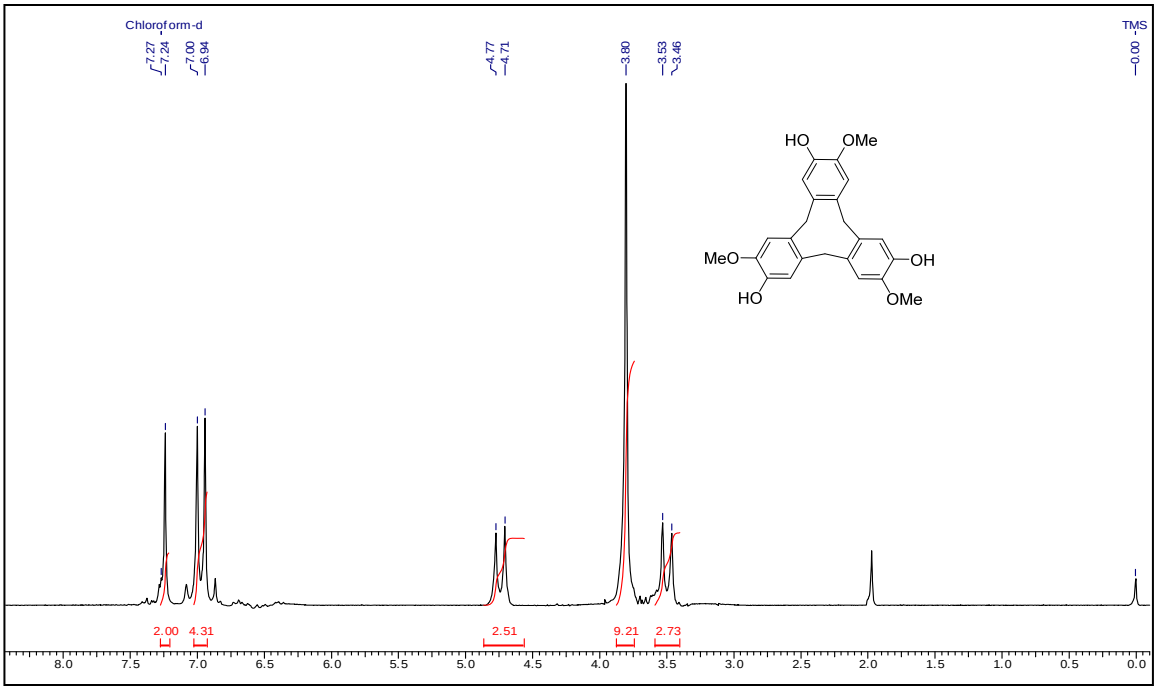
^{13}C NMR Spectrum of **66** in $CDCl_3$ (50 MHz)



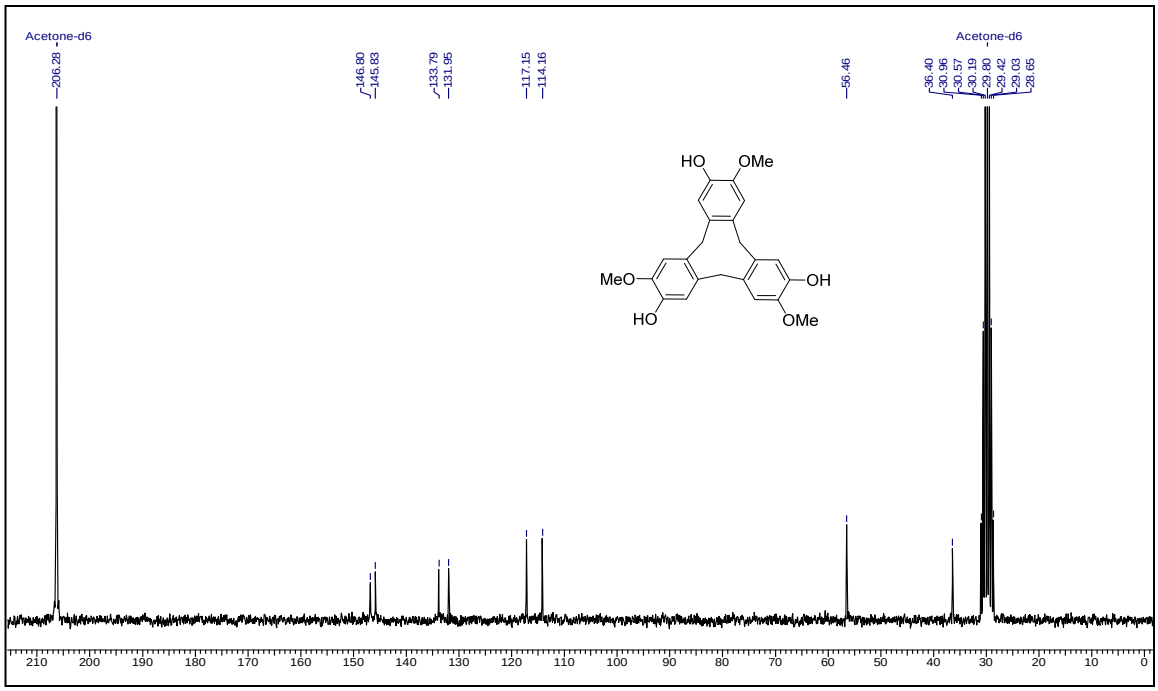
^{1}H NMR Spectrum of **73** in $CDCl_3$ (200 MHz)



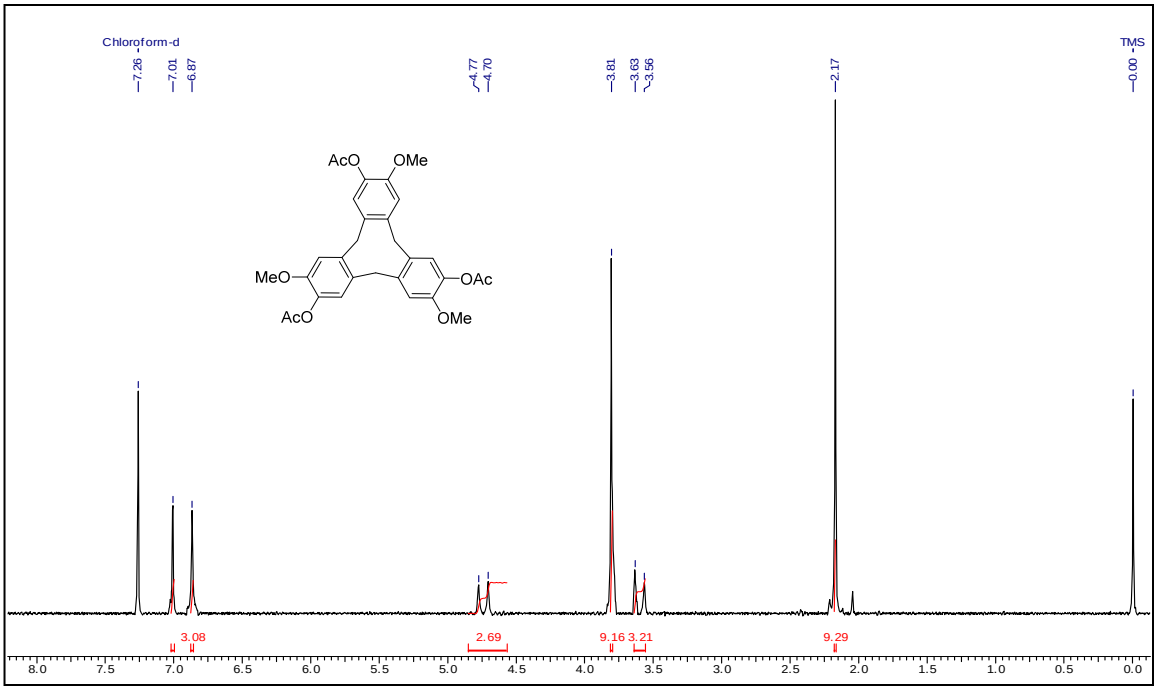
^{13}C NMR Spectrum of **73** in $CDCl_3$ (50 MHz)



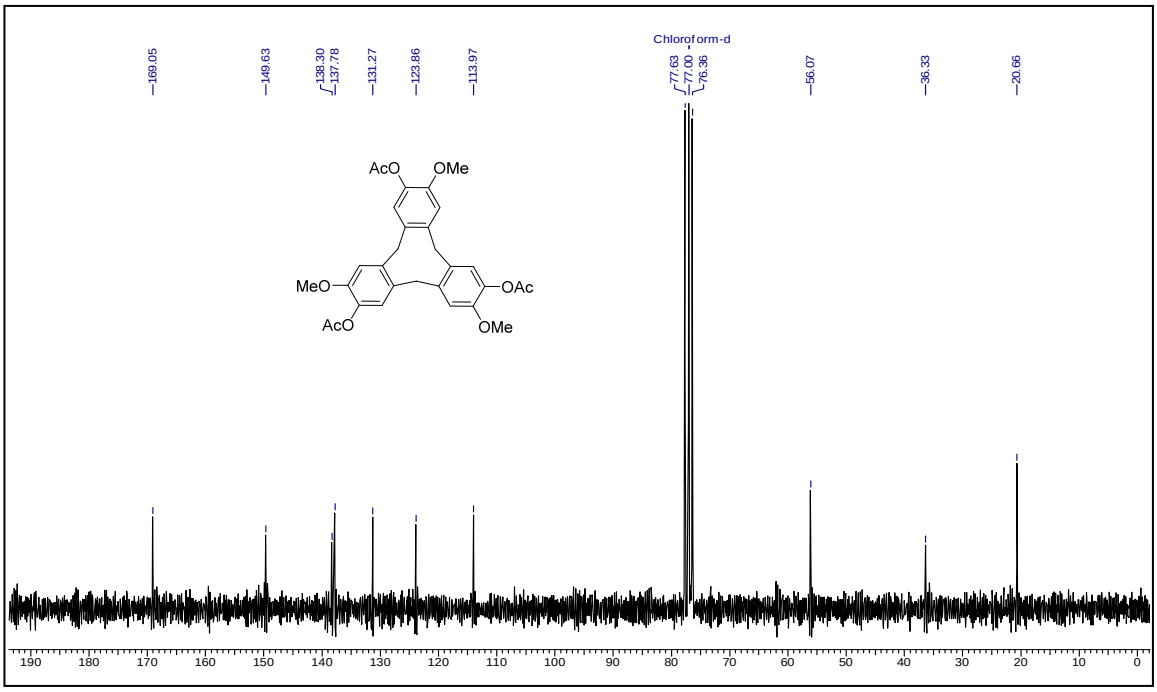
^{1}H NMR Spectrum of **67** in $CDCl_3$ (200 MHz)



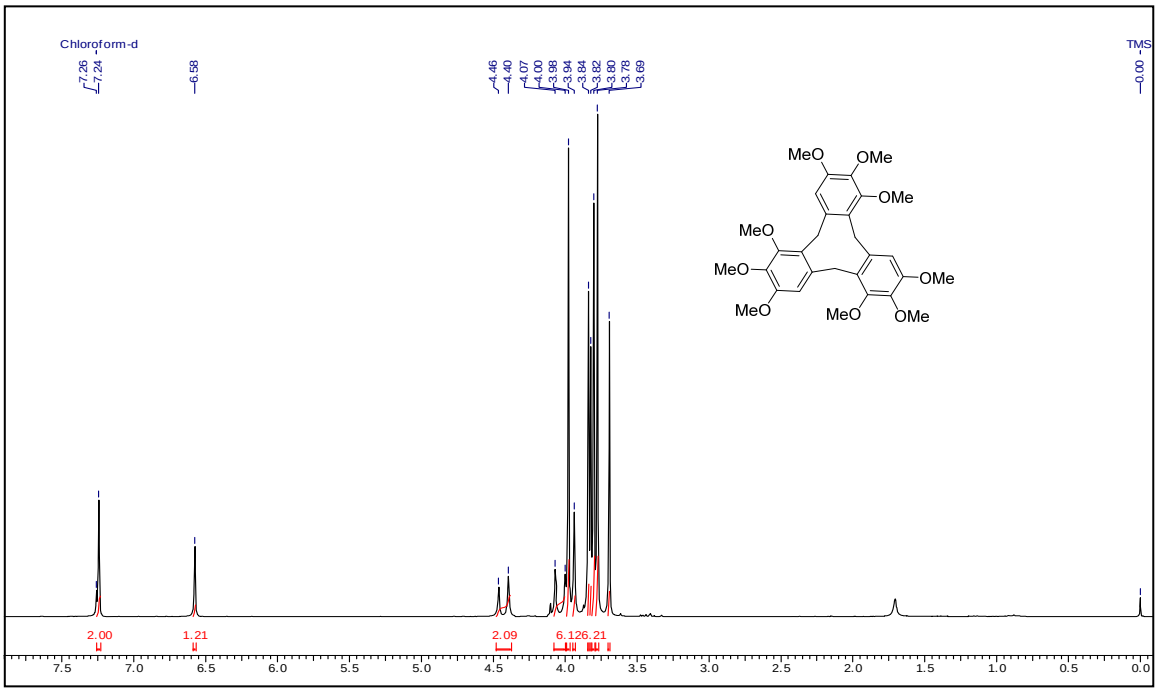
^{13}C NMR Spectrum of **67** in Acetone-d_6 (50 MHz)



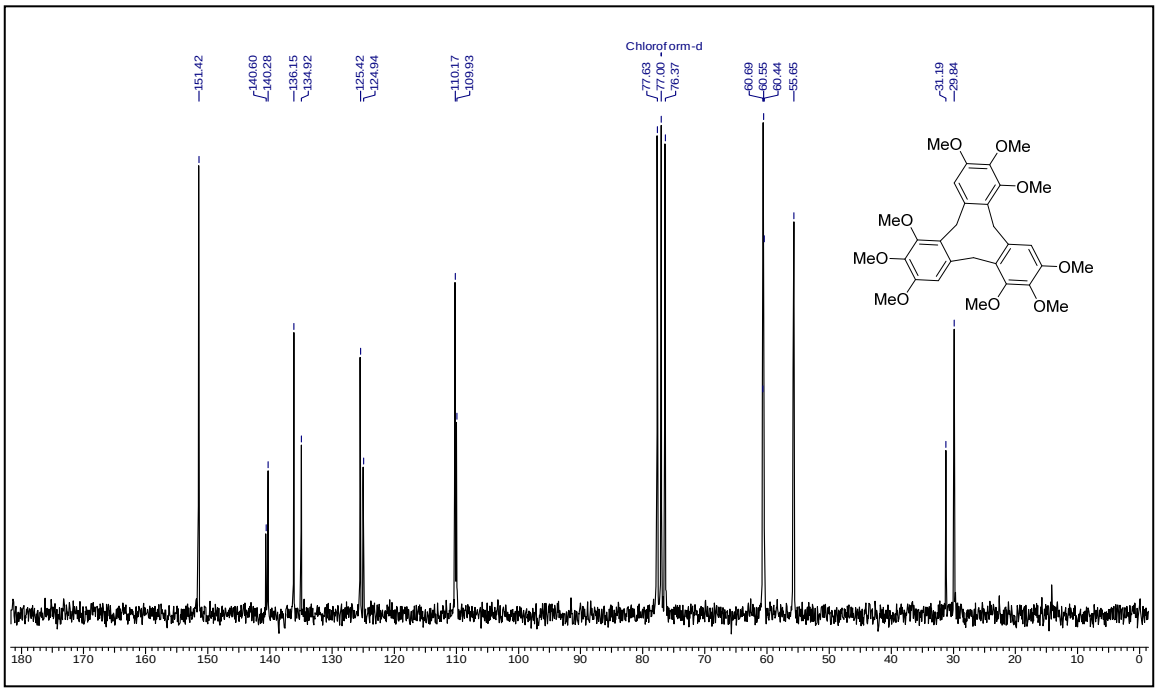
^{1}H NMR Spectrum of **68** in $CDCl_3$ (200 MHz)



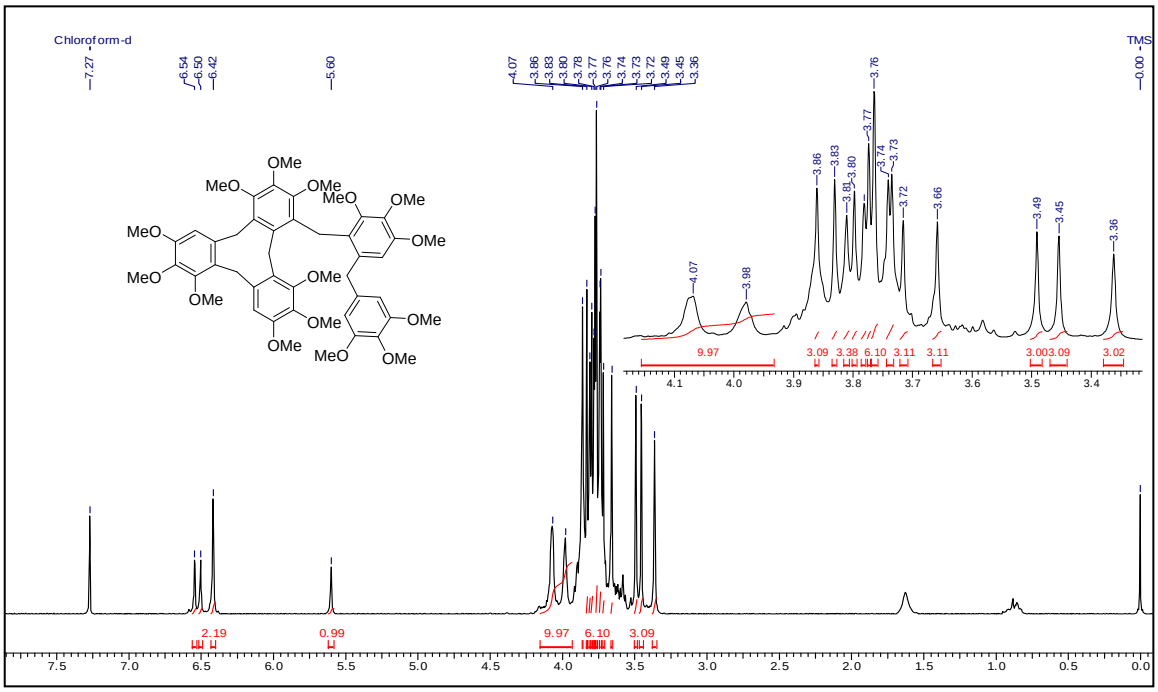
^{13}C NMR Spectrum of **68** in $CDCl_3$ (50 MHz)



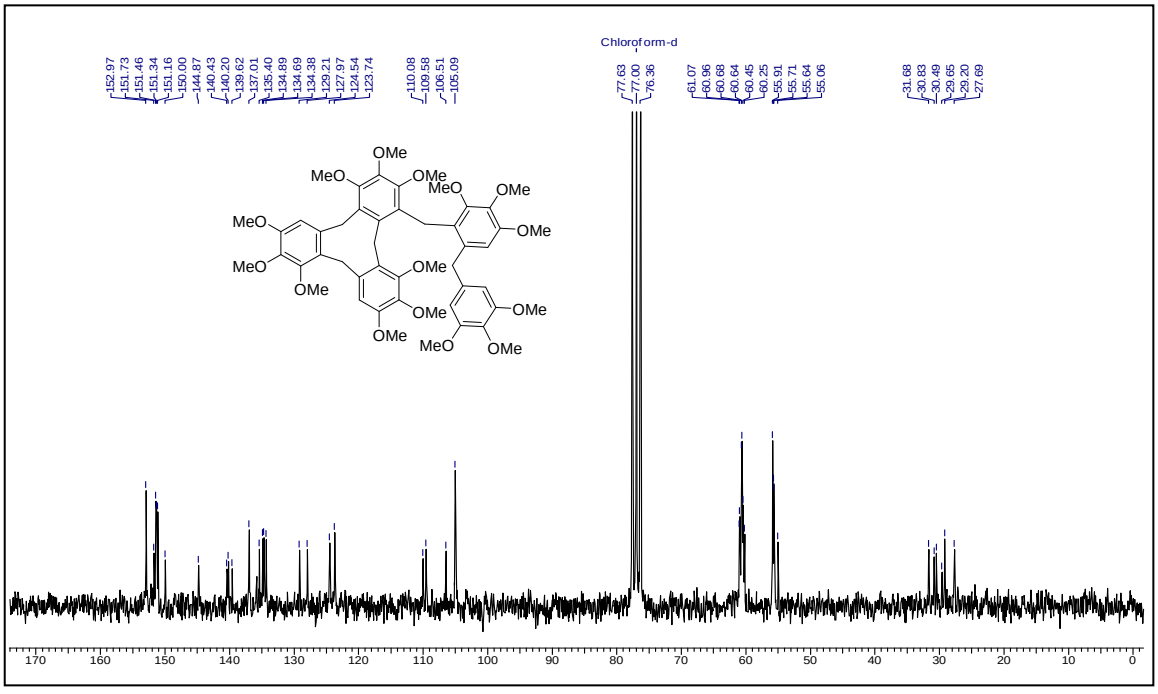
^{1}H NMR Spectrum of **69** in $CDCl_3$ (200 MHz)



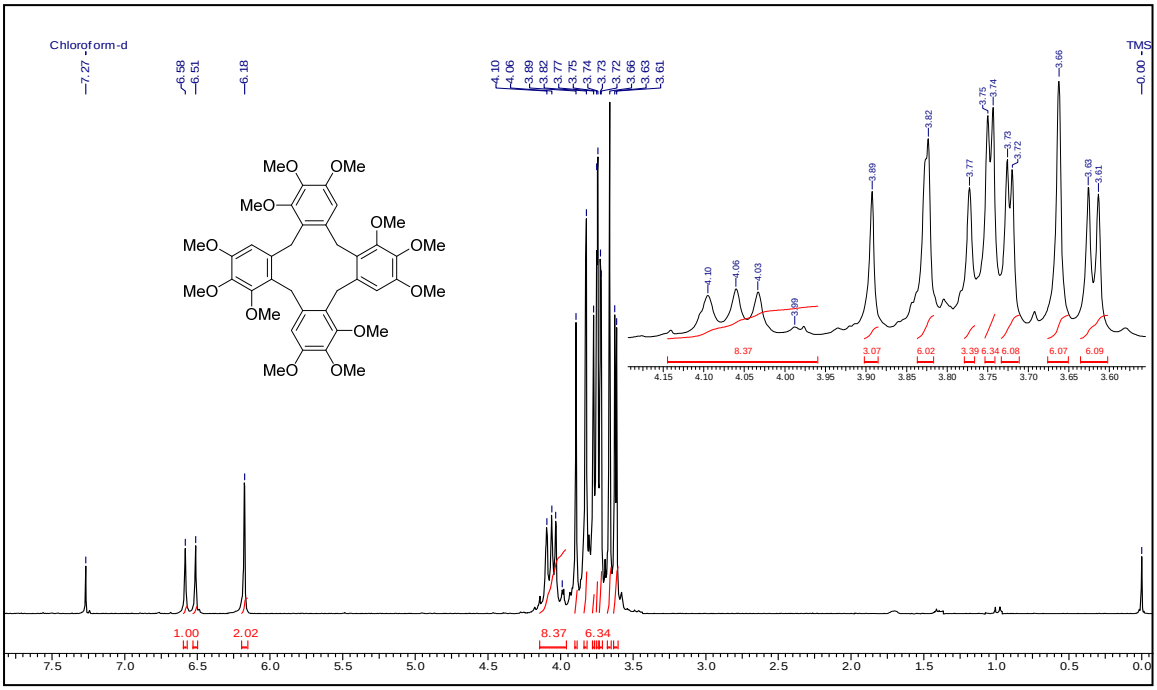
^{13}C NMR Spectrum of **69** in $CDCl_3$ (50 MHz)



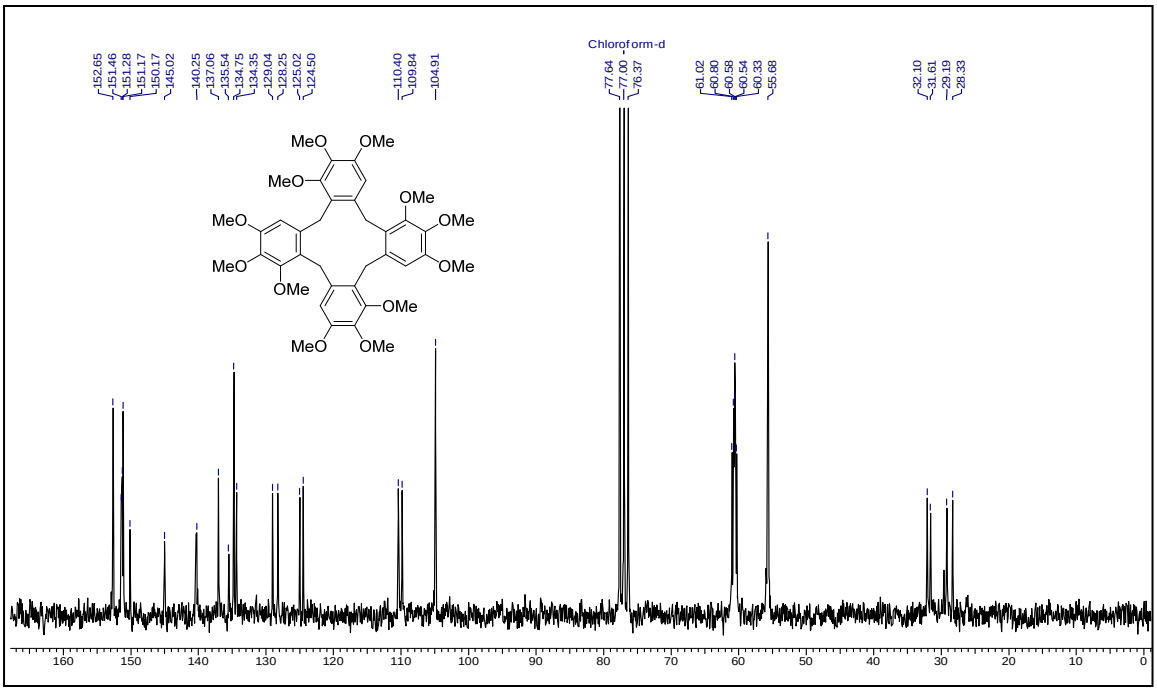
^{1}H NMR Spectrum of **74** in $CDCl_3$ (200 MHz)



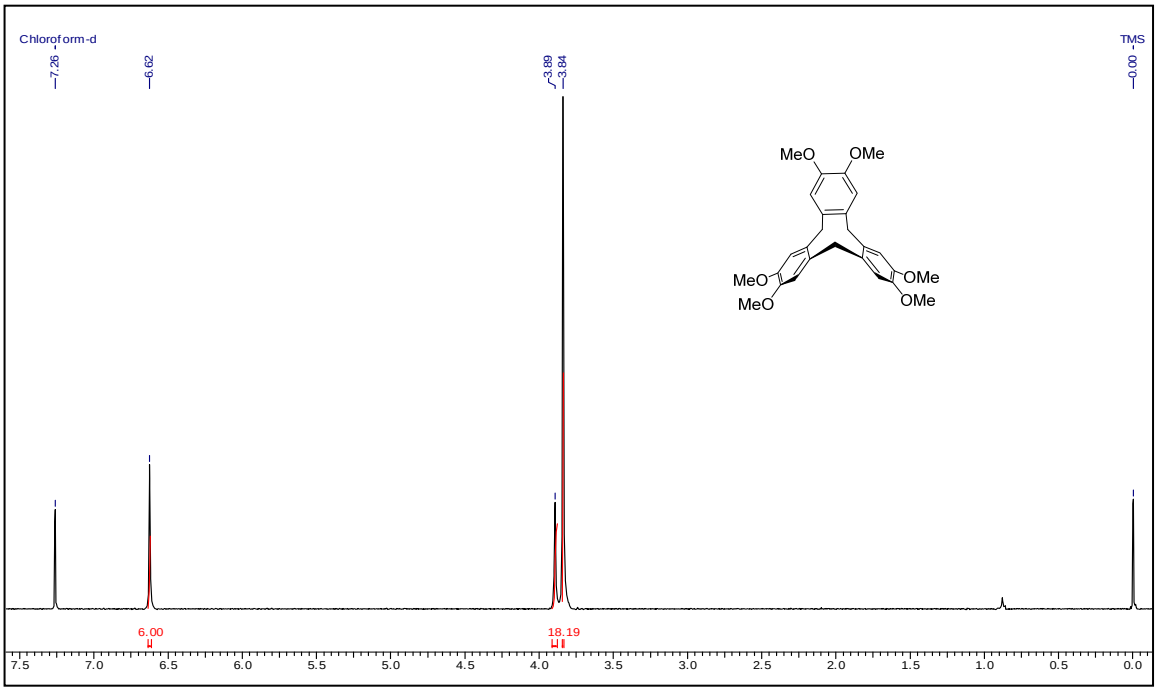
^{13}C NMR Spectrum of **74** in $CDCl_3$ (50 MHz)



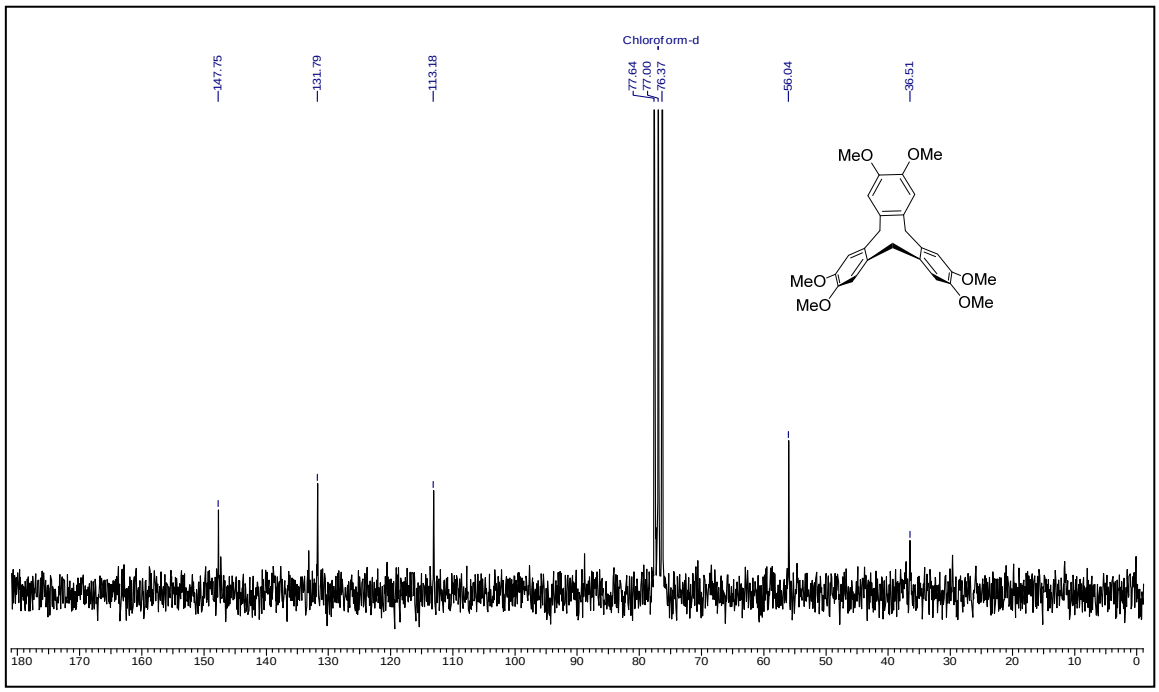
^{1}H NMR Spectrum of **75** in $CDCl_3$ (200 MHz)



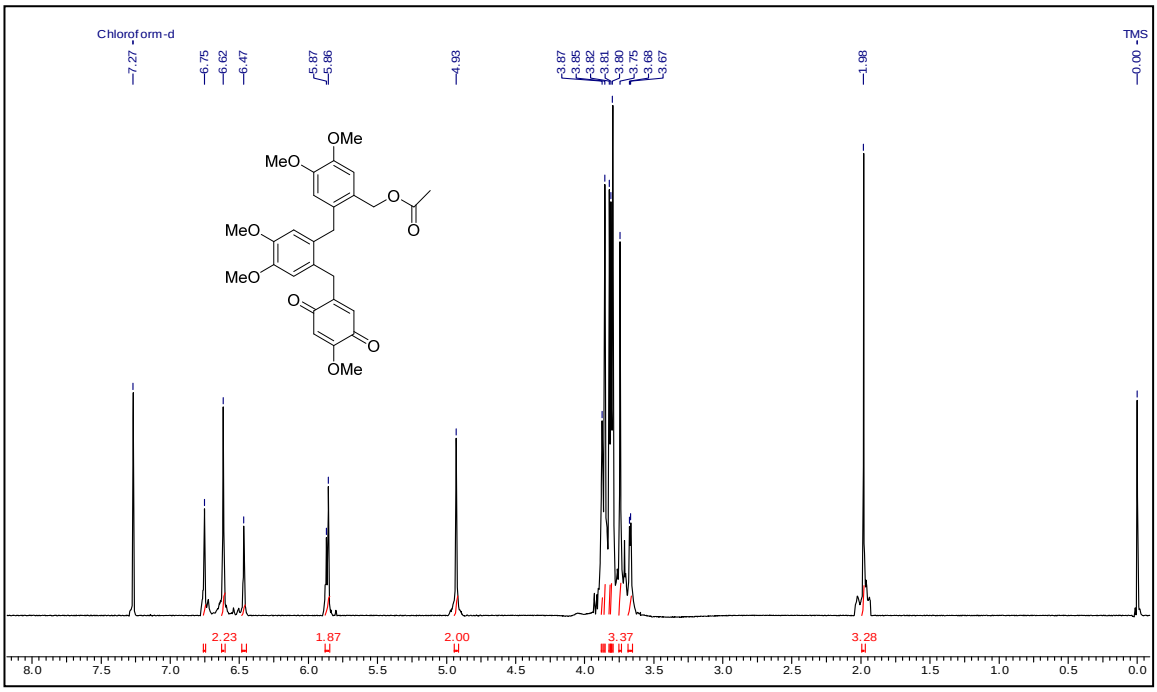
^{13}C NMR Spectrum of **75** in $CDCl_3$ (50 MHz)



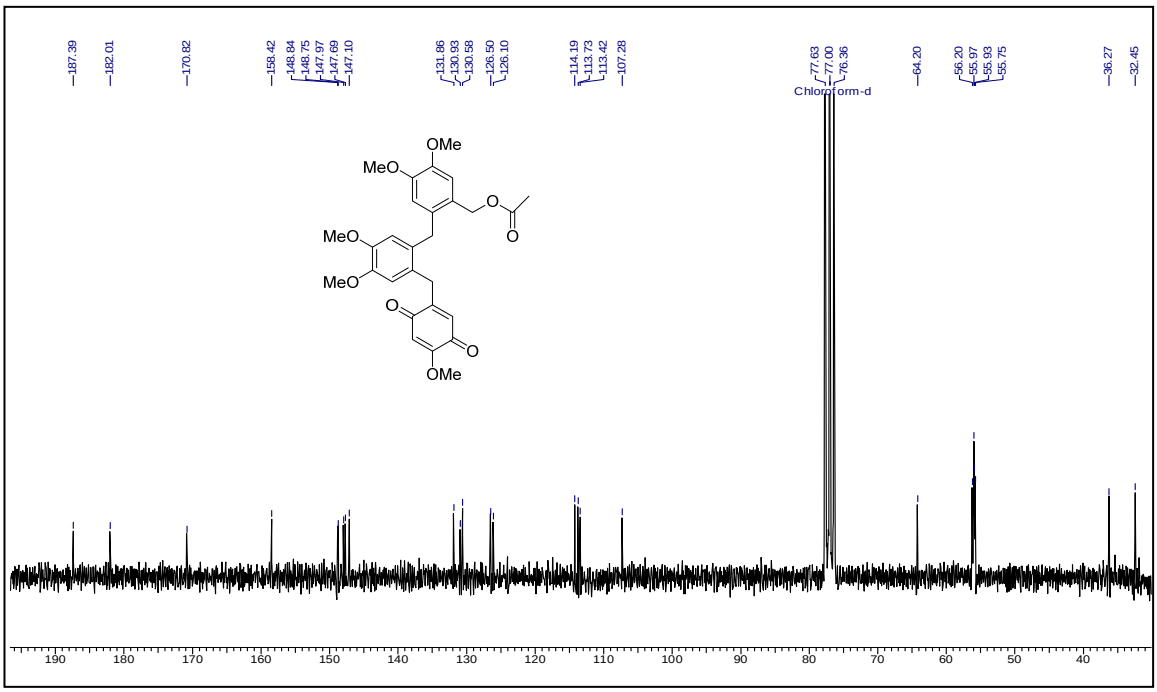
^{1}H NMR Spectrum of **66(S)** in $CDCl_3$ (200 MHz)



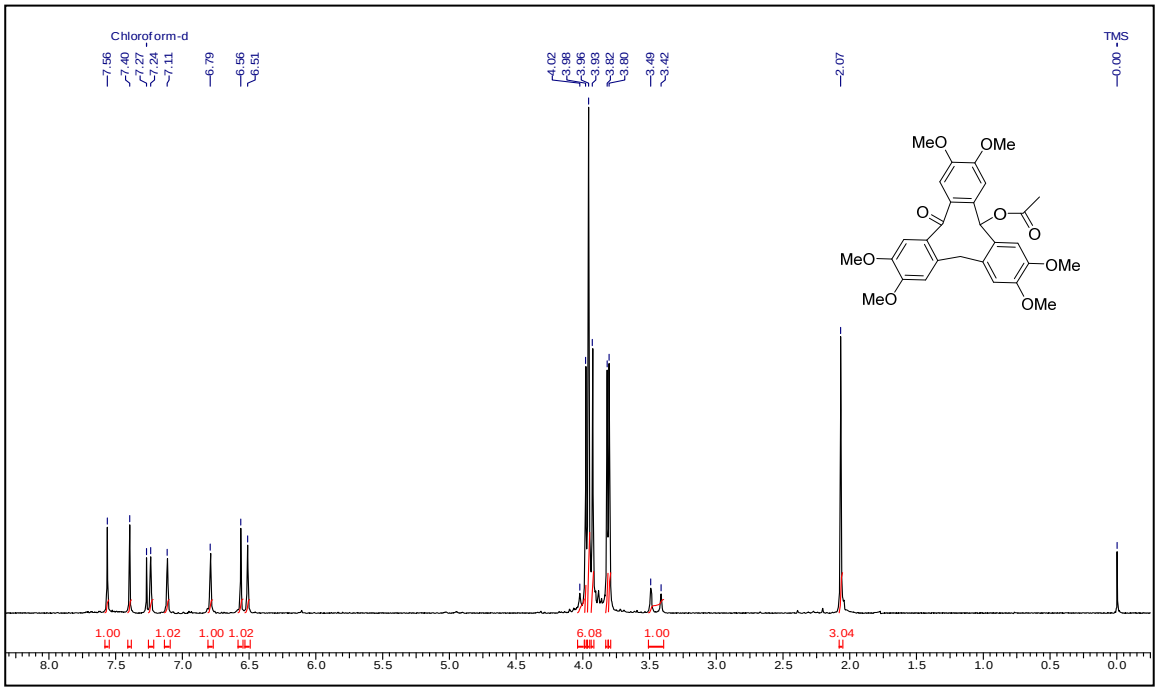
^{13}C NMR Spectrum of **66(S)** in $CDCl_3$ (50 MHz)



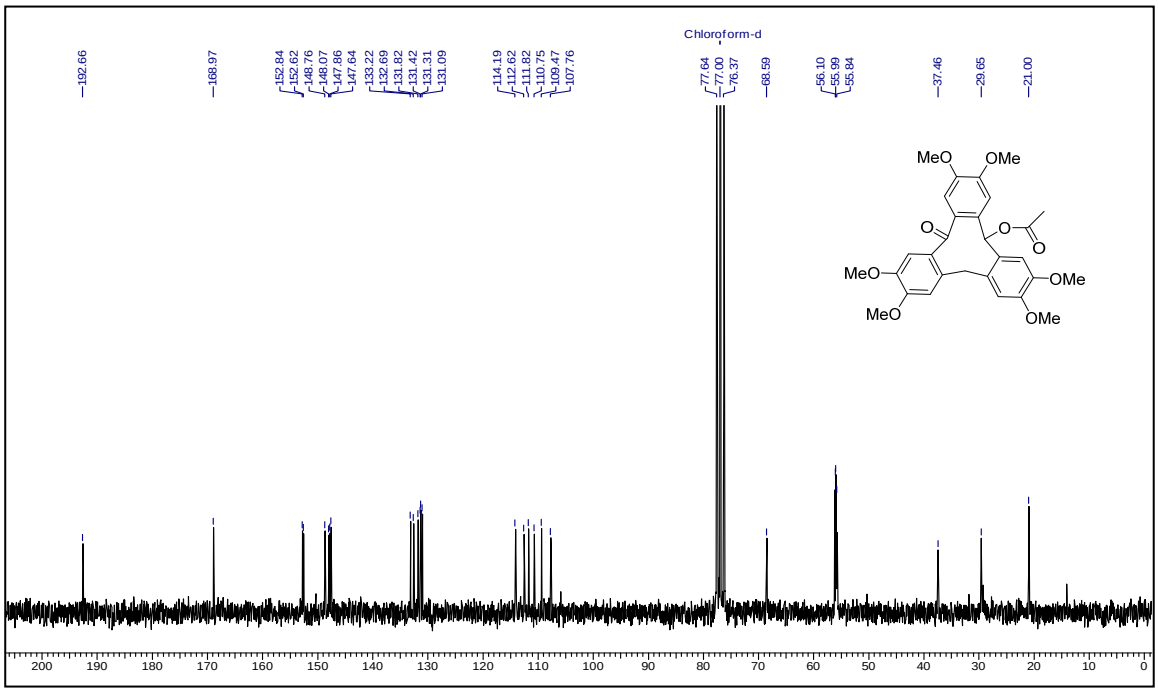
^{1}H NMR Spectrum of **76** in $CDCl_3$ (200 MHz)



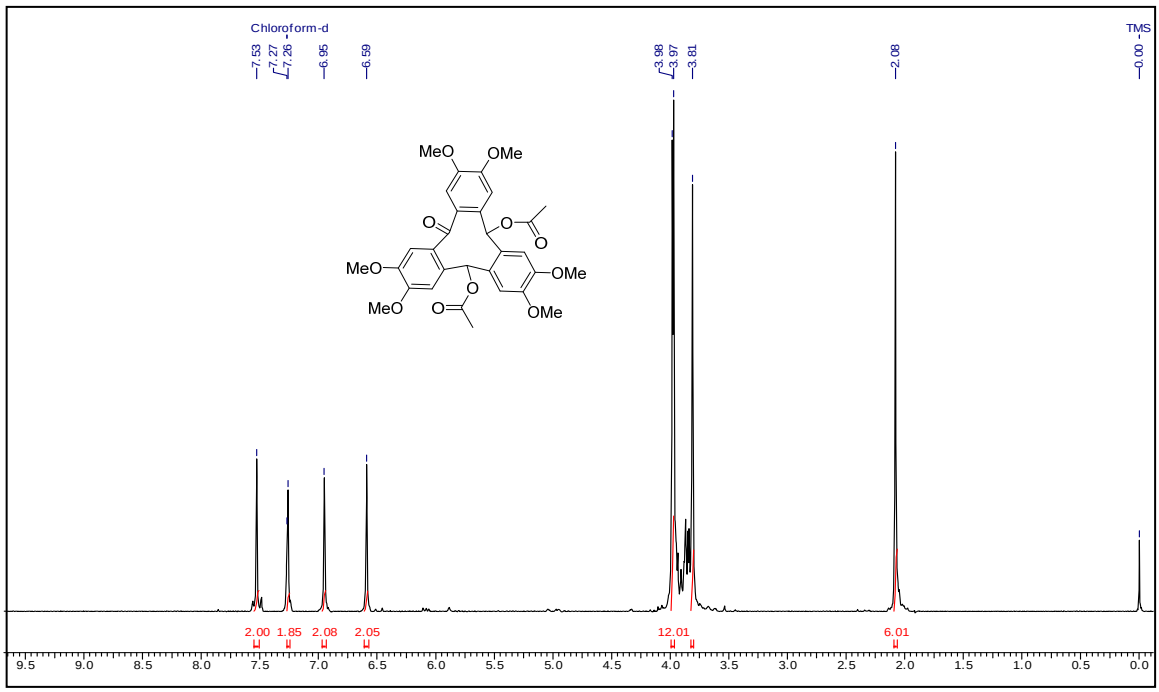
^{13}C NMR Spectrum of **76** in $CDCl_3$ (50 MHz)



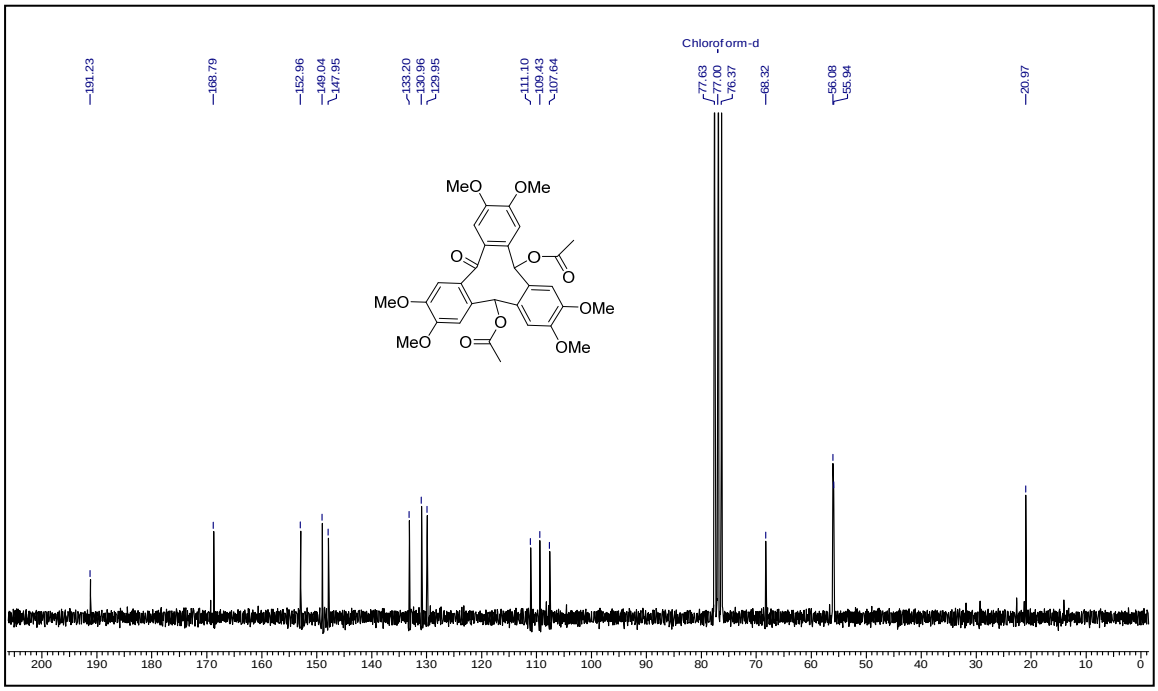
^{1}H NMR Spectrum of **77** in $CDCl_3$ (200 MHz)



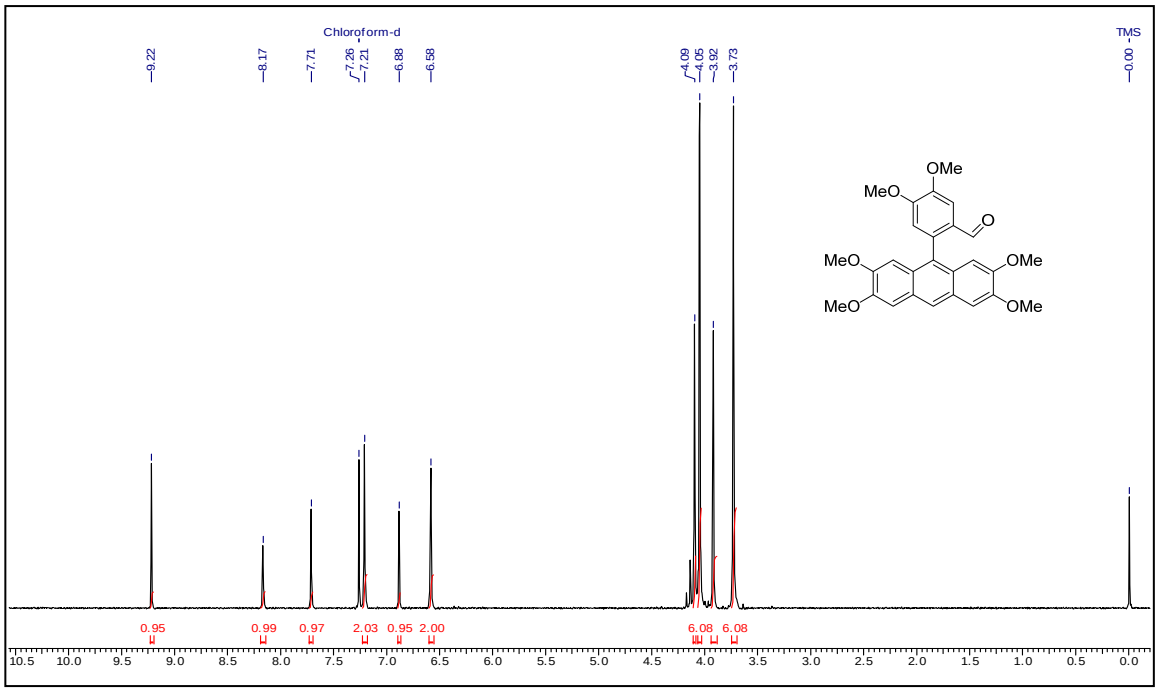
^{13}C NMR Spectrum of **77** in $CDCl_3$ (50 MHz)



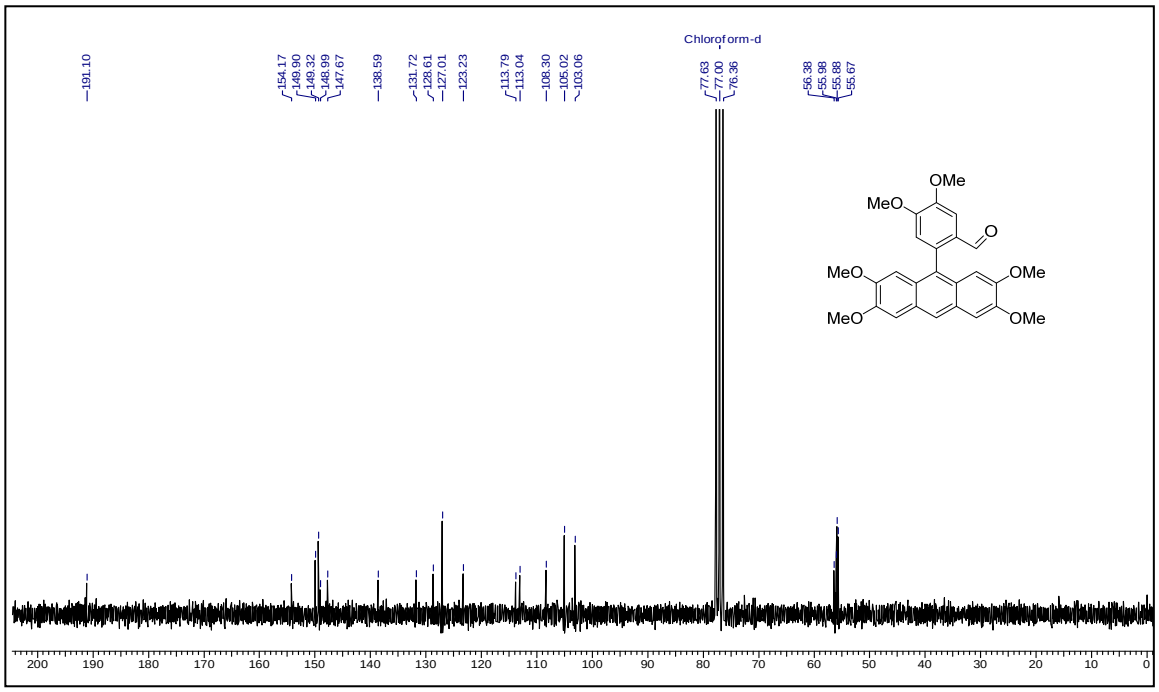
^{1}H NMR Spectrum of **78** in $CDCl_3$ (200 MHz)



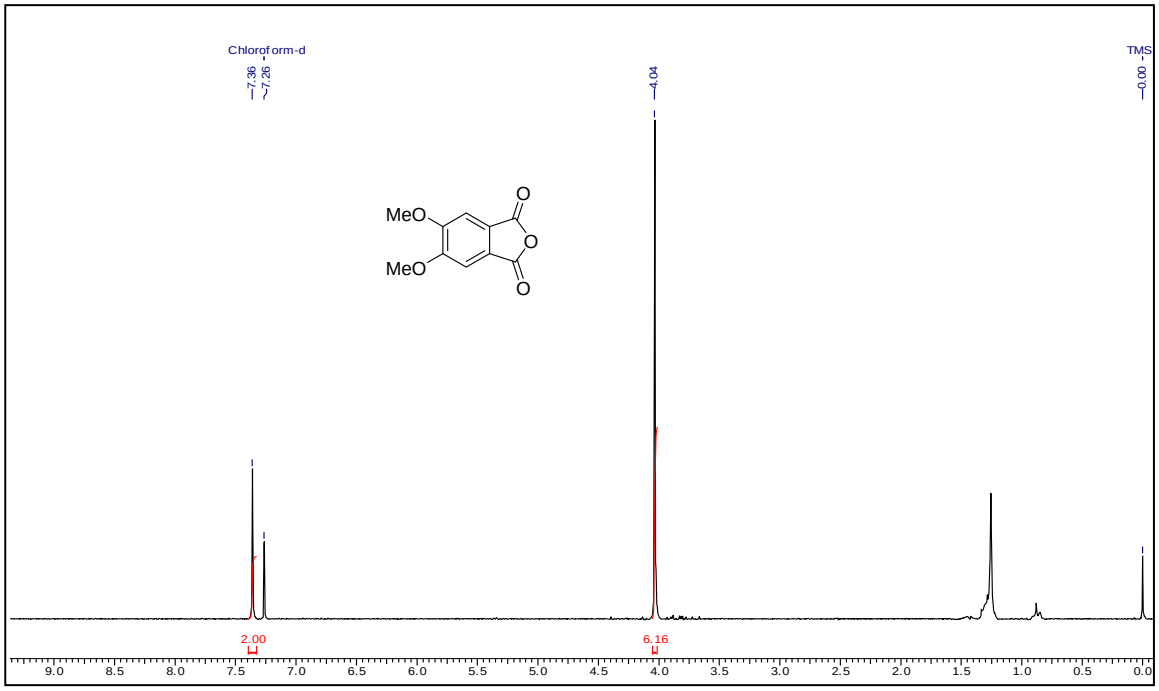
^{13}C NMR Spectrum of **78** in $CDCl_3$ (50 MHz)



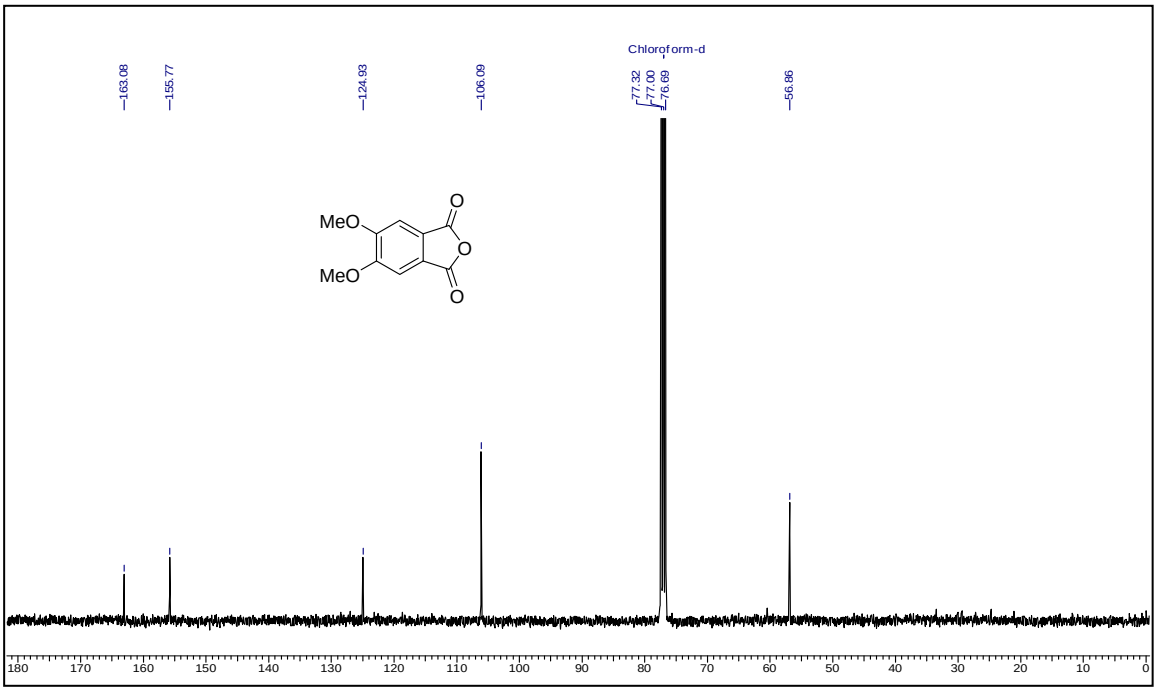
^{1}H NMR Spectrum of **79** in $CDCl_3$ (200 MHz)



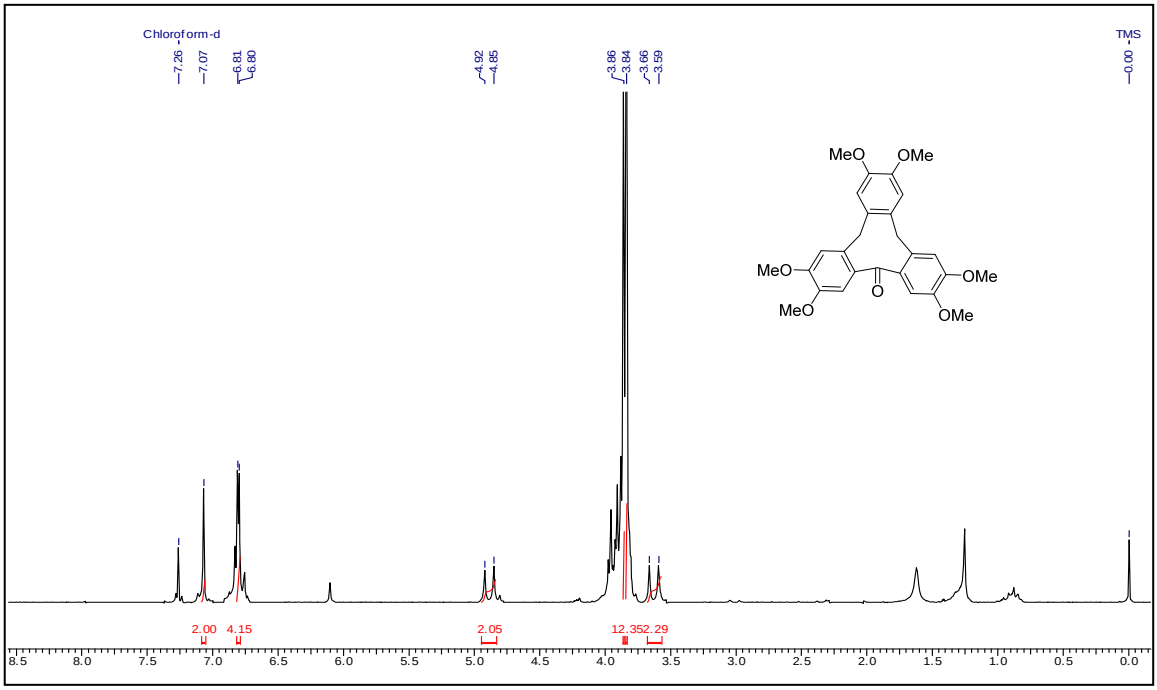
^{13}C NMR Spectrum of **79** in $CDCl_3$ (50 MHz)



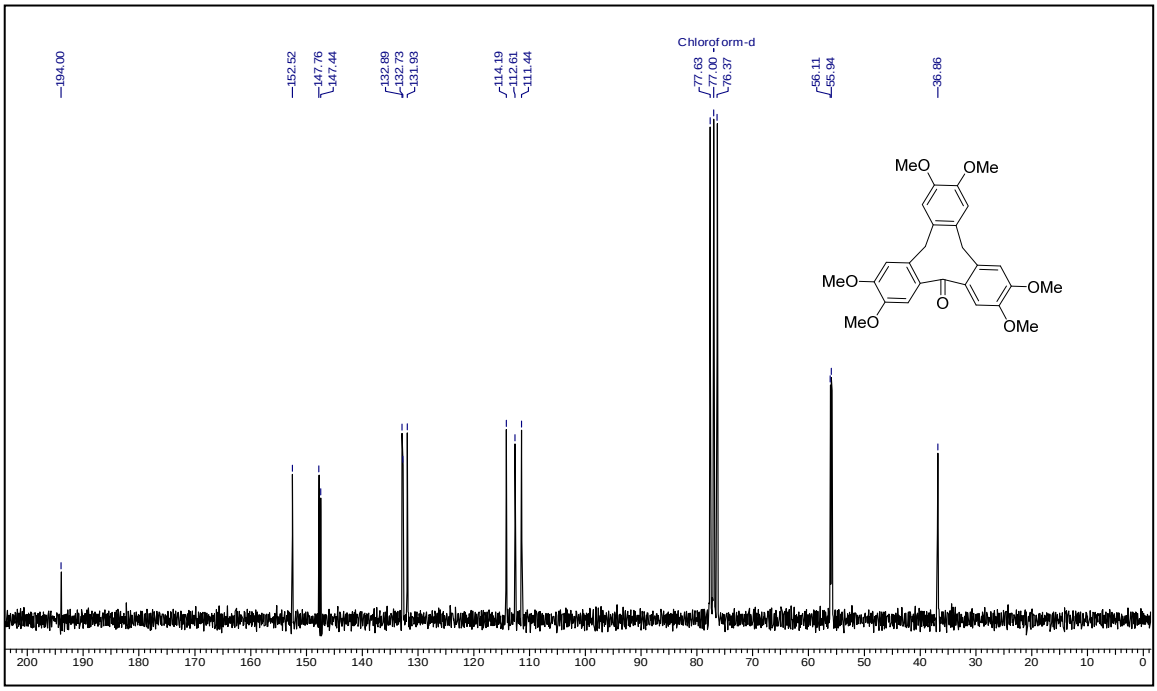
^{1}H NMR Spectrum of **80** in $CDCl_3$ (200 MHz)



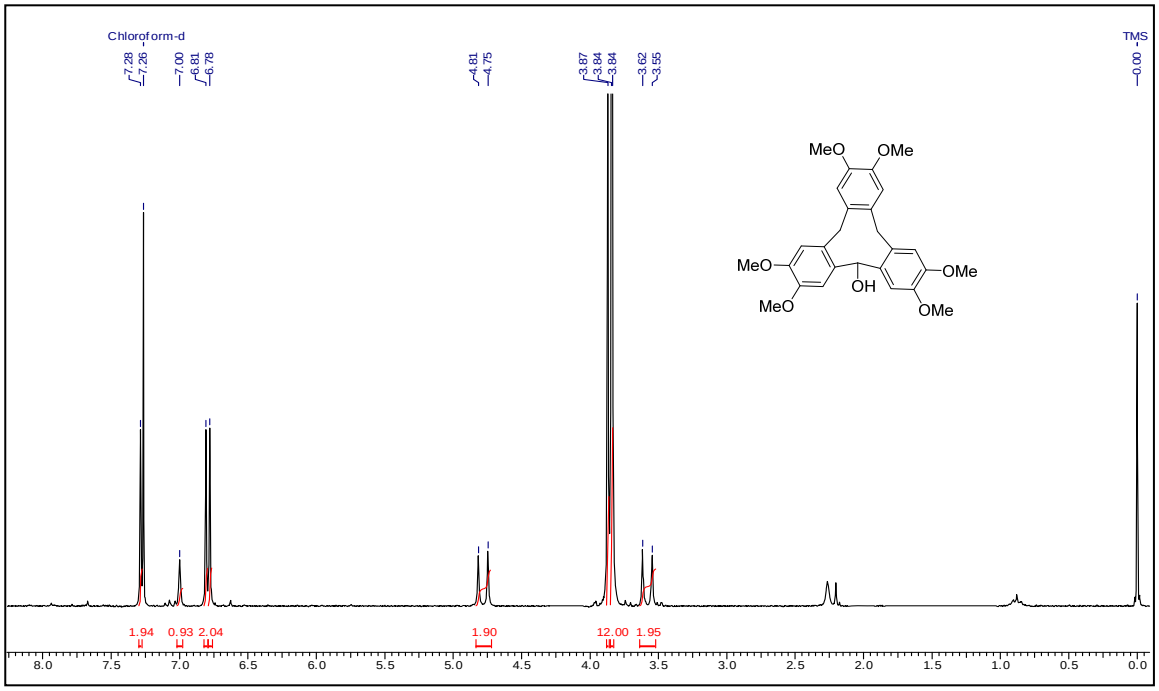
^{13}C NMR Spectrum of **80** in $CDCl_3$ (50 MHz)



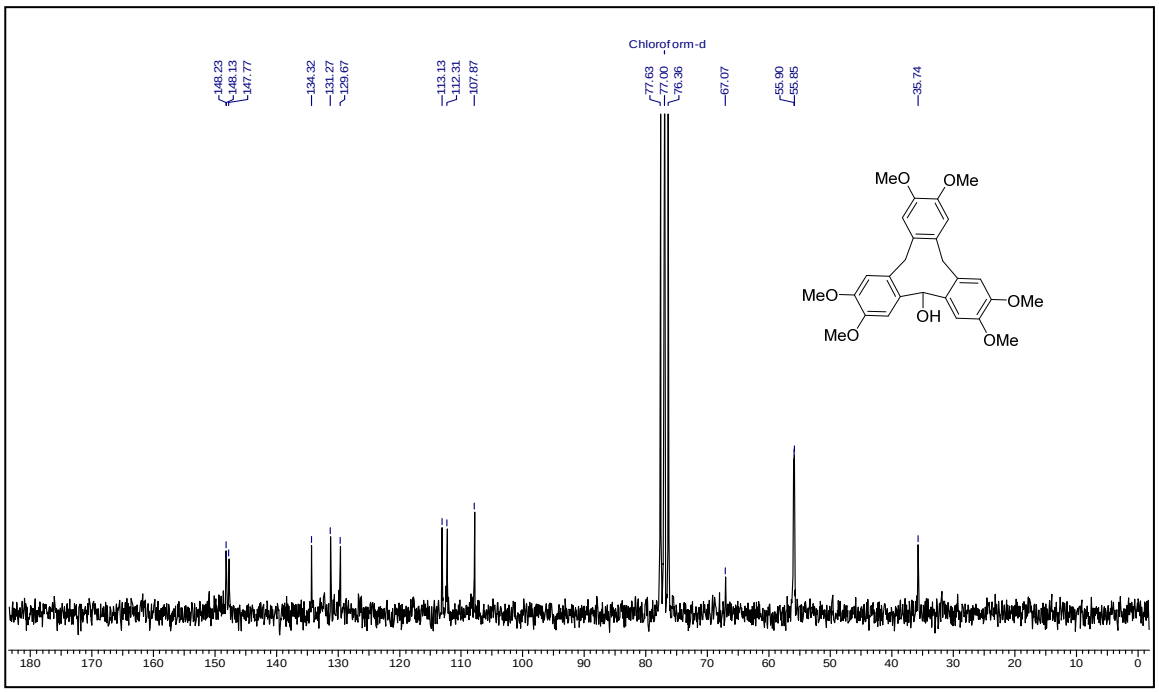
^{1}H NMR Spectrum of **70** in $CDCl_3$ (200 MHz)



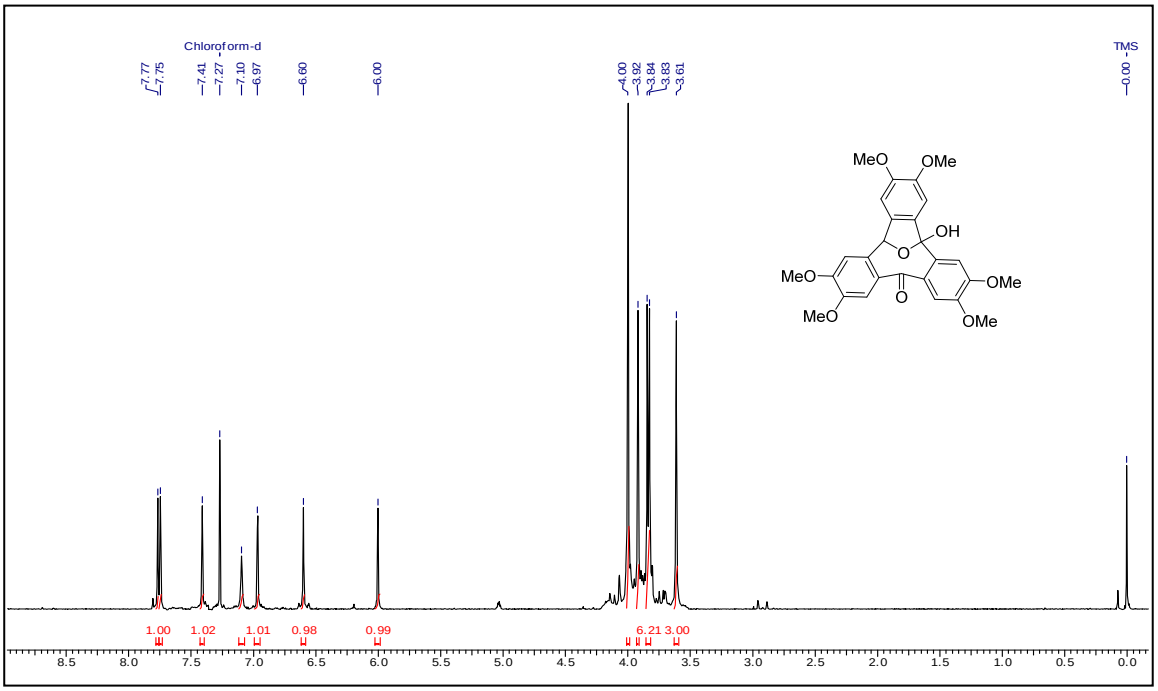
^{13}C NMR Spectrum of **70** in $CDCl_3$ (50 MHz)



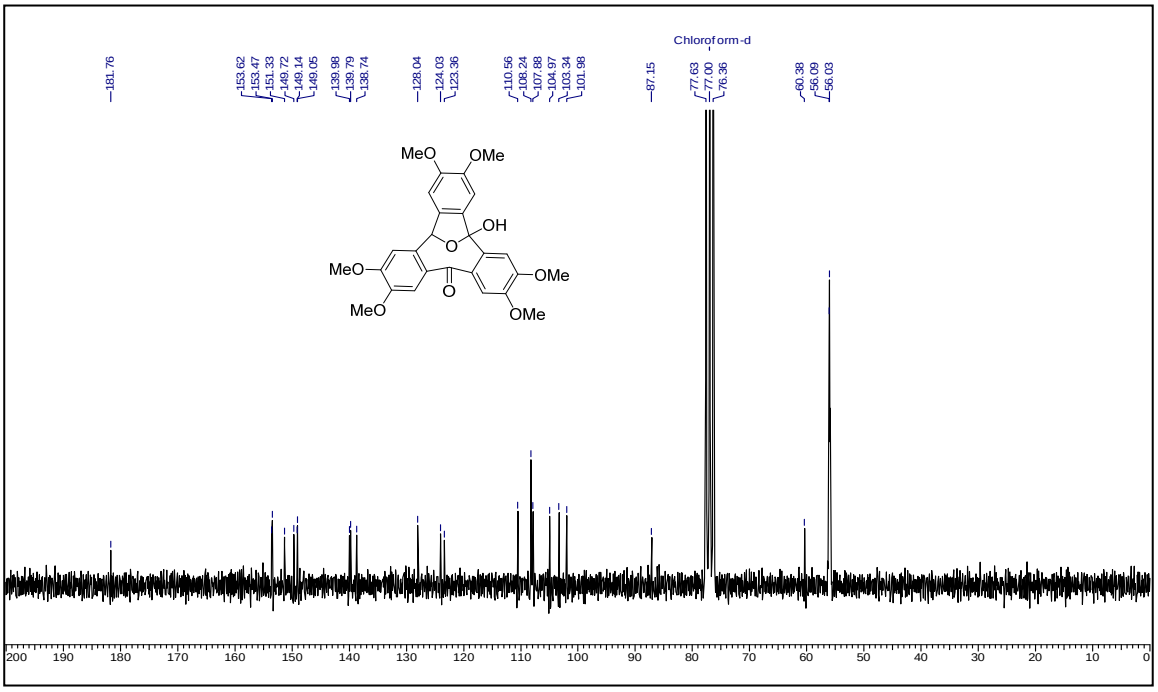
^{1}H NMR Spectrum of **82** in $CDCl_3$ (200 MHz)



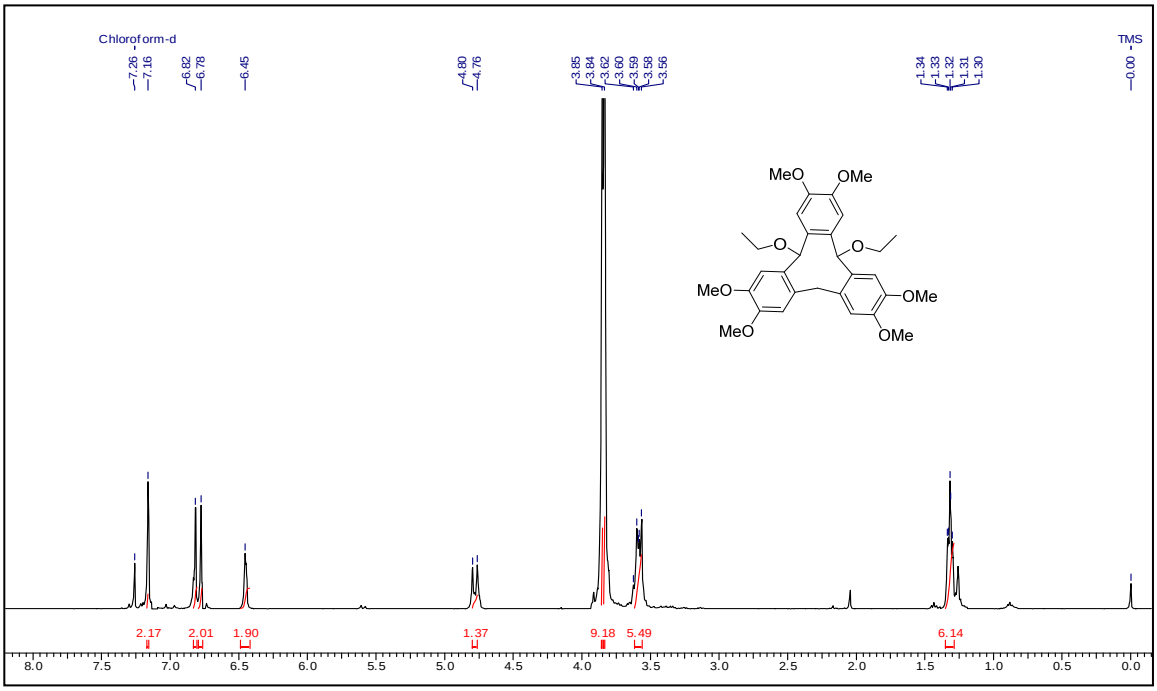
^{13}C NMR Spectrum of **82** in $CDCl_3$ (50 MHz)



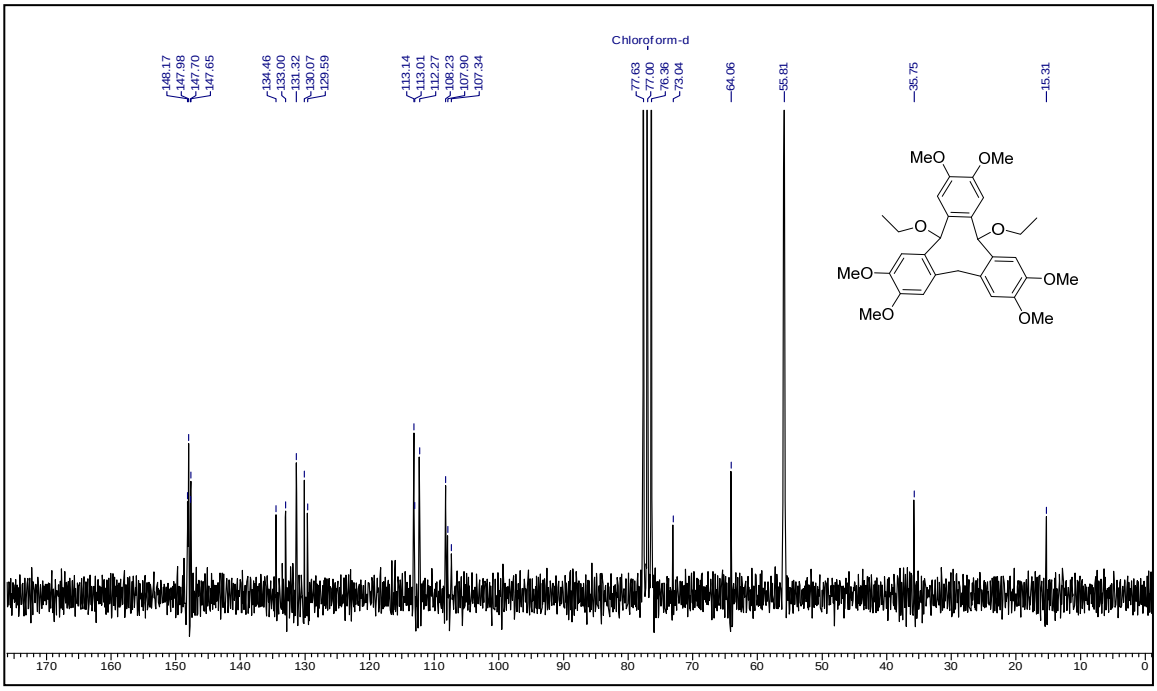
^{1}H NMR Spectrum of **83** in $CDCl_3$ (200 MHz)



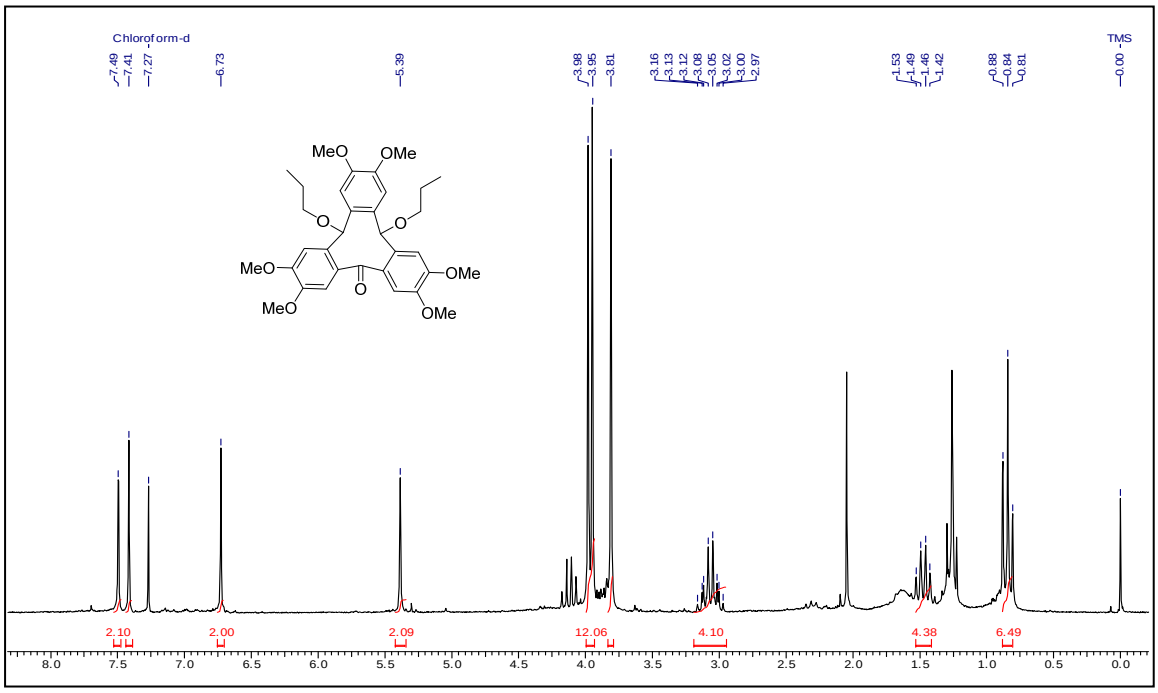
^{13}C NMR Spectrum of **83** in $CDCl_3$ (50 MHz)



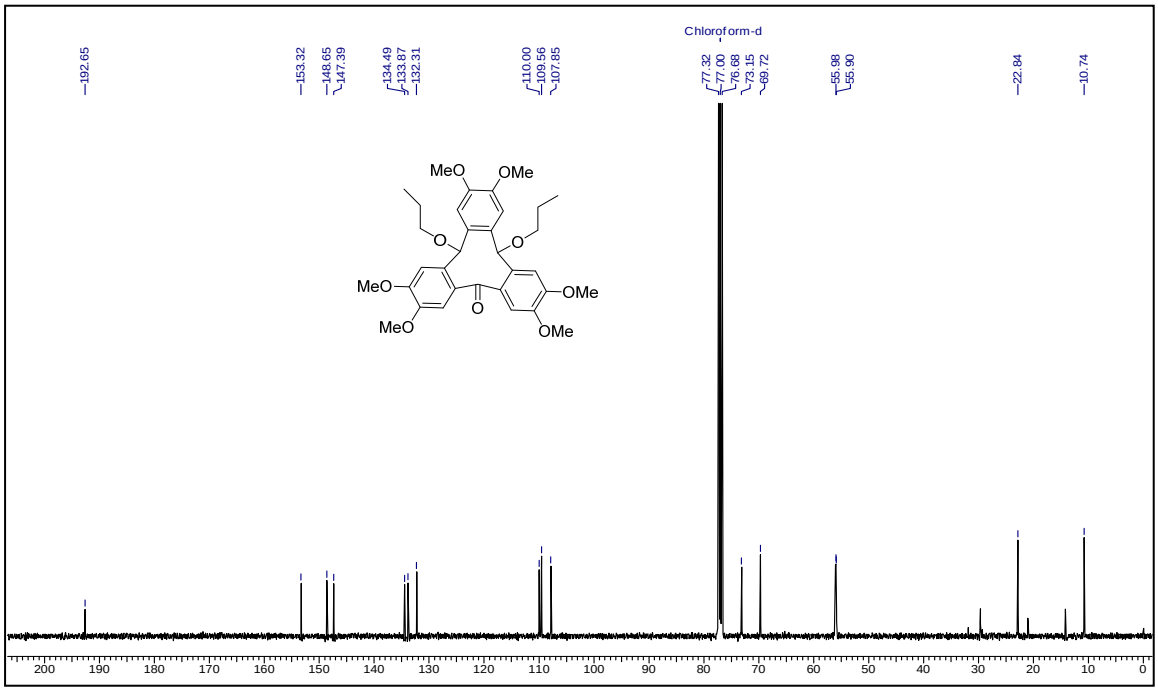
^{1}H NMR Spectrum of **84** in $CDCl_3$ (200 MHz)



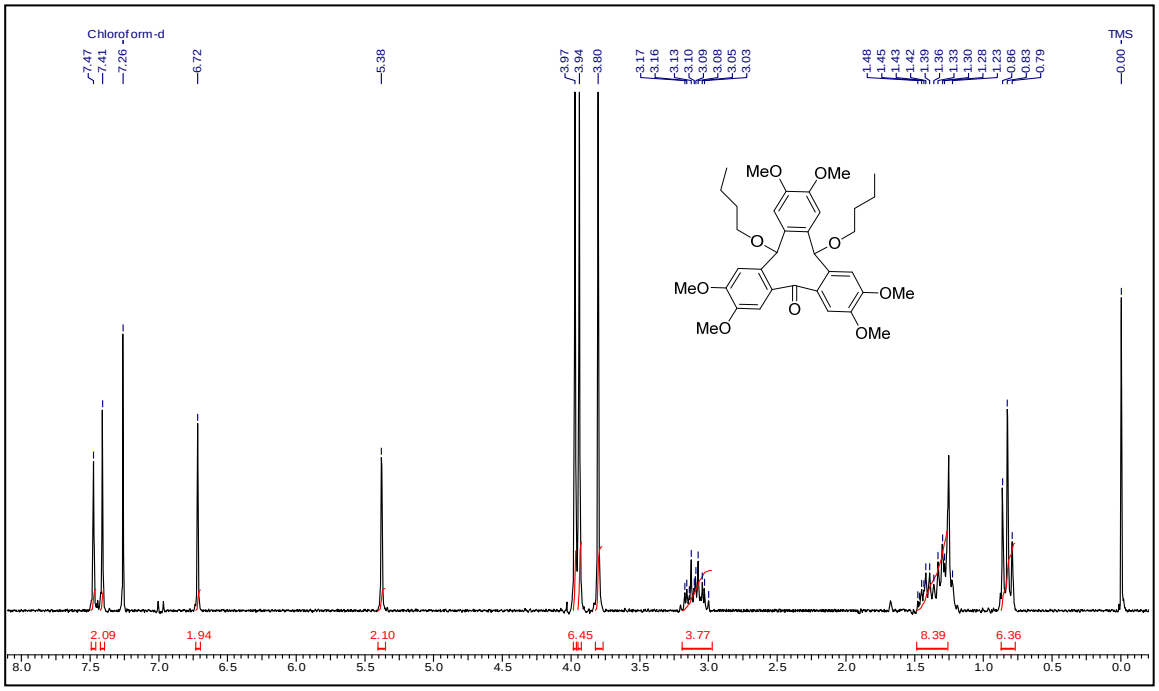
^{13}C NMR Spectrum of **84** in $CDCl_3$ (50 MHz)



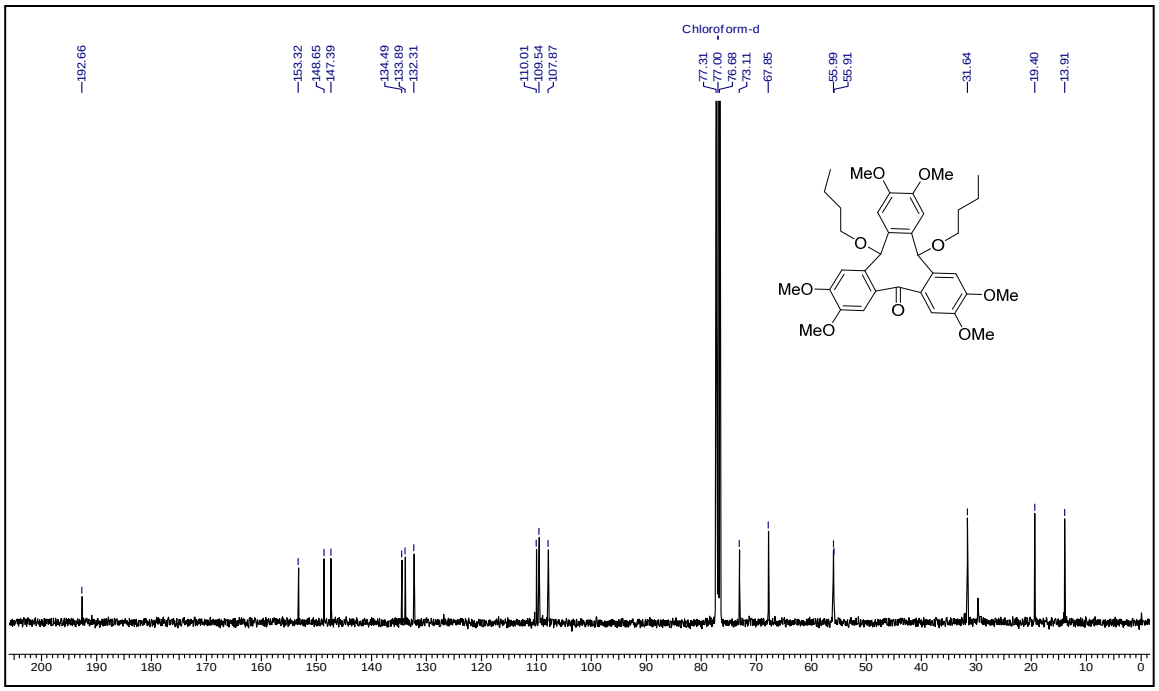
^{1}H NMR Spectrum of **85** in $CDCl_3$ (400 MHz)



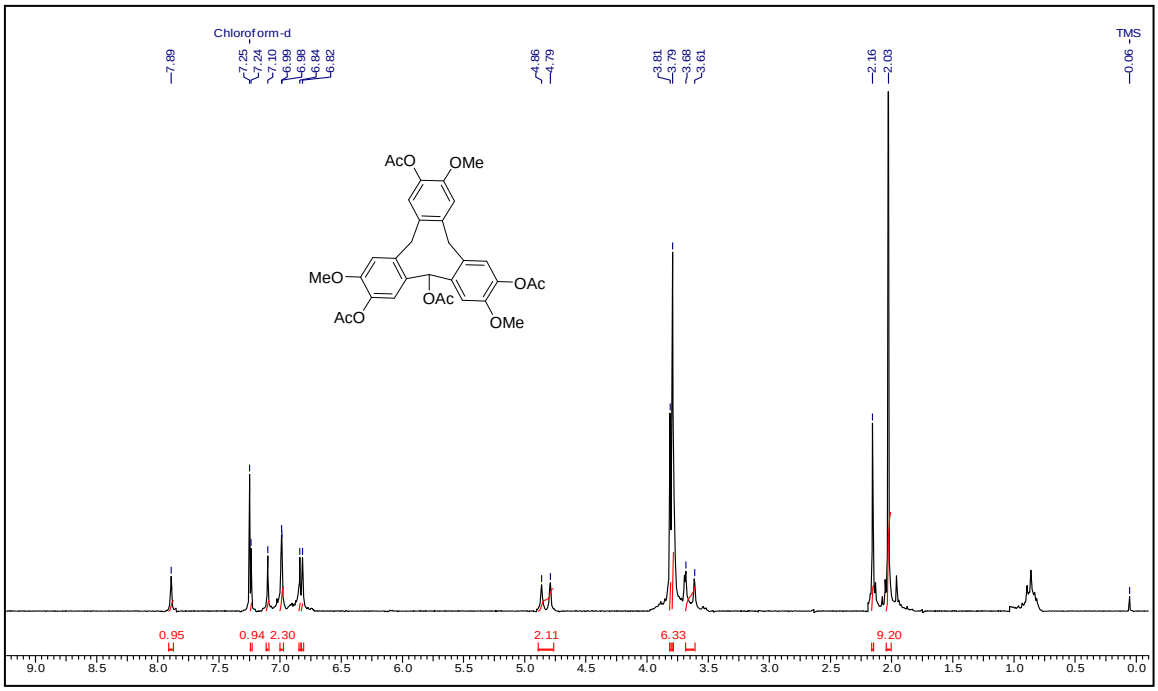
^{13}C NMR Spectrum of **85** in $CDCl_3$ (100 MHz)



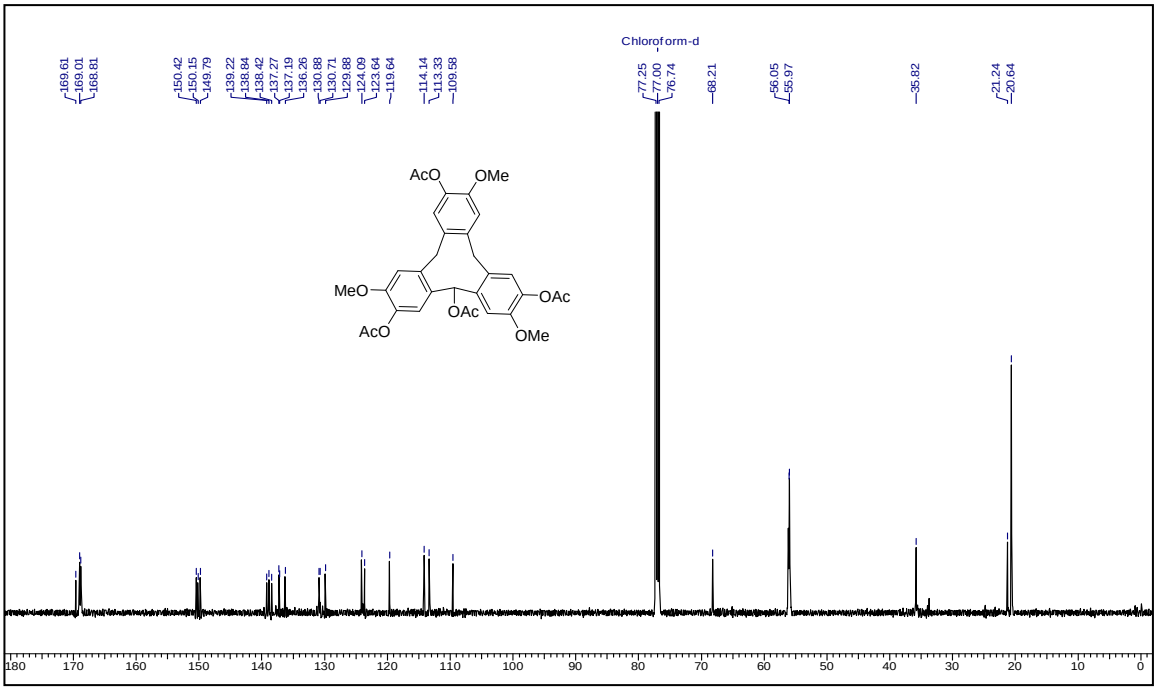
^{1}H NMR Spectrum of **86** in $CDCl_3$ (400 MHz)



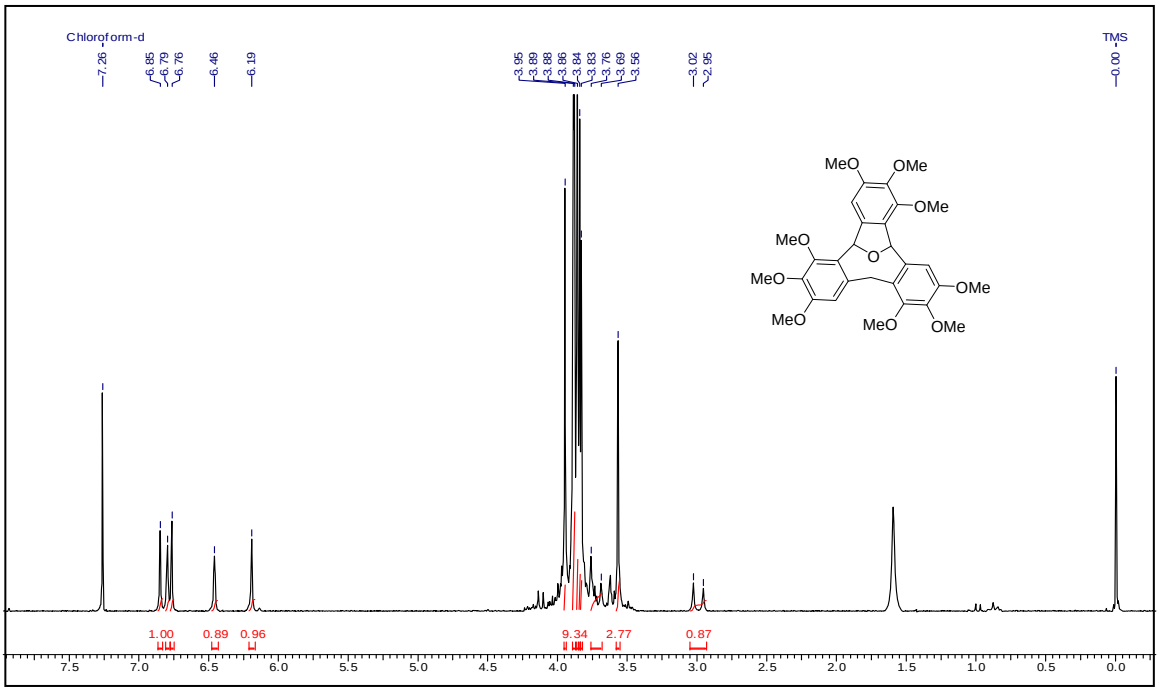
^{13}C NMR Spectrum of **86** in $CDCl_3$ (100 MHz)



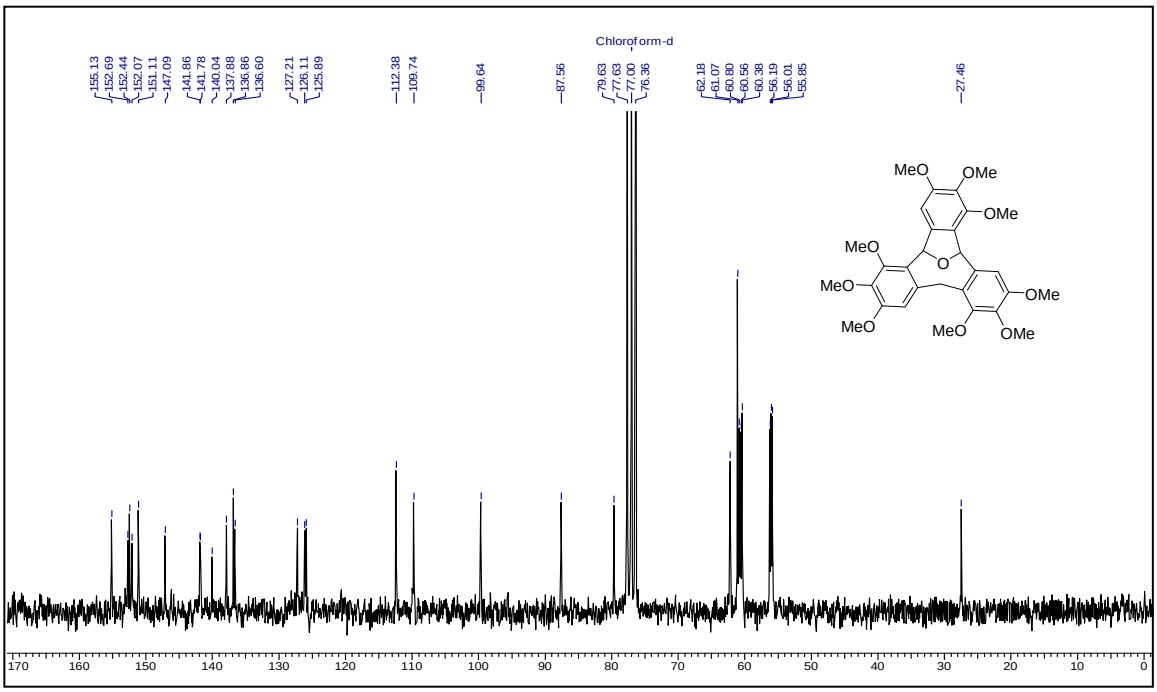
^{1}H NMR Spectrum of **87** in $CDCl_3$ (200 MHz)



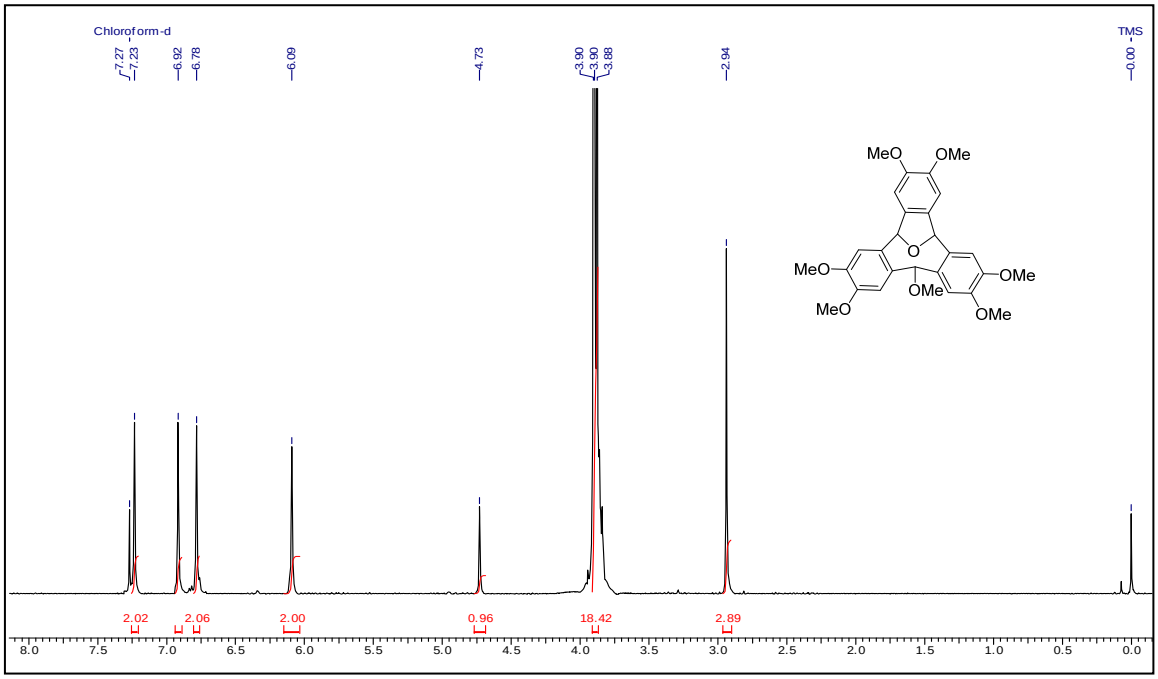
^{13}C NMR Spectrum of **87** in $CDCl_3$ (50 MHz)



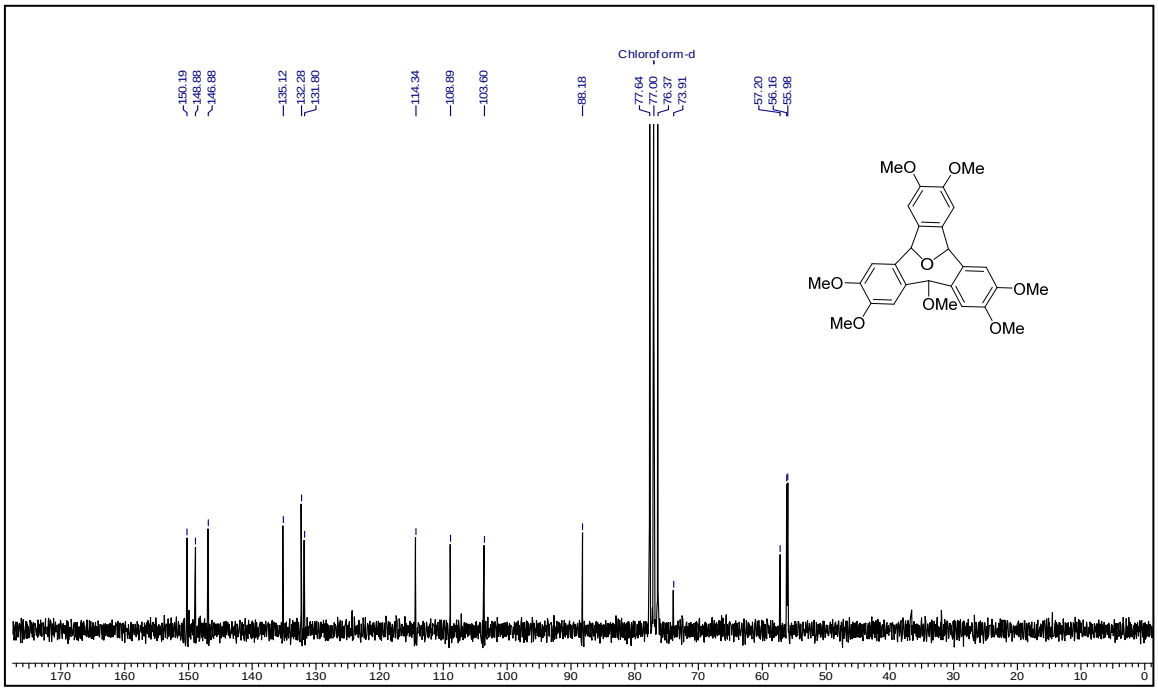
^{1}H NMR Spectrum of **88** in $CDCl_3$ (200 MHz)



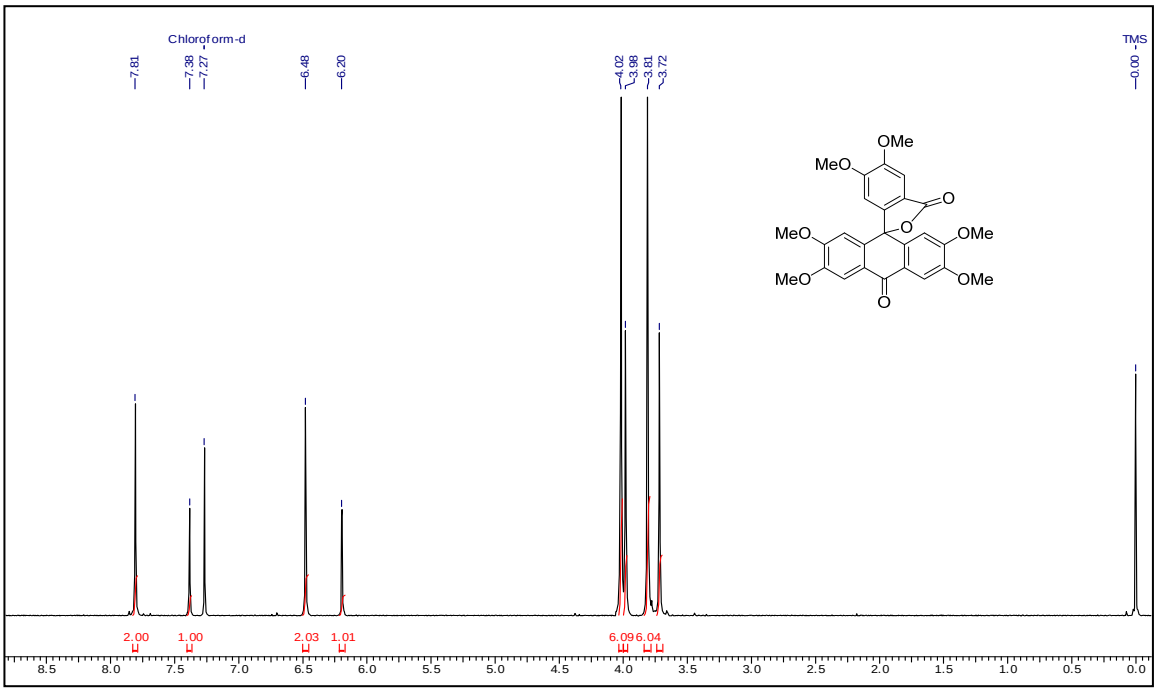
^{13}C NMR Spectrum of **88** in $CDCl_3$ (50 MHz)



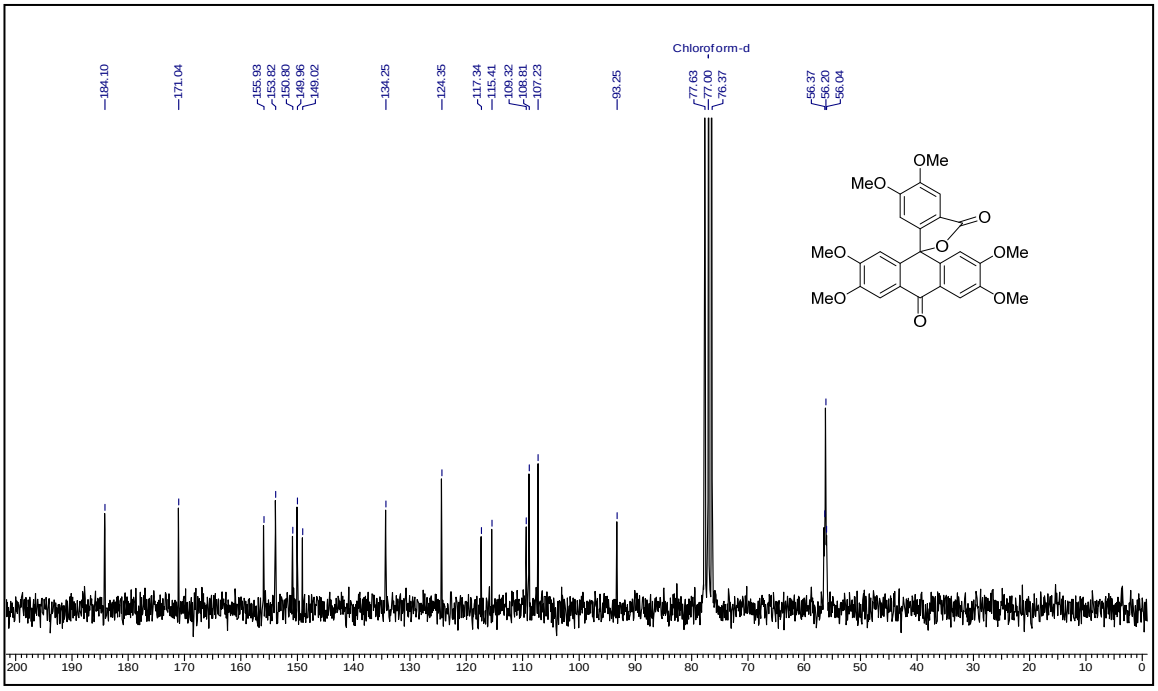
^{1}H NMR Spectrum of **89** in $CDCl_3$ (200 MHz)



^{13}C NMR Spectrum of **89** in $CDCl_3$ (50 MHz)



^{1}H NMR Spectrum of **72** in $CDCl_3$ (200 MHz)



^{13}C NMR Spectrum of **72** in $CDCl_3$ (50 MHz)

LIST OF PUBLICATIONS:

Patent:

1) Ramana.C.V.; **Senthilkumar. B**; Onepot process for the conversion of aroyl chlorides to acyl thioureas, *PCT/IN**2013**/000758.*

Publications

1) **Senthilkumar**, **B.;** Gonnade, R.G.; Ramana, C.V. Pd-catalyzed Benzylic C-H oxidation of cyclotriveratrylene – Product Diversity. *Org. Biomol. Chem.* **2014**, *13*, 2323–2329.

2) **Senthilkumar. B**.; Cornea, S.; Riehle, R.; Torchilin, V.; Degterev, A.; Ramana, C.V. Synthesis of Thiourea, 1, 2, 4-Triazole and Imidazo[1, 2, 4]triazole analogs of PITENIN-1: small molecule antagonists of PIP3 signaling *(communicated)*

Erratum