# Electrochemically Promoted Regioselective C3─H Trifluoromethylation of *2H*-Indazoles

A Thesis

Submitted to

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fulfillment of the requirements for the MSc Programme

By

**Ajit Kumar Sahu**

**Indian Institute of Science Education and Research Pune**
**Dr. Homi Bhabha Road,**
**Pashan, Pune 411008, INDIA.**

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**Supervisor: Prof. Ramakrishna G. Bhat**

# Certificate

This is to certify that this dissertation entitled "**Electrochemically Promoted Regioselective C3─H Trifluoromethylation of 2*H*-Indazoles***"* towards the partial fulfillment of the MSc program at the Indian Institute of Science Education and Research, Pune represents work carried out by **Ajit Kumar Sahu** at Indian Institute of Science Education and Research under the supervision of **Prof. Ramakrishna G. Bhat**, Department of Chemistry, during the academic year 2023-2024.

**Prof. Ramakrishna G. Bhat**

Committee:

Prof. Ramakrishna G. Bhat

Dr. Boopathy Gnanaprakasam

“This thesis is dedicated to…

my family and friends”

# Declaration

I hereby declare that the matter embodied in the report entitled “**Electrochemically Promoted Regioselective C3─H Trifluoromethylation of 2*H*-Indazoles**” are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Science Education & Research (IISER) Pune, under the supervision of **Prof. Ramakrishna G. Bhat** and the same has not been submitted elsewhere for any other degree. Wherever others contribute, every effort is made to indicate this clearly, with due reference to the literature and acknowledgment of collaborative research and discussions.

Ajit Kumar Sahu.

**Ajit Kumar Sahu**

Roll: 20226205

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**Ajit Kumar Sahu**

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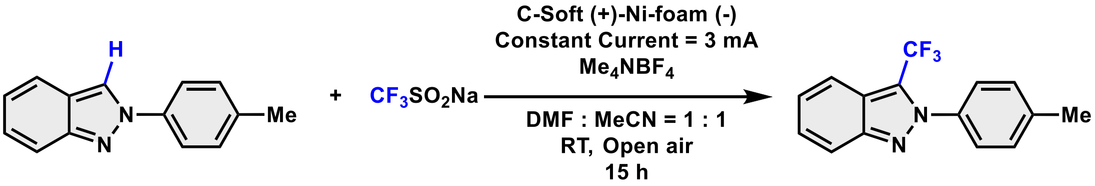
# ABSTRACT

Trifluoromethyl-substituted heterocyclic compounds are an essential class of organofluorocompounds with significant applications in agriculture, medicine, and organic synthesis. As a result, an array of techniques using a variety of radical, nucleophilic, and electrophilic trifluoromethylating agents have been devised. In previous methodologies, expensive transition metal catalysts were employed, along with the use of oxidants in stoichiometric amounts, and carried out at elevated temperatures. In this thesis, a green and sustainable approach having oxidant-free and transition metal-free conditions has been outlined for the electrochemically activated regioselective C3─H trifluoromethylation of 2*H*-indazoles, using $CF_3SO_2Na$ as the trifluoromethyl source. A diverse library of trifluoromethylated products incorporating an array of functionalities has been successfully synthesized in moderate to good yields. A plausible reaction mechanism has been proposed based on control experiment and cyclic voltammetry experiment.



## 1. INTRODUCTION

In the past decade, organic electrosynthesis has gained recognition as a technique capable of meeting several crucial criteria necessary for developing environmentally sustainable processes in society.[1] Electro-organic synthesis is a robust method based on redox principles, utilizing electrical current and electrodes as the leading agents in reactions.[2] This current, constituted by the movement of electrons, represents a sustainable reagent for facilitating oxidation and reduction processes at the electrode surface.[3-5] In an organic electrochemical process, organic molecules undergo activation through the addition or removal of electrons at the electrode surface via a heterogeneous process.[2] The electrodes play a pivotal role in these transformations, constituting heterogeneous chemical interaction between a substrate in a liquid electrolyte setting and an electrode surface that is usually solid. This electrolyte system typically comprises supporting electrolytes and a chemically inert solvent, which enhances the conductivity of electricity.[2] The supporting electrolyte, which could be an acid, base, or salt, aids in establishing an electrochemical double layer on the surface of the electrode.[2] Oxidation reactions involve the loss of an electron from the substrate and are referred to as anodic conversions and occur at the anode, while the reduction reactions involve the addition of an electron to the substrate through a single electron transfer (SET) process and are referred to as cathodic conversions which occur at the cathode.[2]

In an electrochemical configuration, a power source is connected to a reaction mixture via an electrode, facilitating electron transfer with the substrate molecule to produce reactive intermediates for subsequent functionalizations. This electrode is termed as the working electrode. An additional electrode, referred to as the counter electrode, is needed to connect the reaction to the other end of the power source in order to complete the circuit. An anode or a cathode may serve as the working electrode, depending on where the reaction with the substrate occurs. Consequently, in anodic oxidation, oxidation occurs at the working electrode while reduction occurs at the cathode, since at the anode, electrons are donated by the substrate; it circulates through the circuit to cathodically reduce protons, solvent molecules, and other species. Thus, every electrochemical reaction can be understood as the result of the conjunction of two half-reactions. An undivided cell, consisting of the working and counter electrodes, is the simplest configuration where electrodes are housed within the same chamber (an undivided cell), circumstances may arise where high-energy intermediates produced at the working anode are prematurely reduced at the cathode and vice versa. This challenge can be addressed using divided cells, in which the anodic and cathodic chambers are separated by a salt bridge or a partially permeable membrane.[6]

The first electro-organic transformation was carried out by Michael Faraday in the 1830s which includes the electrolysis of acetic acid.[7] The first electrochemical oxidation was reported by Kolbe in 1847 (*Kolbe electrolysis*), which involves the electrolysis of carboxylic acids or their salts at the anode to produce alkyl radicals, then subsequently undergo dimerization or other reactions, leading to the formation of beneficial organic compounds.[8] This method has found wide applications in organic synthesis, particularly for the production of various hydrocarbons and derivatives. In 1845, the dehalogenation of trichloromethane sulfonic acid, reported by Schoebein, was the first electrochemical reduction.[9] The Tafel rearrangement for the preparation of hydrocarbons, a widely recognized cathodic reduction method, was developed in 1907.[10]

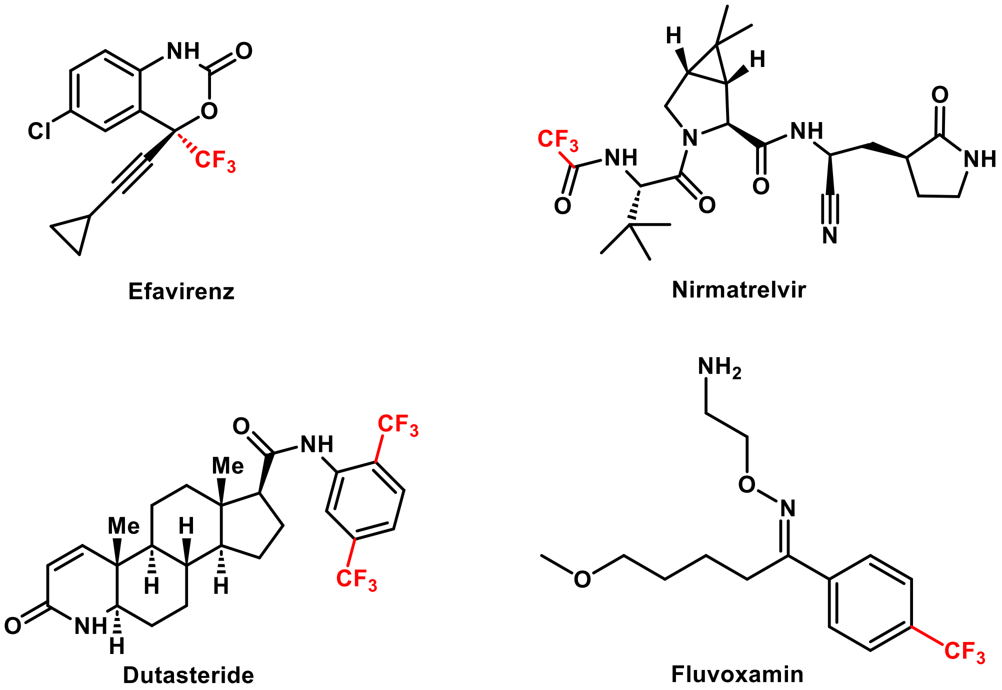
## 1.1. C–H Functionalization

C−H functionalization reactions offer significant potential for streamlining synthetic routes by eliminating the need for pre-functionalization of both coupling partners. This feature has the potential to decrease the number of synthetic steps, which would enhance the overall atom economy of chemical reactions. However, achieving selective cleavage of unactivated C−H bonds poses a significant challenge in the field of organic synthesis. To overcome this challenge, researchers often resort to the use of precious metal catalysts in substantial loadings, stoichiometric metal-based oxidants, elevated temperatures, and manipulations of directing groups. These strategies facilitate the functionalization of specific C−H bonds and promote the desired transformations. Despite these endeavours, attaining high selectivity and efficiency in C−H functionalization reactions continues to be a subject of ongoing and rather challenging scholarly investigation. The reliance on precious metal catalysts, high temperatures, and other demanding conditions can limit the scalability, cost-effectiveness, and environmental sustainability of C−H functionalization processes.

Therefore, ongoing research efforts aim to develop more efficient, selective, and sustainable methods for C−H functionalization, with the goal of enabling practical applications in synthetic chemistry.[11]

Indeed, electrochemical methods represent a sustainable and elegant approach to organic synthesis. They offer several advantages over traditional chemical methods, making them a green alternative in many synthetic routes. Electrochemical methods operate under benign conditions, typically at ambient temperature and atmospheric pressure, reducing energy consumption and minimizing environmental impact.[12] They often exhibit high efficiency and selectivity, allowing precise control over reaction pathways and product formation. This can lead to reduced waste and improved overall yields.[13] Electrochemical synthesis can bypass the formation of unstable intermediates, thereby reducing the risk of side reactions and enhancing the safety profile of the process.[14] By harnessing electricity as the driving force for chemical transformations, electrochemical methods can eliminate the need for hazardous reagents and byproducts, resulting in safer and cleaner synthetic processes. The use of electrochemical methods in organic synthesis represents a promising strategy for achieving sustainable and environmentally friendly chemical transformations, with potential applications across various industries, including pharmaceuticals, materials science, and fine chemicals manufacturing. Fluorine is the smallest substituent capable of replacing hydrogen, and the C−F bond has long been regarded as an excellent surrogate for the C−H bond, with minimal steric effects.[15] A direct fluorination of the parent molecule stands as a straightforward method for synthesizing organofluorine compounds. However, an alternative strategy involves incorporating small polyfluorinated units, such as trifluoromethyl ($-CF_3$) and difluoromethyl ($-CHF_2$) groups, into the core structure.[16]

Among the various fluorine-containing groups, such as the trifluoromethyl group holds particular significance in organic synthesis. It shows very strong electron-withdrawing properties and its inclusion in any target molecule will improve its physical and chemical properties.[17] Trifluoromethyl groups possess unique electronic structures and reactivity compared to alkyl groups like methyl. With an electronegativity analogous to chlorine, which has an electronegativity value of 3.2 and is comparable in size to an isopropyl (*i*-Pr) group, $CF_3$ differs significantly.[18] For instance, fluvoxamine, which performs as an antidepressant, and nirmatrelvir/ritonavir, which is sold under the name of Paxlovid, have proven to be pivotal in the antiviral treatment of COVID-19. Some drugs containing the $CF_3$ group are shown in Figure 1.



**Efavirenz** **Nirmatrelvir** **Dutasteride** **Fluvoxamin**

**Figure 1.** Some drugs containing trifluoromethyl group.

Trifluoromethyl-substituted heterocyclic compounds represent a vital class of organofluorocompounds, holding significant importance in organic synthesis, medicine, and agriculture.[19] Heterocyclic scaffolds hold a distinctive position in both natural product chemistry and synthetic organic chemistry. Serving as precursors to numerous biologically active compounds, their significance has led to a considerable emphasis on developing methods to functionalize these systems. Indazole is one of the many heterocyclic chemicals with significant biological effects, and its derivatives demonstrate a broad variety of biological functions, including antiviral, antimicrobial, anti-tumour, anticancer, anti-inflammatory, anticonvulsant, and many other properties.[20] Indazole can act as a bioisostere of other aromatic heterocycles such as benzimidazole, benzotriazole, and indole.[21] Indazole-containing compounds can interact with various biological targets, including enzymes, receptors, and ion channels. For example, indazole derivatives have been developed as kinase inhibitors for cancer treatment and other diseases.[22] This versatility makes indazole scaffolds valuable in drug discovery and development. Indazole, initially described by noble laureate Hermann Emil Fisher as a "pyrazole ring fused with the benzene ring," has been subject to extensive study, given its intriguing biological and chemical characteristics. Belonging to the family of azoles, indazole consists of carbon, hydrogen, and nitrogen atoms. Also referred to as isoindazolone or benzpyrazole, it belongs to a class of heterocyclic chemical compounds that have two nitrogen atoms. With an aromatic heterocyclic system due to the presence of 10 π-electrons which is analogous to the pyrazole molecule, indazole shares similarities with pyridine and pyrrole.[23] Indazole derivatives hold pharmacological significance as they serve as the foundational structure for various drug molecules. For instance, Granisetron, a $5HT_3$ receptor antagonist, is utilized as an anti-emetic in cancer.[23]

**Axitinib**

**Pazopanib hydrochloride**

**Neuroprotective sodium channel modulator**

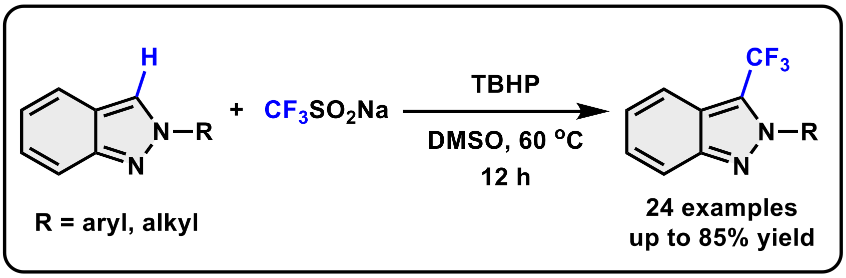
**Highly selective ligand for the ERβ**

**Figure 2.** Some drugs containing indazole moiety

Drugs such as axitinib and pazopanib hydrochloride (Figure 2) contain indazole in their skeleton structure and are used as anti-cancer drugs for treating renal cell carcinoma.[24] The drug granisetron is used to aid chemotherapeutic vomiting.[25a] C3-substituted indazoles are also utilized as a very specific ligand for estrogen receptor β (ERβ), as shown in Figure 3.25b. Numerous methods have been developed for producing indazole moieties.[26] However, a limited number of approaches are available for the functionalization of indazoles.[27]

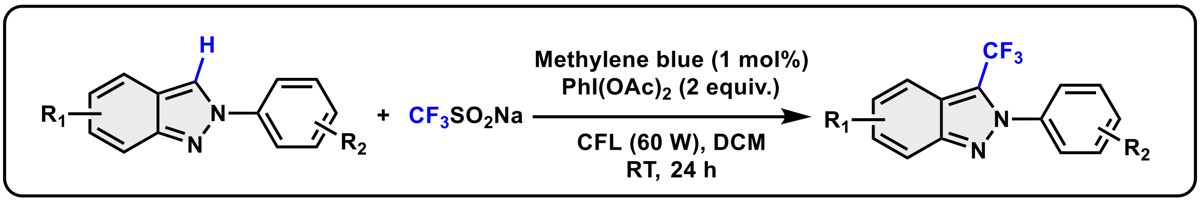
## 1.2. Previous reports on trifluoromethylation of 2*H*-indazole:

In 2018, Hajra and coworkers reported a method for trifluoromethylation of 2*H*-indazole with moderate to high yields, where tert-butyl hydroperoxide (TBHP) is used as the oxidant and $CF_3SO_2Na$ as the trifluoromethyl source. They reacted 2-phenyl-2*H*-indazole with sodium trifluoromethane sulfinate (Langlois' reagent), and tert-butyl hydrogen peroxide (TBHP). The reaction was carried out at a high temperature of 60°C in dimethyl sulfoxide (DMSO) for 12 hours. Despite achieving high functional group tolerance, benign reaction conditions, scalability, and regioselectivity, it is notable that stoichiometric amounts of oxidant have been utilized (Scheme 1).[28]



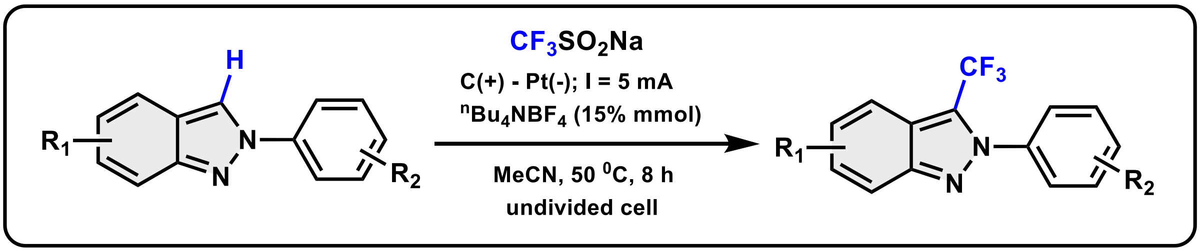
**Scheme 1**. Metal-free trifluoromethylation of Indazole.

In 2019, Sharada and coworkers introduced a visible-light-promoted, regioselective C–H trifluoromethylation of 2*H*-indazoles. 2-phenyl-2*H*-indazole was used as the model substrate in this procedure, $CF_3SO_2Na$ which is also known as the Langlois reagent as the trifluoromethylating agent and phenyliodine (III) diacetate (PIDA) as the oxidant and methylene blue was employed as a photocatalyst. The reaction was carried out in dichloromethane (DCM) and exposed to irradiation using a 60 W compact fluorescent light (CFL) at room temperature for a duration of 24 hours. While the process demonstrated efficacy, its application is restricted by limited substrate compatibility, and it necessitates the use of the super stoichiometric amount of oxidant (Scheme 2).[29]



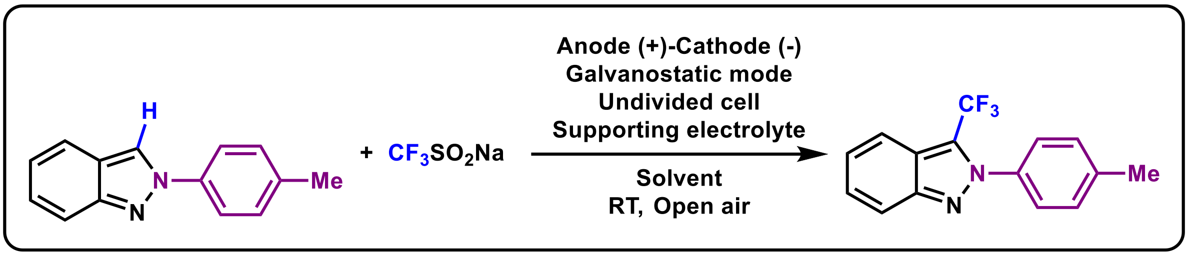
**Scheme 2**. Trifluoromethylation of 2H-Indazole under transition metal free photoredox catalyst.

In the year of 2021, Xie and coworkers described an electrochemically mediated regioselective C—H trifluoromethylation of 2*H*-indazoles using 2-phenyl-2*H*-indazole and $CF_3SO_2Na$ as model substrates, a reaction was conducted employing platinum serving as the cathode and carbon as the anode. The supporting electrolyte used was $^nBu_4NBF^4$, and for 8 h, the reaction was conducted at 50 °C in MeCN as the solvent. Despite its effectiveness, this approach has many limitations, such as the use of expensive electrodes, limited substrate applicability and performed at an elevated temperature (Scheme 3).[30]



**Scheme 3**. Electrochemically mediated trifluoromethylation of 2H-indazole derivatives using $CF_3SO_2Na$.

These techniques have drawbacks, including the utilization of stoichiometric oxidants, organic solvents, lengthy reaction durations, and restricted substrate application, even if they were carried out in a metal-free environment. Hence, the need for a trifluoromethylation strategy with benign reaction conditions, efficient atom economy, and environmental sustainability is of great importance. Therefore, we hypothesized that the desired product could be achieved by utilizing inexpensive electrode materials and conducting the reaction at room temperature (Scheme 4).



**Scheme 4**: Hypothesized reaction condition.

## 2. Results and Discussion

To investigate the validity of our hypothesis, we initiated our investigation by employing 2-(*p*-tolyl)-2*H*-indazole **1a** as the model substrate, Langlois' reagent i.e., sodium trifluoromethanesulfinate ($CF_3SO_2Na$) as the trifluoromethyl source and $Bu_4NPF_6$ as the supporting electrolyte, in an undivided cell setup where nickel foam serving as the cathode and carbon soft as the anode. The reaction was conducted in acetonitrile (MeCN) at room temperature under a constant supply of 5 mA current using a potentiostat. The desired product **2a** was successfully isolated in a 42% yield using the standard reaction conditions (Table 1, Entry 1).

The selection of electrode materials has been an essential factor in the effectiveness of the reaction in the field of electrosynthesis. As a result, a thorough analysis of several electrode materials was conducted to see how they affected the reaction. In the experimentation, it was observed that when carbon rods were used both as the anode and cathode or when nickel foam was employed as the anode, no product was obtained (Table 1, Entry 2 and 5). However, when a carbon rod was employed as the anode and nickel as the cathode, the product was obtained with a yield of 41% (Table 1, Entry 3), furthermore, when a carbon rod was utilized as the anode and platinum as the cathode, a yield of 34% for the product was achieved (Table 1, Entry 4).

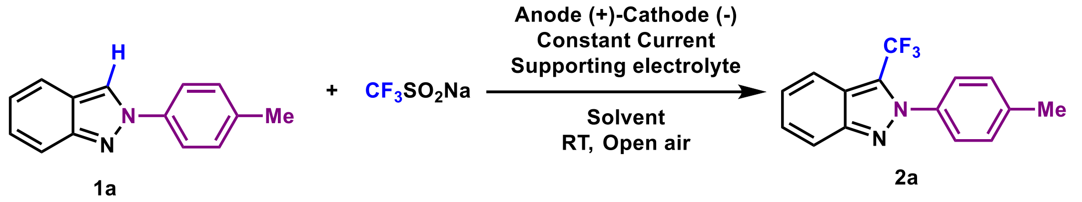
After identifying the optimum electrode combination of nickel foam serving as the cathode and carbon soft as the anode, the next step in the process was to screen different supporting electrolytes. When tetrabutylammonium tetrafluoroborate ($Bu_4NBF_4$) was used, it produced a 34% yield of the intended product **2a** (Table 1, Entry 6). However, with tetrabutylammonium bromide ($Bu_4NBr$), tetrabutylammonium iodide ($Bu_4NI$), and tetraethylammonium chloride ($Et_4NCl$) as supporting electrolytes, no product **2a** was obtained (Table 1, Entry 7-9). With tetramethylammonium tetrafluoroborate ($Me_4NBF_4$), we achieved the desired product with the maximum yield, reaching 62% (Table 1, Entry 10). However, when $Bu_4NClO_4$ was employed as the supporting electrolyte, the product's yield was only 37% (Table 1, Entry 11). Using lithium perchlorate ($LiClO_4$) as the supporting electrolyte, the product was obtained with a lower yield of **2a** in 27% (Table 1, Entry 12).

Subsequently, with tetramethylammonium tetrafluoroborate as a supporting electrolyte, we also varied the constant current in order to comprehend its influence on the reaction. When a constant current of 3 mA was employed, we got a better yield of 66% (Table 1, Entry 13). We further increased the constant current value to 10 mA and the yield dropped to 47% (Table 1, Entry 14).

Additionally, the impact of the solvent on the reaction was examined. MeCN was selected as the solvent primarily for the convenience it offered in the workup procedure, even though DMF produced more yield. We also experimented with different ratios of solvents. When only MeCN was used as the solvent, a yield of 66% was obtained for the product (Table 1, Entry 10). Similarly, employing only DMF as the solvent resulted in an increased yield of 68% (Table 1, Entry 15). In contrast, $MeNO_2$ as the solvent led to the formation of only trace amounts of the desired product (Table 1, Entry 16). In DMSO, a yield of 65% was achieved (Table 1, Entry 17). Furthermore, when a 2:1 ratio of DMF and MeCN was used as the solvent mixture, it resulted in a 60% yield of the product (Table 1, Entry 18). On the other hand, a 1:2 ratio of DMF and MeCN as the solvent mixture yielded a slightly lesser yield of 55% (Table 1, Entry 19). Among the various combinations tested, a mixture consisting of a 1:1 ratio of each solvent (DMF and MeCN) yielded the highest result (Table 1, Entry 20).

Further explorations revealed that increasing the amount of $CF_3SO_2Na$ had a significant and positive impact on the product yield, and hence, we conducted the reaction using different concentrations of $CF_3SO_2Na$. Using 1.5 equivalents of $CF_3SO_2Na$, a 67% yield of the product **2a** has been achieved. With 2 equivalents of $CF_3SO_2Na$, we obtained product **2a** with 76% yield (as shown in Table 1, entry 22). The utilization of 1.5 equivalents of $CF_3SO_2Na$, yielded the product with 54% yield (Table 1, Entry 23), while employing 3 equivalents of $CF_3SO_2Na$, led to 72% yield

## Table 1: Optimization of reaction conditions[a]



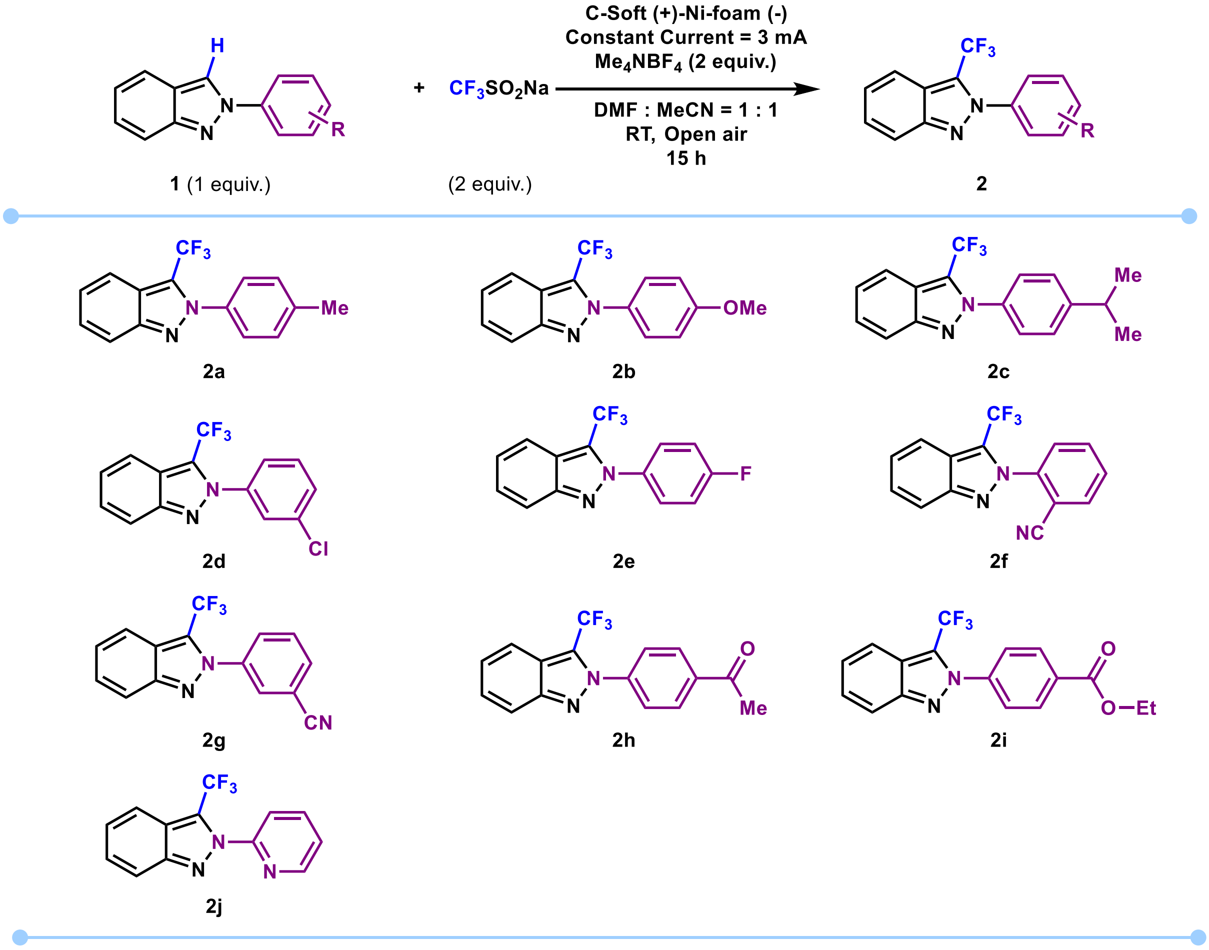
| Entry | Electrodes (+)/ (-) | Supporting Electrolyte | Current (mA) | Solvent | Yield[b] % |
|---|---|---|---|---|---|
| 1 | C-soft (+)/Ni-foam (-) | $Bu_4NPF_6$ | 5 | MeCN | 42 |
| 2 | C-rod (+)/C-rod (-) | $Bu_4NPF_6$ | 5 | MeCN | ND |
| 3 | C-rod (+)/Ni (-) | $Bu_4NPF_6$ | 5 | MeCN | 41 |
| 4 | C-soft (+)/Pt (-) | $Bu_4NPF_6$ | 5 | MeCN | 34 |
| 5 | Ni-foam (+)/C (-) | $Bu_4NPF_6$ | 5 | MeCN | ND |
| 6 | C-soft (+)/Ni-foam (-) | $Bu_4NBF_4$ | 5 | MeCN | 34 |
| 7 | C-soft (+)/Ni-foam (-) | $Bu_4NI$ | 5 | MeCN | ND |
| 8 | C-soft (+)/Ni-foam (-) | $Bu_4NBr$ | 5 | MeCN | ND |
| 9 | C-soft (+)/Ni-foam (-) | $Bu_4NCl$ | 5 | MeCN | ND |
| 10 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 5 | MeCN | 62 |
| 11 | C-soft (+)/Ni-foam (-) | $Bu_4NClO_4$ | 5 | MeCN | 37 |
| 12 | C-soft (+)/Ni-foam (-) | $LiClO_4$ | 5 | MeCN | 27 |
| 13 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | MeCN | 66 |
| 14 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 10 | MeCN | 47 |
| 15 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF | 68 |
| 16 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | $MeNO_2$ | trace |
| 17 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMSO | 65 |
| 18 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (2:1) | 60 |
| 19 | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (1:2) | 55 |
| **20** | **C-soft (+)/Ni-foam (-)** | **$Me_4NBF_4$** | **3** | **DMF: MeCN (1:1)** | **78 (72)[c]** |
| 21[d] | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (1:1) | 67 |
| 22[e] | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (1:1) | 76 |
| 23[f] | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (1:1) | 54 |
| 24[g] | C-soft (+)/Ni-foam (-) | $Me_4NBF_4$ | 3 | DMF: MeCN (1:1) | 72 |

[a] **Reaction conditions:** 2-(*p*-tolyl)-2*H*-indazole **1a** (1 equiv.), $CF_3SO_2Na$ (2 equiv.), supporting electrolyte (2 equiv.), solvent (3 mL), anode(+), cathode(-), constant current (I), room temperature (rt), and open air. [b] Determined by $^1H$ NMR analysis using 1,3,5-Trimethoxybenzene as an internal standard. [c] Isolated yield after column chromatography. [d] $CF_3SO_2Na$ (1.5 equiv.). [e] $CF_3SO_2Na$ (3 equiv.). [f] $Me_4NBF_4$ (1 equiv.). [g] $Me_4NBF_4$ (3 equiv.). ND = Not detected.

(Table 1, Entry 24). When 2 equivalents of both reagents were used a maximum yield of 78% was achieved (Table 1, Entry 20).

After the systematic screening of different electrode combinations, supporting electrolytes, solvents and other reaction conditions, when carbon soft as anode and Ni-foam as a cathode are dipped in the solution containing 2-(*p*-tolyl)-2*H*-indazole **1a** (1.0 equiv.), $CF_3SO_2Na$ (2.0 equiv.) and supporting electrolyte $Me_4NBF_4$ (2.0 equiv.) in DMF: MeCN (1:1, 3 mL) at a constant at a constant current supply of 3 mA in an undivided cell setup proved to be the optimum reaction condition for the synthesis of desired trifluoromethylated product **2a** ( Table 1, Entry 20).

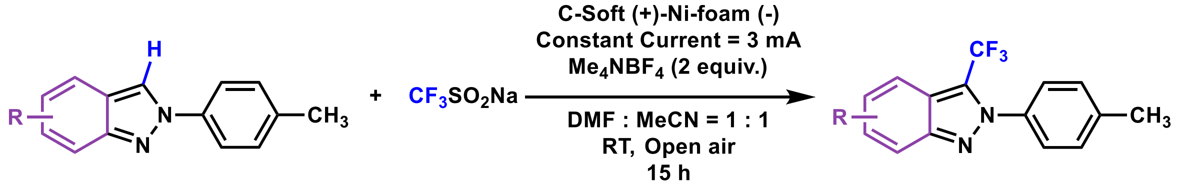
**Table 2:** Substrate Scope for the trifluoromethylated 2*H*-Indazole:



[a]**Reaction conditions: 1a** (1 equiv.), $CF_3SO_2Na$ (2 equiv.), $Me_4NBF_4$ (2 equiv.), solvent (3 mL), C-soft (+), Ni-foam (-), a constant current of 3 mA, room temperature (rt), and open air. [b]Yields are determined by $^1H$ NMR analysis using 1,3,5- Trimethoxybenzene as an internal standard.

With the optimized reaction conditions in hand, we proceeded to explore the broader substrate applicability of this protocol. For this, we have examined various amine partners having electron-withdrawing as well as electron-donating substituents, and we obtained the corresponding desired product in moderate to good yield. Trifluoromethylated 2*H*-Indazole derivatives bearing electron-donating groups such as -CH$_3$, -OCH$_3$, and -$^i$Pr at the *para*-position of the aryl ring resulted in excellent yield (**2a**–**2c**). At the same time, electron-withdrawing substituents at the *p*-position provided a lesser yield for the product. Halogen substituents at the meta and para positions of the 2-phenyl-2*H*-indazole moiety have been obtained with moderate yield (**2d**, **2e**). Notably, even highly electron-withdrawing groups, such as -CN at the ortho and meta position on the 2-phenyl-2*H*-indazole scaffold, were well tolerated in this transformation (**2f**, **2g**).

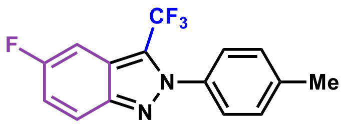
**Table 3:** Substrate Scope for the trifluoromethylated 2H-Indazole:



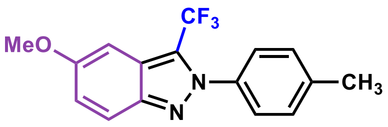
**1aa** (1 equiv.)

(2 equiv.)

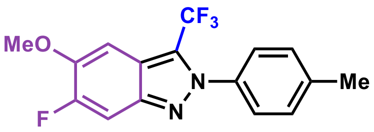
**3**



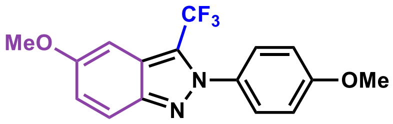
**3a**



**3b**



**3c**

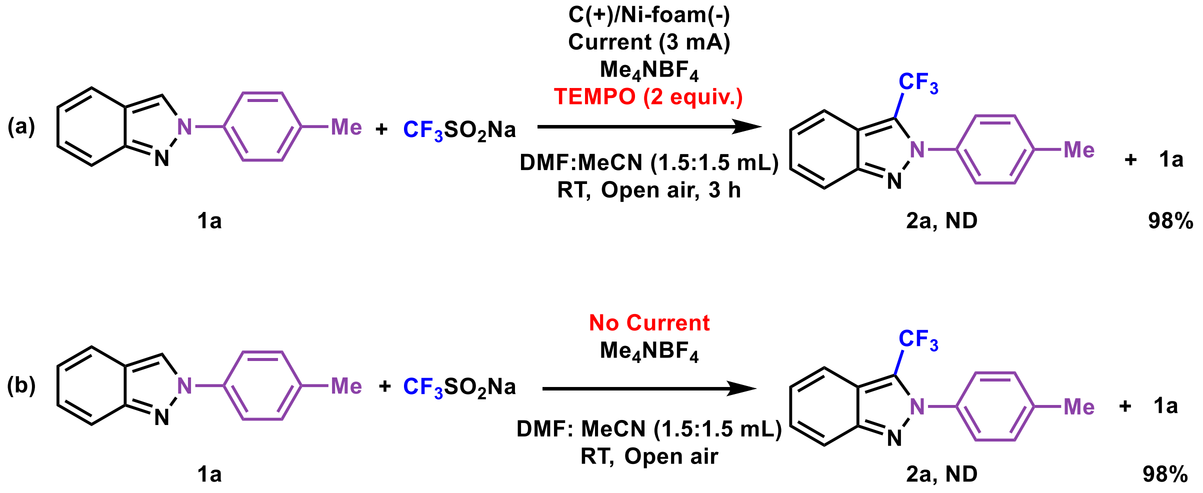


**3d**

[a]**Reaction conditions: 1aa** (1 equiv.), CF$_3$SO$_2$Na (2 equiv.), Me$_4$NBF$_4$ (2 equiv.), solvent (3 mL), C-soft (+), Ni-foam (-), a constant current of 3 mA, room temperature (rt), and open air. [b]Yields are determined by $^1$H NMR analysis using 1,3,5- Trimethoxybenzene as an internal standard.

We also directed our focus towards screening various C5 and C6 substituted 2*H*-indazoles to investigate the protocol's generality and practicality. In this regard, different C5 and C6 substituted 2*H*-Indazole derivatives containing both electron-withdrawing and electron-donating substituents resulted in a moderate to good yield. Electron activating groups such as -$CH_3$ and - $OCH_3$ at the C5 position of the 2H-Indazole on treatment with $CF_3SO_2Na$ using the optimum reaction condition provided the desired trifluoromethylated product in good yield (**3a**, **3b**). Halogen substitutions like -F and -Cl at the C5 position resulted in a moderate to good yield for the product. C5 (-$OCH_3$) and C6 (-F) substitutions on the same molecule have also been obtained in good yield **3c**. We have also synthesized the precursor molecule **3d** for the highly selective ligand for estrogen receptor β (Erβ), which is shown in Figure 2.

We carried out several control experiments to obtain a mechanistic understanding of this protocol (Scheme 5). First, we performed the radical trapping experiment using **1a** and $CF_3SO_2Na$ under the optimized reaction condition in the presence of radical trapping agent TEMPO, and we did not observe the formation of desired product 2a, whereas we recovered 98% of the starting material **1a**. This result suggests that the reaction is going via a radical mediated process (Scheme 5, a). Further, we also performed the reaction while maintaining the optimum reaction condition without the constant current supply and did not observe the formation of the desired product; instead, 98% of the starting material was recovered (Scheme 5, b). This proves this reaction to be an electrochemically mediated process.



**Scheme 5.** Control Experiments

A cyclic voltammetry experiment was performed to obtain the redox potentials of 2-(*p*-tolyl)-2*H*-indazole **1a** and $CF_3SO_2Na$ using glassy carbon as the working electrode, platinum-plated counter electrode, and Ag/AgCl reference electrode (samples were made in an acetonitrile electrolyte solution with substrate concentrations of 10 mM and 100 mM $Me_4NBF_4$. Data were recorded at a 100 mV/s scan rate). From the cyclic voltammograms, the oxidation potential of **1a** was found to be 1.81 V ($E_{ox}$), and for $CF_3SO_2Na$, it was 1.33 V ($E_{ox}$). These experimental data clearly suggest that **1a** and $CF_3SO_2Na$ will undergo oxidation at the carbon-soft anode.

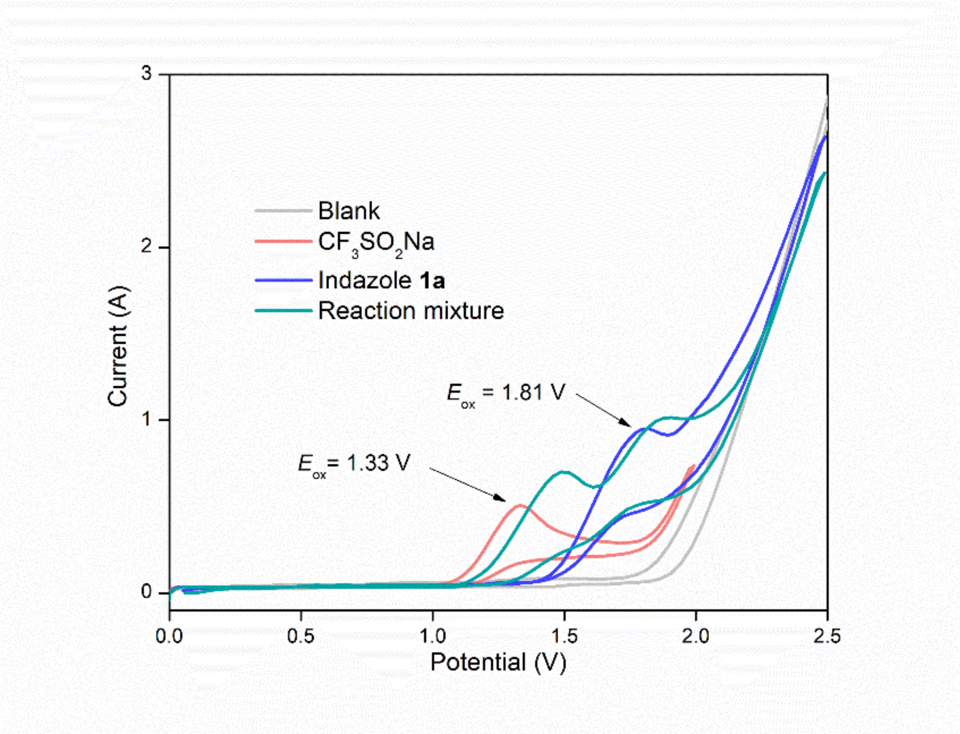
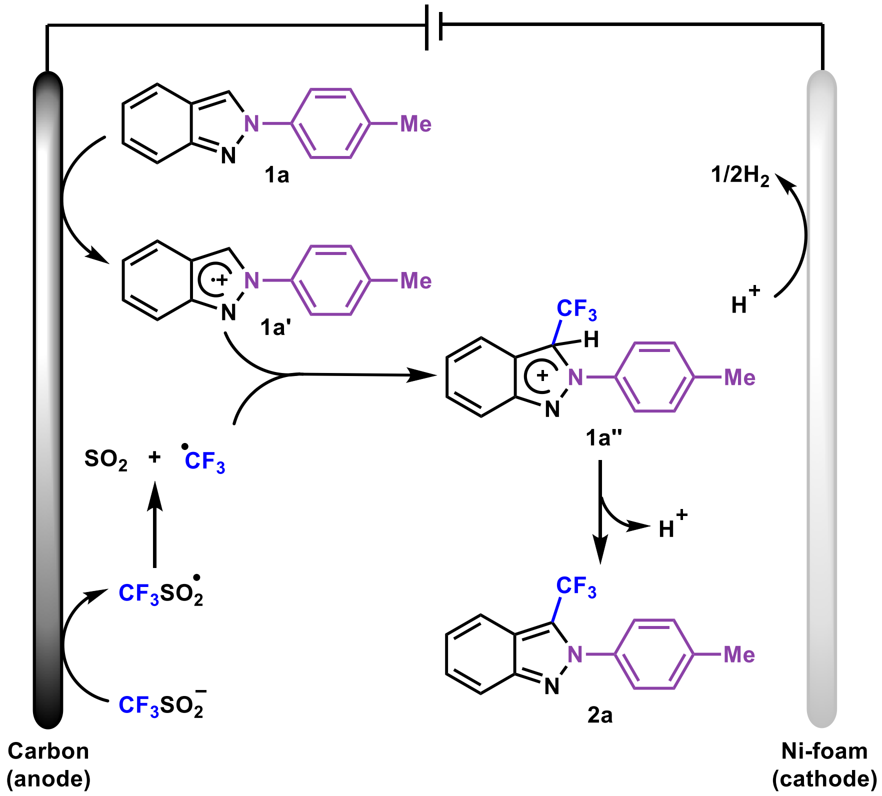


**Figure 3.** Cyclic Voltammograms

From the results of the various control experiments, cyclic voltammograms, and the preceding literature, we proposed a plausible mechanism (Scheme 6). The 2-(*p*-tolyl)-2*H*-indazole **1a** and $CF_3SO_2Na$ under the optimized reaction condition are getting oxidized at the anode surface. The $CF_3SO_2^-$ is oxidized to $CF_3SO_2^\bullet$ which further undergoes $SO_2$ evolution to generate trifluoromethyl radical. Additionally, **1a** is also oxidized to the corresponding radical cation **1a'**. The trifluoromethyl radical and **1a'** undergoes radical coupling reaction to generate 2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-

indazole cation **1a”**. The 2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole cation **1a”** undergoes rearomatization via deprotonation to give the desired product 2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole **2a**. To maintain electroneutrality the released proton is undergoing reduction at the cathode to generate dihydrogen ($H_2$).



**Scheme 6.** Plausible Reaction Mechanism

## 3. Conclusion:

In summary, we have reported a sustainable approach for the synthesis of trifluoromethylated 2*H*-Indazole derivatives using $CF_3SO_2Na$ as the trifluoromethyl source applying a galvanostatic mode of operation. The synthetic utility of this protocol has proved to be compatible with a wide range of 2*H*-Indazole derivatives containing electronically neutral, rich, and withdrawing substituents to afford the desired trifluoromethylated 2*H*-Indazole product in moderate to good yield. The cyclic voltammetry studies and control experiments provided insights into the plausible mechanism of the reaction. We are devoted to expanding the substrate applicability of this protocol, and to know more about the practical utility of this protocol, we are aiming to perform various post-synthetic application studies. Our goal is to synthesize biologically active compounds using this protocol.

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## 5. Experimental Section:

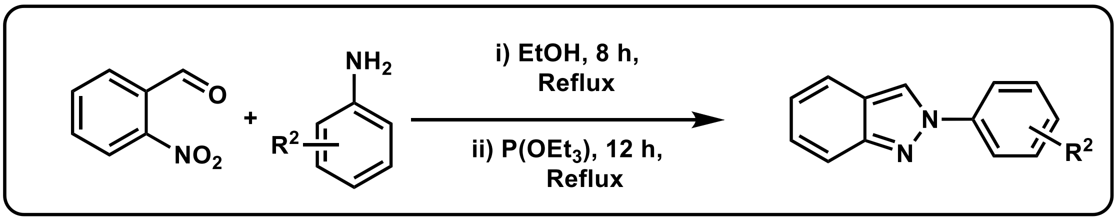
### 5.1. General Information:

**Reagent Information:** All reactions were conducted using distilled and dried solvents, and oven-dried glassware was employed unless stated otherwise. Commercially purchased reagents were used as received unless specified otherwise. Thin-layer chromatographic (TLC) analysis was performed using silica gel 60 $GF_{254}$ pre-coated aluminium-backed plates (2.5 mm), with detection under UV light. Column chromatographic purification of products was carried out using silica gel (100-200 mesh), with a gradient elution of petroleum ether and ethyl acetate mixture**.**

**Analytical Information:** All isolated compounds were characterized via $^1$H NMR and $^{13}$C{$^1$H} NMR spectroscopy. The Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$, with trimethylsilane (TMS) as the internal standard. $^1$H NMR spectra were recorded at 400 MHz, and $^{13}$C{$^1$H} NMR spectra were obtained at 100 MHz (Bruker and Jeol) unless otherwise specified. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for $^1$H NMR and relative to the central $CDCl_3$ (δ = 77.16 ppm) resonance for $^{13}$C NMR spectroscopy. For 1H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) are given in Hz and integration. Additionally, $^{13}$C{$^1$H} NMR spectra were recorded with complete proton decoupling. $^{19}$F NMR spectra were recorded at 377 MHz. Mass samples were subjected to analysis by high-resolution mass spectrometry (HRMS) using ESI TOF.

### 5.2. Preparation of Starting Materials:

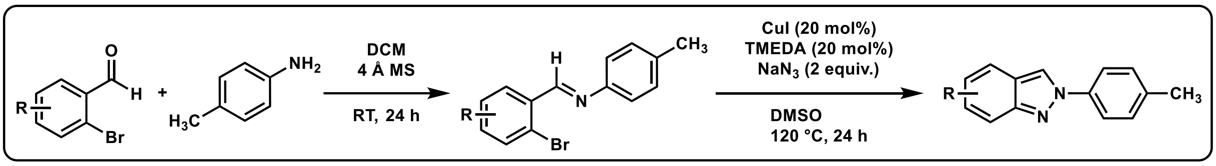
### 5.2.A. General Procedure-A for the synthesis of 2-phenyl-2*H*-indazole derivatives:



2*H*-Indazoles are synthesized following the literature procedure.[31] In an oven-dried round bottom flask, 2-nitrobenzaldehyde (1 g, 1 equiv., 6.62 mmol) and aniline

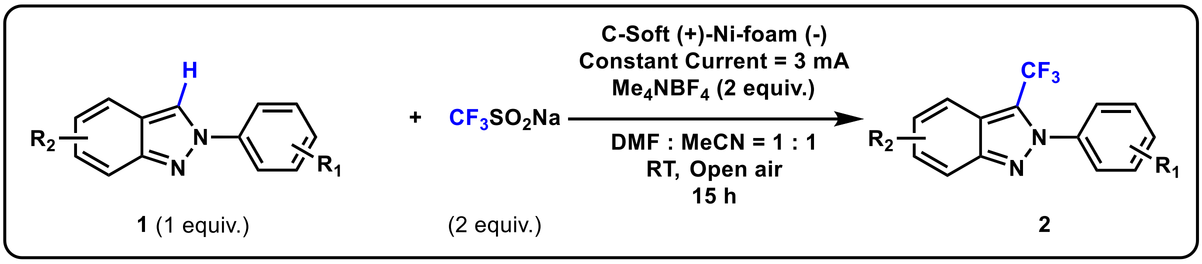
(1 equiv., 6.62 mmol) were taken and refluxed for 8 hours in ethanol (25 mL). The resulting solid was filtered and dried under reduced pressure. The obtained solid was then used in the next step without further purification and subjected to reflux for 12 hours in triethyl phosphite (4 mL). The completion of the reaction was monitored using thin-layer chromatography (TLC). The resulting mixture was then separated using $CH_2Cl_2$ and ice. The organic layer was dried and filtered using anhydrous $Na_2SO_4$, concentrated under reduced pressure, and purified by column chromatography using petroleum ether/ ethyl acetate to obtain the corresponding product.

### 5.2.B. General Procedure-B for the synthesis of 2*H*-Indazole:



2*H*-Indazoles are synthesized following the literature procedure.[32] To an oven-dried round-bottom flask, 2-bromo aryl aldehydes (1 equiv., 3.73 mmol), p-toluidine (1 equiv., 3.73 mmol), and 4 Å molecular sieves were added. Then, it was stirred for 24 hours at room temperature in dichloromethane as the solvent. The mixture was filtered through Celite and subsequently dried under reduced pressure to yield the imines. These imines were utilized in the subsequent step without undergoing further purification. To obtain the desired 2*H*-Indazole derivatives, sodium azide (2 equiv.), copper iodide (20 mol%), and TMEDA (20 mol%) were added to the desired amine in dry DMSO. The reaction mixture was allowed to stir for 24 h at 120 °C. The reaction was monitored using thin-layer chromatography (TLC). After the completion of the reaction, the resulting reaction mixture was filtered through Celite using $CH_2Cl_2$, and the organic layer was separated via workup using $CH_2Cl_2$ and ice. The residue was purified on silica gel column chromatography using petroleum ether/ ethyl acetate as the eluent.

### 5.2.C General Procedure-C for trifluoromethylated 2*H*-Indazole derivatives:

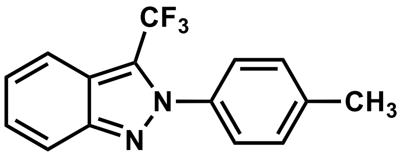


In a reaction tube, compound **1** (1 equiv., 75 mg), $CF_3SO_2Na$ (2 equiv.), and $Me_4NBF_4$ (2 equiv.) were dissolved in a 1:1 mixture of dimethylformamide and acetonitrile (6 mL). Carbon soft was utilized as the anode and nickel foam as the cathode, with electrodes immersed in the reaction mixture. A constant current of 3 mA was applied using a potentiostat, and the reaction was allowed to proceed with stirring for 12 hours at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion of the reaction, acetonitrile was evaporated, and the organic layer was extracted with dichloromethane and ice, followed by concentration under reduced pressure. The resulting residue underwent purification via silica gel column chromatography using petroleum ether/ethyl acetate as the eluent to obtain the pure product.

**Figure 4.** Reaction setup

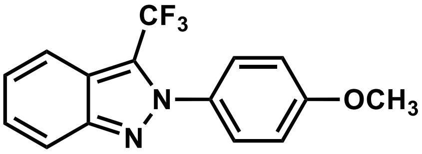
## 6. Characterisation Data

### 2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole



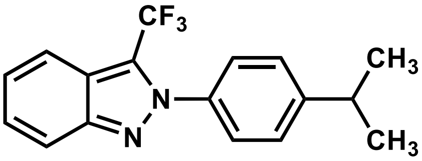
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.84–7.81 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (ddd, *J* = 9.0, 6.6, 1.1 Hz, 1H), 7.35–7.33 (m, 2H), 7.32–7.28 (m, 1H), 2.47 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 148.2, 140.3, 137.2, 129.8, 127.2, 126.0, 125.1, 123.7 (q, *J* = 39.5 Hz), 121.6, 121.1 (q, *J* = 268.8), 119.5, 118.5, 21.4. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.56. HRMS (ESI TOF) *m/z* for $C_{15}H_{12}F_3N_2$ [M + H]$^+$ calcd. 277.0953, found 277.0951.

### 2-(4-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole



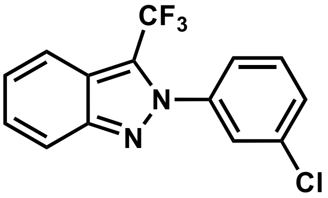
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.83–7.80 (m, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.40 (ddd, *J* = 9.0, 6.7, 1.1 Hz, 1H), 7.31–7.27 (m, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 160.8, 148.1, 132.6, 127.5, 127.2, 125.0, 123.8 (q, *J* = 39.5 Hz), 121.6, 121.1 (q, *J* = 268.8 Hz), 119.5 (q, *J* = 1.9 Hz), 118.5, 114.3, 55.7. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.67. HRMS (ESI TOF) *m/z* for $C_{15}H_{12}F_3N_2O$ [M + H]$^+$ calcd. 293.0902, found 293.0897.

### 2-(4-isopropylphenyl)-3-(trifluoromethyl)-2*H*-indazole



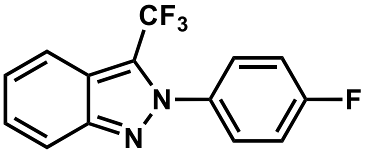
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.84–7.80 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.41–7.38 (m, 3H), 7.32–7.28 (m, 1H), 3.03 (hept, *J* = 7.0 Hz, 1H), 1.32 (d, *J* = 6.9 Hz, 6H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 151.1, 148.2, 137.4, 127.3, 127.2, 126.0, 125.0, 123.7 (q, *J* = 40.2 Hz), 121.6, 121.1 (q, *J* = 268.9 Hz), 119.5 (q, *J* = 1.9 Hz), 118.5, 34.1, 24.0. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.55. HRMS (ESI TOF) *m/z* for $C_{17}H_{16}F_3N_2$ [M + H]$^+$ calcd. 305.1266, found 305.1261.

**2-(3-chlorophenyl)-3-(trifluoromethyl)-2*H*-indazole**



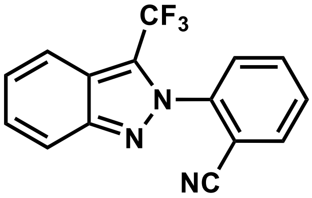
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.84–7.80 (m, 2H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.55 (ddd, *J* = 6.1, 3.0, 2.0 Hz, 1H), 7.50 (dd, *J* = 5.0, 2.0 Hz, 2H), 7.43 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.34–7.30 (m, 1H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 148.5, 140.6, 135.0, 130.4, 130.2, 127.7, 126.7, 125.5, 124.4, 123.8 (q, *J* = 39.8 Hz), 121.8, 120.9 (q, *J* = 269.1 Hz), 119.5 (q, *J* = 1.9 Hz), 118.6. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.39. HRMS (ESI TOF) *m/z* for $C_{14}H_9ClF_3N_2$ [M + H]$^+$ calcd. 297.0406, found 297.0403.

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



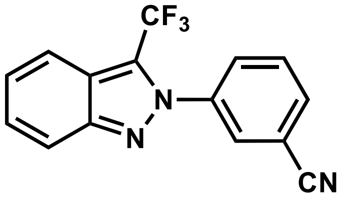
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.84 – 7.80 (m, 2H), 7.59–7.56 (m, 2H), 7.42 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H), 7.33–7.29 (m, 1H), 7.26–7.22 (m, 2H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 163.39 (d, *J* = 250.6 Hz), 148.36, 135.73 (d, *J* = 3.3 Hz), 128.25 (d, *J* = 9.0 Hz), 127.58, 125.38, 124 (q, *J* = 39.6 Hz), 121.68, 121.0 (q, *J* = 269.0 Hz), 119.51 (q, *J* = 1.9 Hz), 118.51, 116.31 (d, *J* = 23.4 Hz). $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.55, -110.19. HRMS (ESI TOF) *m/z* for $C_{14}H_9F_4N_2$ [M + H]$^+$ calcd. 281.0702, found 281.0695.

**2-(3-(trifluoromethyl)-2*H*-indazol-2-yl)benzonitrile**



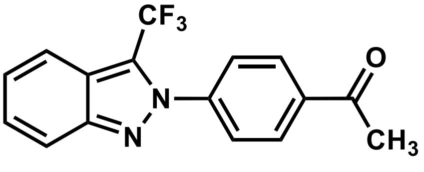
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.89 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.85–7.78 (m, 3H), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.47–7.43 (m, 1H), 7.36–7.32 (m, 1H). $^{13}$C{$^1$H} NMR (100 MHz, Chloroform-*d*): δ (ppm) 149.0, 141.2, 133.8, 133.4, 131.0, 128.5, 128.1, 126.0, 124.8 (q, *J* = 39.7 Hz), 121.5, 120.7 (q, *J* = 268.9 Hz), 119.4 (q, *J* = 1.7 Hz), 118.8, 114.7, 112.5. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -55.26. HRMS (ESI TOF) *m/z* for $C_{15}H_9F_3N_3$ [M + H]$^+$ calcd. 288.0749, found 288.0749.

**3-(3-(trifluoromethyl)-2H-indazol-2-yl)benzonitrile (AKS-I-3CN_NH2)**



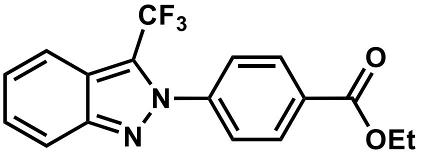
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.93 (d, *J* = 1.8 Hz, 1H), 7.88–7.80 (m, 4H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.45 (ddd, *J* = 8.9, 6.6, 1.0 Hz, 1H), 7.36–7.32 (m, 1H). $^{13}$C{$^1$H} NMR (101 MHz, Chloroform-*d*): δ (ppm) 148.8, 140.4, 133.5, 130.5 (d, *J* = 1.6 Hz), 130.3, 129.8, 128.1, 125.9, 123.9 (q, *J* = 39.9 Hz), 122.0 (d, *J* = 1.4 Hz), 121.2 (q, *J* = 244.4 Hz), 119.5 (q, *J* = 1.6 Hz), 118.6, 117.4, 113.9. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.18. HRMS (ESI TOF) *m/z* for $C_{15}H_9F_3N_3$ [M + H]$^+$ calcd. 288.0749, found 288.0748.

**1-(4-(3-(trifluoromethyl)-2H-indazol-2-yl)phenyl)ethan-1-one**



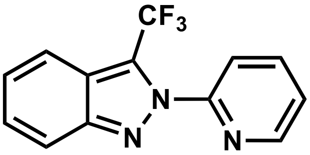
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 8.16–8.13 (m, 2H), 7.83 (ddt, *J* = 8.9, 2.0, 1.2 Hz, 2H), 7.74–7.72 (m, 2H), 7.43 (ddd, *J* = 9.0, 6.7, 1.1 Hz, 1H), 7.34–7.30 (m, 0H), 2.69 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 196.9, 148.7, 143.2, 138.1, 130.2, 129.3, 127.8, 126.4, 125.6, 122.0, 120.9 (q, *J* = 269.2 Hz), 119.5 (q, *J* = 2.0 Hz), 118.6, 26.9. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.20. HRMS (ESI TOF) *m/z* for $C_{16}H_{12}F_3N_2O$ [M + H]$^+$ calcd. 305.0902, found 305.0899.

**ethyl 4-(3-(trifluoromethyl)-2*H*-indazol-2-yl)benzoate**



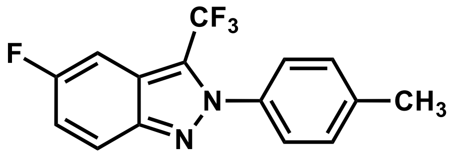
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 8.26–8.22 (m, 2H), 7.84–7.81 (m, 2H), 7.70–7.68 (m, 2H), 7.43 (ddd, *J* = 9.1, 6.7, 1.1 Hz, 1H), 7.32–7.29 (m, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 165.6, 148.6, 143.1, 132.0, 131.4, 130.6, 127.8, 126.2, 125.5, 123.8 (q, *J* = 39.7 Hz), 120.9 (q, *J* = 269.0 Hz), 119.6 (q, *J* = 1.9 Hz), 118.6, 61.7, 14.4. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.25. HRMS (ESI TOF) *m/z* for $C_{17}H_{14}F_3N_2O_2$ [M + H]$^+$ calcd. 335.1007, found 335.1010.

**2-(pyridin-2-yl)-3-(trifluoromethyl)-2*H*-indazole**



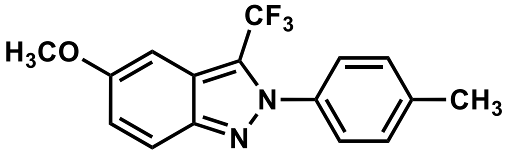
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 8.63 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.96 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1H), 7.90 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.86 (dq, *J* = 8.7, 1.3 Hz, 1H), 7.82 (dt, *J* = 8.9, 1.0 Hz, 1H), 7.47–7.39 (m, 2H), 7.29 (ddd, *J* = 8.7, 6.6, 0.9 Hz, 1H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 152.0, 148.5, 148.4, 138.7, 127.7, 125.4, 124.4, 123.2 (q, *J* = 40.9 Hz), 122.4, 121 (q, *J* = 268.8 Hz), 120.0 (q, *J* = 2.4 Hz), 119.1, 118.6. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.68. HRMS (ESI TOF) *m/z* for $C_{13}H_9F_3N_3$ [M + H]$^+$ calcd. 264.0749, found 264.0747.

**5-fluoro-2-(p-tolyl)-3-(trifluoromethyl)-2*H*-indazole**



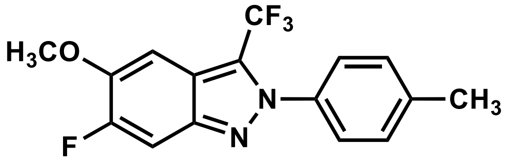
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.80 (ddd, *J* = 9.4, 4.6, 0.7 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.40 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.21 (td, *J* = 9.2, 2.4 Hz, 1H), 2.47 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 160.2 (d, *J* = 244.7 Hz), 145.6, 140.54, 137.1, 129.8, 125.9, 124.1 (q, *J* = 39.6 Hz), 120.9 (q, *J* = 268.9 Hz), 120.9 (d, *J* = 10.1 Hz), 119.2 (d, *J* = 29.1 Hz), 102.6 (q, *J* = 2.0 Hz), 102.3 (d, *J* = 2.0 Hz), 21.4. $^{19}$F NMR (377 MHz, Chloroform-*d*) δ -54.78, -114.76. HRMS (ESI TOF) *m/z* for $C_{15}H_{11}F_4N_2$ $[M + H]^+$ calcd. 295.0858, found 295.0852.

**5-methoxy-2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole**



$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.69 (dd, *J* = 9.4, 0.7 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.34–7.30 (m, 2H), 7.09 (dd, *J* = 9.4, 2.4 Hz, 1H), 6.96 (dt, *J* = 2.3, 1.1 Hz, 1H), 3.89 (s, 3H), 2.46 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*) δ 157.4, 145.1, 140.1, 137.4, 129.7, 125.9, 122.7, 122.5, 122.2 (q, *J* = 1.5 Hz), 121.4 (q, *J* = 268.4 Hz), 119.9, 95.3 (q, *J* = 2.1 Hz), 55.6, 21.4. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.44. HRMS (ESI TOF) *m/z* for $C_{16}H_{14}F_3N_2O$ $[M + H]^+$ calcd. 307.1058, found 307.1056.

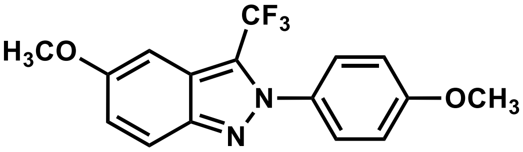
**6-fluoro-5-methoxy-2-(*p*-tolyl)-3-(trifluoromethyl)-2*H*-indazole**



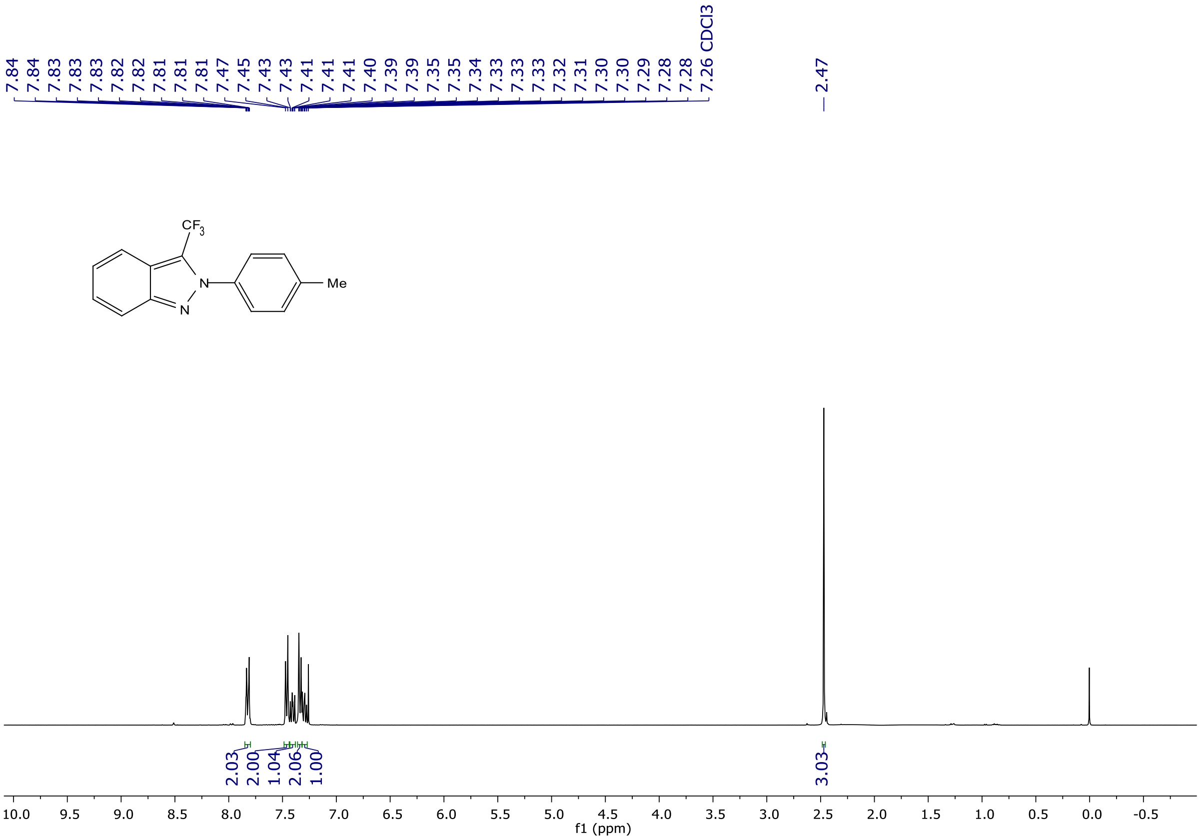
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.43–7.41 (m, 3H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.05 (dd, *J* = 8.0, 1.4 Hz, 1H), 3.98 (s, 3H), 2.46 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 154.6 (d, *J* = 252.4 Hz), 148.5 (d, *J* = 15.3 Hz), 143.4 (d, *J* = 12.2 Hz), 140.2, 137.1, 129.6, 126.3–125.5 (m), 121.9 (d, *J* = 198.3 Hz), 121.1 (q, *J* = 268.8 Hz), 118.4, 102.9 (d, *J* = 21.7 Hz), 97.8–97.5 (m), 56.3, 21.4. $^{19}$F NMR (377

MHz, Chloroform-d): δ (ppm) -54.62, -128.87. HRMS (ESI TOF) *m/z* for $C_{16}H_{13}F_4N_2O$ $[M + H]^+$ calcd. 325.0964, found 325.0961.

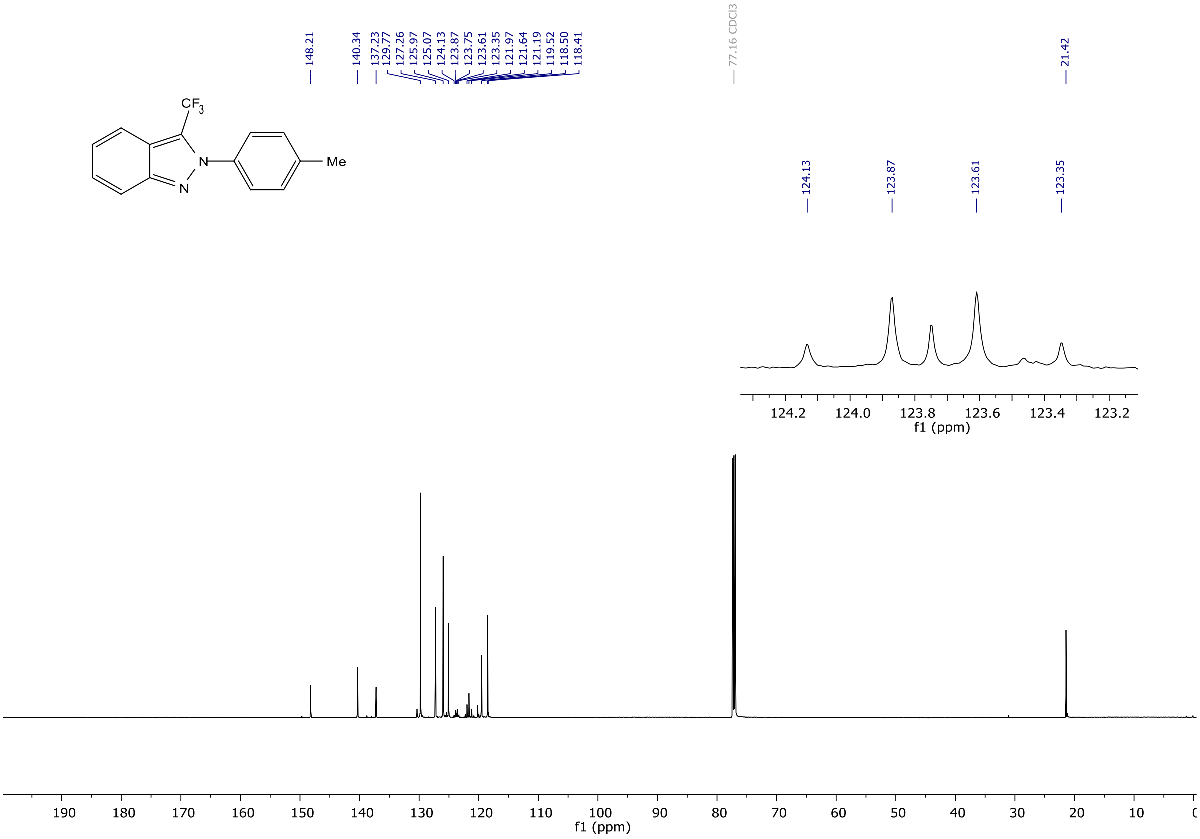
**5-methoxy-2-(4-methoxyphenyl)-3-(trifluoromethyl)-2*H*-indazole**



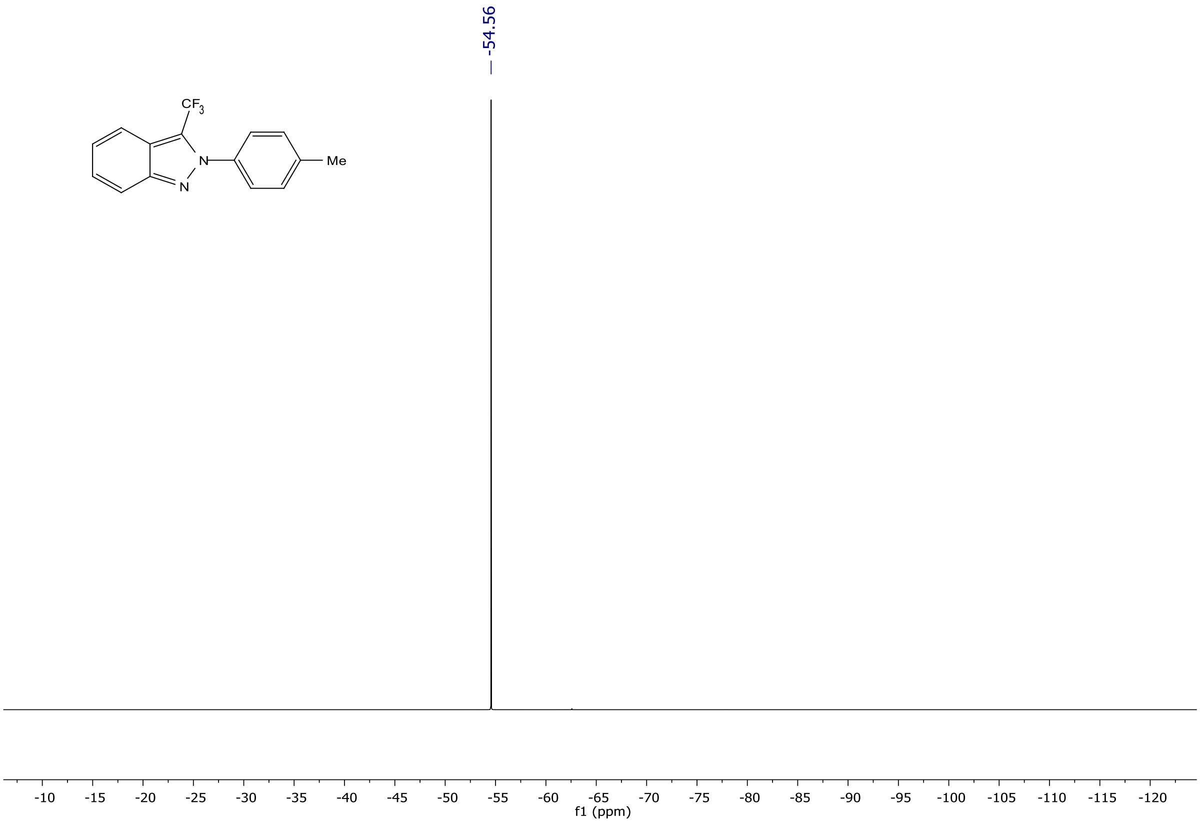
$^1$H NMR (400 MHz, Chloroform-*d*): δ (ppm) 7.69 (dd, *J* = 9.3, 0.7 Hz, 1H), 7.48–7.46 (m, 2H), 7.09 (dd, *J* = 9.4, 2.3 Hz, 1H), 7.04–7.00 (m, 2H), 6.95 (dt, *J* = 2.4, 1.1 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, Chloroform-*d*): δ (ppm) 160.6, 157.3, 145.0, 132.7, 127.4, 122.6, 122.1, 121.3 (q, *J* = 268.5 Hz), 119.8, 114.3, 114.2, 95.3 (q, *J* = 2.0 Hz), 55.7, 55.6. $^{19}$F NMR (377 MHz, Chloroform-*d*): δ (ppm) -54.56. HRMS (ESI TOF) *m/z* for $C_{16}H_{14}F_3N_2O_2$ $[M + H]^+$ calcd. 323.1007, found 323.1011.



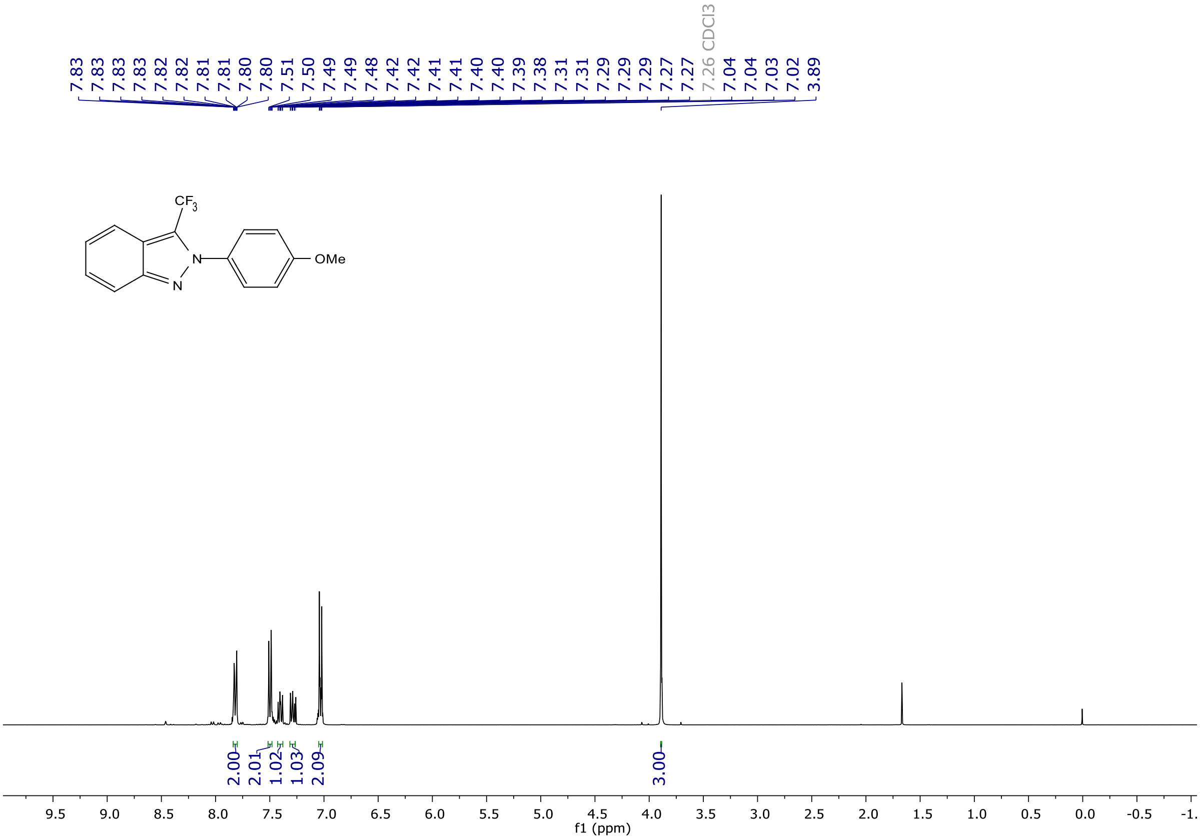
$^1$H NMR spectrum of **2a**, $CDCl_3$, 400 MHz



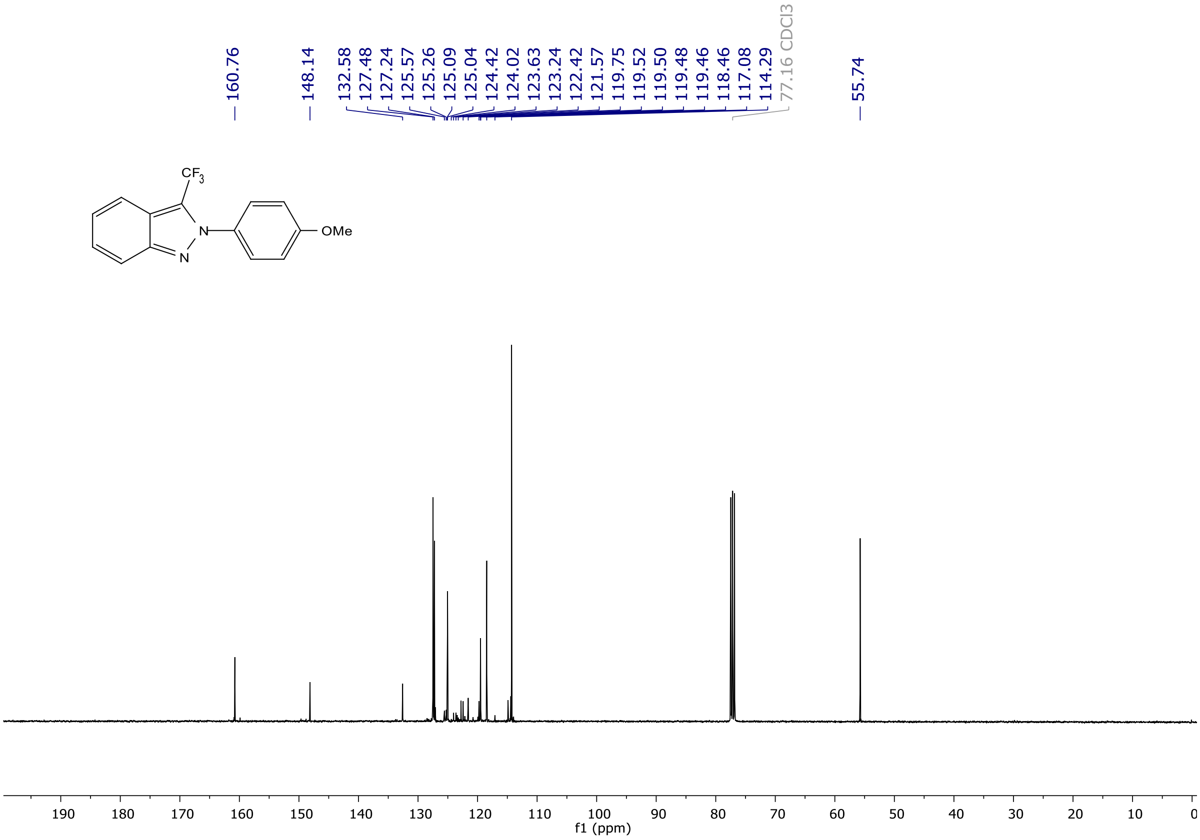
$^{13}C\{^1H\}$ NMR spectrum of **2a**, $CDCl_3$, 100 MHz



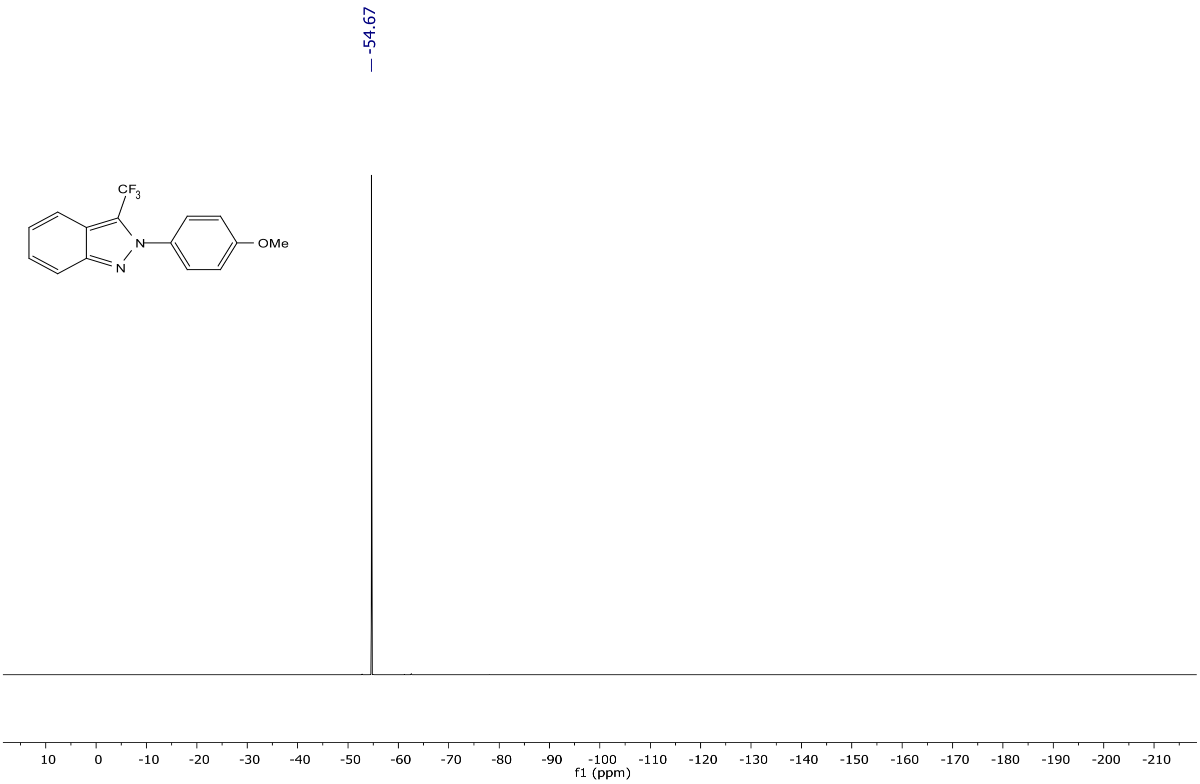
$^{19}F\{^1H\}$ NMR spectrum of **2a**, $CDCl_3$, 377 MHz



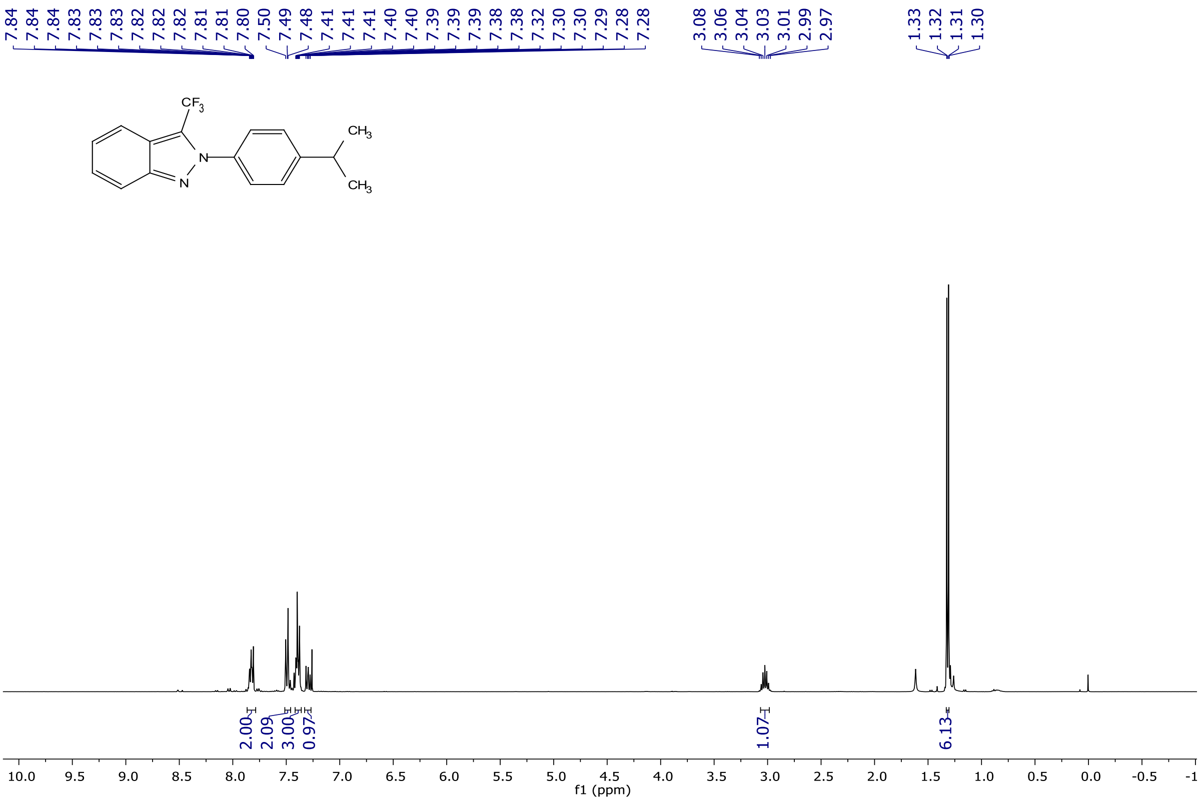
$^{1}$H NMR spectrum of **2b**, $CDCl_3$, 400 MHz



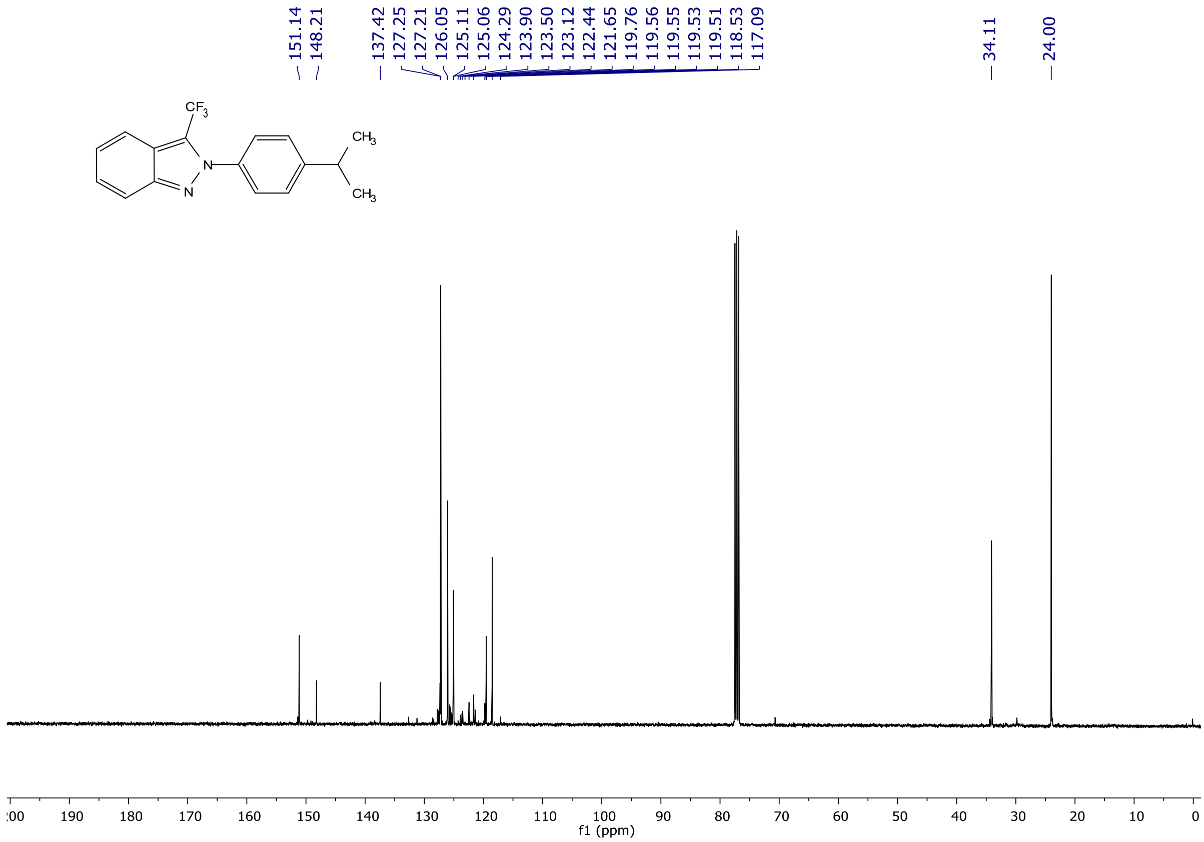
$^{13}C\{^{1}H\}$ NMR spectrum of **2b**, $CDCl_3$, 100 MHz



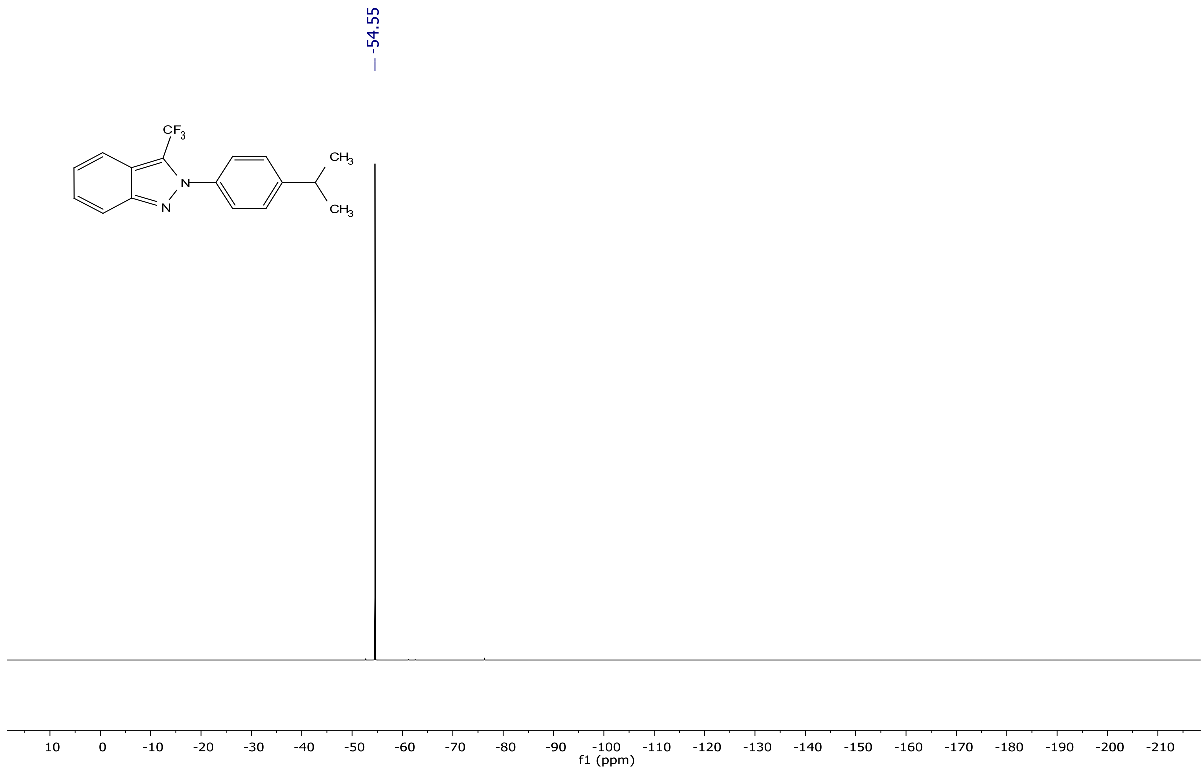
$^{19}$F{$^{1}$H} NMR spectrum of **2b**, CDCl$_3$, 377 MHz



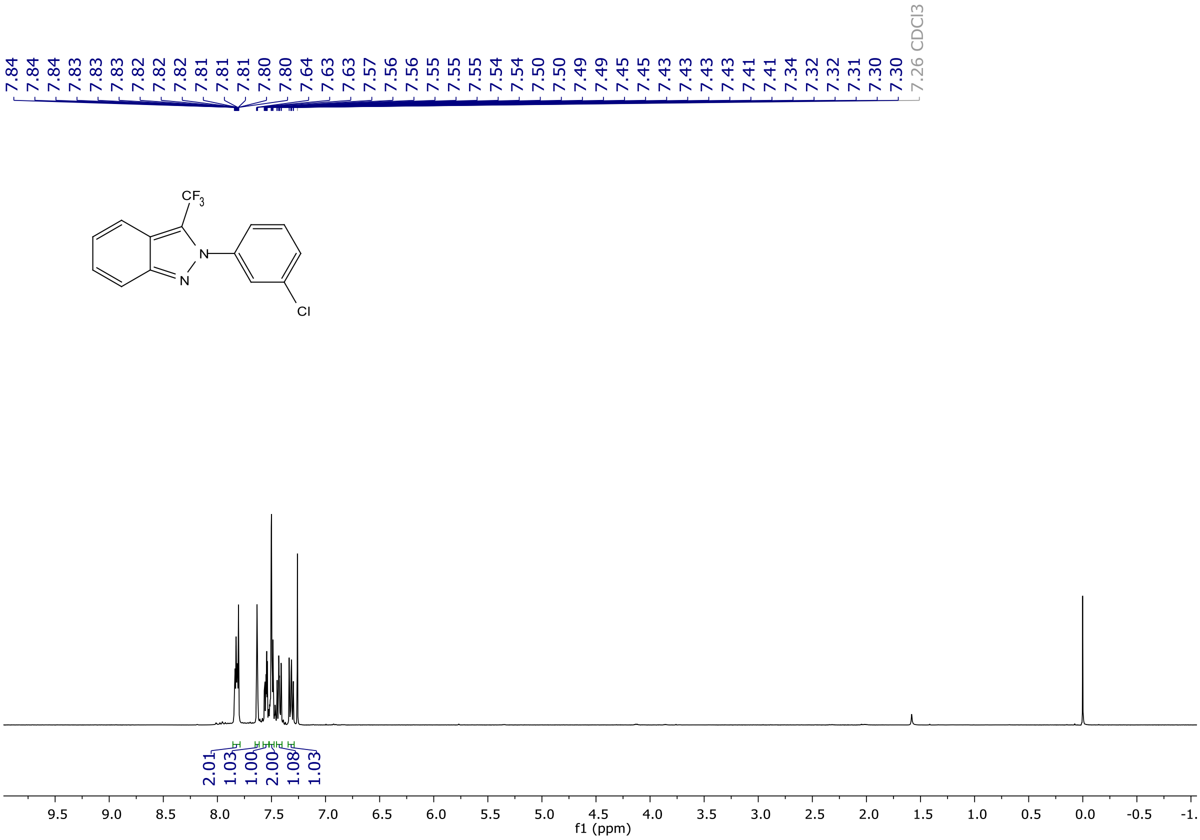
$^{1}$H NMR spectrum of **2c**, CDCl$_3$, 400 MHz



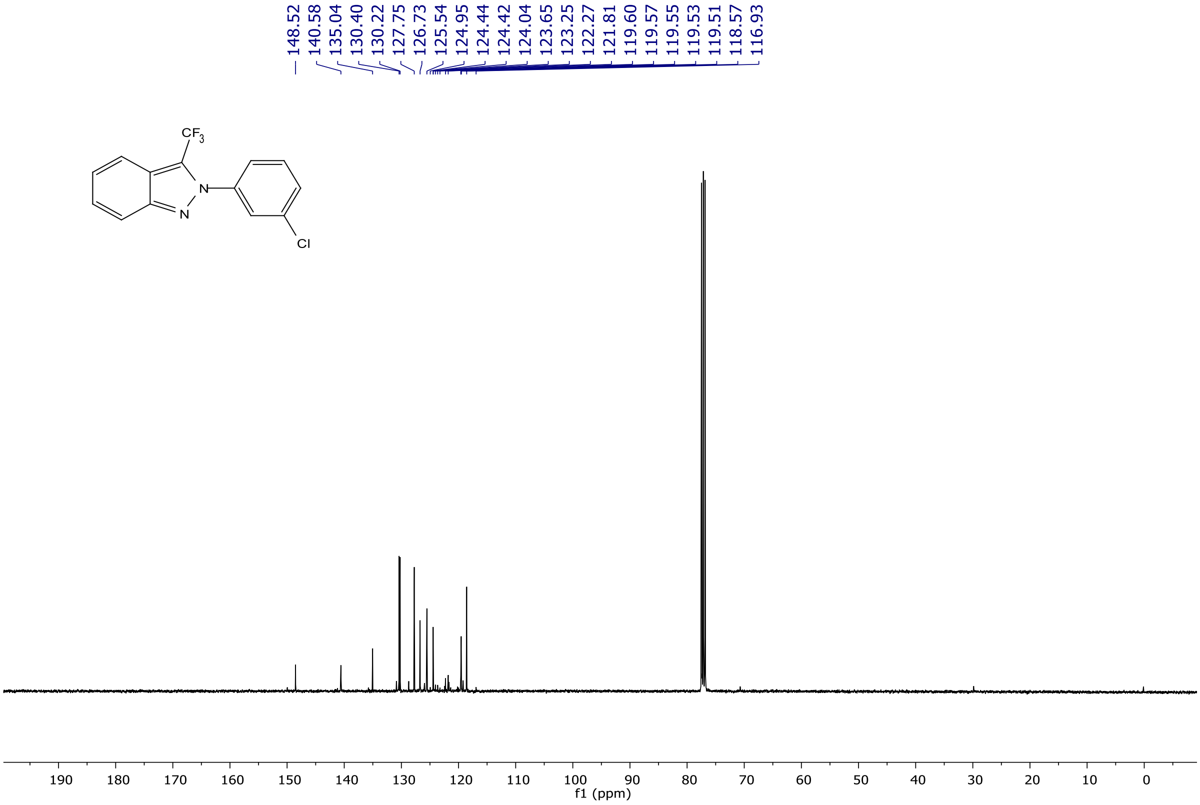
$^{13}C\{^{1}H\}$ NMR spectrum of **2c**, $CDCl_3$, 100 MHz



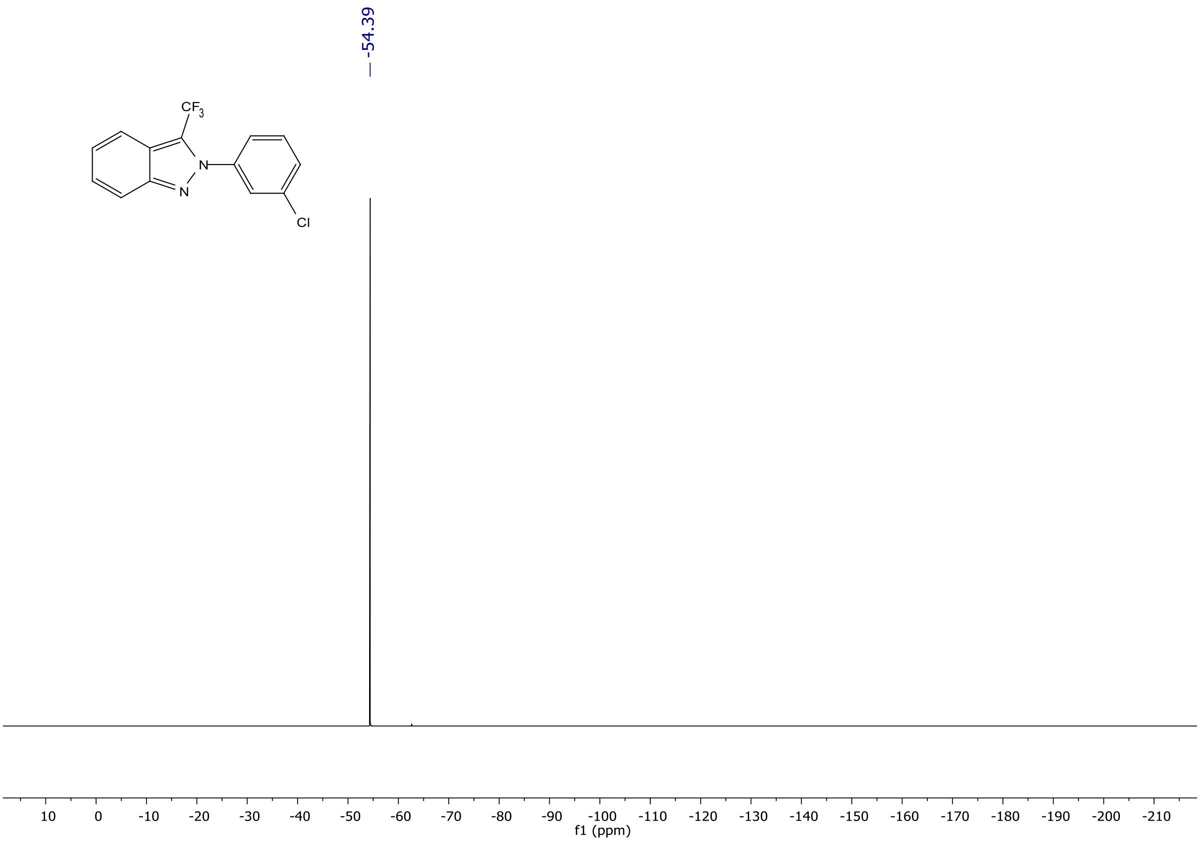
$^{19}F\{^{1}H\}$ NMR spectrum of **2c**, $CDCl_3$, 377 MHz



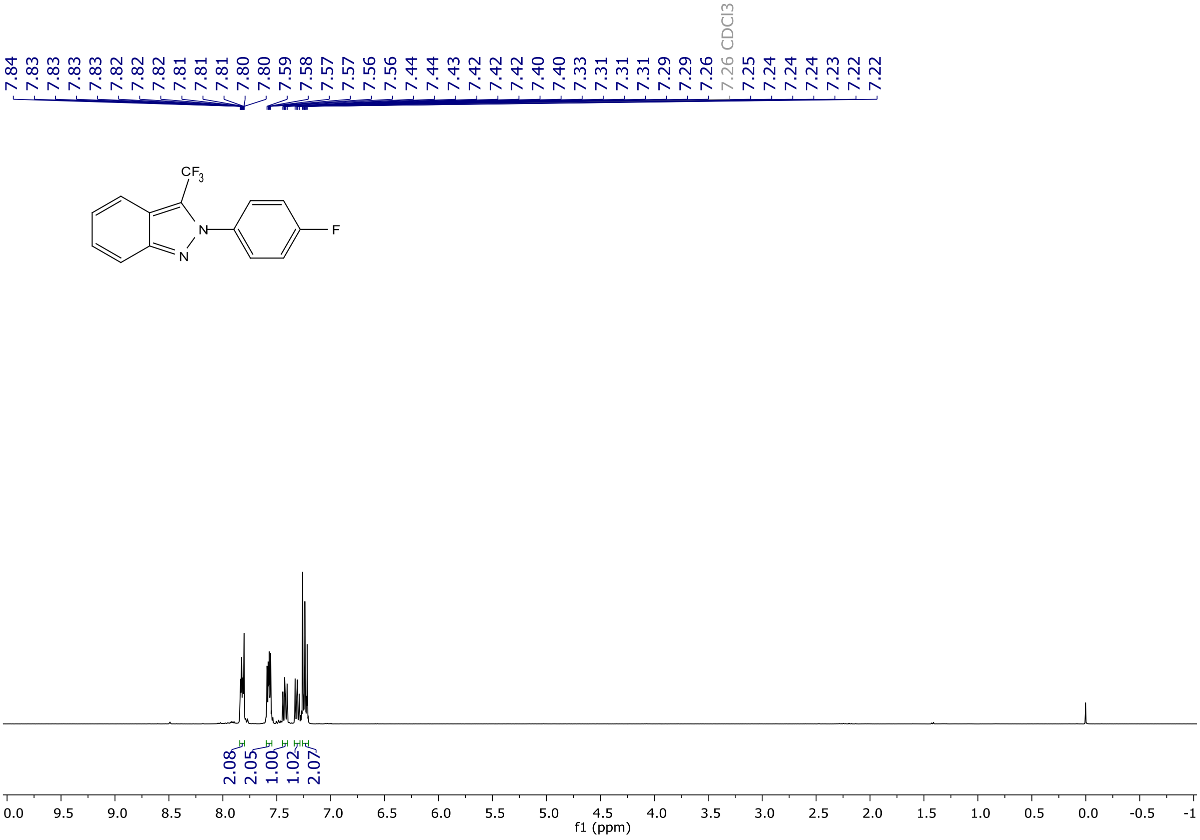
$^1$H NMR spectrum of **2d**, CDCl$_3$, 400 MHz



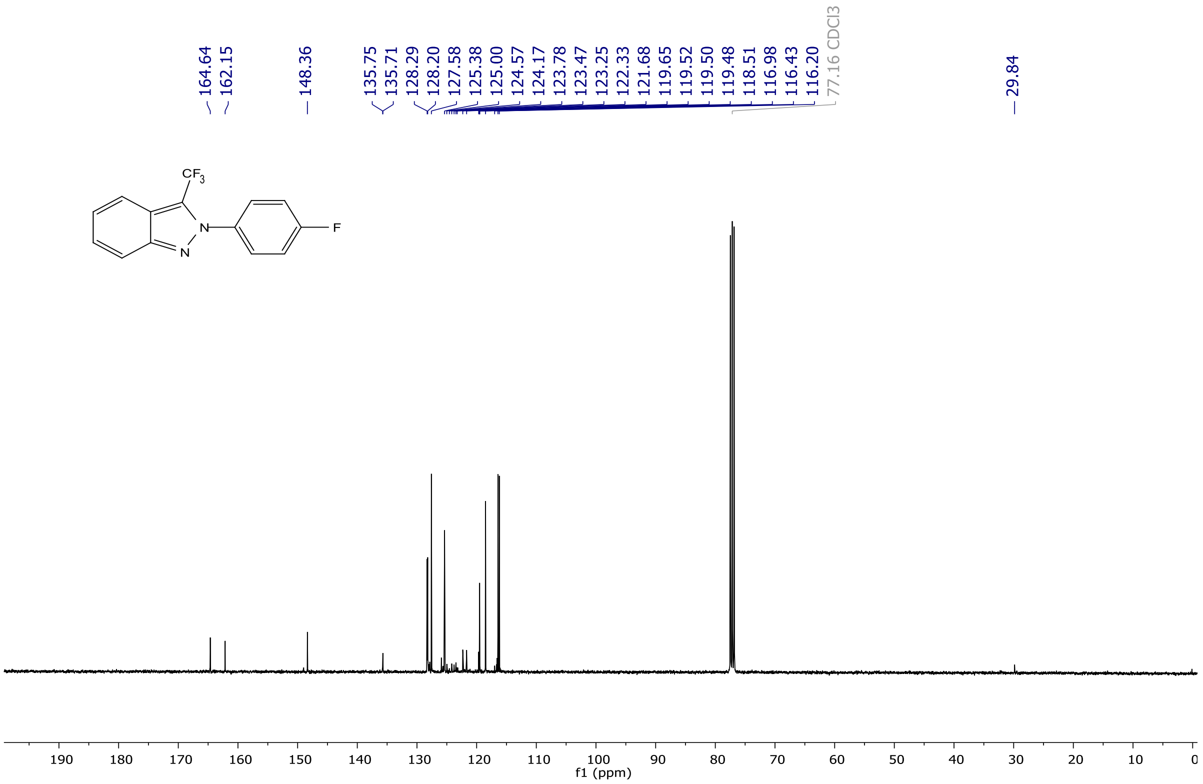
$^{13}$C{$^1$H} NMR spectrum of **2d**, CDCl$_3$, 100 MHz



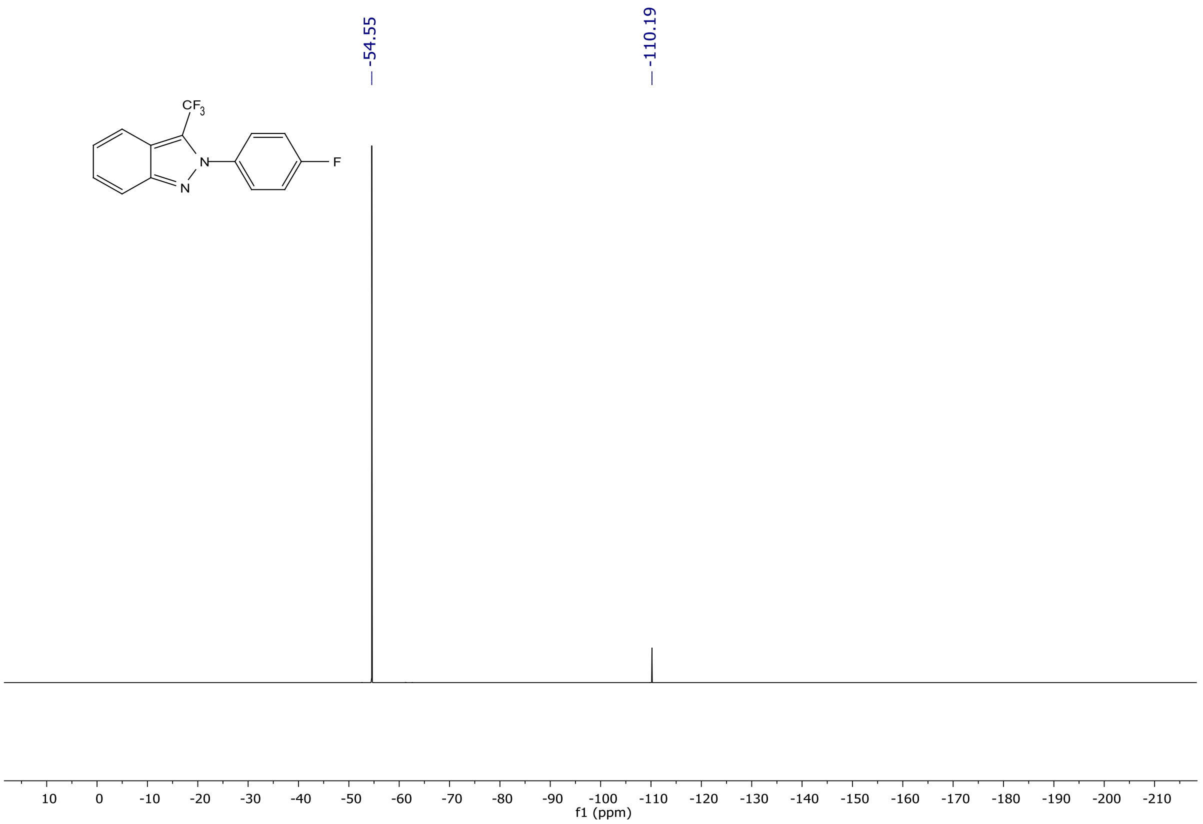
$^{19}$F{$^{1}$H} NMR spectrum of **2d**, CDCl$_3$, 377 MHz



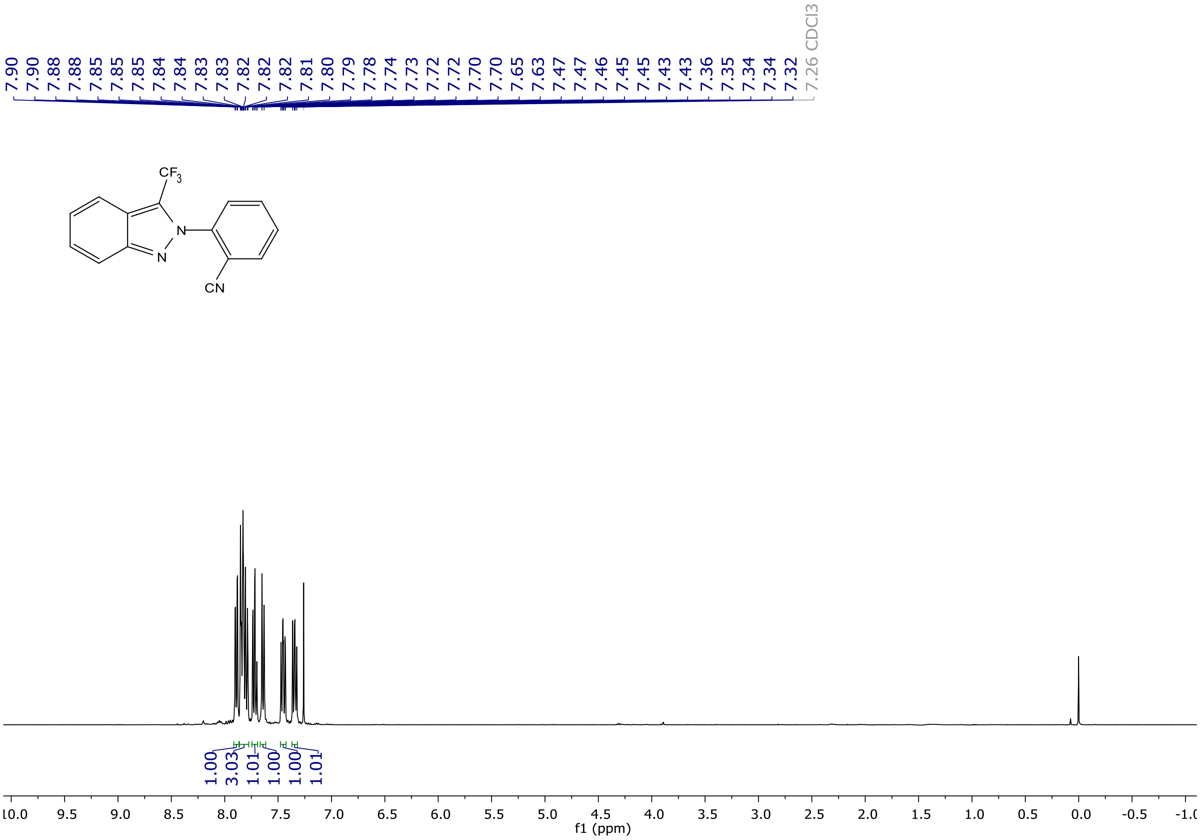
$^{1}$H NMR spectrum of **2e**, CDCl$_3$, 400 MHz



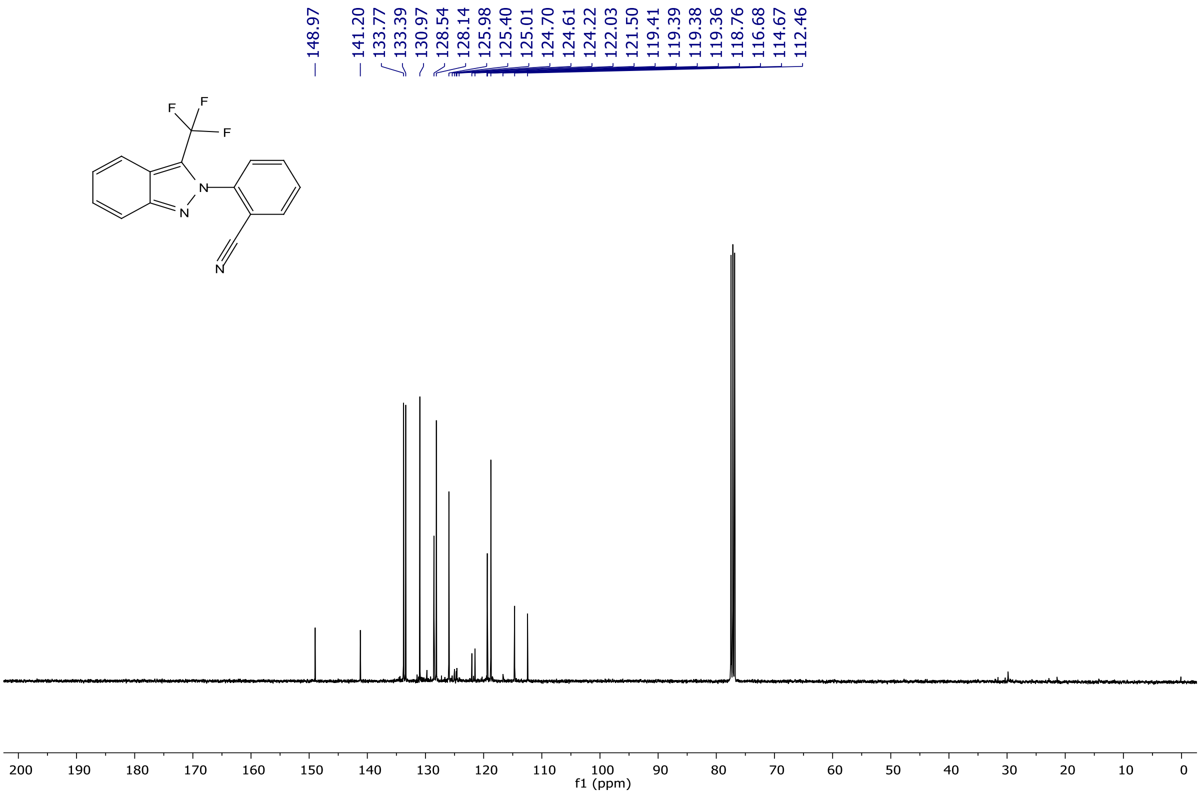
$^{13}$C{$^{1}$H} NMR spectrum of **2e**, CDCl$_3$, 100 MHz



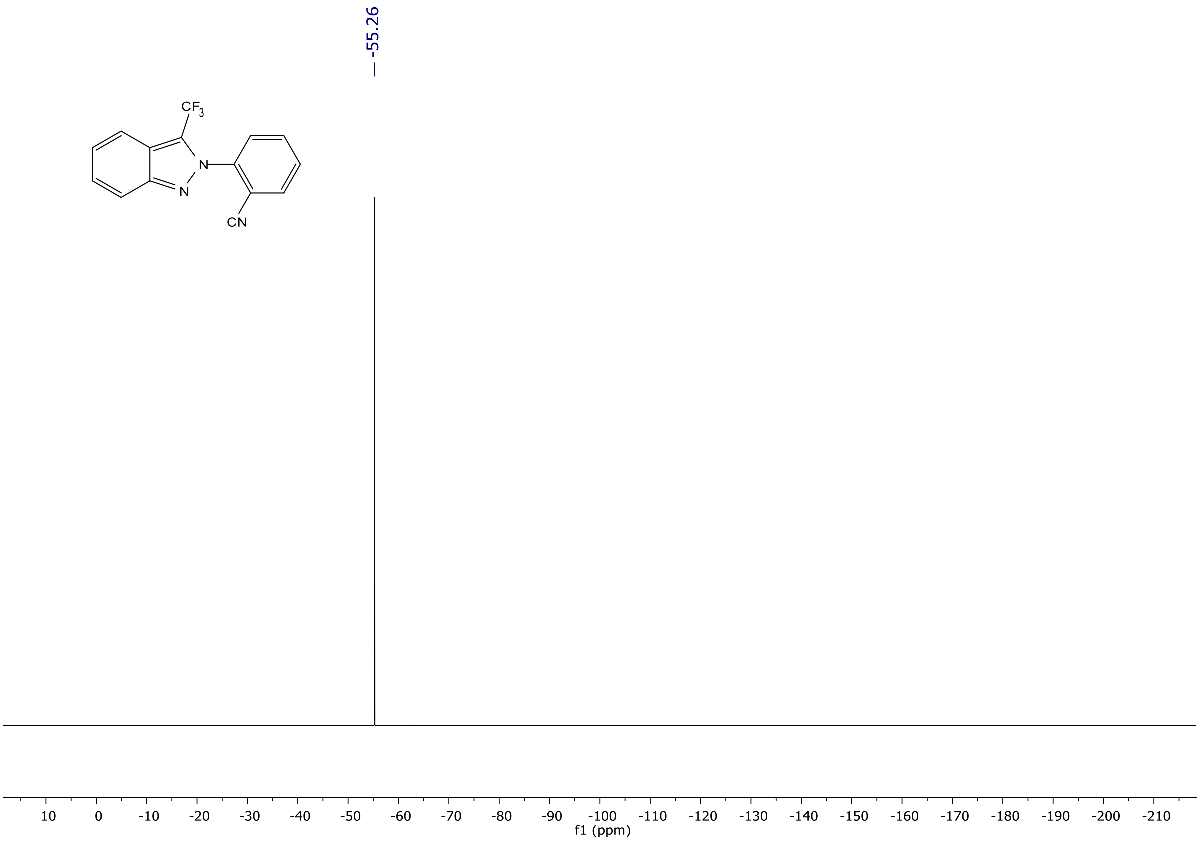
$^{19}$F{$^{1}$H} NMR spectrum of **2e**, CDCl$_3$, 377 MHz



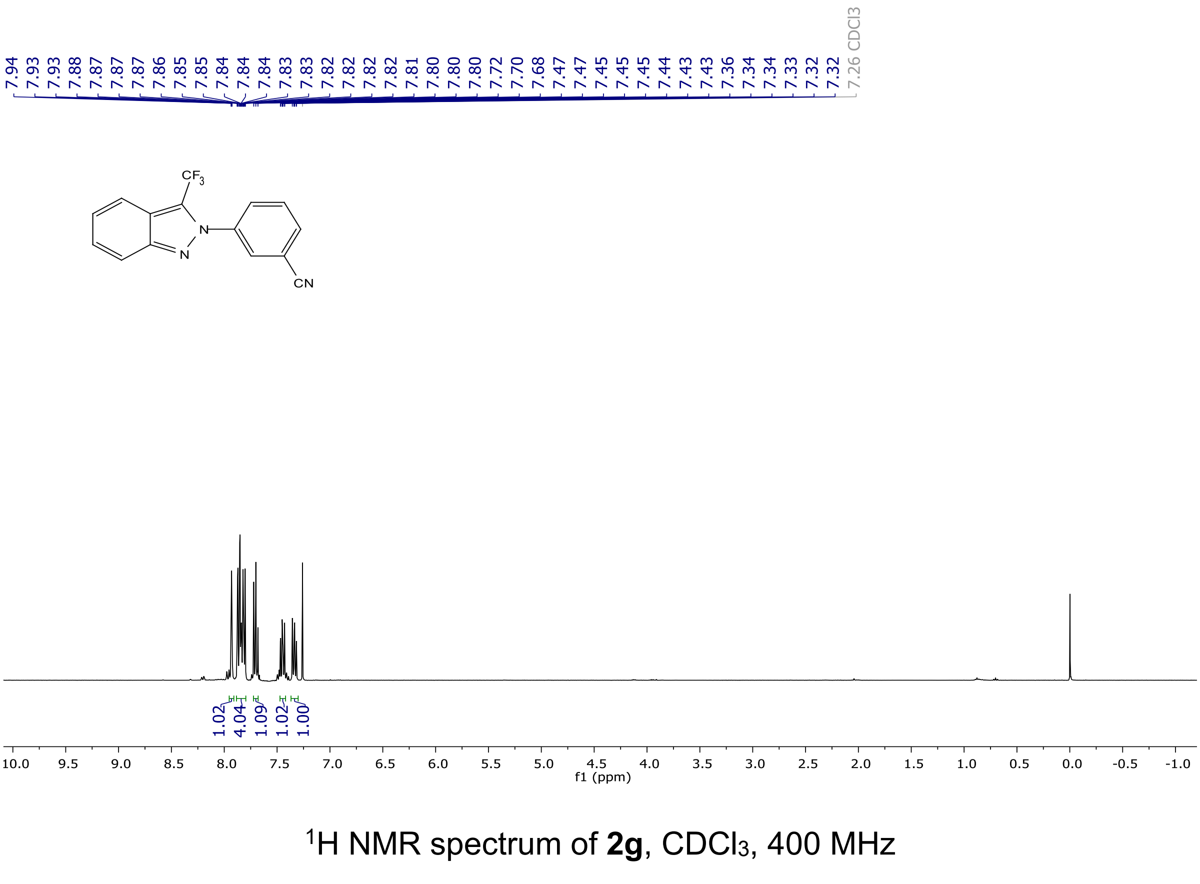
$^{1}$H NMR spectrum of **2f**, CDCl$_3$, 400 MHz



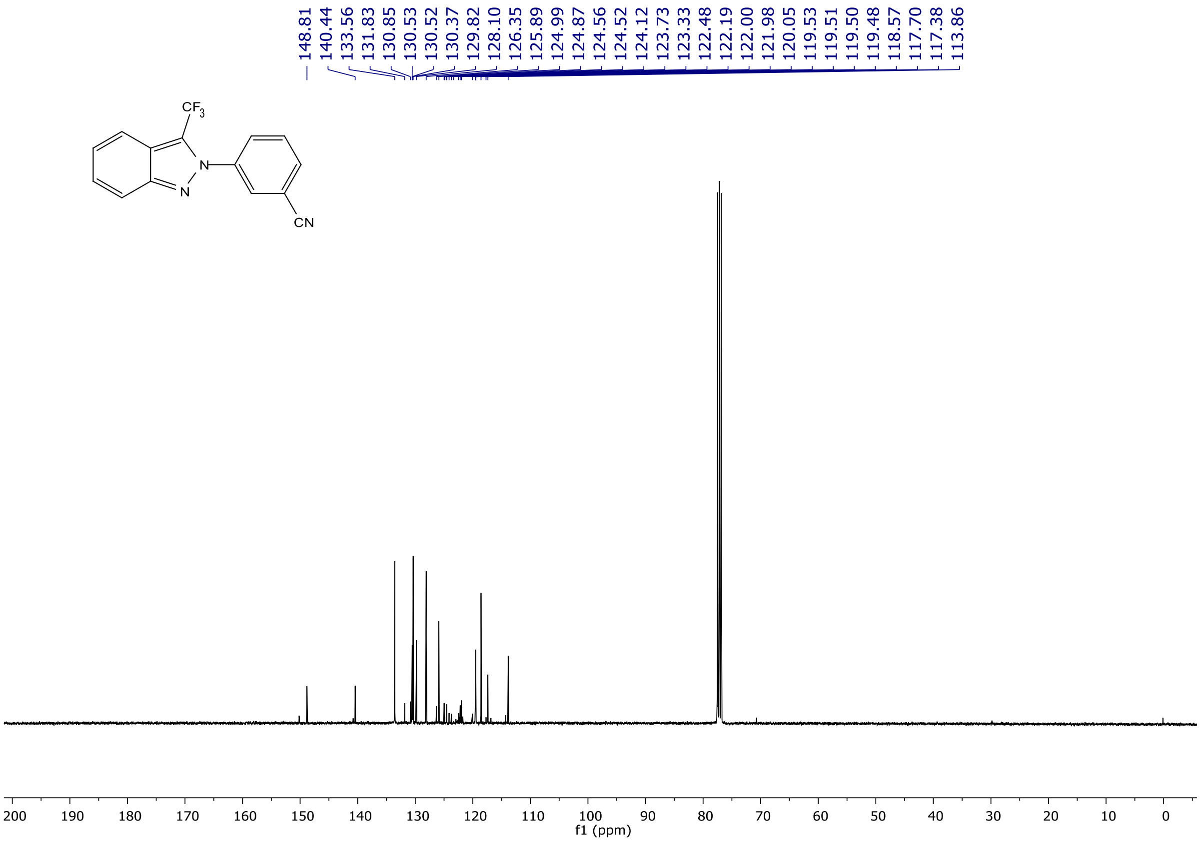
$^{13}$C{$^{1}$H} NMR spectrum of **2f**, CDCl$_3$, 100 MHz



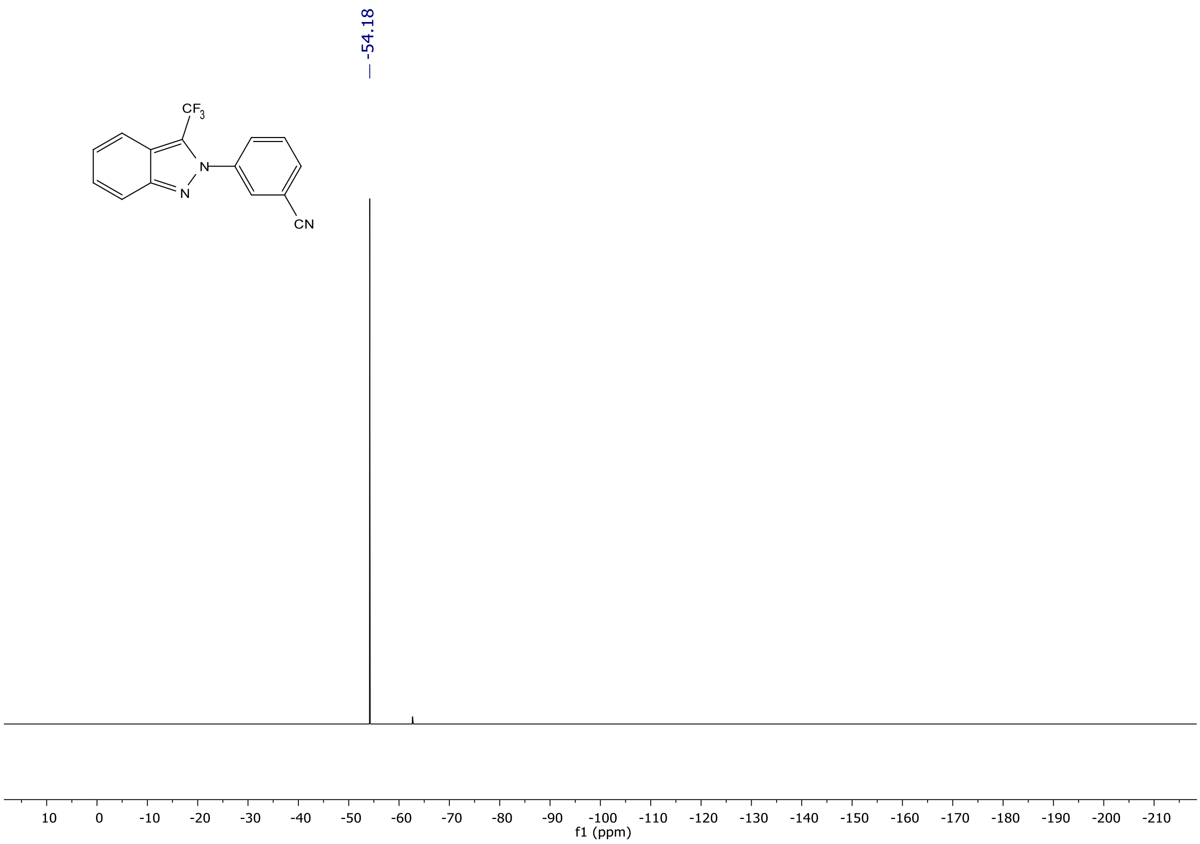
$^{19}F\{^1H\}$ NMR spectrum of **2f**, $CDCl_3$, 377 MHz



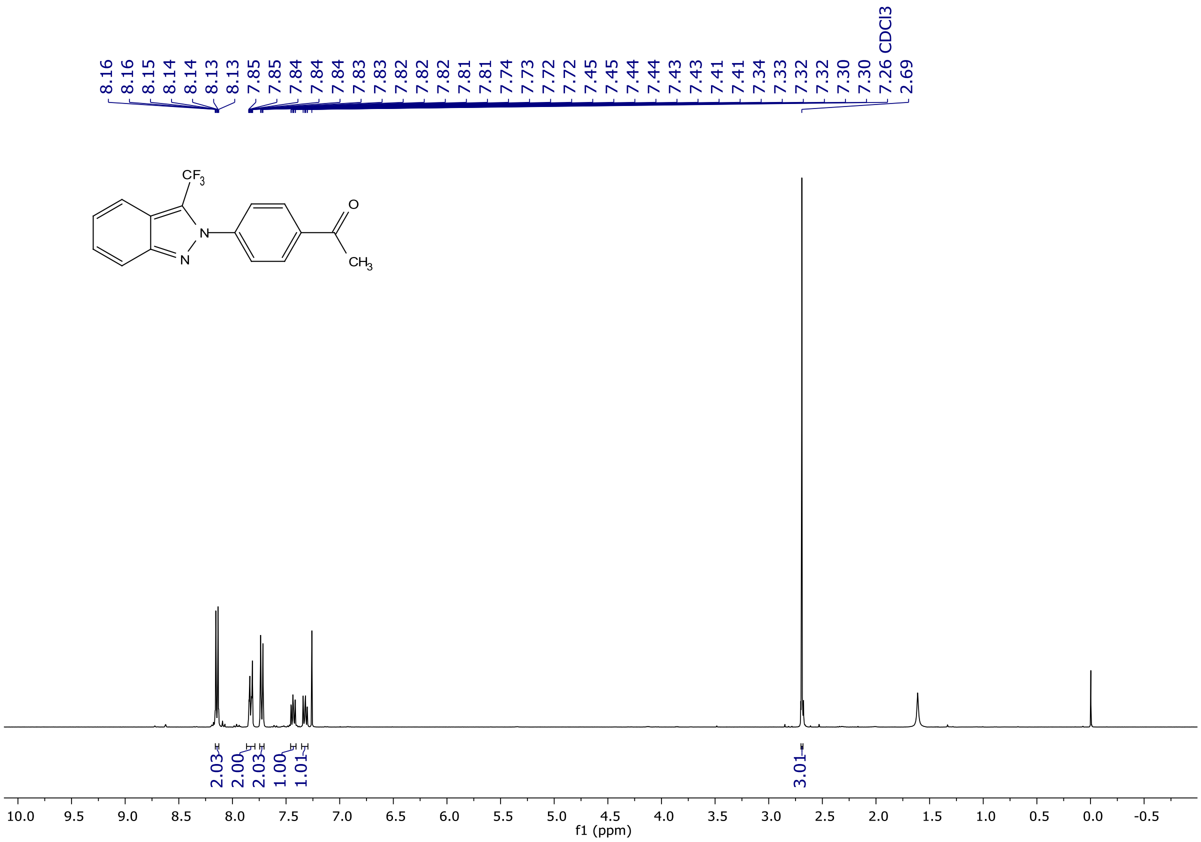
$^1H$ NMR spectrum of **2g**, $CDCl_3$, 400 MHz



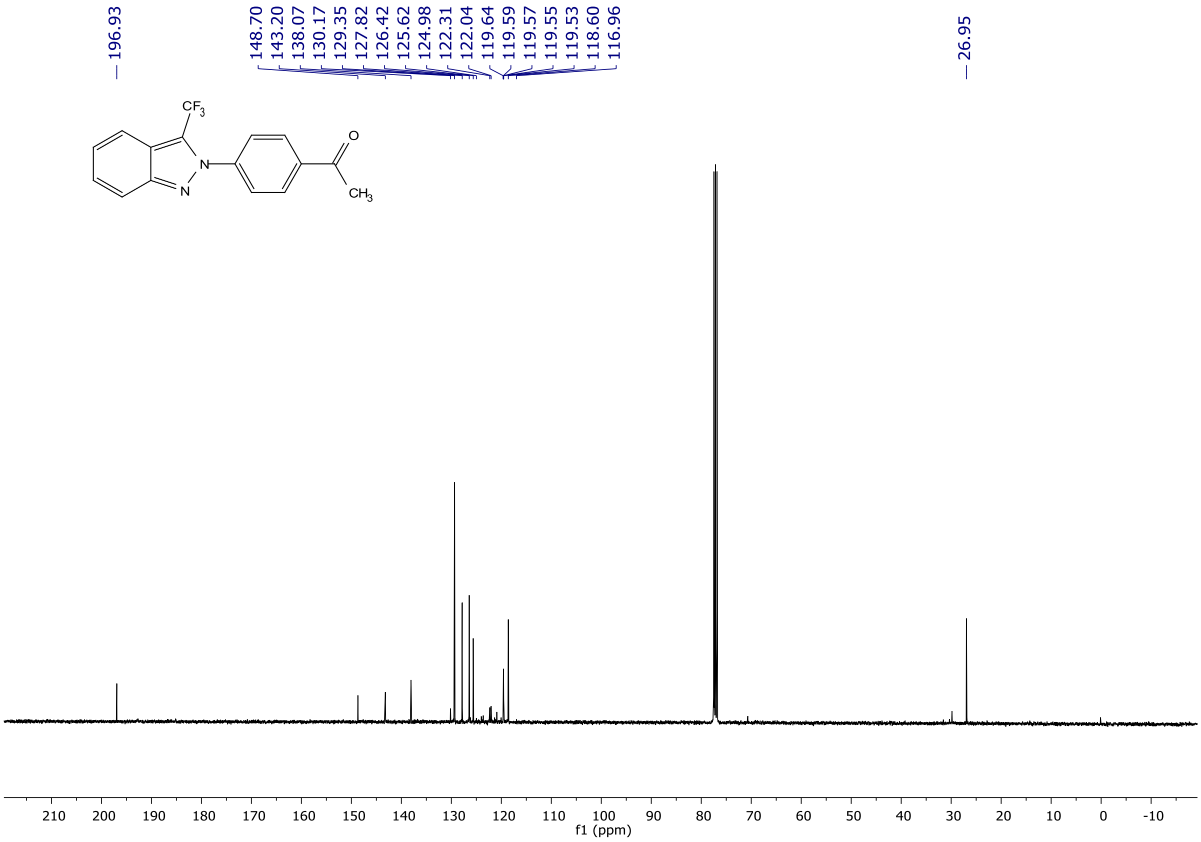
$^{13}$C{$^{1}$H} NMR spectrum of **2g**, CDCl$_3$, 100 MHz



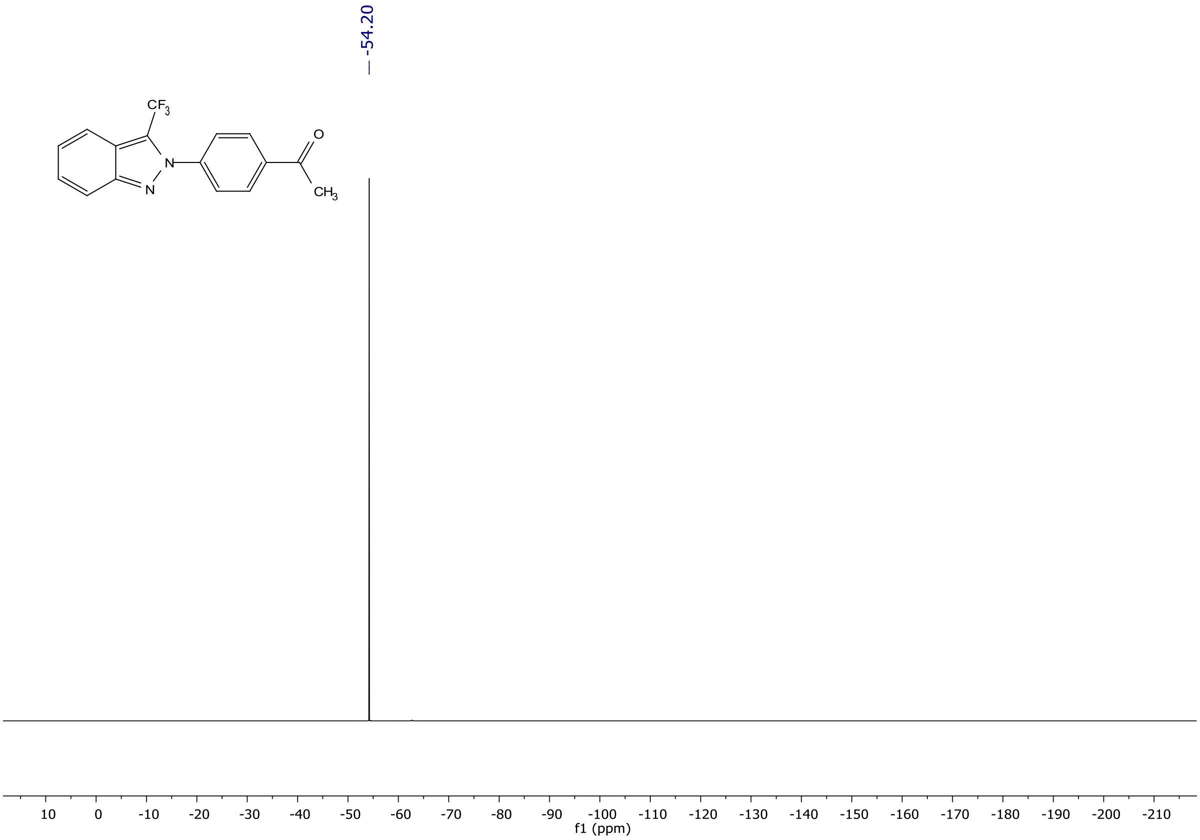
$^{19}$F{$^{1}$H} NMR spectrum of **2g**, CDCl$_3$, 377 MHz



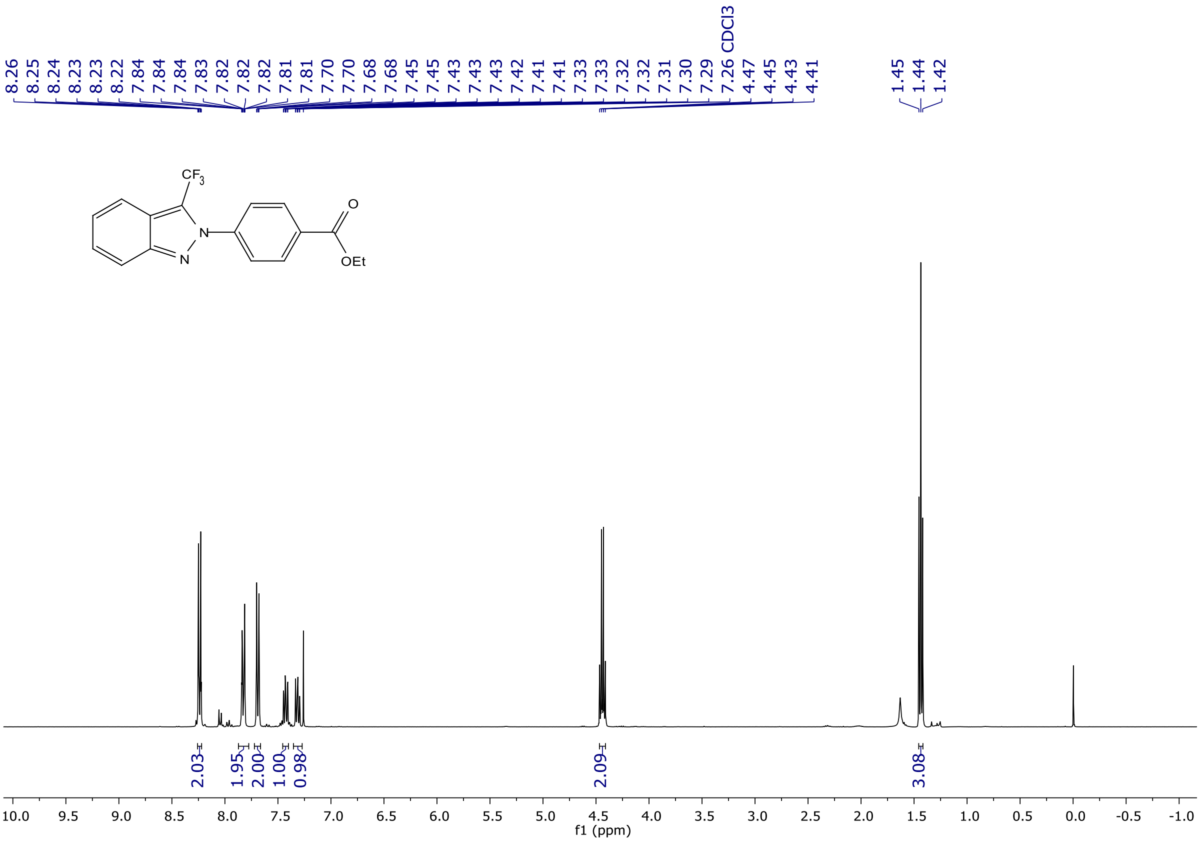
$^1$H NMR spectrum of **2h**, CDCl$_3$, 400 MHz



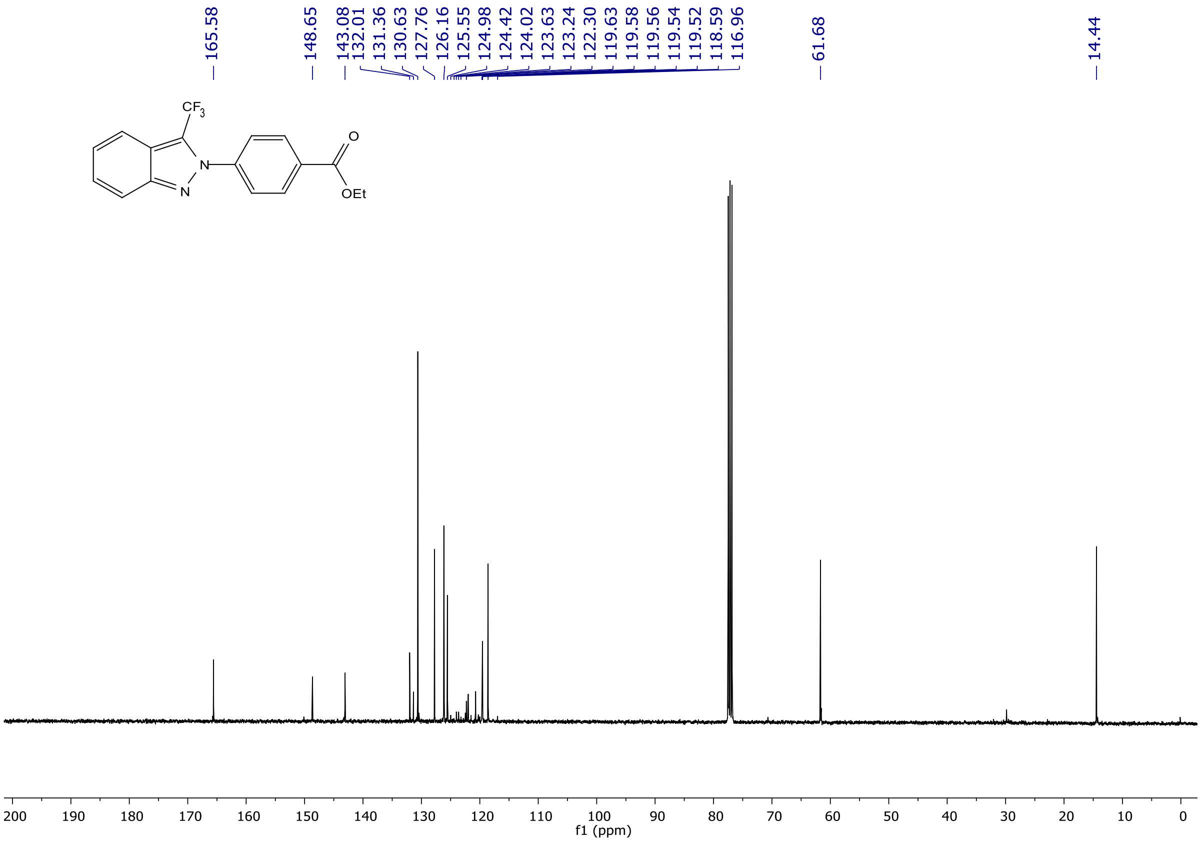
$^{13}$C{$^1$H} NMR spectrum of **2h**, CDCl$_3$, 100 MHz



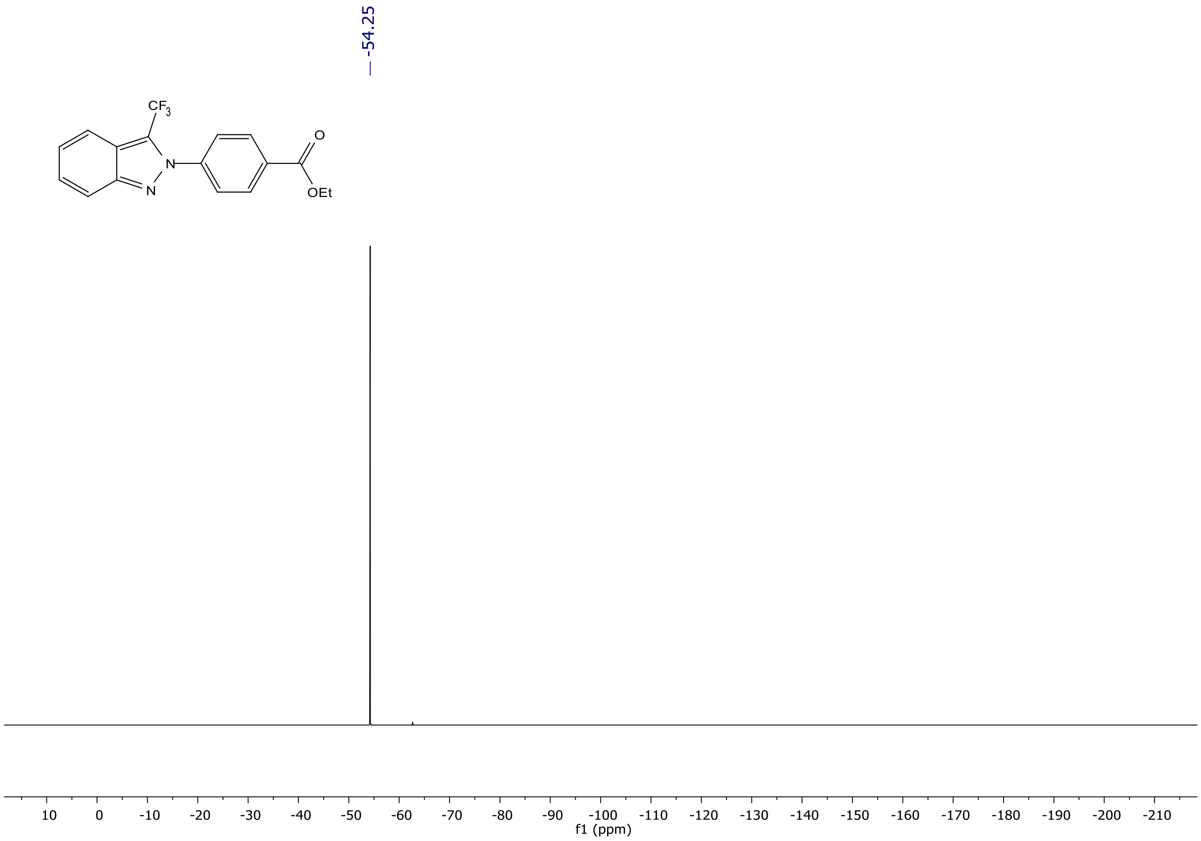
$^{19}F\{^{1}H\}$ NMR spectrum of **2h**, $CDCl_3$, 377 MHz



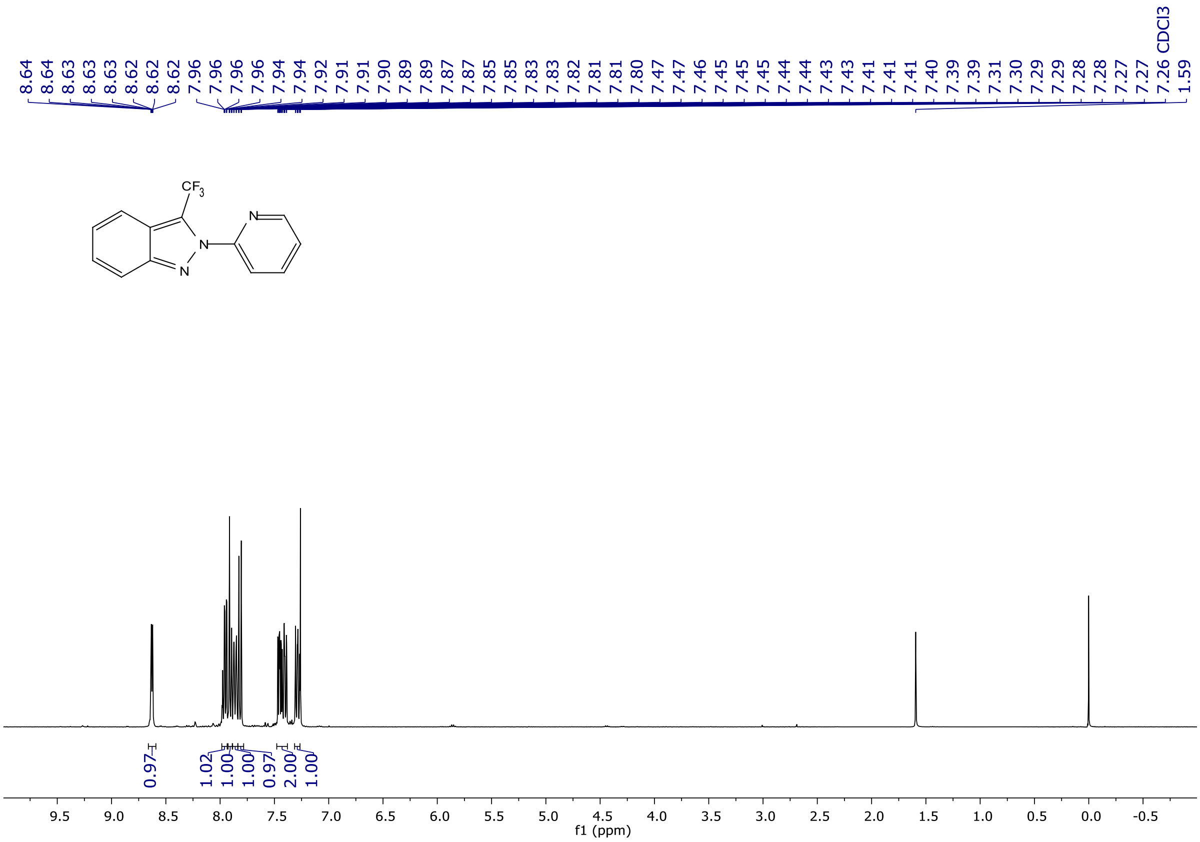
$^{1}H$ NMR spectrum of **2i**, $CDCl_3$, 400 MHz



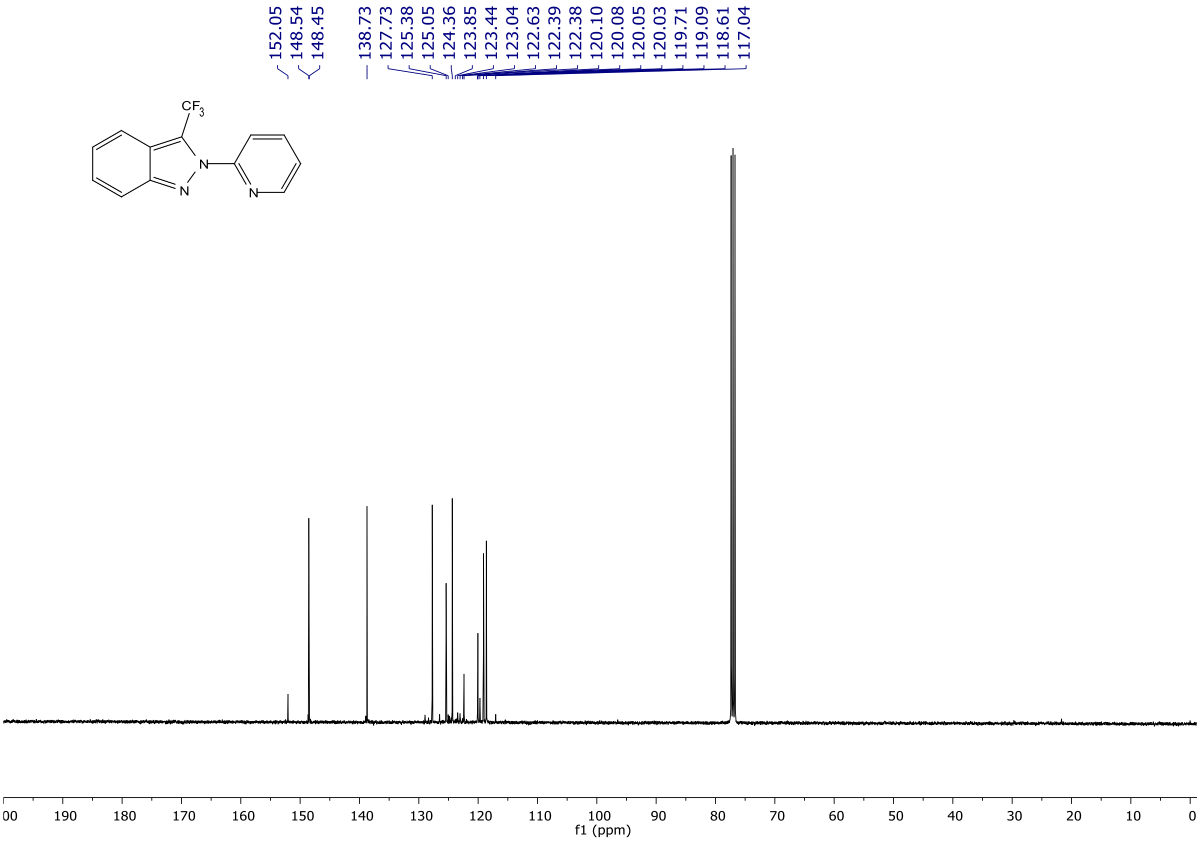
$^{13}$C{$^{1}$H} NMR spectrum of **2i**, CDCl$_3$, 100 MHz



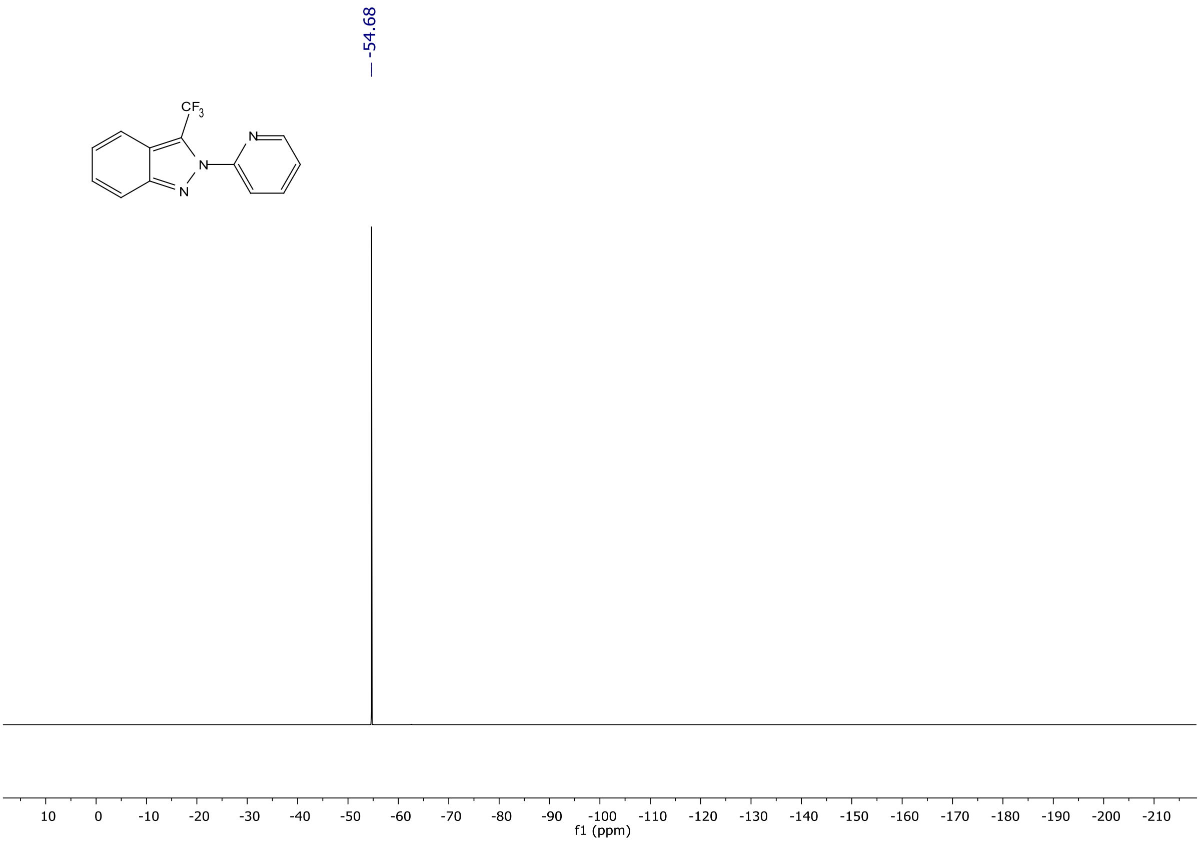
$^{19}$F{$^{1}$H} NMR spectrum of **2i**, CDCl$_3$, 377 MHz



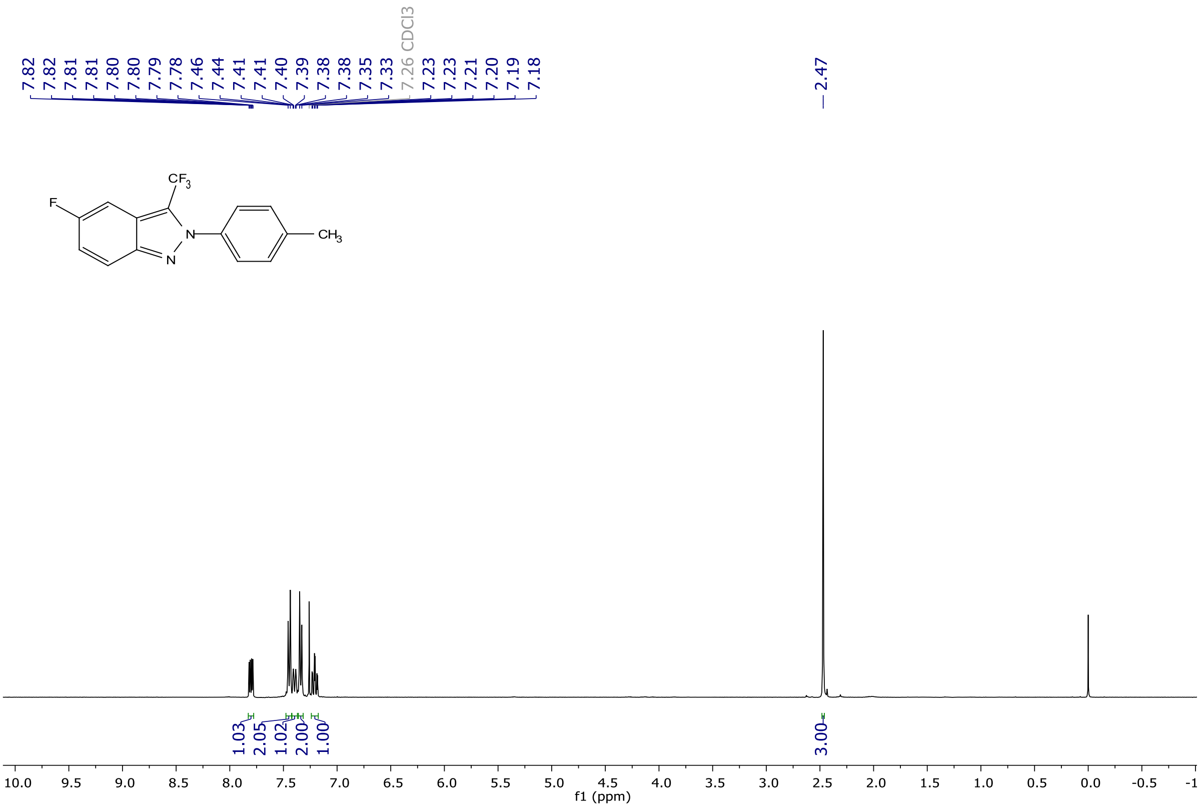
$^1$H NMR spectrum of **2j**, CDCl$_3$, 400 MHz



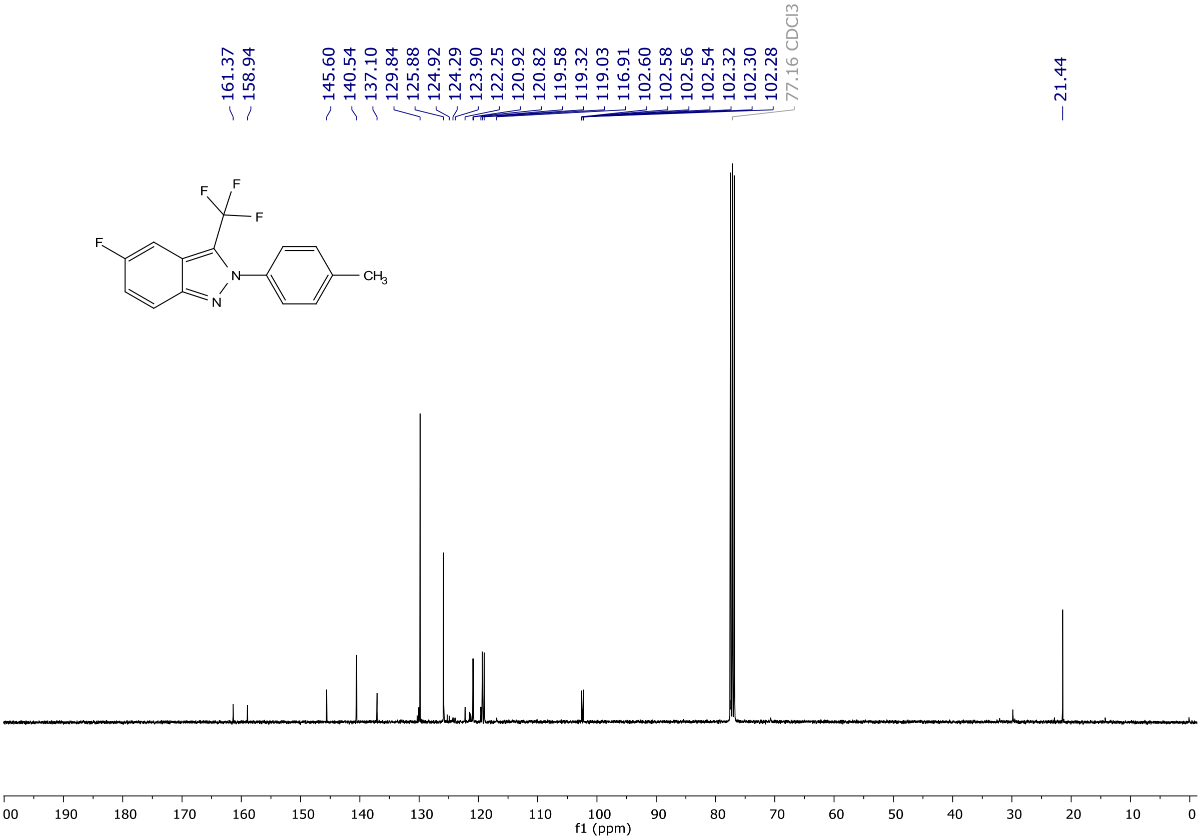
$^{13}$C{$^1$H} NMR spectrum of **2j**, CDCl$_3$, 100 MHz



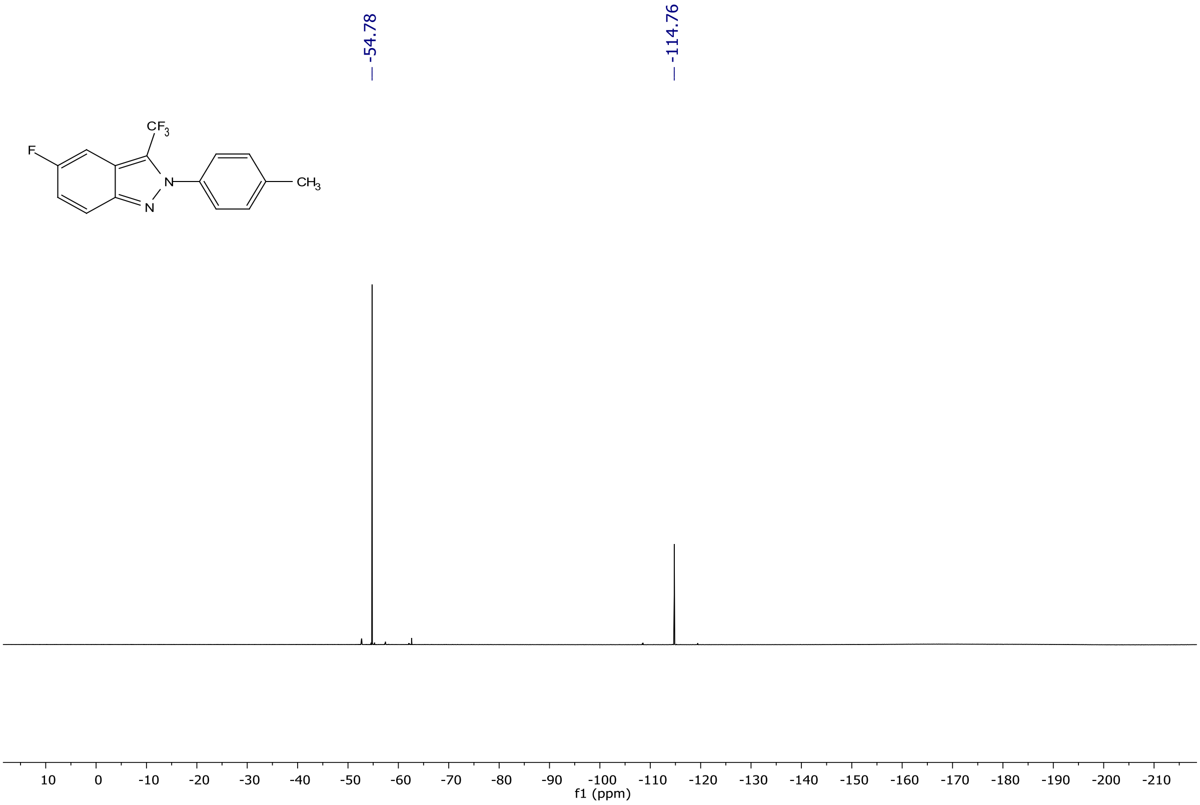
$^{19}F\{^1H\}$ NMR spectrum of **2j**, $CDCl_3$, 377 MHz



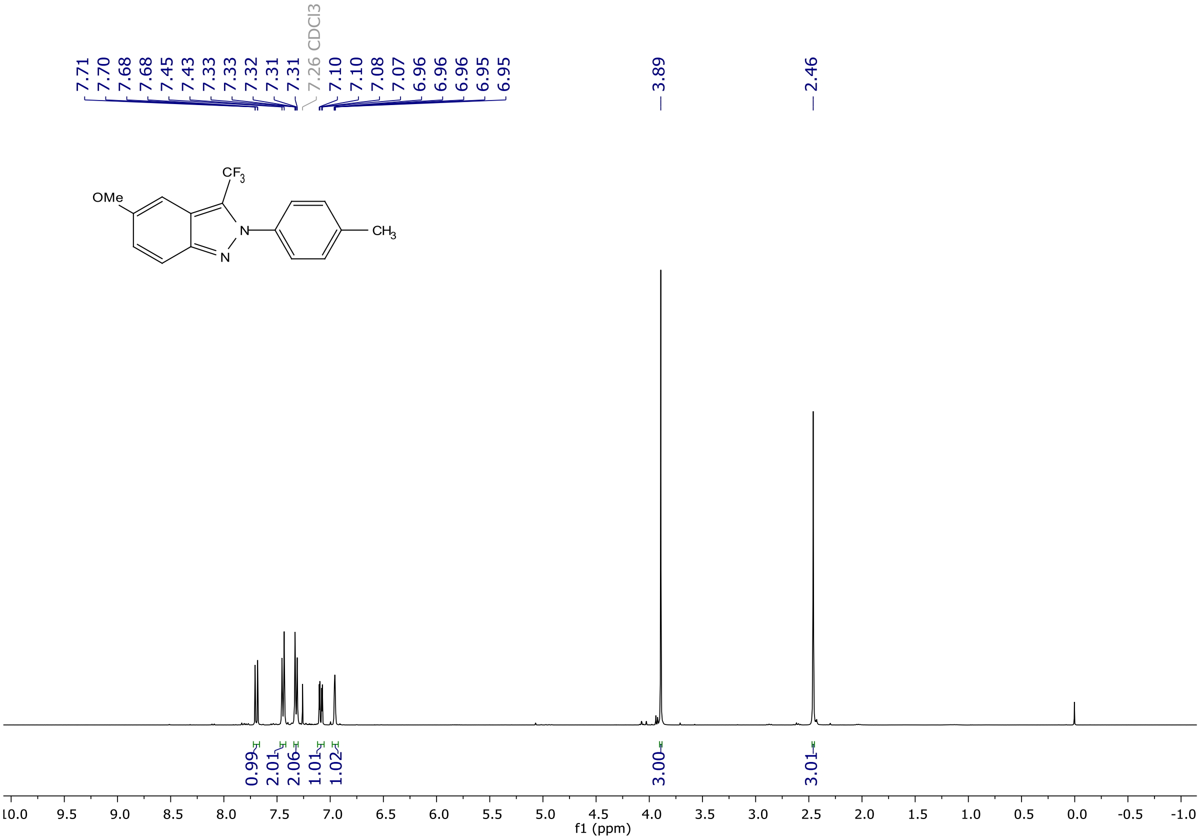
$^1$H NMR spectrum of **3a**, CDCl$_3$, 400 MHz



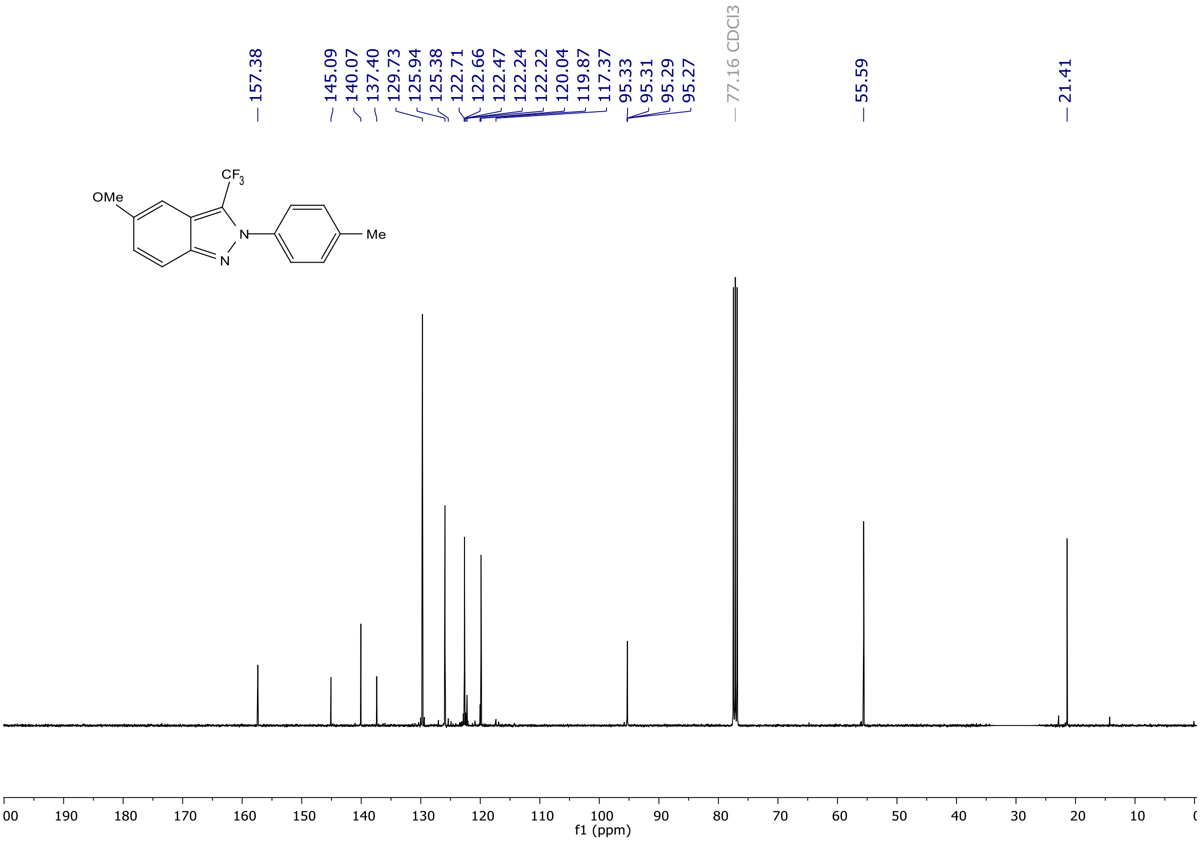
$^{13}$C{$^1$H} NMR spectrum of **3a**, CDCl$_3$, 100 MHz



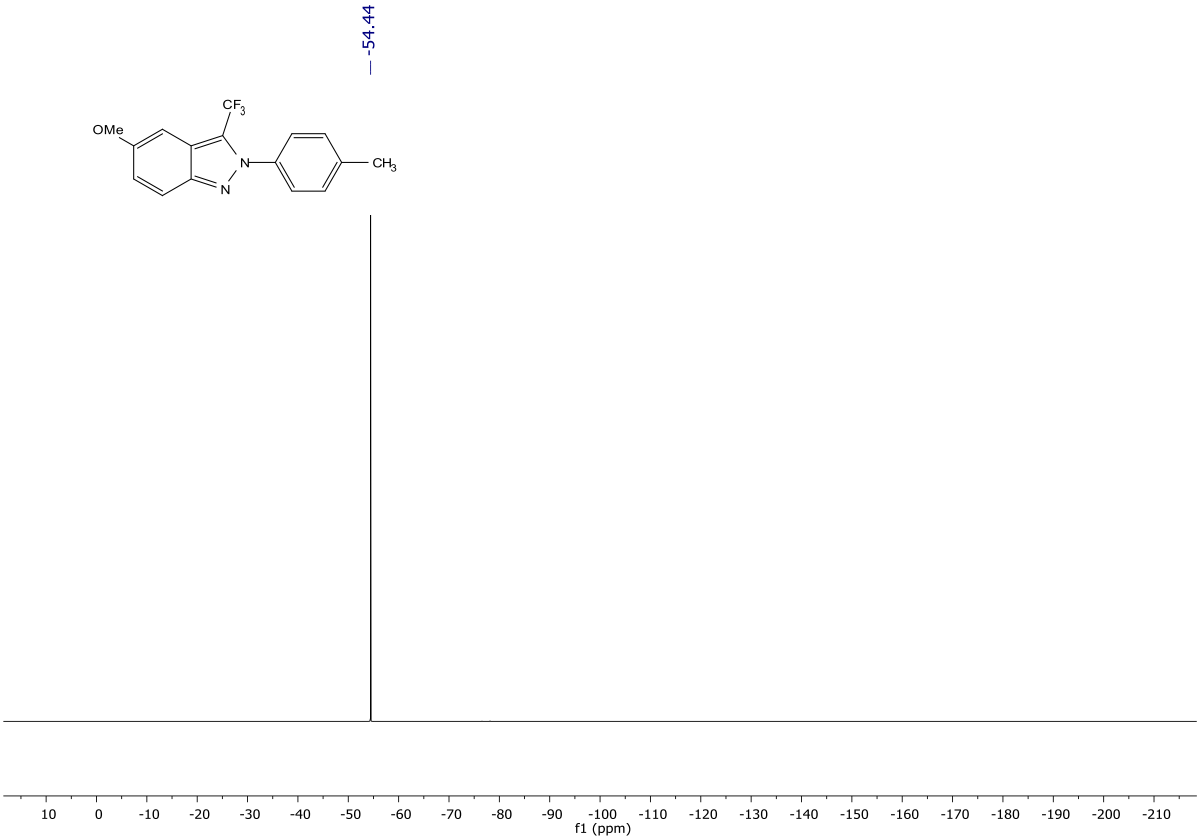
$^{19}$F{$^1$H} NMR spectrum of **3a**, CDCl$_3$, 377 MHz



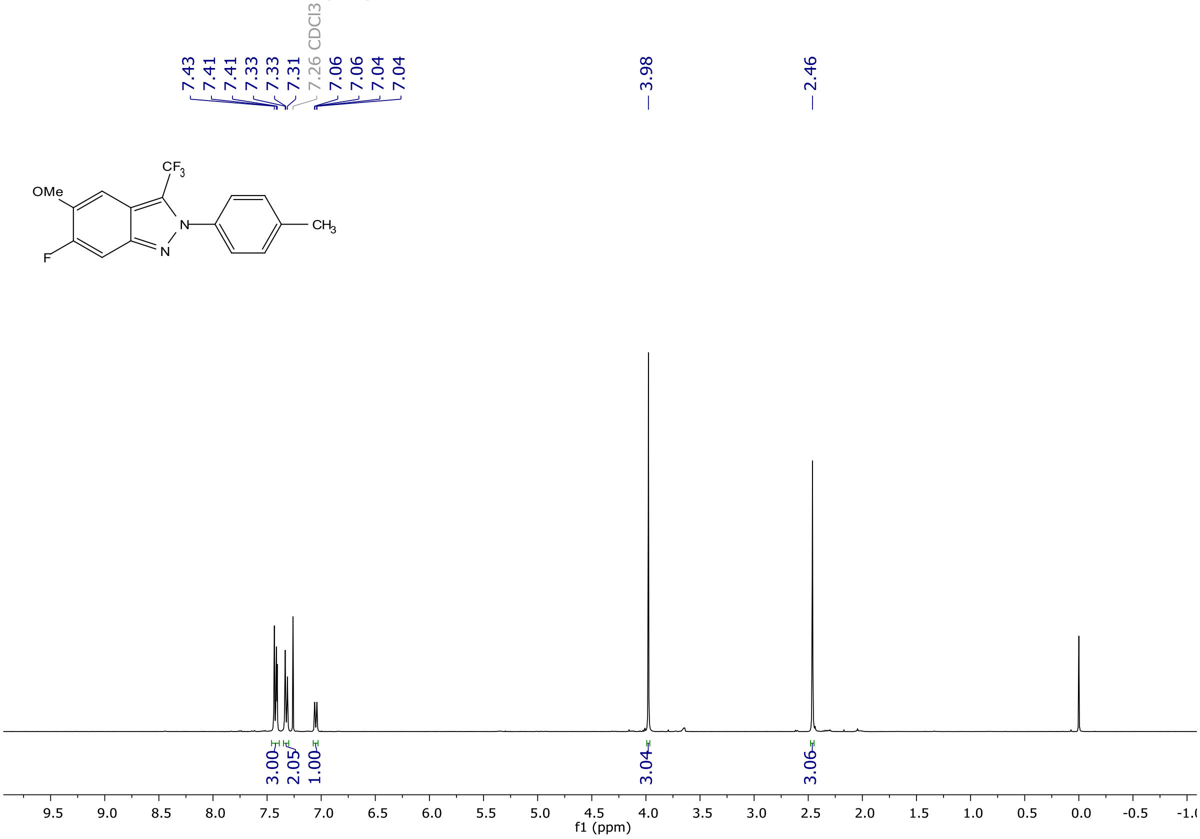
$^1$H NMR spectrum of **3b**, CDCl$_3$, 400 MHz



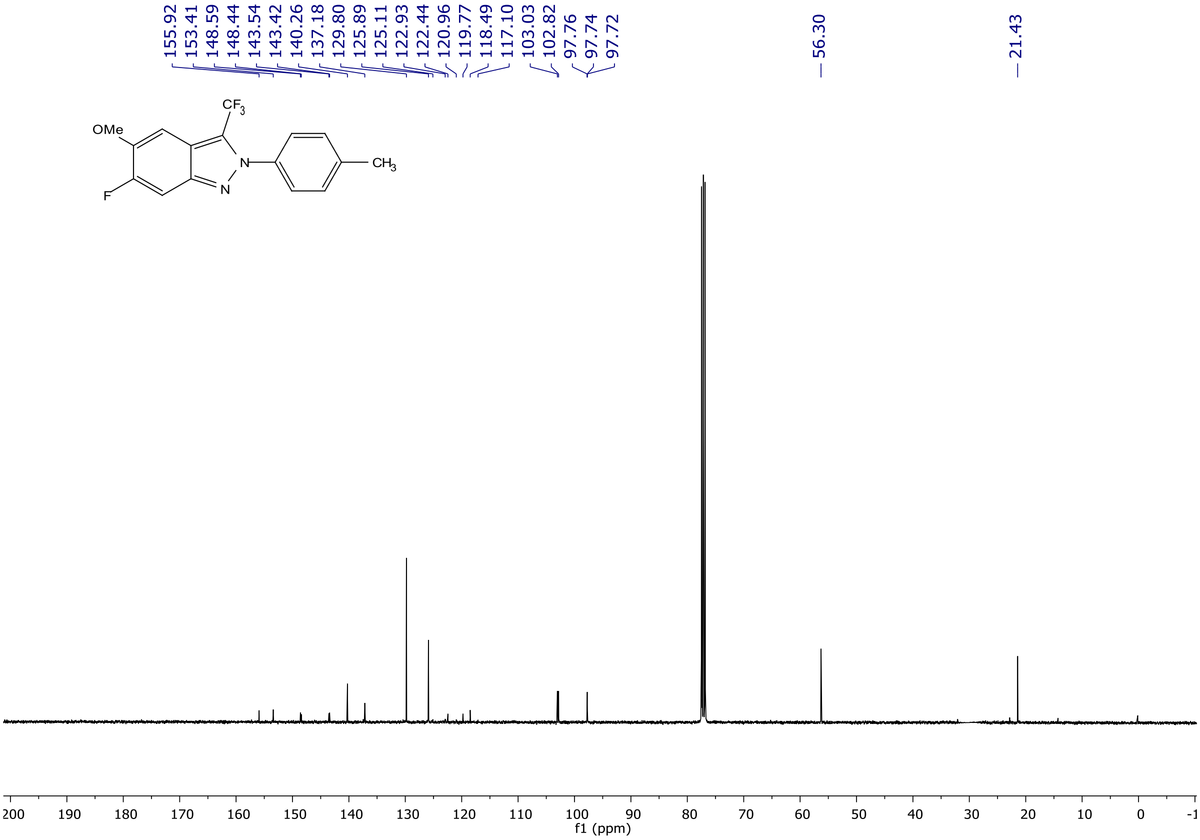
$^{13}$C{$^1$H} NMR spectrum of **3b**, CDCl$_3$, 100 MHz



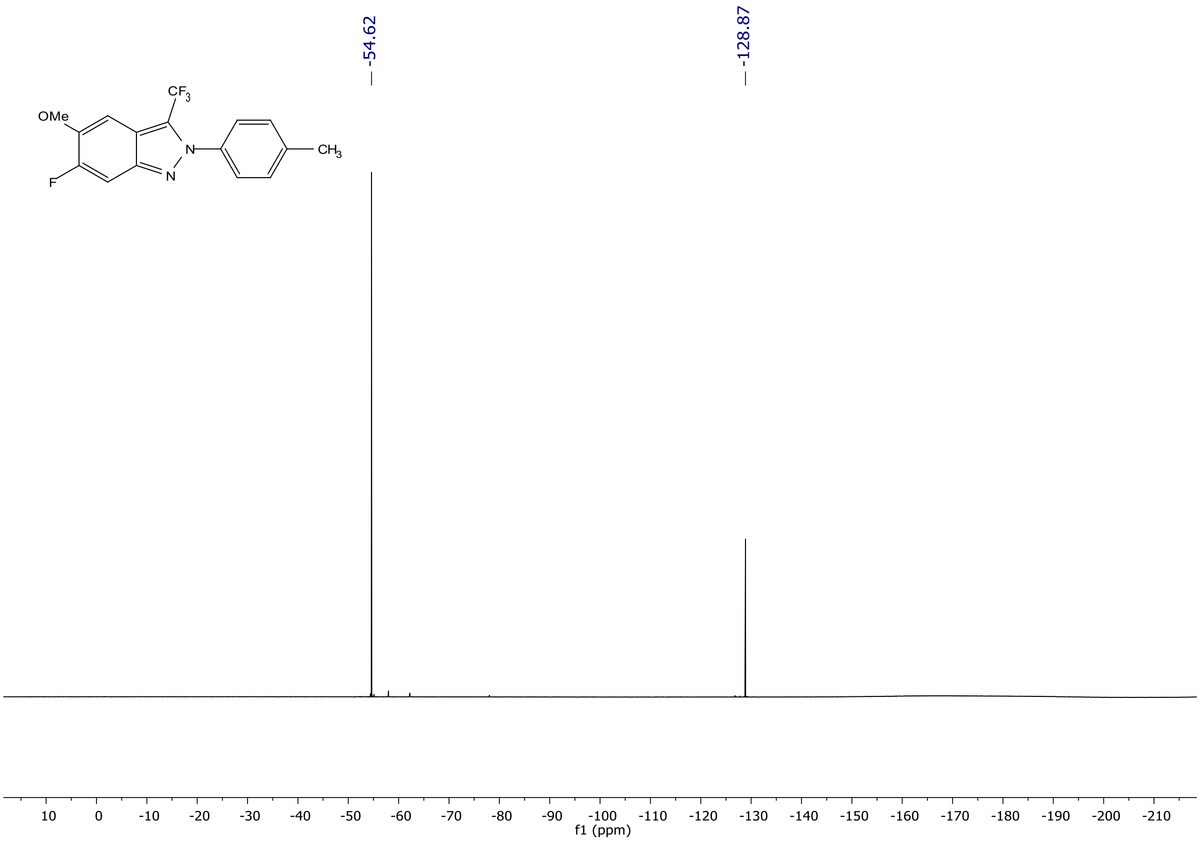
$^{19}F\{^{1}H\}$ NMR spectrum of **3b**, $CDCl_3$, 377 MHz



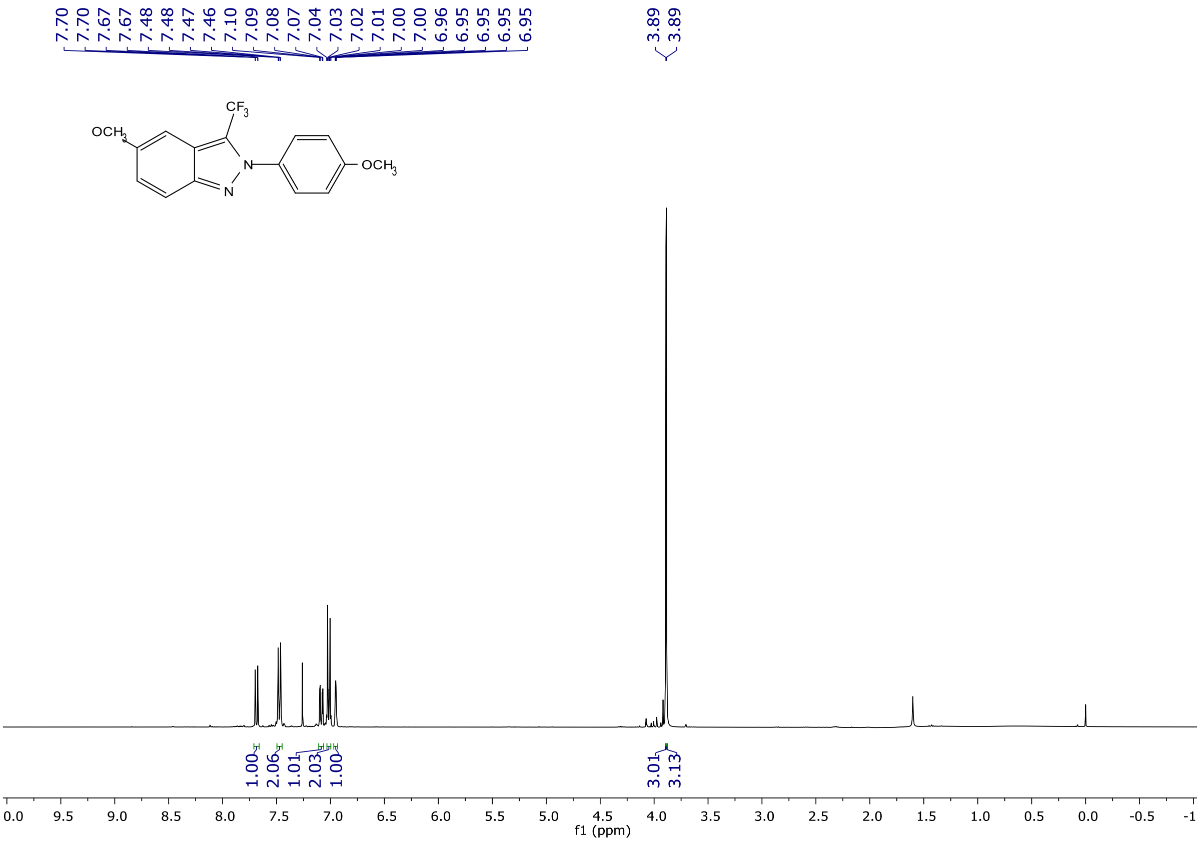
$^{1}H$ NMR spectrum of **3c**, $CDCl_3$, 400 MHz



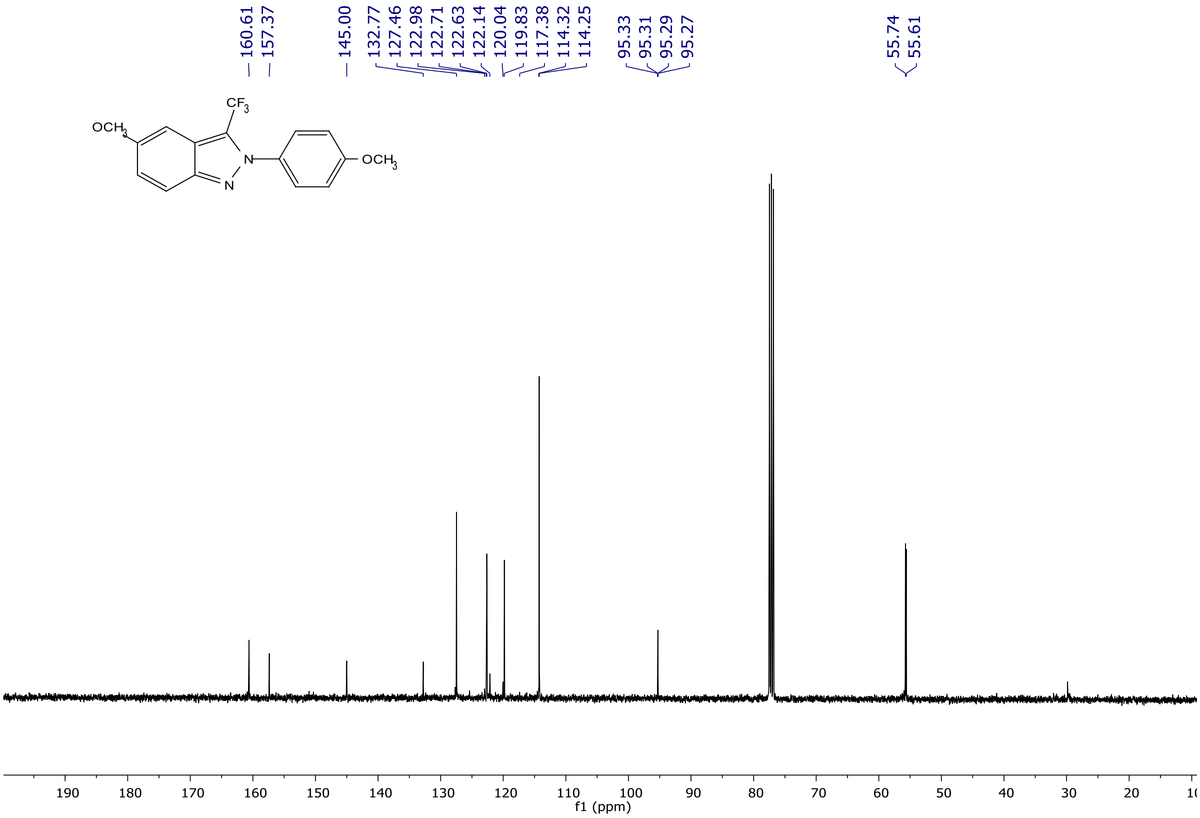
$^{13}$C{$^{1}$H} NMR spectrum of **3c**, CDCl3, 100 MHz



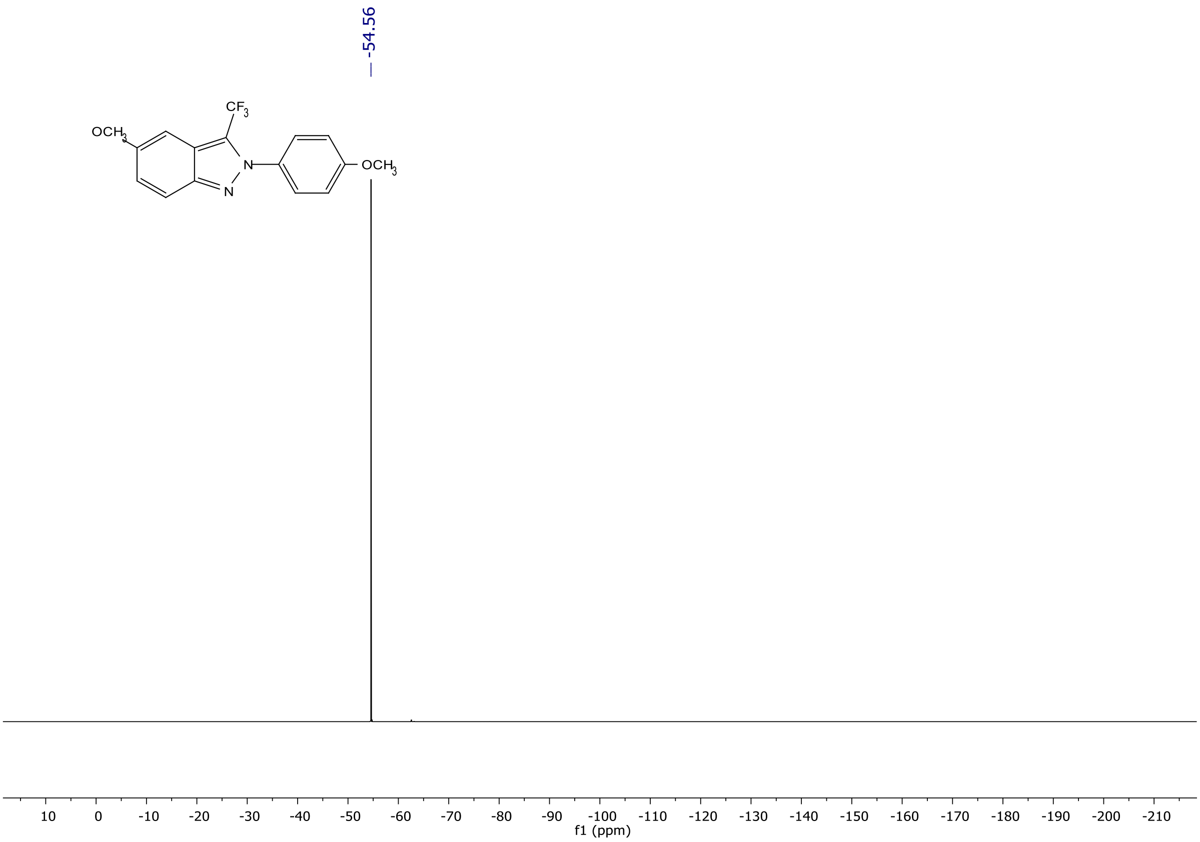
$^{19}$F{$^{1}$H} NMR spectrum of **3c**, CDCl3, 377 MHz



$^{1}$H NMR spectrum of **3d**, CDCl$_3$, 400 MHz



$^{13}$C{$^{1}$H} NMR spectrum of **3d**, CDCl$_3$, 100 MHz



$^{19}F\{^{1}H\}$ NMR spectrum of **3d**, $CDCl_3$, 377 MHz