Sustainable Approaches for the site-selective C-H Functionalization of 2*H*-Indazoles

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~Dedicated to~

My Beloved Family

and

Friends

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- ***Murugan A (முருகன். அ)***

ABSTRACT

Introduction

Heterocyclic moieties are a prominent feature present in natural products, drug molecules and known for their various properties. Especially nitrogen heterocycles are of particular interest in medicinal chemistry, due to their diverse and significant biological properties. Nature has displayed infinite diversity to incorporate these heterocycle scaffolds into a complex structure through evolution. Natural products confine to be the greatest inspiration in drug discovery. The structural complexity and variety of natural products demand developing efficient synthetic methods in green, and sustainable manner was achieved via C-H functionalization/activation.

Construction of C-C and C-X bonds via C-H bond activation/functionalization has attracted considerable attention in the past decades. However, selective C-H activation has been a challenging task, owing to the ubiquitous nature of the C-H bond in organic molecules. In this aspect, along with transition-metal catalyzed C-H functionalization, recently alternative, metal-free versions have become very important due to economic and environmental concerns. A highly atom economical, efficient and yet environmentally friendly method has been the prime synthetic target to be achieved by the chemists for synthesizing complex heterocycles, since last few decades. Inspired by this, more recent research has been focused on the C-H functionalization of Heteroarenes/arenes, especially radical C-H functionalization become fascinating sustainable method. In this context, we were inspired to take up the challenge of developing novel regioselective C-H functionalization of Heteroarenes to the synthesis of functionalized privileged heterocyclic scaffolds.

Accordingly, we have developed a sustainable approach for the site-selective C-H functionalization of 2*H*-indazoles.

The proposed content of the Thesis

Chapter 1: Introduction

Chapter 2: Iron-promoted C3-H nitration of 2*H*-indazole: Direct access to 3-nitro-2*H*-indazoles

Chapter 3: Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition metal-free photoredox catalysis

Description of the research work

Chapter 1: Introduction

In this chapter, we have described introduction about the hetrocycles, photoredox catalysis, sustainable chemistry, and hypervalent compounds.

Chapter 2: Iron-promoted C3-H nitration of 2*H*-indazole: Direct access to 3-Nitro-2*H*-indazoles

In this chapter, we have described the C3-H nitration of 2H-indazole via radical mechanistic pathway in a regioselective manner. We have also described the dual role of iron nitrate as nitro source and promoter.

Direct C-H functionalization has become a reliable and robust method for various transformations, *i.e.* carbon-hydrogen bond to carbon-carbon and carbon-heteroatom bond to construct complex molecules due to its high step- and atom-economy. Recently, direct C-H functionalization via radical pathway has been a rapidly expanding area of research and has emerged as a promising and sustainable approach towards molecular construction often complementary to traditional methods. Despite these developments selective C-H functionalization via radical pathway is still in its infancy and controlling the reactivity, chemo/regioselectivity of radical species for the selective C-H functionalization require efforts to find more mild and proper methods which pose many opportunities and challenges to address.

Owing to the ubiquitous nature of heteroarenes in agrochemicals and pharmaceuticals, the direct C-H functionalization of heteroarenes is a highly attractive strategy providing a short route for complex molecules as well as for late-stage functionalization (LSF) of bioactive molecular scaffolds and hence offers tremendous opportunities for chemists. Among them, C-H functionalization of heteroarenes *via* radical pathway is one of the most appealing and straightforward strategies.

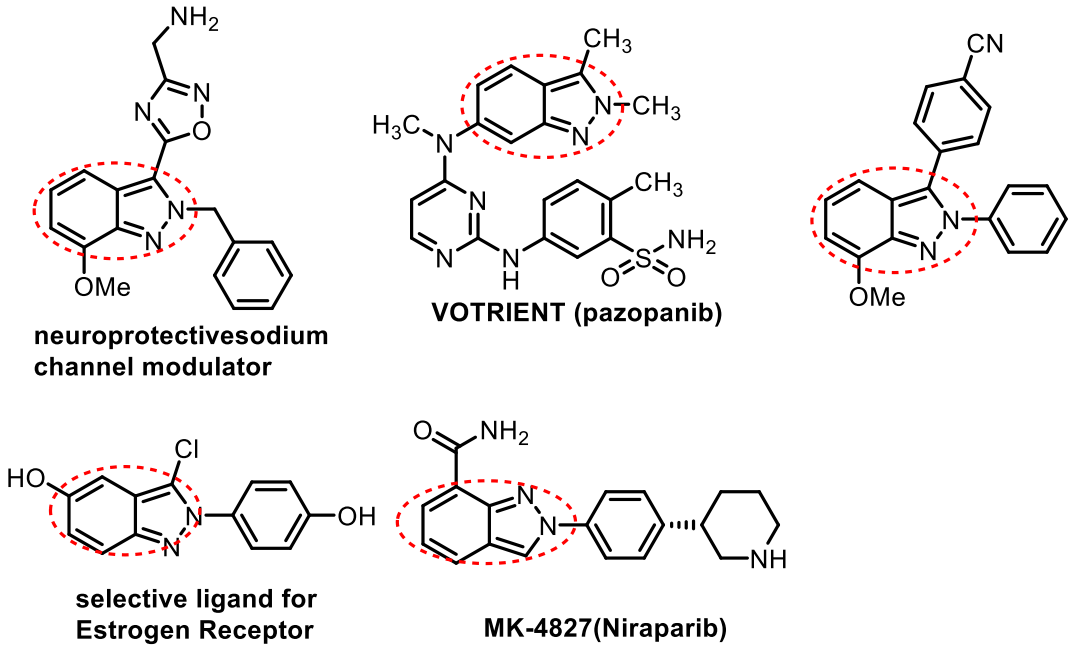
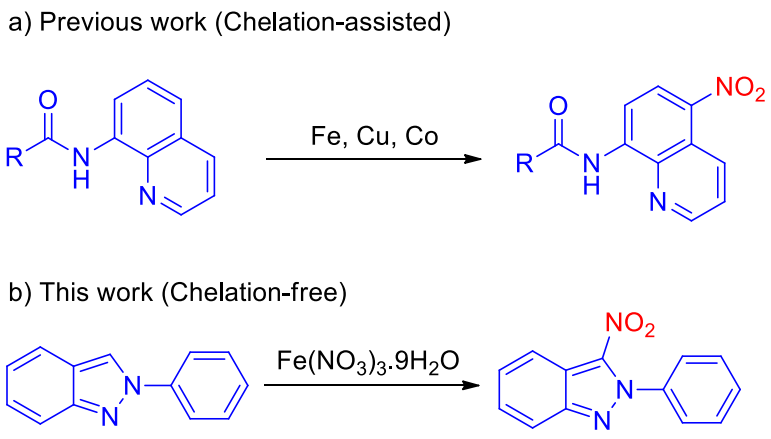


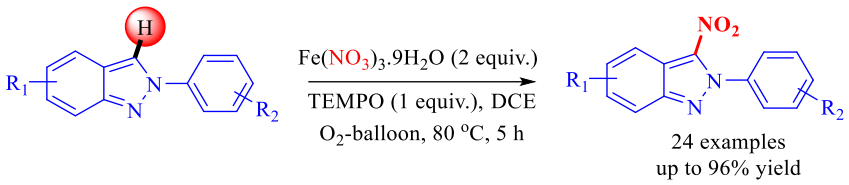
Figure 1. A representative example of biologically active C3-H functionalized 2*H*-indazole based molecules

Heteroaromatic nitro compounds are of great significance due to their importance as crucial precursors in organic synthesis and their potential for further transformations. In recent years, several chemists achieved a transition-metal-catalyzed radical C-H nitration on arenes/heteroarenes by using various nitro source, such as $AgNO_2$, ^tBuONO, $Cu(NO_3)_2$ and $Fe(NO_3)_3.9H_2O$. among all metal nitrates, $Fe(NO_3)_3.9H_2O$ as non-toxic, inexpensive and green reagent is well known for the various radical nitration strategies such as, nitration on olefins, allenes and imines. However, it is an application on aromatic nitration is rare, except recent nitration on 8-aminoquinoline. Hence, there is a broad scope for the development of strategies for radical nitration of arenes and heteroarene.



Scheme 1 Radical C-H nitration of Heteroarene

As an essential class of heteroarenes, indazole motifs are embedded in pharmaceuticals with a broad range of biological activities, including antitumor, antimicrobial, anti-inflammatory, and HIV-protease inhibition. Hence, there have been extensive efforts directed towards the synthesis of indazole derivatives. The recent emergence of radical C-H functionalization as a new paradigm in contemporary chemistry and as a part of our research program on C-H functionalization and indazole chemistry, we were interested in developing radical C-H functionalization as a new approach for the functionalized indazoles. Recently, Wu *et al.* have demonstrated the regioselective C-H functionalization of 8-aminoquinoline through theoretical data calculations. Accordingly, we plan to support our findings in radical C-H functionalization through quantum chemical calculations. Herein, we are delighted to disclose for the first time, a radical C-H functionalization of 2*H*-indazole through $Fe(NO_3)_3.9H_2O$ promoted C3-H nitration.

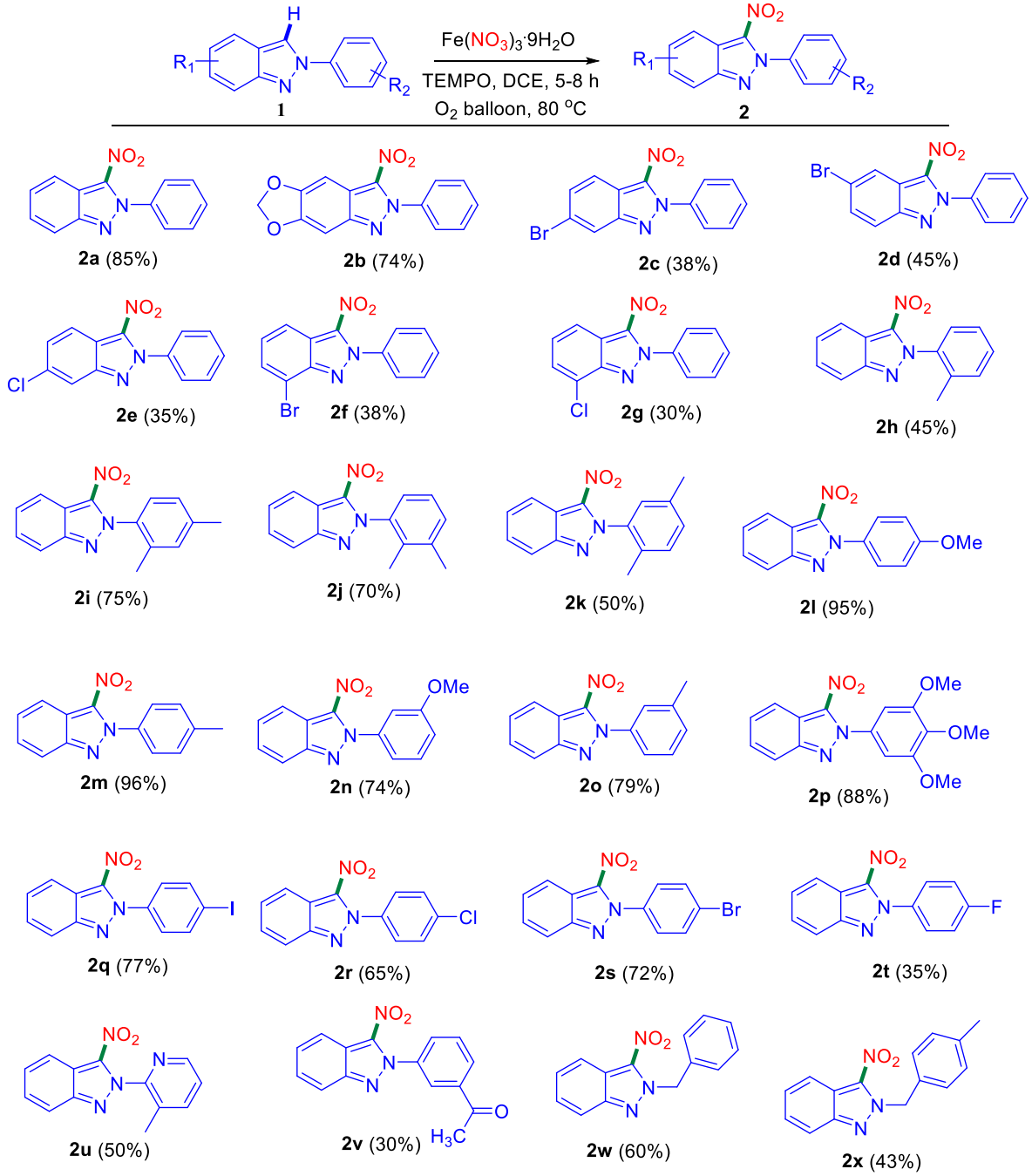


Scheme 2

To manifest this, initially we have started to optimise the nitration, we started with 2*H*-indazole performed the reaction. We found the $Fe(NO_3)_3.9H_2O$ as nitro source and TEMPO as an oxidant in DCE solvent under heating best yield of the product.

After the optimised condition in hand, we next examined the scope of this methodology with different substituted 2H-indazole systems (Table 1). The methylenedioxy substitution gave good yield when compared to halo substitution at 5th, 6th and 7th position of 2*H*-indazole **2c-g**. Next, we examined the scope of substrates with various substitutions (halogen, alkyl, alkoxy) on amine partner of 2*H*-indazoles resulting in desired products with moderate to excellent yield. Having benzyl group in place of aryl on 2nd position of 2*H*-indazole **2w** & **x** did not show any improvement in the yield. Unfortunately, amine partner bearing electron withdrawing groups, such as nitro, nitrile and ester groups did not afford the desired products **2aa-ac**. Also, 2*H*-indazoles with alkyl substitution at 2nd position **2ad** & **2ae** could not provide the nitration product. Furthermore, our attempts to carry out nitration on other heteroarenes (indole **3a**, imidazole **3b**, 1*H*-indazole **3c**) went in vain.

Table 1: Substrates Scope for the C3-Nitration of 2*H*-Indazole [a,b]

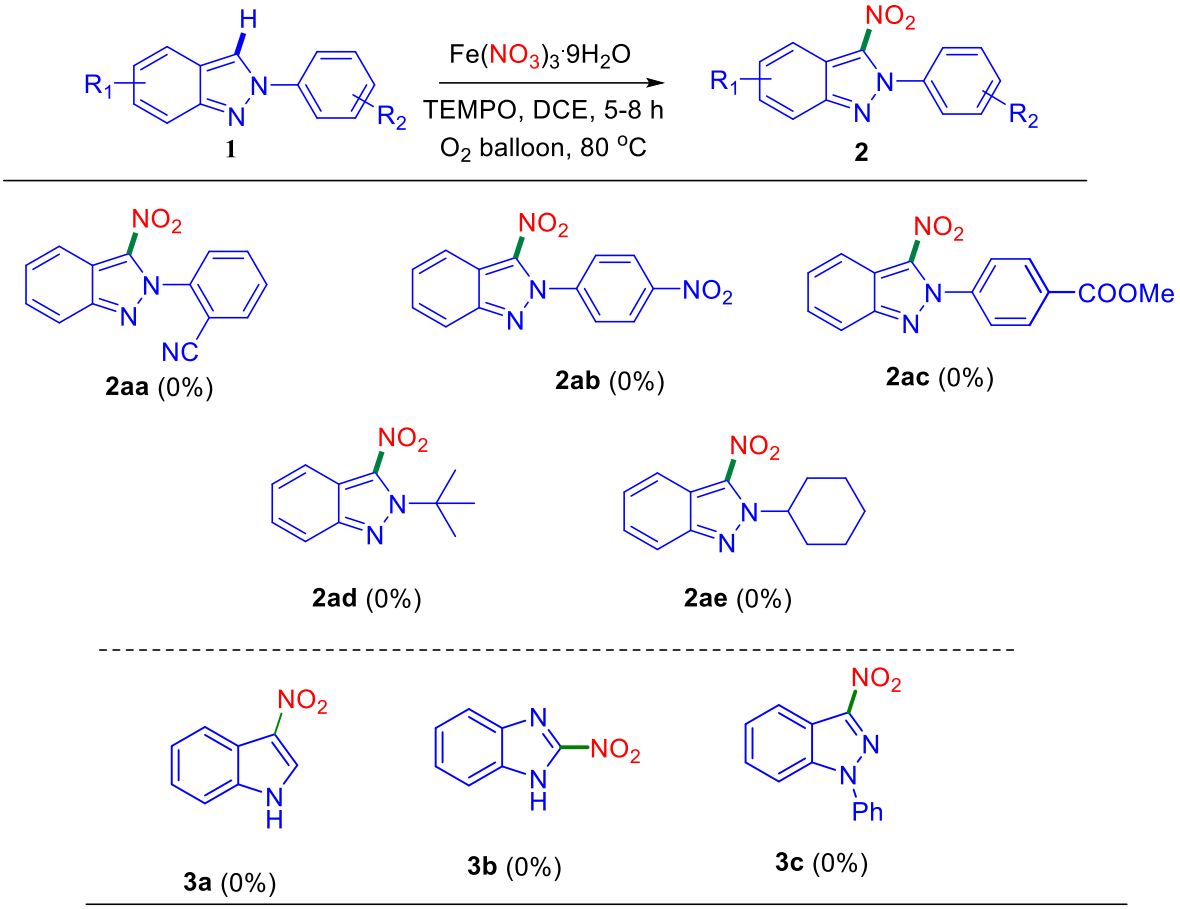


[a]Conditions: 1a (1 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (2 mmol), TEMPO (1 mmol), DCE (2 mL), oxygen balloon, 80 °C, 5–8 h. [b]Isolated yield of chromatographically pure products.

Based on the experiments performed for the optimization of reaction conditions shown in Table 1, we observed that other nitro-sources failed to give any nitro product, hence in order to prove the role of $Fe(NO_3)_3.9H_2O$, we planned to examine the reaction with metal-free nitro

source, however, in the presence of Fe/Cu as a promotor which resulted in good yield thus indicating the dual role of $Fe(NO_3)_3.9H_2O$. Furthermore, the reaction in the absence of any promotor with metal-free nitrate(TBN), did not afford the desired product. Hence, the promoter is necessary for the nitration of indazole at the C3 position.

Table 2: Substrates Scope for the C3-Nitration of 2*H*-Indazole [a,b]



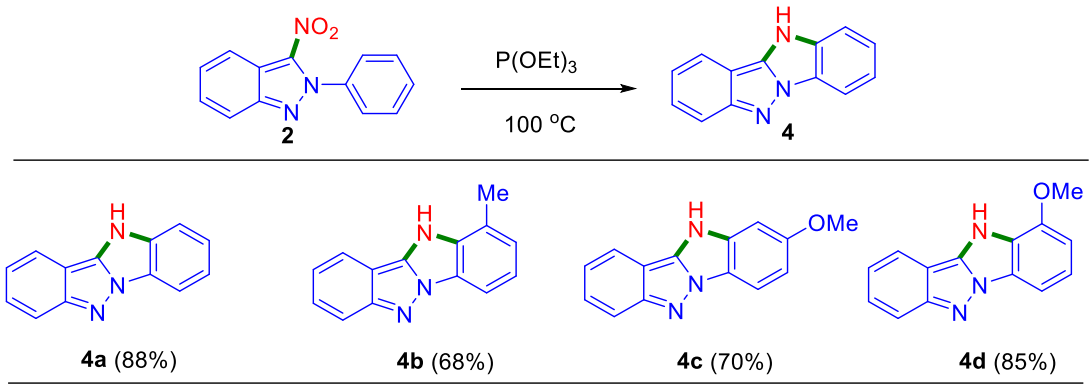
[a]Conditions: 1a (1 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (2 mmol), TEMPO (1 mmol), DCE (2 mL), oxygen balloon, 80 °C, 5–8 h. [b]Isolated yield of chromatographically pure products.

To prove the radical pathway, we performed HR-MS analysis of crude reaction mixture, which shows 2,2,6,6-tetramethylpiperidin-1-ol. To know the role of oxygen, we have conducted a couple of control experiments. We obtained the desired product in 10% and 15% yield when the reaction is carried out in the absence of O_2 and TEMPO respectively. However, these experiments are not conclusive. When we performed the reaction in the presence of an excess amount of TEMPO (2 equiv) under an argon atmosphere, which resulted in 80% yield of the desired product, this indicates that the presence of oxygen reduces the amount of TEMPO significantly (optimized condition, *i.e.* one equiv of TEMPO under oxygen atmosphere). From

these experiments, we can conclude that 'O_2' might be involved, either in the recycle of TEMPO (TEMPOH to TEMPO) or in direct oxidation of intermediate B to intermediate C. Finally, to confirm the C3-functionalization of 2*H*-indazole, we performed the reaction with C3 substituted 2*H*-indazole under standard conditions, which did not afford any nitro-substituted 2*H*-indazole. The X-ray crystallography analysis of compound **3v** further supports the nitration at the C3 position.

After we synthesised various C3-nitro 2*H*-indazoles, we have successfully demonstrated the synthetic utility of nitro indazoles by the synthesis of bio-relevant benzimidazoindazole through reductive cyclization.

Table 3: Application of Nitroindazole: Synthesis of Benzimidazoindazole [a,b]



[a]Reaction conditions: **2a** (0.1 mmol), $P(OEt)_3$ (1 mL), 100 °C, 1 h. [b]Isolated yield of chromatographically pure products.

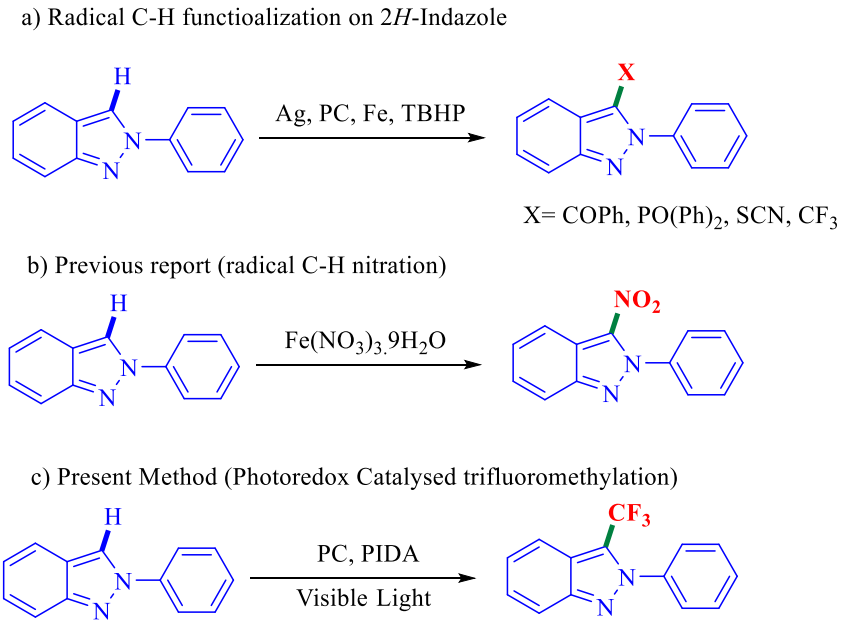
We have successfully developed a novel protocol for the regioselective radical C-H nitration of 2*H*-indazoles. The method offers chelation-free C-H nitration on 2*H*-indazole by using the inexpensive and nontoxic $Fe(NO_3)_3.9H_2O$ under mild conditions. Moreover, the mechanistic pathway was inferred based on control experiments and quantum chemical calculations. The synthetic utility of nitroindazoles was demonstrated by the synthesis of bio-relevant benzimidazoindazoles.

Chapter 3: Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition metal-free photoredox catalysis

In this chapter, we have discussed the synthesis of trifluoromethylated 2H-indazole via transition-metal-free photoredox catalysis. This protocol has key features like regioselective C-H trifluoromethylation, chelation-free and metal-free C-H functionalization and inexpensive, benchtop-stable CF_3 radical source and also scale-up synthesis for this methodology.

The halo-organic compounds are typically considered as sites of high electron density because of their high electronegativity. In general, the halogen atoms can form attractive interaction due to electron donor sites (*i.e.* nucleophiles). Among them, the C-F bond finds important applications in the field of synthetic, medicinal chemistry. This comes out due to fluorine's similar size to hydrogen but significantly with increased electronegativity. In this context, the trifluoromethyl group has significant structural motifs in agrochemical, pharmaceutical, drug candidates and it can enhance their chemical and metabolic stability, increase lipophilicity and bioavailability, and also trifluoromethyl containing organic compounds are commonly applied in a material like liquid crystals.

Over the past decade, due to the importance of trifluoromethylation process several methods have been developed by using various radical, nucleophilic, and electrophilic trifluoromethylating agents such as CF_3I, CF_3SO_2Cl, CF_3COOH, Ruppert-Prakash reagent ($TMSCF_3$), Tognis' reagent, Umemotos' reagent and Baran reagent/Langlois' ($(CF_3SO_2)_2Zn$ /CF_3SO_2Na,). Among these reagents, Langlois' reagent is a benchtop-stable, cheapest, easy to handle and convenient reagent for trifluoromethylation reaction. Hence, there is a broad scope for the development of strategies for the radical trifluoromethylation of heteroarenes.

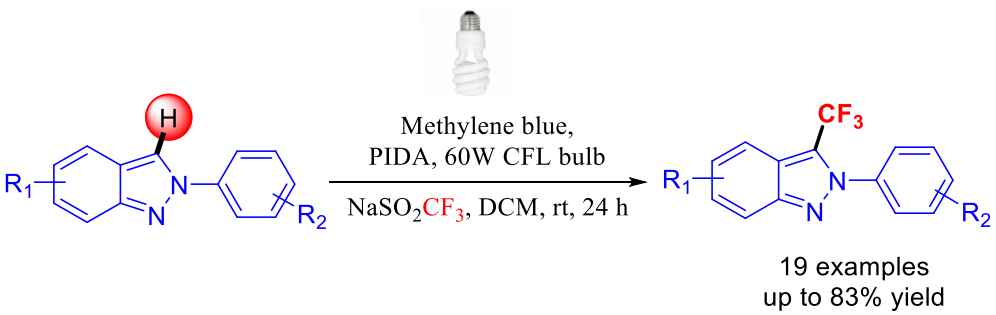


Scheme 3 Regioselective radical C-H nitration of Heteroarene

In recent years, the visible light induced photoredox catalytic activation of organic molecules has been established as a powerful strategy in modern organic synthesis with providing an attractive feature, like mild environmentally begin, excellent functional group tolerance, and high reactivity. In photoredox catalysis, metal complexes and organic dyes as photocatalysts can involve on single-electron-transition (SET) process upon irradiation with visible light. Moreover, the usage of organic dyes is inexpensive and easy to handle as photoredox catalysts, and hence this would be an excellent substitute to inorganic transition metal photocatalyst.

Nitrogen-containing heterocycle compounds have gained significant importance in natural products and exhibit a wide range of biological activities. Among them, indazoles are broadly known for their bioactivities such as antitumor, antimicrobial, anti-inflammatory, anti-HIV, anti-platelet and anti-contraceptive. Considering the immense importance of derivatives of 2*H*-indazoles, an extensive effort has been devoted to the synthesis and functionalization of 2*H*-indazole. Recently, Oh's group have reported the silver catalysed direct acyl radical addition to 2*H*-indazole and Hajra *et al.* have also realised the construction of carbon-phosphorus (C-P) and carbon-sulfur (C-S) bond formations on indazole under mild reaction condition (Scheme 3a). Very recently, Hajra and co-workers described a new approach for direct C3-trifluoromethylation of 2*H*-indazole mediated by peroxides (Scheme 3a). The transition metal catalyst, peroxides and high temperatures have been hindered for the C3-H

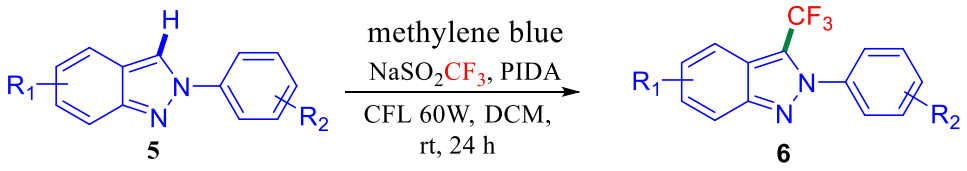
functionalization of 2*H*-indazole and finding to the synthesis of C3-H functionalized 2*H*-indazole is scarce.

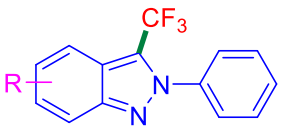


Scheme 4

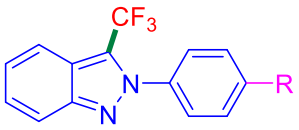
Moreover, in recent years' metal-free radical C-H functionalization has been paid much attention by several synthetic chemists. Due to the latest appearance of radical C–H functionalization as a new paradigm in contemporary chemistry and as part of our investigation on C–H functionalization and indazoles chemistry. Herein, report a novel metal-free visible light promoted organic dye catalysed regioselective C3-trifluoromethylation on 2*H*-indazole.

Table 4. Substrate scope for the C3-trifluoromethylation of 2*H*-indazole [a,b]

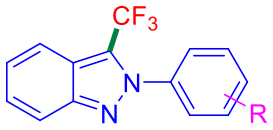




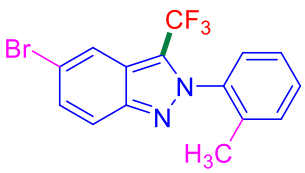
R = H	**6a**	75%
R = 6-Cl	**6b**	35%
R = 6-Br	**6c**	37%
R = 5-Br	**6d**	43%



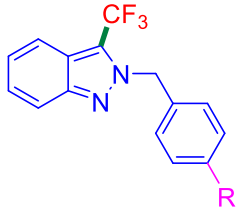
R = F	**6e**	45%
R = Cl	**6f**	53%
R = Br	**6g**	62%
R = I	**6h**	68%



R = *o*-CH_3	**6i**	45%
R = *o*-OMe	**6j**	42%
R = *m*-CH_3	**6k**	64%
R = *m*-OMe	**6l**	70%
R = *p*-CH_3	**6m**	83%
R = *p*-OMe	**6n**	83%
R = *m*-(CO)CH_3	**6o**	40%
R = *o*, *m*, *p*-OCH_3	**6p**	80%



6q (42%)



R = H	**6r**	55%
R = CH_3	**6s**	45%

[a]Reaction Conditions: 1a (1 mmol), methylene blue (1 mol%), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24h. [b]Isolated yield of chromatographically pure products.

After the established optimized reaction condition in our hand, we have examined the substrate scope of this protocol with various 2*H*-indazoles. Initially, we checked the halogen substitution on 2*H*-indazole (**6b**-**h**). The presence of halogen at C-5 and C-6 positions of 2*H*-indazoles (**6b-d**) gave poor yields. On the other hand, the halogen substitution in the *para* position of the amine partner of 2*H*-indazoles (**6e**-**h**) gave 45% to 68% yields. Likewise, the amine partner of 2*H*-indazoles bearing electron-donating groups (-Me, -OMe) resulted in the products with excellent yields (**6k**-**n** & **6p**) this may be due to the increased electron density at C3-position of 2*H*-indazole. This observation resembled with our earlier report. However, the electron donating groups (-Me, -OMe) at *ortho* position (**6i**-**j**) gave moderate yield; this is due to the steric hindrance of the *ortho* substitution. We observed poor yields when the electron-withdrawing group was present on 2*H*-indazole (**6o**) since the electron density at C3-position decreased. In the case of benzylamine partner, the C3-H trifluoromethylated indazoles (**6r-s**) were obtained in low yields.

We have successfully demonstrated a novel photoredox catalysed regioselective C-H trifluoromethylation of 2*H*-indazoles. This protocol offers the transition metal-free photoredox catalysed C3-H trifluoromethylation with an inexpensive and benchtop-stable Langlois' reagent under mild reaction conditions. The present methodology will gain much significance in organic chemistry, pharmaceutical chemistry, and material science.

ABBREVIATIONS

Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
BHT	Butylated hydroxytoluene
BQ	1,4-Benzoquinone
°C	Degree Celsius
CAN	Ceric Ammonium Nitrate
CAS	Chemical Abstracts Service
CFL	Compact Fluorescent Lamp
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarization transfer
DFMS	Zinc Difluoromethanesulfinate
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
dt	Doublet of triplet
DTBP	Di-tert-butyl Peroxide or DTBP
FDA	Food and Drug Administration
FTIR	Fourier-Transform Infrared Spectroscopy

HMPA	Hexamethylphosphoramide
HR-MS	High Resolution Mass Spectrometry
Hz	hertz
IR	Infrared Spectroscopy
IUPAC	The International Union of Pure and Applied Chemistry
J	Coupling Constant (in NMR Spectroscopy)
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
mg	Milligram
min	Minute(s)
mp	Melting Point
n.d.	Not Detected
NMEs	New Molecular Entities
NMR	Nuclear Magnetic Resonance
nr	No reaction
Nu	Nucleophile
O	*Ortho*
P	*Para*
PIDA	(Diacetoxyiodo)benzene
q	Quartet (spectral)
R	Alkyl
Rf	Retention factor
Rt	Room temperature

SET	Single-Electron Transfer
TBHP	tert-Butyl hydroperoxide
TBN	tert-Butyl nitrite
Temp	Temperature
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TEMPOH	2,2,6,6-tetramethylpiperidin-1-ol
TLC	Thin Layer Chromatography
TMSCF3	Trimethyl(trifluoromethyl)silane
TMSN3	Trimethylsilyl azide
W	watts
δ	Chemical shift in parts per million

CHAPTER 1

Introduction

1. 1. Application of Heterocycle compounds

Heterocycle compounds are an essential class of compounds, not only due to their natural abundance but also because of their chemical and biological significance. Natural product scaffolds have been well recognized as "privileged heterocycle structures" in terms of their ability to be the basis for successful drugs. An assessment of all FDA approved new molecular entities (NMEs) reveals that natural products and their derivatives represent over one-third of all NMEs. Such scaffolds can be used as cores moieties of compounds libraries. In this context, several organic chemists have paid much attention to the synthesis of heterocyclic compounds via new synthetic methodology which is also an attractive and challenging area.[1]

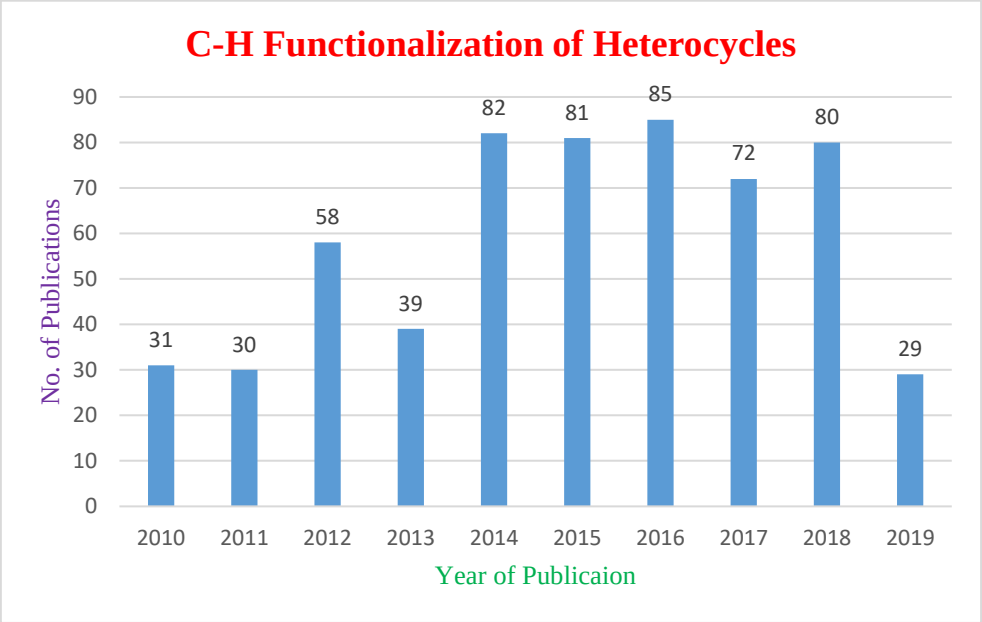


Figure 1: Recent publications in C-H functionalization

In recent years, the direct C-H functionalization of inert C-H bonds has become an important and powerful ideal method for the carbon-carbon and carbon-heteroatom bond formations. In the continuation, the modern radical reactions emerge in the 1980s have

flourished recently. In general, the radical reactions are relatively performed under mild reaction conditions with high atom economy which is very popular in recent days. Moreover, the radical C-H functionalization provides a new pathway to construct heterocycles and functionalization of heteroarenes.[2]

1. 2. Photoredox Catalysis

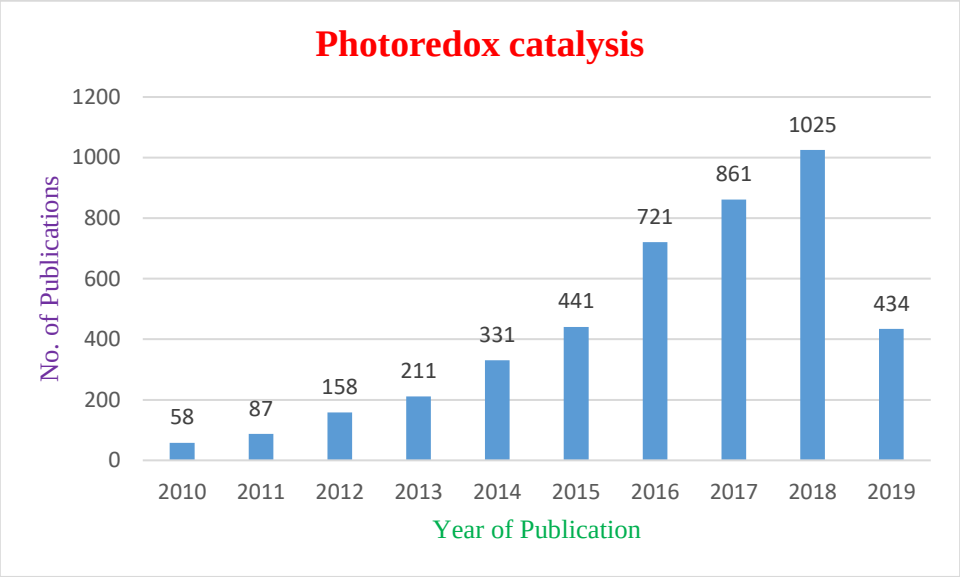


Figure 2: Recent publications in Photoredox catalysis

In the field of photochemistry, exponential growth has been observed in organic synthesis over the past decade (Figure 2). Organic photochemical reactions play a crucial role in the perspectives of green and sustainable chemistry. The light has always been regarded as an inexpensive, abundant, nonpolluting, and endlessly renewable reagent for chemists to utilize in organic reactions. In particular, in comparison with conventional thermal reactions, which usually only shows a singlet state whereas, photochemical reactions can include singlet and triplet states. Photoredox catalysis is not only helpful in attaining good yield of the products but also increases the specificity of organic reactions and exhibits excellent functional group tolerance. Visible light-mediated photoredox catalysis uses its ability to introduce single electron transfer (SET) processes in organic molecules similar to that of conventional radical chemistry. Controlling chemical reactions to produce a set of distinct valuable compounds selectively is a significant synthetic challenge, and photoredox catalysis is a great alternative to the conventional methods of generating radicals. In this way, organic photochemical reactions have become popular and useful tools in organic synthesis and attracted considerable attention in organic chemistry since in the early 20th

century. Furthermore, the photocatalysis are generally classified into three types: transition-metal complexes, organic dyes and semiconductor.[3]

1. 3. Sustainable Chemistry

Figure 3: Recent publications in Sustainable Chemistry

Efficiency and selectivity are the paramount foundations in sustainable approaches, which play a major role in modern organic synthesis. The activation of inactive and ubiquitous C-H bonds has raised as the more dominant strategy for the design and development of sustainable synthetic processes. As frequently happens in chemical research, advancement or innovations in methodological development for making the novel methods more sustainable in the vision of their potential applications. The achievement of sustainable approaches for C-H functionalization reactions is intended to achieve via many different strategies: a) invention of processes that have no necessary of the directing group; b) decreased use of additives or replacement of waste producing additives with "greener" alternatives; c) recovery and reuse of the catalyst, often by moving from homogeneous to heterogeneous conditions; d) replacing expensive and polluting transition-metal-catalyst with more environmentally-friendly metal-catalyst; e) reduce the use of solvent and/or change to use of common reaction solvent with a more sustainable approach. Due to the awareness of environmental concerns, several chemists have been paying much attention to the development of sustainable strategies around the globe.[4]

1. 4. Hypervalent Iodine compounds

The Iodine(I) is commonly considered to belong to the nonmetal category. Iodine atoms are large in size due to which the bonding in Iodine compounds varies from light main-group elements, and it can form more one bond, which is named as a hypervalent bond. Compounds of Iodine in higher oxidation states are termed as hypervalent iodine compounds.[5] Among them, organoiodine reagents particularly organoiodine(III) reagents have emerged as versatile and environmentally benign reagents in organic synthesis. Structure and reactivity of organoiodine reagents are generally similar to that of the transition-metal catalysts. Notably, the reactions of organoiodine reagents are usually accounted by ligand exchange, oxidative addition, reductive elimination and ligand coupling. One of the best example is umpolung reactions which allow transformations by reversing the inherent polarity of one reactant and group transfer reactions have evolved as an efficient tool for organic chemists to realize difficult changes uncommonly. In general, hypervalent Iodine reagents are used in several chemical transformations such as catalysis, promoter, oxidant, atom insertion, and group transfer reagent. Owing to the significance of hypervalent Iodine reagents, many researchers explore the application of hypervalent iodine reagents (figure 4).[6]

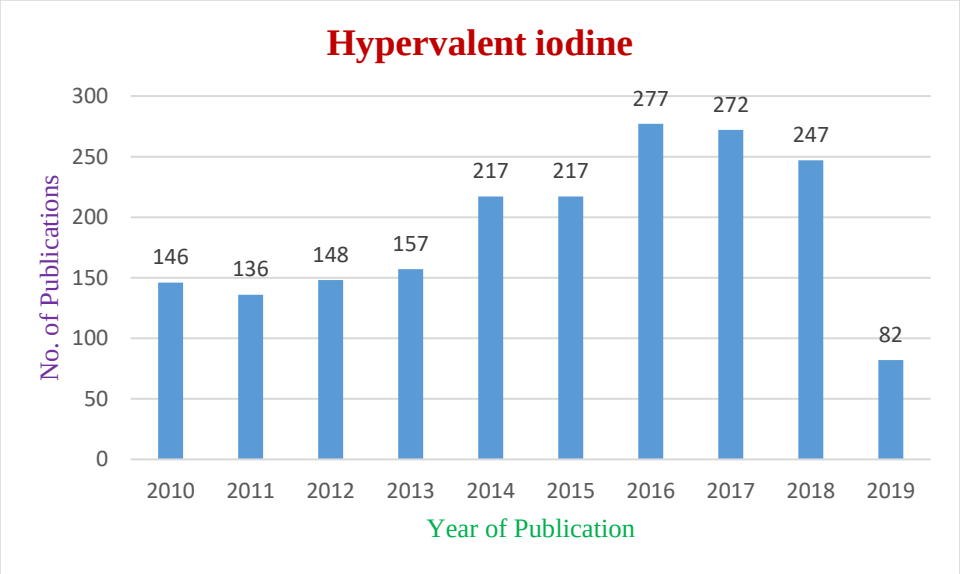


Figure 4: Recent publications in hypervalent iodine

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CHAPTER 2

Iron-Promoted C3-H Nitration of 2*H*-Indazole: Direct access to 3-Nitro-2*H*-Indazoles

2. 1. INTRODUCTION

N-Containing heterocycles constitute a significant part of natural products and their wide use in the field of medicinal chemistry is obvious by the fact that most of these are bioactive and have significant applications as drug molecules.[1] Among nitrogen-containing heterocycles, indazoles have drawn special attention in various fields like academia and the pharmaceutical industry.[2] Indazole heterocycle is normally referred to by its trivial name as 1*H*-indazole (CAS registry number 271-244-3), its systematic IUPAC name benzo[*c*]pyrazole is not used in the *Ring Index* or *Chemical* Abstract and alternative names for indazole such as 1,2-benzodiazole are not in use. Indazoles are known to exist in 3 isomeric forms (Figure 1).

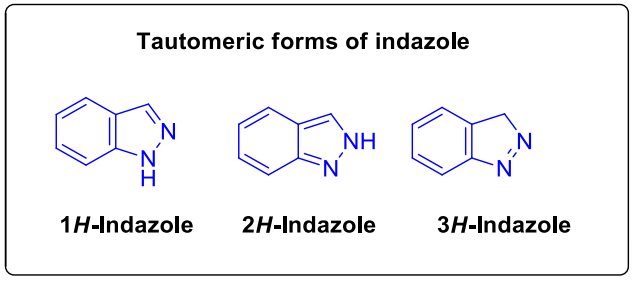


Figure 1

Natural products bearing an indazole structure are rare in nature[3,] and at present only two examples are known: nigellicine[4a] and nigellidine.[4b] However, many synthetic indazoles are known and gaining a lot of importance in the field of medicinal and organic chemistry as they exhibit a broad spectrum of pharmacological and biological activities.[2] 2*H*-Indazoles are widely used in pharma sector than 1*H*-indazoles due to their potent bioactivities like anti-tumour,[5] anti-microbial,[6] anti-inflammatory,[7] HIV protease inhibition,[8] anti-depressant,[9] anti-platelet[10] *etc*. Besides, indazoles are known to be efficient bioisosteres of indoles and benzimidazoles in pharmaceutical chemistry.[11] Bioactive compounds containing 2*H*-indazoles

have been found to have potential activity towards the imidazoline I_2-receptor[12] and 5-HT1A receptors.[13] Some examples of biologically active molecules containing an indazole nucleus include a neuroprotective voltage-dependent sodium channel modulator, oxadiazolylindazole[11b] a selective ligand for the estrogen receptor,[14] MK-4827 used as an anticancer agent,[15] and pazopanib, a tyrosine kinase inhibitor[16] (Figure 2). Although many derivatives of indazole show biological activity, no special toxicity has been reported and no special handling precautions have been recommended. The biodegradability of indazole is included in an ecological survey of heterocyclic compounds.[17]

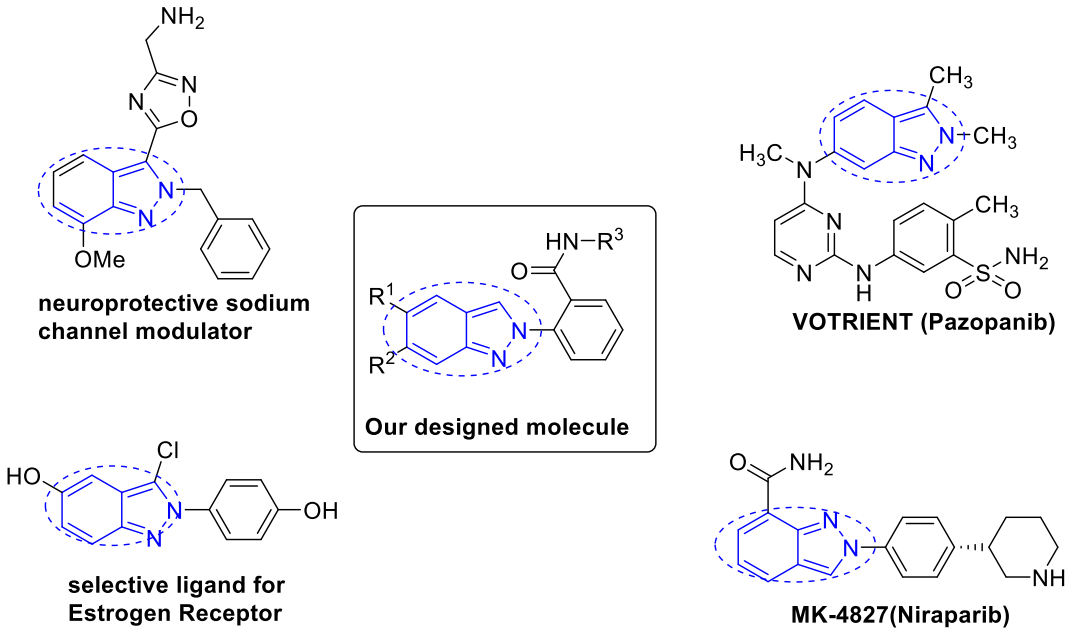


Figure 2. Biologically active molecules have 2*H*-indazole scaffold.

Hence, considering the potent bioactivities of compounds possessing a 2*H*-indazole core, several groups have paid much attention to the development of newer and economic methods for the selective synthesis of 2*H*-indazoles.[18] Despite the importance of indazoles in the pharmaceutical sector, only a limited number of approaches for the regioselective synthesis of *N*-substituted indazoles are available. However, the first report for the synthesis of 2*H*-indazole was in 1880.[19] Indeed, publications in the early years of the 20th century, and many recent publications have described improvements in the methods for synthesis of indazoles. Even though few promising strategies have been established for the selective synthesis of 2*H*-indazoles, most of the synthetic reports favoured the formation of a thermodynamically stable compound, *i.e.* 1*H*-indazole or a mixture of 1*H*- and 2*H*-indazoles with low regioselectivities.[20]

2.2. BACKGROUND

2.2.1. C-H functionalization methods for 2*H*-indazoles

Functionalization of heteroarenes, especially indazoles *via* C-H Functionalization is a powerful alternative approach to the cross-coupling reactions resulting in privileged structural motifs which are of great relevance in further modifications into diverse bioactive molecular scaffolds of importance in agrochemicals and pharmaceuticals. There is a great contest for the development of C3-functionalization of pyrazoles and indazoles due to their reactivity (Figure 3).[21]

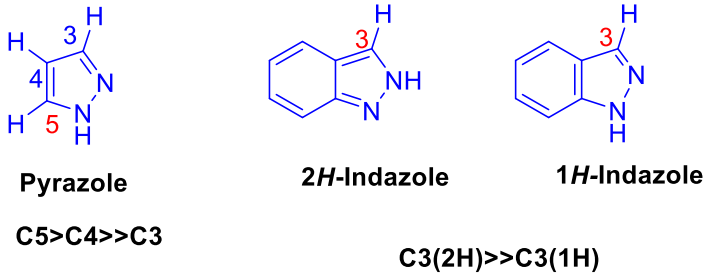
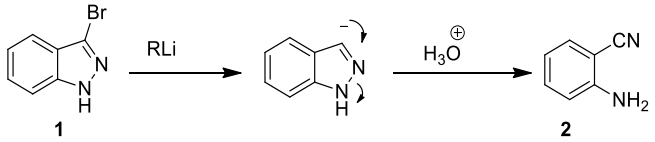


Figure 3

In recent years, transition metal-catalyzed C-H functionalization of heteroarene has gained considerable attention. These reactions can potentially provide concise routes for constructing bi(hetero)aryls as well as late-stage diversification to bioactive heterocyclic scaffolds. As a result, extensive efforts have been directed towards the development of practical and efficient catalytic systems for the direct arylation of indazole and pyrazole (Figure 3).[22]

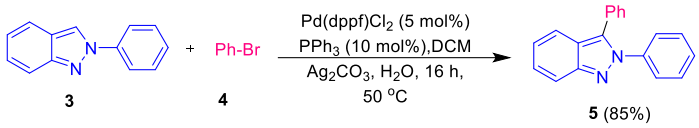
Though lithiation or magnesiation at the C-3 position of indazole has been reported, it involves haloindazoles and drastic conditions. Moreover, these reactions are demanding to owe to the facile fragmentation of these heterocycles leading to aminonitriles (Scheme 1).[23]



Scheme 1

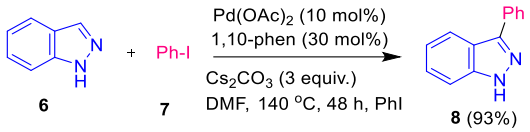
Furthermore, by traditional cross-coupling, zincated indazoles have been employed in transition metal-catalyzed reaction to provide C3-functionalized indazoles.[24] Very recently, there have been reports on C3-functionalization of 2*H*-indazoles.

Direct arylation: Greaney *et al.* have developed an efficient and eco-friendly method for direct arylation of 2*H*-indazole **3** at C3-position (Scheme 2).[25]



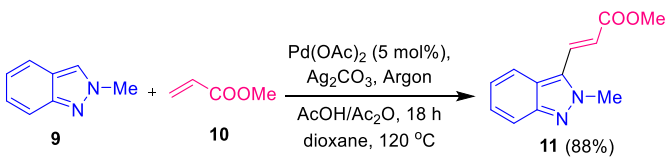
Scheme 2

Later, in 2013 Jin-Quan Yu and co-workers[26] reported a practical Pd-catalyzed direct C-3 arylation of indazole **3** and pyrazole **6** with PhI **7** or PhBr **7** without using Ag additives as halide scavengers. The use of toluene, chlorobenzene, trifluoromethylbenzene and mesitylene as the solvent was found to be crucial for selectivity and reactivity. The importance of this method compared to other methods is the achievement of arylation for 1*H*-indazoles **6** along with 2*H*-indazole and further application for the first total synthesis of natural product nigellidine hydrobromide (Scheme 3).[26]



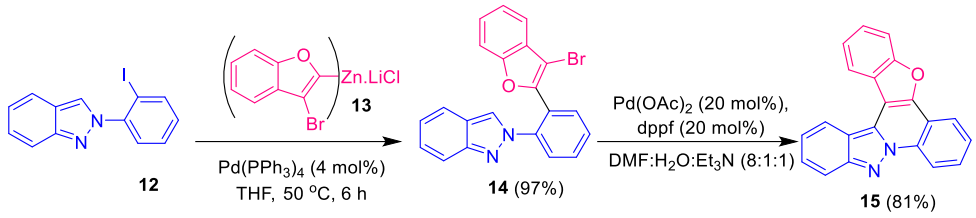
Scheme 3

Heck strategy: Very recently, Saïd El Kazzouli and co-workers have disclosed a new oxidative palladium-catalyzed alkenylation of 2*H*-indazole **9** derivatives with various olefins **10**. The use of $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant promoted the selective C3-monoalkenylation of 2*H*-indazoles affording the desired products **11** in good yields. (Scheme 4).[27]



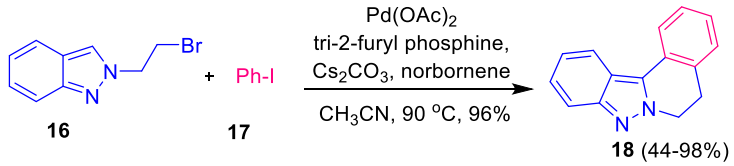
Scheme 4

Cross-coupling reactions: Knochel *et al.* have synthesized polycyclic heteroaromatics **15** bearing an indazole unit using domino cross-coupling reaction and C-H functionalization of 2*H*-indazole (Scheme 5). [28]



Scheme 5

Annulation reaction: Mark Lautens *et al*. have developed annulation process involving a one-pot norbornene-mediated palladium-catalyzed sequence whereby an alkyl-aryl bond and aryl-heteroaryl bond are successively formed through two C-H bond activations (Scheme 6).[29] They also presented subsequent functionalizations of the resulting polycyclic compounds **18** through cross-coupling reactions.

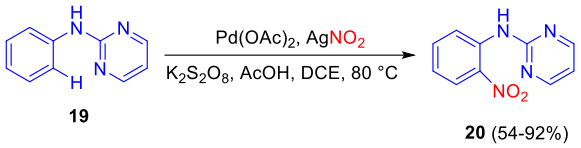


Scheme 6

Regardless of these developments, there has been rare precedence of direct C-H functionalization is leading to annulated indazoles which are highly commendable and challenging. By aiming for this, we envisioned to develop a new and innovative method for the synthesis of 2*H*-indazoles and their further functionalization leading to annulated indazoles.

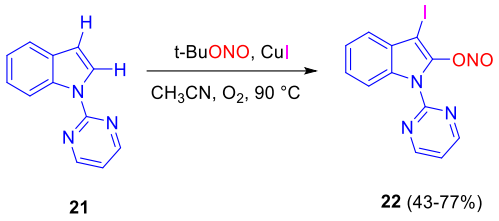
2.2.2. Radical C-H Nitration Methods

Manmohan Kapur *et al*. developed an efficient method for the synthesis of *ortho* nitro-substituted aniline **19** via a palladium(II)-catalyzed regioselective C-H nitration of anilines **20**. They have used easily removable pyrimidine as a directing group (Scheme 7).[30]



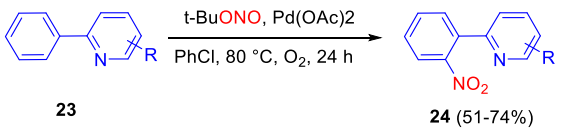
Scheme 7

Later in 2018, Chao Jiang *et al*. have reported a copper-mediated oxidative strategy for the synthesis of nitro functionalized indole **22** through dual C-H functionalization indole **21**. The domino process proceeds smoothly under aerobic conditions with high regioselectivity and broad substrate scope (Scheme 8).[31]



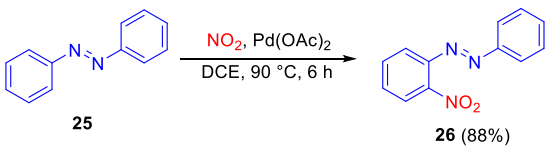
Scheme 8

Ning Jiao and co-workers have developed a palladium-catalyzed synthesis of nitroarenes **24** *via* direct C-H nitration of arenes **23** with readily available *tert*-butyl nitrite (TBN). In this method, the author demonstrated with different directing groups such as pyridine, pyrimidine, pyrazole, pyridol, pyridyl ketone, oxime, and azo groups can be employed in these novel transformations (Scheme 9).[32]



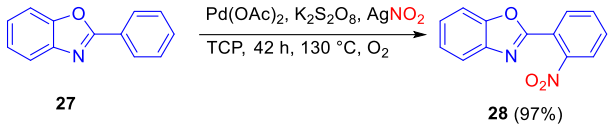
Scheme 9

Peipei Sun *et al*. developed a palladium-catalyzed the synthesis of ortho nitro-substituted azo benzene **26** direct *ortho*-nitration of azoarenes **25** using NO_2 gas. In this method, NO_2 has been used as both nitro source and oxidant for the first time (Scheme 10).[33]



Scheme 10

Yang-JieWu *et al*. developed a palladium-catalyzed chelation-assisted synthesis of nitro arenes **28** through *ortho* C-H nitration of 2-arylbenzoxazoles **27**. This method exhibits high regioselectivity and the reaction could tolerate several functional groups like F, Cl, Br, CH_3, CH_3O affords the desired nitration product (Scheme 11).[34]

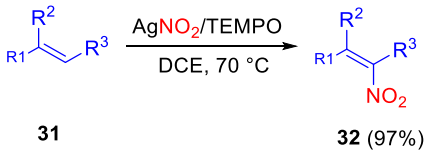


Scheme 11

Malapaka Chandrasekharam and co-workers reported an unprecedented copper-catalyzed synthesis of nitro anilines **30** *via* in situ formations of azidation–oxidation of anilides **29**. This nitration method achieved by employing $TMSN_3$ and TBHP without the exclusion of air or moisture (Scheme 12).[35]

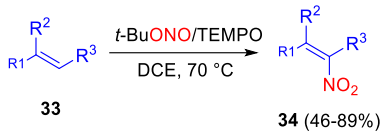
Scheme 12

Debabrata Maiti *et al*. developed the regio- and stereoselective nitration olefins **31** for the synthesis of nitroolefins **32**. Here, it was found that the combination of $AgNO_2$ and TEMPO could promote the nitration reaction (Scheme 13).[36]



Scheme 13

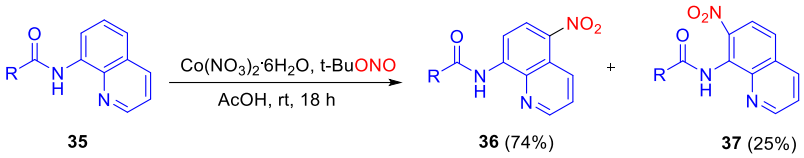
Later in 2013, the same author Debabrata Maiti *et al*. demonstrated the stereoselective nitration of olefins **33** for the synthesis of nitroolefins **34** under metal-free conditions. In this method, *tert*-butyl nitrite (TBN) used as a metal-free nitro source, and the TEMPO plays oxidant role combine with aerobic oxygen (Scheme 14).[37]



Scheme 14

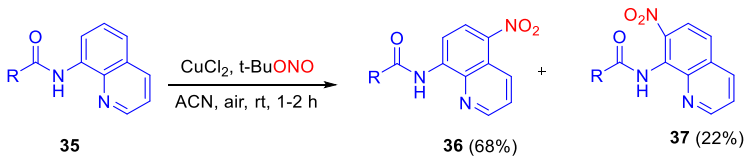
2.2.2. Chelation assisted radical C-H Nitration Methods

Xavi Ribas *et al*. demonstrated the first example of cobalt-catalysed distant C-H nitration of 8-Aminoquinolines **35** for the synthesis of nitro functionalized quinolones **36** & **37**. This method proceeds through a single electron transfer mechanism and uses inexpensive *tert*-butyl nitrite (TBN) as nitro source (Scheme 15).[38]



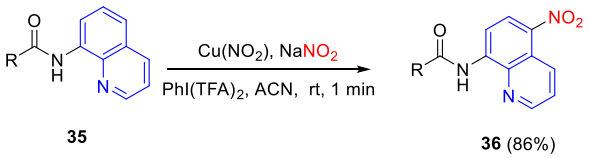
Scheme 15

Later in 2016, Dipankar Koley *et al*. developed a mild, rapid and efficient method for the synthesis of nitro-substituted quinolones **36** & **37** *via* copper-catalysed C-H nitration of 8-aminoquinolines **35** using sodium nitrite as the nitro source. This reaction could complete at room temperature (Scheme 16).[39]



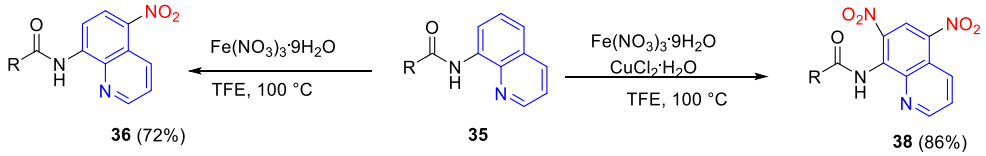
Scheme 16

In 2016, Pengfei Zhang and co-workers reported an efficient synthesis of selective 5-nitro quinolone **36** through copper-catalysed remote C-H nitration of 8- amidoquinolines **35** using *tert*-butyl nitrite as a nitrating agent. This method is applicable for arene, heteroarene, aliphatic carboxamide derivatives (Scheme 17).[40]



Scheme 17

Xuesen Fan *et al*. developed a copper catalyzed achievement of Mono- and Bisnitration of 8-amino quinoline amides **35** via controlled by the chelating group. Here, $Fe(NO_3)_3{\cdot}9H_2O$ plays a dual role as both chelating promoter and nitration reagent. Moreover, the author performed the reaction with copper to obtain bisnitration of quinolones (Scheme 18).[41]



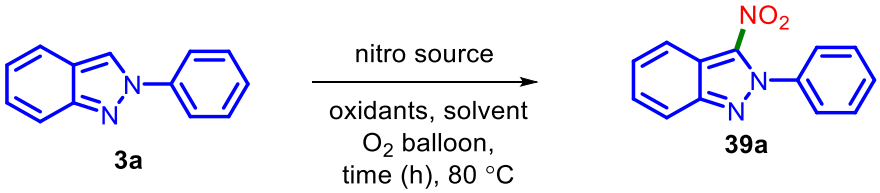
Scheme 18

Accordingly, based on the previous literature reports, herein, we are delighted to disclose for the first time, a regioselective radical C-H functionalization of 2*H*-indazole through $Fe(NO_3)_3.9H_2O$ promoted C3-H nitration.

2.3. RESULTS AND DISCUSSION

Encouraged by our previous report in radical C-H nitration chemistry,[36, 37, 41] we envisioned the iron-promoted C3-H nitration on 2*H*-indazole. Herein, iron nitrate plays the dual role of promoter and nitro source. To achieve our goal, we initiated our preliminary experiments with 2*H*-indazole (**3a**) as a model substrate and $Fe(NO_3)_3.9H_2O$ as a nitro source with MeCN as a solvent at 80 ºC under molecular oxygen atmosphere (Table 1, entry 1). As expected, C3-nitro functionalized product (**39a**) was obtained albeit in very poor yield. In order to improve the yield, we screened various nitro-sources (Table 1, entry 2-8). However, we did not observe any satisfactory yields. Next, we turned to the use of oxidant (2,2,6,6-tetramethylpiperidin-1-yl)oxidant (TEMPO) in the reaction. Surprisingly, we found the expected product with very good yield in the presence of TEMPO (Table 1, entry 9).

Table 1 Optimization of reaction conditions for the synthesis of **39a**[a]

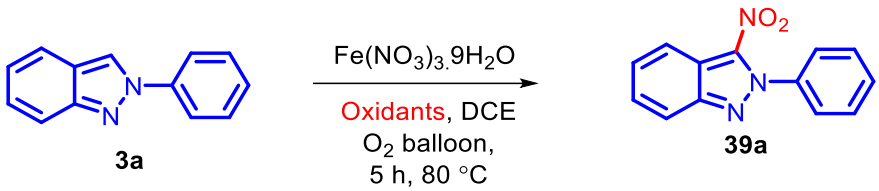


entry	nitro source	oxidants	solvent	time (h)	yield (%)[b]
1	$Fe(NO_3)_3.9H_2O$	-	MeCN	5	15
2	$Ni(NO_3)_2.6H_2O$	-	MeCN	5	trace
3	CAN	-	MeCN	5	trace
4	^tBuONO	-	MeCN	5	n.d.[c]
5	$AgNO_3$	-	MeCN	5	n.d.[c]
6	$AgNO_2$	-	MeCN	5	n.d.[c]
7	$NaNO_2$	-	MeCN	5	n.d.[c]
8	$Cu(NO_3)_2 \cdot 3H_2O$	-	MeCN	5	10
9	$Fe(NO_3)_3.9H_2O$	TEMPO	MeCN	5	65
10	**$Fe(NO_3)_3.9H_2O$**	**TEMPO**	**DCE**	**5**	**85**
11	$Fe(NO_3)_3.9H_2O$	TEMPO	$CHCl_3$	5	55
12	$Fe(NO_3)_3.9H_2O$	TEMPO	DMF	12	nr[d]

13	$Fe(NO_3)_3.9H_2O$	TEMPO	DMSO	12	n.d.[c]
14	$Fe(NO_3)_3.9H_2O$	TEMPO	dioxane	12	n.d.[c]
15	$Fe(NO_3)_3.9H_2O$	TEMPO	toluene	12	n.d.[c]
16	$Fe(NO_3)_3.9H_2O$	TEMPO	H_2O	12	n.d.[c]
17	$Fe(NO_3)_3.9H_2O$	TEMPO	EtOH	12	n.d.[c]
18	$Fe(NO_3)_3.9H_2O$	TEMPO	MeOH	12	n.d.[c]
19	$Fe(NO_3)_3.9H_2O$	TEMPO	DCE	5	60[d]

[a]Reaction conditions: 1a (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 ºC, 5 – 12 h. [b]Isolated yield of chromatographically pure products. [c]Starting materials recovered. [d]Reaction carried out in open air.

Table 2. Optimization of oxidants[a]

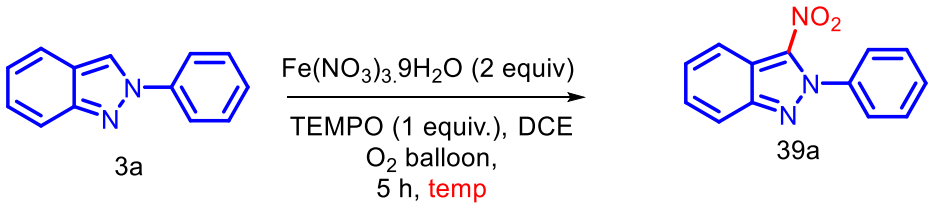


entry	oxidants (equiv)	yield (%)[b]
1	TBHP (1)	n.d.
2	DTP (1)	n.d.
3	DDQ (1)	10
4	TEMPO (0.5)	40
5	TEMPO (1)	85
6	TEMPO (1.5)	85
7	TEMPO (2)	85

[a]Reaction conditions: 1a (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 ºC, 5 – 12 h. [b]Isolated yield of chromatographically pure products.

Further, our attempts of replacing the TEMPO with other oxidants went in vain (Table 2). Afterwards, we also screened the reaction with different solvents (Table 1, entry 10-18) and variation of temperature (Table 3). Interestingly, we observed the formation of a product with very good yield in the case of DCE as a solvent (Table 1, entry 10). Notably, when we performed the reaction in the open air, we observed the formation of the expected product with moderate yield (Table 1, entry 19). Subsequently, with encouraging this results, we screened the reaction with different equivalents of nitro-sources and oxidants (Table 2 & 4). From these experiments, we concluded that two equiv of nitro source and one equiv of oxidant is necessary for complete conversion of the starting materials.

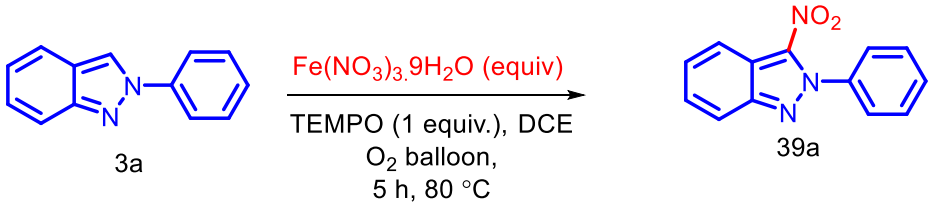
Table 3. Optimization of temperature[a]



entry	temp (°C)	yield (%)[b]
1	40	trace
2	60	62
3	80	85
4	100	80

[a]Reaction conditions: 1a (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 °C, 5 – 12 h. [b]Isolated yield of chromatographically pure products.

Table 4. Optimization of nitro source



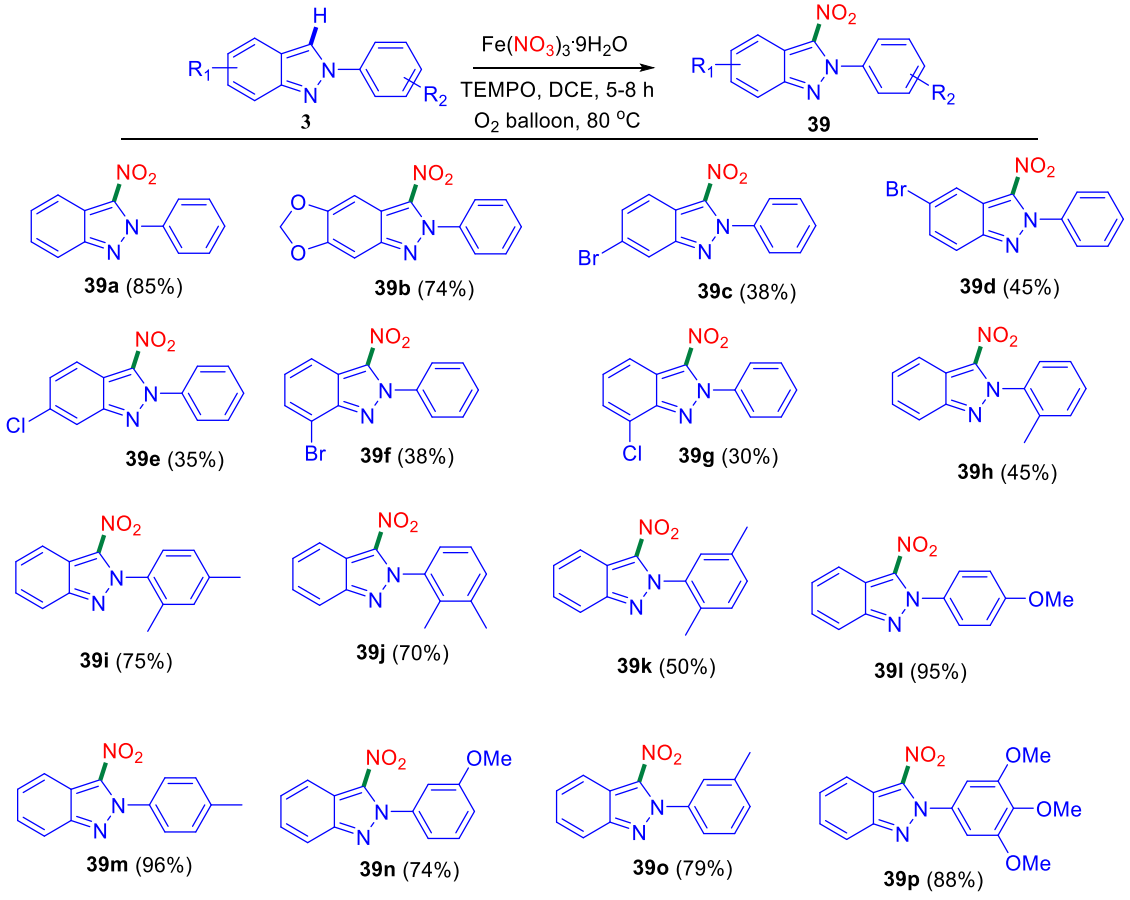
Entry	Nitro source (equiv)	Yield (%)[b]
1	$Fe(NO_3)_3.9H_2O$ (0.5)	15

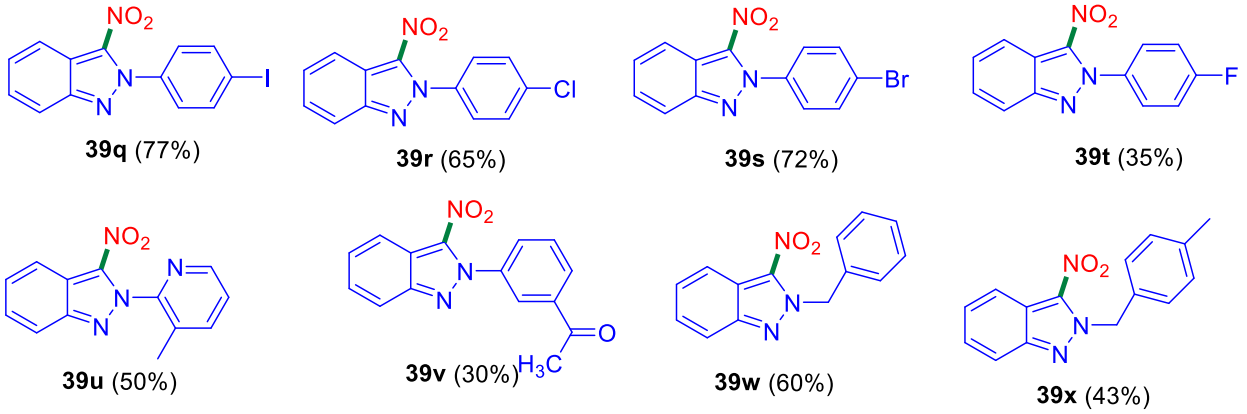
2	$Fe(NO_3)_3.9\ H_2O$ (1)	33
3	$Fe(NO_3)_3.9H_2O$ (2)	85
4	$Fe(NO_3)_3.9H_2O$ (3)	85

[a]Reaction conditions: **1a** (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 °C, 5 – 12 h. [b]Isolated yield of chromatographically pure products.

With the optimised conditions in hand, we next examined the scope of this methodology with different substituted 2*H*-indazole systems (Table 5). The methylenedioxy substitution gave good yield when compared to halo substitution at C5, C6 and C7 position of 2*H*-indazole **39c-g**. Next, we examined the scope of substrates with various substitutions (halogen, alkyl, alkoxy) on amine partner of 2*H*-indazoles resulting in the desired products with moderate to good yield. Having benzyl group in place of aryl on C2 position of 2*H*-indazole **39w** & **x** did not show any improvement in the yield.

Table 5: Substrates Scope for the C3-Nitration of 2*H*-Indazole [a,b]

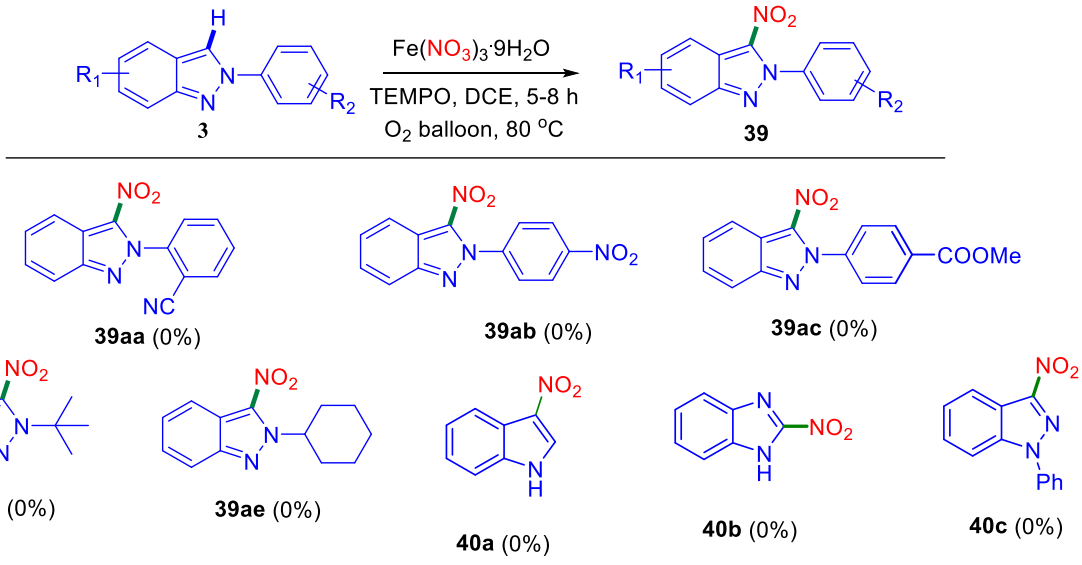




[a]Conditions: **1a** (1 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (2 mmol), TEMPO (1 mmol), DCE (2 mL), oxygen balloon, 80 °C, 5–8 h. [b]Isolated yield of chromatographically pure products.

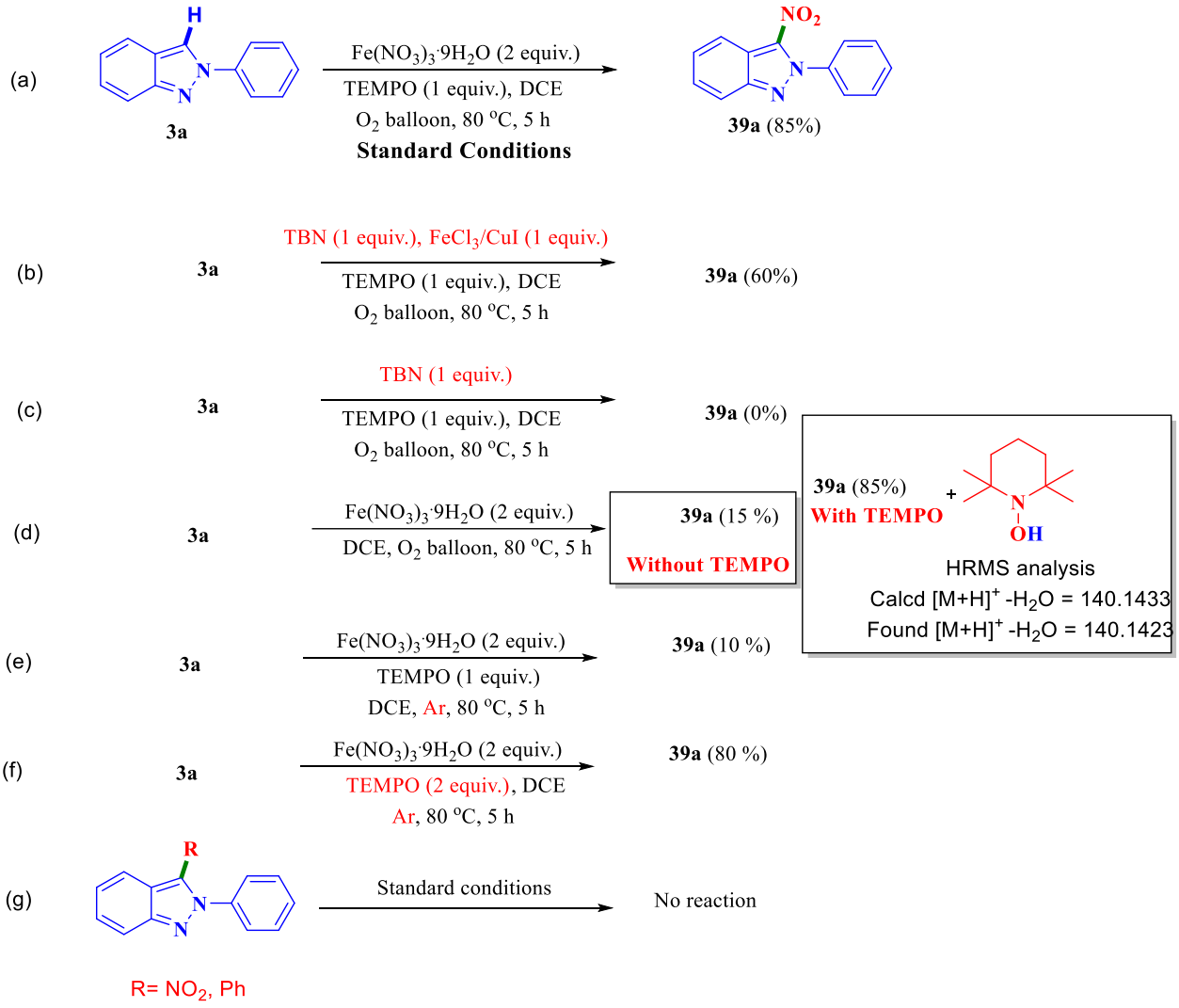
Unfortunately, amine partner bearing electron withdrawing groups (Table 6) such as nitro, nitrile and ester groups did not afford the desired products **39aa-ac**. Also, 2*H*-indazoles with alkyl substitution at C2 position **39ad** & **ae** could not provide the nitration product. Furthermore, our attempts to carry out nitration on other heteroarenes (indole, imidazole, 1*H*-indazole) went in vain.

Table 6: Substrates Scope for the C3-Nitration of 2*H*-Indazole [a,b]



[a]Conditions: 1a (1 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (2 mmol), TEMPO (1 mmol), DCE (2 mL), oxygen balloon, 80 °C, 5–8 h. [b]Isolated yield of chromatographically pure products.

Based on the experiments performed for the Optimization of reaction conditions shown in Table 1, we observed that other nitro-sources failed to give any nitro product. Hence in order to prove the role of $Fe(NO_3)_3.9H_2O$, we planned to examine the reaction with the metal-free nitro source. However, in the presence of Fe/Cu as a promotor which resulted in good yield (Scheme 19b). Thus indicating the dual role of $Fe(NO_3)_3.9H_2O$. Furthermore, the reaction in the absence of any promotor with metal-free nitrate(TBN) did not afford the desired product (Scheme 19c). Hence, the promotor is necessary for the nitration of indazole at the C3 position.

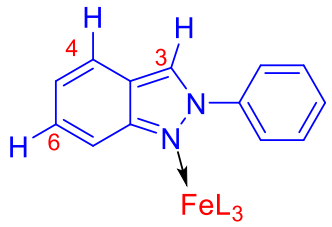


Scheme 19: Control Experiments and Mechanistic studies

To prove the radical pathway, we performed HR-MS analysis of crude reaction mixture which showed 2,2,6,6-tetramethylpiperidin-1-ol. To know the role of oxygen, we have conducted

a couple of control experiments. We obtained the desired product in 10% and 15% yield when the reaction is carried out in the absence of O_2 and TEMPO respectively (Scheme 19e & d). However, these experiments were not conclusive. When we performed the reaction in the presence of an excess amount of TEMPO (2 equiv) under an argon atmosphere, which resulted in 80% yield of the desired product (Scheme 19f). This indicates that the presence of oxygen reduces the amount of TEMPO significantly (optimised condition *i.e.* one equiv of TEMPO under oxygen atmosphere). From these experiments, we can conclude that 'O_2' might be involved, either in the recycle of TEMPO (TEMPOH to TEMPO) or the oxidation of intermediate B to intermediate C. Finally, to confirm the C3-functionalization of 2*H*-indazole, we performed the reaction with C3 substituted 2*H*-indazole under standard conditions (Scheme 19g), which did not afford any nitro-substituted 2*H*-indazole. The X-ray crystallography analysis of compound **39v** further supports the nitration at the C3 position.

Table 7: Charge Distribution and pz Orbital Occupancy of the C3, C4 and C6 Atoms in the Structure A



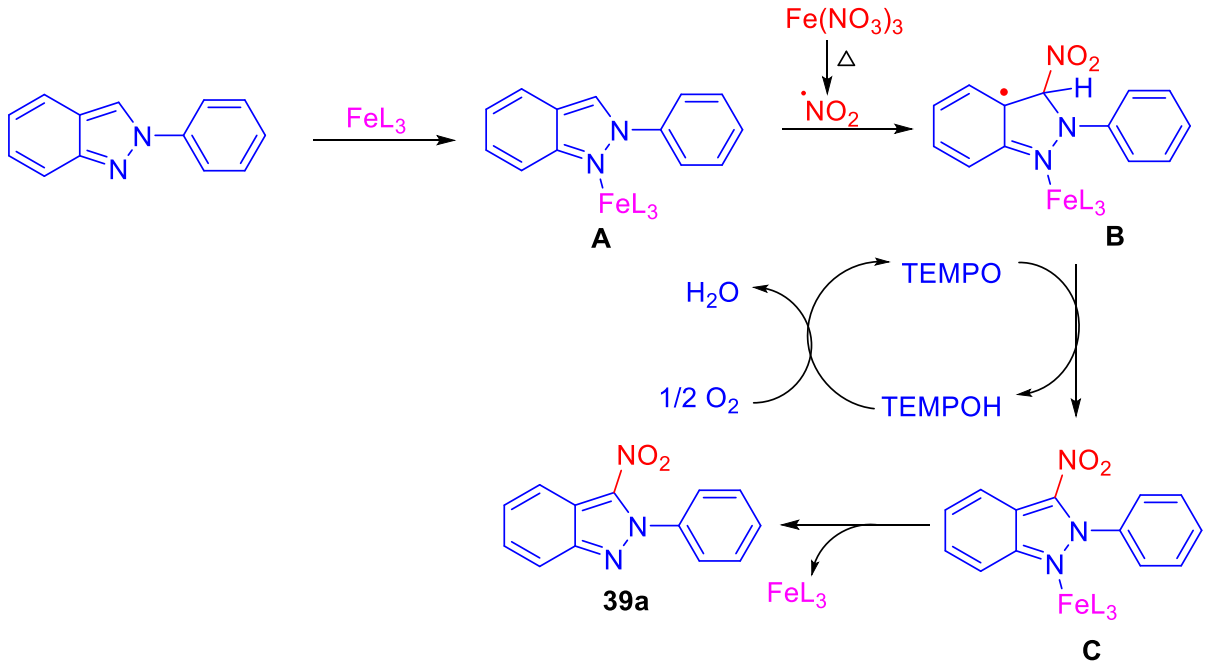
A

Atom	Hirshfeld	p_z orbital occupancy
C3	-0.025	0.997
C4	-0.037	0.990
C6	-0.027	0.980

To further support our finding, we carried out quantum chemical calculations[41] to investigate the charge distribution on indazole. The theoretical data of atoms (C3, C4, C6) on the Fe coordinated indazole intermediate **A** is shown in Table 2. The charges of the C3, C4 and C6 as calculated were found to be -0.025, -0.027 and -0.037 respectively. The charges include a contribution from all valance electron and based on the literature precedence[42] the p_z orbital

occupancy would be the more effective way to assess the reactivity of a specific atom. Among different atoms, the largest p_z orbital occupancy at C3 carbon atom implicates that C3 may be the most likely electrophilic reactive site. Thus, the theoretical calculations support the only C3-H nitration on 2*H*-indazole.

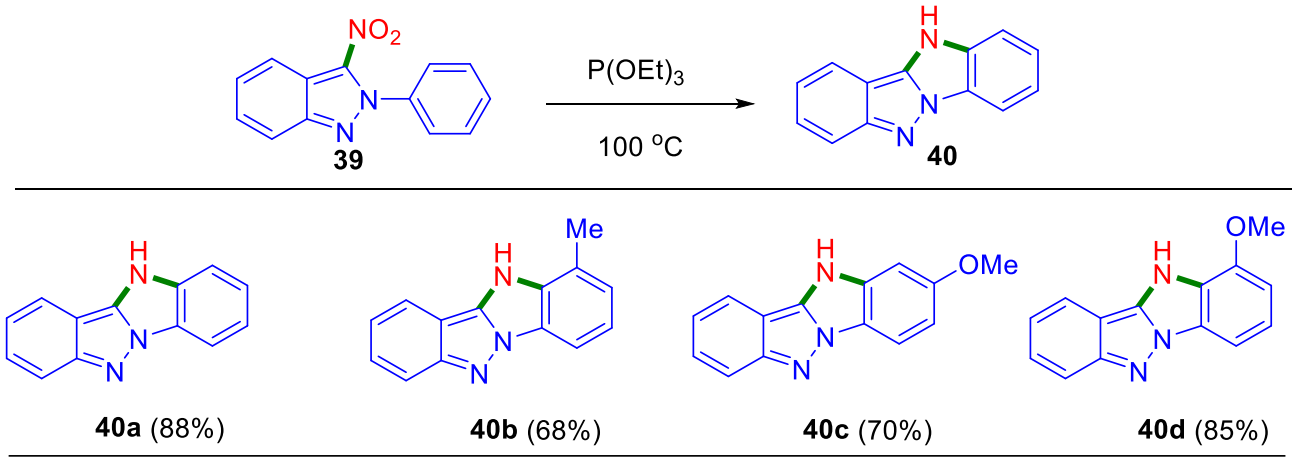
Based on the control experiments, literature reports[41,42] and quantum chemical calculations, we proposed a plausible reaction mechanism for the synthesis of 3-nitro-2-phenyl-2*H*-indazole as depicted in Scheme 20. Initially, coordination of 2-phenyl-2*H*-indazole with $Fe(NO_3)_3.9H_2O$ led to formation of intermediate **A**. Meanwhile, the nitro radical ($NO_2^{\cdot}$) generated from $Fe(NO_3)_3.9H_2O$ under thermal conditions[19] would react at the electrophilic reactive site of the intermediate **A** in order to generate an intermediate **B**. The combination of TEMPO/O_2 is involved in oxidation by the abstract of a hydrogen radical[20] from C3 position of intermediate **B** leading to formation of intermediate **C**, which eventually provides the desired product **39a**.



Scheme 20 Plausible Mechanism

After the synthesis of various C3-nitro 2*H*-indazoles, we successfully demonstrated the synthetic utility of nitroindazoles by the synthesis of bio-relevant benzimidazoindazole through reductive cyclization.[43]

Table 8: Application of Nitroindazole: Synthesis of Benzimidazoindazole [a,b]



40a (88%) **40b** (68%) **40c** (70%) **40d** (85%)

[a]Reaction conditions: **2a** (0.1 mmol), $P(OEt)_3$ (1 mL), 100 °C, 1 h. [b]Isolated yield of chromatographically pure products.

2.4. CONCLUSIONS

We have successfully developed a novel protocol for the radical C-H nitration of 2*H*-indazoles. The method offers chelation-free C-H nitration on 2*H*-indazole by using the inexpensive and nontoxic $Fe(NO_3)_3.9H_2O$ under mild conditions. Moreover, the mechanistic pathway was inferred based on control experiments and quantum chemical calculations. The synthetic utility of nitroindazoles was demonstrated by the synthesis of the bio-relevant benzimidazoindazoles.

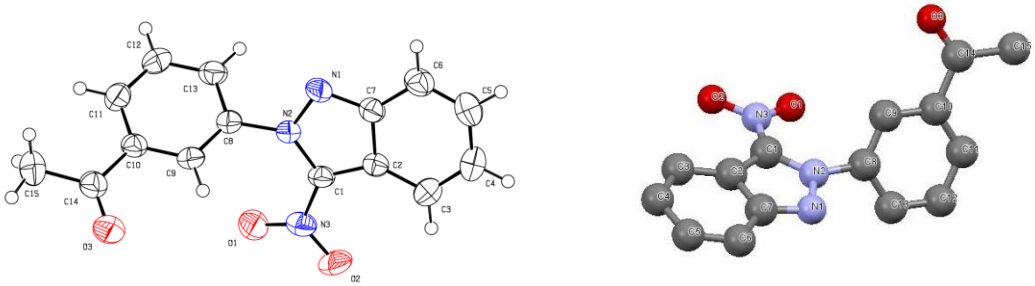
2.5. EXPERIMENTAL SECTION

General Considerations

IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometers at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of the triplet)]. In the ^{1}H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. *o*-Azidobenzaldehydes were prepared by using literature known procedures. All dry solvents were used, toluene was dried over sodium metal and DMSO, CH_3CN and DMF were dried over calcium hydride

Single crystal X-ray data

Figure 1: X-ray crystal structure data for 1-(3-(3-nitro-2H-indazol-2-yl)phenyl)ethanone (39v) CCDC: 1825398



Identification code	exp_7218
Empirical formula	$C_{15}H_{11}N_3O_3$
Formula weight	281.27
Temperature/K	293(2)
Crystal system	Triclinic
Space group	P-1
a/Å	7.8053(18)
b/Å	8.2606(17)
c/Å	11.869(2)
α/°	91.064(17)
β/°	108.89(2)

γ/°	113.92(2)
Volume/Å^3	651.9(3)
Z	2
ρ_{calc}g/cm^3	1.4329
μ/mm^{-1}	0.103
F(000)	292.1
Crystal size/mm^3	0.06 × 0.04 × 0.02
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.9 to 58.02
Index ranges	-10 ≤ h ≤ 9, -10 ≤ k ≤ 11, -16 ≤ l ≤ 15
Reflections collected	5672
Independent reflections	2992 [R_{int} = 0.0387, R_{sigma} = 0.0936]
Data/restraints/parameters	2992/0/190
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0643, wR_2 = 0.1059
Final R indexes [all data]	R_1 = 0.1431, wR_2 = 0.1401

Mass data for Intermediate

Figure 2: The HR-MS data for the intermediate 2,2,6,6-tetramethylpiperidin-1-ol

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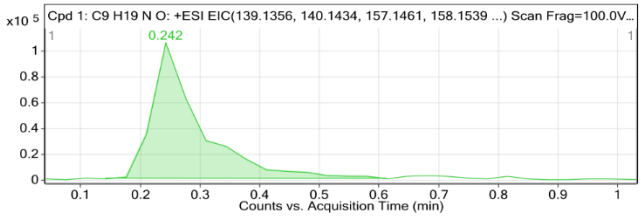
Dept Of Chemistry
HRMS Report

Data File	AVM-472-00.d	**Sample Name**	AVM-472
Position	P2-A7	**Acq Method**	HRMS_Dual ESI_POS_SD_Agilent.m
Acquired Time	29-Feb-16 2:39:22 PM	**DA Method**	SD_IITH.m
Sample Group		**Info.**	
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.00 (B5042.2)		

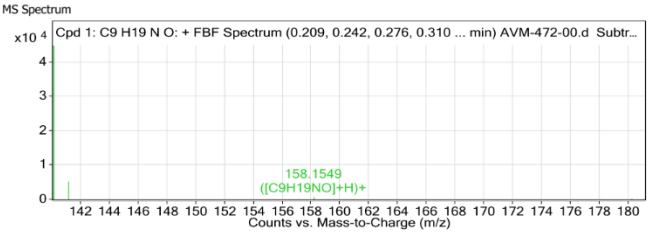
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C9 H19 N O	0.242	157.1458	44827	C9 H19 N O	157.1467	-5.81	C9 H19 N O	C9 H19 N O

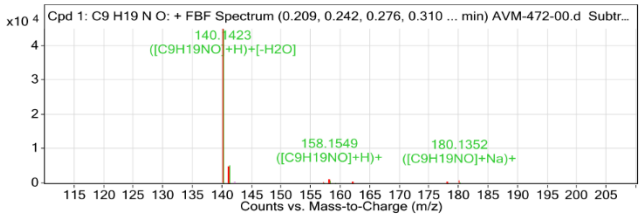
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C9 H19 N O	140.1423	0.242	Find By Formula	157.1458



MS Spectrum



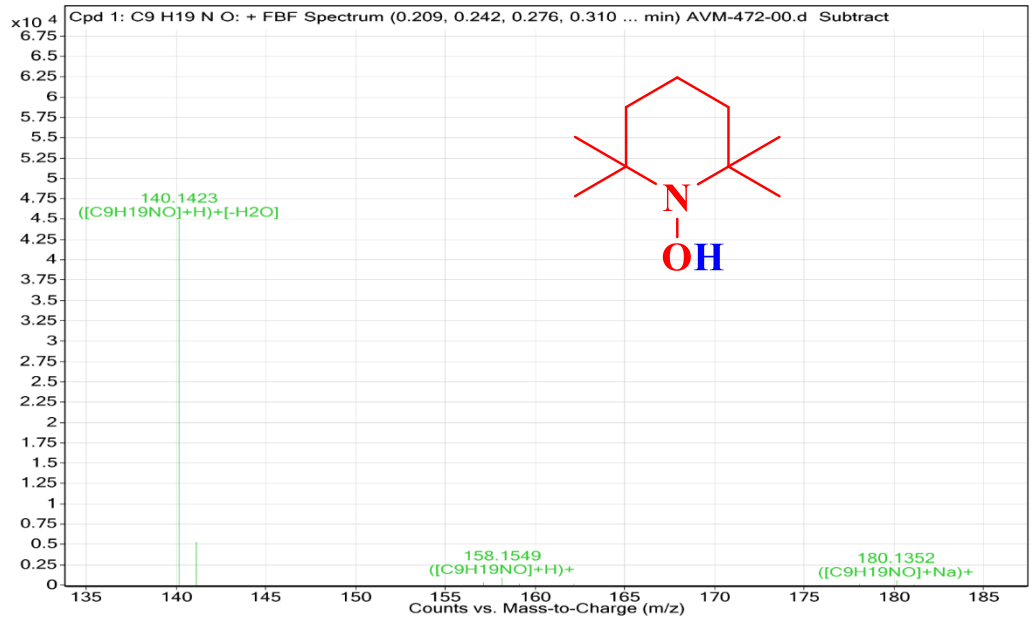
MS Zoomed Spectrum



MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
140.1423	1	44826.87	C9H19NO	(M+H)+[-H2O]
141.146	1	5354.23	C9H19NO	(M+H)+[-H2O]
157.1497	1	267.72	C9H19NO	M+

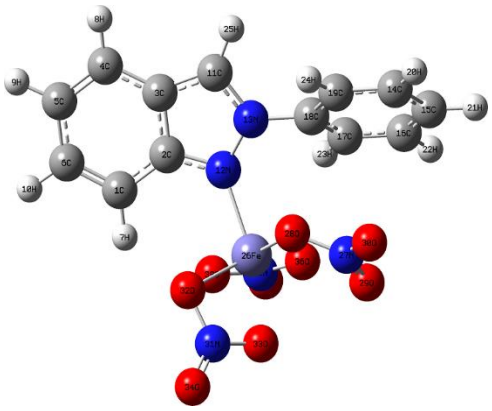
Sample Name	AVM-472	**Position**	P2-A7	**Instrument Name**	HRMS_Q-ToF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	AVM-472-00.d	**ACQ Method**	HRMS_Dual ESI_POS_SD	**Comment**		**Acquired Time**	29-Feb-16 2:39:22 PM



Quantum Chemical Calculations

The quantum chemical calculations were carried out using Gaussian 09 program[6]. The structure was optimized at the M06L[7] meta–GGA level of theory with pseudopotential SDD[8] and 6-31G(d,p) basis set for Fe and other atoms, respectively. The optimized structure has no imaginary frequency. The Hirshfeld[9] charges of atoms were computed at the M06L/6-31G(d,p) level on the optimized structures. NBO[10] analysis for the optimized structure was performed at M06L/6-31G(d,p) level with NBO 3.1 implemented in Gaussian 09 program.

Structure of the optimized complex obtained from quantum chemical calculations



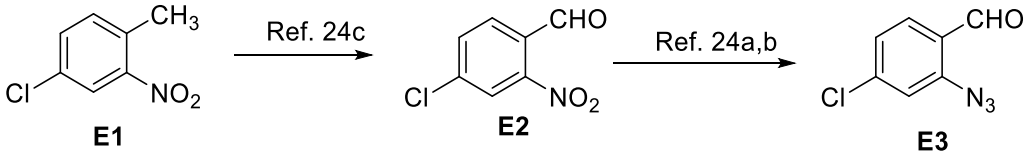
C	-3.25737059	-0.26317235	0.15537335
C	-2.12105211	-1.08645954	0.05472907
C	-2.24061046	-2.46082910	-0.30425429
C	-3.50795582	-3.03394241	-0.53477404
C	-4.61050878	-2.22066052	-0.41977990
C	-4.48042682	-0.85025907	-0.08353318
H	-3.17114055	0.78560819	0.41130060
H	-3.60290499	-4.08355760	-0.79518153
H	-5.60150845	-2.62910452	-0.59088678
H	-5.37725499	-0.24239073	-0.01160570
C	-0.92985015	-2.93884585	-0.32242889
N	-0.80879949	-0.76637995	0.24886865

N	-0.11683233	-1.91691481	-0.00483580
C	3.42711681	-2.73723174	-0.64078236
C	4.03195600	-2.20847111	0.49759050
C	3.25941205	-1.58455206	1.47336666
C	1.88007088	-1.49001345	1.32290760
C	1.29489768	-2.00798354	0.17167927
C	2.05270901	-2.63347214	-0.81508939
H	4.02944360	-3.20412671	-1.41350106
H	5.10870566	-2.27315372	0.61782539
H	3.72632282	-1.16665373	2.35949827
H	1.26633286	-1.01803317	2.08134699
H	1.57268925	-2.98315305	-1.72428217
H	-0.51865741	-3.92551742	-0.47662357
Fe	-0.07272603	1.06649261	0.03455566
N	2.41881777	0.87706622	-1.17642875
O	1.13349963	0.43596668	-1.24780993
O	2.72977842	1.55791098	-0.21092276
O	3.13050515	0.50765078	-2.08988154
N	-0.71459750	2.89309849	-1.37842420
O	-1.33476908	1.74705232	-1.30970204
O	0.28134957	2.93459279	-0.56363555
O	-1.04719097	3.78491264	-2.10458958
N	-0.29522157	1.65209272	2.37751609
O	0.81425144	1.32259318	1.79539708
O	-0.38942459	1.93178182	3.54056436
O	-1.28238024	1.64427547	1.54642546

Procedure for synthesis of azidoaldehyde and 2*H*-indazoles

All small scale dry reactions were carried out using the standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon, nitrogen and oxygen atmosphere wherever necessary. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ˚C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material). All 2-azidobenzaldehydes (**E1-E3** and **E5**) except **E4** have been synthesized by using literature known procedures.[44]

Synthesis of 2-azido-4-chlorobenzaldehyde (E4):

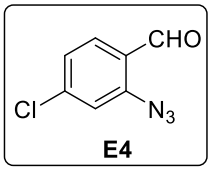


To a stirring solution of 2-nitro-4-chlorobenzaldehyde **E2** (1.0 equiv) in HMPA was added sodium azide (2.0 equiv). The reaction mixture was stirred at ambient temperature and monitored by TLC. After consumption of the starting material, the mixture was diluted with ice-cold water and extracted with diethyl ether (3 × 25 mL). The ether layer was washed with water (3 × 25 mL), brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude compound, which was further purified by column chromatography to give the final analytically pure product (82% yield).

Physical State : White solid

Yield : 80%

Mp : 84–86 ˚C



IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 2408, 2342, 1679, 1591, 841, 816.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 10.22 (s, 1H), 7.88 (d, 1H, J = 8.3 Hz), 6.89 (dd, 1H, J_a = 8.3 and J_b = 1.5 Hz), 6.81 (d, 1H, J = 1.5 Hz).

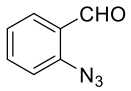
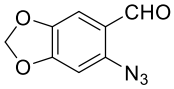
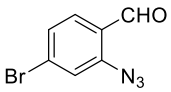
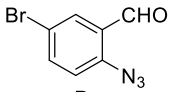
^{13}C NMR ($CDCl_3$, 100 MHz): 187.1 (s, -CHO), 147.4 (s, Ar-C), 144.8 (s, Ar-C), 130.9 (d, Ar-CH), 123.9 (s, Ar-C), 115.5 (d, Ar-CH), 109.1 (d, Ar-CH).

HR-MS (ESI+) *m/z* calculated for $[C_7H_4ClN_3O]^+ = [M]^+$: 181.0037; found: 181.0030.

Preparation of halo substituted azidoaldehyde

The following 2-azido aldehydes are known in the literature.

Table 9: Synthesis of 2-azido aldehydes.

 A	 B	 C	 D

The following 2-Azido-4-chlorobenzaldehyde (E) was synthesized using the below strategy.

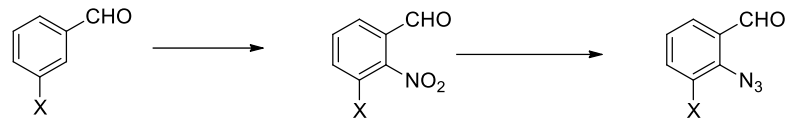
Step 1: A solution of 4-chloro-2-nitrotoluene (1.0 equiv) in DMF.DMA (3.0 equiv) was refluxed at 140°C for two days. The reaction mixture was then cooled to rt. The imine was then added dropwise to a solution of $NaIO_4$ (3.0 equiv) in DMF (13 mL) and H_2O (25 mL). The reaction mixture was then stirred at rt for 4 h. The solid formed was filtered off and washed with toluene (2 x 15 mL). The combined organic layer was washed with water (30 mL) and then with brine (10 mL). The solvent was completely removed and the resulting crude product was recrystallized from hexane to afford pure aldehyde as brown solid (90% yield).

The following 2-Azido-3-halobenzaldehyde (f &g) was synthesized using the below strategy

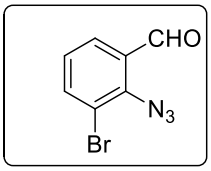
Step 1: To a mixture of H_2SO_4 (16 mL) and conc. nitric acid (2 mL) was slowly added aldehyde such that the temperature of the reaction mixture was maintained below 10 °C. After the addition was complete (40 min), the reaction mixture was stirred for an additional 30 min at 5-10 °C, and then poured onto crushed ice (100 mL). On slow warming of this mixture with stirring (30

min) a yellow precipitate formed, which was filtered and washed with water until the filtrate was no longer acidic to litmus. The precipitate was air dried to give 83 g of a yellow amorphous solid.

Step 2: To a stirring solution of 2-Nitro-3-halobenzaldehyde (1.0 equiv) in HMPA was added sodium azide (2.0 equiv). The reaction mixture was stirred at ambient temperature and monitored by TLC. Once the starting material had disappeared, the mixture was diluted with ice-cold water and extracted with diethyl ether (3 × 25 mL). The ether layer was washed with water (3 × 25 mL), brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product, which was further purified by column chromatography to give the final analytically pure product (85% yield).



2-Azido-3-bromobenzaldehyde (f)



Physical State : Yellow solid

Yield : 82%

Mp : 80−82 °C

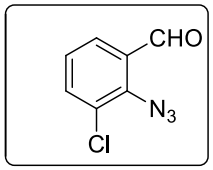
IR (MIR-ATR, 4000−600 cm−1) υmax = 2886, 2118, 1680, 1611, 1483, 1298, 1248, 1192, 1001, 815, 690.

^{1}H NMR (CDCl3, 400 MHz) δ_H = 10.32 (s, 1H), 7.56 (d, 1H, J = 2.4 Hz), 7.32 - 7.18 (m, 3H);

^{13}C NMR (CDCl3, 100 MHz) = 187.6, 139.4, 126.1, 120.7, 118.4.

HR-MS (ESI+) m/z calculated for [C7H5BrN3O]+ = [M]+ 225.96105, found 225.96108.

2-Azido-3-chlorobenzaldehyde (g)



Physical State : Lemon solid

Yield : 78%

Mp : 82−84 °C

IR (MIR-ATR, 4000−600 cm−1) υ_{max} = 2922, 2886, 2130, 1680, 1572, 1485, 1304, 1192, 1000, 940, 815, 690, 563.

^{1}H NMR (CDCl3, 400 MHz) δ_H = 10.32 (s, 1H), 7.57 (d, 1H, J = 2.0 Hz), 7.33 - 7.17 (m, 2H).

^{13}C NMR (CDCl3, 100 MHz) = 187.6, 139.4, 137.5, 127.7, 126.1, 120.7, 118.4.

HR-MS (ESI+) m/z calculated for [C7H4ClN3O]+ = [M]+ 182.01157, found 182.01155.

General procedure (GP-I) for the synthesis of 2-phenyl-2*H*-indazole:

Azidobenzaldehyde **1** (1 mmol), aniline **2** (1 mmol) were taken in a 10 mL oven dried schlenck tube and it was closed with stopcock with argon balloon and placed in an external heating oil bath at 120 ˚C for 1-3 hrs (oil bath temperature). After completion of the starting material, the mixture was cooled to room temperature and was purified on a silica gel column chromatography (hexane/ethylacetate 90:10) which furnished the respective products **1a-x.**

1. General procedure (GP-II) for the synthesis of 3-nitro-2-phenyl-2*H*-indazole:

In an oven dried 10 ml schlenck tube, under an oxygen atmosphere, 2-phenyl-2*H*-indazole **2a-v** (1 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2 mmol), TEMPO (1mmol), were added and followed by addition of DCE (5 mL). The resulting reaction mixture was stirred at 80 °C for 5-10h under an oxygen atmosphere. Progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was quenched by addition of aq. NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in a vacuum. Purification of the residue on a silica gel column chromatography using petroleum

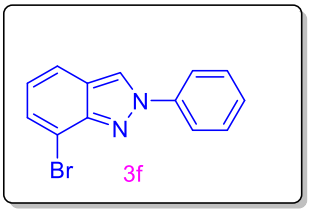
ether/ethyl acetate as (petroleum ether/ethylacetate 97:3 to 95:5) eluent furnished the product nitro indazole **39a-v**.

2. General procedure (GP-II) for the synthesis of Indazolo[2,3-a]quinazoline:

In an oven dried 10 ml schlenck tube, under an argon atmosphere, C3-nitro indazole **3a, 3m, 3l and 3k** (1mmol) and $P(OEt_3)$ (1mL) were added. The resulting reaction mixture was stirred at 80 °C for 1h. Progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was quenched by addition of aq. NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in a vacuum. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as (petroleum ether/ethylacetate 97:3 to 95:5) eluent furnished the product benzimidazoindazole **40a-d.**

Characterization Data of the Products

7-bromo-2-phenyl-2*H*-indazole(3f)



Physical state : Brown Solid

Yield : 86%

Mp : 90-92 ℃

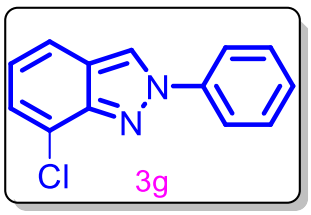
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}=3127, 3073, 2924, 2373, 2113, 1635, 1540, 1501, 1291, 903, 806, 729, 645.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H =8.34 (s, 1H), 7.93 - 7.84 (m, 2H), 7.79 (td, 1H, J = 1.0, 9.3 Hz), 7.59 - 7.49 (m, 2H), 7.45 - 7.37 (m, H), 7.32 (dd, 1H, J = 1.0, 2.0 Hz), 7.02 (dd, 1H, J = 2.2, 9.0 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): 148.0, 140.3, 134.5, 129.6, 128.1, 122.8, 121.0, 120.9, 119.9, 119.8, 107.9.

HR-MS (ESI+) m/z calculated for $[C_{13}H_{19}BrN_2]^+ = [M+H]^+$: 274.0053; found: 274.0053.

7-chloro-2-phenyl-2*H*-indazole(3g)



Physical state : Yellowish Brown Solid

Yield : 76%

Mp : 88-90 ℃

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3051, 2925, 2372, 2115, 1522, 1279, 903, 806, 726, 649.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.02 (dd, 1H), 7.32 (dd, 1H), 7.39 - 7.45 (m, 1H), 7.47 - 7.59 (m, 2H), 7.73 - 7.83 (m, 1H), 7.83 - 7.95 (m, 2H), 8.34 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): 148.0, 140.3, 134.5, 129.6, 128.1, 122.8, 121.0, 120.9, 120.0, 119.8, 107.9.

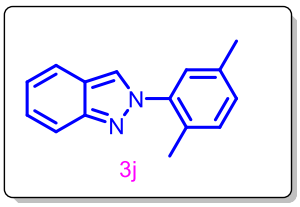
HR-MS (ESI+) m/z calculated for $[C13H10ClN2]^+ = [M+H]^+$: 182.0115; found: 182.0121.

2-(2,5-dimethylphenyl)-2H-indazole(3j)

Physical state : Brown Solid

Yield : 85%

Mp : 60-62 ℃



3j

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3057, 2921, 2858, 1624, 1518, 1469, 1383, 1345, 1292, 1263, 1132, 814, 783, 755, 611.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.11 (s, 1H), 7.86 (d, 1H, *J* = 8.8 Hz), 7.77 (d, 1H, *J* = 8.3 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.34 - 7.11 (m, 4H), 2.41 (s, 3H), 2.24 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 149.3, 140.1, 136.5, 131.1, 130.4, 129.9, 127.2, 126.4, 124.3, 122.1, 122.0, 120.4, 117.9, 20.8, 17.5.

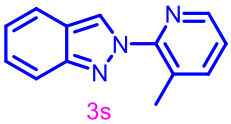
HR-MS (ESI+) m/z calculated for $[C_{15}H_{15}N_2]^+ = [M+H]^+$: 223.1230; found: 223.1231.

2-(3-methylpyridin-2-yl)-2*H*-indazole(3s)

Physical state : Brownish Yellow Solid

Yield : 80%

Mp : 96-98 ℃



3s

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3062, 2921, 2853, 1700, 1655, 1606, 1562, 1515, 1473, 1312, 1143, 1057, 947, 908, 789, 755, 735.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.95 (s, 1H), 8.31 - 8.10 (m, 1H), 7.97 (m, 1H), 7.73 - 7.49 (m, 2H), 7.28 - 7.15 (m, 1H), 7.05 - 6.77 (m, 2H), 2.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 151.9, 150.5, 150.2, 148.0, 127.5, 123.8, 122.6, 122.3, 121.2, 120.7, 118.0, 114.5, 21.2.

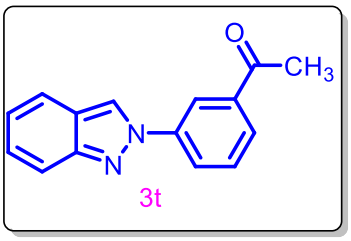
HR-MS (ESI+) m/z calculated for $[C_{13}H_{12}N_3]^+ = [M+H]^+$: 210.1026; found: 210.1027.

1-(3-(2*H*-indazol-2-yl) phenyl) ethan-1-one(3t)

Physical State : Yellow Solid

Yield : 80%

Mp : 62-64 ℃



IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3062, 2911, 1682, 1586, 1517, 1441, 1387, 1354, 1255, 1052, 782, 752, 733, 682, 589, 541.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.57 - 8.43 (m, 2H), 8.21 - 8.13 (m, 1H), 7.99 (dd, 1H, *J* = 1.0, 7.8 Hz), 7.81 (dd, 1H, *J* = 1.0, 8.8 Hz), 7.75 - 7.70 (m, 1H), 7.64 (t, 1H, *J* = 7.8 Hz), 7.40 - 7.31 (m, 1H), 7.19 - 7.09 (m, 1H), 2.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 197.0, 150.0, 140.9, 138.4, 130.0, 127.5, 127.2, 125.2, 123.0, 122.8, 120.5, 120.2, 118.0, 26.8.

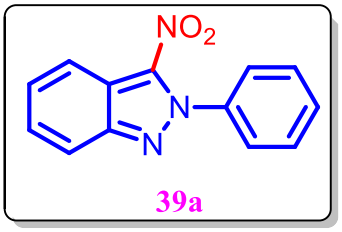
HR-MS (ESI+) m/z calculated for $[C_{15}H_{13}N_20]^+$ = $[M+H]^+$: 237.1022; found: 237.1016.

3-nitro-2-phenyl-2*H*-indazole (39a)

Physical State : Lemon yellow Solid

Yield : 52 mg, 85%

Mp : 110-112 ℃



IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3076, 2922, 2851, 1594, 1557, 1490, 1460, 1440, 1382, 1321, 1301, 1266, 1206, 821, 754, 691.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.23 (dt, 1H, J_a=8.3 and J_b= 1.2 Hz), 7.90-7.88 (m, 1H), 7.59-7.51 (m, 7H).

^{13}C NMR ($CDCl_3$, 100 MHz): 147, 139, 130, 129, 129, 128, 125, 120, 119, 118.

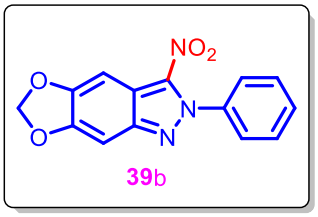
HR-MS (ESI+) m/z calculated for $[C_{13}H_{10}N_3O_2]^+$ = $[M+H]^+$: 240.0768; found: 240.0774.

3-nitro-2-(m-tolyl)-2*H*-indazole (39b)

Physical Sate : Yellow Solid

Yield : 44 mg, 74%

Mp : 86-88 ℃



39b

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2990, 2882, 1992, 1504, 1476, 1340, 1202, 839, 724, 678;

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.55-7.52 (m, 3H), 7.50-7.47 (m, 2H), 7.45 (s, 1H), 7.07 (s, 1H), 6.12 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): 151.3, 150.6, 145, 139.6, 129.7, 129.1, 125.8, 115.8, 102.1, 95.7, 95.4.

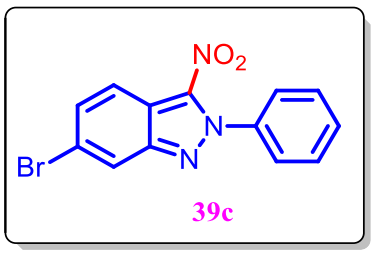
HR-MS (ESI+) m/z calculated for $[C_{14}H_{10}N_3O_4]^+$ = $[M+H]^+$: 284.0666; found: 284.0670.

6-bromo-3-nitro-2-phenyl-2*H*-indazole (39c)

Physical Sate : Yellow Solid

Yield : 22 mg, 38%

Mp : 86-88 ℃



39c

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3106, 2991, 2881, 2314, 1989, 1548, 1504, 1392, 1325, 1207, 816, 725.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.12-8.02 (m, 2H), 7.62-7.58 (m, 4H), 7.52-7.50 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): 147.7, 139.1, 132.5, 130.3, 129.3, 125.8, 122.4, 121.7, 121.6, 116.6.

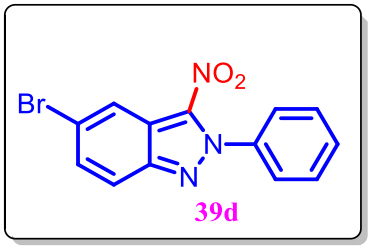
HR-MS (ESI+) m/z calculated for $[C_{13}H_9BrN_3O_2]^+$ = $[M+H]^+$: 317.9873; found: 317.9871.

5-bromo-3-nitro-2-phenyl-2*H*-indazole (39d)

Physical Sate : Golden yellow Solid

Yield : 26 mg, 45%

Mp : 102-104 ℃



39d

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3108, 2873, 2683, 2308, 1989, 1972, 1633, 1539, 1509, 1372, 1341, 1263, 807, 730,701.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.35 (s, 1H), 7.94-7.80 (m, 2H), 7.70-7.65 (m, 1H), 7.56-7.50 (m, 2H), 7.45-7.34 (m, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): 148.1, 130.5, 129.7, 129.3, 128.3, 125.8, 123.9, 122.5, 121.0, 119.8, 119.7, 116.0.

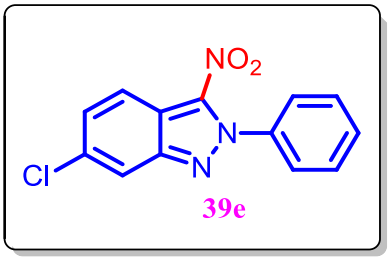
HR-MS (ESI+) m/z calculated for $[C_{13}H_9BrN_3O_2]^+$ = $[M+H]^+$: 317.9873; found: 317.9874.

6-chloro-3-nitro-2-phenyl-2*H*-indazole (39e)

Physical Sate : Brownish orange Solid

Yield : 21 mg, 35%

Mp : 98-100 ℃



39e

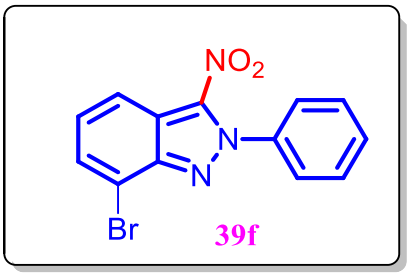
IR (MIR-ATR, 4000–600 cm^{-1}): *υmax* = 3055, 2931, 2119, 1687, 1593, 1540, 1492, 1395, 1326, 1263, 731, 702.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.20 (d, 1H, *J* = 8.3 Hz), 7.62 - 7.54 (m, 3H), 7.54 - 7.49 (m, 2H), 7.47 (d, 1H, *J* = 1.5 Hz), 7.20 (dd, 1H, *Ja* = 2.0 and *Ja* = 8.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): 147.5, 140.9, 139.2, 130.2, 129.2, 125.8, 122.9, 122.1, 115.8, 106.6.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9BrN_3O_2]^+$ = $[M+H]^+$: 317.9873; found: 317.9871.

7-bromo-3-nitro-2-phenyl-2*H*-indazole (39f)



Physical Sate : Golden yellow Solid

Yield : 28 mg, 38%

Mp : 102-104 ℃

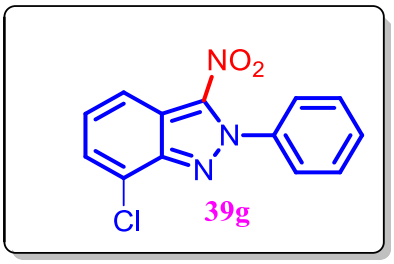
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2921, 2851, 2113, 1648, 1492, 1386, 1345, 1304, 1249, 1182, 893, 808, 757, 645.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.93 - 7.75 (m, 2H), 7.67 - 7.47 (m, 6H), 7.15 (dd, J = 2.0, 9.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): 145.3, 141.7, 139.4, 130.2, 129.2, 125.8, 122.8, 121.5, 119.1, 107.8.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9BrN_3O_2]^+$ = $[M+H]^+$: 317.9873; found: 317.9876.

7-chloro-3-nitro-2-phenyl-2*H*-indazole (39g)



Physical Sate : Orange Solid

Yield : 18 mg, 30%

Mp : 104-106 ℃

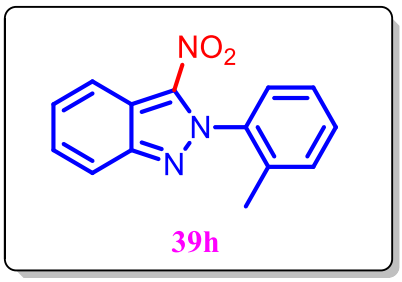
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2921, 2851, 2110, 1594, 1490, 1387, 1303, 1248, 1302, 1147, 907, 834, 738, 688, 600.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.93 - 7.78 (m, 2H), 7.64 - 7.49 (m, 5H), 7.19 - 7.13 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): 145.3, 141.7, 139.4, 130.2, 129.2, 125.8, 122.8, 121.5, 119.1, 107.8.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9BrN_3O_2]^+$ = $[M+H]^+$: 317.9873; found: 317.9870.

3-nitro-2-(*o*-tolyl)-2*H*-indazole (39h)



39h

Physical Sate : Brown Solid;

Yield : 27 mg, 45%

Mp : 60-62 ℃

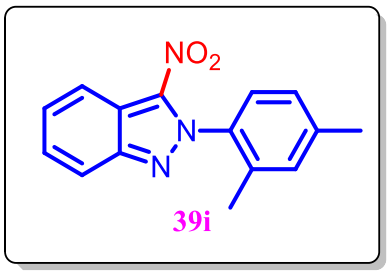
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2923, 2854, 1498, 1459, 1385, 1318, 1202, 821, 755, 720, 635.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.27-8.25 (m, 1H), 7.91-7.89 (m, 1H), 7.59-7.47 (m, 3H), 7.42-7.37 (m, 2H), 7.32-7.30 (m, 1H), 2.05 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 147.5, 139.0, 134.6, 131.0, 128.9, 128.3, 126.8, 126.3, 120.4, 119.4, 117.3, 17.1.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_2]^+$ = $[M+H]^+$: 254.0924; found: 254.0927.

2-(2,4-dimethylphenyl)-3-nitro-2*H*-indazole (39i)



39i

Physical Sate : Brown Solid

Yield : 45 mg, 75%

Mp : 120-122 ℃

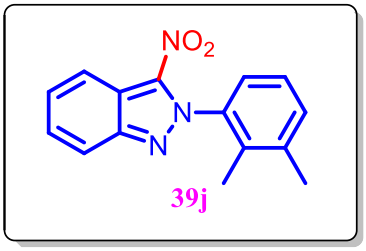
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3018, 2923, 2203, 1558, 1499, 1386, 1319, 1212, 1118, 1042, 826, 755, 612.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.25 - 8.23 (m, 1H) 7.90 - 7.87 (m, 1H) 7.46 - 7.61 (m, 2H) 7.15 - 7.23 (m, 3H) 2.44 (s, 3H) 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.39, 140.48, 136.60, 134.19, 131.65, 128.81, 128.25, 127.45, 126.11, 120.48, 119.44, 117.40, 21.32, 17.02.

HR-MS (ESI+) m/z calculated for $[C_{15}H_{14}N_3O_2]^+$ = $[M+H]^+$: 268.1081; found: 268.1083.

2-(2,3-dimethylphenyl)-3-nitro-2*H*-indazole (39j)



Physical Sate : Brown Solid

Yield : 42 mg, 70%

Mp : 140-142 ℃

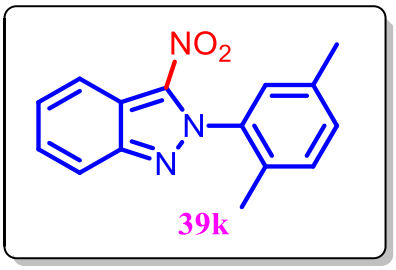
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3073, 2981, 2317, 1558, 1501, 1474, 1388, 1321, 1199, 822, 755.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.22 - 8.28 (m, 1H), 7.86 - 7.92 (m, 1H), 7.49 - 7.61 (m, 2H), 7.38 (d, 1H, *J* = 7.82 Hz), 7.27 - 7.30 (m, 1H), 7.16 (d, 1H, *J* = 7.82 Hz), 2.39 (s, 3H), 1.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.38, 139.14, 138.46, 133.22, 131.71, 128.85, 128.29, 126.18, 124.01, 120.48, 119.45, 117.33, 20.25, 13.96.

HR-MS (ESI+) m/z calculated for $[C_{15}H_{14}N_3O_2]^+$ = $[M+H]^+$: 268.1081; found: 268.1083.

2-(2,5-dimethylphenyl)-3-nitro-2*H*-indazole (39k)



Physical Sate : Orange Solid

Yield : 30 mg, 50%

Mp : 68-70 ℃

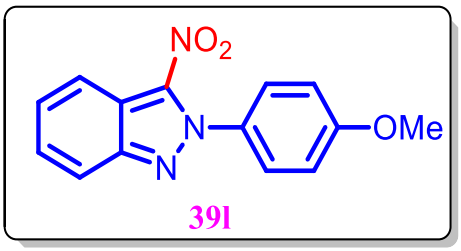
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3032, 2916, 1938, 1610, 1489, 1385, 1306, 1196, 821, 784, 750.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.22 - 8.28 (m, 1H), 7.86 - 7.93 (m, 1H), 7.48 - 7.60 (m, 2H), 7.24 - 7.32 (m, 2H), 7.13 (s, 1H), 2.39 (s, 3H), 2.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.4, 138.9, 136.8, 131.3, 131.1, 130.8, 128.8, 128.3, 126.7, 120.5, 119.4, 117.3, 20.8, 16.6.

HR-MS (ESI+) m/z calculated for $[C_{15}H_{14}N_3O_2]^+$ = $[M+H]^+$: 268.1081; found: 268.1074.

2-(4-methoxyphenyl)-3-nitro-2*H*-indazole (39l)



39l

Physical Sate : Yellow solid

Yield : 57 mg, 95%

Mp : 130-132 ℃

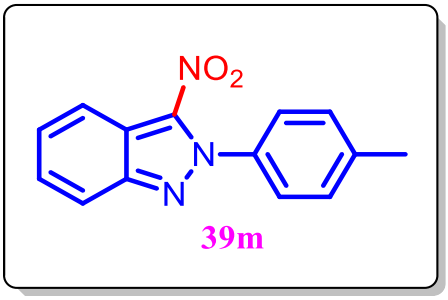
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2993, 2944, 2839, 1800, 1602, 1509, 1387, 1324, 1301, 1255, 832, 749.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.17 - 8.22 (m, 1H), 7.84 - 7.89 (m, 1H), 7.48 - 7.55 (m, 2H), 7.42 - 7.48 (m, 2H), 7.03 - 7.07 (m, 2H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 160.7, 147.1, 132.3, 128.8, 128.3, 127.1, 120.4, 119.3, 118.2, 114.3, 55.7.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_3]^+$ = $[M+H]^+$: 270.0873; found: 270.0877.

3-nitro-2-(*p*-tolyl)-2*H*-indazole (39m)



39m

Physical Sate : Light yellow solid

Yield : 58 mg, 96%

Mp : 148-150 ℃

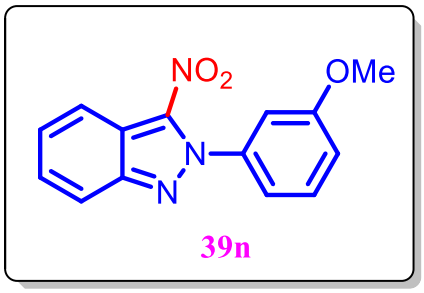
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3075, 2992, 2945, 2315, 1537, 1509, 1389, 1324, 1301, 1209, 1145, 820, 750, 663.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.21 (dt, 1H, *J*= 8.31, 1.22 Hz), 7.80 - 7.95 (1H, m), 7.45 - 7.63 (2H, m), 7.32 - 7.45 (4H, m), 2.48 (3H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 147.2, 140.4, 137.0, 129.8, 128.9, 128.3, 125.6, 120.4, 119.4, 118.2, 21.4.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_2]^+$ = $[M+H]^+$: 254.0924; found: 254.0925.

2-(3-methoxyphenyl)-3-nitro-2*H*-indazole (39n)



39n

Physical Sate : Yellow solid

Yield : 44 mg, 74%

Mp : 120-122 ℃

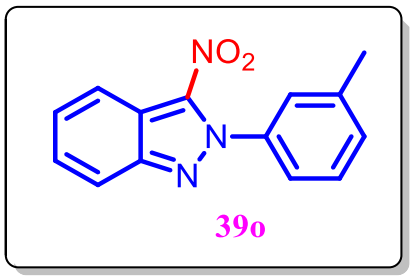
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3075, 2942, 2836, 2317, 1606, 1495, 1437, 1386, 1319, 1242, 1206, 1132, 1035, 821, 754.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.12 - 8.22 (m, 1H), 7.80 - 7.90 (m, 1H), 7.40 - 7.58 (m, 3H), 7.01 - 7.14 (m, 3H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 160.1, 147.3, 140.4, 130.0, 129.0, 128.4, 120.4, 119.4, 118.1, 118.1, 116.2, 111.5, 55.7.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_3]^+$ = $[M+H]^+$: 270.0873; found: 270.0873.

3-nitro-2-(*m*-tolyl)-2*H*-indazole (39o)



39o

Physical Sate : Lemon yellow solid

Yield : 48 mg, 79%

Mp122 : 124 ℃

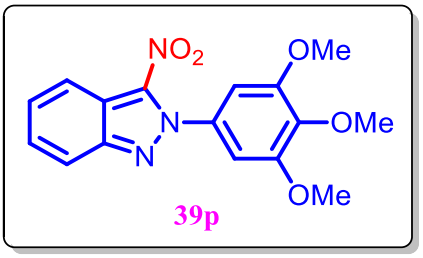
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 2952, 2830, 1504, 1449, 1385, 1320, 1196, 1117, 822, 754, 654.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.15 - 8.24 (m, 1H), 7.82 - 7.90 (m, 1H), 7.40 - 7.55 (m, 3H), 7.27 - 7.40 (m, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 139.5, 139.5, 130.9, 129.0, 128.9, 128.4, 126.3, 122.9, 120.4, 119.3, 118.2, 21.3.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_2]^+$ = $[M+H]^+$: 254.0924; found: 254.0925.

3-nitro-2-(3,4,5-trimethoxyphenyl)-2*H*-indazole (39p)



39p

Physical Sate : Reddish yellow solid

Yield : 50 mg, 88%

Mp : 142-144 ℃

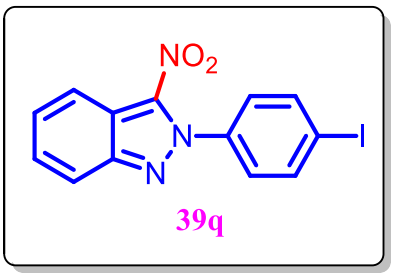
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3002, 2943, 2832, 1600, 1503, 1461, 1334, 1309, 1126, 838, 752.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.21 (d, 1H, *J* = 7.34 Hz), 7.88 (d, 1H, *J* = 7.83 Hz), 7.49 - 7.59 (m, 2H), 6.74 (s, 2H), 3.94 (s, 3H), 3.89 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 153.5, 147.2, 139.4, 134.9, 129.1, 128.5, 120.4, 119.3, 118.1, 103.6, 61.1, 56.4.

HR-MS (ESI+) m/z calculated for $[C_{16}H_{16}N_3O_5]^+$ = $[M+H]^+$: 330.1084; found: 330.1089.

2-(4-iodophenyl)-3-nitro-2*H*-indazole (39q)



39q

Physical Sate : Yellow solid

Yield : 44 mg, 77%

Mp : 136-138 ℃

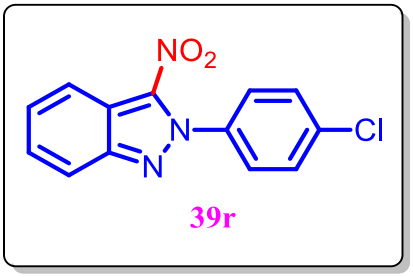
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3065, 2922, 2852, 2203, 1495, 1386, 1322, 1207, 779, 727.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.21 (d, 1H, *J* = 8.3 Hz), 7.97 - 7.82 (m, 3H), 7.60 - 7.47 (m, 2H), 7.28 (d, 2H, *J* = 8.3 Hz, 2H.

^{13}C NMR (100 MHz, $CDCl_3$): 147.6, 139.2, 138.4, 129.3, 128.7, 127.6, 120.4, 119.4, 118.3, 96.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9N_3O_2I]^+$ = $[M+H]^+$: 365.9734; found: 365.9739.

2-(4-chlorophenyl)-3-nitro-2*H*-indazole (39r)



39r

Physical Sate : Yellow solid

Yield : 39 mg, 65%

Mp : 132-134 ℃

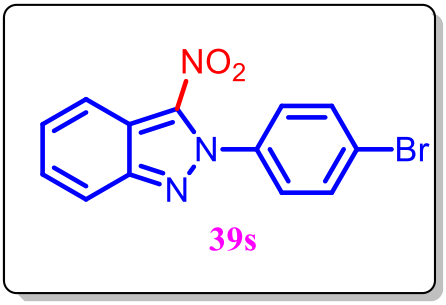
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3054, 2922, 2854, 1771, 1684, 1572, 1507, 1457, 1264, 730, 702, 518.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.21 (d, 1H, *J* = 8.31 Hz), 7.88 (d, 1H, *J* = 8.31 Hz), 7.45 - 7.58 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.5, 137.9, 136.3, 129.5, 129.3, 128.7, 127.2, 120.4, 119.4, 118.3.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9N_3O_2Cl]^+$ = $[M+H]^+$: 274.0378; found: 274.0387.

2-(4-bromophenyl)-3-nitro-2*H*-indazole (39s)



39s

Physical Sate : Yellow solid

Yield : 42 mg, 72%

Mp : 160-162 ℃

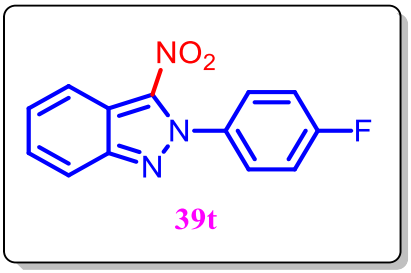
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3159, 3098, 2919, 1929, 1770, 1494, 1387, 1310, 1207, 832, 752, 604, 582.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.22 (d, 1H, *J* = 8.80 Hz), 7.88 (d, 1H, *J* = 8.31 Hz), 7.71 (d, 2H, *J* = 8.31 Hz), 7.47 - 7.59 (m, 2H), 7.42 (d, 2H, *J* = 8.31 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 147.5, 138.4, 132.4, 129.3, 128.7, 127.5, 124.3, 120.4, 119.4.

HR-MS (ESI+) m/z calculated for $[C_{13}H_9N_3O_2Br]^+$ = $[M+H]^+$: 317.9873; found: 317.9869.

2-(4-fluorophenyl)-3-nitro-2*H*-indazole (39t)



39t

Physical Sate : Yellow solid

Yield : 21mg, 35%

Mp : 190-192 ℃

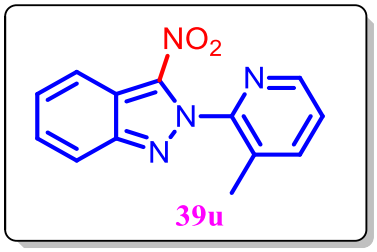
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3076, 2923, 2853, 1599, 1505, 1493, 1391, 1312, 1236, 1312, 1264, 1209, 838, 753, 731.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.22 (dt, 1H, J_a= 8.31 and J_b= 1.22 Hz), 7.85 - 7.90 (m, 1H), 7.48 - 7.58 (m, 4H), 7.23 - 7.30 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 164.5, 162.0, 147.4, 135.5, 129.2, 128.6, 128.0, 127.9, 120.4, 119.4, 118.2, 116.4, 116.2.

HR-MS (ESI+) m/z calculated for $[C_{13}H_8N_3O_2F]$ + = $[M+H]^+$: 258.0673; found: 258.0676.

2-(3-methylpyridin-2-yl)-3-nitro-2*H*-indazole (39u)



39u

Physical Sate : Brown solid

Yield : 30 mg, 50%

Mp : 86-88 ℃

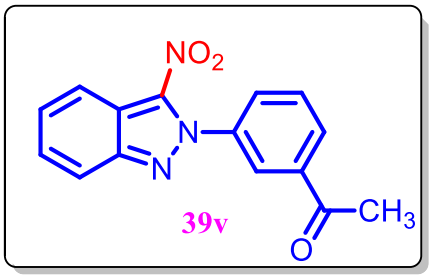
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3074, 2925, 1503, 1461, 1392, 1322, 1304, 1210, 1072, 821, 794, 750.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.13 - 8.19 (m, 1H), 7.84 - 7.92 (m, 2H), 7.46 - 7.54 (m, 3H), 7.37 (d, 1H, J = 7.34 Hz), 2.61 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 159.0, 151.0, 147.5, 139.0, 128.9, 128.6, 124.8, 120.1, 119.5, 118.0, 117.0, 24.1.

HR-MS (ESI+) m/z calculated for $[C_{13}H_{11}N_4O_2]^+$ = $[M+H]^+$: 255.0877; found: 255.0884.

1-(3-(3-nitro-2*H*-indazol-2-yl)phenyl)ethanone (39v)



Physical Sate : Yellow Solid

Yield : 18 mg, 30%

Mp : 168-170 ℃

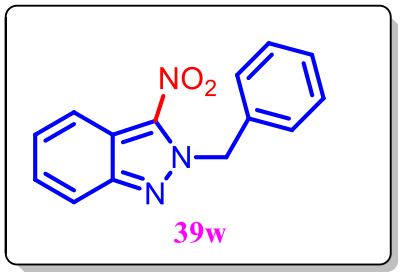
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}=3073, 2930, 1980, 1686, 1536, 1499, 1388, 1305, 1250, 1142, 822, 754, 688, 588.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.25 - 8.09 (m, 3H), 7.91 - 7.84 (m, 1H), 7.76 - 7.66 (m, 2H), 7.60 - 7.48 (m, 2H), 2.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): 196.3, 147.6, 140.0, 138.1, 130.3, 129.8, 129.6, 129.4, 128.8, 125.9, 120.4, 119.4, 118.2, 26.7.

HR-MS (ESI+) m/z calculated for $[C_{15}H_{12}N_3O_2]^+$ = $[M+H]^+$: 282.0873; found: 282.0879.

2-benzyl-3-nitro-2*H*-indazole (39w)



Physical Sate : Yellowish brown solid

Yield : 36 mg, 60%

Mp : 74-76 ℃

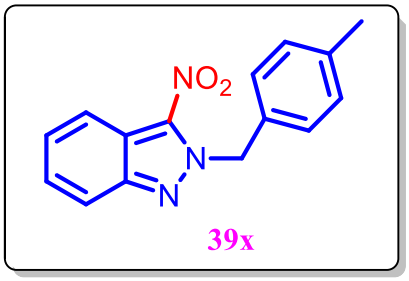
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3150, 3036, 1559, 1495, 1440, 1408, 1334, 1287, 1245, 1173, 821, 754, 707.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.12 - 8.18 (m, 1H), 7.84 - 7.89 (m, 1H), 7.43 - 7.51 (m, 2H), 7.28 - 7.38 (m, 5H), 6.13 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 146.5, 134.5, 128.9, 128.7, 128.6, 128.1, 127.9, 120.5, 119.2, 118.3, 58.2.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O_2]^+$ = $[M+H]^+$: 254.0924; found: 254.0917.

2-(4-methylbenzyl)-3-nitro-2*H*-indazole (39x)



39x

Physical Sate : Dark yellow solid

Yield : 26 mg, 43%

Mp : 82-84 ℃

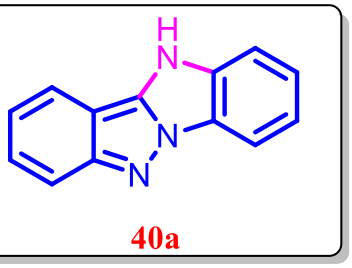
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3029, 2924, 2854, 1950, 1561, 1495, 1441, 1400, 1335, 1291, 1245, 1170, 1099, 823, 752, 732.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.19 - 8.11 (m, 1H), 7.89 - 7.82 (m, 1H), 7.51 - 7.41 (m, 2H), 7.27 (d, 2H, *J* = 7.8 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 6.09 (s, 2H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 146.4, 138.5, 131.6, 129.5, 128.6, 128.1, 127.8, 120.4, 119.2, 118.4, 58.0, 21.2.

HR-MS (ESI+) m/z calculated for $[C_{15}H_{14}N_3O_2]^+$ = $[M+H]^+$: 268.1081; found: 268.1094.

11*H*-benzo [4,5] imidazole[1,2-*b*]indazole (40a)



40a

Physical Sate : Red solid

Yield : 38 mg, 88%

Mp : 40-42 ℃

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3398, 3065, 2924, 2853, 1990, 1744, 1585, 1502, 1270, 1148, 1071, 774, 686.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.02 - 8.07 (m, 2 H), 7.90 (m, 1 H), 7.85 (m, 1 H), 7.70 (m, 1 H), 7.50 - 7.62 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): 153.2, 152.3, 133.6, 133.4, 132.5, 130.9, 129.3, 123.7, 117.1, 116.9, 113.2.

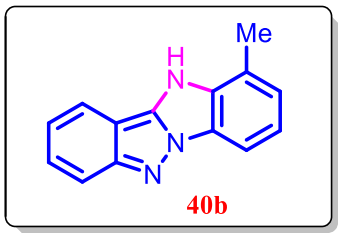
HR-MS (ESI+) m/z calculated for $[C_{13}H_{10}N_3]^+$ = $[M+H]^+$: 208.0869; found: 208.0865.

1-methyl-11*H*-benzo[4,5]imidazo[1,2-*b*]indazole(40b)

Physical Sate : Red solid

Yield : 28 mg, 68%

Mp : 42-44 °C



40b

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3053, 3922, 2854, 2230, 1593, 1477, 1433, 1264, 1095, 883, 764, 734, 686.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.82 - 7.91 (m, 4H), 7.70 (m, 1H), 7.55 (m, 1H), 7.40 - 7.46 (m, 1H), 7.34 - 7.38 (m, 1H), 2.47 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 152.3, 139.2, 133.6, 133.3, 133.3, 130.7 129.1, 123.8, 121.3, 117.2, 116.9, 112.9, 21.3.

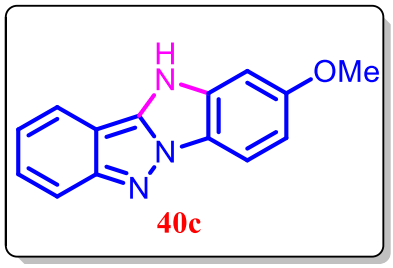
HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3]^+$ = $[M+H]^+$: 222.1026; found: 222.1030.

2-methoxy-11*H*-benzo[4,5]imidazo[1,2-*b*]indazole(40c)

Physical Sate : Red solid

Yield : 30 mg, 70%

Mp : 100–102°C



40c

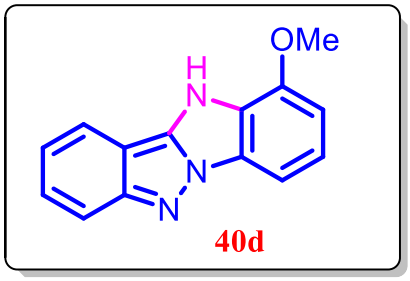
IR (MIR-ATR, 4000–600 cm^{-1}): υmax= 3398, 3091, 2955, 2923, 2230, 2172, 1598, 1504, 1262, 1146, 1023, 838, 768, 743, 604.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H =8.00 - 8.06 (m, 2H), 7.80 - 7.90 (m, 2H), 7.64 - 7.71 (m, 1H), 7.47 - 7.53 (m, 1H), 7.01 - 7.07 (m, 2H), 3.91 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 163.3, 153.5, 146.8, 133.5, 133.3, 130.2, 125.9, 117.1, 117.0, 114.4, 112.6, 55.7.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O]^+$ = $[M+H]^+$: 238.0975; found: 238.0982.

1-methoxy-11*H*-benzo[4,5]imidazo[1,2-b]indazole(40d)



40d

Physical Sate : Red solid

Yield : 37 mg, 85%

Mp : 64-66 °C

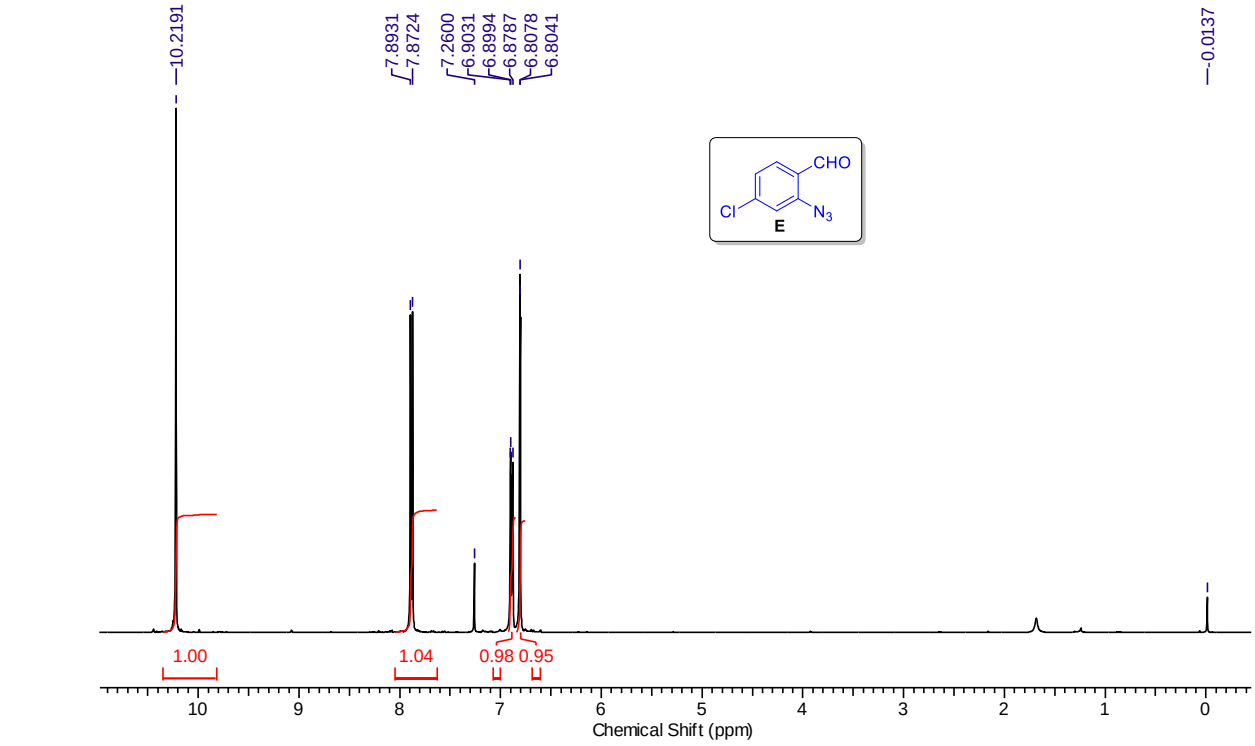
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max}= 3398, 3077, 2934, 2229, 1989, 1955, 1601, 1487, 1478, 1284, 1257, 1132, 1040, 862, 766, 681.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.94 - 7.82 (m, 2H), 7.74 - 7.64 (m, 2H), 7.60 - 7.53 (m, 2H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.11 (td, *J* = 1.7, 8.4 Hz, 1H), 3.91 (s, 3H).

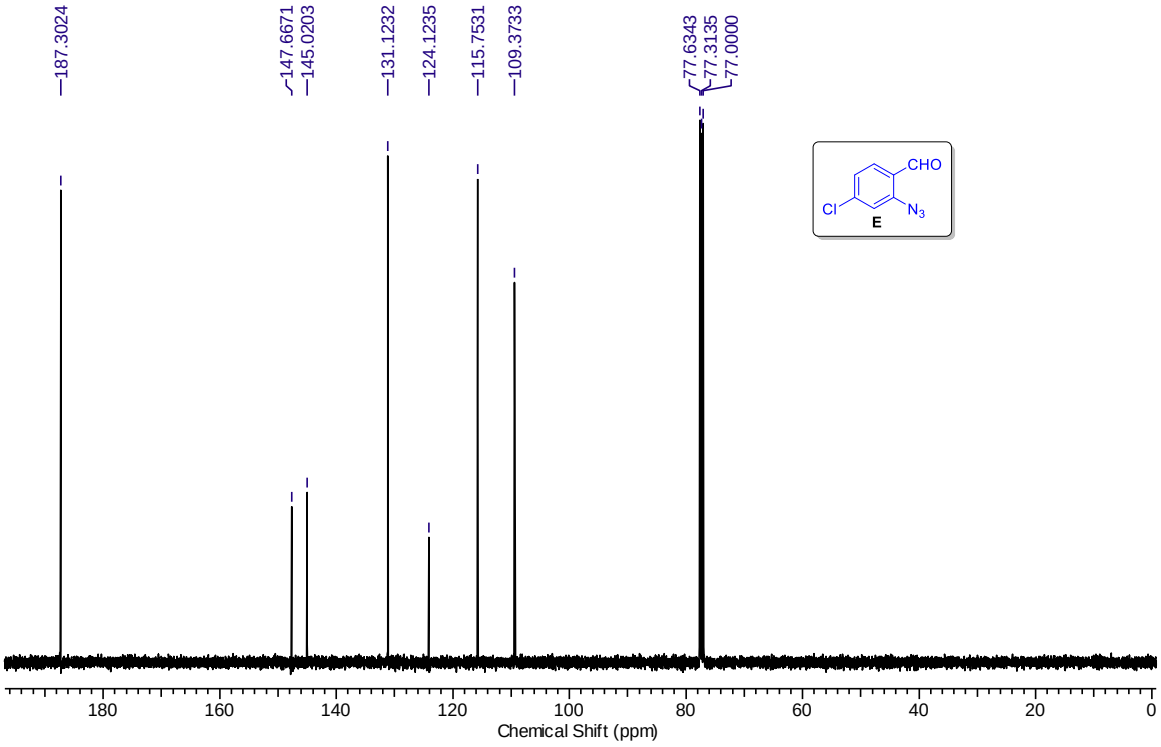
^{13}C NMR (100 MHz, $CDCl_3$): 160.4, 153.5, 153.1, 133.7, 133.4, 130.9, 130.0, 119.5, 118.3, 117.2, 116.9, 113.2, 106.1, 55.5.

HR-MS (ESI+) m/z calculated for $[C_{14}H_{12}N_3O]^+ = [M+H]^+$: 238.0975; found: 238.0980.

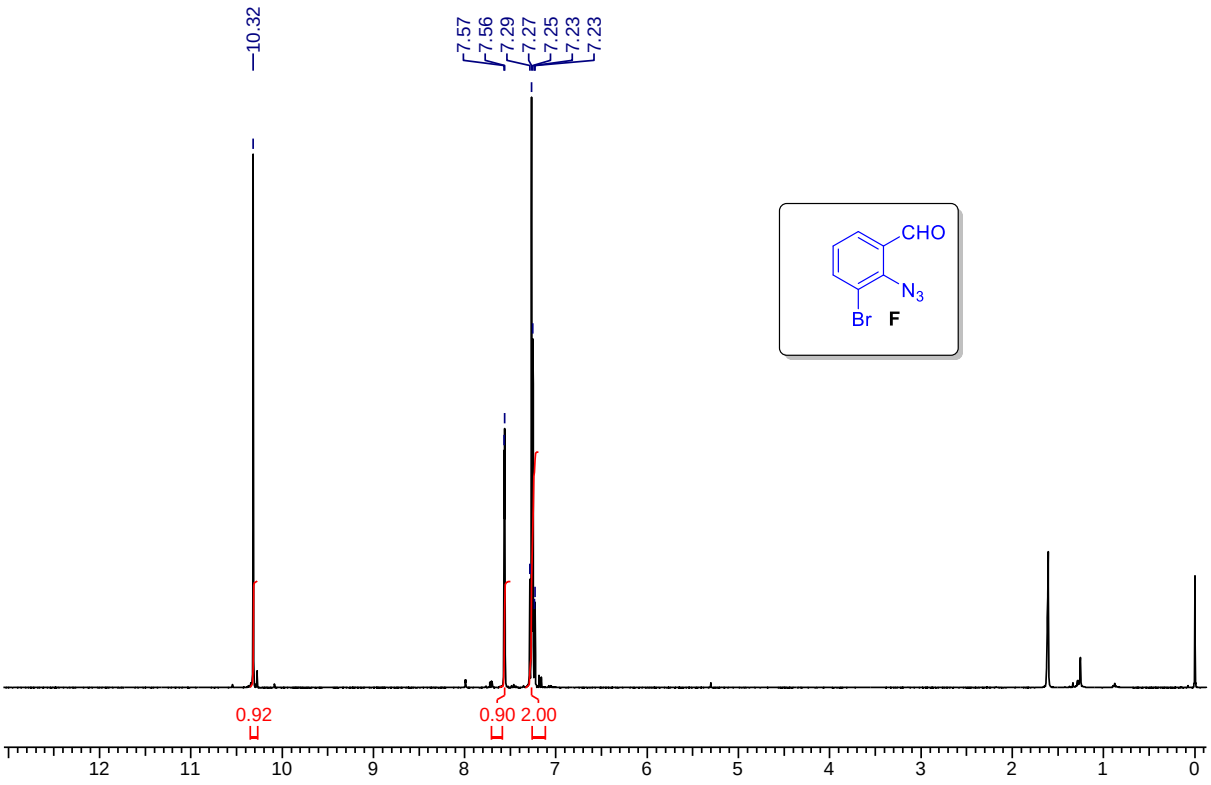
Copies of ^{1}H, ^{13}C NMR spectra for all the compounds



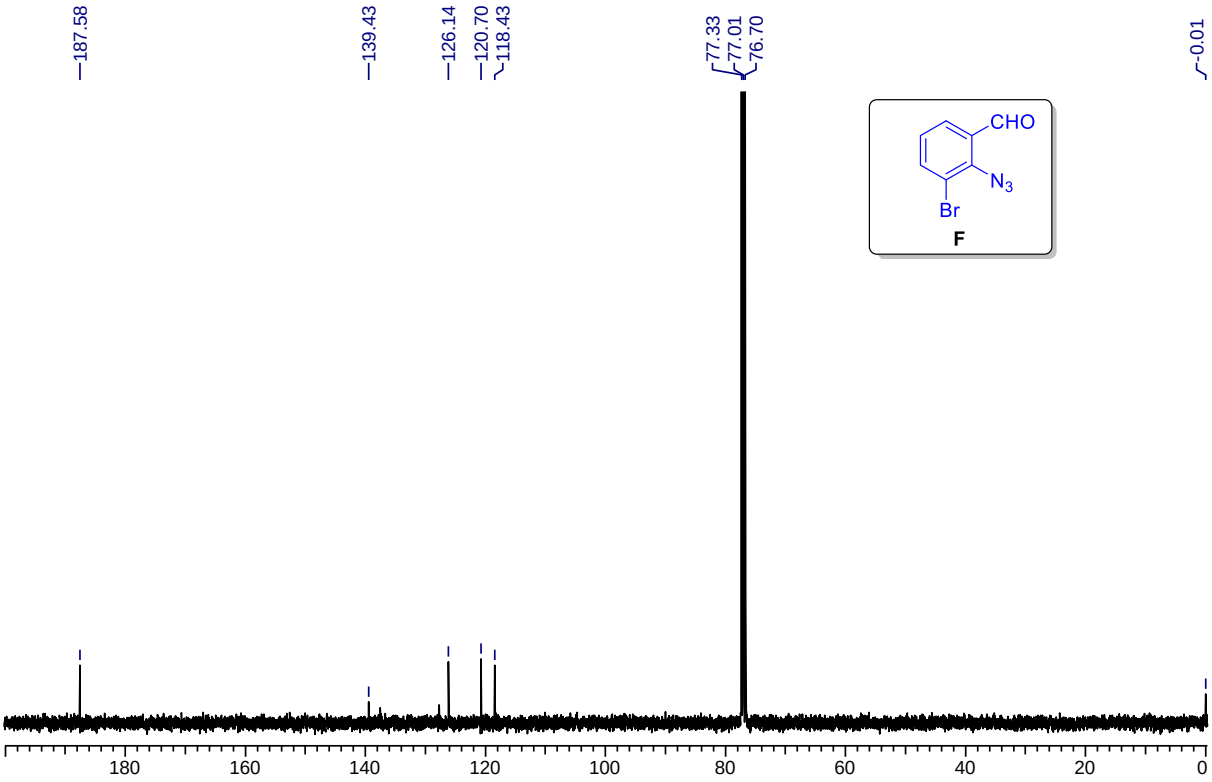
^{1}H NMR (400 MHz) spectrum of compound **E** in $CDCl_3$



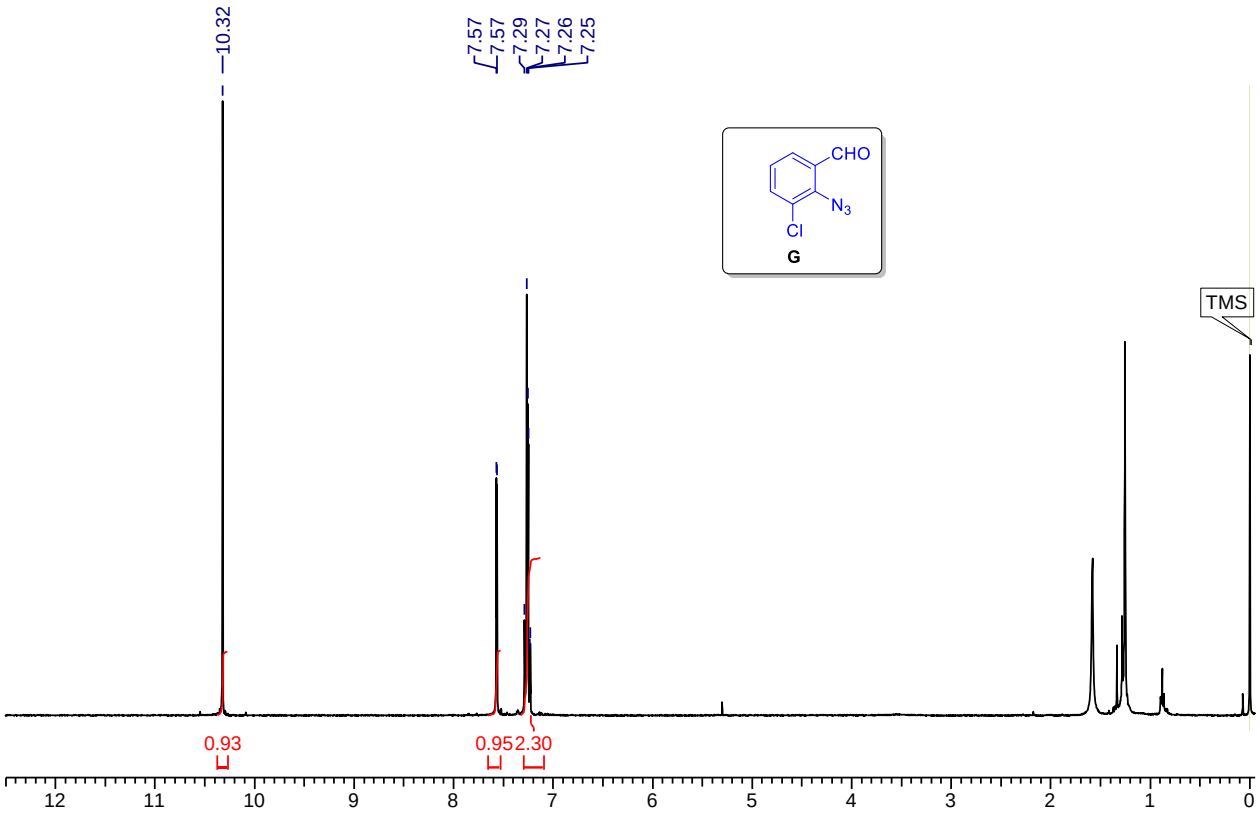
^{13}C NMR (100 MHz) spectrum of compound **E** in $CDCl_3$



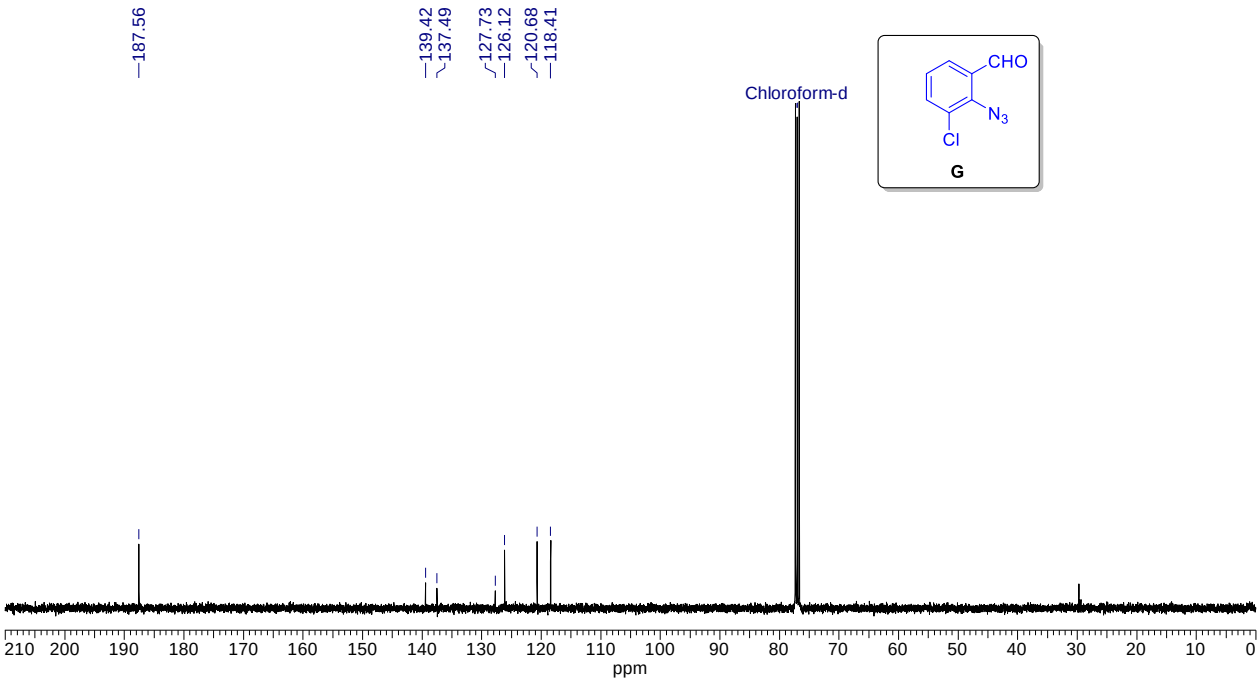
^{1}H NMR (400 MHz) spectrum of compound **F** in $CDCl_3$



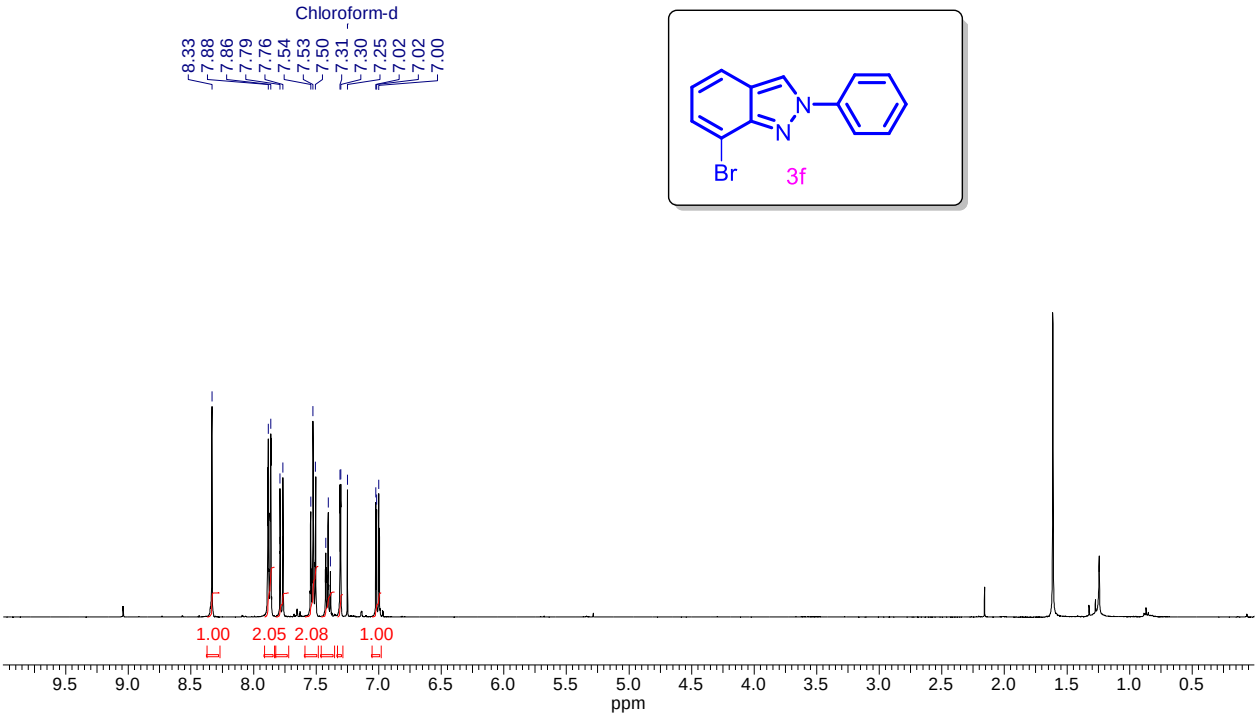
^{13}C NMR (100 MHz) spectrum of compound F in $CDCl_3$



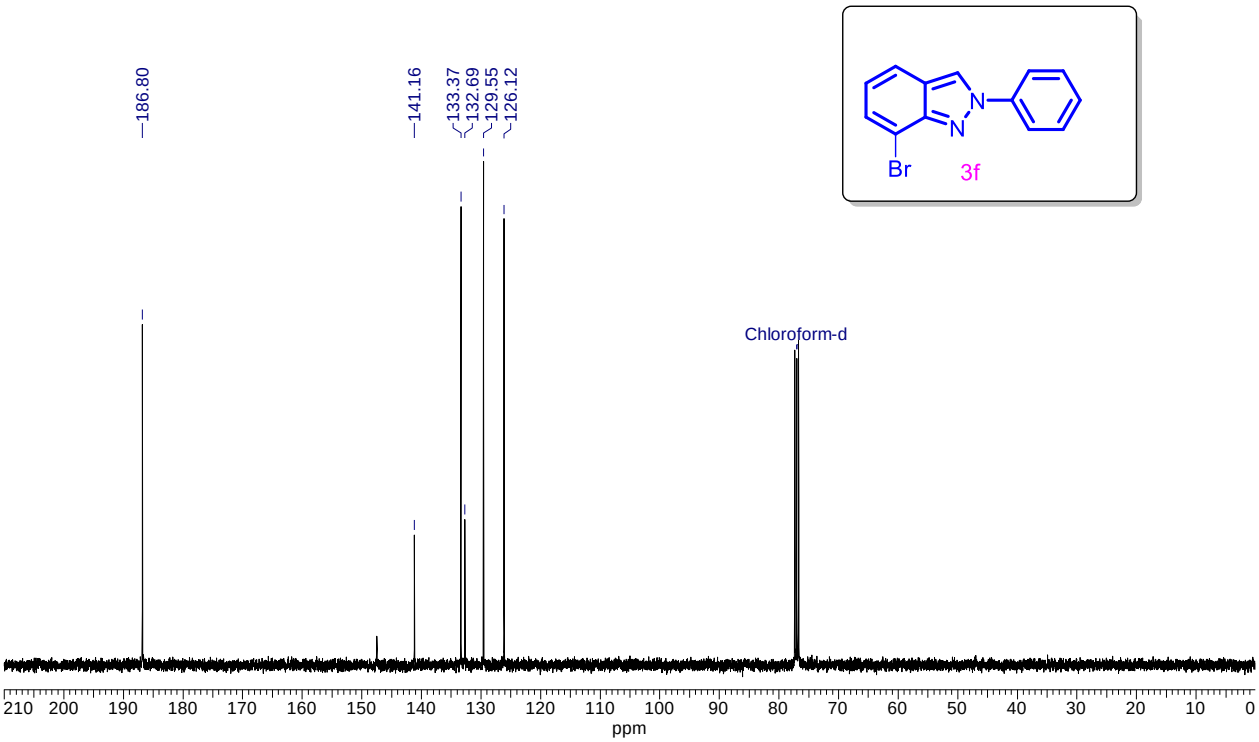
^{1}H NMR (400 MHz) spectrum of compound **G** in $CDCl_3$



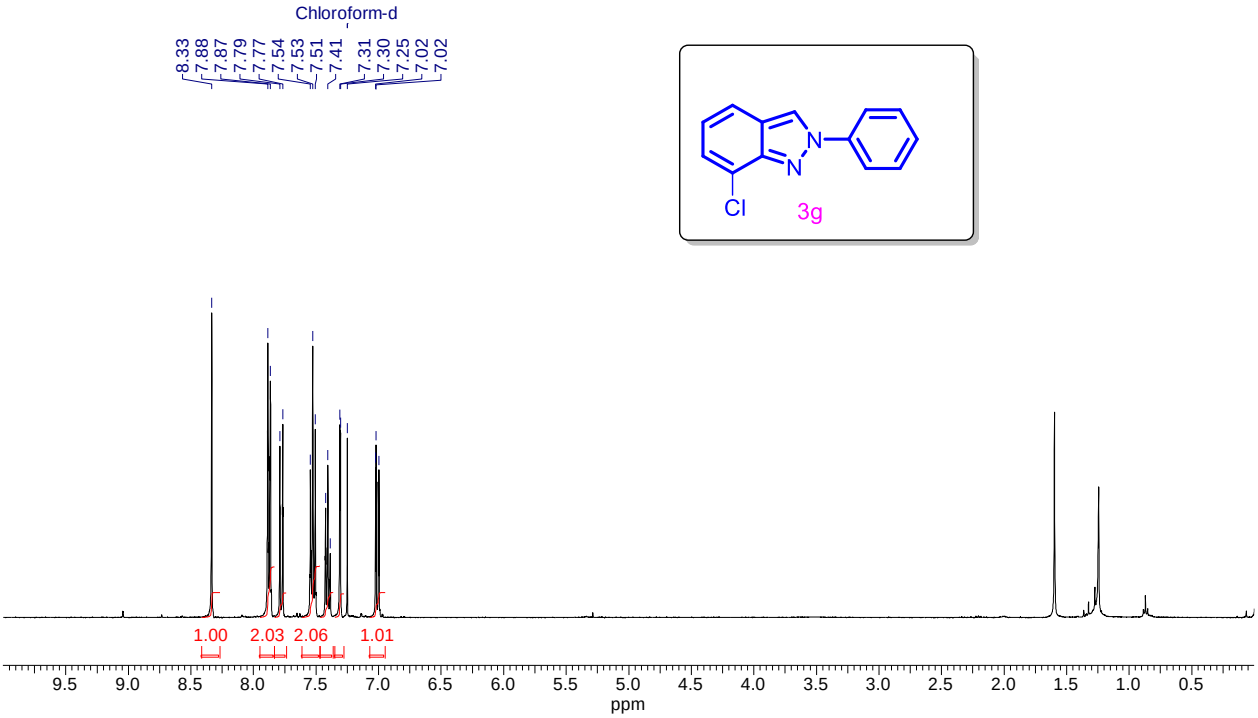
^{13}C NMR (100 MHz) spectrum of compound **G** in $CDCl_3$



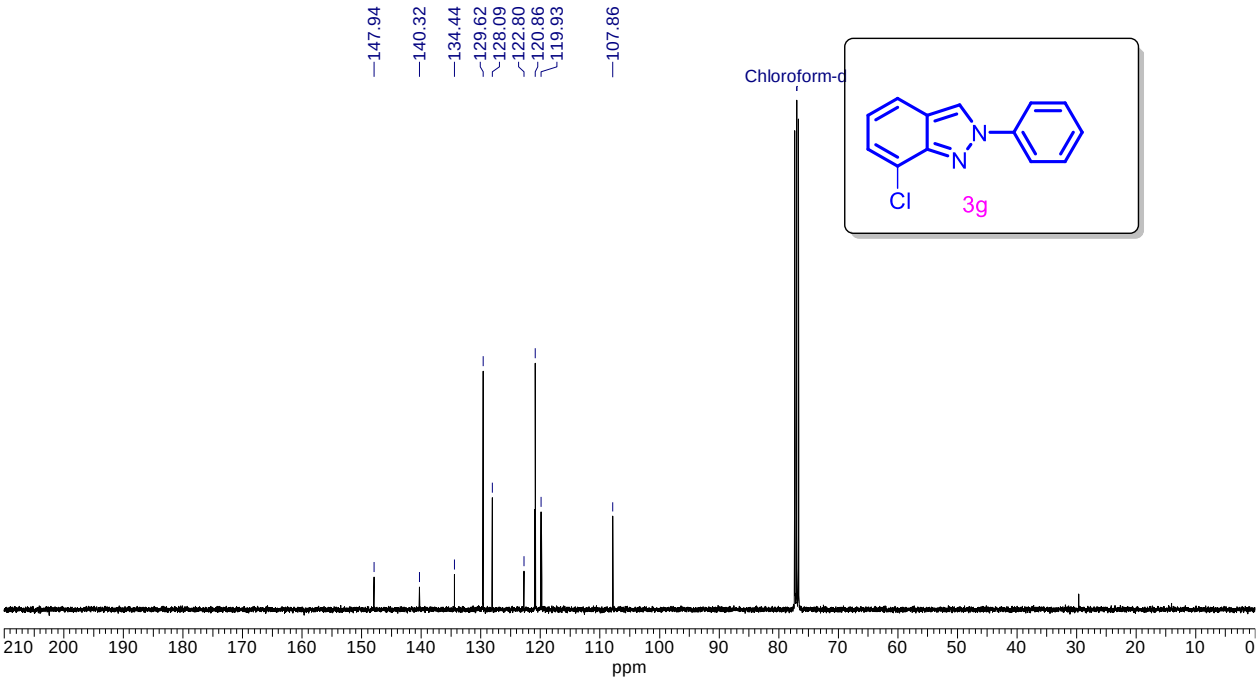
^{1}H NMR (400 MHz) spectrum of compound **3f** in $CDCl_3$



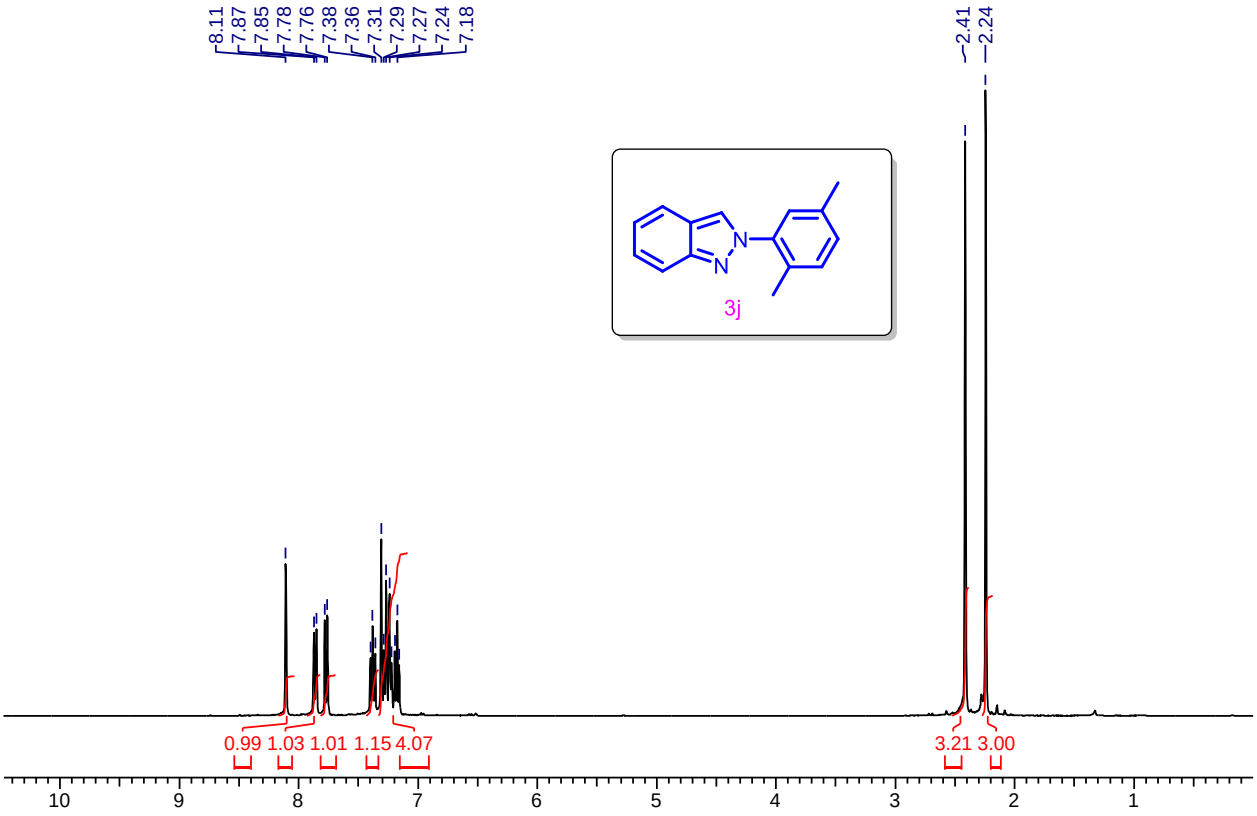
^{13}C NMR (100 MHz) spectrum of compound **3f** in $CDCl_3$



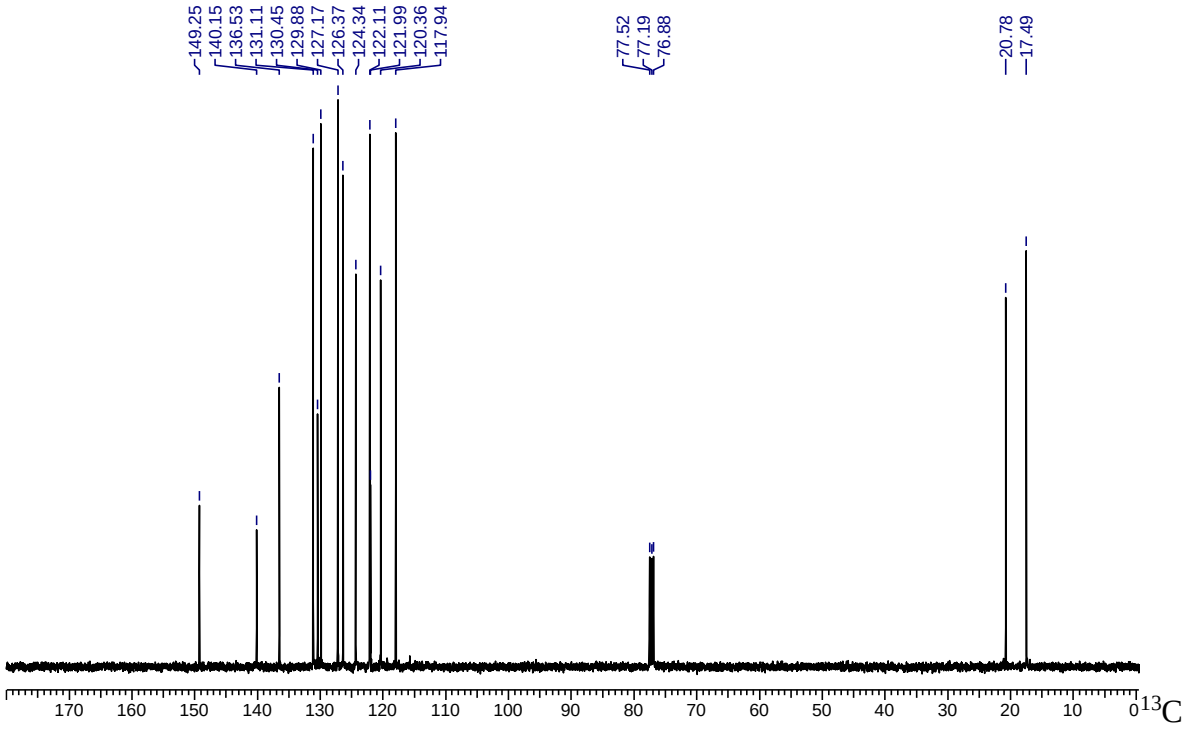
^{1}H NMR (400 MHz) spectrum of compound **3*g*** in $CDCl_3$



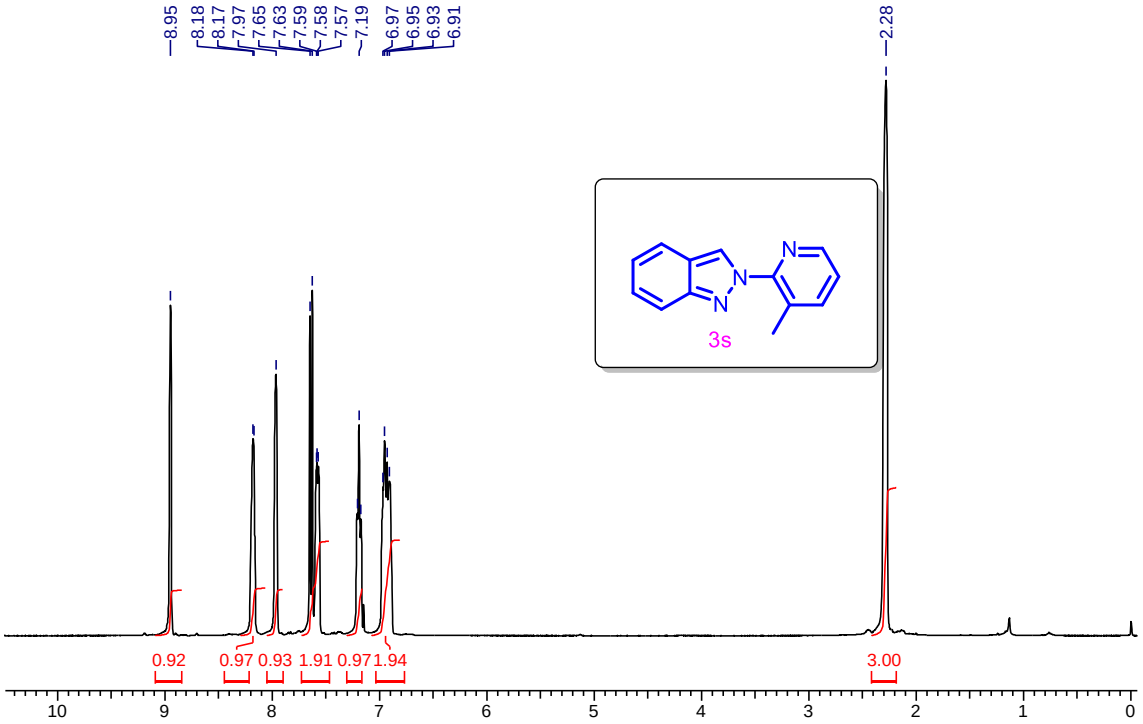
^{13}C NMR (100 MHz) spectrum of compound **3g** in $CDCl_3$



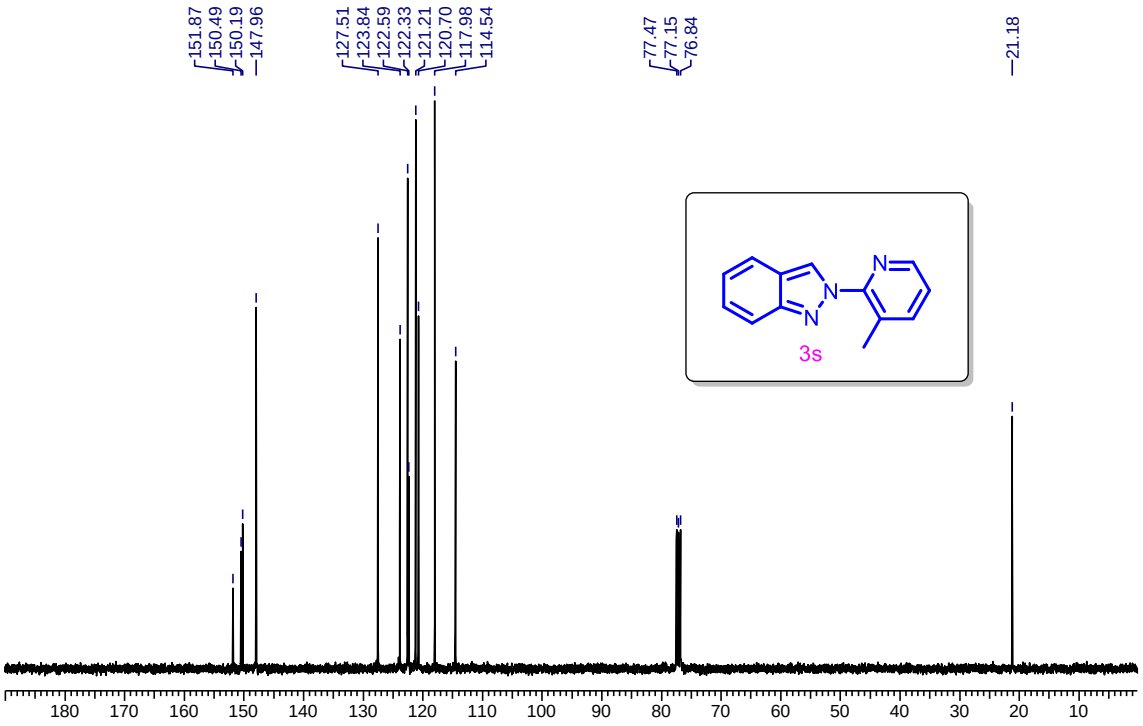
^{1}H NMR (400 MHz) spectrum of compound **3j** in $CDCl_3$



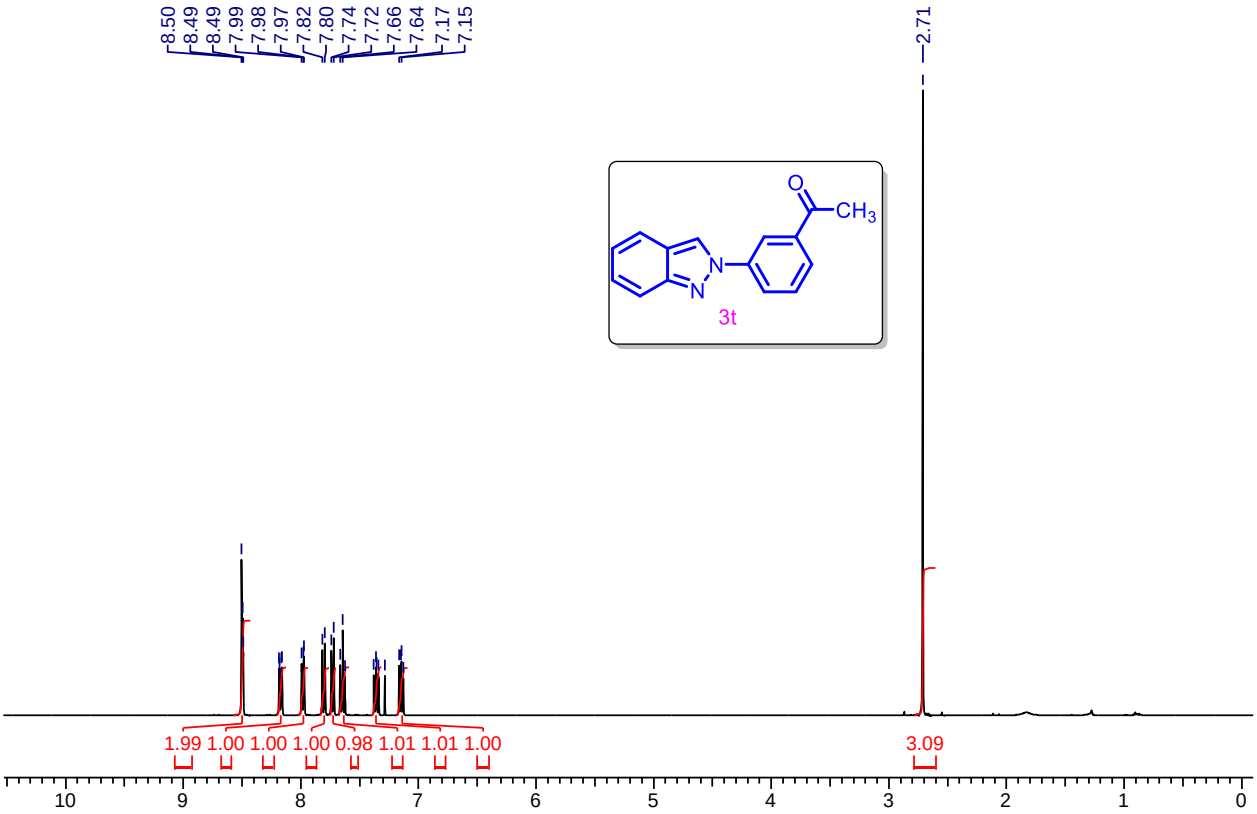
^{13}C ^{13}C NMR (100 MHz) spectrum of compound **3j** in $CDCl_3$



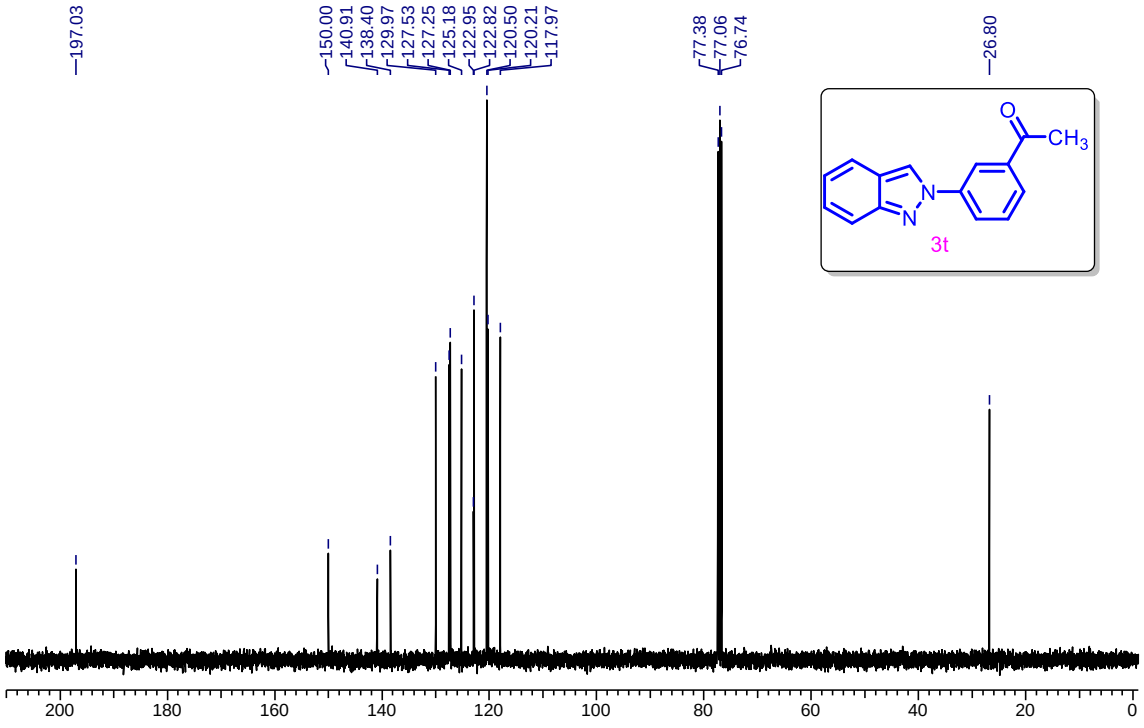
^{1}H NMR (400 MHz) spectrum of compound **3s** in $CDCl_3$



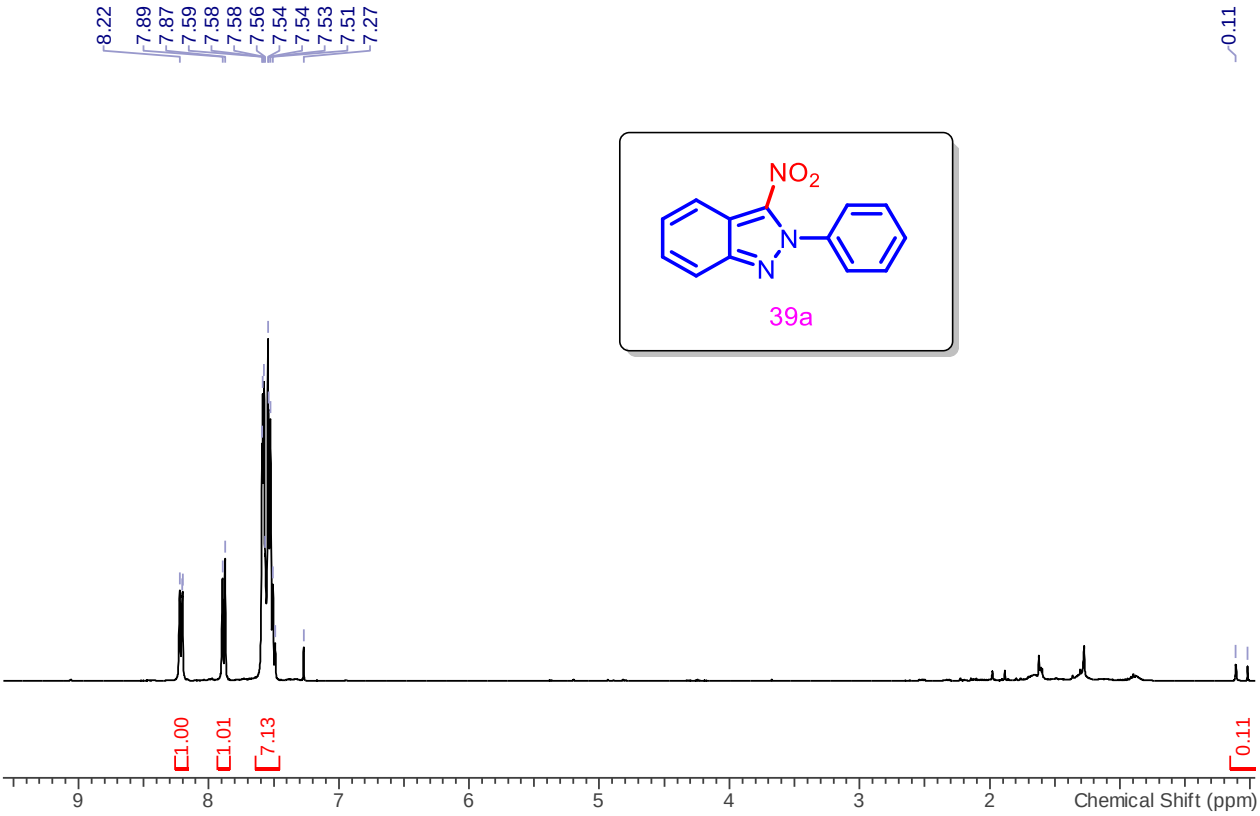
^{13}C NMR (100 MHz) spectrum of compound ***3s*** in $CDCl_3$



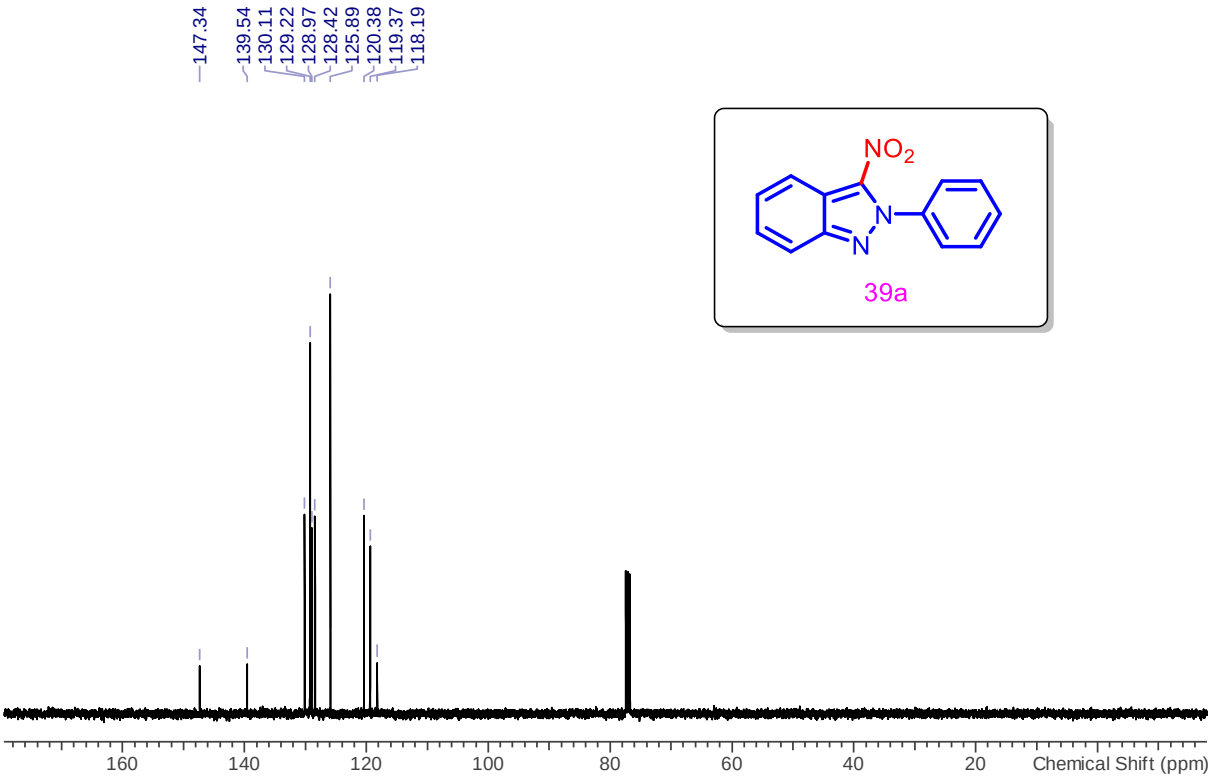
^{1}H NMR (400 MHz) spectrum of compound **3t** in $CDCl_3$



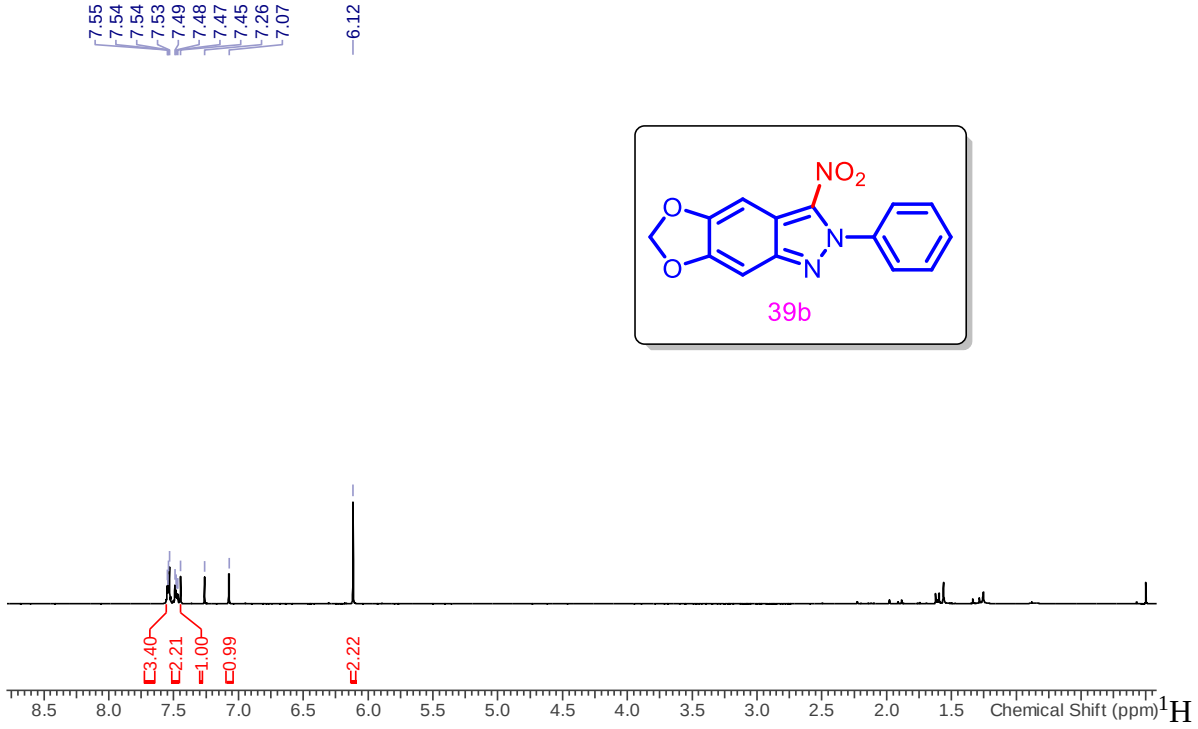
^{13}C NMR (100 MHz) spectrum of compound **3t** in $CDCl_3$



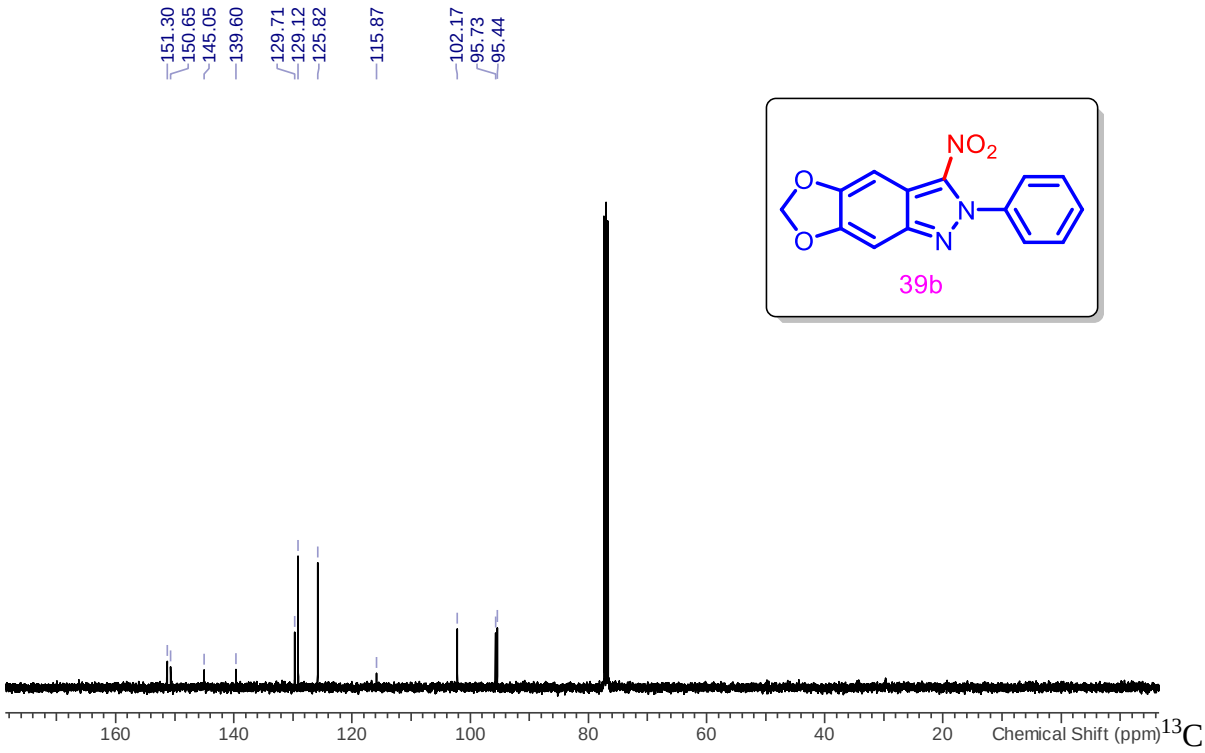
^{1}H NMR (400 MHz) spectrum of compound **39a** in $CDCl_3$



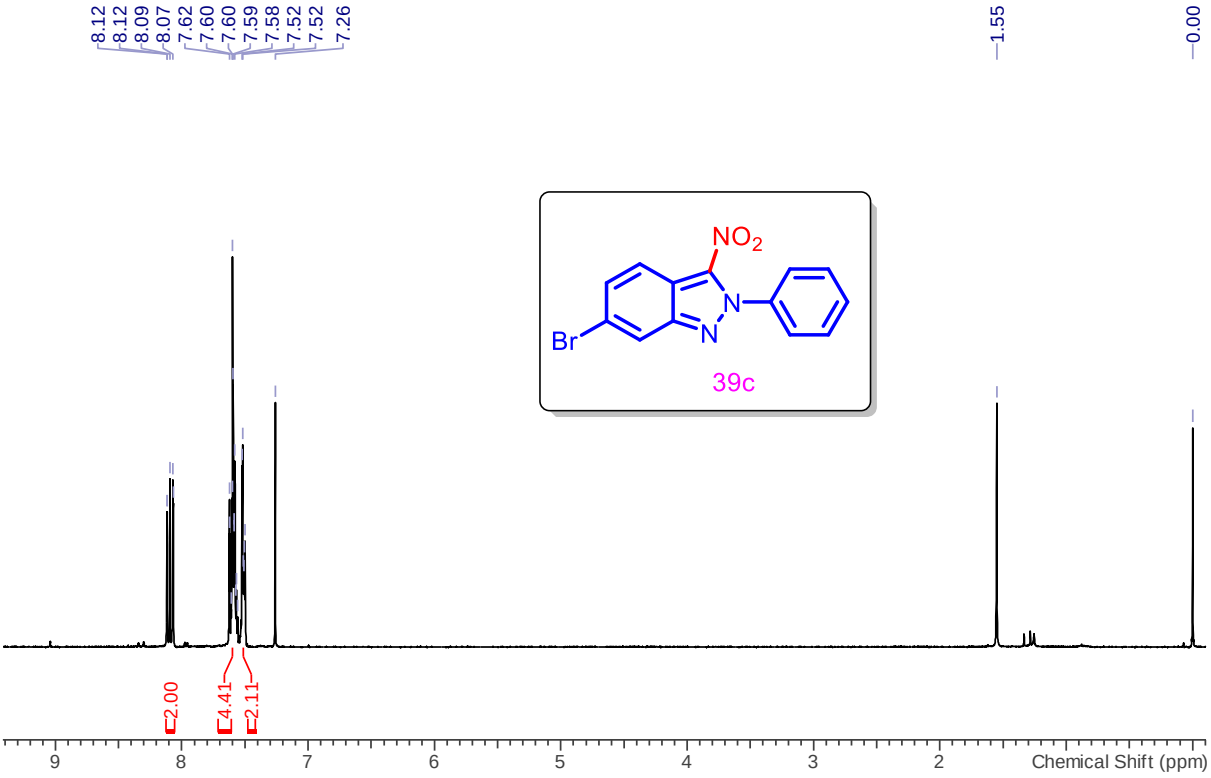
^{13}C NMR (100 MHz) spectrum of compound **39a** in $CDCl_3$



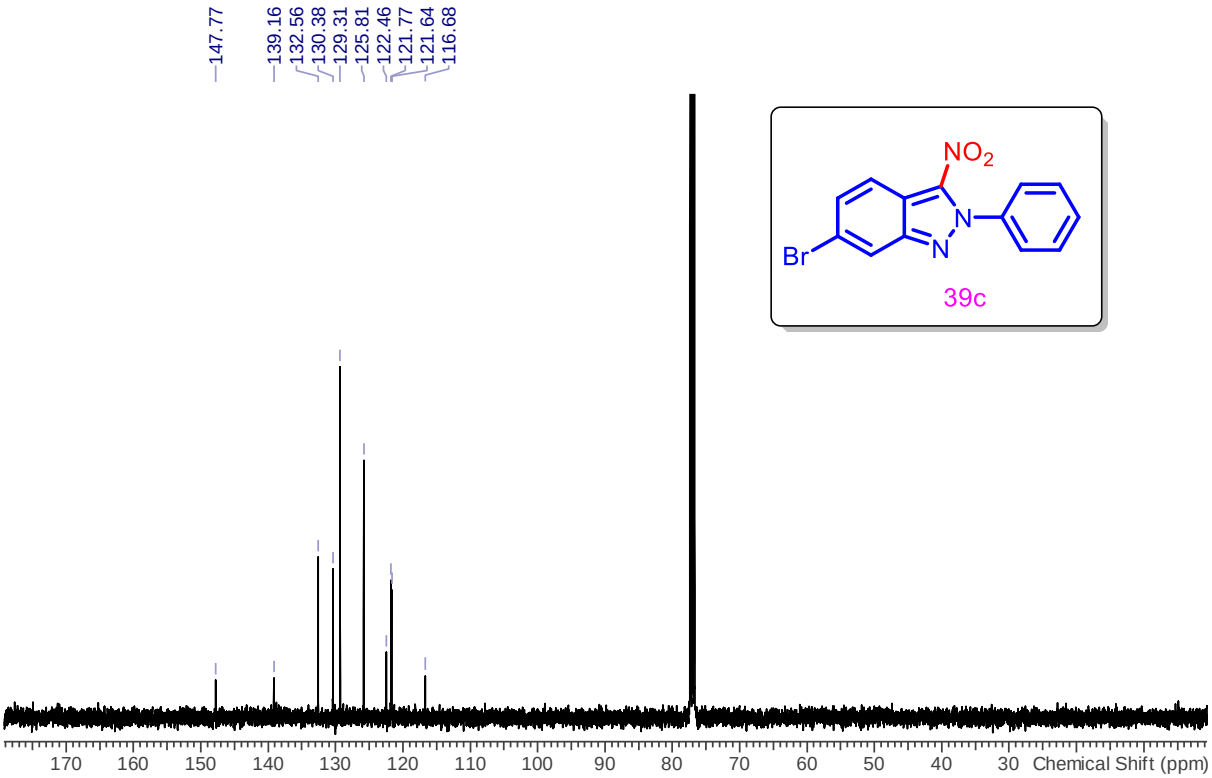
^{1}H NMR (400 MHz) spectrum of compound **39b**in $CDCl_3$



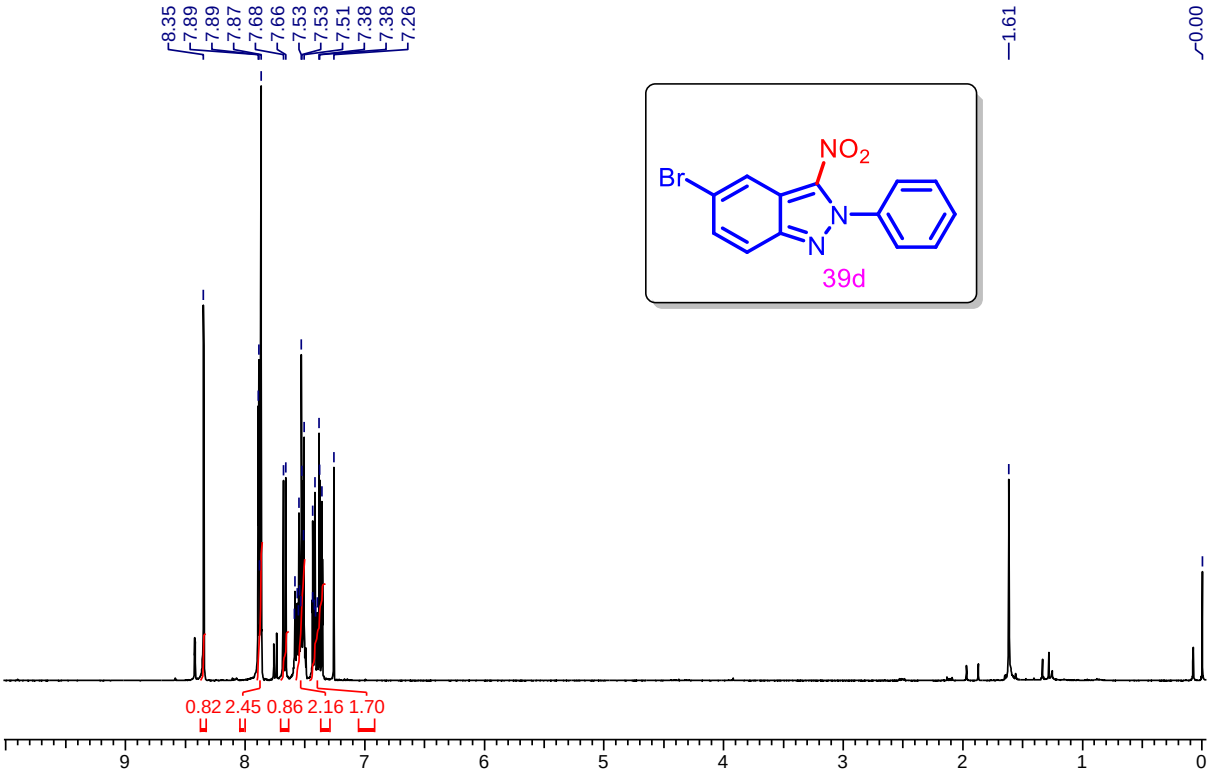
^{13}C NMR (100 MHz) spectrum of compound **39b** in $CDCl_3$



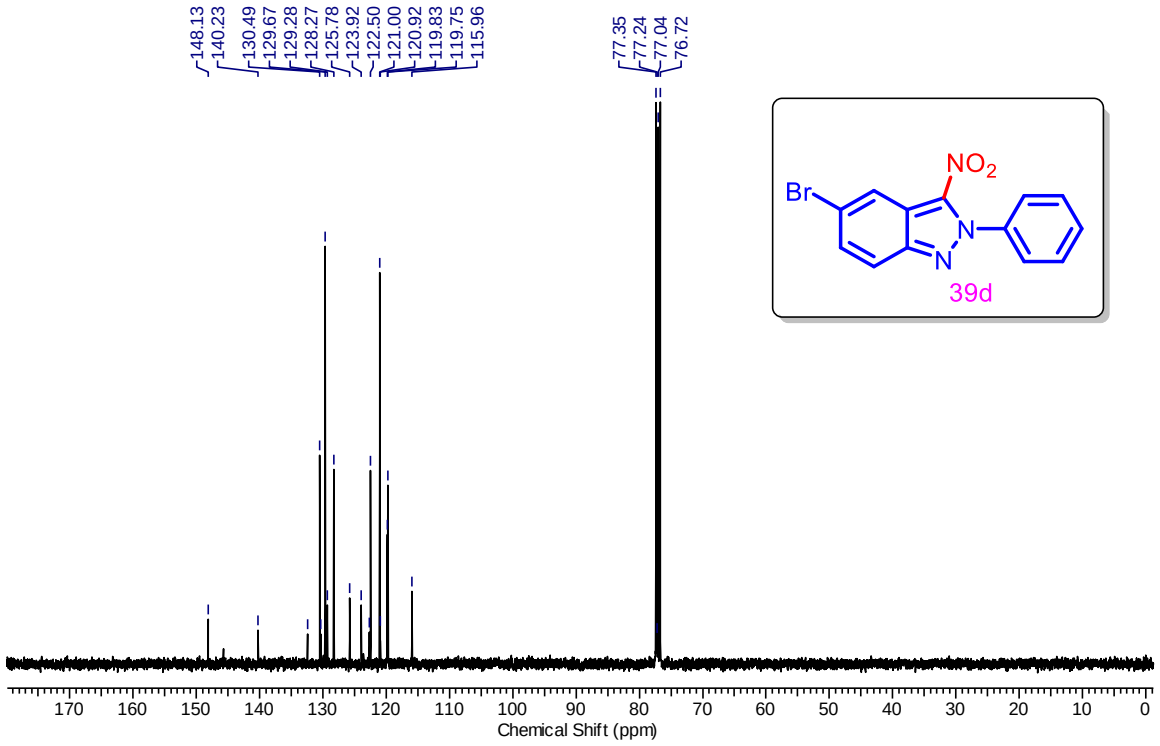
^{1}H NMR (400 MHz) spectrum of compound **39c**in $CDCl_3$



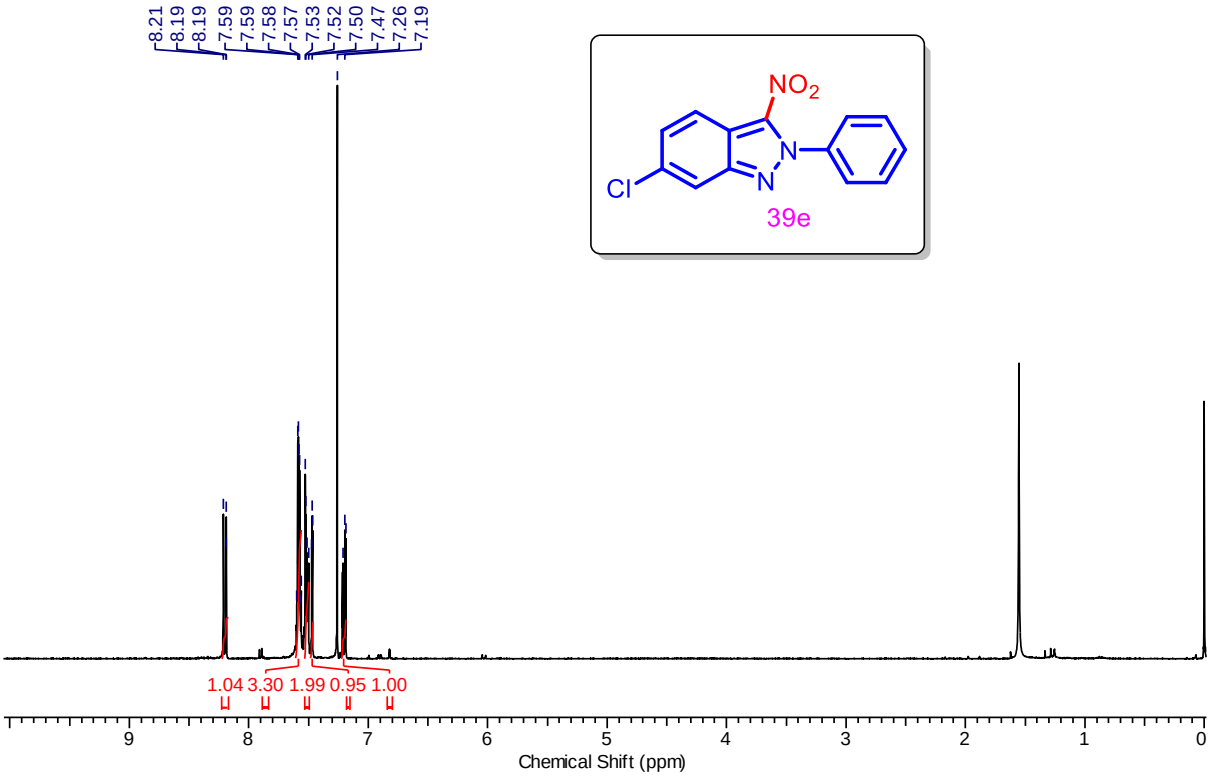
^{13}C NMR (100 MHz) spectrum of compound **39c** in $CDCl_3$



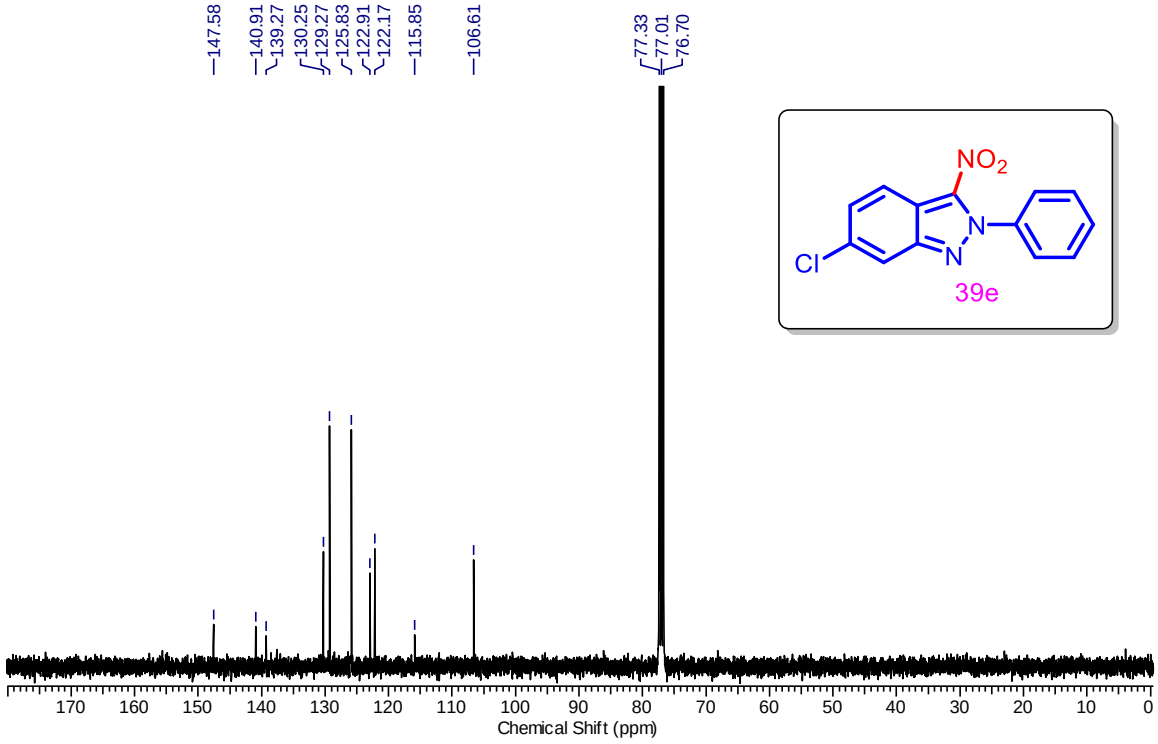
^{1}H NMR (400 MHz) spectrum of compound **39d** in $CDCl_3$



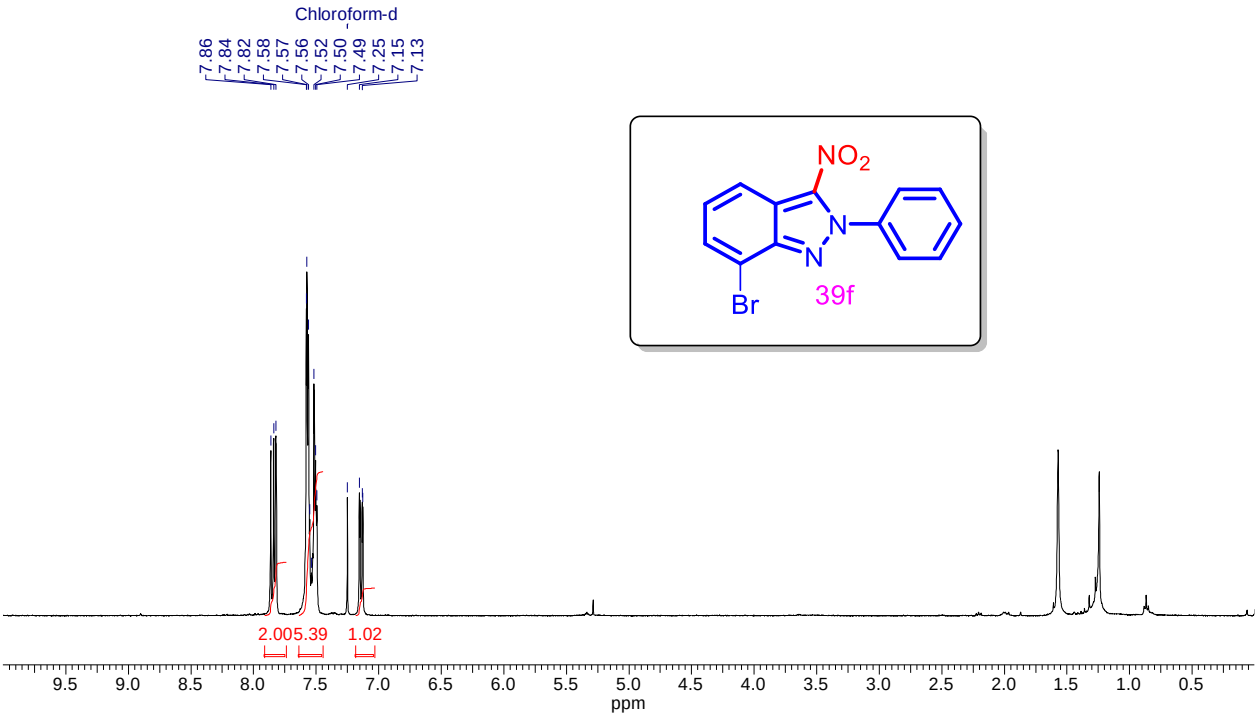
^{13}C NMR (100 MHz) spectrum of compound **39d** in $CDCl_3$



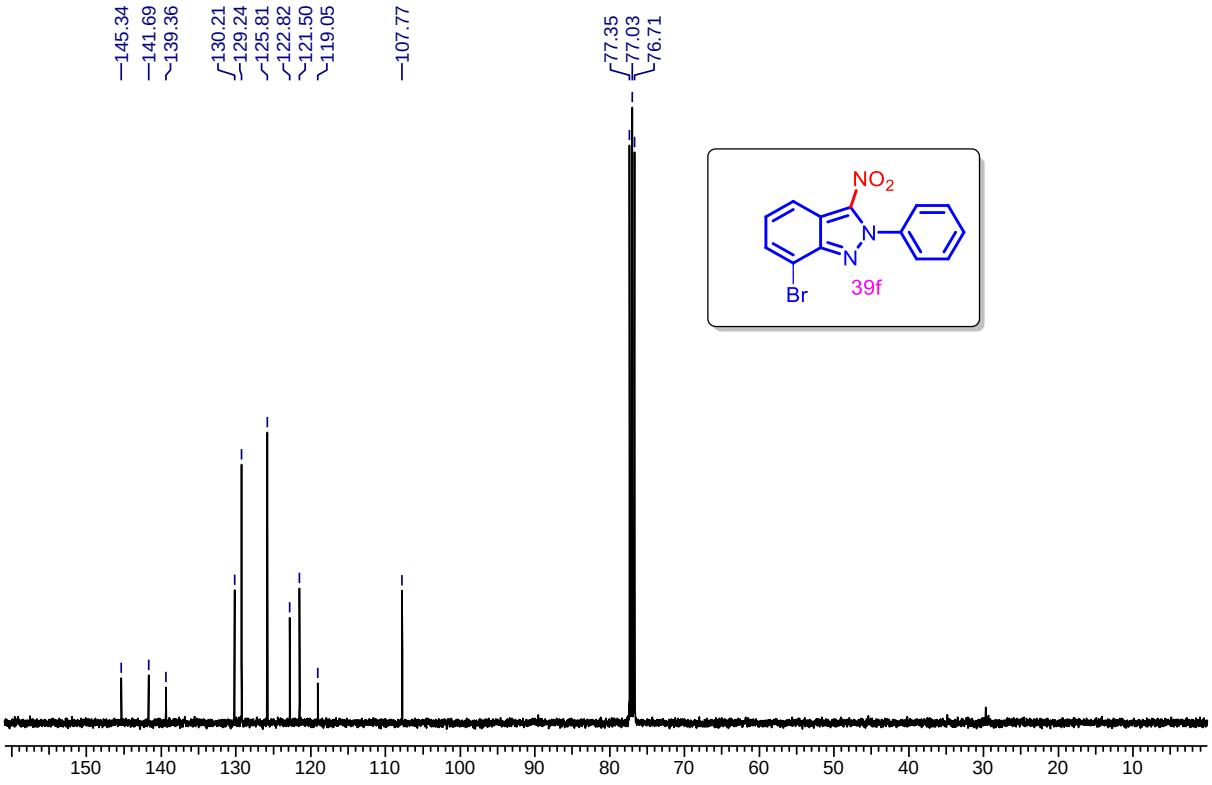
^{1}H NMR (400 MHz) spectrum of compound **39e** in $CDCl_3$



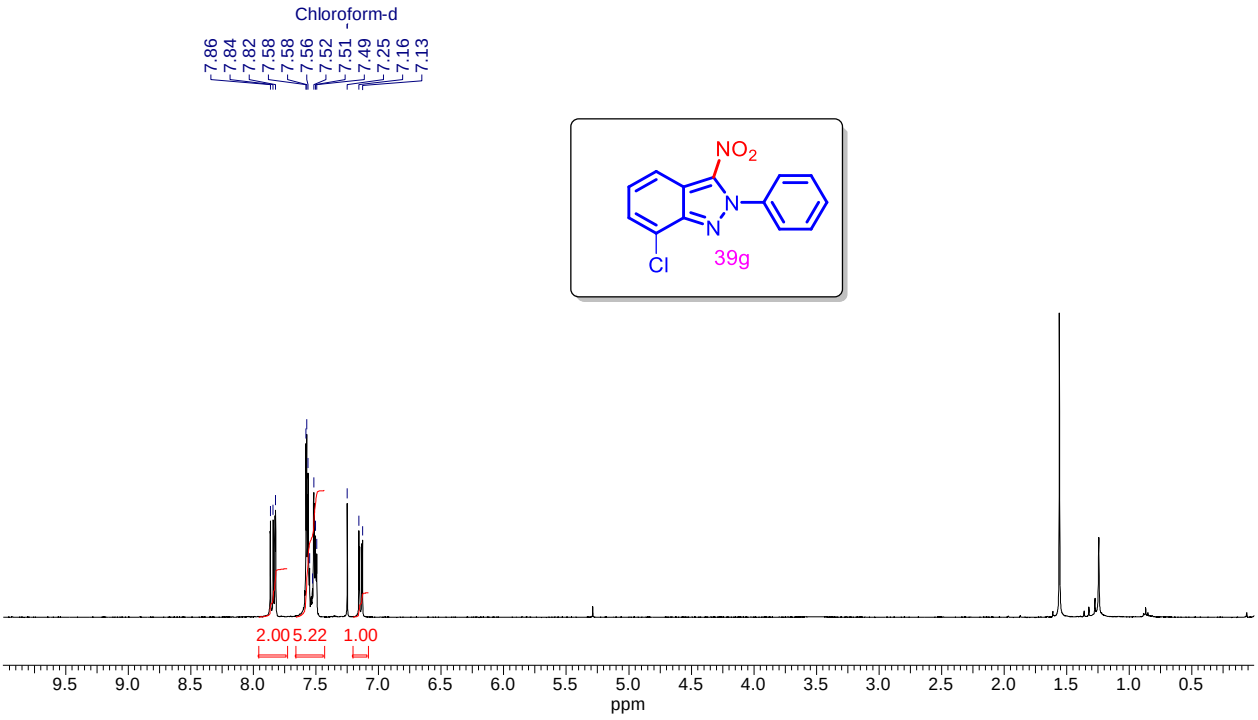
^{13}C NMR (100 MHz) spectrum of compound **39e** in $CDCl_3$



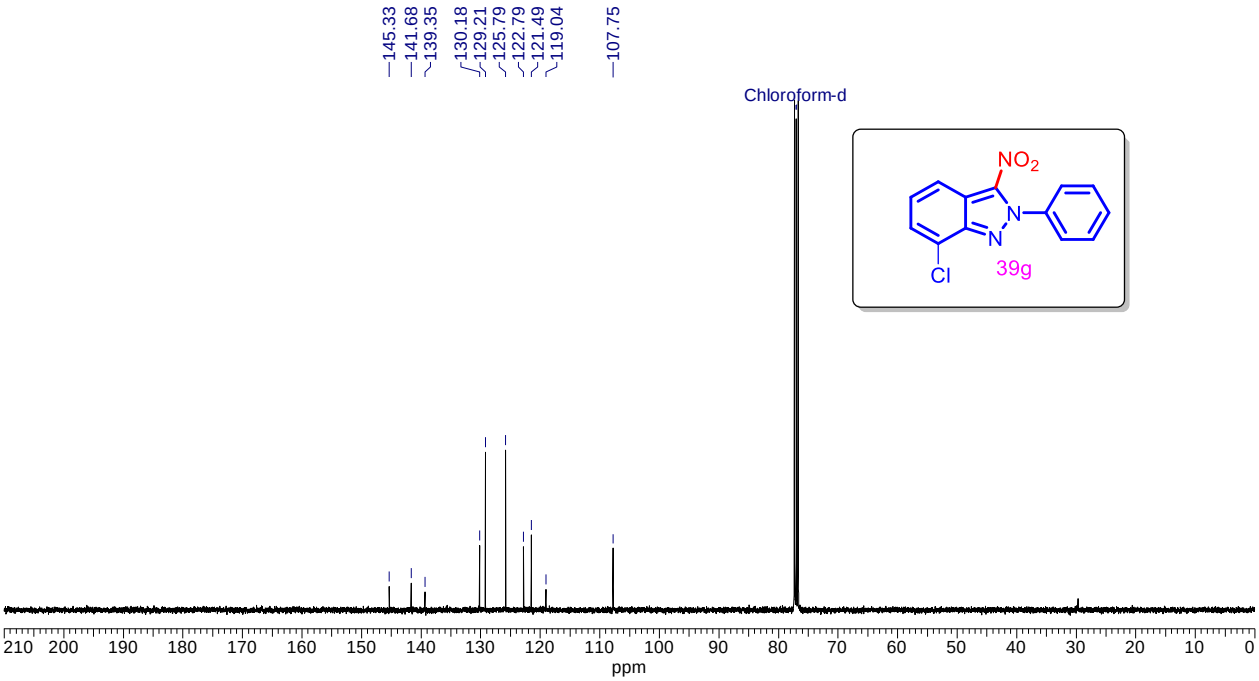
^{1}H NMR (400 MHz) spectrum of compound **39f** in $CDCl_3$



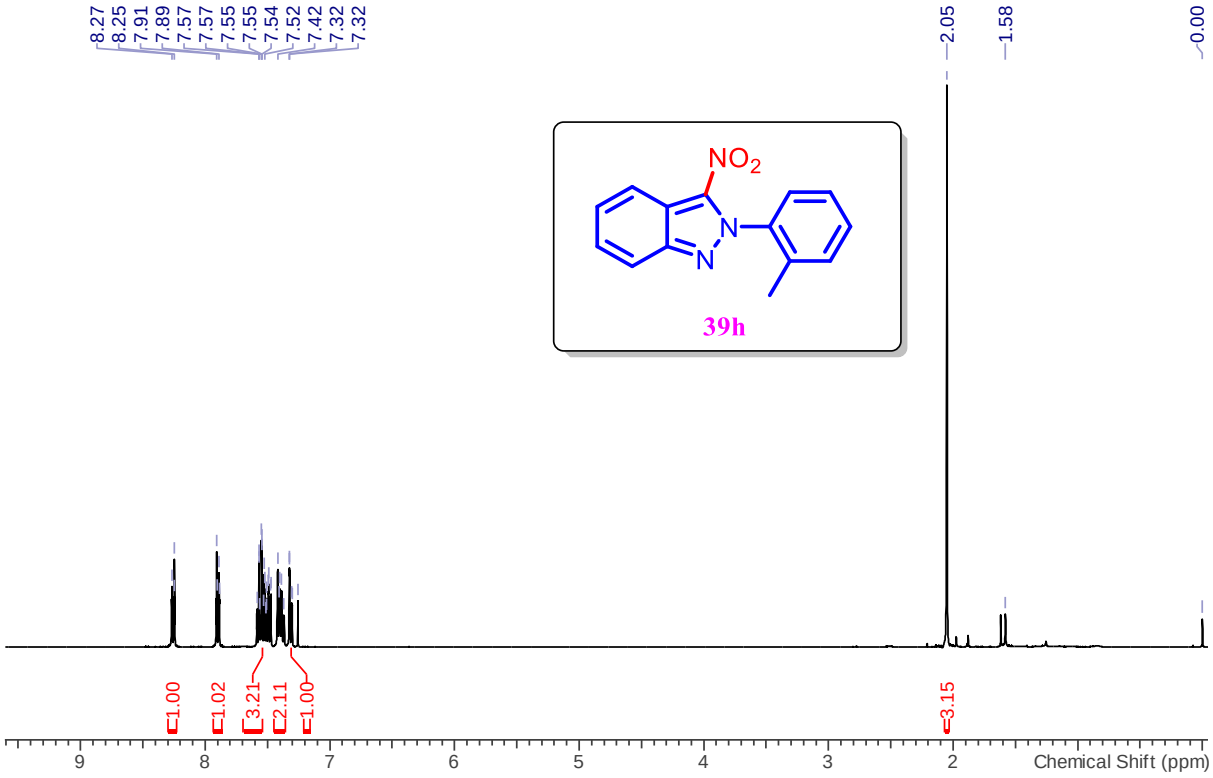
^{13}C NMR (100 MHz) spectrum of compound **39f** in $CDCl_3$



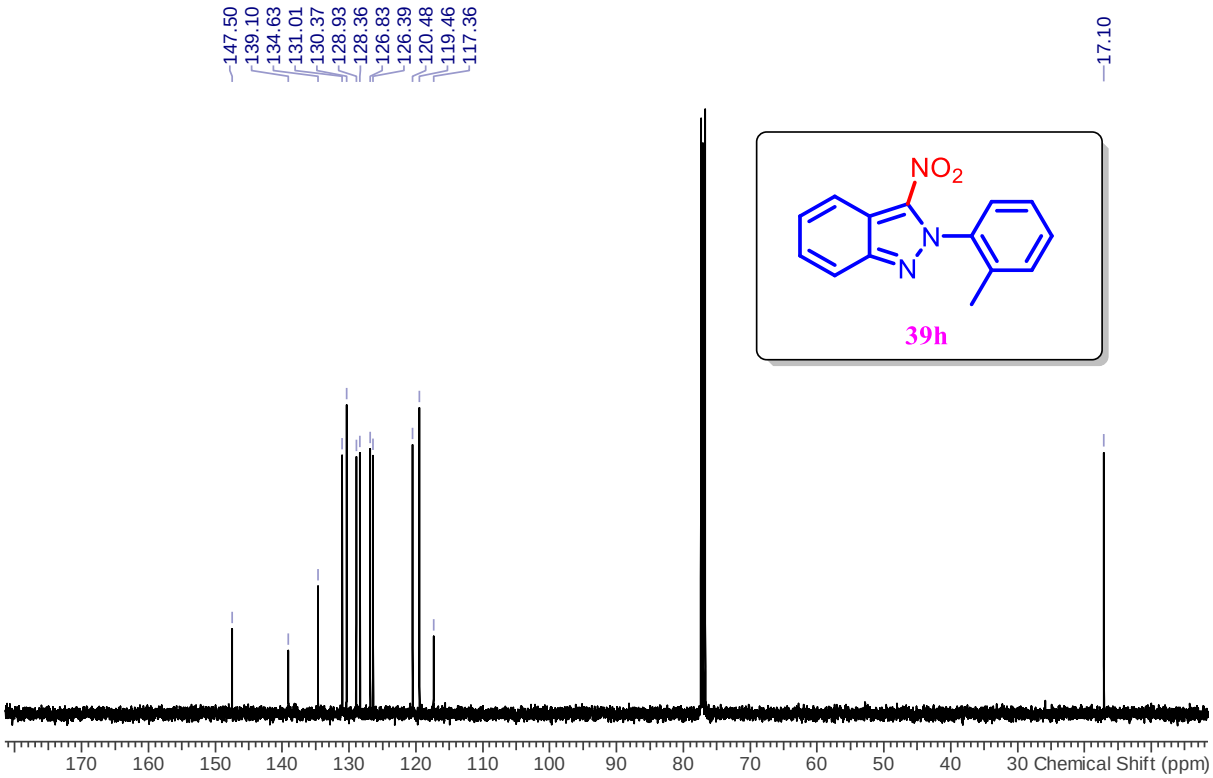
^{1}H NMR (400 MHz) spectrum of compound **39g** in $CDCl_3$



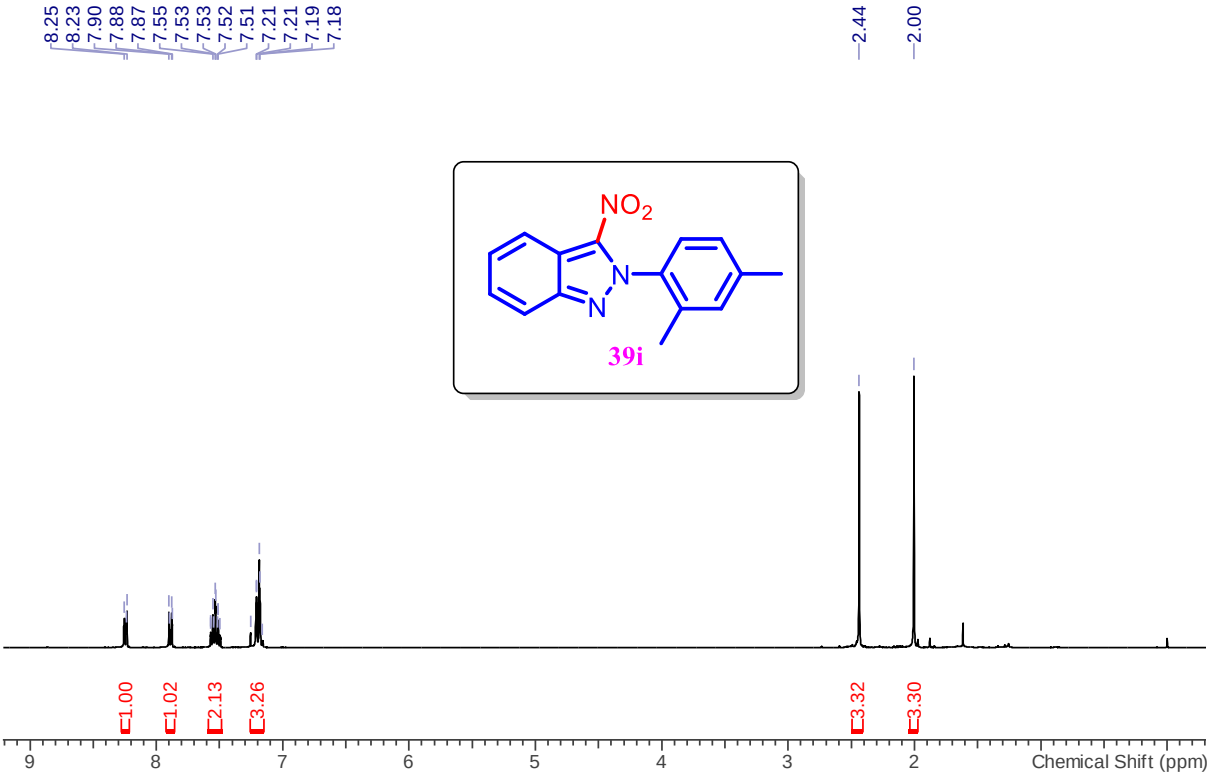
^{13}C NMR (100 MHz) spectrum of compound **39g** in $CDCl_3$



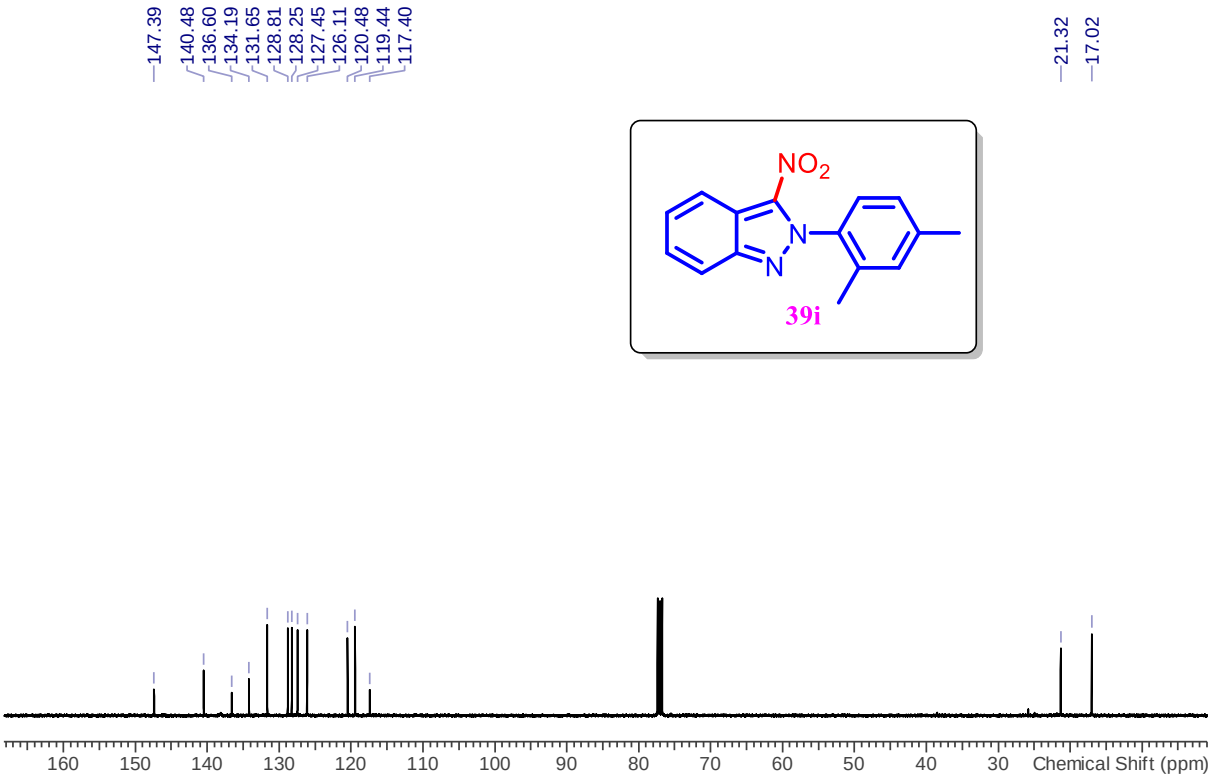
^{1}H NMR (400 MHz) spectrum of compound **39h** in $CDCl_3$



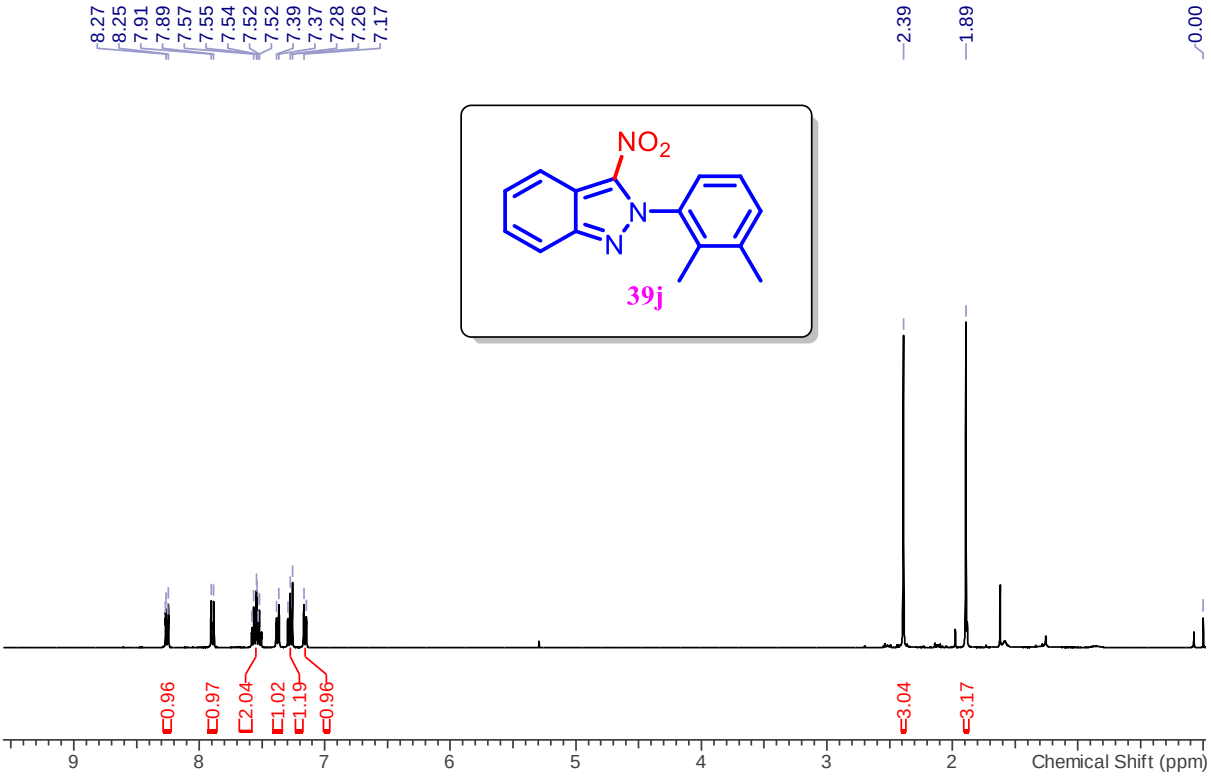
^{13}C NMR (100 MHz) spectrum of compound **39h** in $CDCl_3$



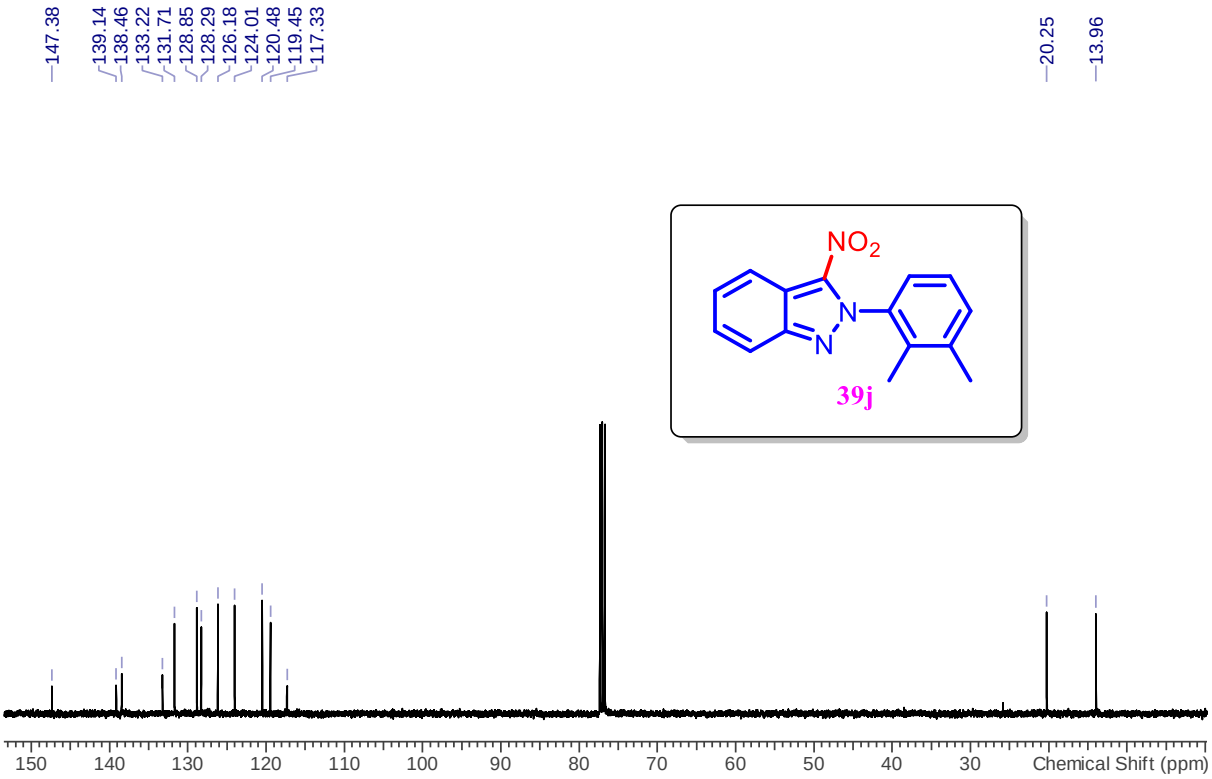
^{1}H NMR (400 MHz) spectrum of compound **39i** in $CDCl_3$



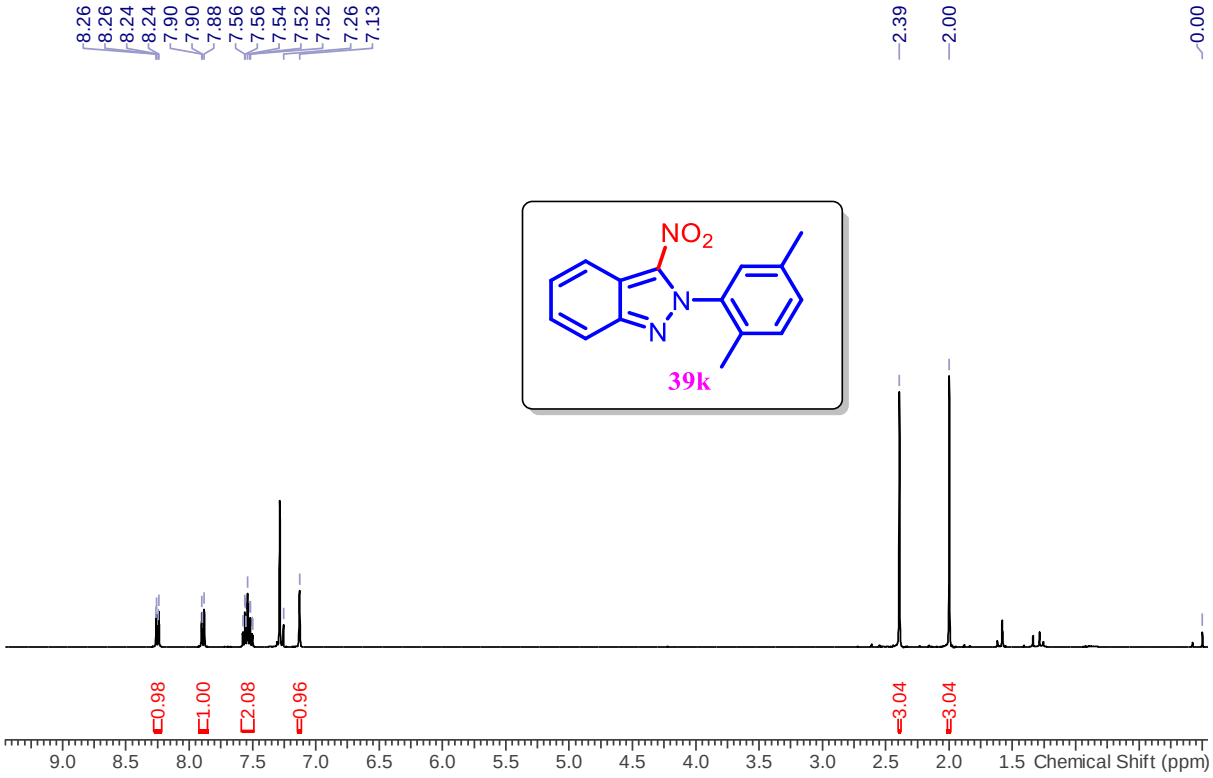
^{13}C NMR (100 MHz) spectrum of compound **39i** in $CDCl_3$



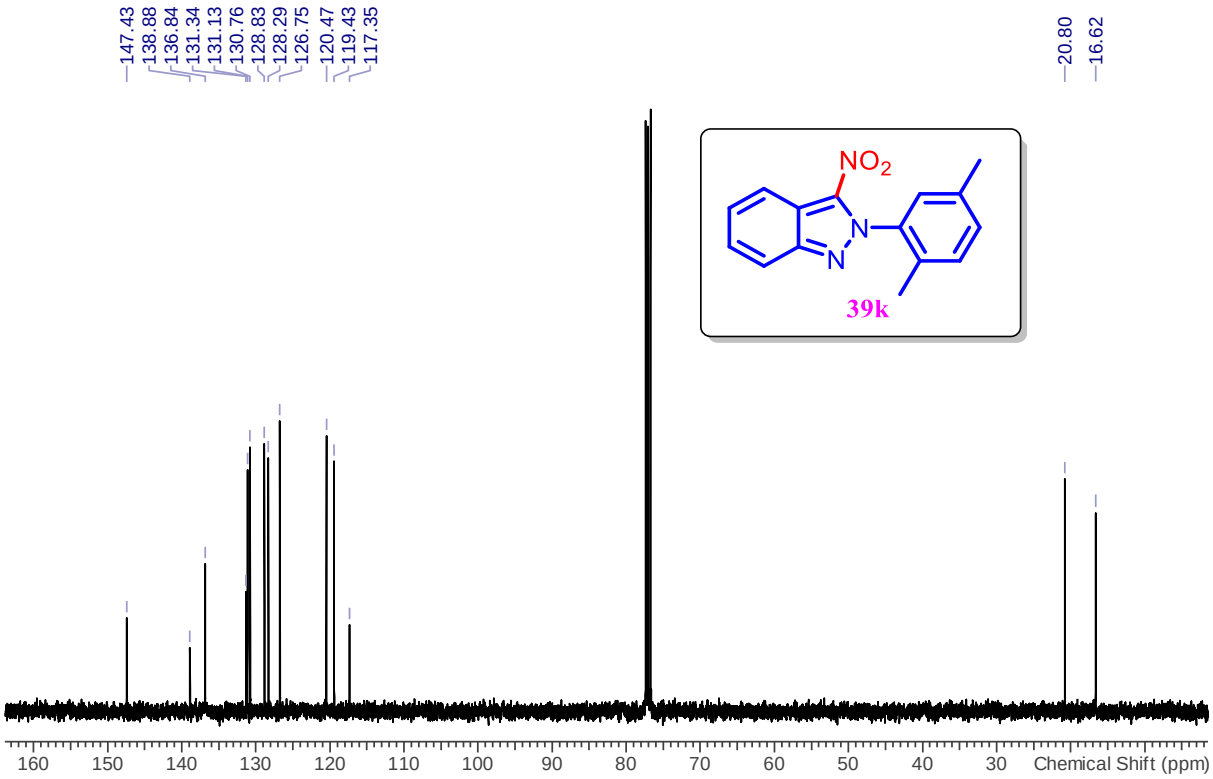
^{1}H NMR (400 MHz) spectrum of compound **39j** in $CDCl_3$



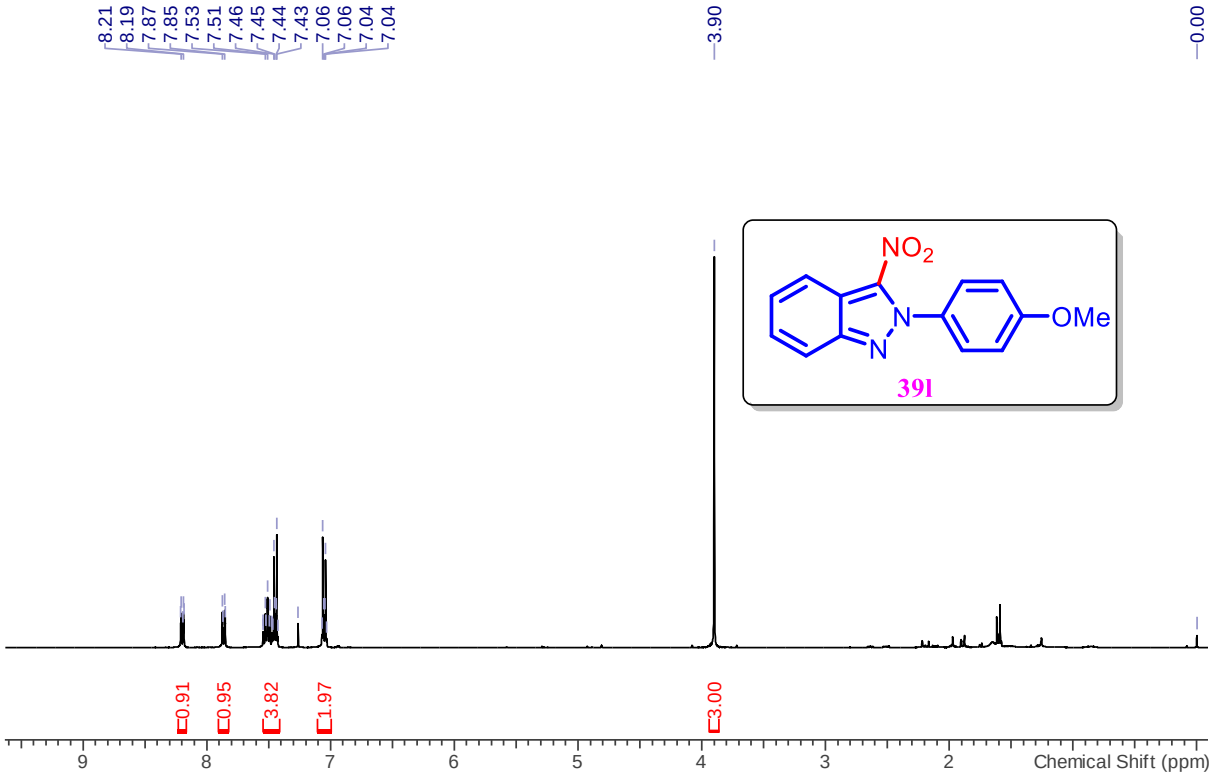
^{13}C NMR (100 MHz) spectrum of compound **39j** in $CDCl_3$



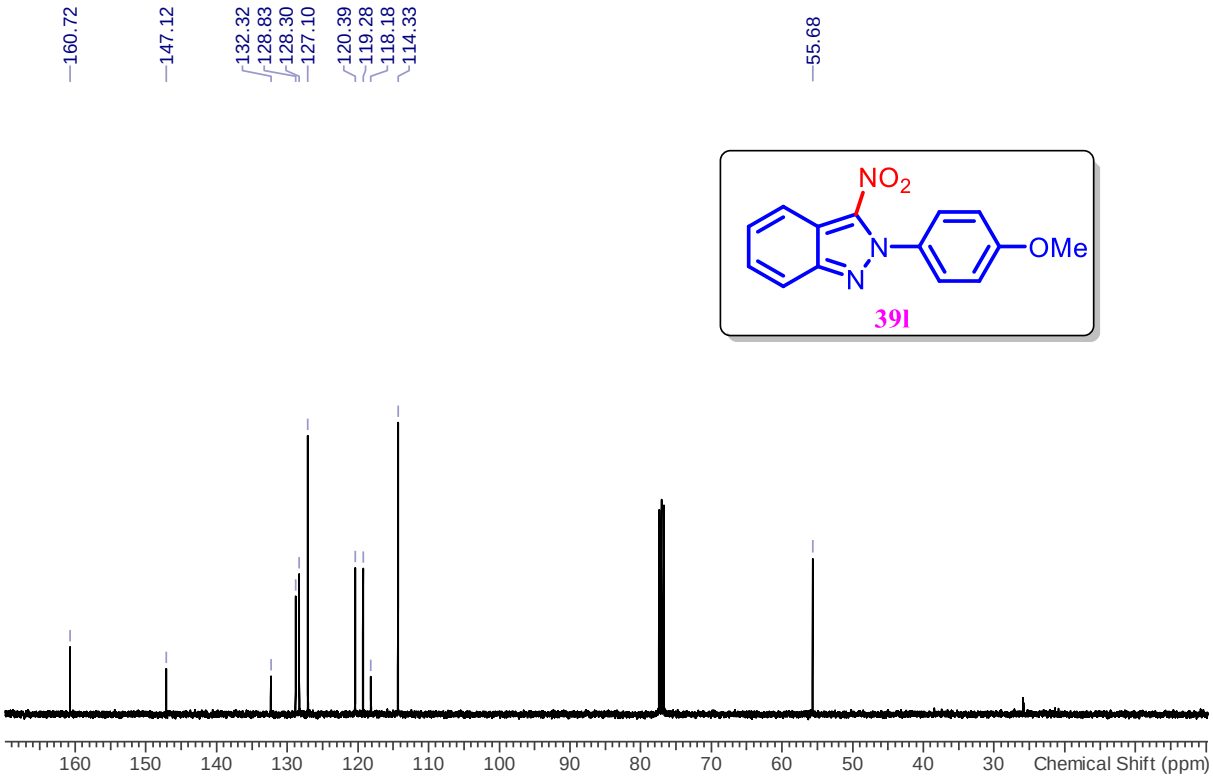
^{1}H NMR (400 MHz) spectrum of compound **39k** in $CDCl_3$



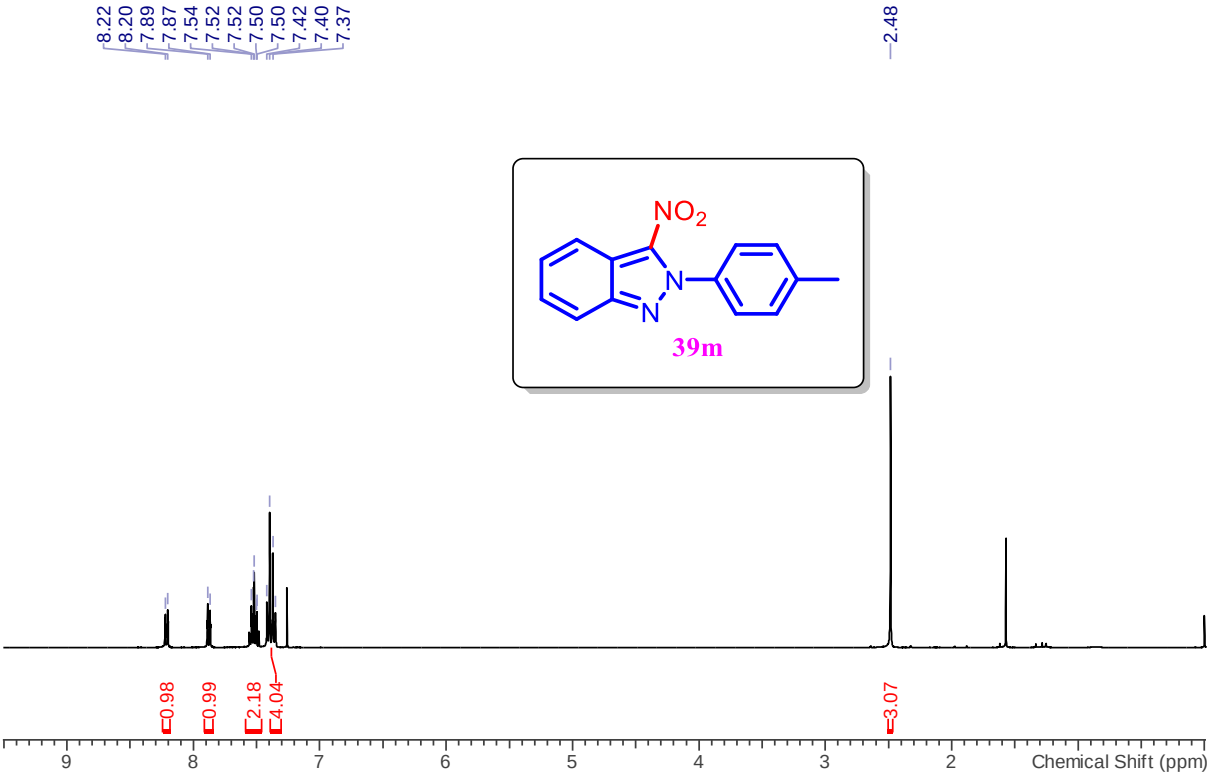
^{13}C NMR (100 MHz) spectrum of compound **39k** in $CDCl_3$



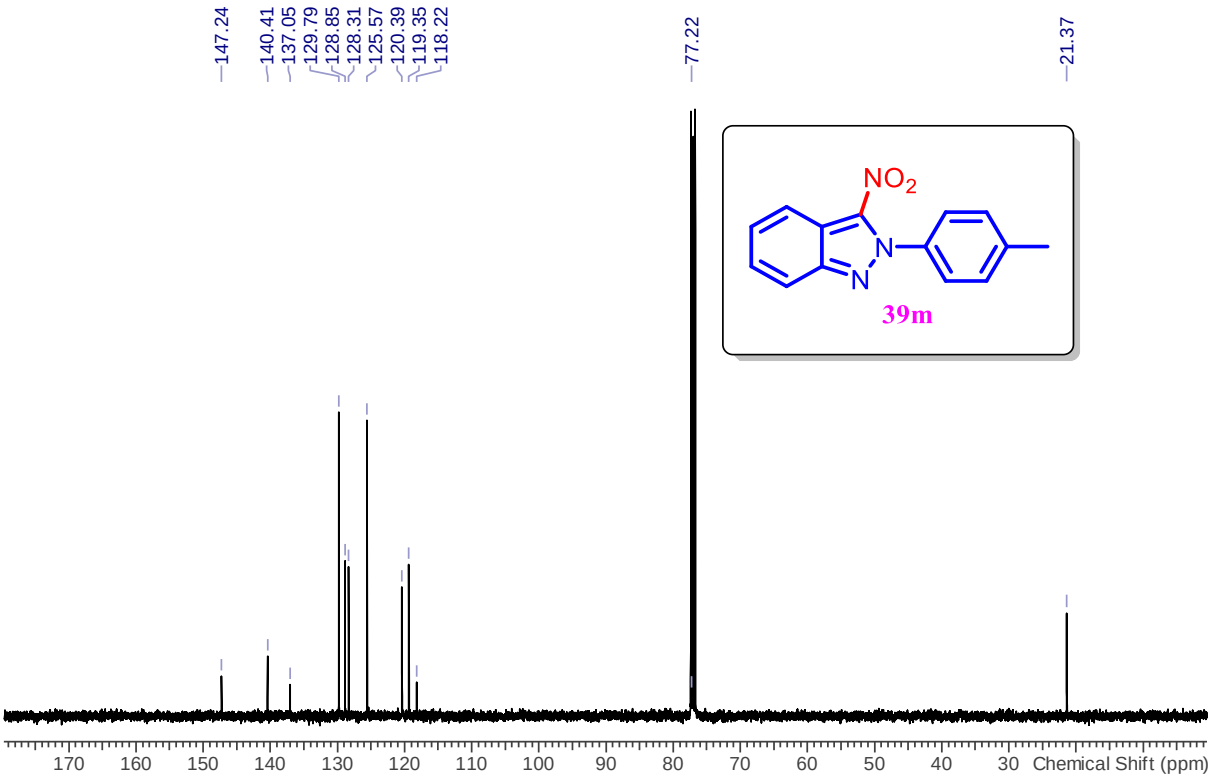
^{1}H NMR (400 MHz) spectrum of compound **39l** in $CDCl_3$



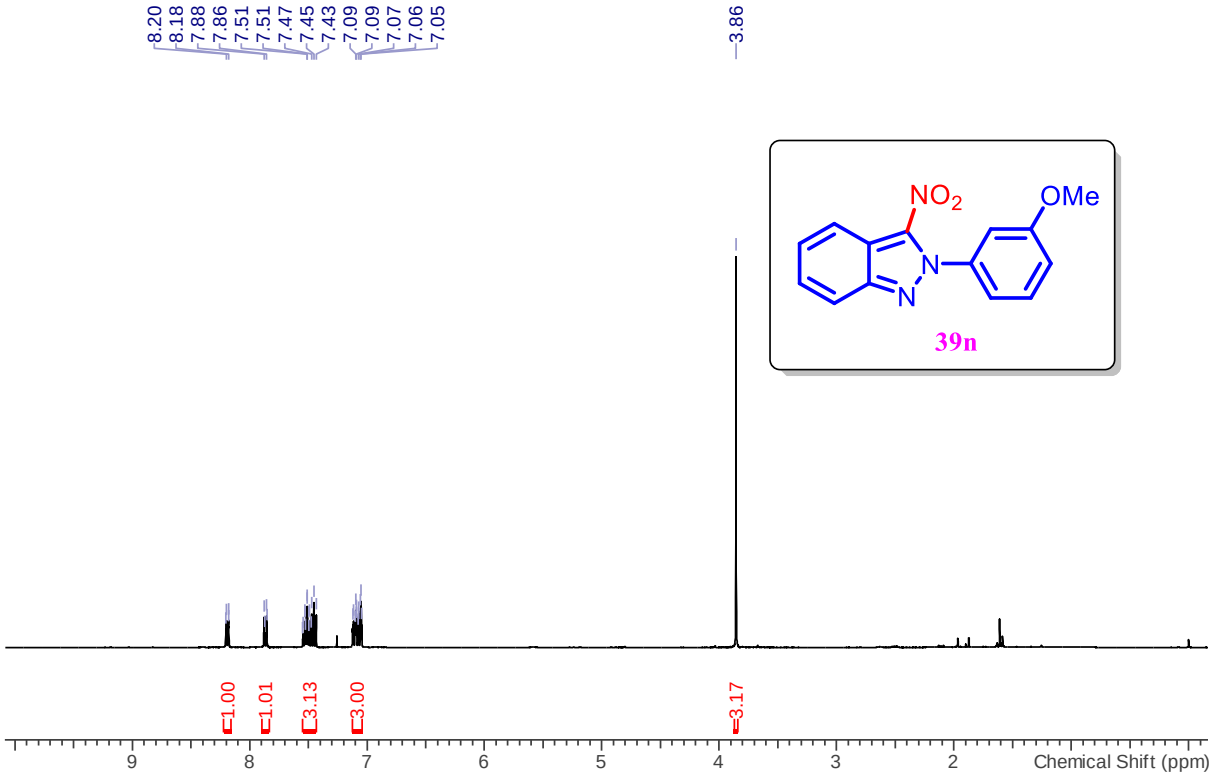
^{13}C NMR (100 MHz) spectrum of compound **39l** in $CDCl_3$



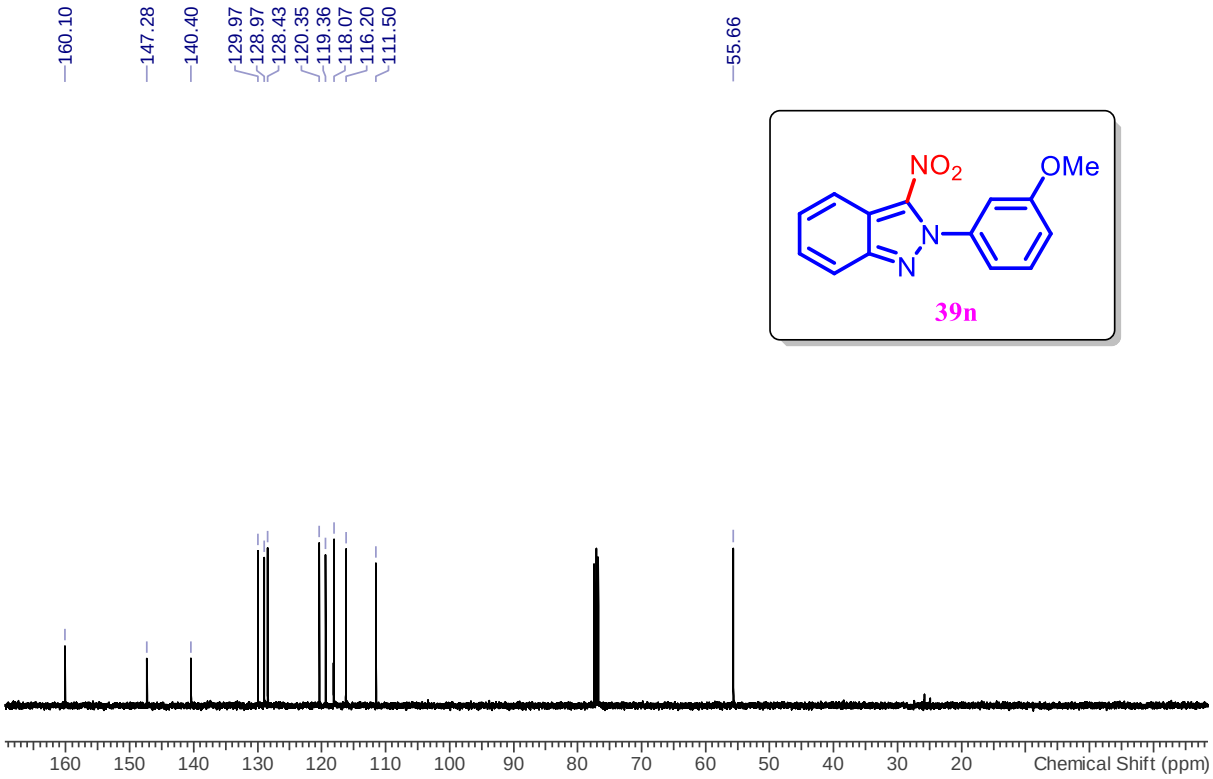
^{1}H NMR (400 MHz) spectrum of compound **39m** in $CDCl_3$



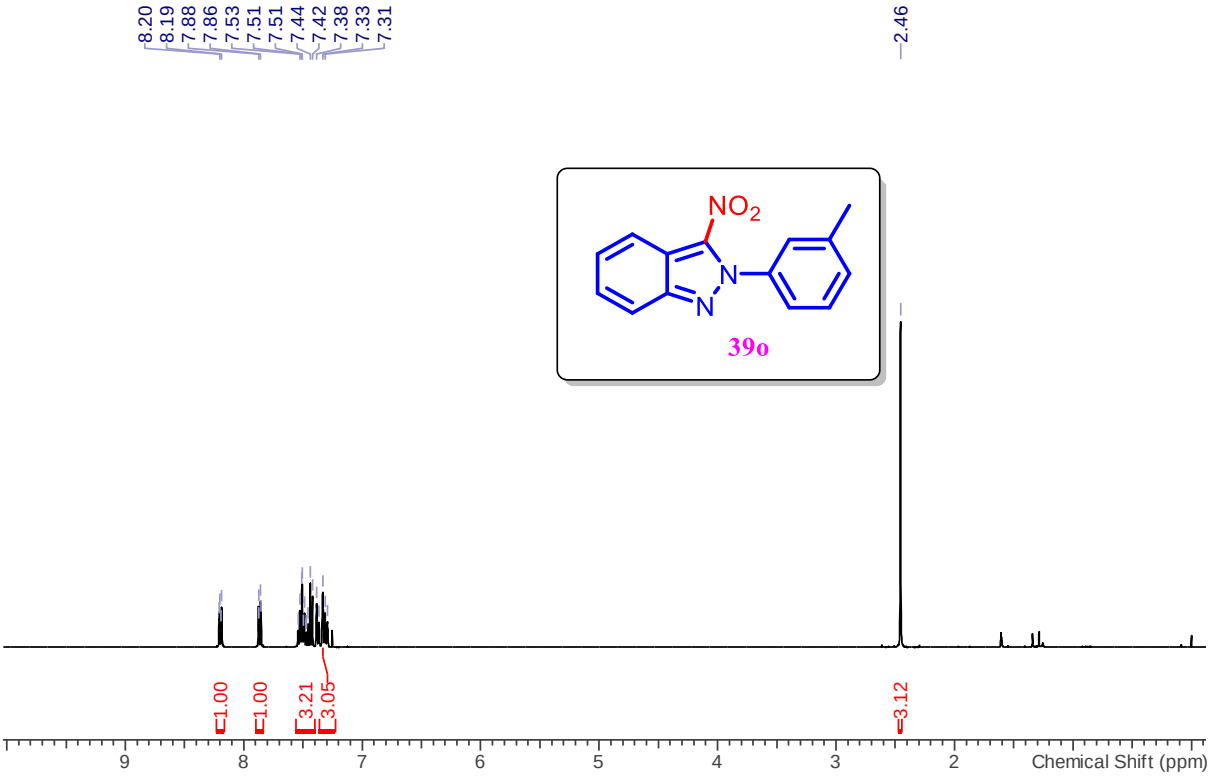
^{13}C NMR (100 MHz) spectrum of compound **39m** in $CDCl_3$



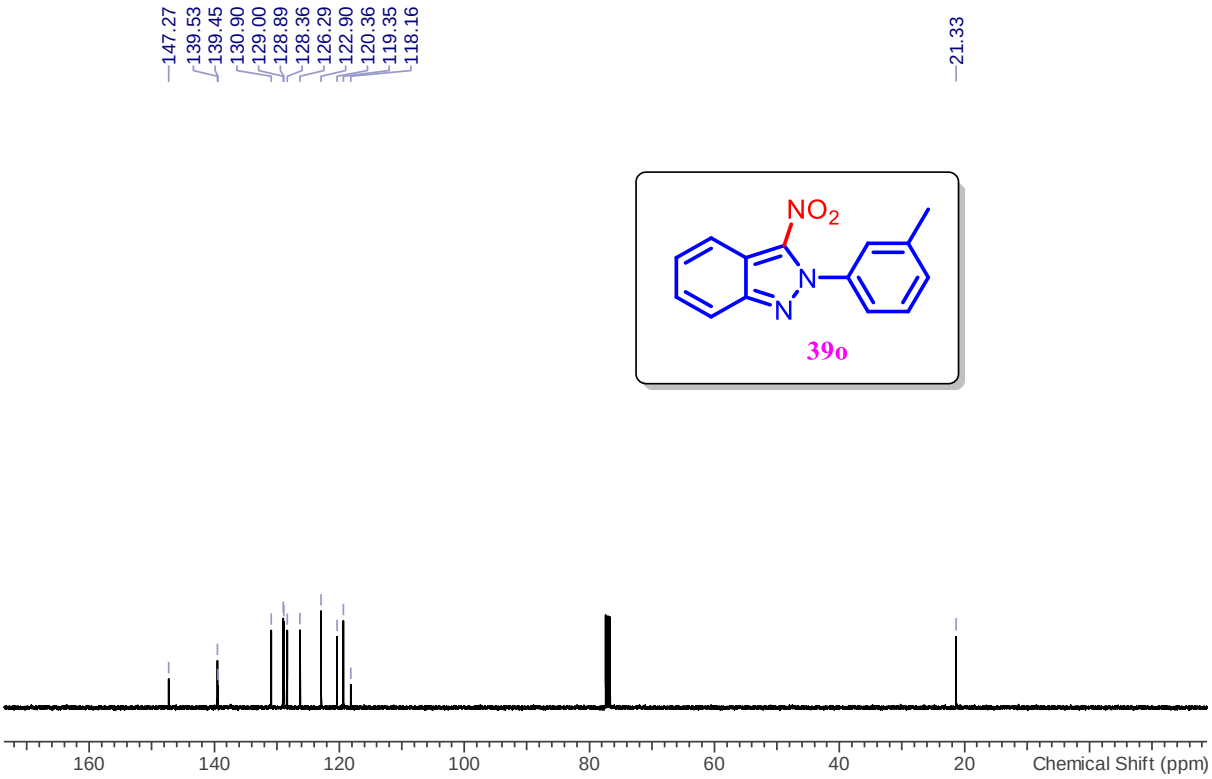
^{1}H NMR (400 MHz) spectrum of compound **39n** in $CDCl_3$



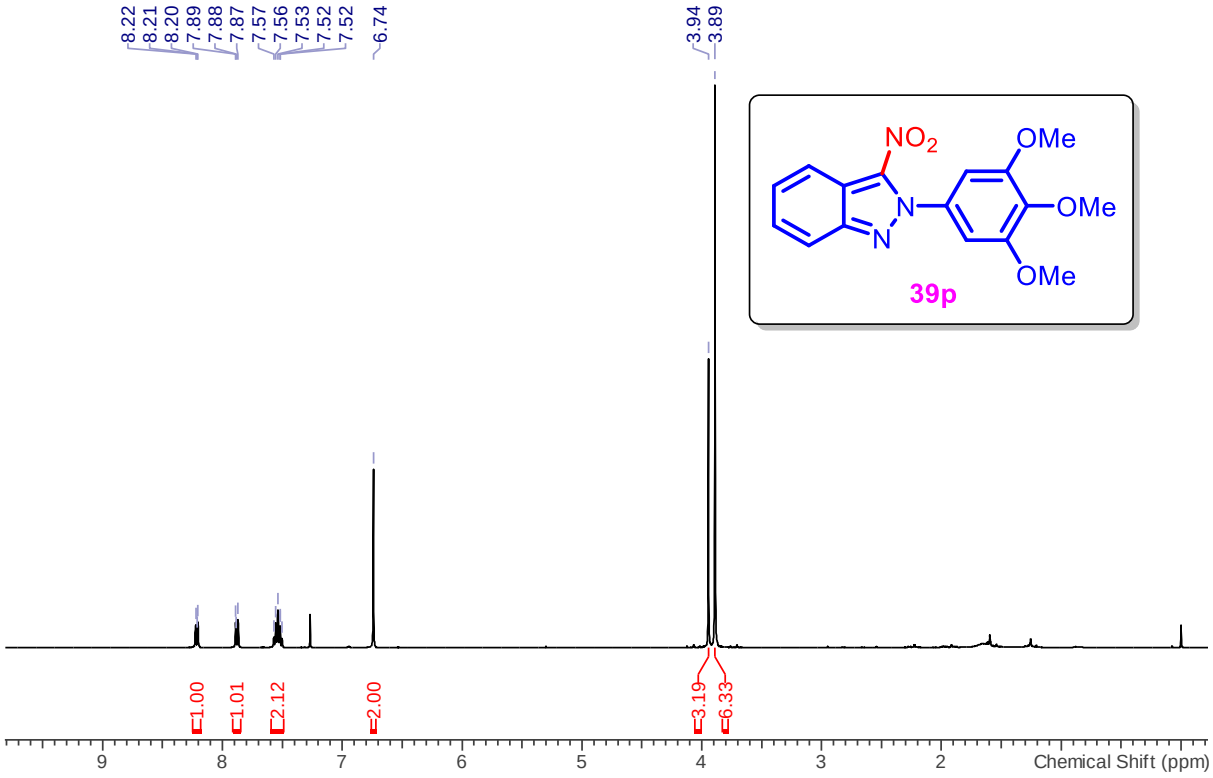
^{13}C NMR (100 MHz) spectrum of compound **39n** in $CDCl_3$



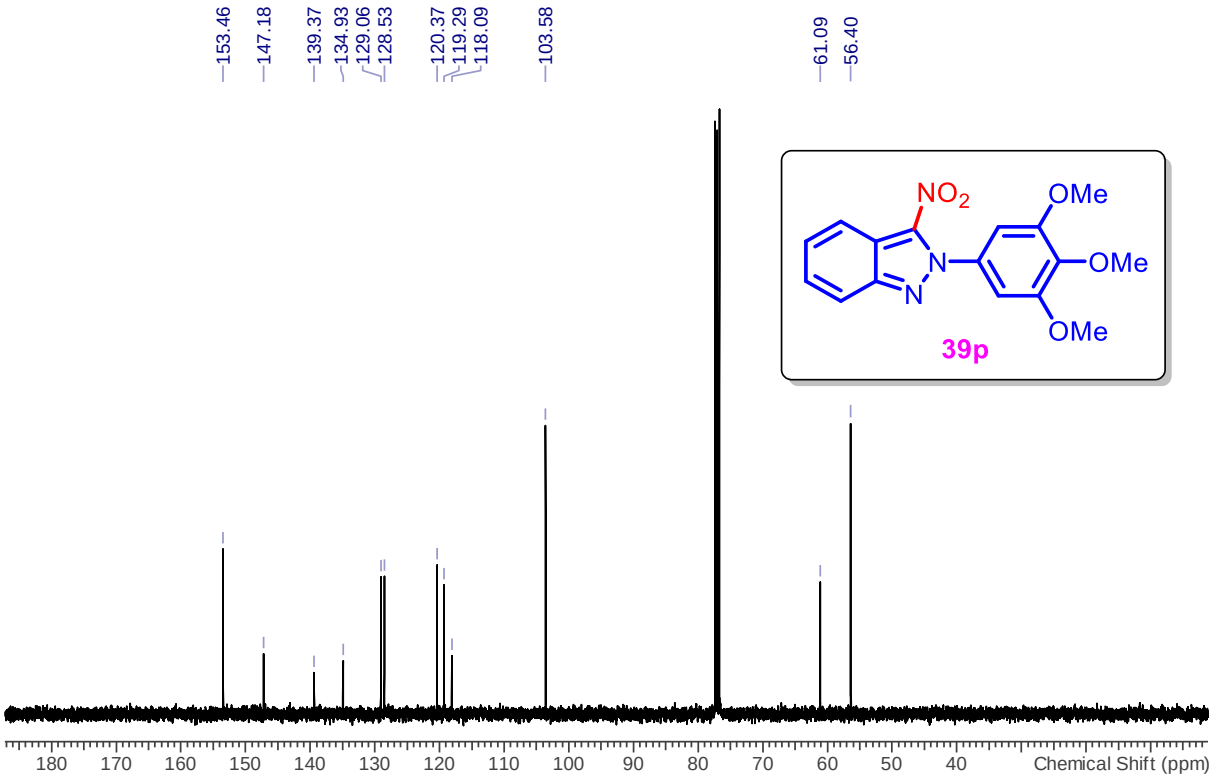
^{1}H NMR (400 MHz) spectrum of compound **39o** in $CDCl_3$



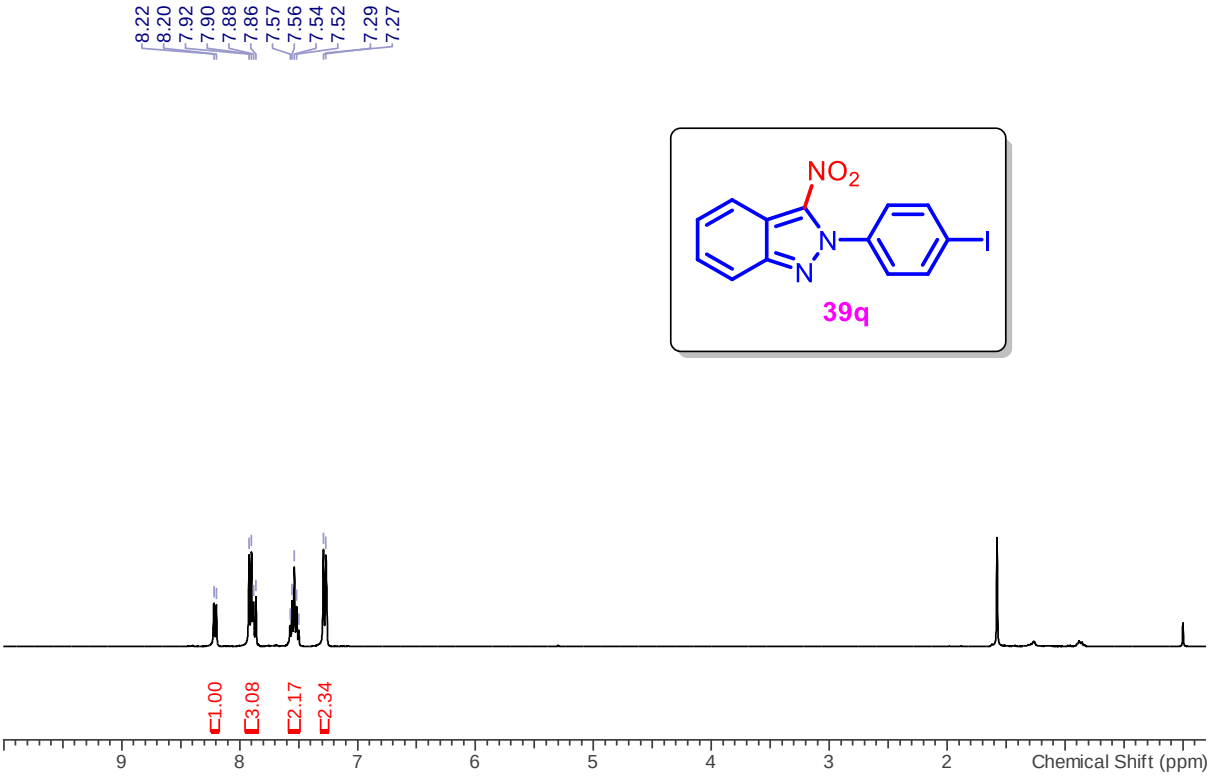
^{13}C NMR (100 MHz) spectrum of compound **39o** in $CDCl_3$



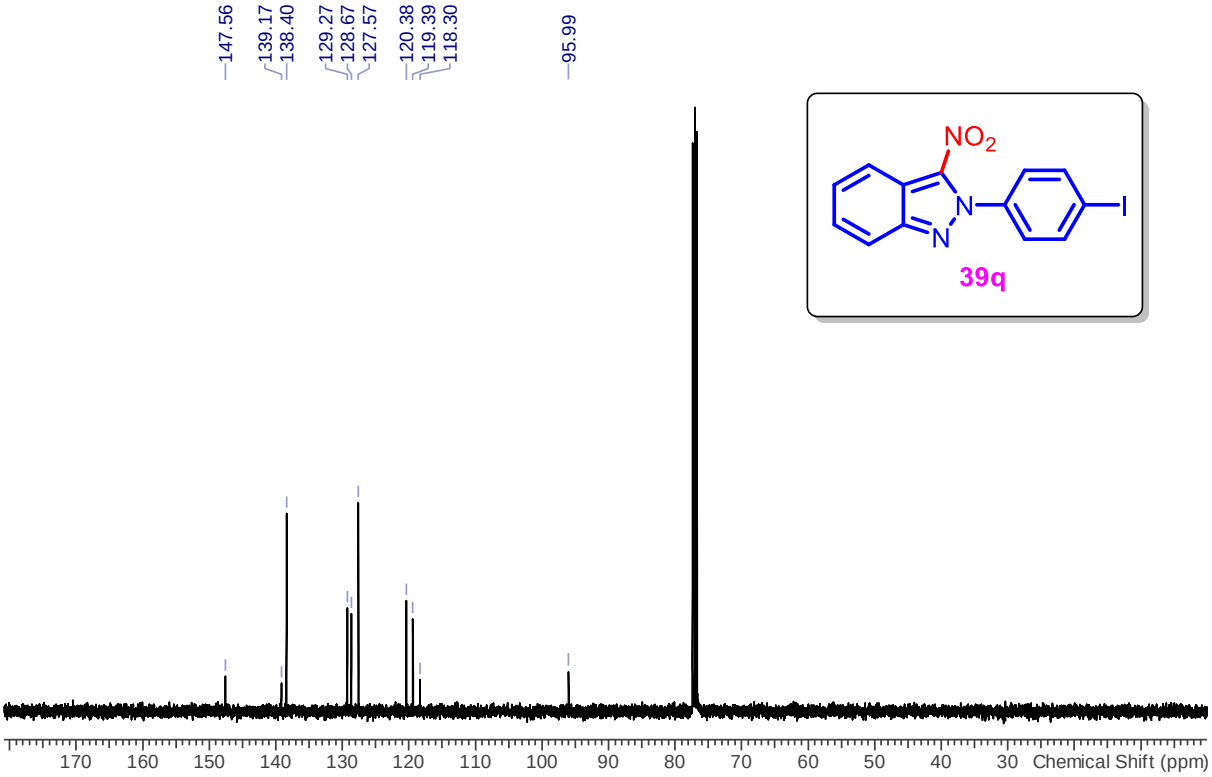
^{1}H NMR (400 MHz) spectrum of compound **39p** in $CDCl_3$



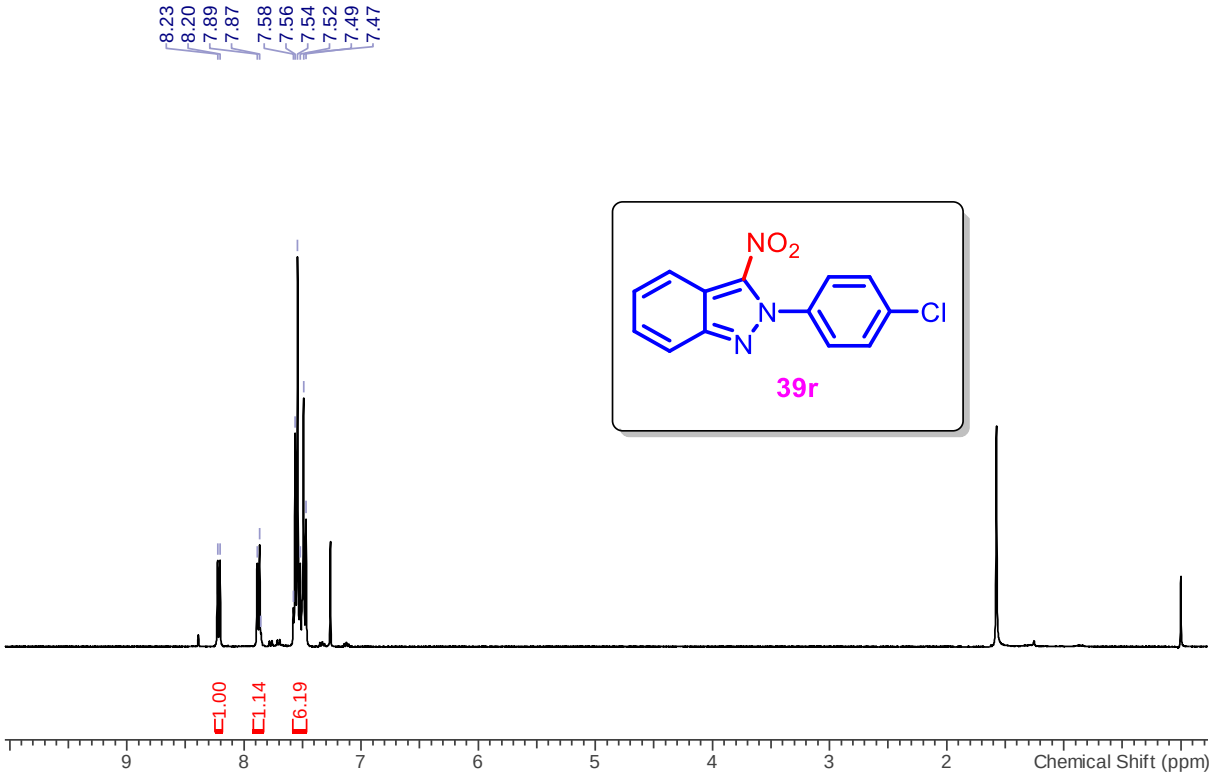
^{13}C NMR (100 MHz) spectrum of compound **39p** in $CDCl_3$



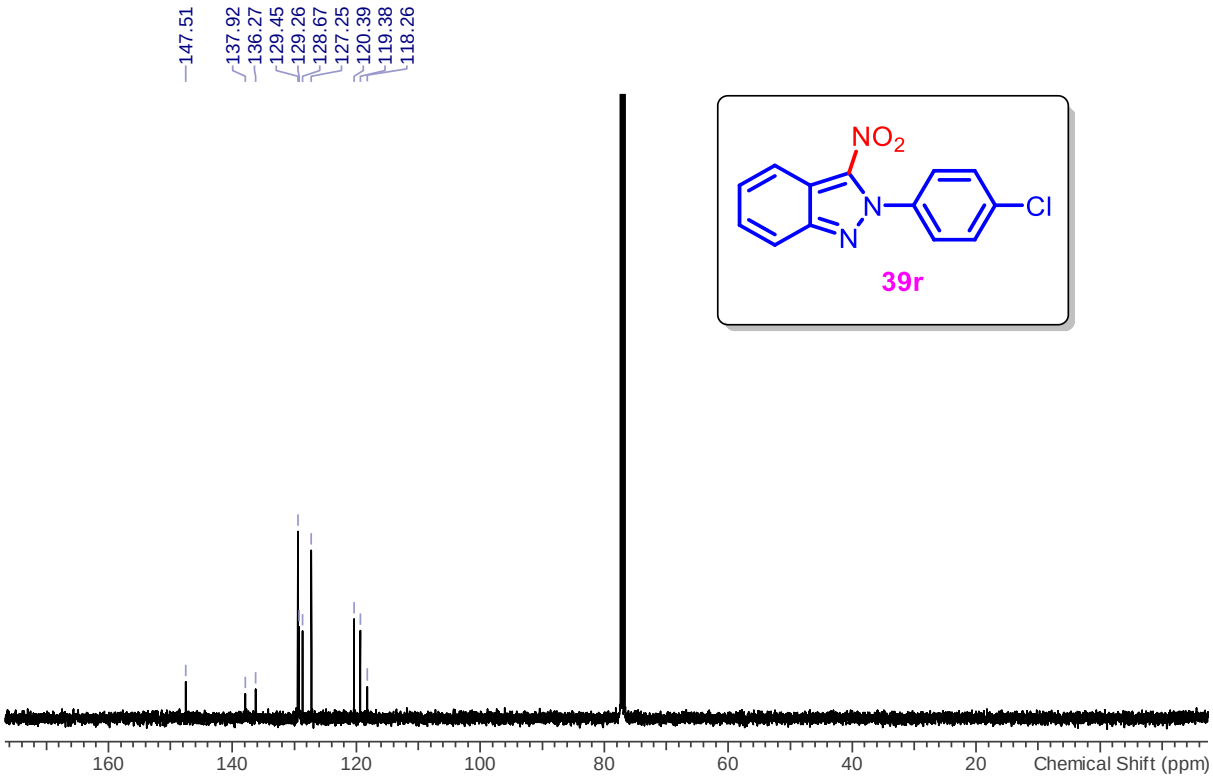
^{1}H NMR (400 MHz) spectrum of compound **39q** in $CDCl_3$



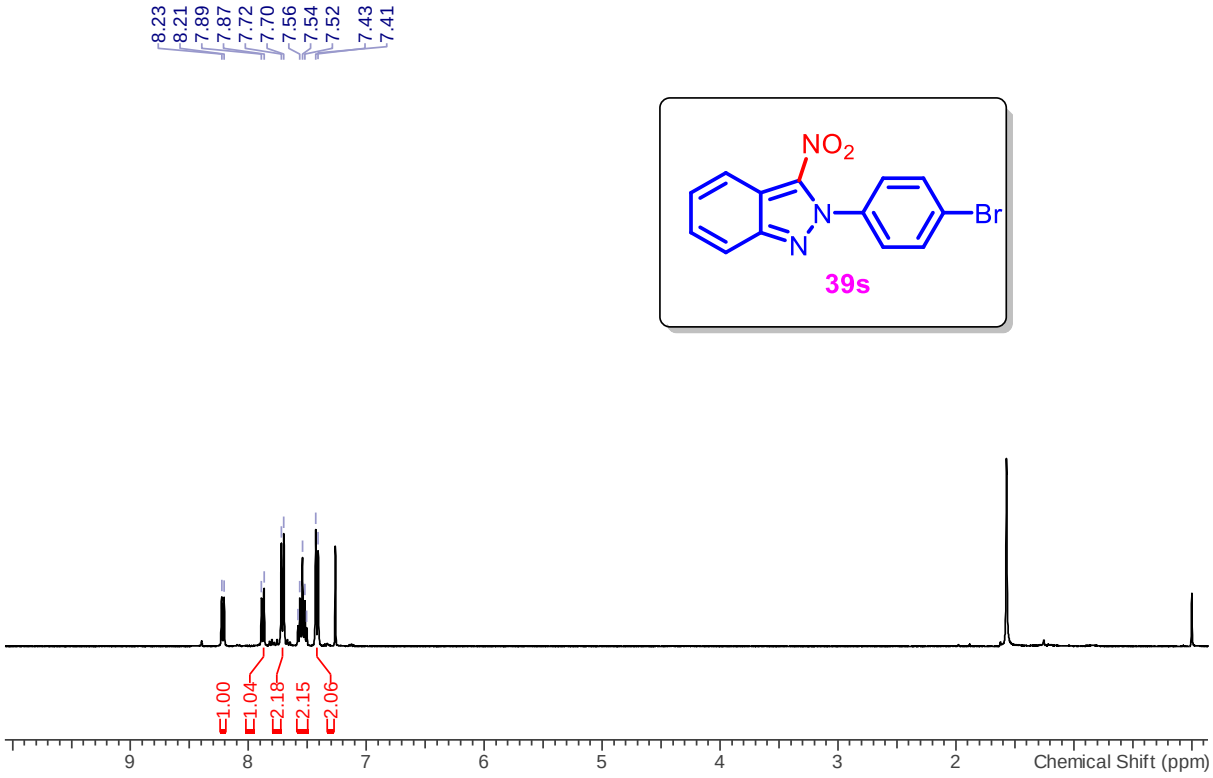
^{13}C NMR (100 MHz) spectrum of compound **39q** in $CDCl_3$



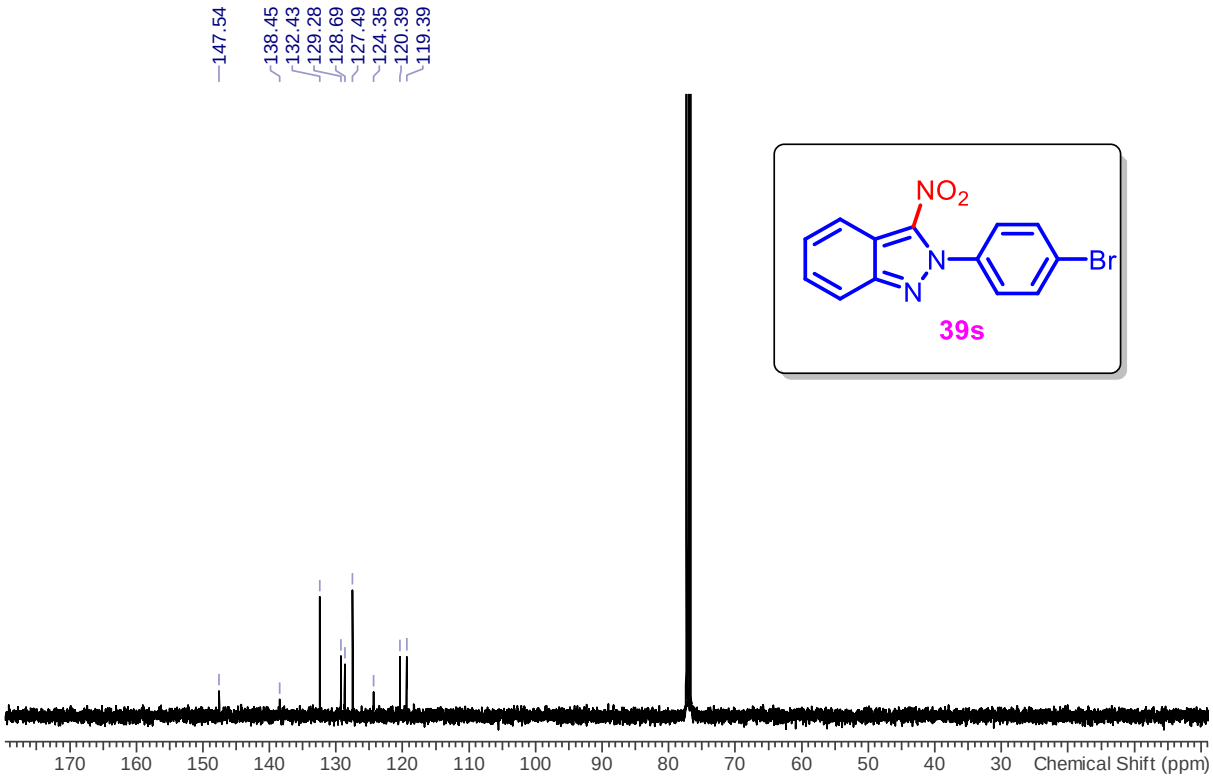
^{1}H NMR (400 MHz) spectrum of compound **39r** in $CDCl_3$



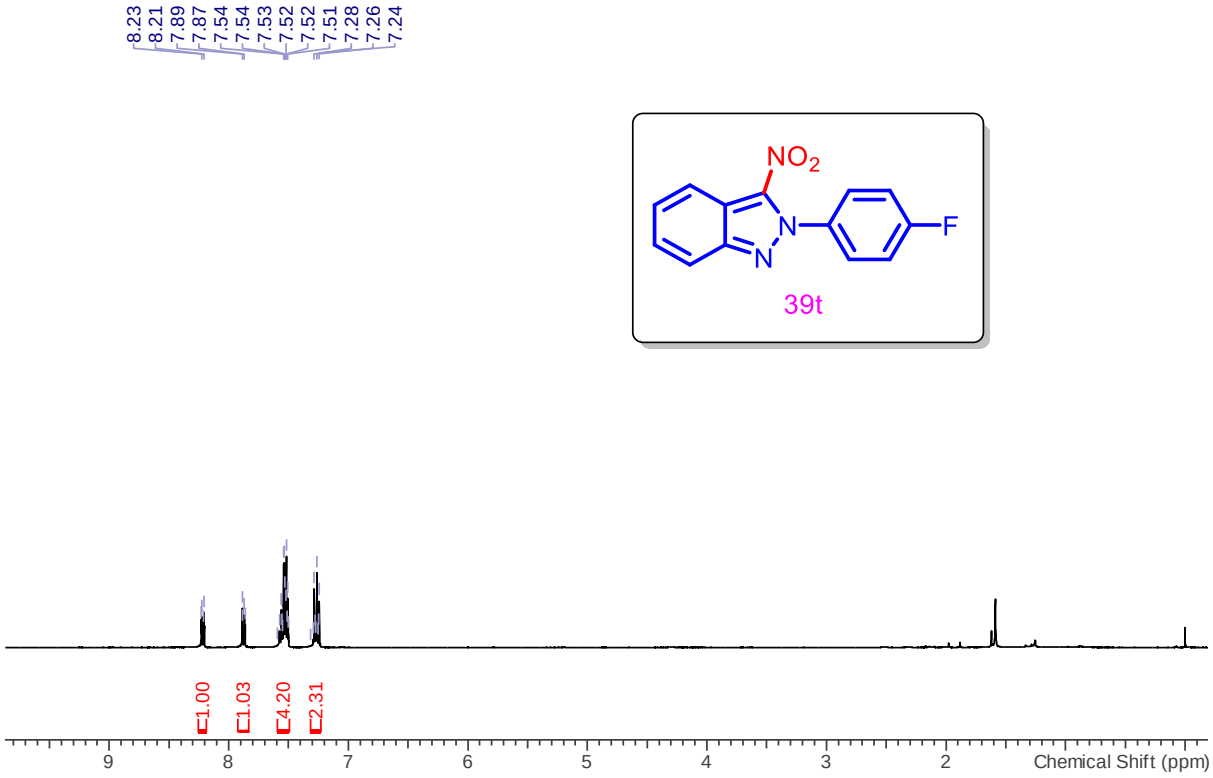
^{13}C NMR (100 MHz) spectrum of compound **39r** in $CDCl_3$



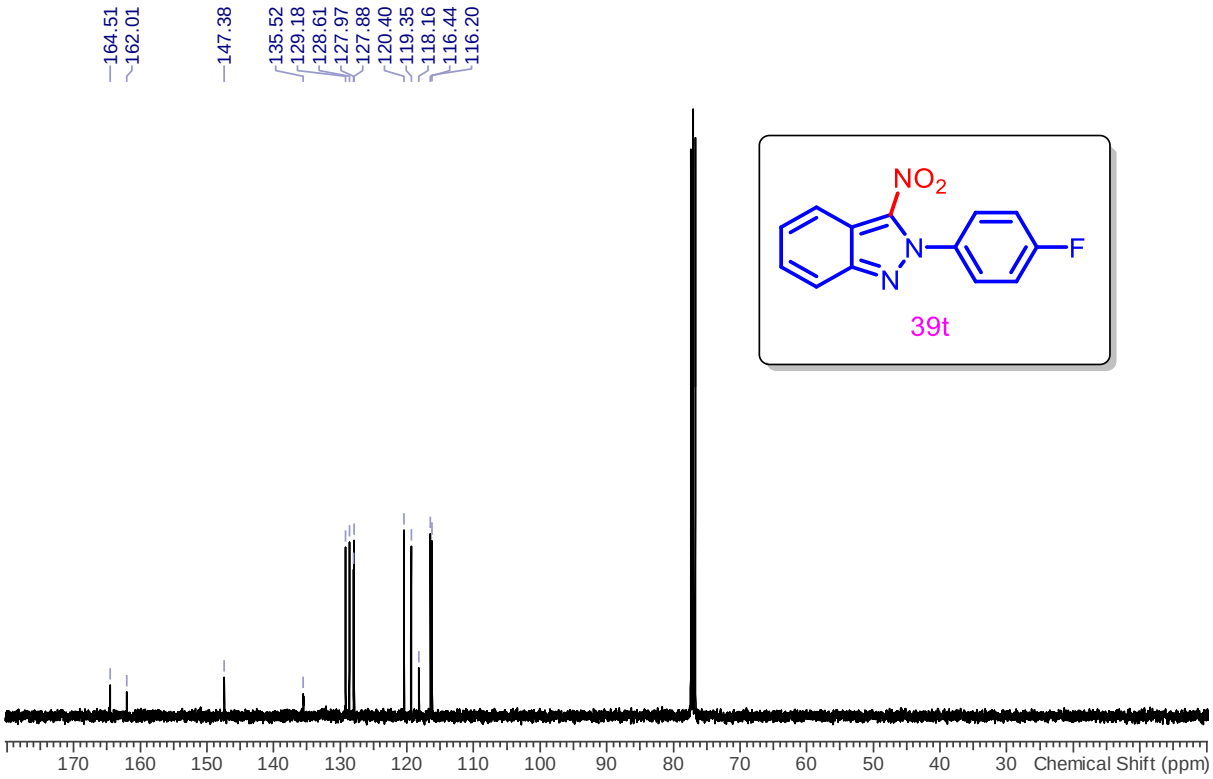
^{1}H NMR (400 MHz) spectrum of compound **39s** in $CDCl_3$



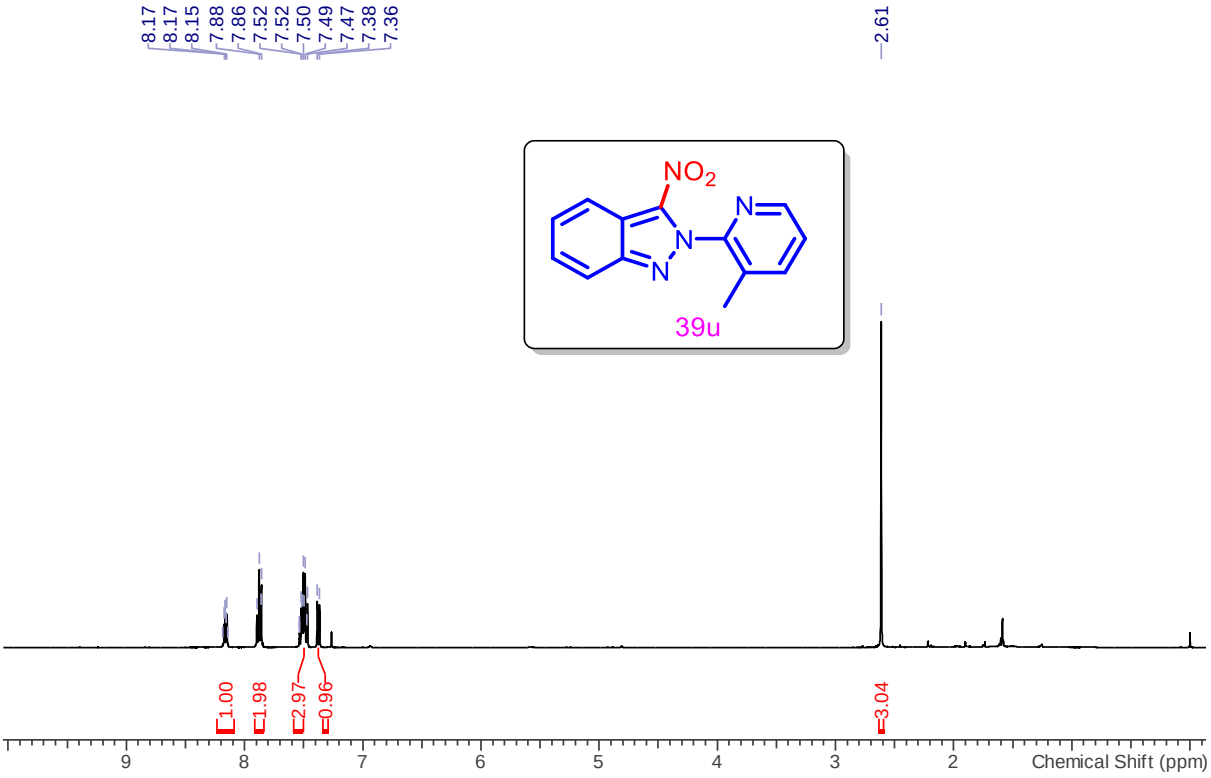
^{13}C NMR (100 MHz) spectrum of compound **39s** in $CDCl_3$



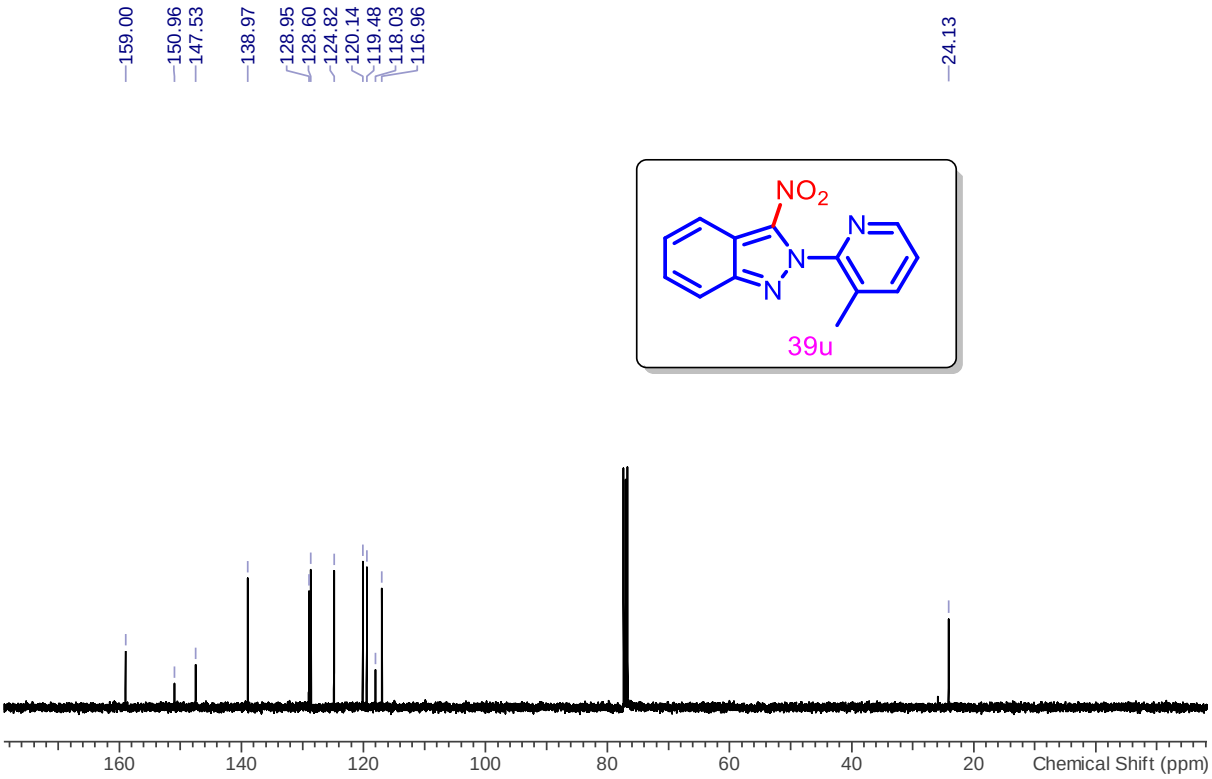
^{1}H NMR (400 MHz) spectrum of compound **39t** in $CDCl_3$



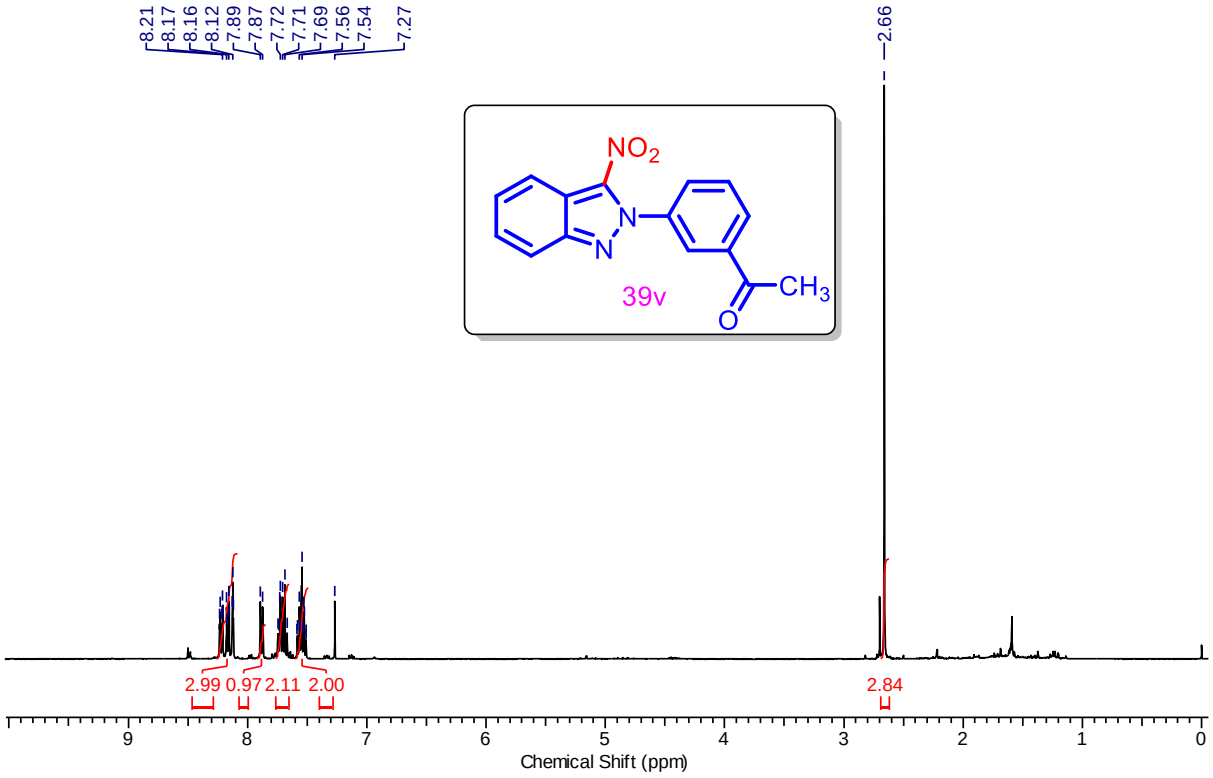
^{13}C NMR (100 MHz) spectrum of compound **39t** in $CDCl_3$



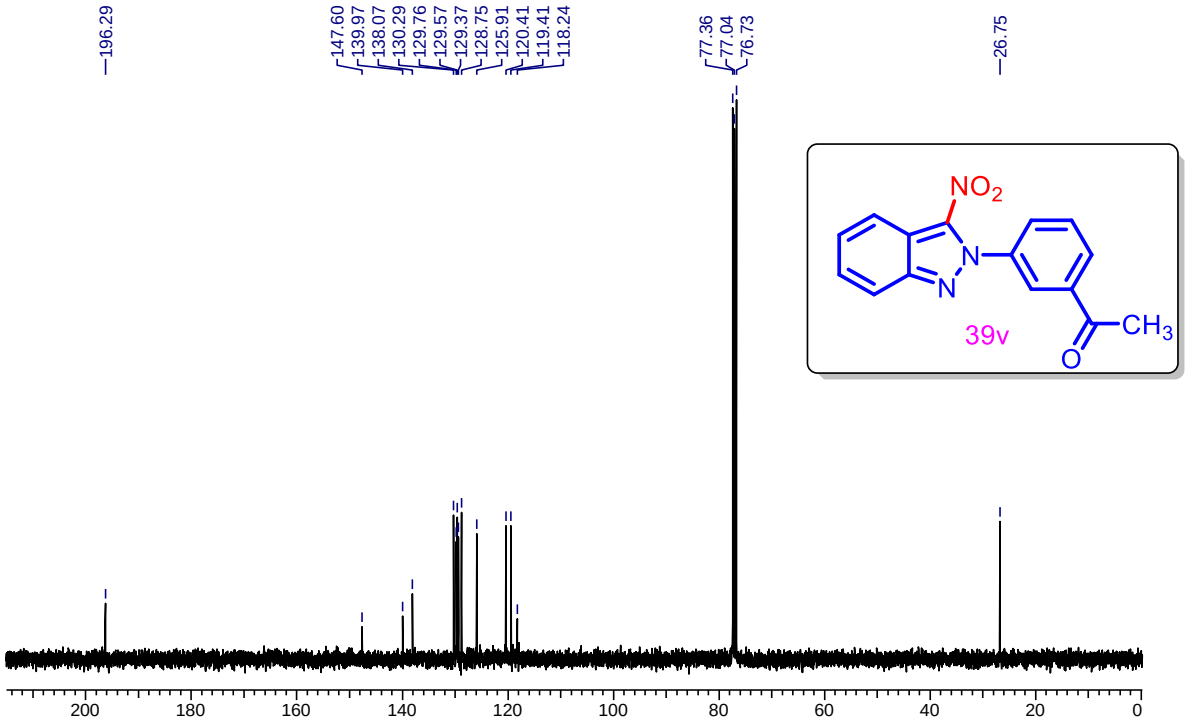
^{1}H NMR (400 MHz) spectrum of compound **39u** in $CDCl_3$



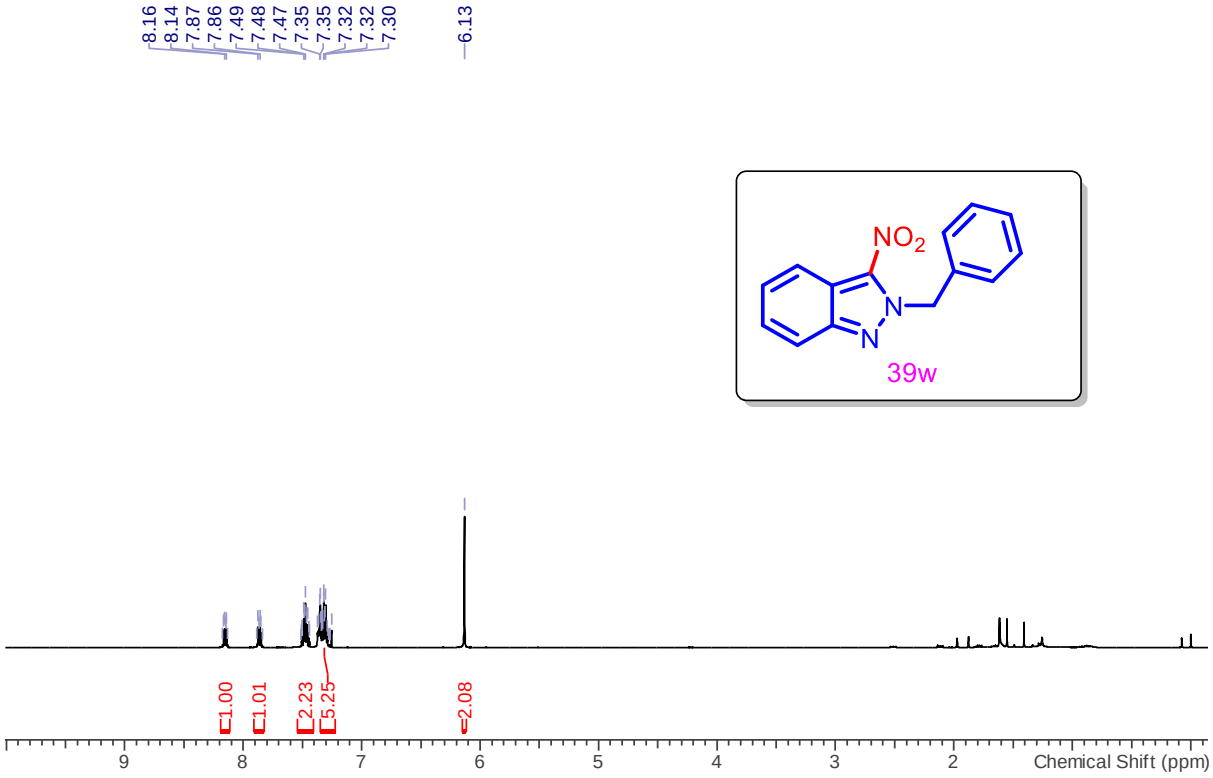
^{13}C NMR (100 MHz) spectrum of compound **39u** in $CDCl_3$



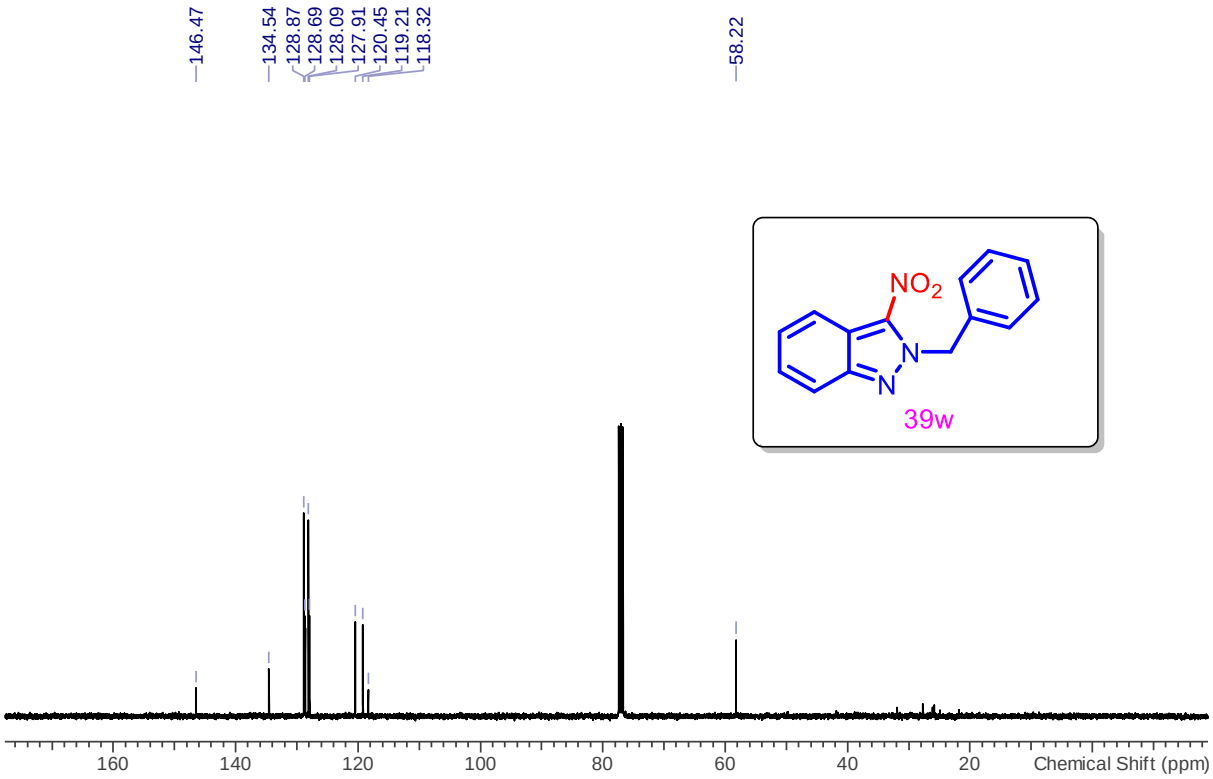
^{1}H NMR (400 MHz) spectrum of compound **39v** in $CDCl_3$



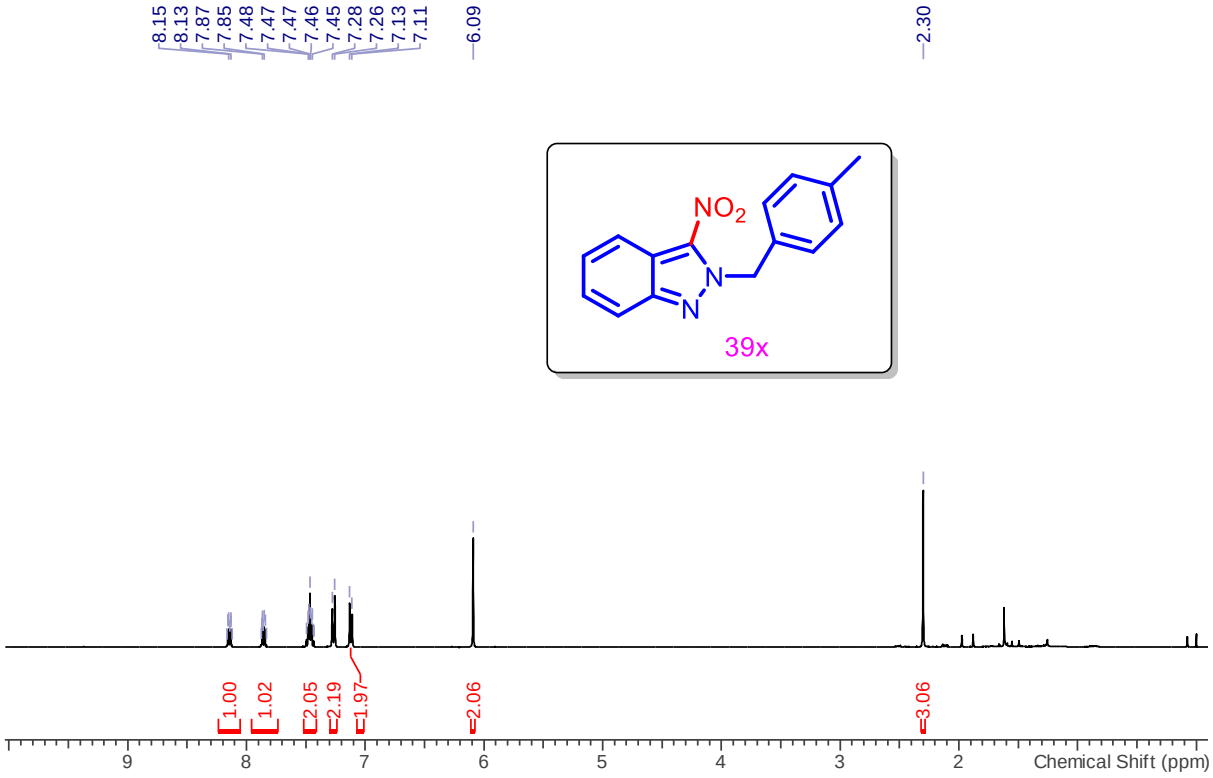
^{13}C NMR (100 MHz) spectrum of compound **39v** in $CDCl_3$



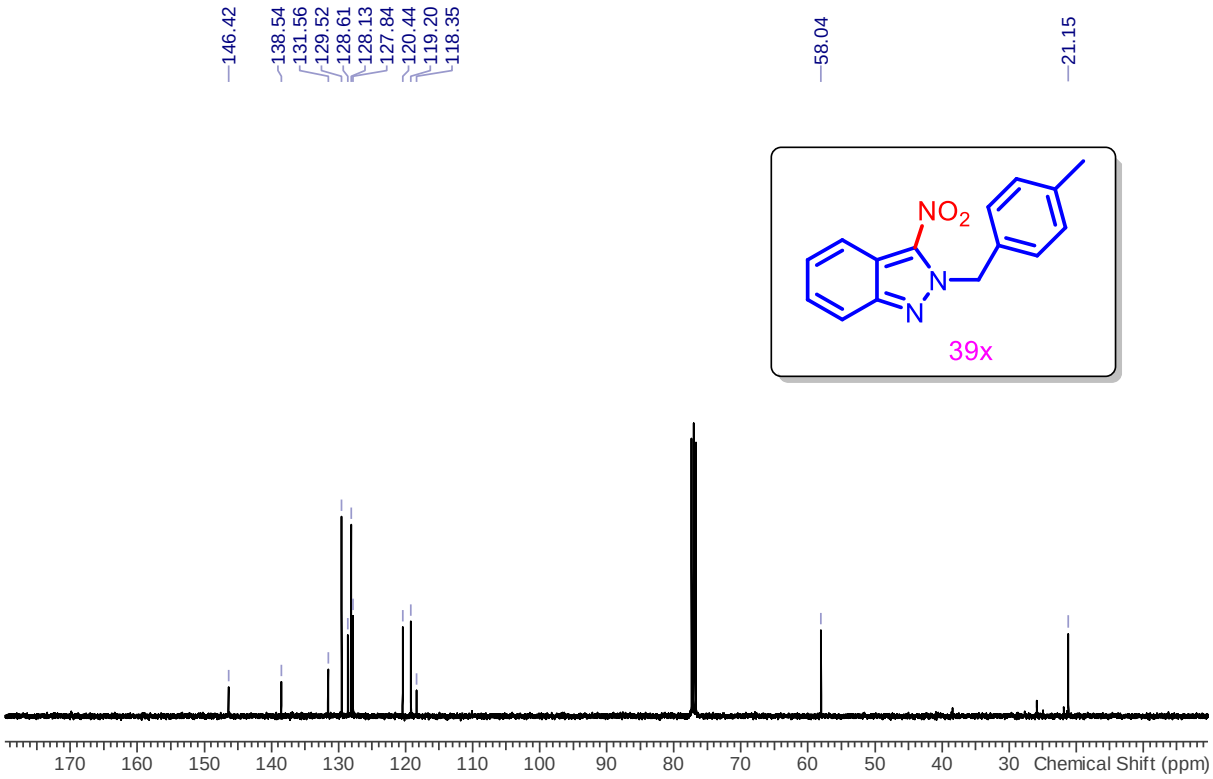
^{1}H NMR (400 MHz) spectrum of compound **39w** in $CDCl_3$



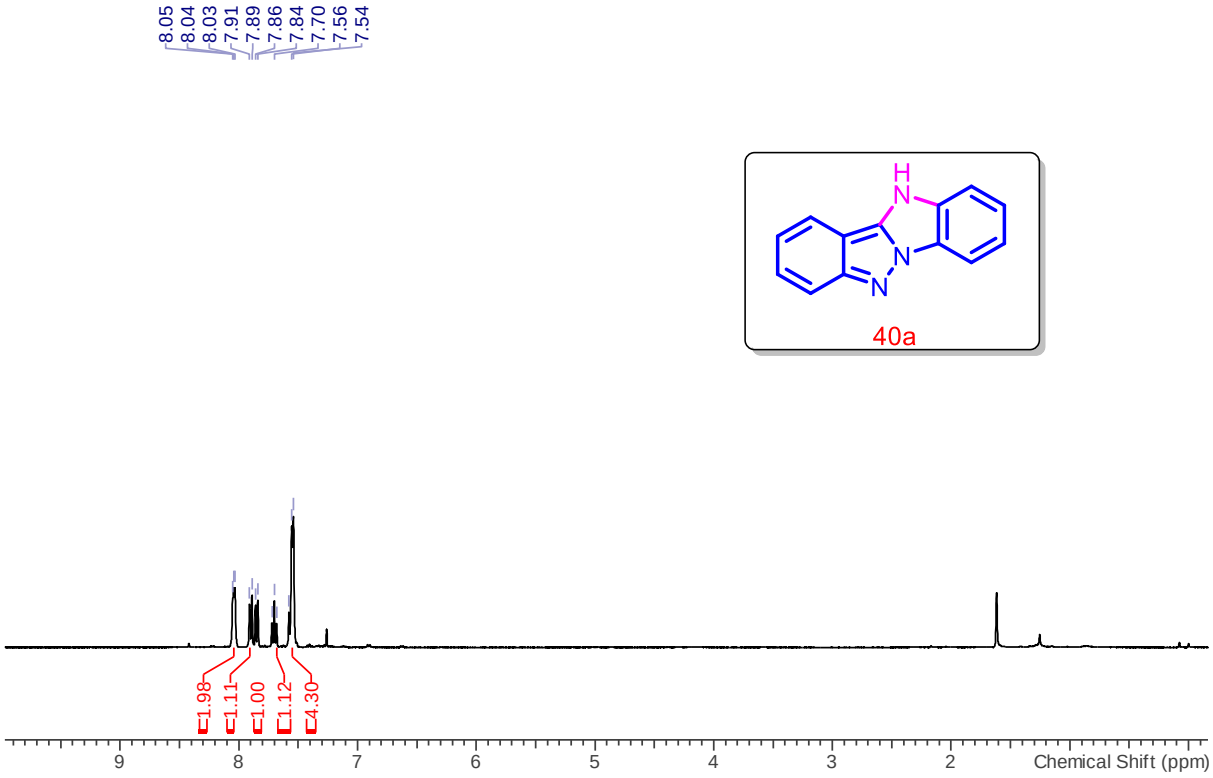
^{13}C NMR (100 MHz) spectrum of compound **39w** in $CDCl_3$



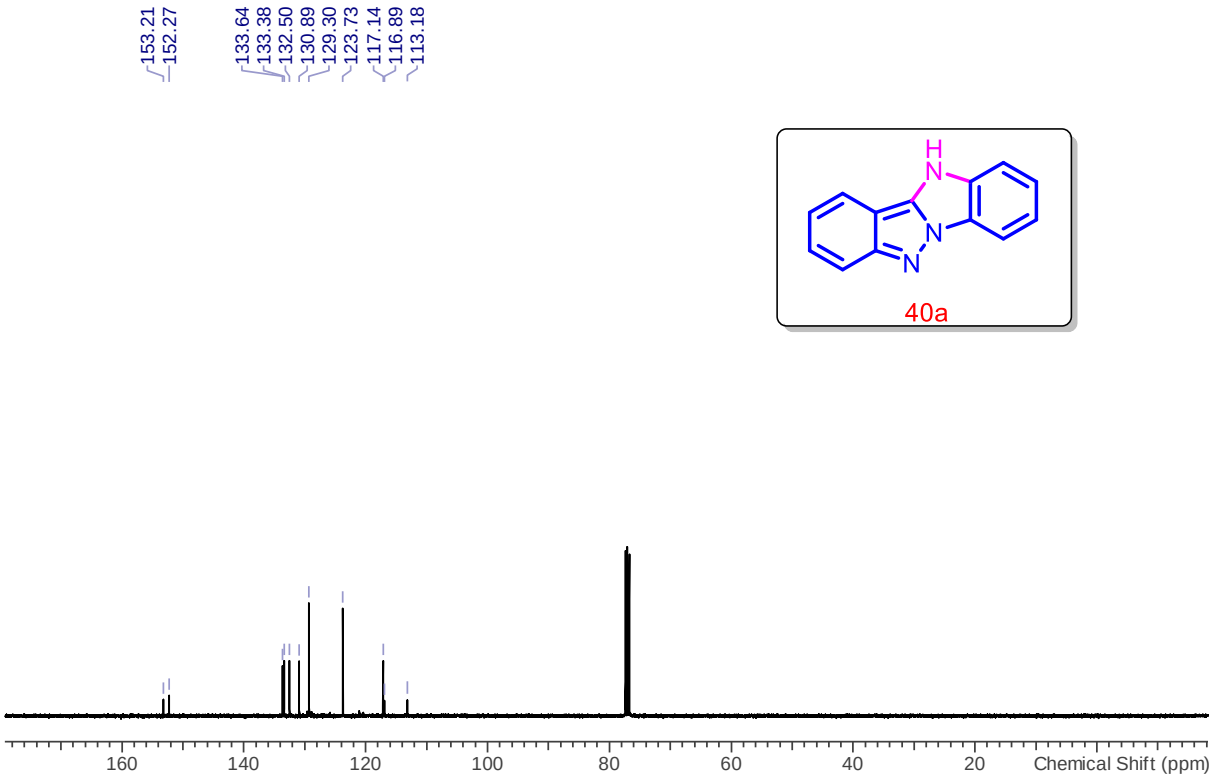
^{1}H NMR (400 MHz) spectrum of compound **39x** in $CDCl_3$



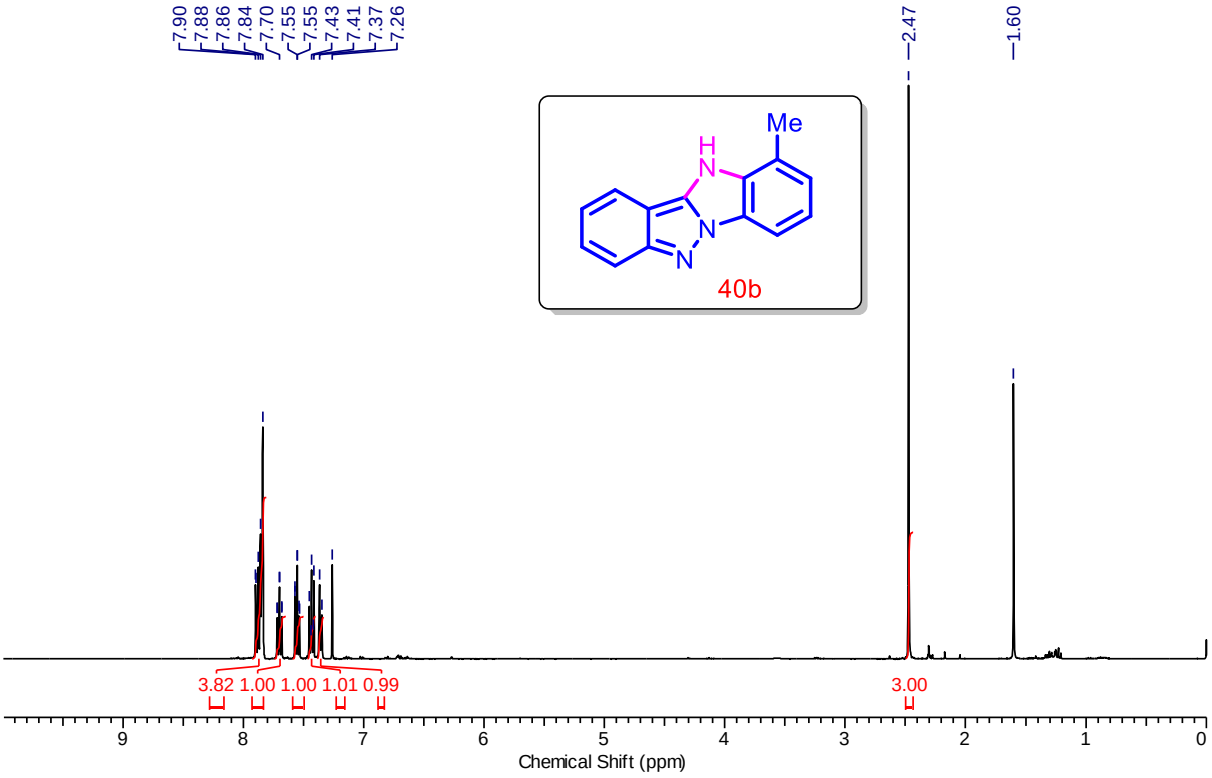
^{13}C NMR (100 MHz) spectrum of compound **39x** in $CDCl_3$



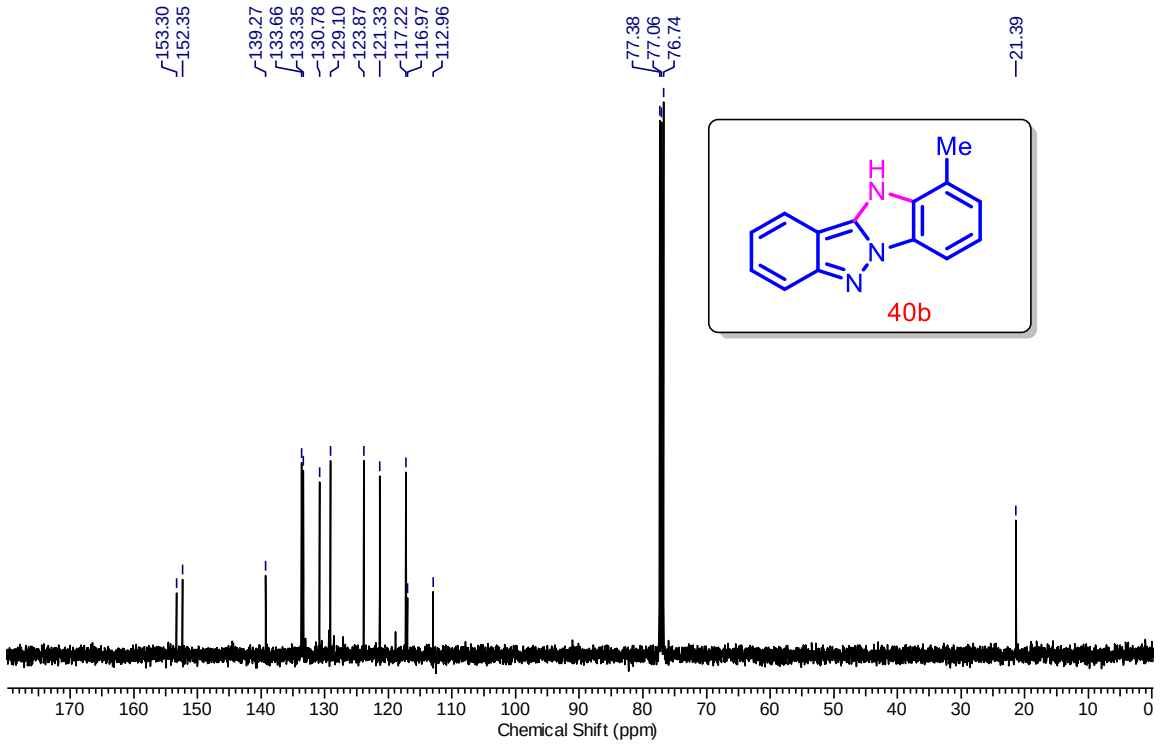
^{1}H NMR (400 MHz) spectrum of compound 40**a** in $CDCl_3$



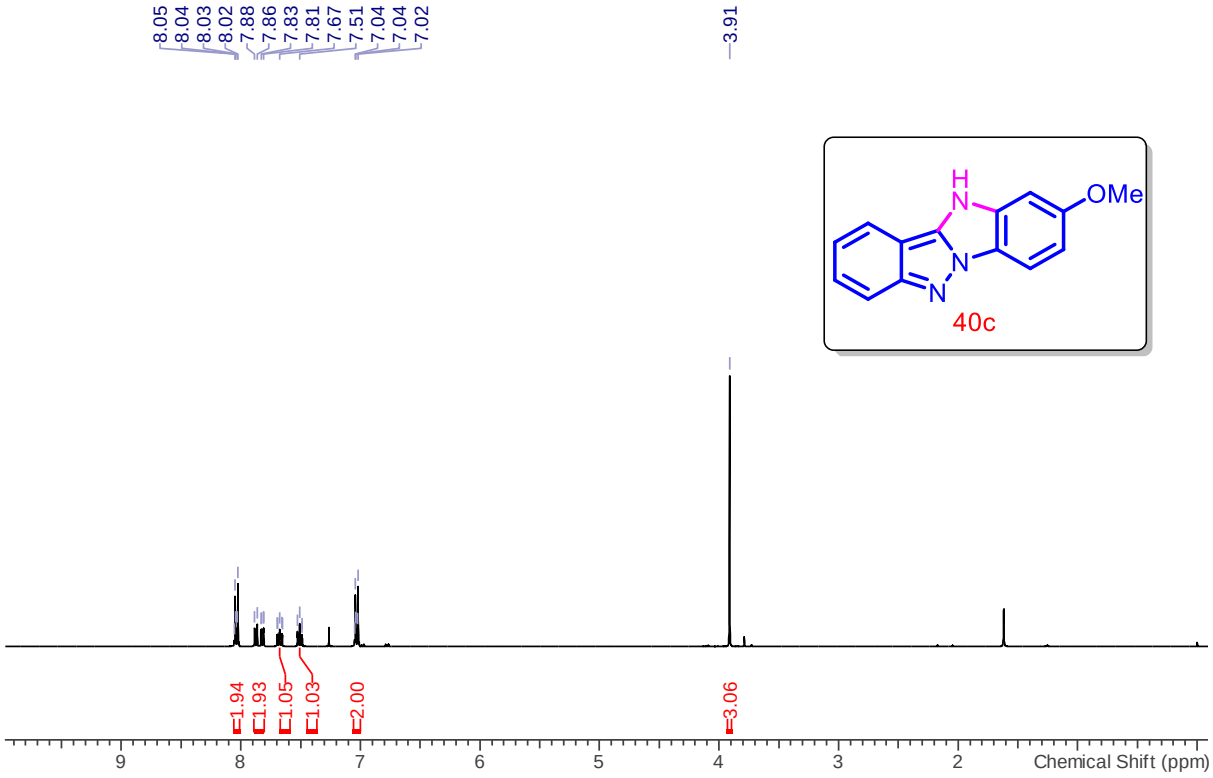
^{13}C NMR (100 MHz) spectrum of compound **40a** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **40b** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **40b** in $CDCl_3$



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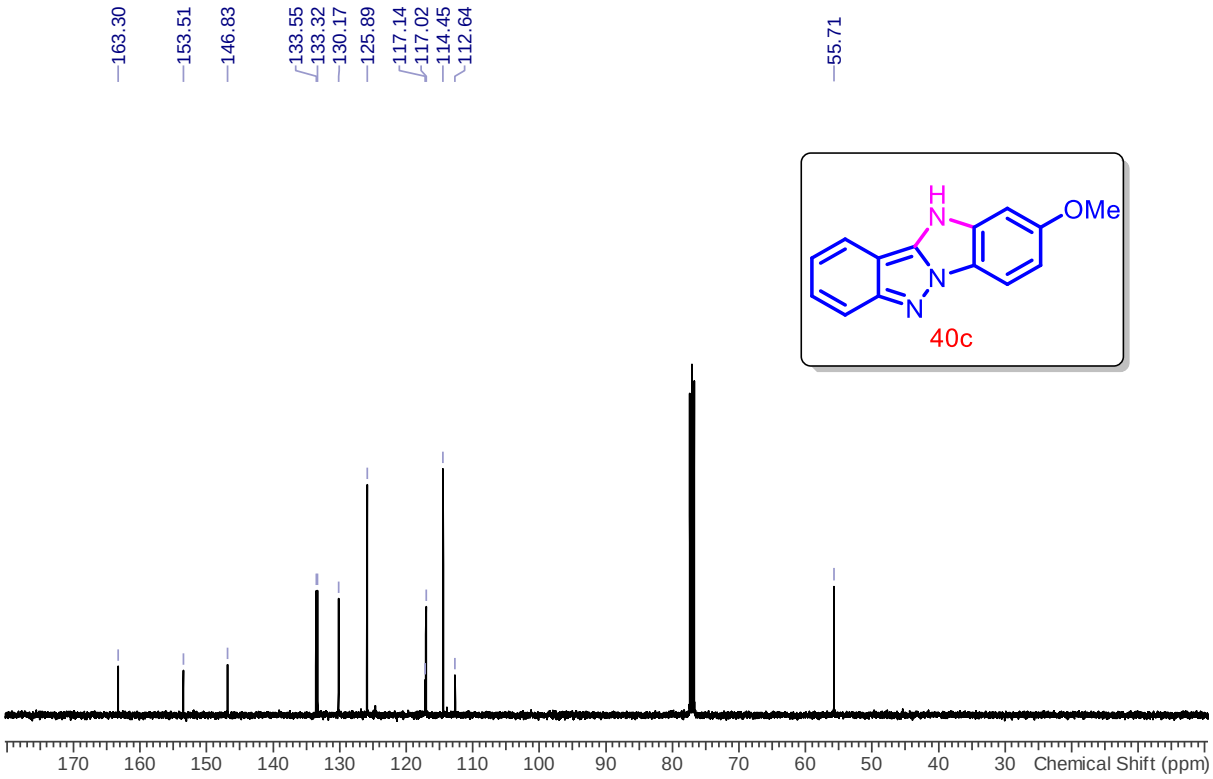
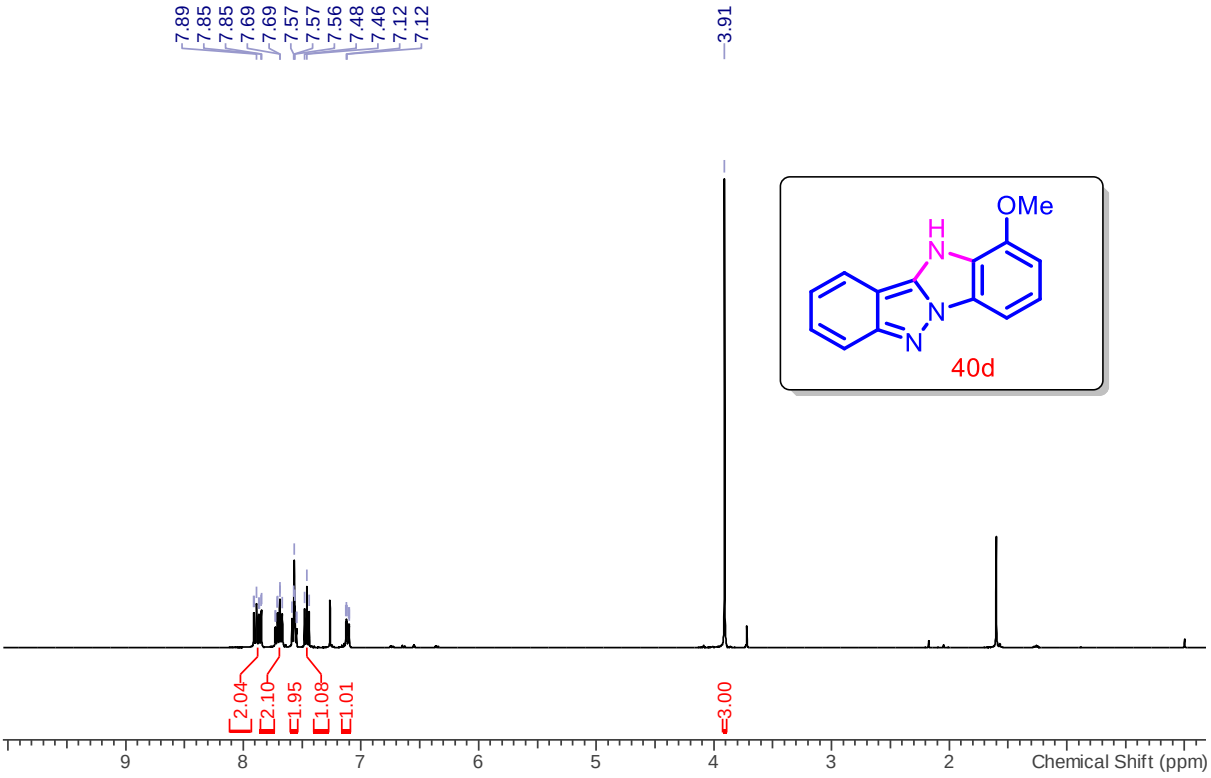
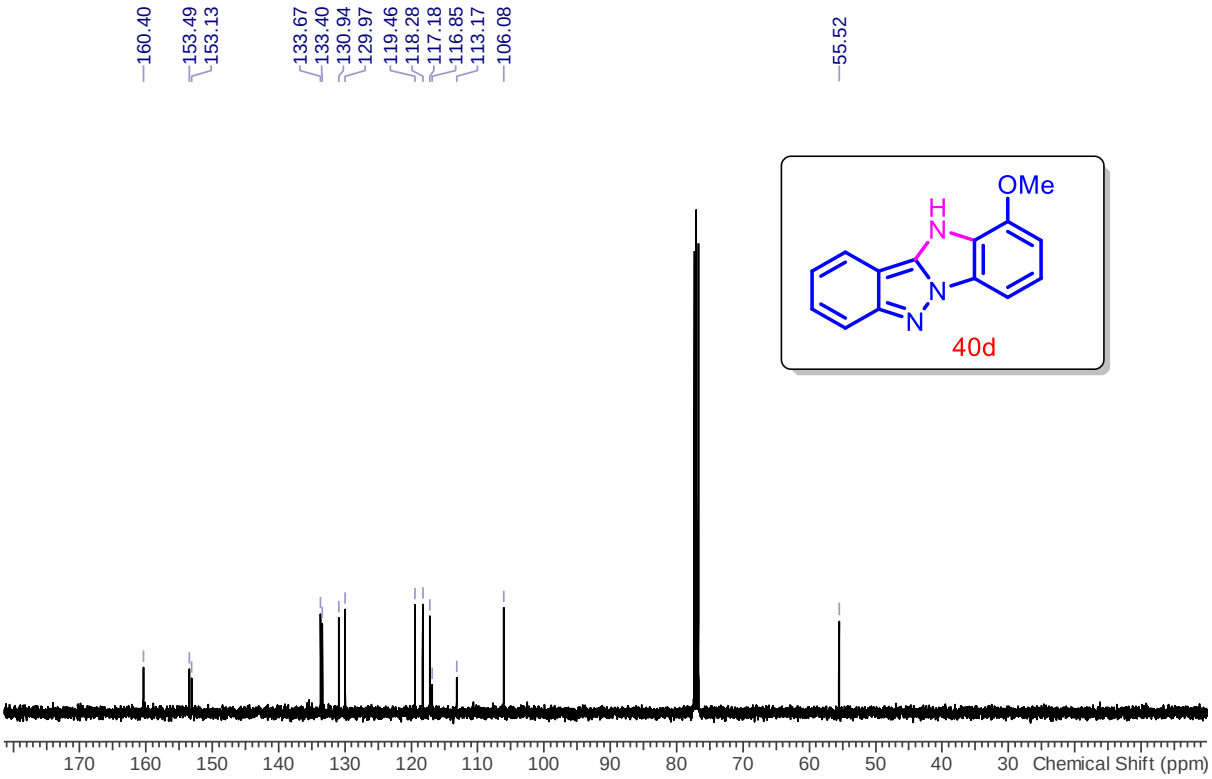


^{13}C NMR (100 MHz) spectrum of compound **40c** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **40d** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **40d** in $CDCl_3$

2.6. REFERENCES

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CHAPTER 3

Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition-metal-free photoredox catalysis

3. 1. Introduction

3. 1. 1. Importance of Fluorine Compounds

Halo-organic compounds are typically considered as sites of high electron density because of their high electronegativity. In general, the halogen atoms can form attractive interaction due to electron donor sites (i.e. nucleophiles).1 Among them, the C-F bond finds important application in the field of synthetic and medicinal chemistry, Which is owed to the similar size and increased electronegativity of fluorine over hyderogen.[2]

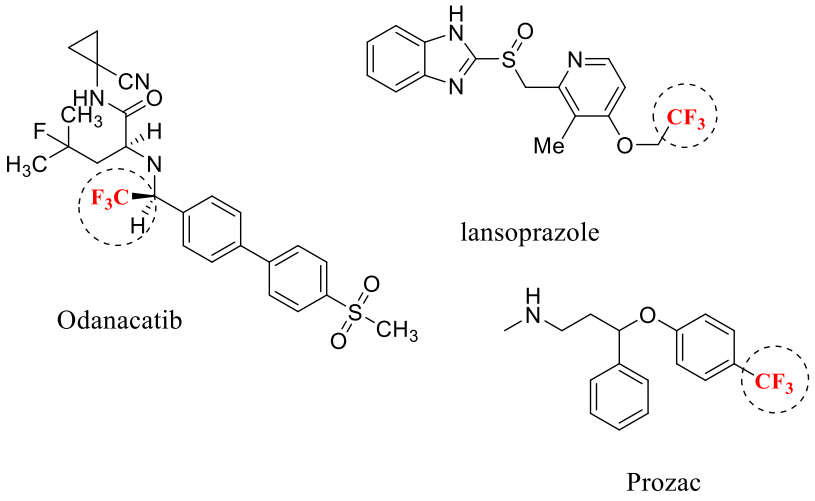


Figure 1. Biologically active Trifluoromethyl Compounds

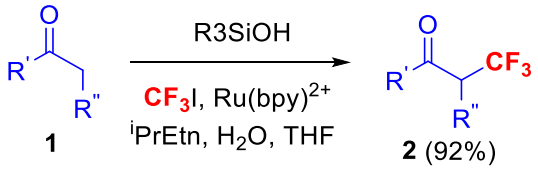
In this context, the trifluoromethyl group represents important structural motif in agrochemicals, pharmaceuticals, and drug candidates. The CF_3 moieties can enhance in metabolic stability, increase lipophilicity, bioavailability, and hydrolytic stability. Further, the trifluoromethyl-containing organic compounds are commonly applied in material such as liquid crystals.[3]

3.2. BACKGROUND

3.2.1. Various Trifluoromethylating Reagents

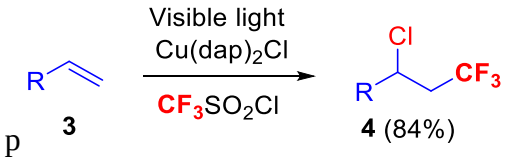
Over the past decade, due to the importance of trifluoromethylation process, several methods have been developed, using various radical, nucleophilic, and electrophilic trifluoromethylating agents such as CF_3I,[4] CF_3SO_2Cl,[5] CF_3COOH,[6] Ruppert-Prakash reagent ($TMSCF_3$),[7] Tognis' reagent,[8] Umemotos' reagent[9] and Baran reagent $(CF_3SO_2)_2Zn$[10] and Langlois' (CF_3SO_2Na).[11]

David W. C. MacMillan *et al*. has developed a mild and operationally simple method for the synthesis of α-trifluoromethylation **2** of enolsilanes **1** and it has been achieved *via* Photoredox catalysis strategy. Here, they have used ruthenium for photocatalysis and trifluoroiodomethane as a trifluoromethyl source (Scheme 1).[4]



Scheme 1

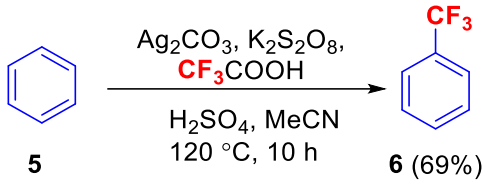
Oliver Reiser *et al*. have developed copper Phenanthroline Photoredox Catalyzed trifluoromethylation of the alkene **3** for the synthesis of trifluoromethyl alkane **4**. In this method, $[Cu(dap)_2]Cl$ plays a dual role such as electron transfer reagent as well as coordinating the reactants in the bond forming processes. Here, they have used CF_3SO_2Cl as a trifluoromethylation source with concurrent loss of sulfur dioxide. (Scheme 2).[5]



p

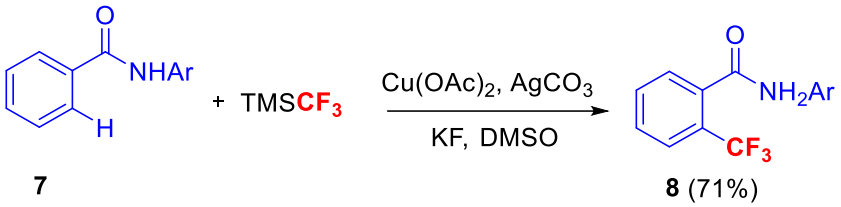
Scheme 2

Yanghui Zhang *et al*. have demonstrated silver- catalysed direct C-H trifluoromethylation of arenes **5** for the synthesis of trifluoromethylarenes **6** using trifluoroacetic acid as a Trifluoromethylating source. (Scheme 3).[6]



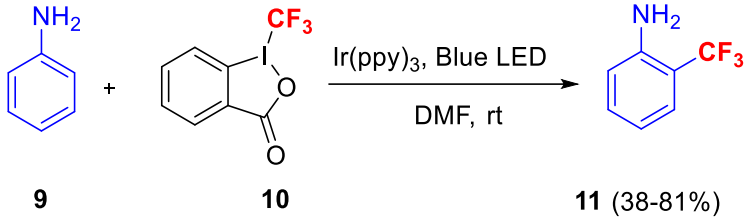
Scheme 3

Jin-Quan Yu and co-workers developed a copper(II)-promoted synthesis of trifluoromethyl substituted arenes **8** through direct *ortho* C-H trifluoromethylation of arenes and heteroarenes **7**. The Ruppert–Prakash reagent ($TMSCF_3$) as a trifluoromethylation reagent and the present copper(II) catalysed C-H activation reaction completes within 30 minutes. (Scheme 4).[7]



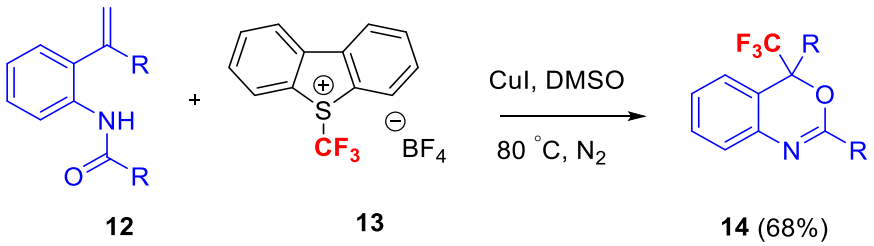
Scheme 4

Jing Ma *et al*. developed the first visible-light induced radical trifluoromethylation of free anilines **9** using iridium as the photocatalyst. In this method, they have used Togni reagent **10** as a CF_3 radical source and it is commercially available and easy to handle (Scheme 5).[8]



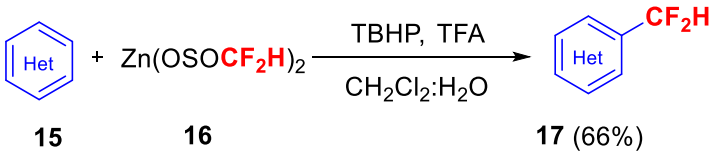
Scheme 5

Sangit Kumar and co-workers reported a copper-catalyzed trifluoromethylation of alkenes **12** to the construction of trifluoromethylated benzoxazines **14** with a simple base and ligand-free condition. In this method, Umemotos' reagent **13** is used as a CF_3 radical source and it involves tandem C–O and C–CF_3 bond constructions (Scheme 6).[9]



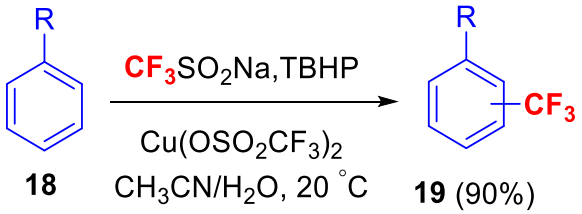
Scheme 6

Yuta Fujiwara et al. invented a new reagent for the difluoromethylation of organic substrates as Baran reagent ($Zn(SO_2CF_2H)_2$, DFMS) **16** and it proceeds through the radical process. Moreover, this method is mild and operationally simple. This method is compatible with a wide range of nitrogen-containing heteroarene substrates of varying complexity (Scheme 7).[10]



Scheme 7

Bernard R. Langlois et al. developed a trifluoromethylation method for the electron-rich aromatic compounds with trifluoromethanesulfinate used as CF_3 radical source. In this method, they have used t-butyl hydroperoxide as an oxidant and catalytic amount copper controlling the monotrifluoromethylation whereas mono- and the bis-trifluoromethylated product was observed almost same as in the absence of copper(II) (Scheme 8).[11]

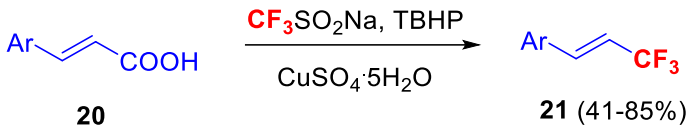


Scheme 8

3.2.2. Trifluoromethylation using Langlois' reagent

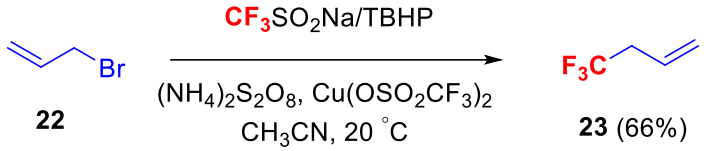
Among these, Langlois' reagent is benchtop-stable, inexpensive, easy to handle and convenient reagent for trifluoromethylation. Despite these developments, the approach for radical trifluoromethylation of arenes and heteroarenes have achieved over the past years.

Zhong-Quan Liu *et al*. developed a copper-catalyzed decarboxylative trifluoromethylation of several α,β-unsaturated carboxylic acids **20** for the synthesis of trifluoromethyl alkenes **21** with Langlois' reagent which is a stable and inexpensive solid, easy to handle reagent for trifluoromethylation (Scheme 9).[12]



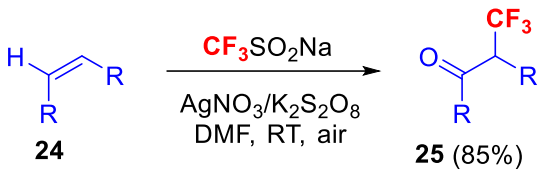
Scheme 9

Bernard R. Langlois and co-workers developed trifluoromethylation of alkene bromide **22** for the synthesis of the corresponding trifluoromethyl substituted alkene **23** using sodium trifluoromethanesulfinate with *t*-butyl hydroperoxide as an oxidant (Scheme 10).[13]



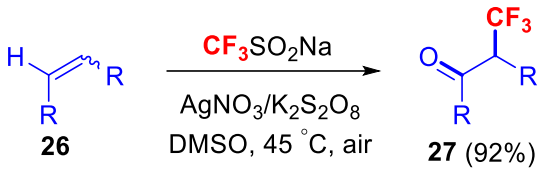
Scheme 10

Debabrata Maiti *et al*. discloses the synthesis of α-CF_3-substituted ketones **25** through oxidative trifluoromethylation of unactivated olefins **24** with inexpensive and stable CF_3SO_2Na as the CF_3 source. This reaction can be carried out in room temperature and open flask (Scheme 11).[14]



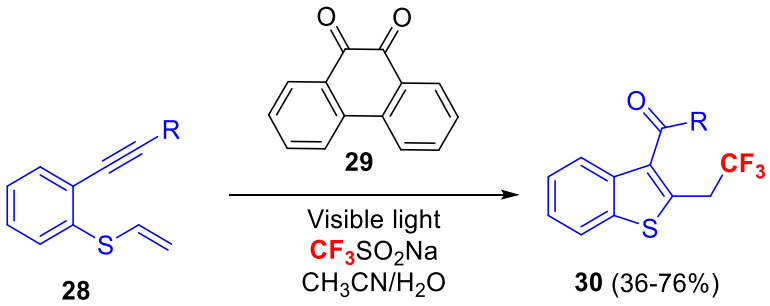
Scheme 11

Aiwen Lei *et al*. discovered the oxytrifluoromethylation of alkenes **27** through an aerobic C_{vinyl}–heteroatom bond oxygenation of unactivated alkene **26**. This method could eliminate the assistance of additional transition-metal catalysts or stoichiometric amounts of organic oxidants and here, molecular oxygen and catalytic amounts of $K_2S_2O_8$ could activate the CF_3SO_2Na (Scheme 12).[15]



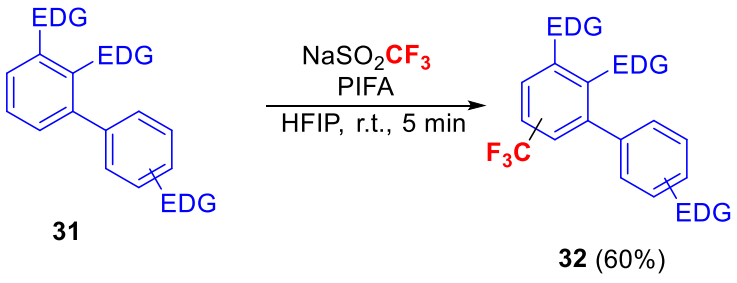
Scheme 12

In 2017, Sangit Kumar *et al*. developed visible-light-induced dehydrogenative cascade trifluoromethylation and oxidation of 1,6-enynes **28** with green solvent water. This method provides an oxidant and metal-free reaction condition for the synthesis of CF_3-containing C3-aryloyl/acylated benzofurans, benzothiophenes, and indoles (Scheme 13).[16]



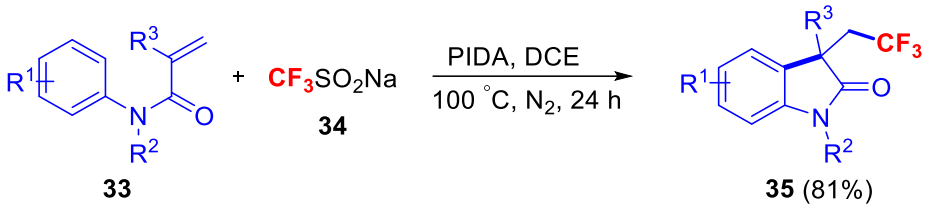
Scheme 13

Norio Shibata **et al**. reported a transition-metal-free direct oxidative trifluoromethylation of unsymmetrical biaryls **31** for the synthesis of CF_3 functionalized biaryls **32** using CF_3SO_2Na as a CF_3 radical source, and they have achieved a simple combination of trifluoromethanesulfinate and phenyliodine bis(trifluoroacetate). This method selectively observed for the electron-rich arenes (Scheme 14).[17]



Scheme 14

Hua Fu *et al*. developed a metal-free synthesis of indolin-2-one **35** through trifluoromethylation and arylation of alkenes **33** and it is a novel, simple and highly efficient method for the synthesis of 3-(trifluoromethyl)-indolin-2-one derivatives. Here, they have used inexpensive and easily stored Langlois' reagent **34** (sodium trifluoromethanesulfinate) as the trifluoromethyl source and iodobenzene diacetate [$PhI(OAc)_2$] as the oxidant (Scheme 15).[18]



Scheme 15

3.2.3. Photoredox catalysis

In recent years, the visible light induced photoredox catalytic activation of organic molecules has been established as a powerful strategy in modern organic synthesis which provide attractive features, like mild, environmentally benign, excellent functional group tolerance, and high reactivity.[19] The photoredox strategy can involve *via* single-electron-transfer (SET) process upon irradiation with visible light using metal complexes and organic dyes as photocatalyst.[20] Moreover, the usage of organic dyes is inexpensive and easy to handle as photoredox catalysts, and hence this would be an excellent substitute to inorganic transition-metal photocatalyst.

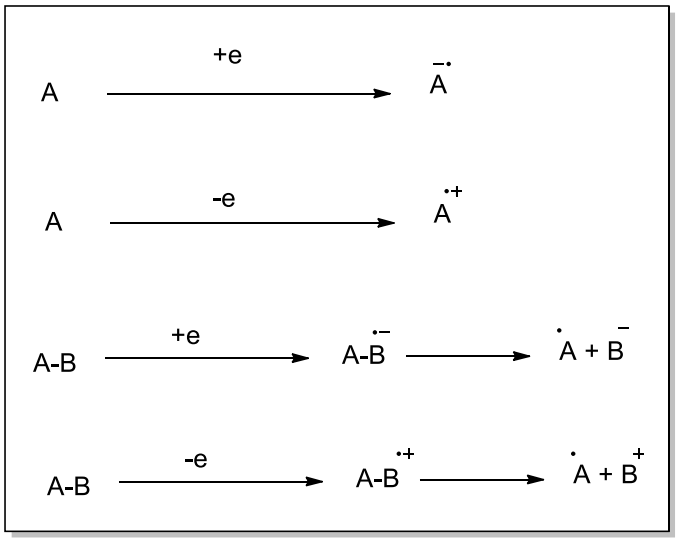


Figure 1. Reactivity Patterns of SET Processes

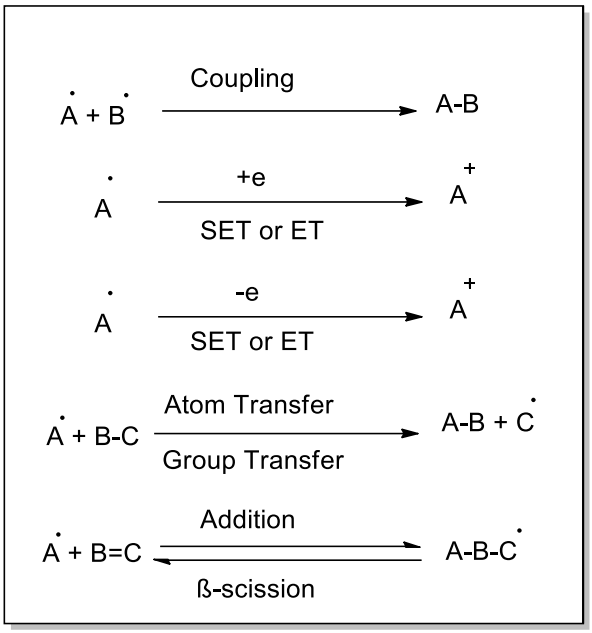
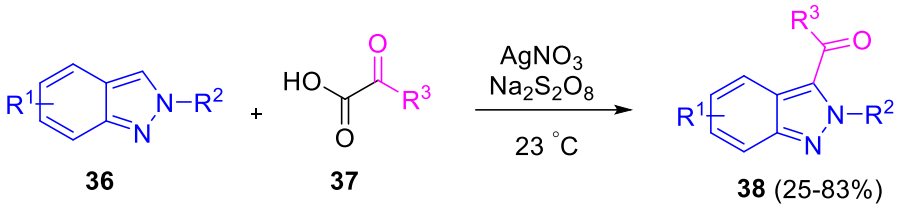


Figure 2. Reactivity Pattern of Radicals

3.2.4. C3-H functionalization of 2*H*-indazole

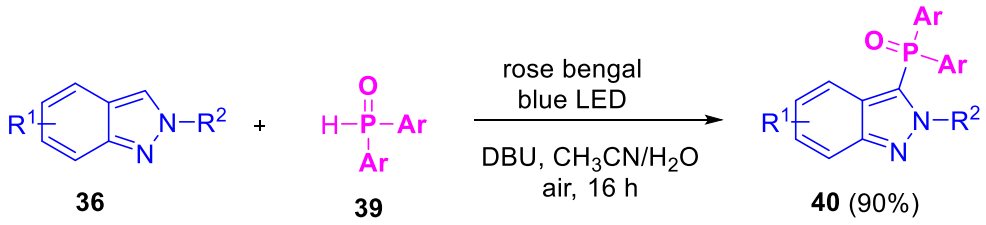
Nitrogen-containing heterocycle compounds have gained significant importance in natural products and they exhibit a wide range of biological activities.[21] Among them, indazoles are broadly known for their bioactivities[22] such as antitumor,[23] antimicrobial,[24] anti-inflammatory,[25] anti-HIV,[26] anti-platelet[27] and anti-contraceptive.[28] Considering the immense importance of derivatives of 2*H*-indazoles, extensive efforts have been devoted for the synthesis and functionalization of 2*H*-indazole.[29]

Kyungsoo Oh *et al*. reported the silver catalyzed the synthesis of acyl functionalized 2*H*-indazole **38** *via* direct acyl radical addition to 2*H*-indazole **36** using Decarboxylative Cross-Coupling of α-Keto Acids **37** (Scheme 16).[30]



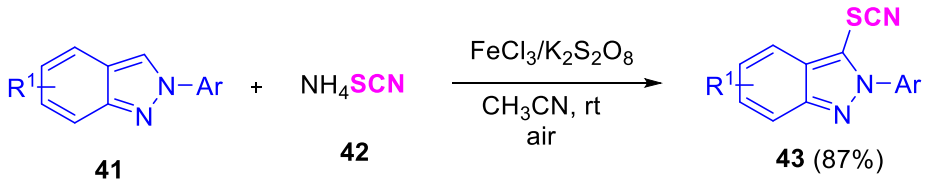
Scheme 16

Later, Alakananda Hajra *et al*. developed a metal-free visible-light-induced phosphonylation of 2*H*-indazoles **36** with diphenylphosphine oxide **39** for the synthesis of phosponyl substituted 2*H*-indazole **40** and they have used rose bengal as an organophotoredox catalyst under ambient air at room temperature (Scheme 17).[31]



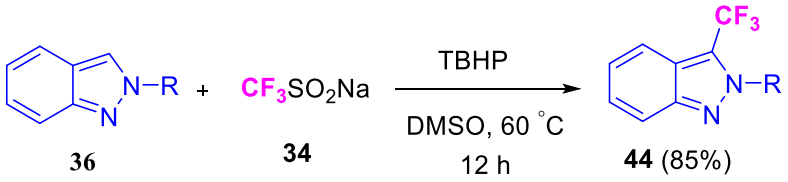
Scheme 17

Recently, Alakananda Hajra *et al*. developed the iron-catalysed synthesis of 2-phenyl-3-thiocyanato-2*H*-indazole **43** through thiocyanation of 2*H*-indazole **41** mediated by Potassium persulfate at environmentally benign reaction conditions (Scheme 18).[32]



Scheme 18

Very recently, Hajra and coworkers described a new approach for the metal-free direct C3-trifluoromethylation of 2*H*-indazole **36** with access to trifluoromethyl functionalized 2*H*-indazole **44** mediated by peroxide. This reaction mechanism proceeds through a radical pathway. (Scheme 19).[33]



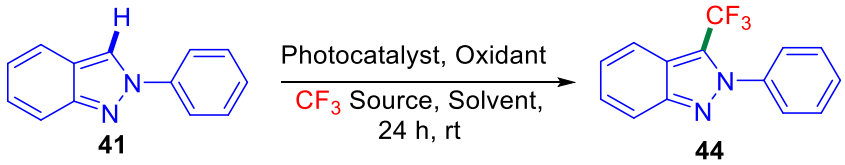
Scheme 19

The transition metal catalyst, peroxides and high temperatures are somewhat disadvantages for the C3-H functionalization of 2*H*-indazoles. Encouraged by the significant advances in the recent radical C-H functionalization,[34] our group initiated the research on the C-H

functionalization of indazoles.[35] Herein, we report a novel metal-free visible light promoted organic dye catalyzed regioselective C3-trifluoromethylation of 2*H*-indazole.

3.3. Results and Discussion

Table 1. Optimization of Reaction Conditions for the Synthesis of 44a[a,b]



entry	catalyst	oxidants	CF_3 Source	Solvent	yield (%)[b]
1	rosebengal	PIDA	$NaSO_2CF_3$	DCM	60
2	rosebengal	$K_2S_2O_8$	$NaSO_2CF_3$	DCM	n.d
3	rosebengal	TBHP	$NaSO_2CF_3$	DCM	n.d
4	rosebengal	IBA-OAc	$NaSO_2CF_3$	DCM	Trace
5	rosebengal	PhIO	$NaSO_2CF_3$	DCM	Trace
6	rosebengal	-	$NaSO_2CF_3$	DCM	ND
7	-	PIDA	$NaSO_2CF_3$	DCM	Trace
8	$Ru(bpy)_3Cl_2$	PIDA	$NaSO_2CF_3$	DCM	Trace
9	$Ir(ppy)_3$	PIDA	$NaSO_2CF_3$	DCM	Trace
10	eosin-Y	PIDA	$NaSO_2CF_3$	DCM	50
11	rhodamine B	PIDA	$NaSO_2CF_3$	DCM	Trace
12	**Methylene blue**	**PIDA**	$NaSO_2CF_3$	**DCM**	**75**
13	azure-B	PIDA	$NaSO_2CF_3$	DCM	55
14	riboflavin	PIDA	$NaSO_2CF_3$	DCM	Trace
15	methylene blue	PIDA	$NaSO_2CF_3$	CH_3CN	30
16	methylene blue	PIDA	$NaSO_2CF_3$	DCE	50
17	methylene blue	PIDA	$NaSO_2CF_3$	Acetone	Trace
18	methylene blue	PIDA	$NaSO_2CF_3$	DMSO	n.d
19	methylene blue	PIDA	$NaSO_2CF_3$	Toluene	n.d
20	methylene blue	PIDA	$NaSO_2CF_3$	MeOH	n.d
21	methylene blue	PIDA	$NaSO_2CF_3$	EtOH	n.d
22	methylene blue	PIDA	$NaSO_2CF_3$	Dioxane	n.d

23	methylene blue	PIDA	$NaSO_2CF_3$	DMF	n.d
24	methylene blue	PIDA	$TMSCF_3$	DCE	n.d
25	methylene blue	PIDA	ICH_2CF_3	DCE	n.d
26	methylene blue	PIDA	CF_3SO_2Cl	DCE	n.d

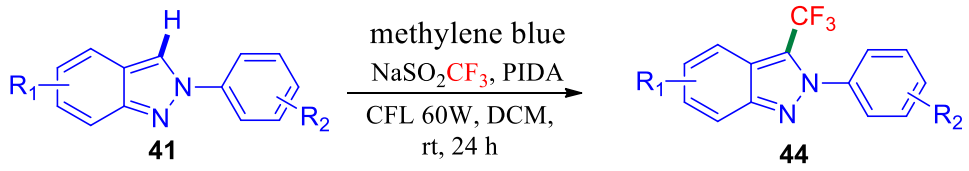
[a]Reaction conditions:**41** (1 mmol), methylene blue (1 mol%), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24h. [b]Isolated yield of chromatographically pure products. n.d= not detected.

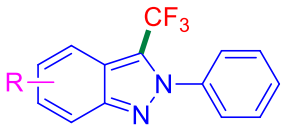
In the initial experiments, we have chosen 2-phenyl-2*H*-indazole as the model substrate, Langlois' reagent as radical CF_3 source and phenyliodine(III) diacetate (PIDA) as an oxidant with 2 mol% rose bengal as a photocatalyst in MeCN and irradiated with 60 W Compact Fluorescent Bulb (CFL) at room temperature for 24 h. Delightfully, we observed C3-trifluoromethylated product **44a** with 60% yield (Table 1, entry 1). Then, the effect of other oxidants such as $K_2S_2O_8$, TBHP, IBA-OAc, and PhIO was examined (table 1, entry 2-5). Unfortunately, our attempts went in vain. To improve the reaction efficiency in terms of yield, we have tested the various photocatalysts. Among all, methylene blue (Table 1, entry 12) was found to be effective photocatalyst and provided the desired product **44a** with 75% yield. Among the solvents screened (table 1, entry 15-23), DCM was found to be the most efficient solvent for this strategy. To improve the yield, a variety of CF_3 sources were examined, but without much success (table 1, entry 24-26).

With the established optimized reaction conditions (table 1, entry 12), we have examined the scope of this protocol with various substitutions on 2*H*-indazoles (table 2). Initially, we checked the halogen substitution on 2*H*-indazole (**44b-h**). The presence of halogen at C5 and C6-positions of 2*H*-indazoles (**44b-d**) gave poor yields. The halogen substituent at *para* position of the amine partner of 2*H*-indazoles (**44e-h**) gave 45% to 68% yields. Likewise, the amine partner of 2*H*-indazoles bearing electron-donating groups (-Me, -OMe) resulted in the products with very good yields (**44i-n** & **44p**). This might be due to the increased electron density at C3-position of 2*H*-indazole. This observation was similar to our earlier report.[27a]

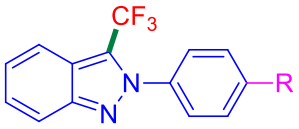
However, the electron donating groups (-Me, -OMe) at *ortho* position (**44i**, **44j**) gave moderate yields; this is due to the steric hindrance of the *ortho* substitution. We observed poor yield, while the electron-withdrawing group substituted on 2*H*-indazole (**44o**), because the electron density might be reduced at C3-position on 2*H*-indazole. In the case of benzylamine partner, the C3-H trifluoromethylated indazoles (**44r, 44s**) were obtained in low yield.

Table 2. Substrate scope for the C3-trifluoromethylation of 2*H*-indazole [a,b]

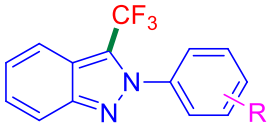




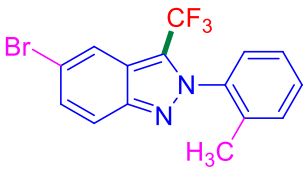
R = H	**44a**	75%
R = 6-Cl	**44b**	35%
R = 6-Br	**44c**	37%
R = 5-Br	**44d**	43%



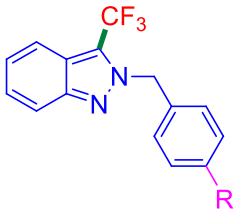
R = F	**44e**	45%
R = Cl	**44f**	53%
R = Br	**44g**	62%
R = I	**44h**	68%



R = *o*-CH_3	**44i**	45%
R = *o*-OMe	**44j**	42%
R = *m*-CH_3	**44k**	64%
R = *m*-OMe	**44l**	70%
R = *p*-CH_3	**44m**	83%
R = *p*-OMe	**44n**	83%
R = *m*-$(CO)CH_3$	**44o**	40%
R = *o, m, p*-OCH_3	**44p**	80%



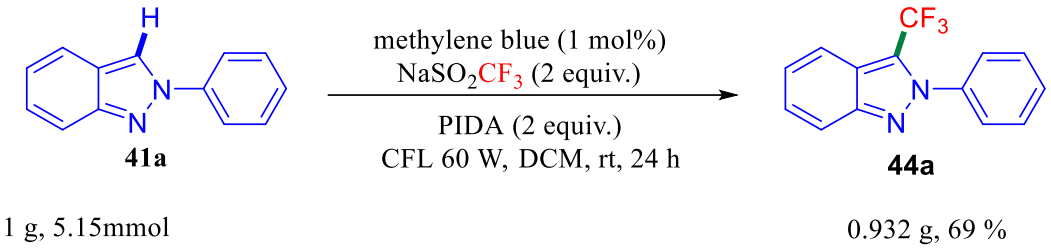
44q (42%)



R = H	**44r**	55%
R = CH_3	**44s**	45%

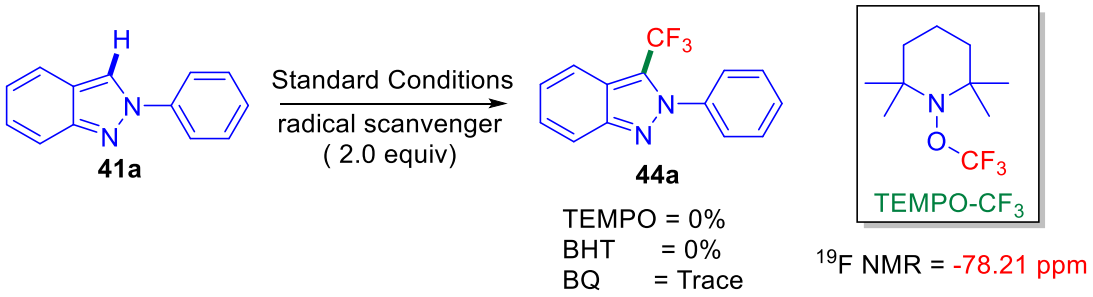
[a]Reaction Conditions: **1a** (1 mmol), methylene blue (1 mol%), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24h. [b]Isolated yield of chromatographically pure products.

Due to the presence of 2*H*-indazole skeleton in various biologically relevant compounds, we have also evaluated the scalability of our protocol. Consequently, when we performed the reaction on 1g scale, it produced the C3-trifluoromethylation of 2*H*-indazole **44a** with 69% yield (Scheme 2).



Scheme 20. Gram-scale synthesis of 2-phenyl-3-(trifluoromethyl)-2*H*-indazole (**44a**).

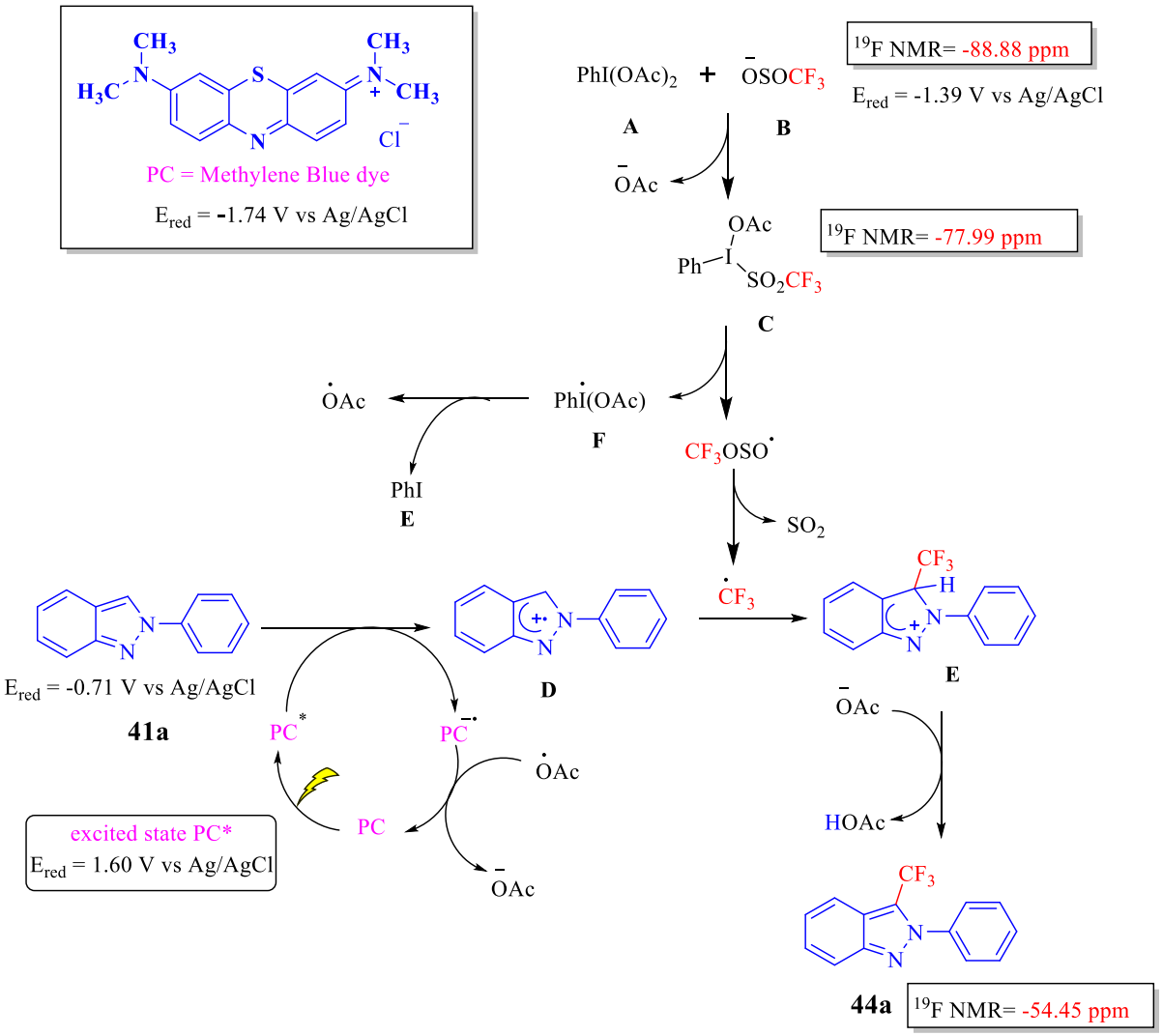
To investigate the reaction mechanism, we performed few control experiments as shown in scheme 21. We observed that 2-phenyl-2*H*-indazole **41a** failed to produce the corresponding trifluoromethylation product **44a** in the presence of radical scavengers such as TEMPO, BHT and BQ. Also, we observed the intermediate **C** and TEMPO-CF_3 adduct in ^{19}F NMR. These results indicate that the reaction mechanism proceeded through the radical pathway as depicted in scheme 4. Moreover, we have performed NMR experiments to confirm intermediates, however we did not observe the peaks corresponding to any hypervalent iodine complexes other than iodobenzene peaks in NMR spectra. In addition, we measured the redox potentials for the 2*H*-indazole **41a** (E_{red} = −0.71 V vs Ag/AgCl), Langlois' reagent (E_{red} = −1.39 V vs Ag/AgCl), photocatalyst (**PC**) (E_{red} = −1.74 V vs Ag/AgCl), using cyclic voltammetry (see SI) and reduction potential for excited state photocatalyst (**PC***) (E_{red} = 1.60 V vs Ag/AgCl).[29] The reduction potentials of 2*H*-indazole and excited state photocatalyst (**PC***) clearly signifies that 2*H*-indazole **41a** has the potential to transfer a single electron to excited state photocatalyst (**PC***), thus supporting the proposed mechanism.



Scheme 21. Control Experiments

Based on the control experiment results and the previous literature reports,[27] a plausible reaction mechanism of the present trifluoromethylation of 2-phenyl-2*H*-indazole is depicted in scheme 22. Initially, the CF_3 radical species would be generated by the reaction of $NaSO_2CF_3$ (**B**) with PIDA (**A**) via intermediate **C**. Meanwhile, the photocatalyst (**PC**) converted to its excited state **PC*** upon the absorption of photons from visible light. The **PC*** produce the

indazole radical cation **D** from the oxidation of indazole along with the generation of photocatalytic radical anion **PC**$^{\bullet-}$ through single-electron-transfer (SET) process. After that, the photocatalyst radical anion (**PC**$^{\bullet-}$) is oxidized to **PC** by reducing acetate radical to acetate anion. Then the generated CF_3 radical would attack intermediate **D** to form intermediate **E** which on deprotonation would result in trifluoromethylation product **44a**.



Scheme 22. Plausible reaction mechanism

3.4. Conclusions

We have successfully demonstrated a novel photoredox catalyzed regioselective C3-H trifluoromethylation of 2*H*-indazoles. This protocol offers the transition metal-free photoredox catalyzed C3-H trifluoromethylation of 2*H*-indazole. This method utilizes an inexpensive and benchtop-stable Langlois' reagent under mild reaction conditions. Further the developed protocol for regioselective trifluoromethylation of 2*H*-indazole would be great significance in pharmaceutical chemistry and material sciences.

3.5. Experimental Section

General Considerations

IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometers at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion concerning either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometers at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of the triplet)]. ^{19}F NMR spectra were recorded on 376 MHz spectrometers at RT in $CDCl_3$. In the ^{1}HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using a Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. All dry solvents were used, toluene was dried over sodium metal and DMSO, CH_3CN and DMF were dried over calcium hydride and which are commercially available.

All small scale dry reactions were carried out using a standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon, nitrogen and oxygen atmosphere wherever necessary. Solvents were distilled before use; petroleum ether with a boiling range of 40 to 60 ˚C was used. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20g per one gram of crude material). All 2-azidobenzaldehydes have been synthesized by using literature known procedures. [29]

General procedure (GP-I) for the synthesis of 2-phenyl-2*H*-indazole

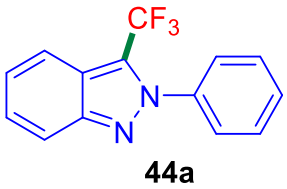
Azidobenzaldehyde **1** (1 mmol), aniline **2** (1 mmol) were taken in a 10 mL oven dried schlenck tube and it was closed with stopcock with argon balloon and placed in an external heating oil bath at 120 ˚C for 1-3 hrs (oil bath temperature). After completion of the starting material, the mixture was cooled to room temperature and was purified on a silica gel column chromatography (hexane/ethylacetate 90:10) which furnished the respective products **41a-s.**

General procedure (GP-II) for the synthesis of 2-phenyl-3-(trifluoromethyl)-2*H*-indazole

In an oven-dried reaction vessel equipped with a magnetic stir bar. Then 2-phenyl-2*H*-indazole (1 mmol), PIDA (2 mmol), sodium triflate (2 mmol) were added and followed by addition of DCM (5 mL). The resulting reaction mixture was irradiated using a 60 W CFL bulb. The progress of the reaction was monitored by TLC until the reaction was completed. The reaction mixture was quenched by addition of aq. NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in a vacuum. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as (petroleum ether/ethylacetate 97:3 to 95:5) eluent furnished the product trifluoromethylated indazoles **44a-s**.

Characterization Data of the Products

2-phenyl-3-(trifluoromethyl)-2*H*-indazole (44a)



44a

Physical State : Dark yellow Solid

Yield : 50 mg, 75%

Mp : 40-42 °C

IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3736, 3673, 3613, 3565, 3032, 2968, 2381, 1734, 1700, 1650, 1556, 1540, 1521, 1508, 1458, 1420, 1218, 1120, 940, 757, 667, 631.

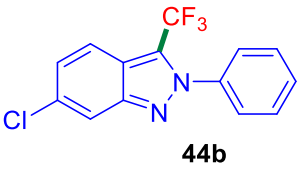
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.79 - 7.87 (m, 2H), 7.52 - 7.63 (m, 5H), 7.39 - 7.45 (m, 1H), 7.28 - 7.34 (m, 1H).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): 148.2, 139.6, 130.0, 29.1, 127.3, 126.1, 125.1, 123.5 (q, J_{C-F} = 40.0 Hz), 121.3 (q, J_{C-F} = 269.0 Hz), 119.4, 118.4.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.5.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_{10}F_3N_2]^+$ = 263.0791; found: 263.0794.

6-chloro-2-phenyl-3-(trifluoromethyl)-2*H*-indazole (44b)



44b

Physical State : Dark orange Solid

Yield : 29 mg, 35%

Mp : 44-46 °C

IR (MIR-ATR, 4000–600 cm^{-1}): *υ*max = 3673, 3613, 3565, 3525, 3068, 2926, 2854, 2355, 1695, 1634, 1596, 1549, 1502, 1470, 1439, 1314, 1290, 1222, 1178, 1126, 1104, 999, 768, 691, 621, 544.

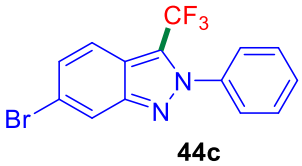
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.73 (d, 1H, J = 8.8 Hz), 7.56 - 7.41 (m, 5H), 7.34 (s, 1H), 6.95 - 6.87 (m, 1H).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.6, 139.3, 135.5, 129.8 (q, J_{C-F} = 36.0 Hz), 127.7, 126.0, 121.4 (q, J_{C-F} = 252.0 Hz), 119.4, 119.3, 105.7.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.7.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9ClF_3N_2]^+$ = 297.0401; found: 297.0408.

6-bromo-2-phenyl-3-(trifluoromethyl)-2*H*-indazole (44c)



44c

Physical State : Yellow Solid

Yield : 27 mg, 37%

Mp : 42-44 °C

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515.

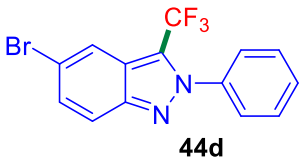
^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04 - 7.98 (m, 1H), 7.71 (dd, 1H, J_a = 1.5 and J_b= 9.8 Hz), 7.62 - 7.51 (m, 5H), 7.38 (dd, 1H, J_a = 1.7 and J_b = 9.0 Hz).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.7, 139.2, 129.8 (q, $J_{C\text{-}F}$ = 42.0 Hz), 128.9, 126.0, 121.9 (q, $J_{C\text{-}F}$ = 268.0 Hz), 120.7, 120.0, 119.2.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.7.

HR-MS(ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9914.

5-bromo-2-phenyl-3-(trifluoromethyl)-2*H*-indazole (44d)



44d

Physical State : Dark yellow Solid

Yield : 31 mg, 43%

Mp : 52-54 °C

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3648, 3588, 3547, 3070, 2924, 2321, 1735, 1596, 1502, 1420, 1271, 1216, 1169, 1124, 1107, 1043, 996, 861, 804, 768, 692, 634, 596.

^1H NMR ($CDCl_3$, 400 MHz) δ_H = 8.01 (s, 1H), 7.70 (d, 1H, J = 9.3 Hz), 7.62 - 7.50 (m, 4H), 7.50 - 7.42 (m, 2H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 146.6, 139.3, 137.9, 132.5, 129.8 (q, $J_{C\text{-}F}$ = 36.0 Hz), 124.6, 123.0, 122.6, 121.9 (q, $J_{C\text{-}F}$ = 248.0 Hz), 120.1, 118.6, 116.5, 112.7.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.6.

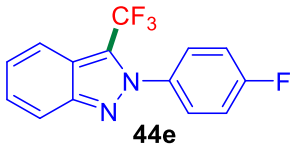
HR-MS(ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9900.

2-(4-fluorophenyl)-3-(trifluoromethyl)-2*H*-indazole (44e)

Physical State : Yellow Solid

Yield : 50 mg, 45%

Mp : 52-54 °C



44e

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3689, 3620, 3568, 3036, 2938, 2321, 1717, 1540, 1502, 1454, 1252, 1216, 1156, 1118, 1107, 1032, 987, 861, 767, 659, 631.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86 - 7.75 (m, 2H), 7.62 - 7.53 (m, 2H), 7.45 - 7.39 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and J_b = 8.3 Hz,), 7.26 - 7.21 (m, 2H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 164.5 (d, J_{C-F} = 249.0 Hz), 149.7, 148.2, 135.6 (d, J_{C-F} = 2.0 Hz), 128.1 (d, J_{C-F} = 9.0 Hz), 127.4, 125.5, 123.6 (q, J_{C-F} = 40.0 Hz), 121.5, 121.0 (q, J_{C-F} = 268.0 Hz), 119.4, 118.4, 116.5 (d, J_{C-F} = 24.0 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz): −54.5, -110.2.

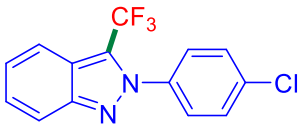
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9F_4N_2]^+$ = 281.0696; found: 281.0690.

2-(4-chlorophenyl)-3-(trifluoromethyl)-2*H*-indazole (44f)

Physical State : Dark yellow solid

Yield : 35 mg, 53%

Mp : 46-48 °C



44f

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3673, 3613, 3547, 3068, 2317, 2089, 1552, 1522, 1498, 1432, 1298, 1220, 1176, 1118, 1089, 1017, 998, 929, 832, 746, 728, 583, 537.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.76 - 7.68 (m, 2H), 7.49 - 7.39 (m, 4H), 7.34 - 7.29 (m, 1H), 7.24 - 7.17 (m, 1H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.0, 136.1, 129.8 (q, J_{C-F} = 47.0 Hz), 127.5, 127.4, 125.7, 123.9, 122.3, 122.2, 121.7, 119.9 (q, J_{C-F} = 231.0 Hz), 118.4.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.3.

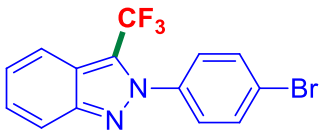
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9ClF_3N_2]^+$ = 297.0401; found: 297.0401.

2-(4-bromophenyl)-3-(trifluoromethyl)-2*H*-indazole (44g)

Physical State : Dark yellow

Yield : 45 mg, 62%

Mp : 44-46 °C



44g

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3673, 3613, 3547, 3068, 1521, 1495, 1432, 1298, 1222, 1176, 1119, 1099, 1068, 1015, 996, 929, 829, 743, 711, 576, 535.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.84 - 7.78 (m, 2H), 7.70 - 7.64 (m, 2H), 7.46 (d, 2H, *J* = 8.3 Hz), 7.43 - 7.37 (m, 1H), 7.31 - 7.25 (m, 1H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.6, 132.8 (q, $J_{C\text{-}F}$ = 43.0 Hz), 127.8, 127.6, 125.3, 124.2, 123.9, 122.5 (q, $J_{C\text{-}F}$ = 223.0 Hz), 119.4, 118.4.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.3.

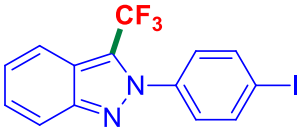
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9900.

2-(4-iodophenyl)-3-(trifluoromethyl)-2*H*-indazole (44h)

Physical State : Light yellow

Yield : 40 mg, 68%

Mp : 100-102 °C



44h

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3736, 3547, 3462, 3032, 2917, 2356, 2154, 1716, 1683, 1556, 1540, 1509, 1362, 1257, 999, 821, 800, 740, 521.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.94 - 7.86 (m, 2H), 7.85 - 7.78 (m, 2H), 7.45 - 7.38 (m, 1H), 7.38 - 7.28 (m, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.3, 138.8 (q, $J_{C\text{-}F}$ = 43.0 Hz), 127.7, 125.3, 123.8, 122.7, 122.2, 121.7, 119.5 (q, $J_{C\text{-}F}$ = 224.0 Hz), 118.4, 95.8.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.3.

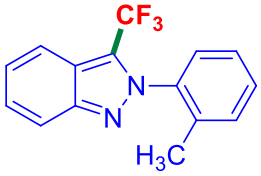
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_9F_3IN_2]^+$ = 388.9757; found: 388.9756.

2-(*o*-tolyl)-3-(trifluoromethyl)-2*H*-indazole (44i)

Physical State : Dark yellow Solid

Yield : 30 mg, 45%

Mp : 52-54 °C



44i

IR (MIR-ATR, 4000–600 cm^{-1}): *υ*max =3057, 2927, 1603, 1564, 1501, 1386, 1337, 1306, 1158, 1114, 1039, 969, 957, 863, 810, 751, 716, 663, 605, 573.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.90 - 7.78 (m, 2H), 7.51 - 7.28 (m, 6H), 2.02 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ = 148.1, 139.6, 138.3, 137.1, 135.8, 130.5, 127.3 (q, J_{C-F} = 36.0 Hz), 125.0, 122.1, 119.4 (q, J_{C-F} = 228.0 Hz), 116.0, 114.9, 16.8.

^{19}F NMR ($CDCl_3$, 376 MHz): −56.2.

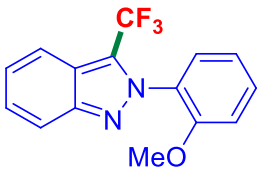
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0952.

2-(2-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole (44j)

Physical State : Yellow Solid

Yield : 27 mg, 42%)

Mp : 40-42 °C



44j

IR (MIR-ATR, 4000–600 cm^{-1}): *υ*max = 3673, 3614, 3525, 2930, 2846, 2316, 1603, 1510, 1437, 1335, 1283, 1202, 1120, 1093, 1021, 966, 804, 753, 653, 603.

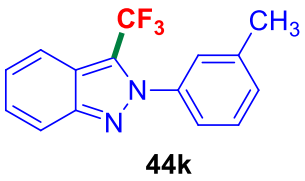
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.03 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 6.8 Hz, 1H), 7.53 (dt, J_a = 1.7 and J_b = 7.9 Hz, 1H), 7.44 (dd, J_a = 1.5 and J_b = 7.8 Hz, 1H), 7.38 - 7.32 (m, 1H), 7.13 - 7.04 (m, 2H), 3.74 (m, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ =154.8, 143.5, 132.0, 128.7, 127.9 (q, J_{C-F} = 42.0 Hz), 125.3, 124.8, 123.9, 123.2, 121.8 (q, J_{C-F} = 267.0 Hz), 119.0, 112.0, 55.7.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.3.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0901.

2-(*m*-tolyl)-3-(trifluoromethyl)-2*H*-indazole (44k)



44k

Physical State : Brown oil

Yield : 43 mg, 64%

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3648, 3565, 3525, 3065, 2924, 2322, 1611, 1592, 1495, 1476, 1431, 1302, 1221, 1202, 1169, 1118, 1016, 880, 787, 745, 693, 693, 627, 605, 521.

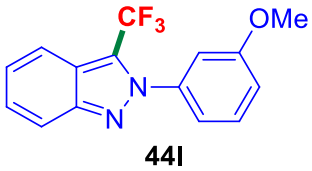
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.74 (d, 2H *J* = 8.8 Hz), 7.39 - 7.24 (m, 5H), 7.20 (dd, 1H, J_a = 7.8 and J_b = 15.2 Hz), 2.37 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 148.2, 139.3, 130.7, 129.5, 128.8, 127.1, 126.7, 125.3, 123.1 (q, $J_{C\text{-}F}$ = 44.0 Hz), 119.6 (q, $J_{C\text{-}F}$ = 250.0 Hz), 118.3, 21.2;

^{19}F NMR ($CDCl_3$, 376 MHz): −54.2.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0960.

2-(3-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole (44l)



44l

Physical State : Brownish yellow Solid

Yield : 53 mg, 80%

Mp : 74-76 °C

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3614, 3547, 2925, 2846, 2323, 2134, 1734, 1593, 1498, 1468, 1288, 1250, 1201, 1163, 1122, 1044, 976, 885, 755, 688, 521.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.45 (t, *J* = 8.3 Hz, 1H), 7.40 - 7.32 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.15 - 7.08 (m, 2H), 3.87 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 160.0, 143.4, 140.0, 129.9, 125.6 (q, $J_{C\text{-}F}$ = 40.0 Hz), 123.7, 122.4, 122.1 (q, $J_{C\text{-}F}$ = 268.0 Hz), 118.5, 116.4, 112.0, 55.6.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.7.

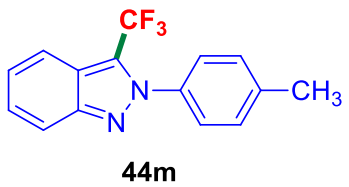
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0901.

2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole (44m)

Physical State : Yellow Solid

Yield : 50 mg, 83%

Mp : 42-44 °C



44m

IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 3673, 3614, 3043, 2925, 2324,1553, 1515, 1471, 1431, 1383, 1298, 1219, 1174, 1117, 1100, 999, 930, 820, 745, 610, 547.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86 - 7.78 (m, 2H), 7.50 - 7.42 (m, 2H), 7.42 - 7.36 (m, 1H), 7.36 - 7.25 (m, 3H), 2.48 - 2.44 (m, 3H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.1, 140.2, 137.2, 130.2, 128.2, 127.1, 125.9 (q, J_{C-F} = 39.0 Hz), 123.8, 122.3, 121.5 (q, J_{C-F} = 267.0 Hz), 119.6, 118.4, 21.3.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.5.

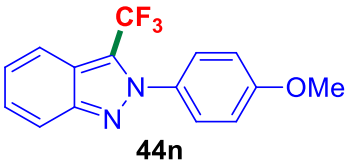
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0948.

2-(4-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole (44n)

Physical State : Yellow Solid

Yield : 53 mg, 83%

Mp : 74-76 °C



44n

IR (MIR-ATR, 4000–600 cm^{-1}): υmax = 2969, 2887, 2839, 2303, 2043, 1608, 1513, 1433, 1299, 1252, 1175, 11148, 1030, 1015, 998, 928, 834, 736, 703, 611, 557, 536.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.85 - 7.79 (m, 2H), 7.53 - 7.47 (m, 2H), 7.43 - 7.37 (m, 1H), 7.32 - 7.24 (m, 1H), 7.07 - 6.99 (m, 2H), 3.89 (s, 3H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 160.6, 148.0, 132.5, 127.4 (q, J_{C-F} = 39.0 Hz), 124.9, 123.5, 122.7, 122.3, 121.4, 119.6 (q, J_{C-F} = 244.0 Hz), 114.8, 55.6.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.6.

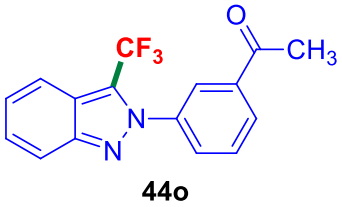
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0891.

1-(3-(3-(trifluoromethyl)-2*H*-indazol-2-yl)phenyl)ethanone (44o)

Physical State : Light brown Solid

Yield : 25 mg, 40%

Mp : 74-76 °C



44o

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3648, 3589, 3504, 3074, 2925, 2323, 1716, 1690, 1589, 1522, 1493, 1430, 1359, 1302, 1256, 1222, 1178, 1149, 1012, 748, 691, 587, 562.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.23 - 8.12 (m, 2H), 7.88 - 7.76 (m, 3H), 7.72 - 7.64 (m, 1H), 7.47 - 7.40 (m, 1H), 7.36 - 7.29 (m, 1H), 2.66 (s, 3H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.4, 148.4, 140.0, 138.0, 130.3, 129.5, 128.2, 127.6, 126.1, 125.4, 123.6 (q, J_{C-F} = 40.0 Hz), 120.5, 119.5 (q, J_{C-F} = 209.0 Hz), 118.4, 26.7.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.2.

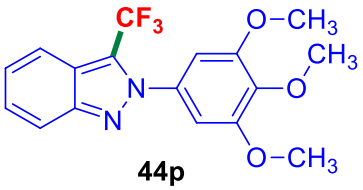
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{16}H_{12}F_3N_2O]^+$ = 305.0896; found: 305.0914.

3-(trifluoromethyl)-2-(3,4,5-trimethoxyphenyl)-2*H*-indazole (44p)

Physical State : Yellow Solid

Yield : 48 mg, 78%)

Mp : 126-128 °C



44p

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3673, 3648, 3565, 2971, 2881, 2835, 1596, 1556, 1505, 1462, 1415, 1307, 1265, 1233, 1170, 1125, 1106, 1016, 945, 897, 837, 794, 733, 702, 613.

^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.87 - 7.78 (m, 2H), 7.46 - 7.38 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and *Jb* = 8.3 Hz,), 6.83 (s, 2 H), 3.93 (s, 3H), 3.90 (s, 6H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ_H = 153.2, 148.0, 139.3, 134.9, 127.3, 125.1 (q, J_{C-F} = 42.0 Hz), 121.5, 119.6 (q, J_{C-F} = 215.0 Hz), 03.8, 61.0, 56.3.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.5.

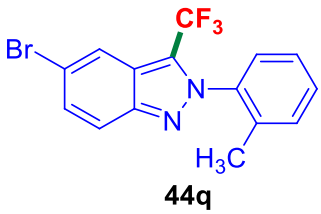
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{17}H_{16}F_3N_2O_3]^+$ = 353.1108; found: 353.1104.

6-bromo-2-(o-tolyl)-3-(trifluoromethyl)-2*H*-indazole (44q)

Physical State : Pale yellow Solid

Yield : 48 mg, 78%

Mp : 82-84 °C



44q

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 8.00 (d, 1H, *J* = 1.0 Hz), 7.88 - 7.79 (m, 1H), 7.77 - 7.70 (m, 1H), 7.67 (d, 1H, *J* = 7.8 Hz), 7.40 - 7.27 (m, 3H), 2.63 (s, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ = 158.3, 150.9, 148.8, 138.9, 129.1, 124.8 (q, J_{C-F} = 44.0 Hz), 122.1, 121.7 (q, J_{C-F} = 246.0 Hz), 120.9, 119.4, 115.6, 23.9.

^{19}F NMR ($CDCl_3$, 376 MHz): −54.5.

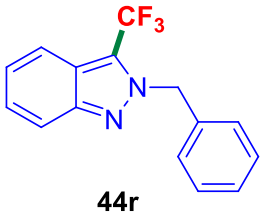
HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{11}BrF_3N_2]^+$ = 355.0052; found: 355.0063.

2-benzyl-3-(trifluoromethyl)-2*H*-indazole (44r)

Physical State : Yellow Solid

Yield : 29 mg, 55%

Mp : 42-44 °C



44r

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max =3673, 3614, 3547, 3067, 3035, 2926, 2323, 1521, 1483, 1436, 1327, 1286, 1219, 1165, 1112, 1036, 970, 881, 746, 706, 627.

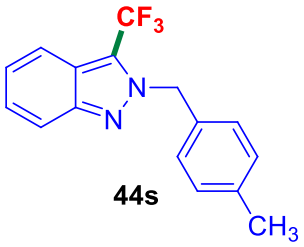
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.82 - 7.72 (m, 2H), 7.39 - 7.19 (m, 7H), 5.73 (s, 2H).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ_H = 147.8, 135.2, 128.9 (q, J_{C-F} = 42.0 Hz), 127.7 (d, J_{C-F} = 8.0 Hz), 126.7, 124.7, 123.7 (q, J_{C-F} = 207.0 Hz), 121.2, 120.0, 119.2, 118.3, 56.3.

^{19}F NMR ($CDCl_3$, 376 MHz): −55.8.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0943.

2-(4-methylbenzyl)-3-(trifluoromethyl)-2*H*-indazole (44s)



44s

Physical State : Brown oil

Yield : 29 mg, 45%

Mp : 90-92 °C

IR (MIR-ATR, 4000–600 cm^{-1}): *v*max = 3673, 3648, 3613, 2925, 2858, 2359, 1717, 1969, 1622, 1539, 1511, 1475, 1433, 1385, 1337, 1305, 1201, 1160, 1123, 1015, 967, 813, 749, 689, 608.

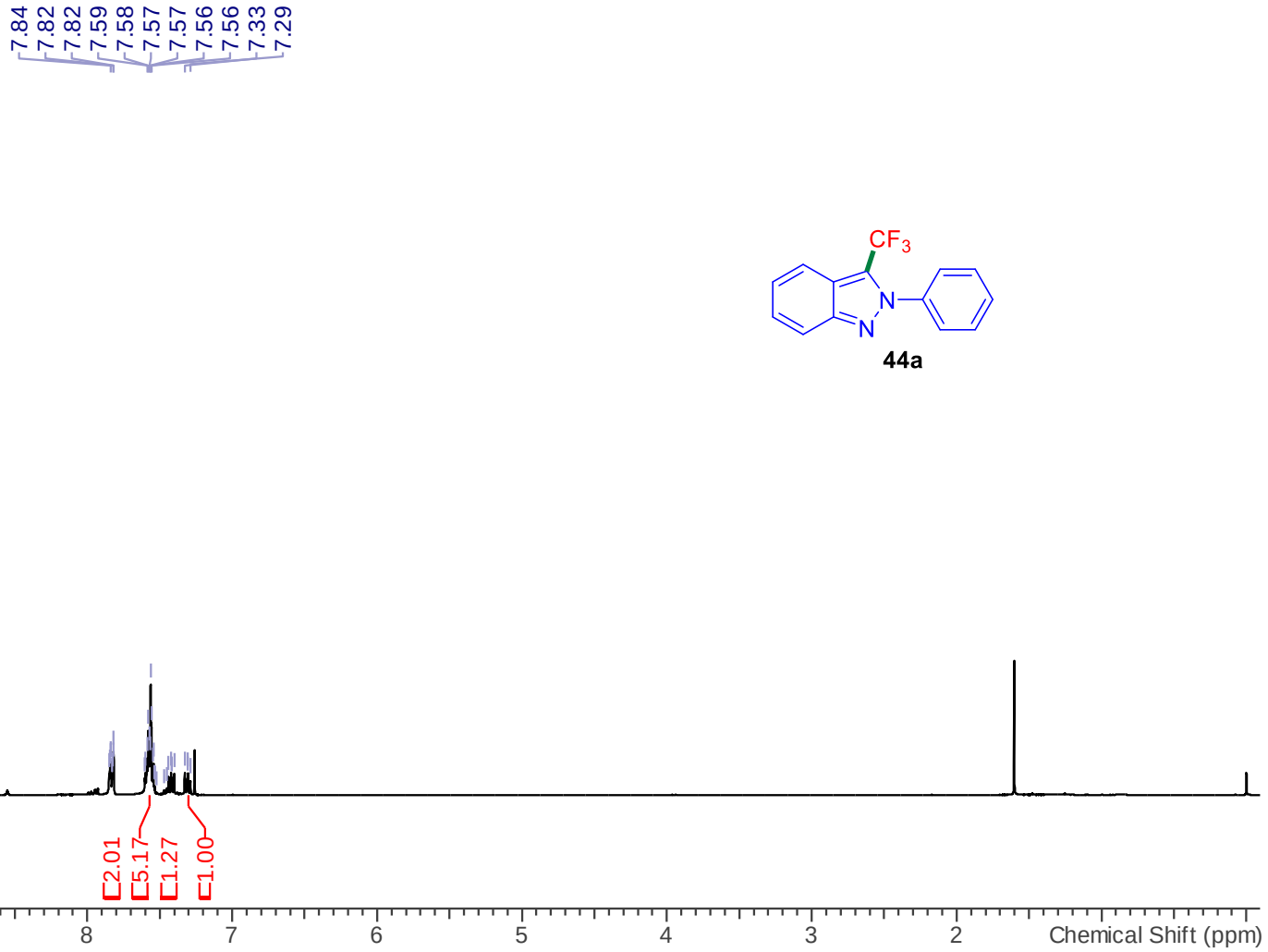
^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.73 - 7.63 (m, 2H), 7.26 (ddd, 1H, J_a = 1.2, J_b = 7.0 and J_c = 8.4 Hz), 7.20 - 7.00 (m, 5H), 5.61 (s, 2H), 2.24 (s, 3H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.8, 138.2, 132.2, 129.4 (q, $J_{C\text{-}F}$ = 44.0 Hz), 127.7 (q, $J_{C\text{-}F}$ = 9.0 Hz), 124.6, 122.6, 121.2 (q, $J_{C\text{-}F}$ = 266.0 Hz), 119.2, 118.3, 56.1, 21.1.

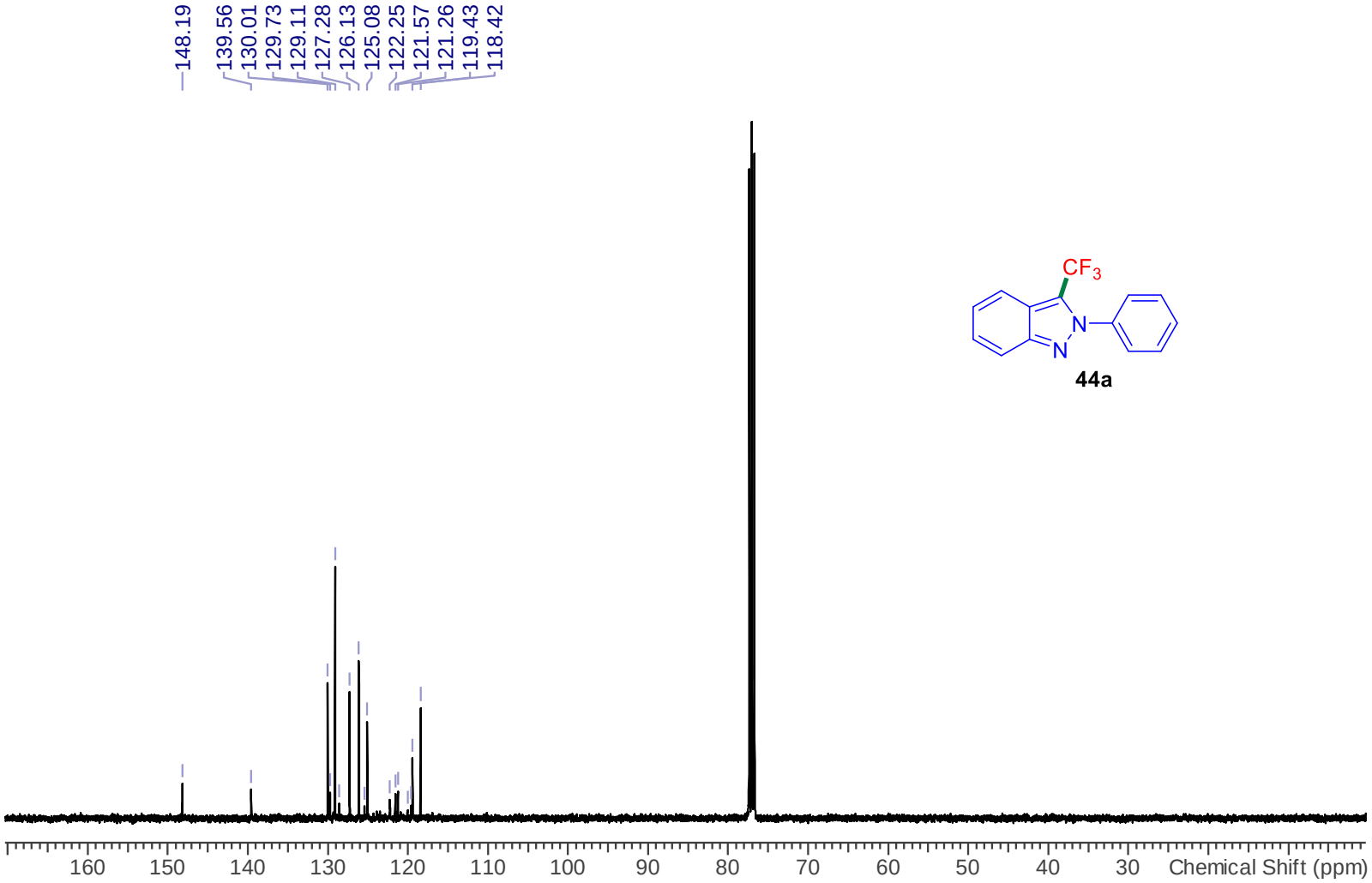
^{19}F NMR ($CDCl_3$, 376 MHz): −55.8.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{16}H_{14}F_3N_2]^+$ = 291.1104; found: 291.1110.

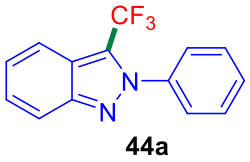
Copies of ^{1}H, ^{13}C, ^{19}F NMR spectra for the all final compounds



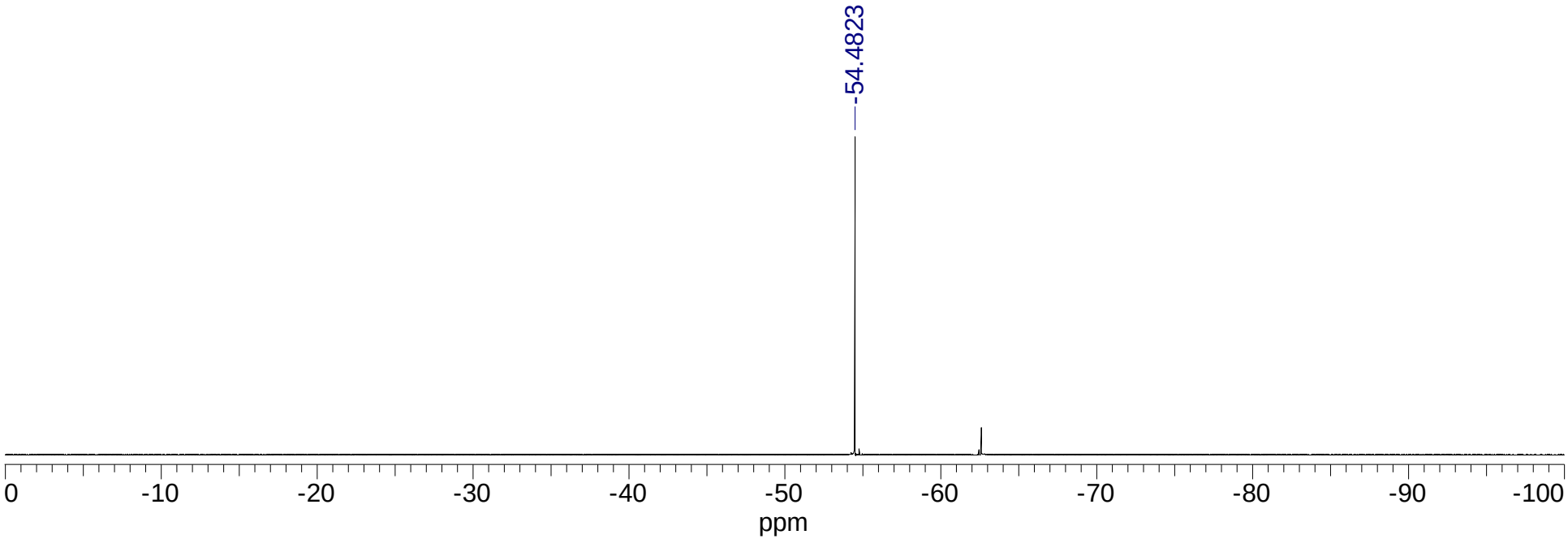
^{1}H NMR (400 MHz) spectrum of compound **44a** in $CDCl_3$



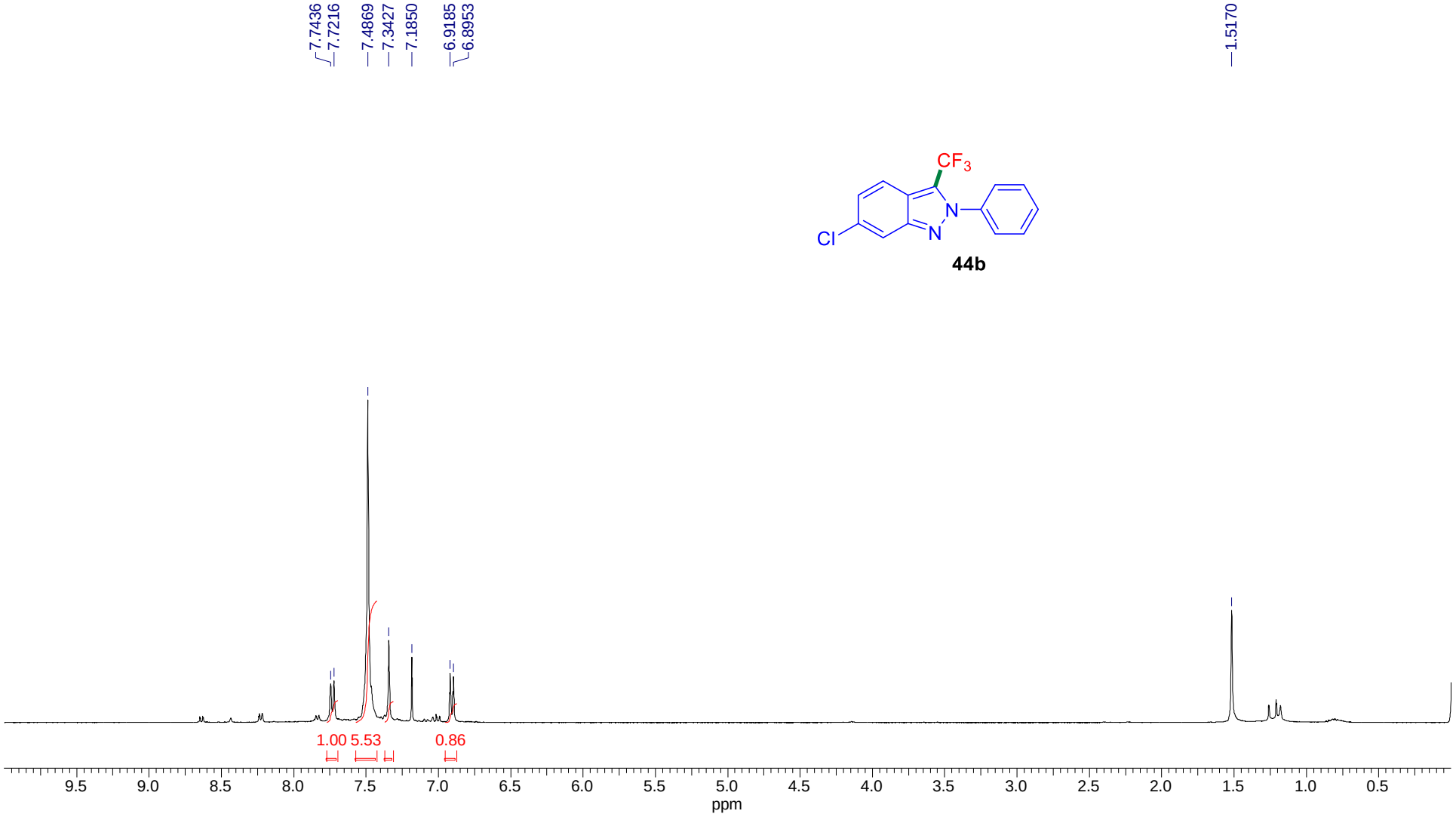
^{13}C NMR (100 MHz) spectrum of compound **44a** in $CDCl_3$



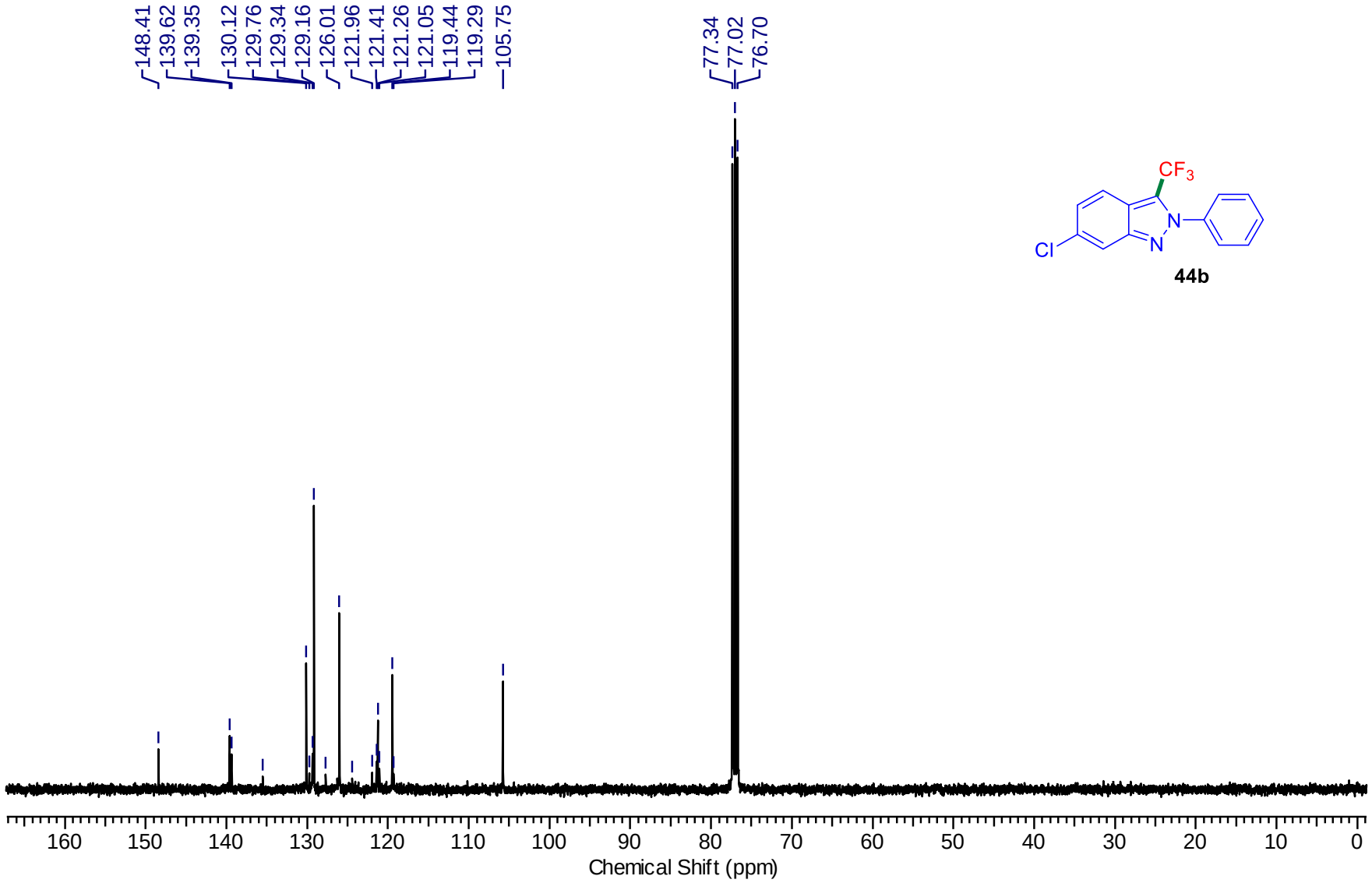
44a



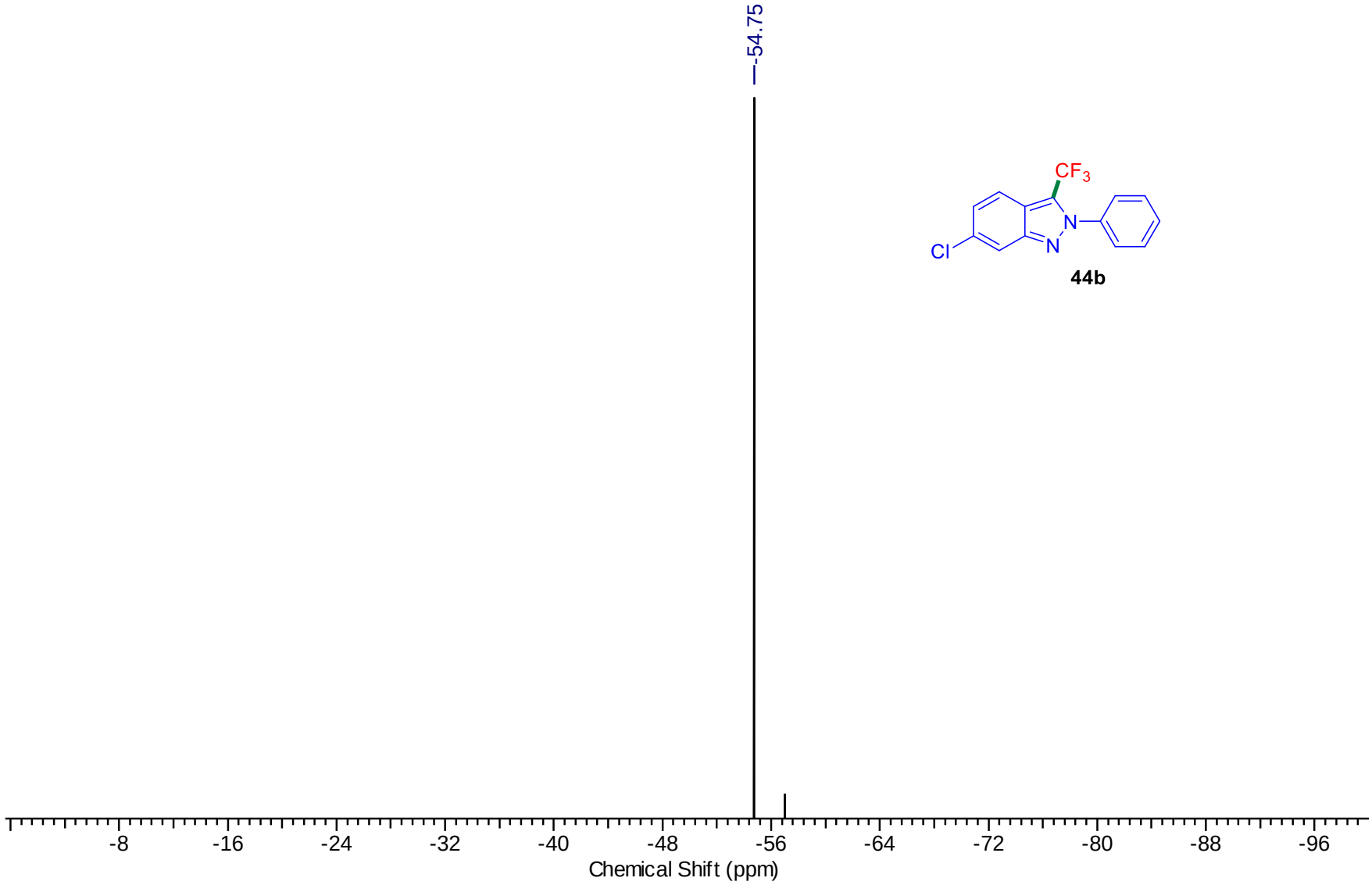
^{19}F NMR (376 MHz) spectrum of compound **44a** in $CDCl_3$



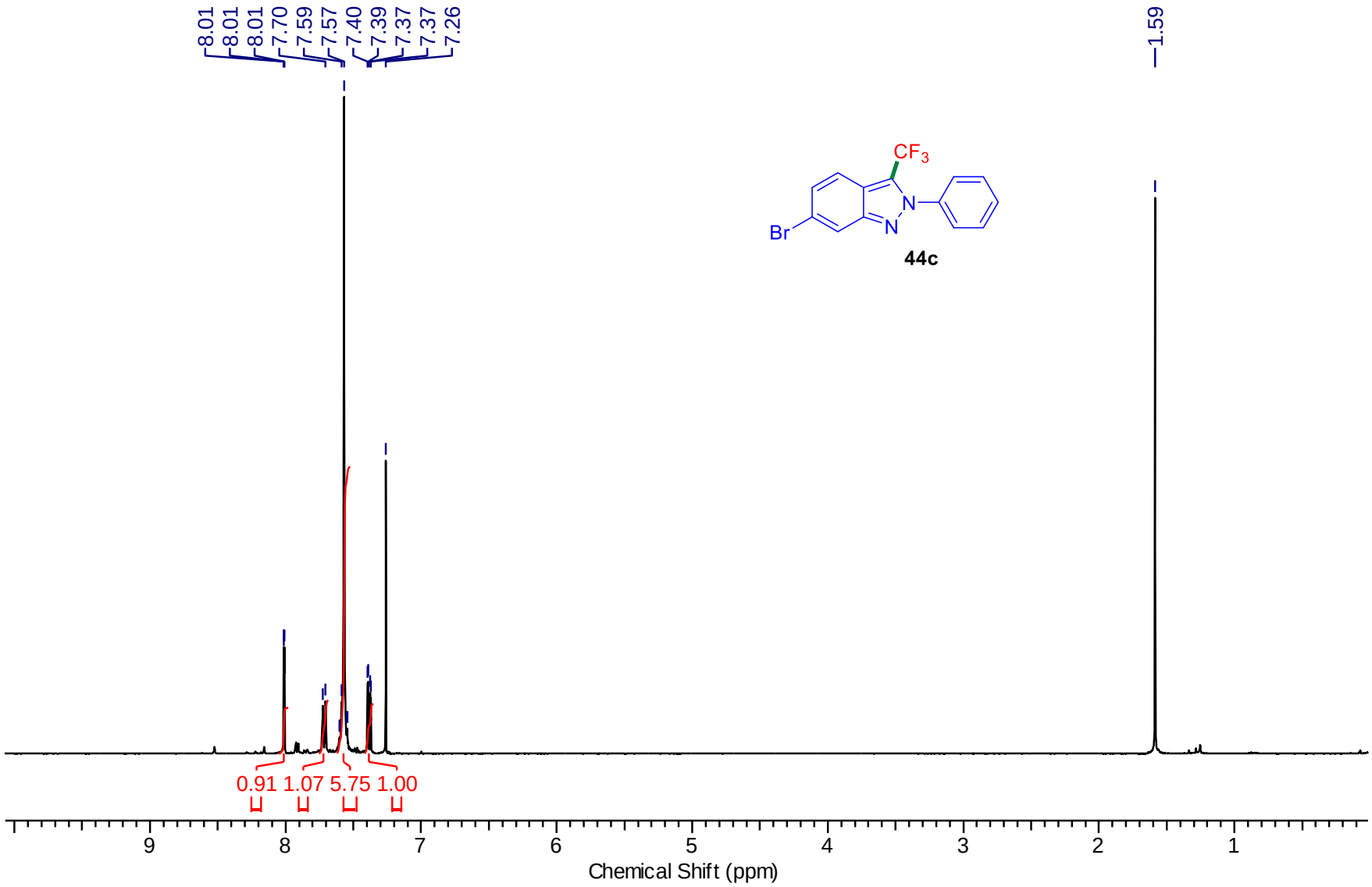
^{1}H NMR (400 MHz) spectrum of compound **44b** in $CDCl_3$



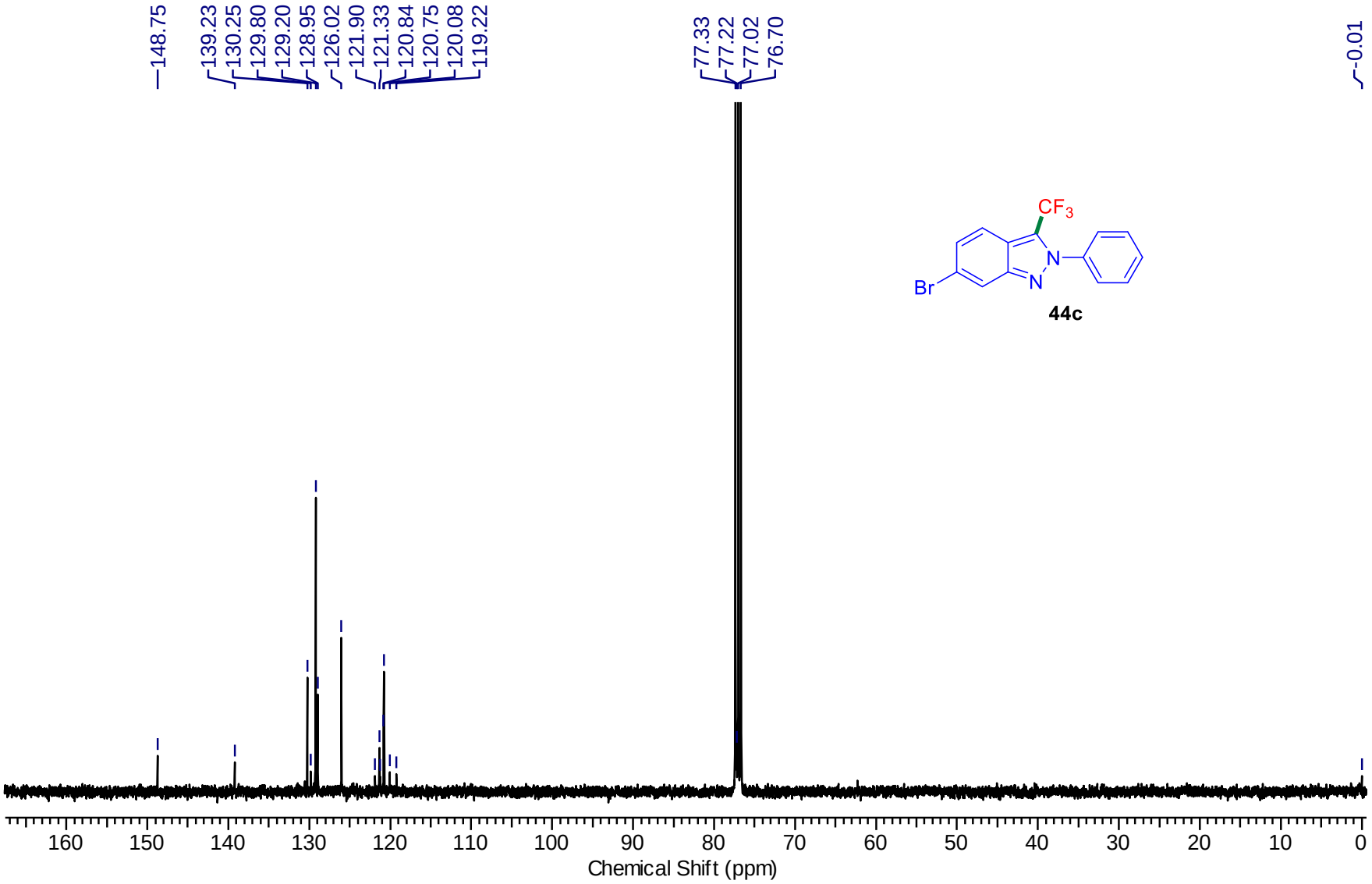
^{13}C NMR (100 MHz) spectrum of compound **44b** in $CDCl_3$



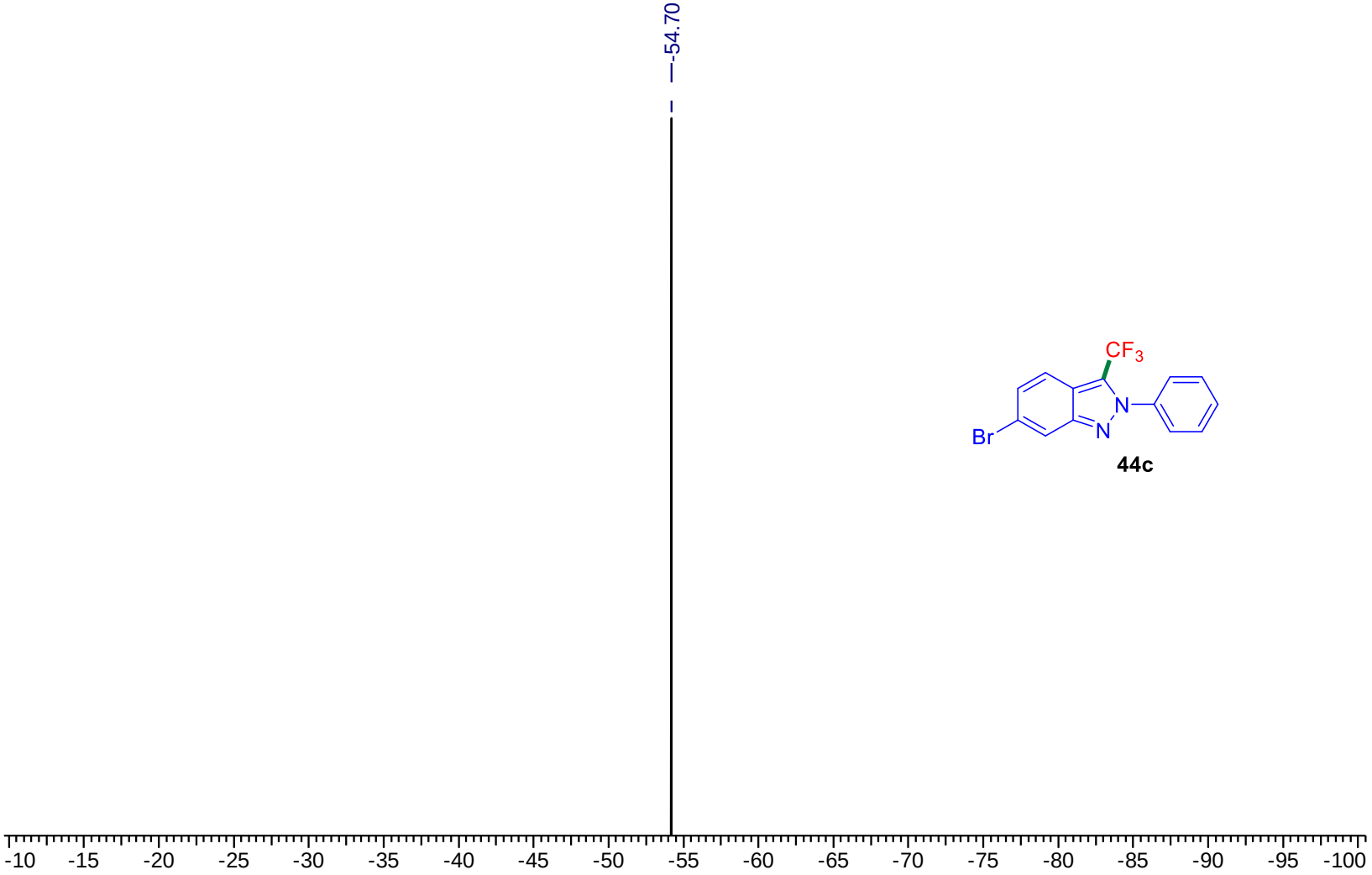
^{19}F NMR (376 MHz) spectrum of compound **44b** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **44c** in $CDCl_3$

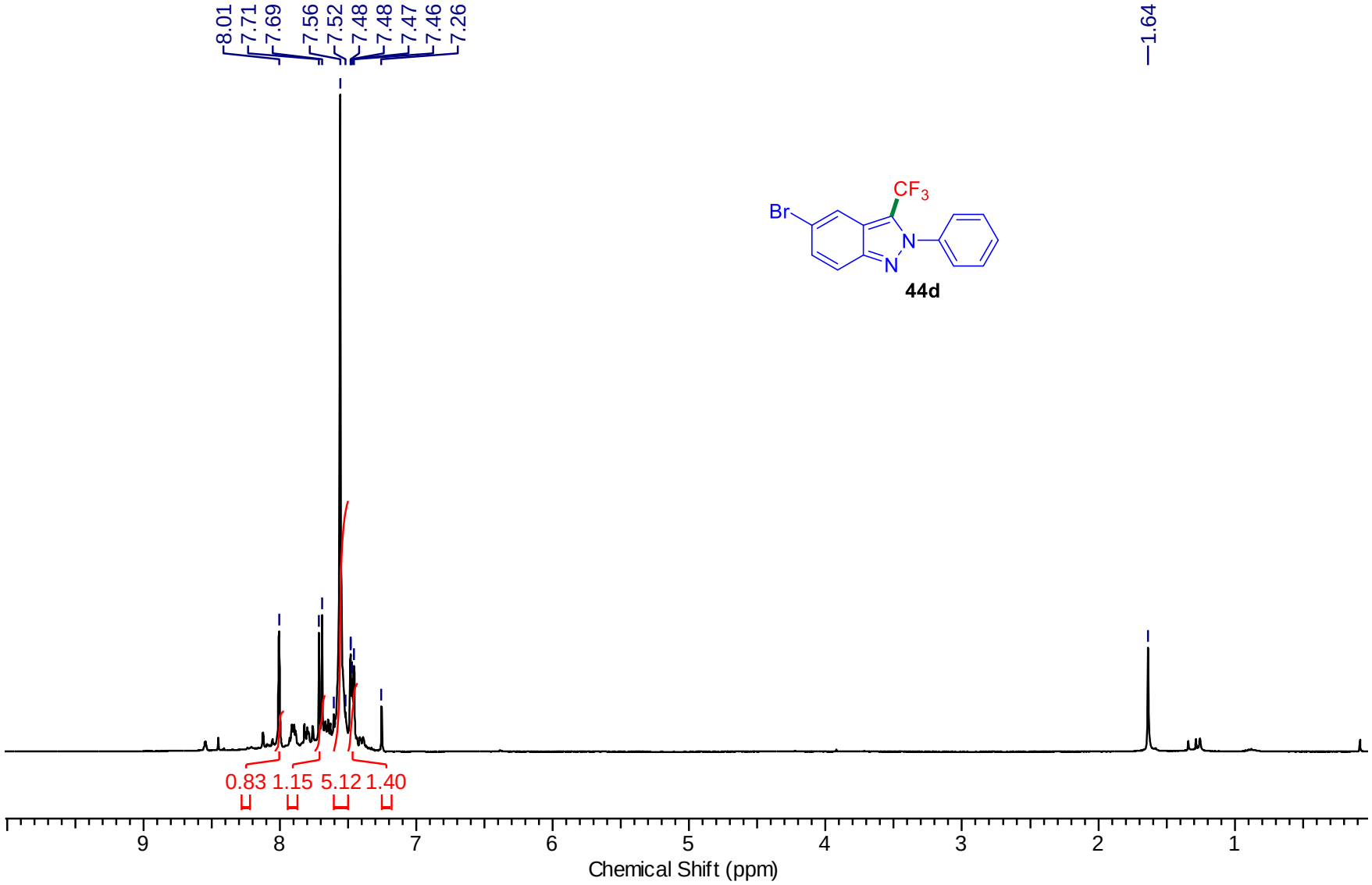


^{13}C NMR (100 MHz) spectrum of compound **44c** in $CDCl_3$

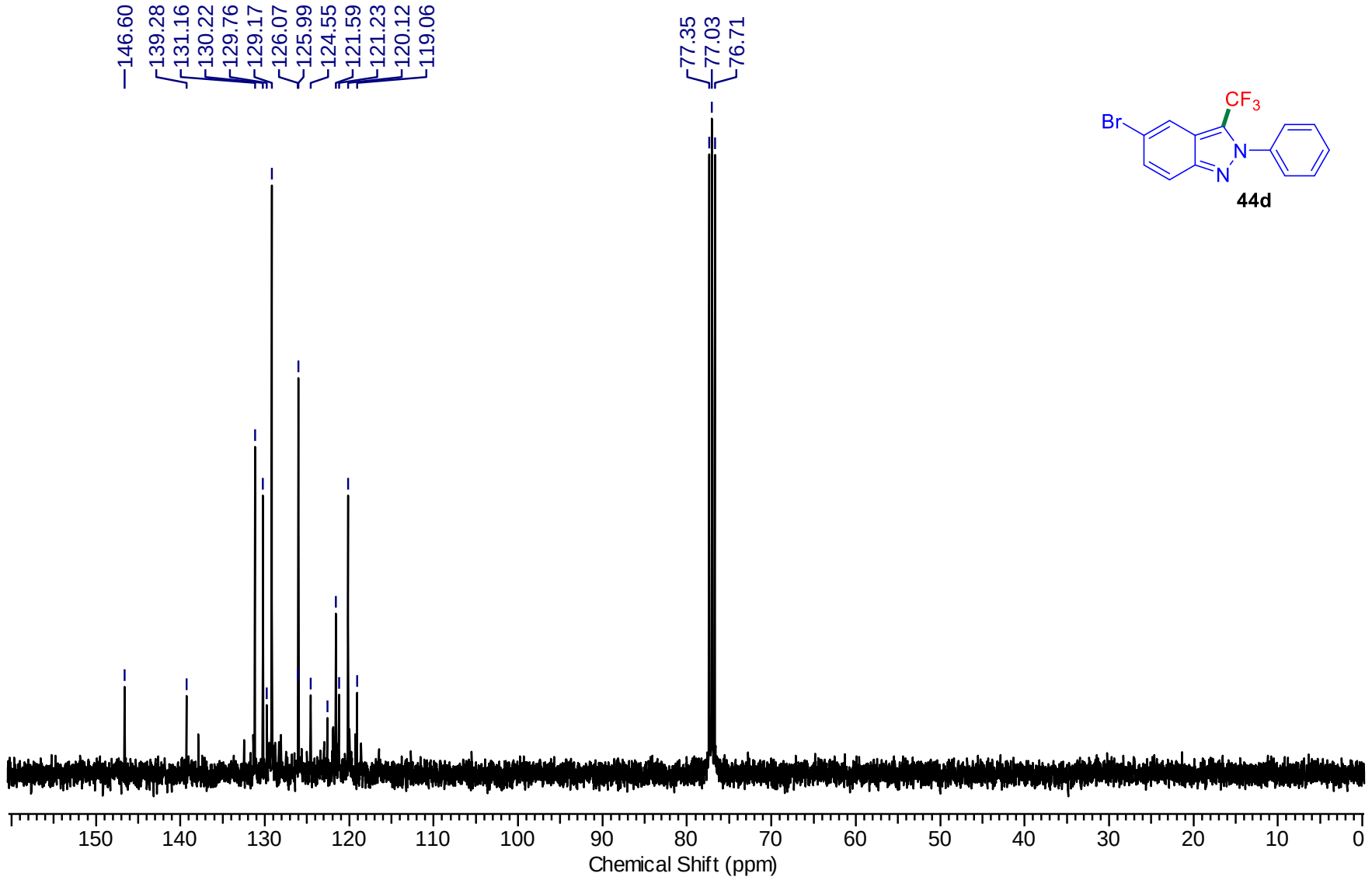


44c

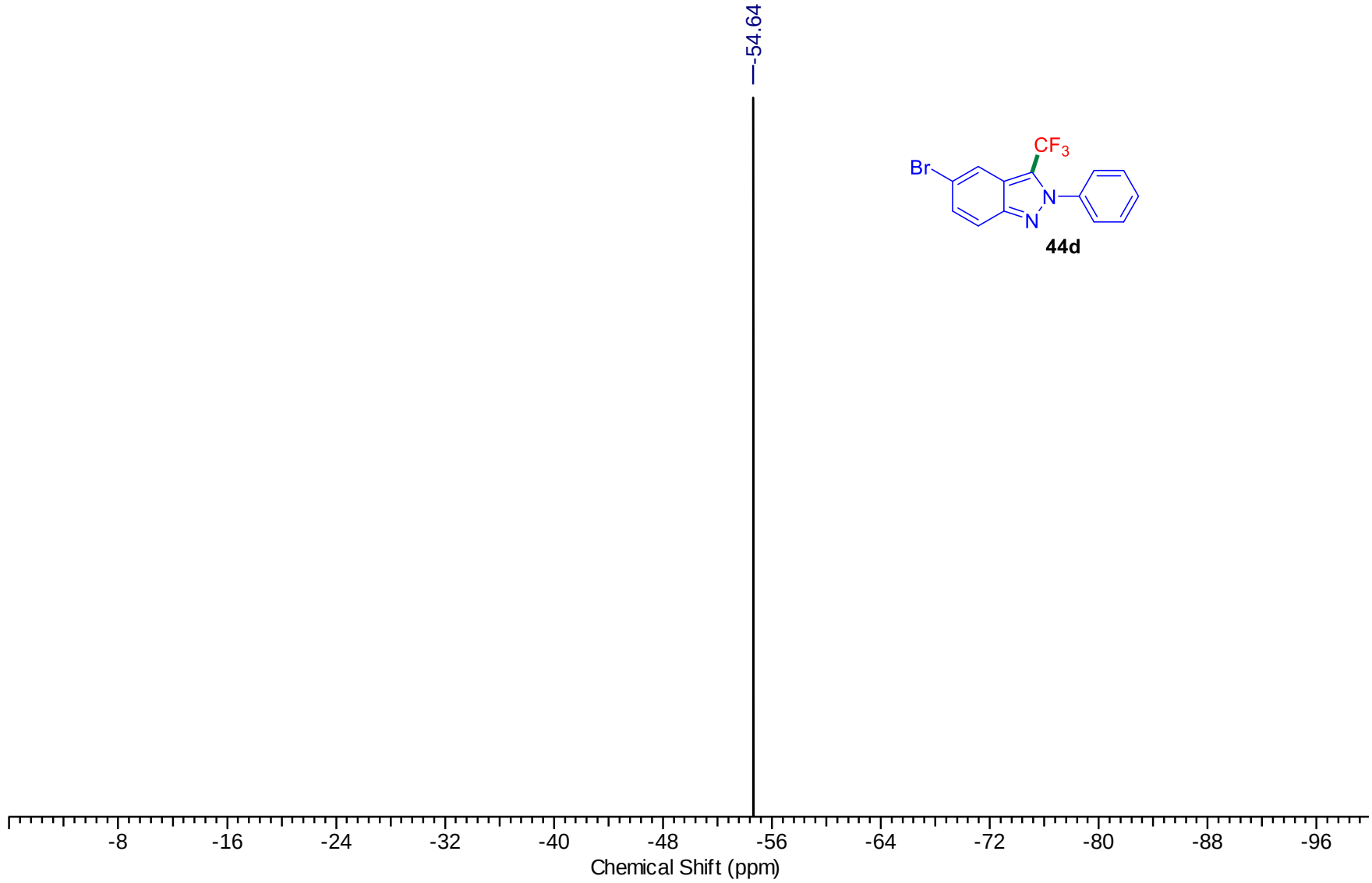
^{19}F NMR (376 MHz) spectrum of compound **44c** in $CDCl_3$



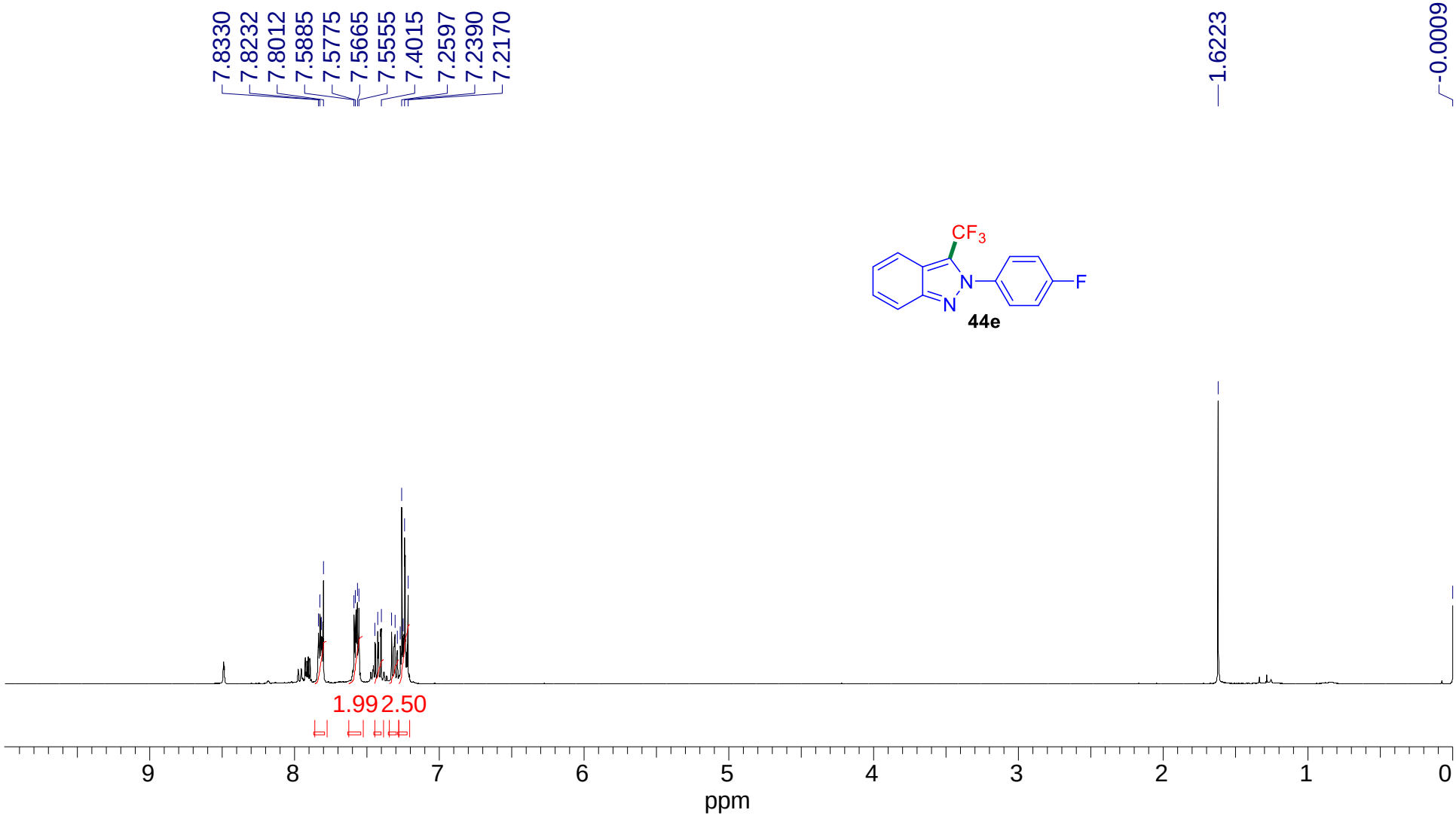
^{1}H NMR (400 MHz) spectrum of compound **44d** in $CDCl_3$



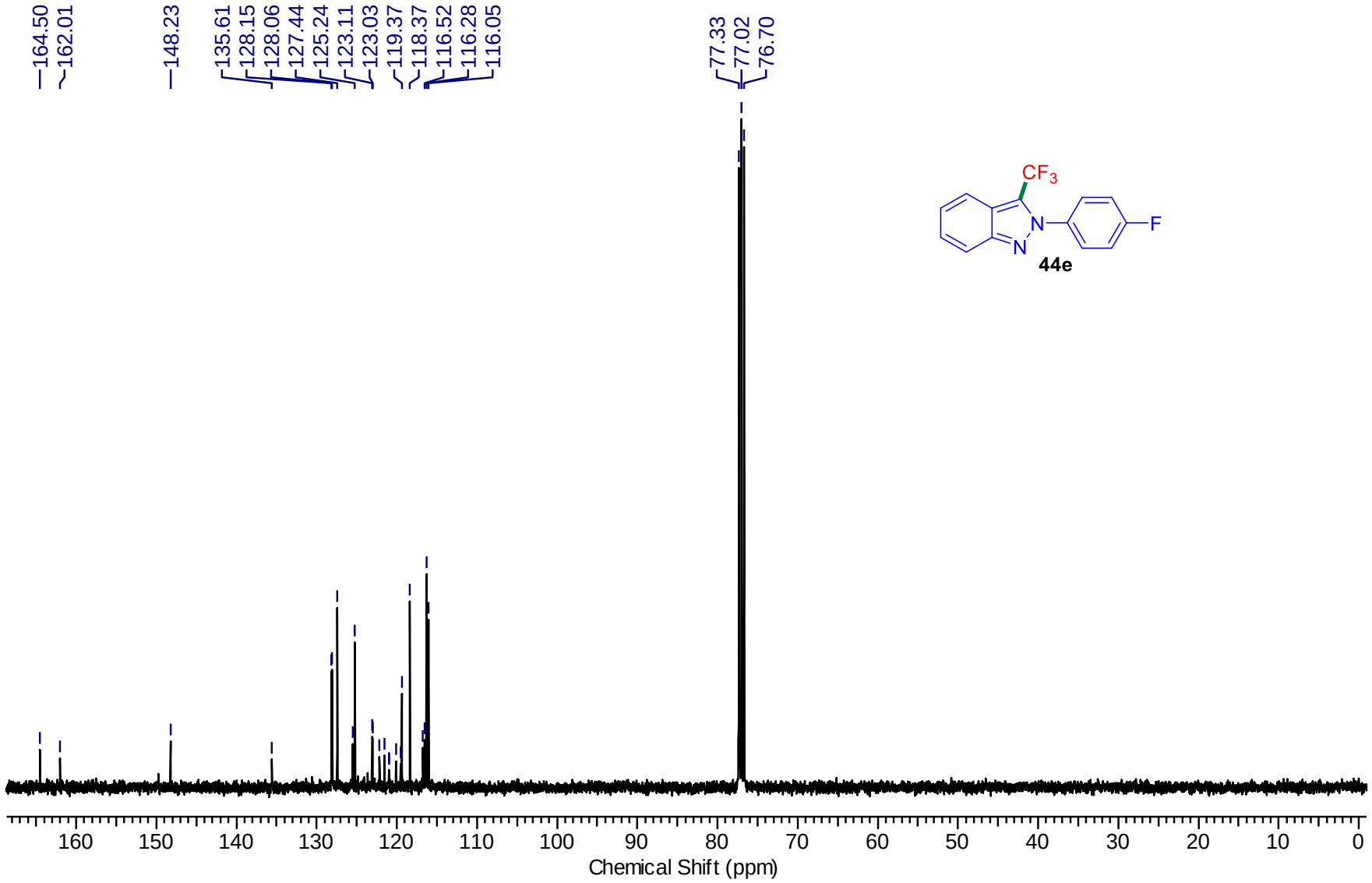
^{13}C NMR (100 MHz) spectrum of compound **44d** in $CDCl_3$



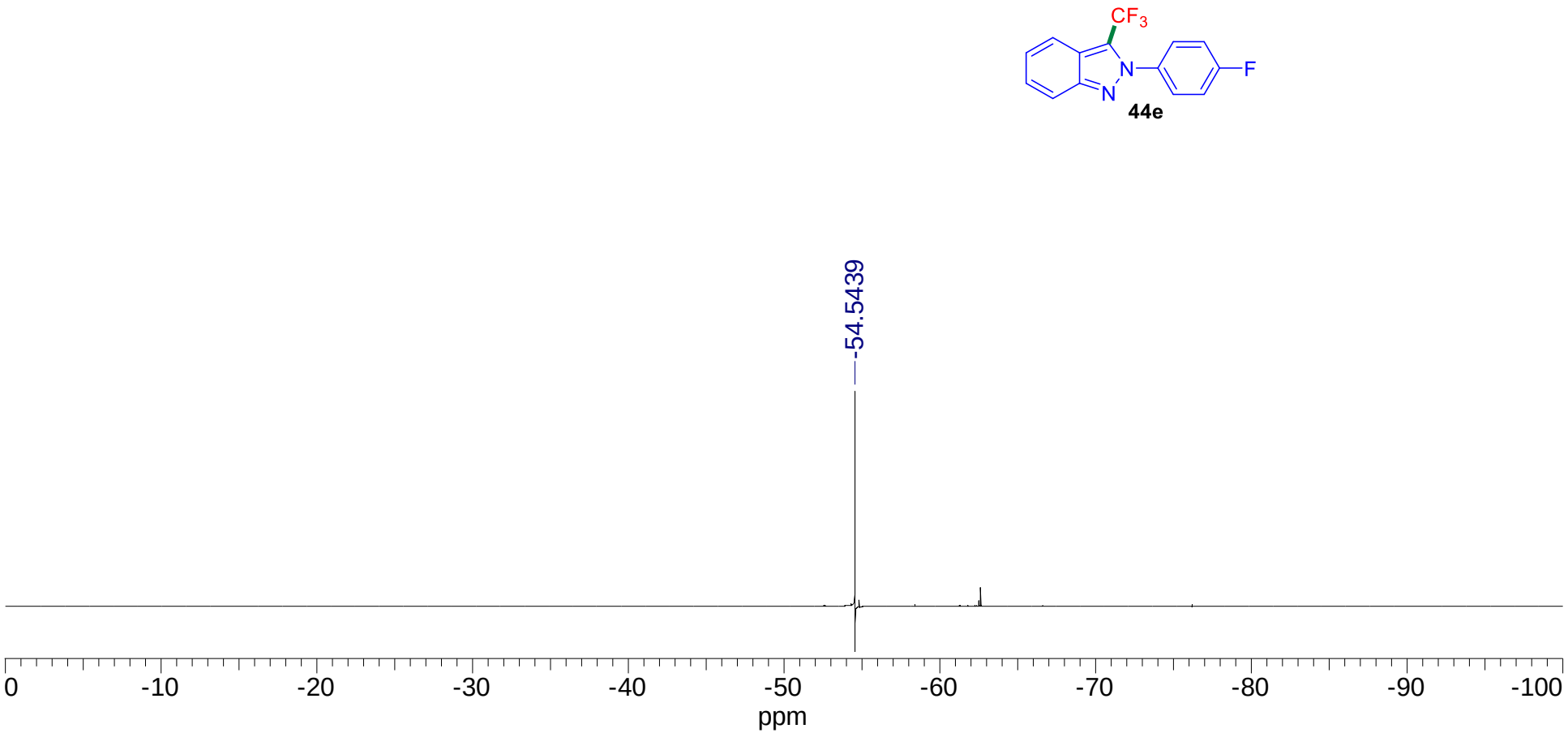
^{19}F NMR (376 MHz) spectrum of compound **44d** in $CDCl_3$



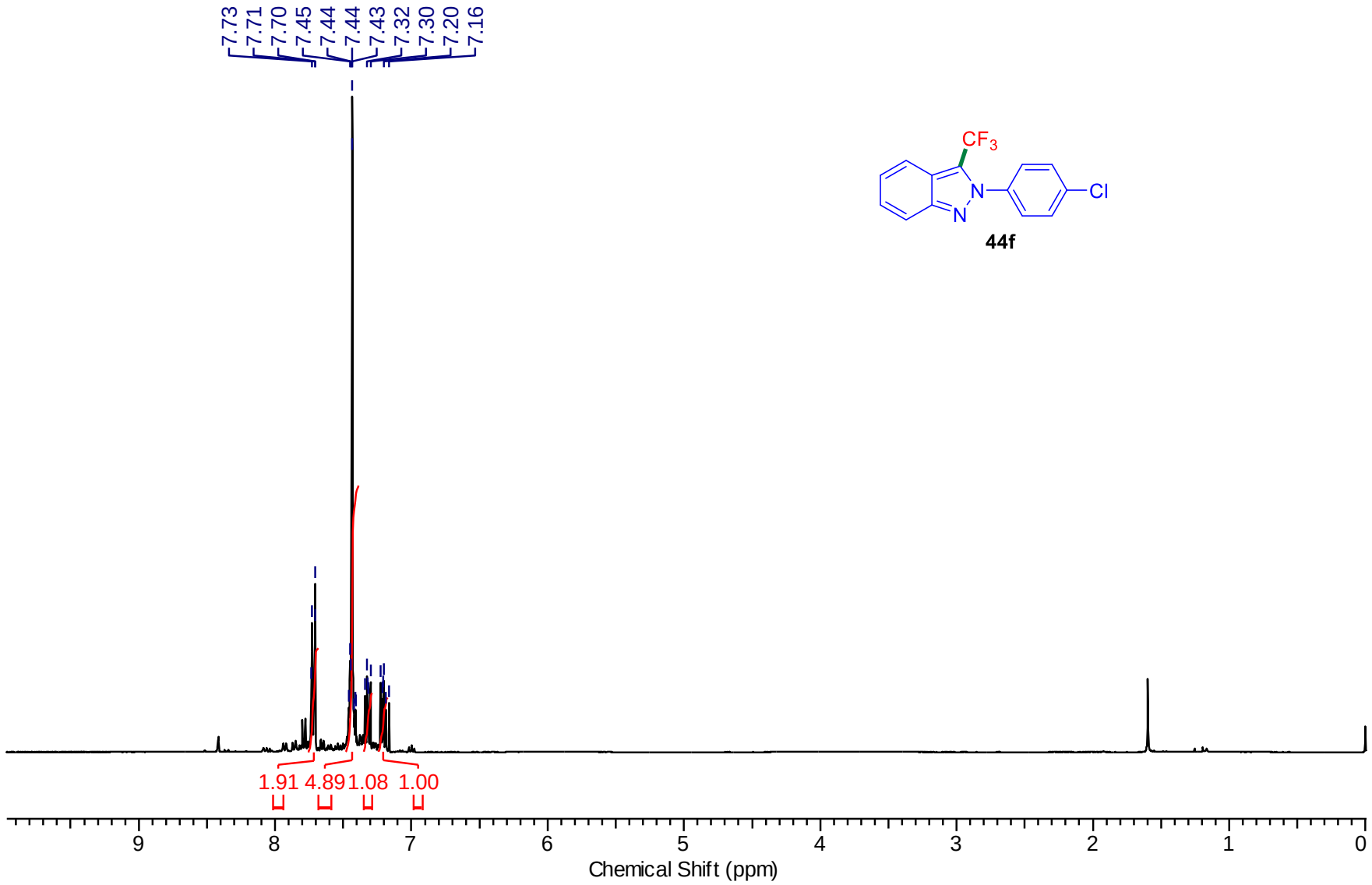
^{1}H NMR (400 MHz) spectrum of compound **44e** in $CDCl_3$



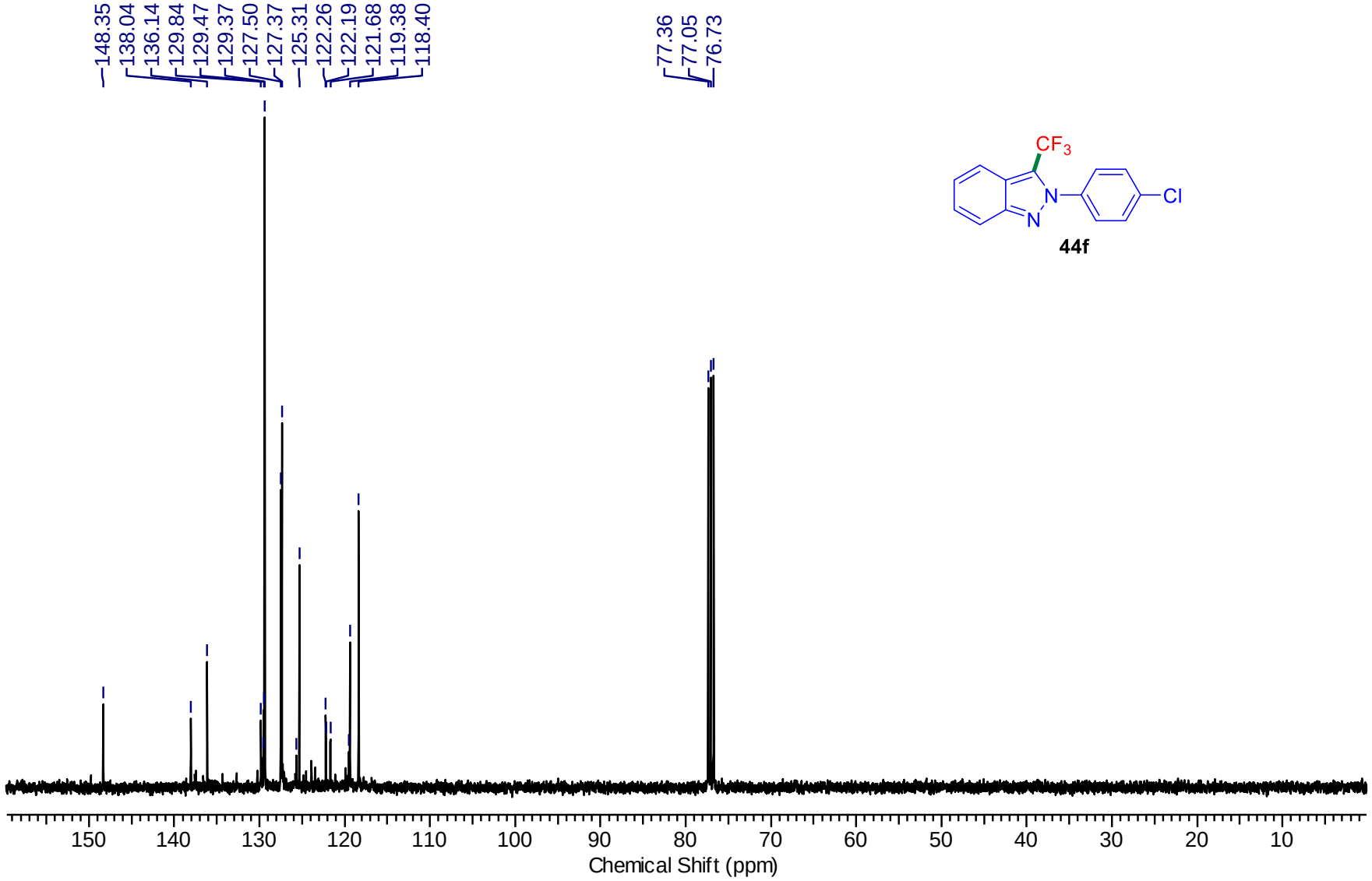
^{13}C NMR (100 MHz) spectrum of compound **44e** in $CDCl_3$



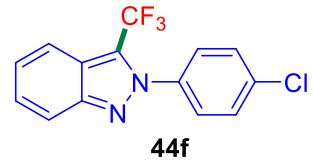
^{19}F NMR (376 MHz) spectrum of compound **44e** in $CDCl_3$



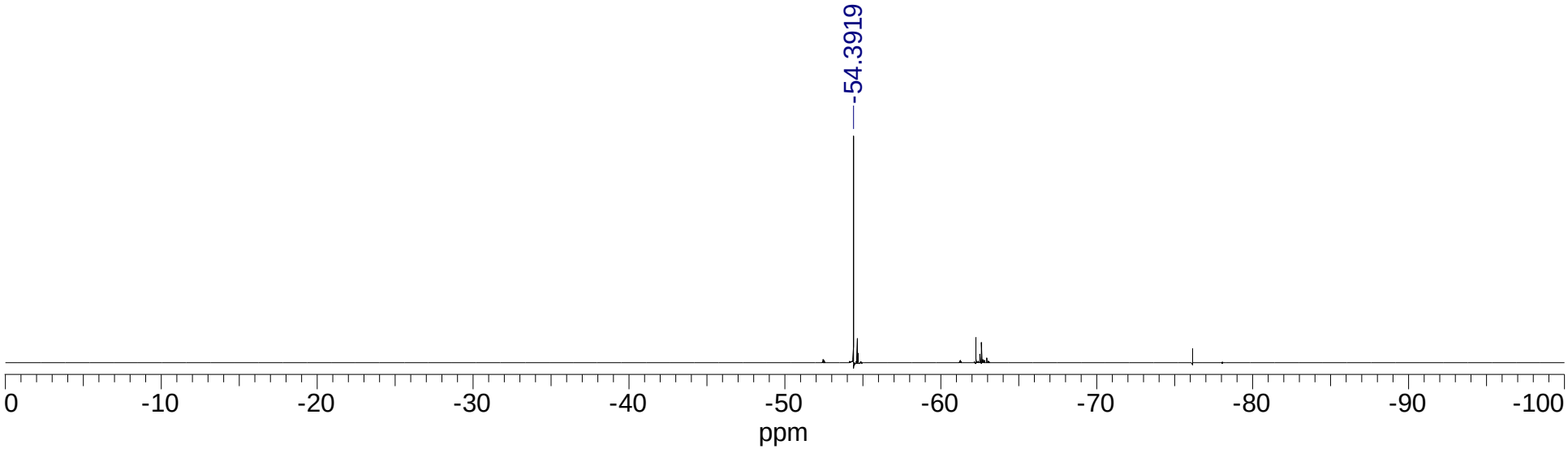
^{1}H NMR (400 MHz) spectrum of compound **44f** in $CDCl_3$



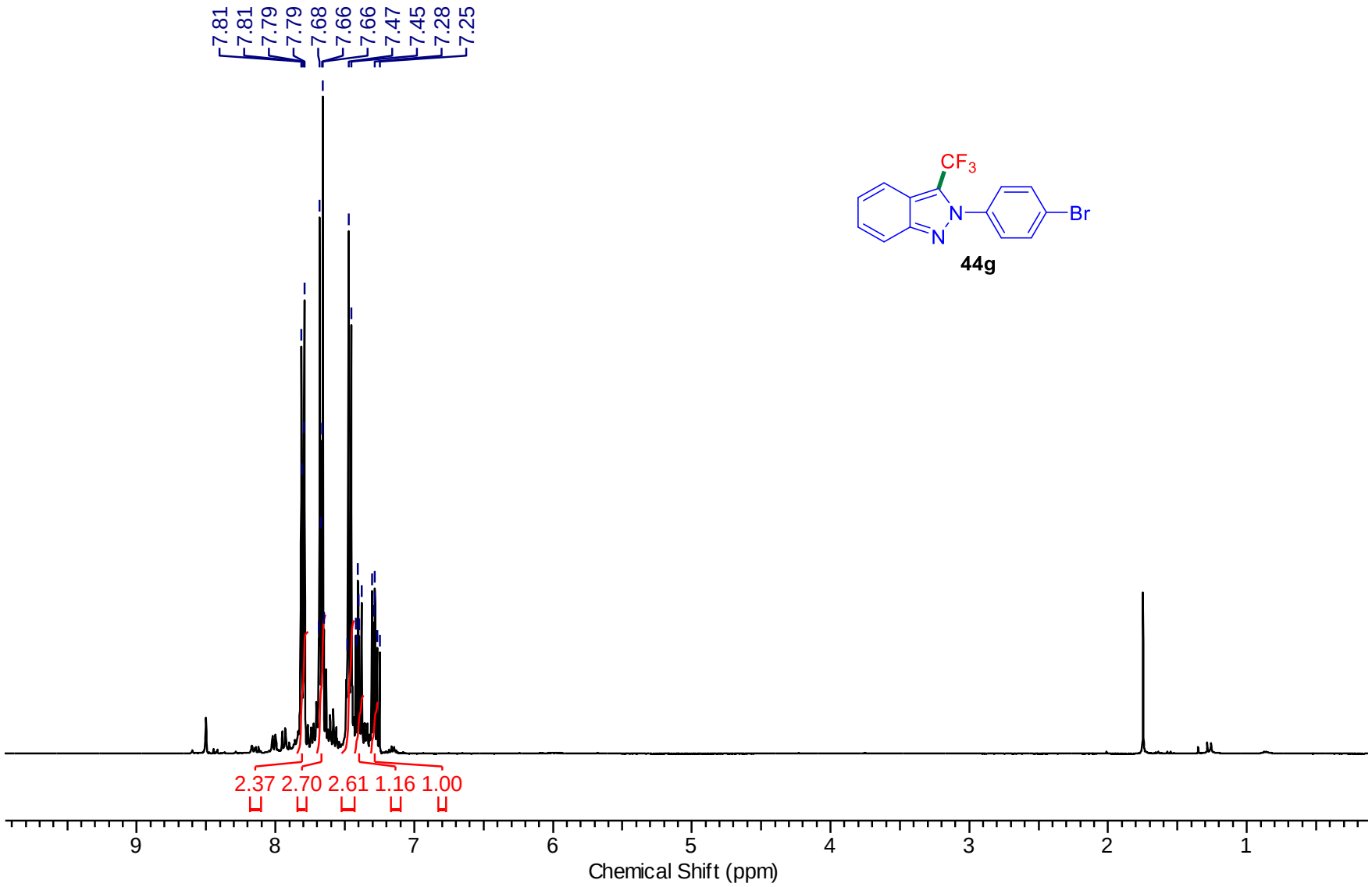
^{13}C NMR (100 MHz) spectrum of compound **44f** in $CDCl_3$



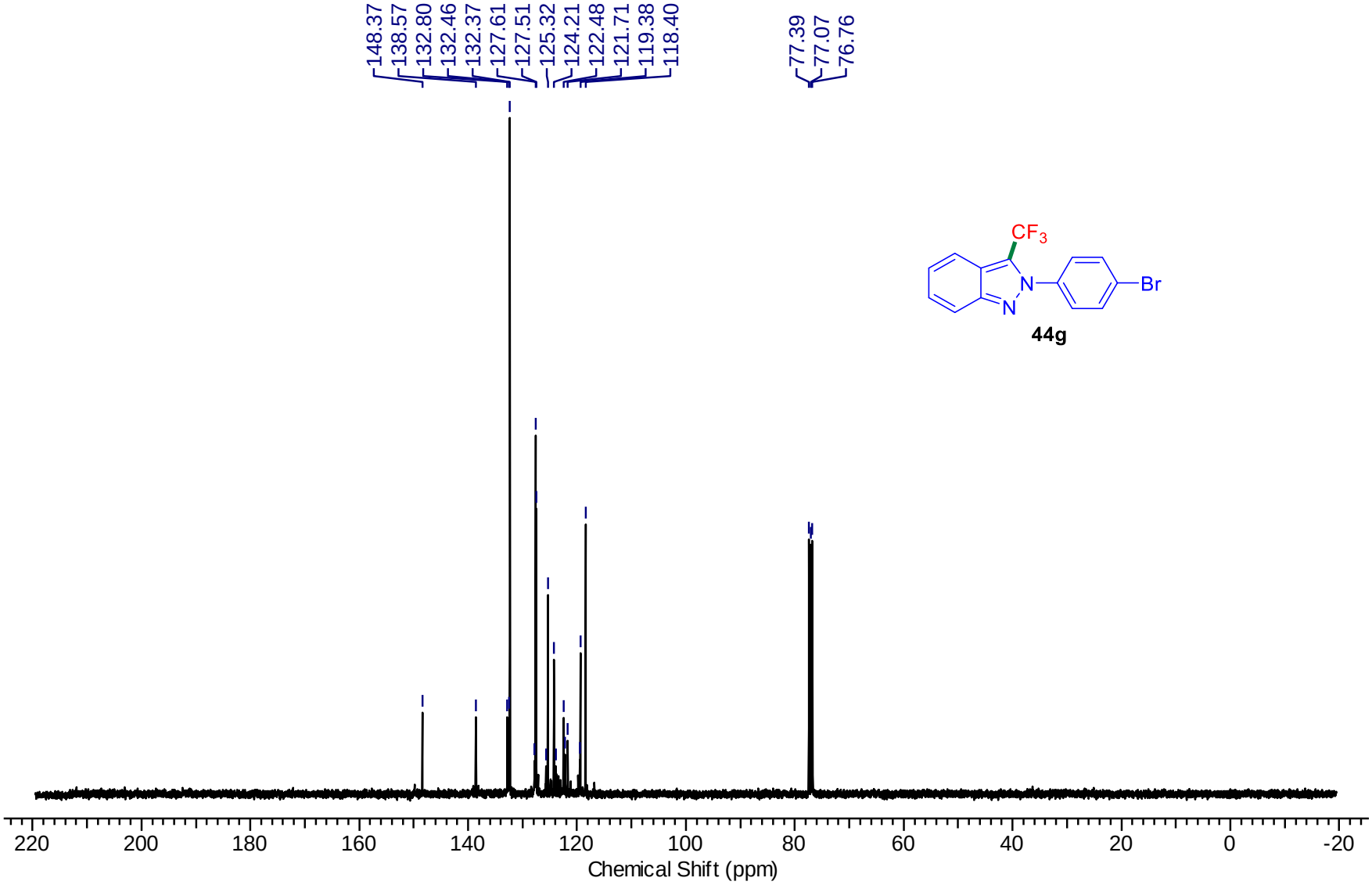
44f



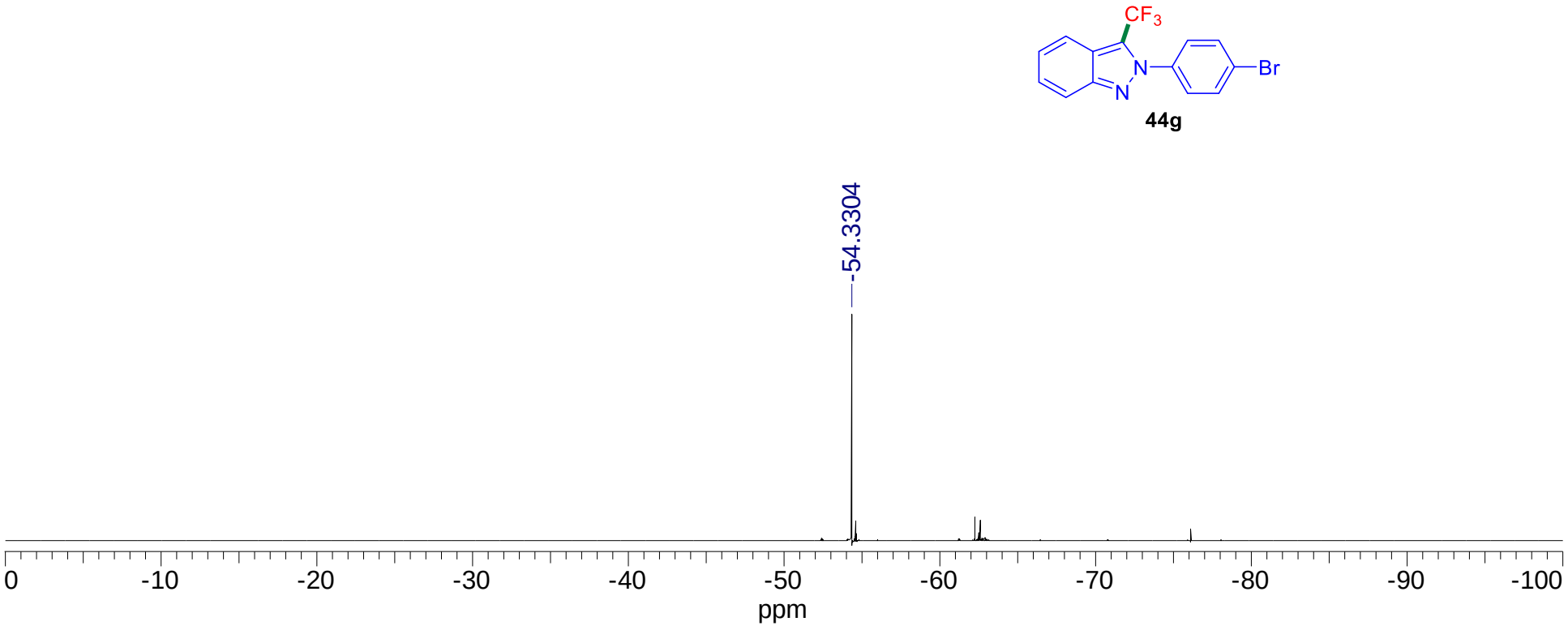
^{19}F NMR (376 MHz) spectrum of compound **44f** in $CDCl_3$



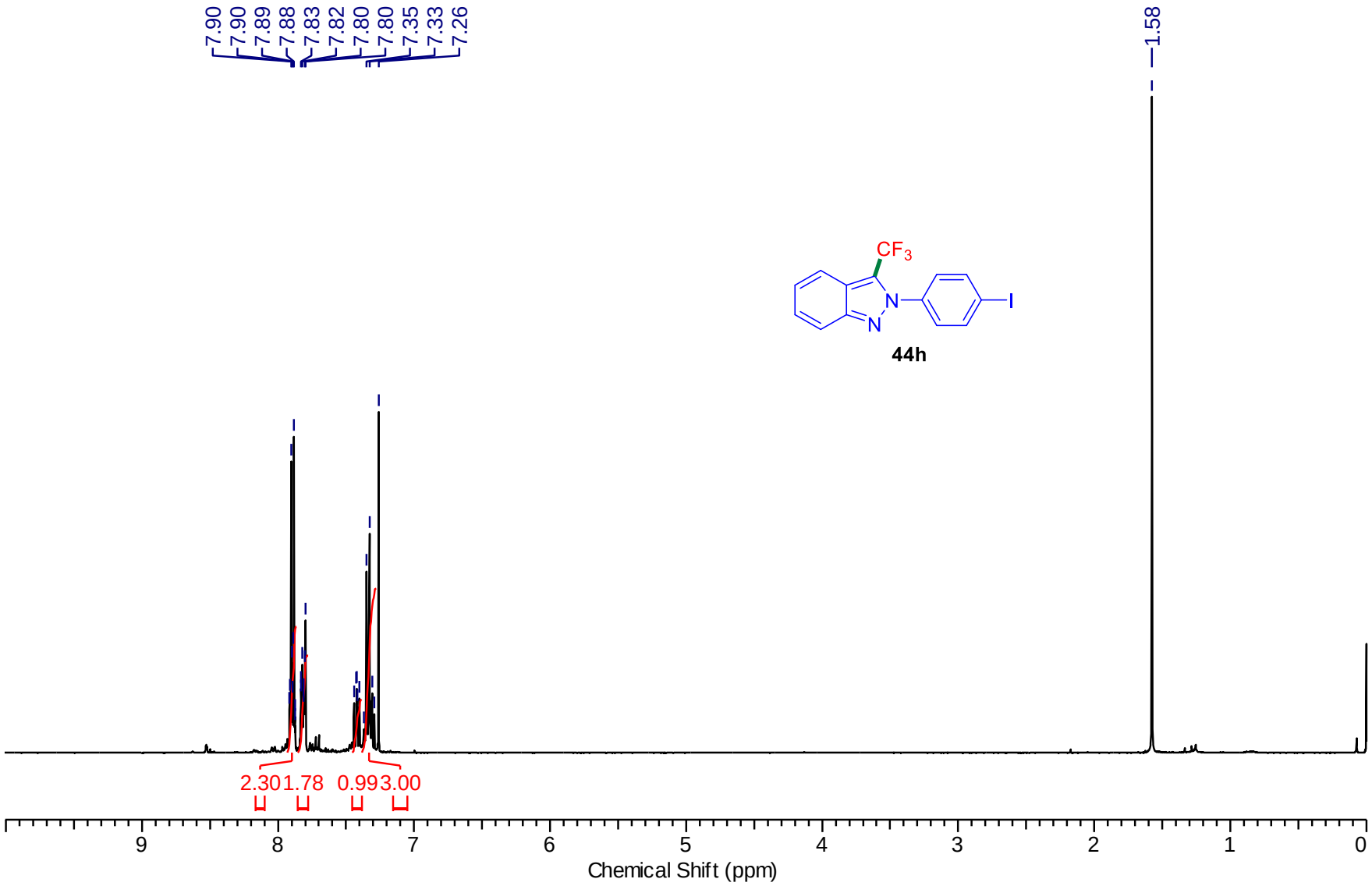
^{1}H NMR (400 MHz) spectrum of compound **44g** in $CDCl_3$



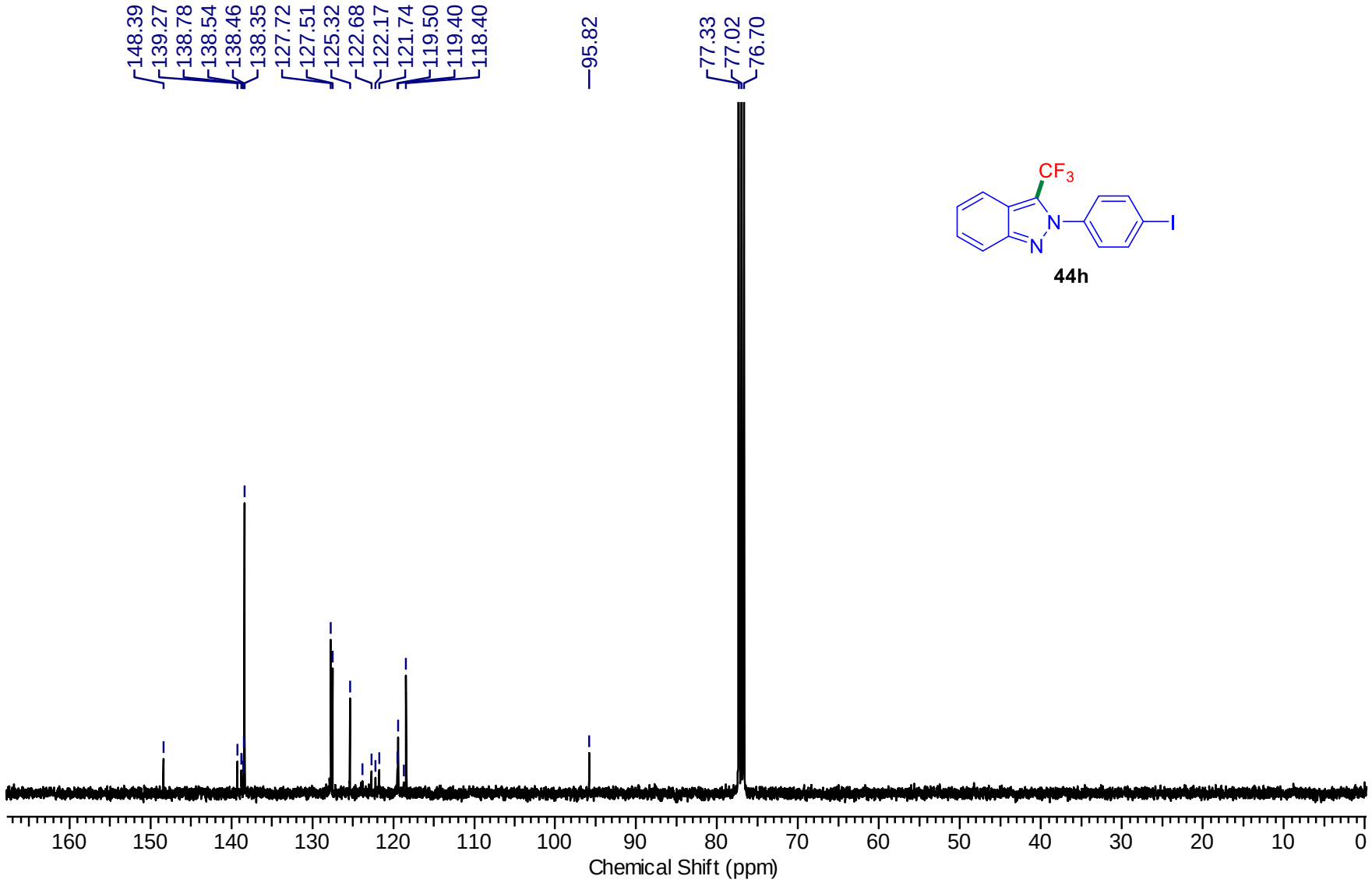
^{13}C NMR (100 MHz) spectrum of compound **44g** in $CDCl_3$



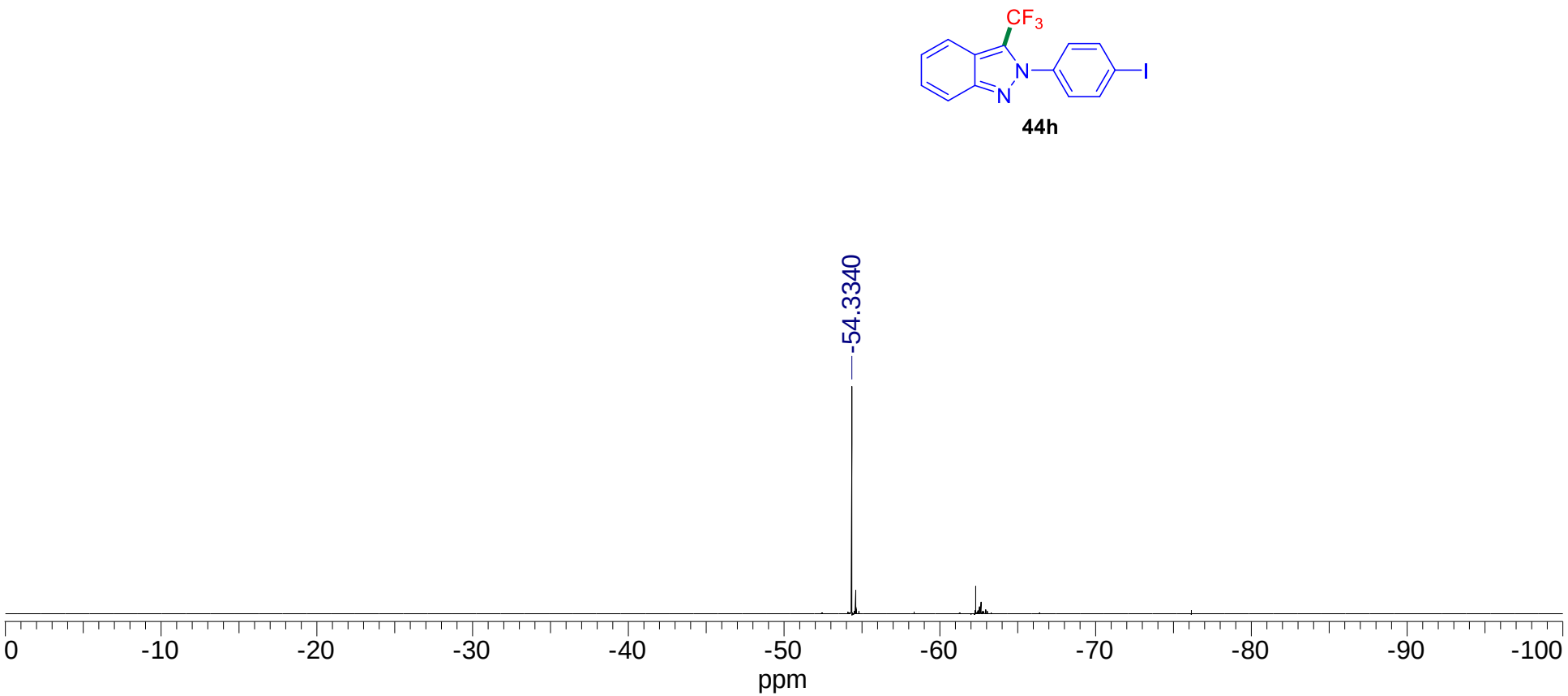
^{19}F NMR (376 MHz) spectrum of compound **44g** in $CDCl_3$



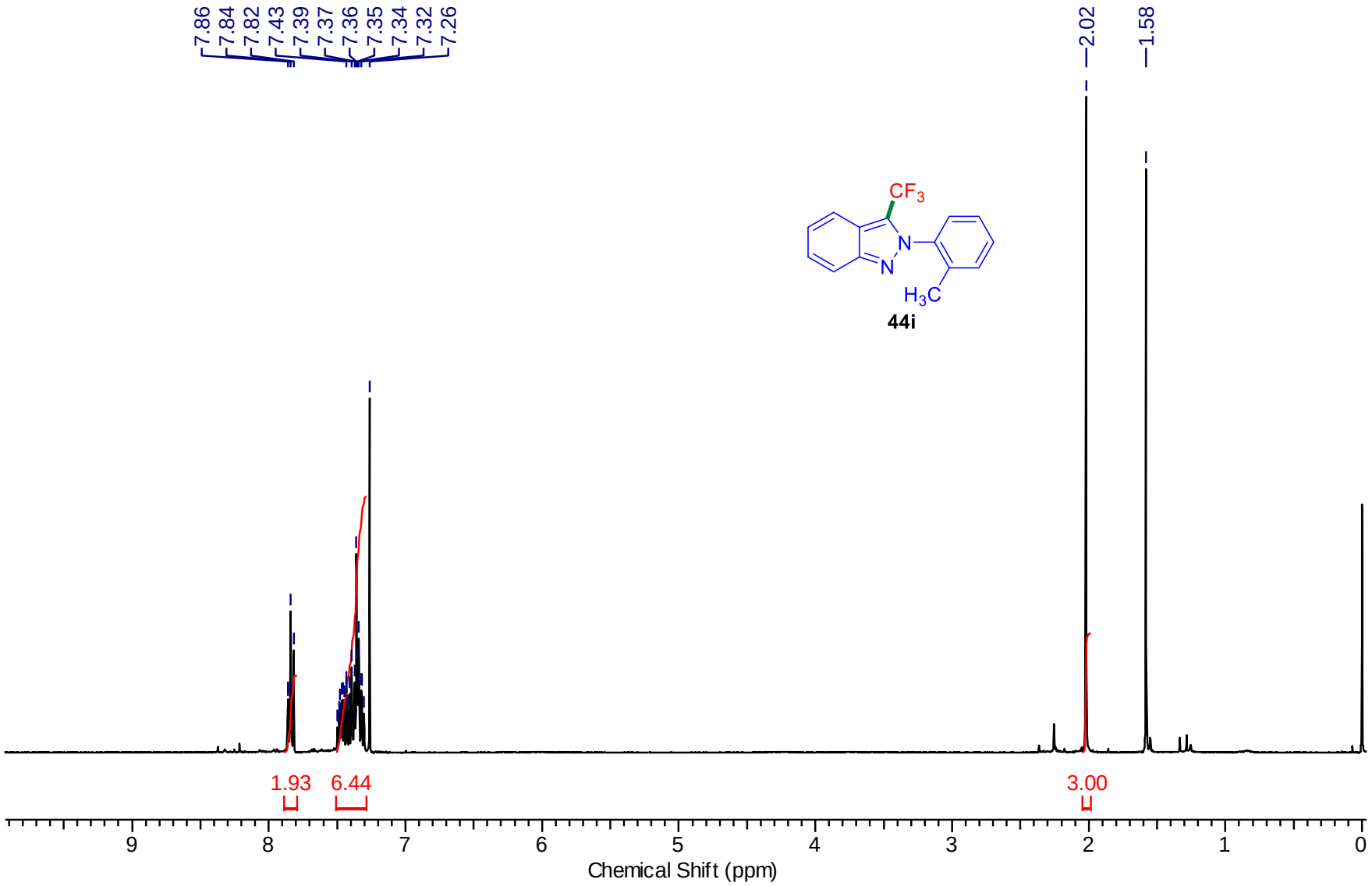
^{1}H NMR (400 MHz) spectrum of compound **44h** in $CDCl_3$



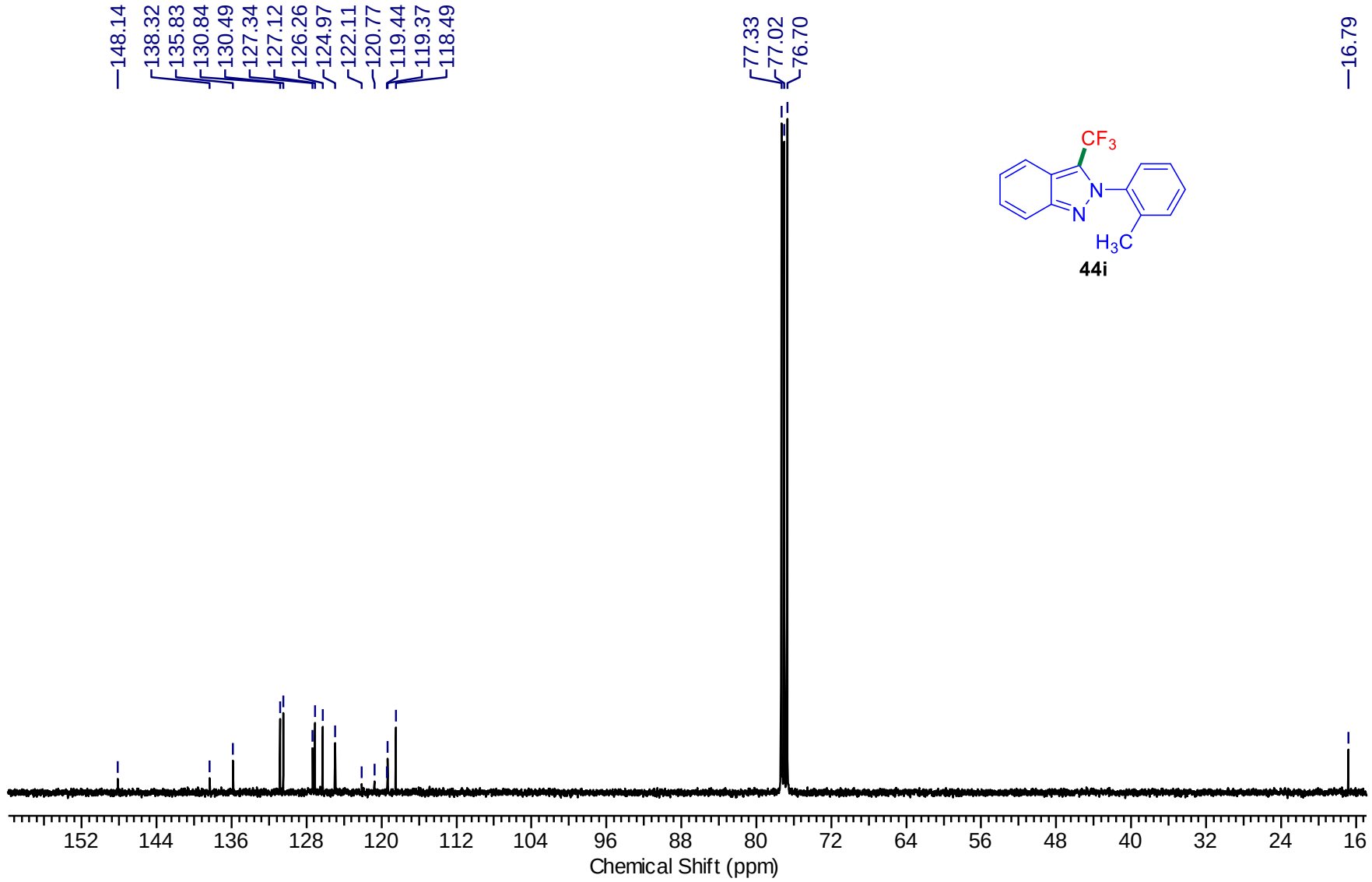
^{13}C NMR (100 MHz) spectrum of compound **44h** in $CDCl_3$



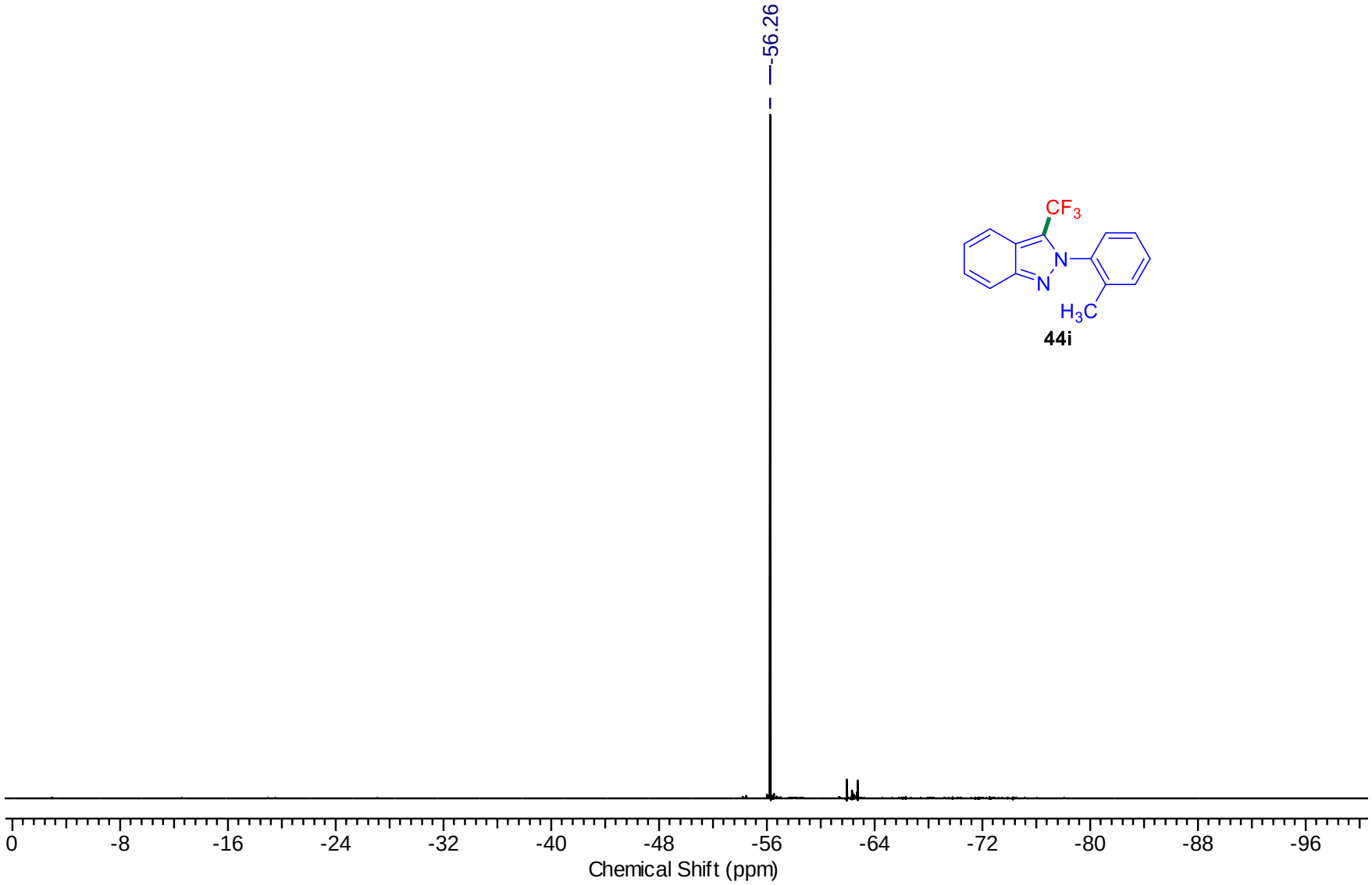
^{19}F NMR (376 MHz) spectrum of compound **44h** in $CDCl_3$



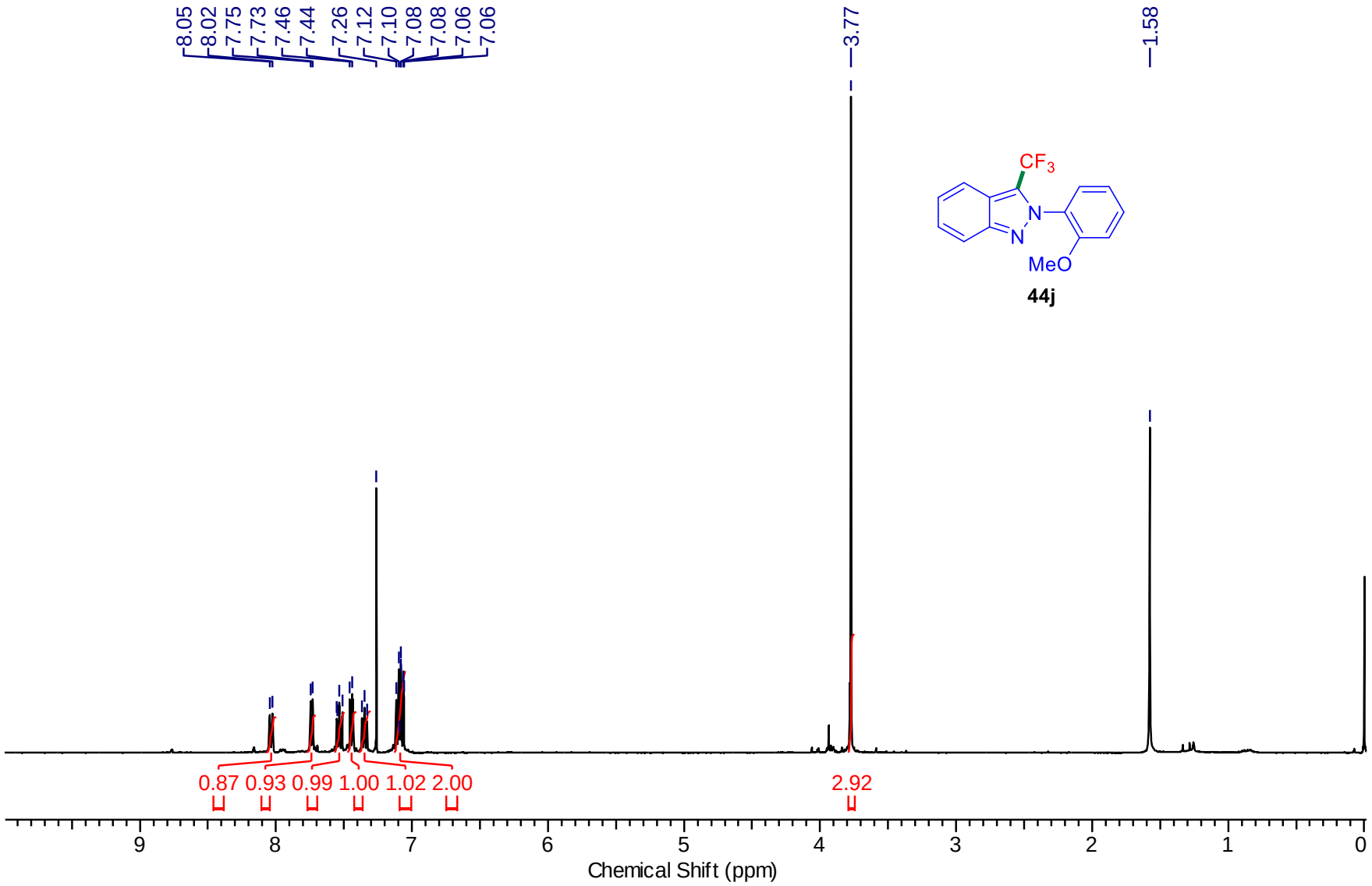
^{1}H NMR (400 MHz) spectrum of compound **44i** in $CDCl_3$



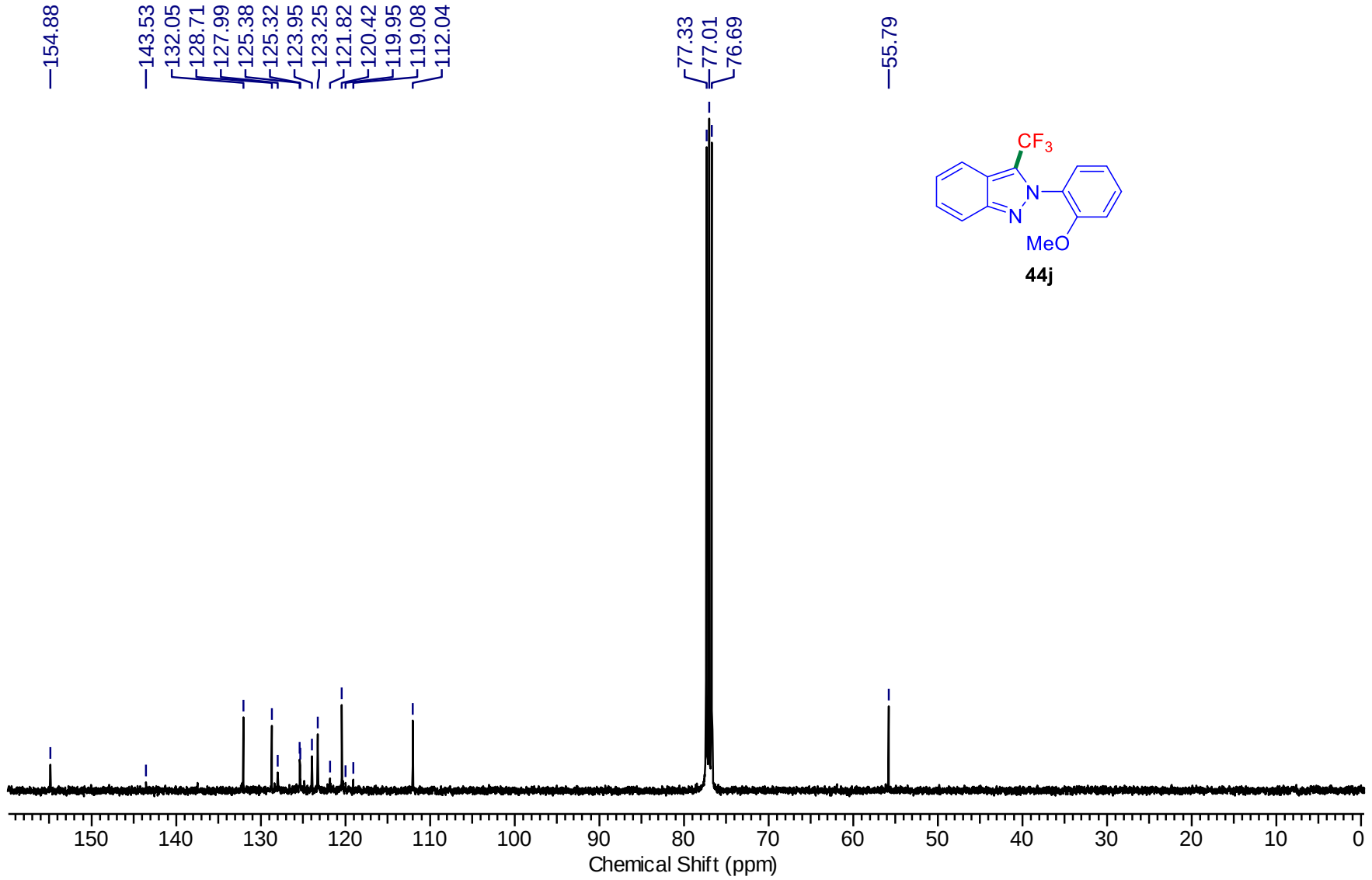
^{13}C NMR (100 MHz) spectrum of compound **44i** in $CDCl_3$



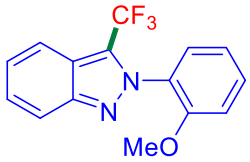
^{19}F NMR (376 MHz) spectrum of compound **44i** in $CDCl_3$



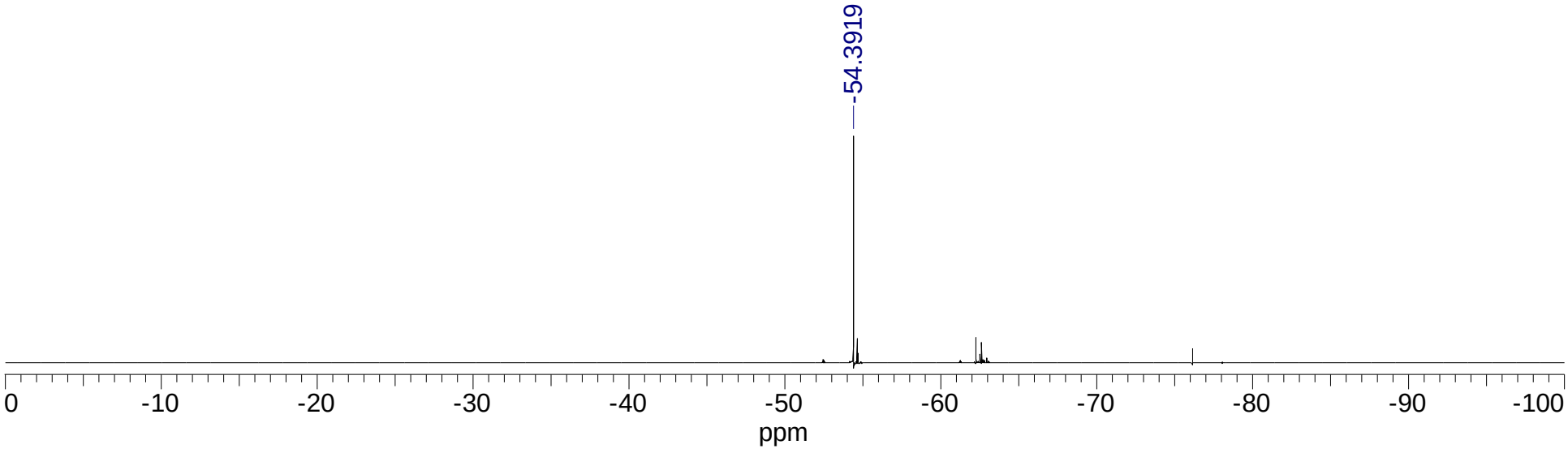
^{1}H NMR (400 MHz) spectrum of compound **44j** in $CDCl_3$



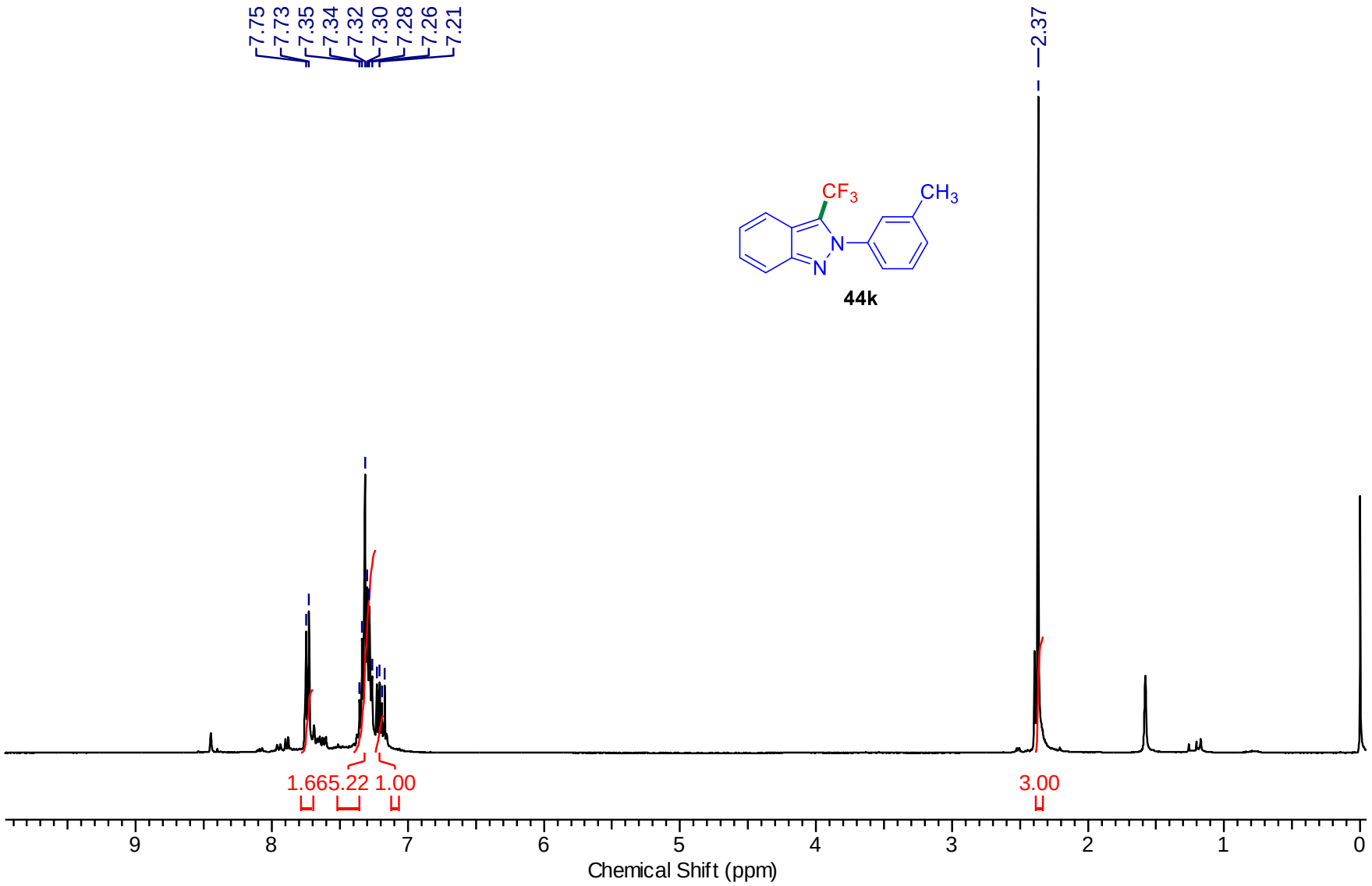
^{13}C NMR (100 MHz) spectrum of compound **44j** in $CDCl_3$



44j



^{19}F NMR (376 MHz) spectrum of compound **44j** in $CDCl_3$



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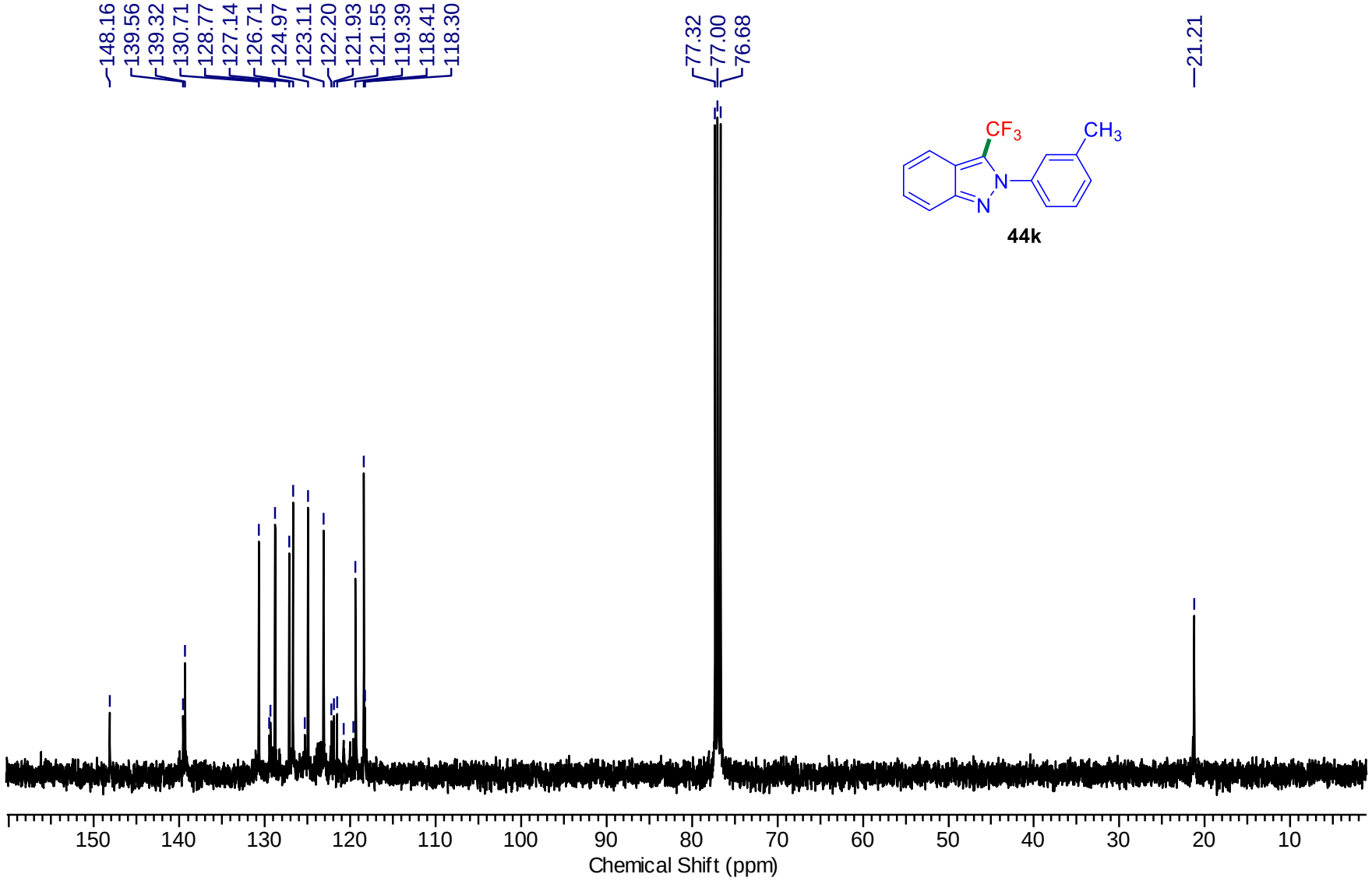

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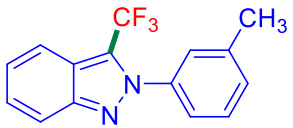
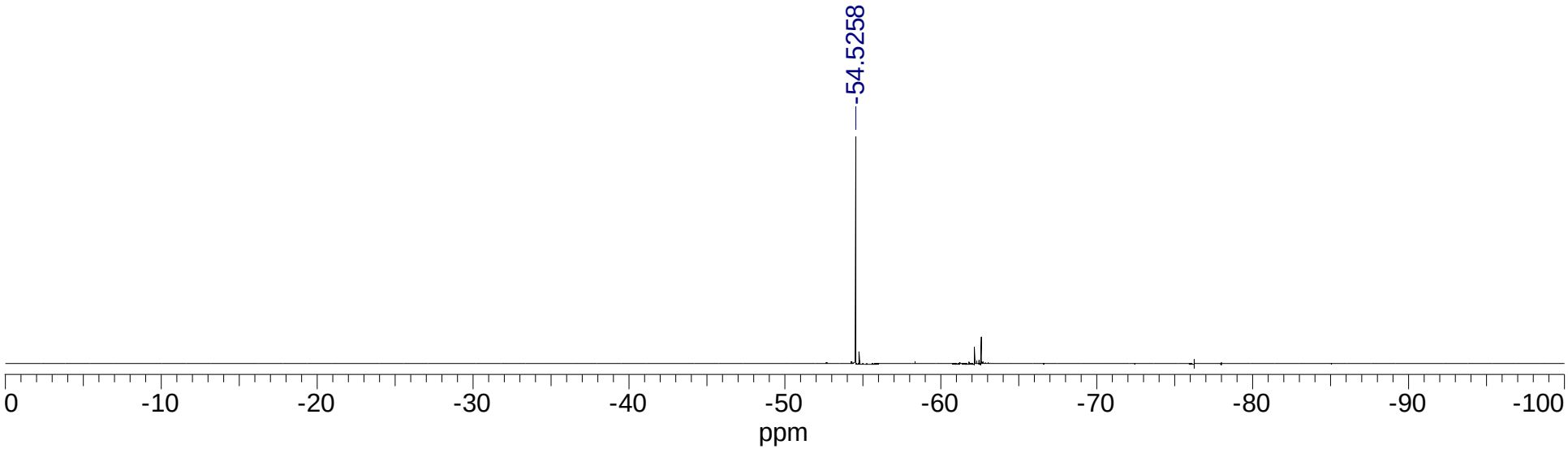
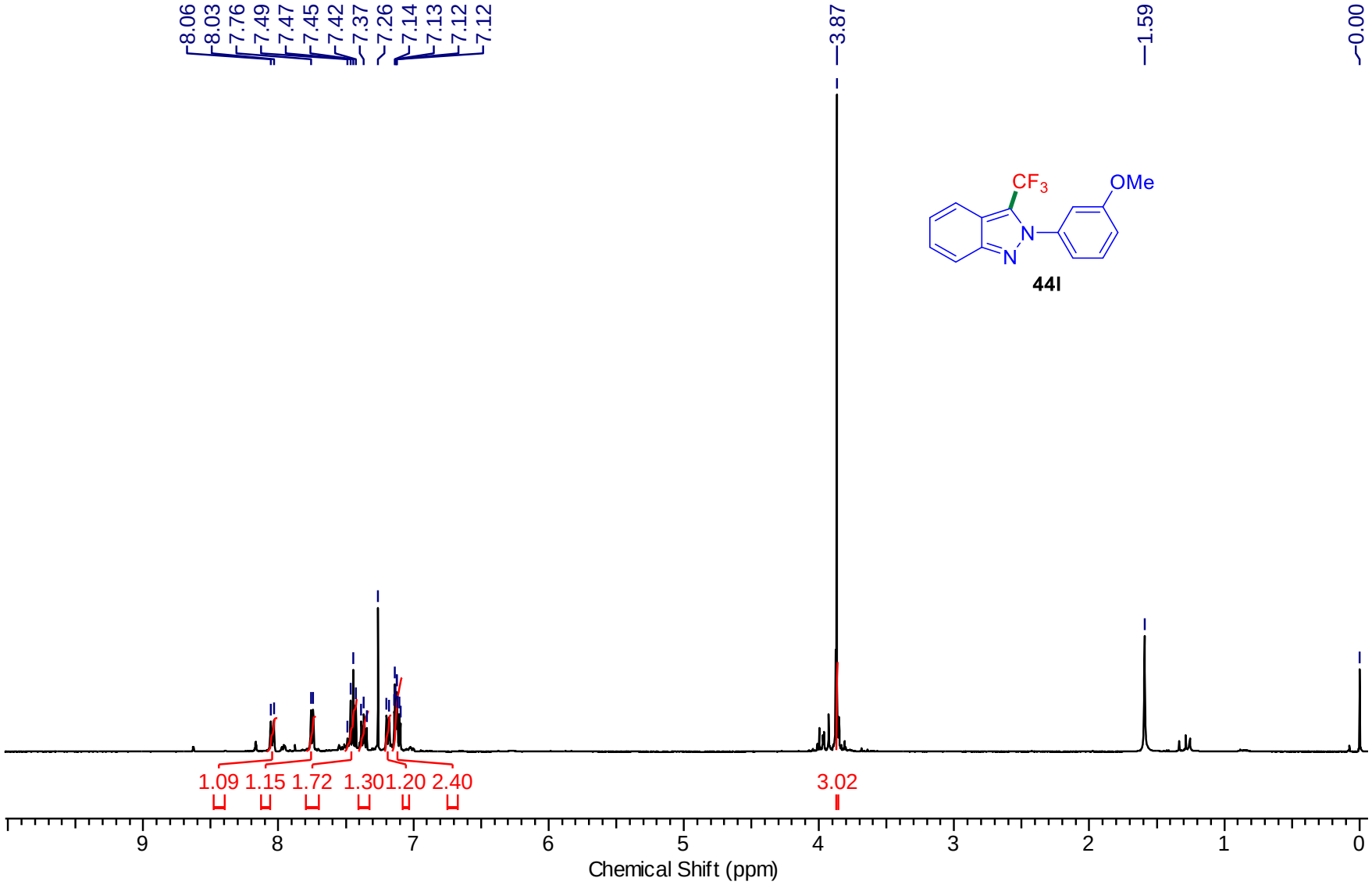


44k



^{19}F NMR (376 MHz) spectrum of compound **44k** in $CDCl_3$



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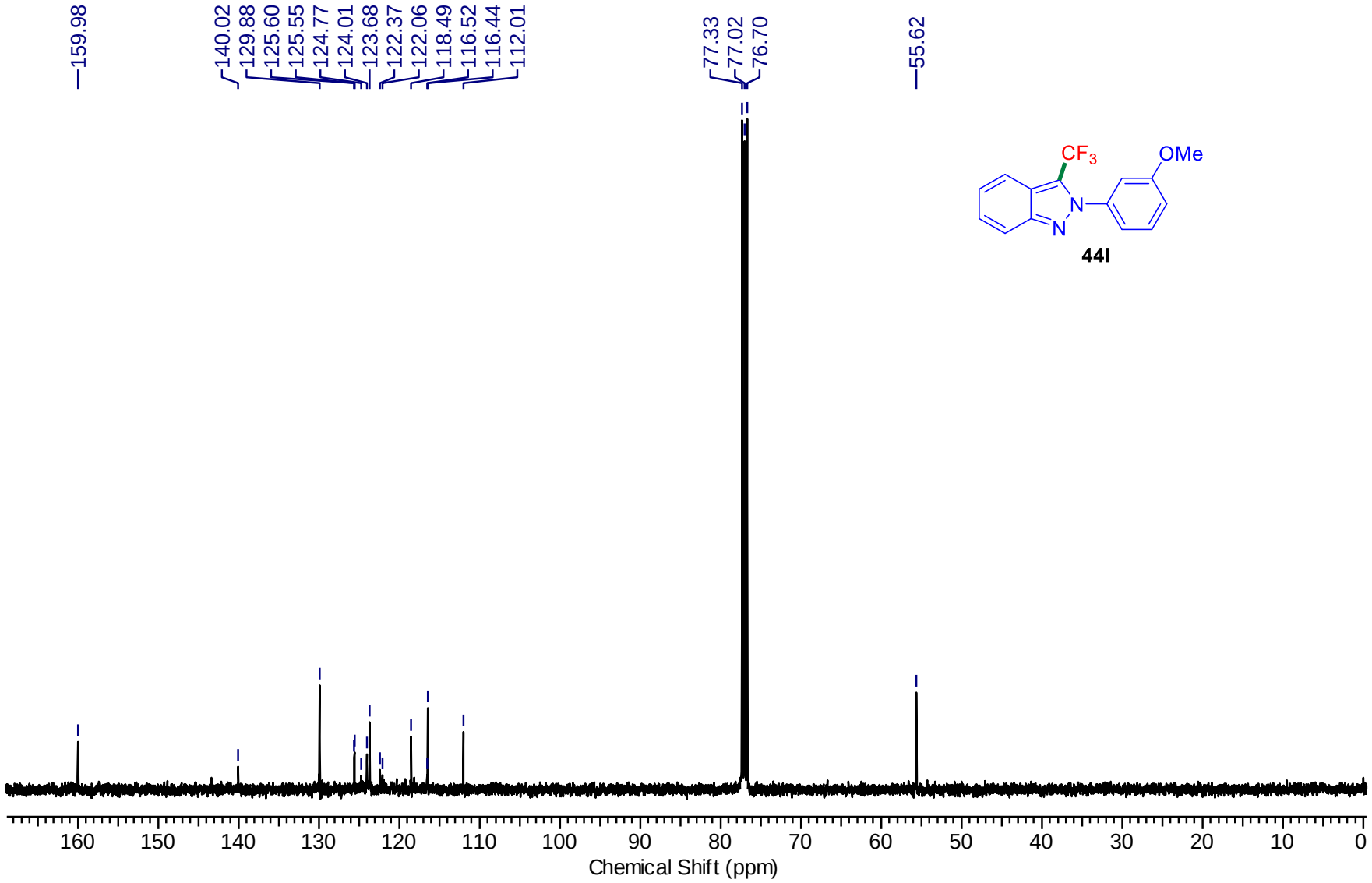

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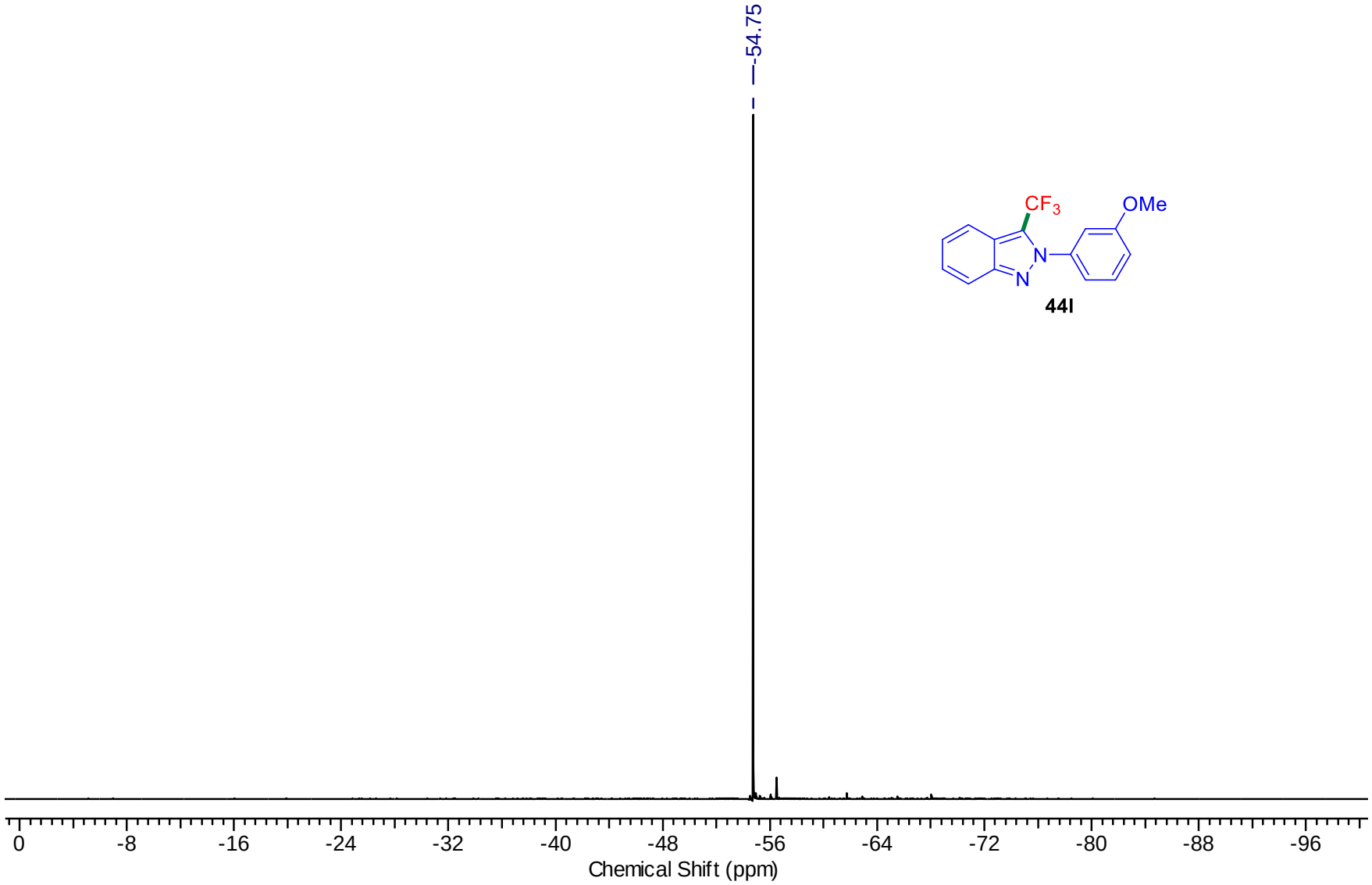

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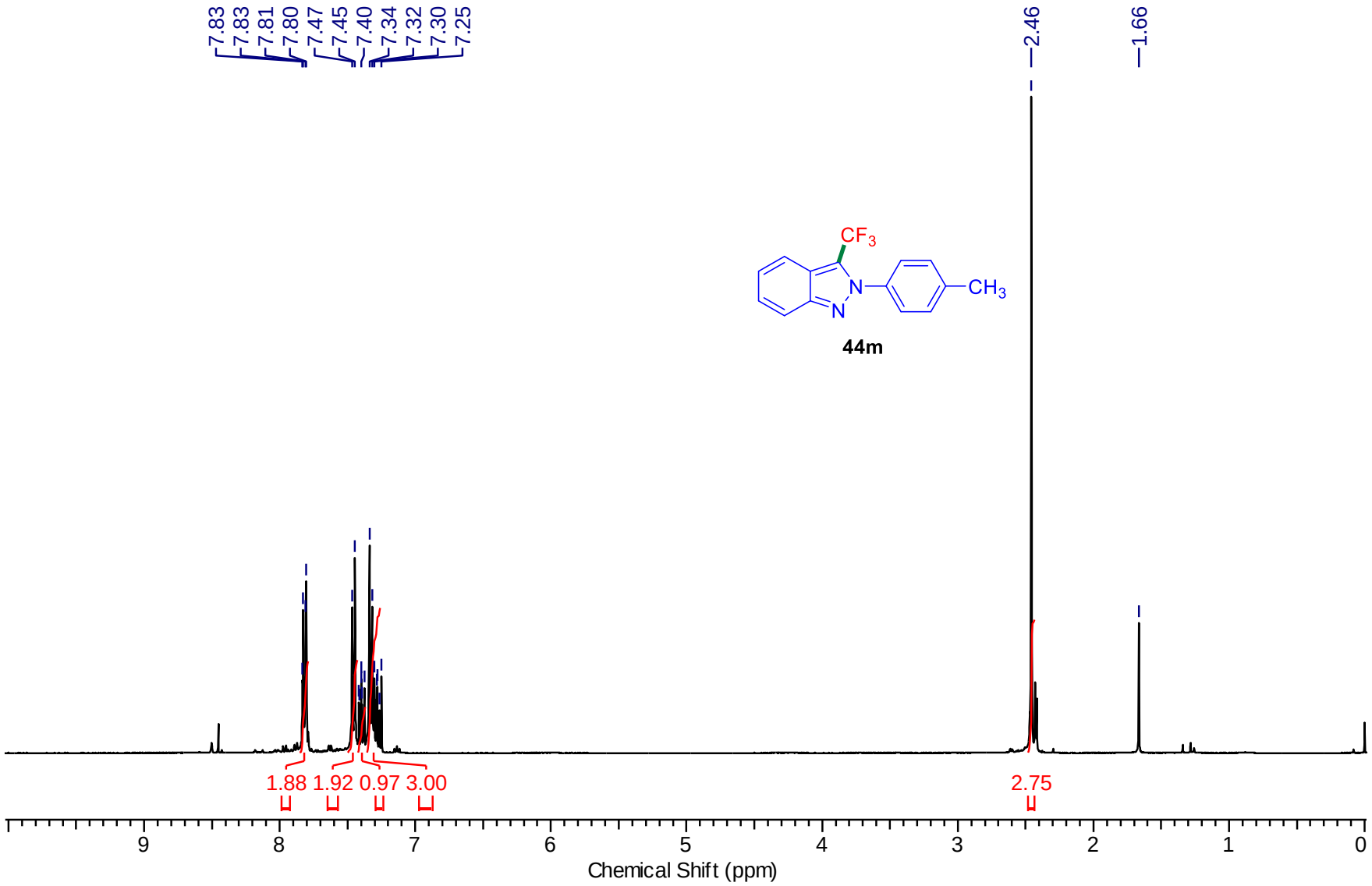

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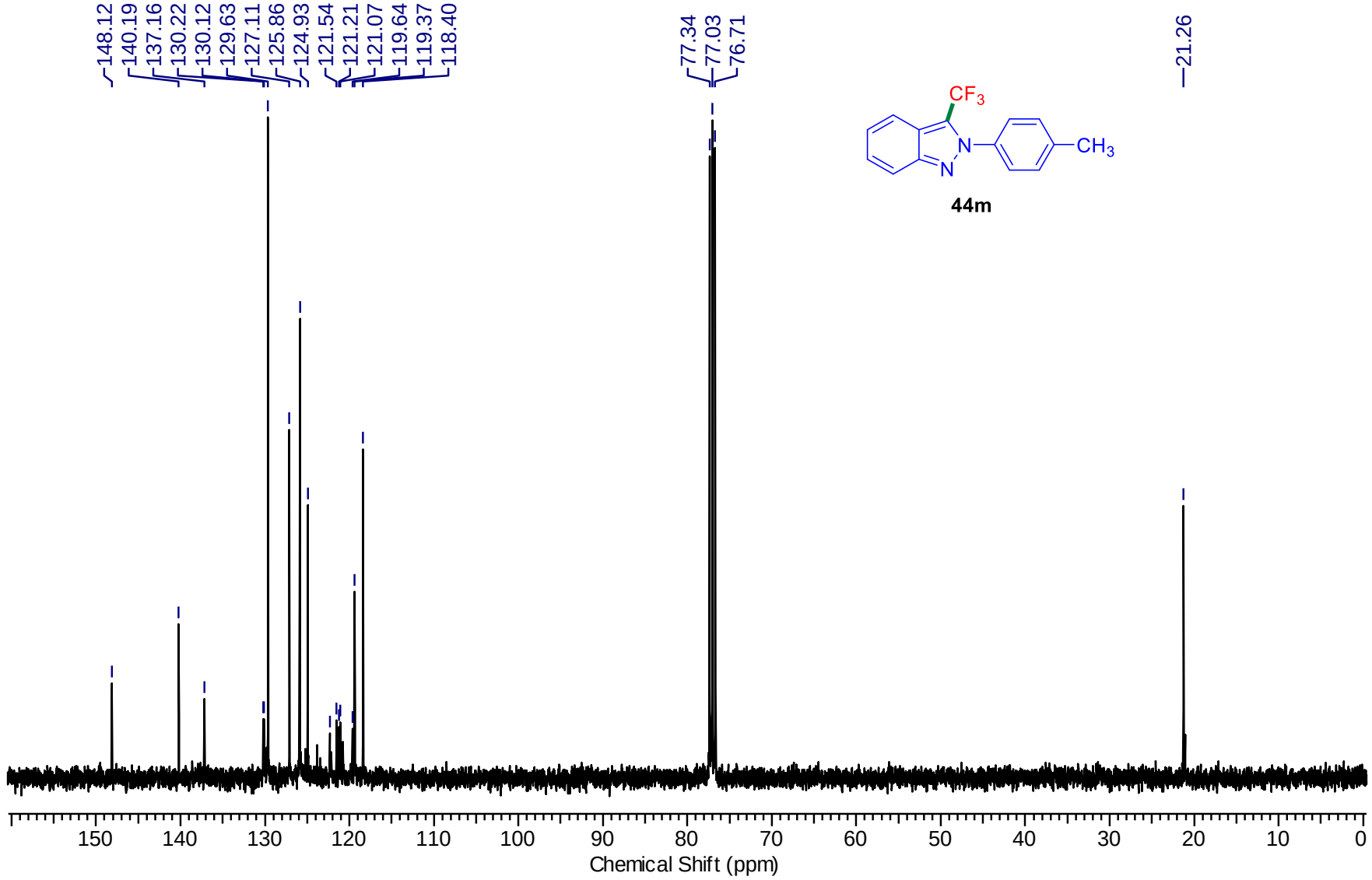

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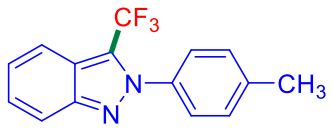
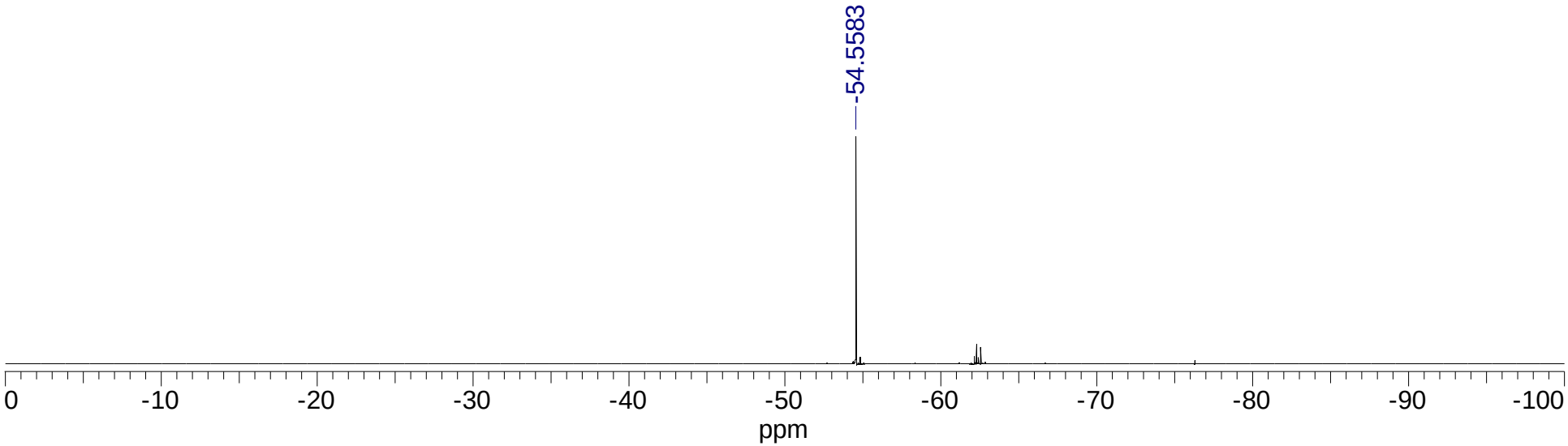


44m



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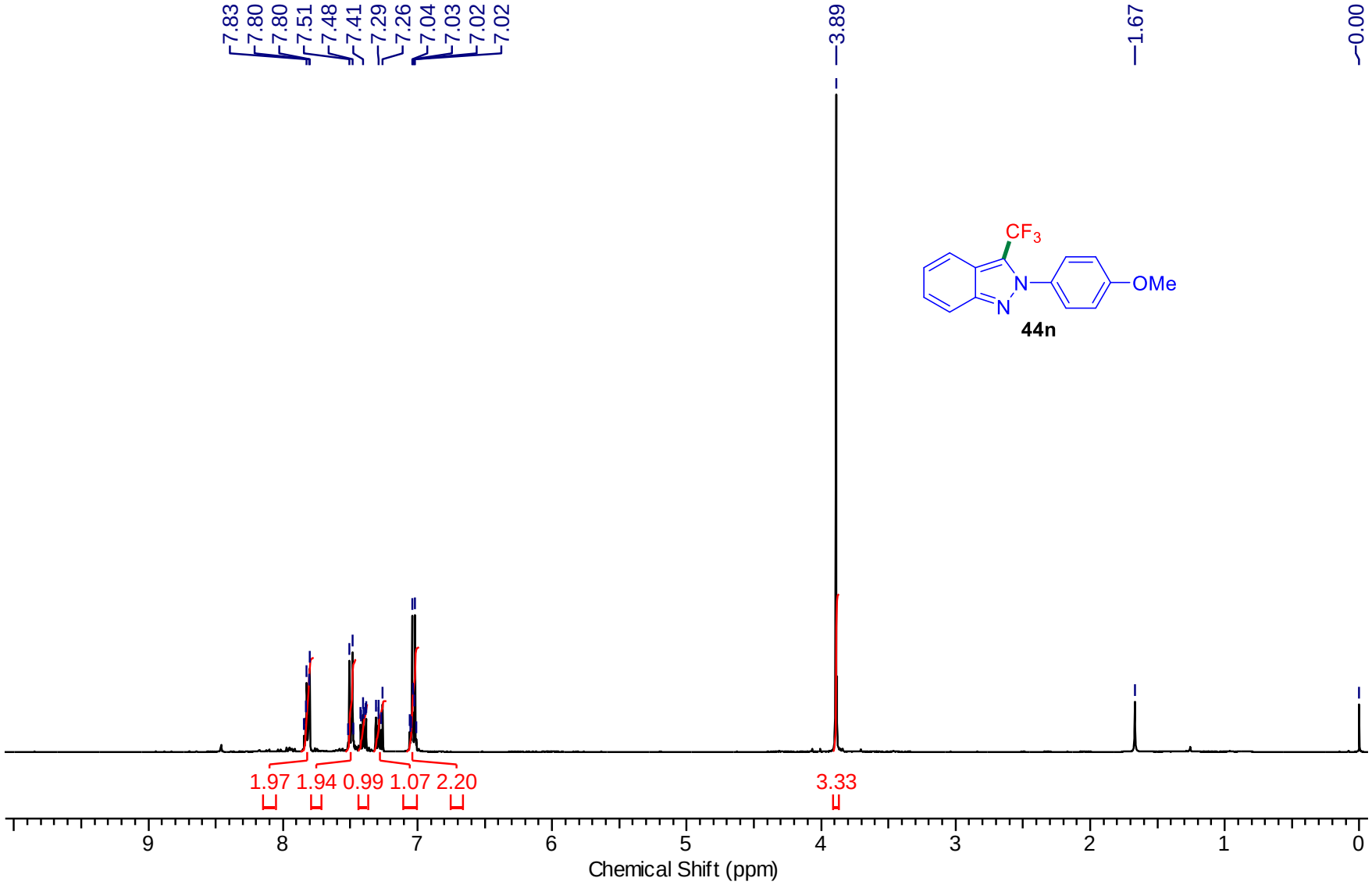

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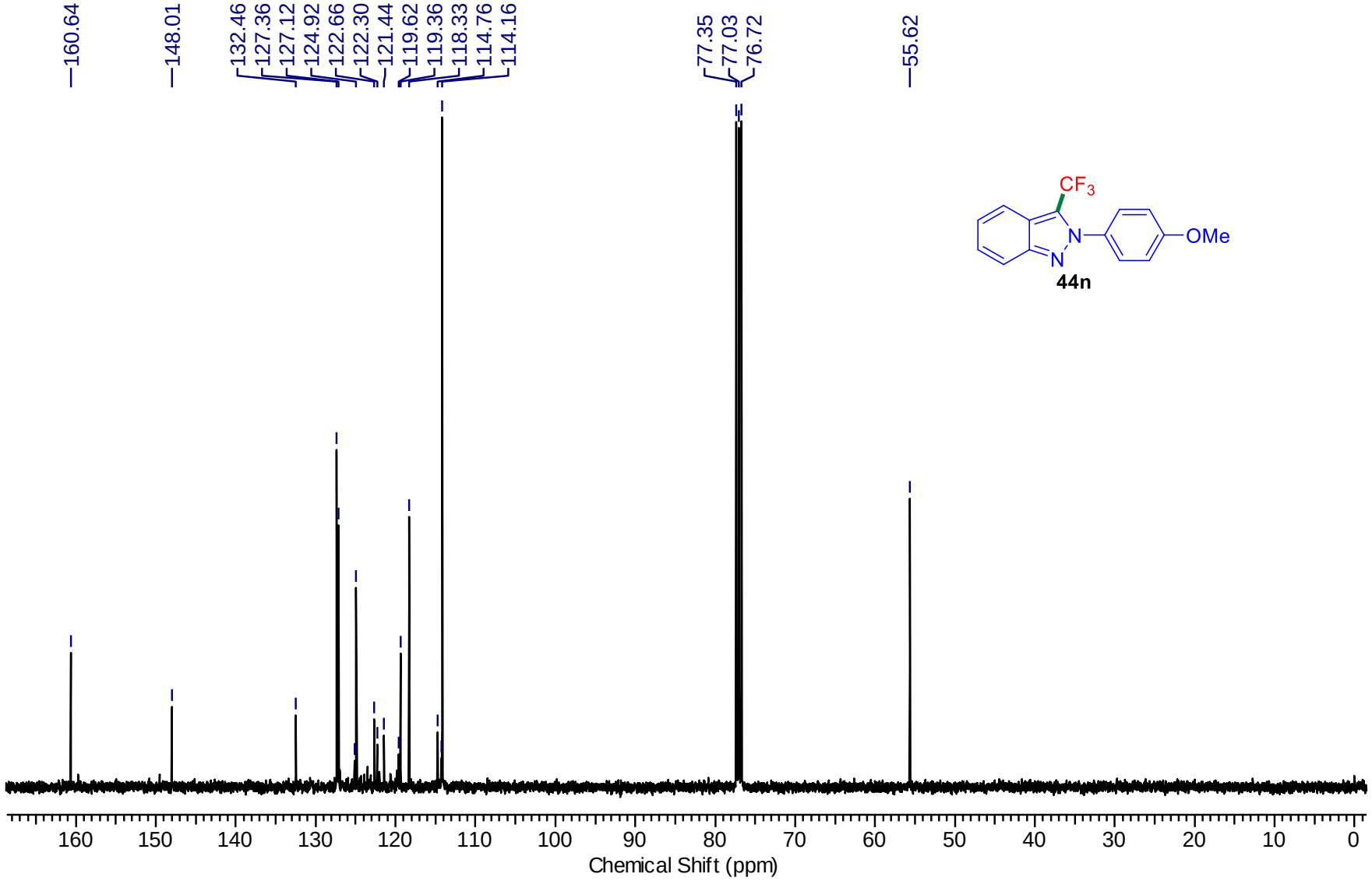
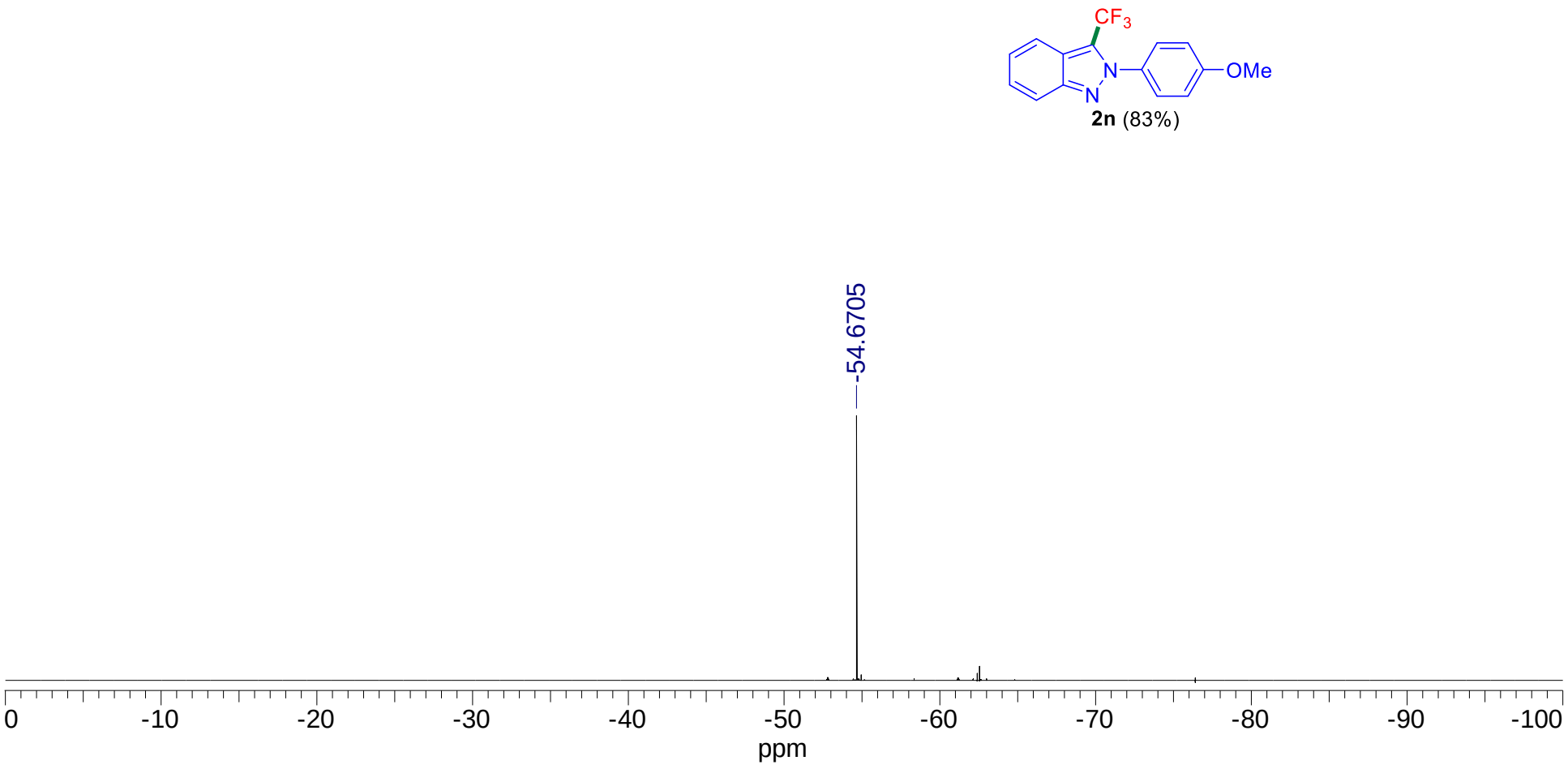


^{13}C NMR (100 MHz) spectrum of compound **44n** in $CDCl_3$



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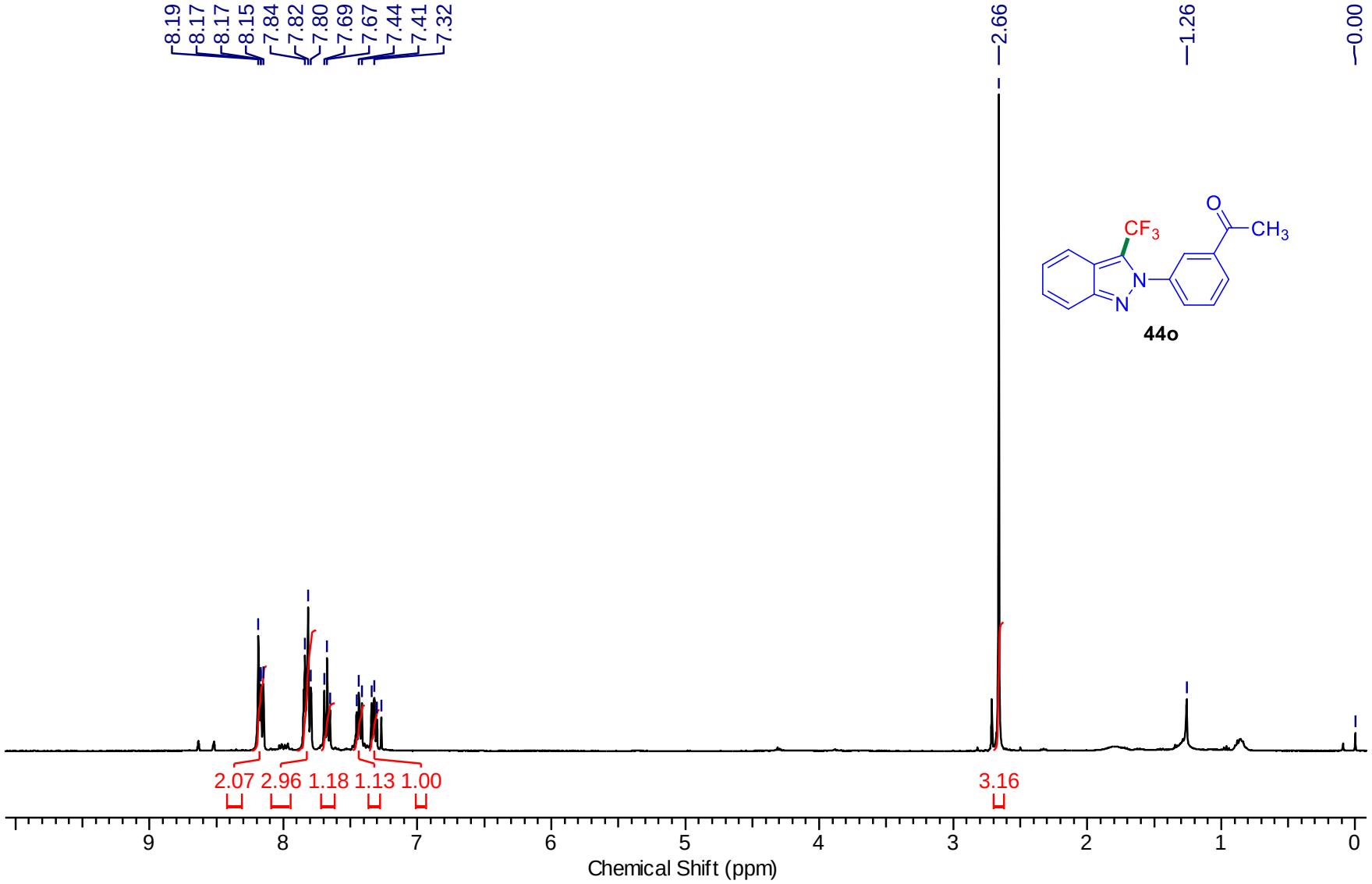
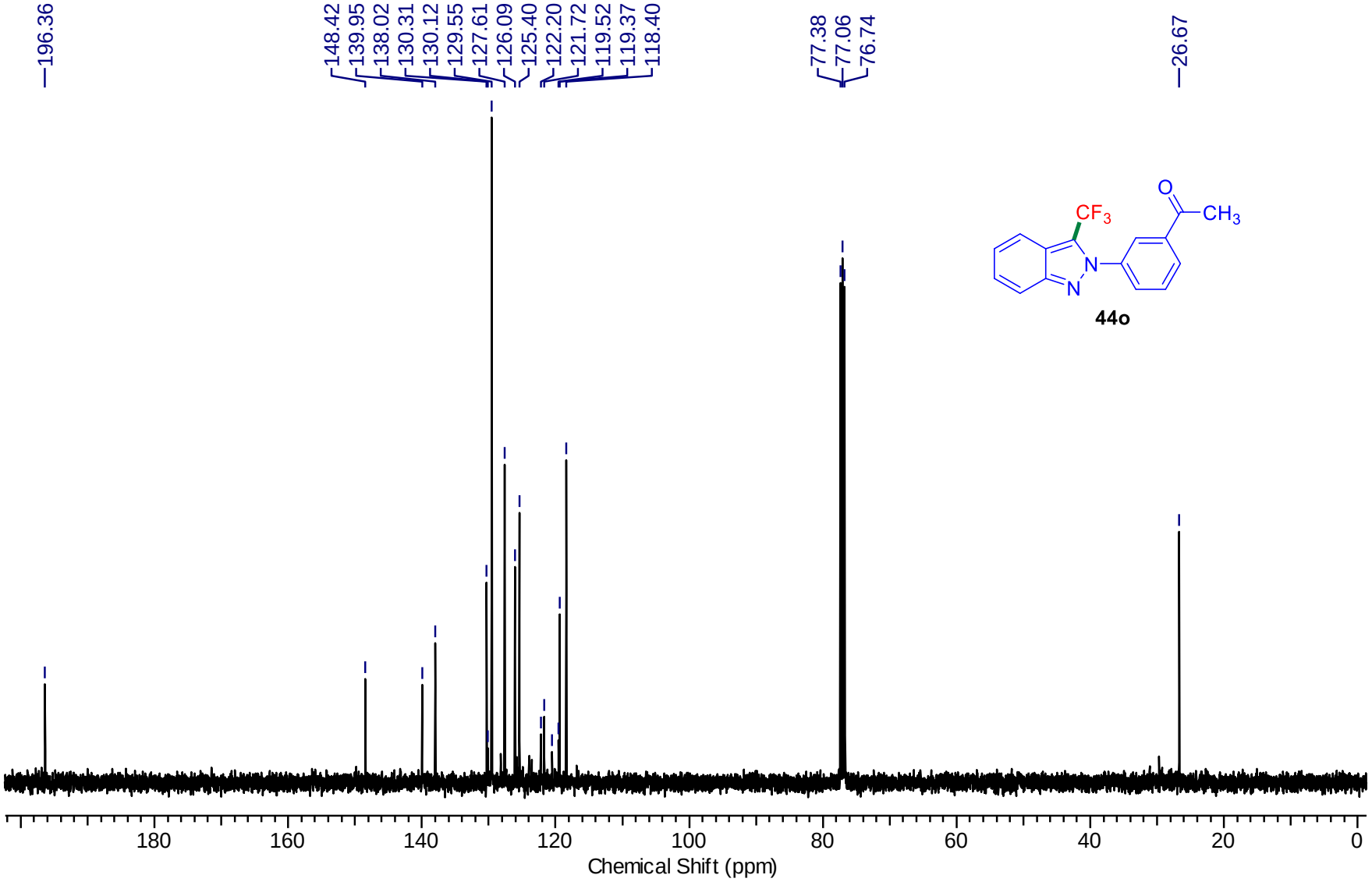


^{1}H NMR (400 MHz) spectrum of compound **44o** in $CDCl_3$



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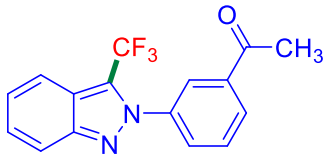

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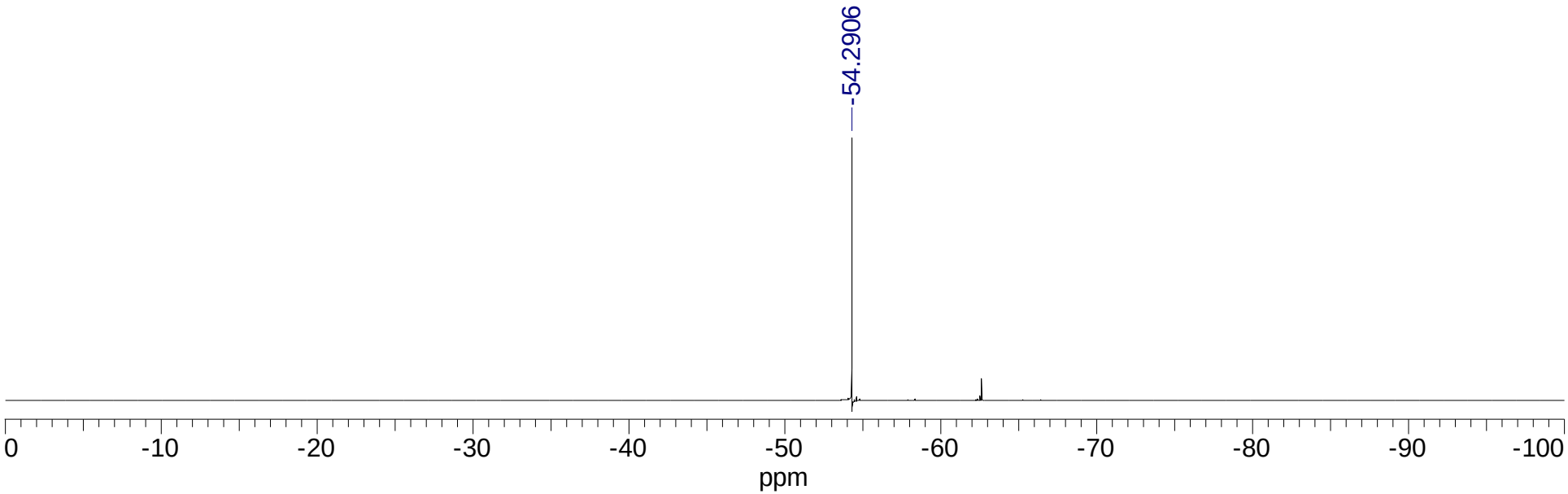

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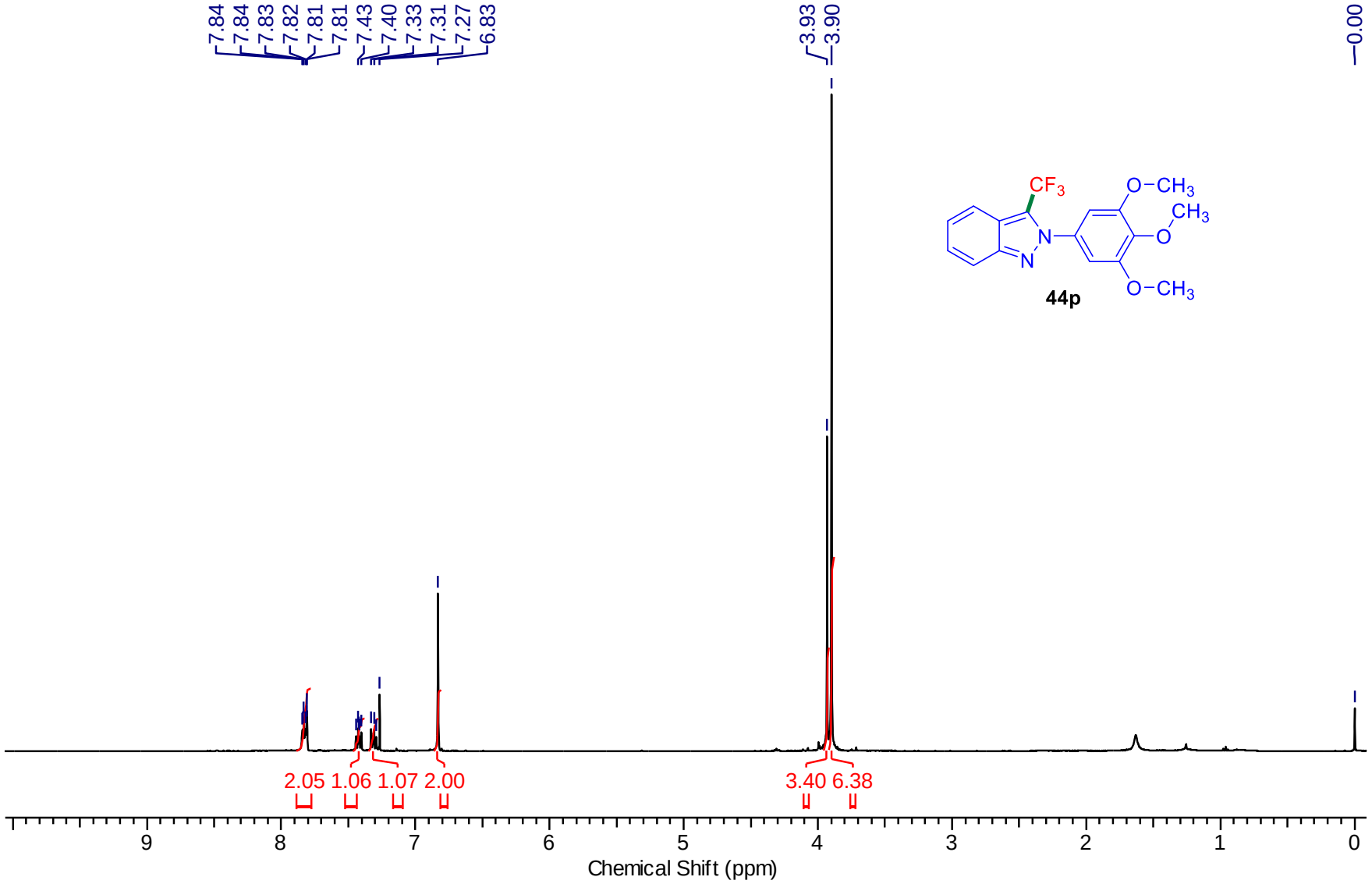

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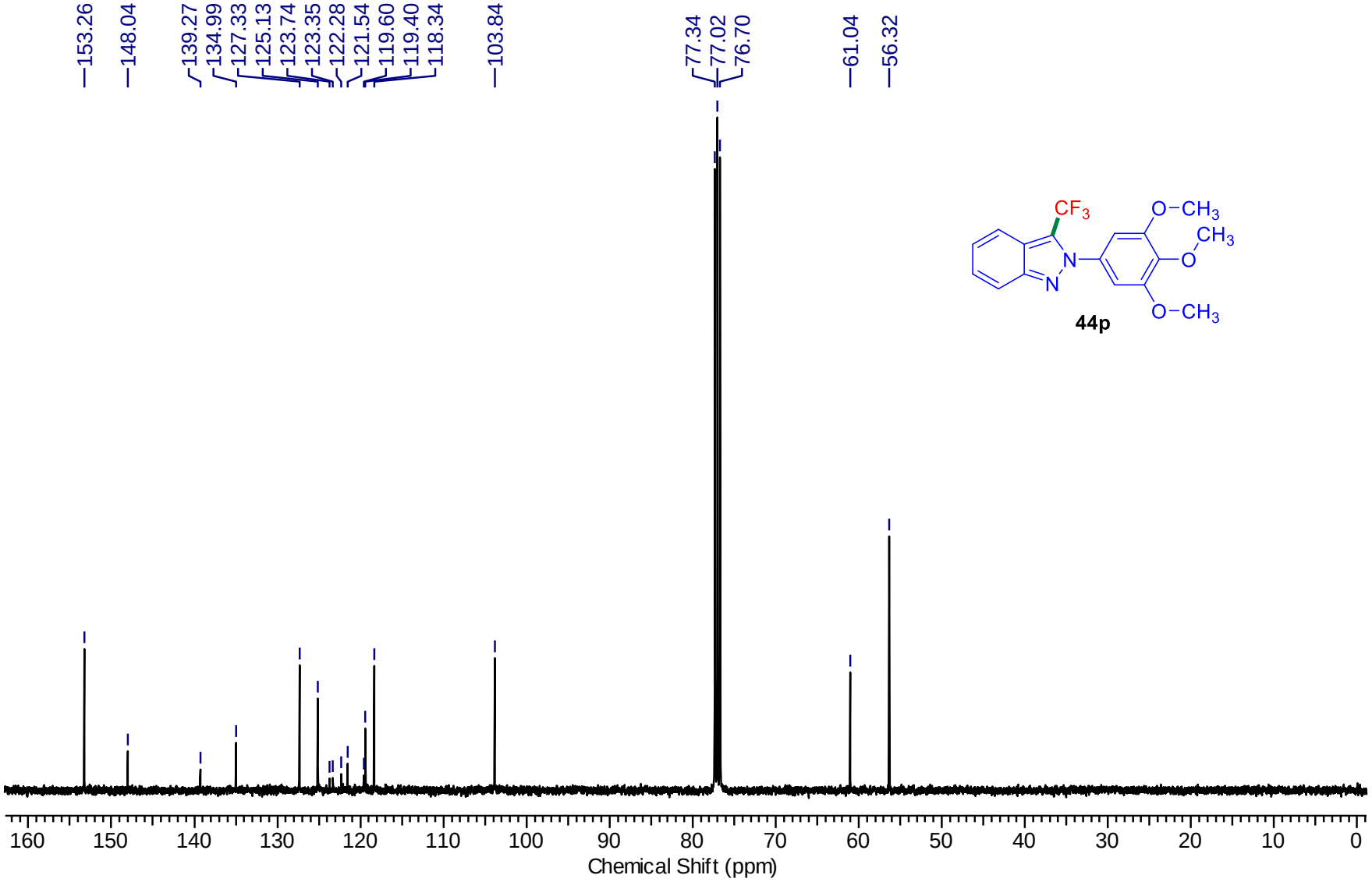

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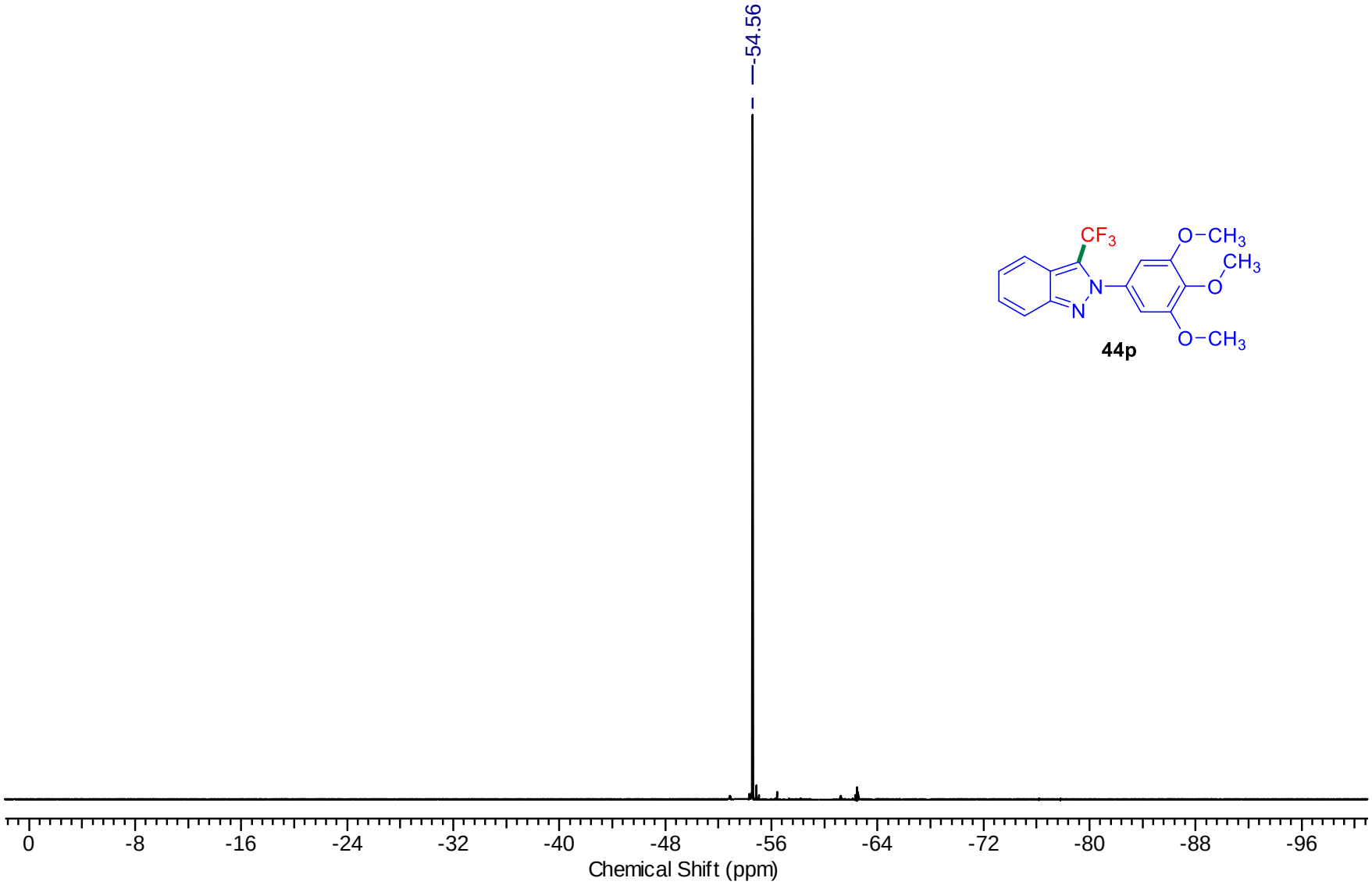

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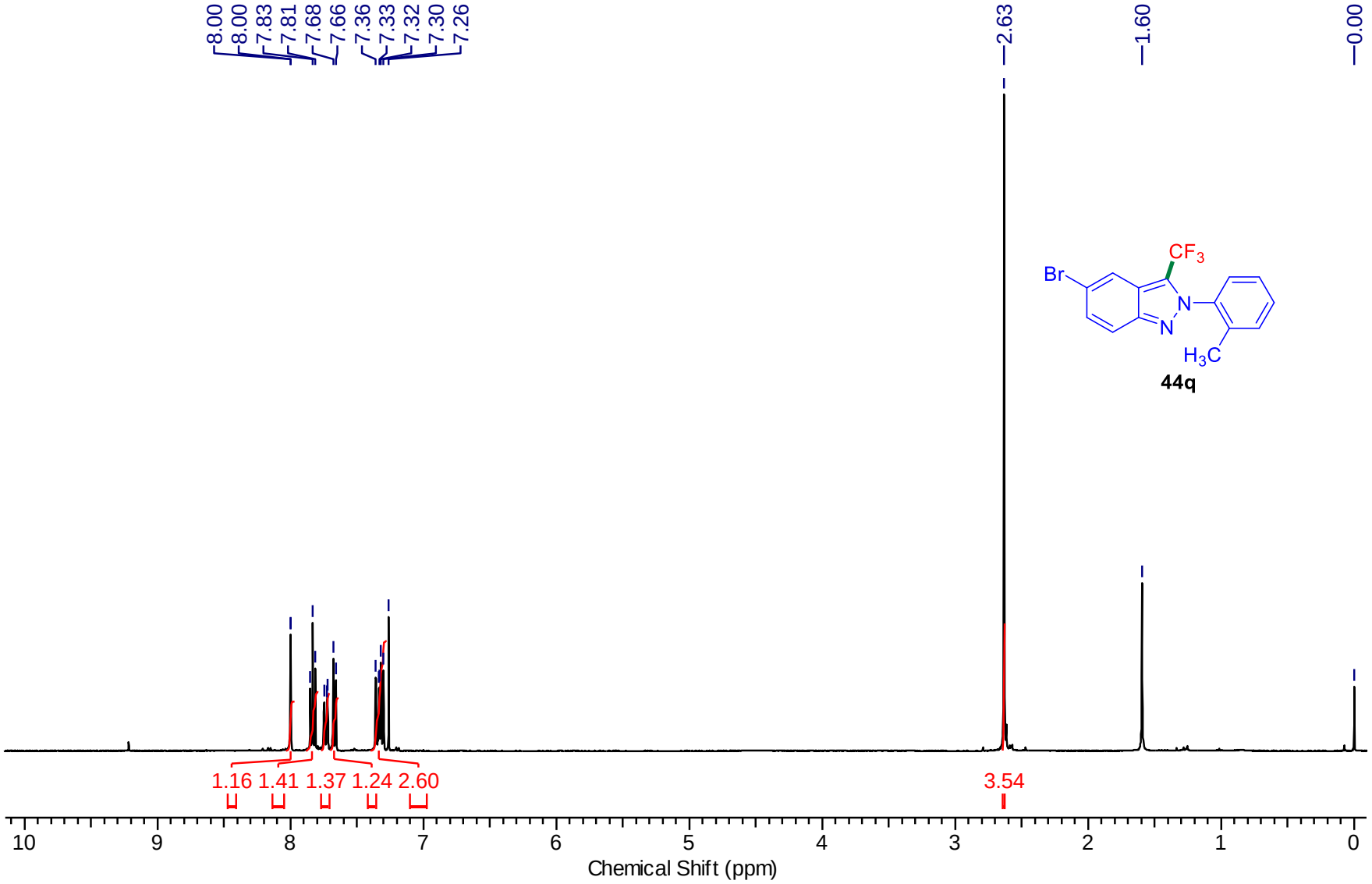
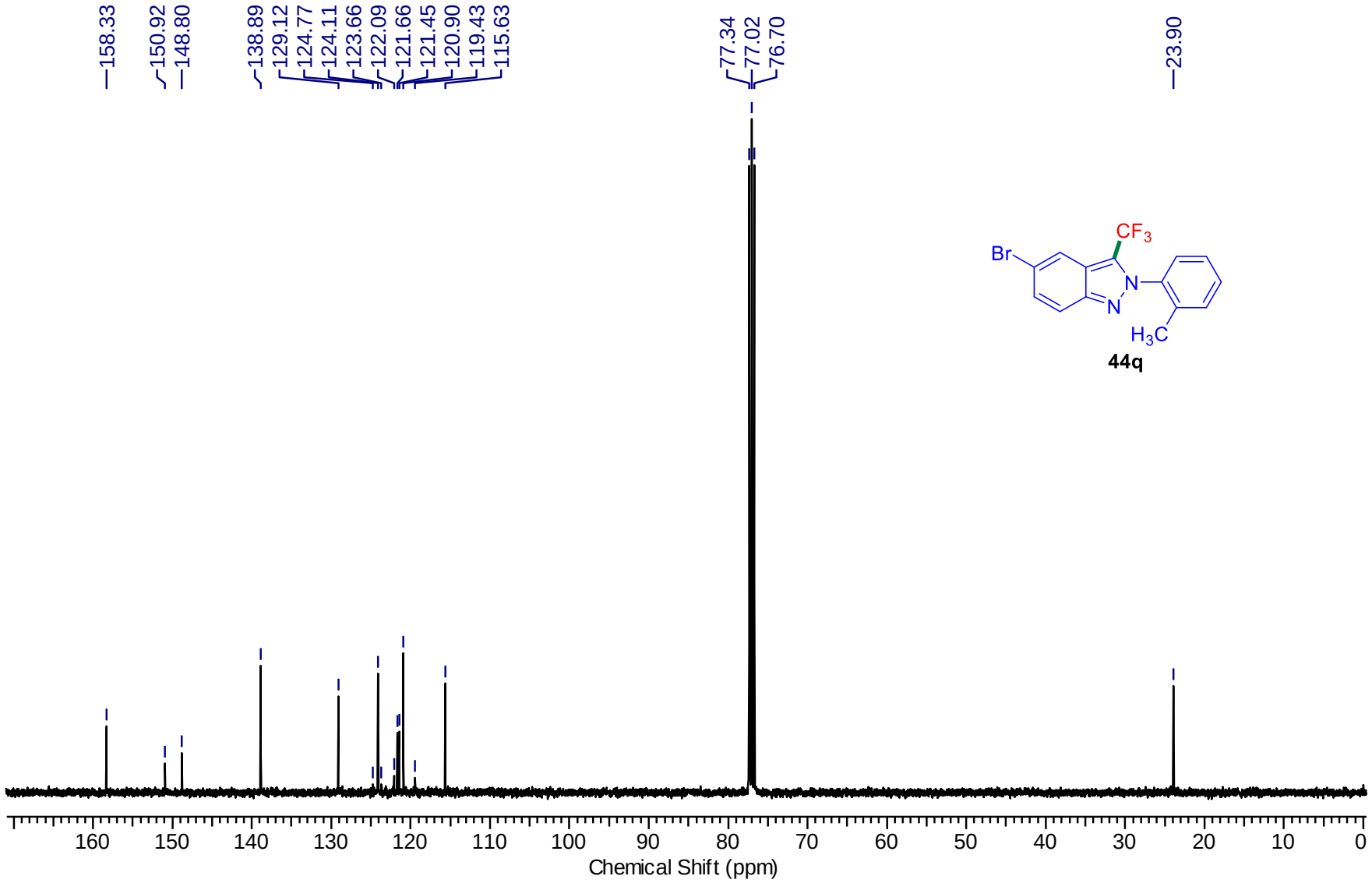


^{1}H NMR (400 MHz) spectrum of compound **44q** in $CDCl_3$



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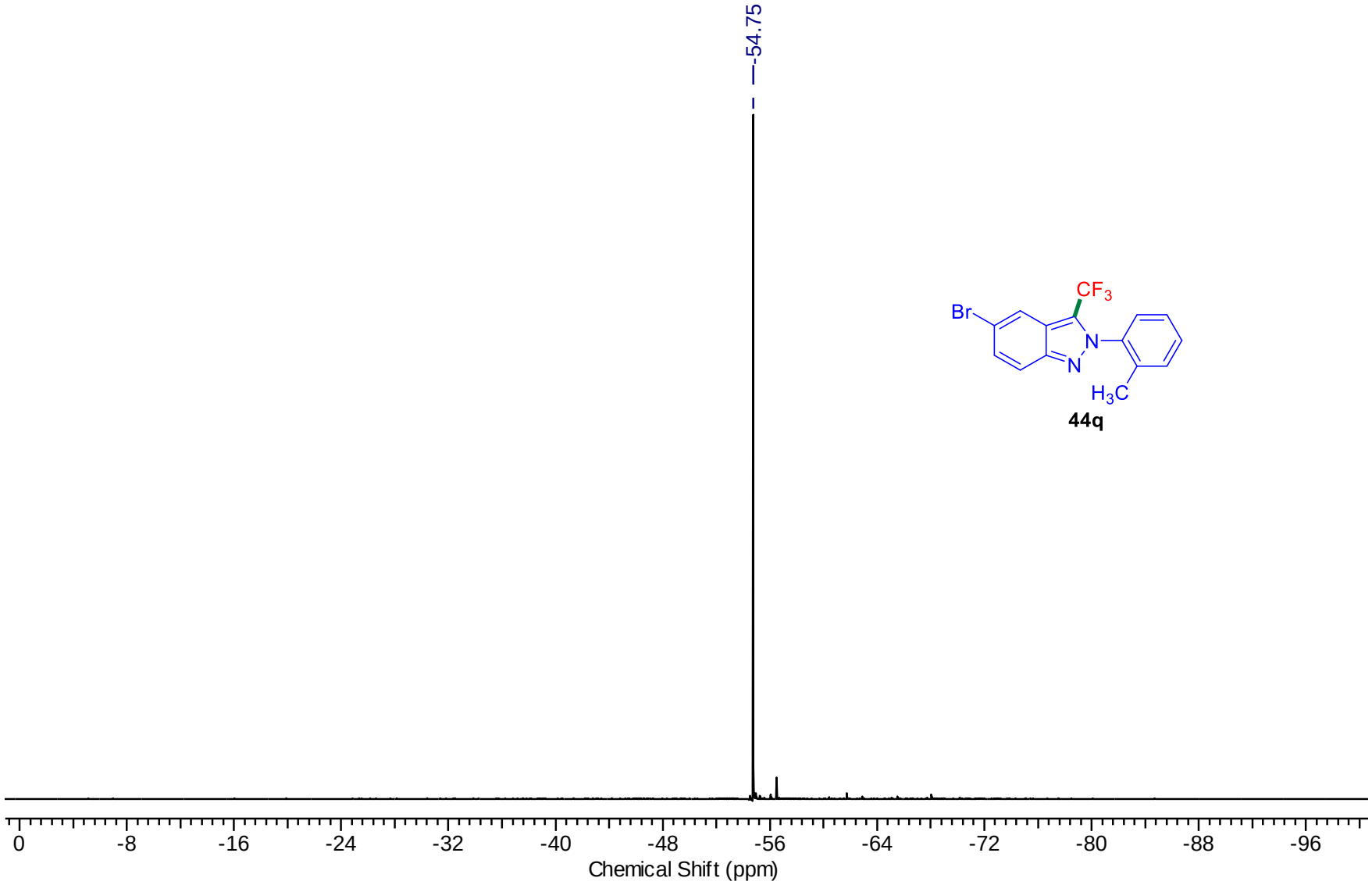

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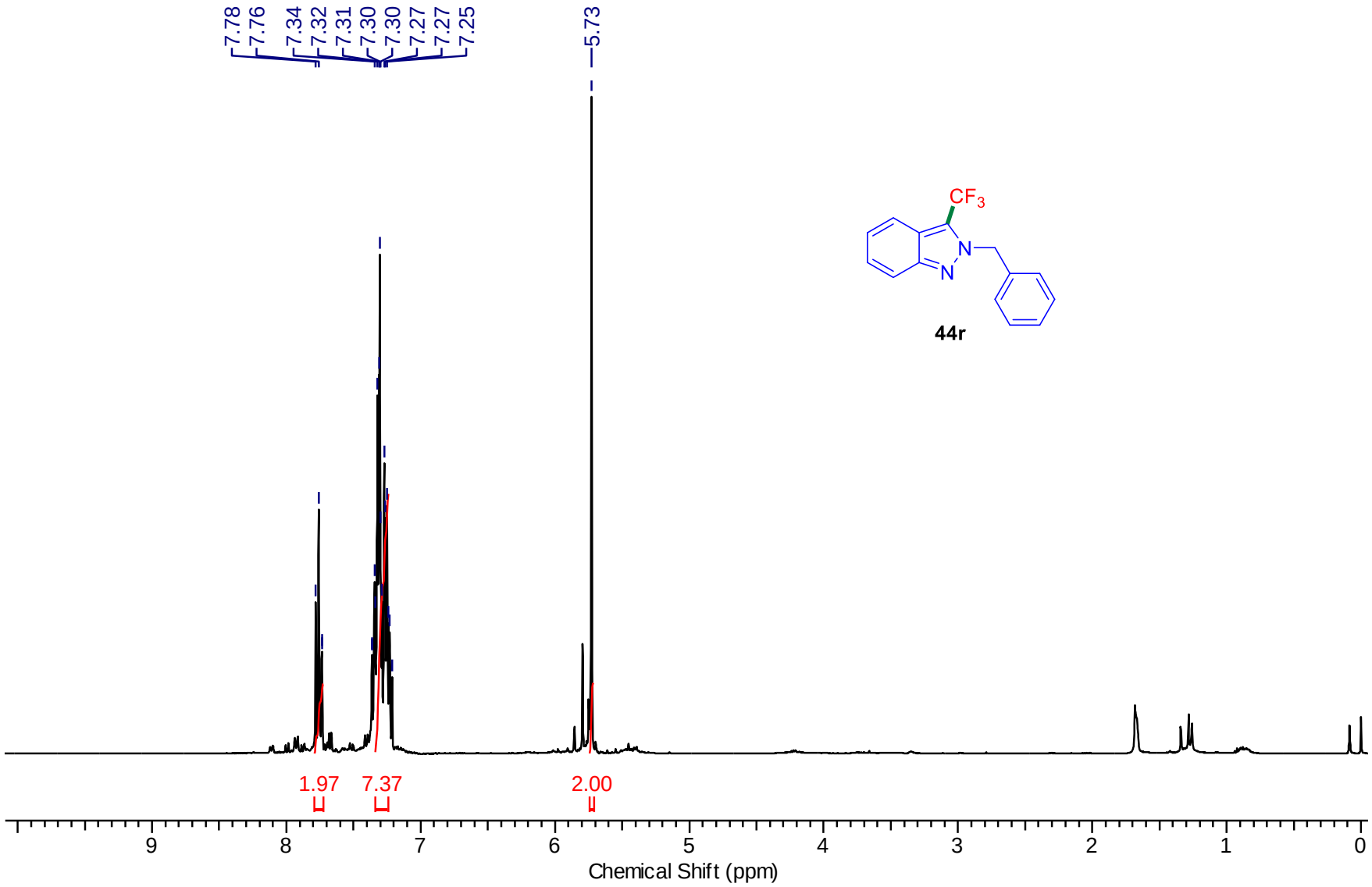
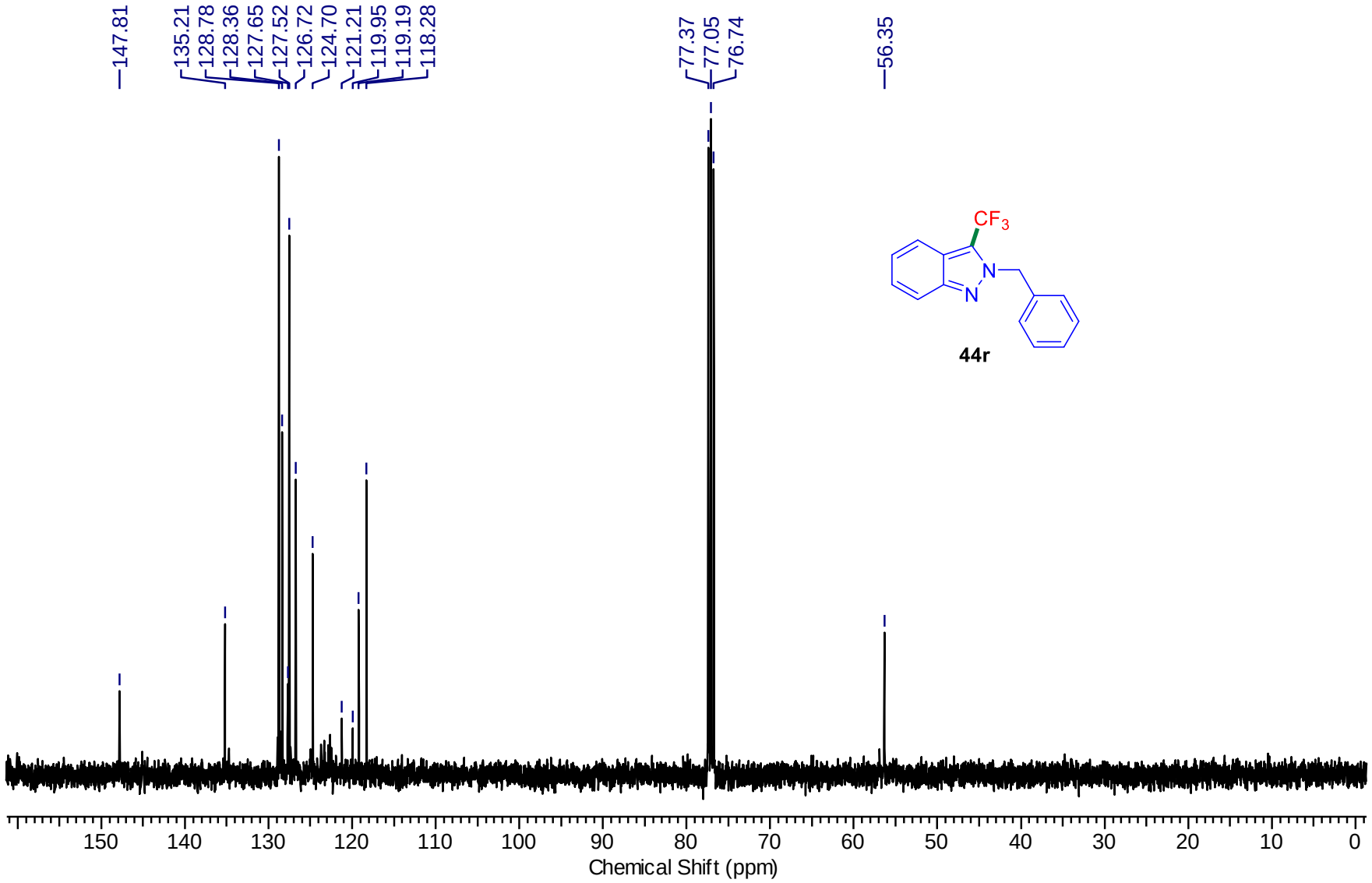


^{1}H NMR (400 MHz) spectrum of compound **44r** in $CDCl_3$



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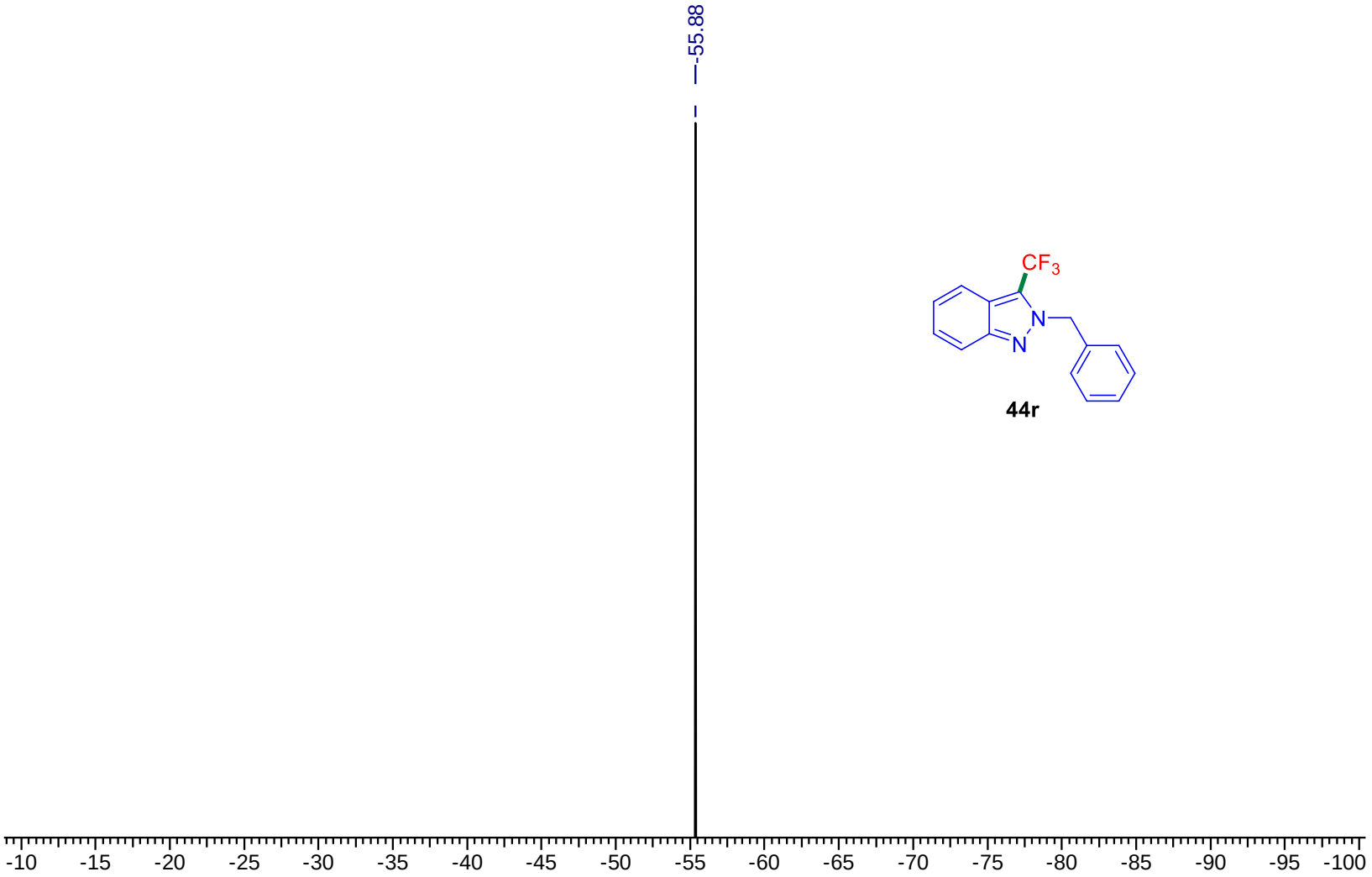

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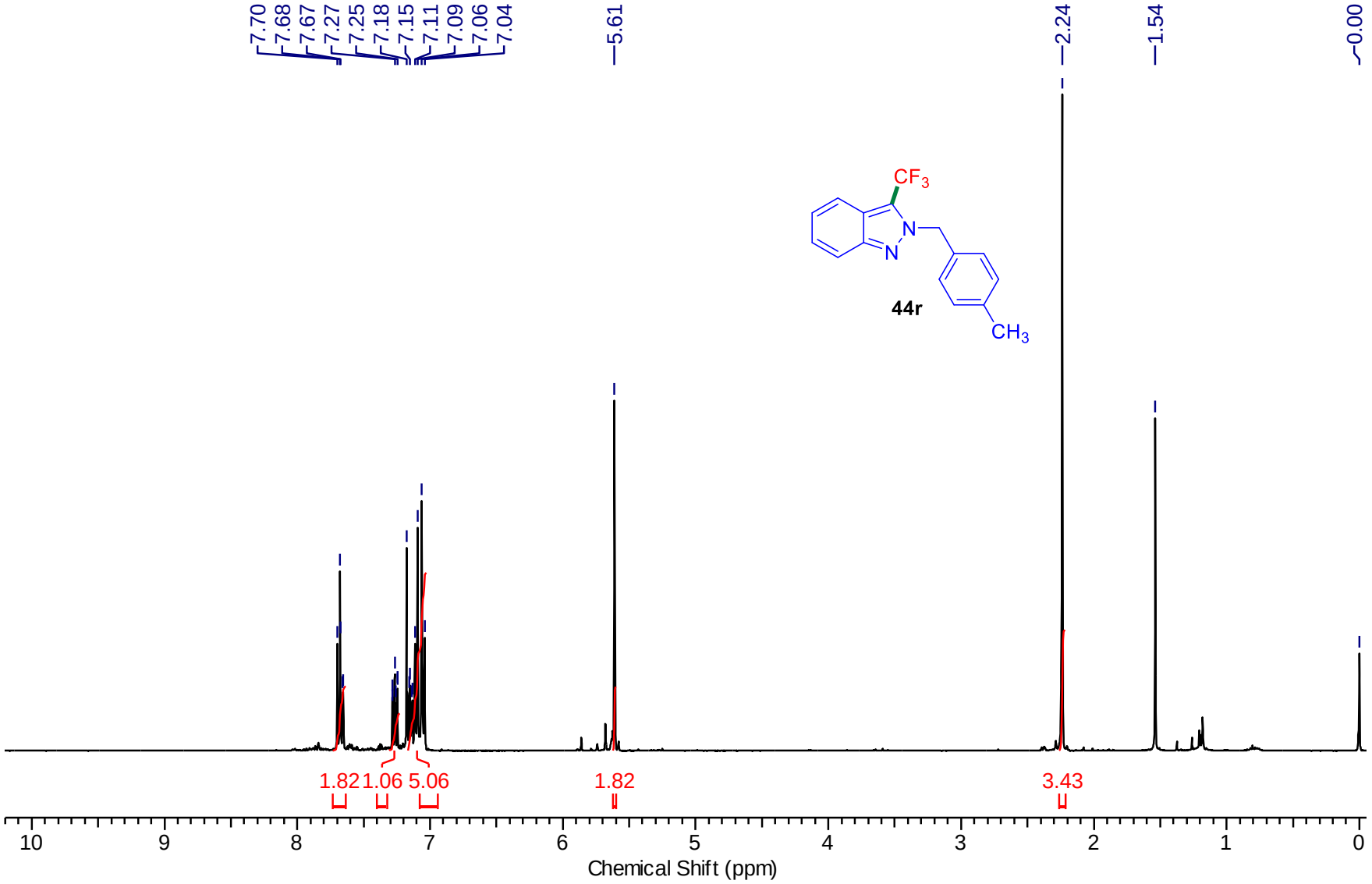
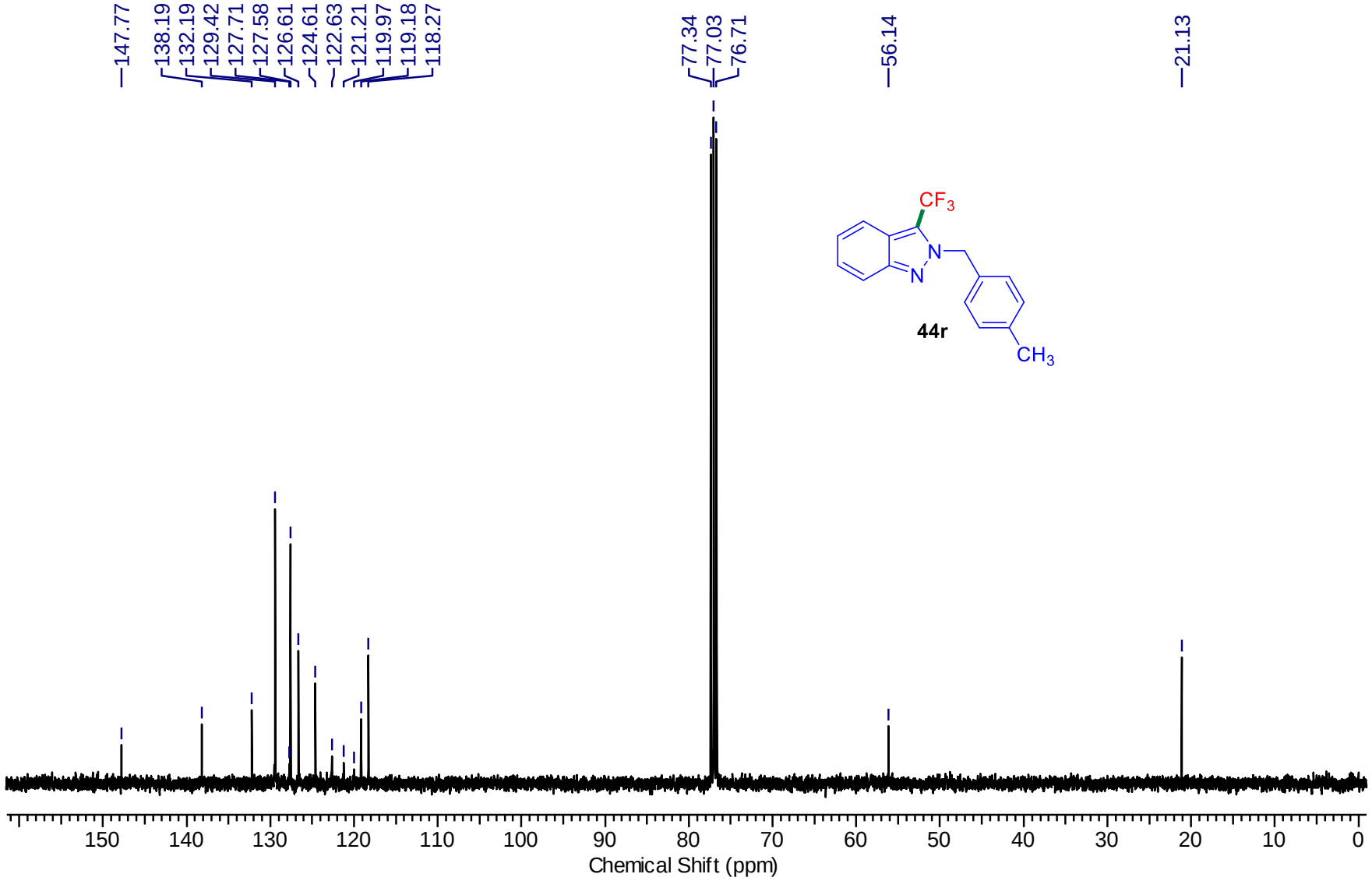
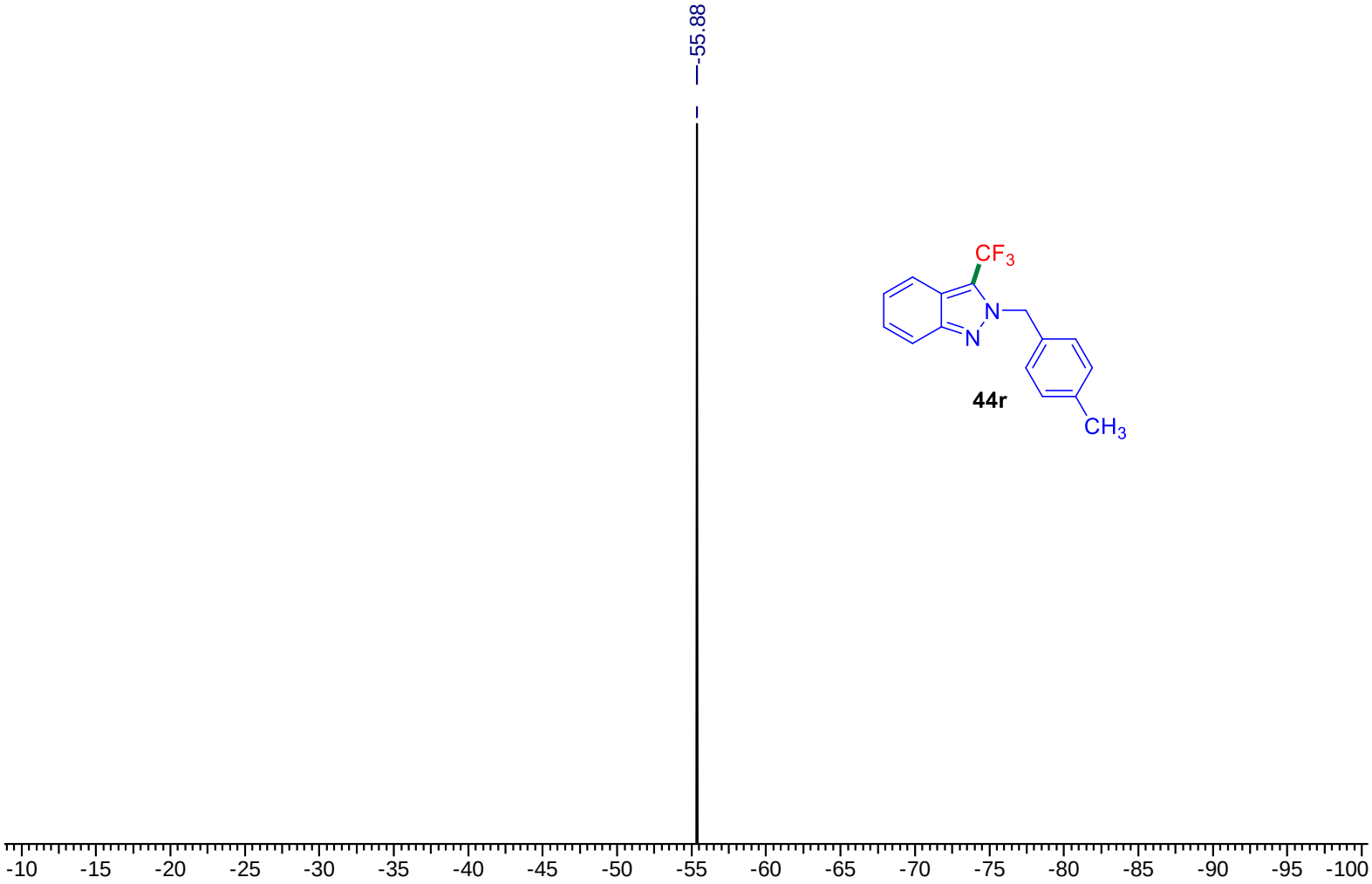


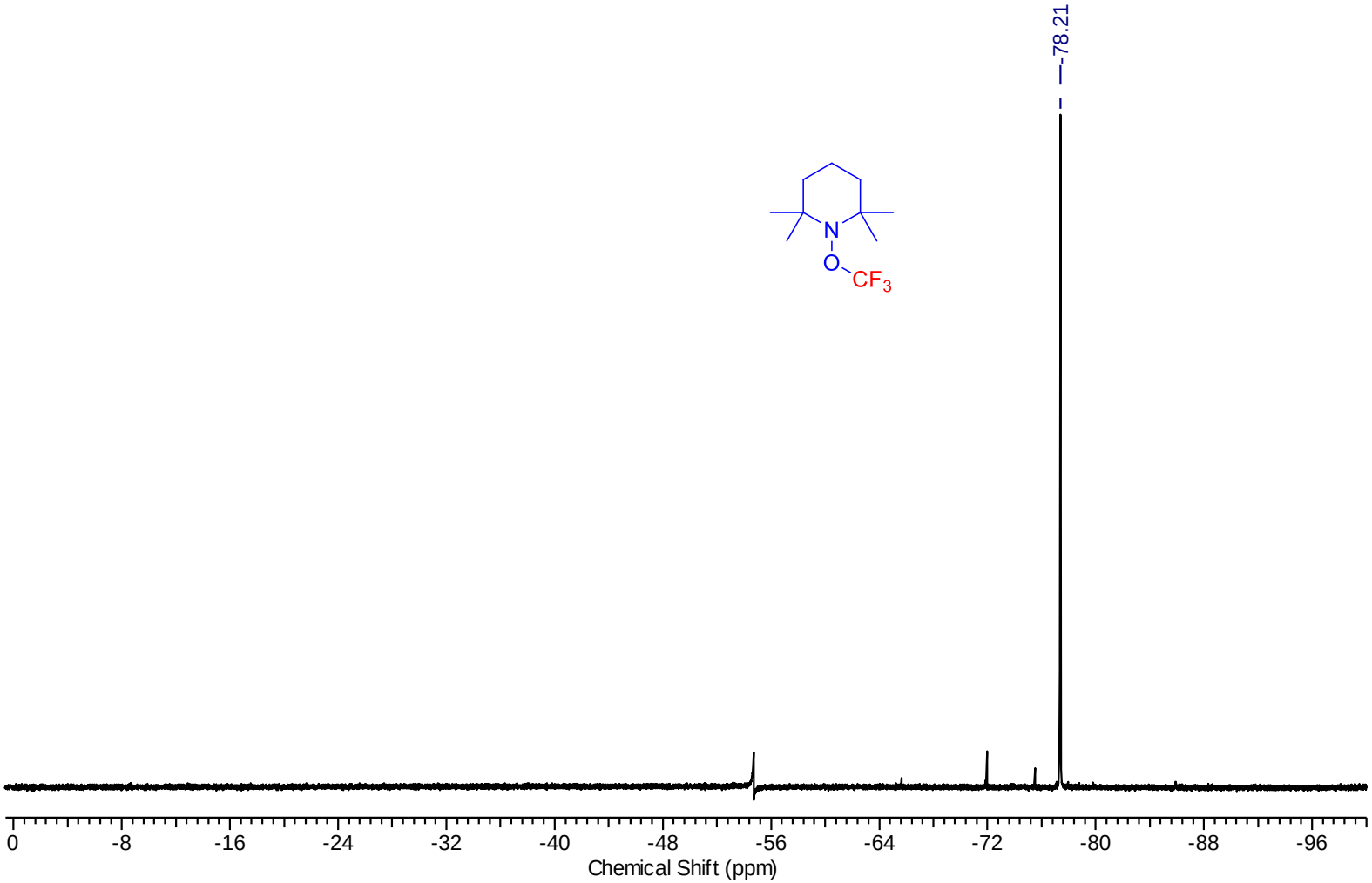
^{1}H NMR (400 MHz) spectrum of compound **44s** in $CDCl_3$



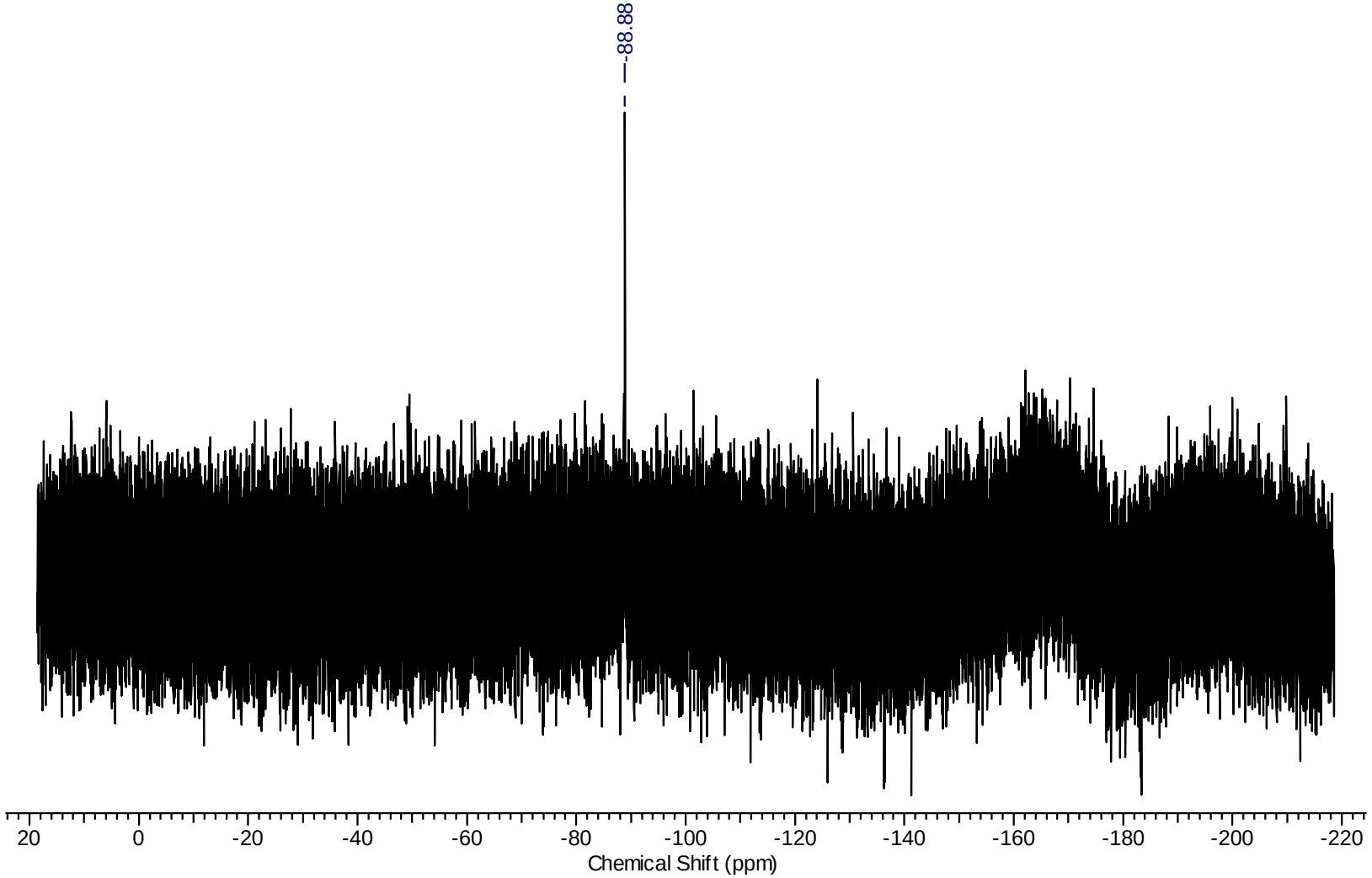
^{13}C NMR (100 MHz) spectrum of compound **44s** in $CDCl_3$



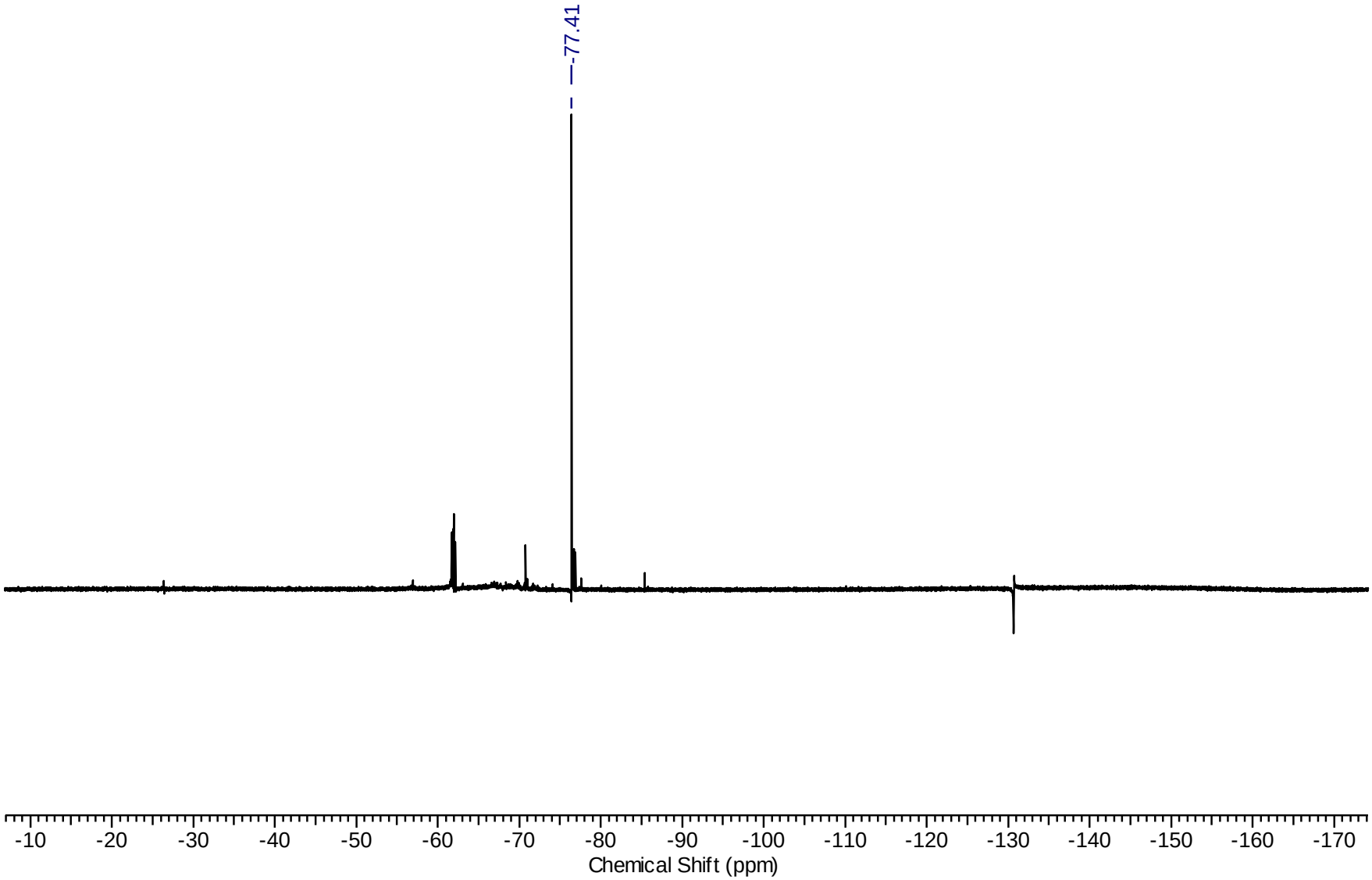
^{19}F NMR (376 MHz) spectrum of compound **44s** in $CDCl_3$



^{19}F NMR (376 MHz) spectrum of compound **TEMPO-CF$_3$** in $CDCl_3$



^{19}F NMR (376 MHz) spectrum of compound **$^{-}$OSOCF$_3$** in $CDCl_3$



^{19}F NMR (376 MHz) spectrum of compound **PhI(OAc)$_2$**

NMR Experiments

We have performed the NMR experiments of i) PIDA and $NaSO_2CF_3$ in $CDCl_3$ solvent and amount of reagents were taken as per standard conditions. In the case of PIDA + $NaSO_2CF_3$, NMR spectra suggested that there is a gradual amount of decomposition of PIDA to Iodobenzene as iodobenzene peaks were detected in the aromatic region of ^1H NMR (highlighted peaks in given NMR spectra, Figure S1). This experiment is carried out for 10 hours, and we did not observe the peaks corresponding to any other hypervalent iodine complexes other than iodobenzene peaks in NMR.

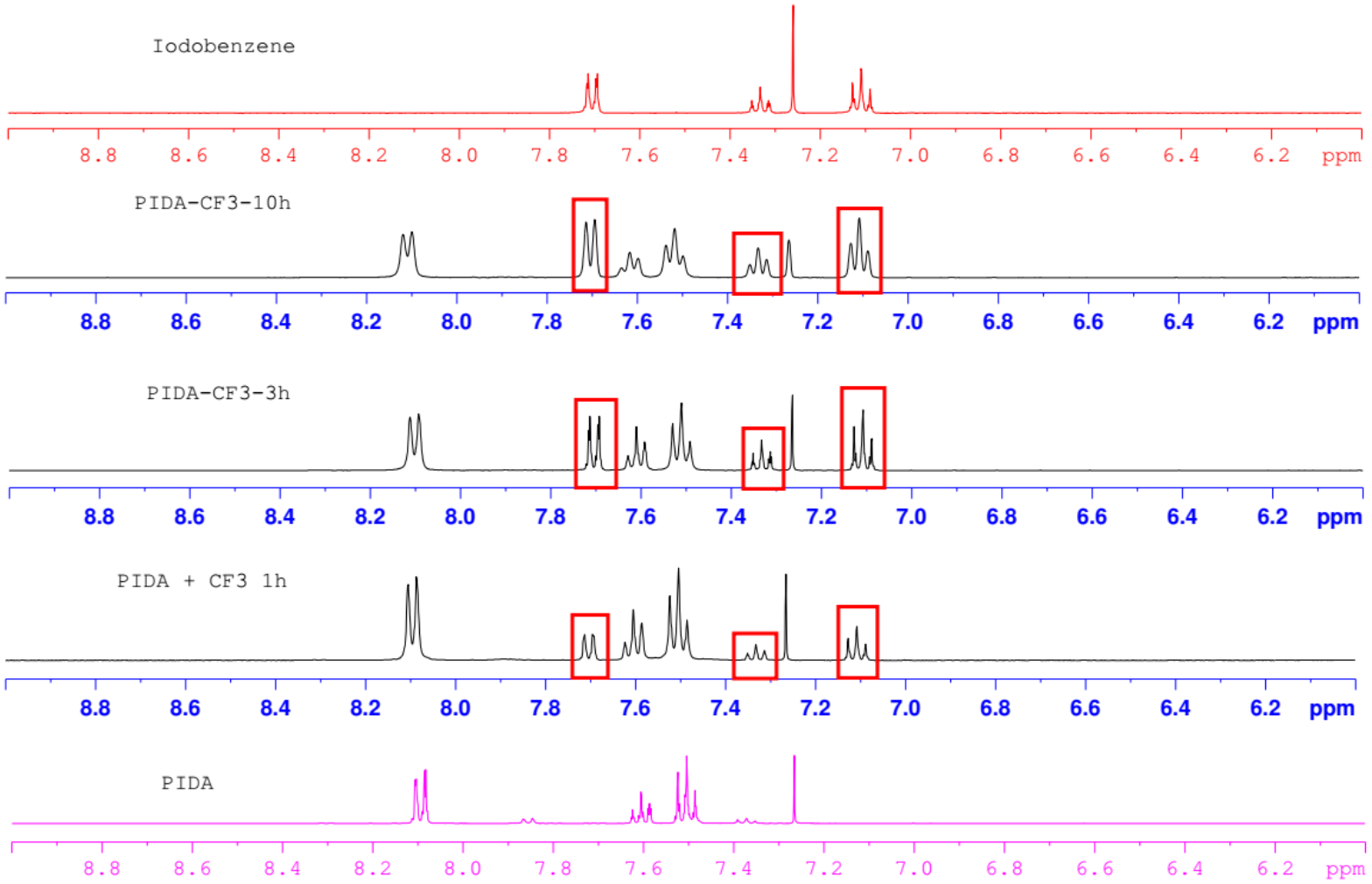


Figure S1. ^{1}H NMR Spectra of PIDA + $NaSO_2CF_3$ at different time intervals

3.6. REFERENCES

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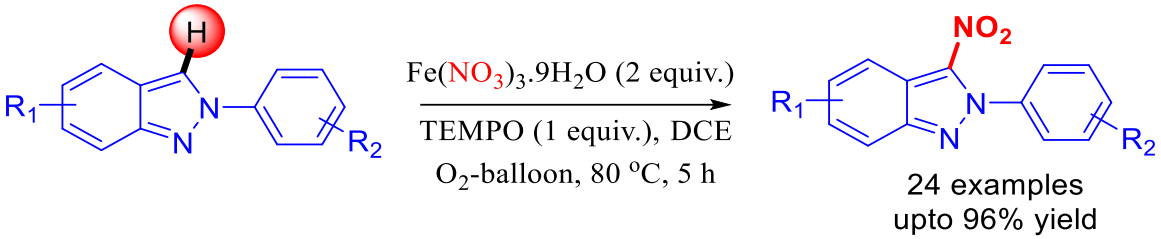
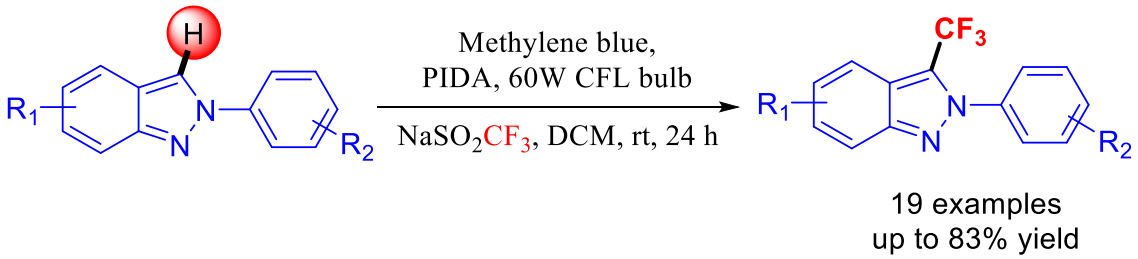
Graphical Abstracts

1. Iron-Promoted C3-H Nitration of 2*H*-Indazole: Direct access to 3-Nitro-2*H*-Indazoles



* Regioselective radical C-H nitration
* Chelation-free C-H functionalization
* Inexpensive and nontoxic nitro source

2. Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition-metal-free photoredox catalysis



* Regioselective radical C-H trifluoromethylation
* Chelation-free and metal-free C-H functionalization
* Inexpensive and benchtop-stable CF_3 radical source
* Scale-up synthesis

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EDUCATION & RESEARCH EXPERIENCE

Ph. D. (Synthetic Organic Chemistry) – Submitted May-**2019**

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Thesis Title: Sustainable Approaches for the site-selective C-H Functionalization of 2*H*-Indazoles

Master of Science (Chemistry) – 2011-2013

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Bachelor of Science (Chemistry) – 2008-2011

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FELLOWSHIPS/AWARDS

- Received **Research Excellence Award-2018** from Indian Institute of Technology Hyderabad.
- Awarded **Senior Research Fellowship (2016-2019)** by University of Grant Commission (UGC), New Delhi, India.
- Awarded **Junior Research Fellowship (2014-2016)** by University of Grant Commission (UGC), New Delhi, India.

AREAS OF SPECIALIZATION

- Photoredox catalyzed selective C-H functionalization
- Hypervalent iodine catalyzed C-H functionalization
- Novel synthetic methodology
- Synthesis of nitrogen enriched and aesthetically molecules

OPERATING INSTRUMENTS AND SKILLS

- Handling air and moisture sensitive chemicals and reactions
- Skills in designing novel routes for the synthesis of novel compounds
- Effective literature study and its application in research
- Analysis of complex organic molecules by using analytical techniques 1H, 13C-NMR IR, spectroscopy, HR-MS, UV visible spectroscopy etc.
- Handling the following instruments NMR, HR-MS, IR.
- Analyzing and solving single crystal X-ray structure with OLEX application
- Excellent skills in the purification of the organic compounds by column chromatography

PUBLICATIONS

1. Regioselective C3-H trifluoromethylation of 2*H*-indazole under transition-metal-free photoredox catalysis. **Arumugavel Murugan,** Venkata Nagarjuna Babu, Ashok Polu, Nagaraj Sabarinathan, Manickam Bakthadoss and Duddu S. Sharada., *J. Org. Chem.* **2019,** *84***,** 7796-7803
2. Iron Promoted C3-H Nitration of 2*H*-Indazole: Direct access to 3- Nitro-2*H*-Indazoles. **Arumugavel Murugan**, Koteswar Rao Gorantla, Bhabani S. Mallik, Duddu S. Sharada. *Org. Biomol. Chem.* **2018**, *16*, 5113-5118.
3. Metal-Free Regioselective Dual C-H Functionalization in a Cascade Fashion: Access to Isocryptolepine Alkaloid Analogues. **Arumugavel Murugan**, Shinde Vidyacharan, Ruma Ghosh and Duddu S. Sharada. *Chem. Select.* **2017**, *2*, 3511–3515.
4. An Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins. Venkata Nagarjuna Babu, **Arumugavel Murugan,** Narenderreddy Katta, Devatha Suman and Duddu S. Sharada., *J. Org. Chem.* **2019,** *84***,**. 6631-6641
5. C(sp^2)−H Functionalization of 2*H*−indazoles at C3-position via palladium(II)−catalyzed isocyanide insertion strategy leading to diverse heterocycles. Shinde Vidyacharan, **Arumugavel Murugan**, and Duddu S. Sharada. *J. Org. Chem.* **2016**, *81*, 2837-2848.

CONFERENCE/SYMPOSIUMS

1. Poster presentation titled “Metal-Free Regioselective Dual C-H Functionalization in a Cascade Fashion: Access to Isocryptolepine Alkaloid Analogues” presented in “21st International Conference on Organic Synthesis (ICOS-21)”, Dec 11-16, 2016 at Indian Institute of Technology (IIT) Bombay, India.
2. Poster presentation titled “Iron Promoted C3-H Nitration of 2*H*-Indazole: Direct access to 3- Nitro-2*H*-Indazoles” presented in JNOST-2018, National Conference on Organic Synthesis, Nov 28-Dec 1, 2018, at Indian Institute of Chemical Technology (IICT), Hyderabad, India.
3. Oral Presentation titled “Sustainable Approaches for site-selective C-H Functionalization of 2*H*-Indazoles” presented in “In House Symposium (IHS-2019)”, March 30, 2019, at Indian Institute of Technology Hyderabad (IITH), India.
4. Poster presentation titled “Regioselective C3–H Trifluoromethylation of 2*H*-Indazole under Transition-Metal-Free Photoredox Catalysis” presented in 20th Tetrahedron Symposium, Jul 18-21, 2019, at Bangkok, Thailand.

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Iron promoted C3–H nitration of 2*H*-indazole: direct access to 3-nitro-2*H*-indazoles†

Arumugavel Murugan, Koteswar Rao Gorantla, Bhabani S. Mallik * and Duddu S. Sharada *

An efficient C3–H functionalization of indazole has been demonstrated. Notably, this method involves chelation-free radical C–H nitration on 2*H*-indazole. The radical mechanism was confirmed by control experiments and quantum chemical calculations. The synthetic utility has been proven by the synthesis of bio-relevant benzimidazoindazoles *via* reductive cyclization.

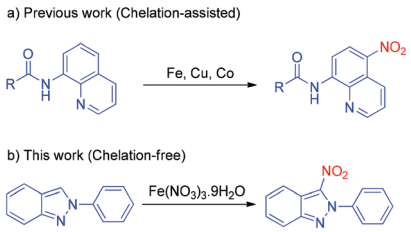
Introduction

Direct C–H functionalization has become a reliable and robust method for various transformations,[1] *i.e.* the carbon–hydrogen bond to the carbon–carbon and carbon–heteroatom bonds to construct complex molecules due to its high step- and atom-economy.[2] Recently, direct C–H functionalization *via* a radical pathway has become a rapidly expanding area of research and has emerged as a promising and sustainable approach towards molecular construction often complementary to traditional methods.[3] Despite these developments selective C–H functionalization *via* a radical pathway is still in its infancy and controlling the reactivity and chemo/regioselectivity of radical species for the selective C–H functionalization requires efforts to find more mild and suitable methods which poses many opportunities and challenges to address.[4]

Owing to the ubiquitous nature of heteroarenes in agrochemicals and pharmaceuticals,[5] the direct C–H functionalization of heteroarenes is a highly attractive strategy providing a concise route for complex molecules as well as for late-stage functionalization (LSF) of bioactive molecular scaffolds and hence offers tremendous opportunities for chemists.[6] Among them, C–H functionalization of heteroarenes *via* a radical pathway is one of the most appealing and straightforward strategies.[7]

Heteroaromatic nitro compounds are of great significance due to their importance as key precursors in organic synthesis[8] and their potential for further transformations. In recent years, several chemists have achieved a transition-metal-catalyzed radical C–H nitration on arenes/heteroarenes by using various nitro sources,[9] such as $AgNO_2$,[9a–d] ^tBuONO,[9e,f] $Cu(NO_3)_2$[9h,i] and $Fe(NO_3)_3{\cdot}9H_2O$.[11d] Among all metal nitrates, $Fe(NO_3)_3{\cdot}9H_2O$ as a non-toxic, inexpensive and green reagent is well known for various radical nitration strategies such as nitration on olefins,[10a–c] allenes[10d] and imines.[10e] However, its application in aromatic nitration is rare, except for a recent nitration on 8-aminoquinoline.[11d] Hence, there is a broad scope for the development of strategies for radical nitration of arenes and heteroarenes (Scheme 1).[11]

As an important class of heteroarenes, indazole motifs are embedded in pharmaceuticals with a broad range of biological activities,[12,13] including antitumor,[14] antimicrobial,[15] anti-inflammatory,[16] and HIV-protease inhibition.[17] Hence, there have been extensive efforts directed towards the synthesis of indazole derivatives. Due to the recent emergence of radical C–H functionalization as a new paradigm in contemporary chemistry and as a part of our research program on C–H functionalization and indazole chemistry,[18] we were interested in developing radical C–H functionalization as a new approach for func-



Scheme 1 Radical C–H nitration of heteroarenes.

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tionalized indazoles. Recently, Wu *et al.* have demonstrated the regioselective C–H functionalization of 8-aminoquinoline through theoretical data calculations.[7e] Accordingly, we planned to support our findings on radical C–H functionalization through quantum chemical calculations. Herein, we are delighted to disclose for the first time a radical C–H functionalization of 2*H*-indazole through $Fe(NO_3)_3{\cdot}9H_2O$ promoted C3–H nitration.

Results and discussion

To achieve our goal, we initiated our preliminary experiments with 2*H*-indazole (**1a**) as a model substrate and $Fe(NO_3)_3{\cdot}9H_2O$ as a nitro source in MeCN as a solvent at 80 °C under an oxygen atmosphere (Table 1, entry 1). As expected, a C3-nitro functionalized product (**2a**) was obtained albeit in very poor yield. Inspired by this result, we screened various nitro sources (Table 1, entries 2–8). However, we did not observe any satisfactory yields.

Next, we turned to the use of the oxidant (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) in the reaction. Surprisingly, we observed the expected product in very good yield in the presence of TEMPO (Table 1, entry 9). Furthermore, our attempts of replacing TEMPO with other oxidants went in vain (Table S1, ESI†).

Furthermore we also screened the reaction with different solvents (Table 1, entries 10–18) and varying temperatures (Table S2, ESI†). Interestingly, we have observed the formation of the product with very good yield in the case of DCE as a solvent (Table 1, entry 10). Notably, when we performed the reaction in open air, we observed the formation of the expected product with moderate yield (Table 1, entry 19). Subsequently, we screened the reaction with different equivalents of nitro sources and oxidants (Tables S1 & S3, ESI†). From these experiments we concluded that 2 equiv. of nitro source and 1 equiv. of oxidant are necessary for the complete conversion of the starting materials.

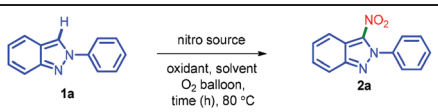
With the optimized conditions in hand, we next examined the scope of this methodology with different substituted 2*H*-indazole systems (Table 2). The methylenedioxy substitution gave good yield when compared to halo substitution at the 5th, 6th and 7th positions of 2*H*-indazoles **2c–g**.

Next, we examined the scope of substrates with various substitutions (halogen, alkyl, alkoxy) on the amine partner of 2*H*-indazoles resulting in desired products with moderate to good yields. Having the benzyl group in place of aryl at the 2nd position of 2*H*-indazoles **2w** & **x** did not show any improvement in the yield.

Unfortunately, amine partner bearing electron withdrawing groups, such as nitro, nitrile and ester groups did not afford the desired products **2aa–ac**. In addition, 2*H*-indazoles with alkyl substitution at the 2nd position of **2ad** & **ae** could not afford the nitration product. Furthermore, our attempts to carry out nitration on other heteroarenes (indole, imidazole, 1*H*-indazole) went in vain.

Based on the experiments performed for the optimization of reaction conditions shown in Table 1, we observed that other nitro sources failed to give any nitro product, hence in order to prove the role of $Fe(NO_3)_3{\cdot}9H_2O$, we planned to examine the reaction with metal free nitro sources, however, in the presence of Fe/Cu as a promotor which resulted in good yield (Scheme 2b), thus indicating the dual role of $Fe(NO_3)_3{\cdot}9H_2O$. Furthermore, the reaction in the absence of any promotor with metal-free nitrate (TBN) did not afford the desired product (Scheme 2c). Hence, the promotor is necessary for the nitration of indazole at the C3 position. To prove the radical pathway, we performed HR-MS analysis of the crude reaction mixture, which showed 2,2,6,6-tetramethylpiperidin-1-ol. To know the role of oxygen, we have conducted a couple of control experiments. We obtained the desired product in 10% and 15% yield when the reaction was carried out in the absence of O_2 and TEMPO respectively (Scheme 2e & d). However, these experiments are not conclusive. When we performed the reaction in the presence of an excess amount of TEMPO (2 equiv.) under an argon atmosphere, 80% yield of the desired product was obtained (Scheme 2f). This indicates that the presence of oxygen reduces the amount of TEMPO significantly (optimized conditions *i.e.* 1 equiv. of TEMPO under an oxygen atmosphere). From these experiments, we can conclude that 'O_2' might involve either in the recycling of TEMPO (TEMPOH to TEMPO) or in the direct oxidation of intermediate **B** to intermediate **C**. Finally, to confirm the C3-functionalization of 2*H*-indazole, we performed the reaction with C3 sub-

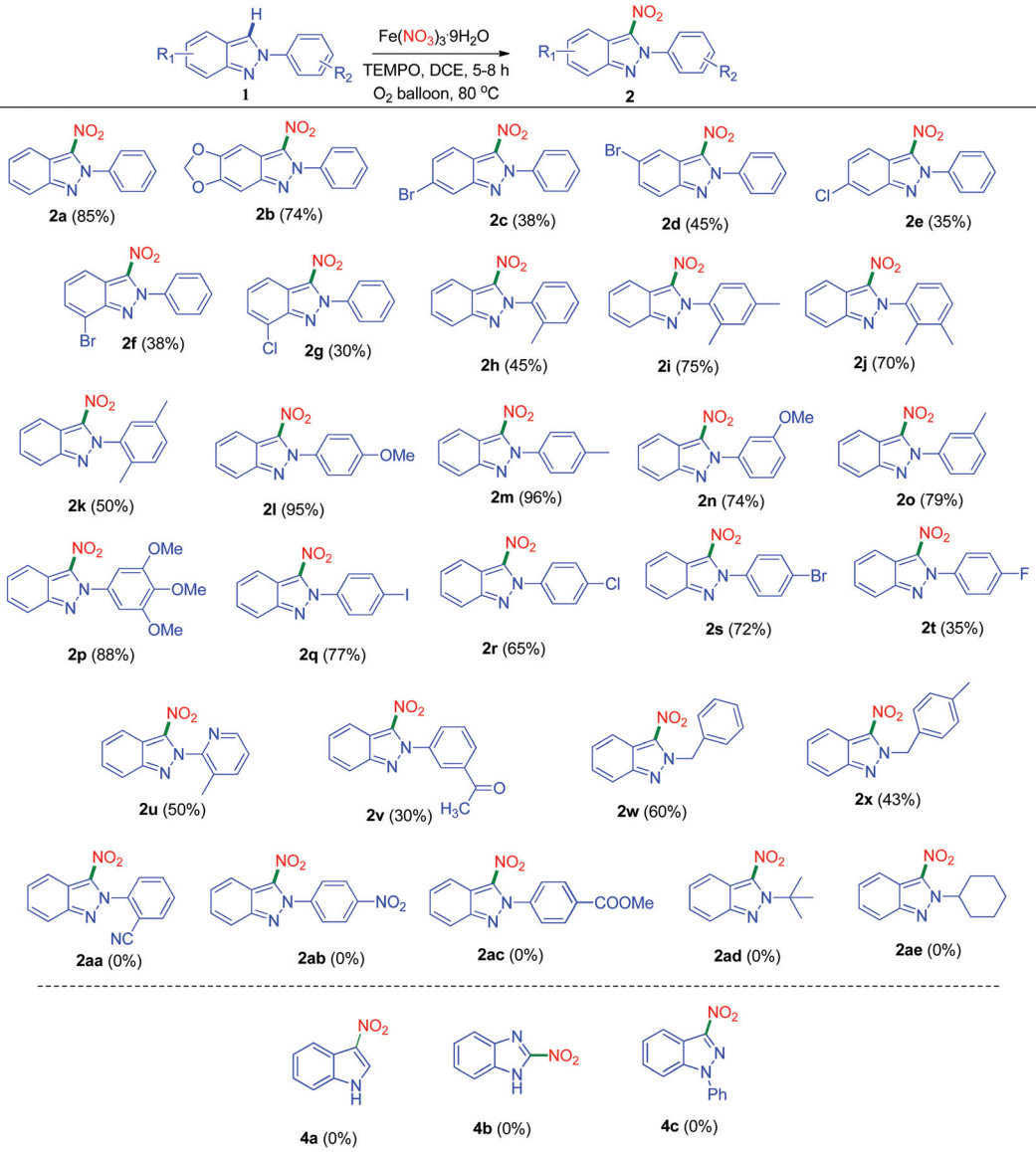
Table 1 Optimization of reaction conditions for the synthesis of **2a**[a]



Entry	Nitro source	Oxidant	Solvent	Time (h)	Yield[b] (%)
1	$Fe(NO_3)_3{\cdot}9H_2O$	—	MeCN	5	15
2	$Ni(NO_3)_2{\cdot}6H_2O$	—	MeCN	5	Trace
3	CAN	—	MeCN	5	Trace
4	^tBuONO	—	MeCN	5	n.d.[c]
5	$AgNO_3$	—	MeCN	5	n.d.[c]
6	$AgNO_2$	—	MeCN	5	n.d.[c]
7	$NaNO_2$	—	MeCN	5	n.d.[c]
8	$Cu(NO_3)_2{\cdot}3H_2O$	—	MeCN	5	10
9	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	MeCN	5	65
10	**$Fe(NO_3)_3{\cdot}9H_2O$**	**TEMPO**	**DCE**	**5**	**85**
11	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	$CHCl_3$	5	55
12	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	DMF	12	nr[d]
13	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	DMSO	12	n.d.[c]
14	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	Dioxane	12	n.d.[c]
15	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	Toluene	12	n.d.[c]
16	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	H_2O	12	n.d.[c]
17	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	EtOH	12	n.d.[c]
18	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	MeOH	12	n.d.[c]
19	$Fe(NO_3)_3{\cdot}9H_2O$	TEMPO	DCE	5	60.[d]

[a] Reaction conditions: **1a** (1 mmol), nitro source (2 mmol), oxidant (1 mmol), solvent (1 mL), oxygen balloon, 80 °C, 5–12 h. [b] Isolated yield of chromatographically pure products. [c] Starting materials recovered. [d] Reaction carried out in open air.

Table 2 Substrate scope for the C3-nitration of 2*H*-indazole[a,b]



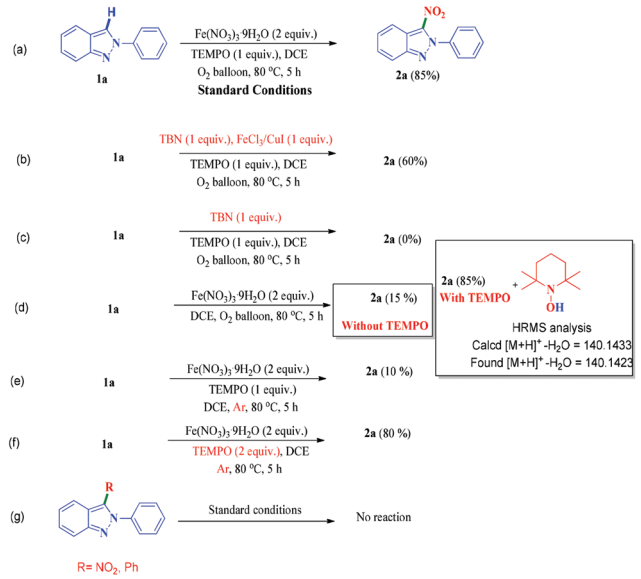
[a] Conditions: **1a** (1 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2 mmol), TEMPO (1 mmol), DCE (2 mL), oxygen balloon, 80 °C, 5–8 h. [b] Isolated yield of chromatographically pure products.

stituted 2*H*-indazole under standard conditions (Scheme 2g), which did not afford any nitro substituted 2*H*-indazole. The X-ray crystallography analysis of compound **2t** further supports the nitration at the C3 position.

To further support our finding, we carried out quantum chemical calculations[7e] to investigate the charge distribution on indazole. The theoretical data of atoms (C3, C4, C6) on the Fe coordinated indazole intermediate **A** are shown in Table 2. The charges of the C3, C4 and C6 as calculated were found to be −0.025, −0.027 and −0.037 respectively (Table 3).

The charges include the contribution from all valance electrons and based on the literature precedence[7e] the p_z orbital occupancy would be a more effective way to assess the reactivity of a specific atom. Among various atoms, the largest p_z orbital occupancy at the C3 carbon atom implicates that C3 may be the most likely electrophilic reactive site. Thus the theoretical calculations support the only C3–H nitration on 2*H*-indazole.

Based on the control experiments, literature reports[7e,9a,11d] and quantum chemical calculations, we have proposed a plausible mechanism for the synthesis of 3-nitro-2-phenyl-2*H*-indazole as depicted in Scheme 3. Initially, coordination of 2-phenyl-2*H*-indazole with $Fe(NO_3)_3{\cdot}9H_2O$ led to the formation of intermediate **A**. Meanwhile, the nitro radical ($NO_2^{\bullet}$) generated from $Fe(NO_3)_3{\cdot}9H_2O$ under thermal conditions[19] would react at the electrophilic reactive site of the intermediate **A** in

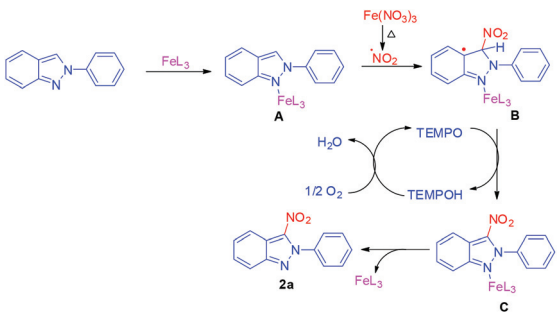


Scheme 2 Control experiments.

Table 3 Charge distribution and p_z orbital occupancy of the C3, C4 and C6 atoms in structure A

Atom	Hirshfeld	p_z orbital occupancy
C3	−0.025	0.997
C4	−0.037	0.990
C6	−0.027	0.980

A

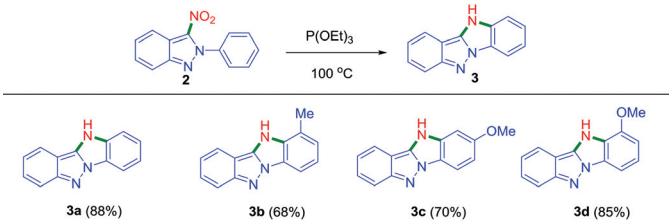


Scheme 3 Plausible mechanism.

order to generate an intermediate **B**. The combination of TEMPO/O_2 is involved in oxidation by the abstraction of a hydrogen radical[20] from the C3 position of intermediate **B** leading to the formation of intermediate **C**, which eventually provides the desired product **2a**.

After we synthesized various C3-nitro 2*H*-indazoles, we successfully demonstrated the synthetic utility of nitro indazoles by the synthesis of bio-relevant benzimidazoindazoles through reductive cyclization (Table 4).

Table 4 Synthesis of benzimidazoindazoles[a,b]



[a] Reaction conditions: **2a** (0.1 mmol), $P(OEt)_3$ (1 mL), 100 °C, 1 h. [b] Isolated yield of chromatographically pure products.

Conclusions

In conclusion we have developed a novel protocol for the radical C–H nitration of 2*H*-indazoles. This method offers chelation-free C–H nitration on 2*H*-indazole by using the inexpensive and nontoxic $Fe(NO_3)_3{\cdot}9H_2O$ under mild conditions. Moreover, the mechanistic pathway was inferred on the basis of control experiments and quantum chemical calculations. The synthetic utility of nitroindazoles was demonstrated by the synthesis of bio-relevant benzimidazoindazoles. This unique radical C–H nitration of 2*H*-indazoles should open new avenues for the C–H functionalization of 2*H*-indazoles and studies in this direction are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Regioselective C3−H Trifluoromethylation of 2*H*-Indazole under Transition-Metal-Free Photoredox Catalysis

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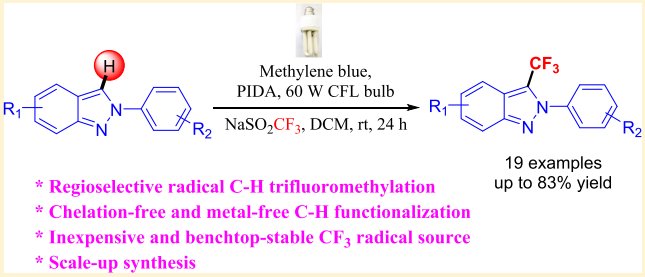
Supporting Information

ABSTRACT: Trifluoromethyl-substituted heteroarenes are biologically active compounds and useful building blocks. In this sequence, we have developed a visible-light-promoted regioselective C3−H trifluoromethylation of 2*H*-indazole under metal-free conditions, which proceeds via a radical mechanism. The combination of photocatalysis and hypervalent iodine reagent provides a practical approach to a library of trifluoromethylated indazoles in 35−83% yields.



INTRODUCTION

Halo-organic compounds are typically considered as sites of high electron density because of their high electronegativity. In general, the halogen atoms can form attractive interaction due to electron donor sites (i.e., nucleophiles).[1] Among them, the C−F bond finds important application in the field of synthetic and medicinal chemistry, which is due to the similar size and increased electronegativity of fluorine over hydrogen.[2] In this context, the trifluoromethyl group represents important structural motif in agrochemicals, pharmaceuticals, and drug candidates. The CF_3 moieties can enhance in metabolic stability, increase lipophilicity, bioavailability, and hydrolytic stability. Further, the trifluoromethyl-containing organic compounds are commonly applied in material such as liquid crystals.[3]

In the past decade, due to the importance of trifluoromethylation process, several methods have been developed, using various radical, nucleophilic, and electrophilic trifluoromethylating agents such as CF_3I,[4] CF_3SO_2Cl,[5] CF_3COOH,[6] the Ruppert−Prakash reagent ($TMSCF_3$),[7] the Togni reagent,[8] the Umemoto reagent,[9] the Baran reagent $(CF_3SO_2)_2Zn$,[10] and the Langlois (CF_3SO_2Na).[11] Among these, the Langlois reagent is benchtop-stable, inexpensive, easy to handle, and convenient for trifluoromethylation.[12] Despite these developments, the approach for radical trifluoromethylation of arenes and heteroarenes has been developed over the past years.[13]

In recent years, the visible-light-induced photoredox catalytic activation of organic molecules has been established as a powerful strategy in modern organic synthesis, which provides attractive features like mild nature, environmentally benign, excellent functional group tolerance, and high reactivity.[14] The photoredox strategy can involve via single electron-transfer (SET) process upon irradiation with visible light using metal complexes and organic dyes as photocatalyst.[15] Moreover, organic dyes are inexpensive and easy to handle as photoredox catalysts, and hence this would be an excellent substitute to inorganic transition-metal photocatalyst.

Nitrogen-containing heterocycle compounds have gained significant importance in natural products and they exhibit a wide range of biological activities.[16] Among them, indazoles are broadly known for their bioactivities[17] such as antitumor,[18] antimicrobial,[19] anti-inflammatory,[20] anti-HIV,[21] antiplatelet,[22] and anticontraceptive.[23] Considering the immense importance of derivatives of 2*H*-indazoles, extensive efforts have been devoted for the synthesis and functionalization of 2*H*-indazole.[24] Recently, Oh et al. have reported the silver-catalyzed direct acyl radical addition to 2*H*-indazole[25a] and Hajra et al. have also realized the construction of carbon−phosphorus (C−P)[25b] and carbon−sulfur (C−S)[25c] bond formations on 2*H*-indazole (Scheme 1a). Very recently, Hajra et al. have described a new approach for the direct C3-trifluoromethylation of 2*H*-indazole mediated by peroxides (Scheme 1a).[25d] The C3−H functionalization of 2*H*-indazoles has few disadvantages such as use of transition-metal catalyst and peroxides and high temperature. Encouraged by the significant advances in the recent radical C−H functionalization,[26] our group initiated the research program on the C−H functionalization of indazoles.[27] Herein, we report a novel metal-free visible-light-promoted organic dye-catalyzed regioselective C3-trifluoromethylation of 2*H*-indazole. An initial

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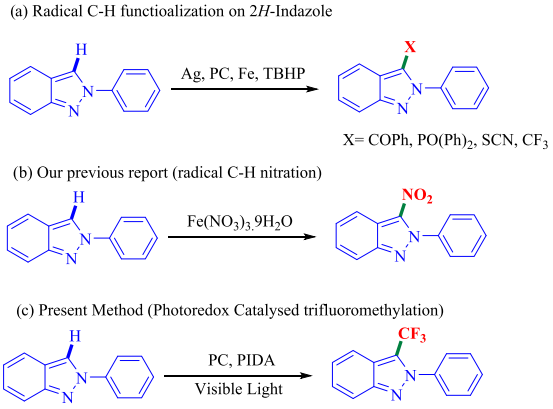
Scheme 1. Regioselective C3−H Functionalization of 2*H*-Indazole



version of this work was deposited in ChemRxiv on 5 March 2019.[28]

RESULTS AND DISCUSSION

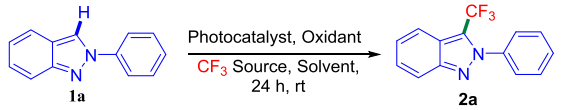
In the initial experiments, we have chosen 2-phenyl-2*H*-indazole as the model substrate, the Langlois reagent as radical CF_3 source, and phenyliodine(III) diacetate (PIDA) as an oxidant with 1 mol % rose bengal as a photocatalyst in MeCN and irradiated with a 60 W compact fluorescent bulb (CFL) at room temperature for 24 h. Delightfully, we observed C3-trifluoromethylated product **2a** with 60% yield (Table 1, entry 1). Then, the effect of other oxidants such as $K_2S_2O_8$, TBHP, IBA-OAc, and PhIO was examined (Table 1, entries 2−5). Unfortunately, our attempts failed. To improve the reaction efficiency in terms of yield, we have tested the various photocatalysts. Among all, methylene blue (Table 1, entry 12) was found to be effective photocatalyst and provided the desired product **2a** with 75% yield. Among the solvents screened (Table 1, entries 15−23), DCM was found to be the most efficient solvent for this strategy. To improve the yield, a variety of CF_3 sources were examined, but without much success (Table 1, entries 24−26).

With the established optimized reaction conditions (Table 1, entry 12), we have examined the scope of this protocol with various substitutions on 2*H*-indazoles (Table 2). Initially, we checked the halogen substitution on 2*H*-indazole (**2b−h**). The presence of halogen at C5 and C6 positions of 2*H*-indazoles (**2b−d**) gave poor yields. The halogen substituent at para position of the amine partner of 2*H*-indazoles (**2e−h**) gave 45−68% yields. Likewise, the amine partner of 2*H*-indazoles bearing electron-donating groups (−Me, −OMe) resulted in the products with very good yields (**2i−n,p**). This might be due to the increased electron density at C3 position of 2*H*-indazole. This observation was similar to our earlier report.[27a]

However, the electron-donating groups (−Me, −OMe) at ortho position (**2i, 2j**) gave moderate yields; this is due to the steric hindrance of the ortho substitution. We observed poor yield when the electron-withdrawing group was substituted on 2*H*-indazole (**2o**) because the electron density might be reduced at C3 position on 2*H*-indazole. In the case of benzylamine partner, the C3-H trifluoromethylated indazoles (**2r, 2s**) were obtained in low yield.

Due to the presence of 2*H*-indazole skeleton in various biologically relevant compounds, we have also evaluated the scalability of our protocol. Consequently, when we performed the reaction on 1 g scale, it produced the C3-trifluoromethylation of 2*H*-indazole **2a** with 69% yield (Scheme 2).

Table 1. Optimization of Reaction Conditions for the Synthesis of 2a[a]



entry	catalyst	oxidants	CF_3 Source	Solvent	yield (%)[b]
1	rose bengal	PIDA	$NaSO_2CF_3$	DCM	60
2	rose bengal	$K_2S_2O_8$	$NaSO_2CF_3$	DCM	n.d
3	rose bengal	TBHP	$NaSO_2CF_3$	DCM	n.d
4	rose bengal	IBA-OAc	$NaSO_2CF_3$	DCM	trace
5	rose bengal	PhIO	$NaSO_2CF_3$	DCM	trace
6	rose bengal		$NaSO_2CF_3$	DCM	n.d
7		PIDA	$NaSO_2CF_3$	DCM	trace
8	$Ru(bpy)_3Cl_2$	PIDA	$NaSO_2CF_3$	DCM	trace
9	$Ir(ppy)_3$	PIDA	$NaSO_2CF_3$	DCM	trace
10	eosin-Y	PIDA	$NaSO_2CF_3$	DCM	50
11	rhodamine B	PIDA	$NaSO_2CF_3$	DCM	trace
12	**methylene blue**	**PIDA**	$NaSO_2CF_3$	**DCM**	**75**
13	azure-B	PIDA	$NaSO_2CF_3$	DCM	55
14	riboflavin	PIDA	$NaSO_2CF_3$	DCM	trace
15	methylene blue	PIDA	$NaSO_2CF_3$	CH_3CN	30
16	methylene blue	PIDA	$NaSO_2CF_3$	DCE	50
17	methylene blue	PIDA	$NaSO_2CF_3$	acetone	trace
18	methylene blue	PIDA	$NaSO_2CF_3$	DMSO	n.d
19	methylene blue	PIDA	$NaSO_2CF_3$	toluene	n.d
20	methylene blue	PIDA	$NaSO_2CF_3$	MeOH	n.d
21	methylene blue	PIDA	$NaSO_2CF_3$	EtOH	n.d
22	methylene blue	PIDA	$NaSO_2CF_3$	dioxane	n.d
23	methylene blue	PIDA	$NaSO_2CF_3$	DMF	n.d
24	methylene blue	PIDA	$TMSCF_3$	DCM	n.d
25	methylene blue	PIDA	ICH_2CF_3	DCM	n.d
26	methylene blue	PIDA	CF_3SO_2Cl	DCM	n.d

[a]Reaction conditions: **1a** (1 mmol), methylene blue (1 mol %), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24 h. [b]Isolated yield of chromatographically pure products. n.d = not detected.

To investigate the reaction mechanism, we performed few control experiments, as shown in Scheme 3. We observed that 2-phenyl-2*H*-indazole **1a** failed to produce the corresponding trifluoromethylation product **2a** in the presence of radical scavengers such as TEMPO, BHT, and BQ. Also, we observed the intermediate **C** and TEMPO-CF_3 adduct in ^{19}F NMR. These results indicate that the reaction mechanism proceeded through the radical pathway, as depicted in Scheme 4. Moreover, we have performed NMR experiments to confirm intermediates; however, we did not observe the peaks corresponding to any hypervalent iodine complexes other than iodobenzene peaks in NMR spectra. In addition, we measured the redox potentials for the 2*H*-indazole **1a** (E_{red} = −0.71 V vs Ag/AgCl), the Langlois reagent (E_{red} = −1.39 V vs Ag/AgCl), photocatalyst (**PC**) (E_{red} = −1.74 V vs Ag/AgCl) using cyclic voltammetry (see SI), and reduction potential for excited-state photocatalyst (**PC***) (E_{red} = 1.60 V vs Ag/AgCl).[29] The reduction potentials of 2*H*-indazole and excited-state photocatalyst (**PC***) clearly signify that 2*H*-indazole **1a** has the potential to transfer a single electron to excited-state photocatalyst (**PC***), thus supporting the proposed mechanism.

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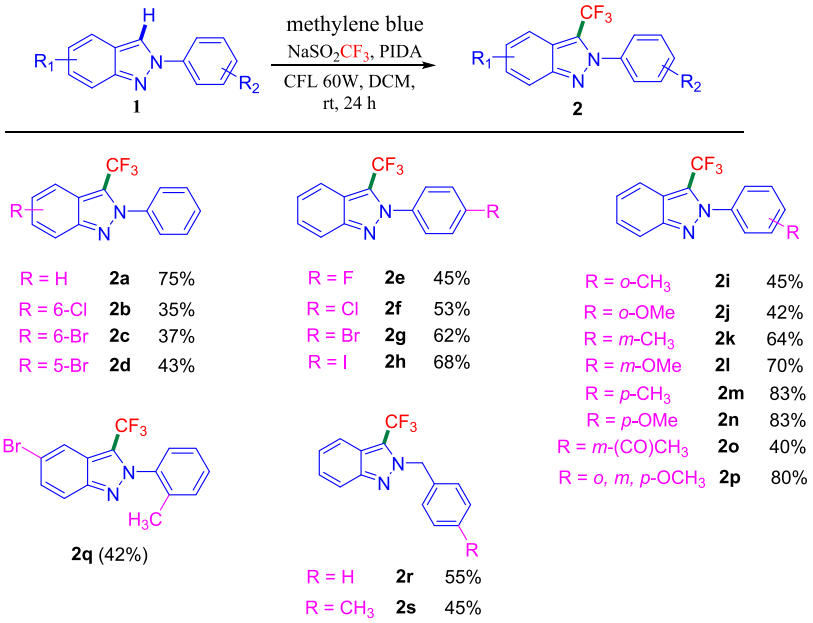
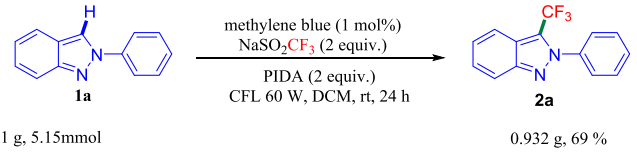
Table 2. Substrate Scope for the C3-Trifluoromethylation of 2*H*-Indazole[a,b]

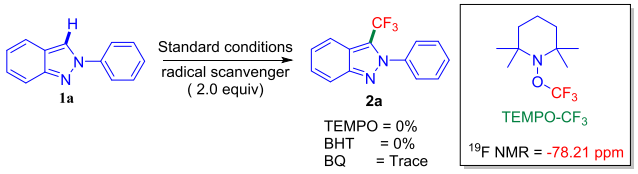


[a]Reaction conditions: **1a** (1 mmol), methylene blue (1 mol %), PIDA (2 mmol), $NaSO_2CF_3$ (2 mmol), DCM (1 mL), 60 W CFL blub, rt, 24 h. [b]Isolated yield of chromatographically pure products.

Scheme 2. Gram-Scale Synthesis of 2-Phenyl-3-(trifluoromethyl)-2*H*-indazole 2a



Scheme 3. Control Experiments



Based on the control experiment results and the literature reports,[27] a plausible reaction mechanism of the present trifluoromethylation of 2-phenyl-2*H*-indazole is depicted in Scheme 4. Initially, the CF_3 radical species would be generated by the reaction of $NaSO_2CF_3$ (**B**) with PIDA (**A**) via intermediate **C**. Meanwhile, the photocatalyst (**PC**) converted to its excited-state **PC*** upon the absorption of photons from visible light. The **PC*** produces the indazole radical cation **D** from the oxidation of indazole along with the generation of photocatalytic radical anion $\mathbf{PC}^{\bullet-}$ through single electron-transfer (SET) process. After that, the photocatalyst radical anion ($\mathbf{PC}^{\bullet-}$) is oxidized to **PC** by reducing acetate radical to acetate anion. Then, the generated CF_3 radical would attack intermediate **D** to form intermediate **E**, which on deprotonation would result in trifluoromethylation product **2a**.

CONCLUSIONS

We have successfully demonstrated a novel photoredox-catalyzed regioselective C3−H trifluoromethylation of 2*H*-indazoles. This protocol offers the transition-metal-free photoredox-catalyzed C3-H trifluoromethylation of 2*H*-indazole. This method utilizes an inexpensive and benchtop-stable Langlois reagent under mild reaction conditions. Further, the developed protocol for regioselective trifluoromethylation of 2*H*-indazole would be of great significance in pharmaceutical chemistry and material sciences.

EXPERIMENTAL SECTION

General Considerations. IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at 295 K in $CDCl_3$; the chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion concerning either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of the triplet)]. In the ^{1}H NMR spectra, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet, and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using a Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. All dry solvents were used, toluene was dried over sodium metal, and DMSO, CH_3CN, and DMF were dried over commercially available calcium hydride.

All small-scale dry reactions were carried out using a standard syringe septum technique. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon, nitrogen, and oxygen atmosphere wherever necessary. Solvents were distilled before use, and petroleum ether with a boiling range of 40−60 °C was used. Acme's silica gel (60−120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material). All 2-azidobenzaldehydes (**A**−**B** and **C**) except **D** have been synthesized by using literature procedures.[30,27c]

General Procedure (GP-I) for the Synthesis of 2-Phenyl-2*H*-indazole.[27f] Azidobenzaldehyde **1** (1 mmol) and aniline **2** (1 mmol) were taken in a 10 mL oven-dried Schlenck tube, which was closed with stopcock with argon balloon and placed in an external heating oil

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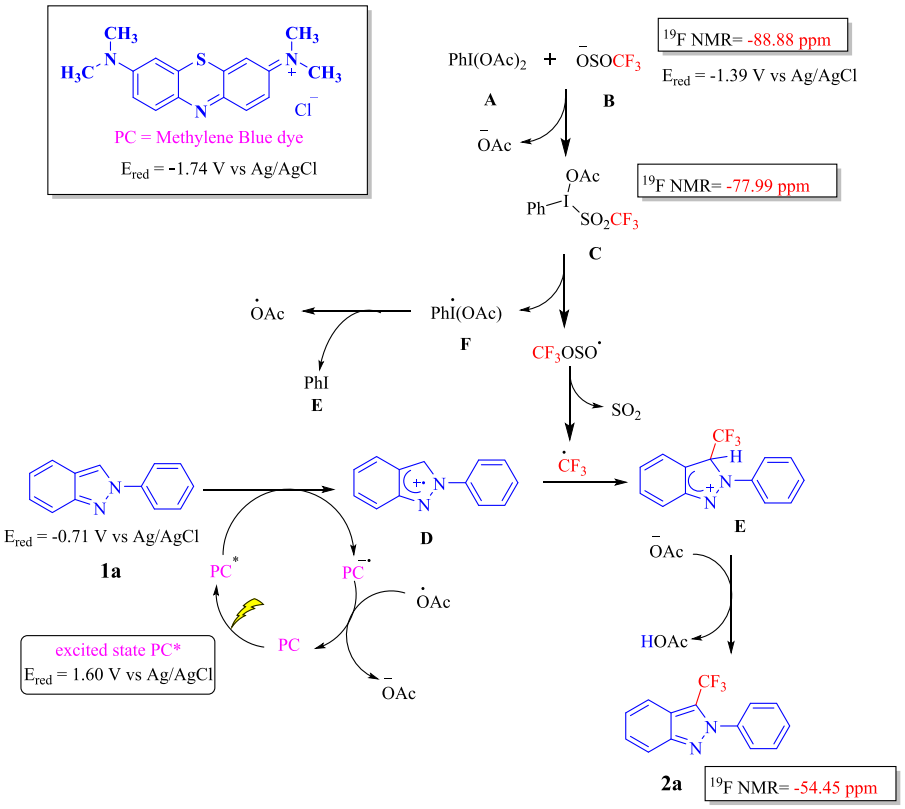
Scheme 4. Plausible Reaction Mechanism



bath at 120 °C for 1−3 h (oil bath temperature). After completion of the starting material, the mixture was cooled to room temperature and was purified on a silica gel chromatography column (hexane/ethyl acetate, 90:10), which furnished the respective products **1a−s**.

General Procedure (GP-II) for the Synthesis of 2-Phenyl-3-(trifluoromethyl)-2*H*-indazole. In an oven-dried reaction vessel charged with 2-phenyl-2*H*-indazole (1 mmol), methylene blue (1 mol %), PIDA (2 mmol) and sodium triflate (2 mmol) were added, followed by addition of DCM (1 mL). The resulting reaction mixture was irradiated using a 60 W CFL bulb. The progress of the reaction was monitored by TLC until the reaction was complete. The reaction mixture was quenched by addition of aq. NH_4Cl solution and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as (petroleum ether/ethyl acetate, 97:3−95:5) eluent furnished the product trifluoromethylated indazoles **2a−s**.

*Characterization Data of the Products. 2-Phenyl-3-(trifluoromethyl)-2H-indazole (**2a**).* Dark yellow solid (50 mg, 75%), mp 40−42 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3736, 3673, 3613, 3565, 3032, 2968, 2381, 1734, 1700, 1650, 1556, 1540, 1521, 1508, 1458, 1420, 1218, 1120, 940, 757, 667, 631; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.79−7.87 (m, 2H), 7.52−7.63 (m, 5H), 7.39−7.45 (m, 1H), 7.28−7.34 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 148.2, 139.6, 130.0, 29.1, 127.3, 126.1, 125.1, 123.5 (q, J_{C-F} = 40.0 Hz), 121.3 (q, J_{C-F} = 269.0 Hz), 119.4, 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $[C_{14}H_{10}F_3N_2]^+$ = 263.0791; found: 263.0794.

*6-Chloro-2-phenyl-3-(trifluoromethyl)-2H-indazole (**2b**).* Dark orange solid (29 mg, 35%), mp 44−46 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3613, 3565, 3525, 3068, 2926, 2854, 2355, 1695, 1634, 1596, 1549, 1502, 1470, 1439, 1314, 1290, 1222, 1178, 1126, 1104, 999, 768, 691, 621, 544; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.73 (d, 1H, *J* = 8.8 Hz), 7.56−7.41 (m, 5H), 7.34 (s, 1H), 6.95−6.87 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.6, 139.3, 135.5, 129.8 (q, J_{C-F} = 36.0 Hz), 127.7, 126.0, 121.4 (q, J_{C-F} = 252.0 Hz), 119.4, 119.3, 105.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.7; HR-MS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $[C_{14}H_9ClF_3N_2]^+$ = 297.0401; found: 297.0408.

*6-Bromo-2-phenyl-3-(trifluoromethyl)-2H-indazole (**2c**).* Yellow solid (27 mg, 37%), mp 42−44 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04−7.98 (m, 1H), 7.71 (dd, 1H, J_a = 1.5 and J_b = 9.8 Hz), 7.62−7.51 (m, 5H), 7.38 (dd, 1H, J_a = 1.7 and J_b = 9.0 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.7, 139.2, 129.8 (q, J_{C-F} = 42.0 Hz), 128.9, 126.0, 121.9 (q, J_{C-F} = 268.0 Hz), 120.7, 120.0, 119.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.7; HR-MS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9914.

*5-Bromo-2-phenyl-3-(trifluoromethyl)-2H-indazole (**2d**).* Dark yellow solid (31 mg, 43%), mp 52−54 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3648, 3588, 3547, 3070, 2924, 2321, 1735, 1596, 1502, 1420, 1271, 1216, 1169, 1124, 1107, 1043, 996, 861, 804, 768, 692, 634, 596; ^1H NMR ($CDCl_3$, 400 MHz) δ_H = 8.01 (s, 1H), 7.70 (d, 1H, *J* = 9.3 Hz), 7.62−7.50 (m, 4H), 7.50−7.42 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 146.6, 139.3, 137.9, 132.5, 129.8 (q, J_{C-F} = 36.0 Hz), 124.6, 123.0, 122.6, 121.9 (q, J_{C-F} = 248.0 Hz), 120.1, 118.6, 116.5, 112.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.6; HR-MS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9900.

*2-(4-Fluorophenyl)-3-(trifluoromethyl)-2H-indazole (**2e**).* Yellow solid (50 mg, 45%), mp 52−54 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3689, 3620, 3568, 3036, 2938, 2321, 1717, 1540, 1502, 1454, 1252, 1216, 1156, 1118, 1107, 1032, 987, 861, 767, 659, 631; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86−7.75 (m, 2H), 7.62−7.53 (m, 2H), 7.45−7.39 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and J_b = 8.3 Hz,), 7.26−7.21 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 164.5 (d, J_{C-F} = 249.0 Hz), 149.7, 148.2, 135.6 (d, J_{C-F} = 2.0 Hz), 128.1 (d, J_{C-F} = 9.0 Hz), 127.4, 125.5, 123.6 (q, J_{C-F} = 40.0 Hz), 121.5, 121.0 (q, J_{C-F} = 268.0 Hz), 119.4, 118.4, 116.5 (d, J_{C-F} = 24.0 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5, −110.2; HR-MS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $[C_{14}H_9F_4N_2]^+$ = 281.0696; found: 281.0690.

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*2-(4-Chlorophenyl)-3-(trifluoromethyl)-2H-indazole (**2f**).* Dark yellow solid (35 mg, 53%), mp 46−48 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3613, 3547, 3068, 2317, 2089, 1552, 1522, 1498, 1432, 1298, 1220, 1176, 1118, 1089, 1017, 998, 929, 832, 746, 728, 583, 537; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.76−7.68 (m, 2H), 7.49−7.39 (m, 4H), 7.34−7.29 (m, 1H), 7.24−7.17 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.0, 136.1, 129.8 (q, $J_{C\text{-}F}$ = 47.0 Hz), 127.5, 127.4, 125.7, 123.9, 122.3, 122.2, 121.7, 119.9 (q, $J_{C\text{-}F}$ = 231.0 Hz), 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{14}H_9ClF_3N_2]^+$ = 297.0401; found: 297.0401.

*2-(4-Bromophenyl)-3-(trifluoromethyl)-2H-indazole (**2g**).* Dark yellow (45 mg, 62%), mp 44−46 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3613, 3547, 3068, 1521, 1495, 1432, 1298, 1222, 1176, 1119, 1099, 1068, 1015, 996, 929, 829, 743, 711, 576, 535; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.84−7.78 (m, 2H), 7.70−7.64 (m, 2H), 7.46 (d, 2H, *J* = 8.3 Hz), 7.43−7.37 (m, 1H), 7.31−7.25 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 138.6, 132.8 (q, $J_{C\text{-}F}$ = 43.0 Hz), 127.8, 127.6, 125.3, 124.2, 123.9, 122.5 (q, $J_{C\text{-}F}$ = 223.0 Hz), 119.4, 118.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{14}H_9BrF_3N_2]^+$ = 340.9896; found: 340.9900.

*2-(4-Iodophenyl)-3-(trifluoromethyl)-2H-indazole (**2h**).* Light yellow (40 mg, 68%), mp 100−102 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3736, 3547, 3462, 3032, 2917, 2356, 2154, 1716, 1683, 1556, 1540, 1509, 1362, 1257, 999, 821, 800, 740, 521; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.94−7.86 (m, 2H), 7.85−7.78 (m, 2H), 7.45−7.38 (m, 1H), 7.38−7.28 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.4, 139.3, 138.8 (q, $J_{C\text{-}F}$ = 43.0 Hz), 127.7, 125.3, 123.8, 122.7, 122.2, 121.7, 119.5 (q, $J_{C\text{-}F}$ = 224.0 Hz), 118.4, 95.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{14}H_9F_3IN_2]^+$ = 388.9757; found: 388.9756.

*2-(o-Tolyl)-3-(trifluoromethyl)-2H-indazole (**2i**).* Dark yellow solid (30 mg, 45%), mp 52−54 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} =3057, 2927, 1603, 1564, 1501, 1386, 1337, 1306, 1158, 1114, 1039, 969, 957, 863, 810, 751, 716, 663, 605, 573; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.90−7.78 (m, 2H), 7.51−7.28 (m, 6H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.1, 139.6, 138.3, 137.1, 135.8, 130.5, 127.3 (q, $J_{C\text{-}F}$ = 36.0 Hz), 125.0, 122.1, 119.4 (q, $J_{C\text{-}F}$ = 228.0 Hz), 116.0, 114.9, 16.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −56.2; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0952.

*2-(2-Methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (**2j**).* Yellow solid (27 mg, 42%), mp 40−42 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3614, 3525, 2930, 2846, 2316, 1603, 1510, 1437, 1335, 1283, 1202, 1120, 1093, 1021, 966, 804, 753, 653, 603; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.03 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.53 (dt, J_a = 1.7 and J_b = 7.9 Hz, 1H), 7.44 (dd, J_a = 1.5 and J_b = 7.8 Hz, 1H), 7.38−7.32 (m, 1H), 7.13−7.04 (m, 2H), 3.74 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ =154.8, 143.5, 132.0, 128.7, 127.9 (q, $J_{C\text{-}F}$ = 42.0 Hz), 125.3, 124.8, 123.9, 123.2, 121.8 (q, $J_{C\text{-}F}$ = 267.0 Hz), 119.0, 112.0, 55.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.3; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0901.

*2-(m-Tolyl)-3-(trifluoromethyl)-2H-indazole (**2k**).* Brown oil (43 mg, 64%). IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3648, 3565, 3525, 3065, 2924, 2322, 1611, 1592, 1495, 1476, 1431, 1302, 1221, 1202, 1169, 1118, 1016, 880, 787, 745, 693, 693, 627, 605, 521; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.74 (d, 2H *J* = 8.8 Hz), 7.39−7.24 (m, 5H), 7.20 (dd, 1H, J_a = 7.8 and J_b = 15.2 Hz), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.2, 139.3, 130.7, 129.5, 128.8, 127.1, 126.7, 125.3, 123.1 (q, $J_{C\text{-}F}$ = 44.0 Hz), 119.6 (q, $J_{C\text{-}F}$ = 250.0 Hz), 118.3, 21.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.2; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0960.

*2-(3-Methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (**2l**).* Brownish yellow solid (53 mg, 80%), mp 74−76 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3614, 3547, 2925, 2846, 2323, 2134, 1734, 1593, 1498, 1468, 1288, 1250, 1201, 1163, 1122, 1044, 976, 885, 755, 688, 521; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.04 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.45 (t, *J* = 8.3 Hz, 1H), 7.40−7.32 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.15−7.08 (m, 2H), 3.87 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 160.0, 143.4, 140.0, 129.9, 125.6 (q, $J_{C\text{-}F}$ = 40.0 Hz), 123.7, 122.4, 122.1 (q, $J_{C\text{-}F}$ = 268.0 Hz), 118.5, 116.4, 112.0, 55.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.7; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0901.

*2-(p-Tolyl)-3-(trifluoromethyl)-2H-indazole (**2m**).* Yellow solid (50 mg, 83%), mp 42−44 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3614, 3043, 2925, 2324,1553, 1515, 1471, 1431, 1383, 1298, 1219, 1174, 1117, 1100, 999, 930, 820, 745, 610, 547; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.86−7.78 (m, 2H), 7.50−7.42 (m, 2H), 7.42−7.36 (m, 1H), 7.36−7.25 (m, 3H), 2.48−2.44 (m, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 148.1, 140.2, 137.2, 130.2, 128.2, 127.1, 125.9 (q, $J_{C\text{-}F}$ = 39.0 Hz), 123.8, 122.3, 121.5 (q, $J_{C\text{-}F}$ = 267.0 Hz), 119.6, 118.4, 21.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0948.

*2-(4-Methoxyphenyl)-3-(trifluoromethyl)-2H-indazole (**2n**).* Yellow solid (53 mg, 83%), mp 74−76 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 2969, 2887, 2839, 2303, 2043, 1608, 1513, 1433, 1299, 1252, 1175, 11148, 1030, 1015, 998, 928, 834, 736, 703, 611, 557, 536; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.85−7.79 (m, 2H), 7.53−7.47 (m, 2H), 7.43−7.37 (m, 1H), 7.32−7.24 (m, 1H), 7.07−6.99 (m, 2H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 160.6, 148.0, 132.5, 127.4 (q, $J_{C\text{-}F}$ = 39.0 Hz), 124.9, 123.5, 122.7, 122.3, 121.4, 119.6 (q, $J_{C\text{-}F}$ = 244.0 Hz), 114.8, 55.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.6; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2O]^+$ = 293.0896; found: 293.0891.

*1-(3-(3-(Trifluoromethyl)-2H-indazol-2-yl)phenyl)ethanone (**2o**).* Light brown solid (25 mg, 40%), mp 74−76 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3648, 3589, 3504, 3074, 2925, 2323, 1716, 1690, 1589, 1522, 1493, 1430, 1359, 1302, 1256, 1222, 1178, 1149, 1012, 748, 691, 587, 562; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.23−8.12 (m, 2H), 7.88−7.76 (m, 3H), 7.72−7.64 (m, 1H), 7.47−7.40 (m, 1H), 7.36−7.29 (m, 1H), 2.66 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 196.4, 148.4, 140.0, 138.0, 130.3, 129.5, 128.2, 127.6, 126.1, 125.4, 123.6 (q, $J_{C\text{-}F}$ = 40.0 Hz), 120.5, 119.5 (q, $J_{C\text{-}F}$ = 209.0 Hz), 118.4, 26.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.2; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{16}H_{12}F_3N_2O]^+$ = 305.0896; found: 305.0914.

*3-(Trifluoromethyl)-2-(3,4,5-trimethoxyphenyl)-2H-indazole (**2p**).* Yellow solid (48 mg, 78%), mp 126−128 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3648, 3565, 2971, 2881, 2835, 1596, 1556, 1505, 1462, 1415, 1307, 1265, 1233, 1170, 1125, 1106, 1016, 945, 897, 837, 794, 733, 702, 613; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.87−7.78 (m, 2H), 7.46−7.38 (m, 1H), 7.31 (dd, 1H, J_a = 6.8 and J_b = 8.3 Hz,), 6.83 (s, 2 H), 3.93 (s, 3H), 3.90 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ_H = 153.2, 148.0, 139.3, 134.9, 127.3, 125.1 (q, $J_{C\text{-}F}$ = 42.0 Hz), 121.5, 119.6 (q, $J_{C\text{-}F}$ = 215.0 Hz), 03.8, 61.0, 56.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{17}H_{16}F_3N_2O_3]^+$ = 353.1108; found: 353.1104.

*6-Bromo-2-(o-tolyl)-3-(trifluoromethyl)-2H-indazole (**2q**).* Pale yellow solid (48 mg, 78%), mp 82−84 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 2116, 2032, 1596, 1540, 1502, 1462, 1432, 1305, 1220, 1179, 1127, 1106, 998, 934, 798, 768, 692, 571, 515; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.00 (d, 1H, *J* = 1.0 Hz), 7.88−7.79 (m, 1H), 7.77−7.70 (m, 1H), 7.67 (d, 1H, *J* = 7.8 Hz), 7.40−7.27 (m, 3H), 2.63 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 158.3, 150.9, 148.8, 138.9, 129.1, 124.8 (q, $J_{C\text{-}F}$ = 44.0 Hz), 122.1, 121.7 (q, $J_{C\text{-}F}$ = 246.0 Hz), 120.9, 119.4, 115.6, 23.9; ^{19}F NMR ($CDCl_3$, 376 MHz): −54.5; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{11}BrF_3N_2]^+ = [M + H]^+$: 355.0052; found: 355.0063.

*2-Benzyl-3-(trifluoromethyl)-2H-indazole (**2r**).* Yellow solid (29 mg, 55%), mp 42−44 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} =3673, 3614, 3547, 3067, 3035, 2926, 2323, 1521, 1483, 1436, 1327, 1286, 1219, 1165, 1112, 1036, 970, 881, 746, 706, 627; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.82−7.72 (m, 2H), 7.39−7.19 (m, 7H), 5.73 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ_H = 147.8, 135.2, 128.9 (q, $J_{C\text{-}F}$ = 42.0 Hz), 127.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.7, 124.7, 123.7

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(q, J_{C-F} = 207.0 Hz), 121.2, 120.0, 119.2, 118.3, 56.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −55.8; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{15}H_{12}F_3N_2]^+$ = 277.0947; found: 277.0943.

*2-(4-Methylbenzyl)-3-(trifluoromethyl)-2H-indazole (**2s**).* Brown solid (29 mg, 45%), mp 90−92 °C; IR (MIR-ATR, 4000−600 cm^{-1}): υ_{max} = 3673, 3648, 3613, 2925, 2858, 2359, 1717, 1969, 1622, 1539, 1511, 1475, 1433, 1385, 1337, 1305, 1201, 1160, 1123, 1015, 967, 813, 749, 689, 608; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 7.73−7.63 (m, 2H), 7.26 (ddd, 1H, J_a = 1.2, J_b = 7.0 and J_c = 8.4 Hz), 7.20−7.00 (m, 5H), 5.61 (s, 2H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ = 147.8, 138.2, 132.2, 129.4 (q, J_{C-F} = 44.0 Hz), 127.7 (q, J_{C-F} = 9.0 Hz), 124.6, 122.6, 121.2 (q, J_{C-F} = 266.0 Hz), 119.2, 118.3, 56.1, 21.1; ^{19}F NMR ($CDCl_3$, 376 MHz): −55.8; HR-MS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $[C_{16}H_{14}F_3N_2]^+$ = 291.1104; found: 291.1110.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00676.

Cyclic voltammetry data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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