Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Silver-mediated Synthesis of Novel 3-CF_3/CN/Phosphonate -substituted Pyrazoles as Pyrrolomycin Analogues from 3-Formylchromones and Diazo Compounds

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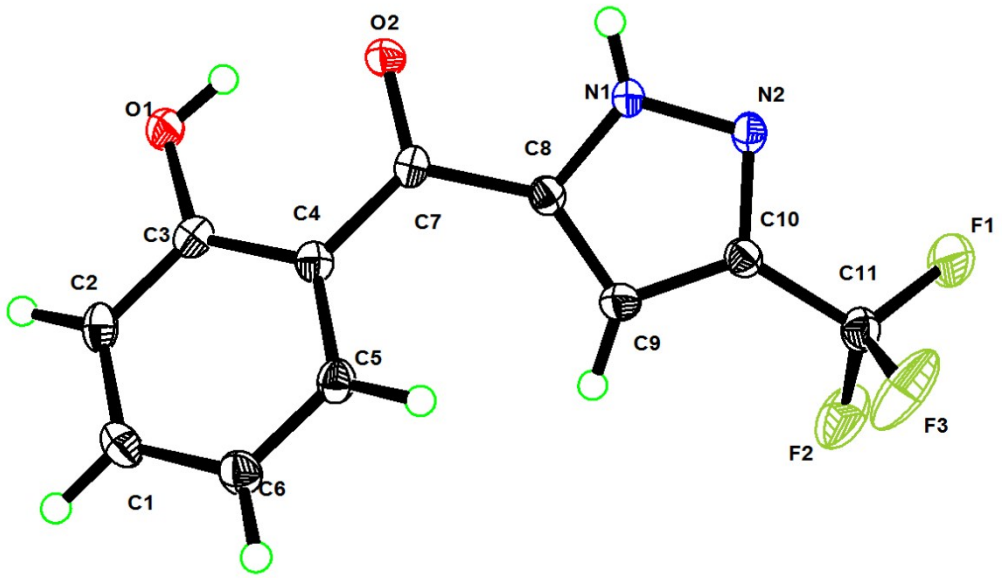

Figure 2. X-ray crystal structure of compound **3a** wherein thermal ellipsoids are drawn at 50% probability level (CCDC-1893699)

Table 1 Crystal data and structure refinement for mo_20180036-PXF-1_0m.

Identification code	mo_20180036-PXF-1_0m
Empirical formula	$C_{11}H_7F_3N_2O_2$
Formula weight	256.19
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.410(2)
b/Å	17.433(7)
c/Å	11.237(4)
α/°	90
β/°	93.290(7)
γ/°	90
Volume/Å^3	1057.9(7)
Z	4

$\rho_{calc}g/cm^3$	1.608
μ/mm-1	0.147
F(000)	520.0
Crystal size/mm^3	0.18 × 0.12 × 0.08
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.318 to 55.802
Index ranges	$-6 \leq h \leq 7$, $-21 \leq k \leq 22$, $-14 \leq l \leq 14$
Reflections collected	8616
Independent reflections	2471 [R_{int} = 0.0818, R_{sigma} = 0.0809]
Data/restraints/parameters	2471/0/168
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0595, wR_2 = 0.1375
Final R indexes [all data]	R_1 = 0.1046, wR_2 = 0.1599
Largest diff. peak/hole / e $Å^{-3}$	0.57/-0.54

Experimental Procedures

General Methods

Unless otherwise noted, all solvents and other reagents are commercially available and used without further purification. All reagents were weighed in air at room temperature. Column chromatography was performed on silica gel (200~300 mesh). NMR spectra were recorded on Varian-MERCURY Plus-400 NMR spectrometer or Bruker AVANCE III 500 NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multipet (m) and broad (br). High-resolution mass spectra (HRMS) were recorded on a Micromass Ultra Q-TOF (ESI) spectrometer. Melting points (m.p) were measured by Büchi 510 melting point apparatus.

Materials: Known compounds **1a-e**,[1] **1f**,[2] **1g**,[1] **1h**,[2] **1i**,[1] **1j**,[3] **1k**,[4] **1l**,[5] **1m** and **1n**,[1] **1o**,[6] **1p**,[2] **1q** [4] and **1r**,[7] **1s**,[4] **1t**,[1] **2c**,[8] and **5**,[9] **6**,[10] **7** [10] were prepared by the literature procedures, and their spectroscopic features are in good agreement with those reported in the literatures.

General procedure for the synthesis of 3a-3t.

2a (1 mmol, 3 eq), ^{t}BuONO (1.1 mmol, 3.3 eq), AcOH (0.2 mmol, 0.6 eq) and 1,4-dioxane (3 mL)/THF (1 mL) were added into a 15 mL sealing tube, sealed, stirred at 55 ^{o}C for 30 minutes. Then, the mixture was cooled to room temperature, **1a** (0.3 mmol, 1 eq), Na_3PO_4 (0.45 mmol, 1.5 eq) and Ag_2O (0.45 mmol, 1.5 eq) were added, and the mixture was stirred at room temperature for 3 hours. The mixture was quenched with saturated solution of NH_4Cl (5 mL) and the resulting insoluble solid was filtered. The filtrate was extracted with EtOAc (10 mL) for 2 times, and the resulting organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude product, which was further purified by silica gel chromatography using an ethyl acetate/petroleum ether (1/60) mixture to afford the desired product.

General procedure for the synthesis of 3u-3z.

A 15 mL sealing tube equipped with a magnetic stir bar was charged with 2-aminoacetonitrile hydrochloride (**2b**) (1.0 mmol) and water (0.2 mL). This solution was cooled to 0 ^{o}C before dropwise addition of an aqueous solution of $NaNO_2$ (1 mmol in 0.3 mL of water). After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Then 1,4-dioxane (3 mL)/THF (1 mL), **1a** (0.3 mmol), Na_3PO_4 (0.45 mmol) and Ag_2O (0.45 mmol) were added successively, and the mixture was stirred at room temperature for an additional 3 h. The mixture was quenched with saturated solution of NH_4Cl (5 mL), and the resulting insoluble solid was filtered. The filtrate was extracted with EtOAc (5 mL) for 2 times, and the resulting organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude product, which was further purified by silica gel

chromatography using an ethyl acetate/petroleum ether (1/30) mixture to afford the desired product.

General procedure for the synthesis of 3a'-3e'.

1j (0.29 mmol), Ag_2O (0.44 mmol) and 1,4-dioxane (5 mL) were added into a 15 mL sealing tube. Then, **2c** (0.44 mmol), Et_3N (0.44 mmol) were added, and the mixture was stirred at room temperature for 3 hours. The mixture was quenched with saturated solution of NH_4Cl (5 mL), and the resulting insoluble solid was filtered. The filtrate was extracted with EtOAc (10 mL) for 3 times, and the resulting organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the crude product, which was further purified by silica gel chromatography using an dichloromethane/methanol gradient mixture to afford the desired product

Procedure for the synthesis of 8.

To a stirred solution of **7** (0.6 mmol) in dimethylformamide (3 mL), $POCl_3$ (0.5 mL) was added dropwise at 0°C over 20-30 mins. After that the mixture was stirred for further 30 mins and then continued at RT for 3-5 hrs. The mixture was treated with ice-cold water (20 mL). The resulting solid was filtered, washed with plenty of water and purified by silica gel chromatography using an dichloromethane/methanol gradient mixture to afford the desired product **8**.

Procedure for the synthesis of 9.

2a (0.6 mmol), ^tBuONO (0.66 mmol), AcOH (0.12 mmol) and 1,4-dioxane (3 mL)/THF (1 mL) were added into a 15 mL sealing tube, sealed, stirred at 55 ^oC for 30 minutes. Then, the mixture was cooled to room temperature, **8** (0.2 mmol), Na_3PO_4 (0.3 mmol) and Ag_2O (0.3 mmol) were added, and the mixture was stirred at room temperature for 3 hours. The mixture was quenched with saturated solution of NH_4Cl (5 mL), and the resulting insoluble solid was filtered. The filtrate was extracted with EtOAc (10 mL) for 3 times, and the resulting organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product, which was further purified by silica gel chromatography using an ethyl acetate/petroleum ether gradient mixture to afford the desired product **9**.

***In vitro* antibacterial assay**

Minimum Inhibitory Concentration (MIC) of compounds were determined by broth microdilution assay according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[4] Briefly, the exponential phase bacterial suspension was diluted with Mueller-Hinton II broth (cation-adjusted, BD 212322) to approximately 5×105 CFU/mL. Then 100 μL each bacterial dilution was distributed in 96-well plates and compounds dissolved in DMSO were diluted by 1:2 serial dilutions to reach concentrations ranging from 256 to 0.125 μg/mL. All tests also included sterile control, DMSO growth control and vancomycin positive control. The 96-well plates were

incubated at 37 °C for 24 h. MIC values were defined as the lowest compound concentration to completely inhibit the bacterial growth.

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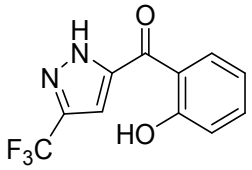
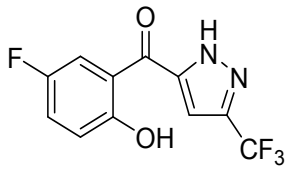
Analytical Characterization Data of Products



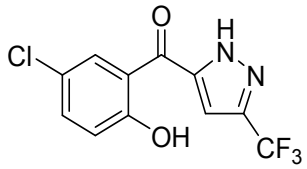
(2-hydroxyphenyl)(3-(trifluoromethyl)-1H-pyrazol-5-yl)methanone (3a)

As a yellow solid (85%). M.p 165-167 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 11.83 (s, 1H), 11.48 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.06 – 7.00 (m, 1H). ^{13}C NMR (125 MHz, Chloroform-d) δ 186.53, 163.32, 140.37, 137.70, 130.93, 120.51 (q, *J* = 269.1 Hz), 119.79, 119.03, 118.34, 108.51. ^{19}F NMR (376 MHz, CDCl3) δ -62.11. HRMS (ESI-) calculated for $C_{11}H_5F_4N_2O_2$ $[M-H]^-$ 255.0387; found, 255.0382.



(5-fluoro-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3b)

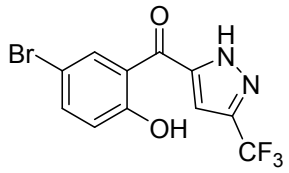
As a yellow solid (67%). M.p 165-167 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.52 (s, 1H), 11.26 (s, 1H), 7.68 (s, 1H), 7.47 – 7.29 (m, 1H), 7.21 (s, 1H), 7.10 (d, *J* = 4.6 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 159.68, 156.10, 154.19, 125.39 (d, *J* = 23.6 Hz), 120.50, 120.31 (d, *J* = 268.0 Hz), 117.63 (d, *J* = 6.6 Hz), 115.53, 108.39. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.20, -122.26. HRMS (ESI^-) calculated for $C_{11}H_5F_4N_2O_2$ $[M-H]^-$ 273.0293; found, 273.0288.



(5-chloro-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3c)

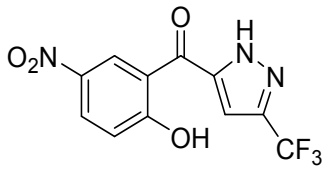
As a yellow solid (88%). M.p 119-121 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.57 (s, 1H), 11.43 (s, 1H), 8.00 (s, 1H), 7.55 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.21 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.56, 161.83, 137.48, 129.82, 124.56, 120.63, 120.30 (d, *J* = 269.2 Hz), 118.83, 108.54. ^{19}F NMR (376 MHz, $CDCl_3$)

δ -62.12. HRMS (ESI$^-$) calculated for $C_{11}H_5ClF_3N_2O_2$ [M-H]$^-$ 288.9997; found, 288.9994.



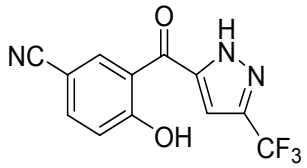
(5-bromo-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3d)

As a yellow solid (88%). M.p 110-112 ^{o}C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.44 (s, 2H), 8.16 (s, 1H), 7.67 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.20 (s, 1H), 7.03 – 7.00 (m, 1H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 185.60, 162.24, 140.22, 132.96, δ 120.97, 120.29 (d, *J* = 269.3 Hz), 119.45, 111.33, 108.55. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.03. HRMS (ESI$^-$) calculated for $C_{11}H_5BrF_3N_2O_2$ [M-H]$^-$ 332.9492; found, 332.9495.



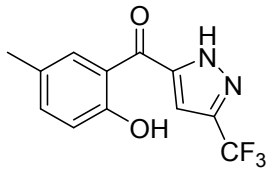
(2-hydroxy-5-nitrophenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3e)

As a yellow solid (82%). M.p 188-190 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.87 (s, 1H), 11.85 (s, 1H), 8.38 – 8.30 (m, 2H), 7.29 (s, 1H), 7.16 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 182.39, 161.83, 141.96, 139.24, 128.49, 126.14, 124.97, 120.98 (d, *J* = 257.6 Hz), 117.50, 108.90. ^{19}F NMR (376 MHz, DMSO) δ -60.40. HRMS (ESI$^-$) calculated for $C_{11}H_5F_3N_3O_4$ [M-H]$^-$ 300.0238; found, 300.0233.



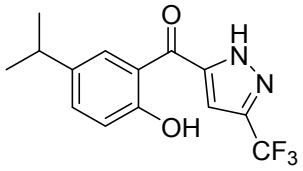
4-hydroxy-3-(3-(trifluoromethyl)-1*H*-pyrazole-5-carbonyl)benzonitrile (3f)

As a yellow solid (82%). M.p 197-199 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.46 (s, 1H), 7.96 (s, 1H), 7.87 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.26 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 183.29, 160.39, 142.49, 137.33, 134.88, 126.38, 121.59 (d, *J* = 266.6 Hz), 119.15, 118.53, 109.43, 101.94. ^{19}F NMR (376 MHz, DMSO) δ -60.39. HRMS (ESI$^-$) calculated for $C_{12}H_5F_3N_3O_2$ [M-H]$^-$ 280.0339; found, 280.0335.



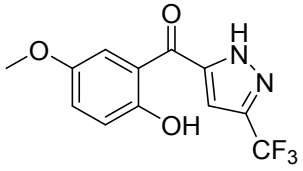
(2-hydroxy-5-methylphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3g)

As a yellow solid (74%). M.p 125-127 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.46 (s, 1H), 11.31 (s, 1H), 7.76 (s, 1H), 7.42 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.17 (s, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 186.23, 161.36, 138.86, 130.28, 129.06, 120.54 (d, *J* = 269.1 Hz), 118.80, 118.00, 108.28, 20.64. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.15. HRMS (ESI^{-}) calculated for $C_{12}H_8F_3N_2O_2$ [M-H]$^{-}$ 269.0543; found, 269.0546



(2-hydroxy-5-isopropylphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3h)

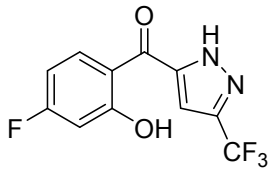
As a yellow solid (83%). M.p 143-145 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.38 (s, 1H), 11.31 (s, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.13 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 2.94 (p, *J* = 7.1 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 186.26, 161.58, 140.47, 140.19, 136.36, 127.85, 120.53 (d, *J* = 268.8 Hz), 118.88, 117.97, 108.12, 33.30, 23.98. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.20. HRMS (ESI^{-}) calculated for $C_{14}H_{12}F_3N_2O_2$ [M-H]$^{-}$ 297.0856; found, 297.0860.



(2-hydroxy-5-methoxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3i)

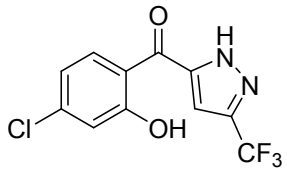
As a yellow solid (75%). M.p 111-113 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.53 (s, 1H), 11.08 (s, 1H), 7.47 – 7.42 (m, 1H), 7.26 – 7.21 (m, 1H), 7.18 (s, 1H), 7.06 (d, *J* = 9.1 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 186.01, 157.76, 152.29, 140.64, 125.47, 120.47 (q, *J* = 269.1 Hz), 119.41, 117.35, 112.97, 107.66,

55.56. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.15. HRMS (ESI^-) calculated for $C_{12}H_8F_3N_2O_3$ $[M-H]^-$ 285.0493; found, 285.0493.



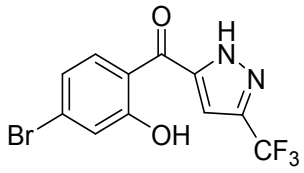
(4-fluoro-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3j)

As a yellow solid (70%). M.p 149-151 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.89 (s, 1H), 11.48 (s, 1H), 8.08 (dd, *J* = 8.5, 6.5 Hz, 1H), 7.17 (s, 1H), 6.82 – 6.72 (m, 2H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.43, 169.33, 167.26, 166.16 (d, *J* = 14.7 Hz), 133.53 (d, *J* = 12.0 Hz), 120.41 (q, *J* = 269.0 Hz), 115.36, 108.44, 108.21, 105.72 (d, *J* = 23.9 Hz). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.13, -96.21. HRMS (ESI^-) calculated for $C_{11}H_5F_4N_2O_2$ $[M-H]^-$ 273.0293; found, 273.0296.



(4-chloro-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3k)

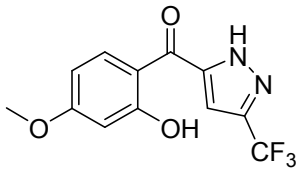
As a yellow solid (84%). M.p 142-144 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.67 (s, 1H), 11.56 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.17 (s, 1H), 7.13 (d, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 8.7, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.79, 163.99, 143.90, 131.91, 120.54, 120.37 (q, *J* = 269.1 Hz), 119.12, 116.83, 108.33. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.13. HRMS (ESI^-) calculated for $C_{11}H_5ClF_3N_2O_2$ $[M-H]^-$ 288.9997; found, 288.9997



(4-bromo-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3l)

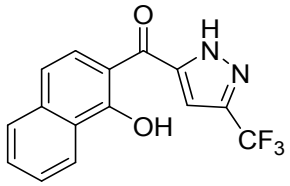
As a yellow solid (70%). M.p 152-154 °C. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.61 (s, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 7.19 – 7.15 (m, 2H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.81, 163.70, 132.59, 131.74, 123.36, 122.26,

120.36 (d, J = 268.9 Hz), 117.14, 108.29. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.10. HRMS (ESI^-) calculated for $C_{11}H_5BrF_3N_2O_2$ $[M-H]^-$ 332.9492; found, 332.9496.



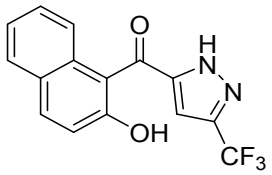
(2-hydroxy-4-methoxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3m)

As a yellow solid (62%). M.p 163-165 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.20 (s, 1H), 11.42 (s, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 6.57 (dd, J = 9.0, 2.5 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 184.27, 167.38, 166.88, 143.89 (d, J = 39.3 Hz), 140.49, 132.51, 120.59 (d, J = 269.0 Hz), 112.20, 109.00, 107.58, 101.38, 55.84. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.18. HRMS (ESI^-) calculated for $C_{12}H_8F_3N_2O_3$ $[M-H]^-$ 285.0493; found, 285.0499.



(1-hydroxynaphthalen-2-yl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3n)

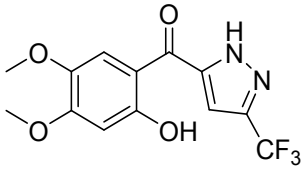
As a yellow solid (70%). M.p 169-171 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.54 (s, 16H), 11.53 (s, 1H), 8.51 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.64 – 7.54 (m, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.26 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.63, 164.91, 144.06 (d, J = 38.0 Hz), 140.54, 137.70, 131.24, 127.61, 126.57, 125.17, 124.72, 124.09, 120.60 (q, J = 269.1 Hz), 119.44, 108.19. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.16. HRMS (ESI^-) calculated for $C_{15}H_8F_3N_2O_2$ $[M-H]^-$ 305.0543; found, 305.0543.



(2-hydroxynaphthalen-1-yl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3o)

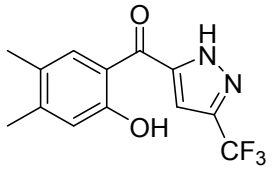
As a yellow solid (68%). M.p 157-159 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.49 (s, 1H), 10.44 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.43 – 7.38 (m,

2H), 7.22 (d, *J* = 9.0 Hz, 2H), 6.83 (s, 1H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 185.73, 160.99, 142.78, 137.42, 131.10, 128.88, 128.69, 127.52, 125.27, 124.85, 120.44 (q, *J* = 269.2 Hz), 119.05, 114.16, 108.93. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.32. HRMS (ESI^-) calculated for $C_{15}H_8F_3N_2O_2$ $[M-H]^-$ 305.0543; found, 305.0547.



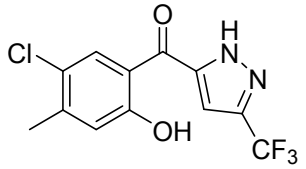
(2-hydroxy-4,5-dimethoxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3p)

As a yellow solid (65%). M.p 187-189 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.20 (s, 1H), 11.42 (s, 1H), 7.37 (s, 1H), 7.11 (s, 1H), 6.56 (s, 1H), 3.97 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 162.27, 158.35, 142.83, 120.54 (d, *J* = 269.6 Hz), 111.29, 110.09, 106.97, 101.02, 56.75, 56.45. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.15. HRMS (ESI^-) calculated for $C_{13}H_{10}F_3N_2O_4$ $[M-H]^-$ 315.0598; found, 315.0600.



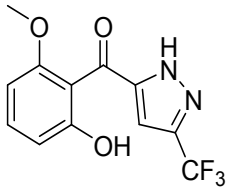
(2-hydroxy-4,5-dimethylphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3q)

As a yellow solid (63%). M.p 144-146 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.51 (s, 1H), 11.42 (s, 1H), 7.69 (s, 1H), 7.15 (s, 1H), 6.90 (s, 1H), 2.32 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 185.5, 161.89, 148.95, 130.59, 128.35, 120.58 (q, *J* = 269.1 Hz), 119.49, 116.18, 107.98, 20.74, 19.13. ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.14. HRMS (ESI^-) calculated for $C_{13}H_{10}F_3N_2O_2$ $[M-H]^-$ 283.0700; found, 283.0700.



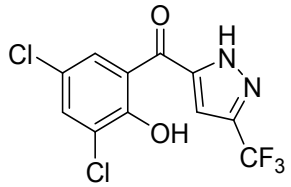
(5-chloro-2-hydroxy-4-methylphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3r)

As a yellow solid (82%). M.p 139-141 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.44 (s, 2H), 7.99 (s, 1H), 7.19 (s, 1H), 7.00 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.01, 161.86, 147.37, 130.21, 125.27, 120.95, 120.39 (d, *J* = 271.2 Hz), 117.09, 108.19, 21.03. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.03. HRMS (ESI^-) calculated for $C_{12}H_7ClF_3N_2O_2$ $[M-H]^-$ 303.0154; found, 303.0158.



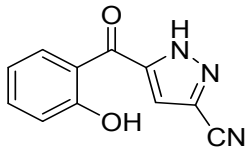
(2-hydroxy-6-methoxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3s)

As a yellow solid (66%). M.p 150-152 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.44 (s, 1H), 10.46 (s, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.43, 162.43, 159.45, 143.59 (q, *J* = 38.6 Hz), 143.03, 136.88, 120.76 (q, *J* = 268.8 Hz), 111.18, 111.00, 108.32, 102.37, 55.47. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -62.31. HRMS (ESI^-) calculated for $C_{12}H_8F_3N_2O_3$ $[M-H]^-$ 285.0493; found, 285.0492.



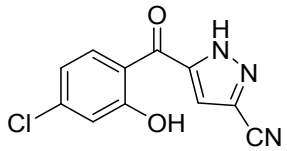
(3,5-dichloro-2-hydroxyphenyl)(3-(trifluoromethyl)-1*H*-pyrazol-5-yl)methanone (3t)

As a yellow solid (63%). M.p 144-146 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.92 (s, 1H), 11.50 (s, 1H), 8.04 (s, 1H), 7.70 – 7.68 (m, 1H), 7.23 (s, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 185.77, 157.59, 136.92, 128.79, 124.69, 124.34, 120.14 (q, *J* = 269.1 Hz), 119.42, 110.00, 108.92. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -61.93. HRMS (ESI^-) calculated for $C_{11}H_4Cl_2F_3N_2O_2$ $[M-H]^-$ 322.9607; found, 322.9608.



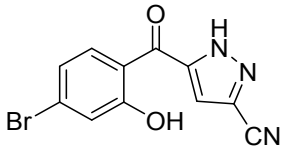
5-(2-hydroxybenzoyl)-1*H*-pyrazole-3-carbonitrile (3u)

As a yellow solid (78%). M.p 199-201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.02 (s, 1H), 10.49 (s, 1H), 7.69 – 7.36 (m, 3H), 7.09 – 6.86 (m, 2H). ^{13}C NMR (150 MHz, Pyridine-d_5) δ 185.95, 160.25, 142.40, 135.23, 130.92, 124.45, 121.92, 119.02, 117.74, 115.49, 114.00. HRMS (ESI$^-$) calculated for $C_{11}H_6N_3O_2$ [M-H]$^-$ 212.0466; found, 212.0469.



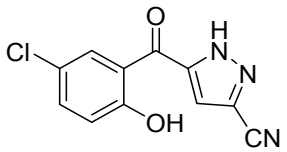
5-(4-chloro-2-hydroxybenzoyl)-1*H*-pyrazole-3-carbonitrile (3v)

As a yellow solid (60%). M.p 166-168 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.03 (s, 1H), 10.88 (s, 1H), 7.52 (d, J = 21.4 Hz, 2H), 7.16 – 6.79 (m, 2H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 186.85, 162.59, 144.73, 142.04, 134.12, 126.26, 123.31, 121.26, 119.71, 117.43, 115.84. HRMS (ESI$^-$) calculated for $C_{11}H_5ClN_3O_2$ [M-H]$^-$ 246.0076; found, 246.0079.



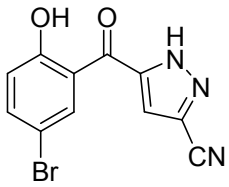
5-(4-bromo-2-hydroxybenzoyl)-1*H*-pyrazole-3-carbonitrile (3w).

As a yellow solid (46%), M.p 195-197 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 11.40 (s, 2H), 7.84 (d, J = 8.4 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.22 (dd, J = 8.4, 1.8 Hz, 1H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 184.97, 160.30, 142.72, 132.07, 128.72, 124.35, 122.19, 121.87, 120.76, 115.49, 113.89. HRMS (ESI$^-$) calculated for $C_{11}H_5BrN_3O_2$ [M-H]$^-$ 289.9571; found, 289.9569.



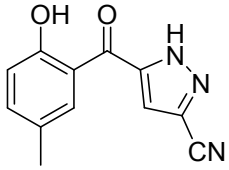
5-(5-chloro-2-hydroxybenzoyl)-1*H*-pyrazole-3-carbonitrile (3x).

As a yellow solid (61%), M.p 198-200 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 11.41 (s, 2H), 7.98 (d, J = 2.6 Hz, 1H), 7.66 (s, 1H), 7.49 (dd, J = 8.8, 2.7 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 184.31, 157.54, 142.96, 133.89, 129.79, 124.78, 124.42, 123.33, 119.22, 115.67, 113.89. HRMS (ESI$^-$) calculated for $C_{11}H_5ClN_3O_2$ [M-H]$^-$ 246.0076; found, 246.0075.



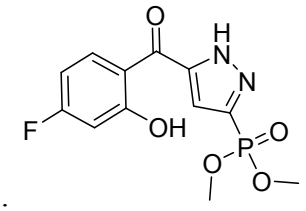
5-(5-bromo-2-hydroxybenzoyl)-1*H*-pyrazole-3-carbonitrile (3y).

As a yellow solid (50%), M.p 185-187 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.08 (d, J = 2.5 Hz, 1H), 7.63 (s, 1H), 7.60 (dd, J = 8.8, 2.5 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 186.17, 159.86, 144.96, 138.65, 134.64, 127.46, 126.39, 121.56, 117.60, 115.84, 112.41. HRMS (ESI$^-$) calculated for $C_{11}H_5BrN_3O_2$ [M-H]$^-$ 289.9571; found, 289.9567.



5-(2-hydroxy-5-methylbenzoyl)-1*H*-pyrazole-3-carbonitrile(3z).

As a yellow solid (66%), M.p 196-198 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 7.76 (d, J = 1.7 Hz, 1H), 7.69 (s, 1H), 7.30 (dd, J = 8.4, 2.2 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 188.05, 160.33, 144.38, 138.24, 132.62, 130.15, 126.53, 123.43, 119.64, 117.43, 115.96, 21.49. HRMS (ESI$^-$) calculated for $C_{12}H_8N_3O_2$ [M-H]$^-$ 226.0622; found, 226.0620.



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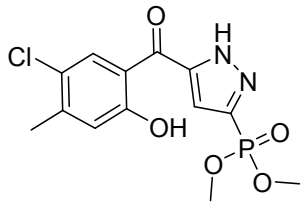
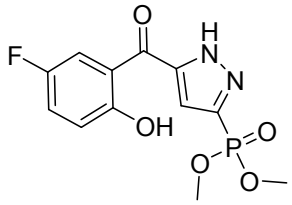
dimethyl (5-(4-fluoro-2-hydroxybenzoyl)-1*H*-pyrazol-3-yl)phosphonate (3a').

As a yellow solid (90%). M.p 185-187 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.67 (s, 1H), 8.79 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 6.69 (ddd, J = 19.7, 9.6, 2.5 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 168.64, 166.93, 166.51 (d, J = 14.5 Hz), 136.01, 115.93, 115.55 (d, J = 18.6 Hz), 107.49 (d, J = 22.1 Hz), 104.85 (d, J = 23.6 Hz), 53.35, 53.31. HRMS (ESI$^+$) calculated for $C_{12}H_{13}FN_2O_5P$ [M+H]$^+$ 315.0541; found, 315.0544.



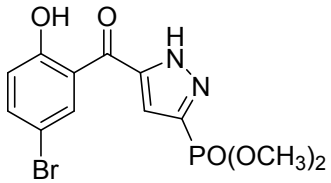
dimethyl (5-(5-chloro-2-hydroxy-4-methylbenzoyl)-1*H*-pyrazol-3-yl)phosphonate (3b').

As a yellow solid (83%), M.p 153-155 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.93 (s, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.06 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 187.95, 160.88, 144.28, 132.31, 123.72, 119.96, 119.38, 115.88 (d, J = 20.0 Hz), 52.60, 52.56, 19.79. HRMS (ESI$^+$) calculated for $C_{13}H_{15}ClN_2O_5P$ $[M+H]^+$ 345.0402; found, 345.0405.



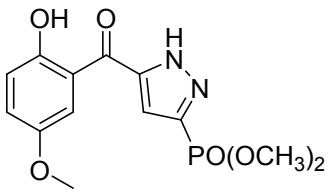
dimethyl (5-(5-fluoro-2-hydroxybenzoyl)-1*H*-pyrazol-3-yl)phosphonate (3c').

As a yellow solid (95%), M.p 163-165 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.62 (d, J = 10.3 Hz, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.15 (dd, J = 9.1, 4.6 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, Pyridine-d_5) δ 188.10, 158.15, 155.59, 153.71, 120.72, 119.03 (d, J = 7.4 Hz), 117.65 (d, J = 24.4 Hz), 116.02 (d, J = 20.2 Hz), 52.59, 52.54. HRMS (ESI$^+$) calculated for $C_{12}H_{13}FN_2O_5P$ $[M+H]^+$ 315.0541; found, 315.0543

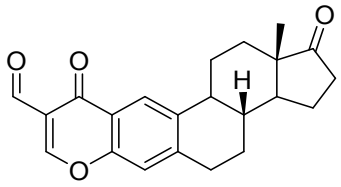


Dimethyl (5-(5-bromo-2-hydroxybenzoyl)-1*H*-pyrazol-3-yl)phosphonate(3d').

As a yellow solid (88%). M.p 178-180 °C. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.84 (s, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.8, 2.5 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (150 MHz, Chloroform-d) δ 188.95, 162.63, 139.14, 135.38, 120.14, 119.94, 115.49 (d, J = 18.3 Hz), 110.61, 53.79, 53.75. HRMS (ESI$^+$) calculated for $C_{12}H_{13}BrN_2O_5P$ $[M+H]^+$ 374.9740; found, 374.9738.

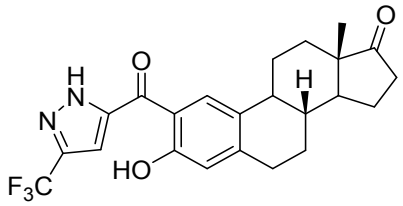


Dimethyl (5-(2-hydroxy-5-methoxybenzoyl)-1*H*-pyrazol-3-yl)phosphonate(3e'). As a yellow solid (84%). M.p 146-148 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.40 (s, 1H), 11.92 (s, 1H), 8.39 (s, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 9.1, 3.0 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, Chloroform-*d*) δ 158.15, 151.74, 124.81, 119.00, 118.27, 115.47 (d, *J* = 18.9 Hz), 55.86, 53.65, 53.61. HRMS (ESI^{+}) calculated for $C_{13}H_{16}N_2O_6P$ $[M+H]^{+}$ 327.0740; found, 327.0743.



(3b*R*,13a*S*)-13a-methyl-1,10-dioxo-1,2,3,3a,3b,4,5,10,11b,12,13,13a-dodecahydrocyclopenta[5,6]naphtho[1,2-*g*]chromene-9-carbaldehyde (8).

As a white solid (40%), M.p 217-219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.88 (s, 1H), 7.99 (s, 1H), 7.50 (s, 1H), 3.11 – 2.96 (m, 2H), 2.48 – 2.31 (m, 3H), 2.15 – 2.04 (m, 1H), 1.99 (d, *J* = 4.5 Hz, 2H), 1.83 (d, *J* = 15.2 Hz, 1H), 1.63 – 1.42 (m, 6H), 0.84 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 219.78, 188.88, 175.10, 163.51, 154.12, 146.06, 139.65, 122.56, 121.50, 120.04, 118.28, 49.95, 47.56, 43.64, 37.32, 35.71, 31.51, 29.42, 25.69, 25.67, 21.49, 13.77. HRMS (ESI^{+}) calculated for $C_{22}H_{23}O_4$ $[M+H]^{+}$ 351.1591; found, 351.1585

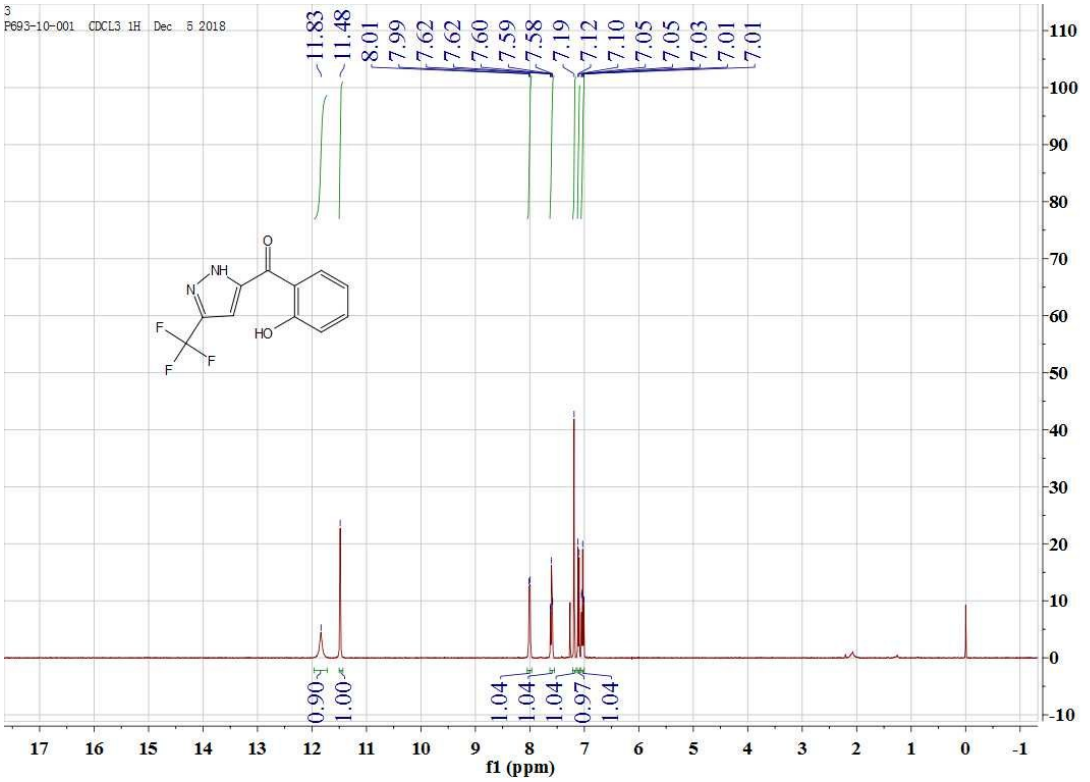


(8*R*,13*S*)-3-hydroxy-13-methyl-2-(3-(trifluoromethyl)-1*H*-pyrazole-5-carbonyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (9) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.68 (s, 1H), 11.36 (s, 1H), 7.90 (s, 1H), 7.10 (s, 1H), 6.83 (s, 1H), 3.04 – 2.89 (m, 2H), 2.54 (dd, *J* = 18.9, 8.6 Hz, 1H), 2.39 – 2.24 (m, 2H), 2.23 – 2.00 (m, 4H), 1.69 – 1.45 (m, 6H), 0.95 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-d) δ 220.43, 186.00, 161.16, 148.70, 132.03, 129.87 (d, J = 36.6 Hz), 127.58, 120.52 (d, J = 269.2 Hz), 118.23, 116.55, 107.80, 50.38, 47.89, 43.55, 38.03,

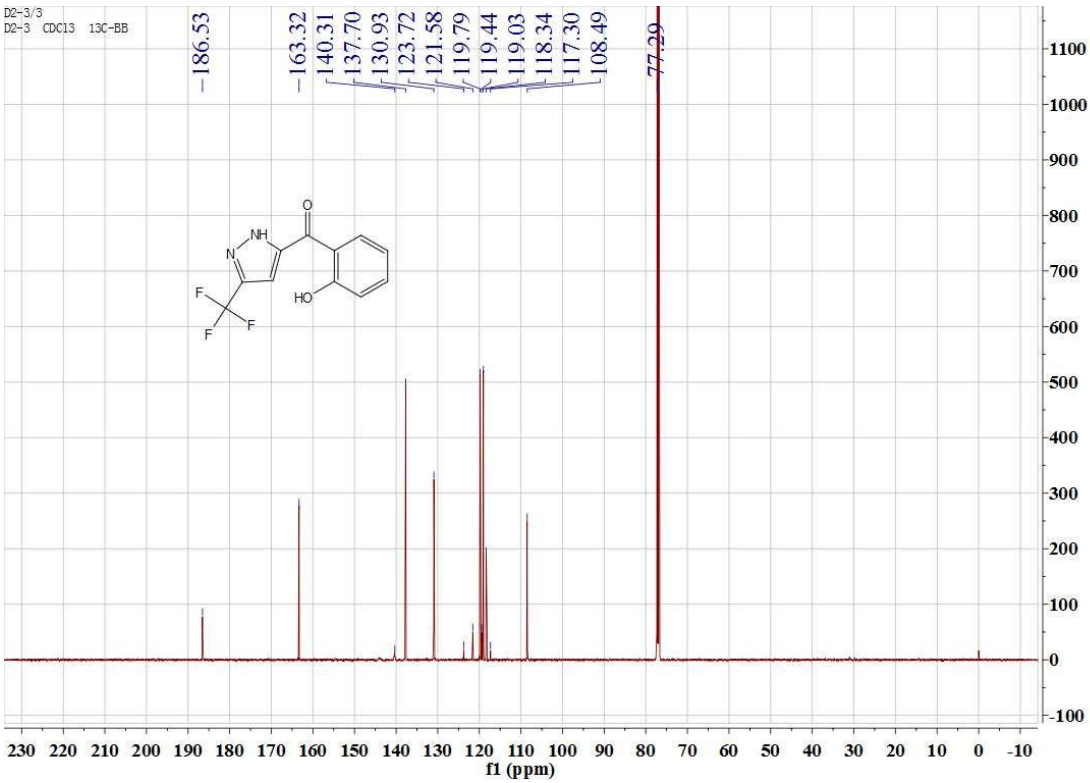
35.82, 31.41, 29.98, 26.04, 25.90, 21.58, 13.82. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.97. HRMS (ESI^-) calculated for $C_{23}H_{23}F_3N_2O_3$ $[M-H]^-$ 431.1588; found, 431.1576.

Copies of 1H NMR, 13C NMR and 19F NMR Spectra for the Products

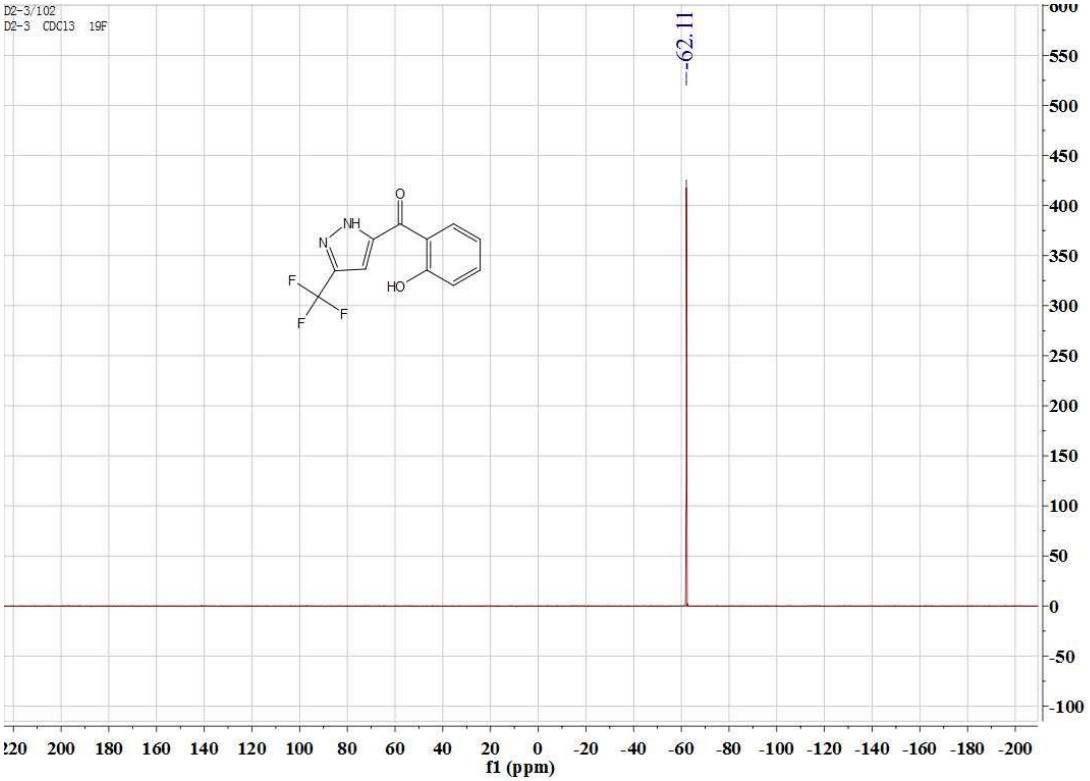
^{1}H NMR spectrum of **3a**



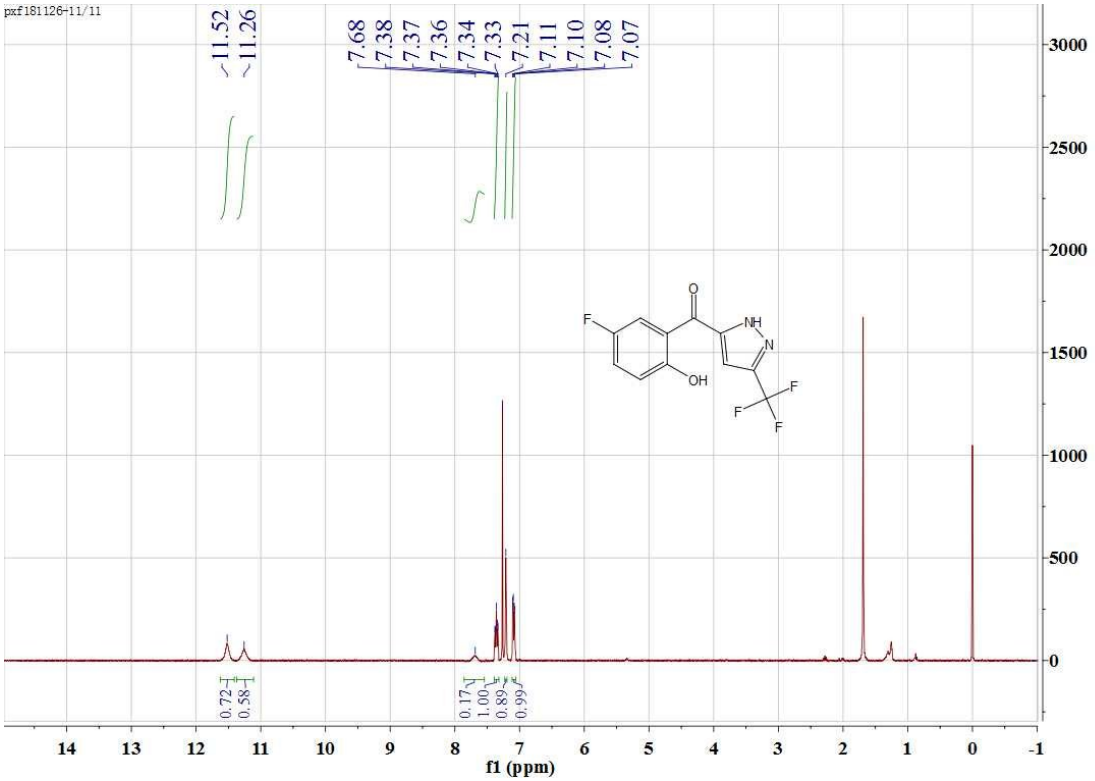
^{13}C NMR spectrum of **3a**



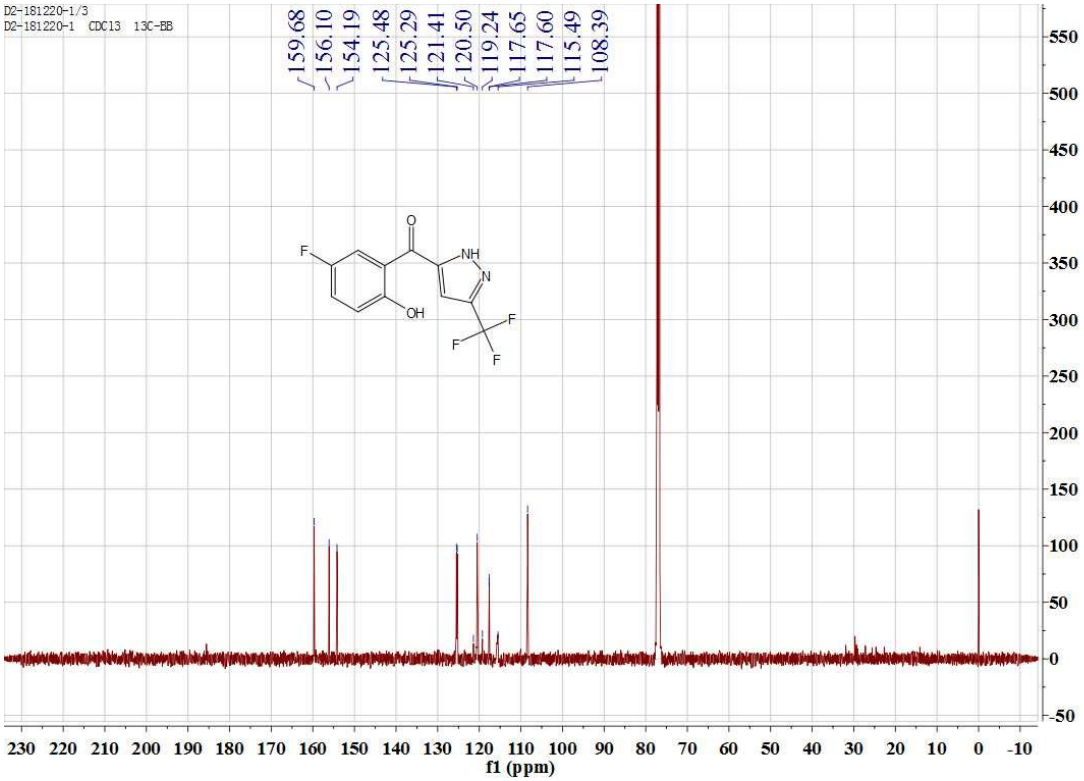
^{19}F NMR spectrum of **3a**



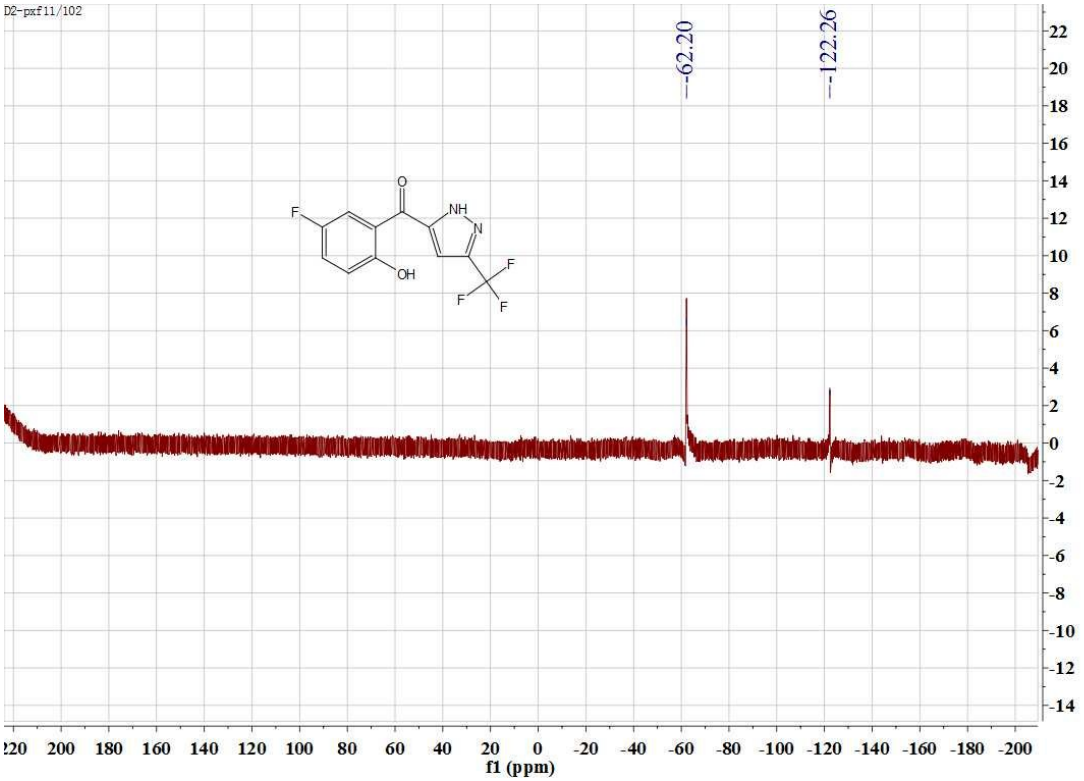
^{1}H NMR spectrum of **3b**



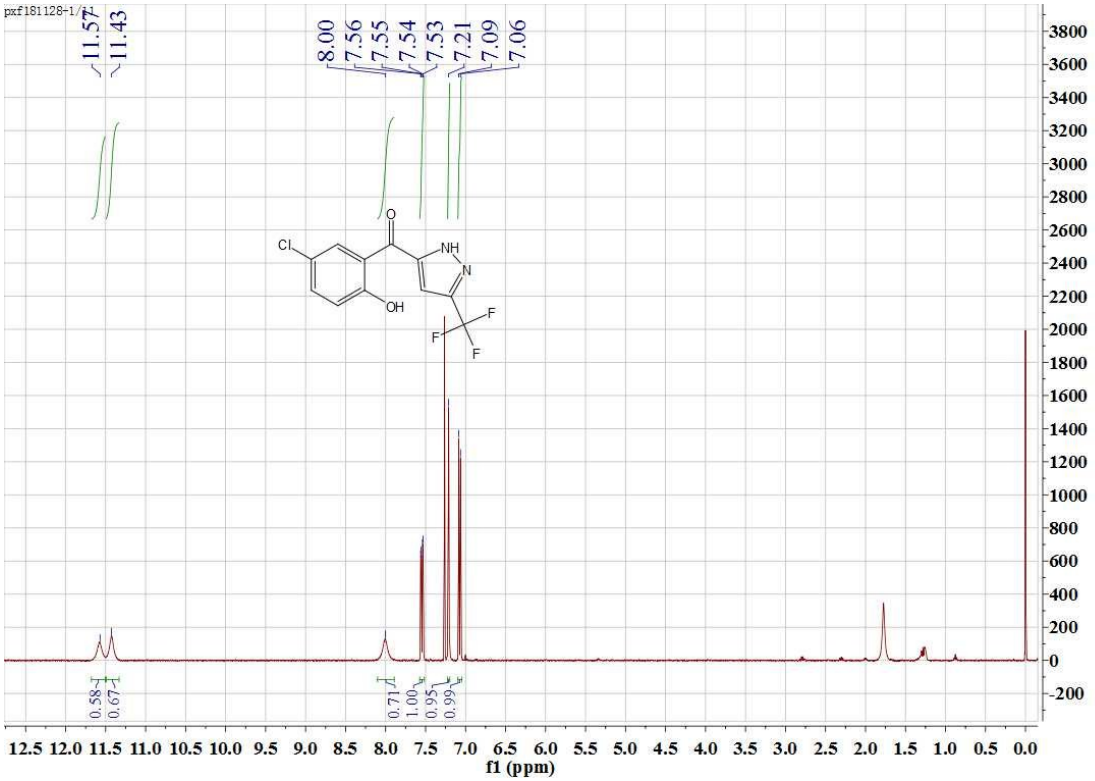
^{13}C NMR spectrum of **3b**



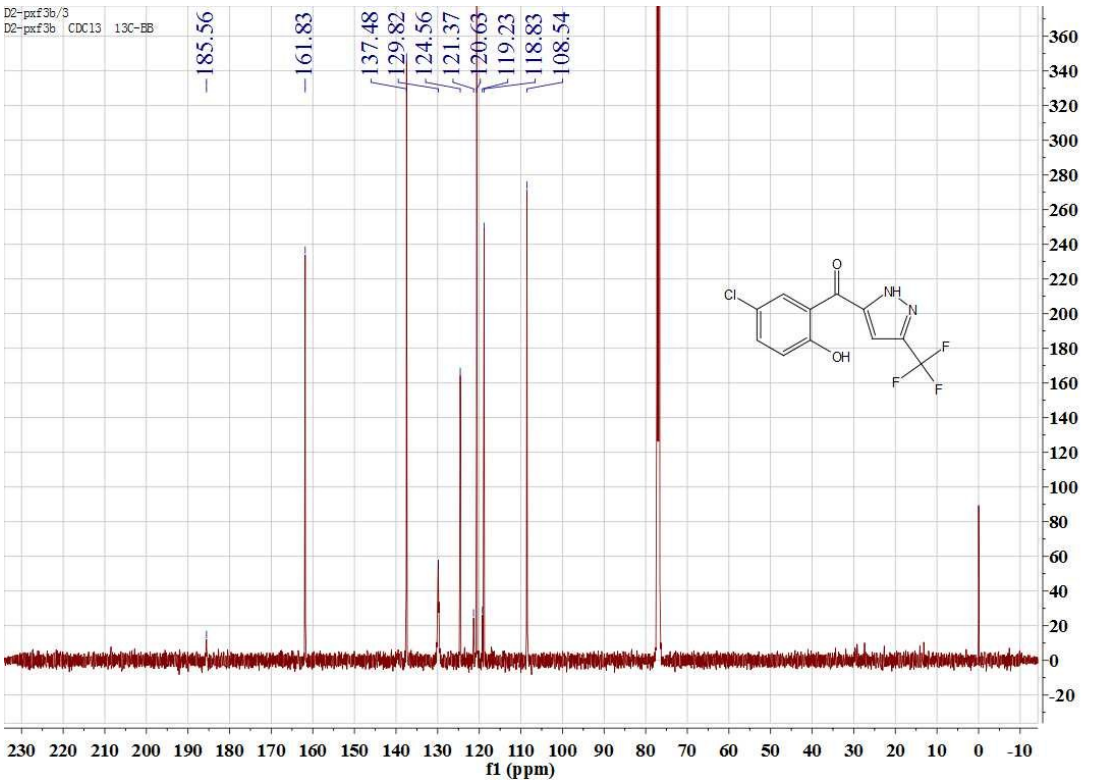
^{19}F NMR spectrum of **3b**



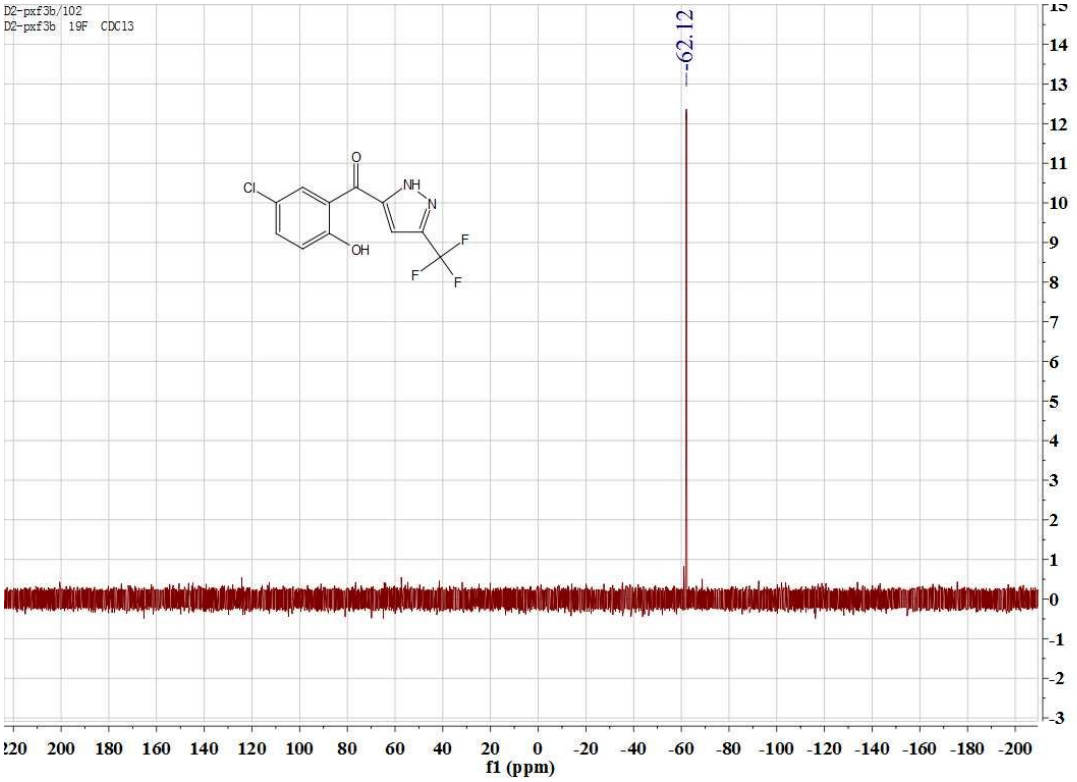
^{1}H NMR spectrum of **3c**



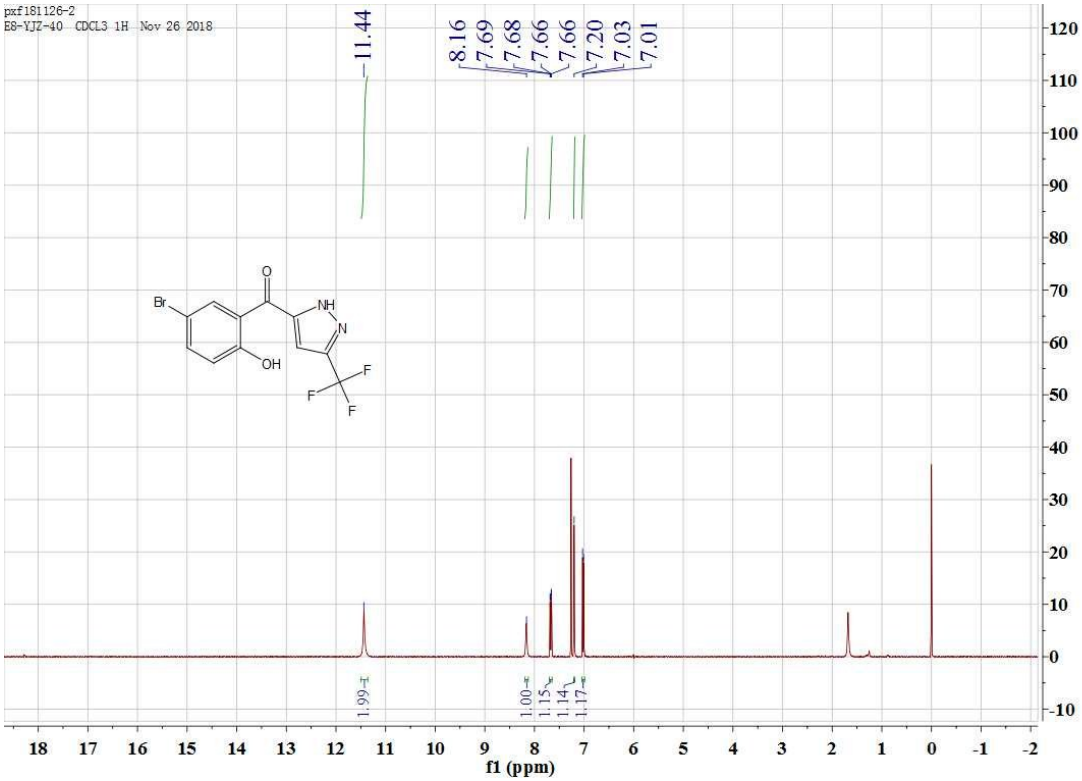
^{13}C NMR spectrum of **3c**



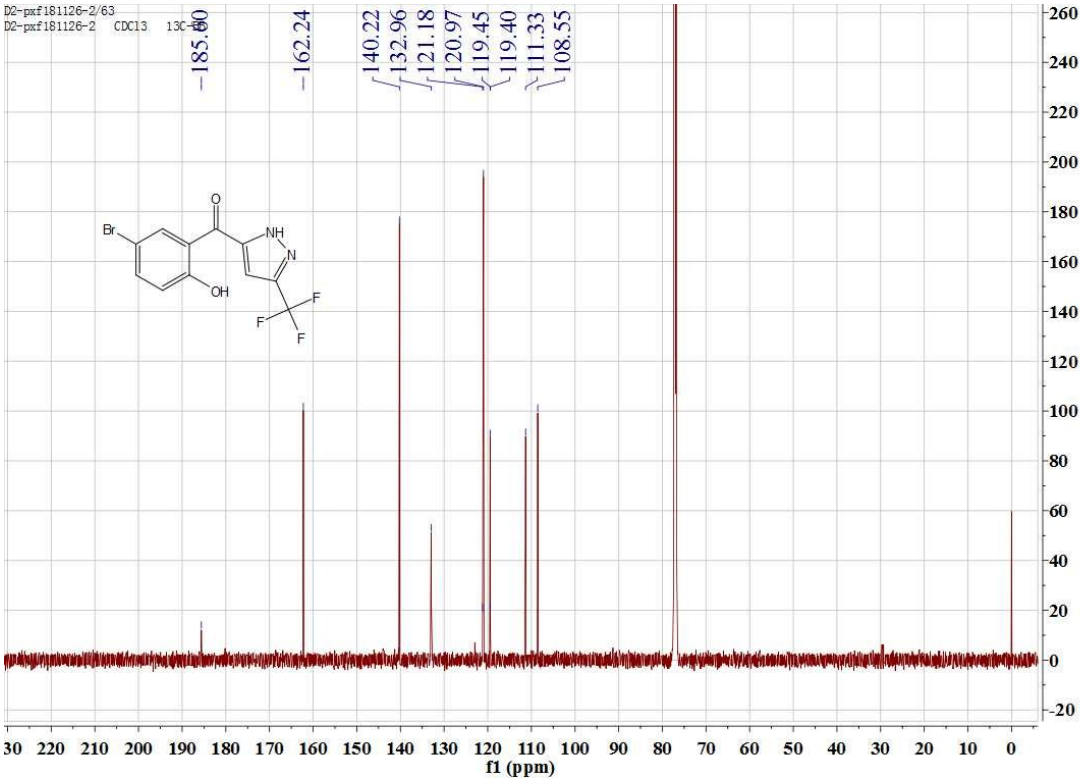
^{19}F NMR spectrum of **3c**



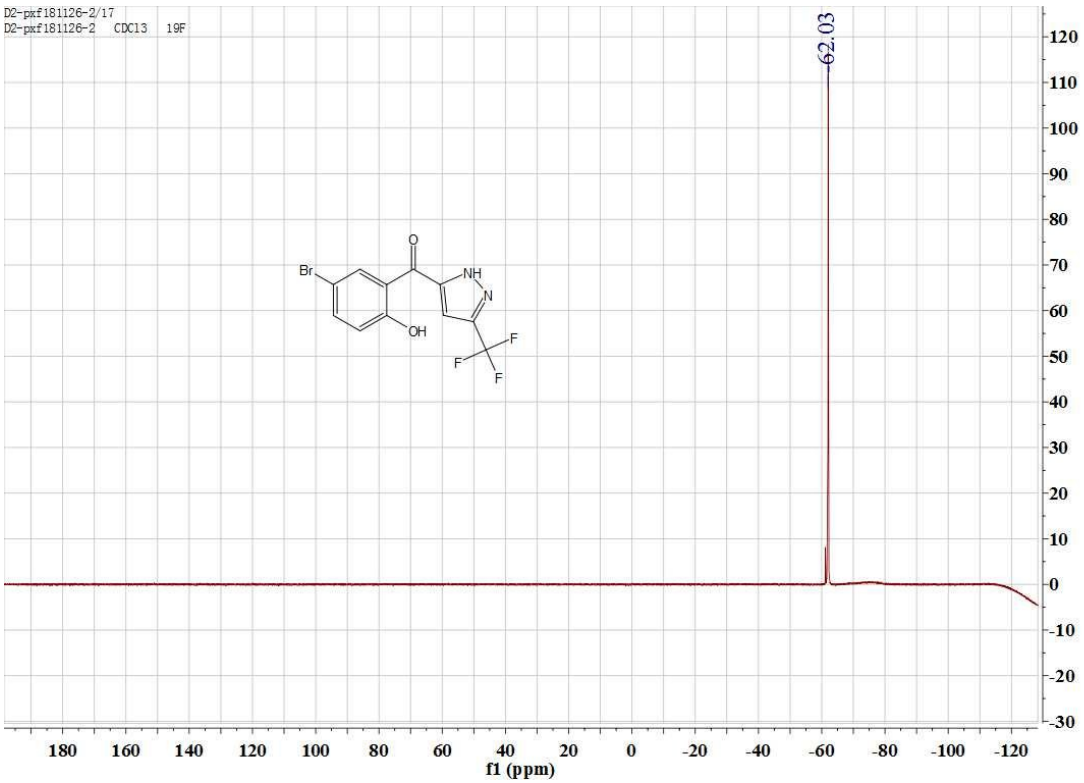
^{1}H NMR spectrum of **3d**



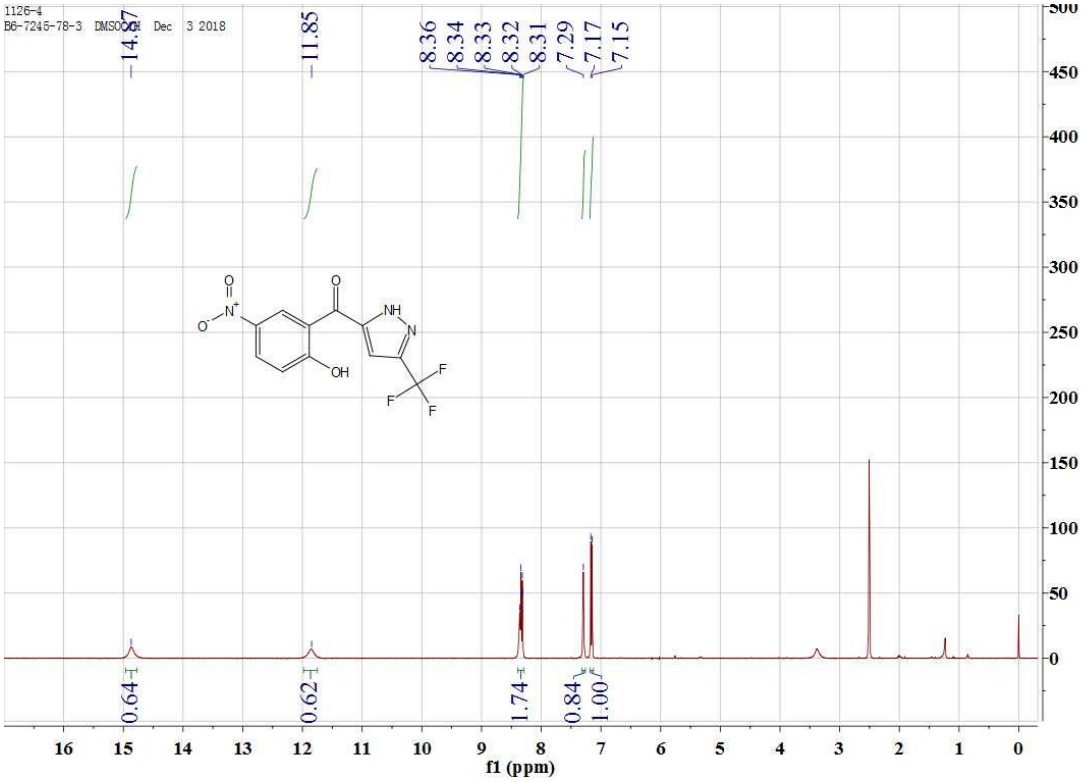
^{13}C NMR spectrum of **3d**



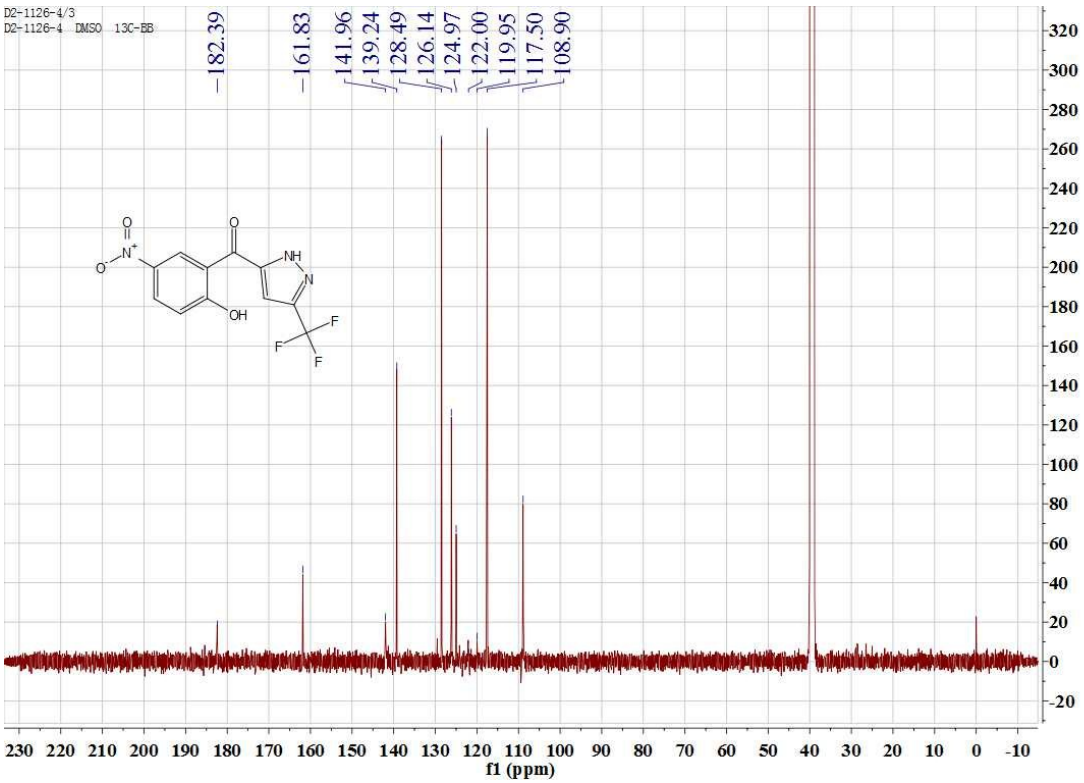
^{19}F NMR spectrum of **3d**



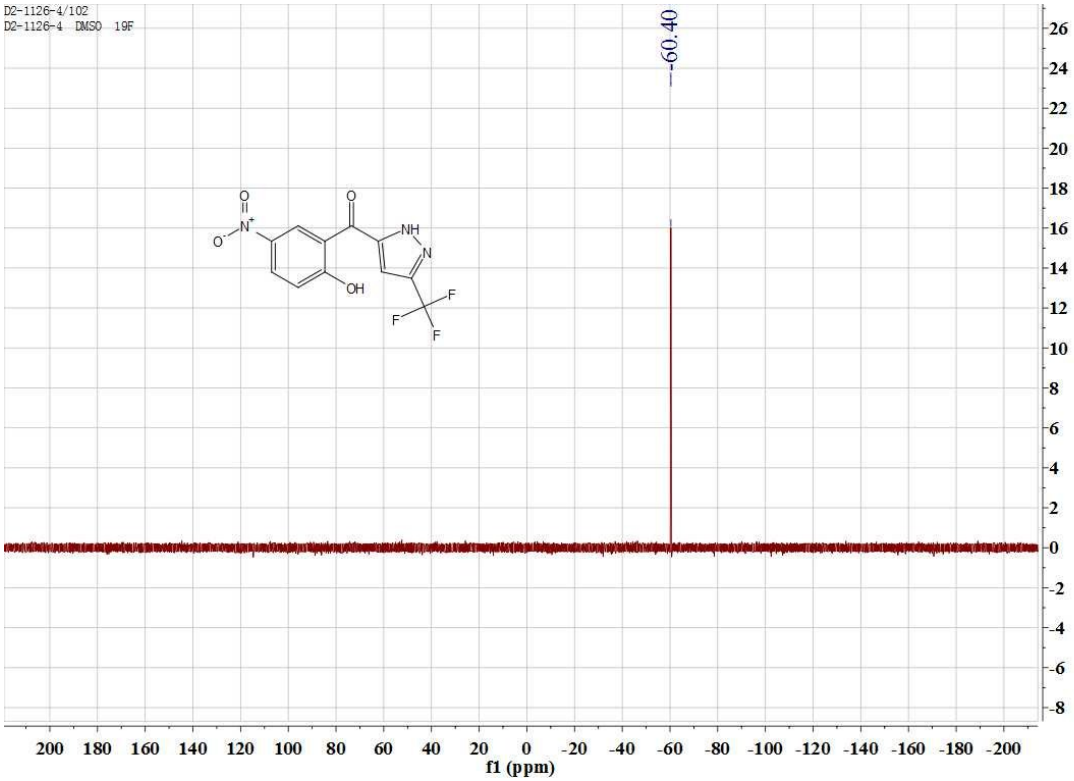
^{1}H NMR spectrum of **3e**



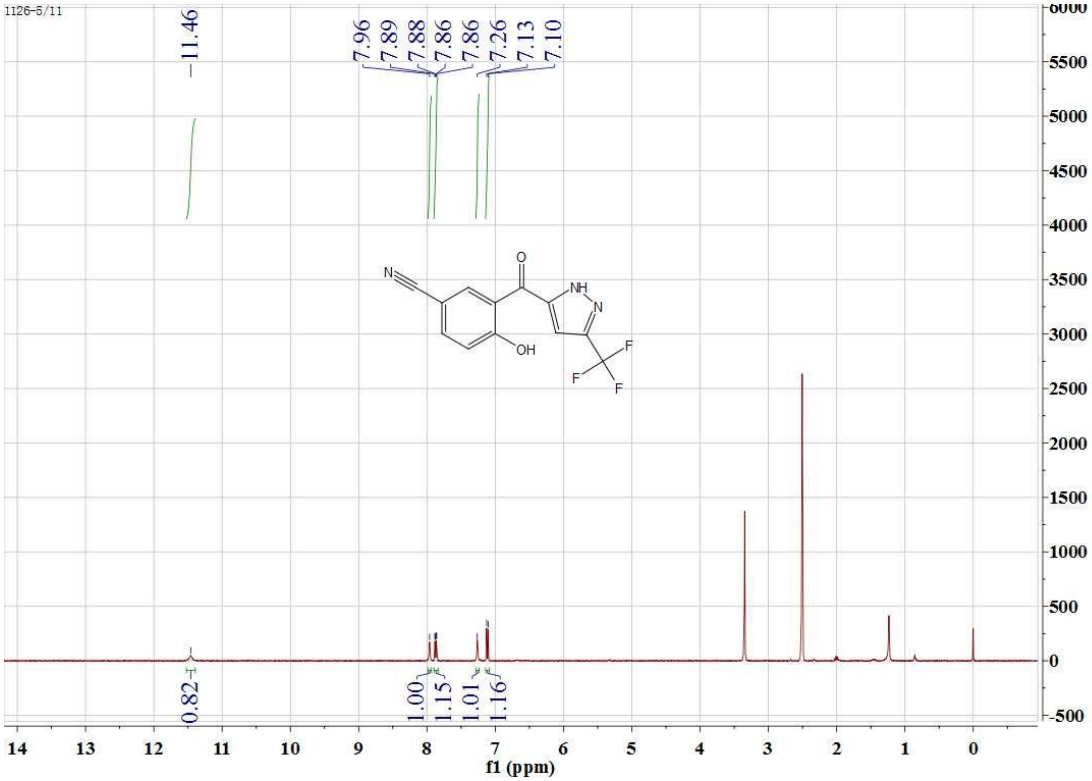
^{13}C NMR spectrum of **3e**



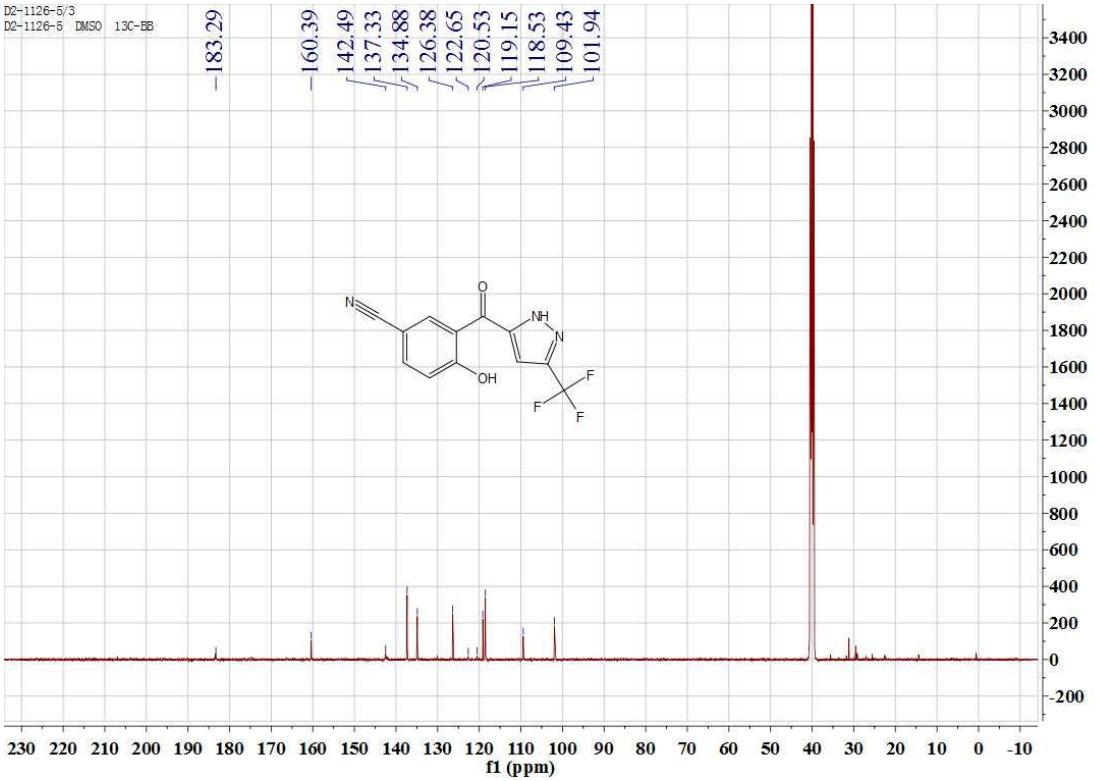
^{19}F NMR spectrum of **3e**



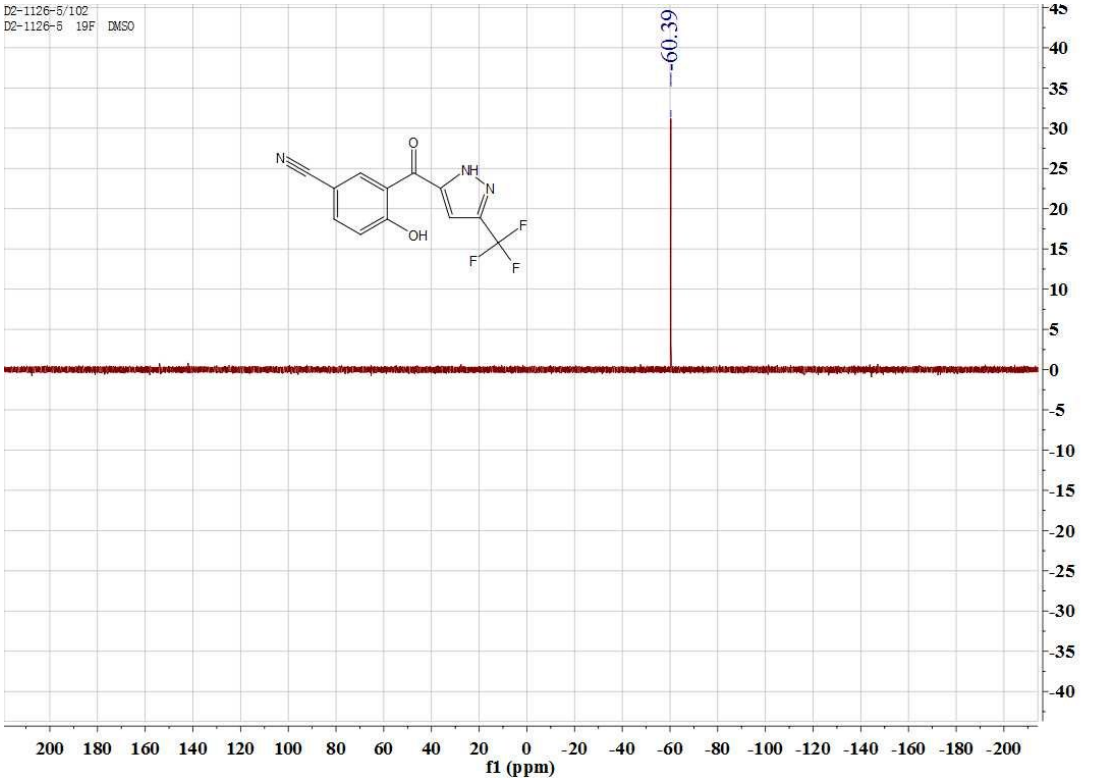
^{1}H NMR spectrum of **3f**



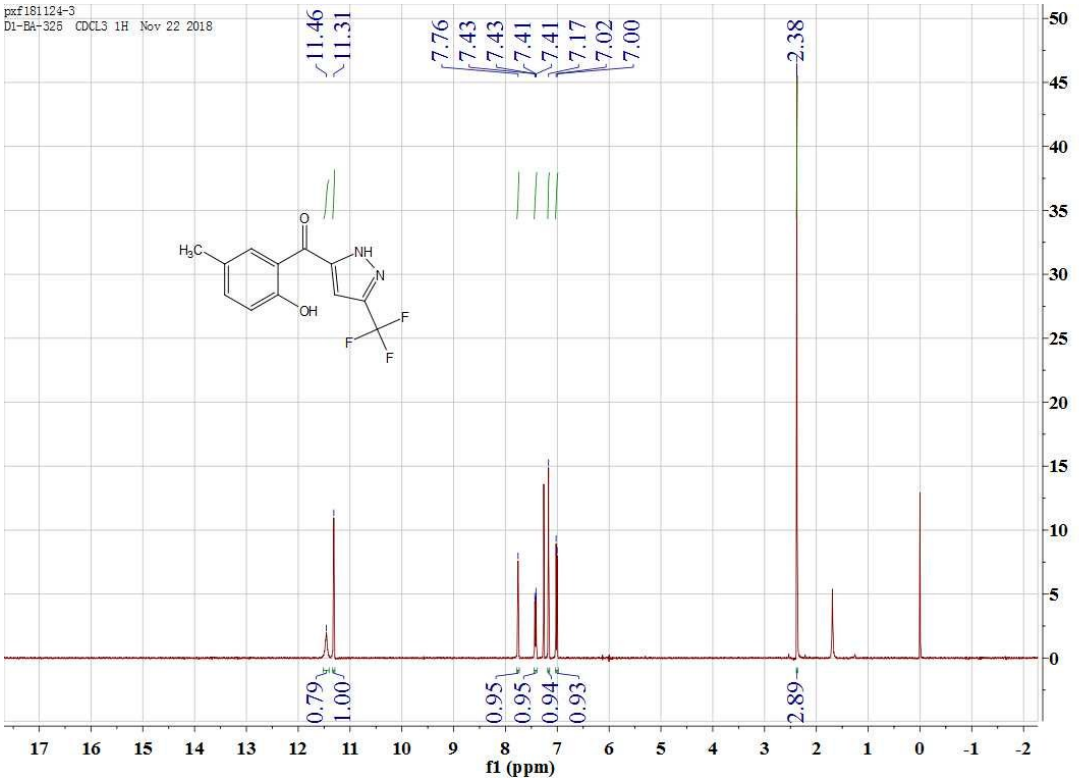
^{13}C NMR spectrum of **3f**



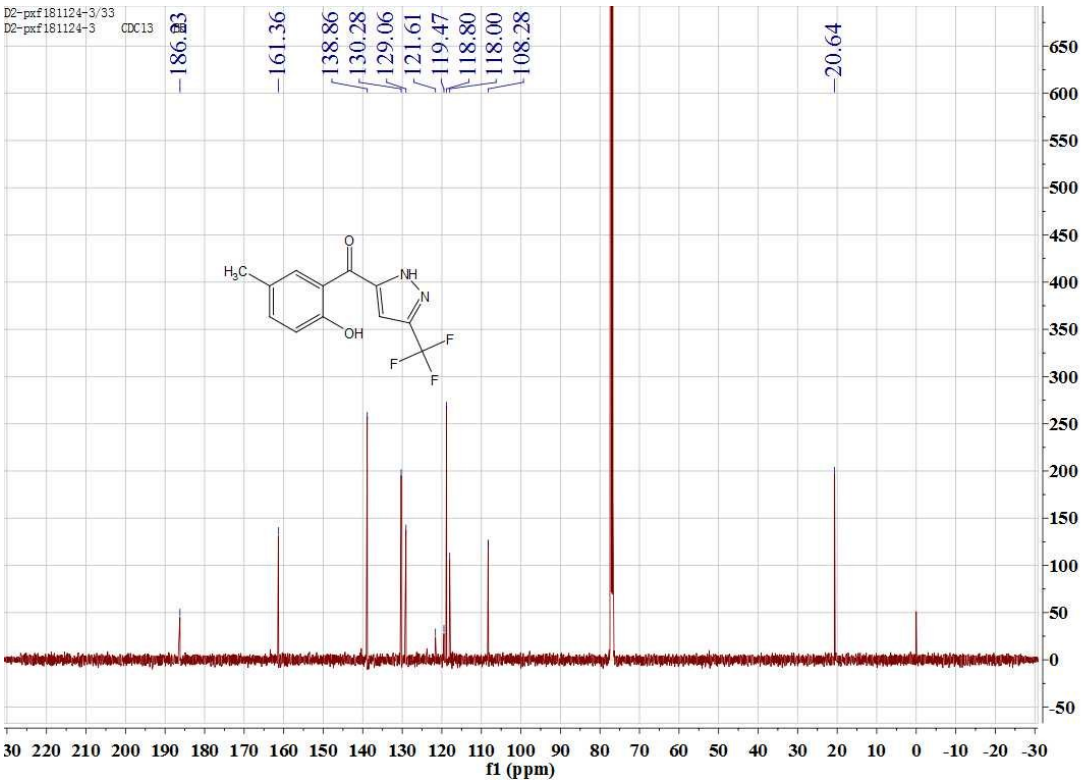
^{19}F NMR spectrum of **3f**



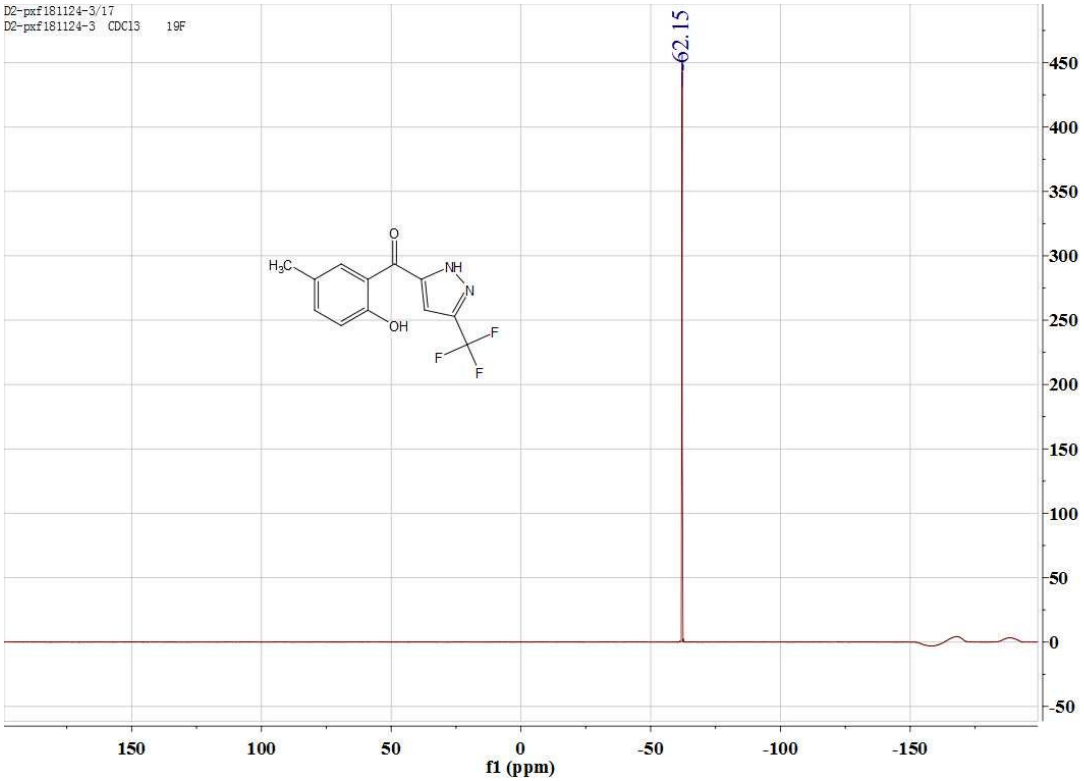
^{1}H NMR spectrum of **3g**



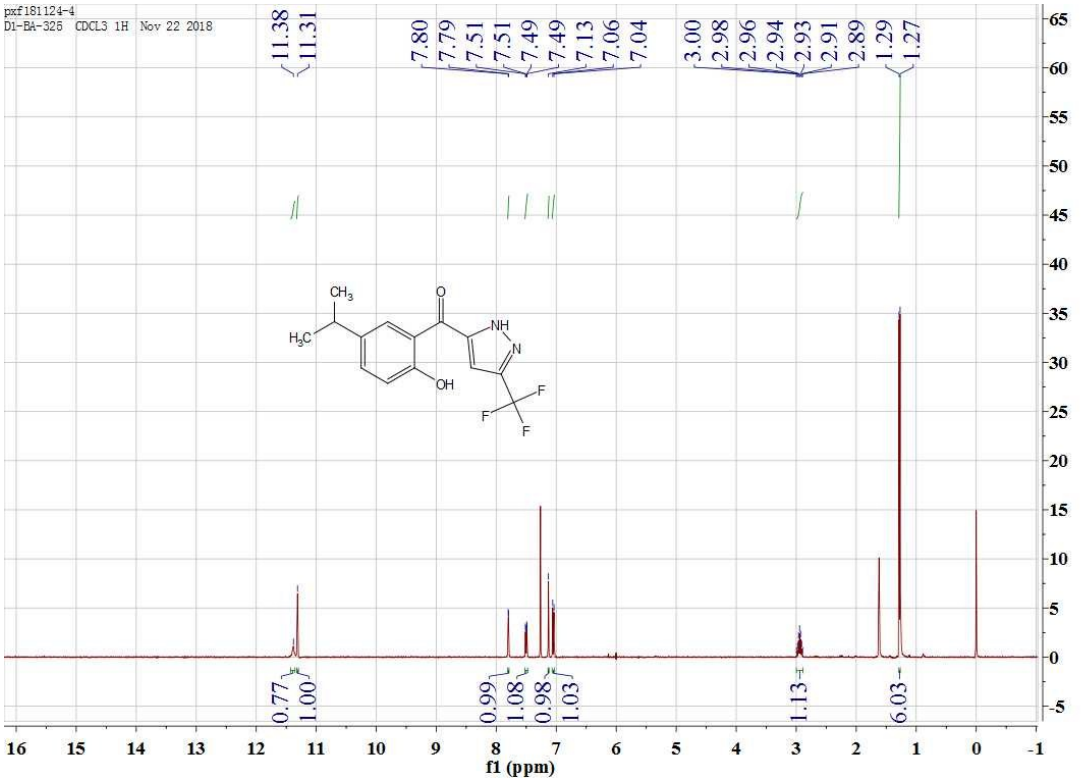
^{13}C NMR spectrum of **3g**



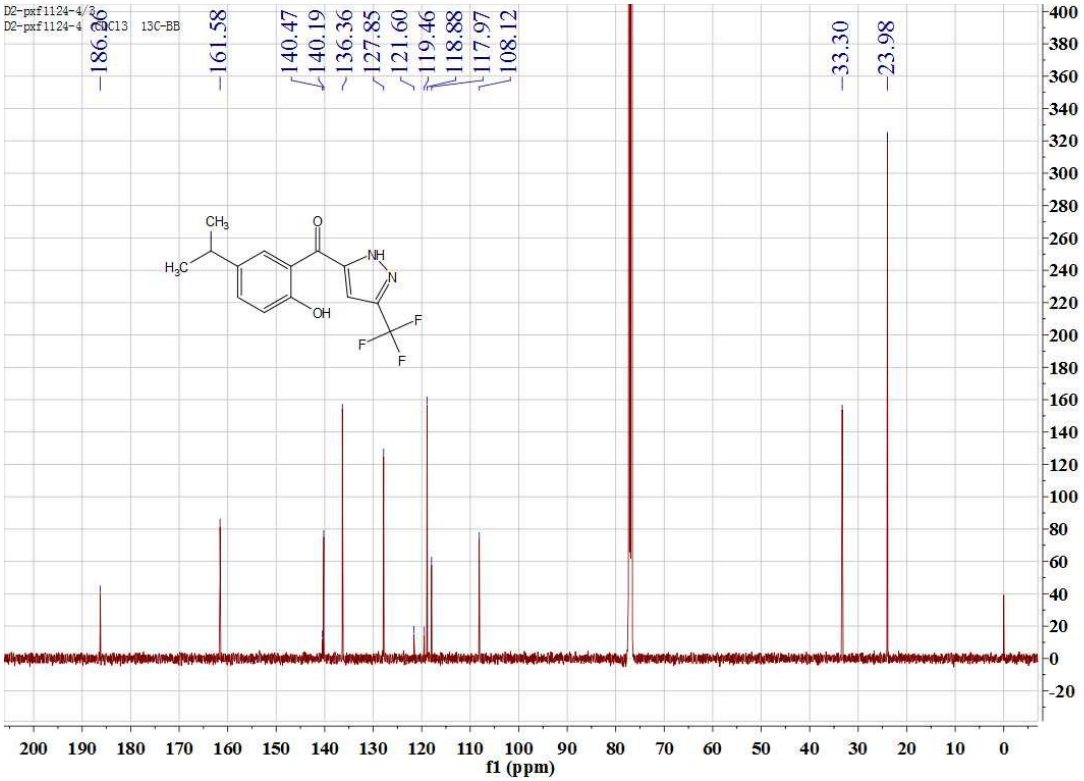
^{19}F NMR spectrum of **3g**



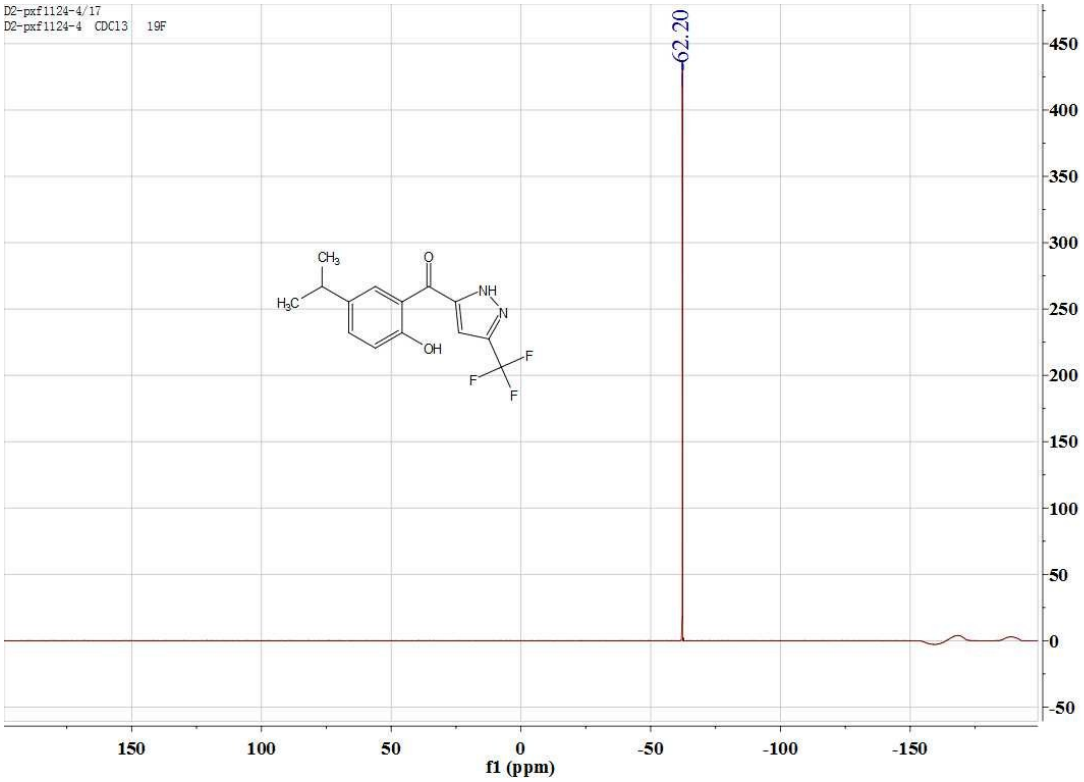
^{1}H NMR spectrum of **3h**



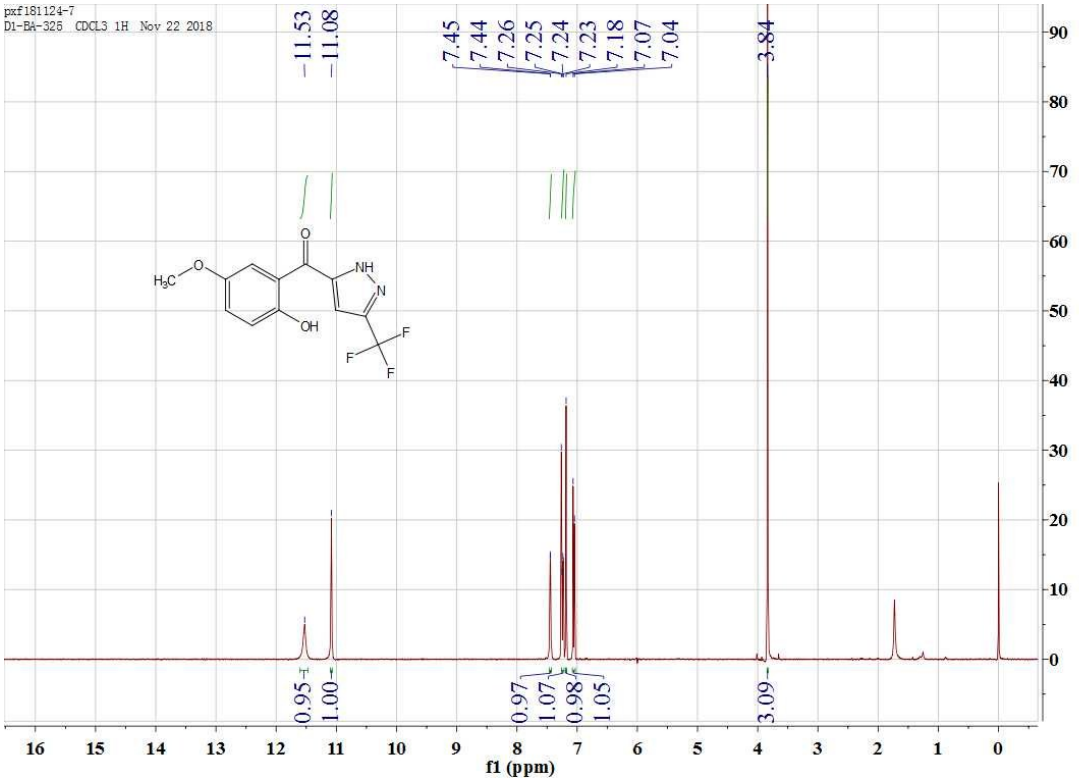
^{13}C NMR spectrum of **3h**



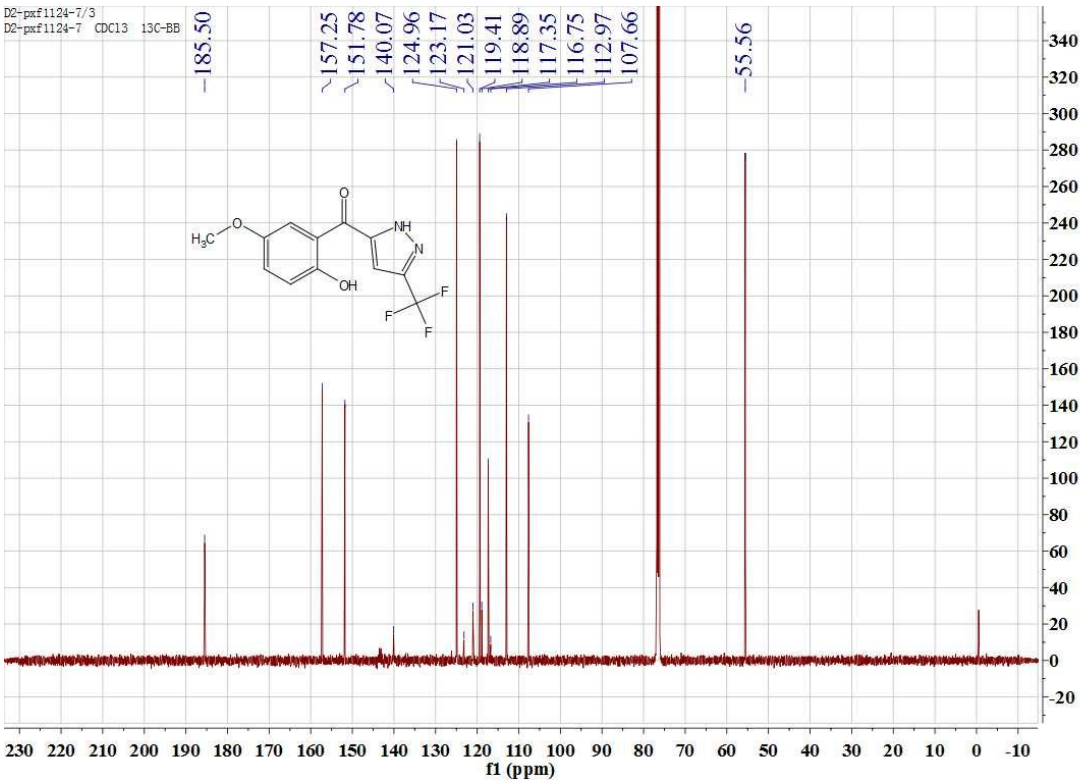
^{19}F NMR spectrum of **3h**



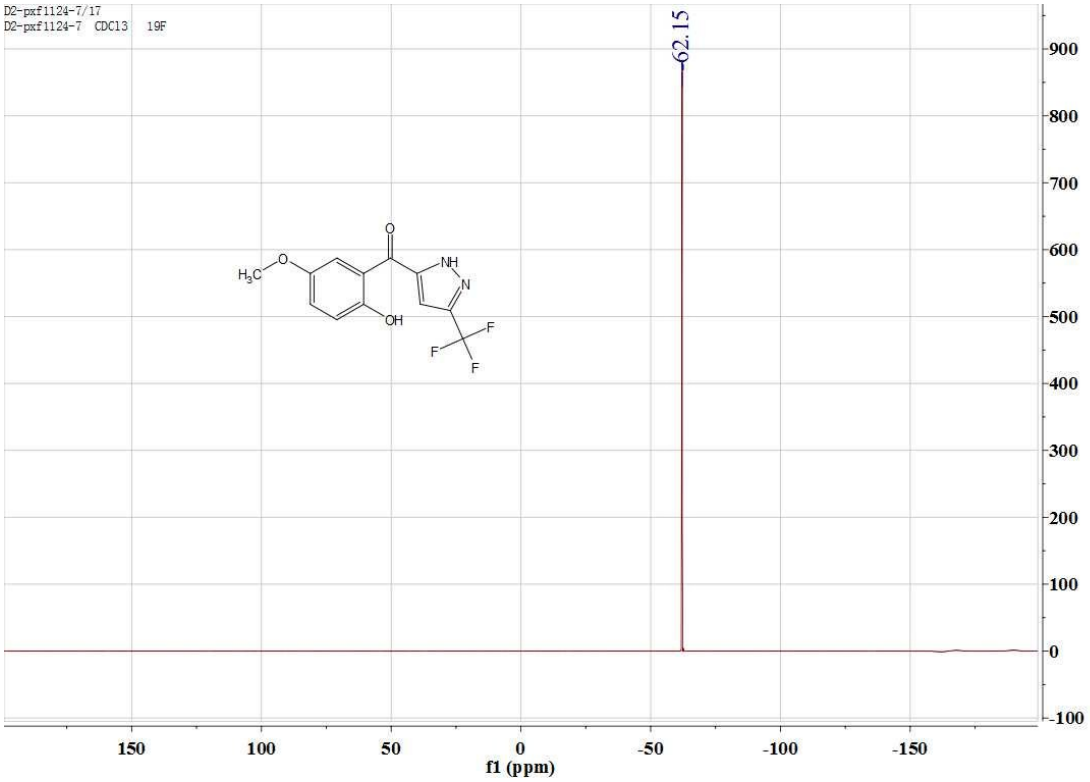
^{1}H NMR spectrum of **3i**



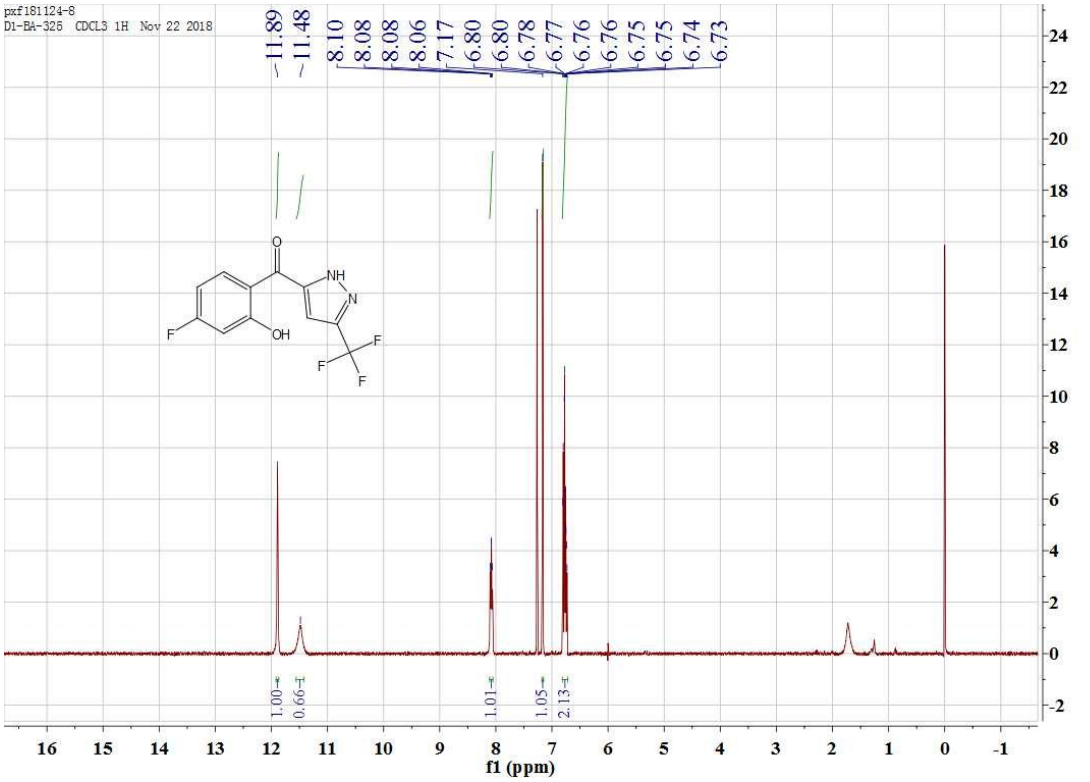
^{13}C NMR spectrum of **3i**



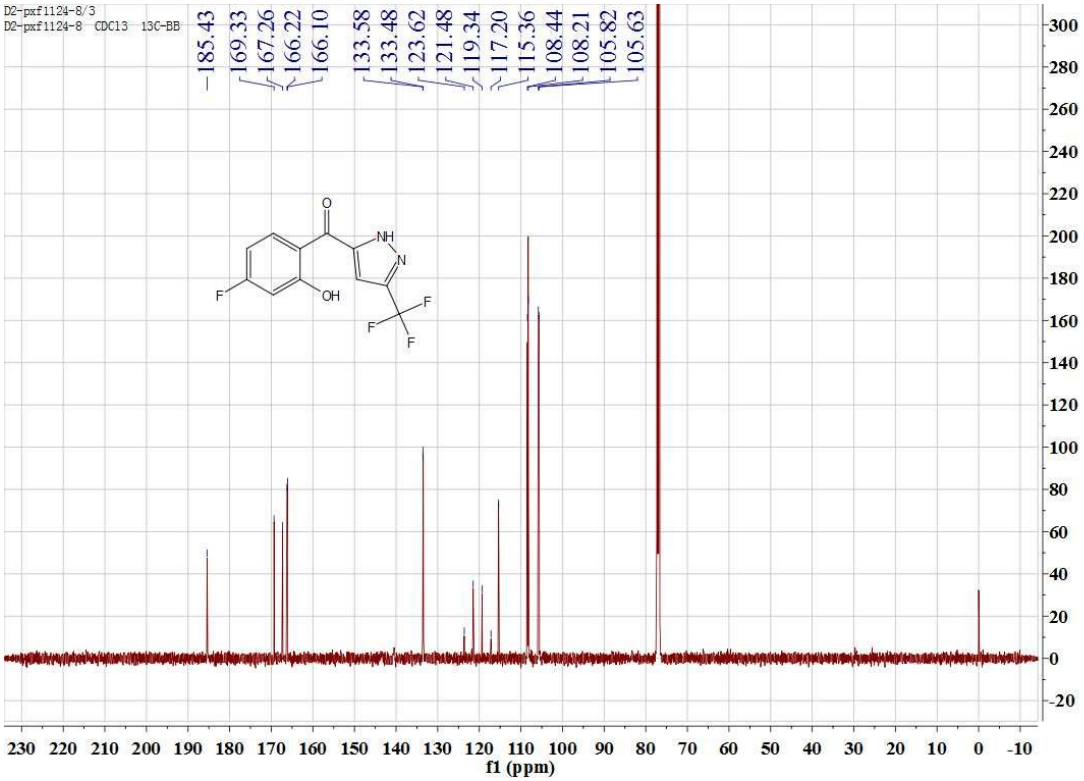
^{19}F NMR spectrum of **3i**



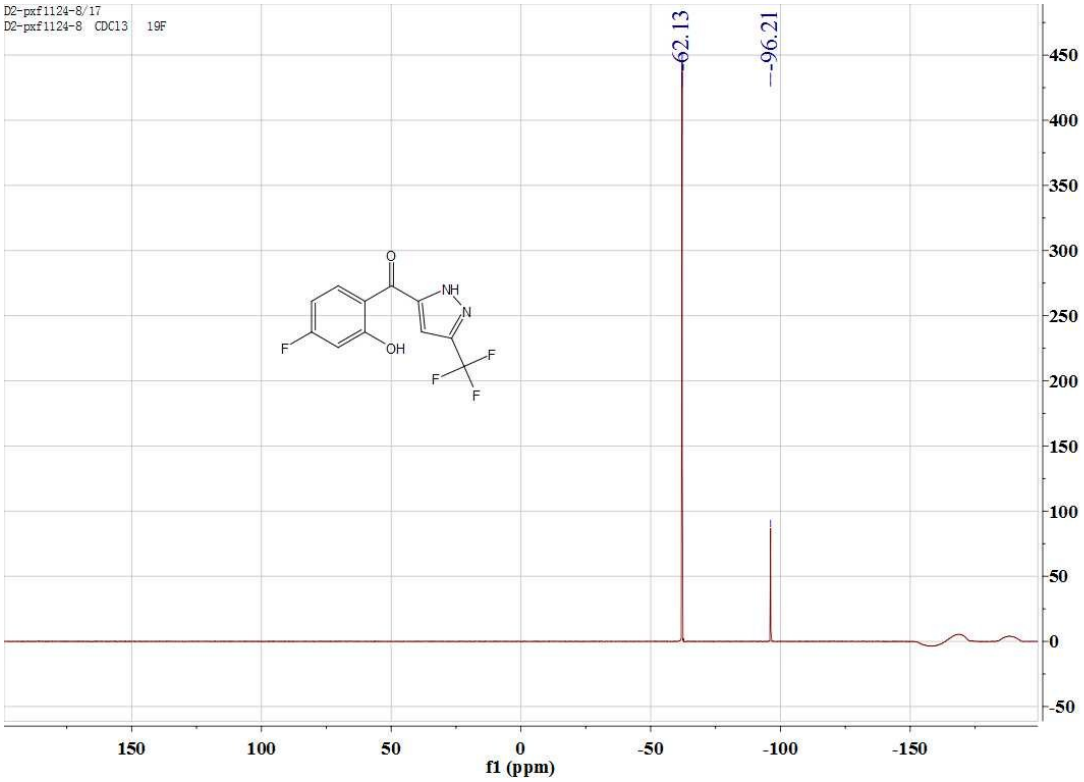
^{1}H NMR spectrum of **3j**



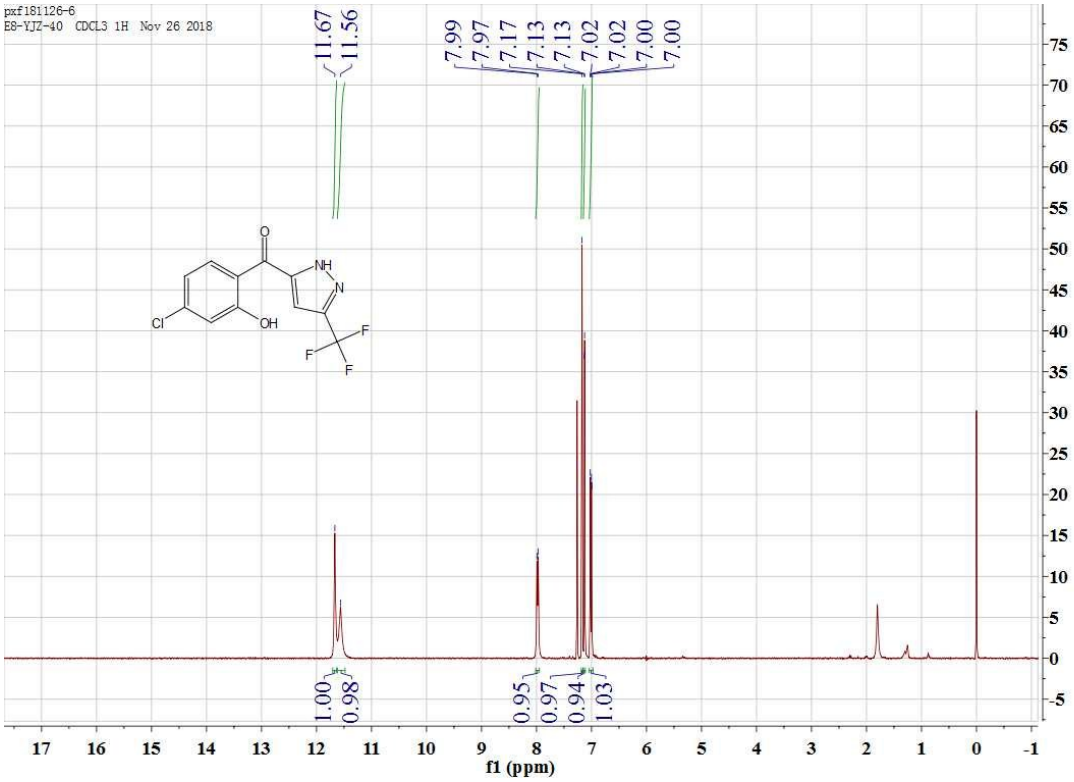
^{13}C NMR spectrum of **3j**



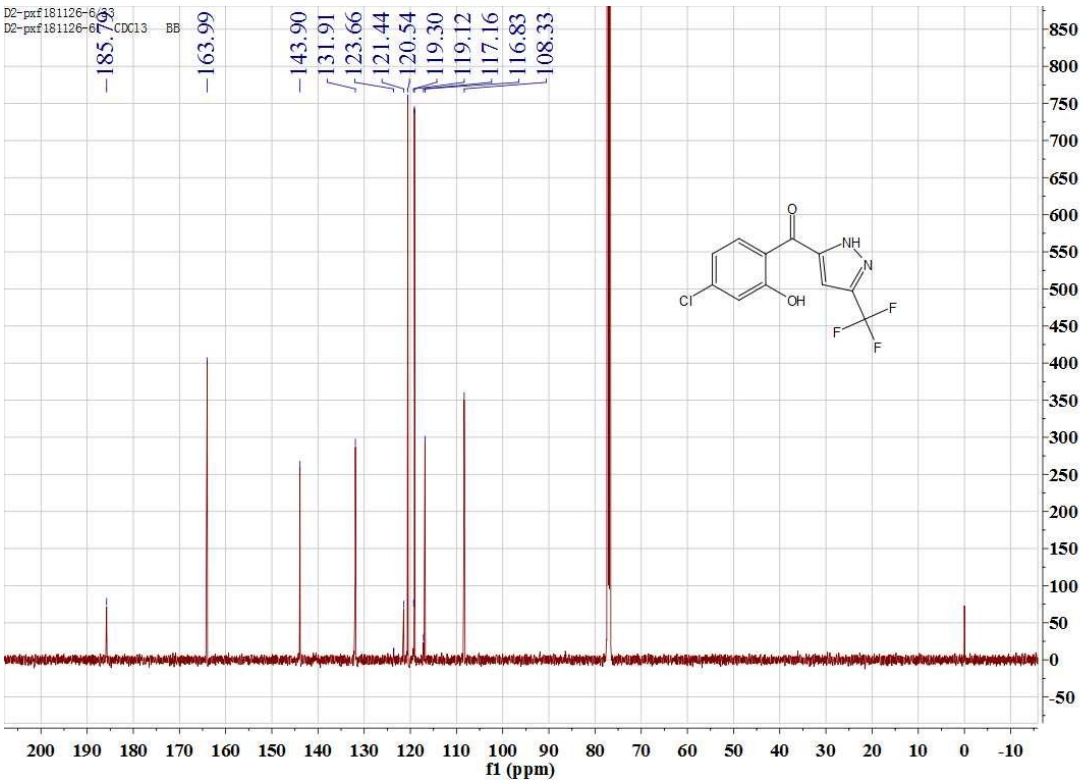
^{19}F NMR spectrum of **3j**



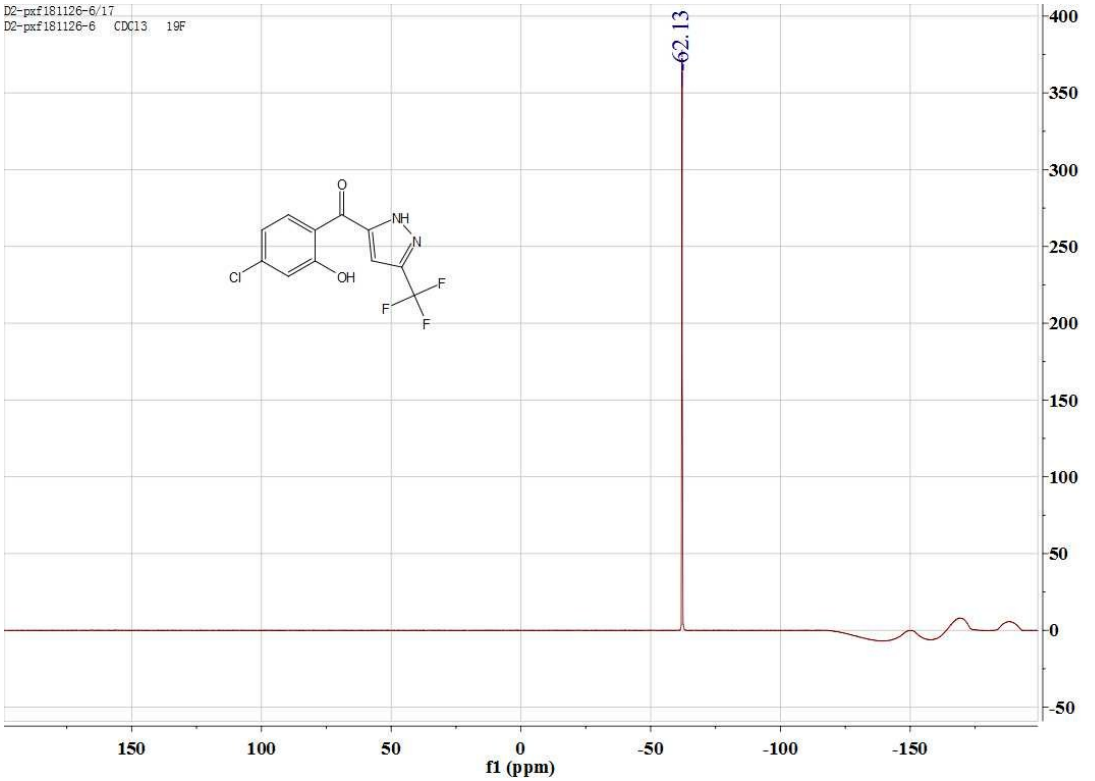
^{1}H NMR spectrum of **3k**



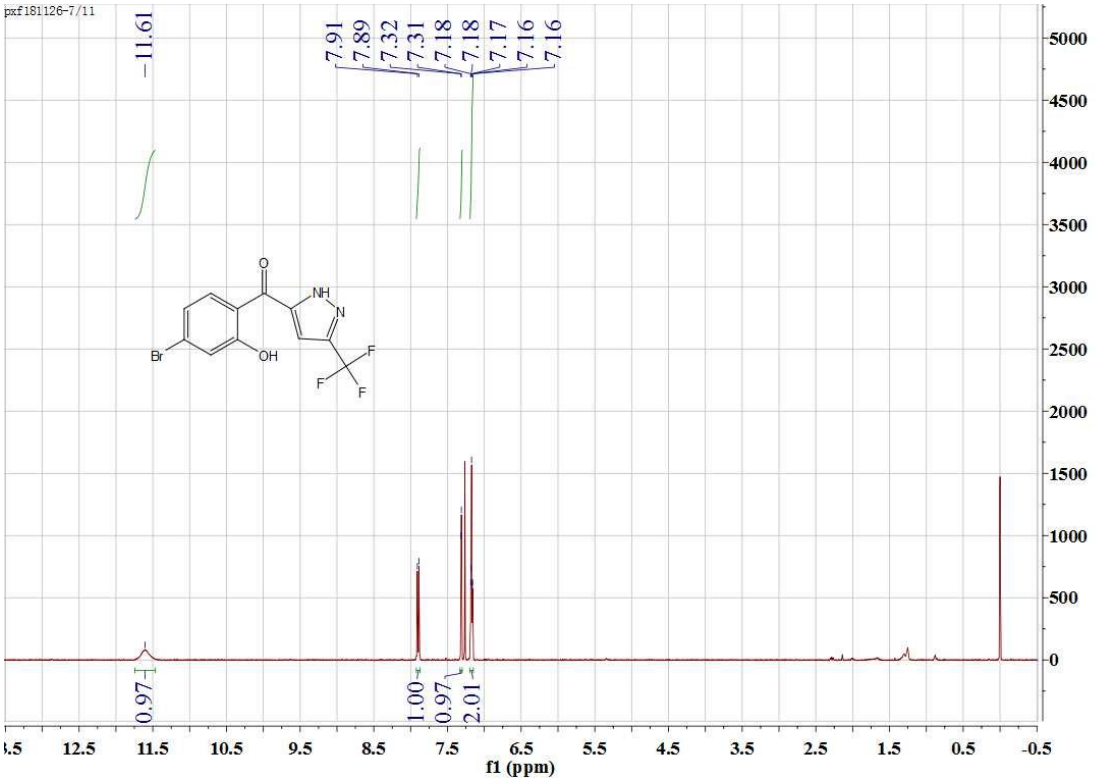
^{13}C NMR spectrum of **3k**



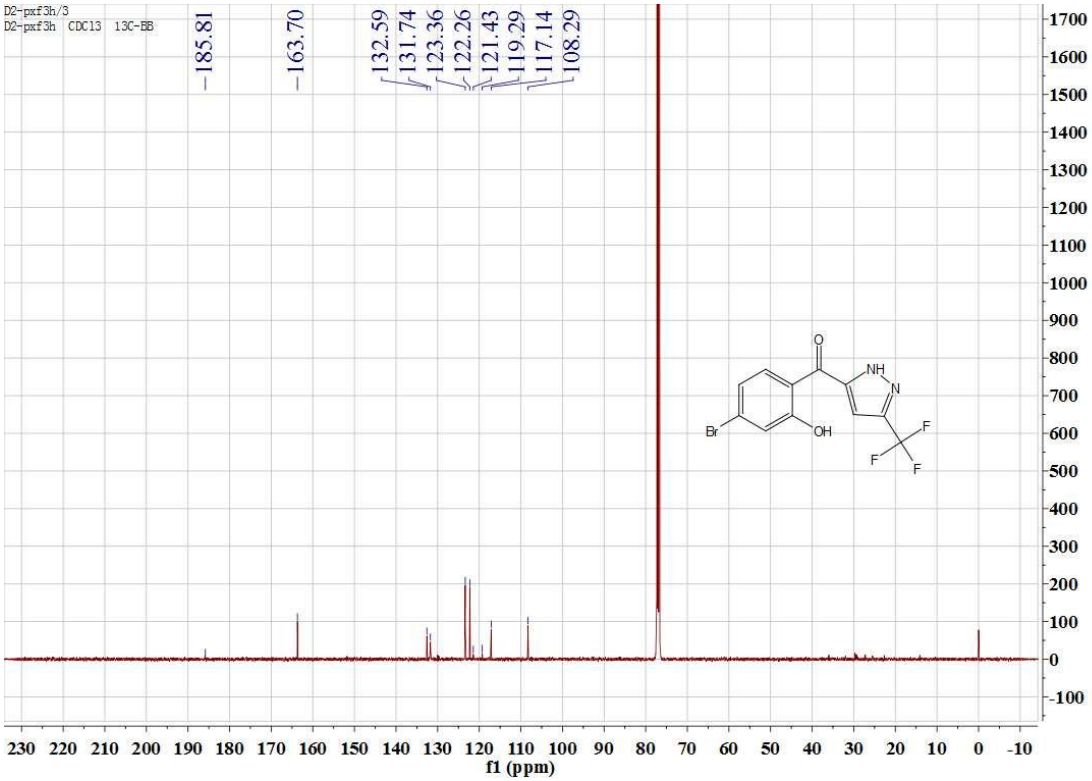
^{19}F NMR spectrum of **3k**



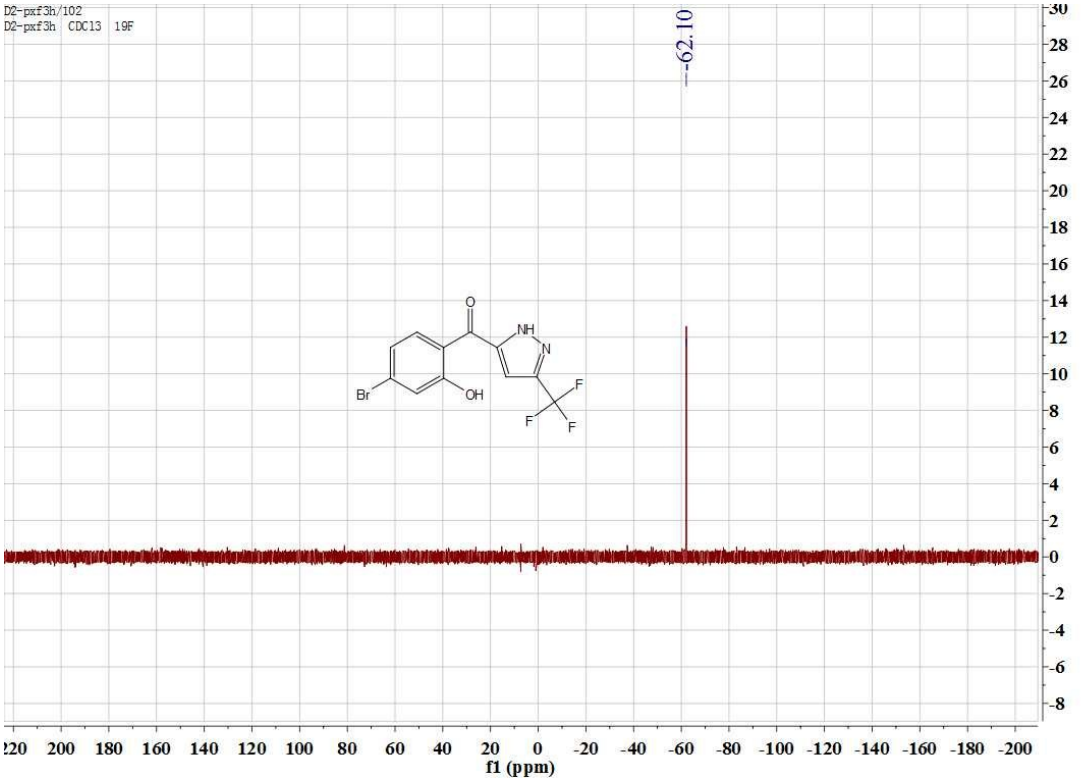
^{1}H NMR spectrum of **3l**



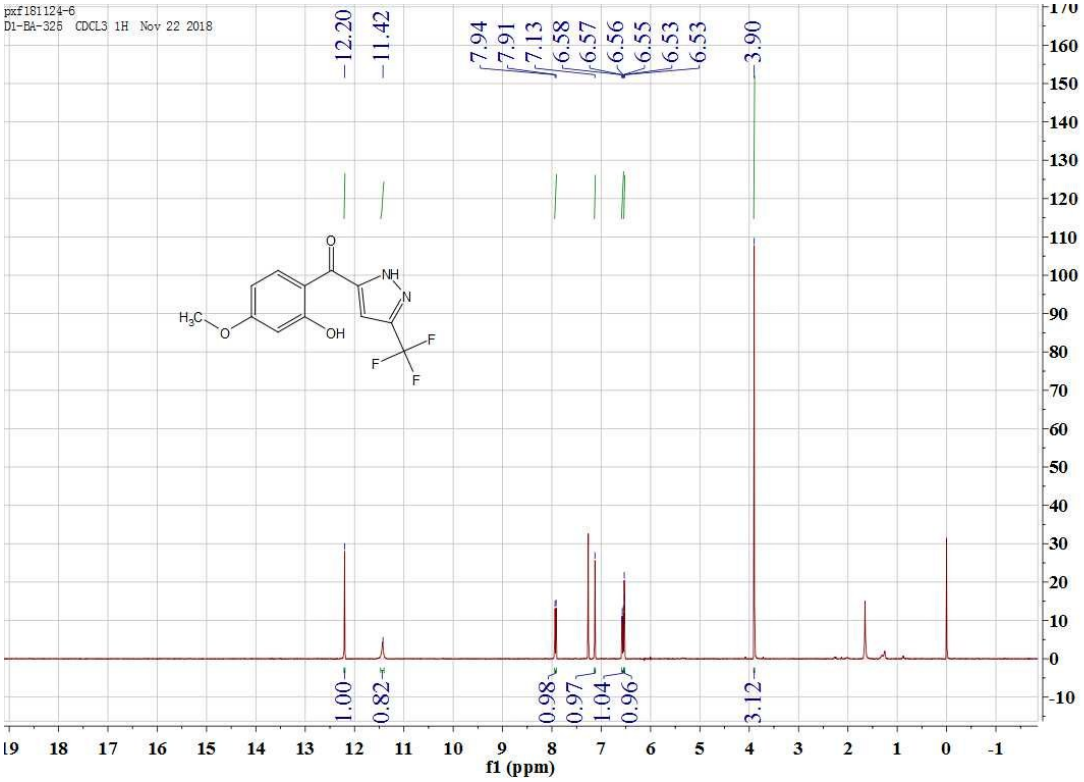
^{13}C NMR spectrum of **3l**



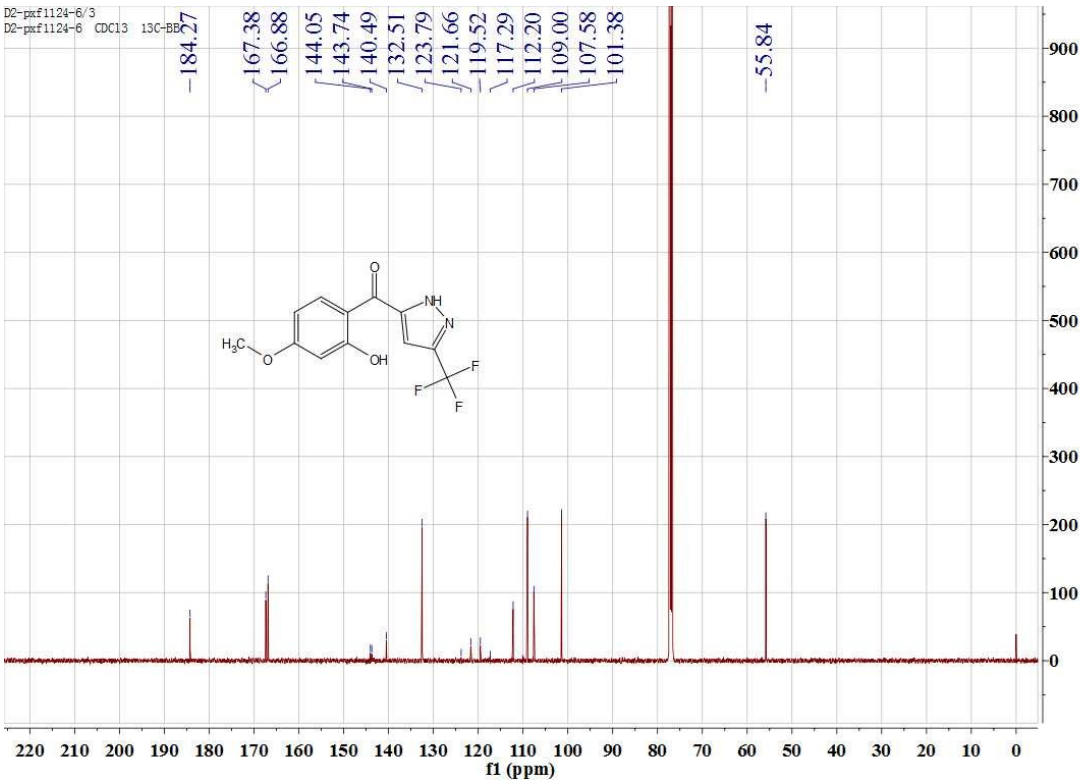
^{19}F NMR spectrum of **3l**



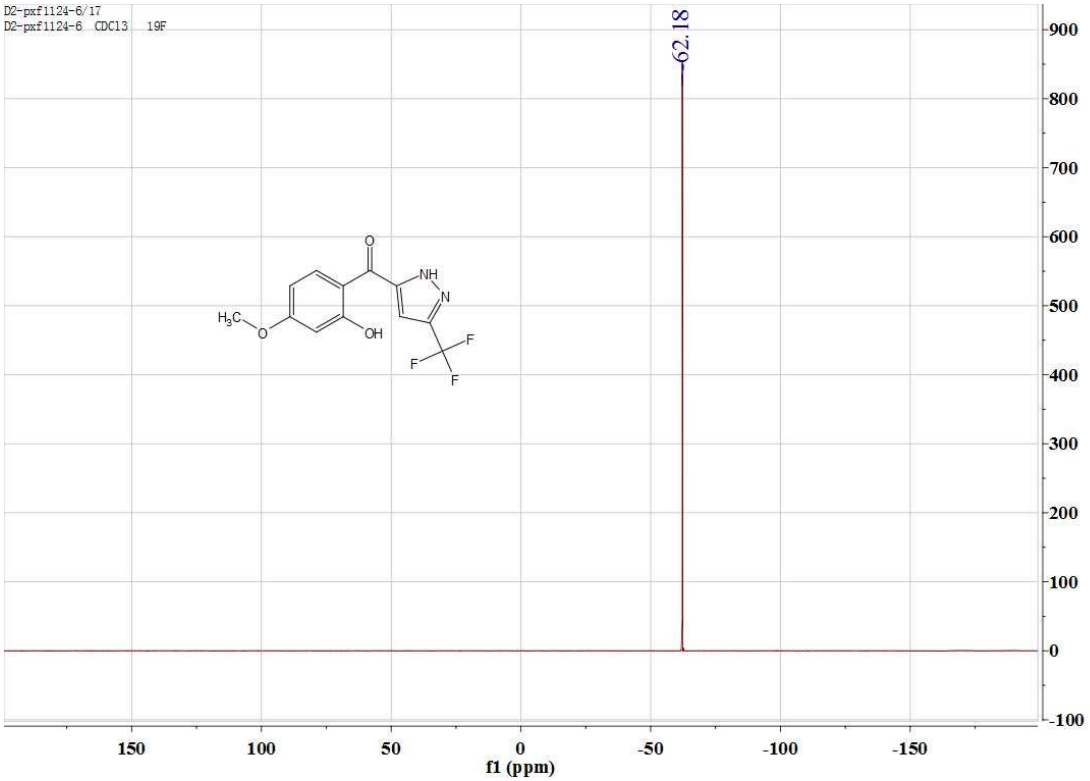
^{1}H NMR spectrum of **3m**



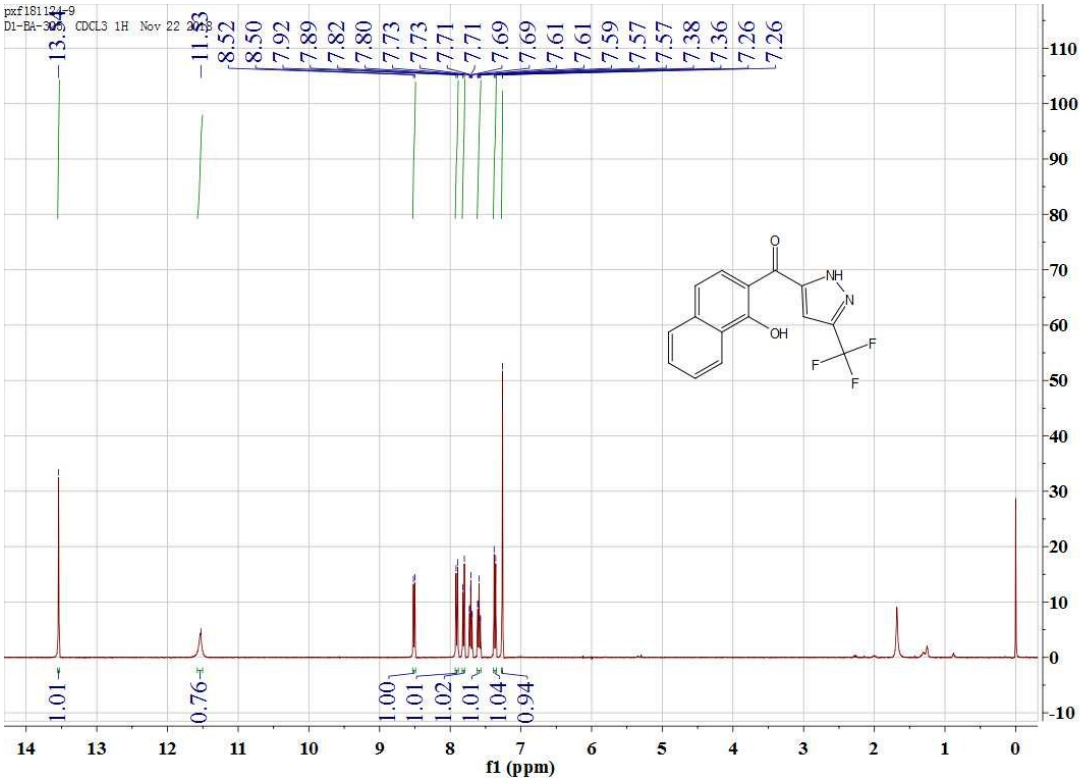
^{13}C NMR spectrum of **3m**



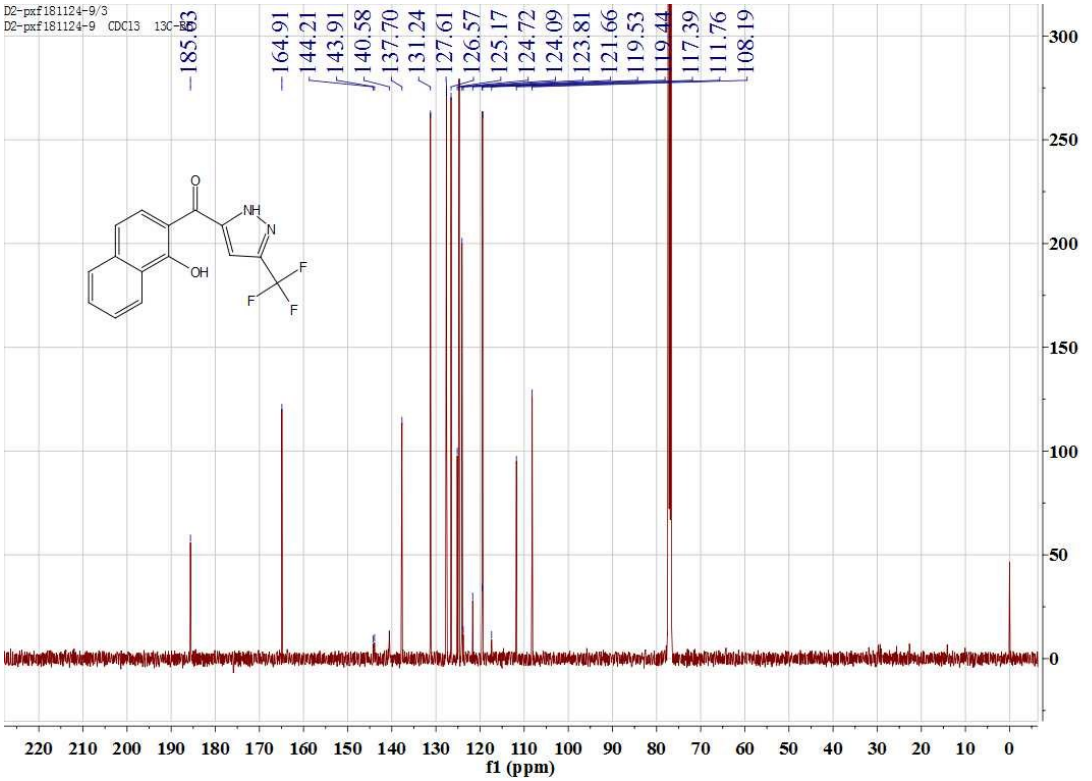
^{19}F NMR spectrum of **3m**



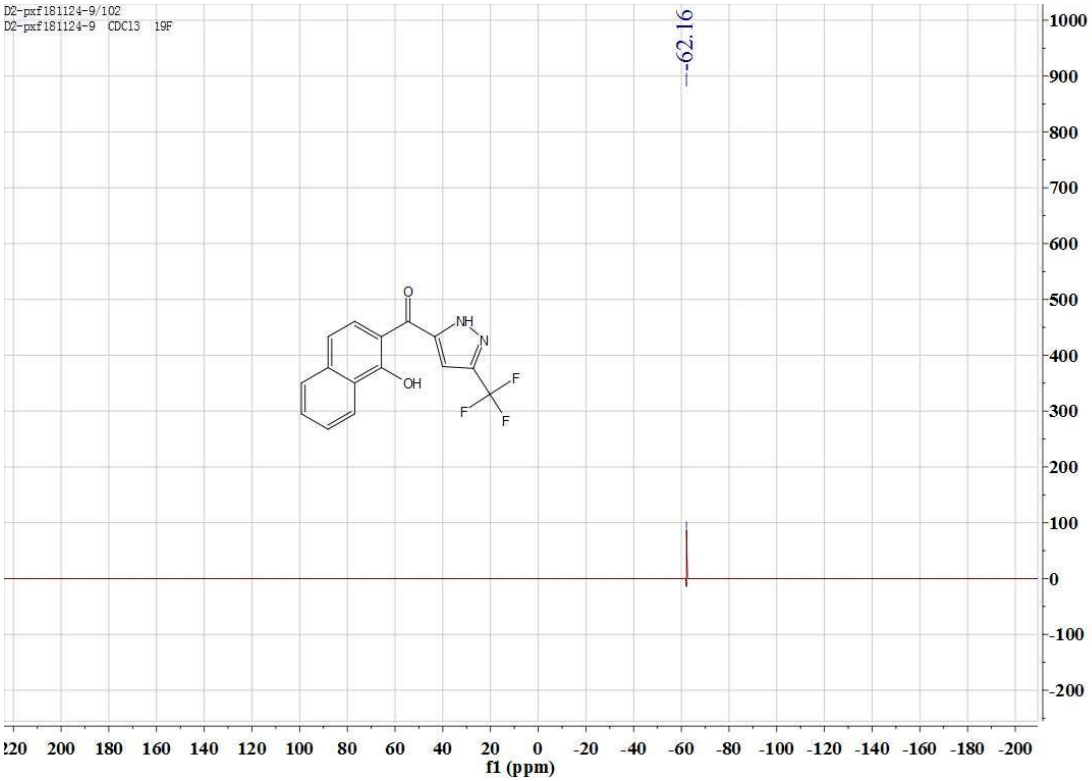
^{1}H NMR spectrum of **3n**



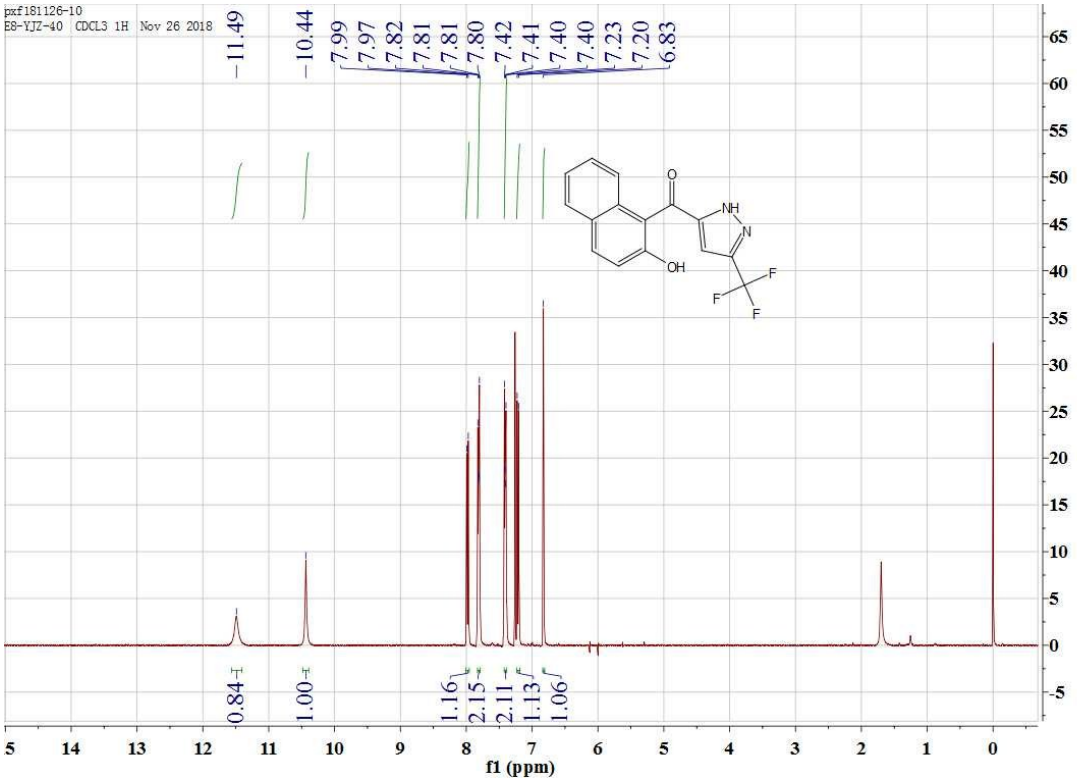
^{13}C NMR spectrum of **3n**



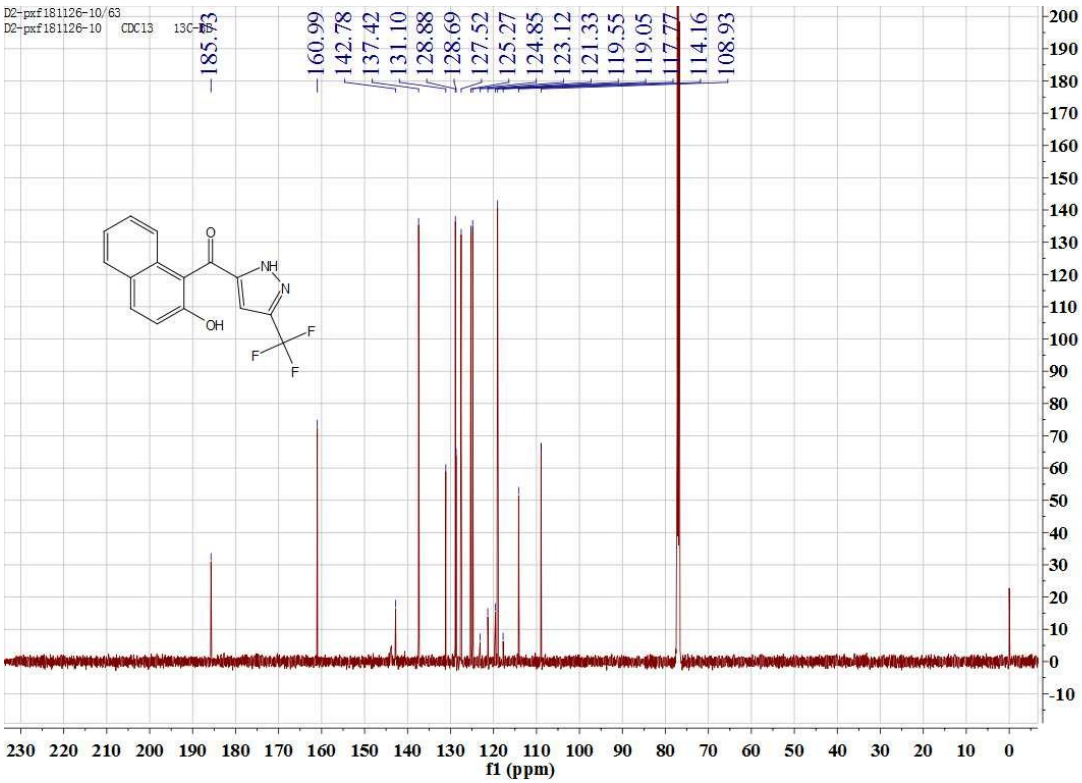
^{19}F NMR spectrum of **3n**



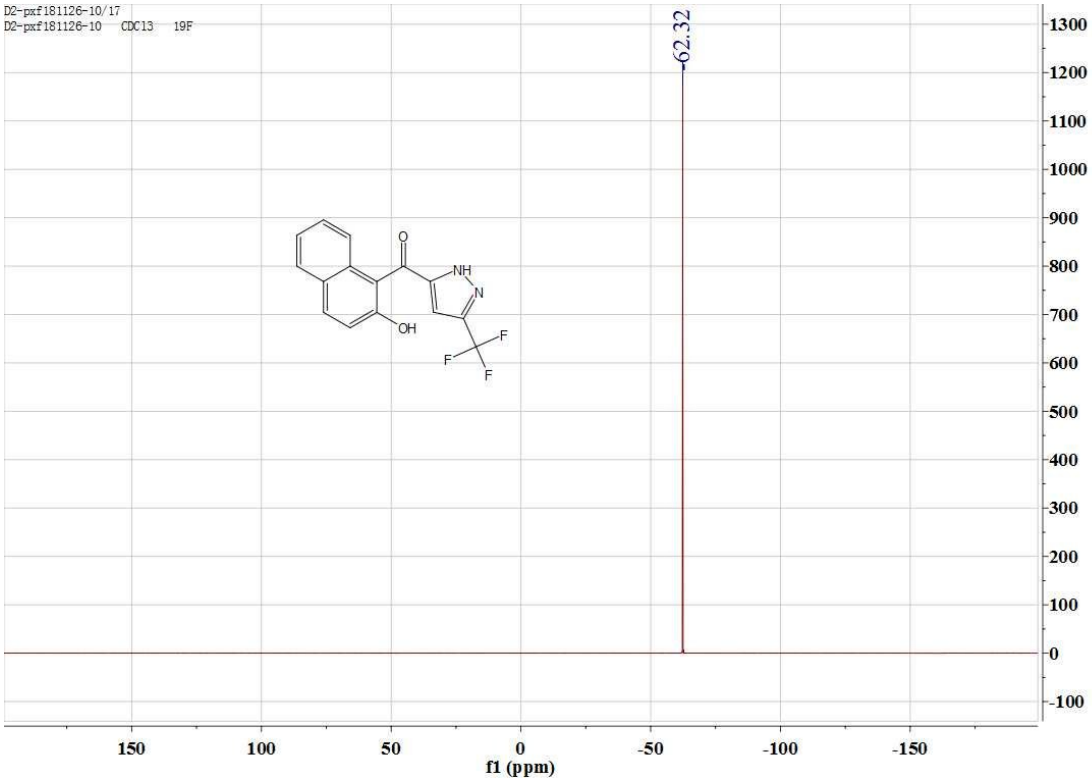
^{1}H NMR spectrum of **3o**



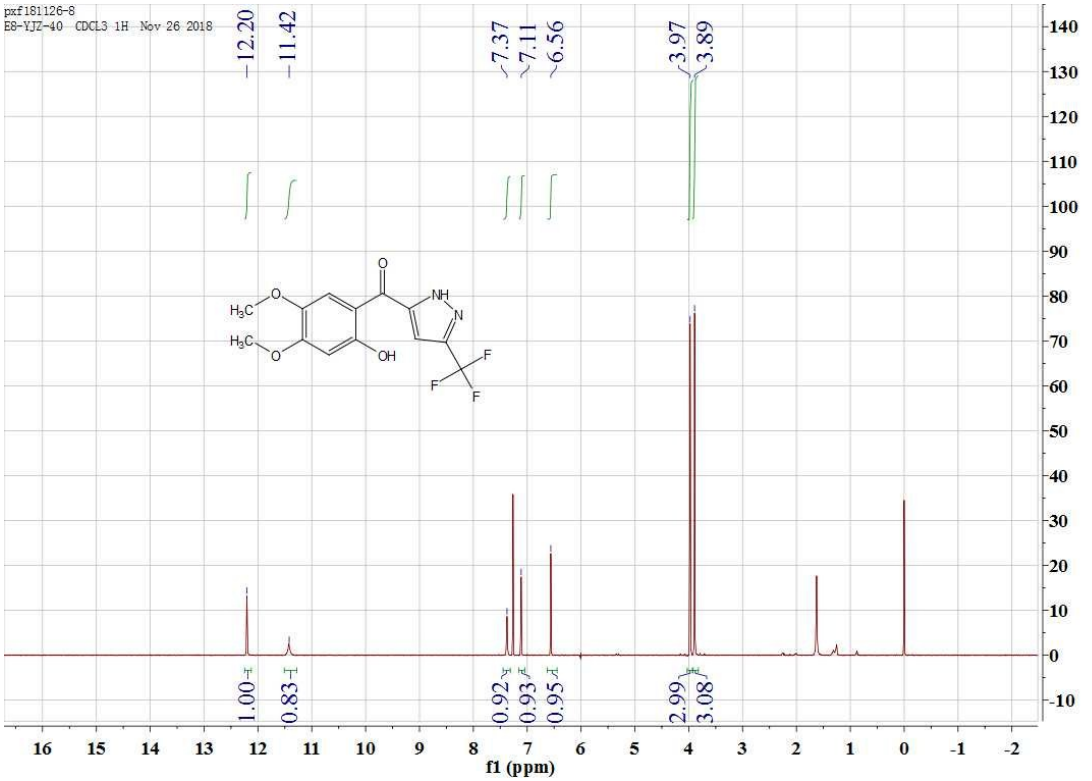
^{13}C NMR spectrum of **3o**



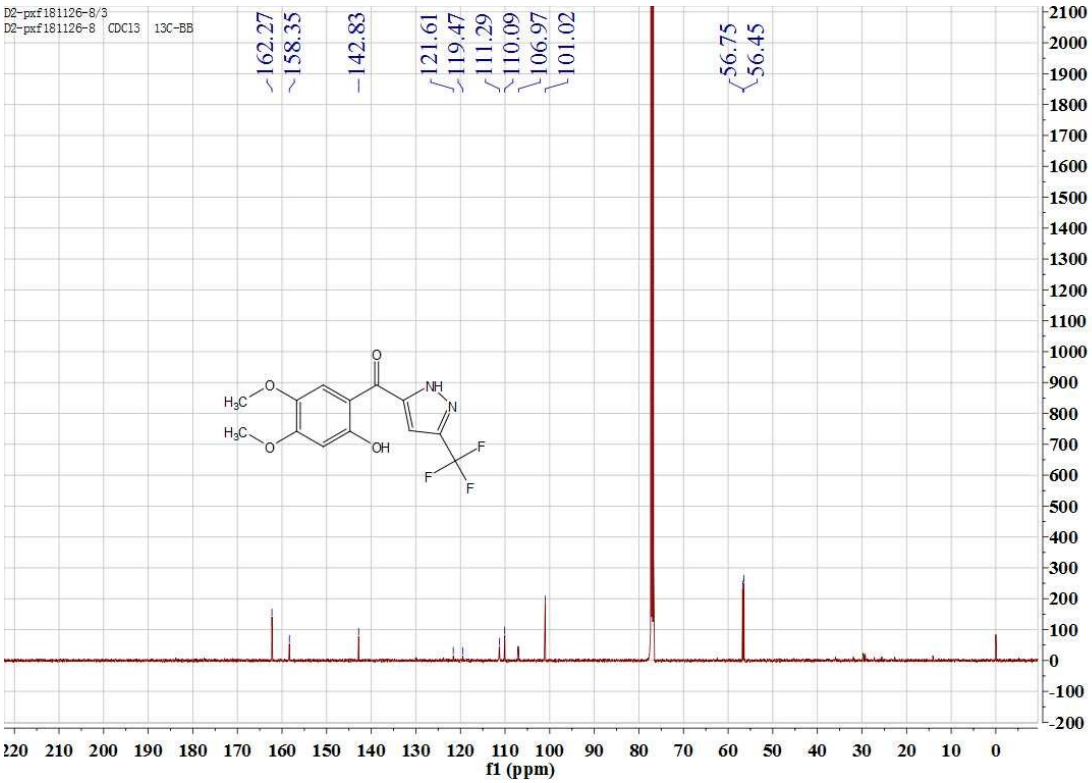
^{19}F NMR spectrum of **3o**



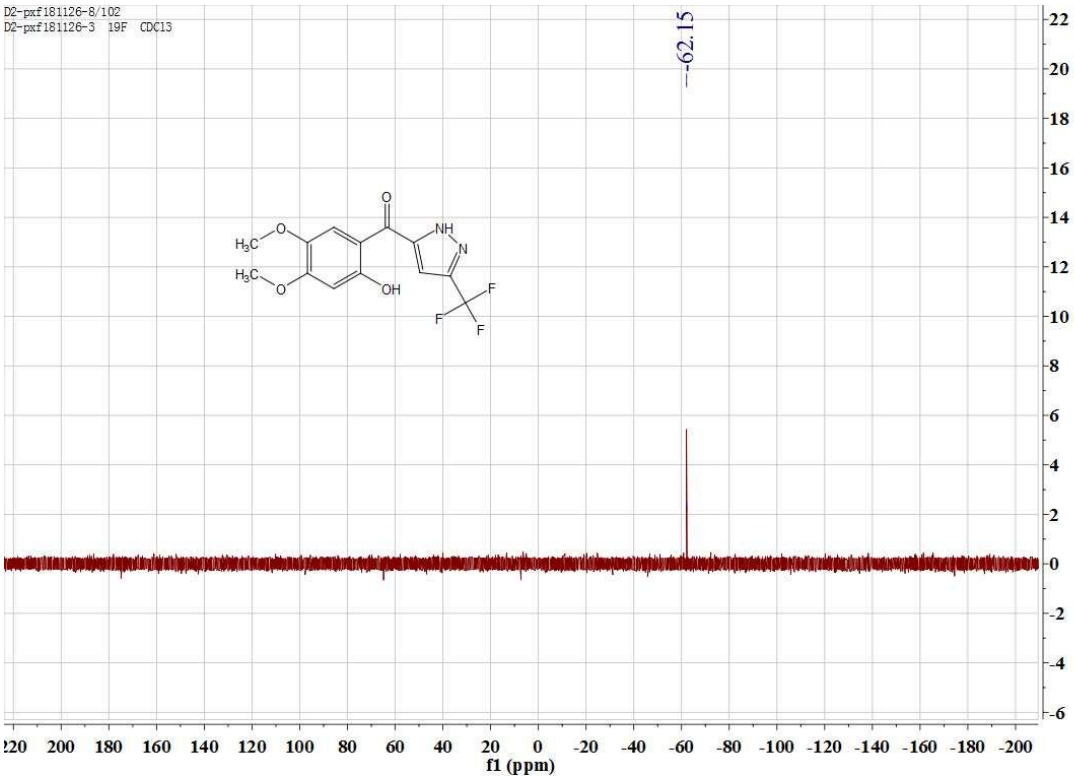
^{1}H NMR spectrum of **3p**



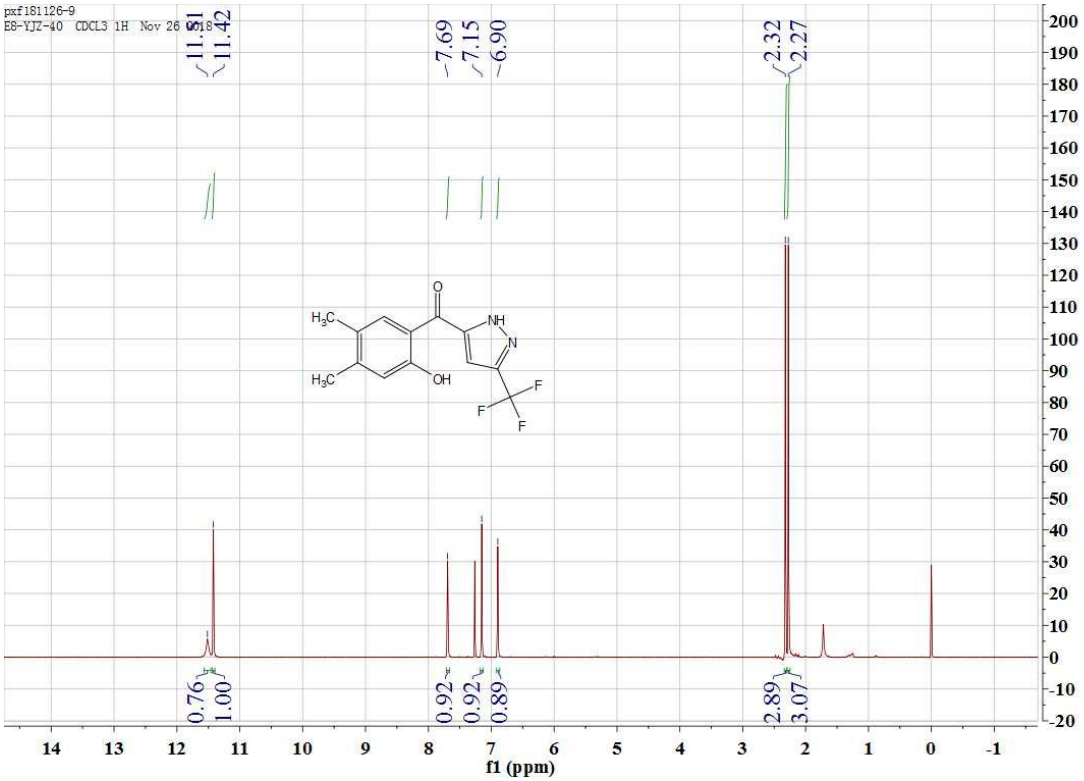
^{13}C NMR spectrum of **3p**



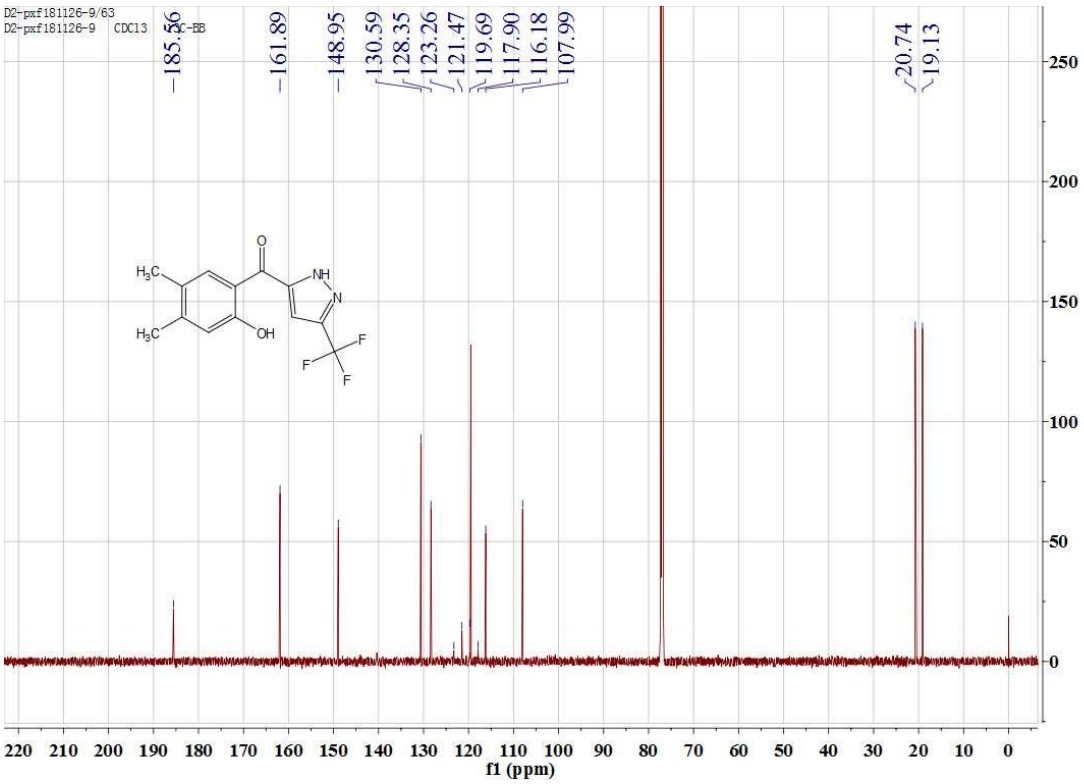
^{19}F NMR spectrum of **3p**



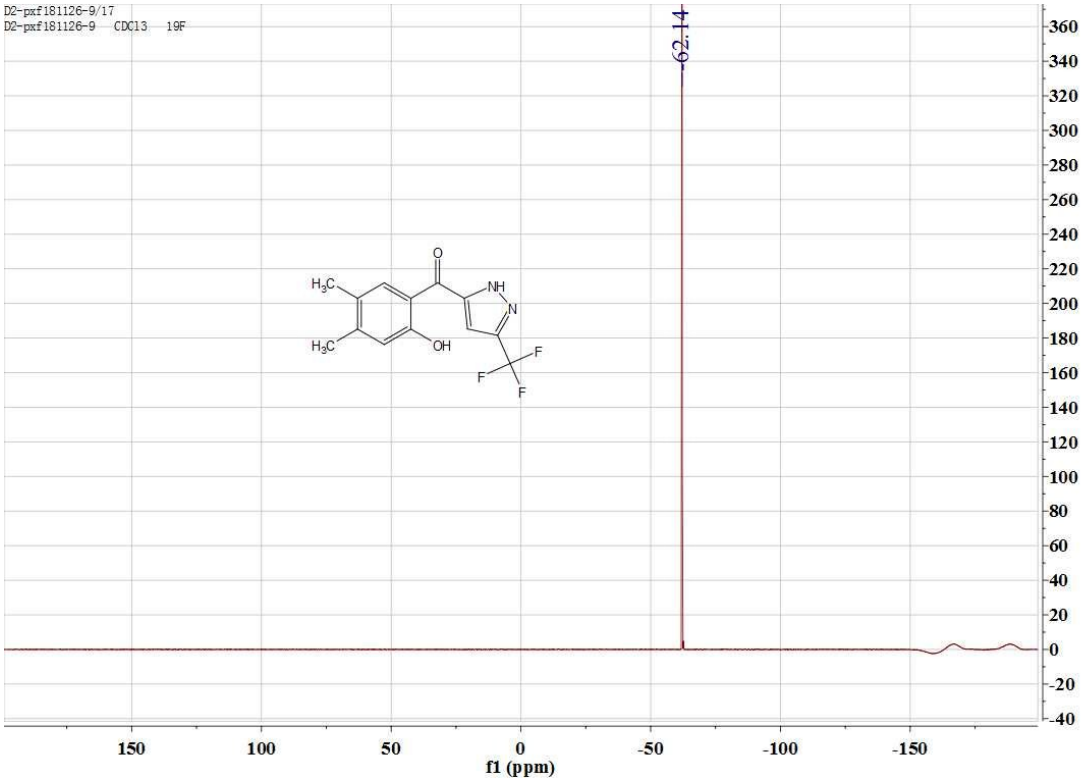
^{1}H NMR spectrum of **3q**



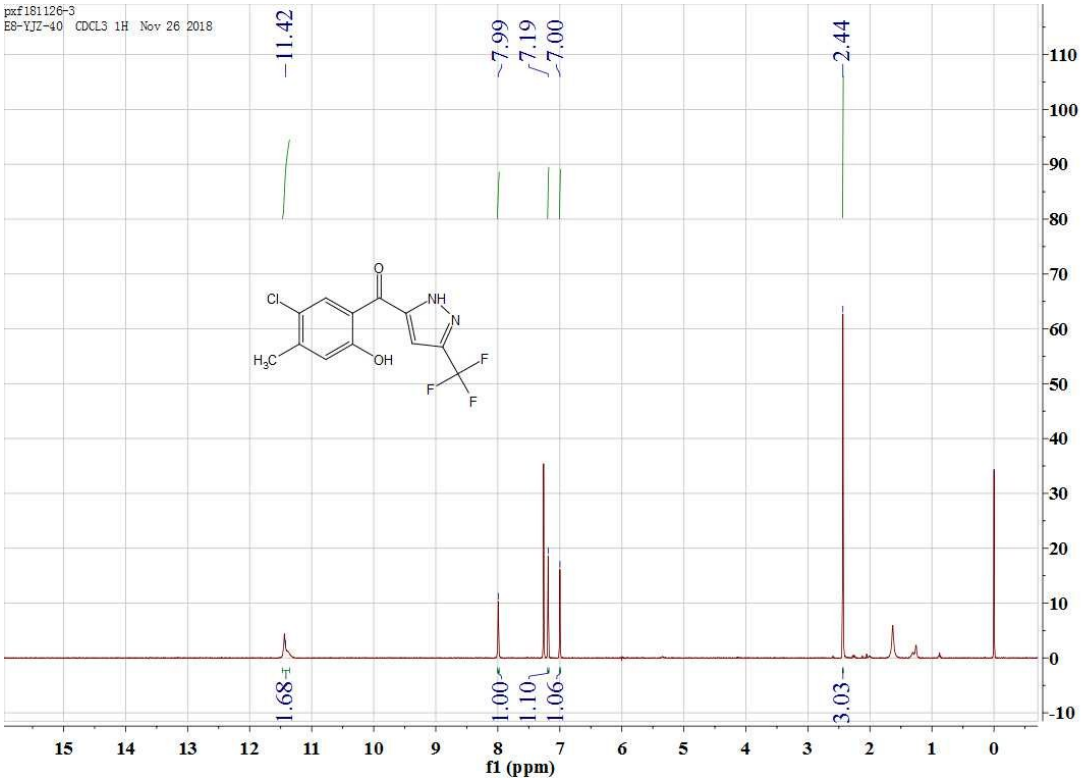
^{13}C NMR spectrum of **3q**



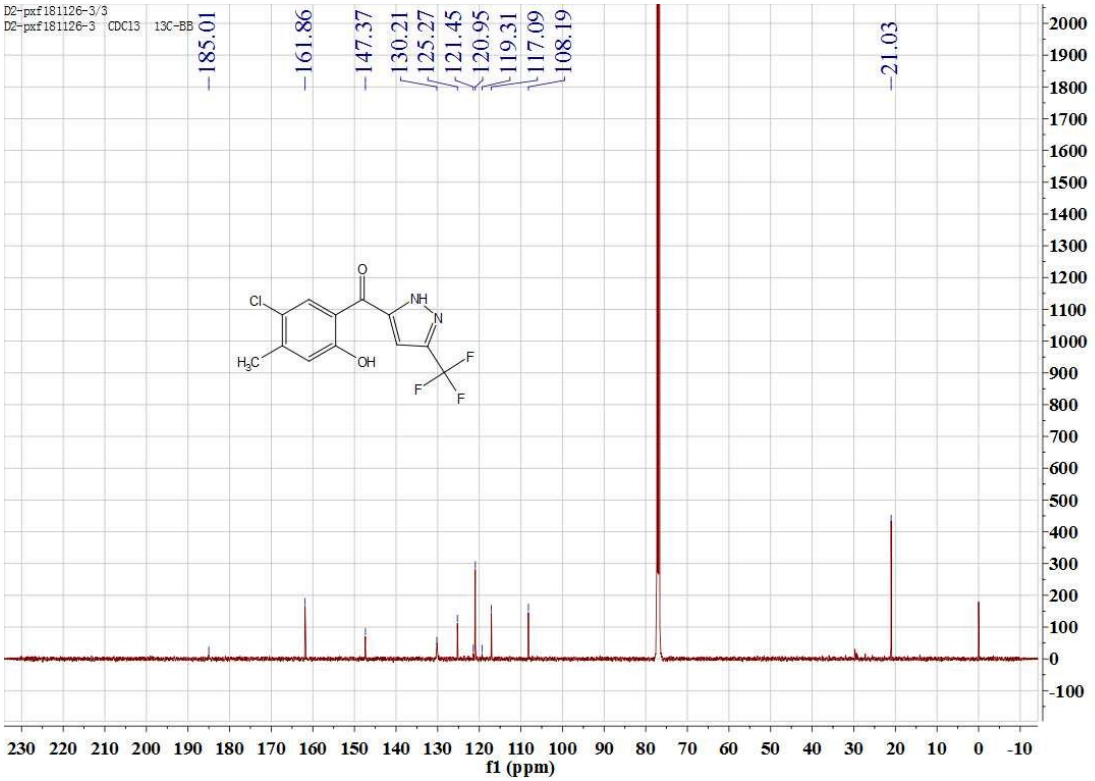
^{19}F NMR spectrum of **3q**



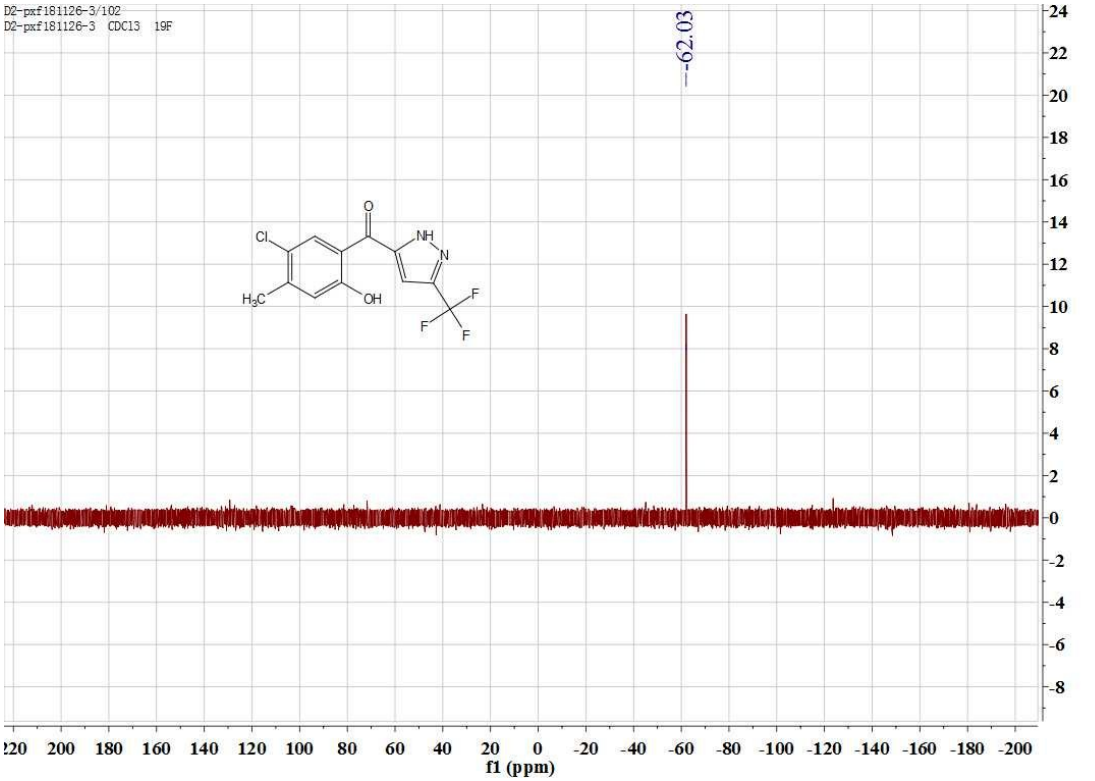
^{1}H NMR spectrum of **3r**



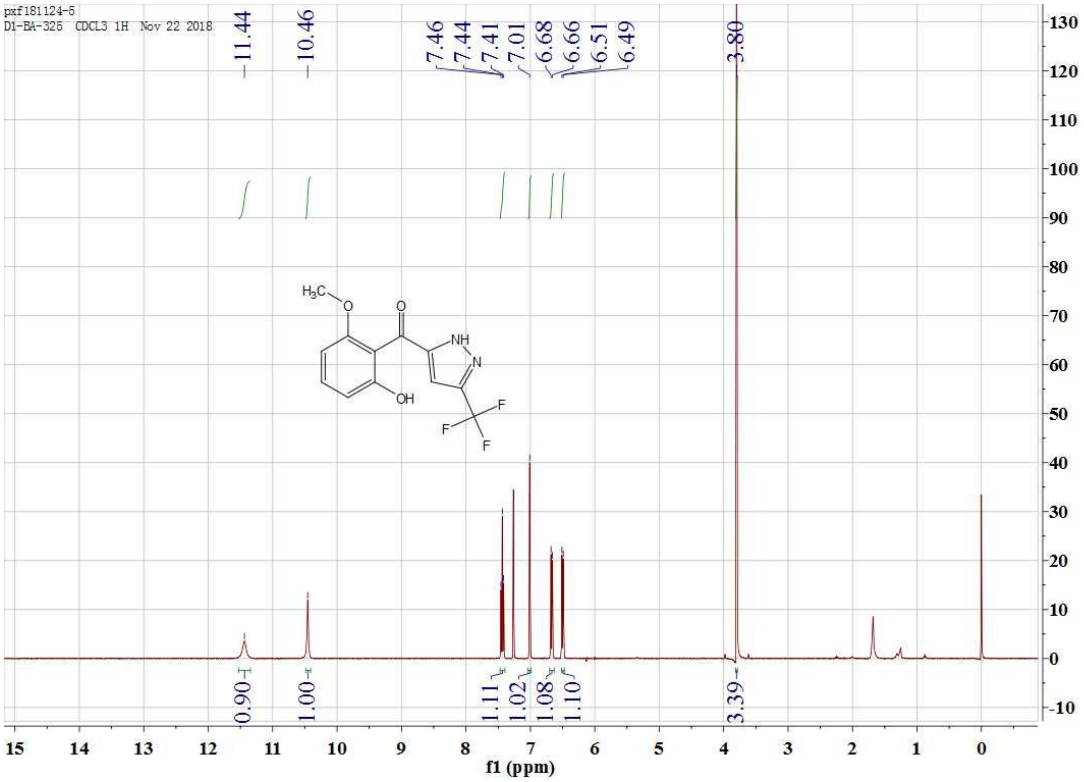
^{13}C NMR spectrum of **3r**



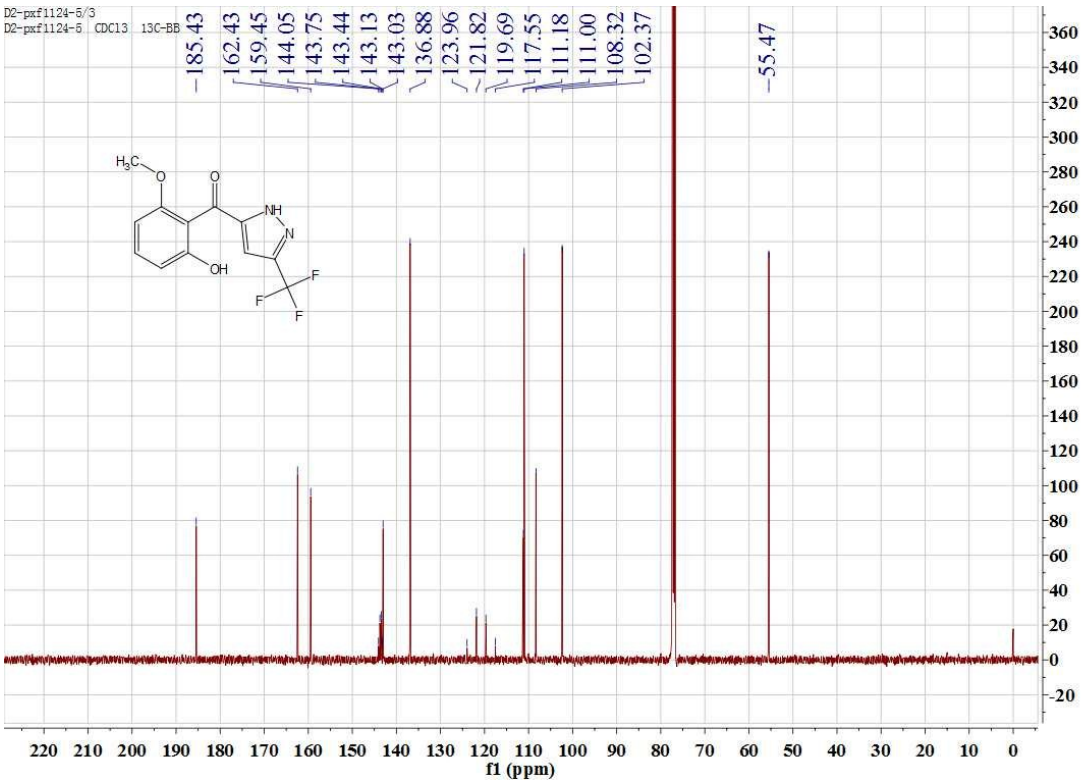
^{19}F NMR spectrum of **3r**



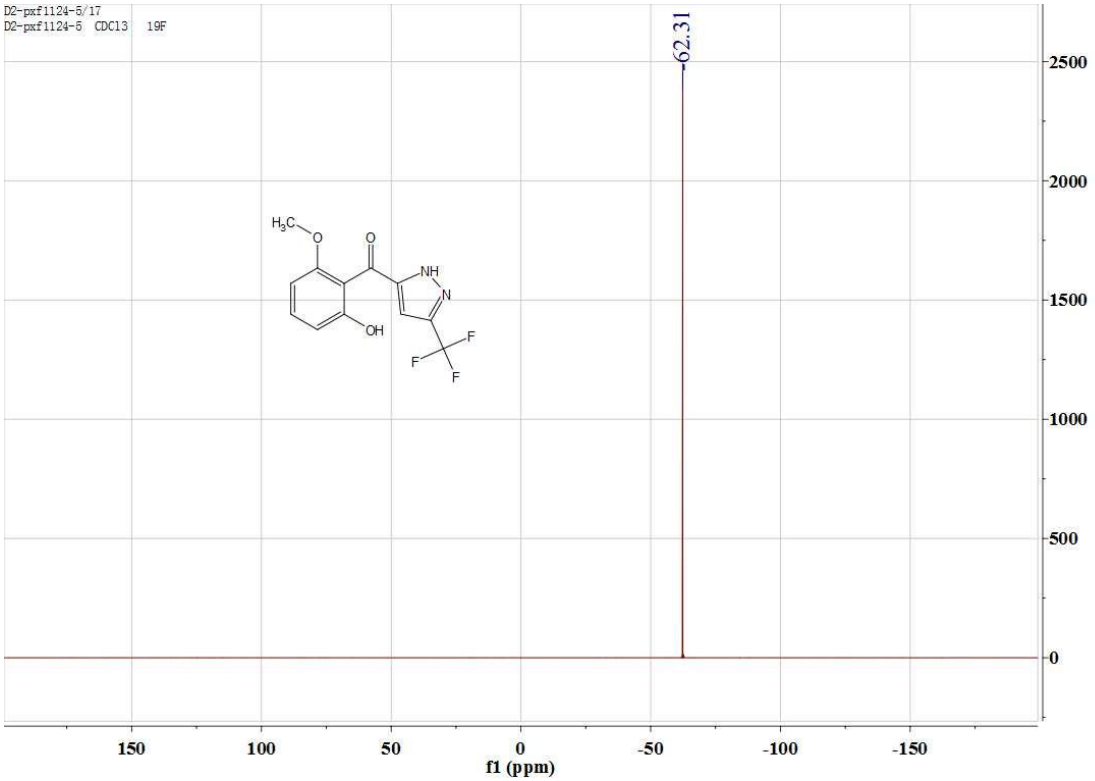
^{1}H NMR spectrum of **3s**



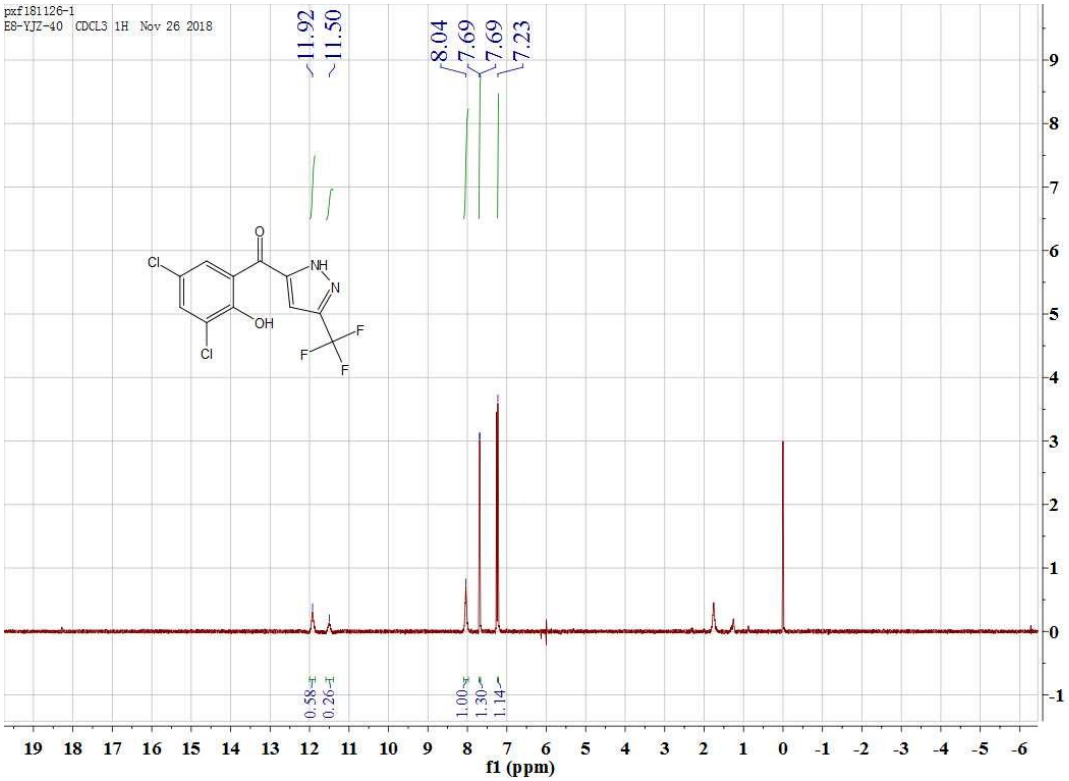
^{13}C NMR spectrum of **3s**



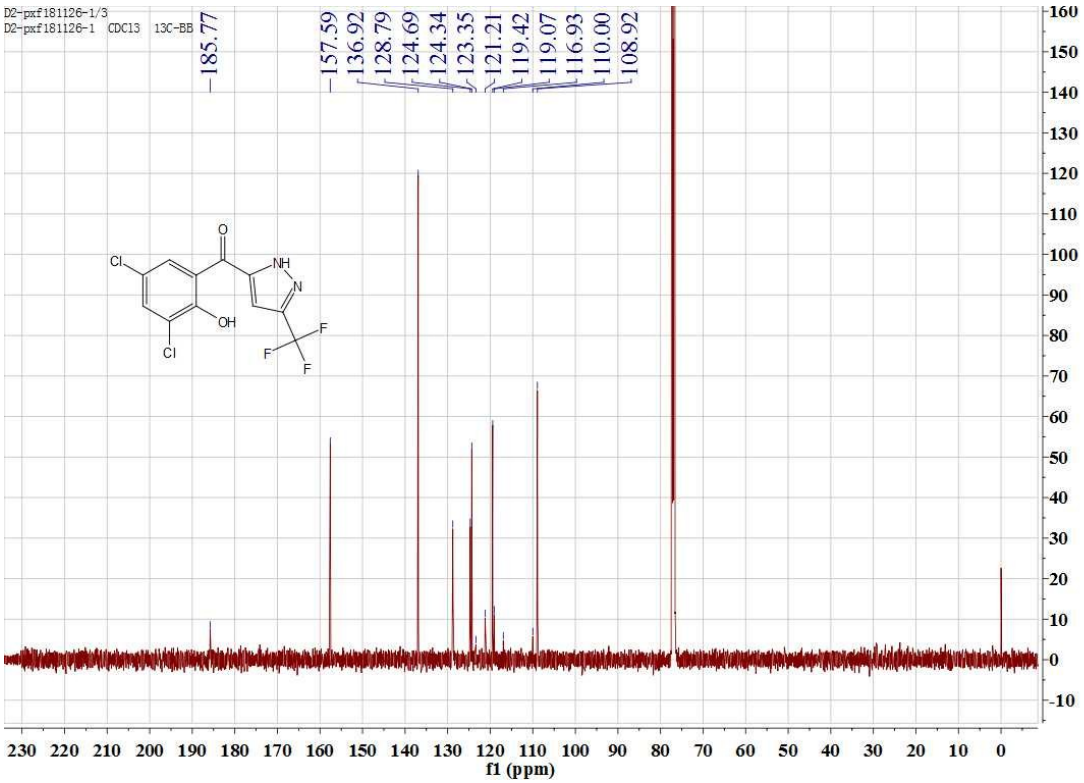
^{19}F NMR spectrum of **3s**



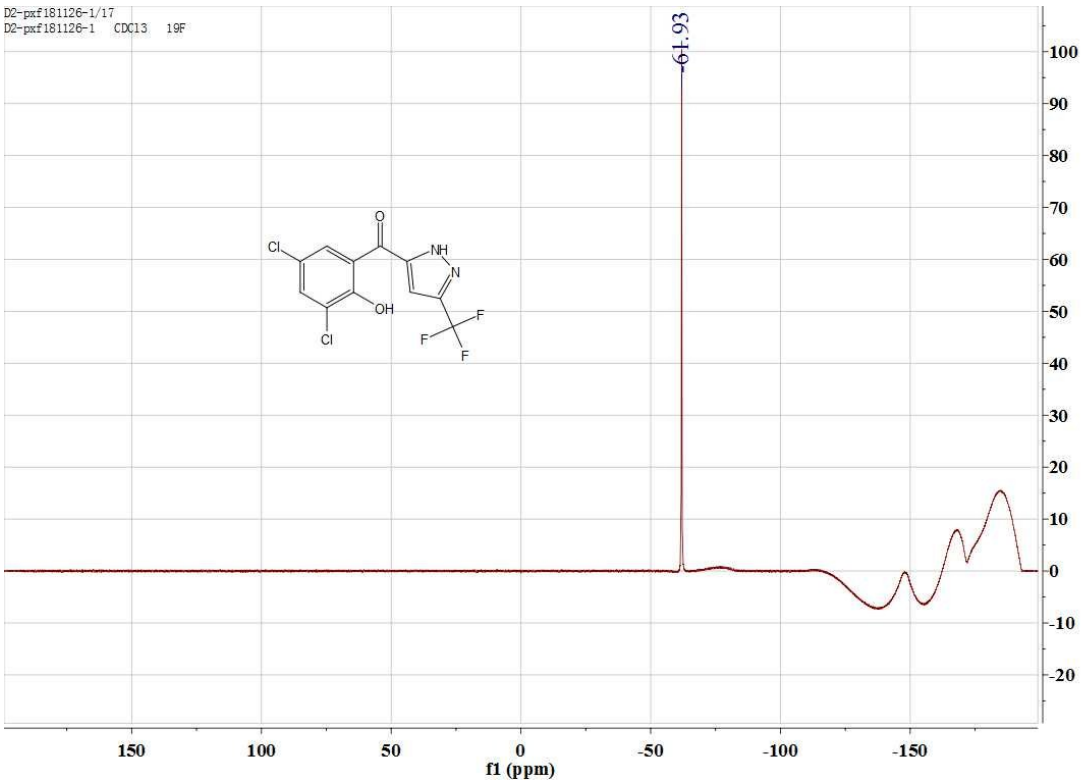
^{1}H NMR spectrum of **3t**



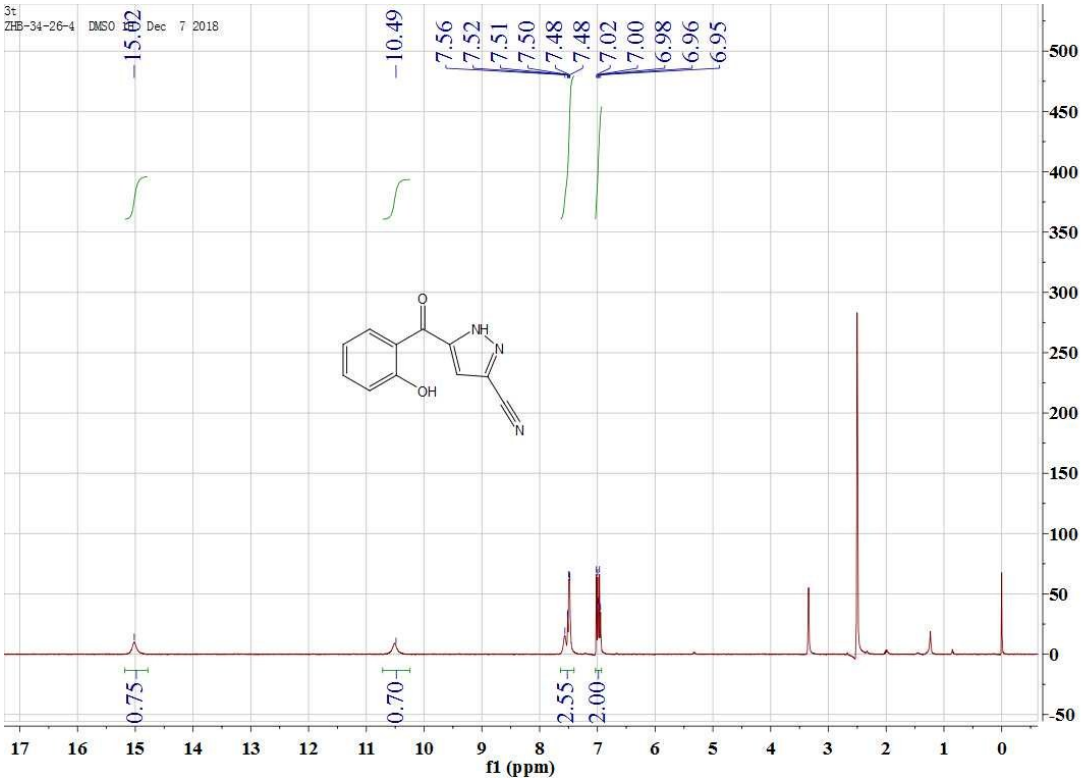
^{13}C NMR spectrum of **3t**



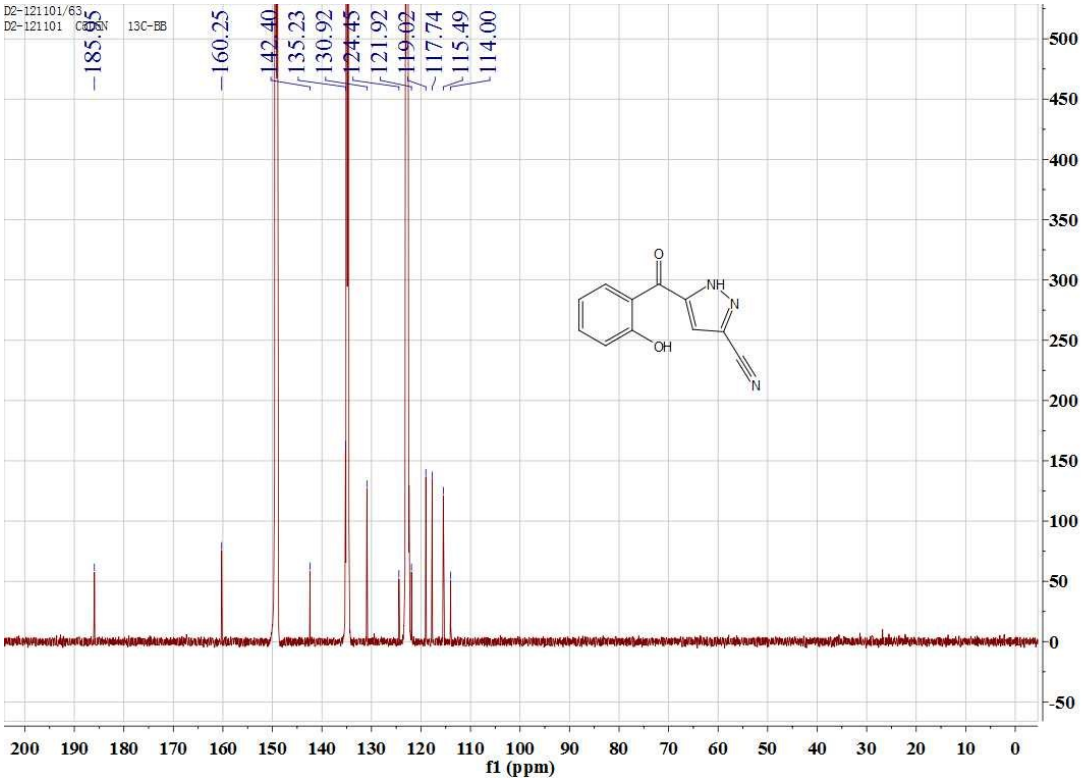
^{19}F NMR spectrum of **3t**



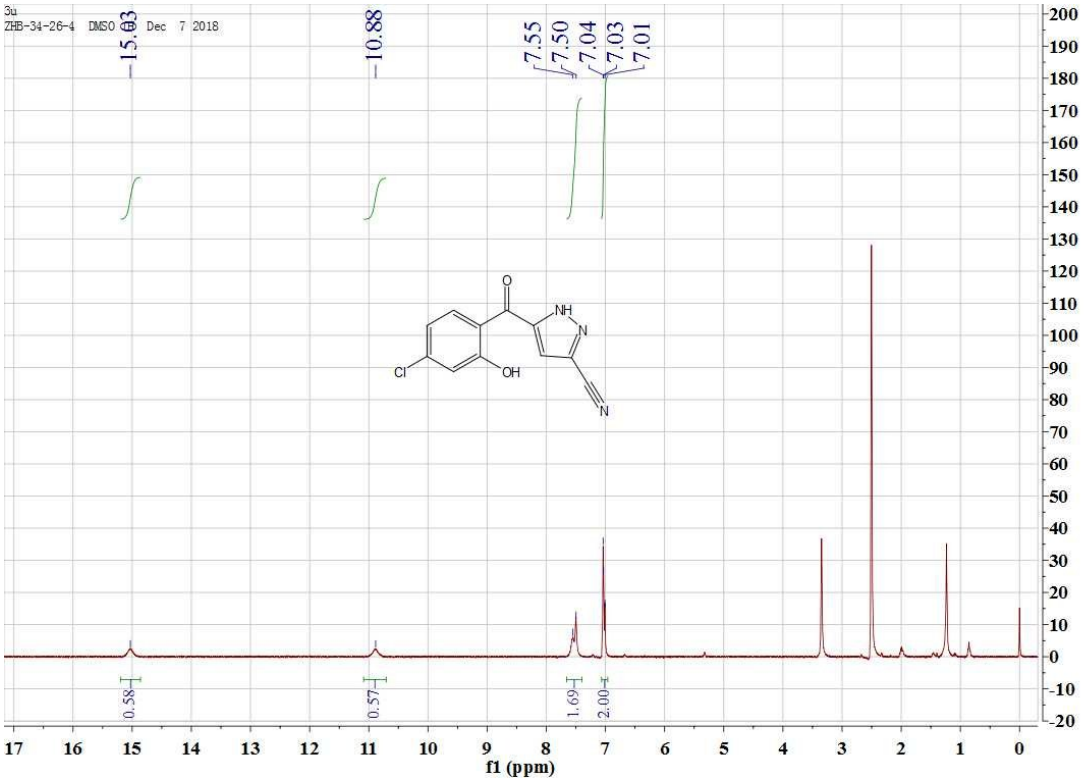
^{1}H NMR spectrum of **3u**



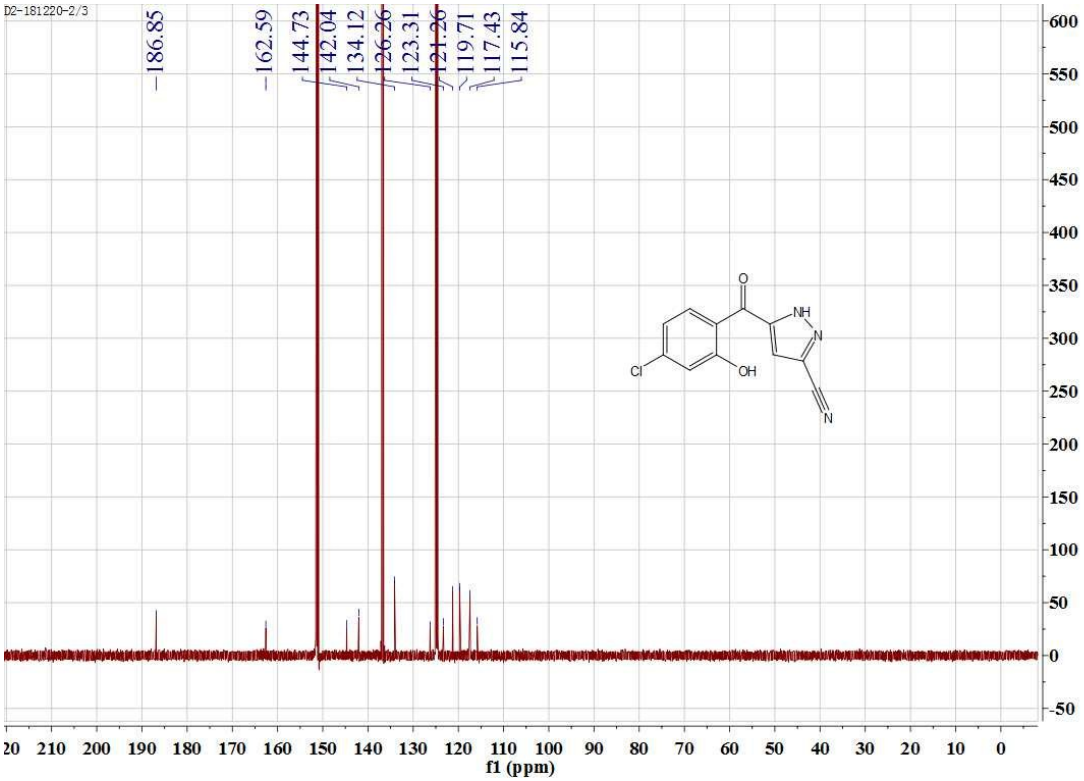
^{13}C NMR spectrum of **3u**



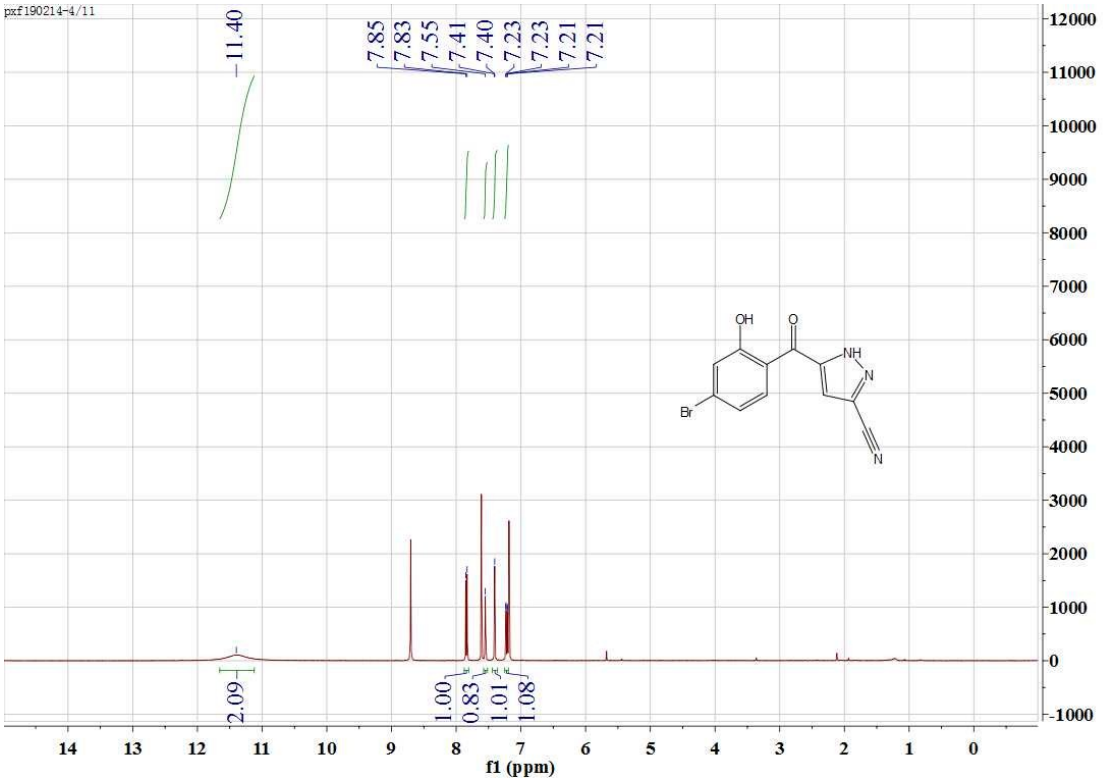
^{1}H NMR spectrum of **3v**



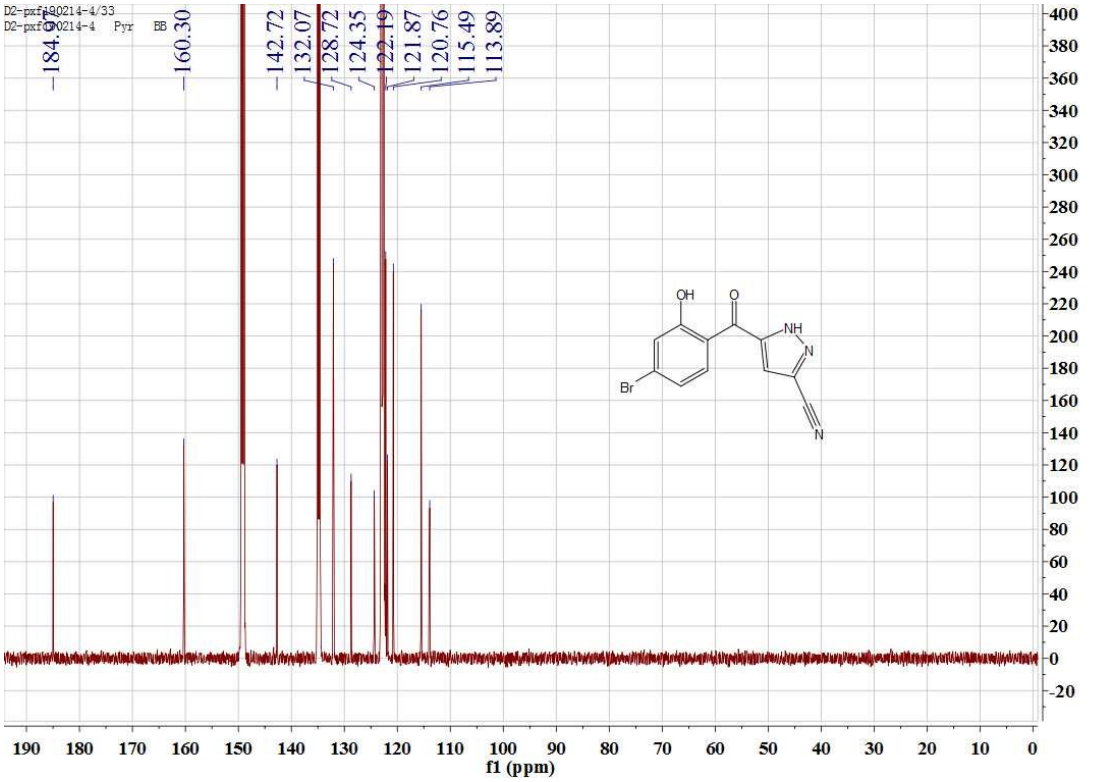
^{13}C NMR spectrum of **3v**



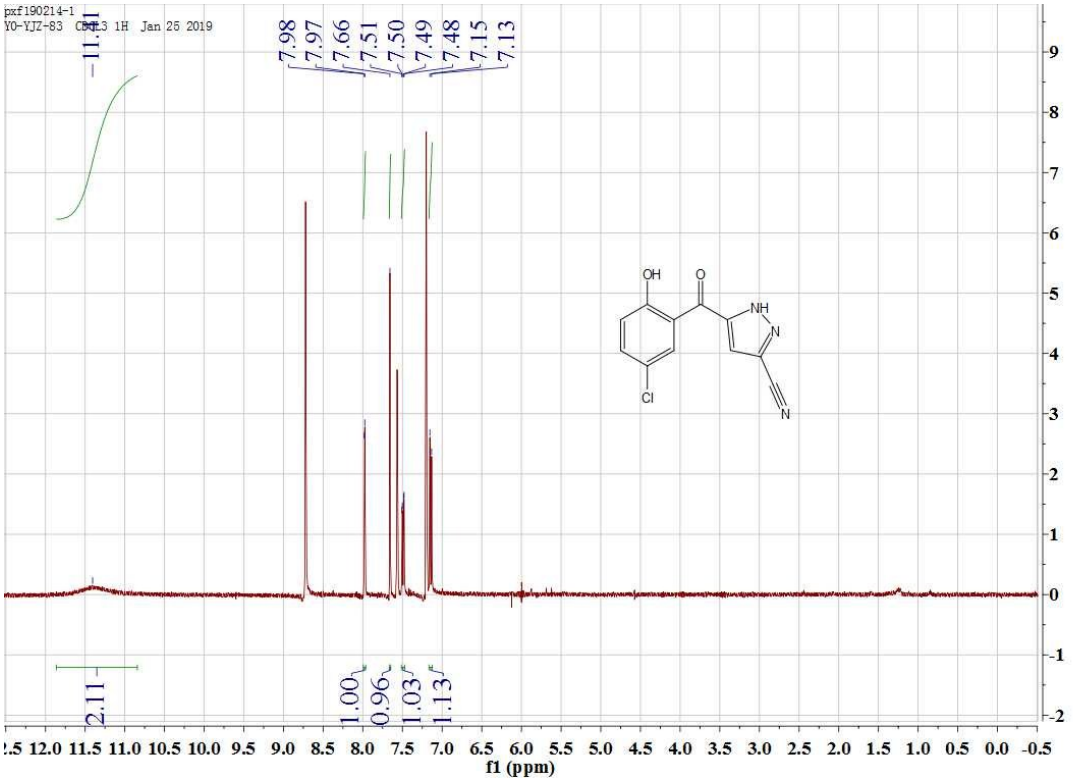
^{1}H NMR spectrum of **3w**



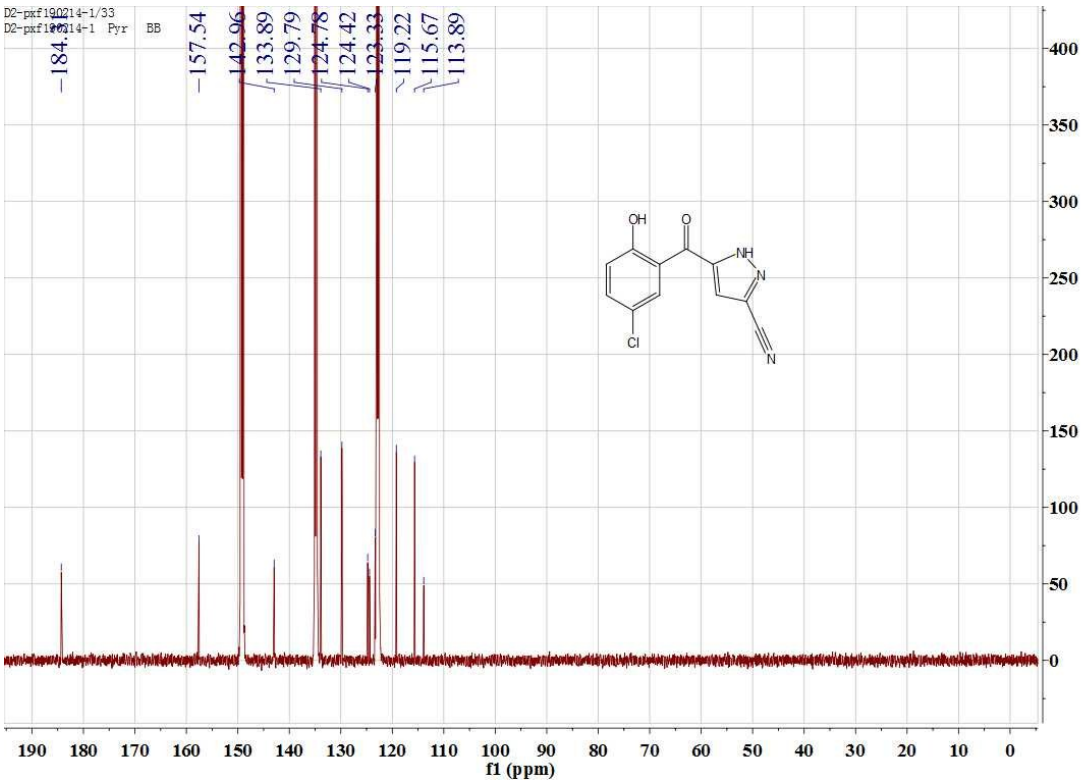
^{13}C NMR spectrum of **3w**



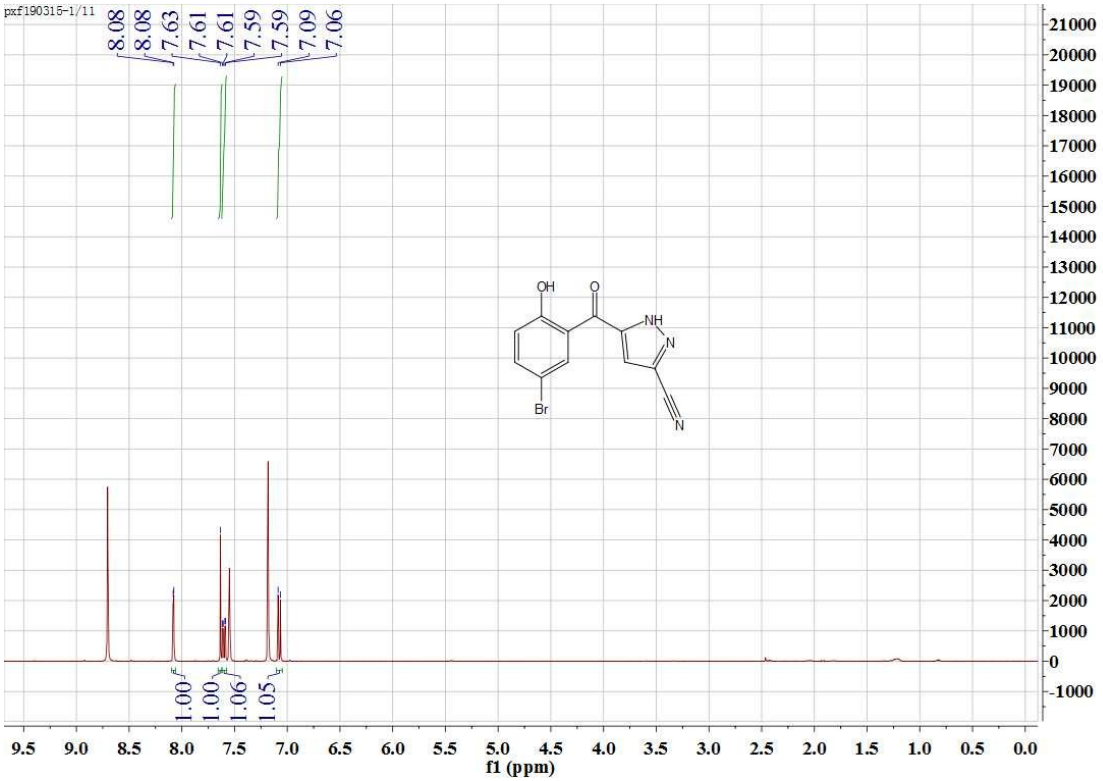
^{1}H NMR spectrum of **3x**



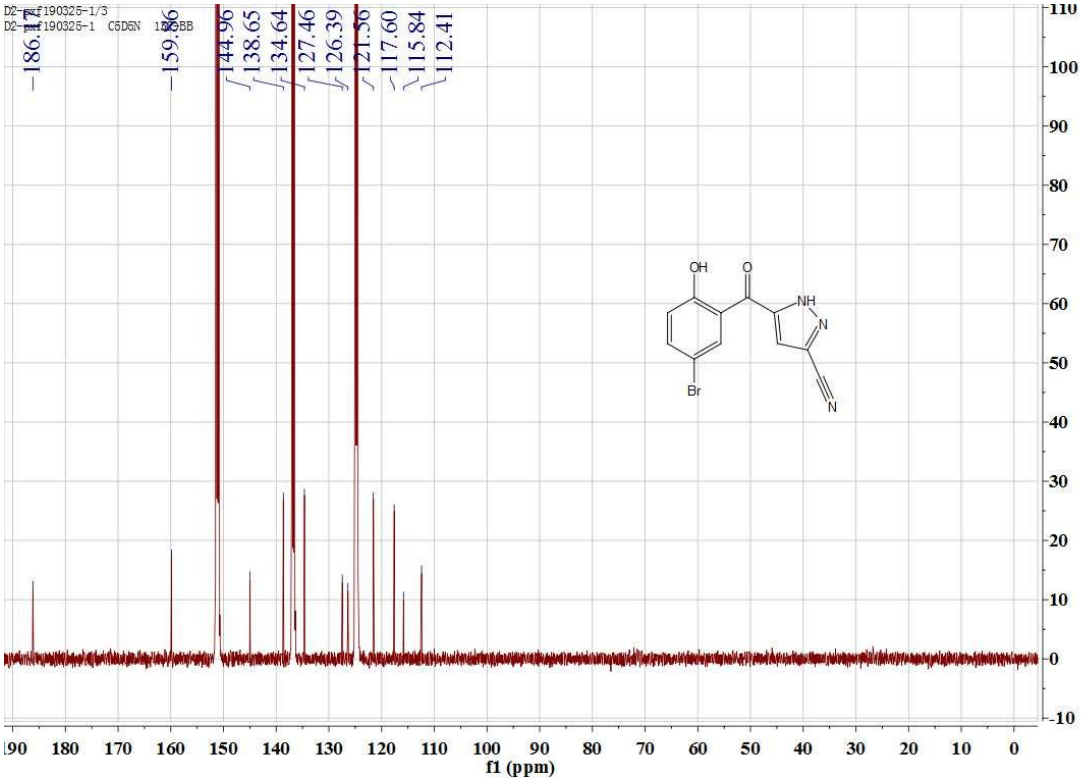
^{13}C NMR spectrum of **3x**



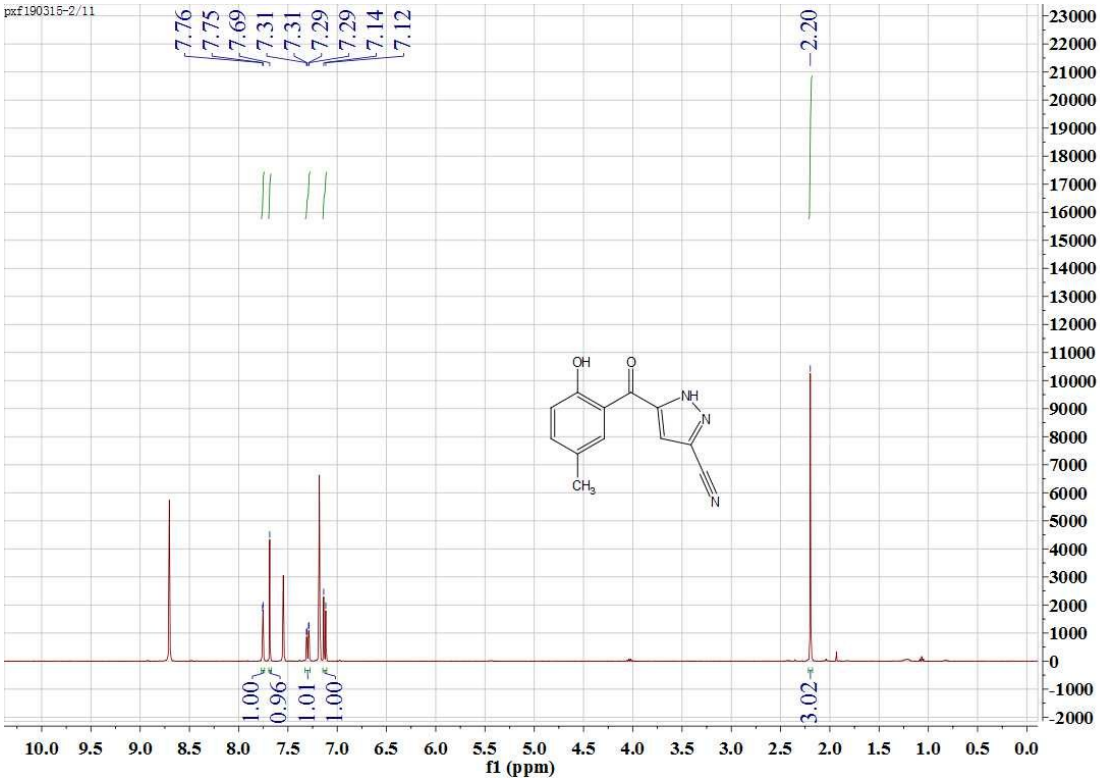
^{1}H NMR spectrum of **3y**



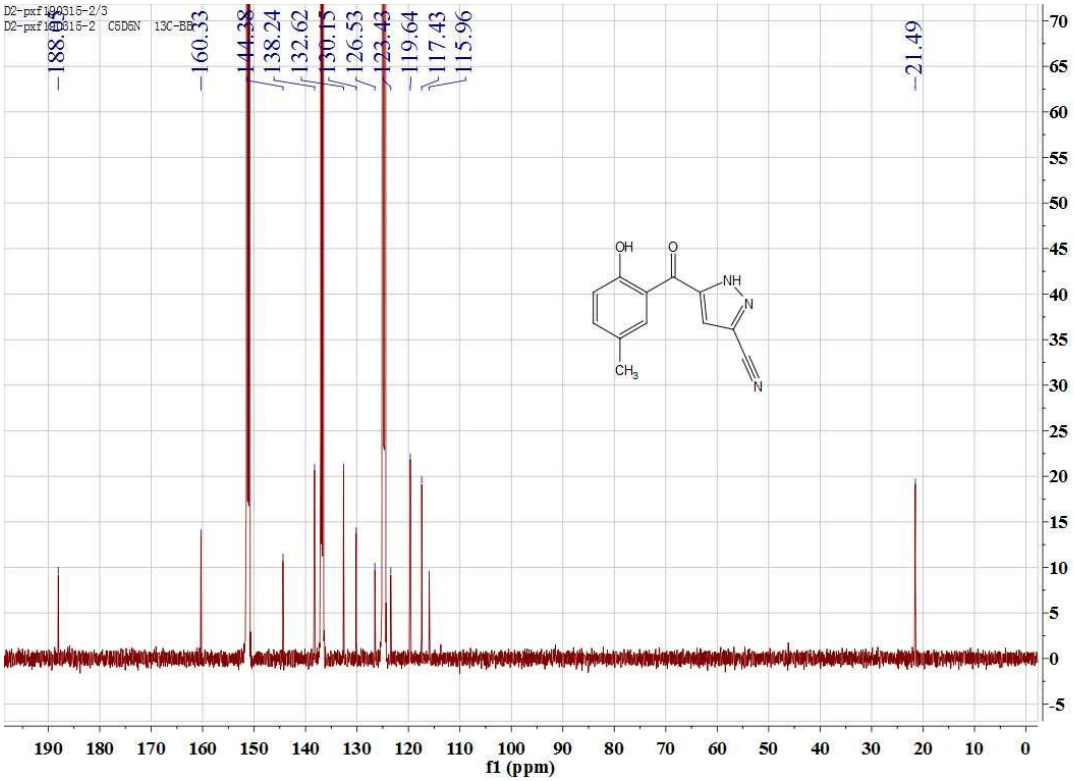
^{13}C NMR spectrum of **3y**



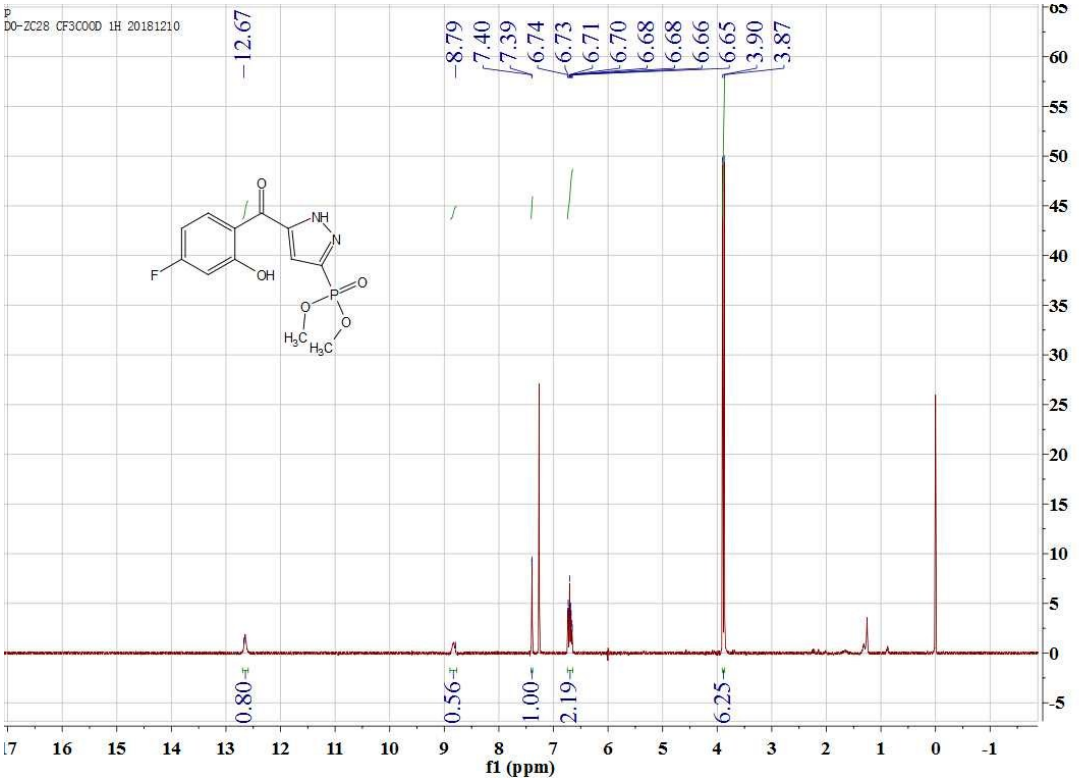
^{1}H NMR spectrum of **3z**



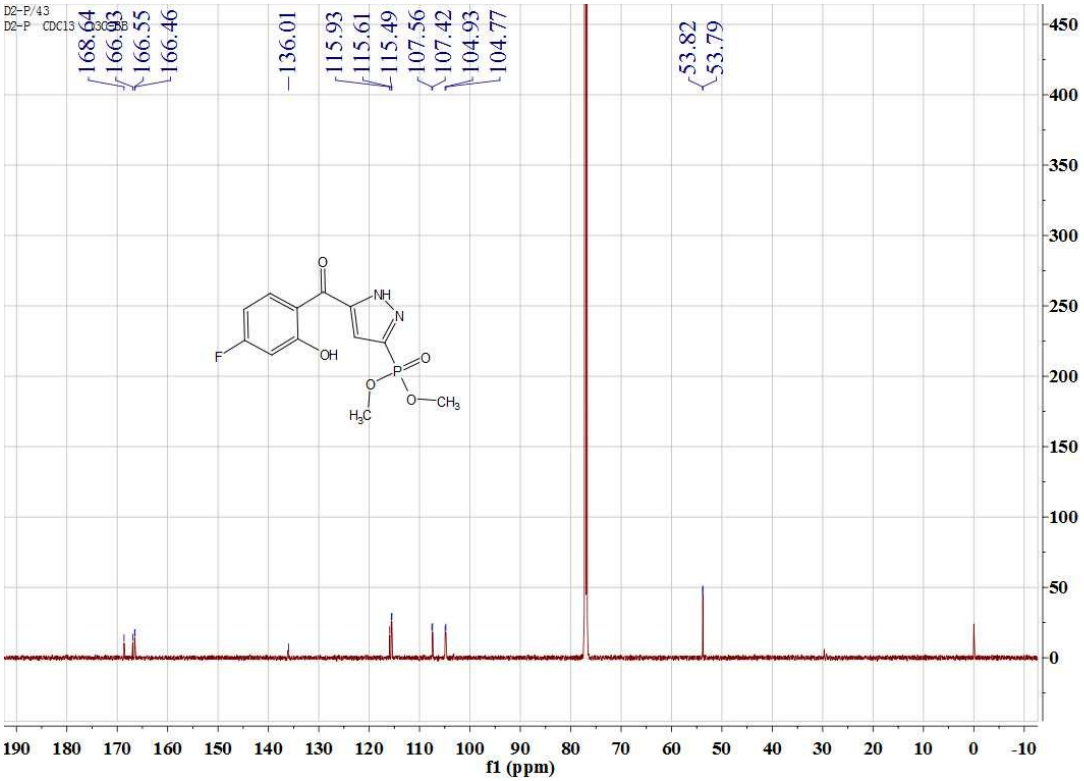
^{13}C NMR spectrum of **3z**



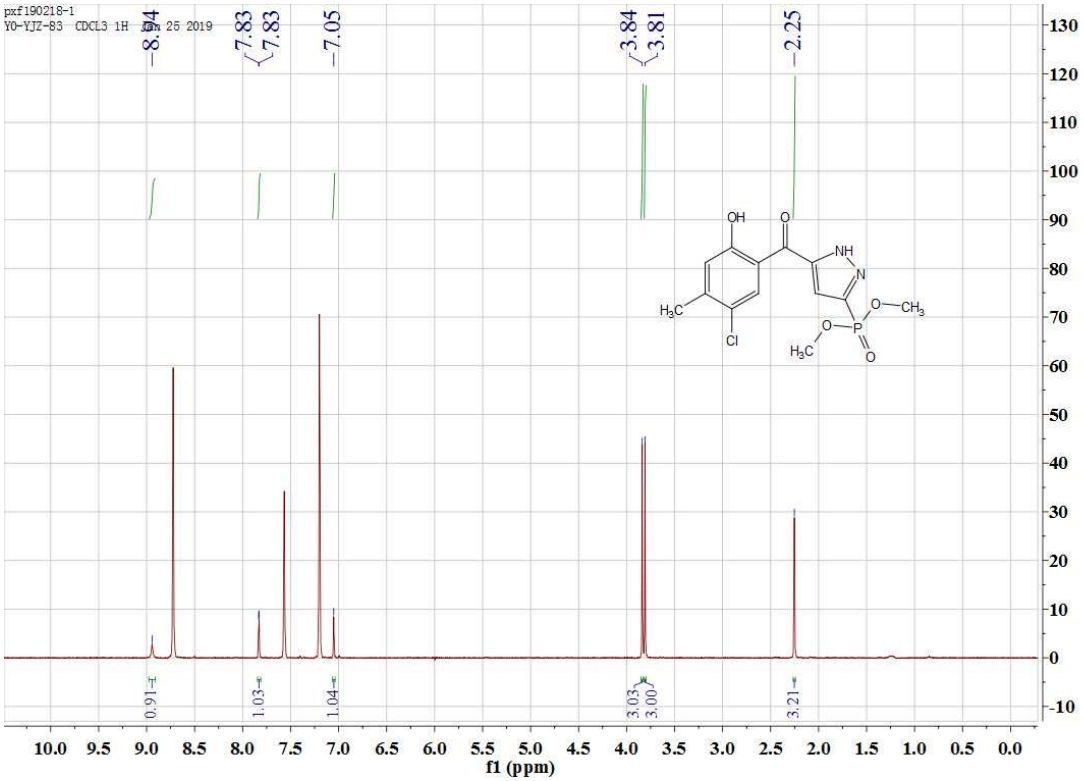
^{1}H NMR spectrum of **3a'**



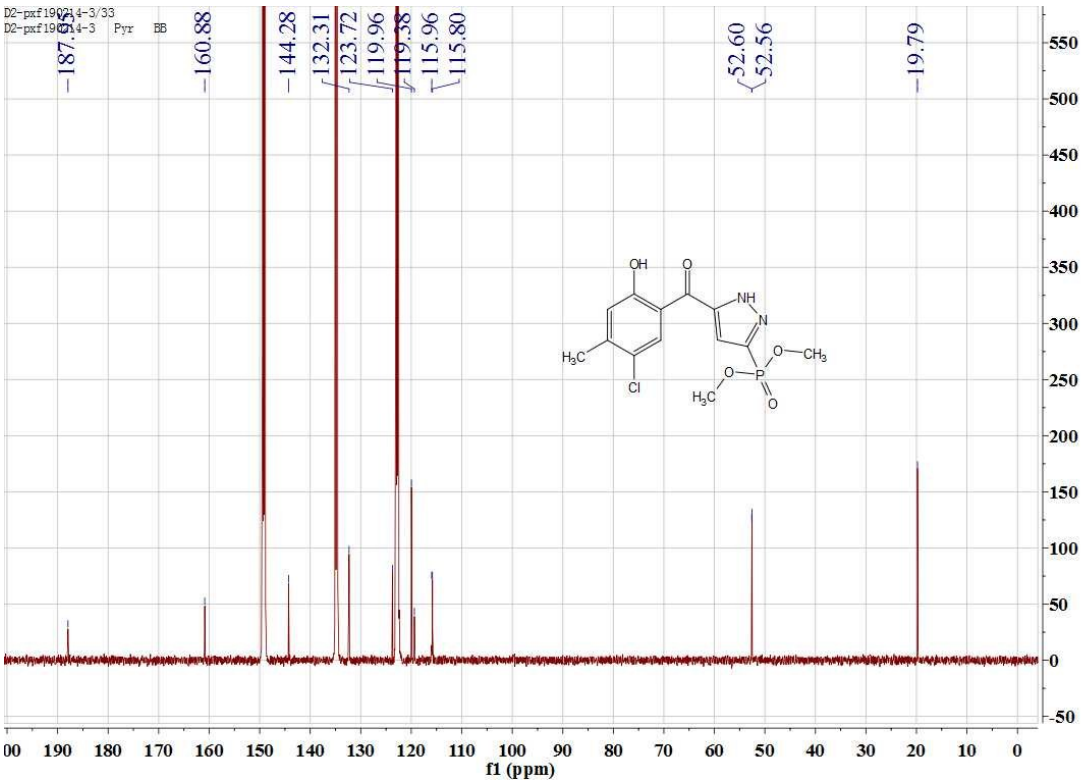
^{13}C NMR spectrum of **3a'**



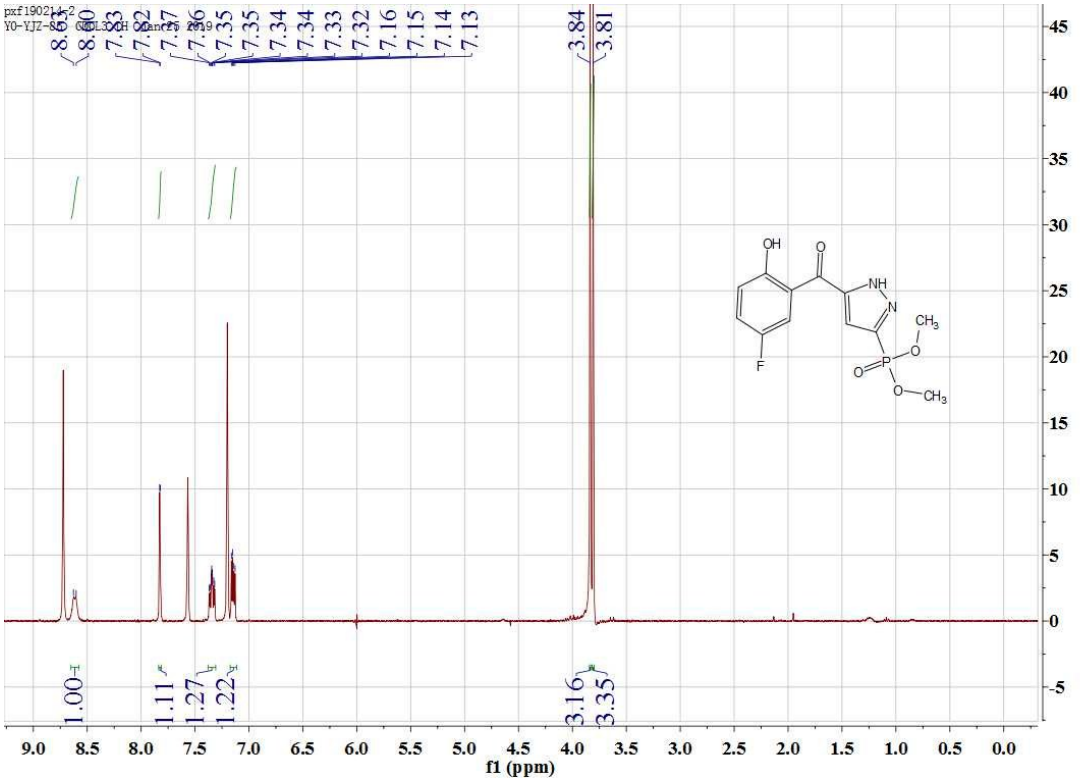
^{1}H NMR spectrum of **3b'**



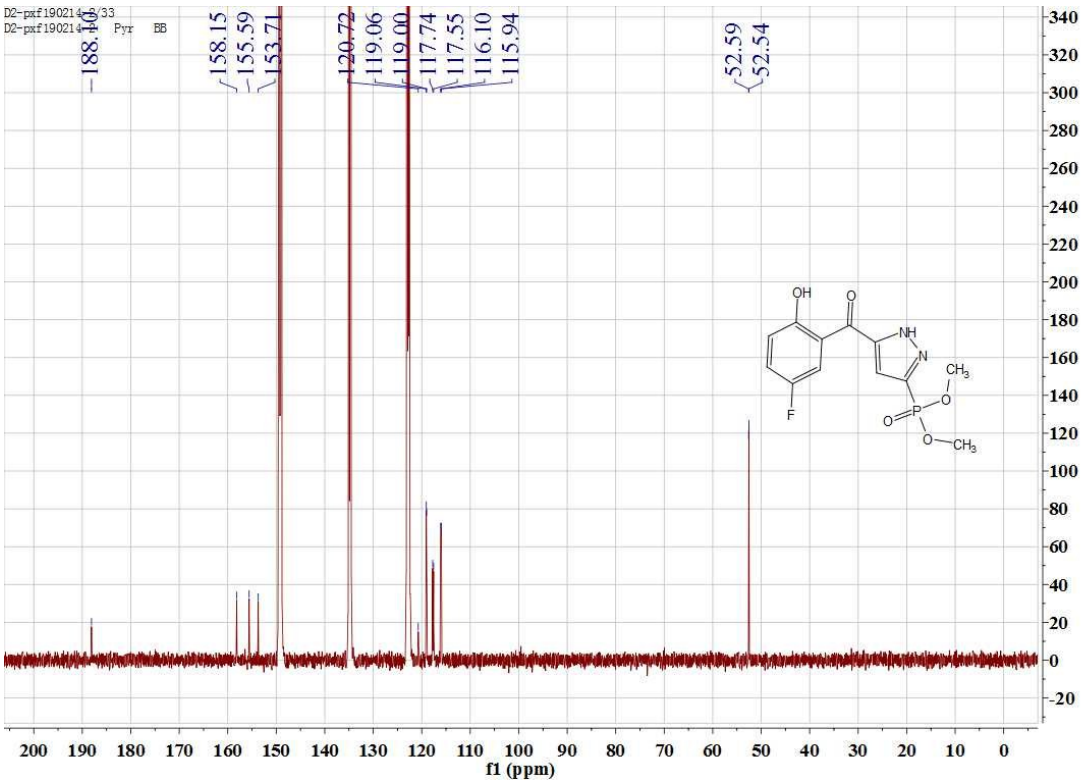
^{13}C NMR spectrum of **3b'**



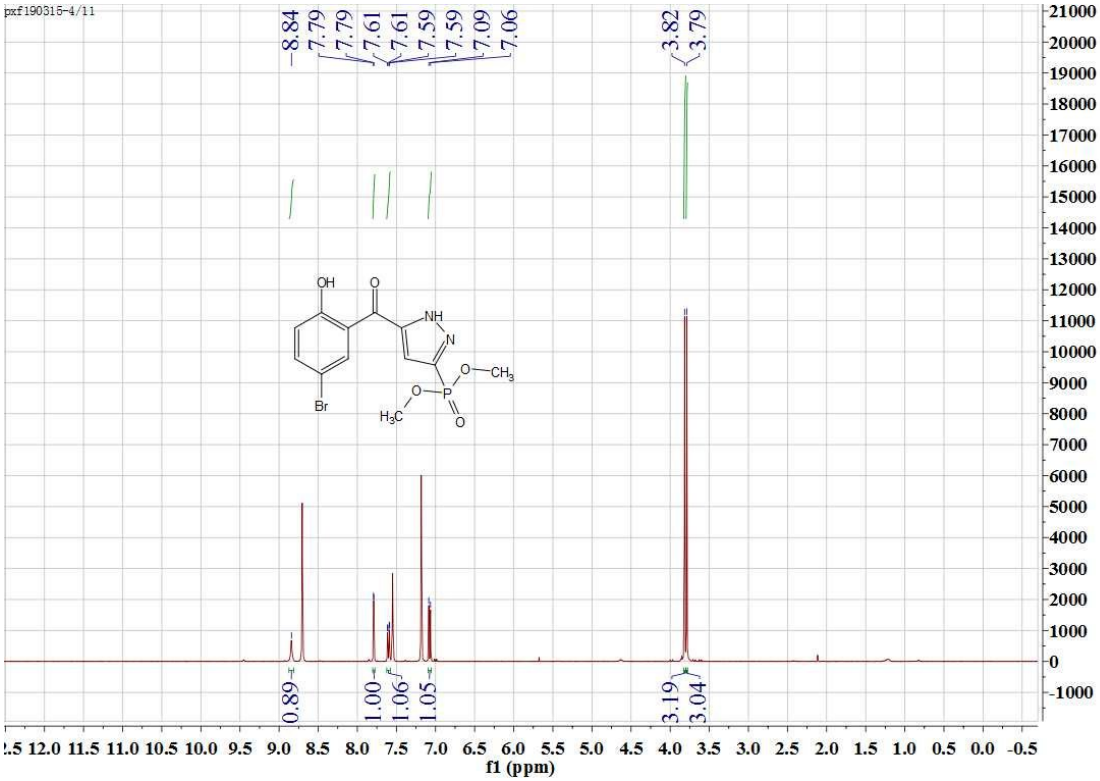
^{1}H NMR spectrum of **3c'**



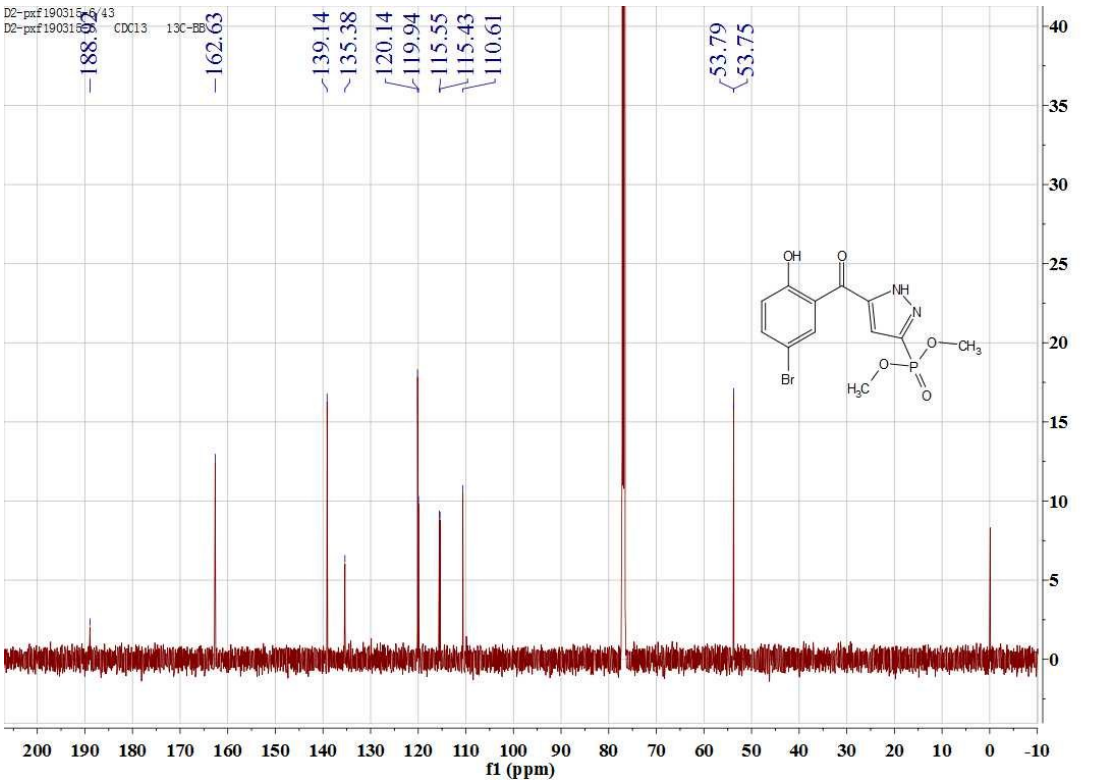
^{13}C NMR spectrum of **3c'**



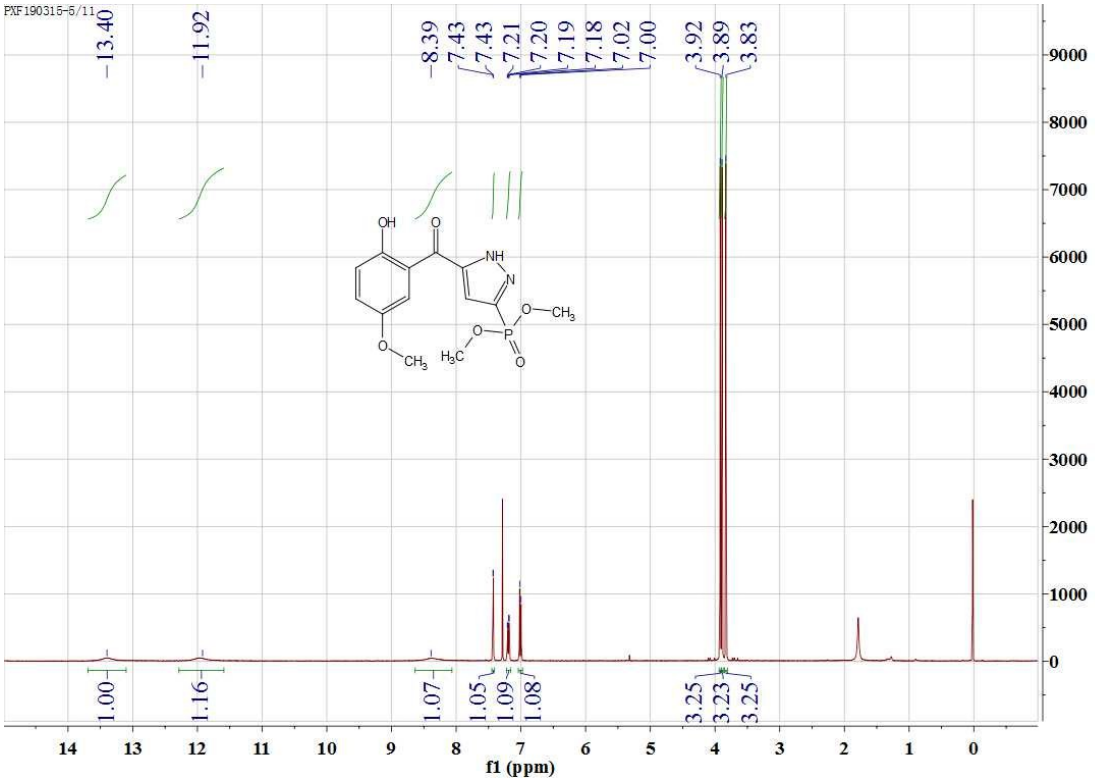
^{1}H NMR spectrum of **3d'**



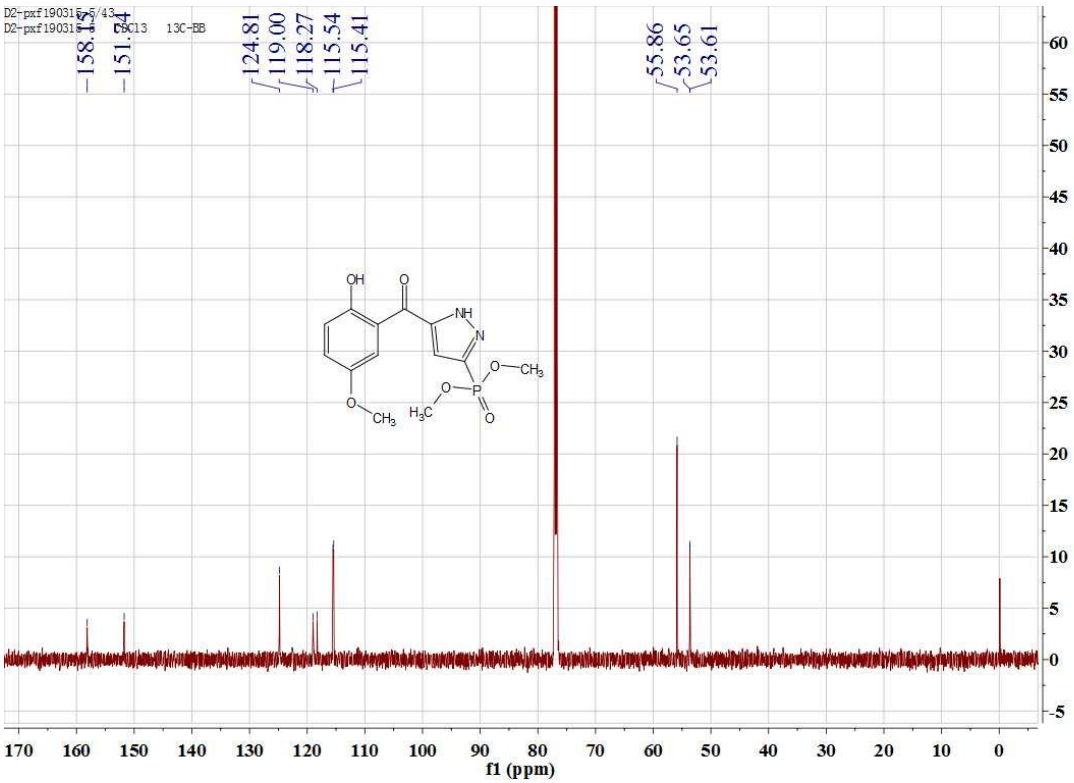
^{13}C NMR spectrum of **3d'**



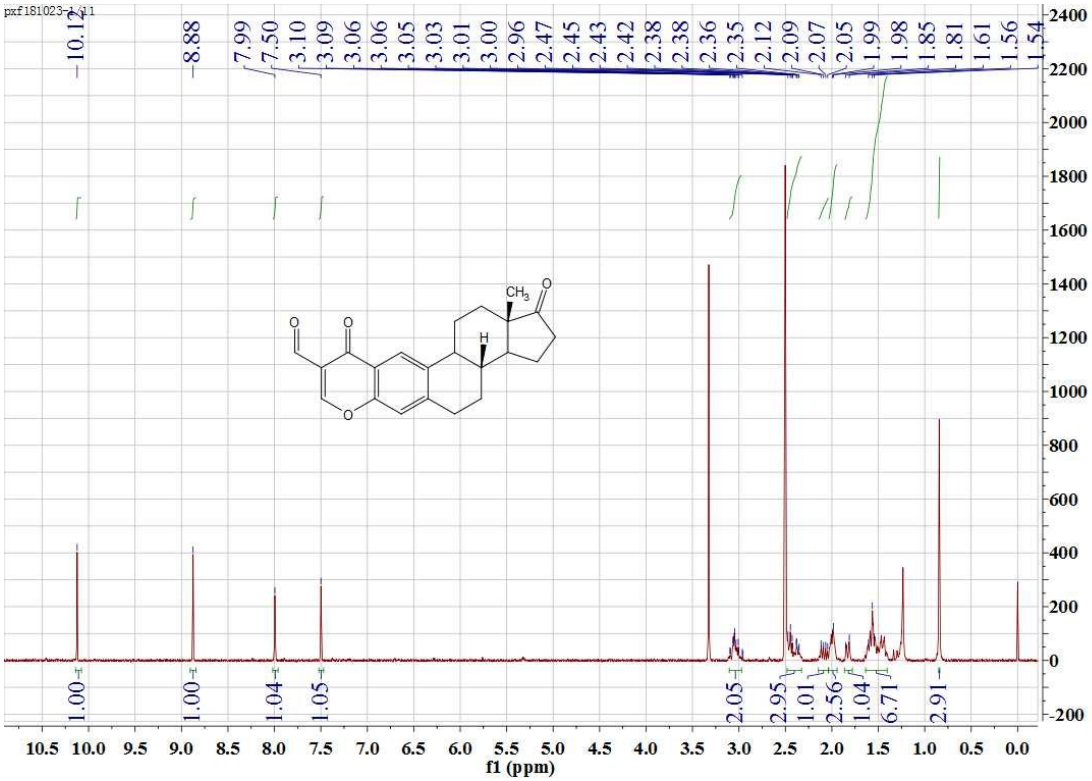
^{1}H NMR spectrum of **3e'**



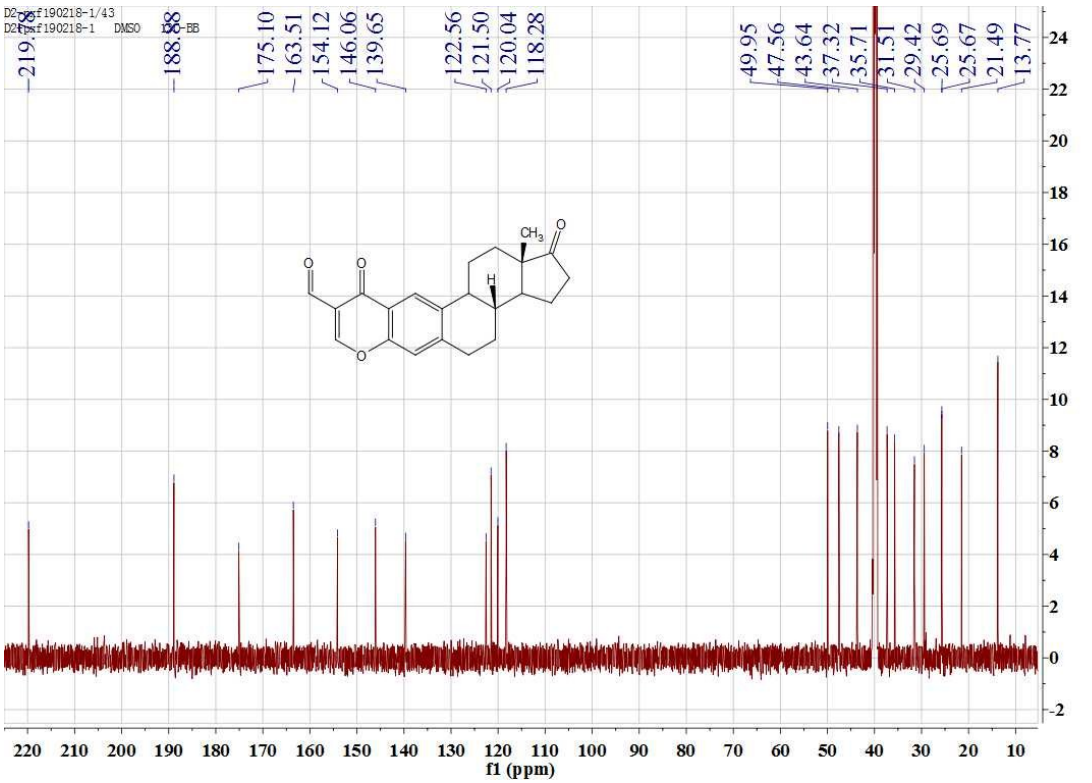
^{13}C NMR spectrum of **3e'**



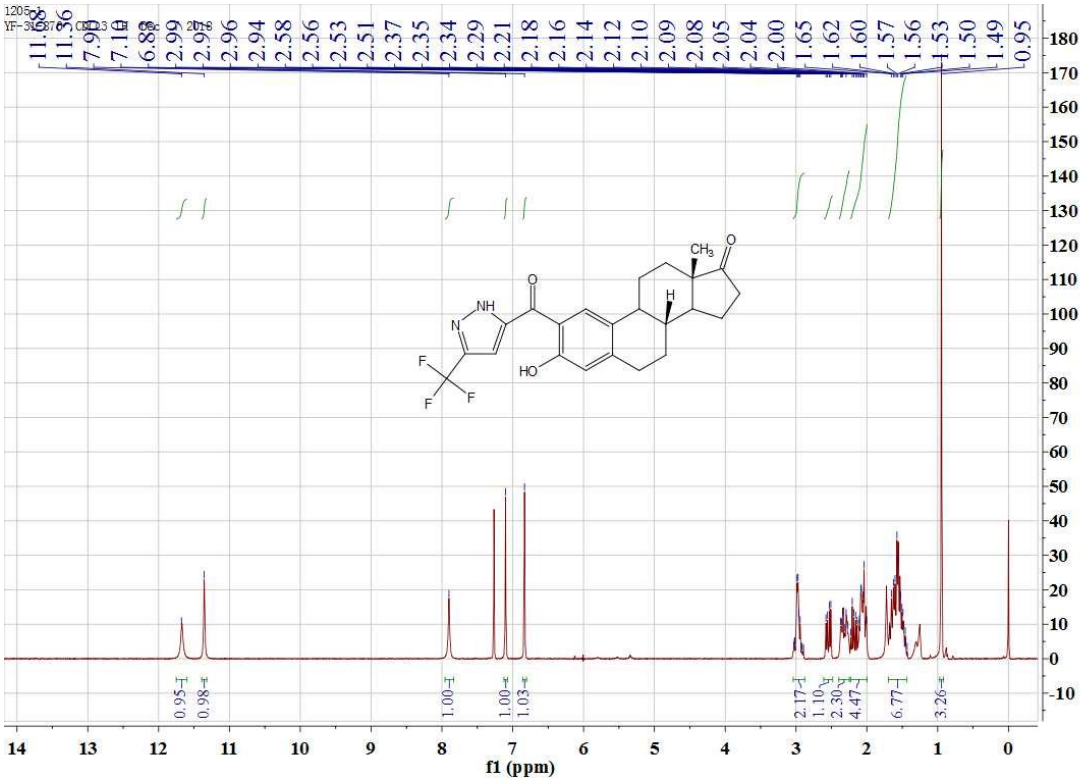
^{1}H NMR spectrum of **8**



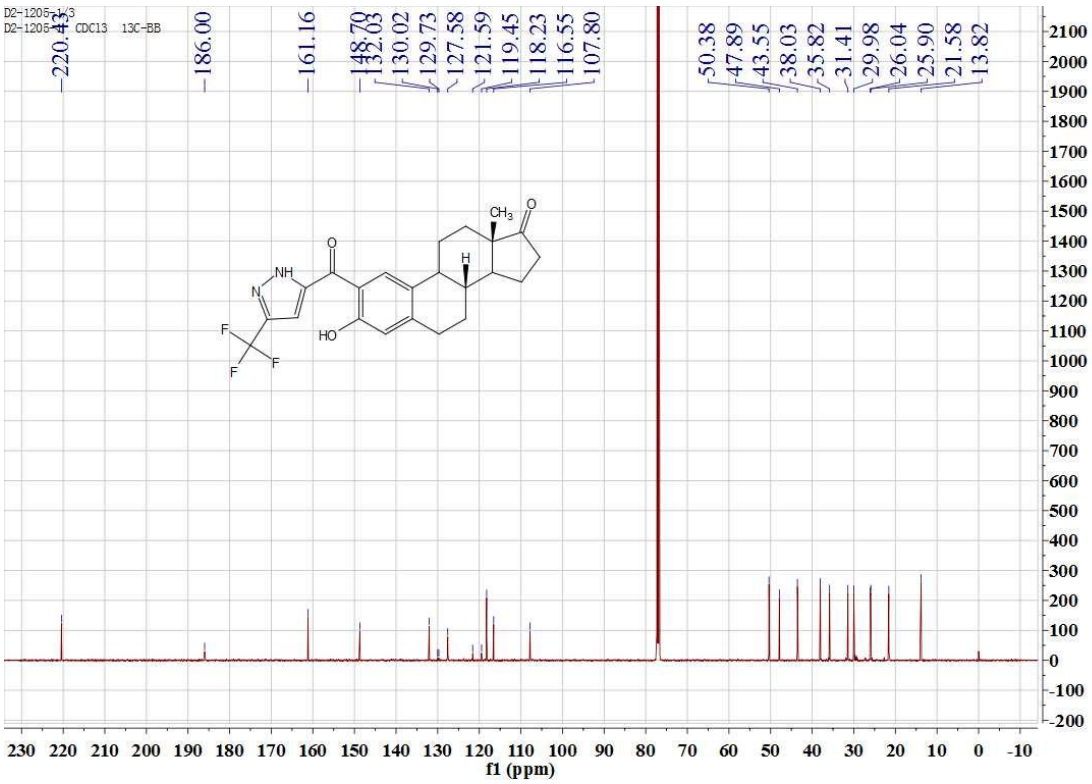
^{1}H NMR spectrum of **8**



^{1}H NMR spectrum of **9**



^{13}C NMR spectrum of **9**



^{19}F NMR spectrum of **9**