

Synthesis of CF₃-Indazoles via Rh(III)-Catalyzed C-H [4+1] Annulation of Azobenzenes with CF₃-Imidoyl Sulfoxonium Ylides

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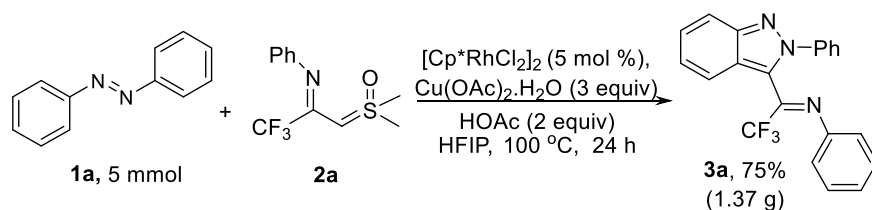
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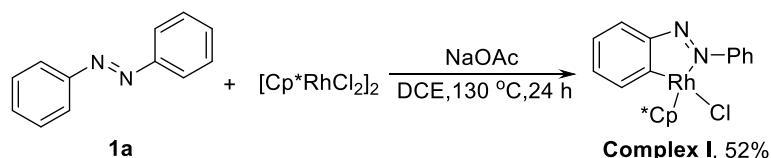
1. Gram-Scale reaction for the synthesis of **3a**



A Schlenk flask was charged with azobenzene **1a** (0.91 g, 5 mmol), CF_3 -imidoyl sulfoxonium ylide **2a** (1.97 g, 7.5 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3 equiv), HOAc (2 equiv) and HFIP (15 mL). Then the mixture was stirred at 100 °C under air atmosphere for 24 h. After being cooled to ambient temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford the desired product **3a** (1.37 g, 75%).

2. Mechanism studies

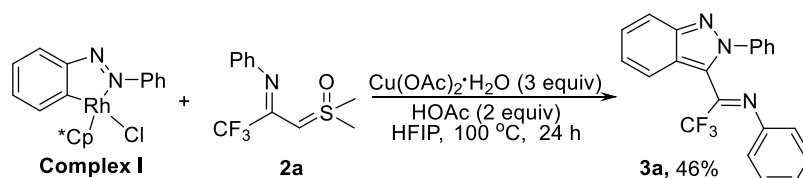
2.1 The preparation of complex **I**^[1]



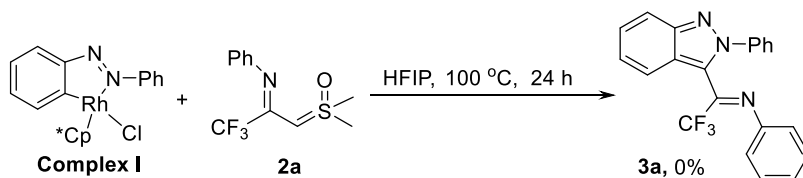
A pressure tube was charged with azobenzene **1a** (36.4 mg, 0.2 mmol), $[\text{Cp}^*\text{RhCl}_2]_2$ (60 mg, 0.1 mmol), NaOAc (32.8 mg, 0.4 mmol) and DCE (1 mL). Then the mixture was stirred at 130 °C under air atmosphere for 24 h. After being cooled to ambient temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford the five-membered cyclorhodium complex **I** (47.1 mg, 52%).

Complex I: ^1H NMR (400 MHz, CDCl_3) δ : 8.18 (dd, $J = 7.7, 1.5$ Hz, 1H), 8.04 – 7.98 (m, 2H), 7.88 (dd, $J = 7.6, 1.3$ Hz, 1H), 7.53 – 7.46 (m, 3H), 7.29 (td, $J = 7.4, 1.5$ Hz, 1H), 7.22 (td, $J = 7.4, 1.3$ Hz, 1H), 1.49 (s, 15H); ^{13}C NMR (101 MHz, CDCl_3) δ : 193.50, 178.61, 165.53, 158.94, 151.43, 143.78, 137.11, 137.00, 130.58, 123.55, 122.87, 122.02, 119.14, 96.08, 96.02, 9.26; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{25}\text{ClIn}_2\text{Rh}$ ($\text{M} + \text{H}$)⁺: 455.0756, found 455.0758.

2.2 The transformation of complex **I**

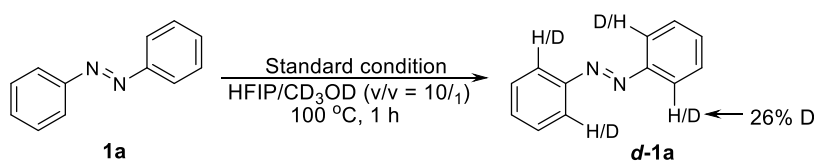


A pressure tube was charged with complex species **I** (90.6 mg, 0.2 mmol), CF_3 -imidoyl sulfoxonium ylide **2a** (78.9 mg, 0.3 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (119.8 mg, 0.6 mmol), HOAc (24 mg, 0.2 mmol) and HFIP (2 mL). Then the mixture was stirred at 100 °C under air atmosphere for 24 h. After being cooled to ambient temperature, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford the desired product **3a** in 46% yield.



A pressure tube was charged with complex species **I** (90.6 mg, 0.2 mmol), CF_3 -imidoyl sulfoxonium ylide **2a** (78.9 mg, 0.3 mmol), and HFIP (2mL). Then the mixture was stirred at 100 $^\circ\text{C}$ under air atmosphere for 24 h. The desired product **3a** was not observed.

2.3 H/D exchange experiments



A pressure tube was charged with azobenzene **1a** (0.2 mmol), CD_3OD (0.2mL), $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3 equiv), HOAc (2 equiv) and HFIP (1 mL). Then the mixture was stirred at 100 $^\circ\text{C}$ under air atmosphere for 1h. After being cooled to ambient temperature, the mixture were filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford the product **d-1a**. The deuterium incorporation of **d-1a** was determined to be 26% by the ^1H NMR analysis (Figure S1).

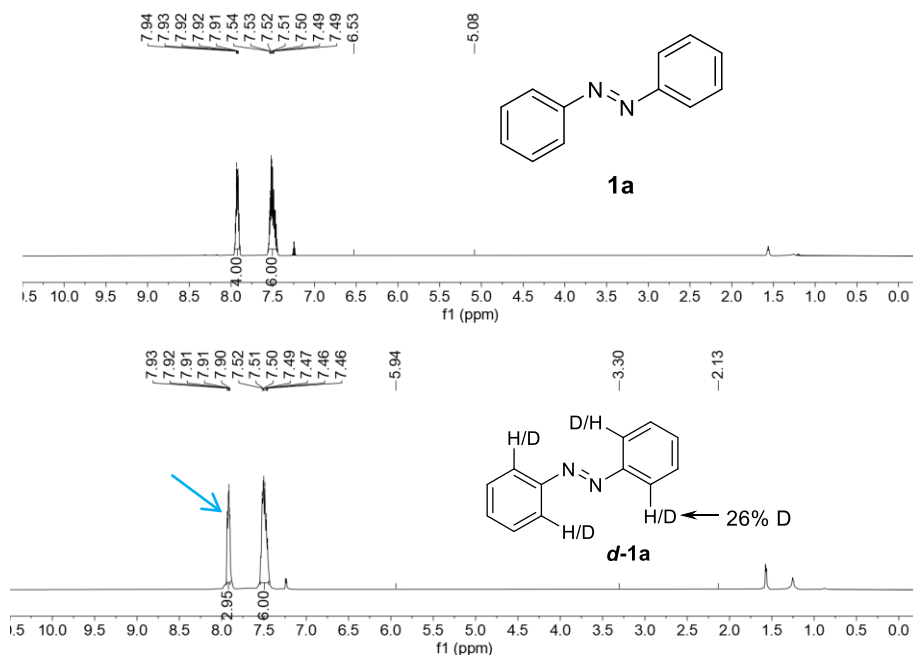
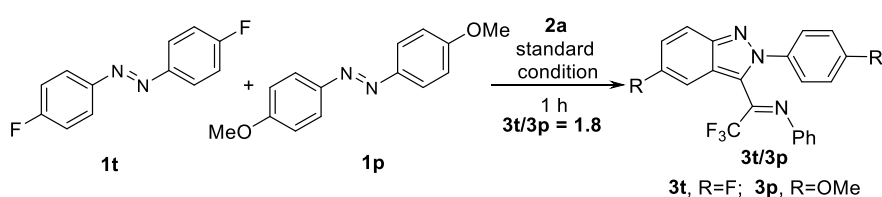


Figure S1. The ^1H NMR of **1a** and **d-1a**

2.4 Competition experiments



A pressure tube was charged with 4-fluoro disubstituted azobenzene **1t** (0.10 mmol),

4-methoxy disubstituted azobenzene **1p** (0.10 mmol), CF₃-imidoyl sulfoxonium ylide **2a** (0.3 mmol), [Cp*RhCl₂]₂ (5 mol%), Cu(OAc)₂·H₂O (3 equiv), HOAc (2 equiv) and HFIP (2 mL). Then the mixture was stirred at 100 °C under air atmosphere for 1h. After being cooled to ambient temperature, the mixture were filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by flash chromatography to afford the mixture of **3t/3p**, and the ratio of **3t/3p** (**3t/3p** = 1.8:1) was determined by the ¹H NMR analysis (**Figure S2**).

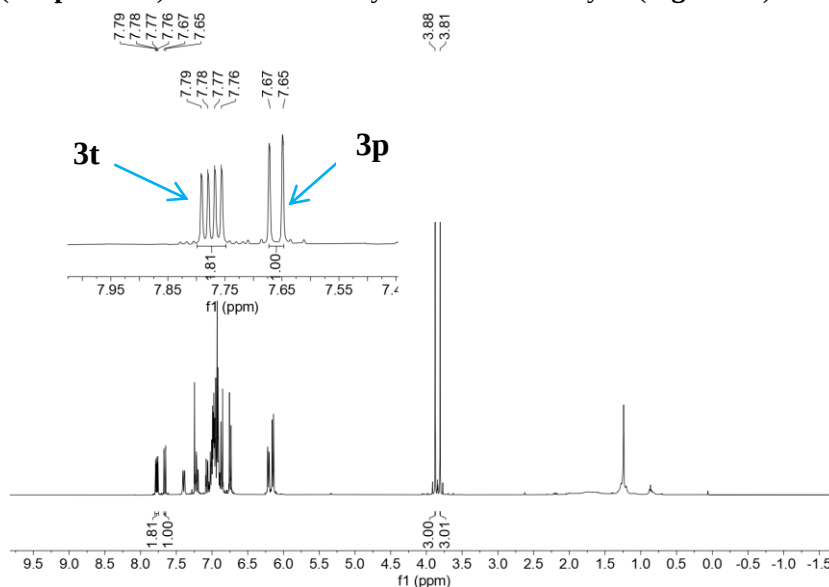
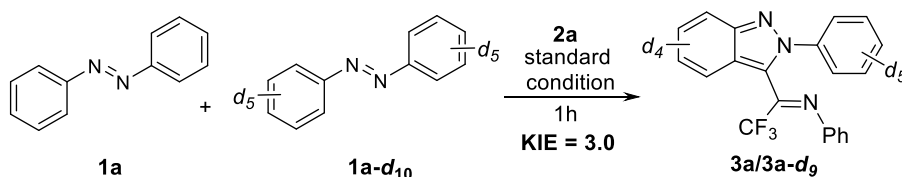


Figure S2. The ¹H NMR of **3t/3p** mixture

2.5 Kinetic isotope effect study



A pressure tube was charged with **1a** (0.10 mmol), **1a-d₁₀** (0.10 mmol), CF₃-imidoyl sulfoxonium ylide **2a** (0.3 mmol), [Cp*RhCl₂]₂ (5 mol%), Cu(OAc)₂·H₂O (3 equiv), HOAc (2 equiv) and HFIP (2 mL). Then the mixture was stirred at 100 °C under air atmosphere for 1 h. After being cooled to ambient temperature, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether as eluent to afford a mixture of product **3a** and **3a-d₉**, which was further analyzed by ¹H NMR spectrum. The ¹H NMR data indicated a kinetic isotope effect (KIE) of 3.0 (**Figure S3**).

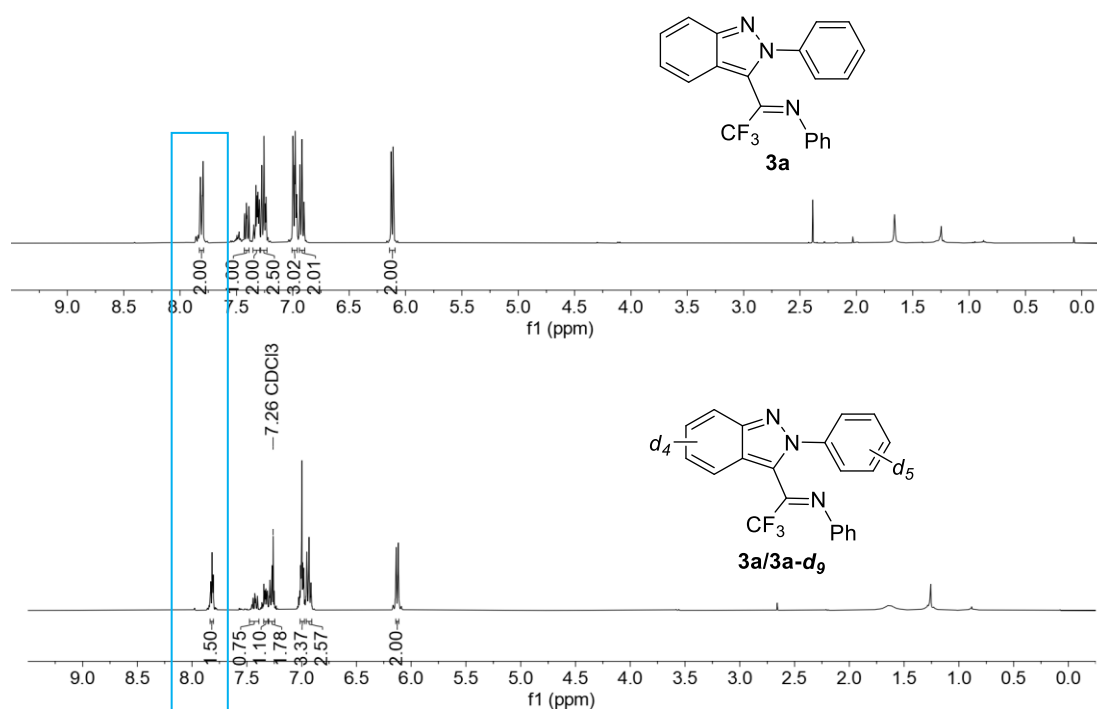


Figure S3. The ^1H NMR of **3a** and **3a/3a-d₉** mixture

3. Cytotoxic Activity Evaluation

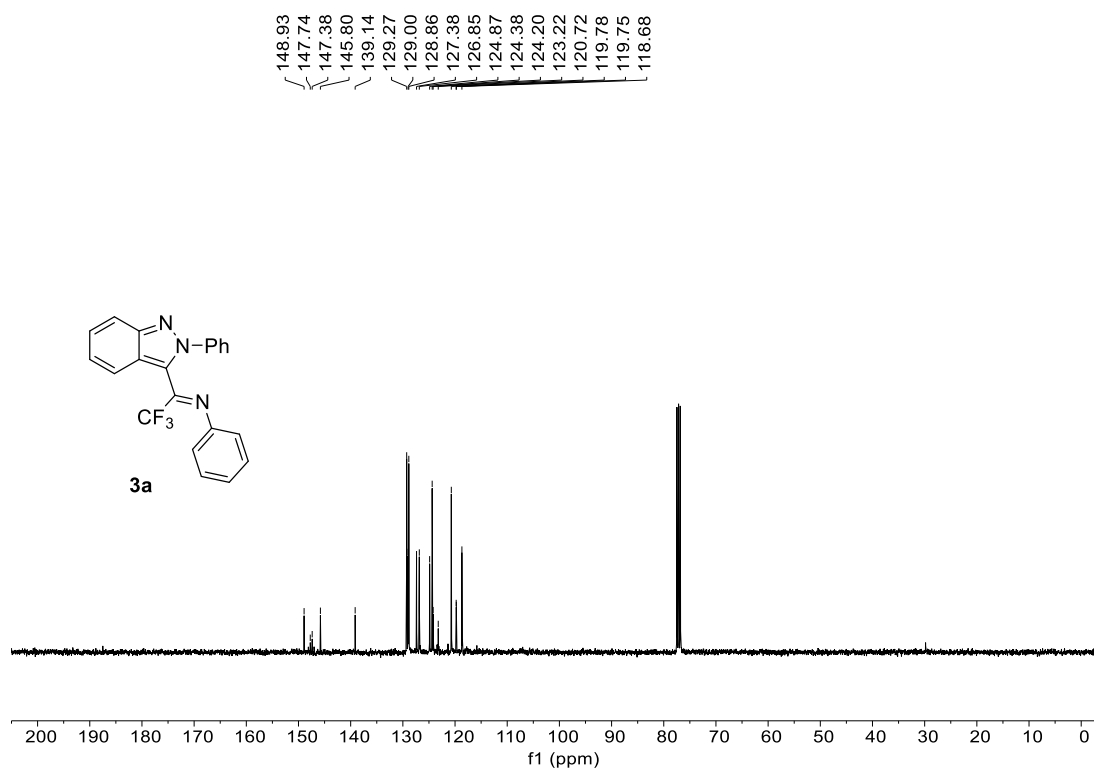
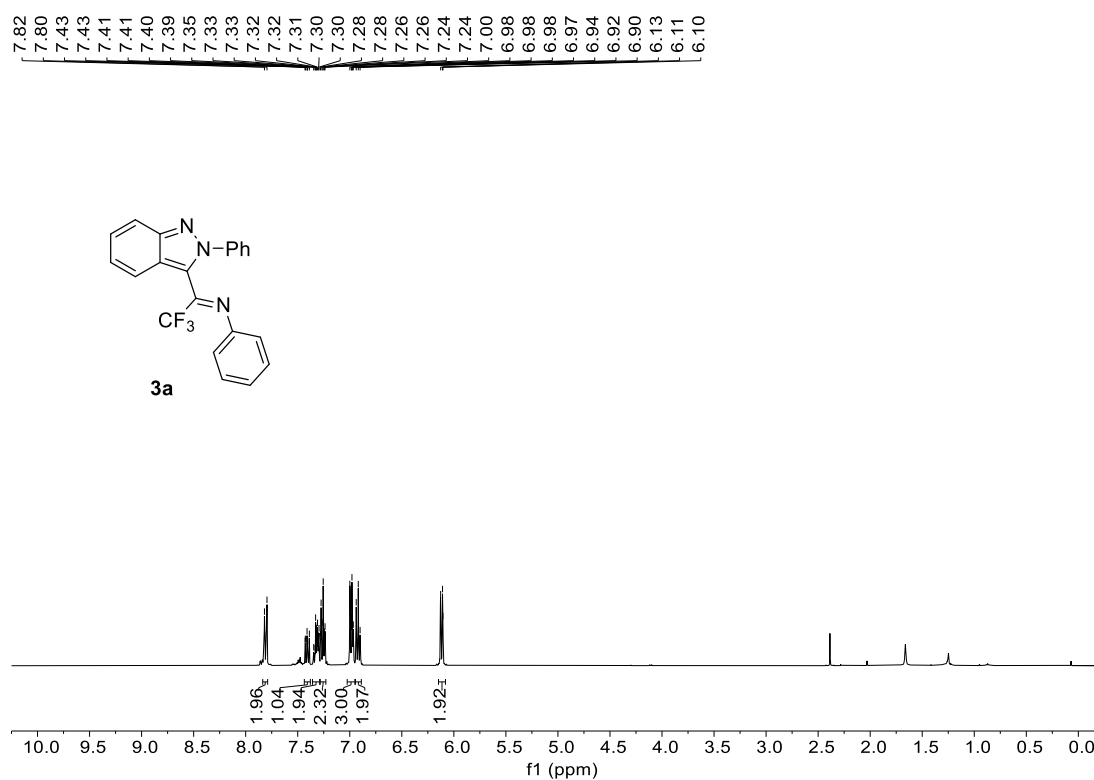
The in vitro cytotoxicity of selected compound against A549 cells (human lung adenocarcinoma cell line), HepG2 cells (human liver carcinoma cell line) and Hela cells (human cervical carcinoma cell line) were evaluated by Cell Counting Kit-8 assay (CCK-8) with Gefitinib as the positive control. Dilute A549, HepG2 or Hela cell suspensions in growth medium to desired density and 100 μL were taken to 96-well plate. These cell lines were cultured with standard methods in DMEM medium containing 20% FBS (Gibco, CA, USA). The tested compounds were dissolved in DMSO and then diluted with 20% FBS DMEM medium to prepare the tested compounds with different concentration gradients. The exponentially growing cells were seeded on 96-well plates (5×10^3 cells per well) and incubated for 24h. Subsequently, cells were treated with designated concentrations of compounds for 24 h. Then, 100 μL mixed solution ($V_{\text{CCK-8}}: V_{\text{DMEM}} = 1:10$) were added to each well, the plates were incubated at 37°C for an additional 3-5 h, and then, absorbance was read at 450 nm. Cell inhibition was calculated using the following formula: Cell inhibition rate = (control OD value - test OD)/(control OD value - blank OD value) $\times 100\%$. The half maximal inhibitory concentration (IC_{50}) values were determined using GraphPad Prism 5 software (Graph Pad, La Jolla, CA, USA).

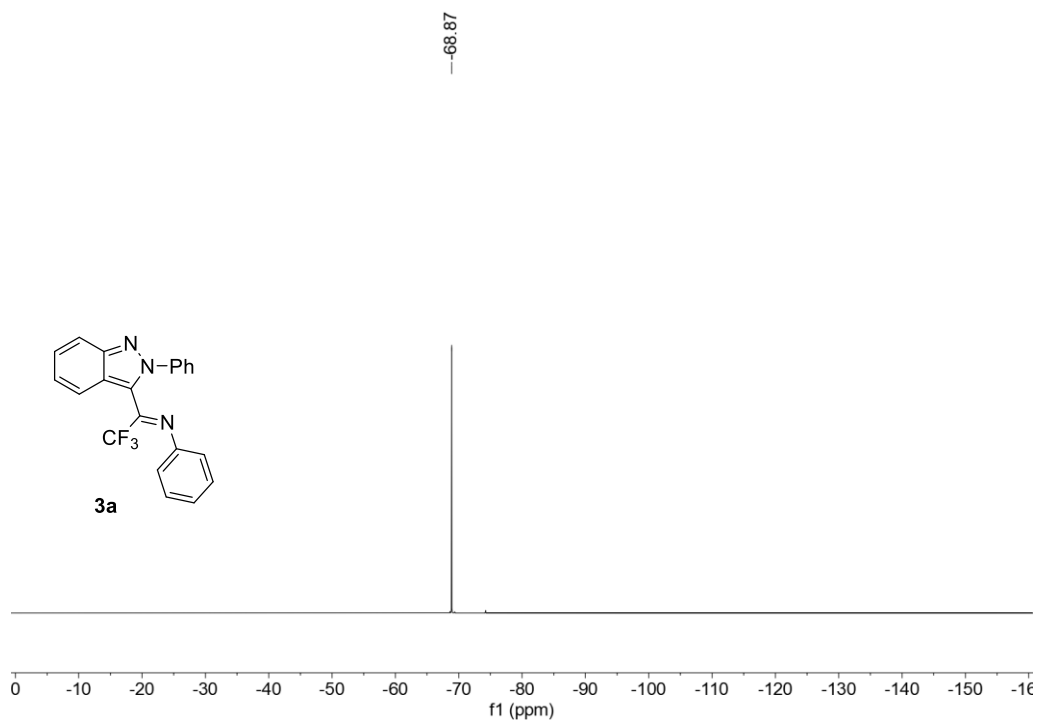
4. References

[1] Cai S.; Lin S.; Yi X.; Xi C. *J. Org. Chem.* **2017**, 82, 512-520.

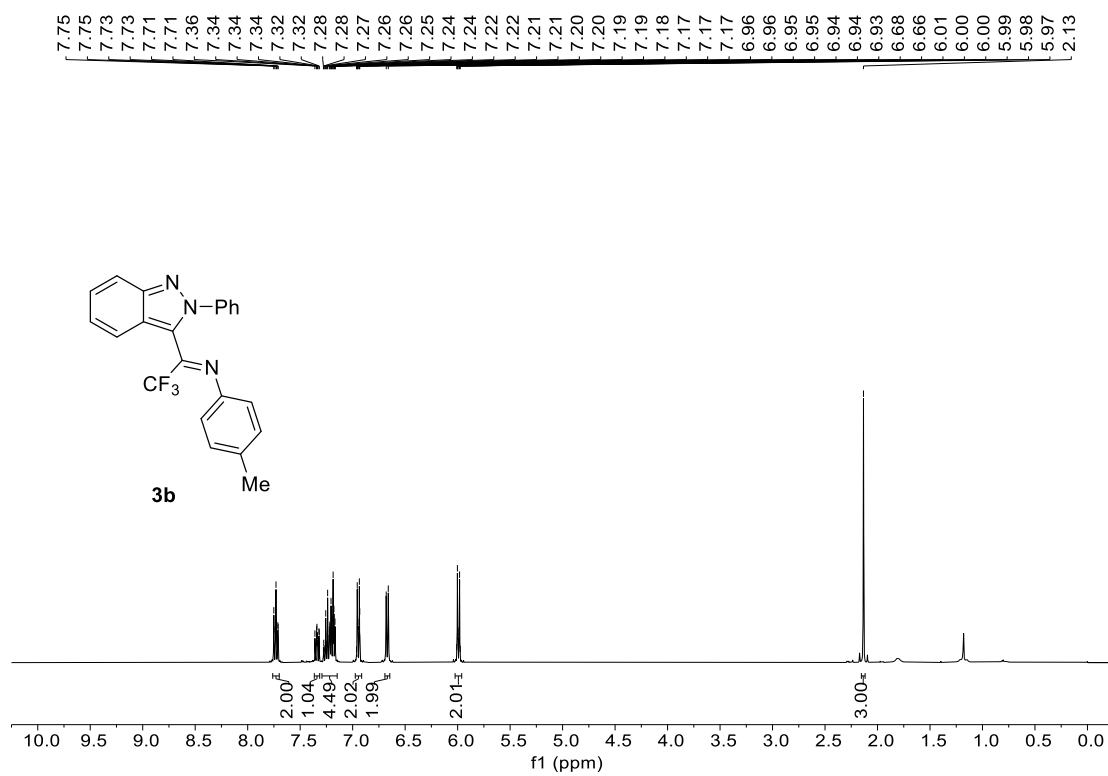
5. ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum for all isolated compounds

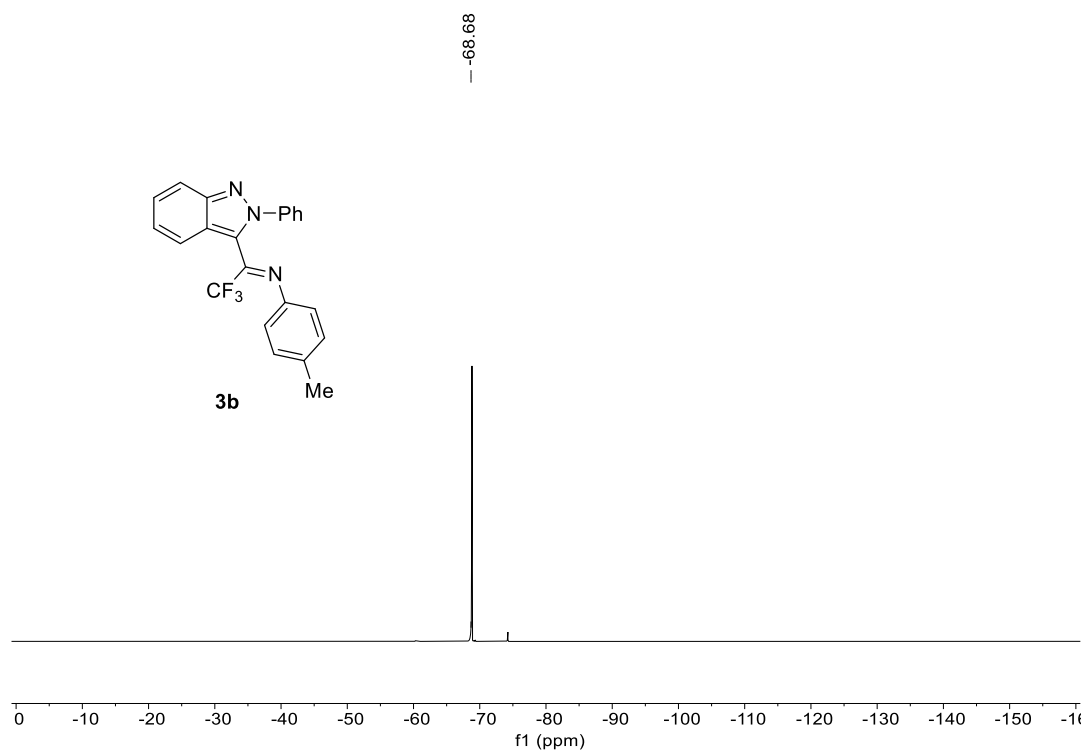
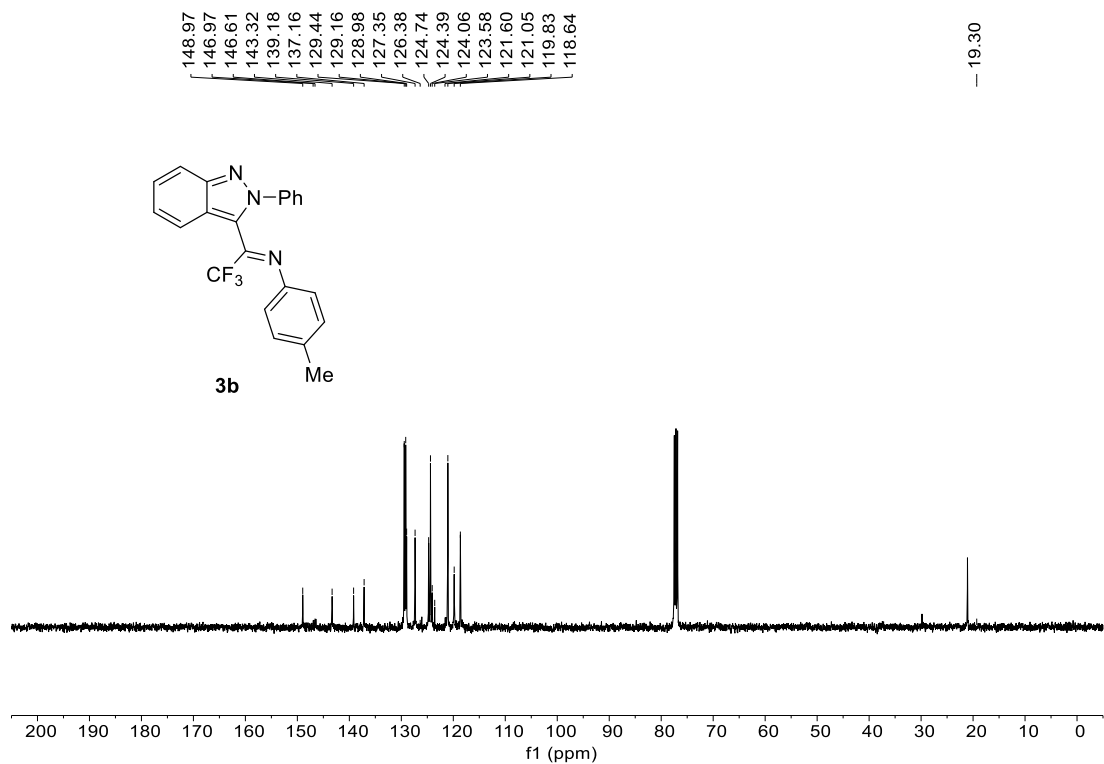
(1) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3a** (using CDCl_3 as solvent)



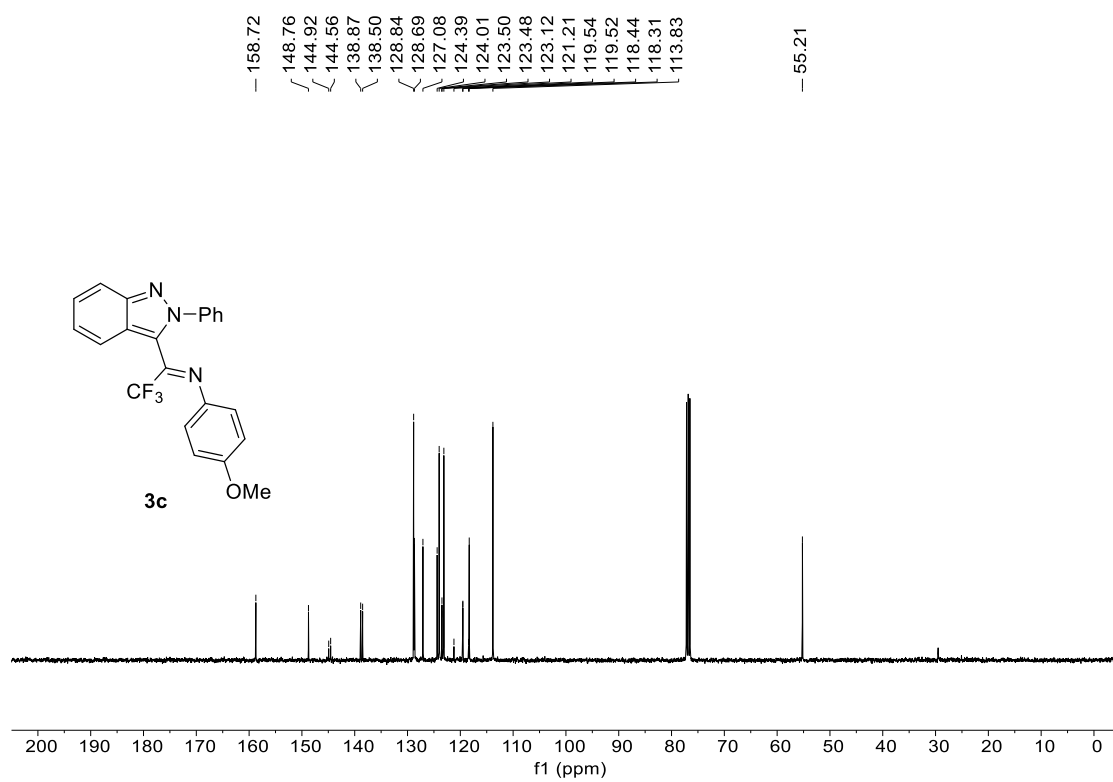
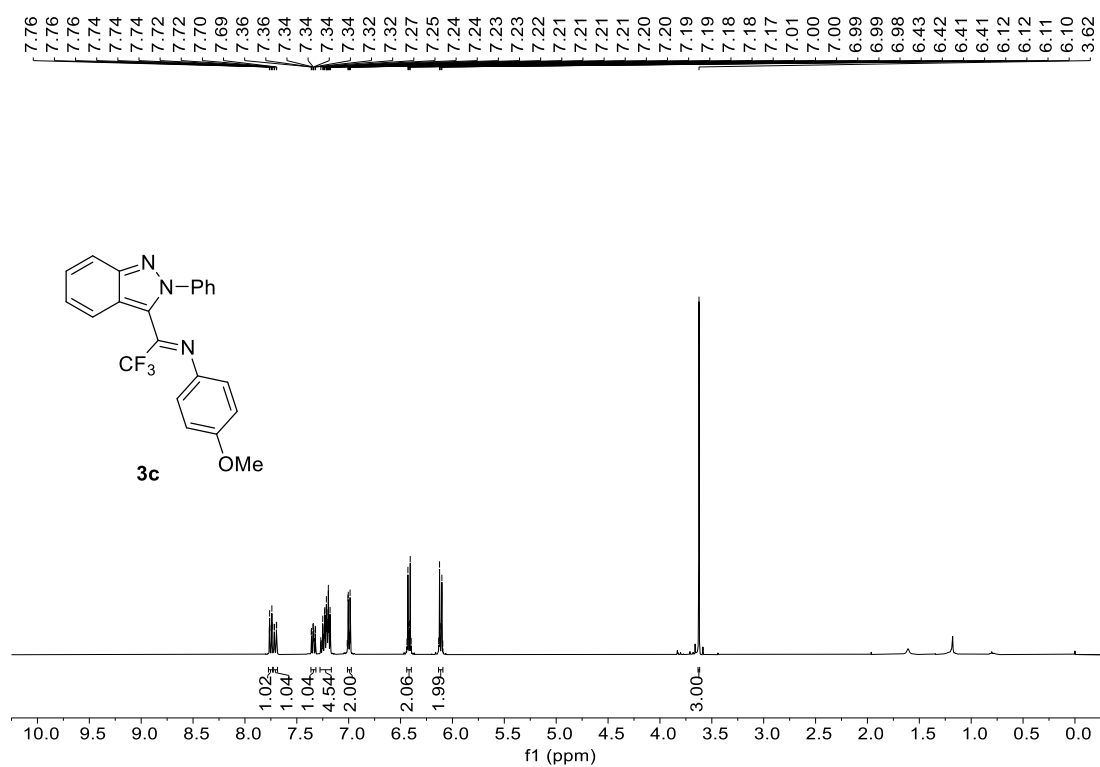


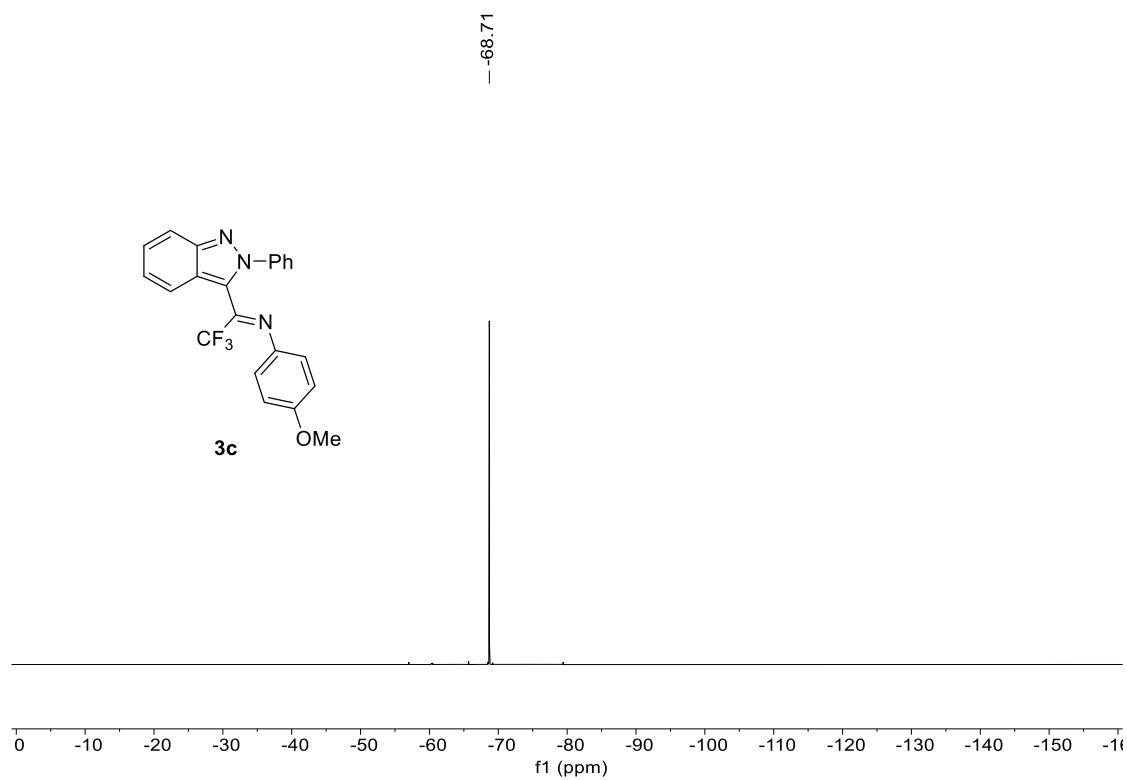
(2) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3b** (using CDCl_3 as solvent)



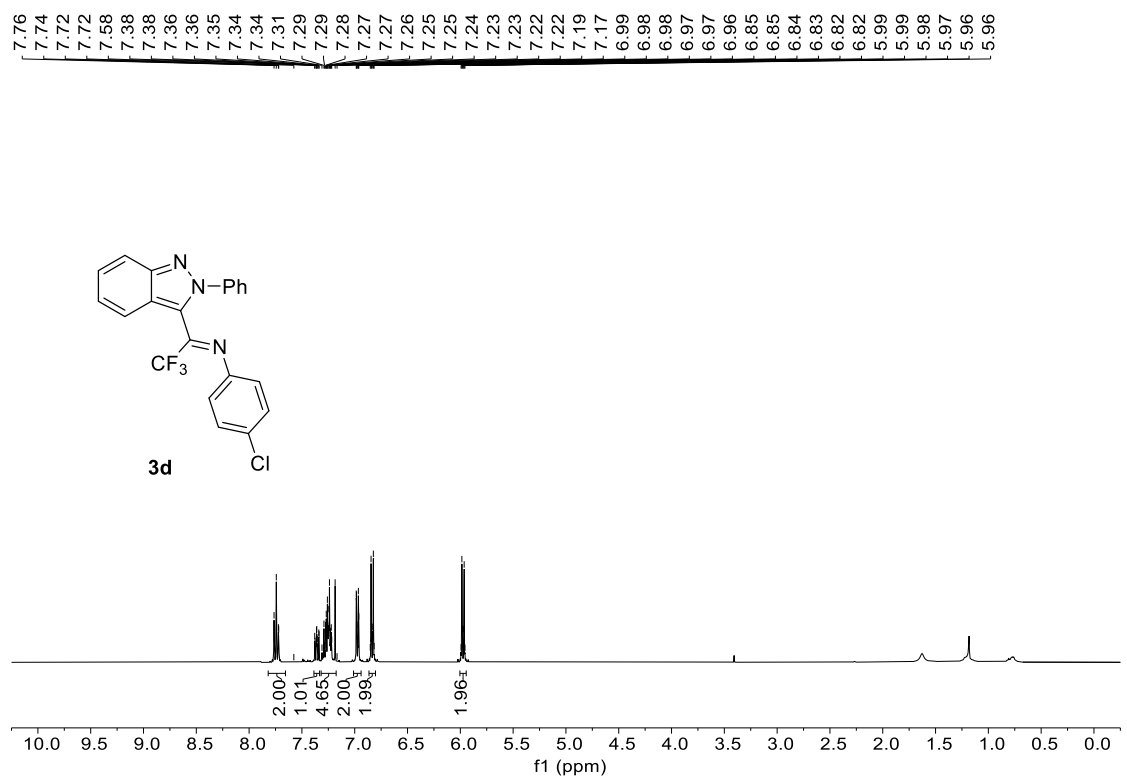


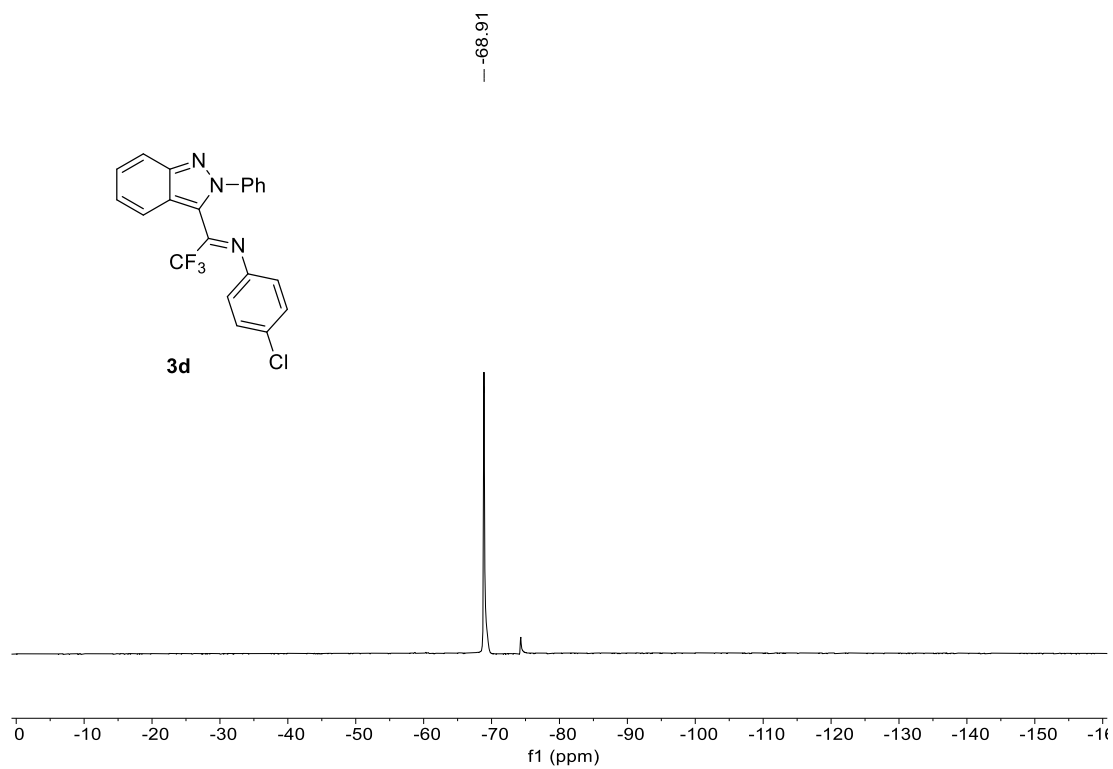
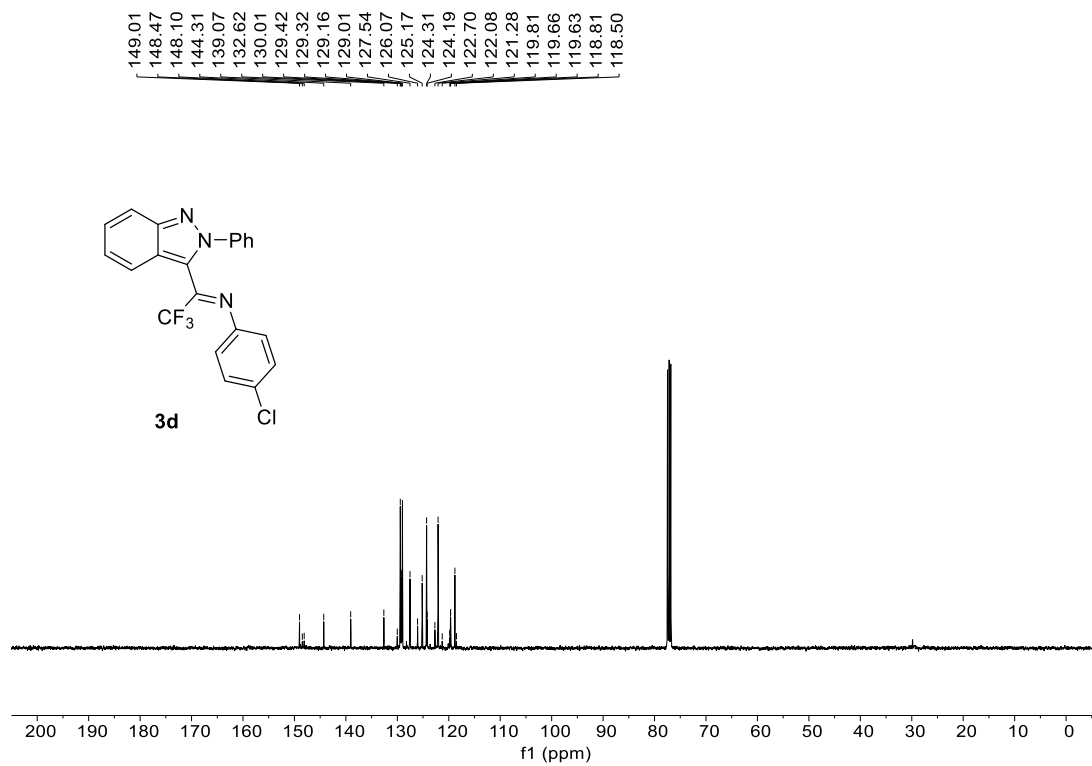
(3) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3c** (using CDCl_3 as solvent)



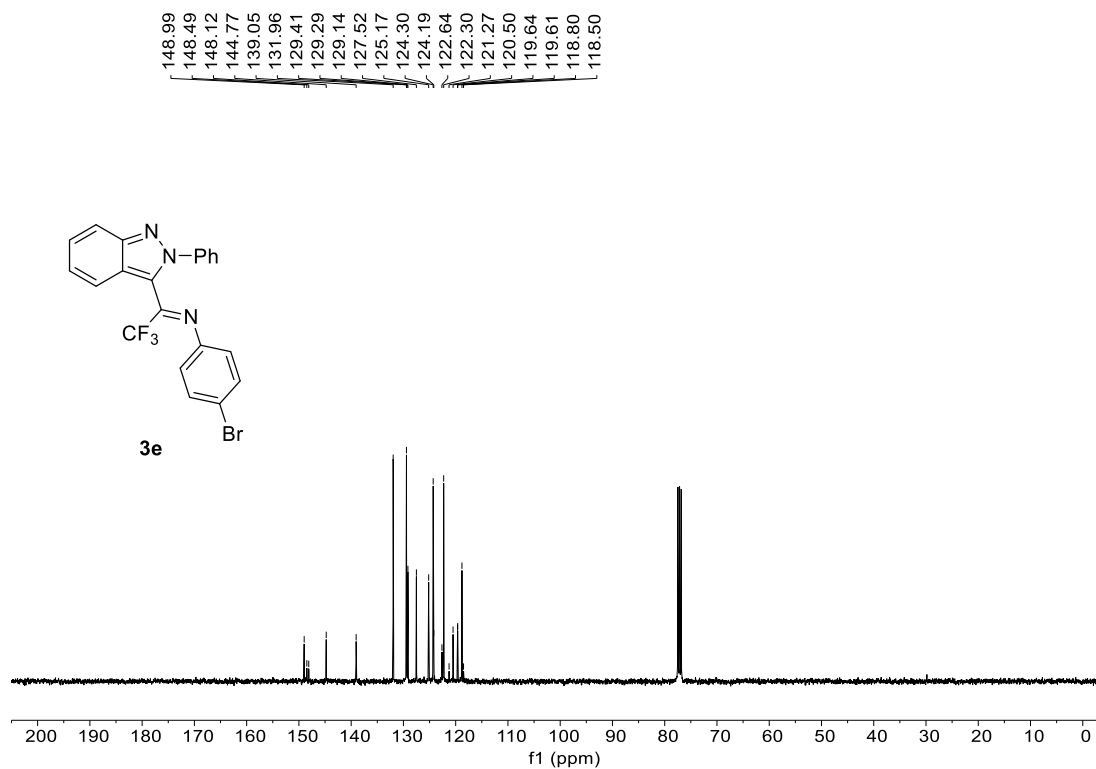
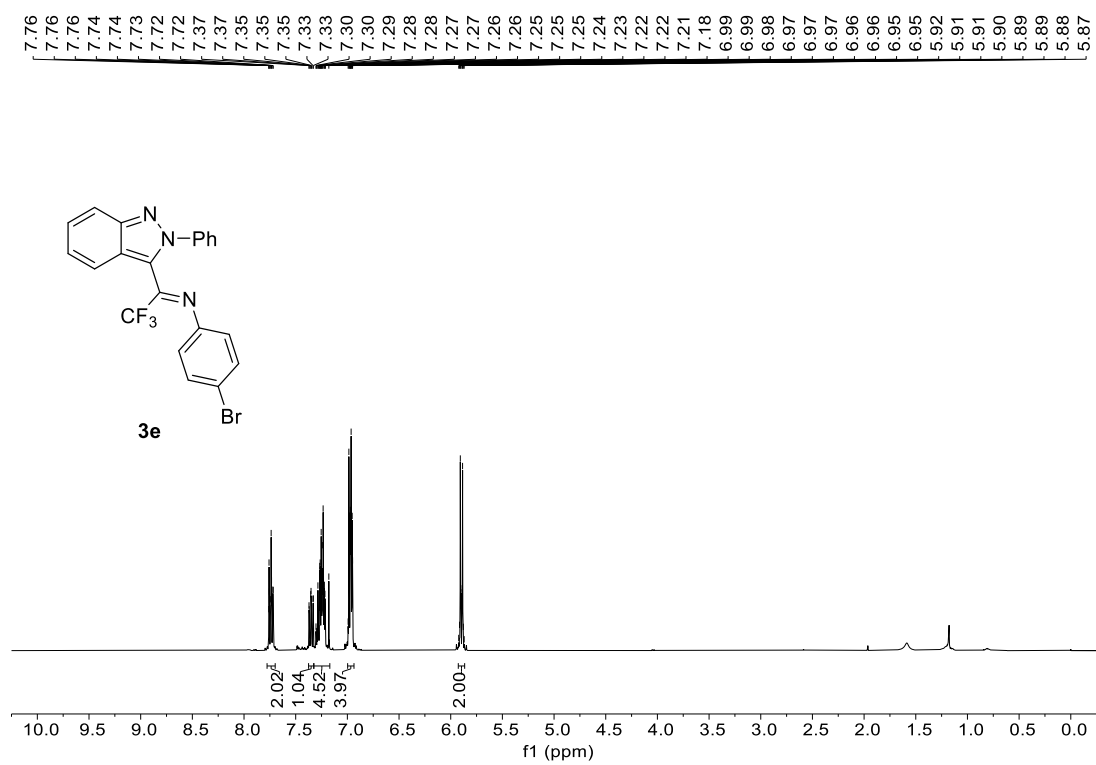


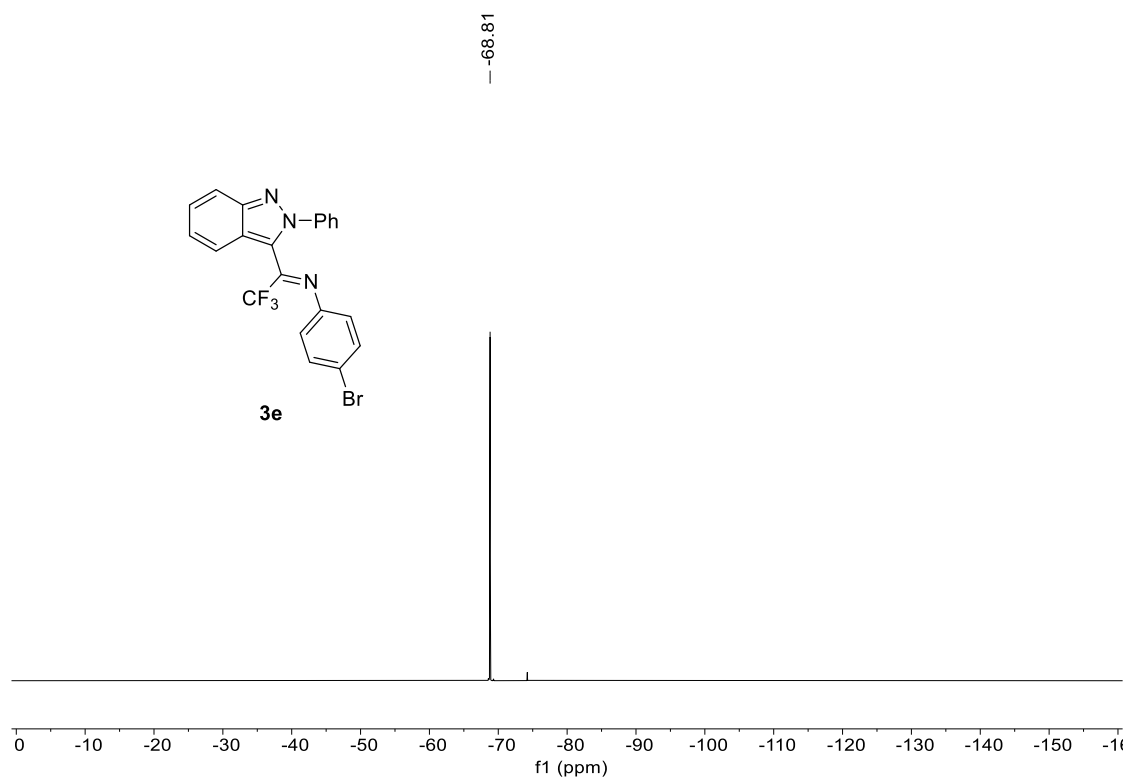
(4) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3d** (using CDCl_3 as solvent)



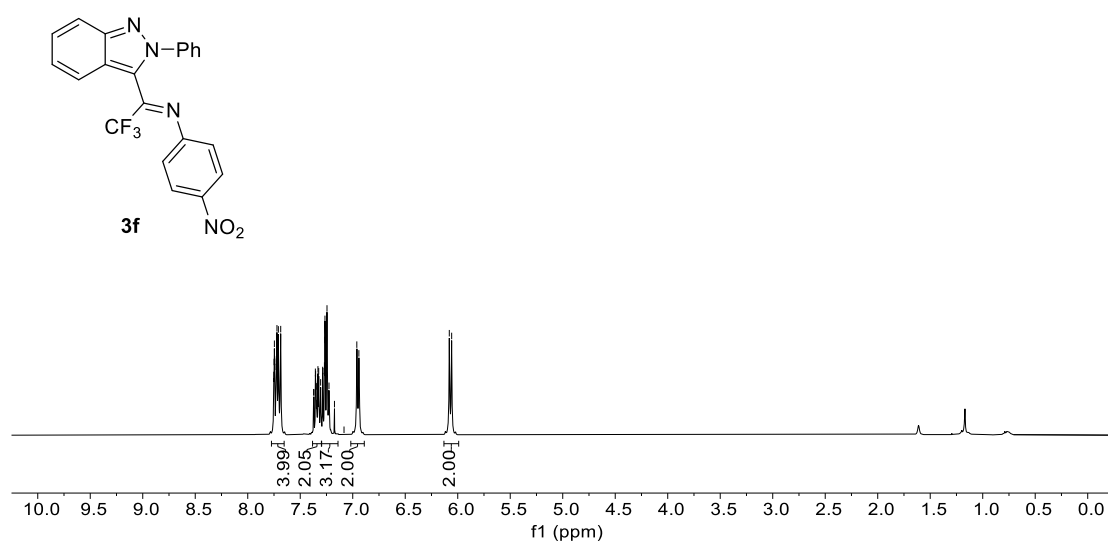
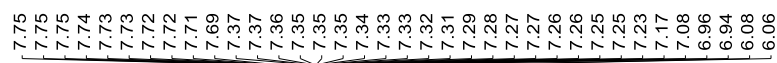


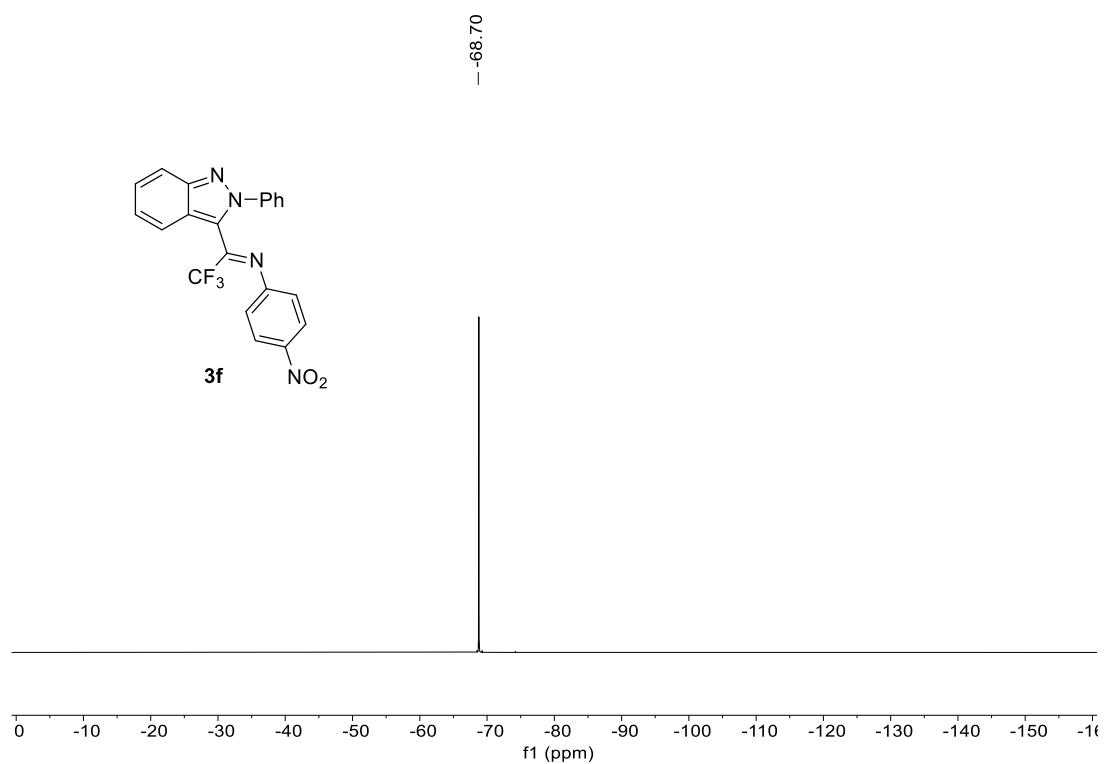
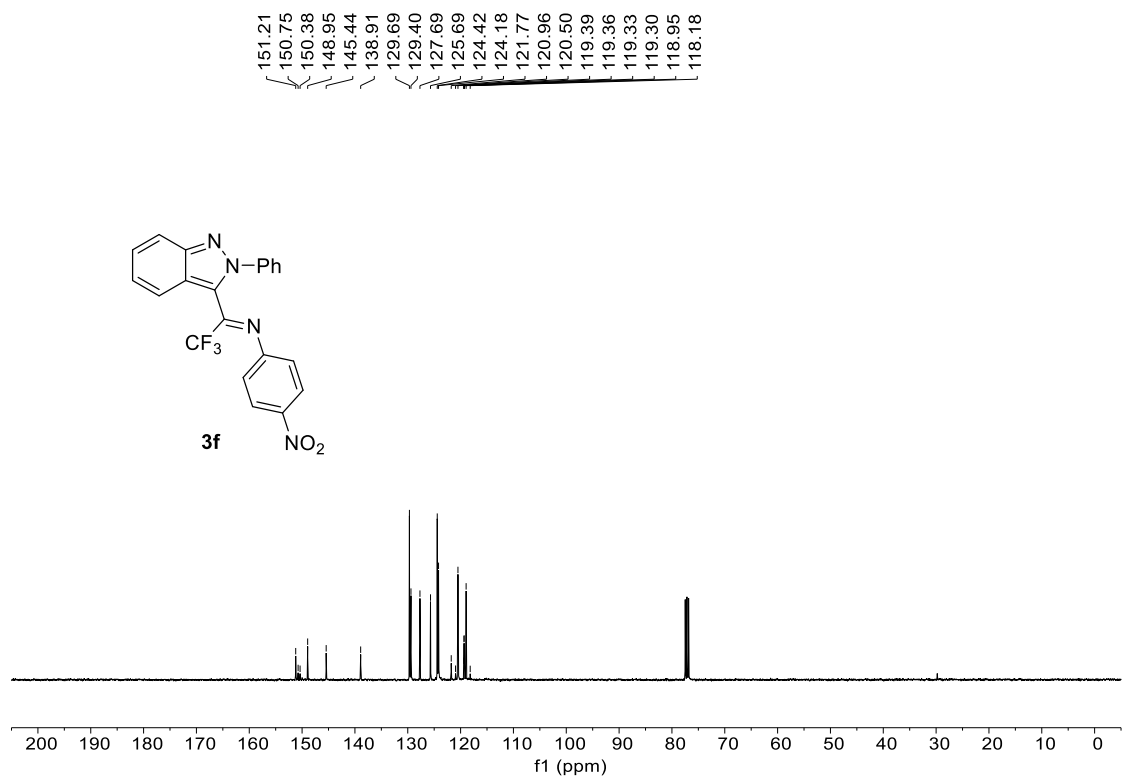
(5) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3e** (using CDCl_3 as solvent)



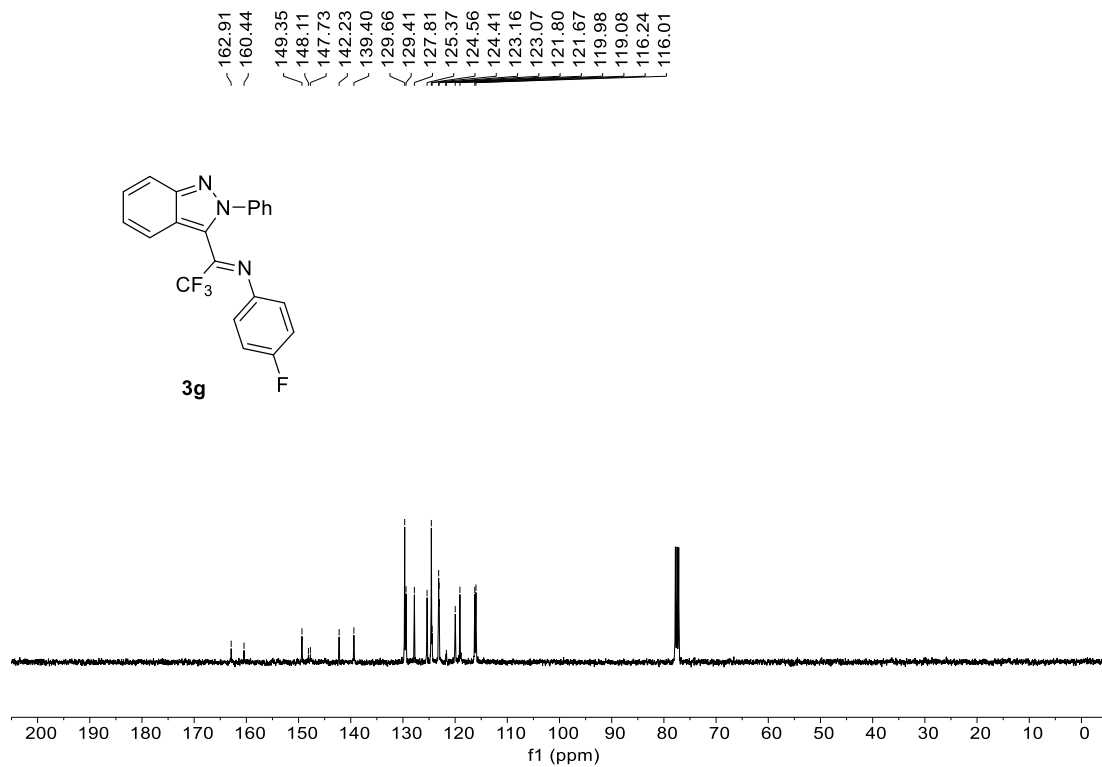
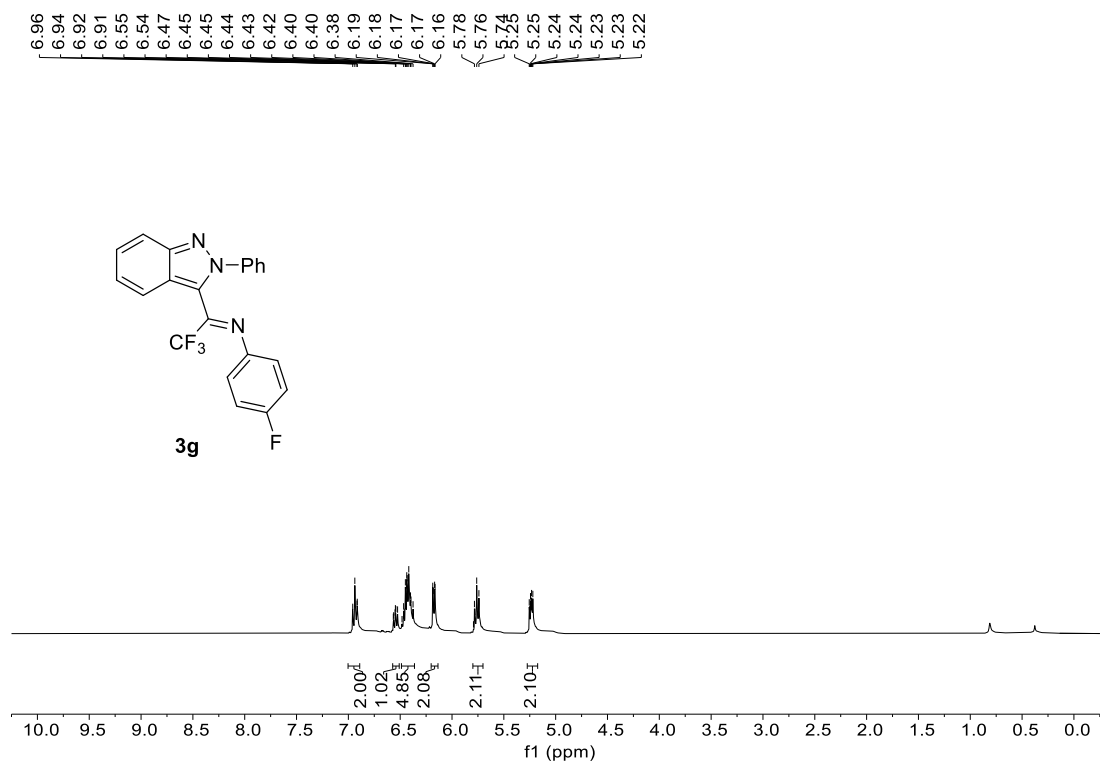


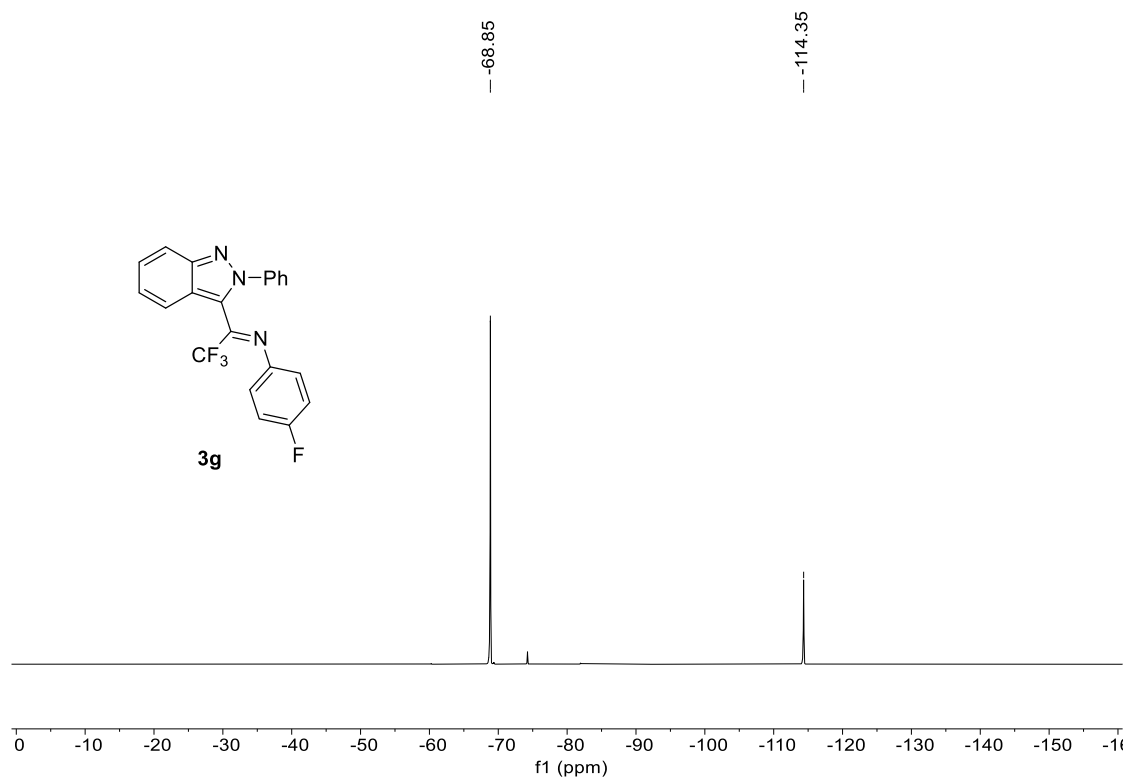
(6) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3f** (using CDCl_3 as solvent)



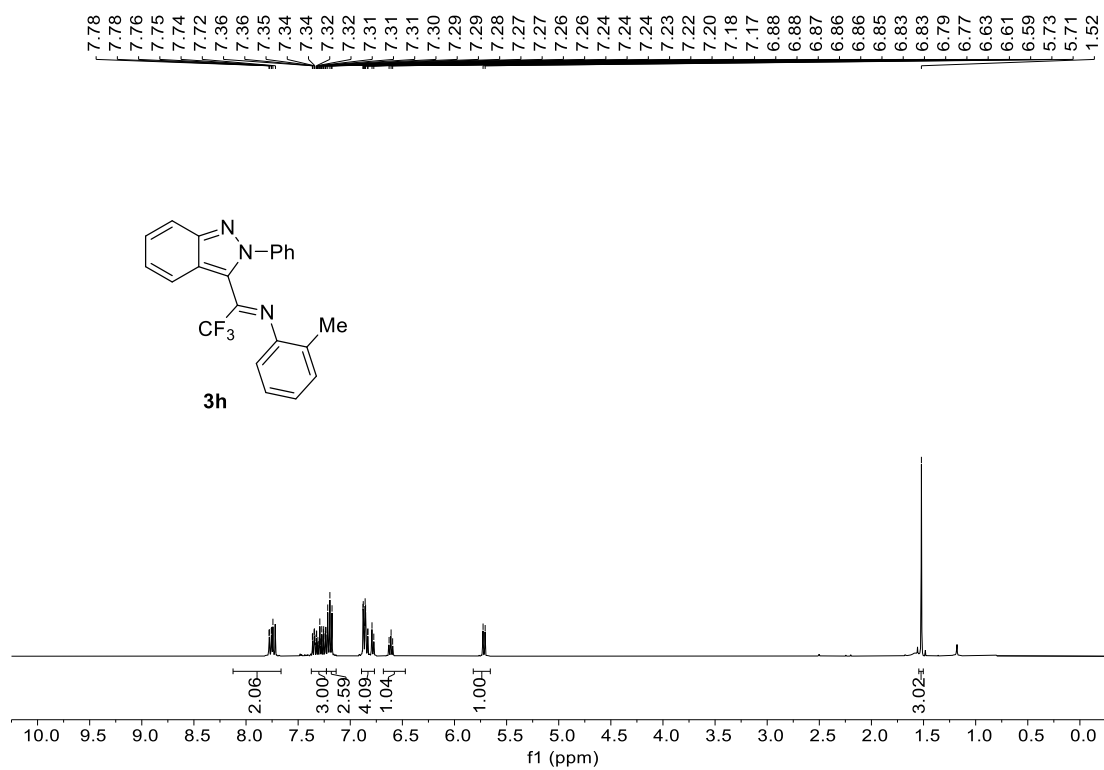


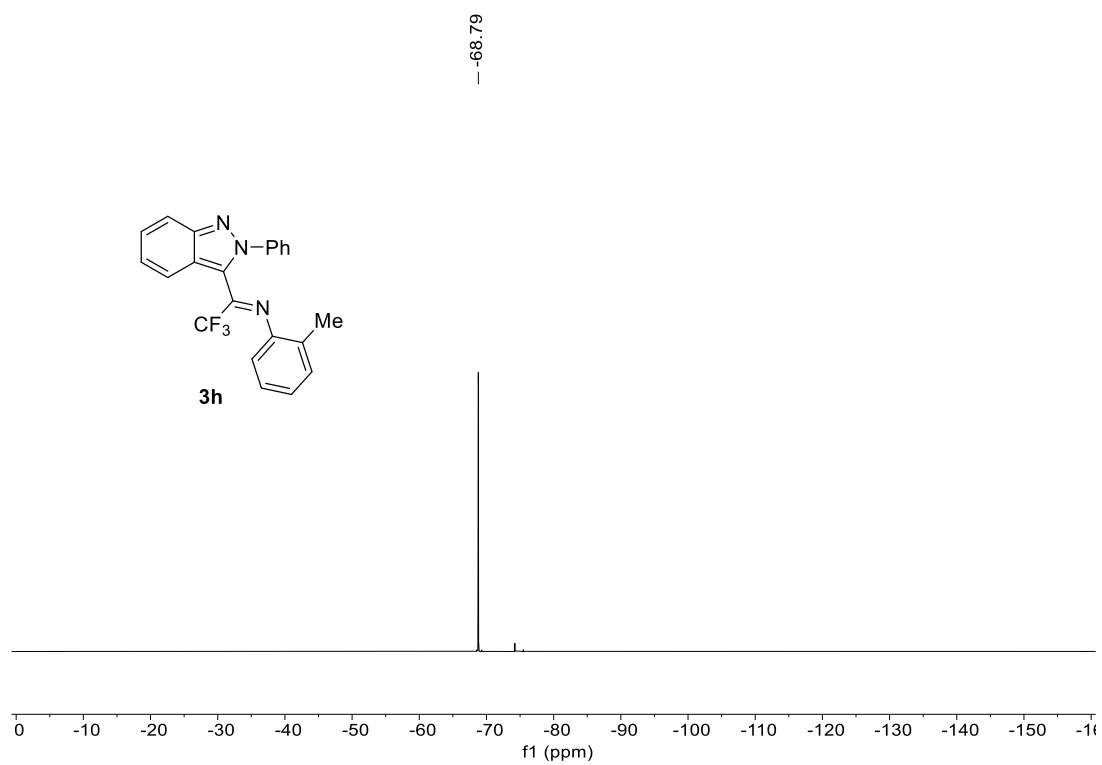
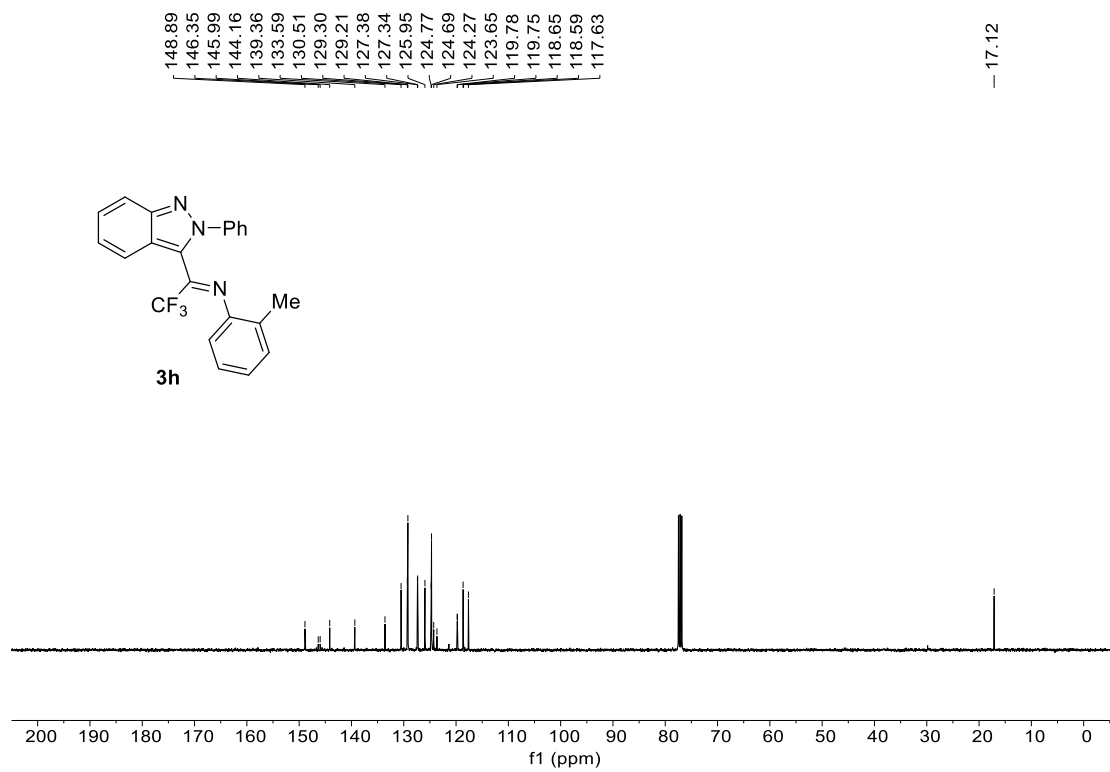
(7) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3g** (using CDCl_3 as solvent)



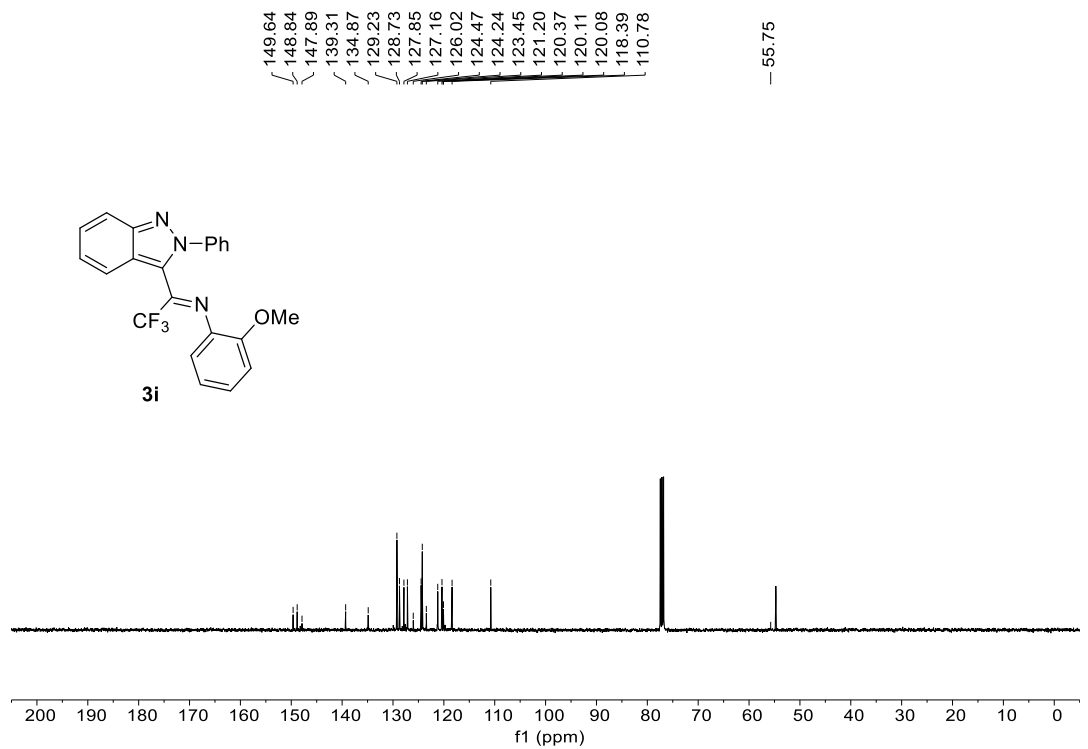
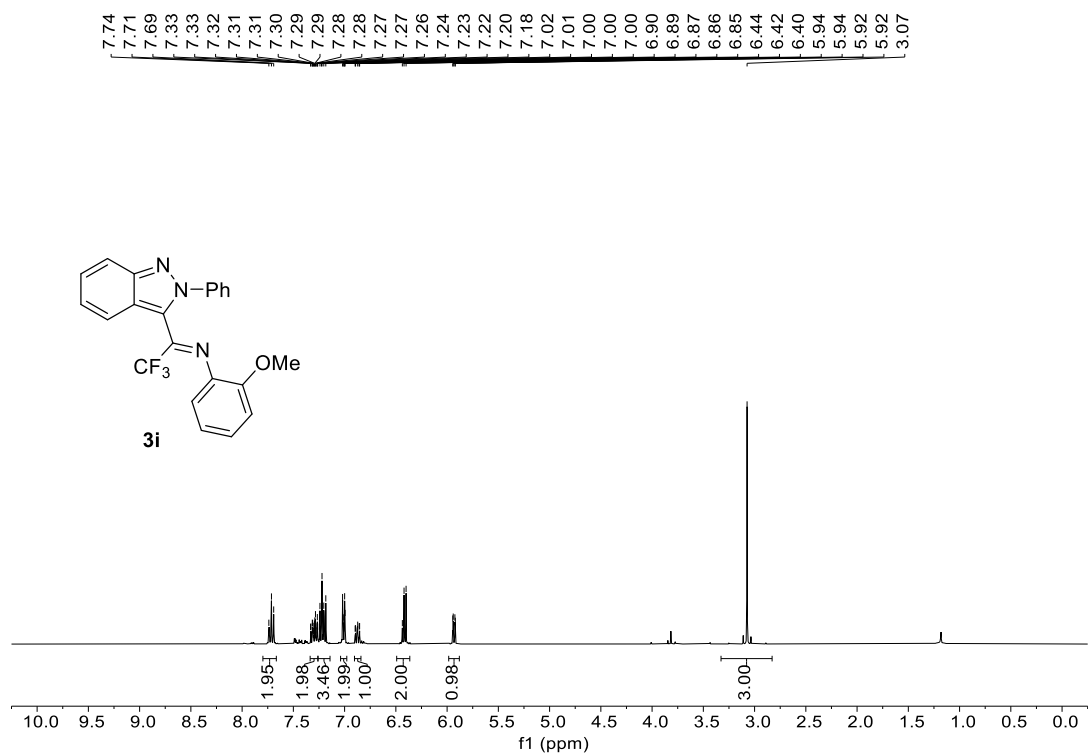


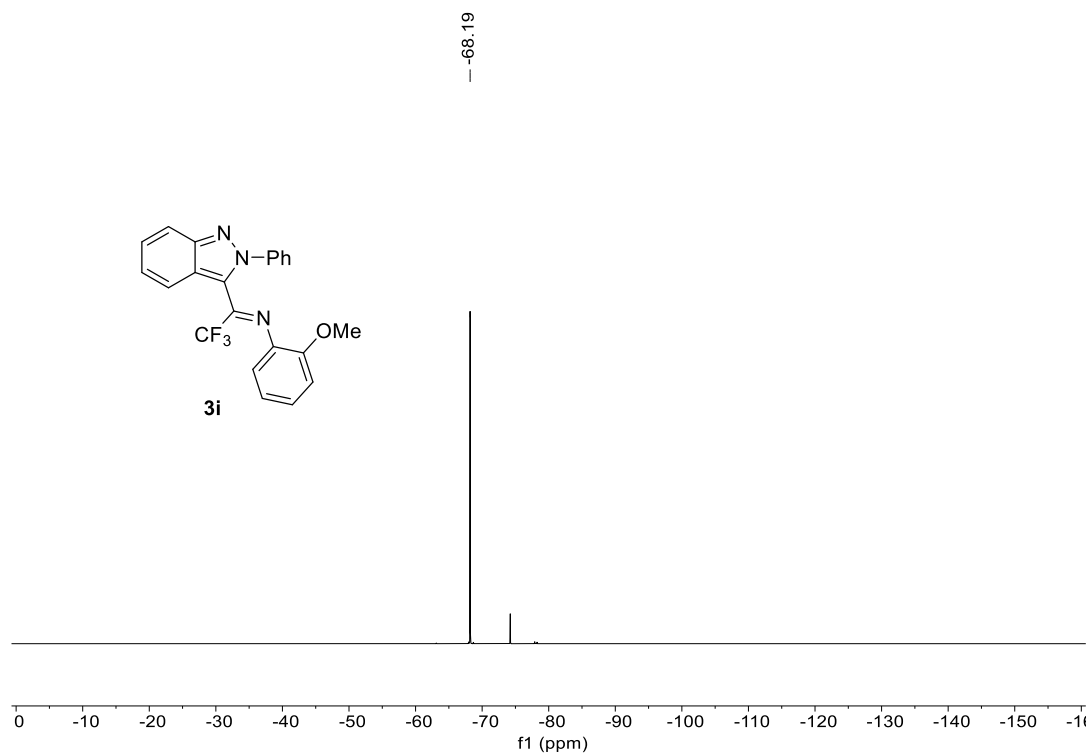
(8) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3h** (using CDCl₃ as solvent)



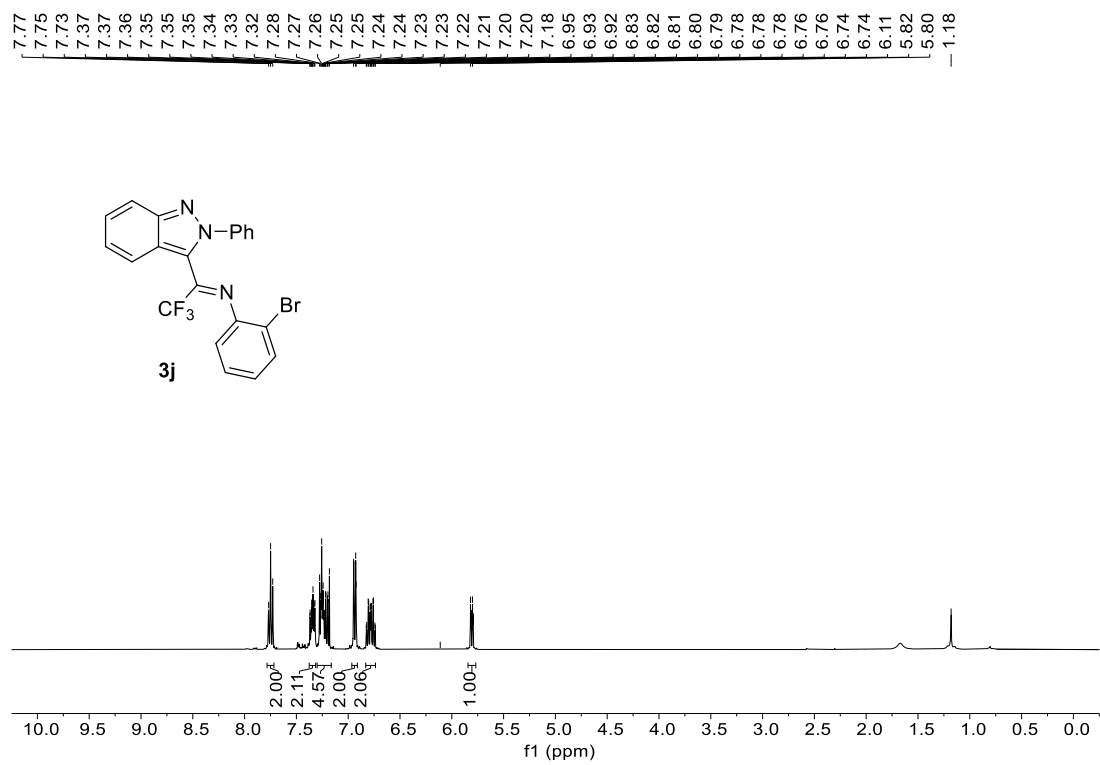


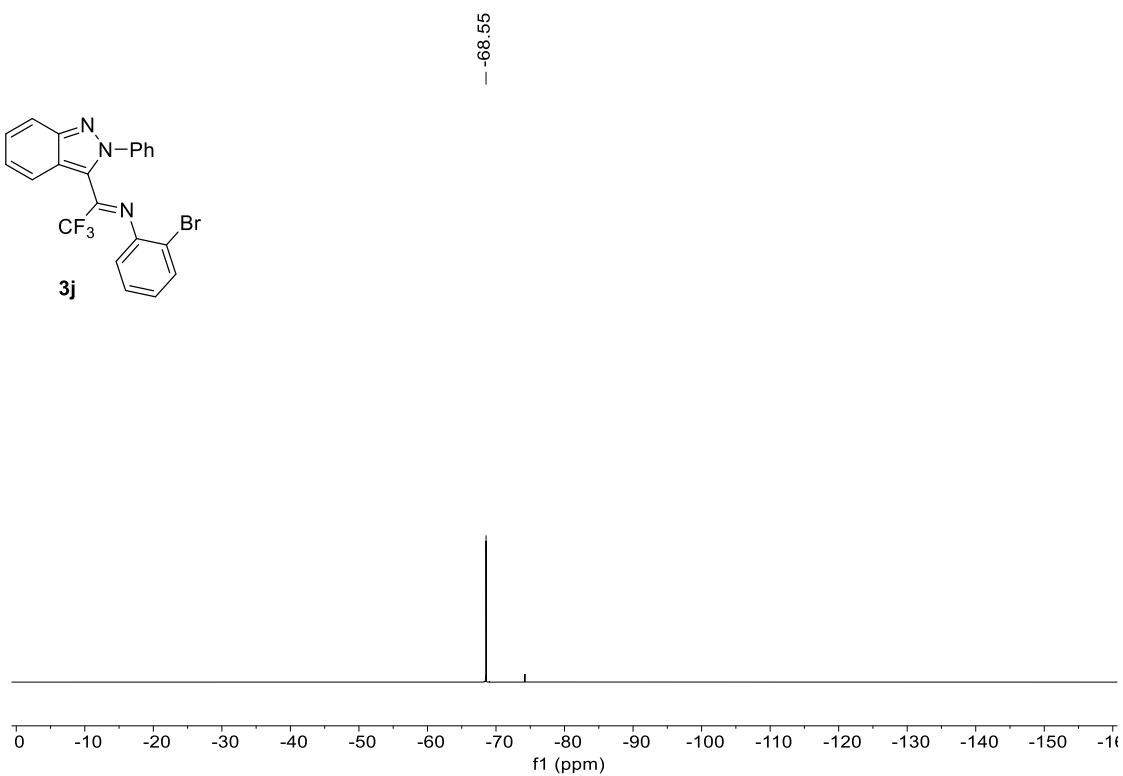
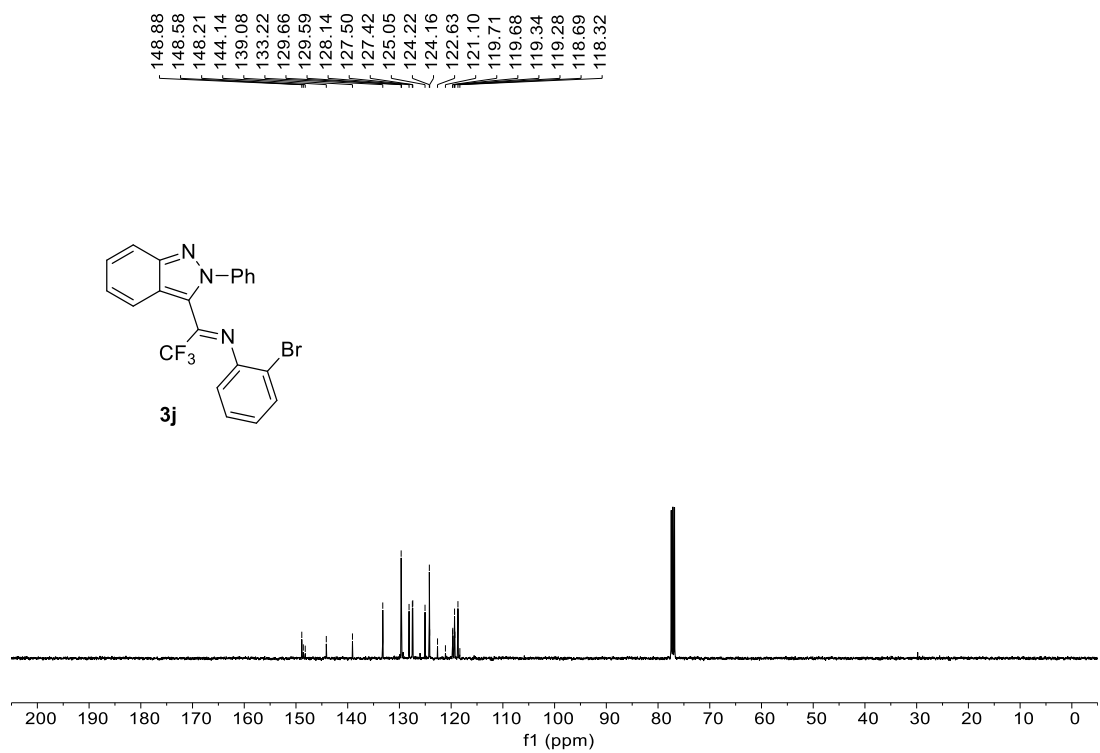
(9) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3i** (using CDCl_3 as solvent)



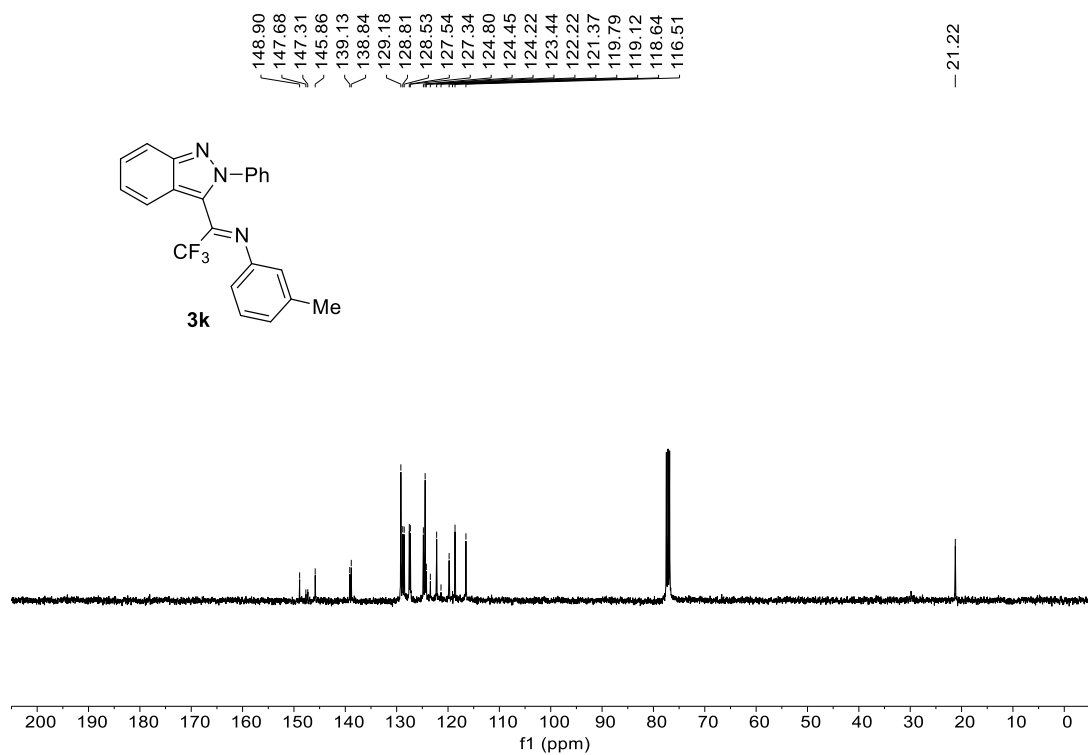
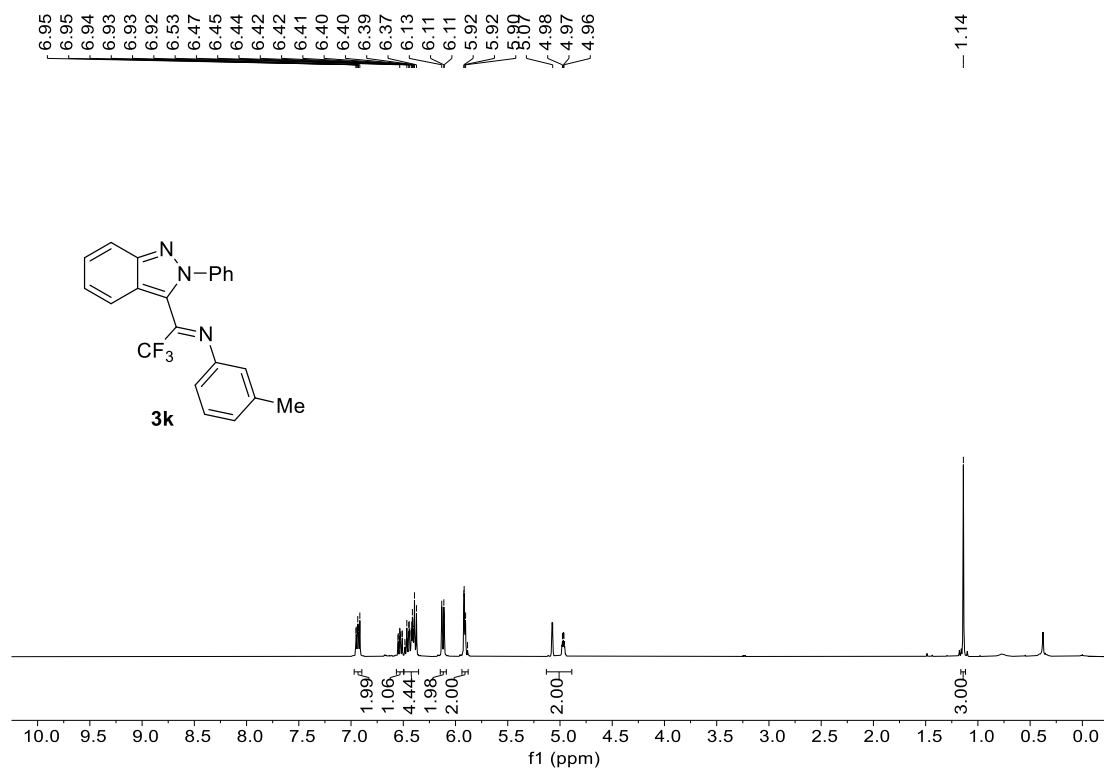


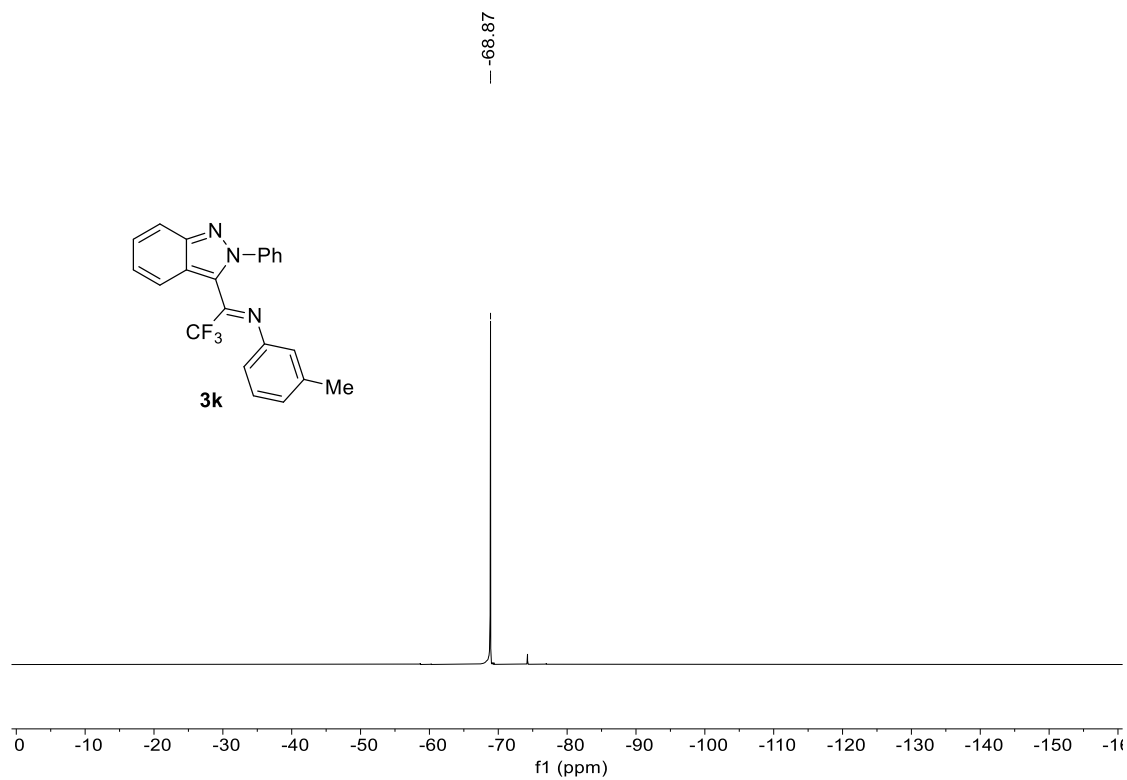
(10) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3j** (using CDCl_3 as solvent)



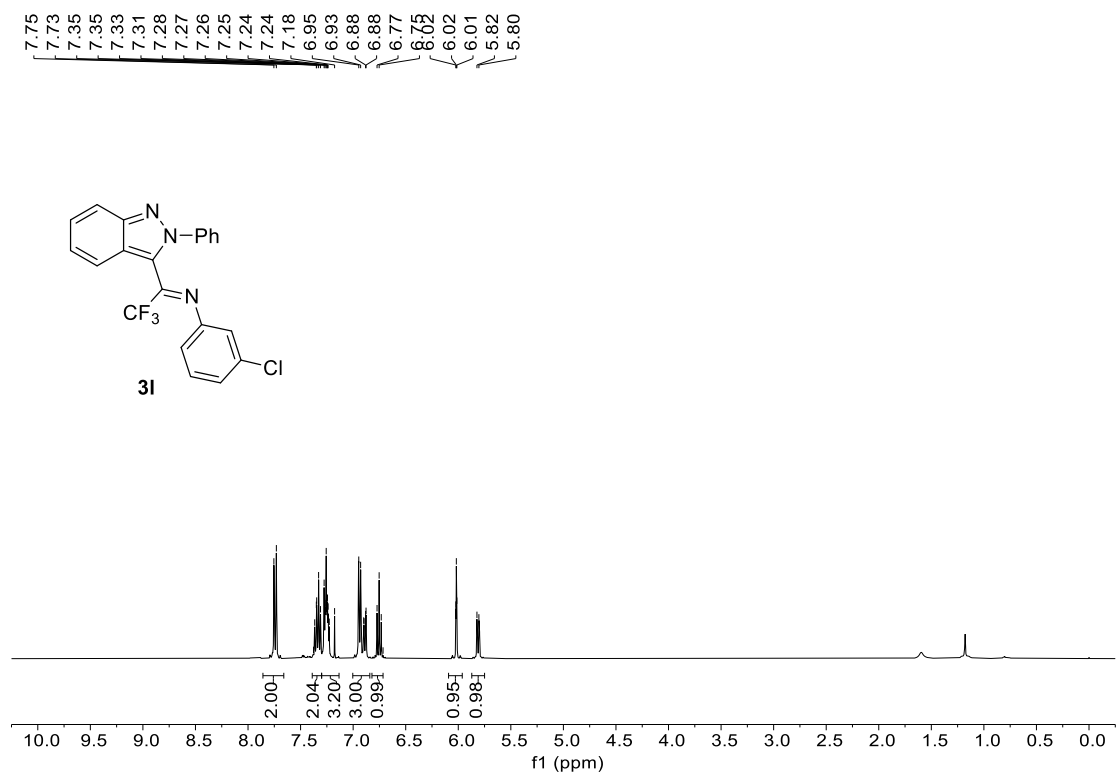


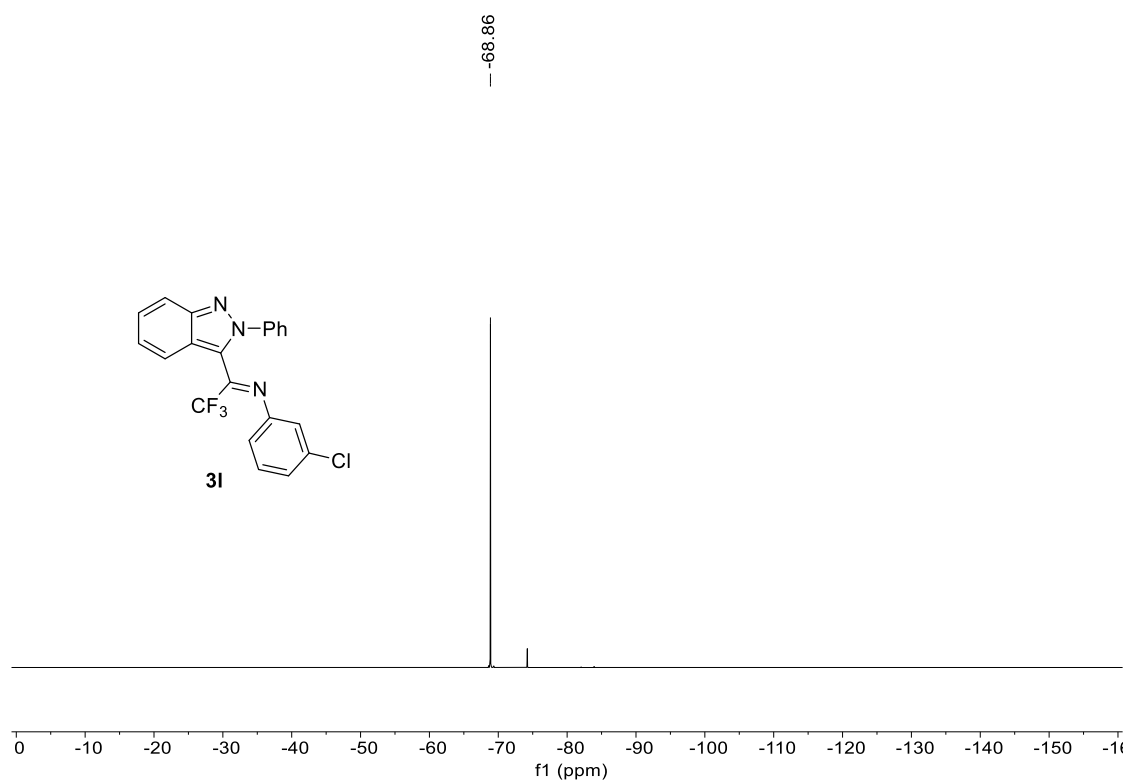
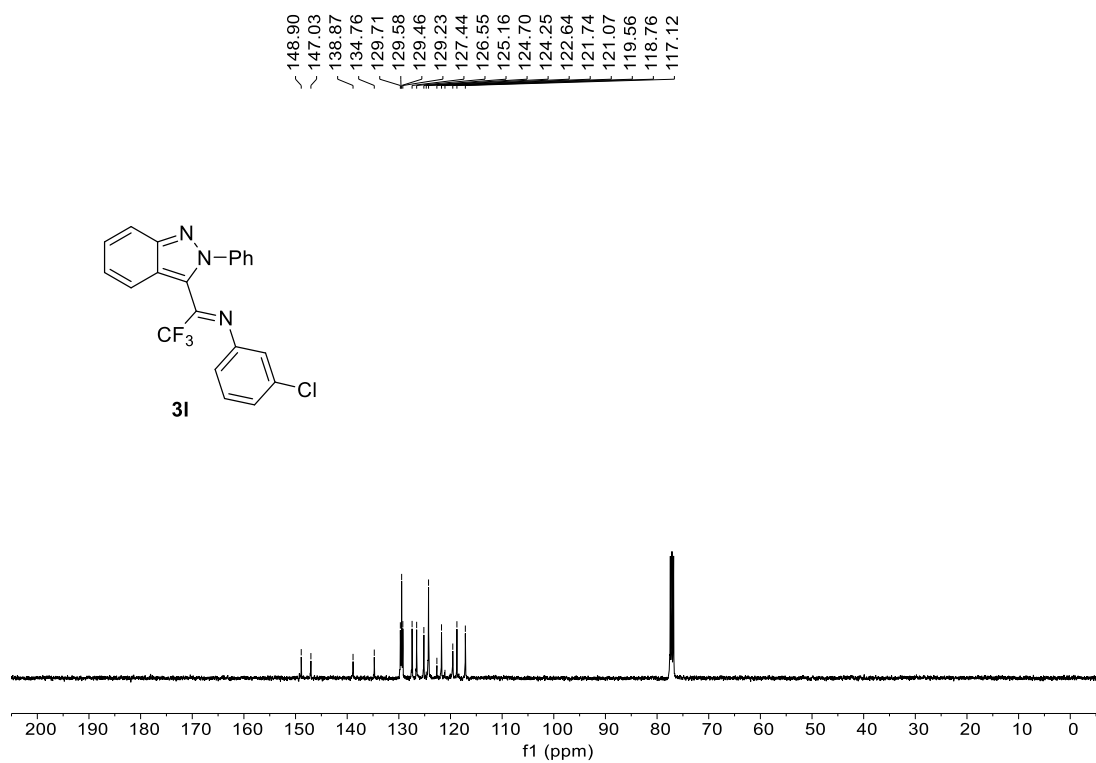
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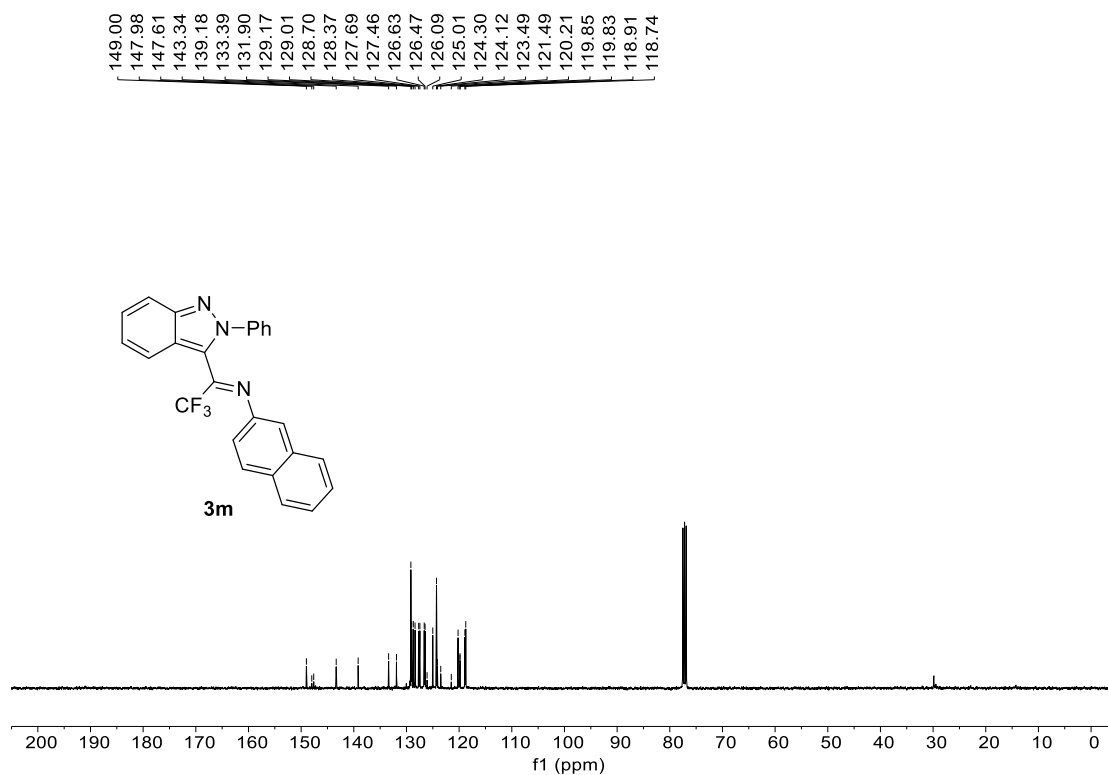
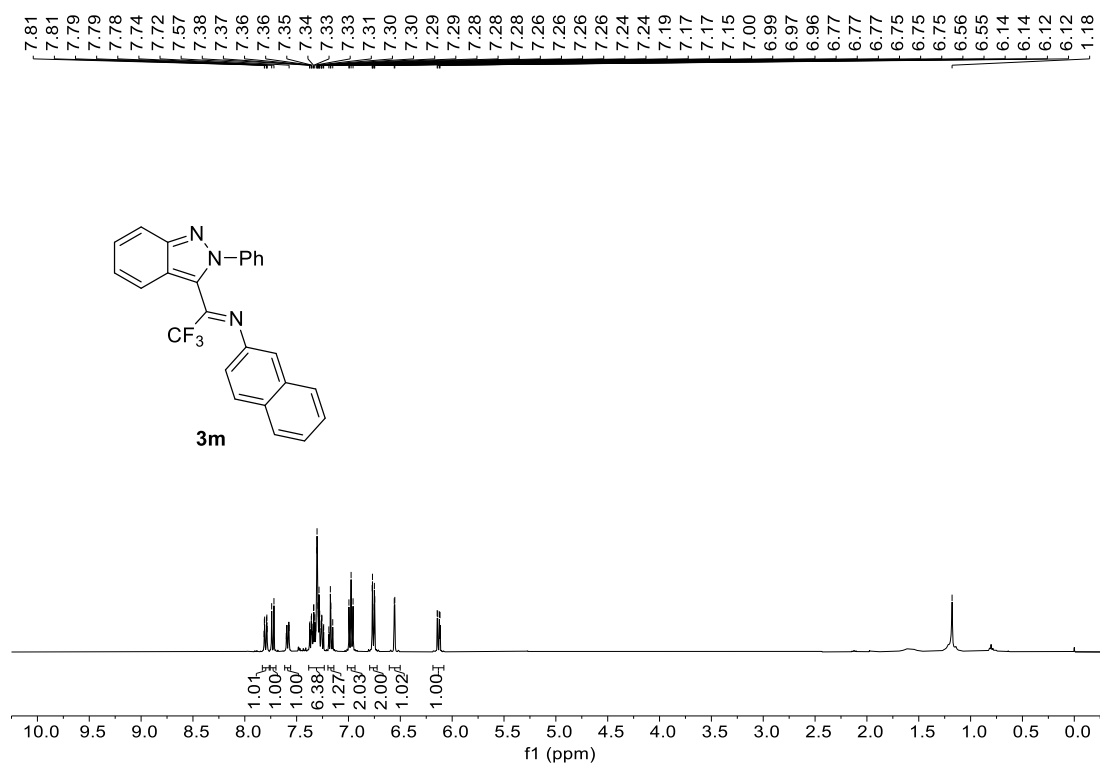


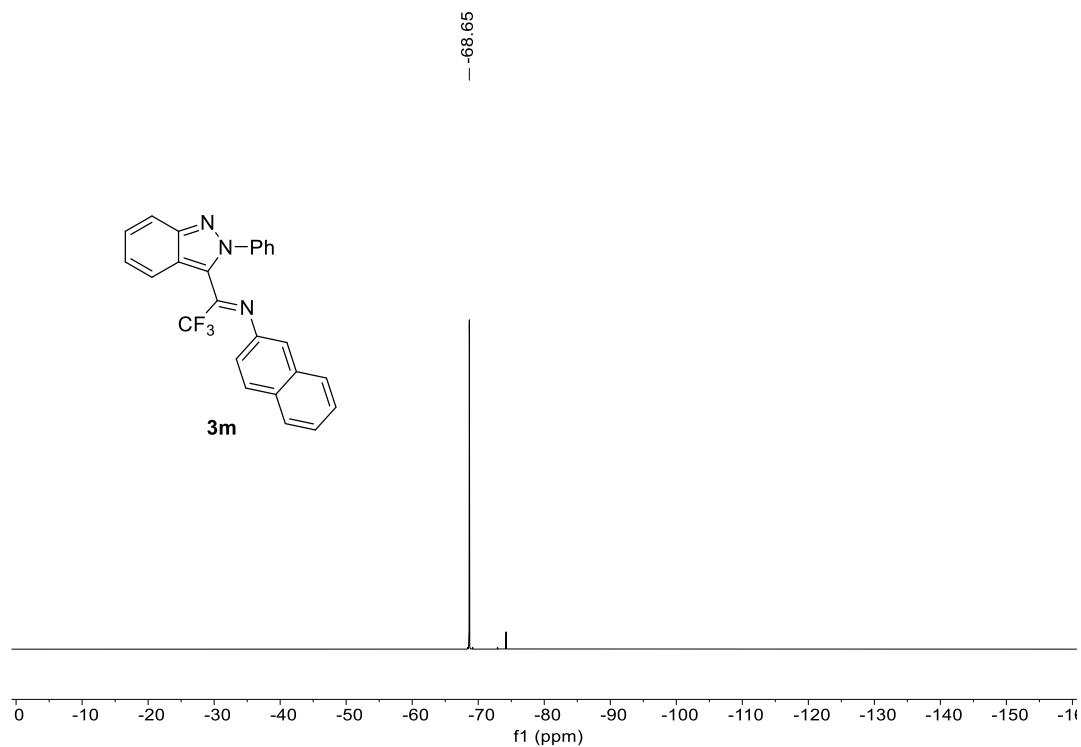
(12) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3l** (using CDCl_3 as solvent)



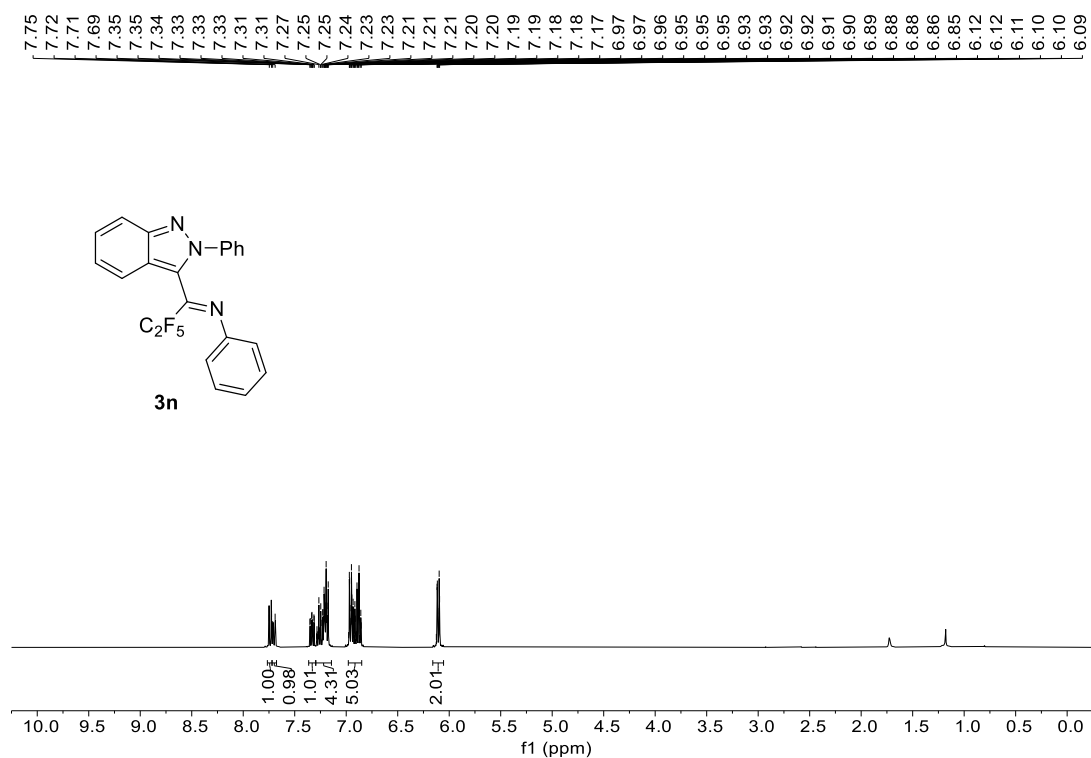


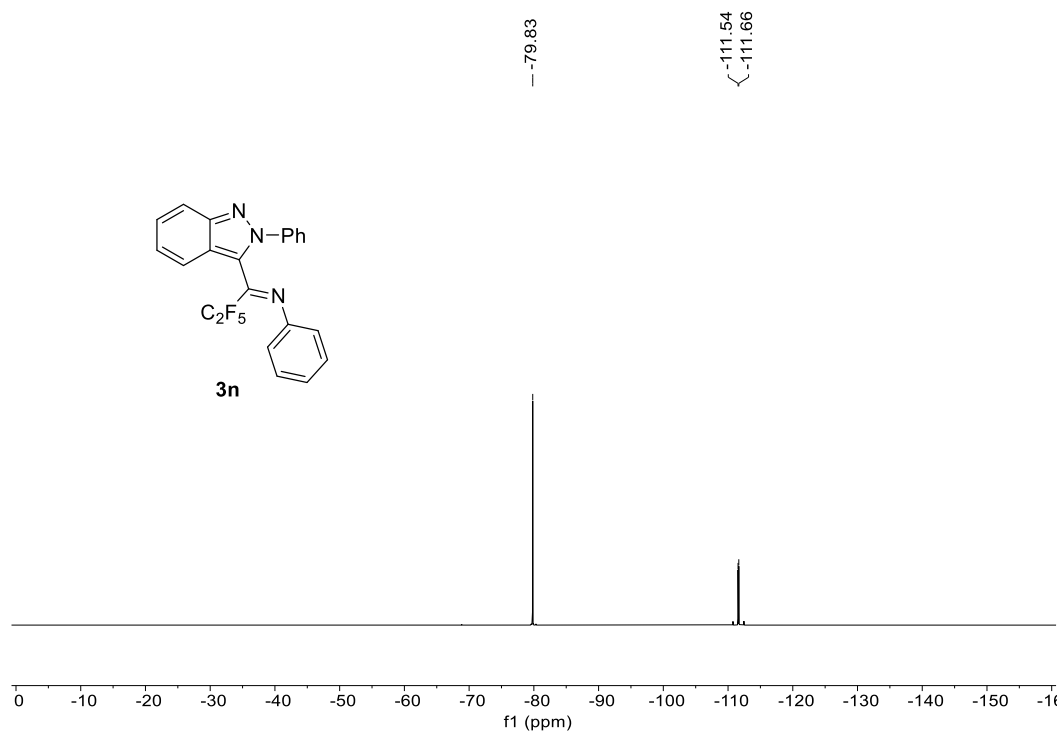
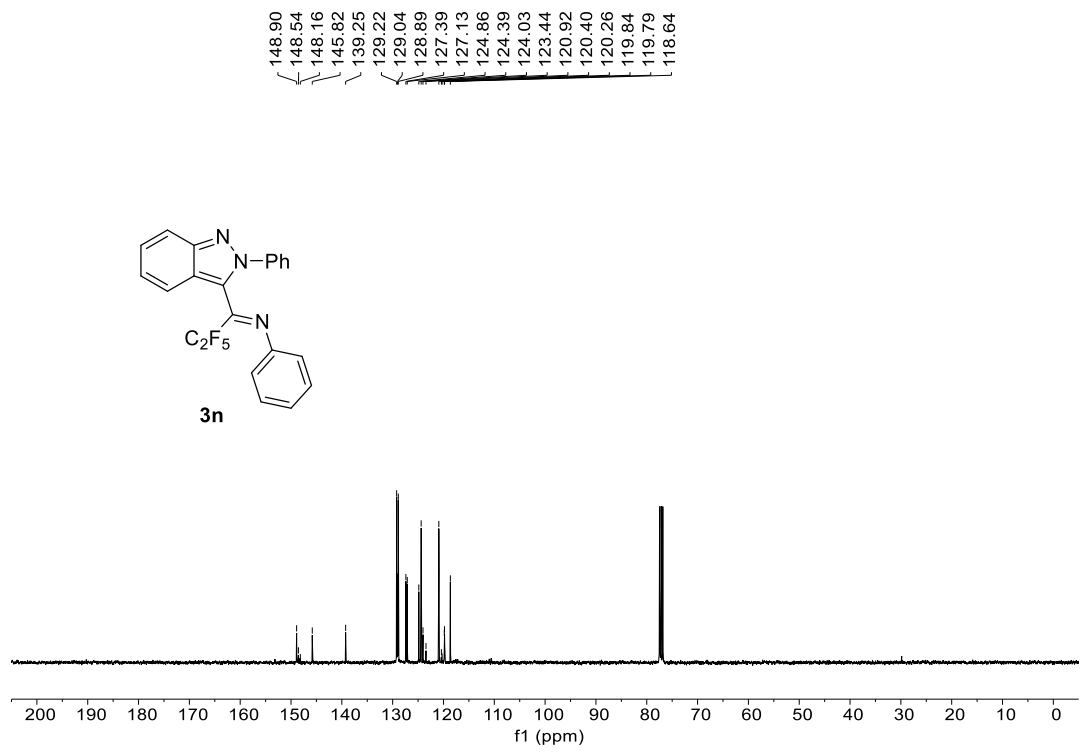
(13) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3m** (using CDCl_3 as solvent)



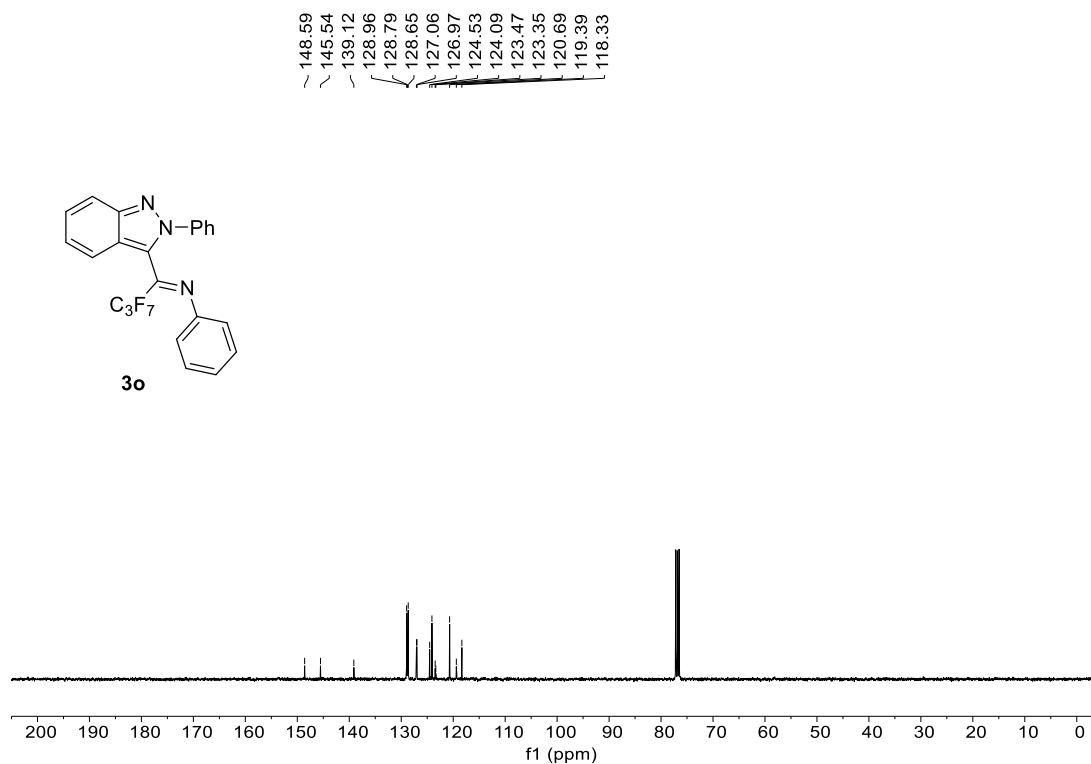
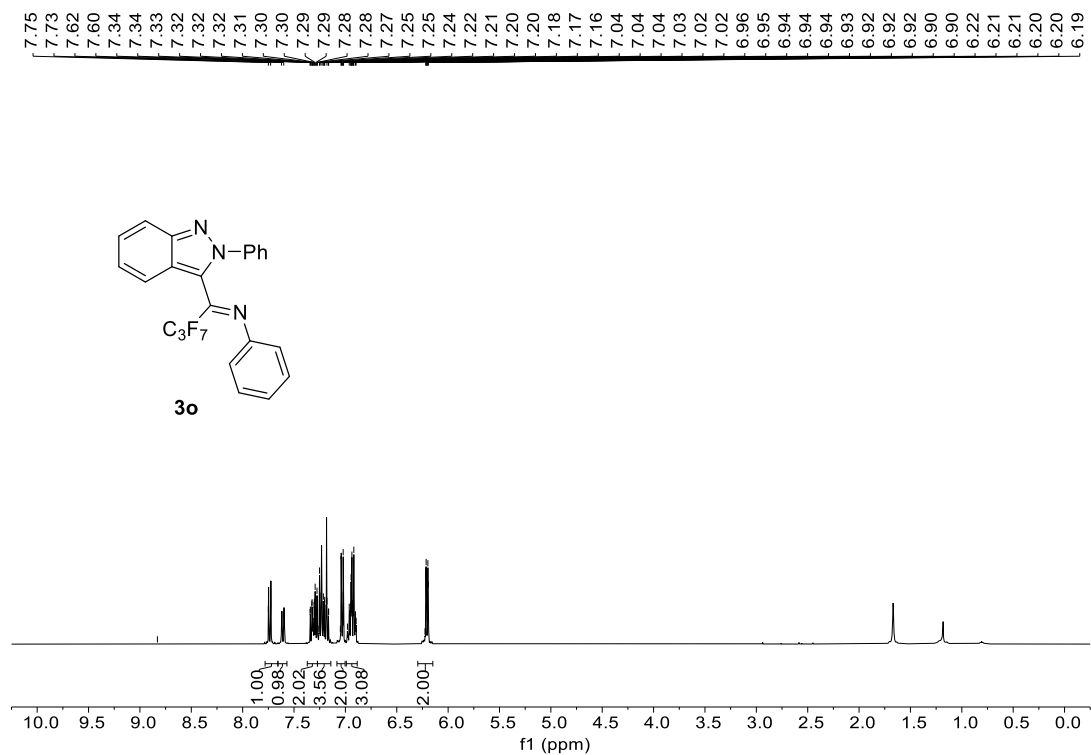


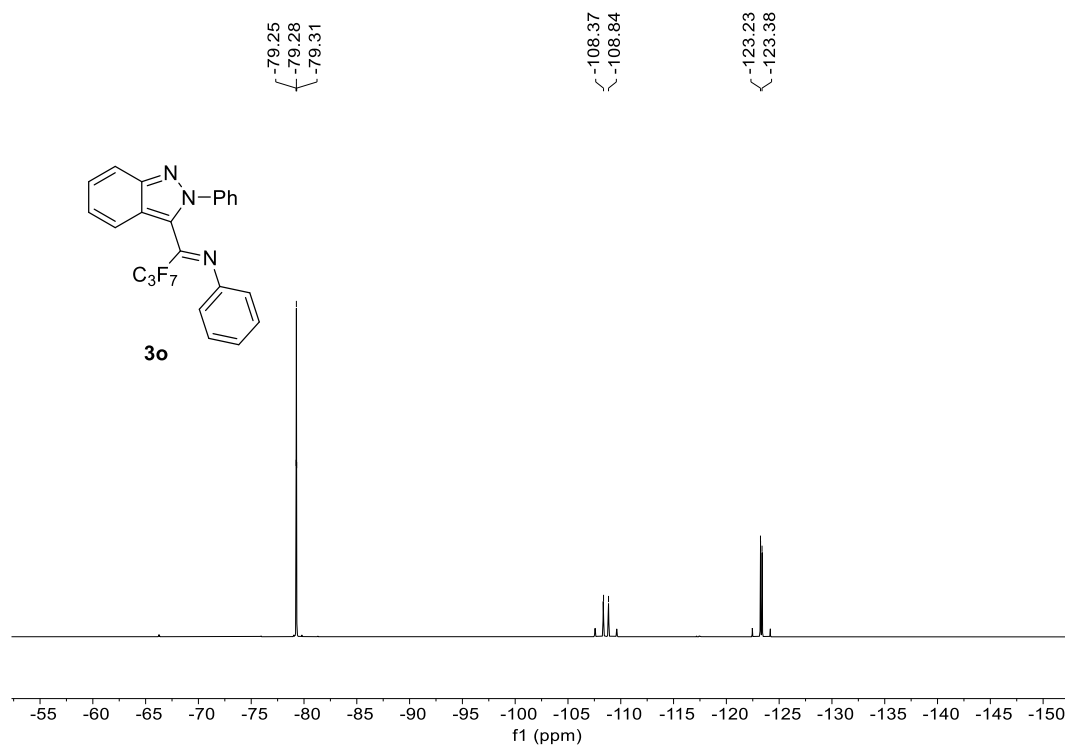
(14) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3n** (using CDCl_3 as solvent)



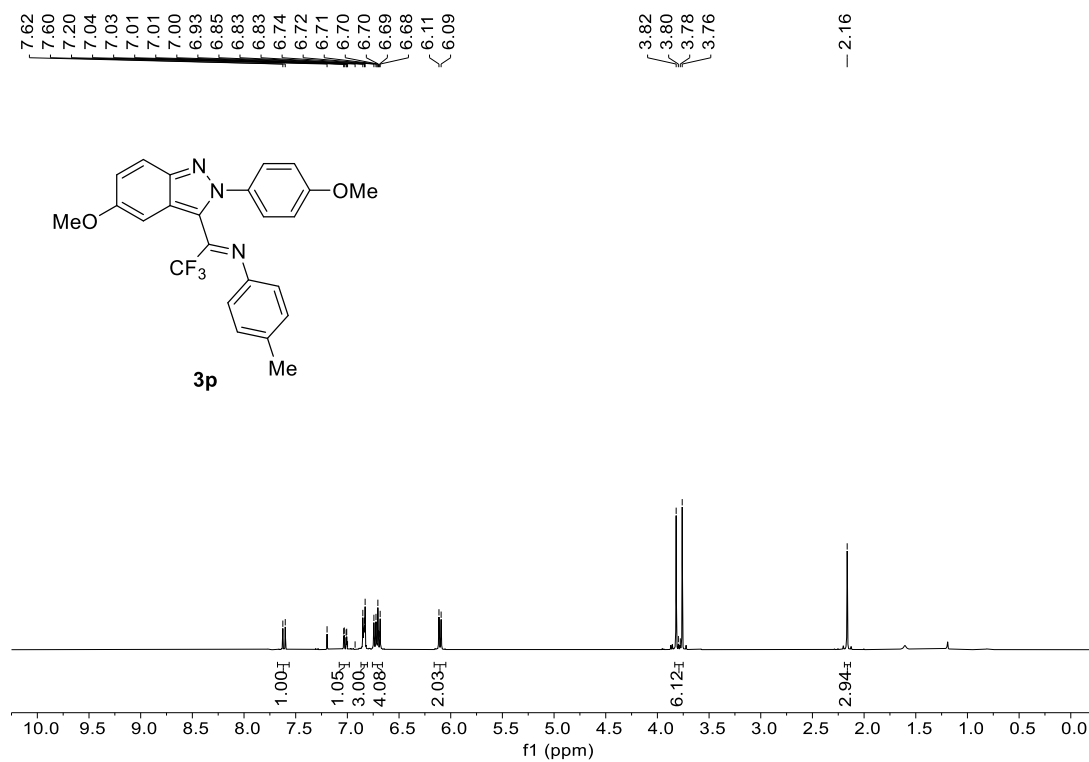


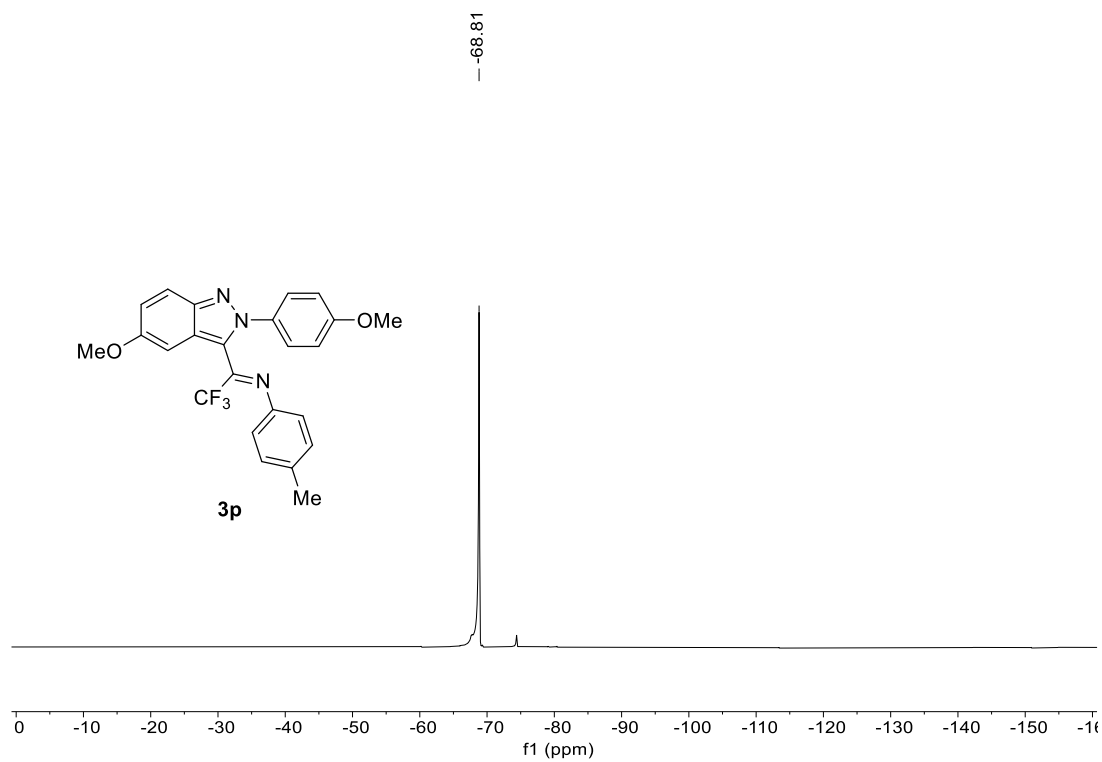
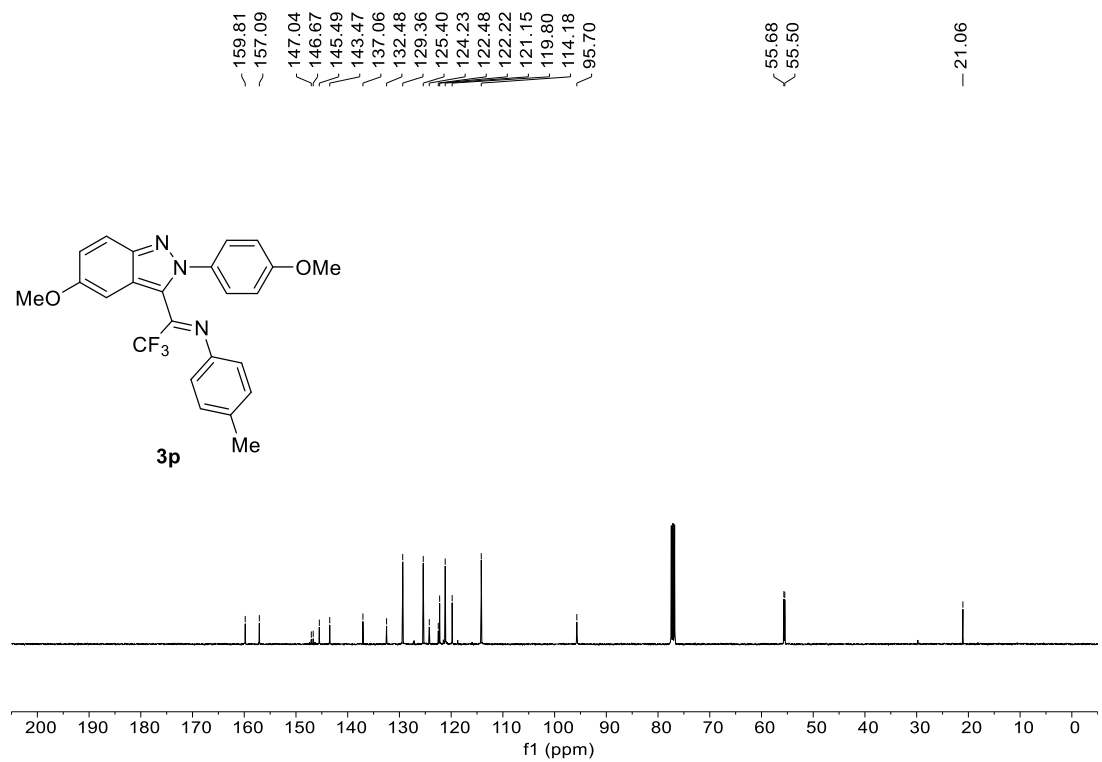
(15) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3o** (using CDCl_3 as solvent)



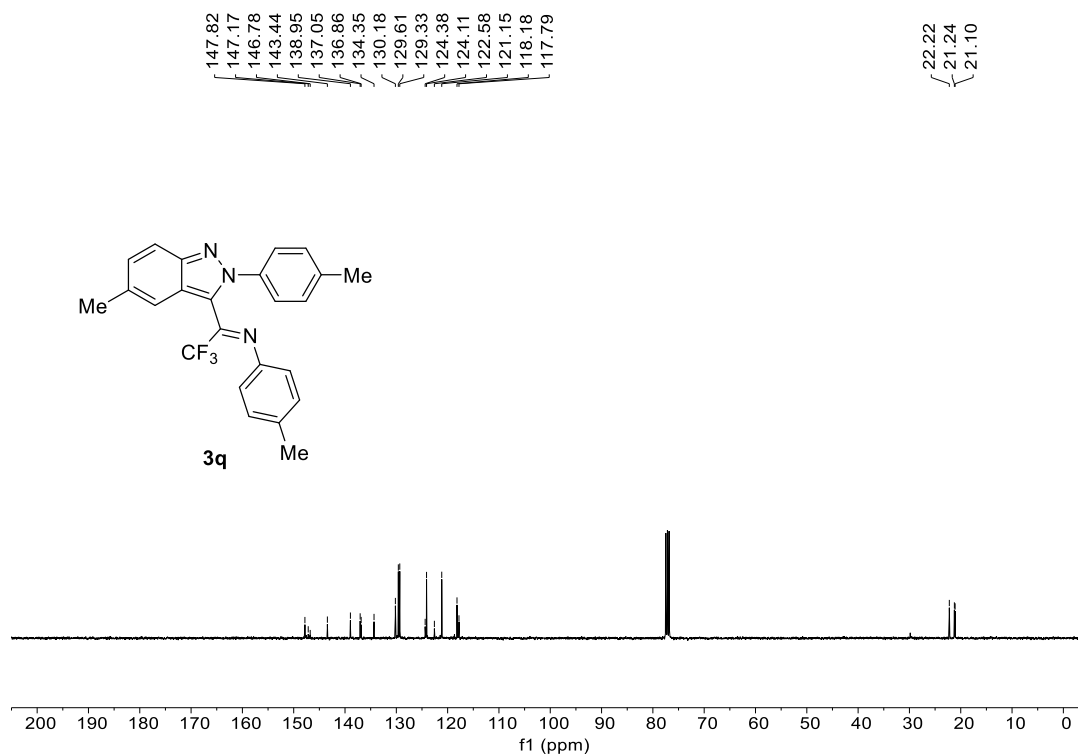
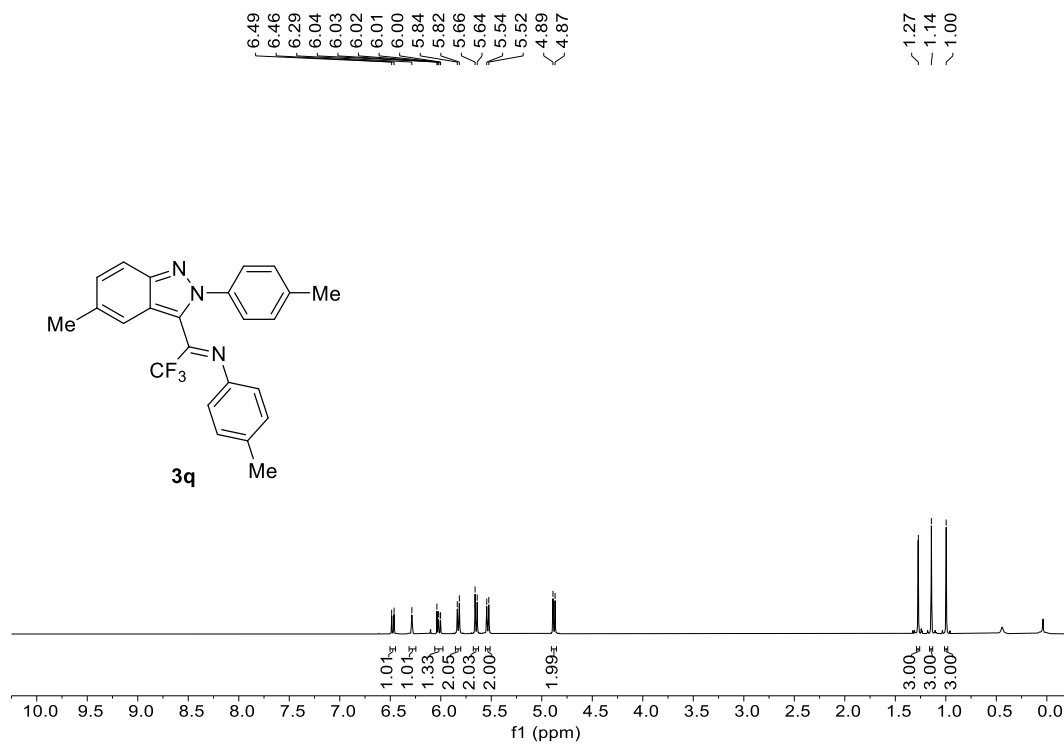


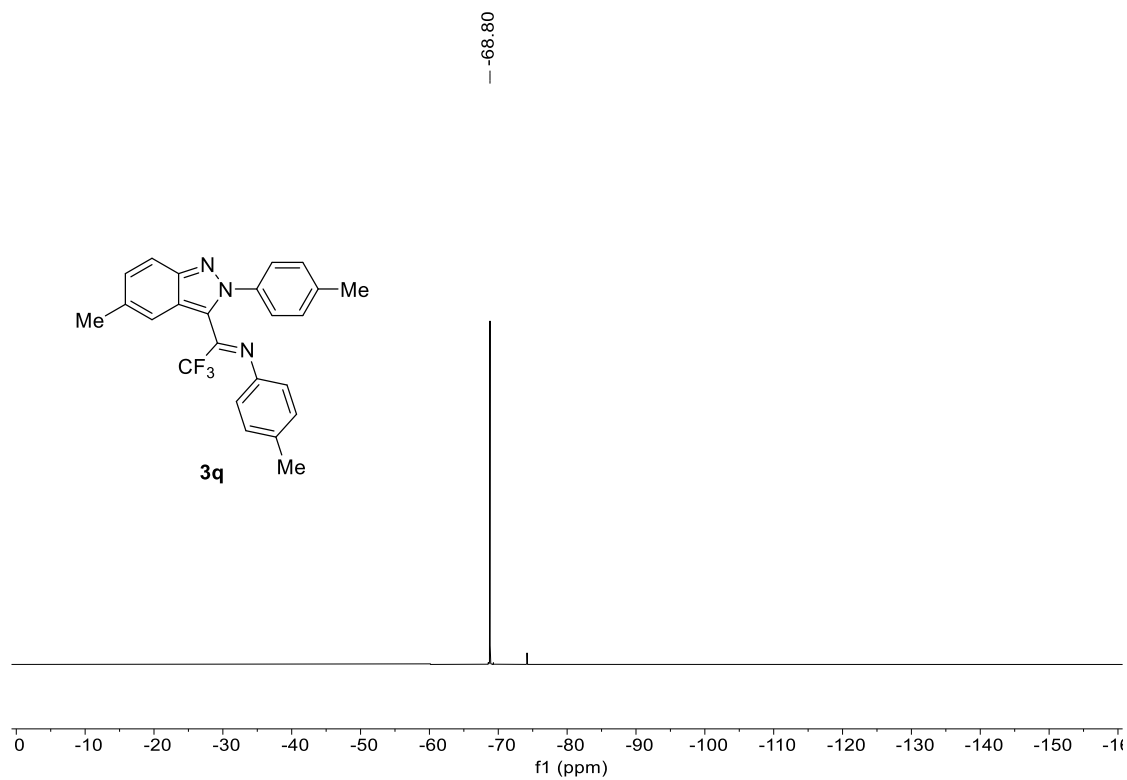
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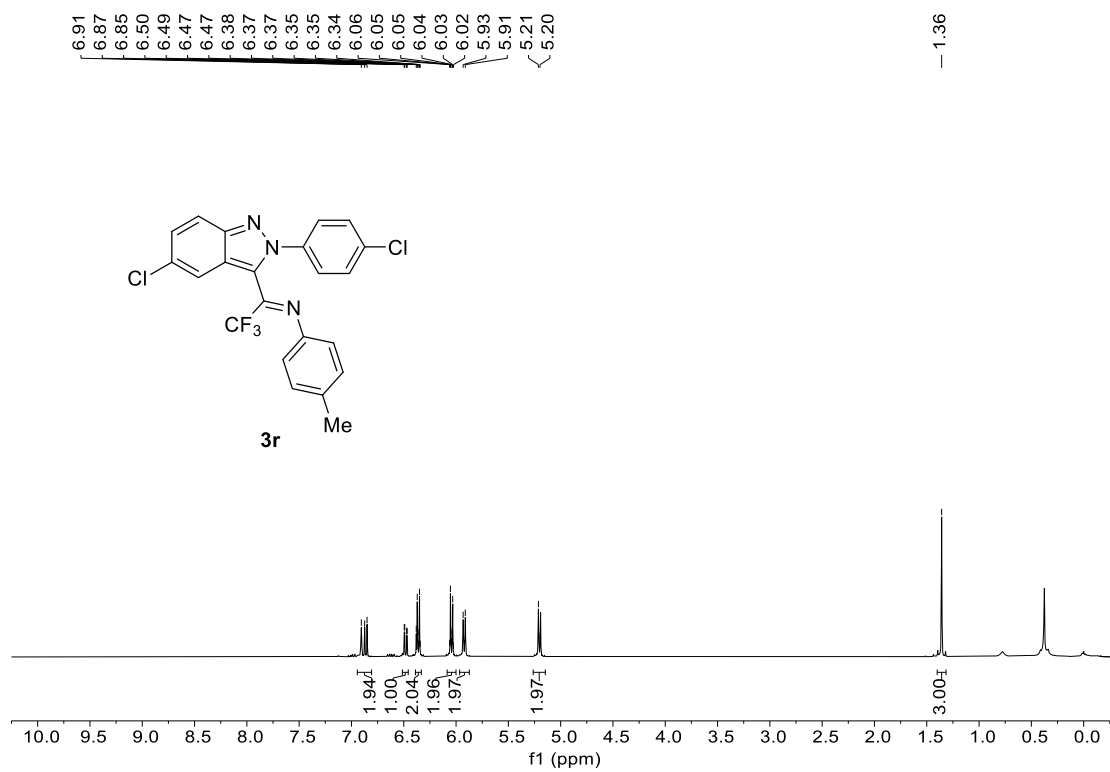


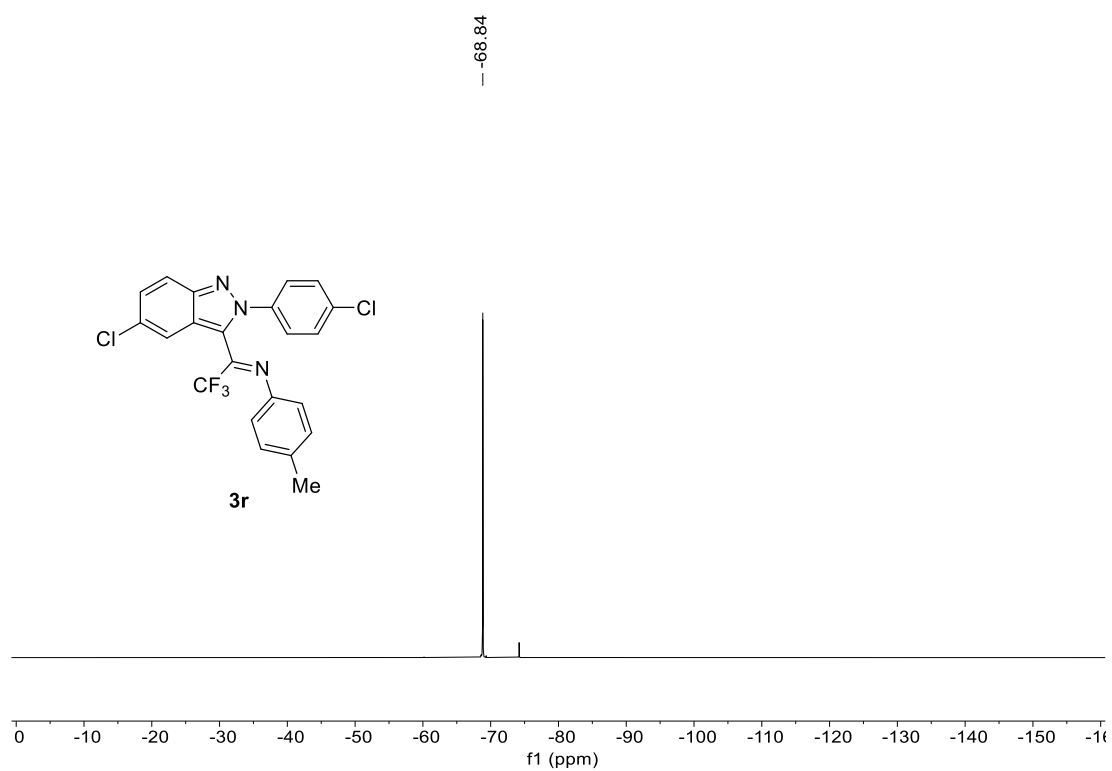
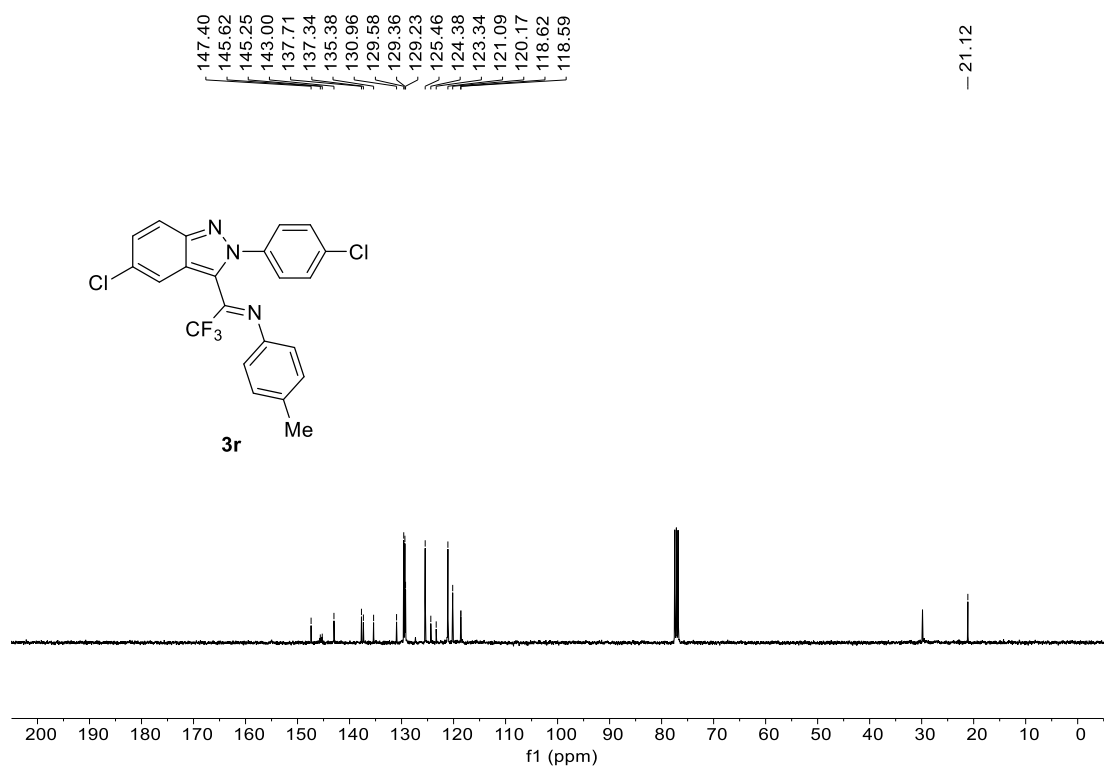
(17) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3q** (using CDCl_3 as solvent)



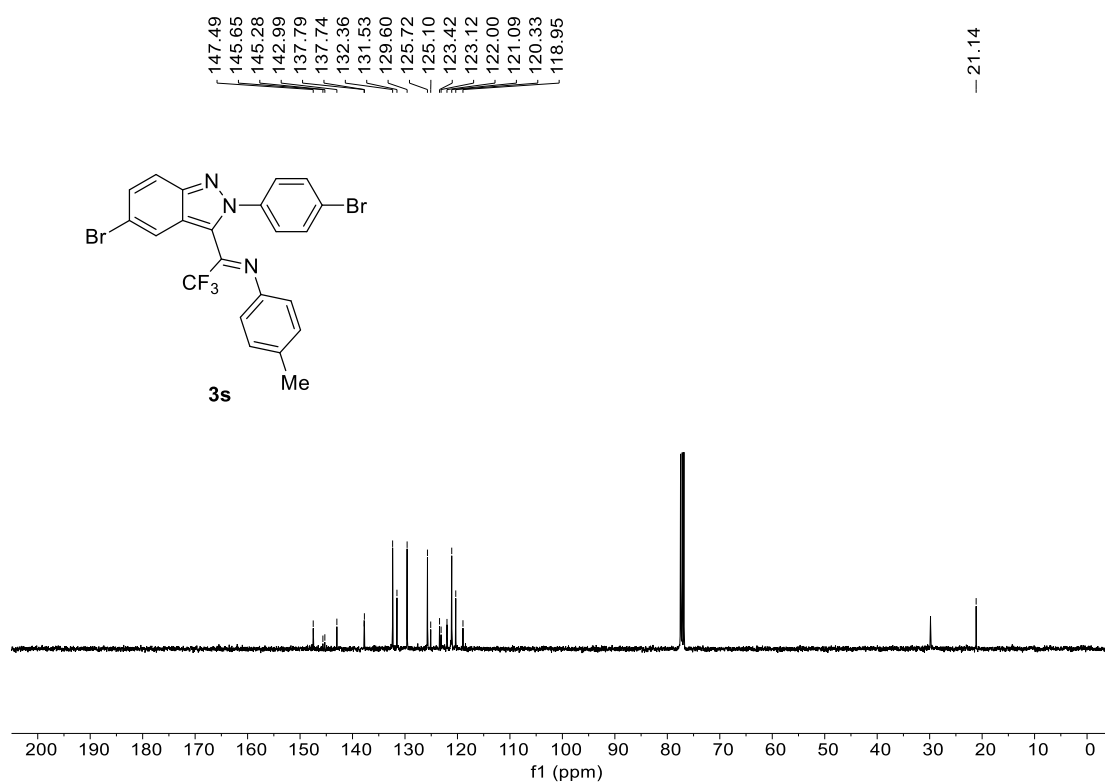
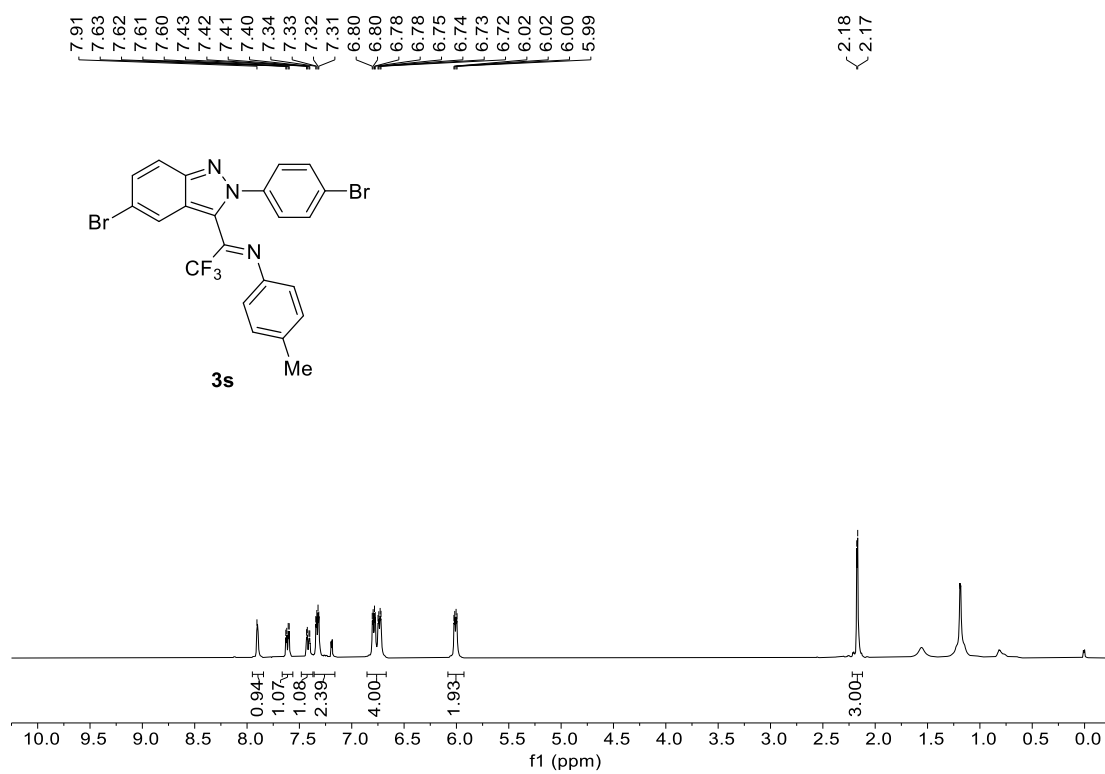


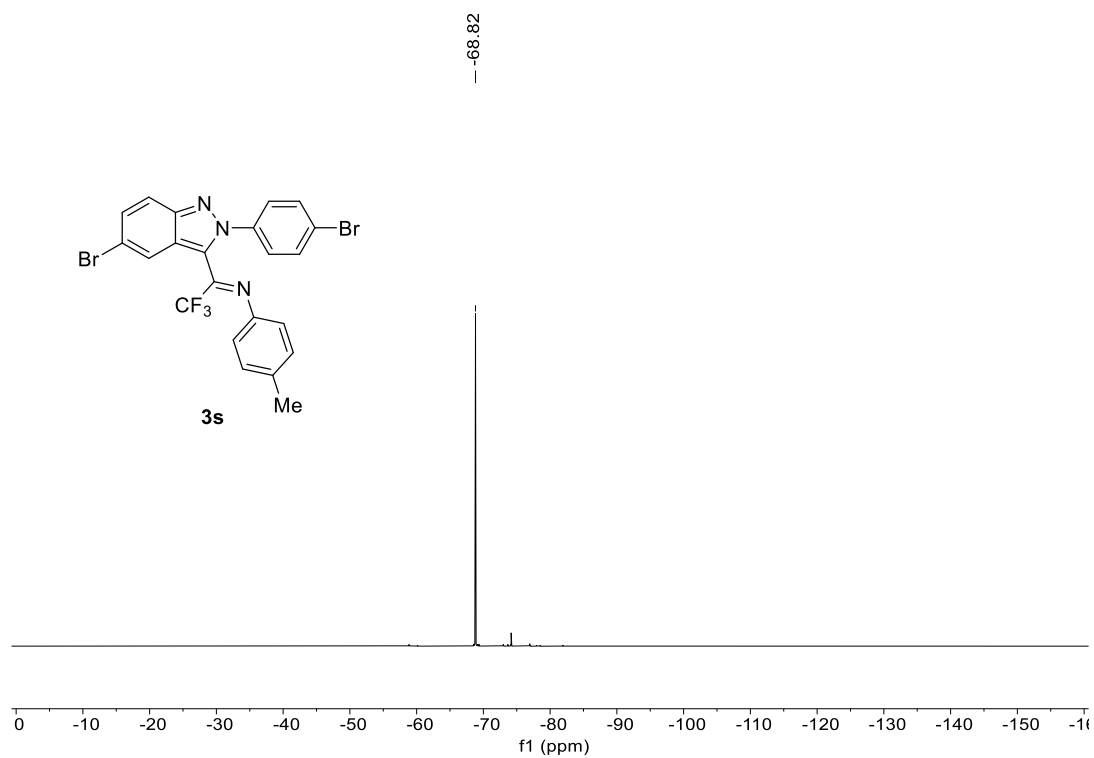
(18) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3r** (using CDCl_3 as solvent)



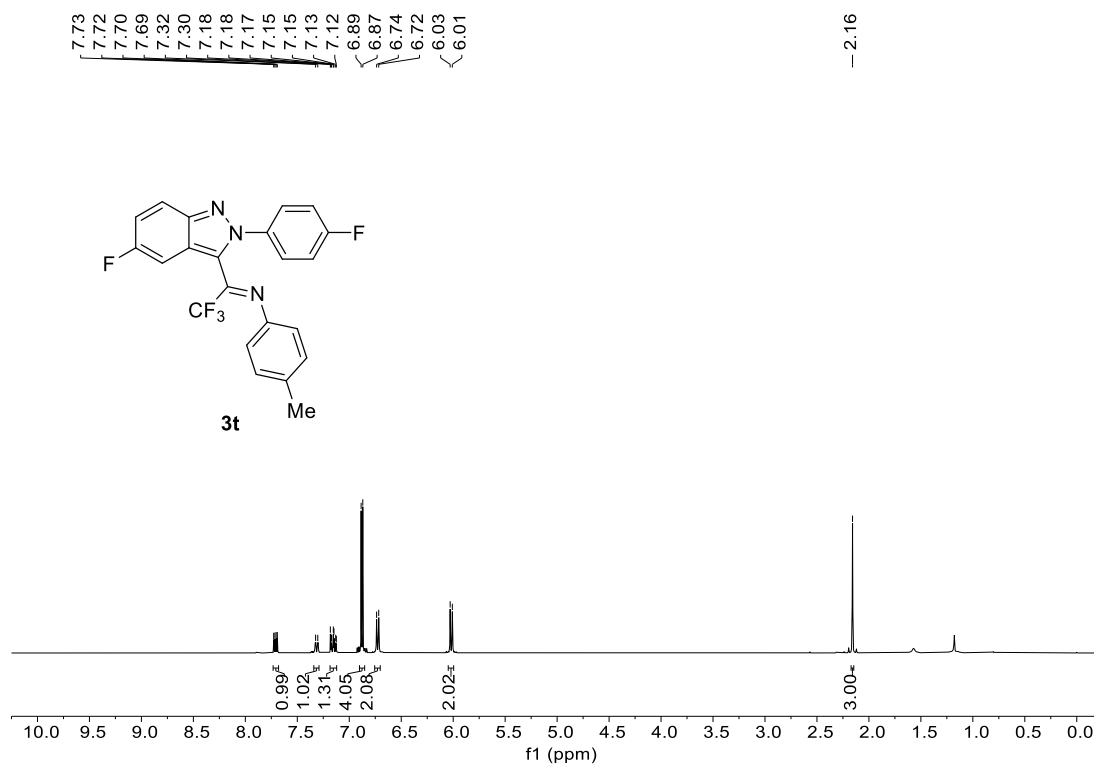


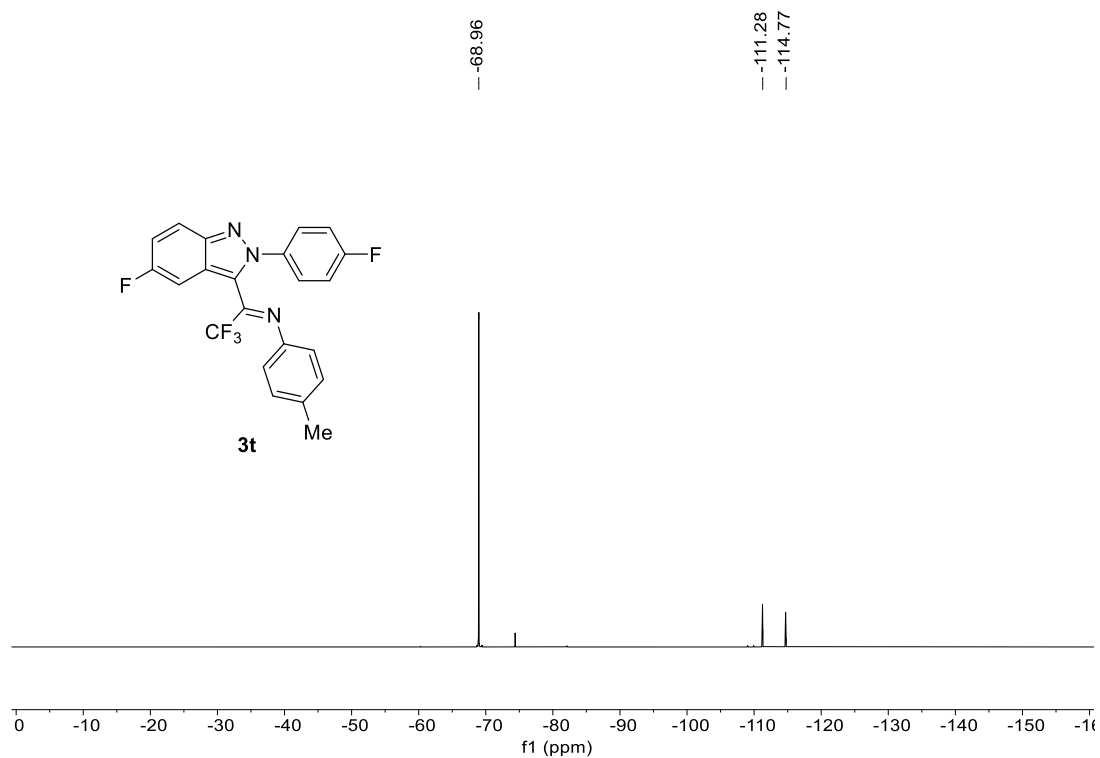
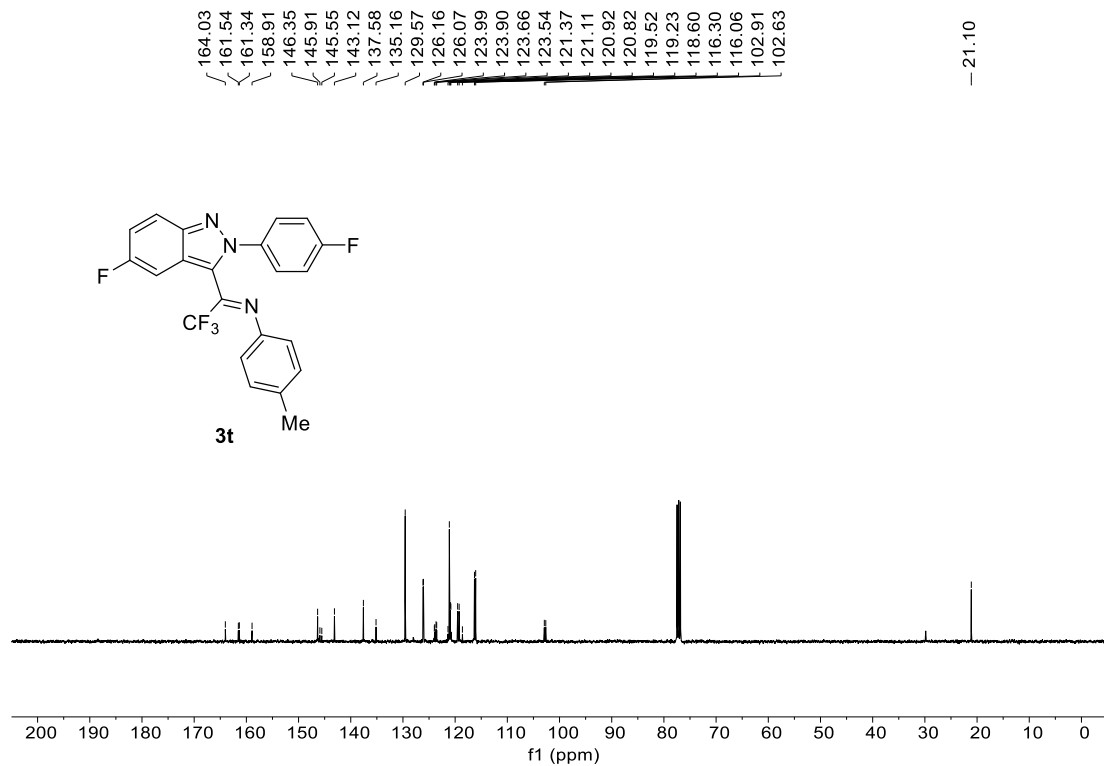
(19) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3s** (using CDCl_3 as solvent)



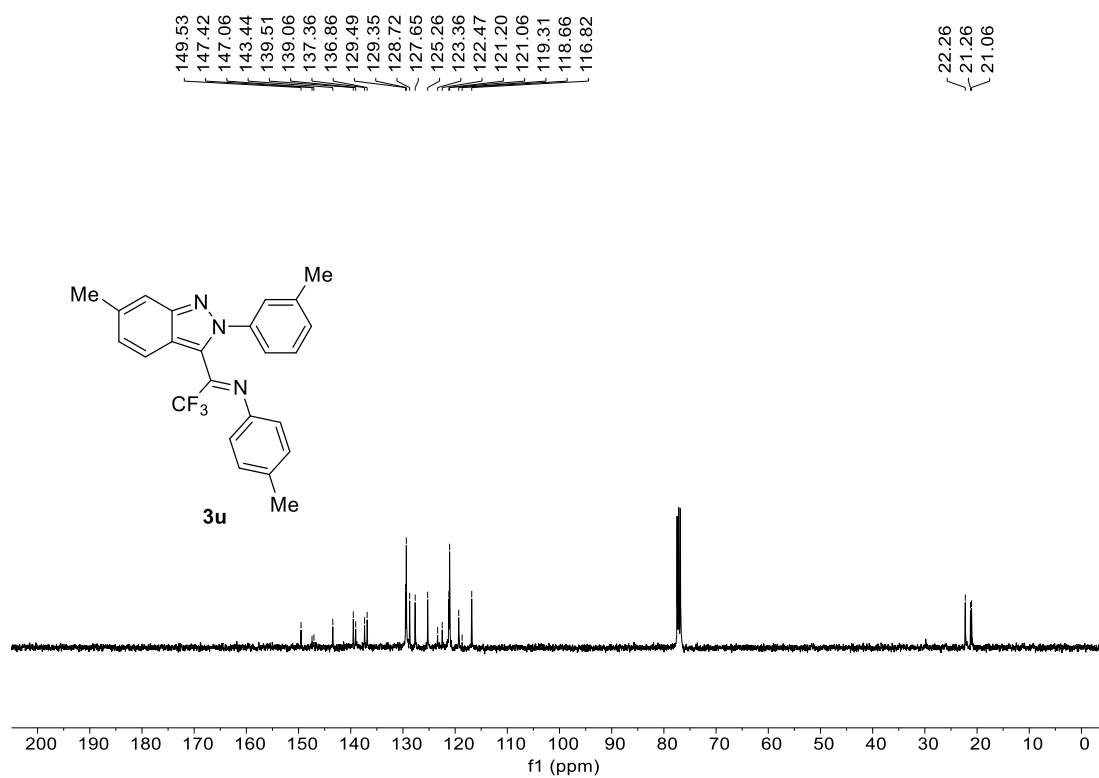
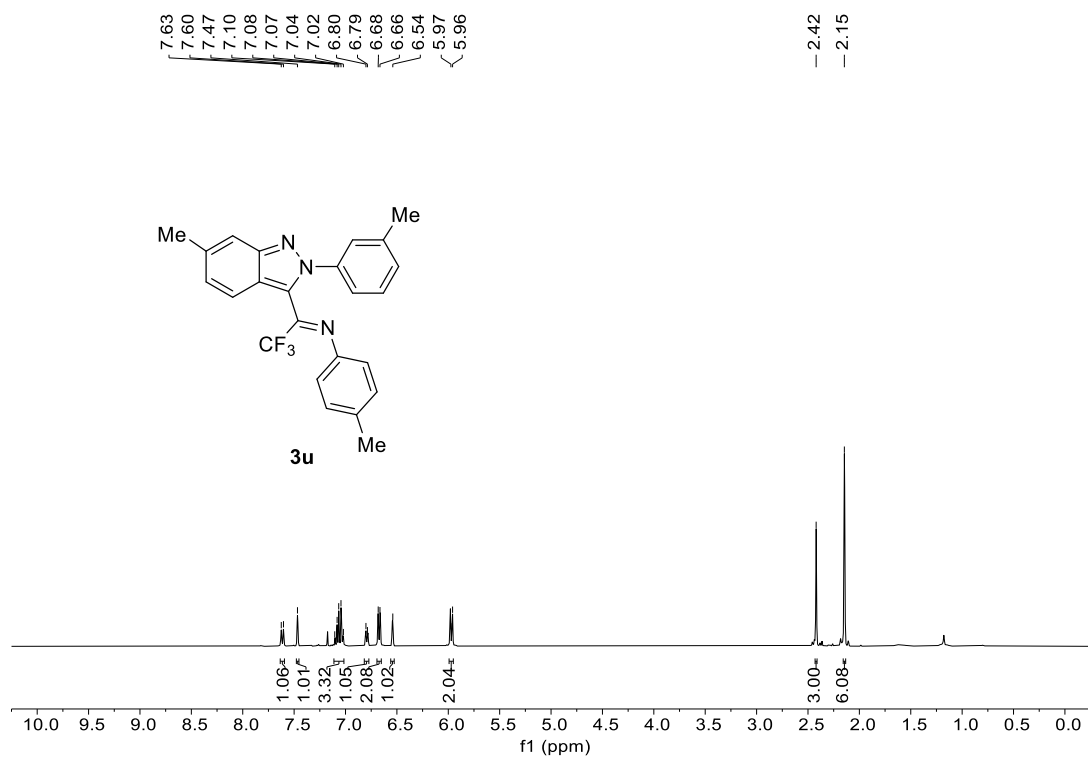


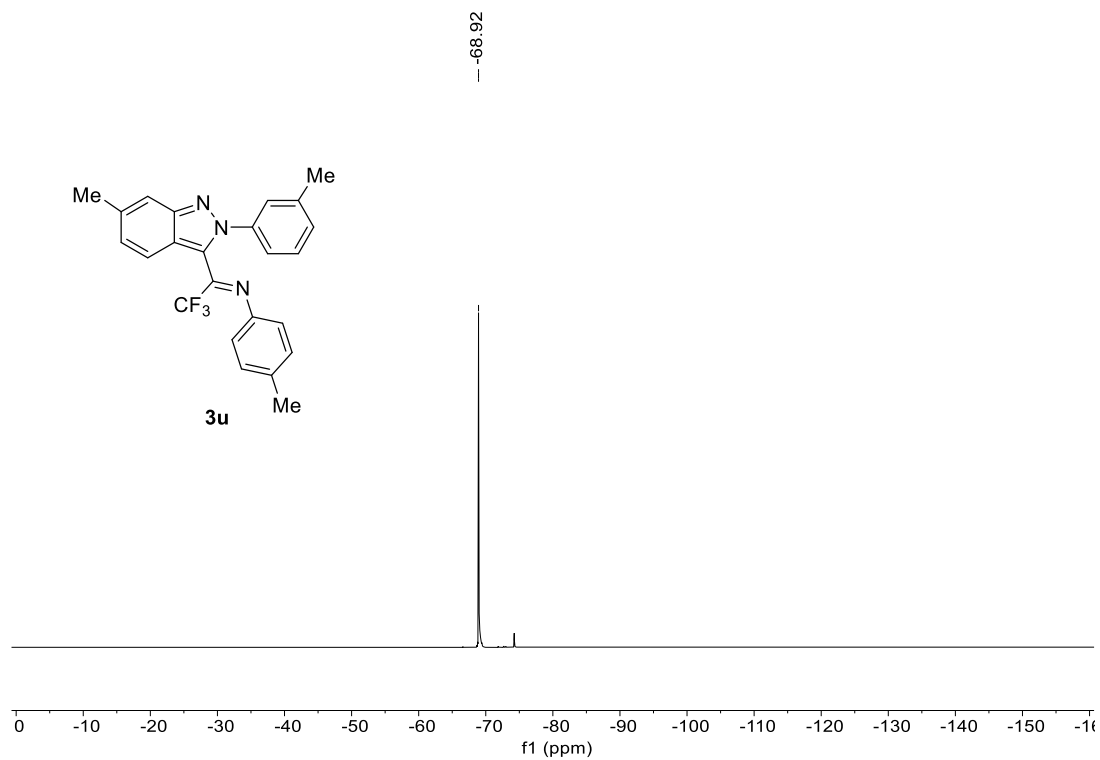
(20) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3t** (using CDCl_3 as solvent)



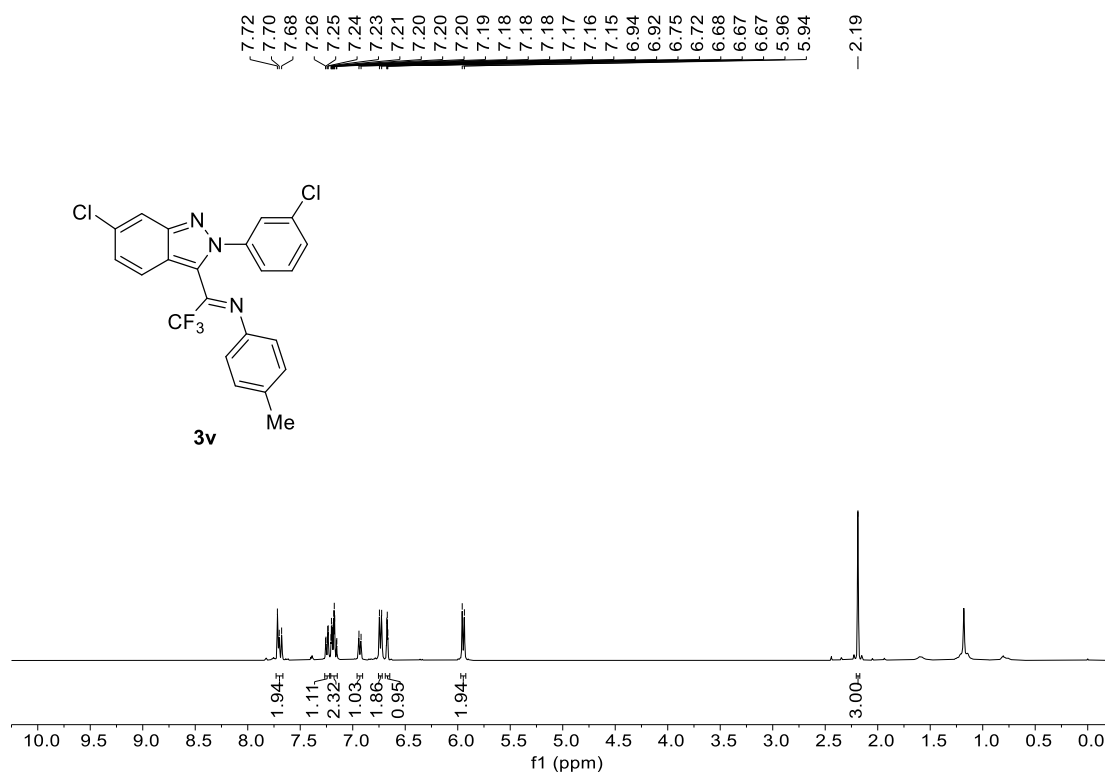


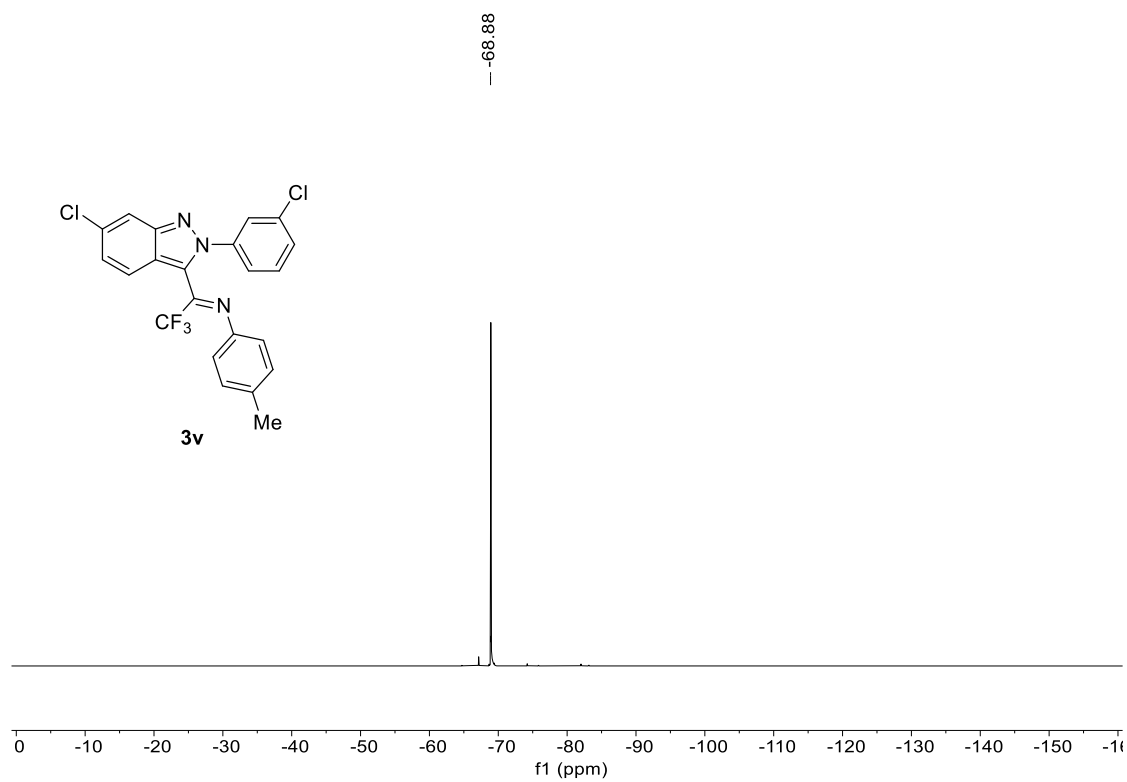
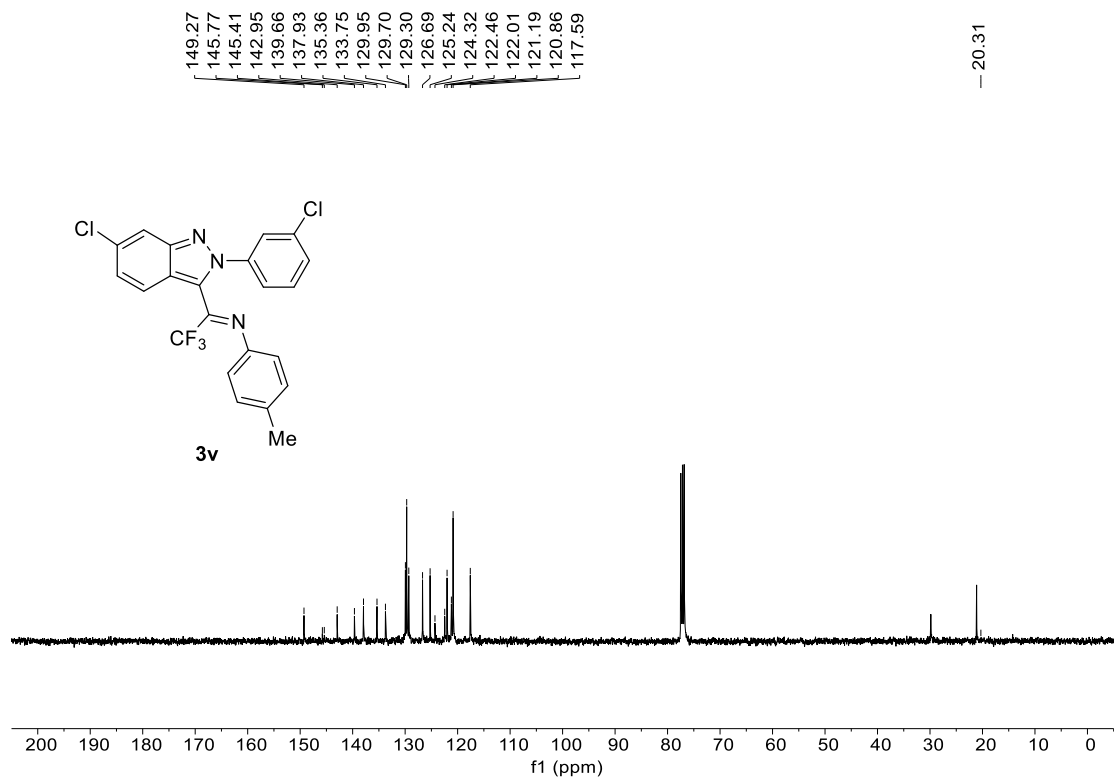
(21) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3u** (using CDCl_3 as solvent)



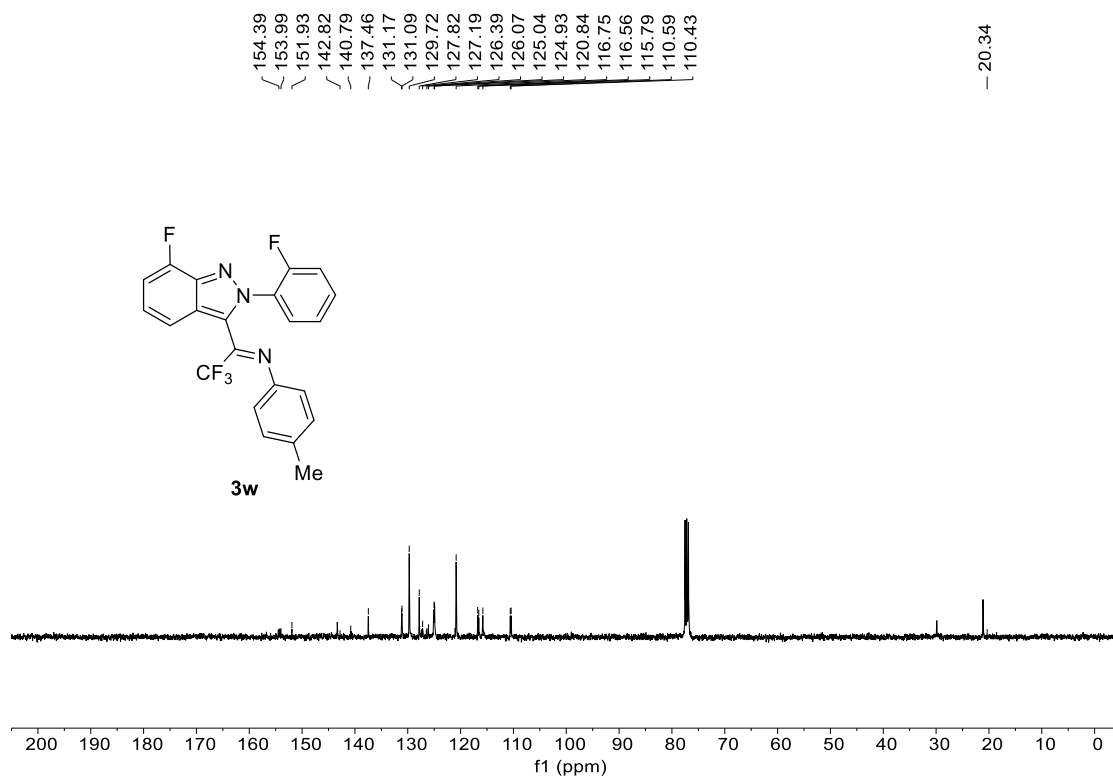
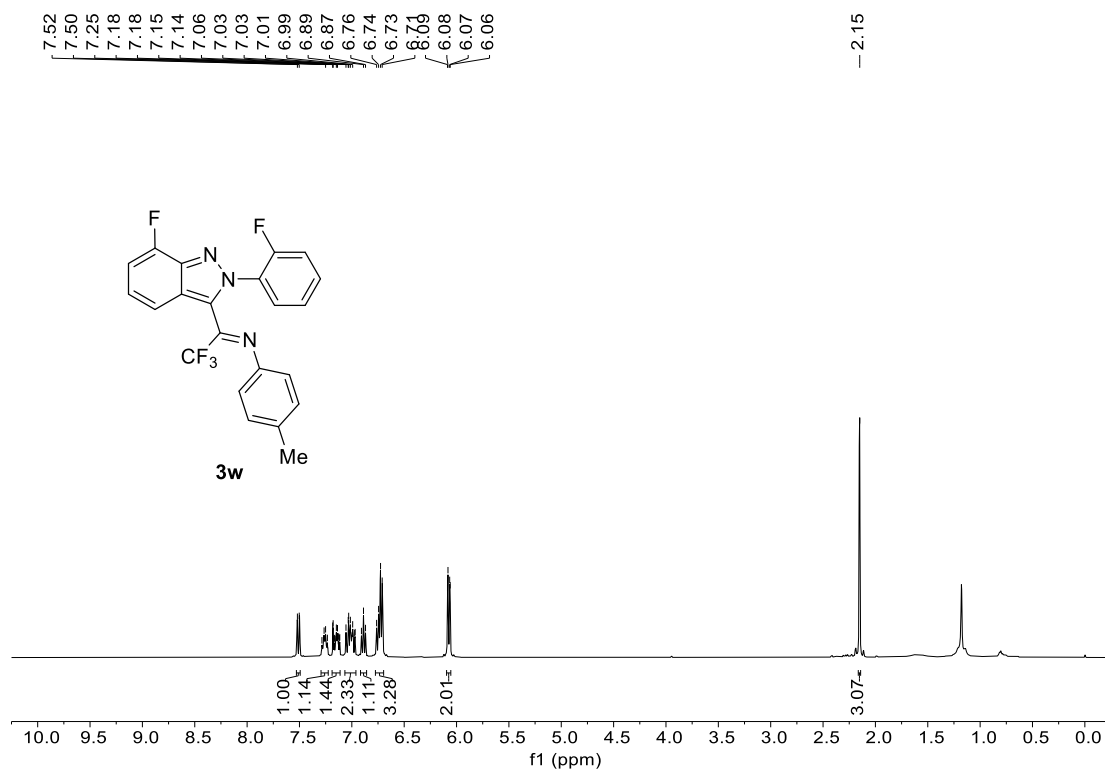


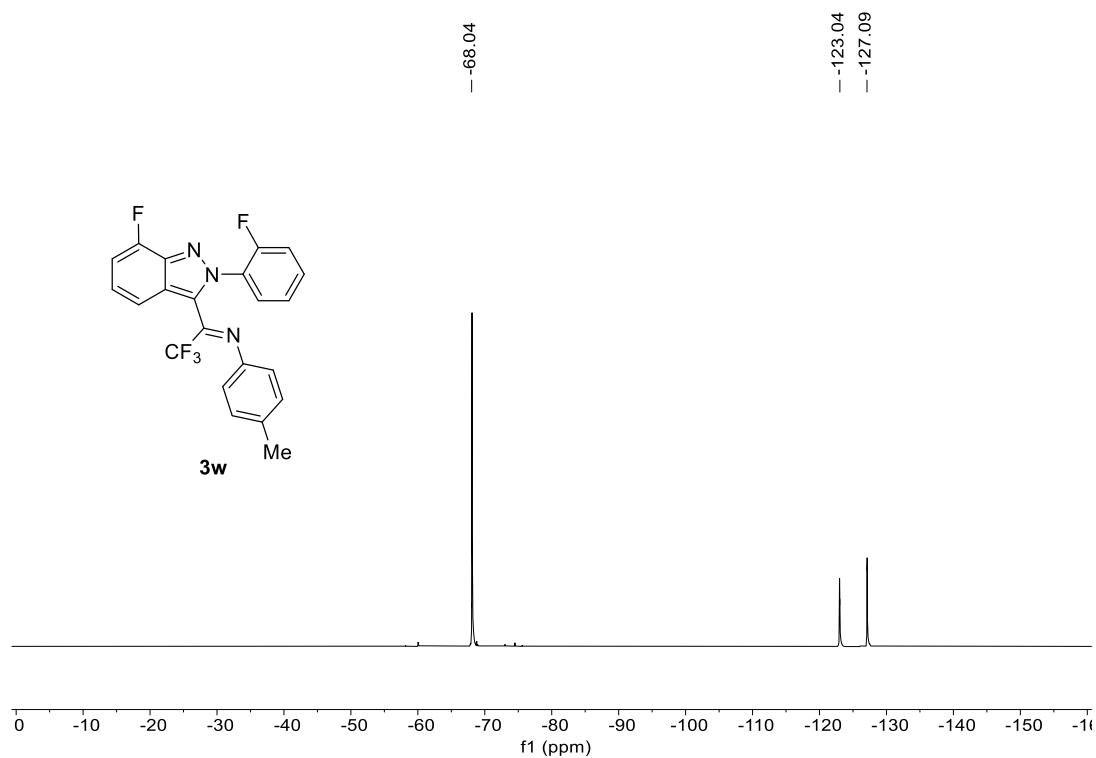
(22) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3v** (using CDCl₃ as solvent)



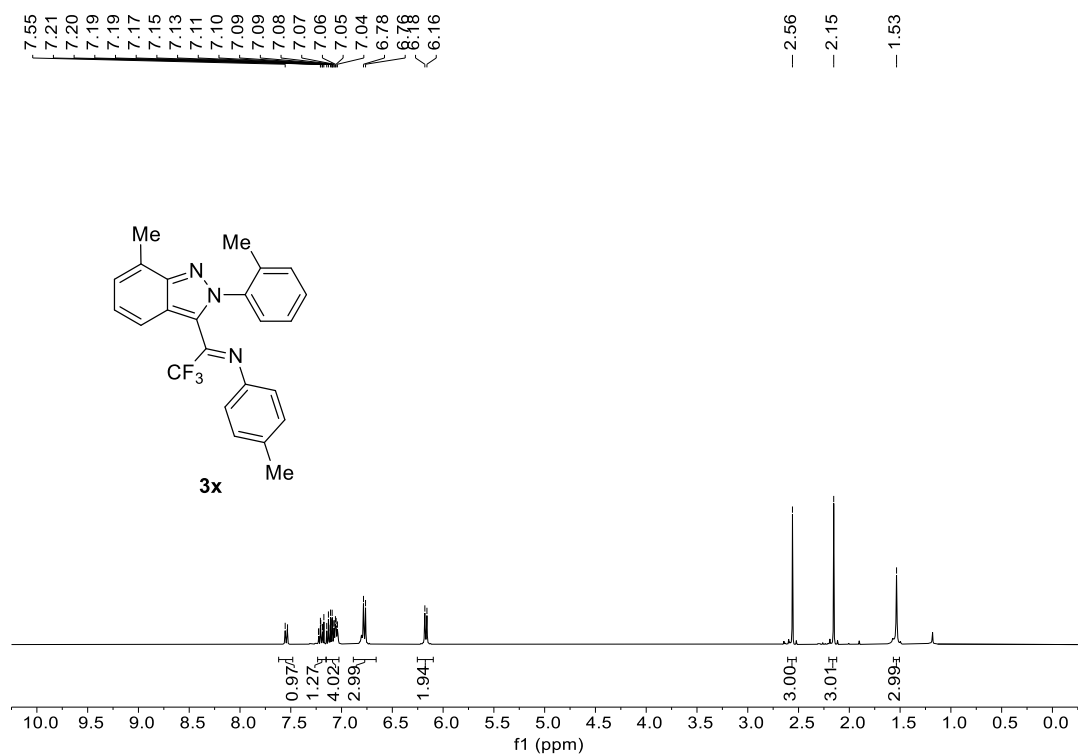


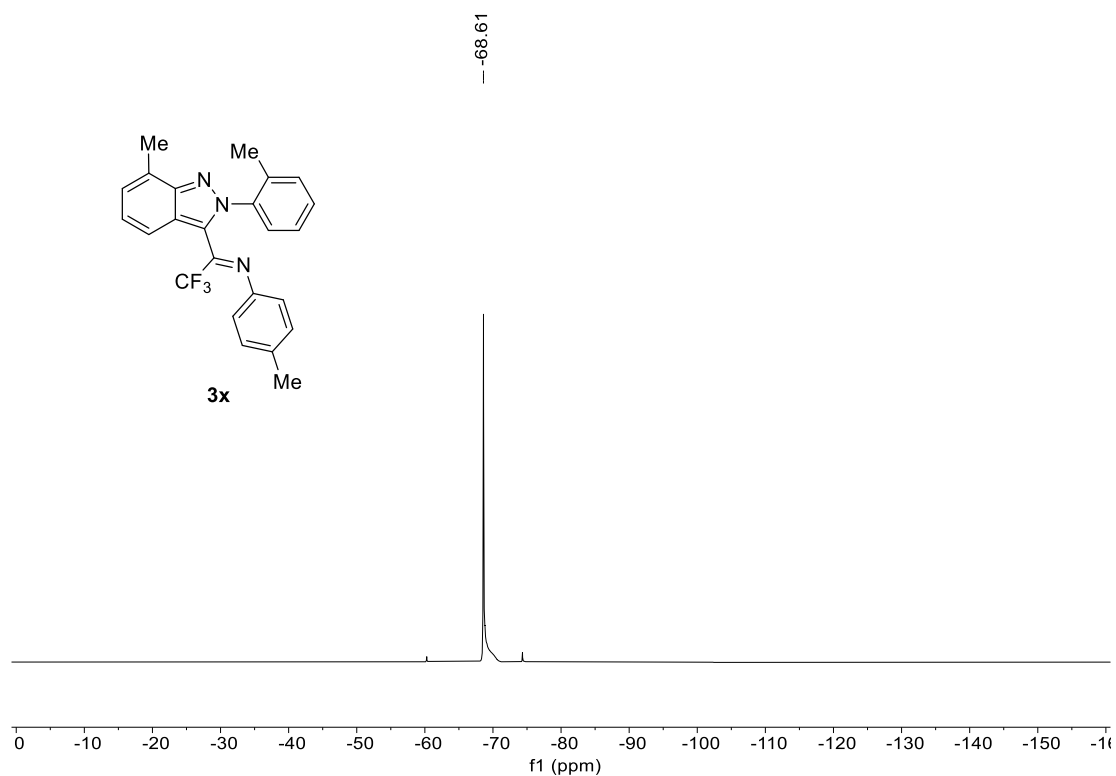
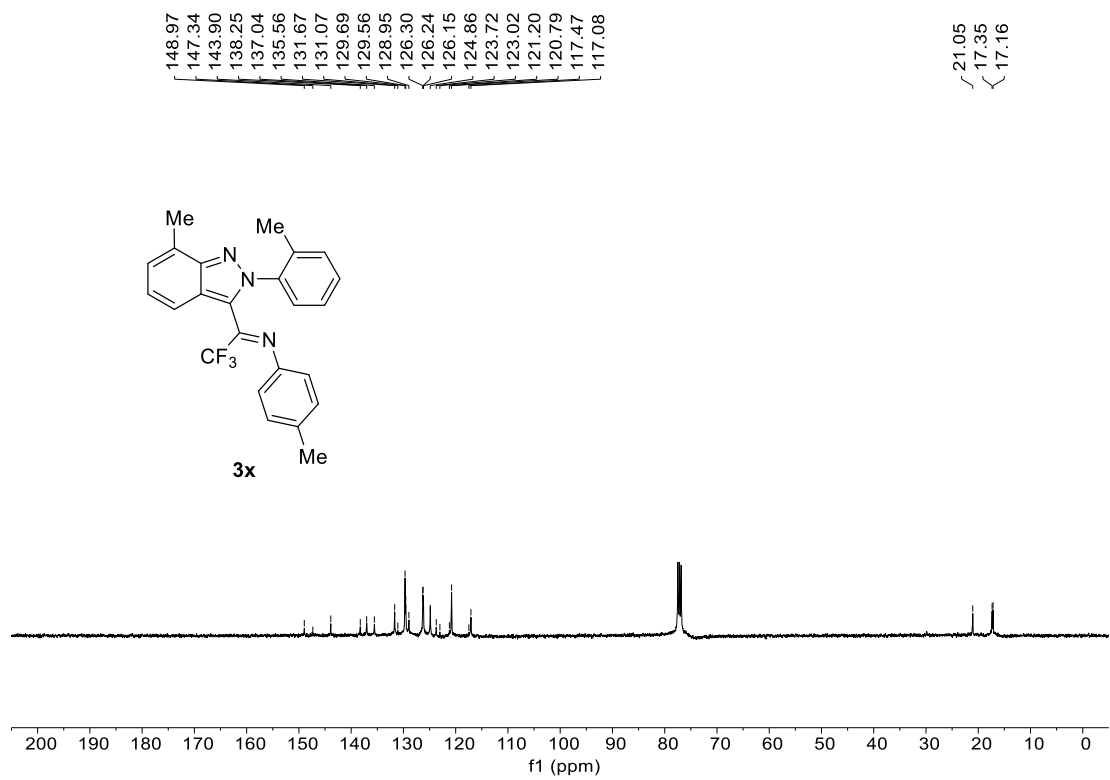
(23) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3w** (using CDCl_3 as solvent)



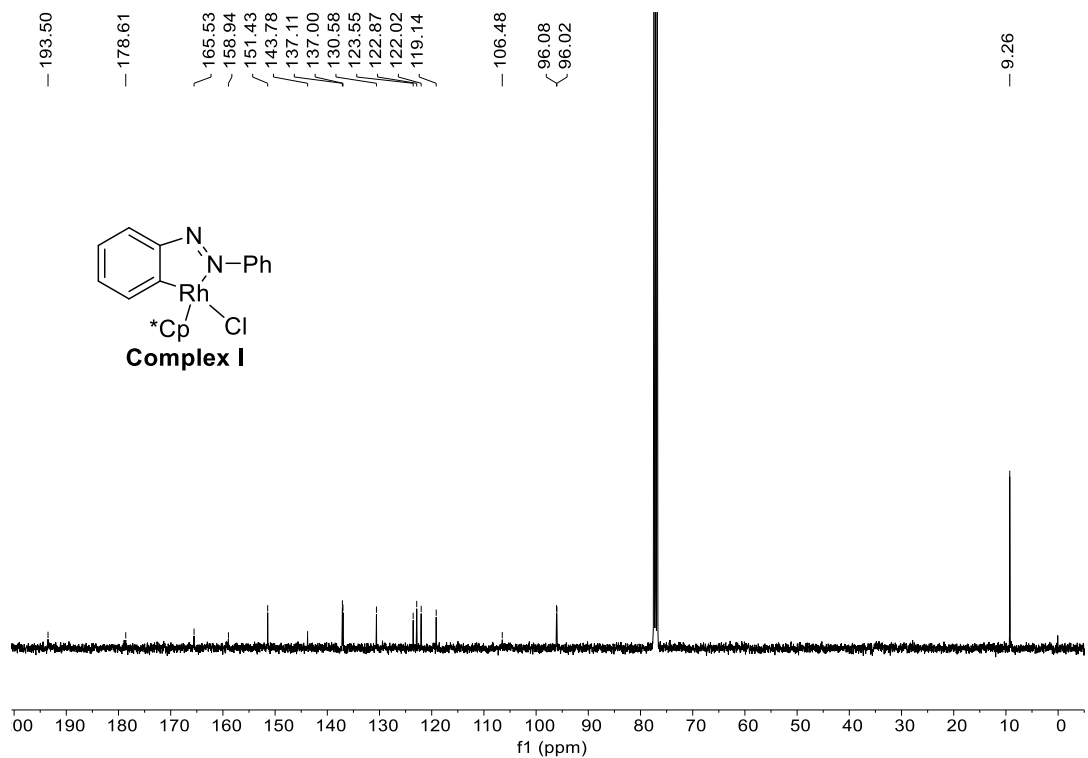
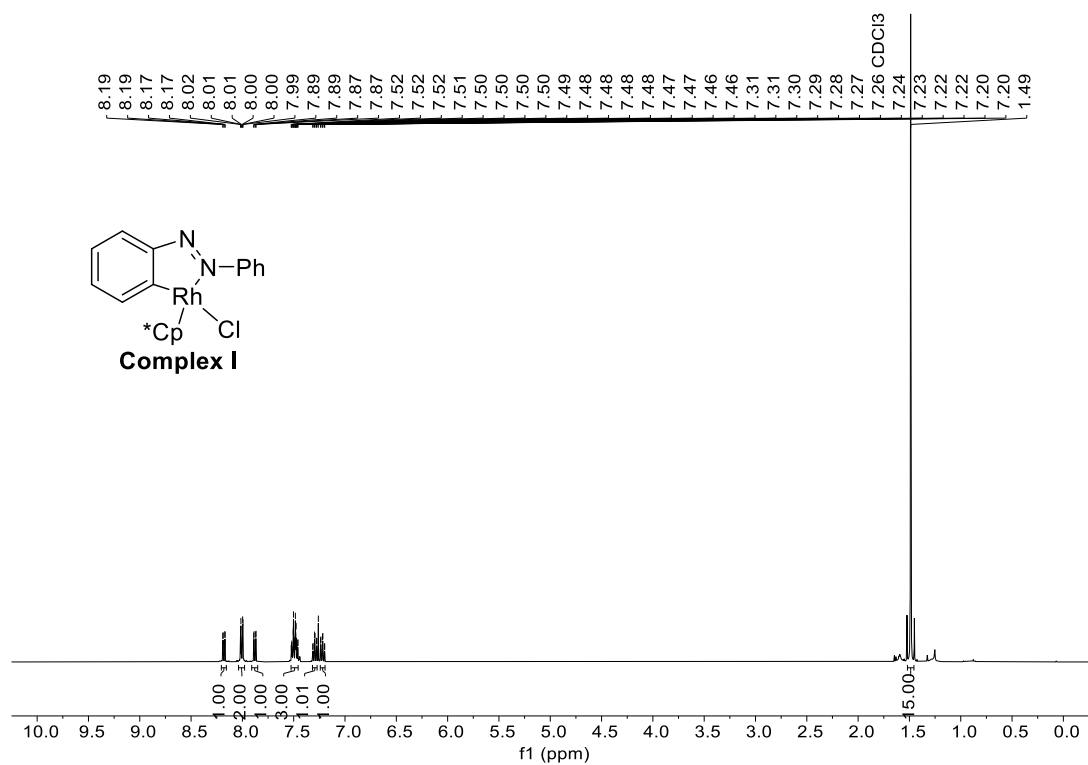


(24) ^1H NMR, ^{13}C NMR and ^{19}F NMR spectrum of **3x** (using CDCl₃ as solvent)





(25) ^1H NMR and ^{13}C NMR of **Complex I** (using CDCl_3 as solvent)



6. HRMS spectrum for all unknown compounds

