

Supporting Information

Copper-Catalyzed Asymmetric Friedel-Crafts Hydroxyalkylation of Pyrazole-4,5-diones with 5-Aminoisoxazoles

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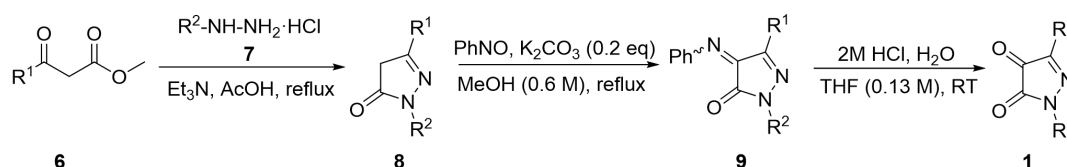
Part I Experimental Section

1.1 General information

^1H NMR and ^{13}C NMR were recorded on Bruker-500 MHz Spectrometer (^1H NMR: 500MHz, ^{13}C NMR: 125MHz, ^{19}F NMR: 470MHz) using TMS as internal reference. The chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz respectively. Uv-Vis Spectrophotometry was carried out on Shimadzu UV-3000. HPLC analysis was carried out on an Agilent 1260 series HPLC with a multiple wavelength detector. Chiralpak AD-H, IC were purchased from Daicel Chemical Industries, LTD. Optical rotations were measured on a PerKinElmerTM Polarimeter (Model 343). HRMS (ESI) were recorded on a WatersTM Q-TOF Premier. Single crystal data was collected at room temperature on a Rigaku Oxford Diffraction SuperNova with an AtlasS2 CCD using Cu K α radiation. Commercially available compounds were used without further purification. Commercially available compounds were used without further purification. All solvents were purified according to the standard procedures unless otherwise noted. Ligands **L**₁-**L**₄^[S1], **L**₁'^[S2], pyrazole-4,5-diones **1**^[S3], 5-aminoisoxazoles **2**^[S4] were prepared according to the literature procedures.

1.2 General procedure for the synthesis of substrate

1.2.1 General procedure for the synthesis of pyrazole-4,5-diones **1a-v**^[S5]



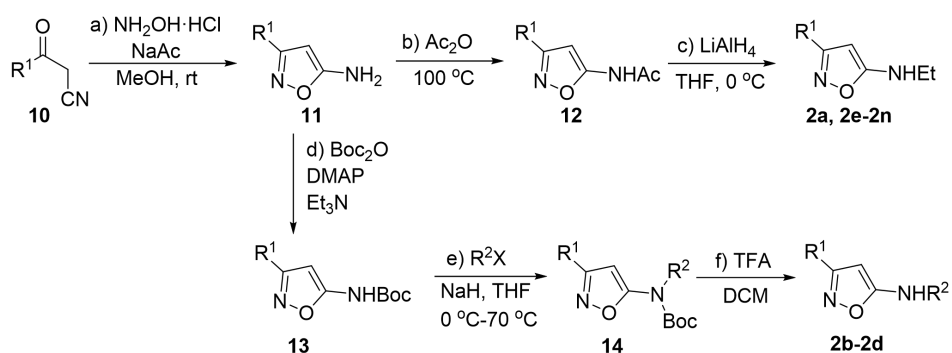
To a solution of **7** (20 mmol, 1.0 equiv.) in glacial acetic acid (30 mL) was added **6** (20 mmol, 1.0 equiv.) and Triethylamine (20 mmol, 1.0 equiv.). The reaction mixture was stirred at 110 °C until TLC (petroleum ether/ ethyl acetate = 2:1) showed complete consumption of the starting material. After cooling to room temperature, the mixture was quenched with a solution of saturated NaHCO_3 and extracted with EtOAc, the organic layer was washed with brine and dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **8**.

Add PhNO (1.0 equiv.) to a solution of pyrazolon derivative **8** (1.0 equiv.) in MeOH (0.6 M) and the K_2CO_3 (0.2 equiv.) was added at once, the mixture was

refluxed for 3 hours. The solvent was removed under reduced pressure and the crude product was directly purified by flash column chromatography (petroleum ether/ ethyl acetate = 30:1) to afford the desired product **9**.

To a solution of pyrazolon-derived phenyl-ketimine **9** in THF (0.13 M), 2 M HCl was added and stirring at room temperature. After stirring for 10 minutes - 5.5 hours, water was added. The reaction mixture was extracted with DCM (3×20 mL) and the combined organic layers were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was directly purified by flash column chromatography (petroleum ether/ ethyl acetate = 20:1) to afford the desired product **1**.

1.2.2 General procedure for the synthesis of 5-aminoisoxazoles **2a-n** [S4]



a) NH₂OH · HCl (1.3 g, 18.8 mmol) and NaOAc (1.55 g, 18.8 mmol) were stirred in MeOH (20 mL) at room temperature for 1 hour and then the compound **10** (6.3 mmol) was added to the mixture. The reaction mixture was stirred at room temperature overnight. Then the reaction mixture was quenched with water and extracted with EtOAc, the organic layer was washed with brine and dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **11**.

b) Compound **11** (500 mg, 3 mmol) was stirred in acetic anhydride (6 mL) at 100 °C for 2h. The reaction mixture was quenched with a solution of saturated NaHCO₃ and extracted with EtOAc, the organic layer was washed with brine and dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **12**.

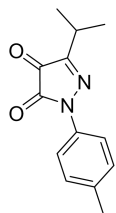
c) The compound **12** (500 mg, 2 mmol) was dried in vacuum and then dissolved in dry THF (10 mL) at 0 °C. Lithium aluminium hydride (240 mg, 6 mmol) was added during 20 minutes. The reaction was then stirred at room temperature overnight. Next, the reaction mixture was quenched by slow addition of 1M NaOH solution at 0 °C. The mixture was stirred for 30 minutes and then filtered through a pad of Celite. The filtrate was extracted with EtOAc, the organic layer was washed with brine and dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **2a, 2e-n**.

d) To a solution of compound **11** (1 g, 4 mmol), Boc₂O (2.3 g, 10 mmol) and DMAP (50 mg, 0.4 mmol) in 30 mL of DCM add triethylamine (1.27 g, 12 mmol) dropwise and stirred overnight at room temperature. The reaction was diluted with DCM. The organic layer was washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. (PE/EA = 10/1) to give compound **13** as a white solid.

e) To a stirred solution of **13** (1 mmol) in dry THF (5 mL) at 0°C, NaH(80 mg, 2 mmol) was added and stirred for 30 min. R₂X (2 mmol) was added dropwise to the reaction mixture. The reaction mixture was then stirred at 70 °C overnight. The reaction mixture was quenched with EtOAc, washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **14**.

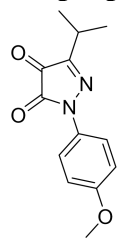
f) To a stirred solution of **14** (1 mmol) in DCM at room temperature, TFA(5 mmol) was added and stirred for 8h. The reaction mixture was quenched with a solution of saturated NaHCO₃ and extracted with DCM, the organic layer was washed with brine and dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography to afford **2b-d**.

3-isopropyl-1-(p-tolyl)-1H-pyrazole-4,5-dione(1d)



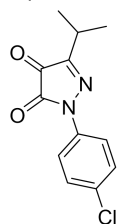
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.75 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 2.94 (hept, J = 6.9 Hz, 1H), 2.37 (s, 3H), 1.33 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.8, 151.1, 149.0, 136.1, 134.6, 129.7, 117.8, 26.9, 21.1, 19.0.

3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazole-4,5-dione(1e)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.75 (m, 2H), 7.00-6.94 (m, 2H), 3.84 (s, 3H), 2.94 (hept, J = 6.9 Hz, 1H), 1.33 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 185.0, 157.8, 151.1, 148.8, 130.3, 119.6, 114.3, 55.5, 26.9, 19.0.

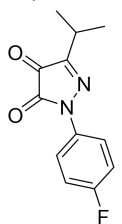
1-(4-chlorophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1f)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.90-7.84 (m, 2H), 7.44-7.38 (m, 2H), 2.96 (hept, J = 7.0 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.2, 151.6, 149.1, 135.5, 131.4,

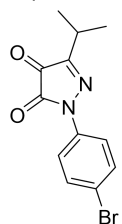
129.3, 118.8, 26.9, 19.0.

1-(4-fluorophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1g)



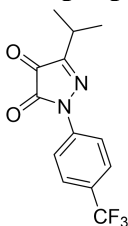
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.91-7.84 (m, 2H), 7.18-7.10 (m, 2H), 2.96 (hept, J = 6.9 Hz, 1H), 1.33 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.4, 160.5 (d, J = 246.3 Hz), 151.4, 149.0, 133.1 (d, J = 3.0 Hz), 119.6 (d, J = 8.4 Hz), 116.0 (d, J = 23.0 Hz), 26.9, 19.0. ¹⁹F NMR (470 MHz, CDCl₃) δ -115.29.

1-(4-bromophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1h)



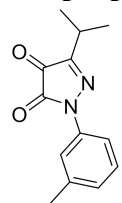
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H), 2.96 (hept, J = 7.0 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.2, 151.6, 149.1, 136.0, 132.2, 119.2, 119.1, 26.9, 19.0.

3-isopropyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4,5-dione(1i)



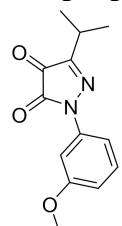
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.9 Hz, 2H), 2.99 (hept, J = 6.9 Hz, 1H), 1.35 (s, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 183.8, 152.0, 149.4, 139.6, 127.8 (q, J = 32.7 Hz), 126.5 (q, J = 4.0 Hz), 123.9 (q, J = 272.0 Hz), 117.3, 27.0, 19.0. ¹⁹F NMR (470 MHz, CDCl₃) δ -62.31.

3-isopropyl-1-(m-tolyl)-1H-pyrazole-4,5-dione(1k)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.51-7.44 (m, 2H), 7.12 (t, J = 7.8 Hz, 1H), 6.90-6.84 (m, 1H), 2.74 (hept, J = 6.9 Hz, 1H), 2.21 (s, 3H), 1.13 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.7, 151.2, 149.2, 139.2, 136.9, 129.0, 127.1, 118.3, 115.0, 26.9, 21.7, 19.1.

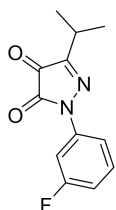
3-isopropyl-1-(3-methoxyphenyl)-1H-pyrazole-4,5-dione(1l)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.74-7.67 (m, 2H), 7.55 (t, J = 8.2 Hz, 1H), 7.01 (ddd, J = 8.3, 2.4, 0.9 Hz, 1H), 4.06 (s, 3H), 3.16 (hept, J = 6.9 Hz, 1H), 1.54 (d, J = 7.0 Hz, 6H). ¹³C NMR (125

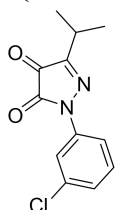
MHz, CDCl₃) δ 183.4, 159.1, 150.2, 148.1, 137.0, 129.0, 110.7, 108.9, 102.5, 54.4, 25.8, 18.0.

1-(3-fluorophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1m)



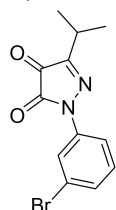
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.75 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 7.67 (dt, J = 10.5, 2.3 Hz, 1H), 7.41 (td, J = 8.3, 6.3 Hz, 1H), 6.97 (tdd, J = 8.3, 2.5, 0.9 Hz, 1H), 2.97 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.0, 162.9 (d, J = 245.5 Hz), 151.6, 149.2, 138.2 (d, J = 10.5 Hz), 130.5 (d, J = 9.1 Hz), 112.9 (d, J = 3.7 Hz), 112.9 (d, J = 21.1 Hz), 105.1 (d, J = 27.5 Hz), 26.9, 19.0. ¹⁹F NMR (470 MHz, CDCl₃) δ -110.38.

1-(3-chlorophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1n)



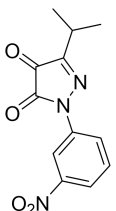
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 7.92-7.90 (m, 1H), 7.86 (ddd, J = 8.3, 2.1, 0.9 Hz, 1H), 7.41-7.34 (m, 1H), 7.24 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H), 2.97 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.0, 151.7, 149.2, 137.9, 135.0, 130.3, 126.2, 117.5, 115.5, 26.9, 19.0.

1-(3-bromophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1o)



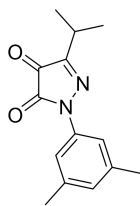
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 8.05 (t, J = 2.0 Hz, 1H), 7.91 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.39 (ddd, J = 8.1, 1.9, 1.1 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 2.97 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 184.0, 151.7, 149.2, 138.0, 130.5, 129.1, 122.9, 120.3, 116.0, 27.0, 19.0.

3-isopropyl-1-(3-nitrophenyl)-1H-pyrazole-4,5-dione(1q)



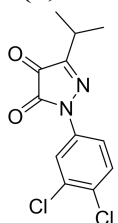
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ¹H NMR (500 MHz, CDCl₃) δ 8.74 (t, J = 2.2 Hz, 1H), 8.38 (ddd, J = 8.2, 2.1, 0.9 Hz, 1H), 8.13 (ddd, J = 8.1, 2.2, 1.0 Hz, 1H), 7.65 (t, J = 8.2 Hz, 1H), 3.02 (hept, J = 6.9 Hz, 1H), 1.37 (d, J = 6.9 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ 183.5, 152.2, 149.4, 148.7, 137.8, 130.3, 122.9, 120.6, 112.3, 27.0, 19.0.

1-(3,5-dimethylphenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1s)



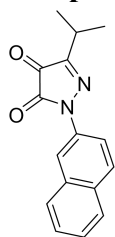
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ^1H NMR (500 MHz, CDCl_3) δ 7.49 (s, 2H), 6.91 (s, 1H), 2.94 (hept, $J = 6.9$ Hz, 1H), 2.37 (s, 6H), 1.33 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 183.7, 150.1, 148.1, 137.9, 135.8, 127.0, 114.5, 25.8, 20.5, 18.0.

1-(3,4-dichlorophenyl)-3-isopropyl-1H-pyrazole-4,5-dione(1t)



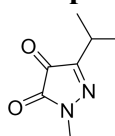
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ^1H NMR (500 MHz, CDCl_3) δ 8.03 (d, $J = 2.5$ Hz, 1H), 7.83 (dd, $J = 8.9, 2.7$ Hz, 1H), 7.50 (d, $J = 9.0$ Hz, 1H), 2.97 (hept, $J = 6.9$ Hz, 1H), 1.35 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 182.6, 150.9, 148.1, 135.1, 132.2, 129.8, 128.6, 118.0, 115.6, 25.9, 17.9.

3-isopropyl-1-(naphthalen-2-yl)-1H-pyrazole-4,5-dione(1u)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red solid. ^1H NMR (500 MHz, CDCl_3) δ 8.32 (s, 1H), 8.04 (dd, $J = 8.9, 2.2$ Hz, 1H), 7.92-7.80 (m, 3H), 7.54-7.43 (m, 2H), 2.96 (hept, $J = 6.9$ Hz, 1H), 1.36 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 184.6, 151.4, 149.3, 134.5, 133.3, 131.5, 129.2, 128.2, 127.8, 126.9, 126.0, 125.6, 116.8, 115.1, 27.0, 19.1.

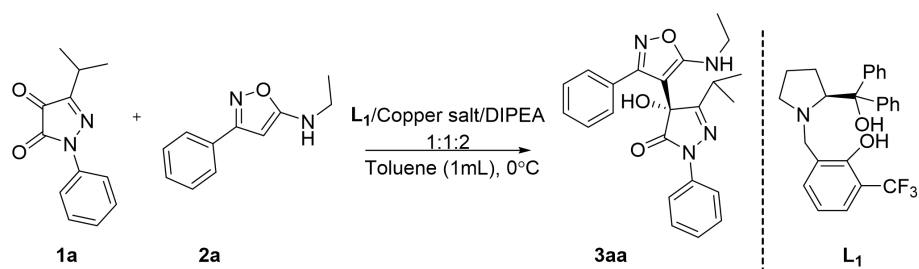
3-isopropyl-1-methyl-1H-pyrazole-4,5-dione(1v)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a red liquid. ^1H NMR (500 MHz, CDCl_3) δ 3.39 (s, 3H), 2.81 (hept, $J = 7.0$ Hz, 1H), 1.24 (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ 185.1, 150.4, 149.1, 31.8, 25.9, 18.4.

1.3 Optimization of reaction conditions.

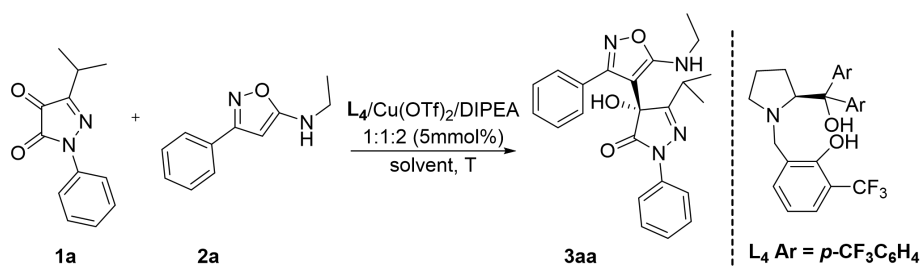
Table S1. Effects of copper salts ^a



Entry	Copper salt	Yield (%) ^b	ee (%) ^c
1	$CuSO_4 \cdot 5H_2O$	93	50
2	$Cu(NO_3)_2 \cdot 3H_2O$	90	50
3	$CuCl_2 \cdot 2H_2O$	92	45
4	$CuBr_2$	85	48
5	$Cu(OAc)_2 \cdot H_2O$	78	18
6	$Cu(OTf)_2$	86	68

^a Unless otherwise noted, the reaction of **1a** (0.1 mmol) and **2a** (0.12 mmol) was performed in the presence of ligand (**L1**, 5 mol%), DIPEA (10 mol%) and copper salt (5 mol%) in solvent (1.0 mL) for 18 h. ^b Yield of the isolated product based on **1a**. ^c Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Table S2. Effects of aprotic polar solvent ^a



Entry	Solvent	T(°C)	Yield (%) ^b	ee (%) ^c
1	Tol	-30	93	99
2	DMF	-30	83	43
3 ^d	DMSO	20	80	49
4	Tol	20	93	70

^a Unless otherwise noted, the reaction of **1a** (0.1 mmol) and **2a** (0.12 mmol) was performed in the presence of ligand (**L4**, 5 mol%), DIPEA (10 mol%) and copper salt (5 mol%) in solvent (1.0 mL) at -30 °C for 18 h. ^b Yield of the isolated product based on **1a**. ^c Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. ^d Due to the high freezing point of DMSO, the reaction was carried out at 20 °C.

1.4 General working procedure

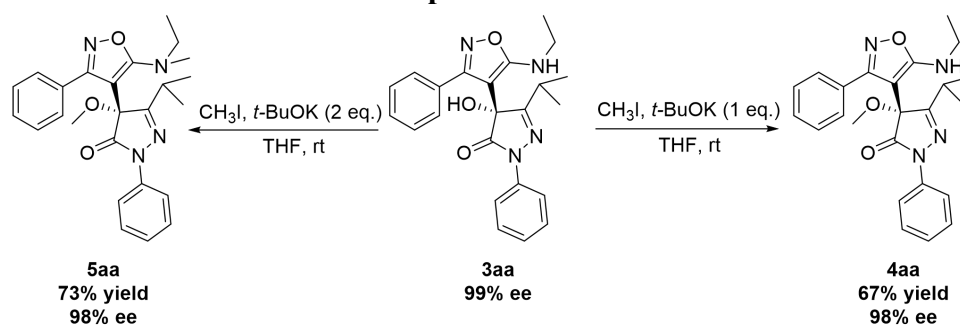
1.4.1 Procedure for the Friedel-Crafts hydroxyalkylation product **3**

A mixture of $\text{Cu}(\text{OTf})_2$ (1.8 mg, 0.005 mmol) and the ligand (**L**₄, 2.8 mg, 0.005mmol) in toluene (1 mL) with DIPEA (1.74 μL , 0.01 mmol) were stirred at room temperature for 2 h. pyrazole-4,5-diones **1** (0.1mmol) was then added and the resulting mixture was cooled to -30°C . After stirring the mixture for 0.5 h, 5-aminoisoxazole **2** (0.12 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the reaction mixture was evaporated in vacuo. Purification of the residue by column chromatography (petroleum ether/ ethyl acetate = 10:1) afforded the desired product **3** as a white solid.

1.4.2 Procedure for the Friedel-Crafts hydroxyalkylation on a gram scale

A mixture of $\text{Cu}(\text{OTf})_2$ (36 mg, 0.01 mmol) and the ligand (**L**₄, 56 mg, 0.01mmol) in toluene (40 mL) with DIPEA (34.8 μL , 0.2 mmol) were stirred at room temperature for 2 h. pyrazole-4,5-diones **1a** (4mmol) was then added and the resulting mixture was cooled to -30°C . After stirring the mixture for 0.5 h, 5-aminoisoxazole **2a** (4.8 mmol) was added in one portion. After the reaction was complete (monitored by TLC), the reaction mixture was evaporated in vacuo. Purification of the residue by column chromatography (petroleum ether/ ethyl acetate = 10:1) afforded the desired product **3aa** as a white solid.

1.4.3 Further transformation of the product **3aa**



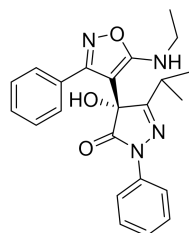
A mixture of **3aa** (40.4 mg, 0.1 mmol), $t\text{-BuOK}$ (11.2mg, 0.1 mmol) and CH_3I (6.2 μL , 0.1 mmol) in THF (1 mL) were stirred at room temperature. After the reaction was complete (monitored by TLC), the reaction mixture was evaporated in vacuo. Purification of the residue by column chromatography (petroleum ether/ ethyl acetate = 20:1) afforded the desired product **4aa** as a white solid.

A mixture of **3aa** (40.4 mg, 0.1 mmol), $t\text{-BuOK}$ (22.4mg, 0.2 mmol) and CH_3I (12.4 μL , 0.2 mmol) in THF (1 mL) were stirred at room temperature. After the

reaction was complete (monitored by TLC), the reaction mixture was evaporated in vacuo. Purification of the residue by column chromatography (petroleum ether/ ethyl acetate = 20:1) afforded the desired product **5aa** as a white solid.

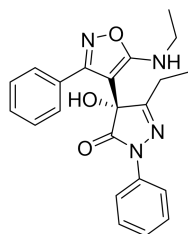
1.5 Experimental data of products

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**3aa**)



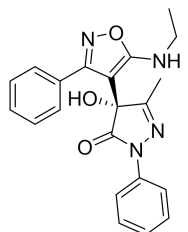
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 34.0 mg, 87% yield; 37.5 mg, 93% yield; mp = 157-159 °C; $[\alpha]_D^{20}$ 218.2 (c = 1.0, CHCl₃, 99% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23°C, UV = 254 nm, t_R = 7.7 min (major), t_R = 9.6 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.58-7.53 (m, 2H), 7.37-7.29 (m, 2H), 7.18-7.06 (m, 6H), 6.59 (t, J = 6.0 Hz, 1H), 6.27 (s, 1H), 3.55-3.43 (m, 2H), 2.80 (hept, J = 6.9 Hz, 1H), 1.34-1.26 (m, 6H), 1.12-1.07 (m, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.4, 169.1, 167.2, 161.6, 138.0, 129.4, 128.9, 128.5, 128.4, 127.9, 124.5, 118.1, 84.7, 77.3, 37.4, 28.3, 20.4, 19.7, 15.3. HRMS (ESI) m/z calcd for C₂₃H₂₄N₄O₃ [M+H]⁺ 405.1921, found 405.1927.

(R)-5-ethyl-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**3ba**)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 36.3 mg, 93% yield; mp = 165-168 °C; $[\alpha]_D^{20}$ 156.7 (c = 1.0, CHCl₃, 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 70:30, flow rate = 0.8 mL/min, T = 18°C, UV = 254 nm, t_R = 8.1 min (major), t_R = 10.0 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.59 (d, J = 8.1 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.23-7.17 (m, 1H), 7.17-7.10 (m, 5H), 6.55 (t, J = 6.1 Hz, 1H), 6.21 (s, 1H), 3.49 (p, J = 6.9 Hz, 2H), 2.53 (dq, J = 17.8, 7.3 Hz, 1H), 2.35 (dq, J = 17.8, 7.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.6, 169.2, 164.5, 161.6, 138.1, 129.4, 129.0, 128.5, 128.4, 127.9, 124.5, 118.1, 84.5, 76.7, 37.4, 20.5, 15.2, 8.5. HRMS (ESI) m/z calcd for C₂₂H₂₂N₄O₃ [M+H]⁺ 391.1765, found 391.1771.

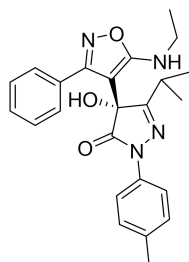
(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**3ca**)



The title compound was prepared according to the general working

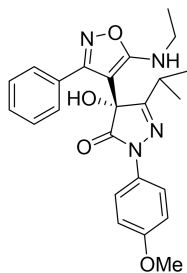
procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 34.6 mg, 92% yield; mp = 170-172 °C; $[\alpha]_D^{20}$ 192.9 (c = 1.0, CHCl₃, 94% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23°C, UV = 254 nm, t_R = 9.4 min (major), t_R = 12.6 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.58-7.52 (m, 2H), 7.37-7.29 (m, 2H), 7.22-7.09 (m, 6H), 6.57 (s, 1H), 6.24 (s, 1H), 3.54-3.45 (m, 2H), 2.02 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.3, 169.3, 161.6, 160.8, 137.9, 129.4, 129.0, 128.5, 128.4, 127.9, 124.5, 118.1, 84.2, 76.5, 37.4, 15.2, 12.3. HRMS (ESI) m/z calcd for C₂₁H₂₀N₄O₃ [M+H]⁺ 377.1608, found 377.1612.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(p-tolyl)-2,4-dihydro-3H-pyrazol-3-one (3da)



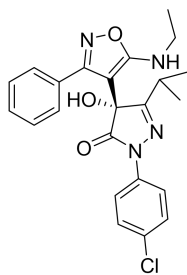
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.8 mg, 93% yield; mp = 158-159 °C; $[\alpha]_D^{20}$ 233.4 (c = 1.0, CHCl₃, 96% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 70:30, flow rate = 1.0 mL/min, T = 8°C, UV = 254 nm, t_R = 7.0 min (major), t_R = 9.7 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.46-7.39 (m, 2H), 7.21-7.07 (m, 7H), 6.59 (t, J = 6.3 Hz, 1H), 6.22 (s, 1H), 3.55-3.43 (m, 2H), 2.78 (hept, J = 6.9 Hz, 1H), 2.31 (s, 3H), 1.34-1.25 (m, 6H), 1.08 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.1, 169.1, 167.0, 161.5, 135.6, 133.9, 129.4, 128.9, 128.8, 128.5, 127.9, 118.3, 84.7, 77.2, 37.4, 28.3, 20.4, 20.1, 19.6, 15.3. HRMS (ESI) m/z calcd for C₂₄H₂₆N₄O₃ [M+Na]⁺ 441.1897, found 441.1898.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(4-methoxyphenyl)-2,4-dihydro-3H-pyrazol-3-one (3ea)



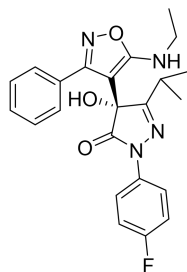
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.3 mg, 93% yield; mp = 158-160 °C; $[\alpha]_D^{20}$ 210.6 (c = 1.0, CHCl₃, 96% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 0.8 mL/min, T = 13°C, UV = 254 nm, t_R = 16.6 min (major), t_R = 22.8 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.46-7.40 (m, 2H), 7.24-7.10 (m, 5H), 6.92-6.86 (m, 2H), 6.58 (t, J = 6.2 Hz, 1H), 6.30-6.10 (m, 1H), 3.79 (s, 3H), 3.55-3.43 (m, 2H), 2.79 (hept, J = 6.9 Hz, 1H), 1.34-1.25 (m, 6H), 1.08 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 170.8, 169.1, 167.0, 161.6, 156.8, 131.3, 129.5, 128.9, 128.5, 127.9, 119.9, 113.4, 84.7, 77.1, 54.8, 37.4, 28.2, 20.4, 19.7, 15.3. HRMS (ESI) m/z calcd for C₂₄H₂₆N₄O₄ [M+H]⁺ 435.2027, found 435.2033.

(R)-2-(4-chlorophenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3fa)



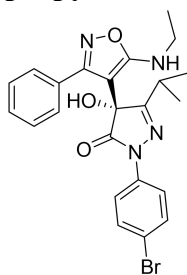
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.3 mg, 92% yield; mp = 176-179 °C; $[\alpha]_D^{20}$ 153.0 (c = 0.5, CHCl₃, 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 8°C, UV = 254 nm, t_R = 17.3 min (major), t_R = 23.2 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.60-7.53 (m, 2H), 7.38-7.32 (m, 2H), 7.19-7.07 (m, 5H), 6.60 (t, J = 6.2 Hz, 1H), 6.31 (s, 1H), 3.56-3.44 (m, 2H), 2.83 (hept, J = 7.0 Hz, 1H), 1.34-1.26 (m, 6H), 1.12 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.3, 169.0, 167.7, 161.5, 136.7, 129.3, 129.0, 129.0, 128.5, 128.4, 127.9, 119.4, 84.5, 77.3, 37.4, 28.2, 20.3, 19.7, 15.3. HRMS (ESI) m/z calcd for C₂₃H₂₃ClN₄O₃ [M+H]⁺ 439.1531, found 439.1534.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-2-(4-fluorophenyl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3ga)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.8 mg, 92% yield; mp = 163-164 °C; $[\alpha]_D^{20}$ 239.7 (c = 1.0, CHCl₃, 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 0.8 mL/min, T = 14°C, UV = 254 nm, t_R = 11.2 min (major), t_R = 14.1 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.59-7.51 (m, 2H), 7.20-7.06 (m, 7H), 6.60 (t, J = 6.3 Hz, 1H), 6.26 (s, 1H), 3.56-3.44 (m, 2H), 2.86-2.78 (m, 1H), 1.31 (m, 6H), 1.12 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.1, 169.0, 167.5, 161.5, 159.4 (d, J = 241.7 Hz), 134.3 (d, J = 2.8 Hz), 129.3, 128.9, 128.5, 127.9, 119.9 (d, J = 8.3 Hz), 114.9 (d, J = 22.7 Hz), 84.6, 77.2, 37.4, 28.2, 20.3, 19.7, 15.2. ¹⁹F NMR (471 MHz, Acetone-d₆) δ -119.35. HRMS (ESI) m/z calcd for C₂₃H₂₃FN₄O₃ [M+H]⁺ 423.1827, found 423.1830

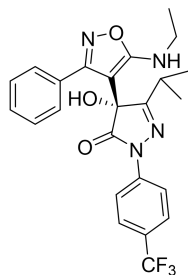
(R)-2-(4-bromophenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3ha)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.8 mg, 91% yield; mp = 176-178 °C; $[\alpha]_D^{20}$ 172.3 (c = 1.0, CHCl₃, 90% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 8°C, UV = 254 nm, t_R = 14.9 min (major), t_R = 18.3 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.55-7.46 (m, 4H), 7.19-7.06 (m, 5H), 6.60 (t, J = 6.3 Hz, 1H), 6.34 (s, 1H), 3.56-3.44 (m, 2H), 2.86-2.80 (m, 1H), 1.34-1.26 (m, 6H), 1.12 (d, J = 6.8 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.4, 169.0, 167.8, 161.5, 137.2, 131.4, 129.3, 129.0, 128.5, 127.9,

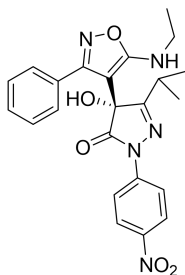
119.8, 116.7, 84.5, 77.3, 37.4, 28.2, 20.3, 19.7, 15.2. HRMS (ESI) m/z calcd for $C_{23}H_{23}BrN_4O_3$ $[M+H]^+$ 483.1026, found 483.1031.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(4-(trifluoromethyl)phenyl)-2,4-dihydro-3H-pyrazol-3-one (3ia)



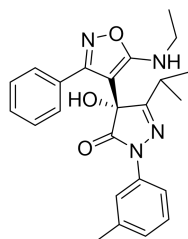
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.4 mg, 92% yield; mp = 152-154 °C; $[\alpha]_D^{20}$ 214.8 (c = 1.0, $CHCl_3$, 93% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 14°C, UV = 254 nm, t_R = 11.8 min (major), t_R = 14.4 min (minor); 1H NMR (500 MHz, Acetone- d_6) δ 7.78 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.14-7.04 (m, 5H), 6.62 (t, J = 6.1 Hz, 1H), 6.34 (s, 1H), 3.56-3.44 (m, 2H), 2.86 (hept, J = 6.9 Hz, 1H), 1.31 (m, 6H), 1.15 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.8, 169.0, 168.2, 161.5, 140.9, 129.2, 128.9, 128.5, 127.9, 125.7 (q, J = 3.8 Hz), 125.4 (q, J = 32.2 Hz), 124.5 (q, J = 271.2 Hz), 117.8, 84.5, 77.4, 37.4, 28.3, 20.3, 19.7, 15.2. ^{19}F NMR (471 MHz, Acetone- d_6) δ -62.44. HRMS (ESI) m/z calcd for $C_{24}H_{23}F_3N_4O_3$ $[M+H]^+$ 473.1795, found 473.1801.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(4-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one (3ja)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.4 mg, 90% yield; mp = 175-176 °C; $[\alpha]_D^{20}$ 228.9 (c = 1.0, $CHCl_3$, 88% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 70:30, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 4.4 min (major), t_R = 6.3 min (minor); 1H NMR (500 MHz, MeOD) δ 8.24-8.17 (m, 2H), 7.85-7.78 (m, 2H), 7.11-7.03 (m, 5H), 3.47 (q, J = 7.1 Hz, 2H), 2.85 (hept, J = 6.9 Hz, 1H), 1.34-1.29 (m, 6H), 1.19 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, MeOD) δ 172.9, 169.3, 169.0, 161.8, 143.8, 142.6, 129.1, 128.3, 128.2, 127.8, 124.0, 117.5, 84.5, 77.3, 37.1, 28.3, 19.8, 19.4, 14.7. HRMS (ESI) m/z calcd for $C_{23}H_{23}N_5O_5$ $[M+H]^+$ 450.1772, found 450.1779.

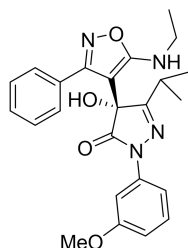
(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(m-tolyl)-2,4-dihydro-3H-pyrazol-3-one (3ka)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.9 mg, 93% yield; mp = 155-156 °C; $[\alpha]_D^{20}$ 144.7 (c = 1.0, $CHCl_3$, 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 14°C, UV = 254 nm, t_R = 11.4 min (major), t_R = 15.5

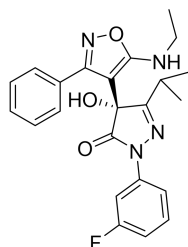
min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.37-7.30 (m, 2H), 7.23-7.07 (m, 6H), 6.96 (d, $J = 7.5$ Hz, 1H), 6.58 (t, $J = 6.3$ Hz, 1H), 6.21 (s, 1H), 3.55-3.43 (m, 2H), 2.80 (hept, $J = 6.9$ Hz, 1H), 2.31 (s, 3H), 1.34-1.26 (m, 6H), 1.09 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.3, 169.1, 167.1, 161.6, 138.0, 137.9, 129.4, 128.9, 128.5, 128.2, 127.9, 125.3, 118.9, 115.6, 84.7, 77.2, 37.4, 28.3, 20.7, 20.4, 19.7, 15.3. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 419.2078, found 419.2085.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(3-methoxyphenyl)-2,4-dihydro-3H-pyrazol-3-one (3la)



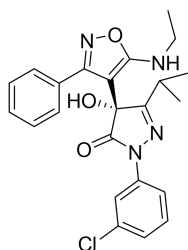
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.4 mg, 93% yield; mp = 162-165 °C; $[\alpha]_{\text{D}}^{20}$ 126.4 ($c = 1.0$, CHCl_3 , 96% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 0.8 mL/min, $T = 13^\circ\text{C}$, UV = 254 nm, $t_{\text{R}} = 13.2$ min (major), $t_{\text{R}} = 17.0$ min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.27-7.21 (m, 1H), 7.21-7.15 (m, 3H), 7.15-7.08 (m, 4H), 6.75-6.70 (m, 1H), 6.59 (t, $J = 6.3$ Hz, 1H), 6.24 (s, 1H), 3.77 (s, 3H), 3.56-3.44 (m, 2H), 2.85-2.76 (m, 1H), 1.34-1.26 (m, 6H), 1.09 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.4, 169.1, 167.1, 161.5, 159.8, 139.1, 129.4, 129.2, 128.9, 128.5, 127.9, 110.4, 109.9, 104.1, 84.7, 77.3, 54.7, 37.4, 28.3, 20.4, 19.6, 15.2. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$ 435.2027, found 435.2033.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-2-(3-fluorophenyl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3ma)



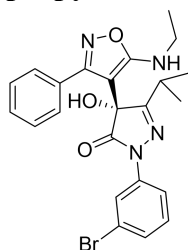
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.0 mg, 90% yield; mp = 164-165 °C; $[\alpha]_{\text{D}}^{20}$ 248.1 ($c = 1.0$, CHCl_3 , 92% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 0.8 mL/min, $T = 16^\circ\text{C}$, UV = 254 nm, $t_{\text{R}} = 8.6$ min (major), $t_{\text{R}} = 11.0$ min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.43 (ddd, $J = 8.3, 2.1, 1.0$ Hz, 1H), 7.40-7.30 (m, 2H), 7.18-7.06 (m, 5H), 6.91 (tdd, $J = 8.4, 2.6, 1.0$ Hz, 1H), 6.60 (t, $J = 6.2$ Hz, 1H), 6.30 (s, 1H), 3.56-3.44 (m, 2H), 2.84 (hept, $J = 6.9$ Hz, 1H), 1.34-1.27 (m, 6H), 1.13 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.5, 169.0, 167.8, 162.5 (d, $J = 242.0$ Hz), 161.5, 139.4 (d, $J = 11.1$ Hz), 130.1 (d, $J = 9.2$ Hz), 129.3, 128.9, 128.5, 127.9, 113.5 (d, $J = 3.5$ Hz), 110.8 (d, $J = 21.3$ Hz), 104.8 (d, $J = 27.5$ Hz), 84.5, 77.4, 37.4, 28.2, 20.3, 19.7, 15.2. ^{19}F NMR (471 MHz, Acetone- d_6) δ -113.43. HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{23}\text{FN}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 423.1827, found 423.1835.

(R)-2-(3-chlorophenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3na)



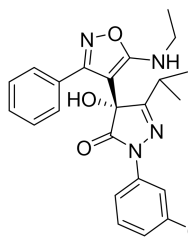
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.3 mg, 92% yield; mp = 154-156 °C; $[\alpha]_D^{20}$ 224.4 (c = 1.0, CHCl₃, 94% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 26°C, UV = 254 nm, t_R = 11.7 min (major), t_R = 16.0 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.58-7.50 (m, 2H), 7.34 (t, J = 8.1 Hz, 1H), 7.21-7.04 (m, 6H), 6.60 (t, J = 6.1 Hz, 1H), 6.32 (s, 1H), 3.55-3.43 (m, 2H), 2.84 (hept, J = 6.9 Hz, 1H), 1.33-1.27 (m, 6H), 1.14 (d, J = 6.9 Hz, 3H). ¹³C NMR (126 MHz, Acetone-d₆) δ 171.5, 169.0, 167.9, 161.5, 139.0, 133.6, 130.0, 129.3, 128.9, 128.6, 127.9, 124.2, 117.6, 116.2, 84.5, 77.4, 37.4, 28.2, 20.3, 19.8, 15.3. HRMS (ESI) m/z calcd for C₂₃H₂₃ClN₄O₃ [M+H]⁺ 439.1531, found 439.1538.

(R)-2-(3-bromophenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3oa)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 44.8 mg, 93% yield; mp = 167-170 °C; $[\alpha]_D^{20}$ 161.0 (c = 1.0, CHCl₃, 93% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 16°C, UV = 254 nm, t_R = 13.7 min (major), t_R = 20.3 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.68 (t, J = 1.9 Hz, 1H), 7.57 (dt, J = 7.9, 1.7 Hz, 1H), 7.35-7.25 (m, 2H), 7.19-7.08 (m, 5H), 6.60 (t, J = 6.3 Hz, 1H), 6.29 (s, 1H), 3.56-3.44 (m, 2H), 2.87-2.81 (m, 1H), 1.31 (m, 6H), 1.15 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.5, 169.0, 168.0, 161.5, 139.1, 130.3, 129.3, 128.9, 128.6, 127.9, 127.2, 121.5, 120.6, 116.6, 84.5, 77.3, 37.4, 28.2, 20.3, 19.8, 15.2. HRMS (ESI) m/z calcd for C₂₃H₂₃BrN₄O₃ [M+H]⁺ 483.1026, found 483.1031.

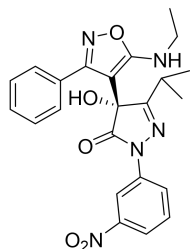
(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(3-(trifluoromethyl)phenyl)-2,4-dihydro-3H-pyrazol-3-one (3pa)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 42.4 mg, 90% yield; mp = 161-164 °C; $[\alpha]_D^{20}$ 283.4 (c = 1.0, CHCl₃, 88% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 5.3 min (major), t_R = 6.8 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.86-7.79 (m, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.15-7.03 (m, 5H), 6.62 (t, J = 6.2 Hz, 1H), 6.33 (s,

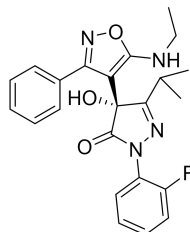
1H), 3.56-3.44 (m, 2H), 2.88 (hept, J = 6.9 Hz, 1H), 1.31 (dt, J = 7.1, 3.7 Hz, 6H), 1.17 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.6, 168.9, 168.2, 161.5, 138.4, 130.1 (q, J = 32.2 Hz), 129.6, 129.2, 128.9, 128.6, 127.8, 124.2 (q, J = 271.2 Hz), 121.3, 120.8 (q, J = 4.1 Hz), 114.3 (q, J = 4.4 Hz), 84.5, 77.4, 37.4, 28.2, 20.3, 19.8, 15.2. ¹⁹F NMR (471 MHz, Acetone-d₆) δ -63.21. HRMS (ESI) m/z calcd for C₂₄H₂₃F₃N₄O₃ [M+Na]⁺ 495.1614, found 495.1620.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(3-nitrophenyl)-2,4-dihydro-3H-pyrazol-3-one (3qa)



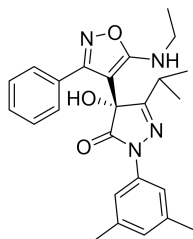
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.9 mg, 91% yield; mp = 157-159 °C; [α]_D²⁰ 257.2 (c = 1.0, CHCl₃, 85% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 18°C, UV = 254 nm, t_R = 12.1 min (major), t_R = 14.0 min (minor); ¹H NMR (500 MHz, MeOD) δ 8.35 (t, J = 2.2 Hz, 1H), 8.00 (ddd, J = 8.2, 2.3, 1.0 Hz, 1H), 7.94 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 7.17-6.92 (m, 5H), 3.47 (q, J = 7.1 Hz, 2H), 2.86 (hept, J = 6.9 Hz, 1H), 1.35-1.29 (m, 6H), 1.21 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, MeOD) δ 172.5, 169.2, 169.0, 161.8, 148.2, 138.4, 129.4, 129.0, 128.4, 128.3, 127.8, 123.4, 118.8, 112.4, 84.5, 77.4, 37.1, 28.2, 19.8, 19.5, 14.7. HRMS (ESI) m/z calcd for C₂₃H₂₃N₅O₅ [M+H]⁺ 450.1772, found 450.1780.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-2-(2-fluorophenyl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3ra)



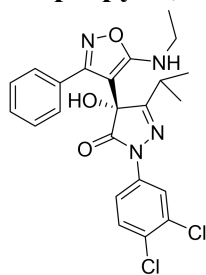
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.6 mg, 80% yield; mp = 157-158 °C; [α]_D²⁰ 115.3 (c = 1.0, CHCl₃, 75% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23°C, UV = 254 nm, t_R = 4.8 min (major), t_R = 10.7 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.42-7.30 (m, 4H), 7.28-7.15 (m, 4H), 6.98 (td, J = 7.7, 1.8 Hz, 1H), 6.60 (t, J = 6.2 Hz, 1H), 6.43 (s, 1H), 3.55-3.43 (m, 2H), 2.74 (hept, J = 6.9 Hz, 1H), 1.33-1.24 (m, 6H), 1.00 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.5, 169.3, 167.2, 161.5, 155.9 (d, J = 251.9 Hz), 129.8, 129.3, 128.8, 128.7, 128.3, 126.4, 124.8 (d, J = 12.0 Hz), 124.0 (d, J = 3.7 Hz), 116.3 (d, J = 19.4 Hz), 84.3, 75.8, 37.4, 28.4, 20.4, 19.3, 15.2. ¹⁹F NMR (471 MHz, Acetone-d₆) δ -119.04. HRMS (ESI) m/z calcd for C₂₃H₂₃FN₄O₃ [M+H]⁺ 423.1827, found 423.1832.

(R)-2-(3,5-dimethylphenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3sa)



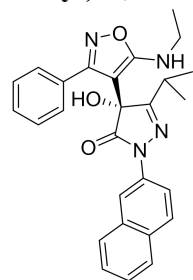
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 39.8 mg, 92% yield; mp = 162-164 °C; $[\alpha]_D^{20}$ 114.6 (c = 1.0, CHCl₃, 94% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 0.8 mL/min, T = 13°C, UV = 254 nm, t_R = 10.2 min (major), t_R = 13.8 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.25-7.16 (m, 1H), 7.16-7.09 (m, 6H), 6.81-6.77 (m, 1H), 6.57 (t, J = 6.2 Hz, 1H), 6.19 (s, 1H), 3.55-3.43 (m, 2H), 2.79 (hept, J = 6.9 Hz, 1H), 2.26 (s, 6H), 1.33-1.25 (m, 6H), 1.09 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.2, 169.1, 167.0, 161.6, 137.8, 137.8, 129.5, 128.9, 128.6, 127.9, 126.2, 116.3, 84.8, 77.2, 37.4, 28.2, 20.6, 20.4, 19.8, 15.3. HRMS (ESI) m/z calcd for C₂₅H₂₈N₄O₃ [M+H]⁺ 433.2243, found 433.2241.

(R)-2-(3,4-dichlorophenyl)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2,4-dihydro-3H-pyrazol-3-one (3ta)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.4 mg, 92% yield; mp = 173-176 °C; $[\alpha]_D^{20}$ 198.7 (c = 1.0, CHCl₃, 87% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 6.6 min (major), t_R = 7.7 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.69 (d, J = 2.3 Hz, 1H), 7.58-7.49 (m, 2H), 7.19-7.07 (m, 5H), 6.61 (t, J = 6.2 Hz, 1H), 6.32 (s, 1H), 3.56-3.44 (m, 2H), 2.89-2.82 (m, 1H), 1.34-1.28 (m, 6H), 1.16 (d, J = 6.8 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.5, 168.9, 168.4, 161.4, 137.5, 131.6, 130.4, 129.2, 128.9, 128.6, 127.9, 126.8, 119.2, 117.6, 84.4, 77.4, 37.4, 28.2, 20.3, 19.8, 15.2. HRMS (ESI) m/z calcd for C₂₃H₂₂Cl₂N₄O₃ [M+H]⁺ 473.1142, found 473.1148.

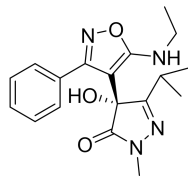
(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-(naphthalen-2-yl)-2,4-dihydro-3H-pyrazol-3-one (3ua)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 42.2 mg, 93% yield; mp = 168-170 °C; $[\alpha]_D^{20}$ 193.1 (c = 1.0, CHCl₃, 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 8.4 min (major), t_R = 12.2 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 8.00 (d, J = 2.1 Hz, 1H), 7.91-7.82 (m, 3H), 7.76 (dd, J = 9.0, 2.1 Hz, 1H), 7.55-7.43 (m, 2H), 7.20-7.12 (m, 2H), 7.11-7.02 (m, 3H), 6.63 (t, J = 6.2 Hz, 1H), 6.29 (s, 1H), 3.58-3.46 (m, 2H), 2.88-2.82 (m, 1H), 1.36-1.25 (m, 6H), 1.16 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.5, 169.1, 167.5, 161.6, 135.6, 133.4, 130.9, 129.4, 128.9, 128.6, 128.2, 127.9, 127.7, 127.6, 126.5, 125.2, 118.1, 115.2, 84.7, 77.3, 37.4, 28.3, 20.4,

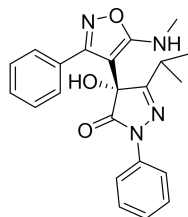
19.8, 15.3. HRMS (ESI) m/z calcd for $C_{27}H_{26}N_4O_3$ $[M+H]^+$ 455.2078, found 455.2084.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-methyl-2,4-dihydro-3H-pyrazol-3-one(3va)



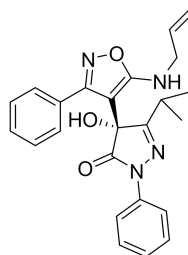
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 30.8 mg, 90% yield; mp = 103-104 °C; $[\alpha]_D^{20}$ 287.9 (c = 1.0, $CHCl_3$, 89% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 7.5 min (major), t_R = 11.3 min (minor); 1H NMR (500 MHz, $CDCl_3$) δ 7.43-7.29 (m, 3H), 7.18-7.02 (m, 2H), 5.93 (s, 1H), 5.80 (s, 1H), 3.51-3.36 (m, 2H), 2.67 (hept, J = 6.8 Hz, 1H), 2.64 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 168.1, 167.4, 160.6, 128.4, 127.7, 127.5, 126.9, 83.3, 59.5, 36.7, 29.6, 27.1, 19.8, 19.3, 14.5. HRMS (ESI) m/z calcd for $C_{18}H_{22}N_4O_3$ $[M+H]^+$ 343.1765, found 343.1769.

(R)-4-hydroxy-5-isopropyl-4-(5-(methylamino)-3-phenylisoxazol-4-yl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ab)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 36.3 mg, 93% yield; mp = 177-179 °C; $[\alpha]_D^{20}$ 217.2 (c = 1.0, $CHCl_3$, 96% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 9.3 min (major), t_R = 13.1 min (minor); 1H NMR (500 MHz, $DMSO-d_6$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.29 (s, 1H), 7.16 (q, J = 7.1 Hz, 2H), 7.09 (t, J = 7.5 Hz, 2H), 7.02 (m, 2H), 6.86 (q, J = 5.0 Hz, 1H), 2.96 (d, J = 5.0 Hz, 3H), 2.69 (hept, J = 7.1 Hz, 1H), 1.21 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $DMSO-d_6$) δ 172.2, 169.4, 168.0, 161.8, 137.8, 129.5, 129.2, 129.0, 128.6, 128.4, 125.1, 118.5, 84.5, 77.1, 29.3, 28.2, 21.1, 20.6. HRMS (ESI) m/z calcd for $C_{22}H_{22}N_4O_3$ $[M+H]^+$ 391.1765, found 391.1771.

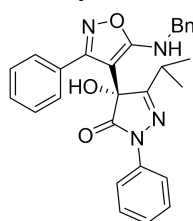
(R)-4-(5-(allylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ac)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 37.5 mg, 90% yield; mp = 151-152 °C; $[\alpha]_D^{20}$ 217.3 (c = 1.0, $CHCl_3$, 93% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 8.6 min (major), t_R = 12.7

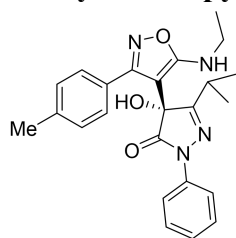
min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.60-7.53 (m, 2H), 7.36-7.28 (m, 2H), 7.21-7.06 (m, 6H), 6.76 (t, $J = 6.5$ Hz, 1H), 6.30 (s, 1H), 6.05 (ddt, $J = 17.2, 10.4, 5.2$ Hz, 1H), 5.38 (dq, $J = 17.2, 1.7$ Hz, 1H), 5.18 (dq, $J = 10.3, 1.6$ Hz, 1H), 4.09 (ddt, $J = 5.0, 5.0, 1.7$ Hz, 2H), 2.80 (hept, $J = 6.9$ Hz, 1H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (126 MHz, Acetone- d_6) δ 171.3, 168.9, 167.1, 161.6, 138.0, 135.6, 129.3, 129.0, 128.5, 128.4, 127.9, 124.5, 118.2, 115.2, 85.0, 77.3, 44.7, 28.3, 20.4, 19.6. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 417.1921, found 417.1925.

(R)-4-(5-(benzylamino)-3-phenylisoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ad)



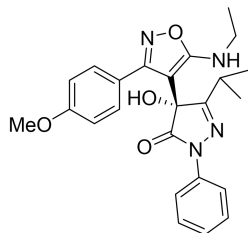
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.3 mg, 93% yield; mp = 171-172 °C; $[\alpha]_{\text{D}}^{20}$ 192.3 ($c = 1.0$, CHCl_3 , 96% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, $T = 23^\circ\text{C}$, UV = 254 nm, $t_{\text{R}} = 12.2$ min (major), $t_{\text{R}} = 17.8$ min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.59-7.53 (m, 2H), 7.53-7.48 (m, 2H), 7.42-7.26 (m, 5H), 7.21-7.05 (m, 7H), 6.40 (s, 1H), 4.73-4.61 (m, 2H), 2.78 (hept, $J = 6.9$ Hz, 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.3, 168.9, 167.2, 161.6, 139.7, 138.0, 129.2, 129.0, 128.5, 128.5, 128.4, 127.9, 127.4, 127.2, 124.6, 118.2, 85.2, 77.3, 46.1, 28.2, 20.4, 19.7. HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}_3$ $[\text{M}+\text{H}]^+$ 467.2078, found 467.2085.

(R)-4-(5-(ethylamino)-3-(p-tolyl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ae)



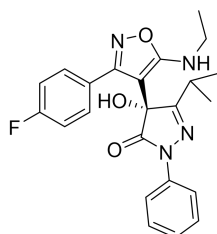
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.9 mg, 93% yield; mp = 164-167 °C; $[\alpha]_{\text{D}}^{20}$ 226.8 ($c = 1.0$, CHCl_3 , 93% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, $T = 20^\circ\text{C}$, UV = 254 nm, $t_{\text{R}} = 11.3$ min (major), $t_{\text{R}} = 15.1$ min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.55-7.49 (m, 2H), 7.36-7.29 (m, 2H), 7.17-7.10 (m, 1H), 7.00-6.95 (m, 2H), 6.86 (d, $J = 7.9$ Hz, 2H), 6.54 (t, $J = 6.2$ Hz, 1H), 6.21 (s, 1H), 3.54-3.42 (m, 2H), 2.88-2.76 (m, 1H), 2.07 (s, 3H), 1.32-1.27 (m, 6H), 1.13 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.3, 168.9, 167.2, 161.6, 138.8, 138.0, 128.5, 128.4, 128.3, 126.3, 124.4, 118.1, 84.9, 77.3, 37.4, 28.2, 20.4, 20.3, 19.9, 15.3. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_3$ $[\text{M}+\text{Na}]^+$ 441.1897, found 441.1905.

(R)-4-(5-(ethylamino)-3-(4-methoxyphenyl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3af)



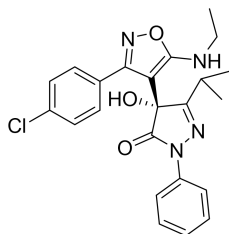
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 39.1mg, 90% yield; mp = 166-169 °C; $[\alpha]_D^{20}$ 262.4 (c = 1.0, CHCl₃, 93% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 70:30, flow rate = 1.0 mL/min, T = 20°C, UV = 254 nm, t_R = 4.1 min (major), t_R = 10.8 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.62-7.55 (m, 2H), 7.39-7.27 (m, 2H), 7.18-7.11 (m, 1H), 7.05-6.98 (m, 2H), 6.63-6.57 (m, 2H), 6.54 (t, J = 6.3 Hz, 1H), 6.19 (s, 1H), 3.53-3.44 (m, 2H), 2.86-2.79 (m, 1H), 1.32-1.29 (m, 6H), 1.15 (d, J = 6.8 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.3, 168.9, 167.3, 161.4, 160.2, 138.1, 129.8, 128.3, 124.4, 121.3, 118.0, 113.3, 85.0, 77.3, 54.5, 37.4, 28.2, 20.4, 19.9, 15.3. HRMS (ESI) m/z calcd for C₂₄H₂₆N₄O₄ [M+H]⁺ 435.2027, found 435.2033.

(R)-4-(5-(ethylamino)-3-(4-fluorophenyl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ag)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 38.4 mg, 91% yield; mp = 163-166 °C; $[\alpha]_D^{20}$ 203.7 (c = 1.0, CHCl₃, 97% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 70:30, flow rate = 0.8 mL/min, T = 23°C, UV = 254 nm, t_R = 9.7 min (major), t_R = 18.5 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.61-7.55 (m, 2H), 7.38-7.29 (m, 2H), 7.18-7.11 (m, 3H), 6.88-6.80 (m, 2H), 6.60 (t, J = 6.2 Hz, 1H), 6.30 (s, 1H), 3.55-3.43 (m, 2H), 2.83 (hept, J = 6.9 Hz, 1H), 1.34-1.28 (m, 6H), 1.15 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.3, 169.0, 167.5, 163.0 (d, J = 246.6 Hz), 160.7, 137.9, 130.8 (d, J = 9.0 Hz), 128.5, 125.5 (d, J = 3.6 Hz), 124.6, 117.9, 114.8 (d, J = 22.0 Hz), 84.9, 77.3, 37.4, 28.2, 20.4, 19.8, 15.2. ¹⁹F NMR (471 MHz, Acetone-d₆) δ -113.52. HRMS (ESI) m/z calcd for C₂₃H₂₃FN₄O₃ [M+H]⁺ 423.1827, found 423.1829.

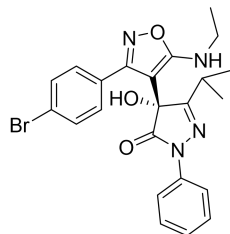
(R)-4-(3-(4-chlorophenyl)-5-(ethylamino)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ah)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.5 mg, 90% yield; mp = 166-168 °C; $[\alpha]_D^{20}$ 208.6 (c = 1.0, CHCl₃, 98% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 19°C, UV = 254 nm, t_R = 10.3 min (major), t_R = 16.5 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.58-7.52 (m, 2H), 7.39-7.31 (m, 2H), 7.19-7.12 (m, 1H), 7.10 (s, 4H), 6.62 (t, J = 6.2 Hz, 1H), 6.26 (s, 1H), 3.55-3.43 (m, 2H), 2.85 (hept, J = 6.9 Hz, 1H), 1.33-1.25 (m, 6H), 1.15 (d, J =

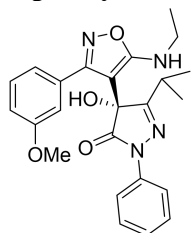
6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.2, 169.1, 167.5, 160.6, 137.8, 134.8, 130.2, 128.5, 128.1, 128.0, 124.6, 117.9, 84.8, 77.2, 37.4, 28.2, 20.4, 19.9, 15.2. HRMS (ESI) m/z calcd for C₂₃H₂₃ClN₄O₃ [M+H]⁺ 439.1531, found 439.1535.

(R)-4-(3-(4-bromophenyl)-5-(ethylamino)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ai)



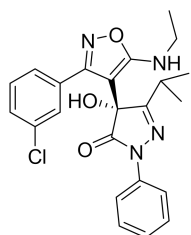
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 43.8 mg, 91% yield; mp = 156-158 °C; [α]_D²⁰ 237.8 (c = 1.0, CHCl₃, 96% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 24°C, UV = 254 nm, t_R = 20.2 min (major), t_R = 30.3 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.58-7.52 (m, 2H), 7.39-7.29 (m, 2H), 7.16-7.08 (m, 5H), 6.59 (t, J = 6.2 Hz, 1H), 6.24 (s, 1H), 3.55-3.43 (m, 2H), 2.80 (hept, J = 6.9 Hz, 1H), 1.34-1.26 (m, 6H), 1.10 (d, J = 6.9 Hz, 3H). ¹³C NMR (126 MHz, Acetone-d₆) δ 171.4, 169.1, 167.2, 161.5, 138.0, 129.4, 128.9, 128.5, 128.4, 127.9, 124.5, 118.1, 84.7, 77.3, 37.4, 28.3, 20.4, 19.7, 15.3. HRMS (ESI) m/z calcd for C₂₃H₂₃BrN₄O₃ [M+H]⁺ 483.1026, found 483.1033.

(R)-4-(5-(ethylamino)-3-(3-methoxyphenyl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3aj)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 40.4 mg, 93% yield; mp = 163-165 °C; [α]_D²⁰ 220.3 (c = 1.0, CHCl₃, 96% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 20°C, UV = 254 nm, t_R = 17.5 min (major), t_R = 21.9 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.55 (dq, J = 7.1, 1.3 Hz, 2H), 7.37-7.28 (m, 2H), 7.17-7.10 (m, 1H), 7.02 (t, J = 7.9 Hz, 1H), 6.73-6.67 (m, 2H), 6.64 (dd, J = 2.6, 1.5 Hz, 1H), 6.59 (t, J = 6.2 Hz, 1H), 6.23 (s, 1H), 3.53 (s, 3H), 3.52-3.45 (m, 2H), 2.83 (hept, J = 6.9 Hz, 1H), 1.33-1.28 (m, 6H), 1.14 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.2, 169.0, 167.2, 161.5, 159.2, 137.9, 130.5, 129.0, 128.3, 124.5, 120.8, 118.2, 114.8, 113.8, 84.6, 77.2, 54.4, 37.4, 28.3, 20.4, 19.8, 15.3. HRMS (ESI) m/z calcd for C₂₄H₂₆N₄O₄ [M+Na]⁺ 457.1846, found 457.1853.

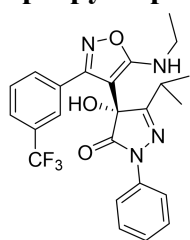
(R)-4-(3-(3-chlorophenyl)-5-(ethylamino)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3ak)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 37.4 mg, 85% yield; mp = 158-160 °C; [α]_D²⁰ 196.5 (c = 1.0, CHCl₃, 94% ee); HPLC:

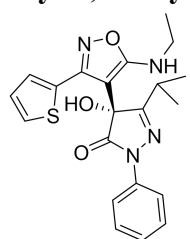
Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 18°C, UV = 254 nm, t_R = 12.3 min (major), t_R = 16.8 min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.59 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.9 Hz, 2H), 7.18-7.02 (m, 5H), 6.65 (t, J = 6.2 Hz, 1H), 6.28 (s, 1H), 3.56-3.44 (m, 2H), 2.84 (hept, J = 6.9 Hz, 1H), 1.31 (dt, J = 7.2, 3.7 Hz, 6H), 1.15 (d, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.2, 169.1, 167.4, 160.3, 137.9, 133.5, 131.2, 129.6, 129.1, 128.5, 128.4, 127.1, 124.6, 118.0, 84.6, 77.2, 37.4, 28.3, 20.4, 19.8, 15.2. HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{23}\text{ClN}_4\text{O}_3$ $[\text{M}+\text{Na}]^+$ 461.1351, found 461.1357.

(R)-4-(5-(ethylamino)-3-(3-(trifluoromethyl)phenyl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3al)



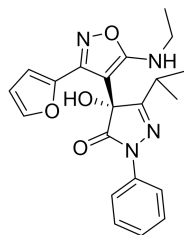
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 39.2 mg, 83% yield; mp = 150-152 °C; $[\alpha]_D^{20}$ 188.6 (c = 1.0, CHCl_3 , 81% ee); HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 23°C, UV = 254 nm, t_R = 5.9 min (major), t_R = 24.1 min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.55-7.50 (m, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.34-7.24 (m, 3H), 7.15-7.10 (m, 1H), 6.67 (t, J = 6.3 Hz, 1H), 6.27 (s, 1H), 3.56-3.46 (m, 2H), 2.88 (hept, J = 6.9 Hz, 1H), 1.32 (dt, J = 7.2, 3.7 Hz, 6H), 1.17 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.1, 169.2, 167.5, 160.4, 137.7, 132.5, 130.3, 129.9 (q, J = 32.6 Hz), 129.0, 128.4, 125.8 (q, J = 3.7 Hz), 125.3 (q, J = 4.1 Hz), 124.5, 123.9 (q, J = 272.1 Hz), 117.7, 84.7, 77.2, 37.4, 28.2, 20.4, 19.7, 15.2. ^{19}F NMR (471 MHz, Acetone- d_6) δ -63.24. HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{23}\text{F}_3\text{N}_4\text{O}_3$ $[\text{M}+\text{Na}]^+$ 495.1614, found 495.1621.

(R)-4-(5-(ethylamino)-3-(thiophen-2-yl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3am)



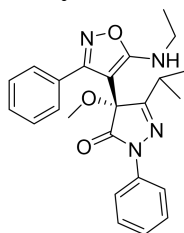
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 35.7 mg, 87% yield; mp = 152-154 °C; $[\alpha]_D^{20}$ 199.3 (c = 1.0, CHCl_3 , 95% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 80:20, flow rate = 1.0 mL/min, T = 16°C, UV = 254 nm, t_R = 14.3 min (major), t_R = 21.3 min (minor); ^1H NMR (500 MHz, Acetone- d_6) δ 7.67 (dd, J = 8.8, 1.3 Hz, 2H), 7.41-7.34 (m, 3H), 7.17 (tt, J = 7.3, 1.2 Hz, 1H), 6.82 (dd, J = 3.7, 1.2 Hz, 1H), 6.72 (dd, J = 5.1, 3.6 Hz, 1H), 6.68 (t, J = 6.5 Hz, 1H), 6.33 (s, 1H), 3.55-3.43 (m, 2H), 2.82 (hept, J = 6.9 Hz, 1H), 1.33-1.27 (m, 6H), 1.14 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, Acetone- d_6) δ 171.2, 169.5, 167.4, 155.6, 138.1, 128.6, 128.5, 128.1, 127.4, 127.0, 124.7, 118.3, 84.8, 77.1, 37.3, 28.4, 20.3, 19.8, 15.2. HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 411.1485, found 411.1490.

(R)-4-(5-(ethylamino)-3-(furan-2-yl)isoxazol-4-yl)-4-hydroxy-5-isopropyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (3an)



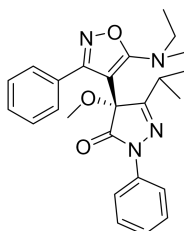
The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1-5/1) to give the product as a white solid. 33.5 mg, 85% yield; mp = 159-162 °C; $[\alpha]_D^{20}$ 162.9 (c = 1.0, CHCl₃, 91% ee); HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 70:30, flow rate = 1.0 mL/min, T = 16°C, UV = 254 nm, t_R = 14.5 min (major), t_R = 32.5 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.89-7.83 (m, 2H), 7.46-7.38 (m, 2H), 7.19 (tt, J = 7.3, 1.2 Hz, 1H), 7.08-7.03 (m, 1H), 6.73 (t, J = 6.2 Hz, 1H), 6.63 (d, J = 3.4 Hz, 1H), 6.41 (s, 1H), 6.36 (dd, J = 3.4, 1.8 Hz, 1H), 3.54-3.42 (m, 2H), 2.77 (hept, J = 6.9 Hz, 1H), 1.32-1.26 (m, 6H), 1.09 (d, J = 6.9 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 171.6, 169.6, 167.0, 152.6, 143.9, 143.5, 138.7, 128.7, 124.4, 118.0, 111.3, 109.8, 83.5, 77.0, 37.4, 28.4, 20.3, 19.7, 15.2. HRMS (ESI) m/z calcd for C₂₁H₂₂N₄O₄ [M+H]⁺ 395.1714, found 395.1718.

(R)-4-(5-(ethylamino)-3-phenylisoxazol-4-yl)-5-isopropyl-4-methoxy-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (4aa)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 10/1) to give the product as a white solid. 28.0 mg, 67% yield; mp = 174-176 °C; HPLC: Daicel Chiralpak AD-H, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 16°C, UV = 254 nm, t_R = 5.4 min (major), t_R = 8.3 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.61-7.55 (m, 2H), 7.39-7.31 (m, 2H), 7.21-7.17 (m, 1H), 7.17-7.13 (m, 1H), 7.13-7.06 (m, 4H), 6.67 (t, J = 6.2 Hz, 1H), 3.47 (dtd, J = 13.3, 7.0, 2.0 Hz, 2H), 3.24 (s, 3H), 2.78 (hept, J = 7.0 Hz, 1H), 1.32-1.27 (m, 6H), 1.12 (d, J = 6.8 Hz, 3H). ¹³C NMR (125 MHz, Acetone-d₆) δ 169.0, 168.7, 165.1, 161.5, 137.6, 129.3, 129.0, 128.6, 128.4, 127.9, 124.9, 118.3, 83.6, 83.1, 52.5, 37.4, 28.4, 19.7, 19.3, 15.3. HRMS (ESI) m/z calcd for C₂₄H₂₆N₄O₃ [M+H]⁺ 419.2078, found 419.2083.

(R)-4-(5-(ethyl(methyl)amino)-3-phenylisoxazol-4-yl)-5-isopropyl-4-methoxy-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (5aa)



The title compound was prepared according to the general working procedure and purified by column chromatography (PE/EA = 20/1) to give the product as a white solid. 31.5 mg, 73% yield; mp = 159-160 °C; HPLC: Daicel Chiralpak IC, hexane: 2-propanol = 90:10, flow rate = 1.0 mL/min, T = 16°C, UV = 254 nm, t_R = 8.9 min (major), t_R = 12.3 min (minor); ¹H NMR (500 MHz, Acetone-d₆) δ 7.81 (d, J = 8.1 Hz, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.38 – 7.27 (m, 3H), 7.25 – 7.17 (m, 3H), 3.61 – 3.37 (m, 2H), 3.17 (s, 3H), 3.07 (s, 3H), 2.48 (hept, J = 6.8 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 0.86 (s, 3H). ¹³C NMR (125 MHz,

Acetone-d₆) δ 171.0, 169.9, 164.6, 163.4, 137.5, 129.7, 129.4, 128.9, 128.8, 128.0, 125.3, 118.6, 83.6, 77.3, 52.4, 49.4, 38.4, 29.0, 20.2, 19.0, 12.6. HRMS (ESI) m/z calcd for C₂₅H₂₈N₄O₃ [M+H]⁺ 433.2234, found 433.2240.

1.6 A plausible structure of the transition state and DFT calculations.

All the calculations were performed using Gaussian 16 software packages.^[S5] The geometry of all reactants and transition states were optimized using the (U)B3LYP^[S6]-D3(Becke-Johnson damping function)^[S7] in toluene (using SMD solvation model^[S8]). In these geometry optimizations, a mixed basis set of SDD^[S9] for Cu, while 6-31G(d)^[S10] for all the other atoms was used. Vibrational frequency analysis was calculated at the same level of theory to validate each structure as either a minimum or a transition state and to evaluate its zero-point energy and thermal corrections at 298 K. For each transition state, the intrinsic reaction coordinate (IRC) analysis was conducted to ensure that it connects the right reactant and product.^[S11] To obtain more accurate energies, solution-phase single point energy calculations were performed at the (U)B3LYP-D3(BJ)/6-311+G(d,p)-SDD level.

Table S3. Thermal correction of Gibbs free energy (TCG, hartree) and single point energies (SP, hartree) in toluene for all species involved in this study

Compounds	TCG	SP	Compounds	TCG	SP
Int-I	0.362192	-2342.895995	TS	0.716866	-3600.298262
1c	0.126058	-646.027257	Int-III	0.71518	-3600.298463
2a	0.172227	-611.30592	(R)-3ca	0.325724	-1257.364543
Int-II	0.711477	-3600.307755			

C	4.51739500	-0.99983800	2.53141400
C	5.48040800	-0.85702000	-0.06932000
C	5.87972900	-0.79215300	2.31683900
H	4.13426400	-1.04880800	3.54825100
C	6.35375400	-0.72049300	1.00902100
H	6.55921700	-0.67986600	3.15515100
H	7.40695700	-0.54810100	0.81750100
O	3.31082800	-1.22606000	-0.92242700
C	5.98455600	-0.74731500	-1.47726300
F	5.39992700	0.27221300	-2.15529900
F	5.76737800	-1.86937300	-2.20128200
F	7.32069300	-0.51567200	-1.51804500
C	-1.02544000	-0.35439000	0.01133000
C	-1.35929800	1.15307700	-0.06993100
C	-0.64437900	1.98000200	-0.94274300
C	-2.38763200	1.72496000	0.69387000
C	-0.90052900	3.34823100	-1.01035000
H	0.11243200	1.54161400	-1.58220500
C	-2.65156300	3.08999800	0.63425300
H	-3.00750200	1.09913000	1.32629400
C	-1.89663400	3.90853800	-0.21005000
H	-0.32765500	3.97614000	-1.68435700
H	-3.44478900	3.51759200	1.23870800
C	-2.35304500	-1.13197100	-0.01030400
C	-3.04009700	-1.18657300	-1.23251700
C	-2.91779300	-1.75999400	1.10323000
C	-4.25229500	-1.85455100	-1.34132100
H	-2.60671700	-0.70201100	-2.09994300
C	-4.13743500	-2.43341300	1.00233700
H	-2.42426100	-1.73724100	2.06786000
C	-4.80611600	-2.48036400	-0.21826100
H	-4.77390900	-1.88675200	-2.29237700
H	-4.56440100	-2.91458900	1.87549900
O	-0.29508400	-0.74891700	-1.12121400
Cu	1.50747500	-0.87383400	-0.88339900
C	-2.21648900	5.37121300	-0.30585400
C	-6.08948100	-3.24500400	-0.35436800
F	-2.59078100	5.88394800	0.88997200
F	-1.16269800	6.09702800	-0.74213700
F	-3.23766100	5.61165100	-1.16374600
F	-6.72247900	-3.40055500	0.83066300
F	-6.95527900	-2.63314700	-1.19534900

F	-5.88519800	-4.48932000	-0.85275600
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1c

C	2.25170100	-0.89868400	0.00116600
C	1.04083500	1.15728400	-0.00140100
C	2.47464100	0.57249900	-0.00088100
O	3.50500900	1.20259000	-0.00189700
O	0.73428200	2.33416900	-0.00301800
N	0.23841400	0.03812300	0.00049600
N	0.98753600	-1.15663100	0.00179800
C	-1.77717000	-1.32629700	-0.00335800
C	-3.16642100	-1.42605800	-0.00350000
C	-3.96383100	-0.28101800	-0.00009000
C	-3.35471900	0.97390100	0.00354600
C	-1.96650900	1.09717300	0.00389500
C	-1.17646900	-0.06081500	0.00034800
H	-1.15855800	-2.21416600	-0.00586900
H	-3.62470800	-2.41092000	-0.00635000
H	-5.04636500	-0.36583300	-0.00028100
H	-3.96119100	1.87507100	0.00624600
H	-1.49974600	2.07203900	0.00665000
C	3.30929600	-1.94298500	0.00260300
H	3.95290900	-1.83618900	-0.87870200
H	3.95184900	-1.83484000	0.88452000
H	2.86170500	-2.93967500	0.00308100

2a

C	-1.79753800	0.20211700	0.03283800
C	-0.60163400	0.88037000	-0.00104100
C	0.37514900	-0.15308100	0.02415400
H	-0.45545200	1.94816800	-0.03500000
O	-1.57202200	-1.12547600	0.06675600
N	-0.17117500	-1.35734000	0.06513500
C	1.84233000	-0.01540000	0.00717000
C	2.66306900	-1.15496600	-0.00713000
C	2.44170100	1.25164100	0.00525600
C	4.04838600	-1.02542800	-0.02266800
H	2.20181200	-2.13676500	-0.00599600
C	3.82989300	1.37858100	-0.01098500
H	1.82308300	2.14344100	0.01860300
C	4.63805400	0.24147700	-0.02502000
H	4.67085400	-1.91582700	-0.03357500

H	4.27912300	2.36777600	-0.01187100
H	5.71983900	0.34048900	-0.03757100
N	-3.09455500	0.61294100	0.08459900
H	-3.23267200	1.57504700	-0.20050800
C	-4.19801800	-0.29778900	-0.22916900
H	-4.16400700	-0.61352600	-1.28277700
H	-4.07246200	-1.19640800	0.38081100
C	-5.52851000	0.37250500	0.08399000
H	-6.35595000	-0.30974900	-0.13581400
H	-5.58328200	0.65650700	1.14028200
H	-5.67189900	1.27528300	-0.52314300

Int-II

C	0.43745400	2.87533800	1.88897100
C	2.18415200	2.40307800	0.34437900
C	2.87055900	3.07813800	1.54389300
C	1.76231100	3.19966500	2.61956200
H	-0.35609700	3.59965300	2.06989700
H	0.06147600	1.89394800	2.16793500
H	2.56065100	2.76452300	-0.61399000
H	3.73698100	2.51962700	1.89954000
H	3.22964200	4.06799200	1.24514000
H	1.92300400	2.49351200	3.43730200
H	1.74430600	4.20443300	3.05041100
N	0.76070600	2.86424200	0.43018500
C	0.58721900	4.23517500	-0.16315400
H	1.23601300	4.95105800	0.35594300
H	0.92534900	4.16386800	-1.20287700
C	-0.84273600	4.69226000	-0.08547700
C	-1.84434900	3.89653400	-0.70448300
C	-1.20169000	5.85424400	0.59554200
C	-3.19524500	4.30779500	-0.57770800
C	-2.53416800	6.26587200	0.68394400
H	-0.42084900	6.44853900	1.06627900
C	-3.52722400	5.48105100	0.10007700
H	-2.79505000	7.17687000	1.21271500
H	-4.56917900	5.77242000	0.17741600
O	-1.55536000	2.81219600	-1.38761400
C	-4.25465600	3.43369400	-1.17414500
F	-4.24443000	2.17413400	-0.65776100
F	-4.13528500	3.29321400	-2.51569800
F	-5.50098500	3.92180400	-0.94954000

C	2.24565500	0.83267900	0.26813600
C	2.14684700	0.14929600	1.65037100
C	3.26228600	0.01614700	2.48211100
C	0.92761300	-0.38334900	2.08500700
C	3.14987700	-0.59648200	3.73236100
H	4.23219800	0.37382200	2.15600000
C	0.81501000	-0.99640800	3.33299200
H	0.05912300	-0.29518100	1.44563800
C	1.92522300	-1.10494900	4.16871900
H	-0.14558000	-1.38774700	3.65613700
H	1.84518900	-1.57848900	5.14090300
C	3.55751500	0.36665700	-0.39334600
C	3.68391100	-1.01040300	-0.64550800
C	4.60175300	1.20843200	-0.78345300
C	4.79436100	-1.52433400	-1.29974800
H	2.89656600	-1.68241600	-0.32331900
C	5.72719400	0.69978400	-1.43827900
H	4.56733100	2.27294900	-0.58403800
C	5.82193100	-0.66334000	-1.70400500
H	4.87128700	-2.59015800	-1.48869700
H	6.52792000	1.36834400	-1.73479300
O	1.19600700	0.40020800	-0.55602300
Cu	-0.24818500	1.59068100	-0.79563600
C	0.05386500	-2.40252700	-2.04116900
C	-0.66246100	-2.48699500	-0.84265600
C	-1.49745100	-3.63032700	-1.02496000
H	-0.43841900	-1.94889600	0.06150400
O	-0.36337000	-3.36892100	-2.88367100
N	-1.36520900	-4.16012100	-2.22463800
C	-2.47237700	-4.17011900	-0.06725400
C	-3.53691900	-4.97157300	-0.50919200
C	-2.35756000	-3.87176000	1.29780800
C	-4.45957900	-5.47258500	0.40406800
H	-3.63399100	-5.18436600	-1.56835800
C	-3.28551300	-4.37222400	2.20810500
H	-1.53882000	-3.25157900	1.64890300
C	-4.33748800	-5.17381600	1.76395100
H	-5.28351000	-6.08755000	0.05372100
H	-3.19468300	-4.12484900	3.26107500
H	-5.06722300	-5.55384600	2.47270600
N	0.95324400	-1.51930700	-2.43976800
H	1.19236800	-0.77765600	-1.75137300

C	1.54962000	-1.48123200	-3.77226400
H	2.33898900	-2.24140200	-3.84244500
H	0.78343200	-1.73777300	-4.51092000
C	-3.07352500	-1.24079300	-2.38957600
C	-2.47659300	-0.31563300	-0.30117300
C	-2.03649100	-0.40464100	-1.75171200
O	-1.13640700	0.27700800	-2.24967100
O	-1.90538500	0.33218500	0.57743100
N	-3.62589700	-1.04729200	-0.25407700
N	-3.96845900	-1.57792100	-1.51707500
C	-5.64920000	-2.05322400	0.63554900
C	-6.48395000	-2.33131400	1.71505100
C	-6.17121400	-1.87286800	2.99543000
C	-5.00872200	-1.12517200	3.18826700
C	-4.15927600	-0.83655100	2.12195000
C	-4.48454300	-1.30660500	0.84231500
H	-5.88138200	-2.41750400	-0.35574300
H	-7.38437400	-2.91546200	1.54853800
H	-6.82688500	-2.09329000	3.83258700
H	-4.75441300	-0.75709600	4.17823600
H	-3.26031100	-0.25592600	2.27452300
C	2.12114400	-0.09502900	-4.04460200
H	2.58229700	-0.07265000	-5.03717000
H	1.33213900	0.66344300	-4.00987600
H	2.88621900	0.16669600	-3.30700800
C	-3.13428800	-1.64415800	-3.81779000
H	-3.06624600	-0.76223100	-4.46520800
H	-2.29658600	-2.30538600	-4.06342600
H	-4.06997700	-2.17104000	-4.01867100
C	4.38316400	-0.75687100	4.57290300
C	6.99029700	-1.21346200	-2.46718400
F	7.36952800	-2.42715600	-2.00544400
F	6.69695500	-1.37763900	-3.78149900
F	8.07053000	-0.40365100	-2.40760800
F	5.19407000	0.32502900	4.48845300
F	5.12459100	-1.82241100	4.18395100
F	4.09318500	-0.93889300	5.88031900

Int-III

C	0.34178700	3.22797400	1.13000800
C	2.09943200	2.42796800	-0.25719200
C	2.75329900	3.46303900	0.67402700

C	1.64848200	3.83513200	1.69405900
H	-0.49370000	3.92683000	1.10818400
H	0.03106900	2.35654900	1.70163600
H	2.43700400	2.52152400	-1.29039800
H	3.65401600	3.08074200	1.15577500
H	3.05131600	4.33999200	0.09117800
H	1.86220900	3.41944900	2.68153000
H	1.56815300	4.92008300	1.80424000
N	0.64884500	2.79644000	-0.26665300
C	0.39154200	3.91289500	-1.24027200
H	1.04257700	4.76620300	-1.01307900
H	0.67731400	3.52690100	-2.22602100
C	-1.04397700	4.35299000	-1.22353100
C	-2.06013600	3.38574900	-1.46517600
C	-1.38742400	5.67844800	-0.96277500
C	-3.41099900	3.82562800	-1.41161300
C	-2.71945700	6.09881400	-0.93923600
H	-0.59195800	6.39753400	-0.77516500
C	-3.72642900	5.16026700	-1.15970200
H	-2.96774700	7.13648500	-0.74092700
H	-4.76833000	5.46068100	-1.12859800
O	-1.79701200	2.13501800	-1.74387400
C	-4.48905600	2.80722000	-1.61442700
F	-4.44251200	1.80951100	-0.69370900
F	-4.43542100	2.21038000	-2.82847200
F	-5.72956600	3.35488200	-1.51388300
C	2.27740700	0.91379600	0.11706300
C	2.20694700	0.65144900	1.63654200
C	3.31961300	0.83931700	2.46163600
C	1.01982500	0.18830800	2.21645100
C	3.23619600	0.60414100	3.83593000
H	4.26687100	1.15398800	2.03806900
C	0.93690100	-0.04664200	3.58934300
H	0.14845600	0.03579300	1.59148900
C	2.04359600	0.16163400	4.41066000
H	0.00099300	-0.39007600	4.02074100
H	1.98552000	-0.01768900	5.47846500
C	3.61808600	0.36237800	-0.40661400
C	3.86697400	-1.00295700	-0.18241700
C	4.54978100	1.08864800	-1.15299600
C	4.96986700	-1.63567100	-0.73713900
H	3.17215700	-1.57349100	0.42418900

C	5.66271400	0.46022000	-1.71876400
H	4.42677800	2.15213600	-1.31943100
C	5.86330400	-0.90396800	-1.52849400
H	5.14079200	-2.69293200	-0.56151400
H	6.36486100	1.03529700	-2.31236600
O	1.27085200	0.19581900	-0.54455700
Cu	-0.30687900	1.16258800	-1.05607400
C	0.42491300	-2.82079200	-1.35528900
C	-0.61004600	-2.38887100	-0.40901800
C	-1.22172100	-3.70688600	-0.07914100
H	-0.23215700	-1.78306300	0.41288700
O	0.27060500	-4.10768800	-1.66739000
N	-0.77963700	-4.67341000	-0.82280000
C	-2.29356700	-3.93399100	0.89481800
C	-3.21228100	-4.98038300	0.70853500
C	-2.42230800	-3.08707800	2.00623300
C	-4.24381500	-5.16909300	1.62206000
H	-3.12038300	-5.61978200	-0.16293500
C	-3.45935000	-3.28046100	2.91533300
H	-1.72459100	-2.27058200	2.15553000
C	-4.37203700	-4.31812800	2.72387600
H	-4.96023100	-5.97003600	1.46634000
H	-3.56517000	-2.60777900	3.76003700
H	-5.19143500	-4.45419900	3.42304300
N	1.34504400	-2.08780100	-1.88933600
H	1.41225200	-1.10831800	-1.48951500
C	2.29355400	-2.54256700	-2.91465600
H	3.13153300	-3.04053000	-2.41529800
H	1.79032700	-3.27998300	-3.54572000
C	-2.73927200	-2.09474700	-1.93798300
C	-2.47376300	-0.70360600	-0.05771700
C	-1.65426000	-1.31216000	-1.21847300
O	-0.96706300	-0.45931900	-1.95949800
O	-2.02274400	0.04717100	0.80441200
N	-3.73558000	-1.19857800	-0.19464500
N	-3.87558700	-2.01534400	-1.34455200
C	-5.93921100	-1.92494000	0.51171700
C	-7.01181700	-1.84246600	1.39619300
C	-7.00333100	-0.91674700	2.44113800
C	-5.91007500	-0.06140700	2.58712300
C	-4.82858300	-0.12571600	1.71019100
C	-4.84380300	-1.06825200	0.67315100

H	-5.93456500	-2.64792200	-0.29301000
H	-7.85757500	-2.51186900	1.26609700
H	-7.84200500	-0.85752900	3.12874500
H	-5.89540900	0.67290000	3.38774200
H	-3.98538200	0.54071900	1.81980900
C	2.78583500	-1.35482700	-3.72984300
H	3.53757200	-1.69215400	-4.44995300
H	1.95968500	-0.88626200	-4.27462700
H	3.24914200	-0.60284500	-3.08547500
C	-2.55580400	-2.80974400	-3.22779400
H	-2.10954000	-2.12652600	-3.95950200
H	-1.87832700	-3.66451300	-3.11732100
H	-3.51661900	-3.16936300	-3.60410200
C	4.46971700	0.77248400	4.67420300
C	6.97163200	-1.62051200	-2.23856000
F	7.51024200	-2.60355400	-1.48222500
F	6.52021000	-2.21431400	-3.37484600
F	7.97467800	-0.79364100	-2.60323600
F	5.19622200	1.84974900	4.29123600
F	5.29529300	-0.29878600	4.57735100
F	4.18330300	0.92756400	5.98553000

(R)-3ca

C	3.08759100	0.43792300	0.05061100
C	1.70967700	0.30292100	-0.02440000
C	1.23152600	1.60941400	0.30034700
H	1.69014500	-1.24973600	-2.20660200
O	3.41102700	1.70014200	0.36405800
N	2.21102700	2.46138900	0.53451200
C	-0.16503100	2.08606800	0.38628600
C	-1.09874800	1.41785700	1.18944800
C	-0.56491400	3.21374000	-0.34270300
C	-2.42119600	1.85499900	1.24074100
H	-0.79011200	0.55904900	1.77644700
C	-1.88644500	3.65171700	-0.28440800
H	0.16222000	3.72921900	-0.96162400
C	-2.81800300	2.96960100	0.50077600
H	-3.14099700	1.31935200	1.85191600
H	-2.19101100	4.52121700	-0.86000900
H	-3.85110300	3.30361300	0.53424400
N	4.08407900	-0.46477600	-0.10910100
H	3.78050900	-1.29230000	-0.61270300

C	5.48231200	-0.06302200	-0.27020600
H	5.62842700	0.47784600	-1.21688400
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C	0.62662900	-1.84105400	0.75334600
C	-0.39239900	-0.70613200	-1.03582800
C	0.99934500	-0.95845000	-0.42116800
O	1.77365300	-1.72312500	-1.35632200
O	-0.59117100	-0.13868600	-2.09659100
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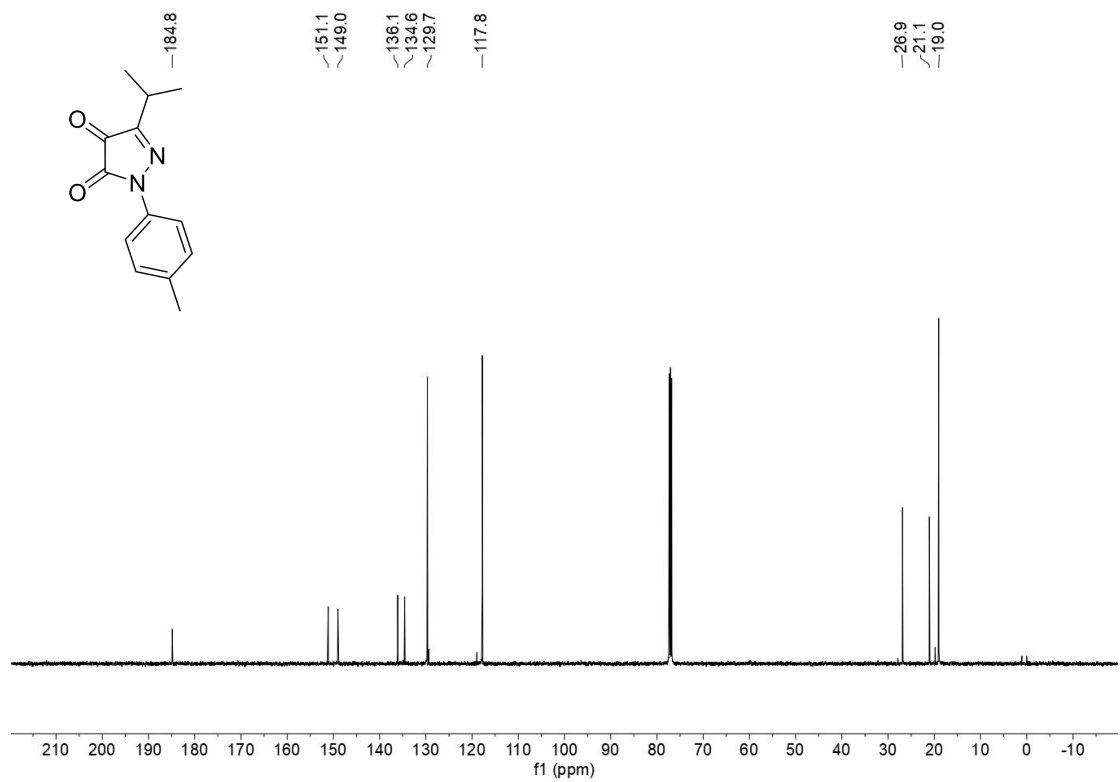
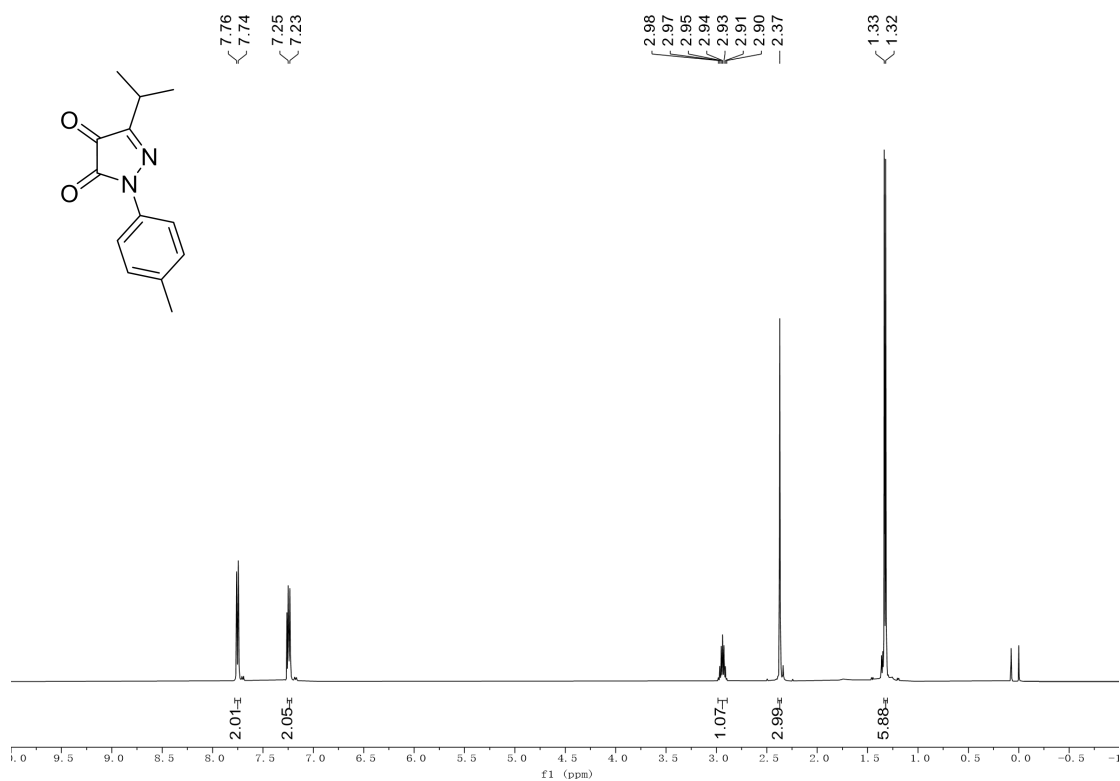
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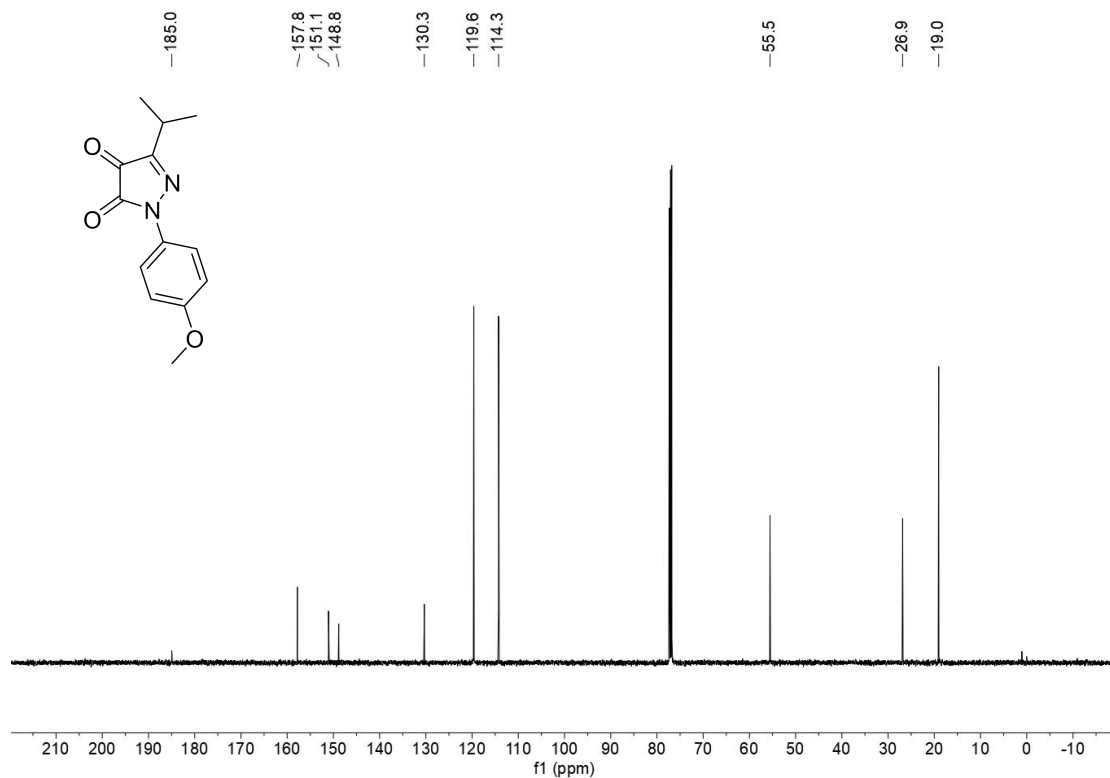
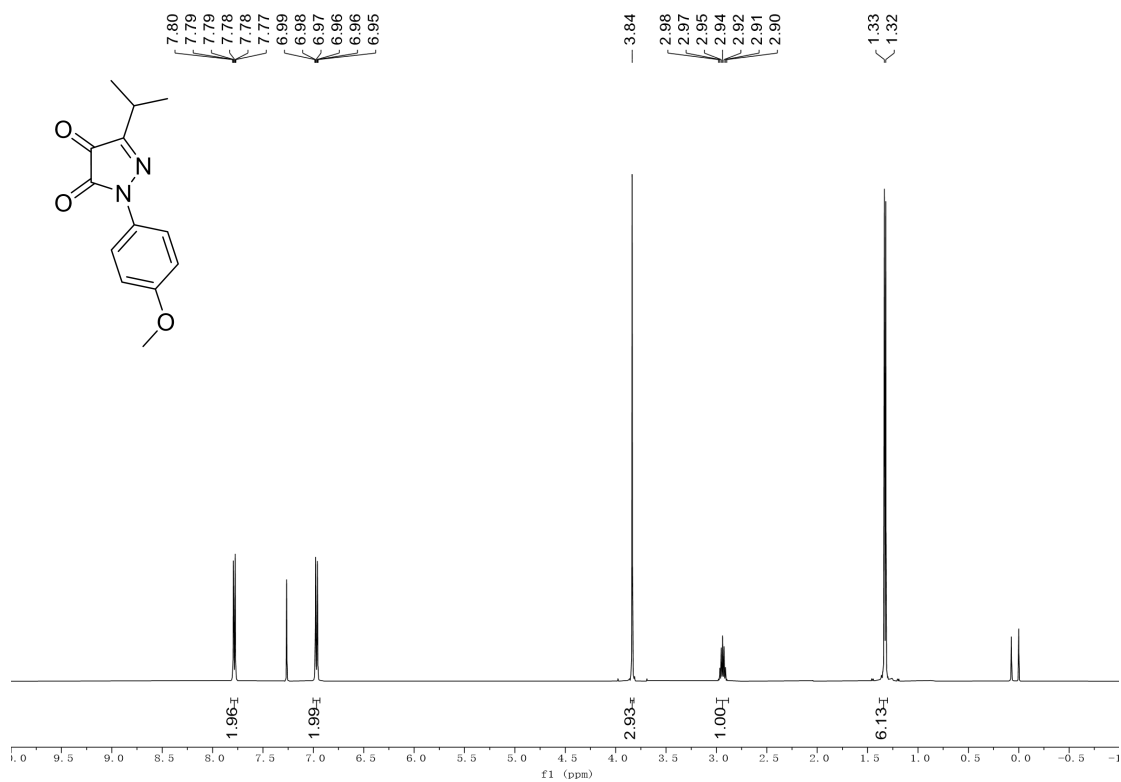
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Part II NMR spectra

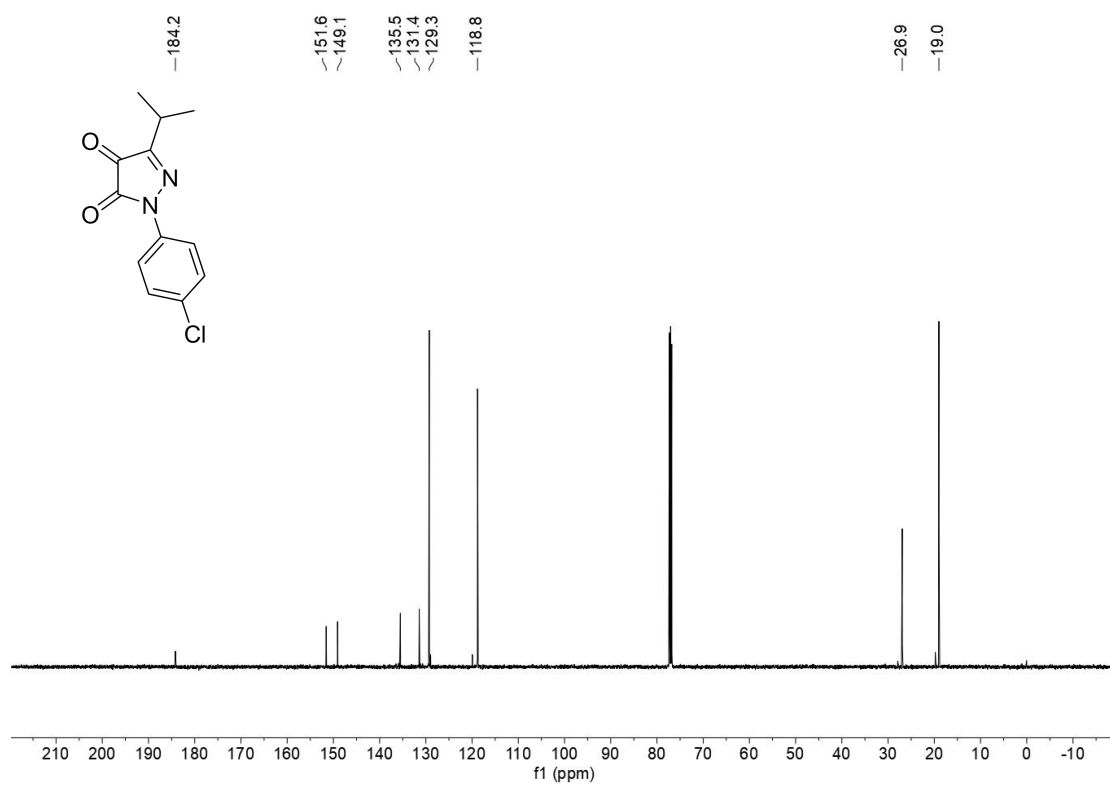
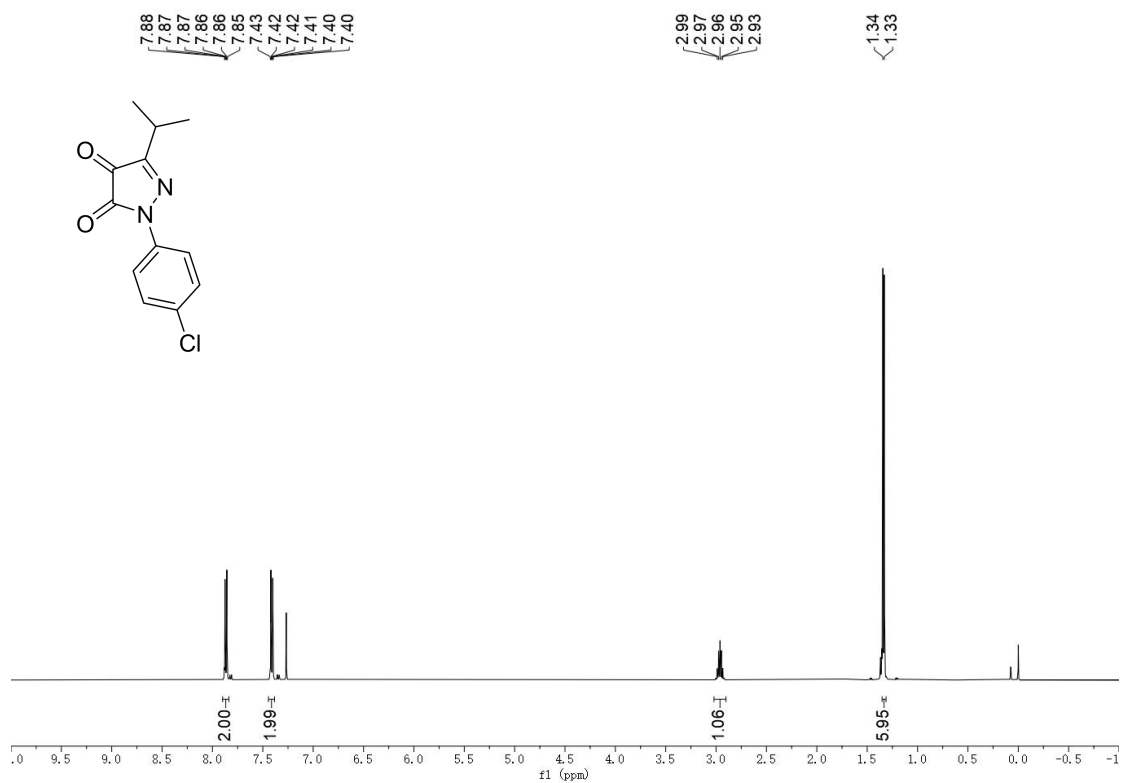
^1H NMR and ^{13}C NMR of **1d**



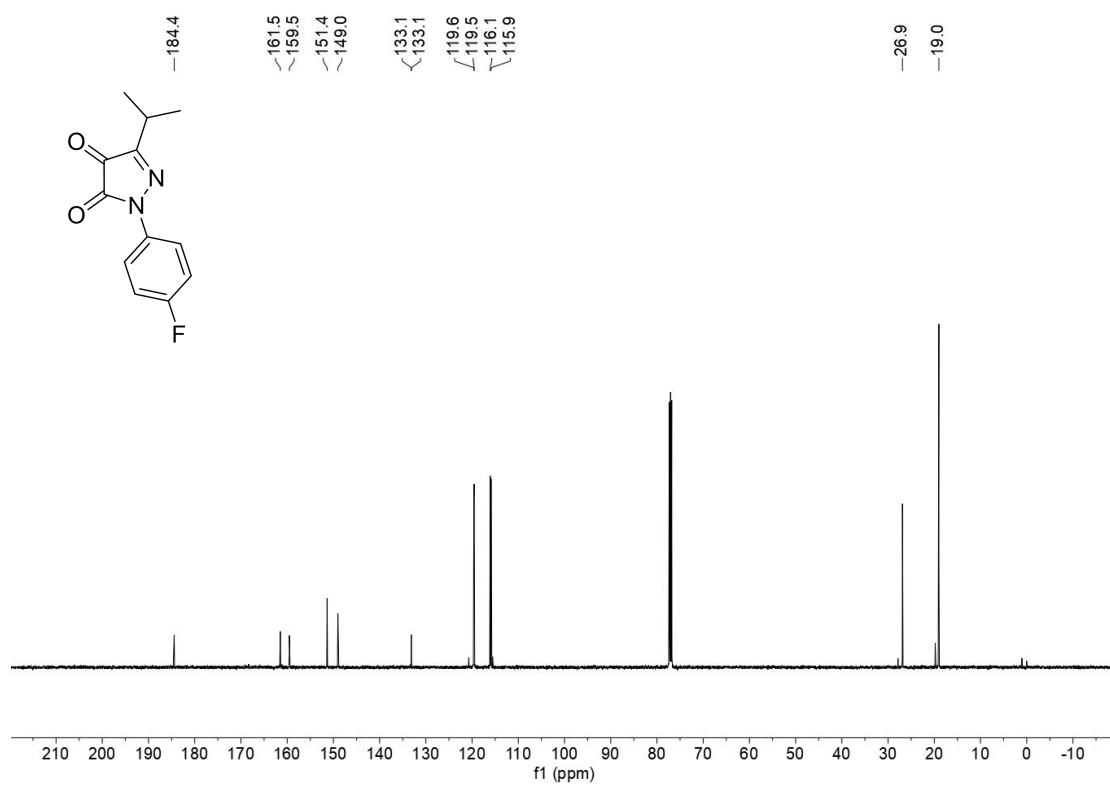
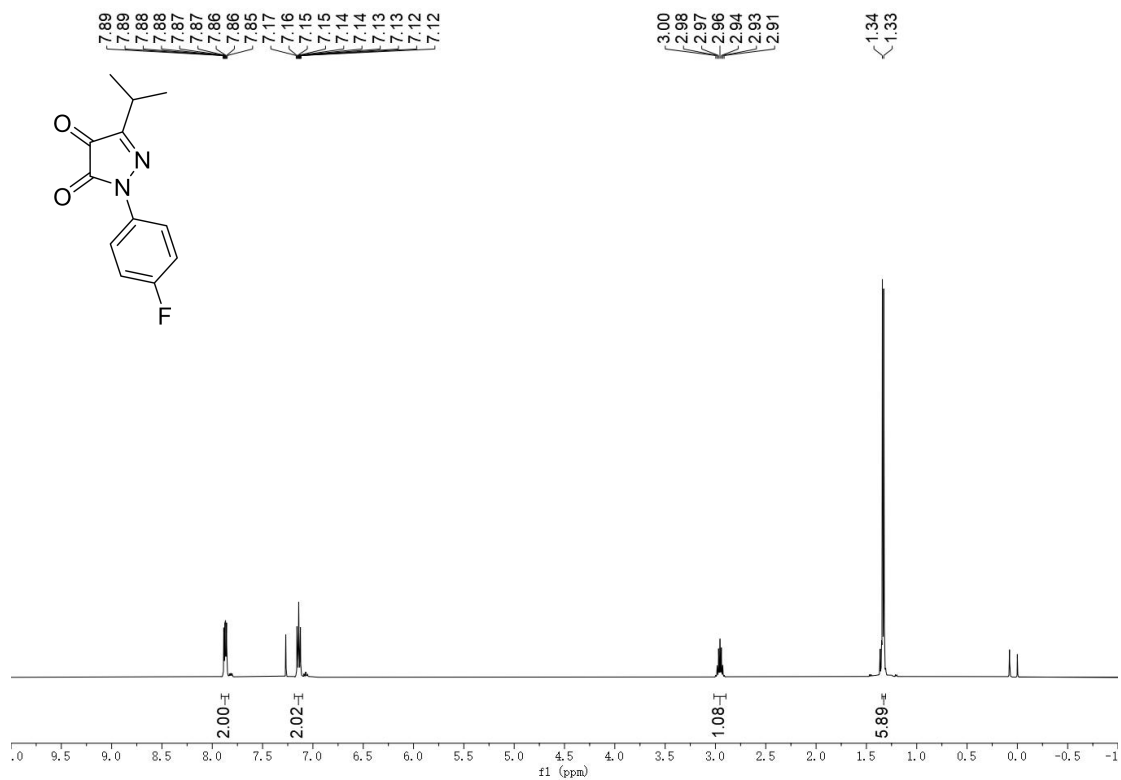
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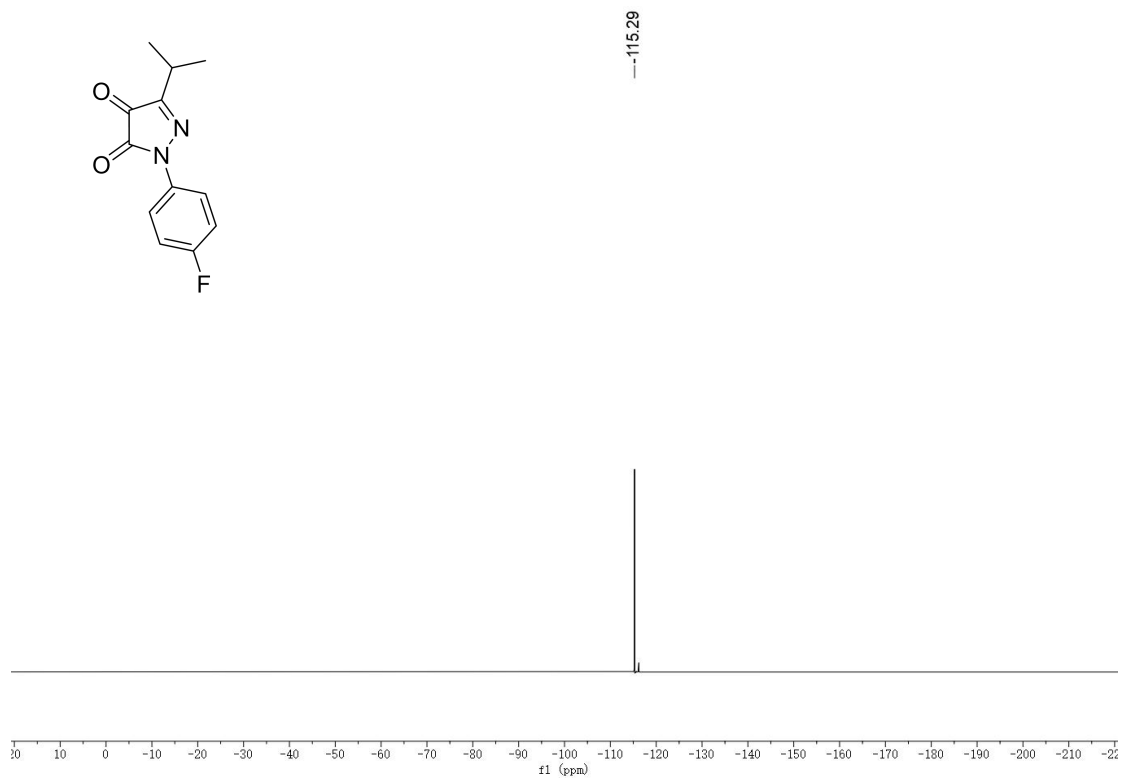


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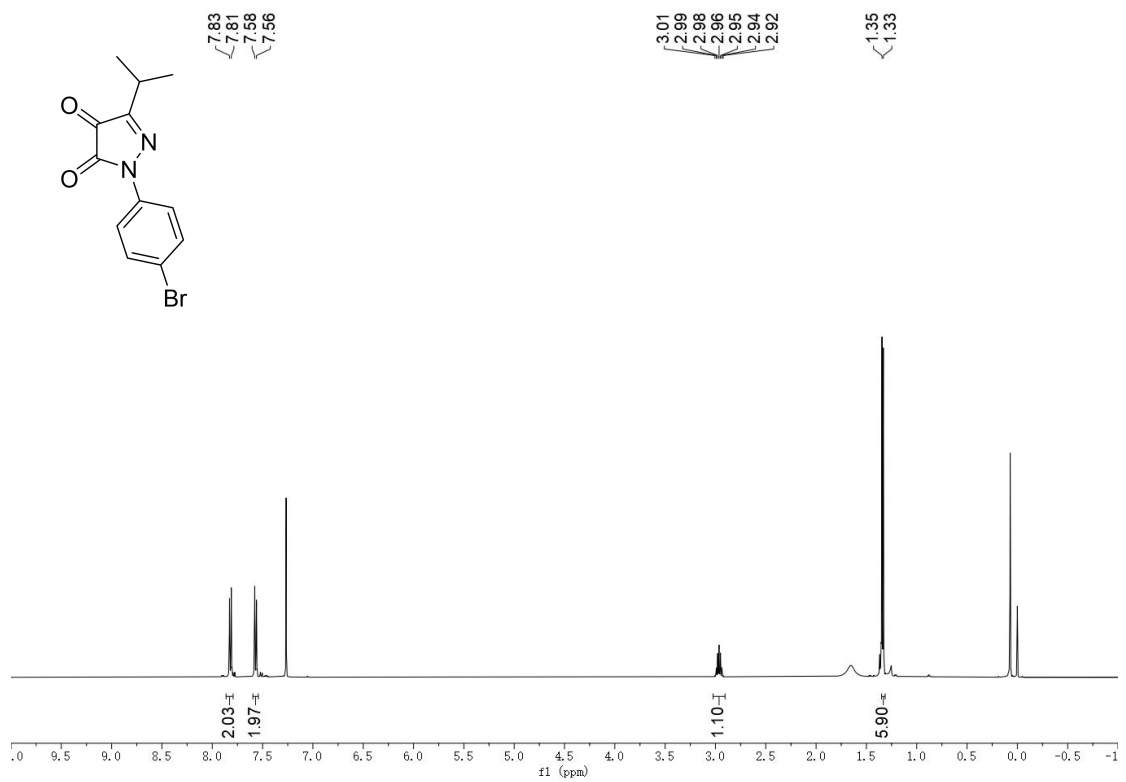


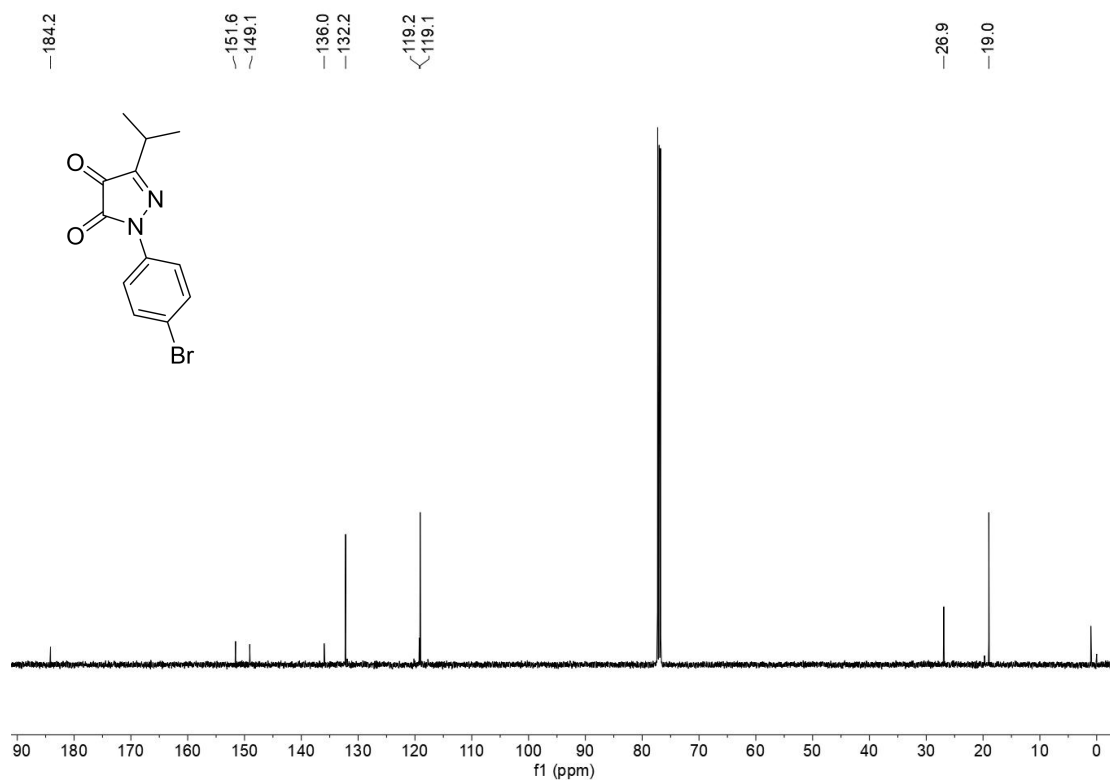
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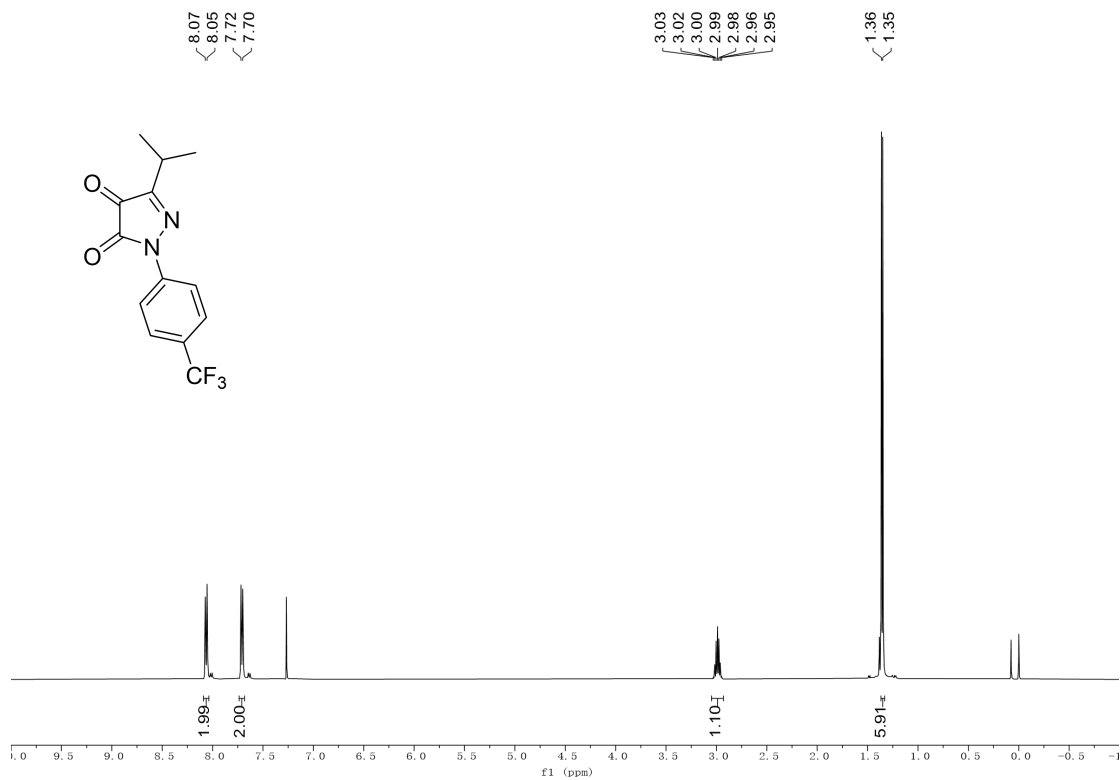


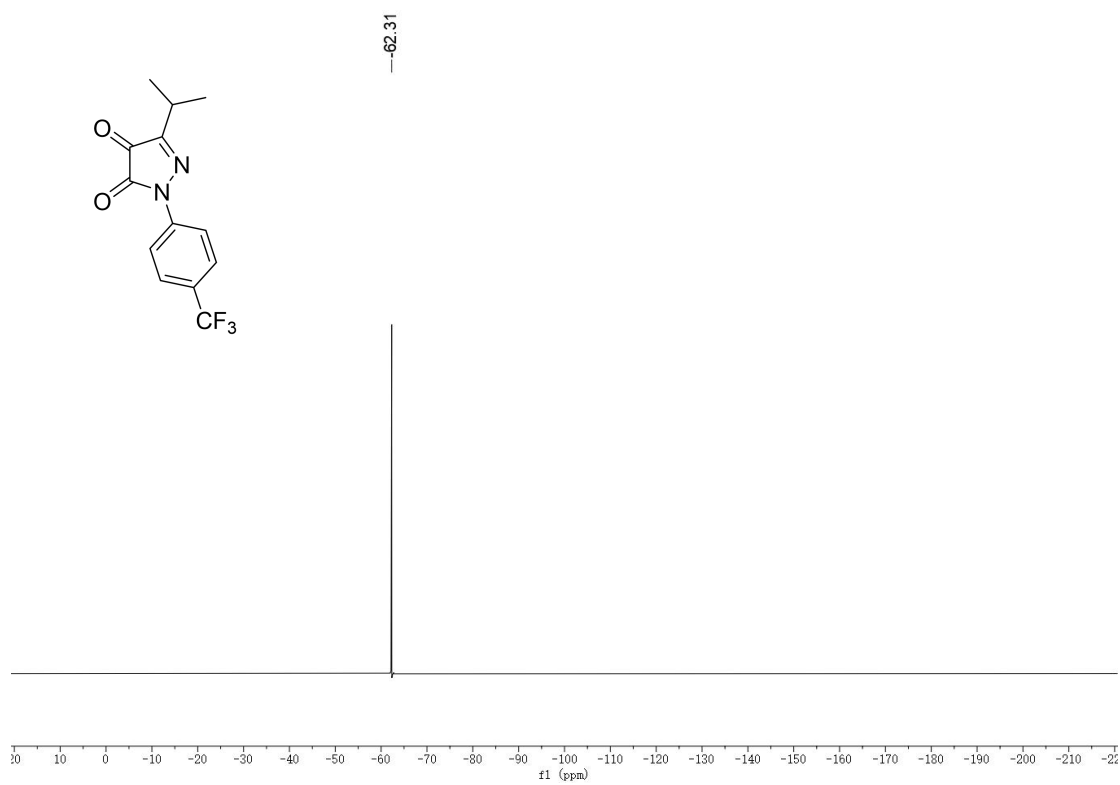
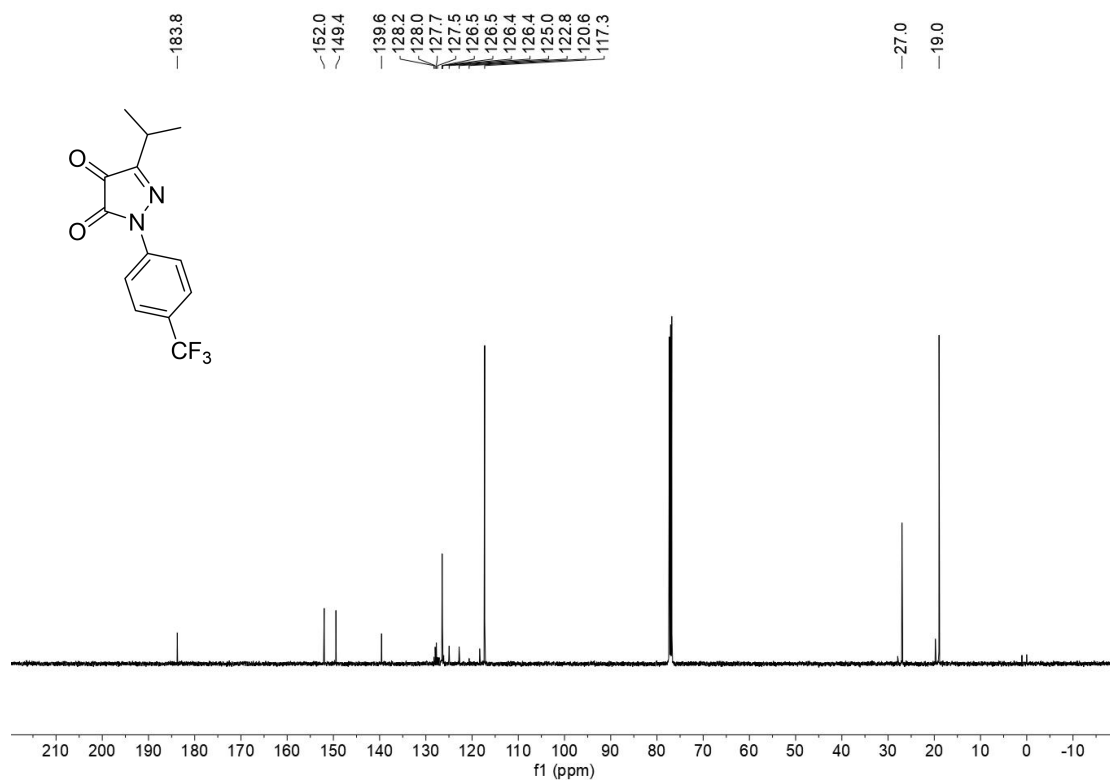
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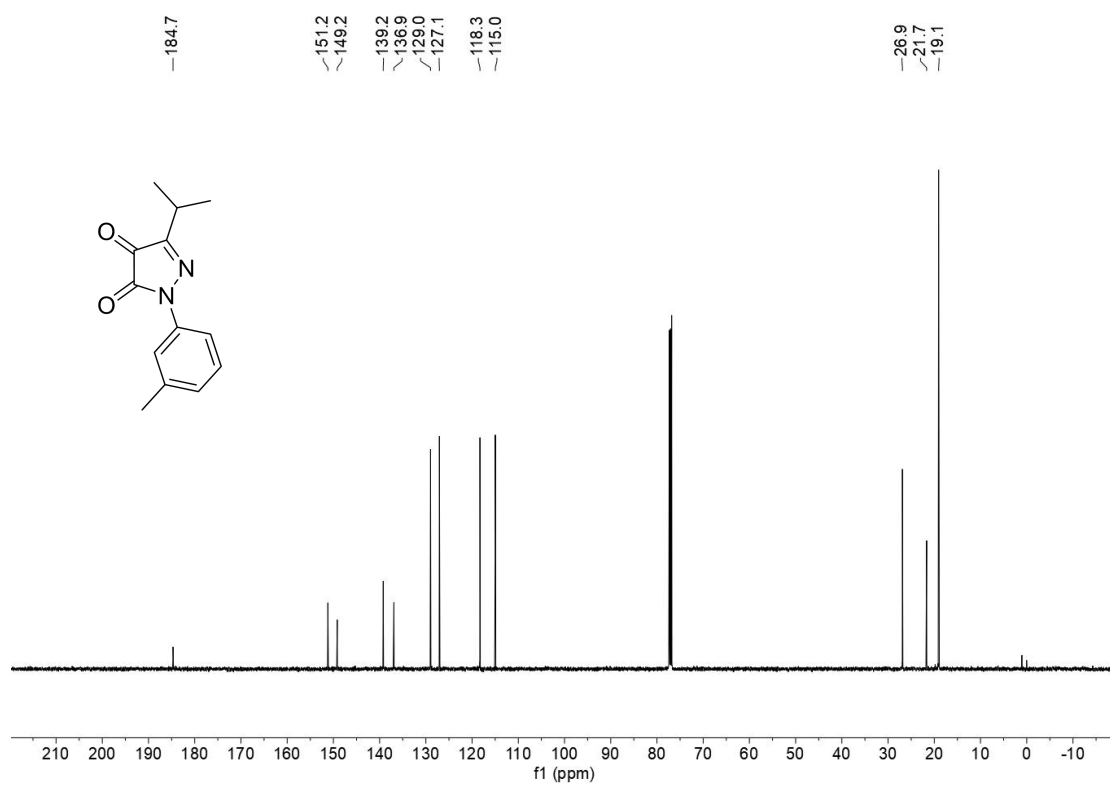
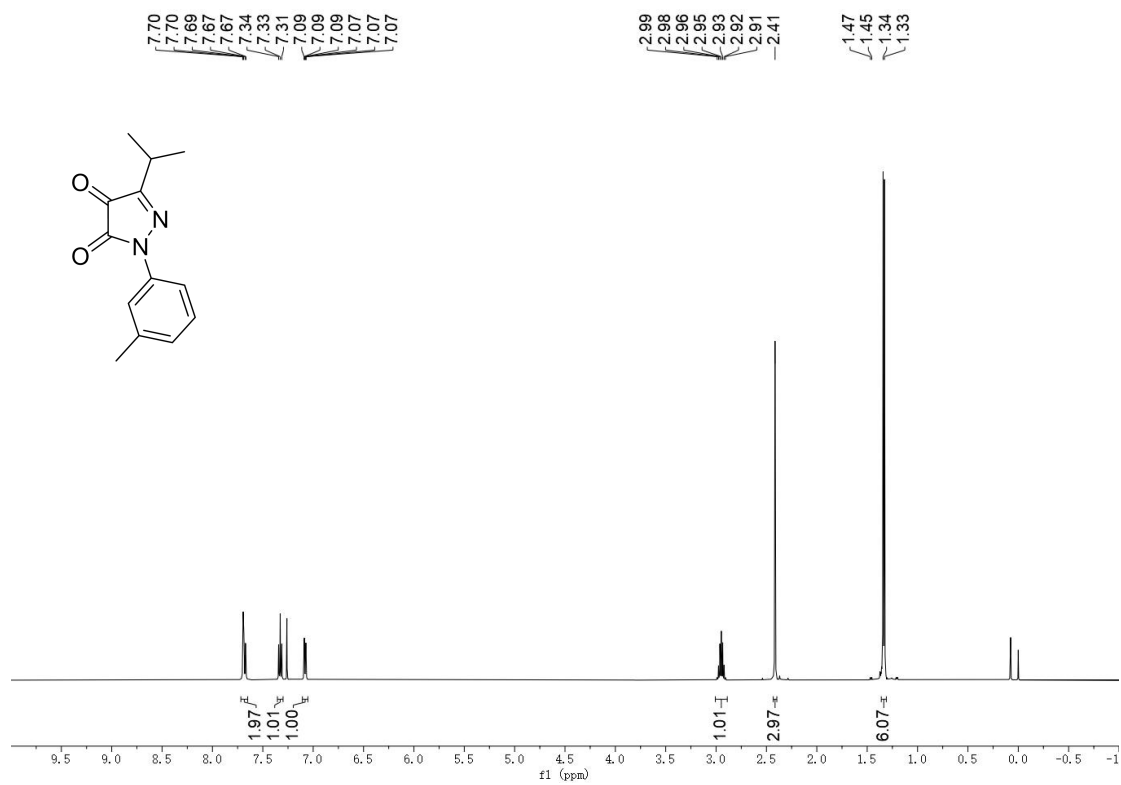


¹H NMR, ¹³C NMR and ¹⁹F NMR of **1i**

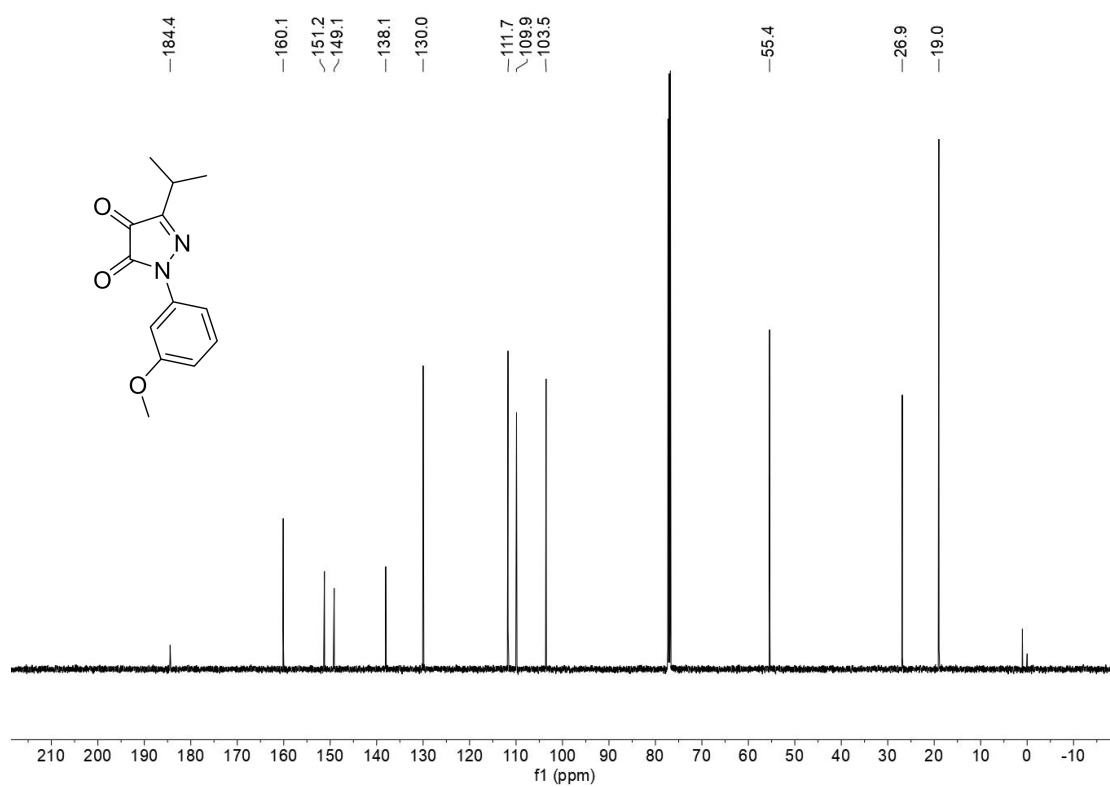
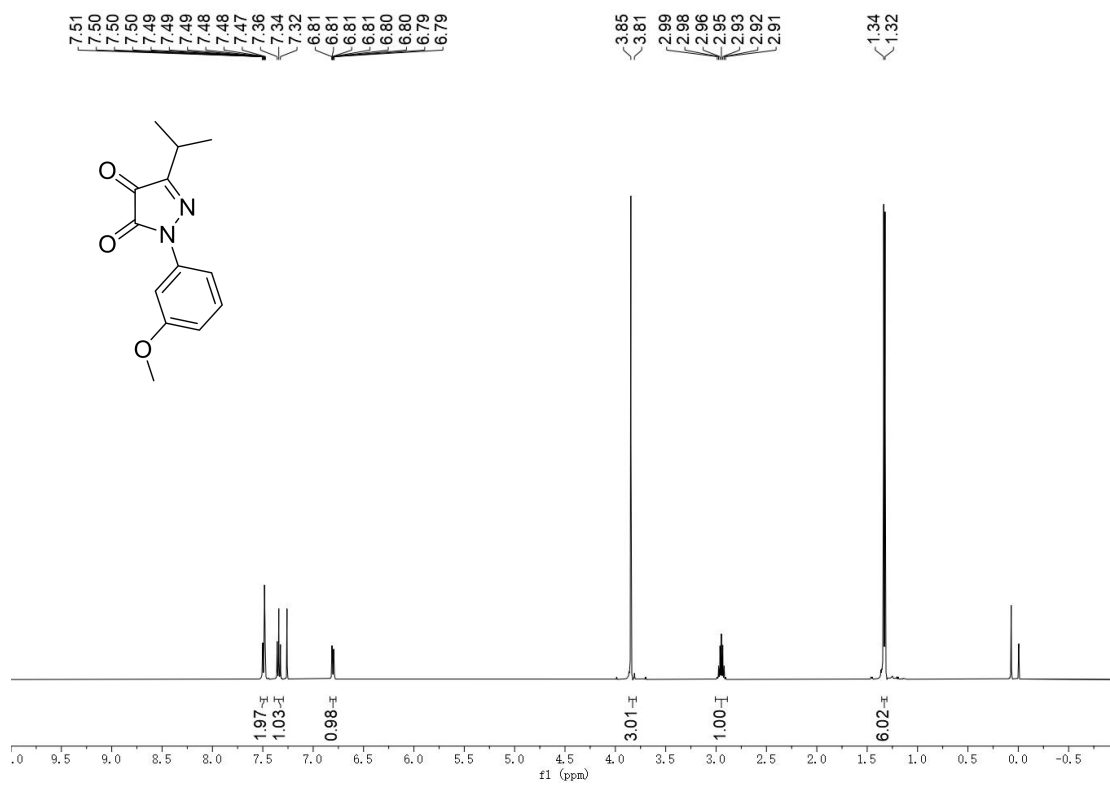




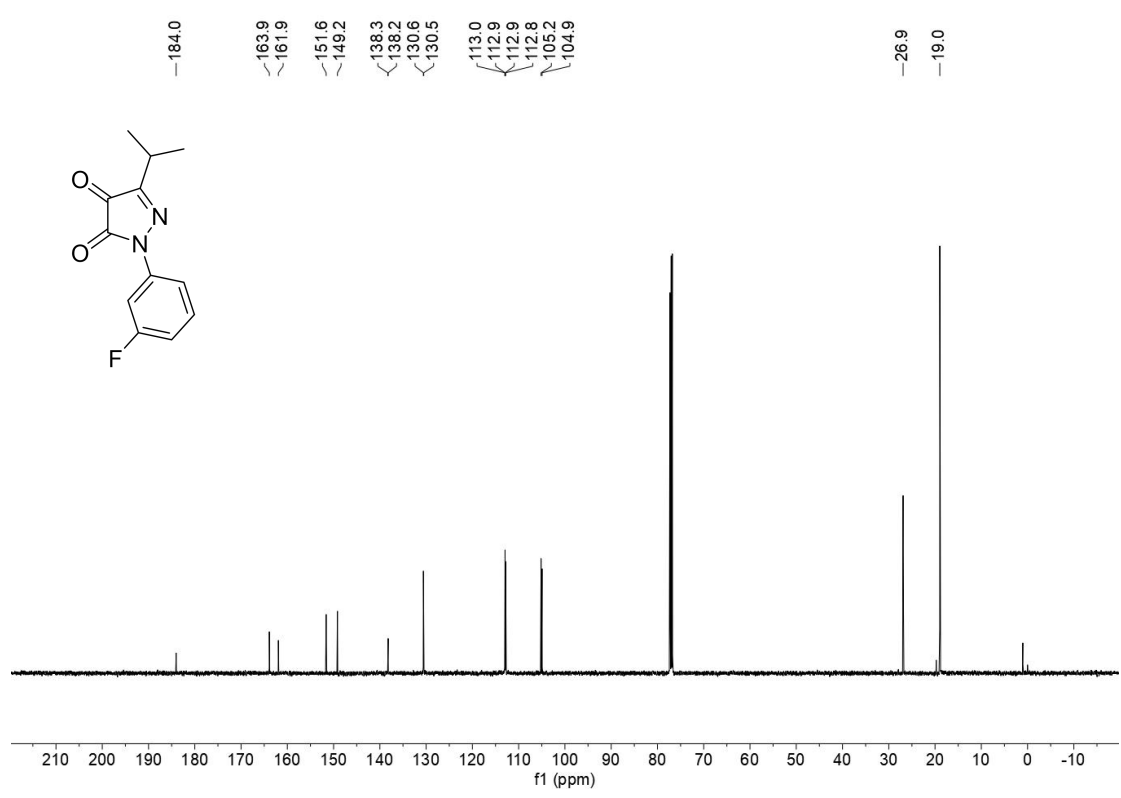
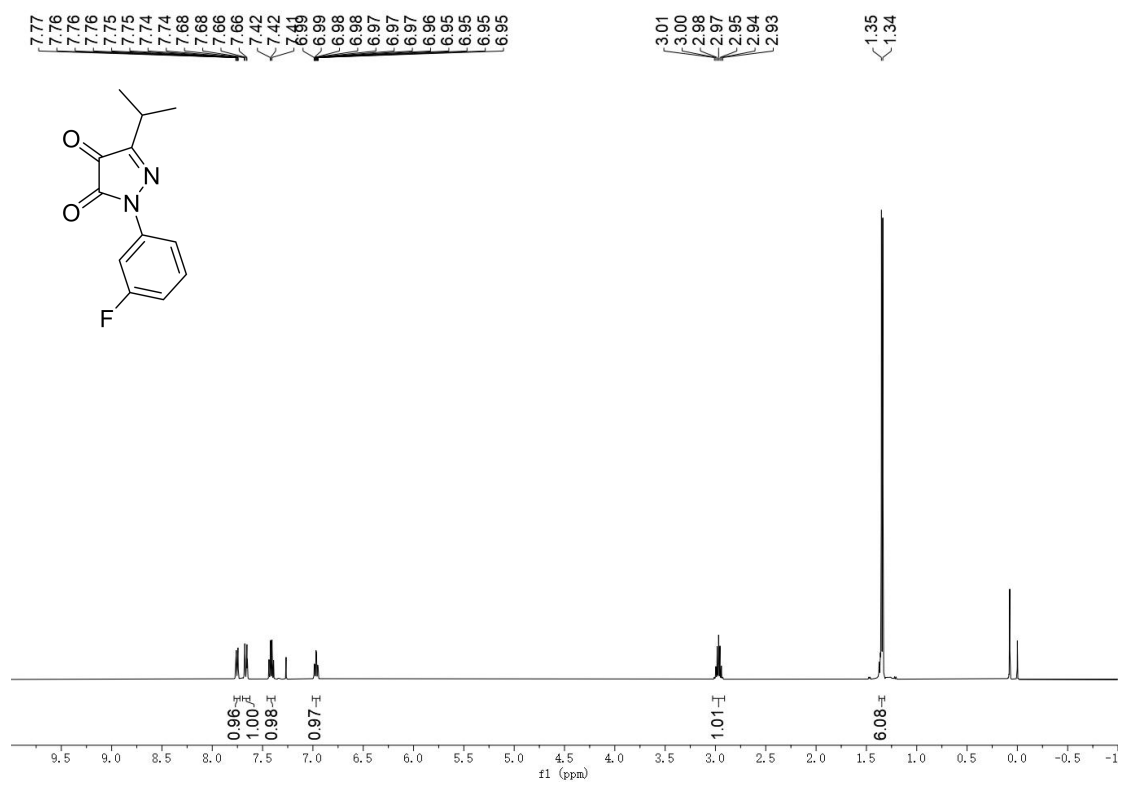
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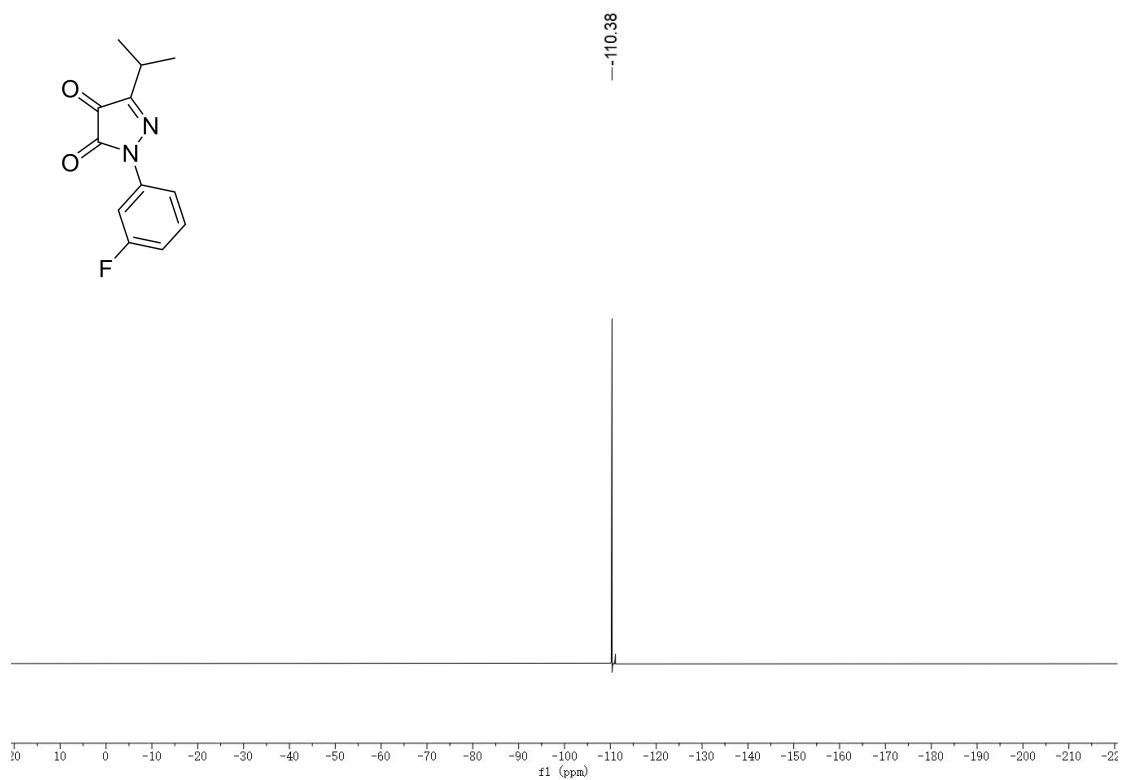


^1H NMR and ^{13}C NMR of **11**

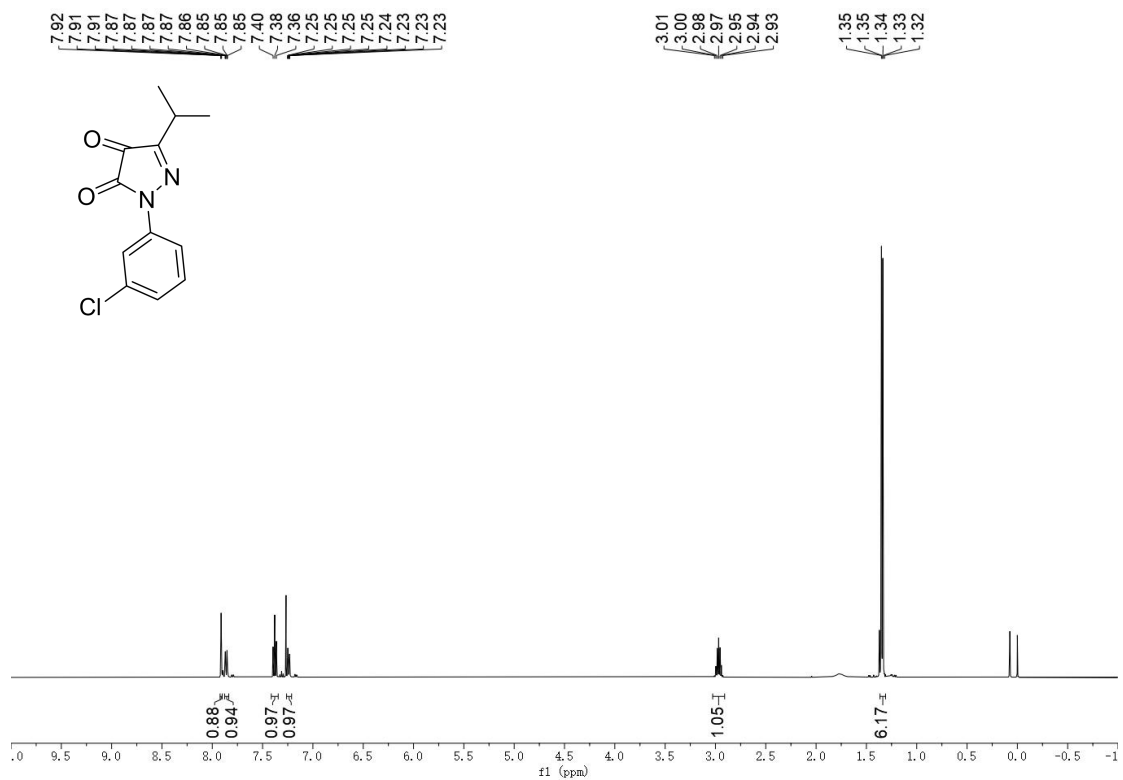


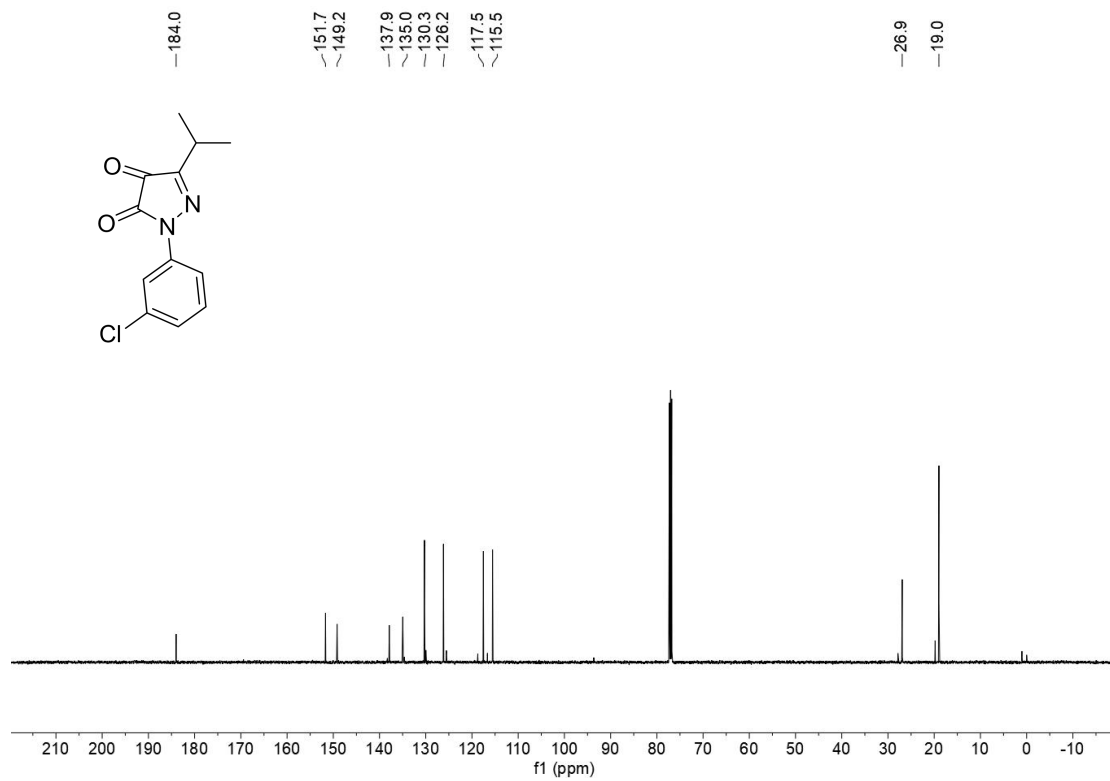
¹H NMR, ¹³C NMR and ¹⁹F NMR of **1m**



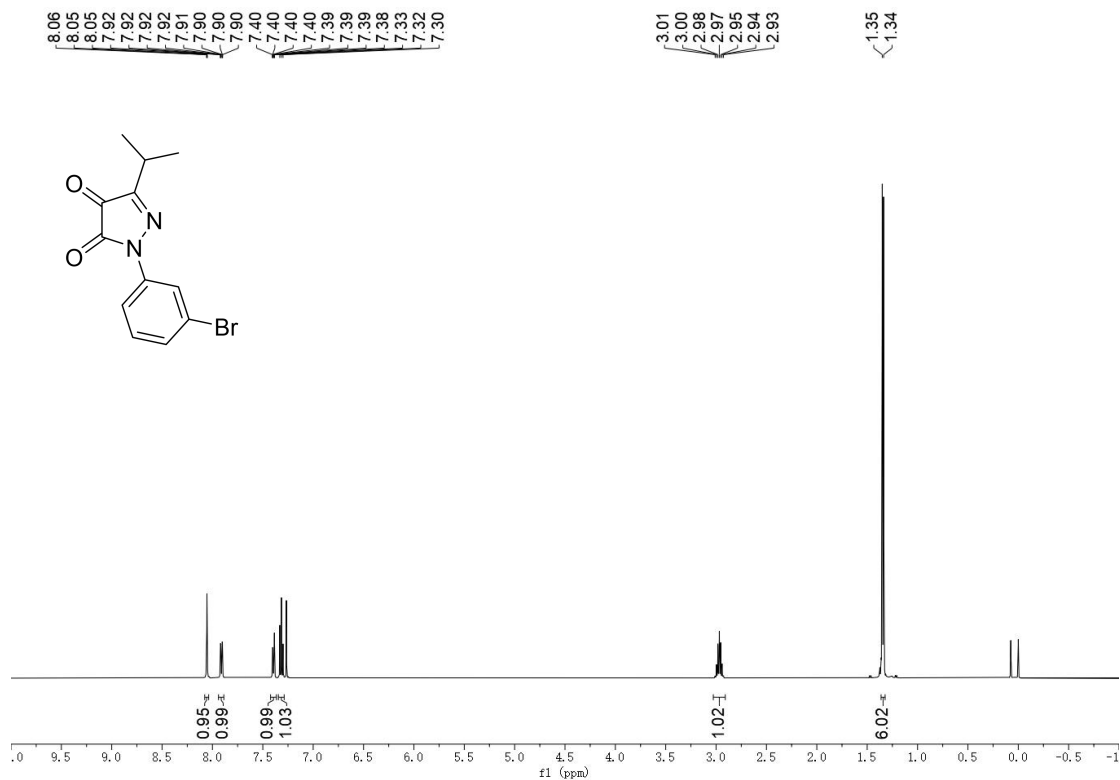


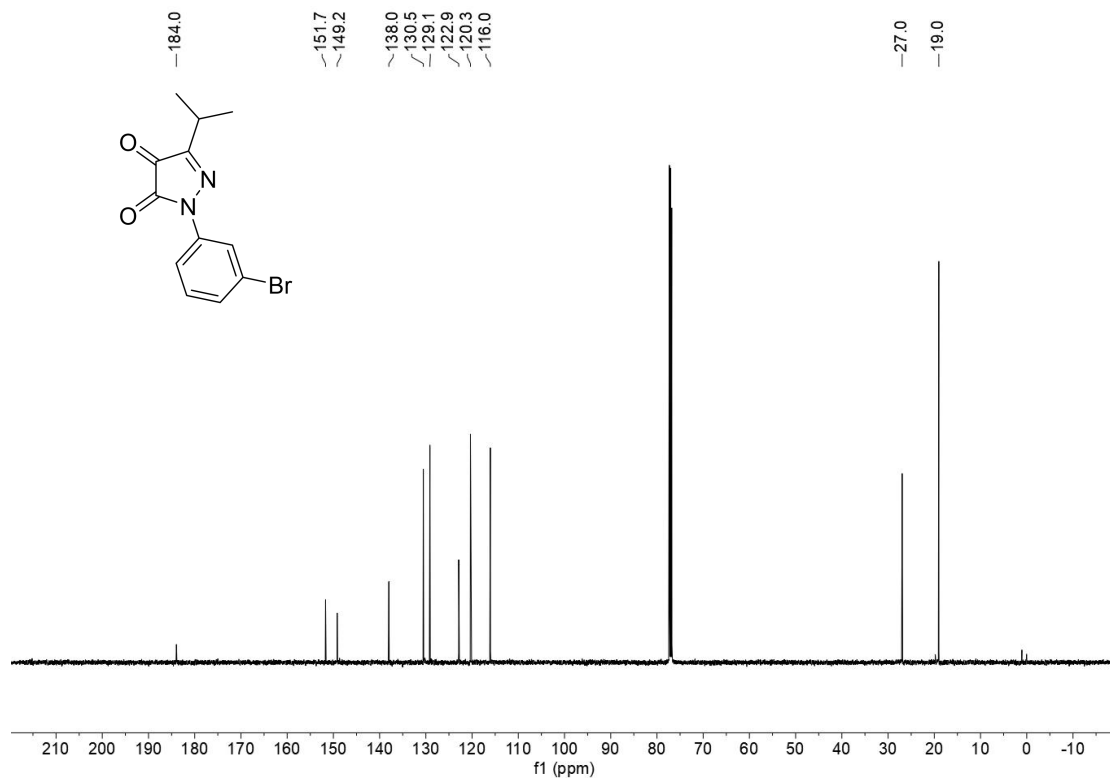
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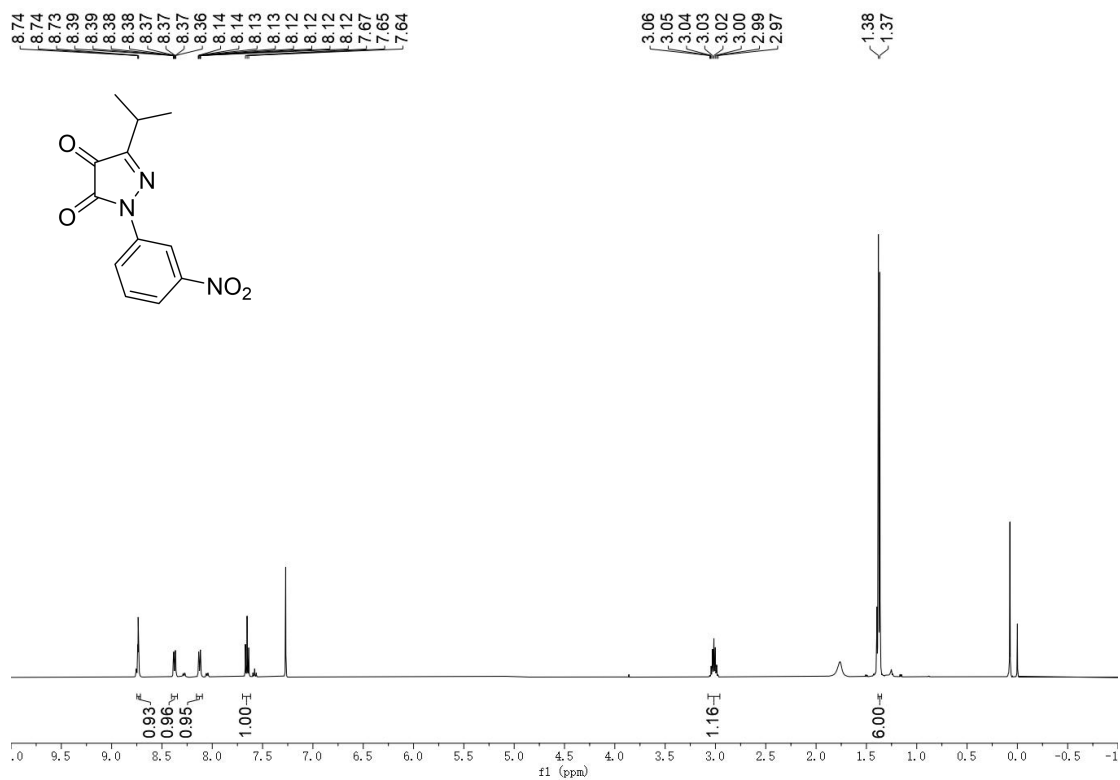


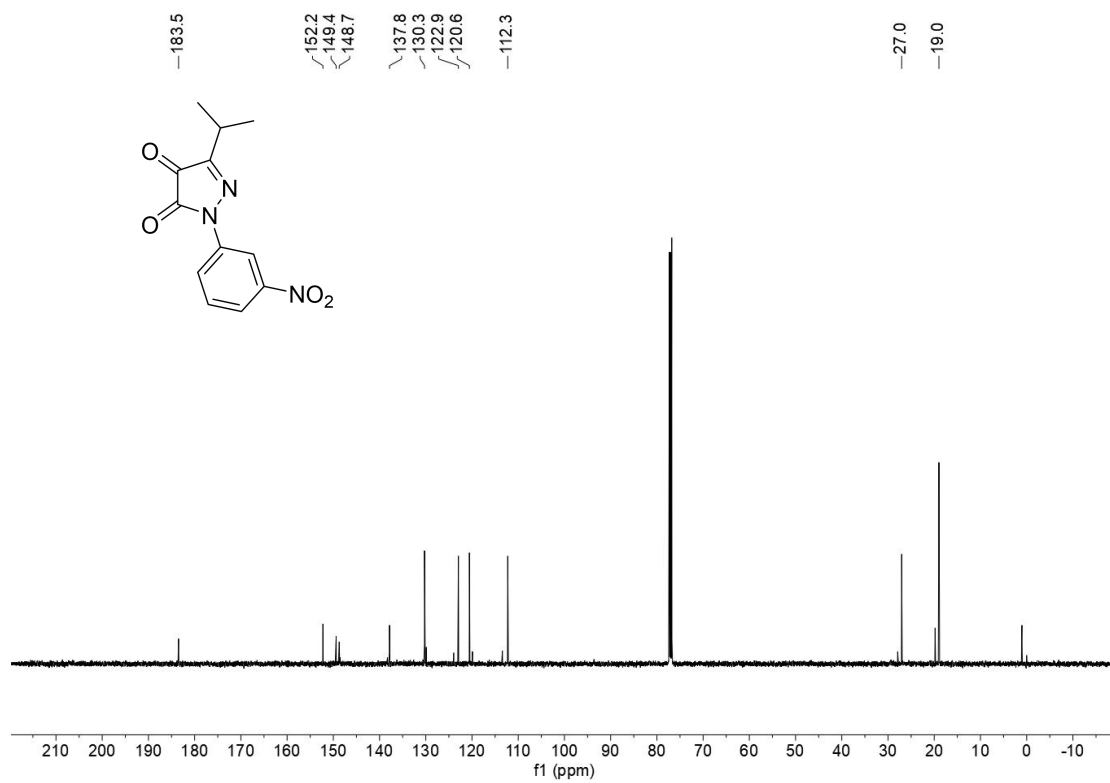
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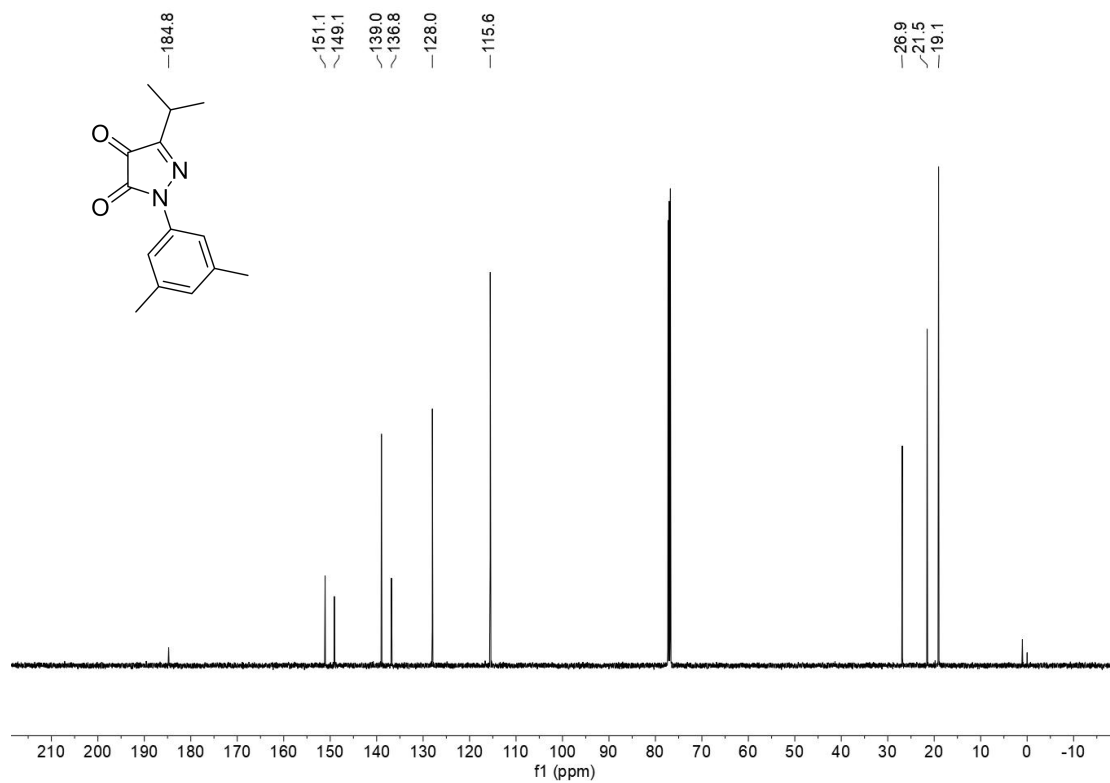
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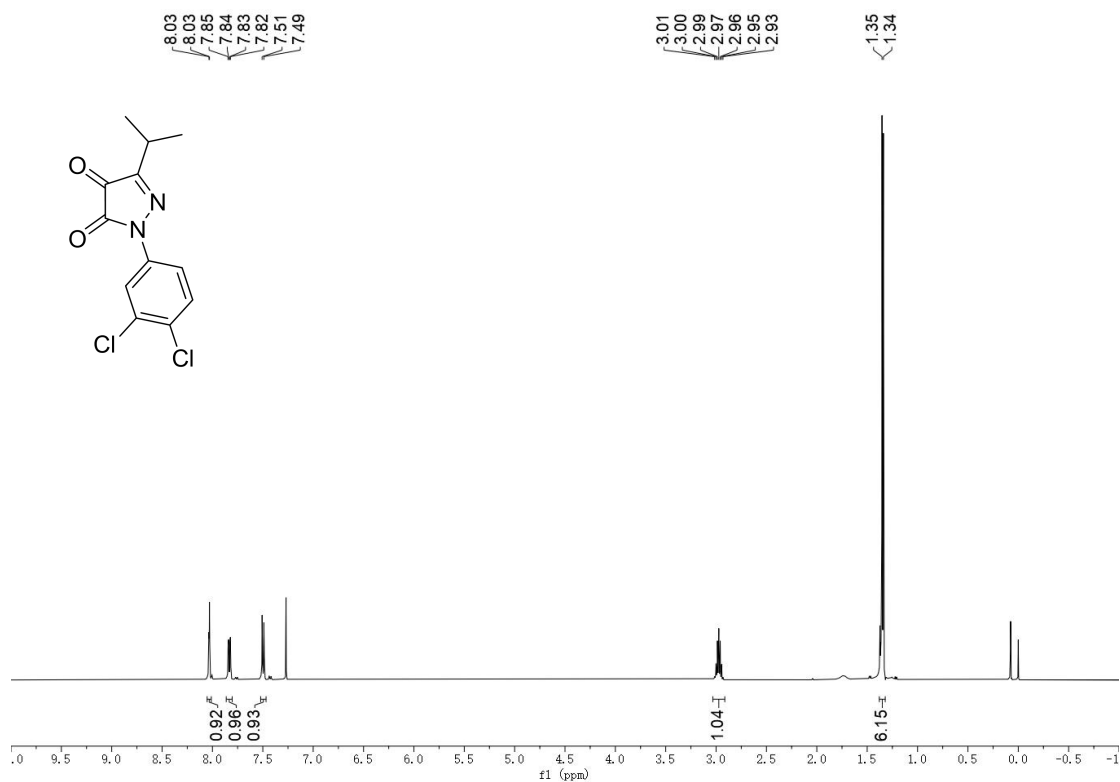


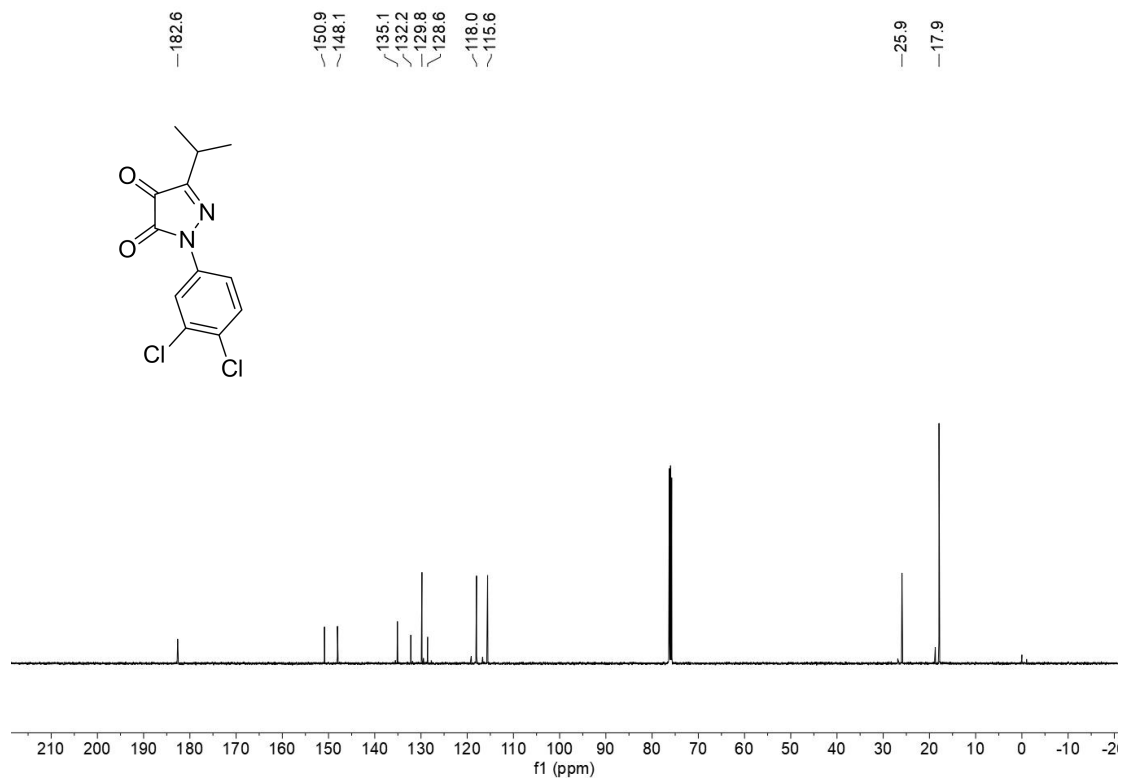
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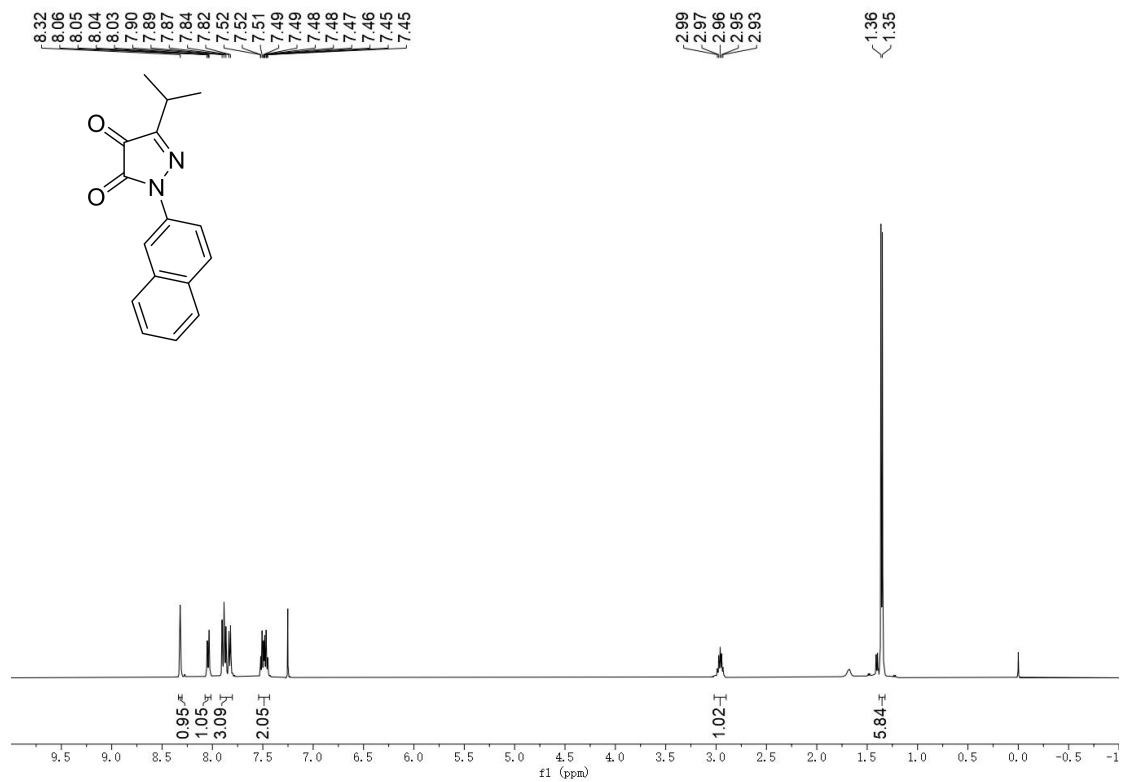


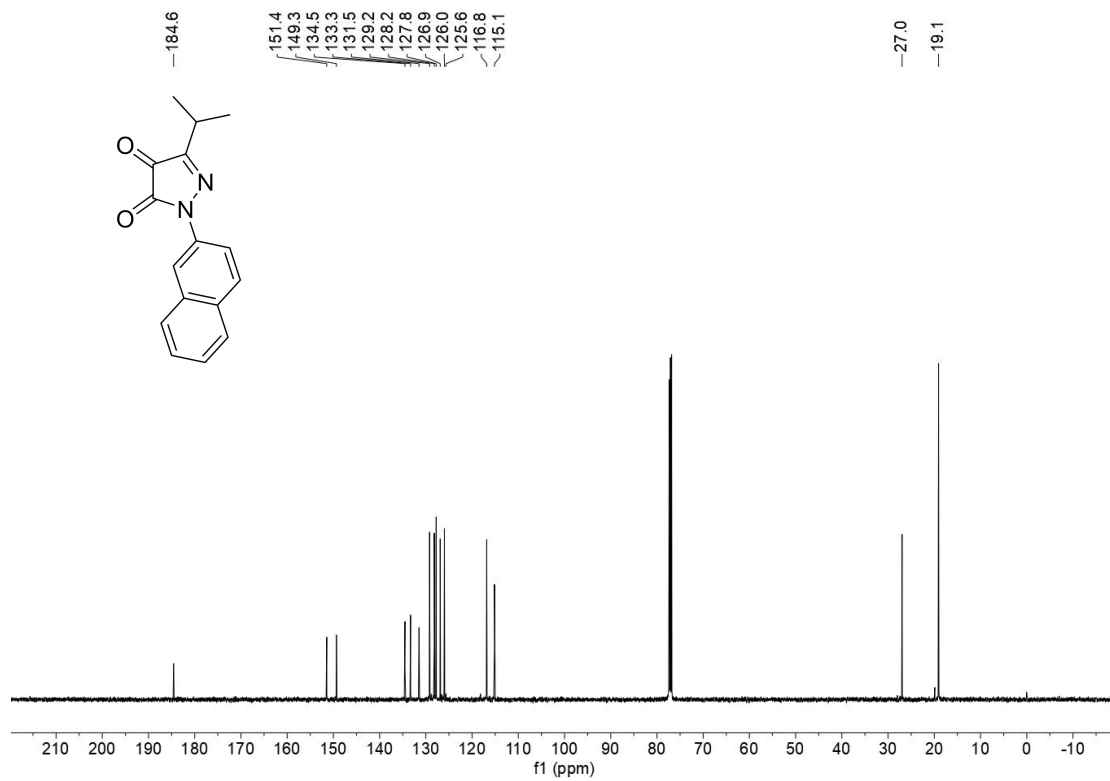
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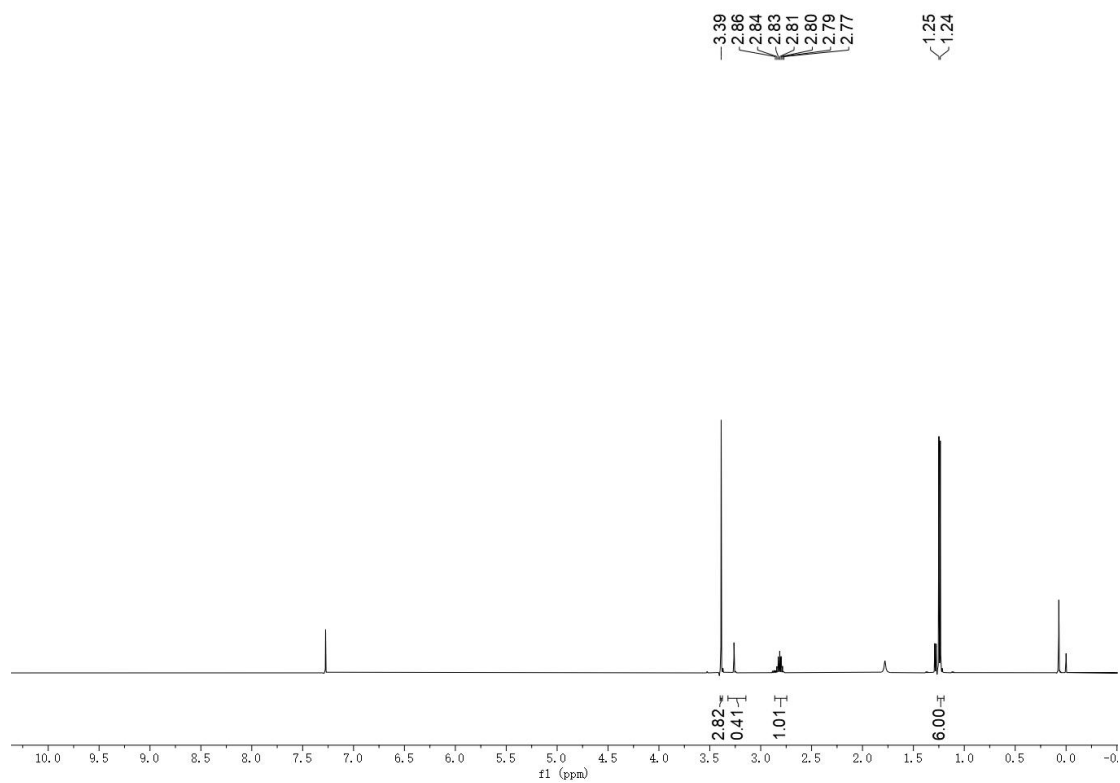


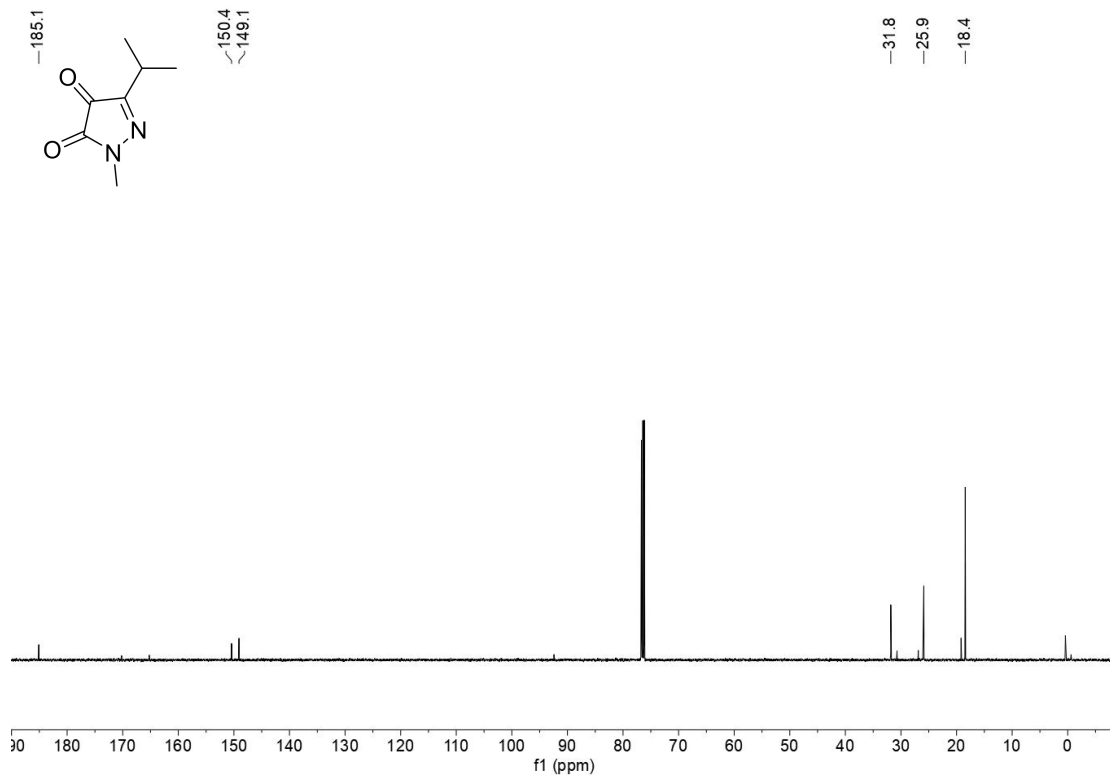
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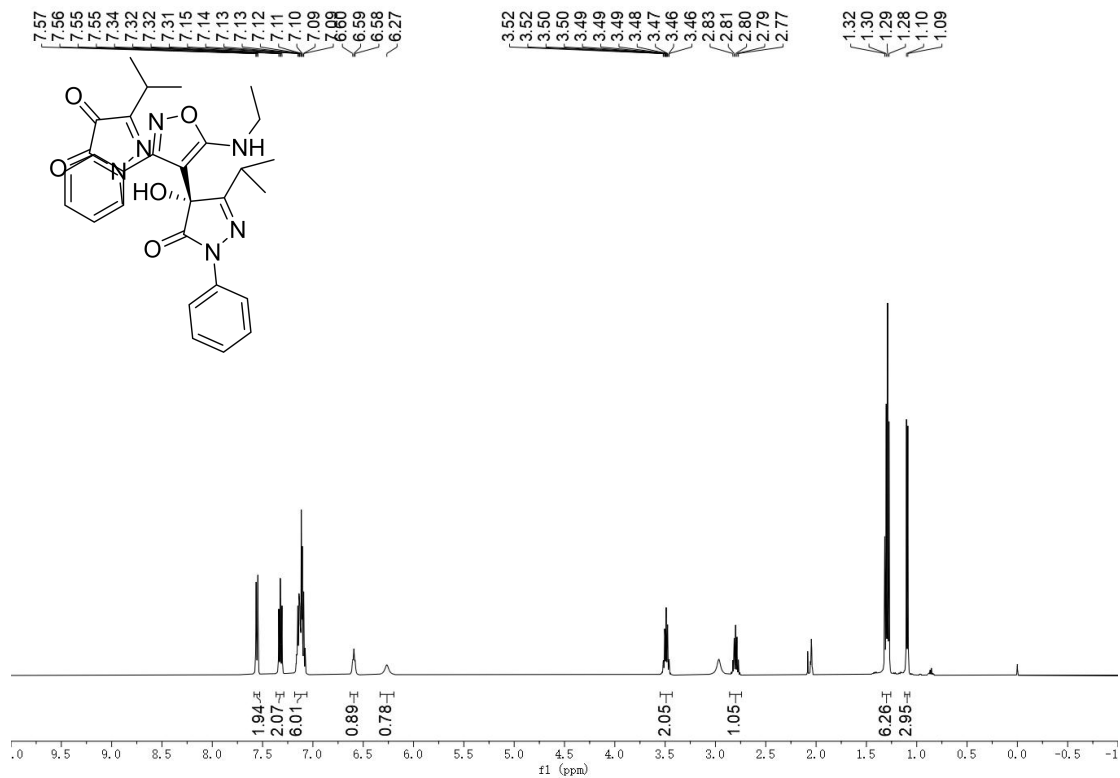


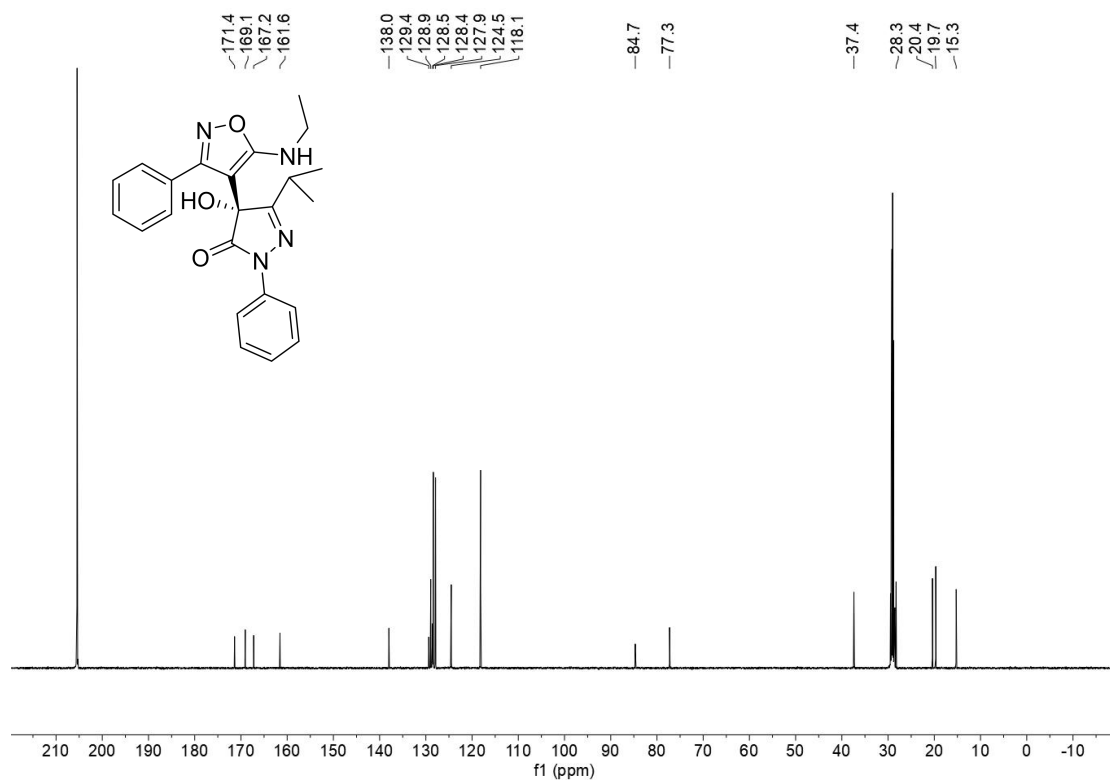
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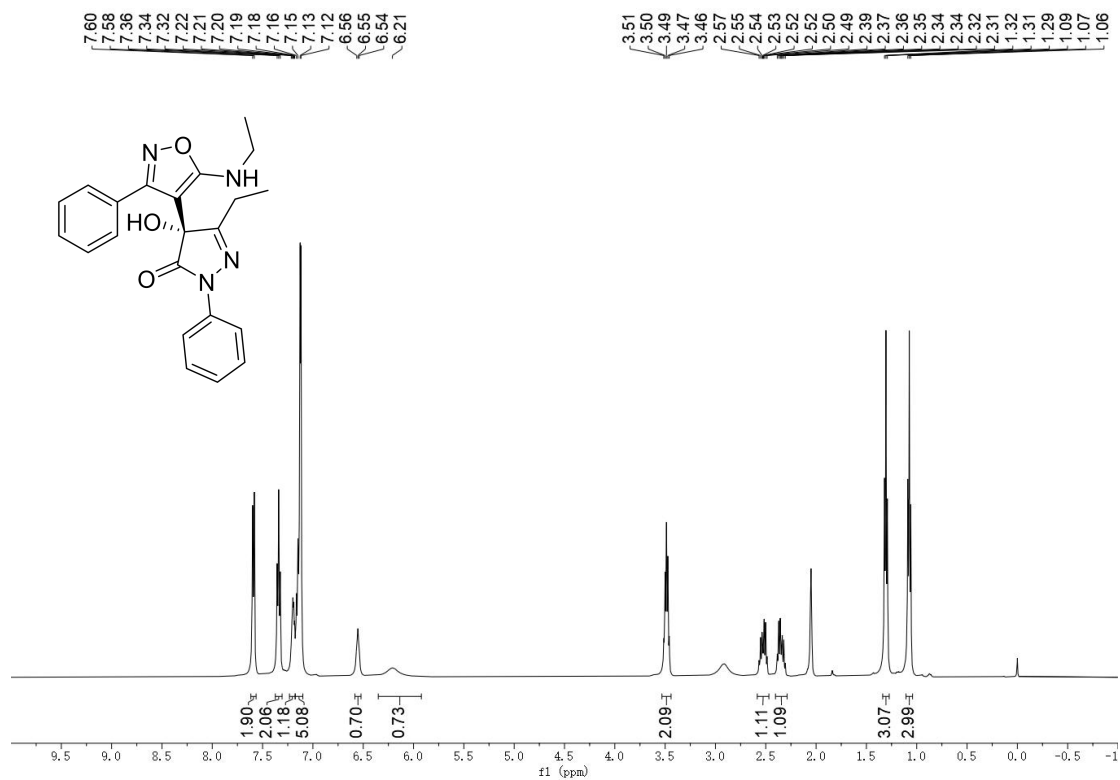


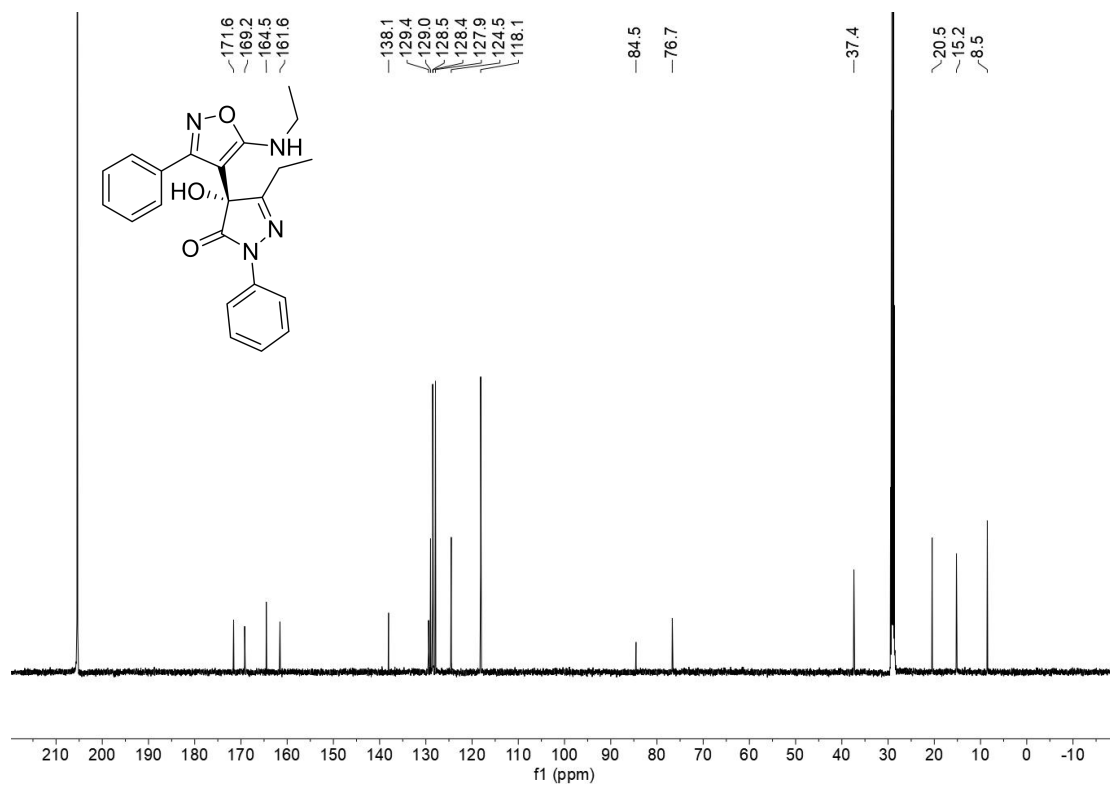
¹H NMR and ¹³C NMR of 3aa



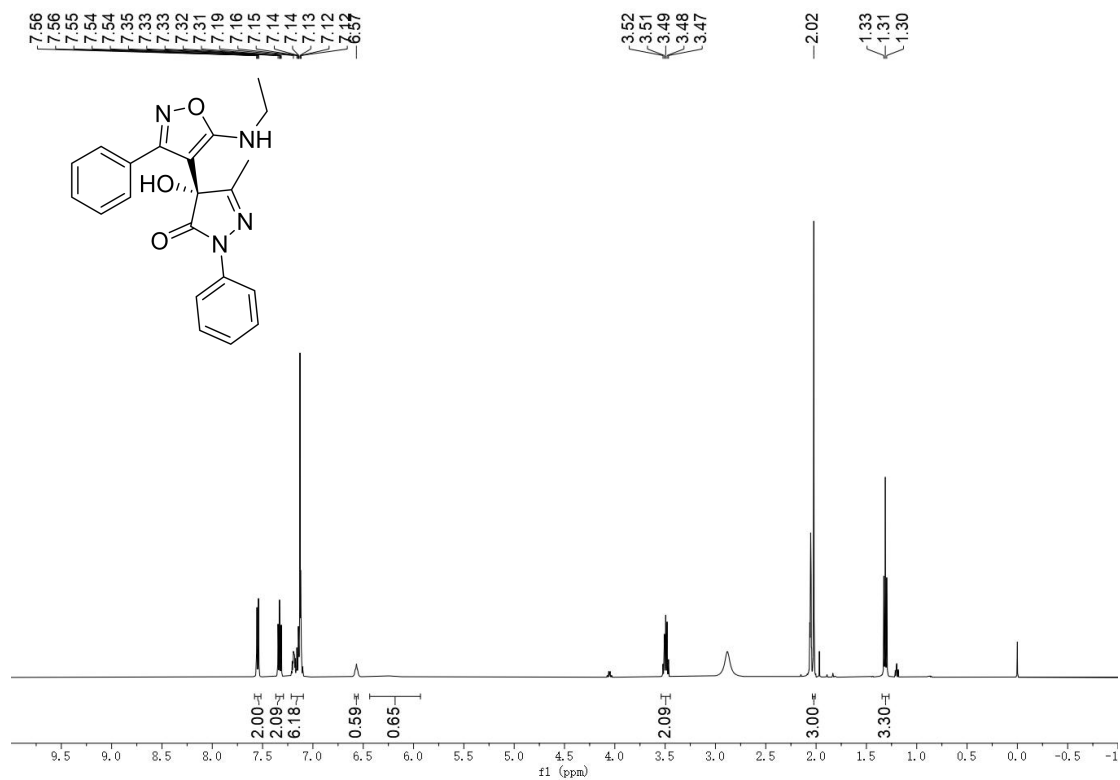


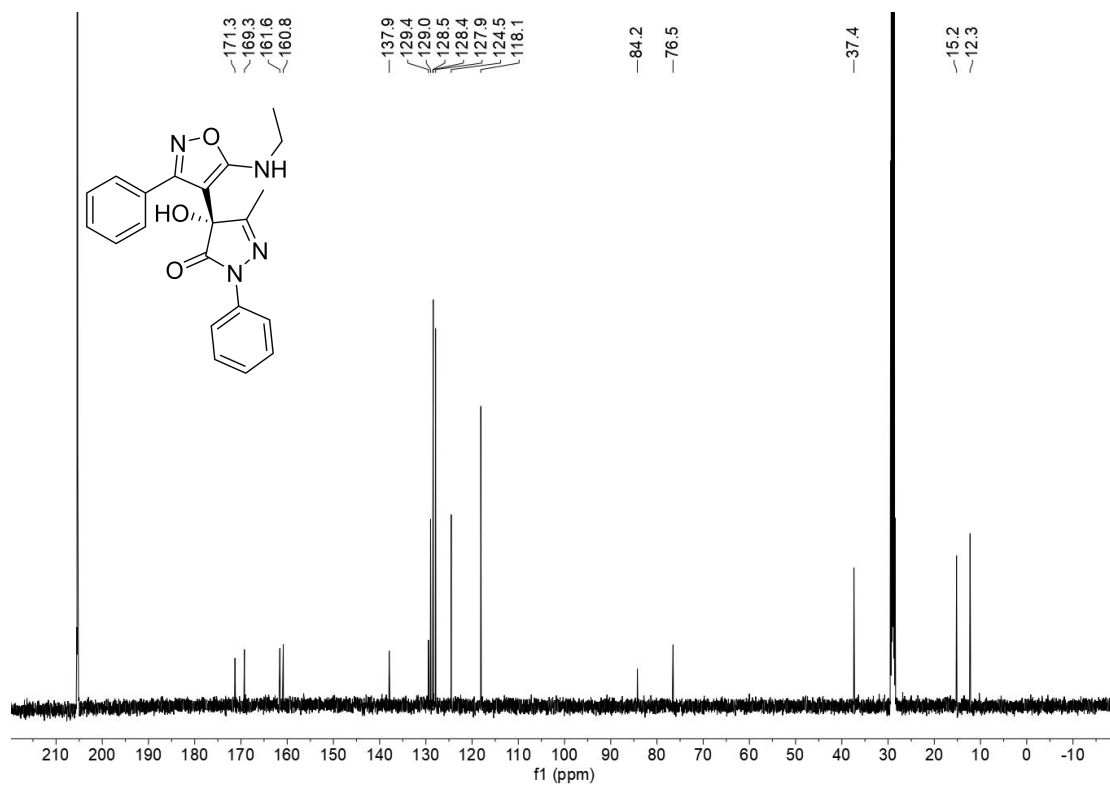
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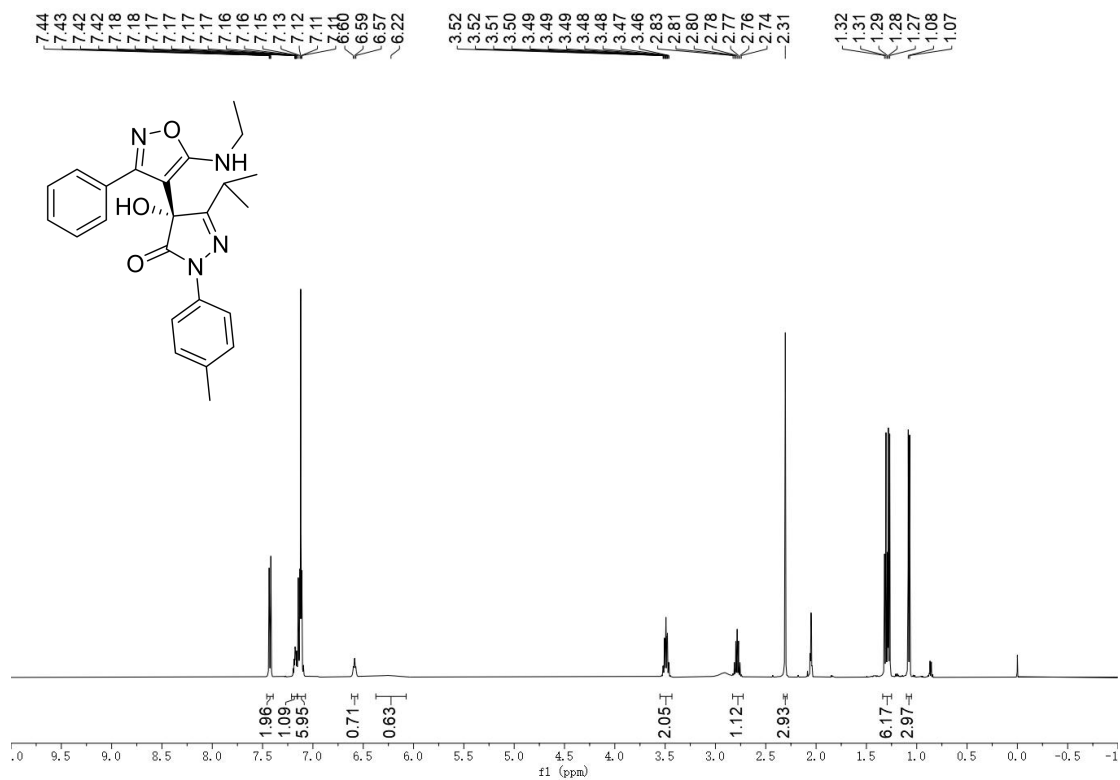


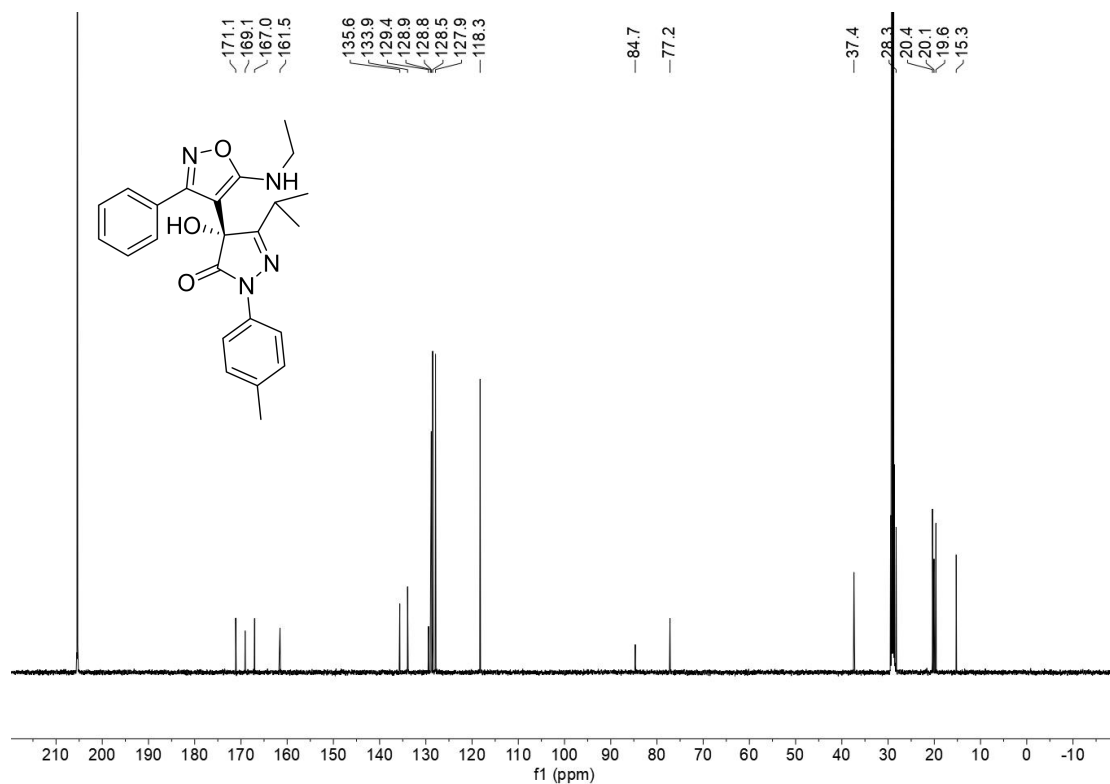
¹H NMR and ¹³C NMR of 3ca



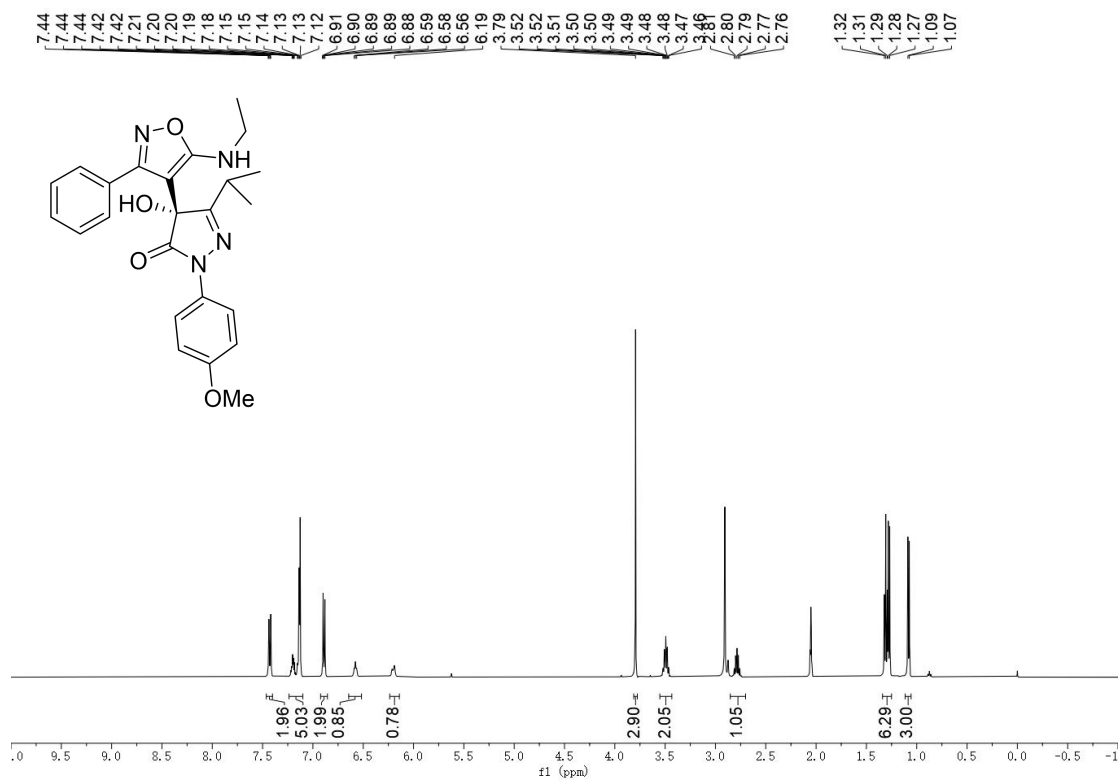


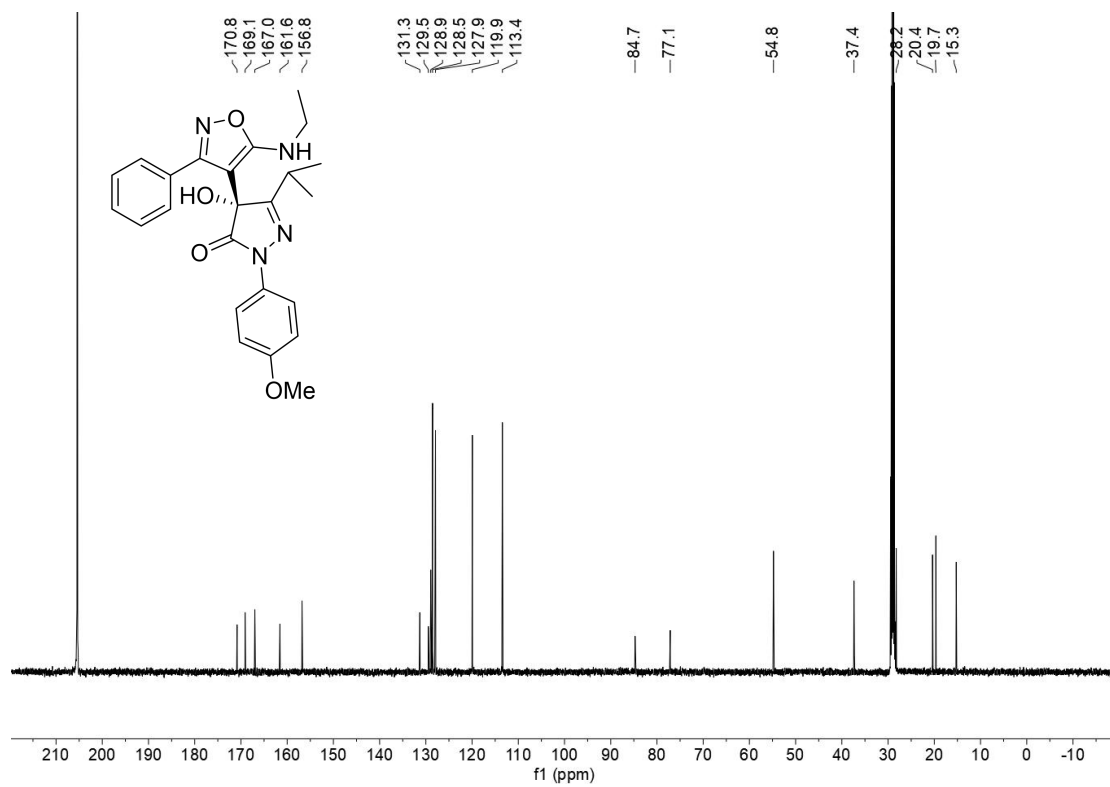
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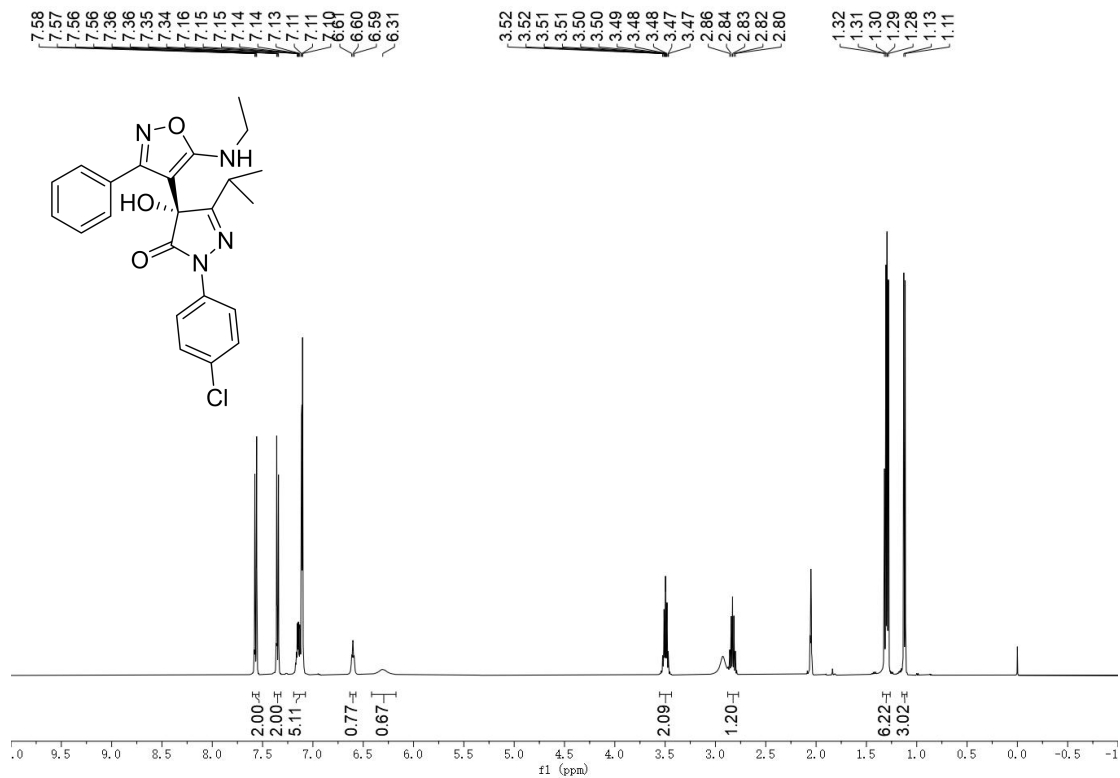


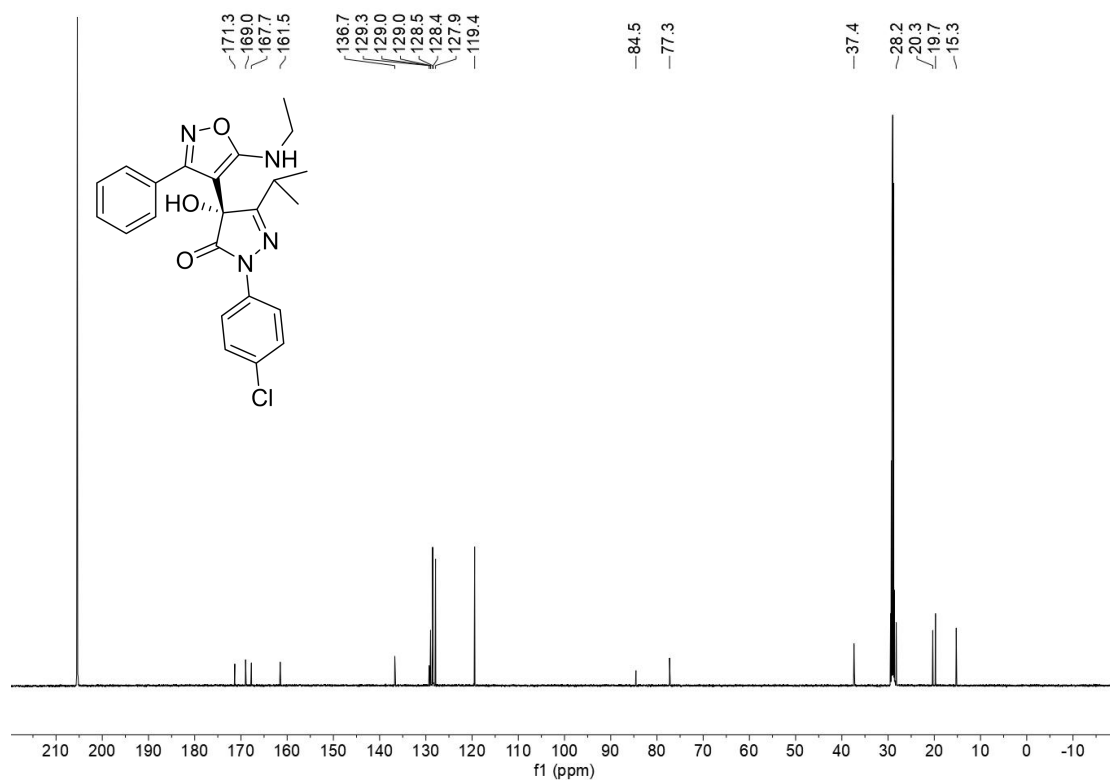
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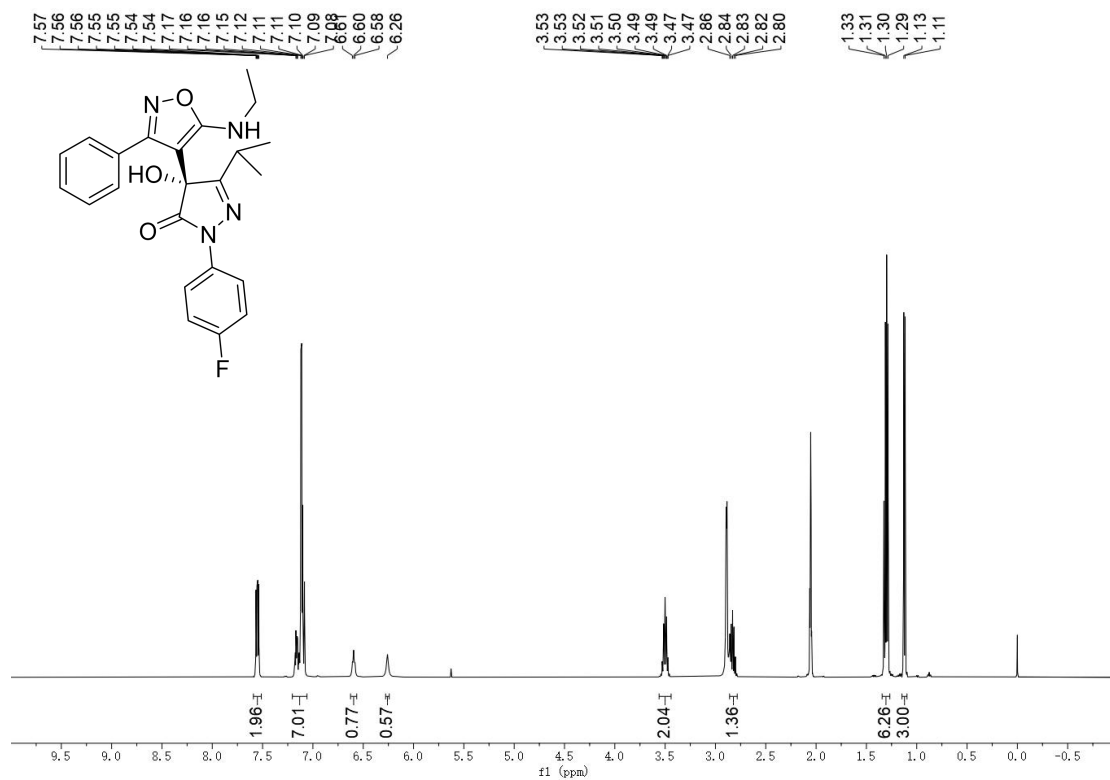


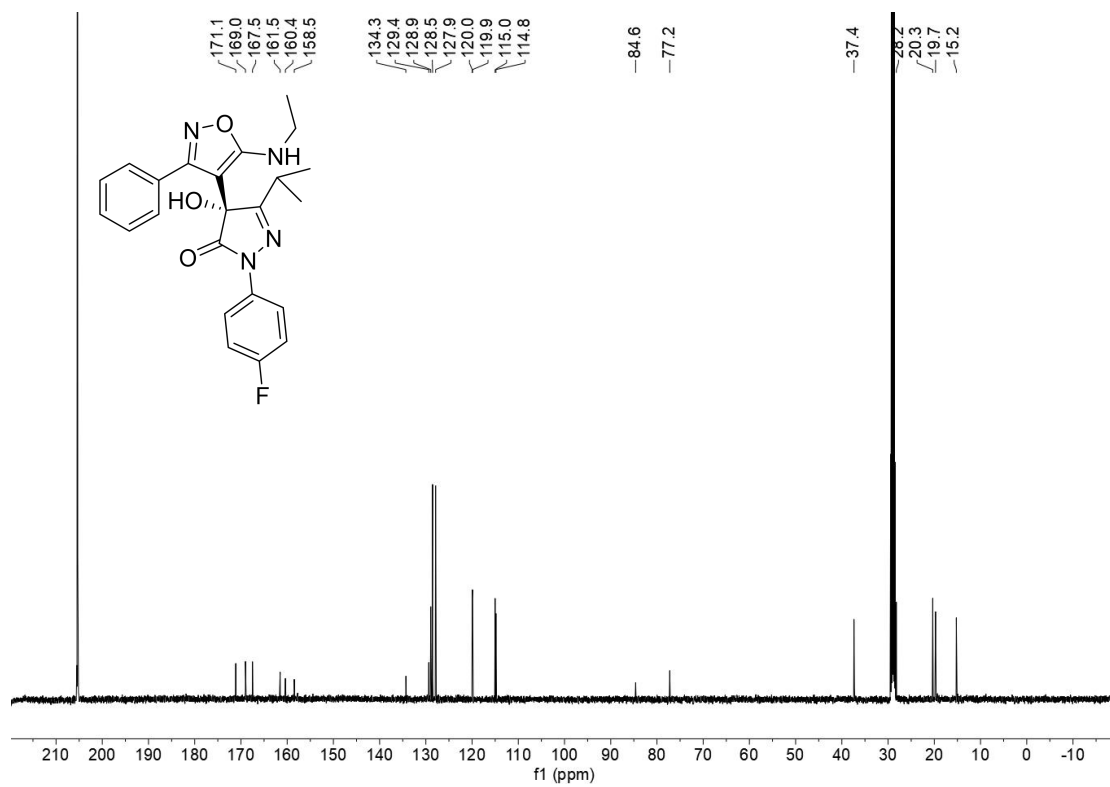
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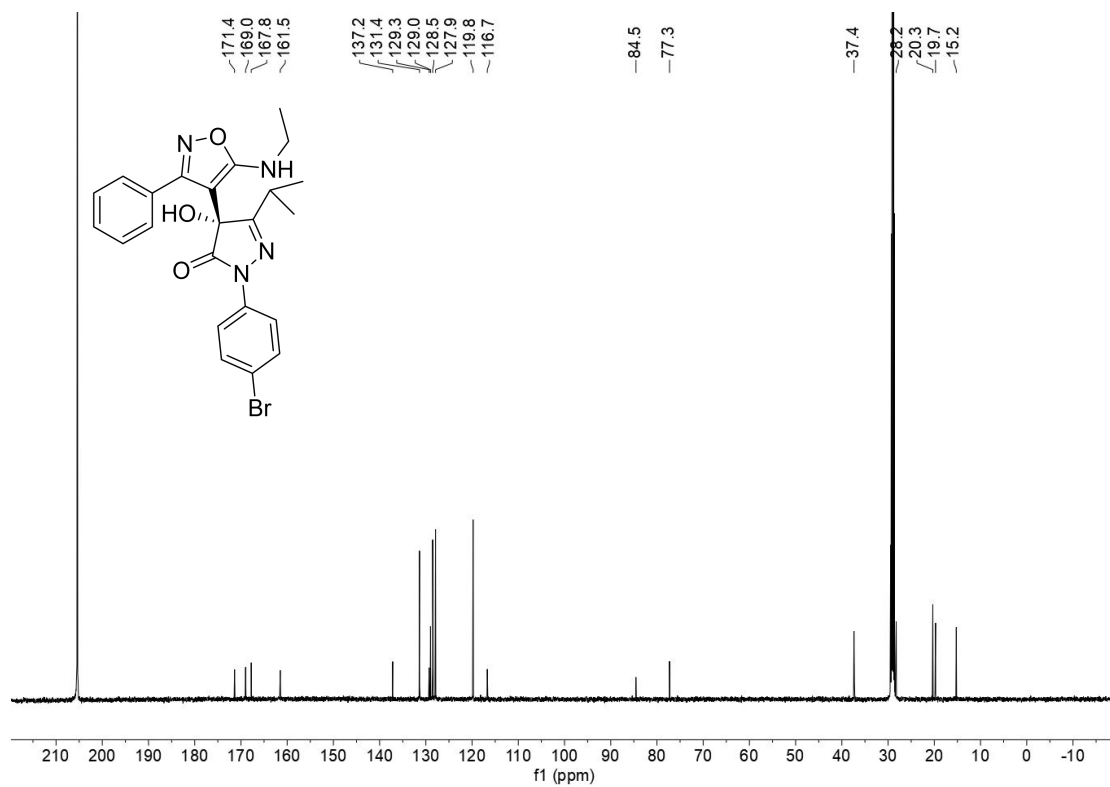
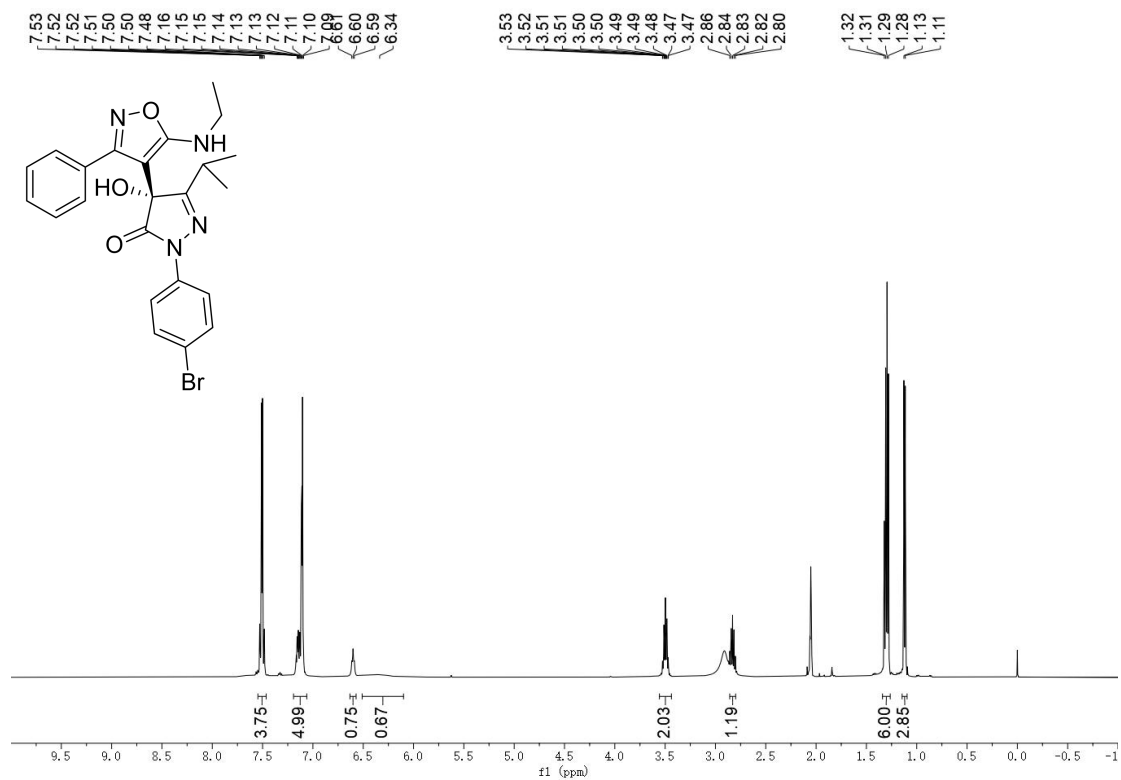


¹H NMR, ¹³C NMR and ¹⁹F NMR of 3ga

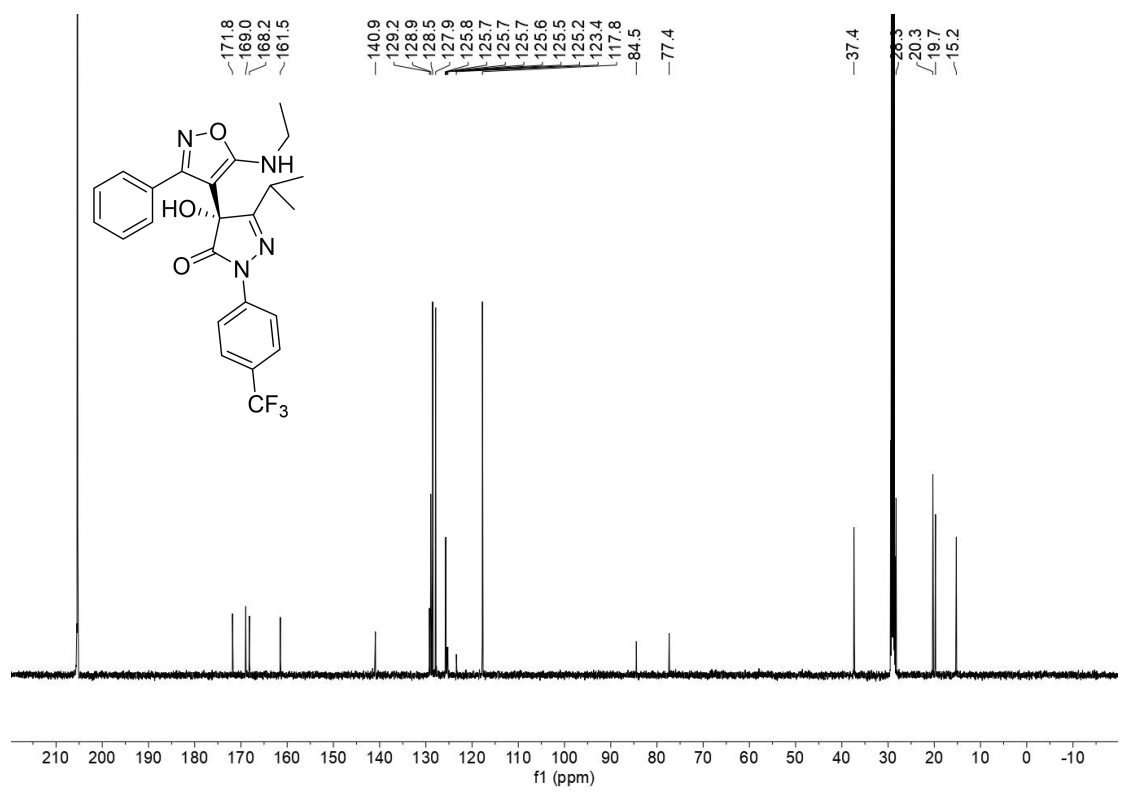
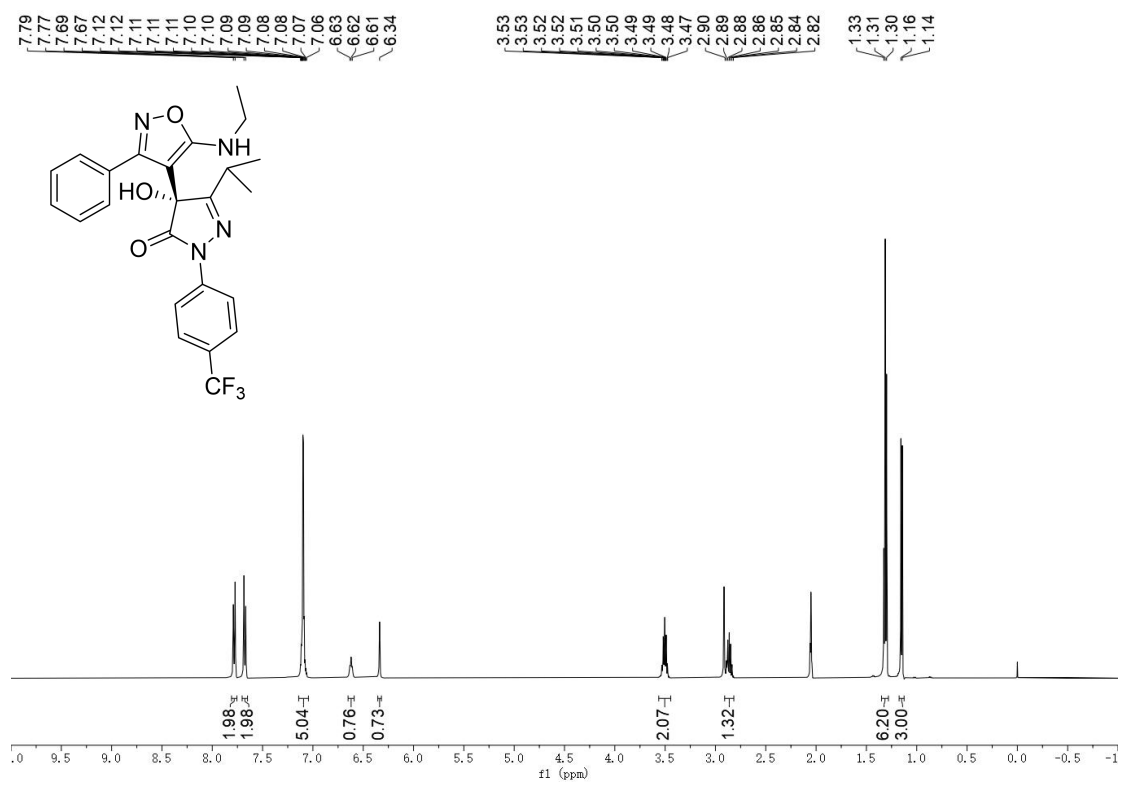


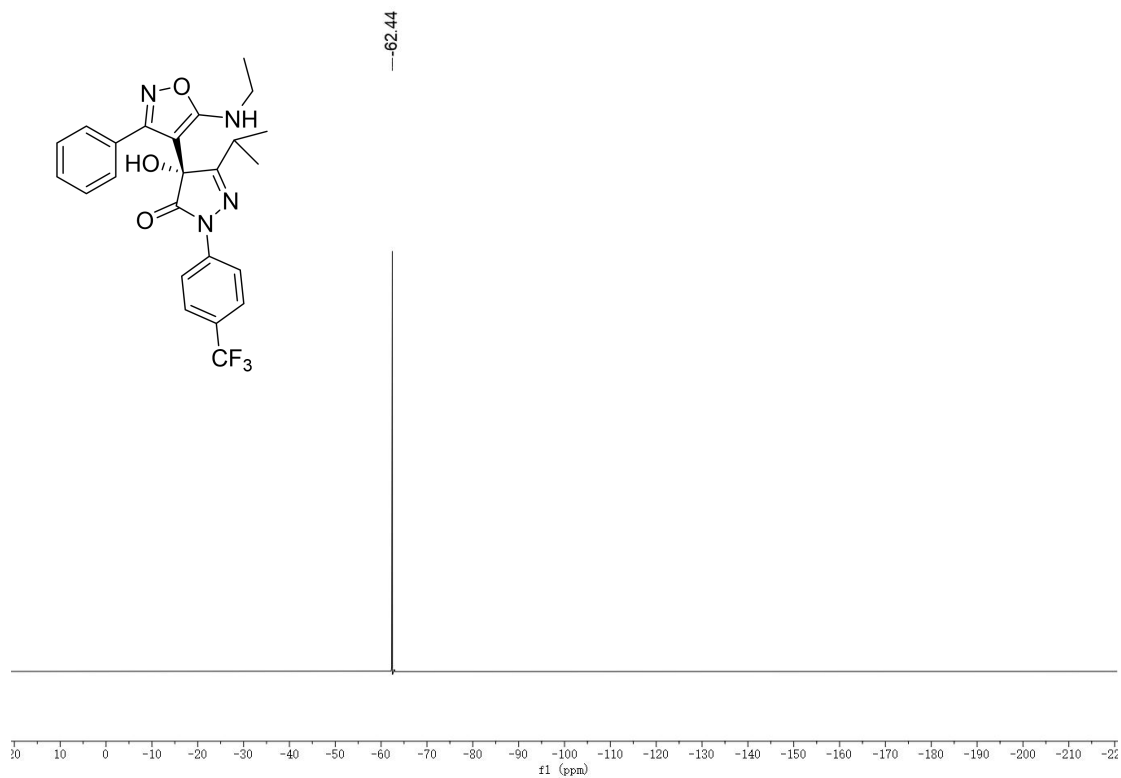


¹H NMR and ¹³C NMR of **3ha**

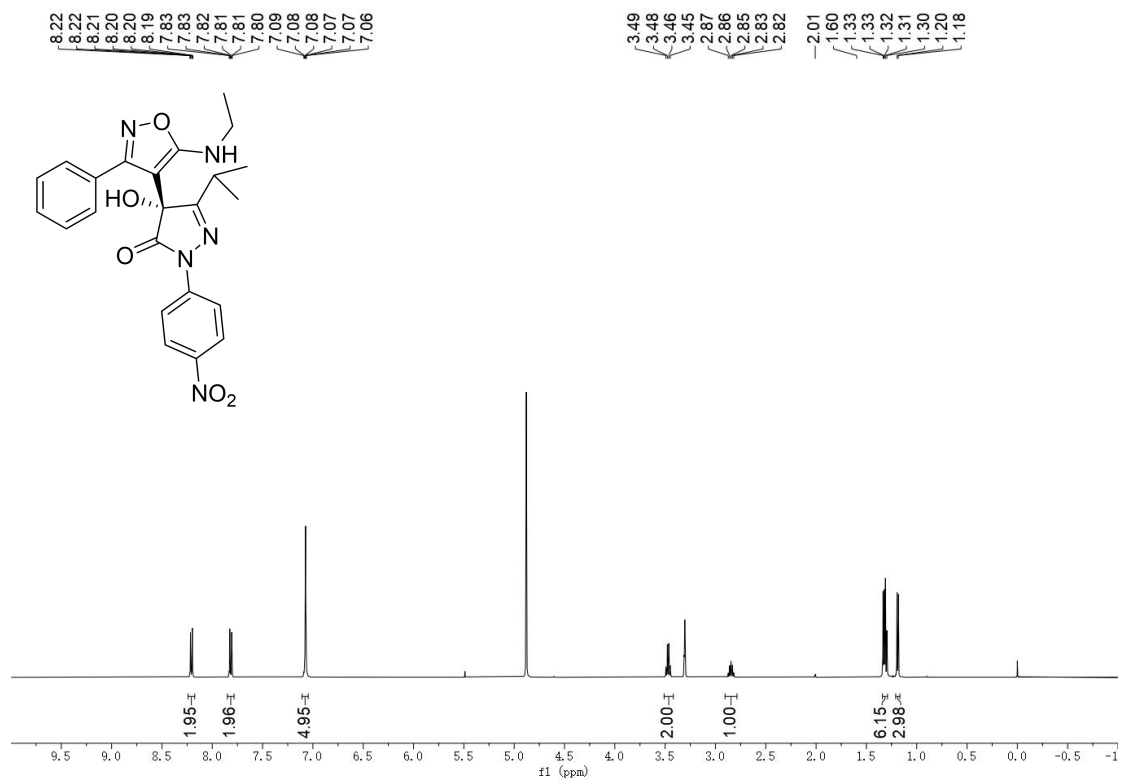


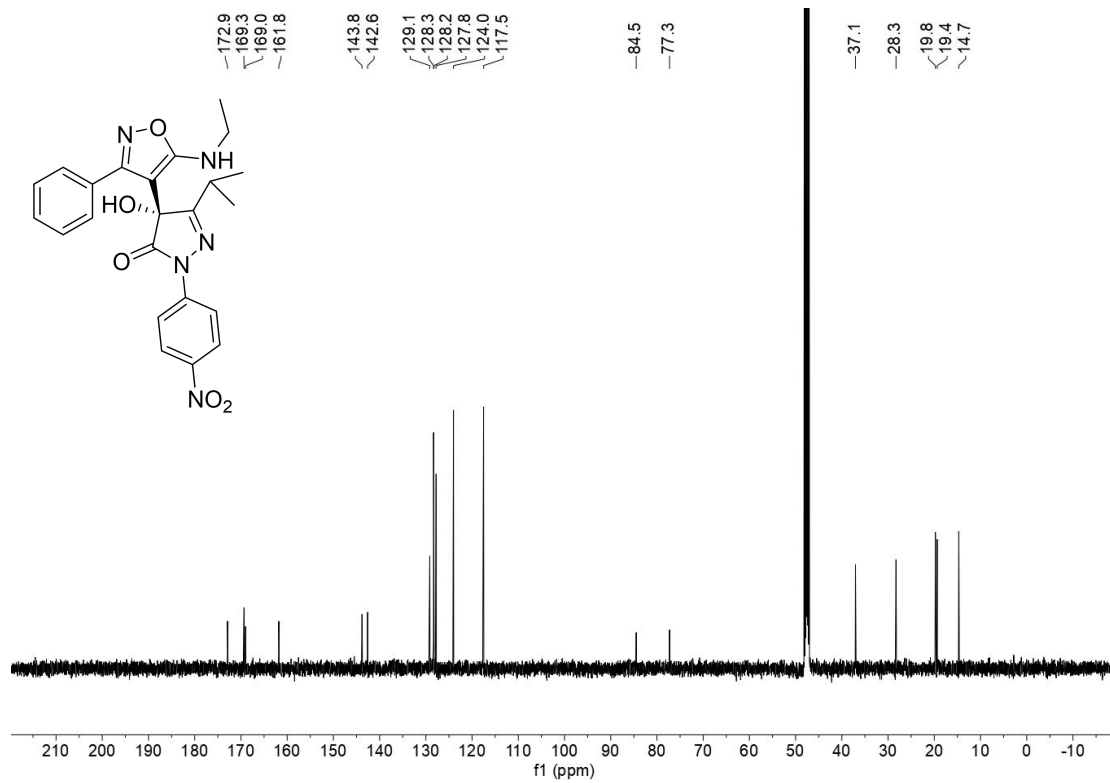
¹H NMR, ¹³C NMR and ¹⁹F NMR of **3ia**



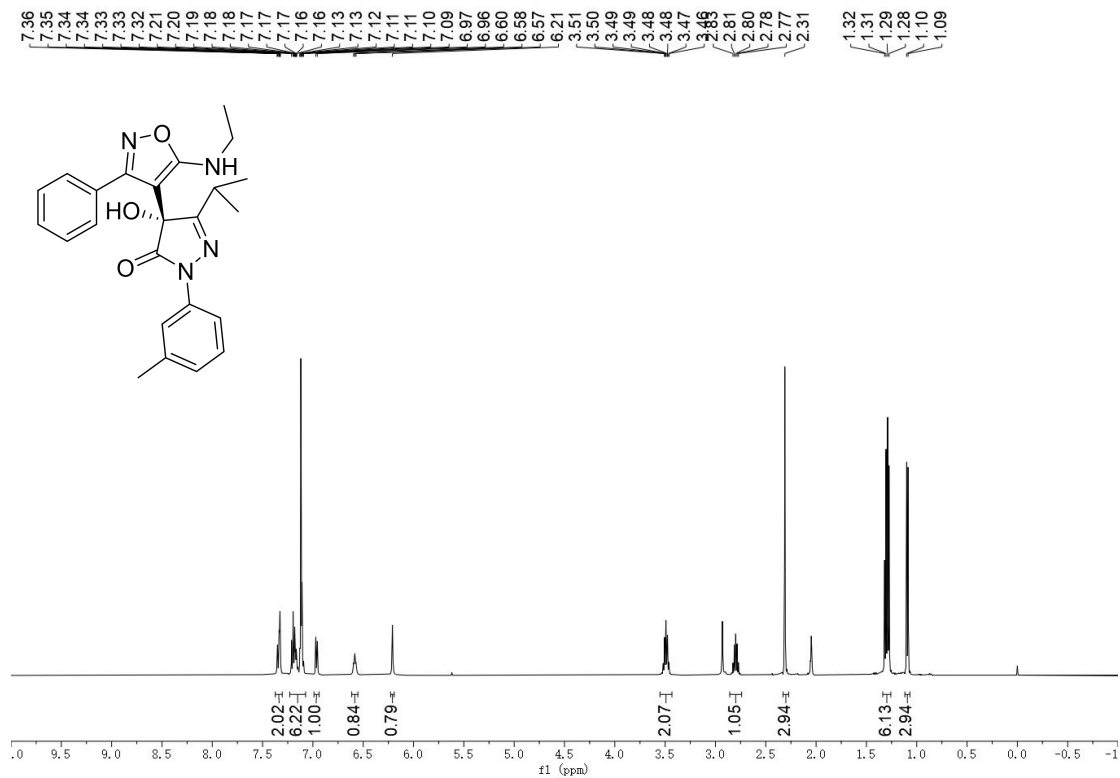


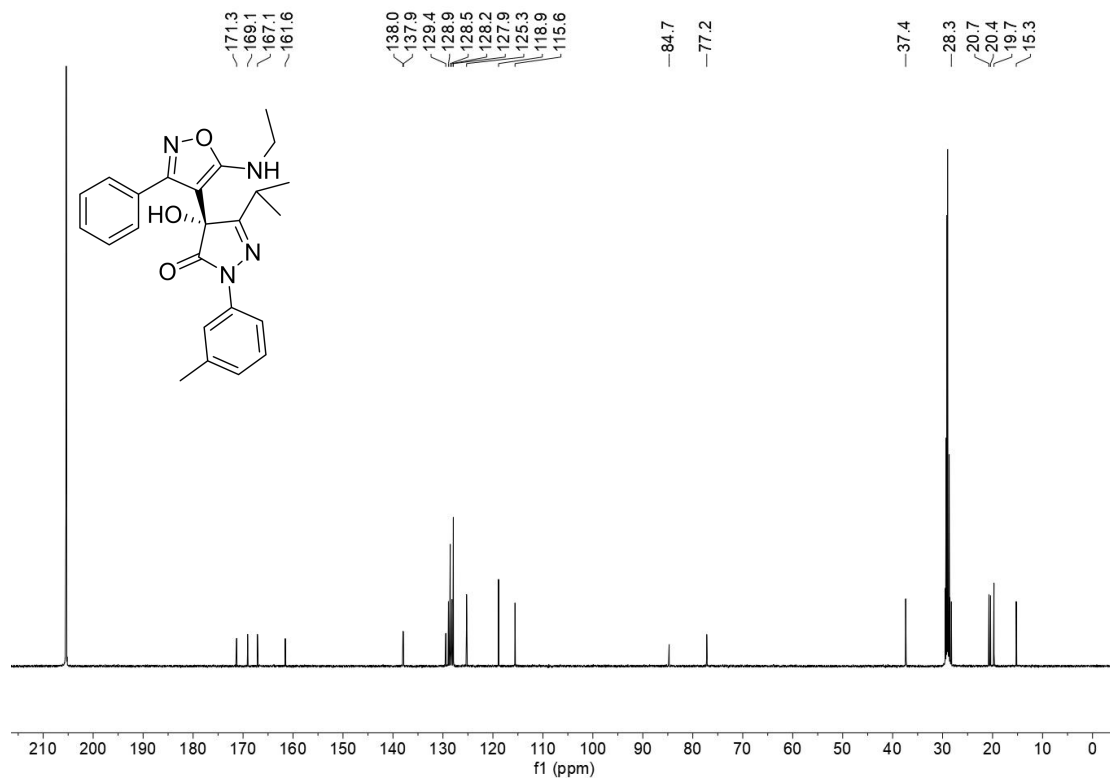
^1H NMR and ^{13}C NMR of **3ja**



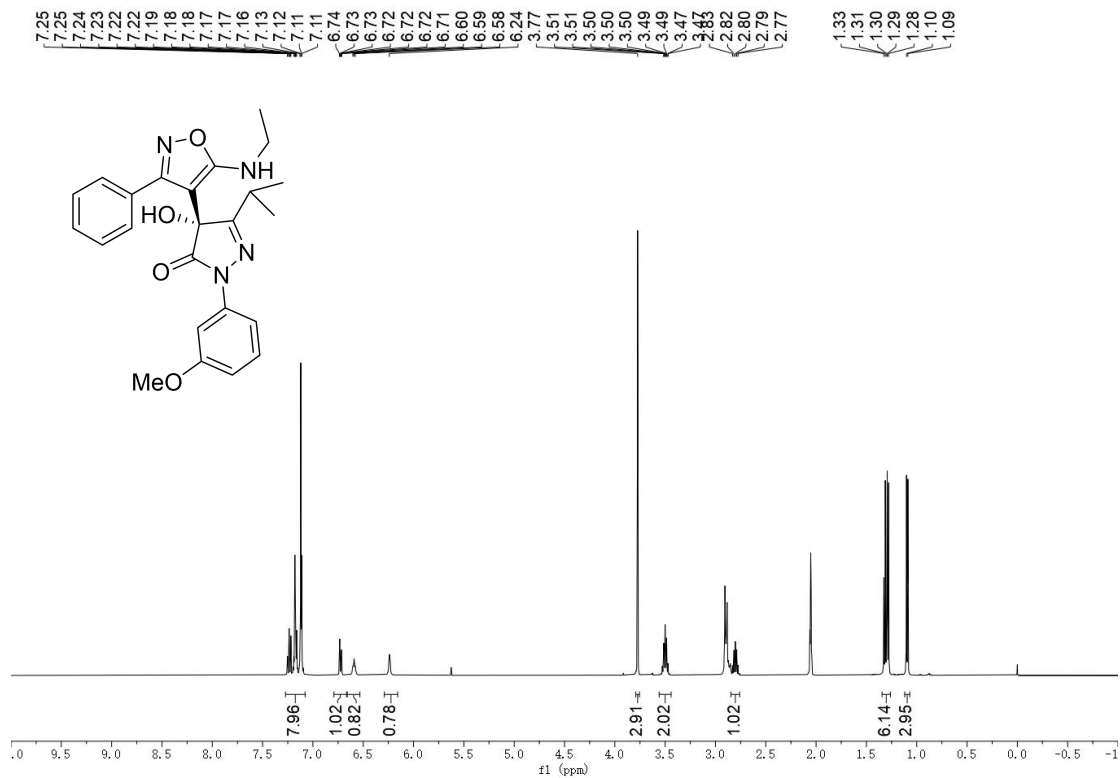


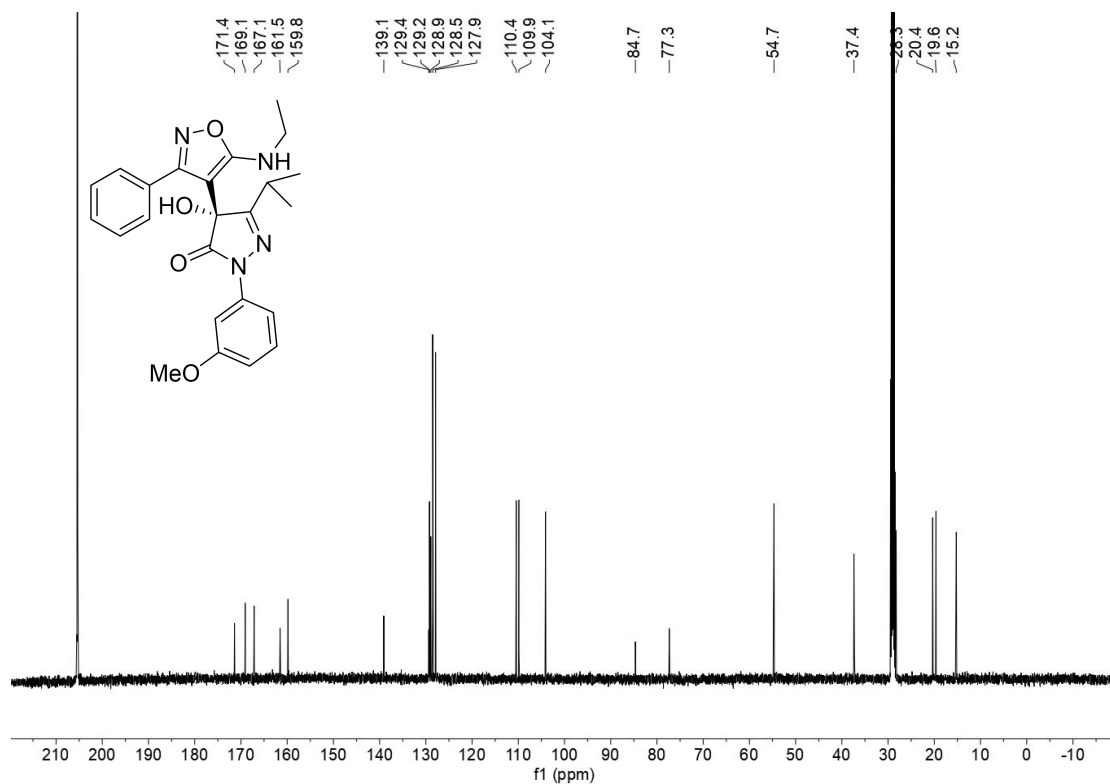
¹H NMR and ¹³C NMR of 3ka



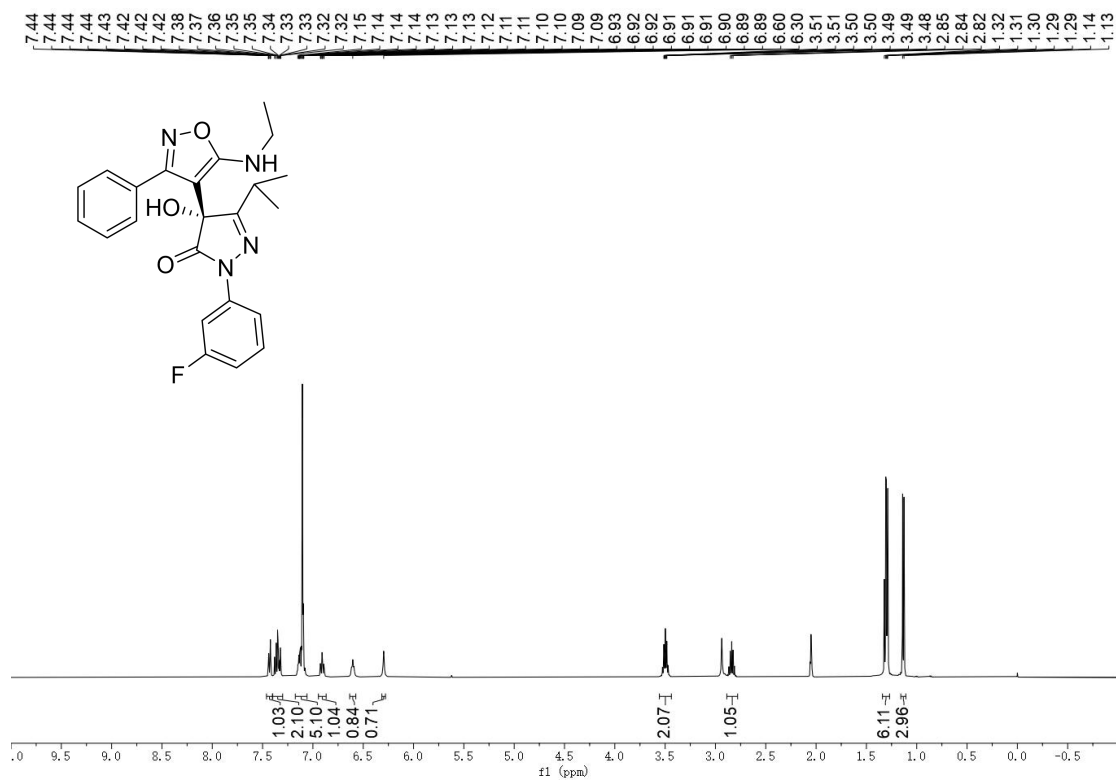


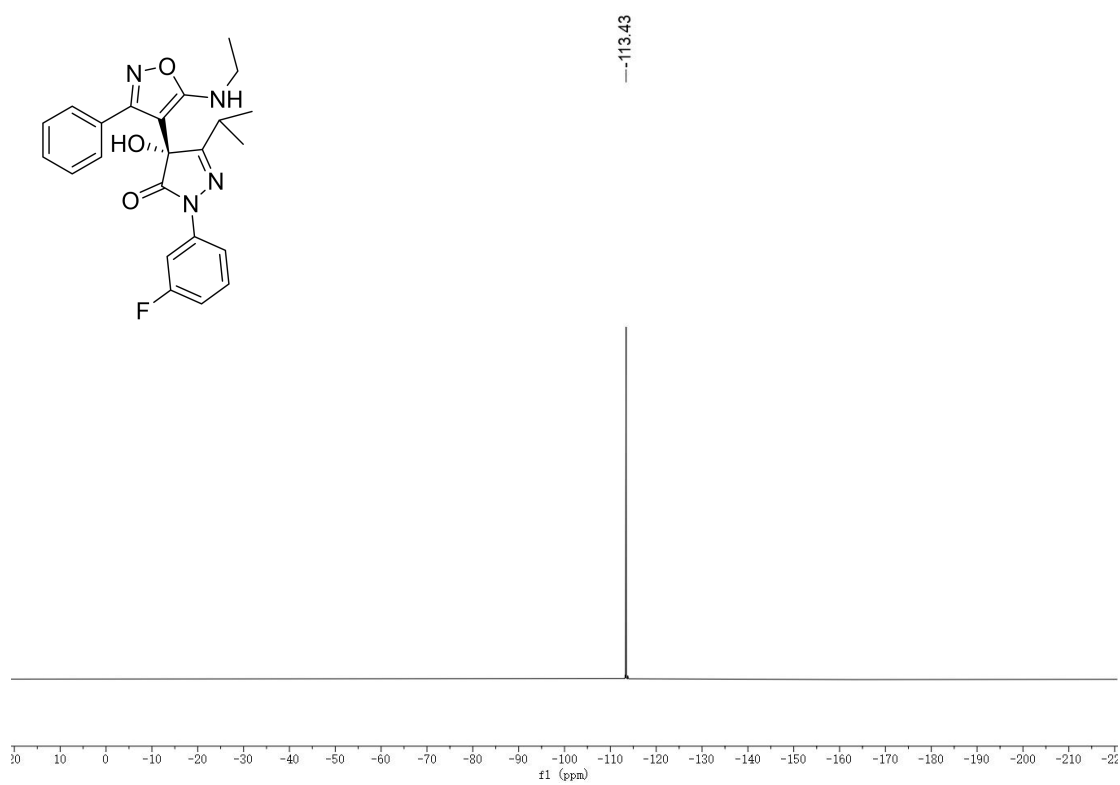
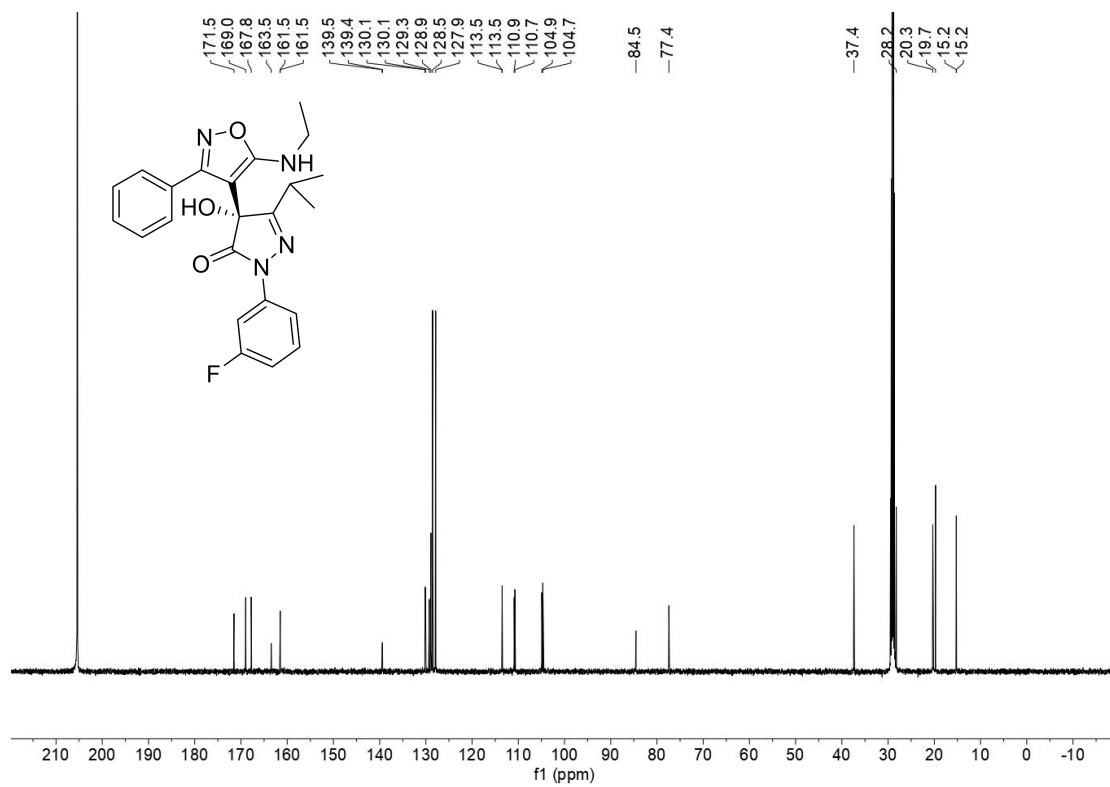
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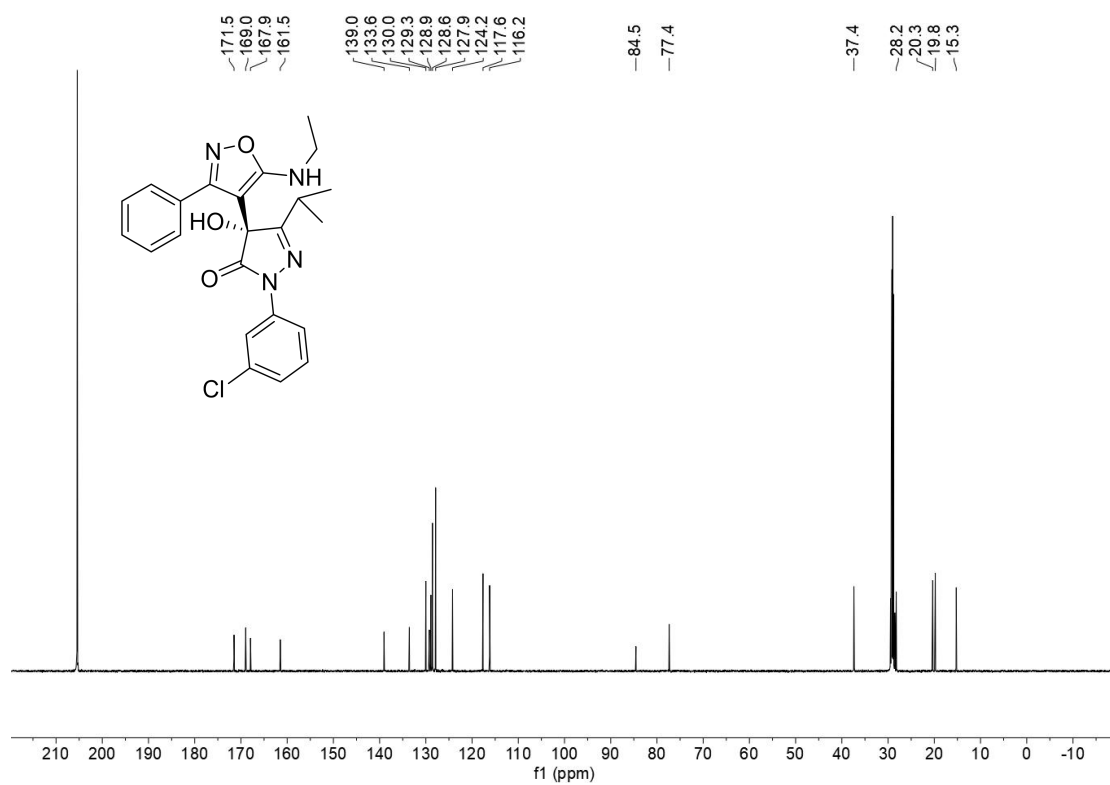
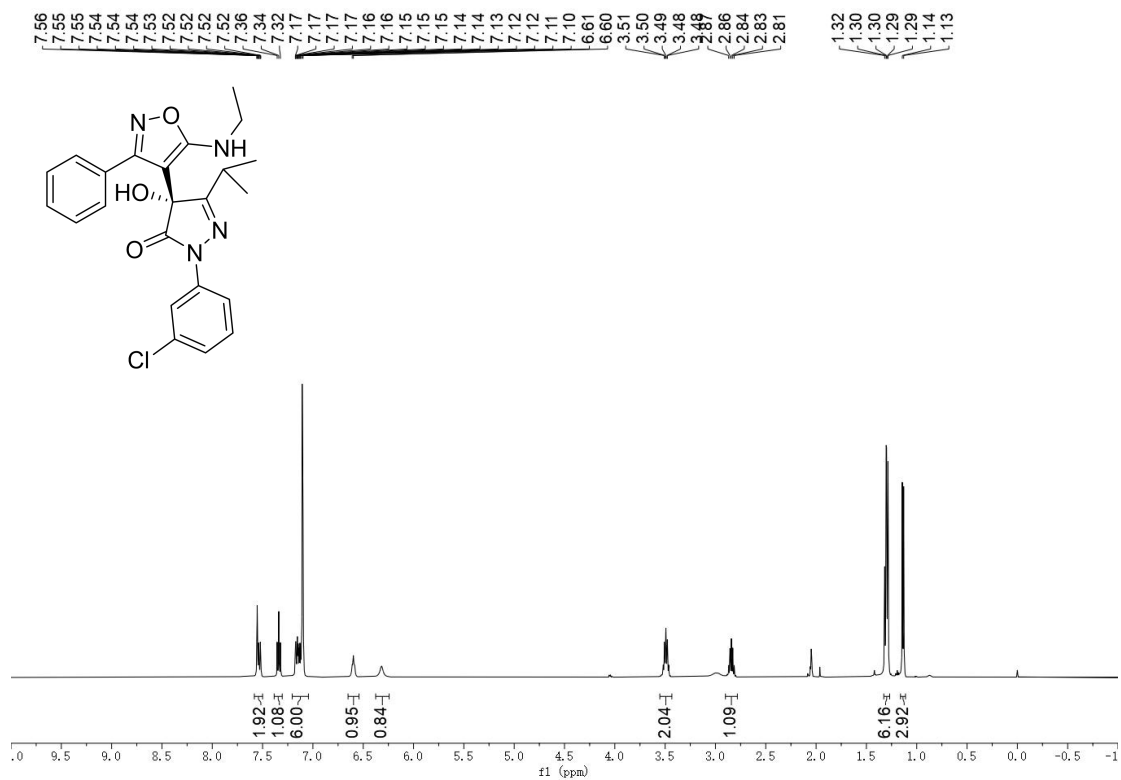


¹H NMR, ¹³C NMR and ¹⁹F NMR of **3ma**

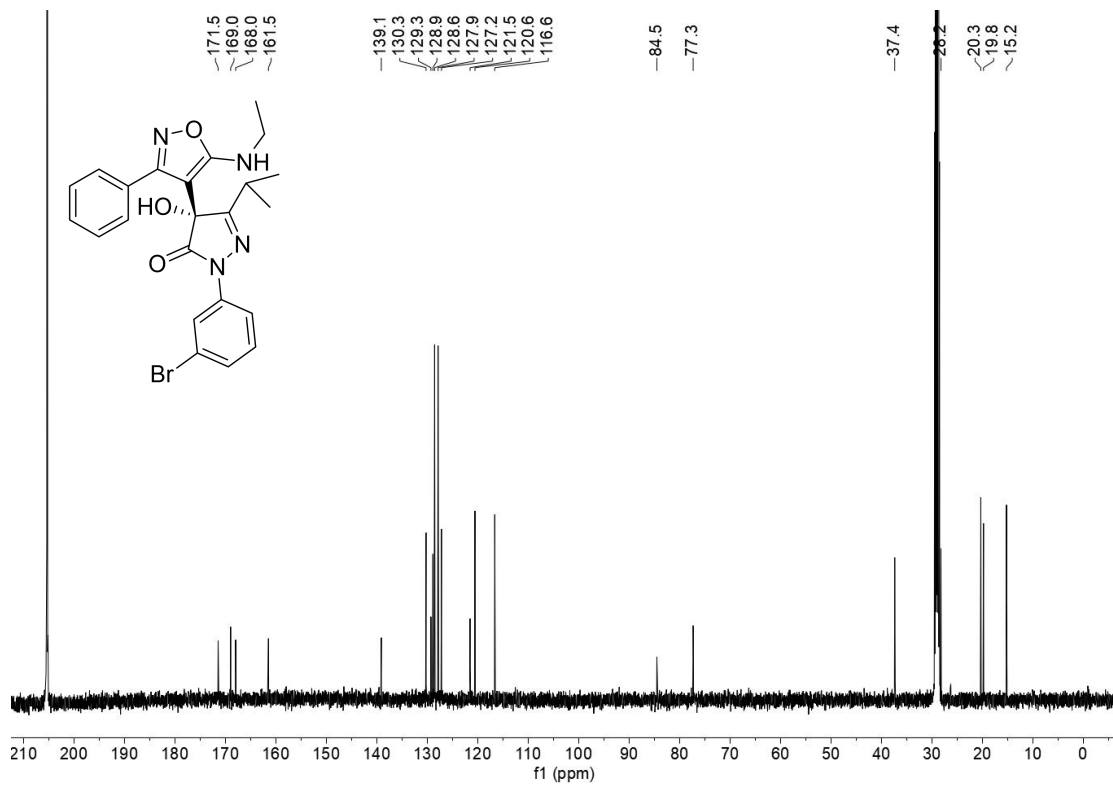
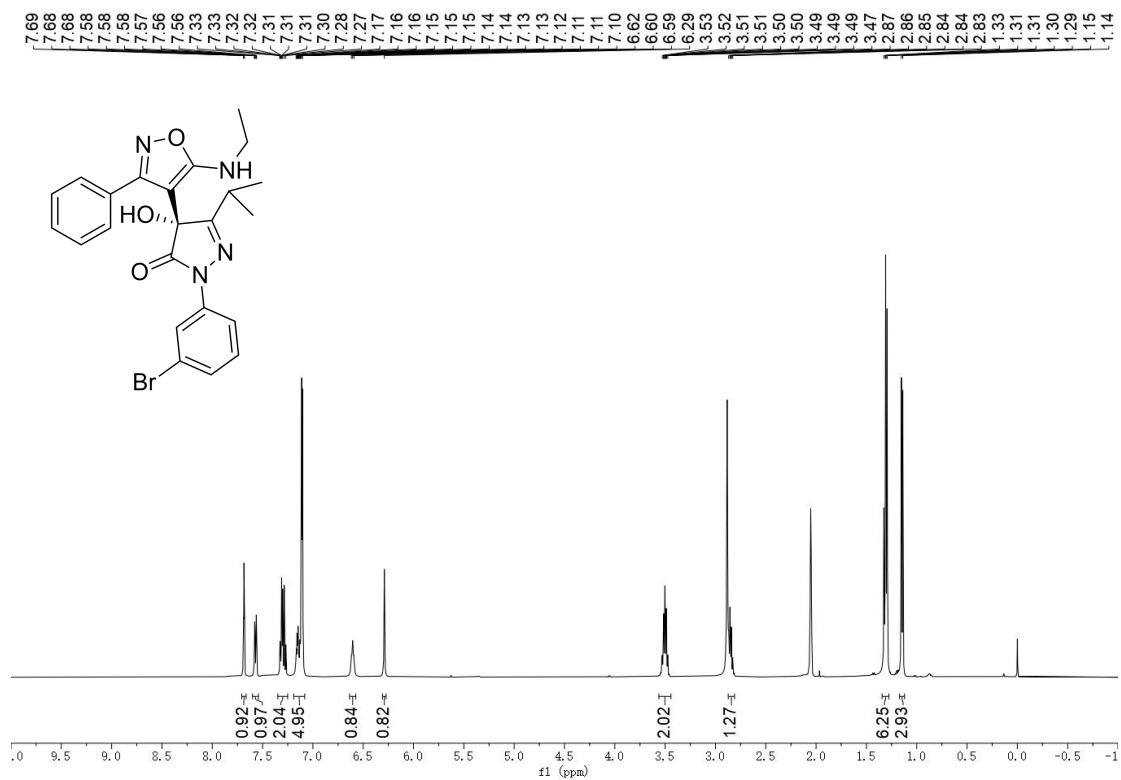




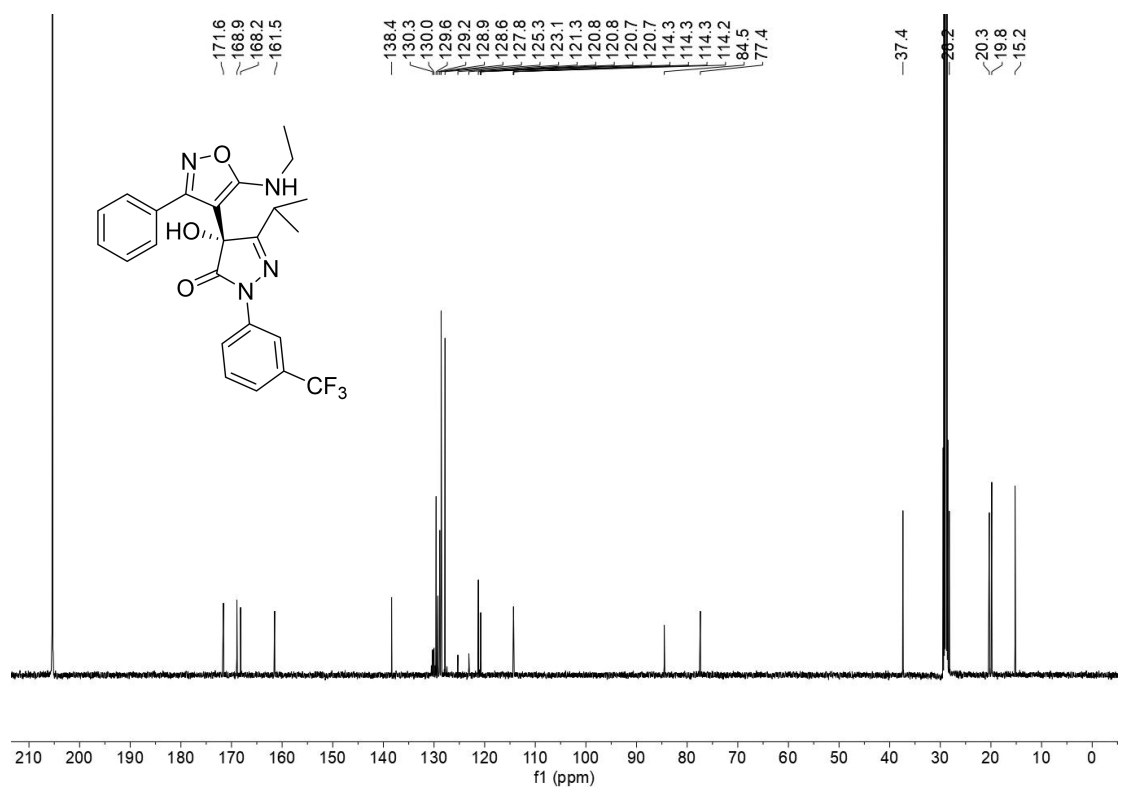
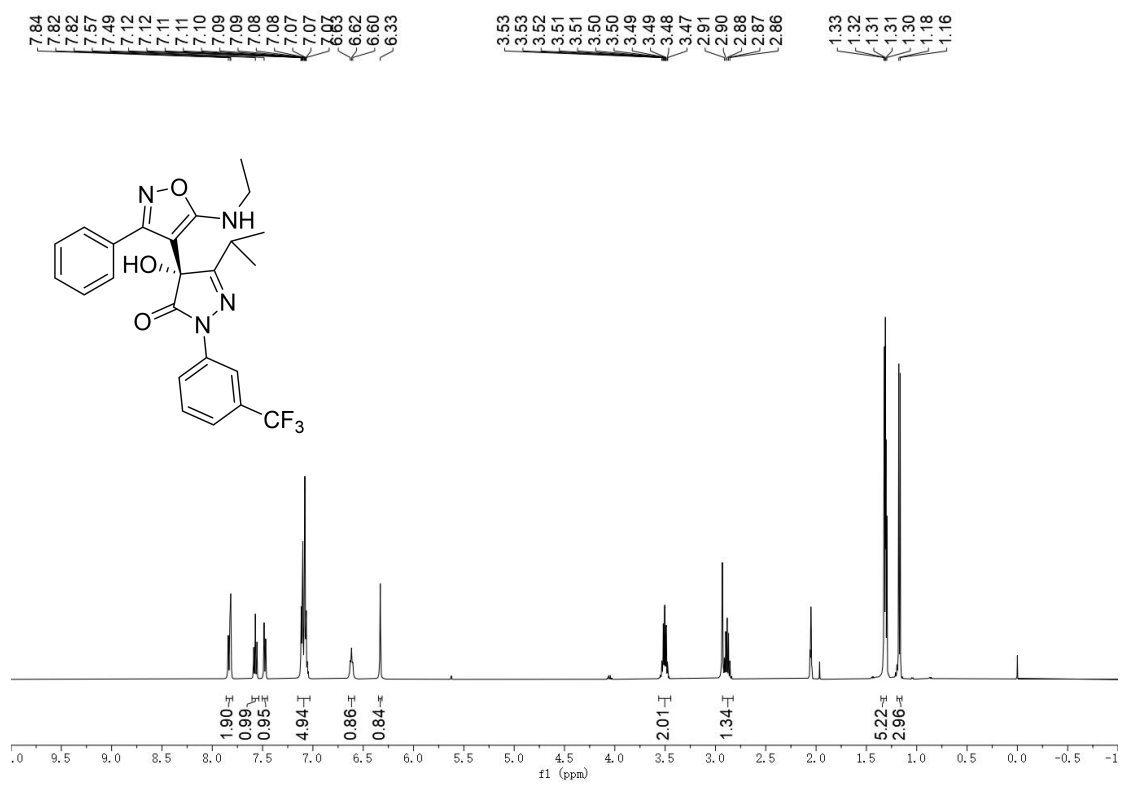
^1H NMR and ^{13}C NMR of **3na**

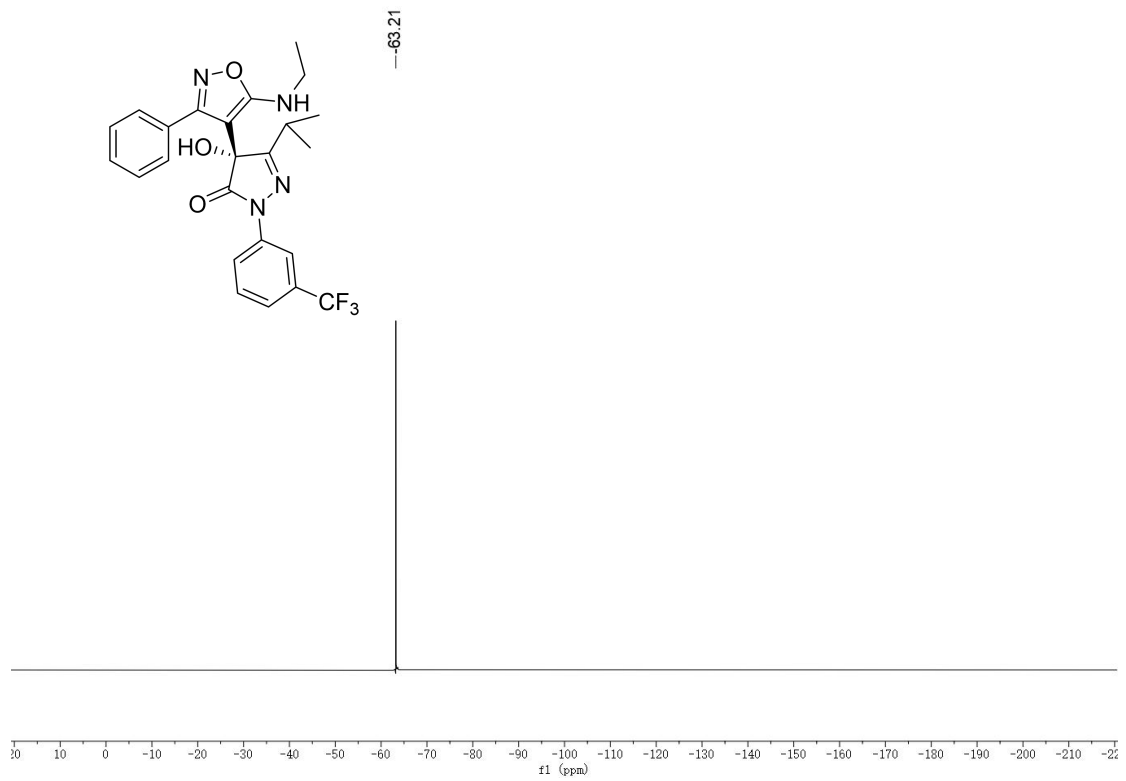


¹H NMR and ¹³C NMR of 30a

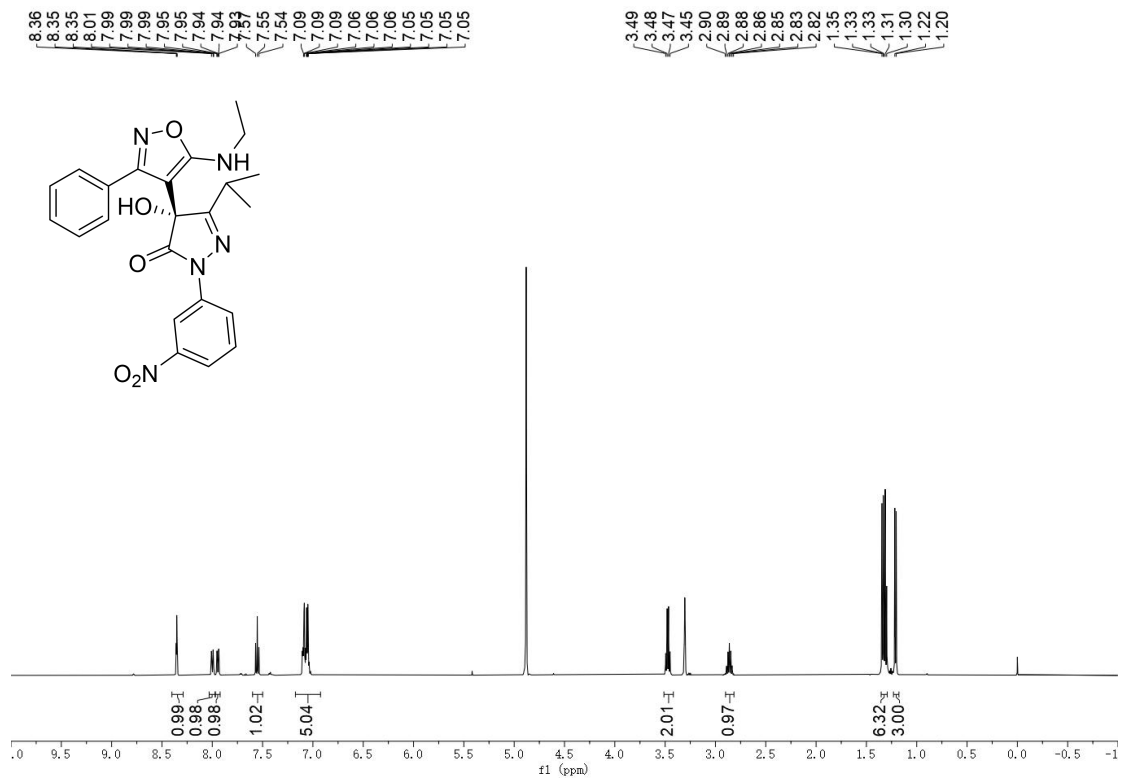


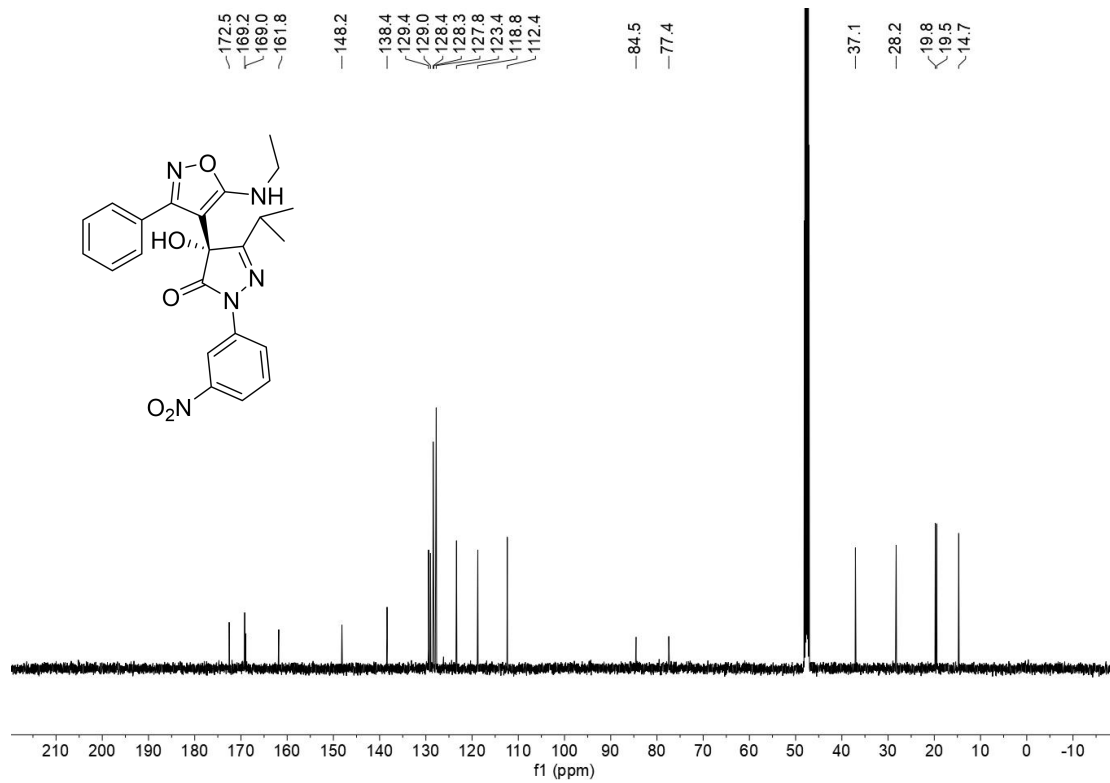
¹H NMR, ¹³C NMR and ¹⁹F NMR of 3pa



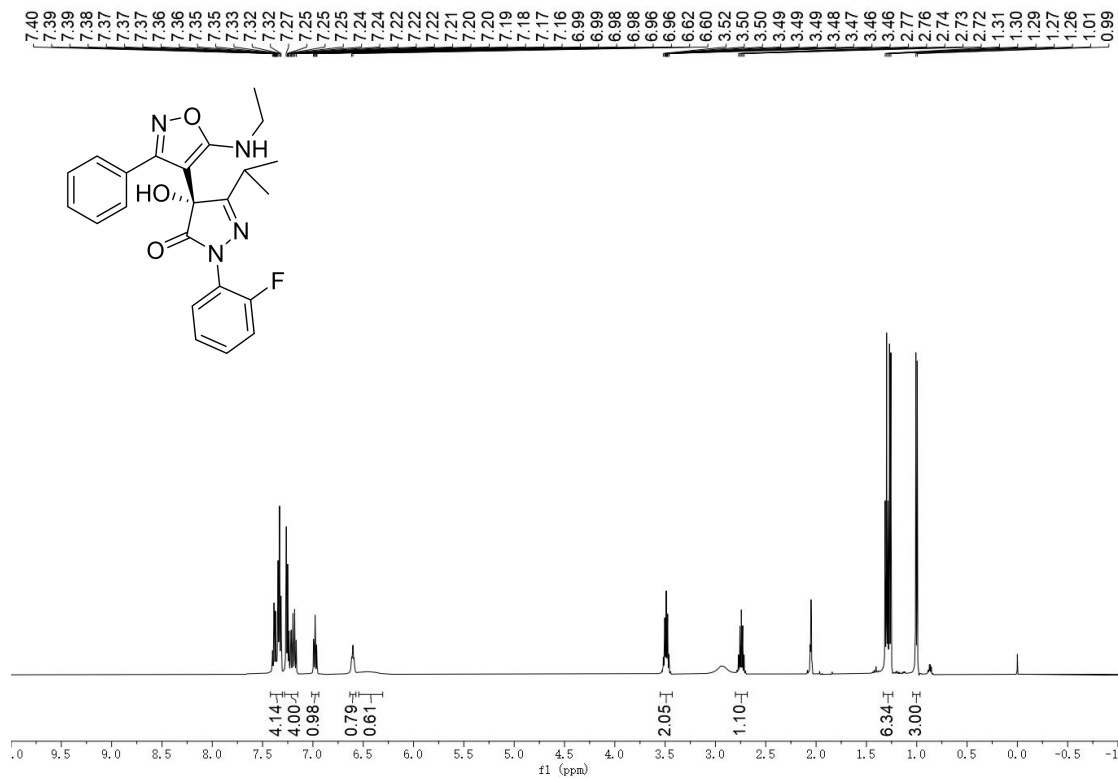


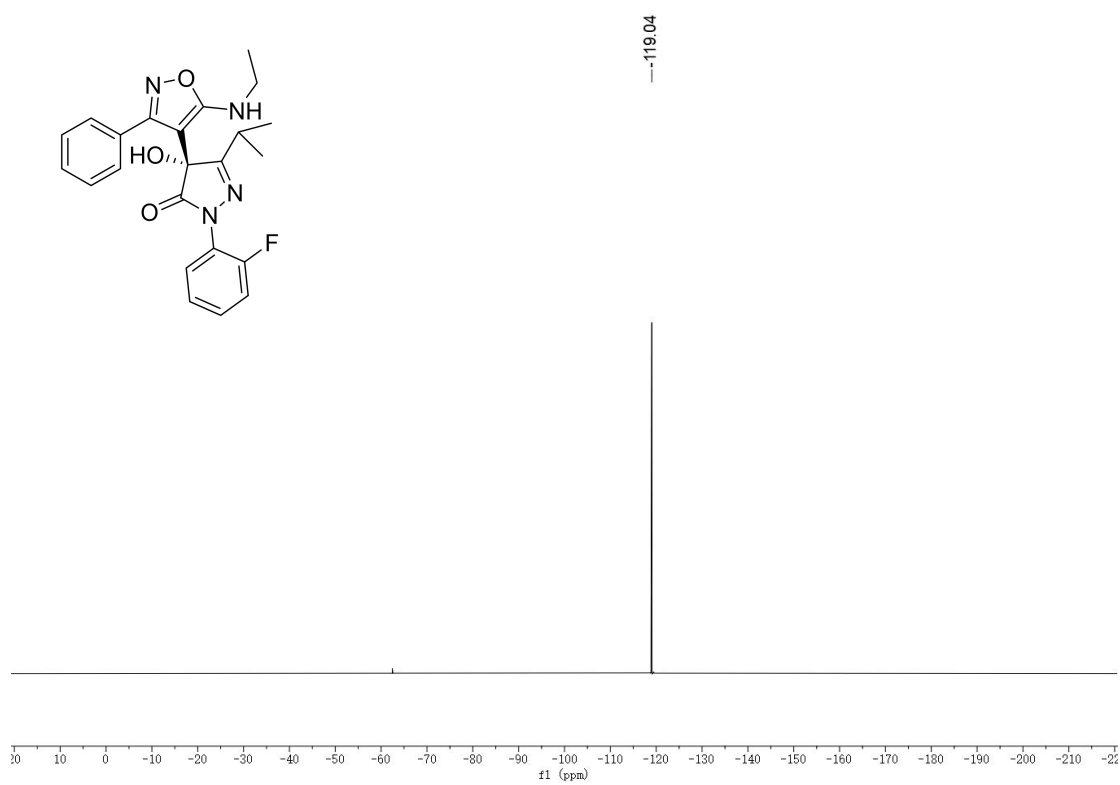
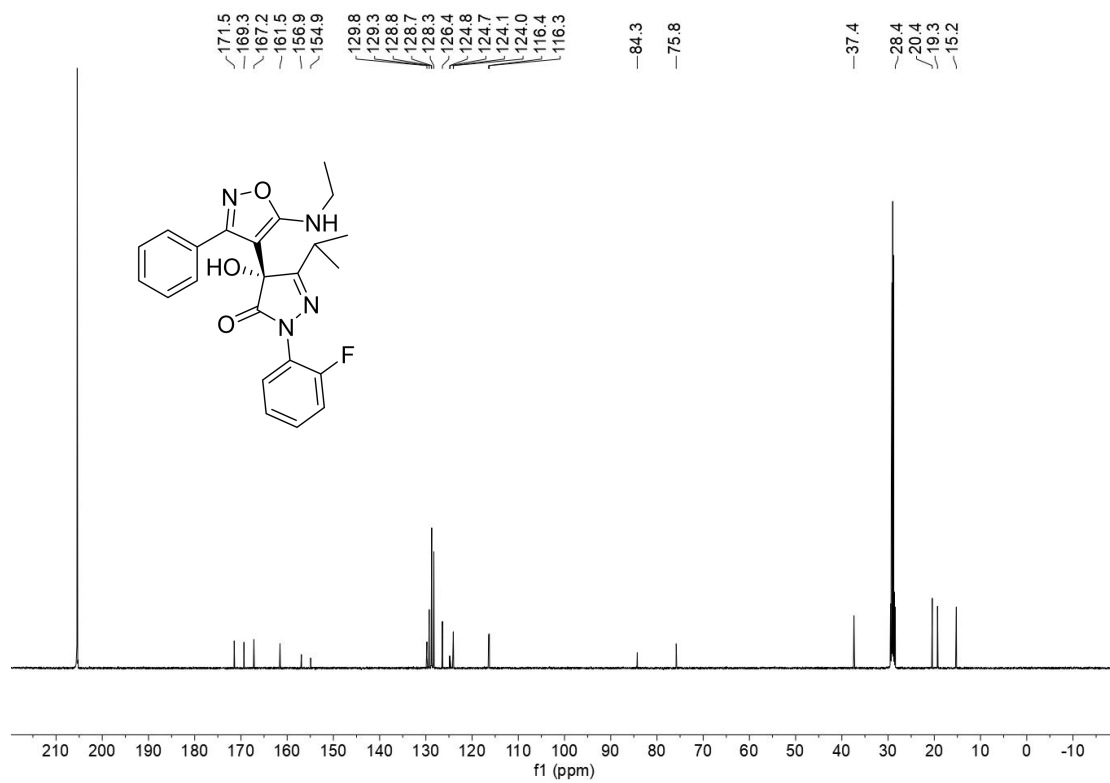
^1H NMR and ^{13}C NMR of **3qa**



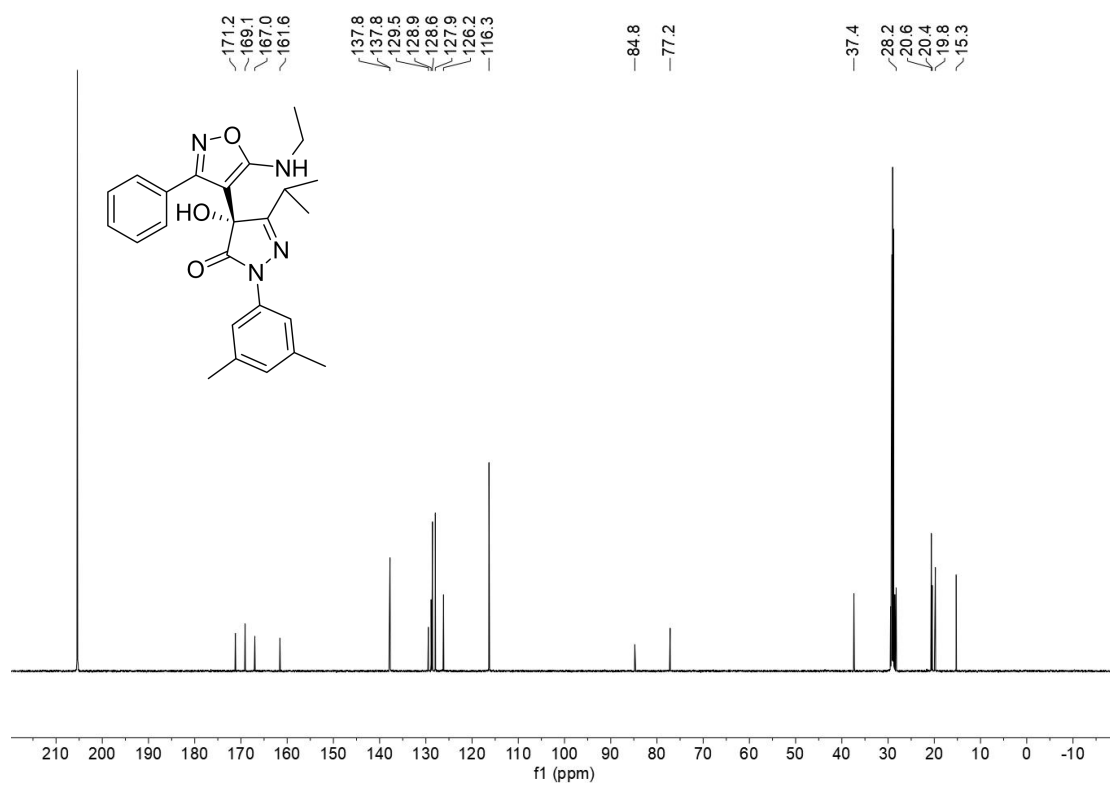
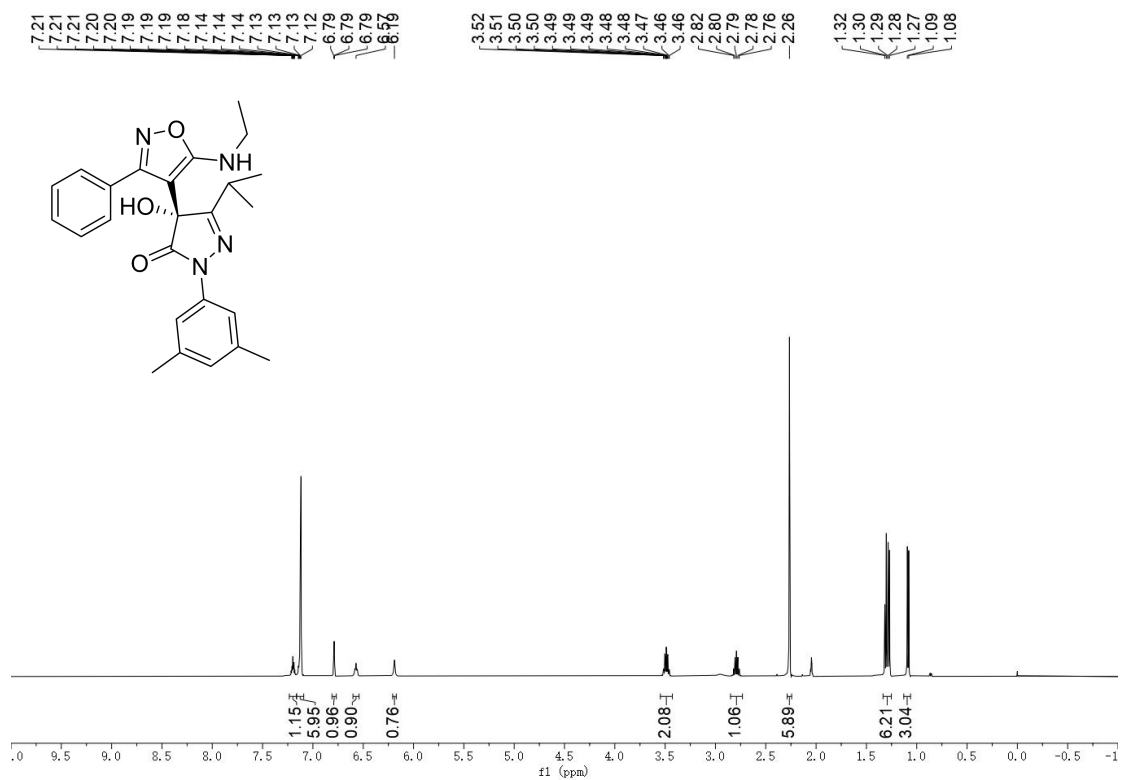


¹H NMR, ¹³C NMR and ¹⁹F NMR of **3ra**

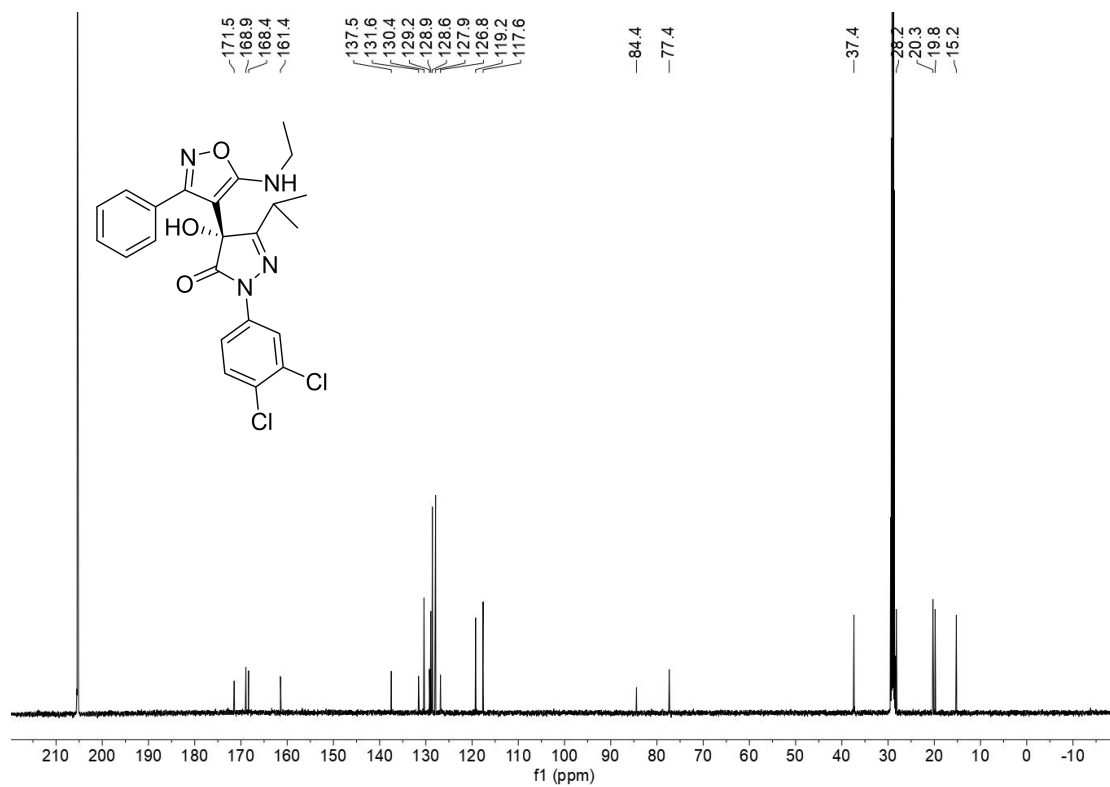
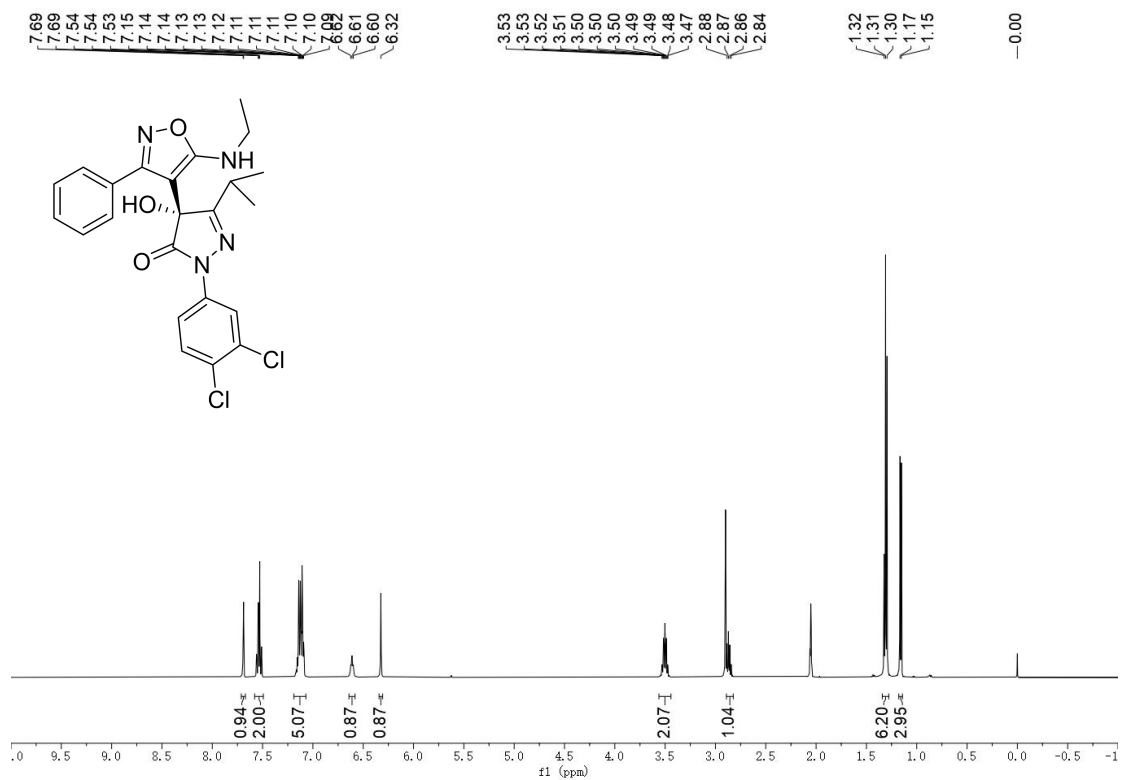




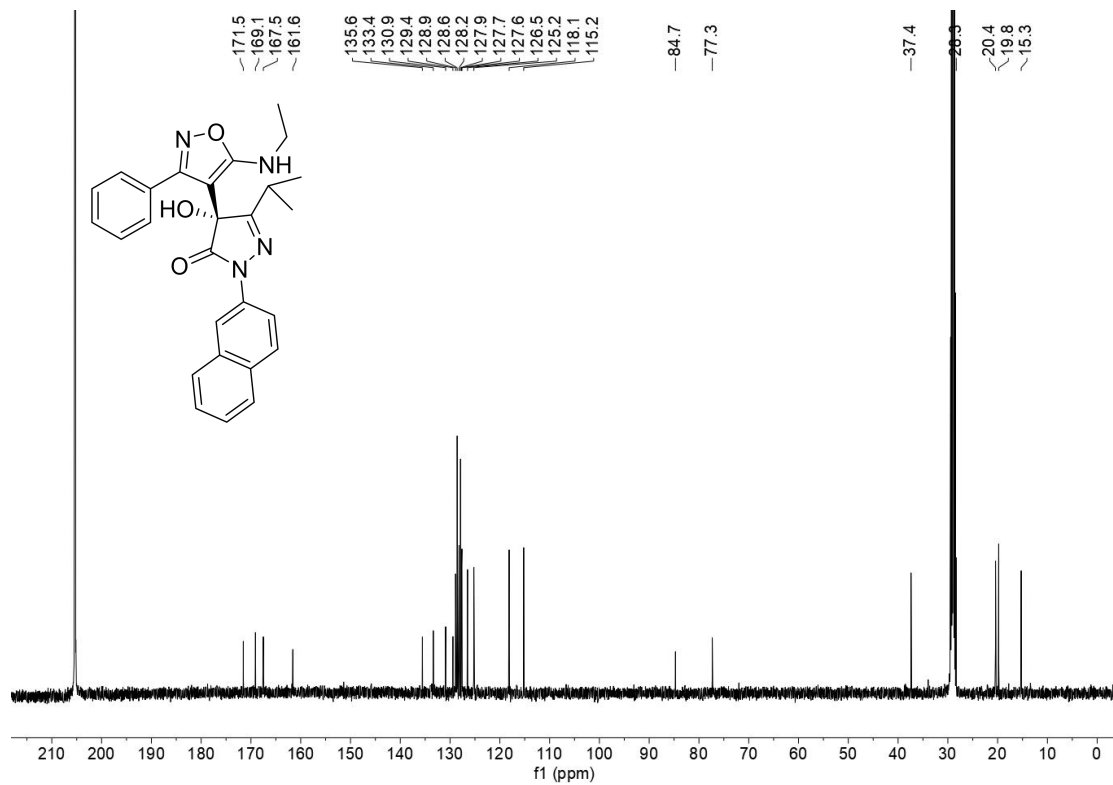
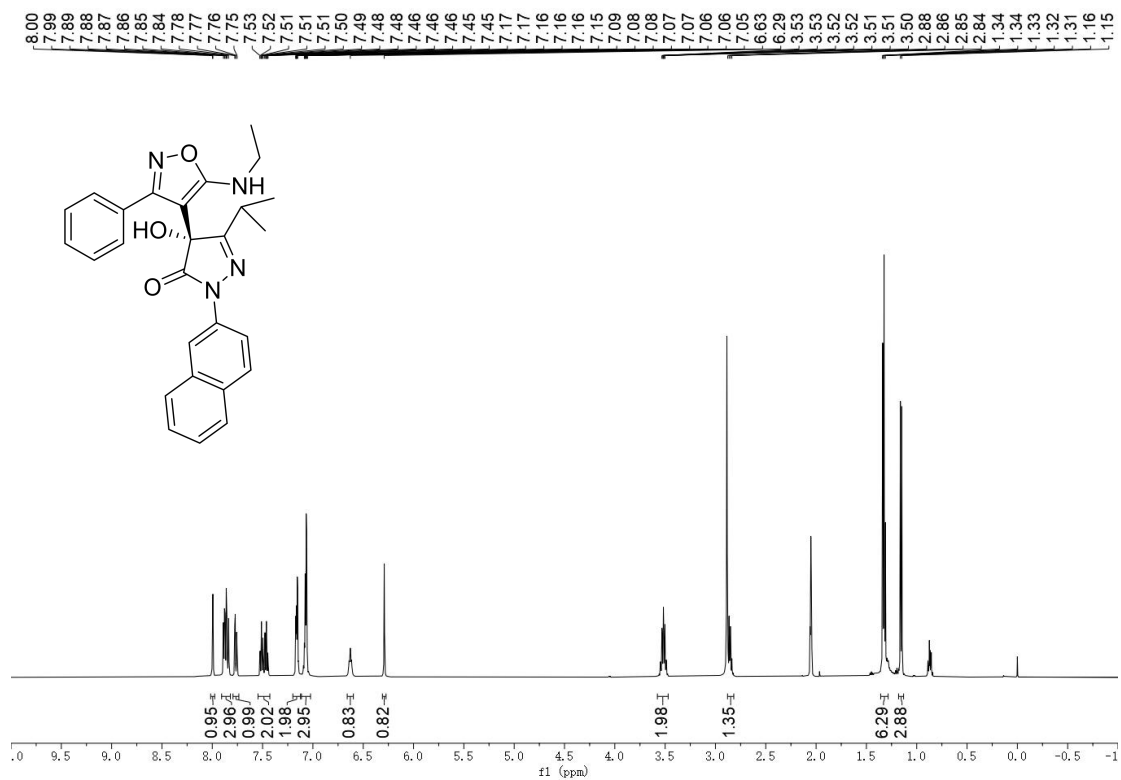
^1H NMR and ^{13}C NMR of **3sa**



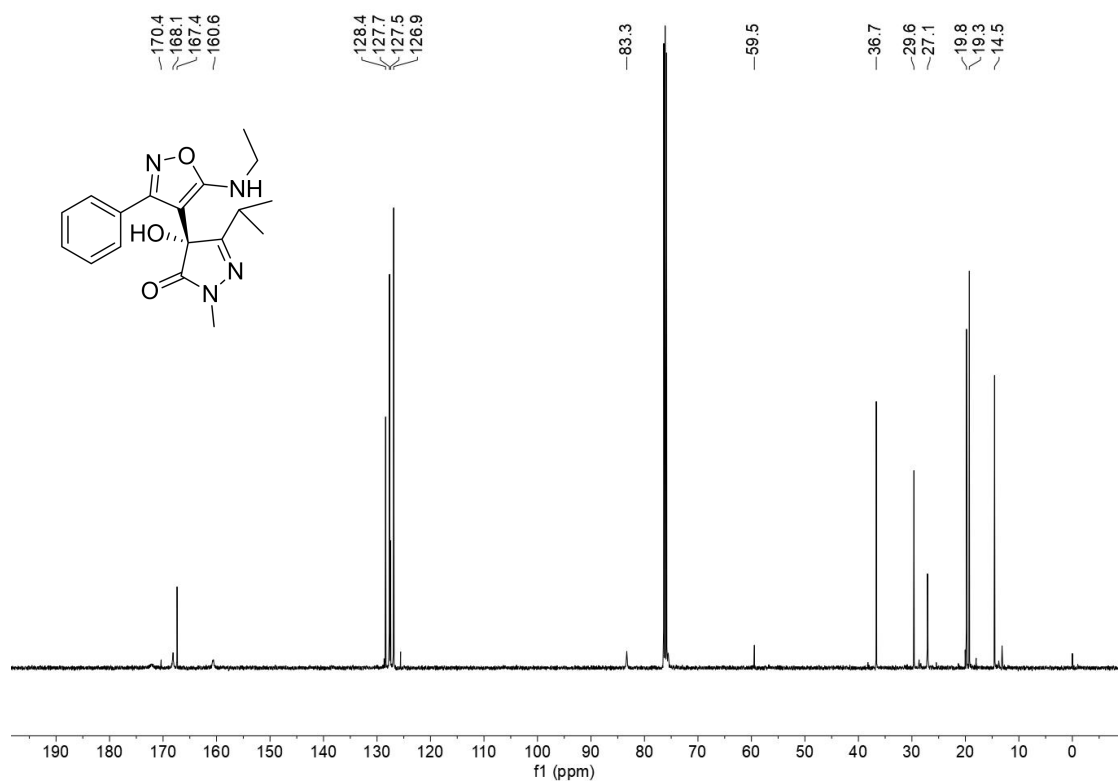
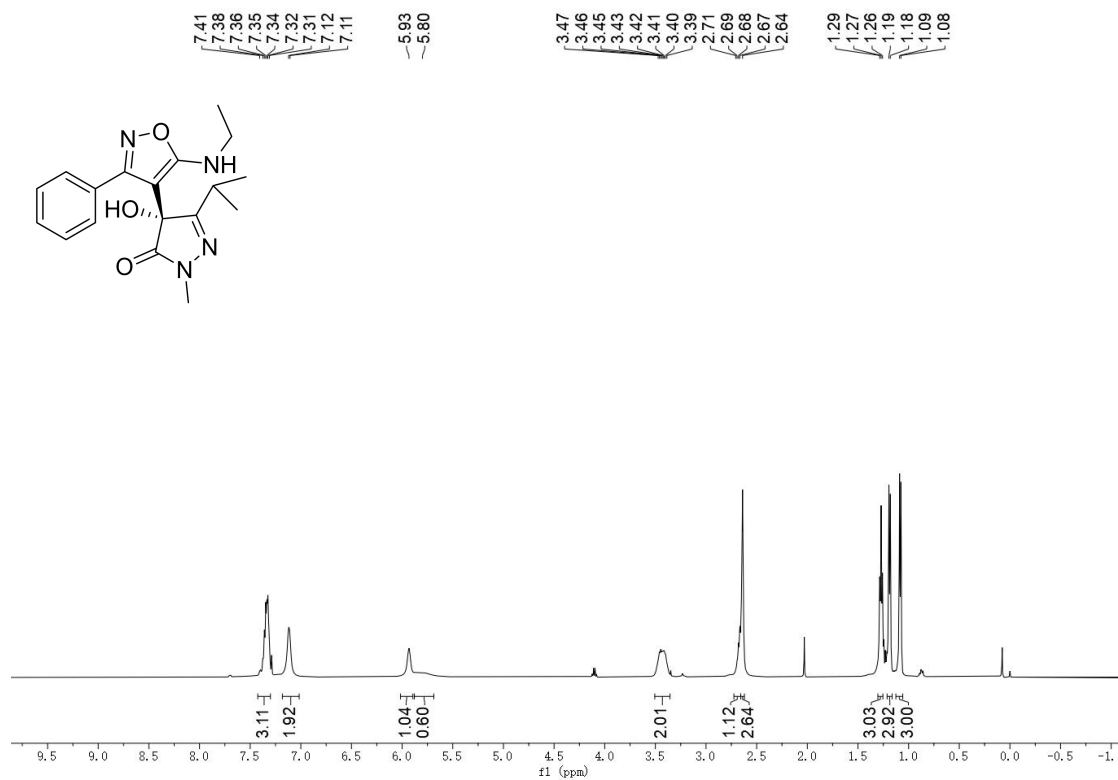
¹H NMR and ¹³C NMR of **3ta**



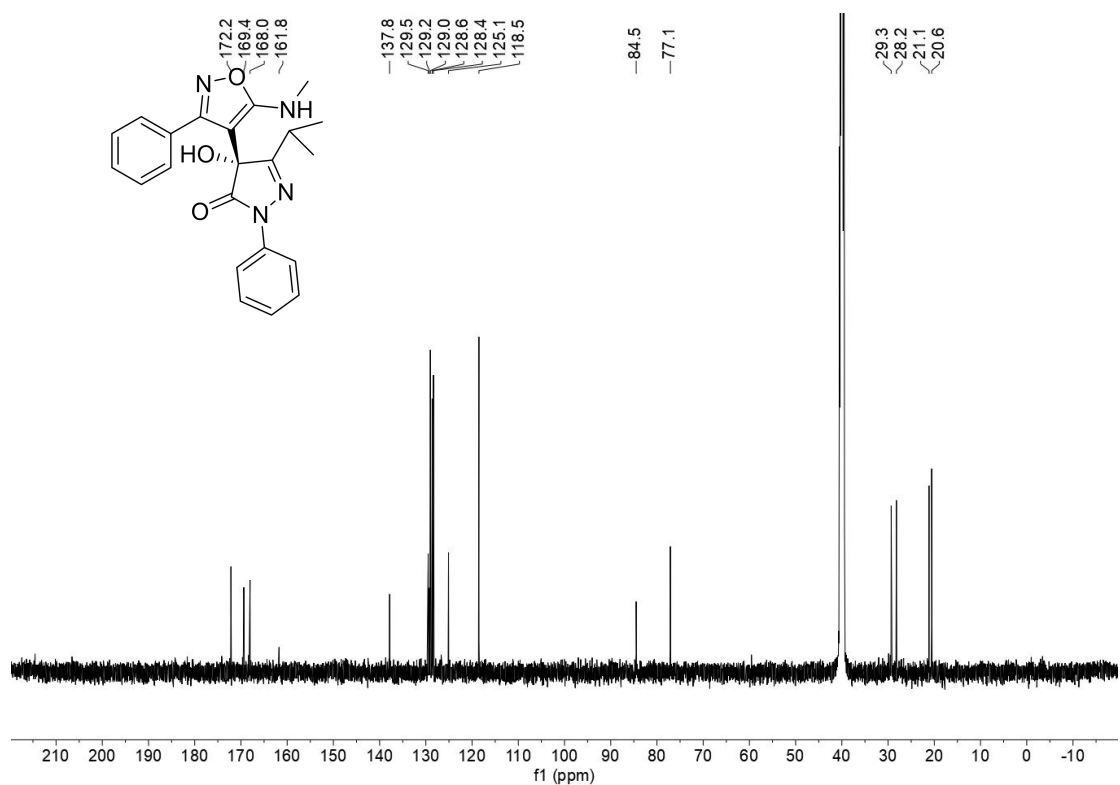
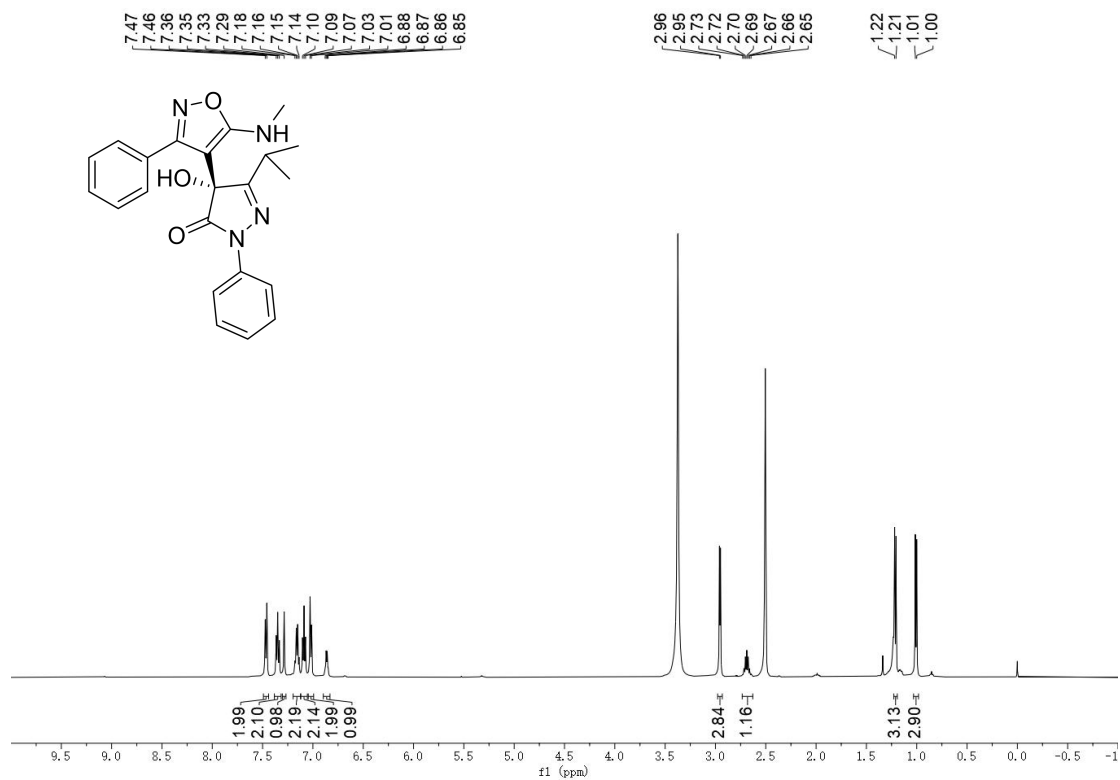
¹H NMR and ¹³C NMR of **3ua**



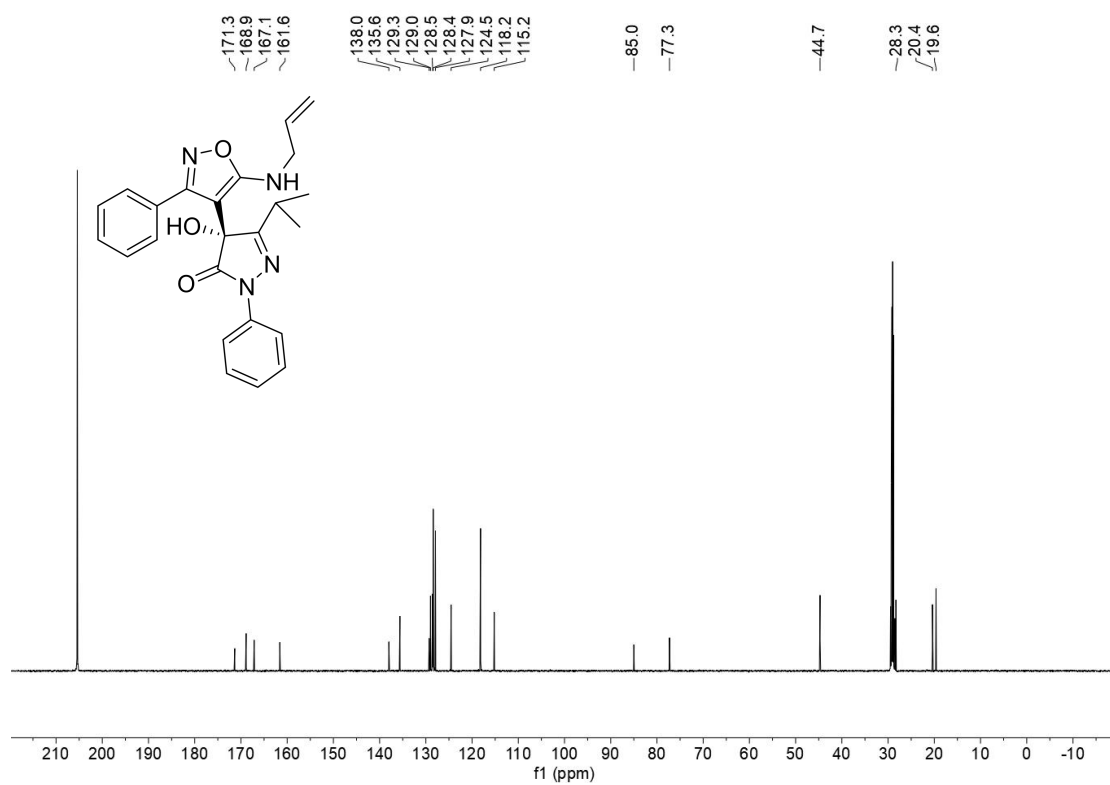
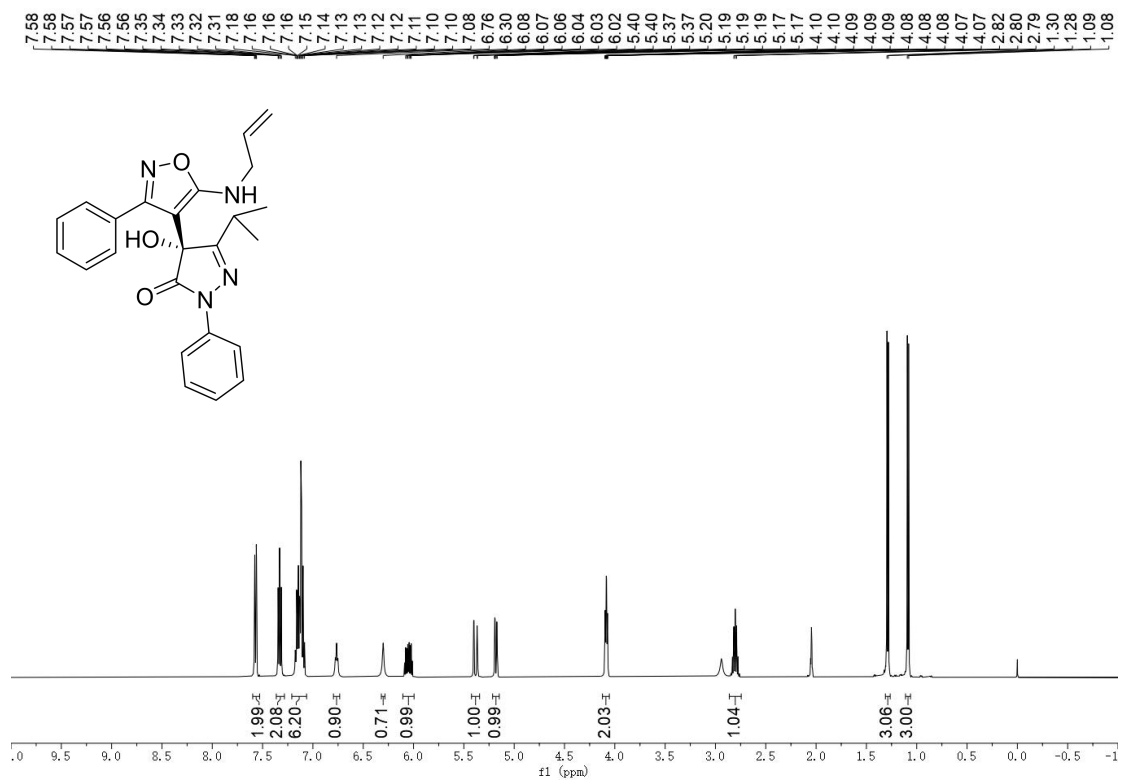
¹H NMR and ¹³C NMR of 3va



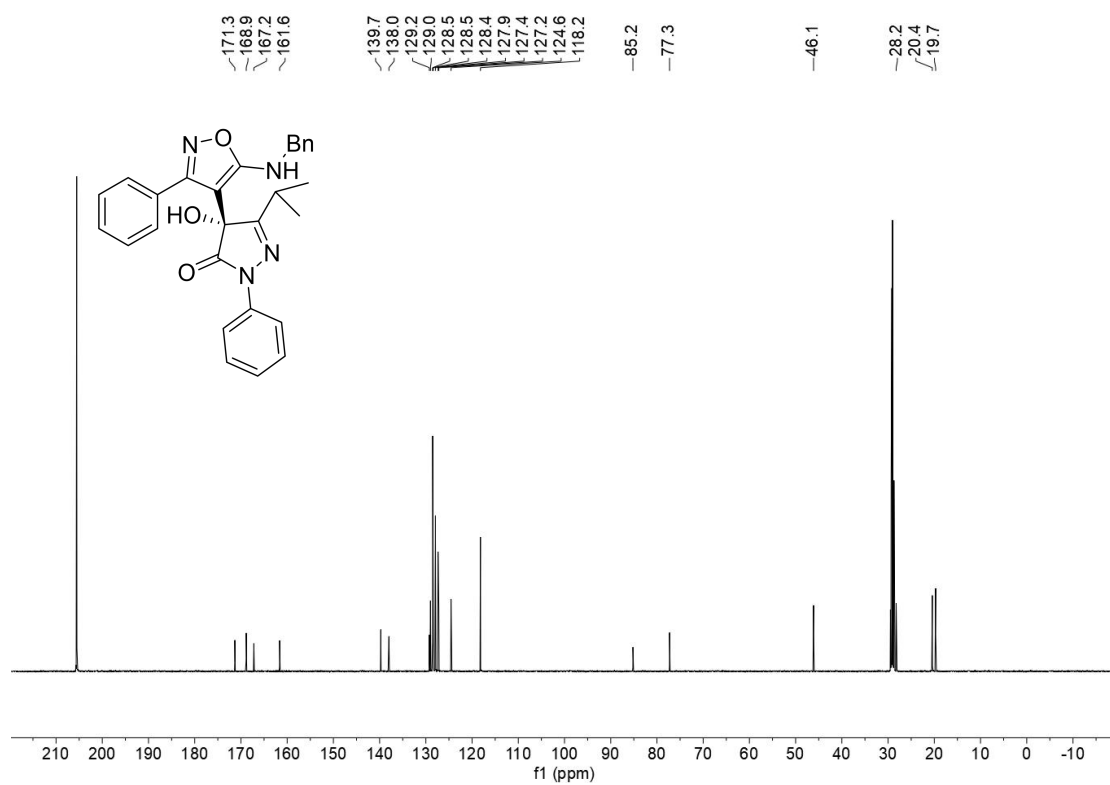
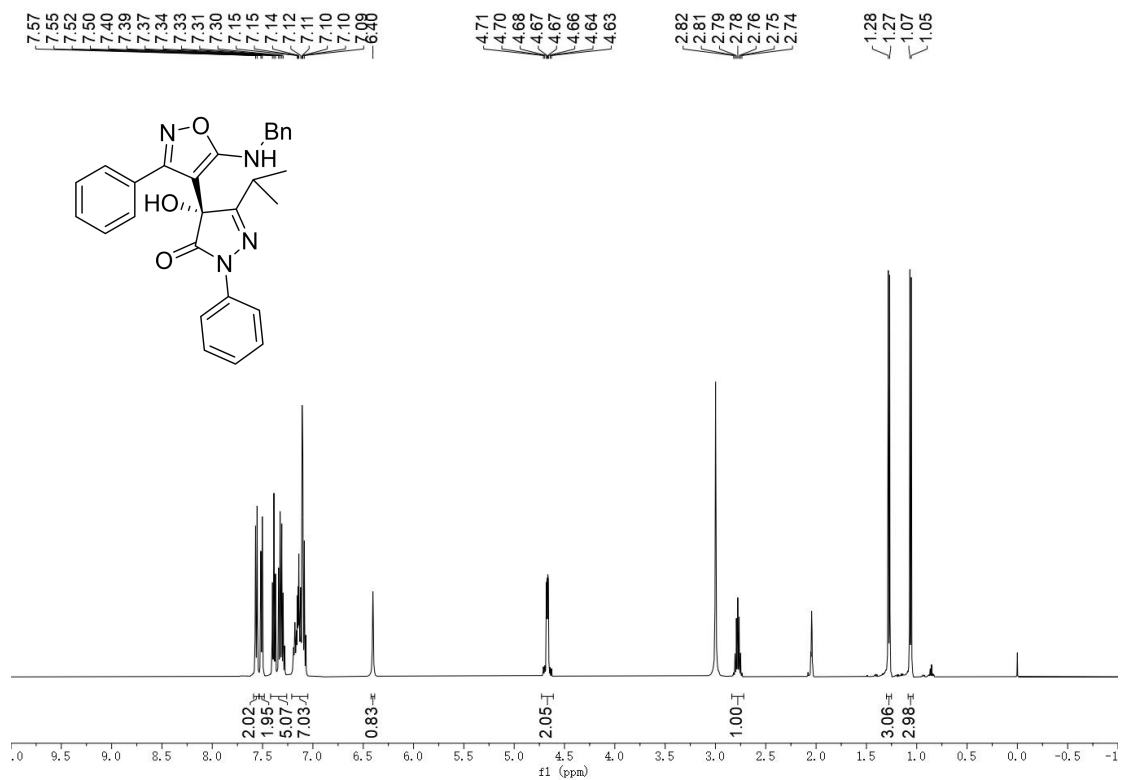
^1H NMR and ^{13}C NMR of **3ab**



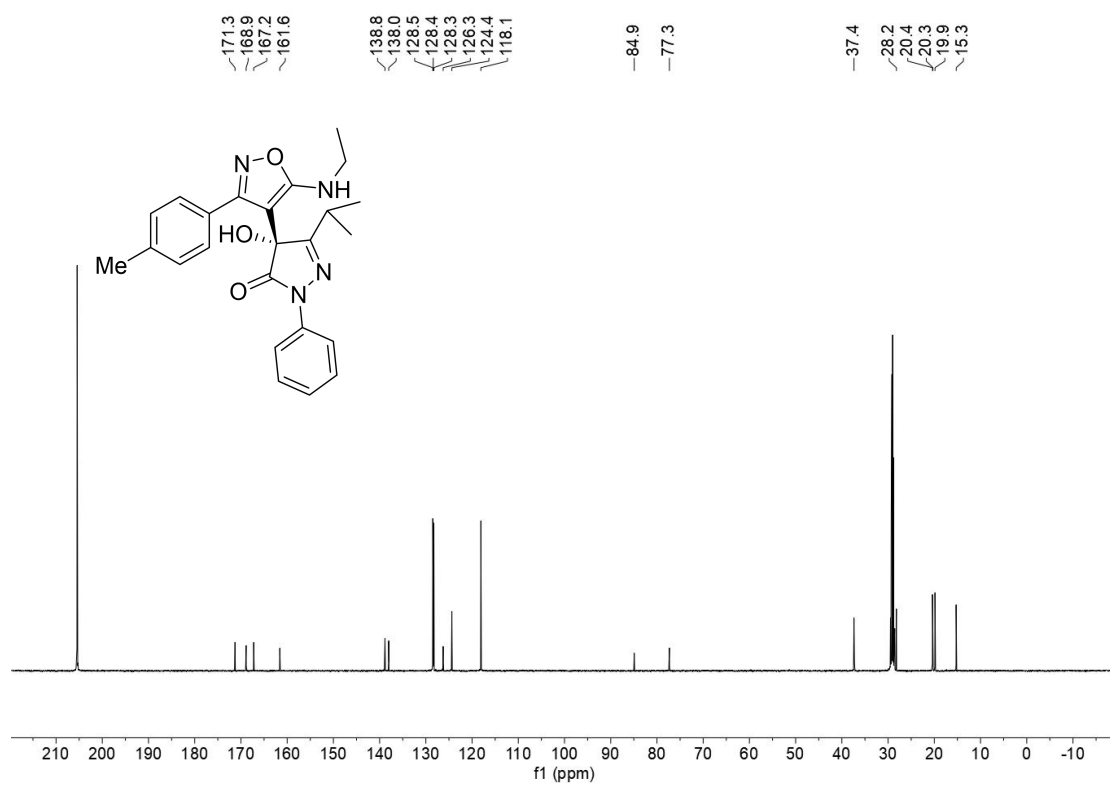
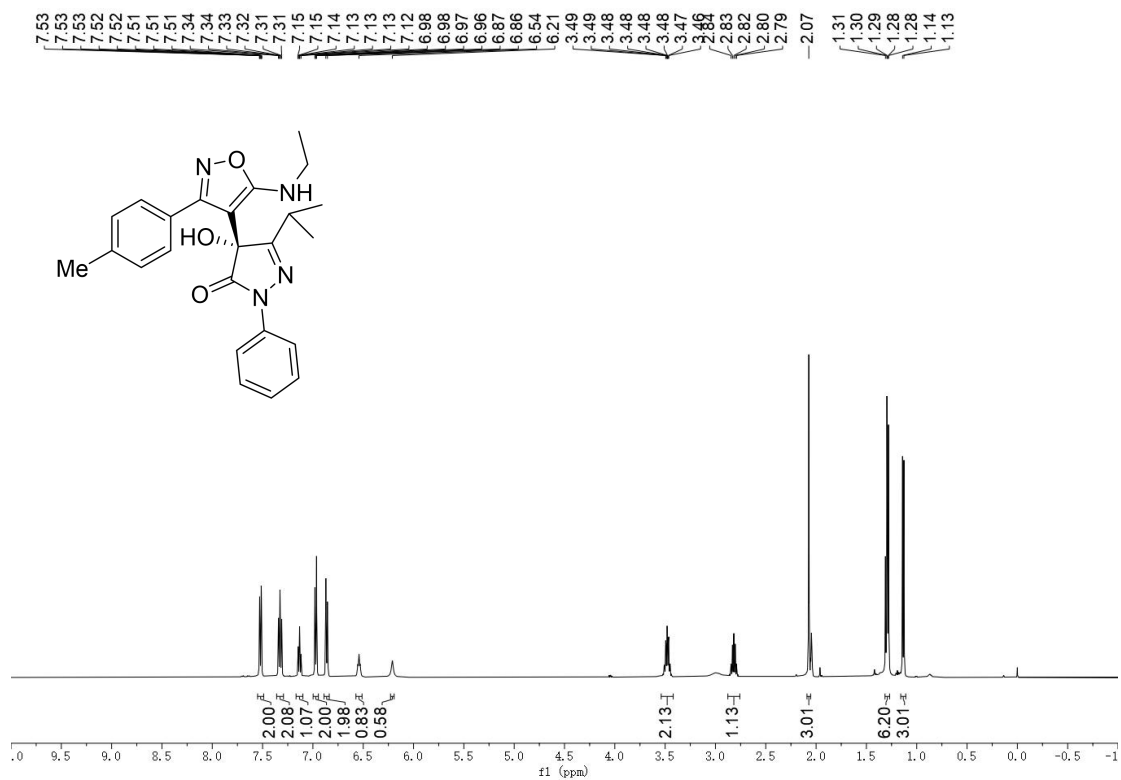
^1H NMR and ^{13}C NMR of **3ac**



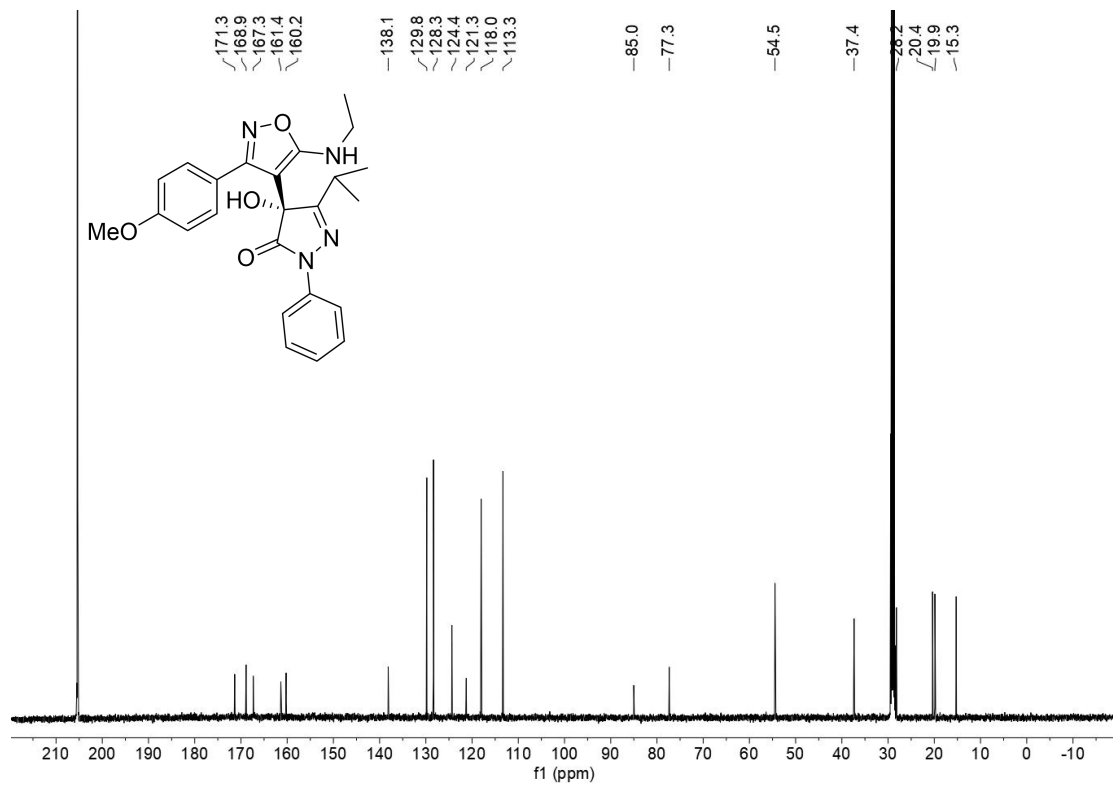
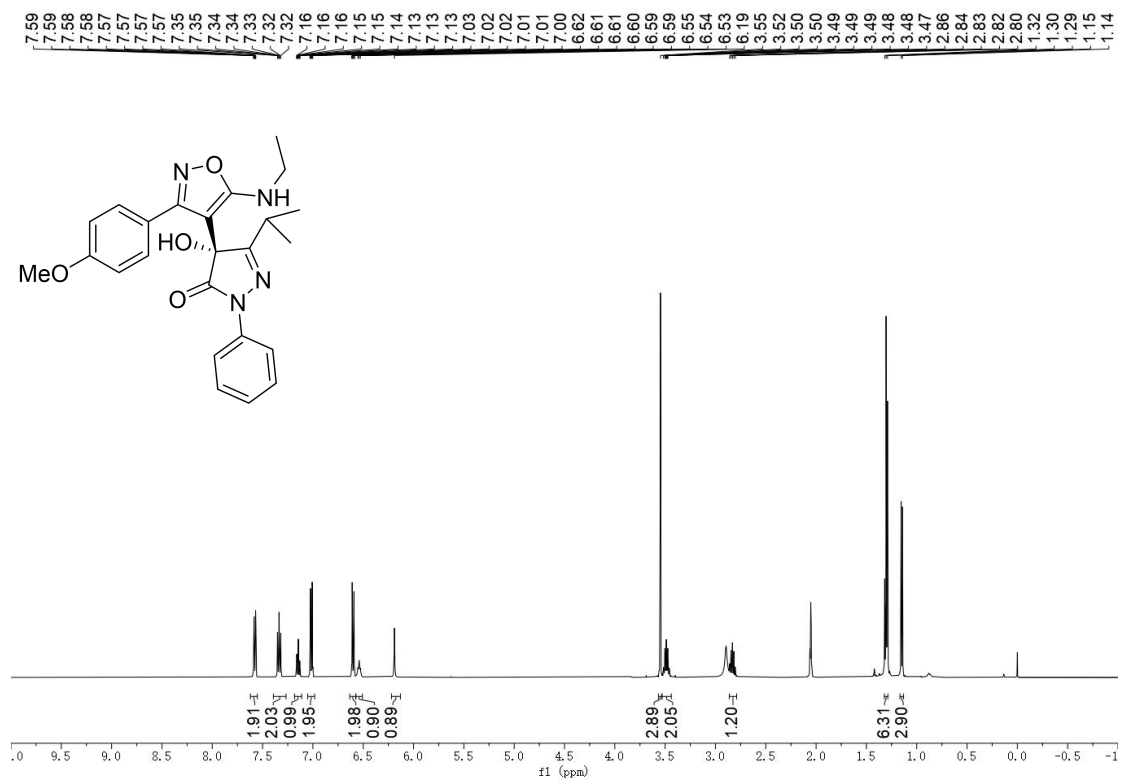
^1H NMR and ^{13}C NMR of **3ad**



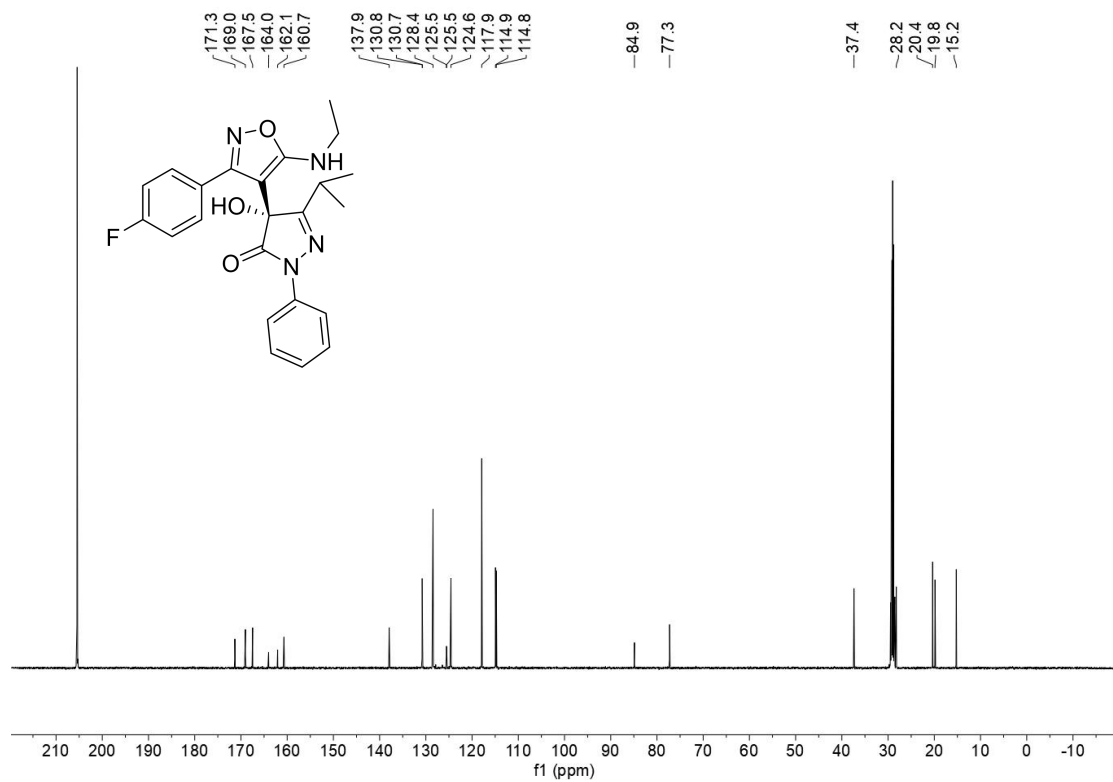
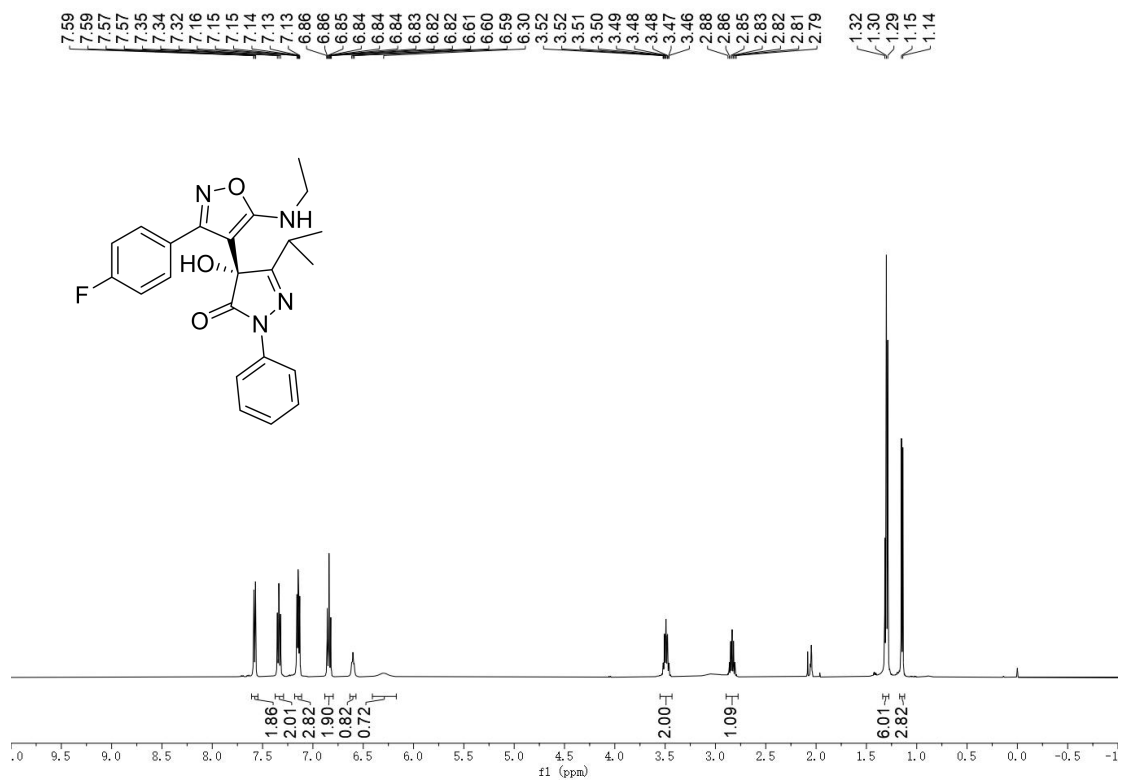
¹H NMR and ¹³C NMR of **3ae**

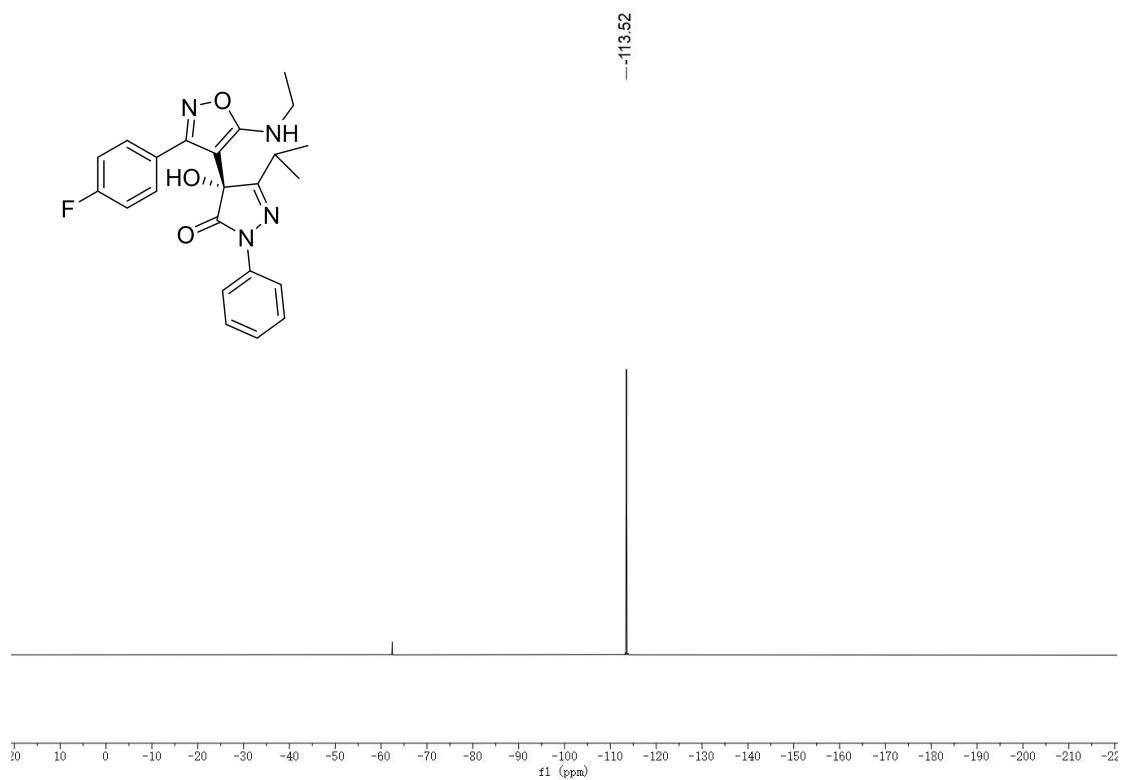


¹H NMR and ¹³C NMR of 3af

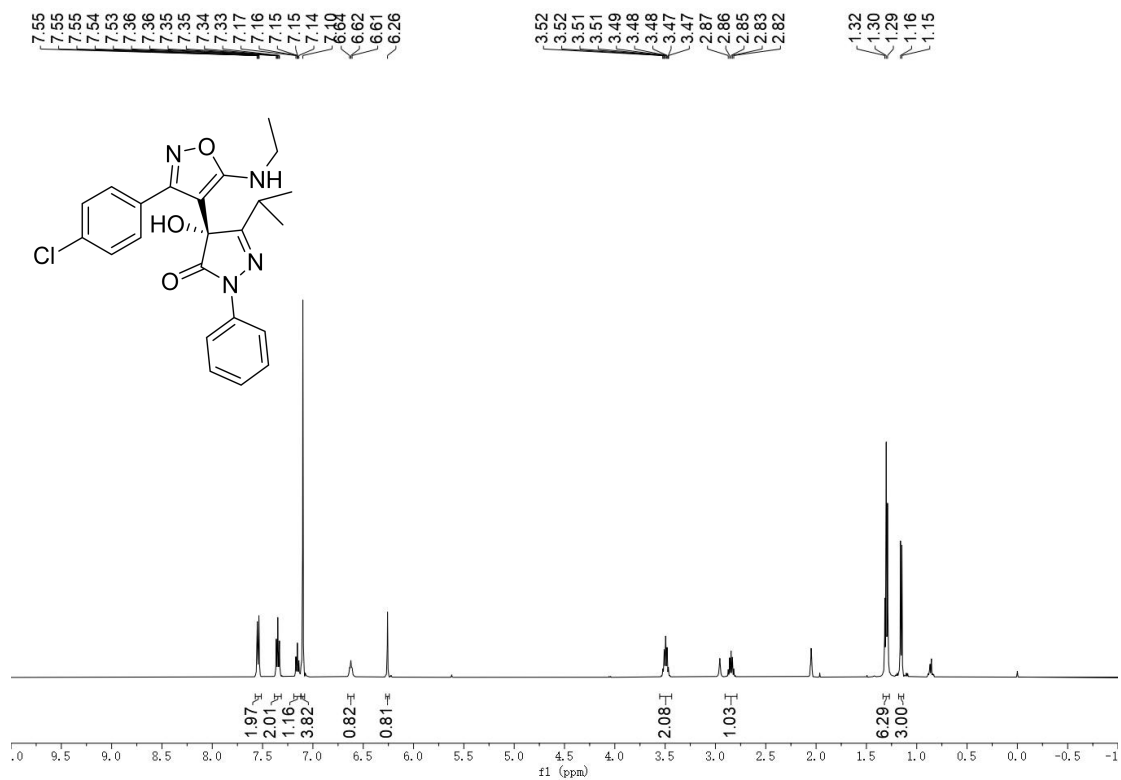


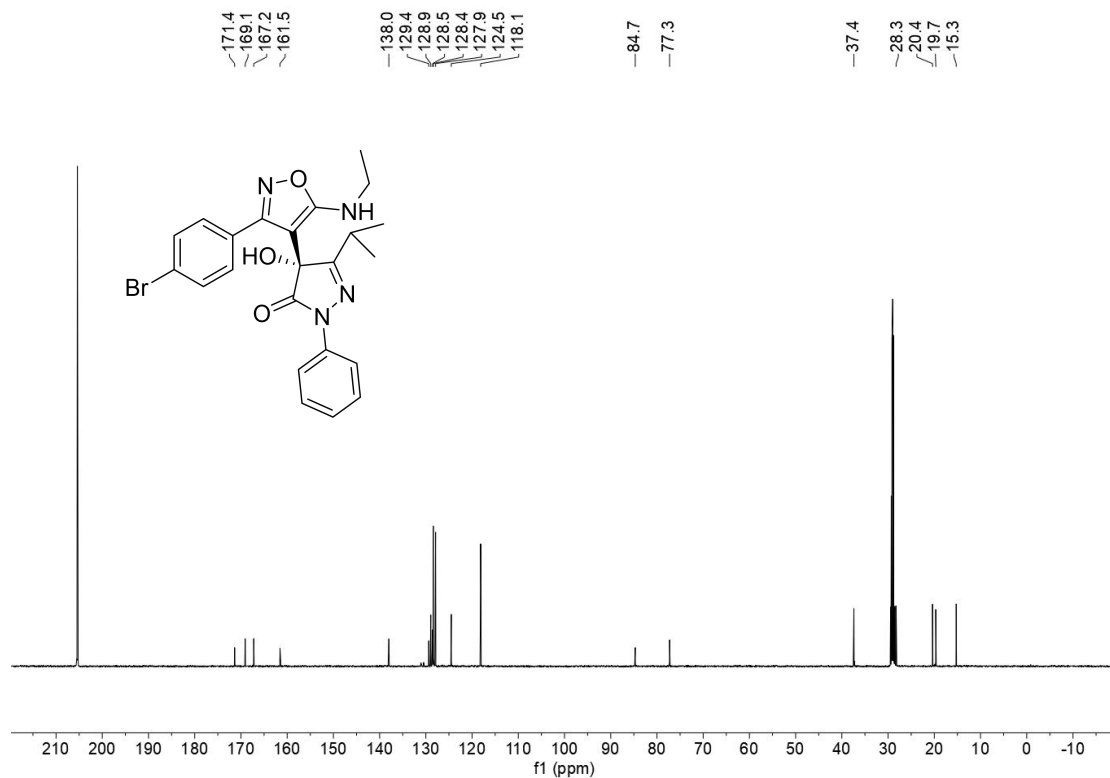
¹H NMR and ¹³C NMR of **3ag**



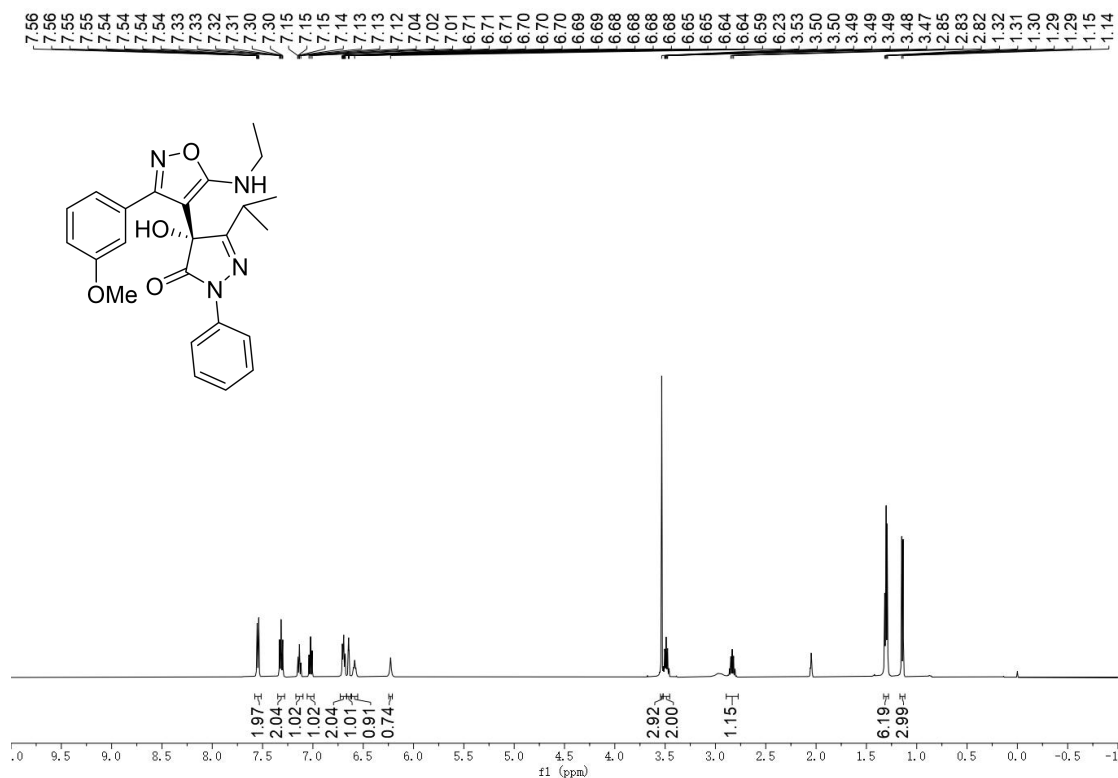


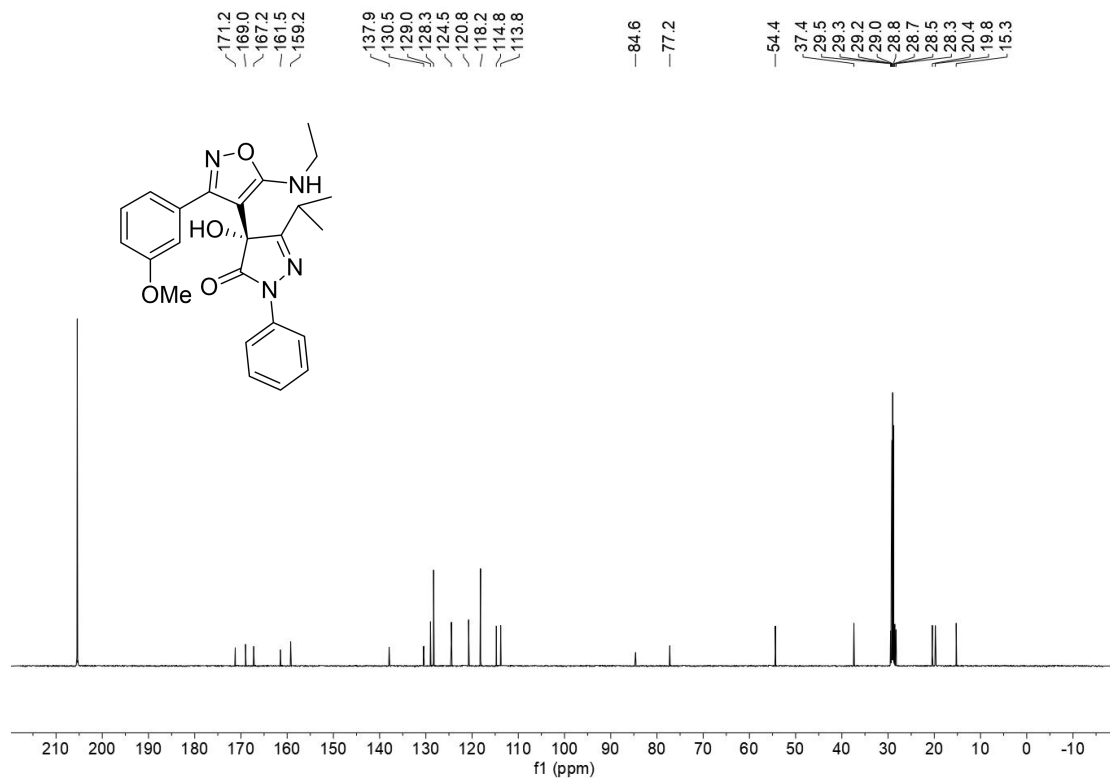
^1H NMR and ^{13}C NMR of 3ah



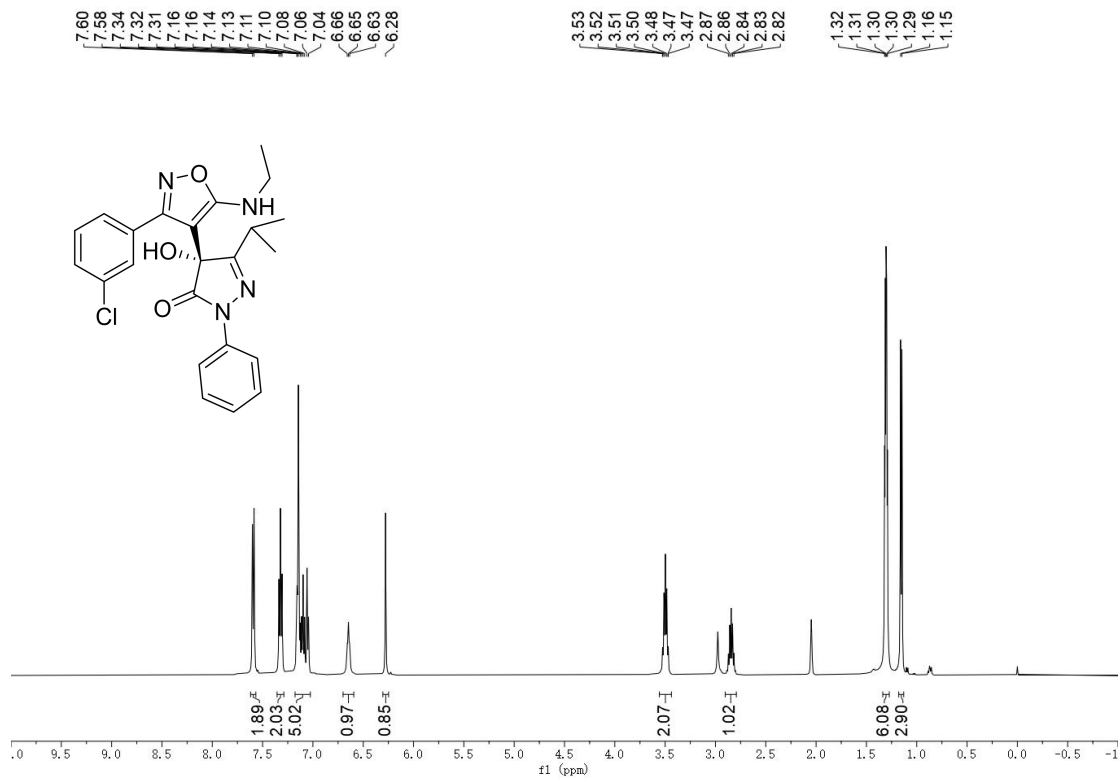


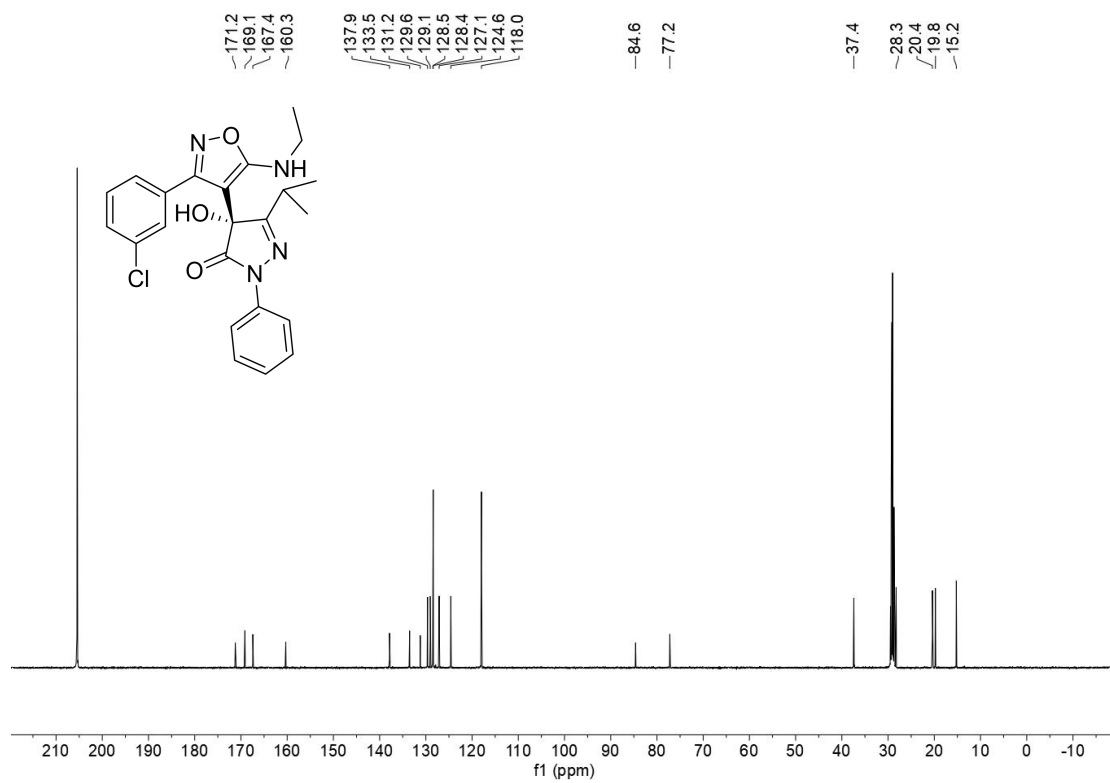
¹H NMR and ¹³C NMR of 3aj



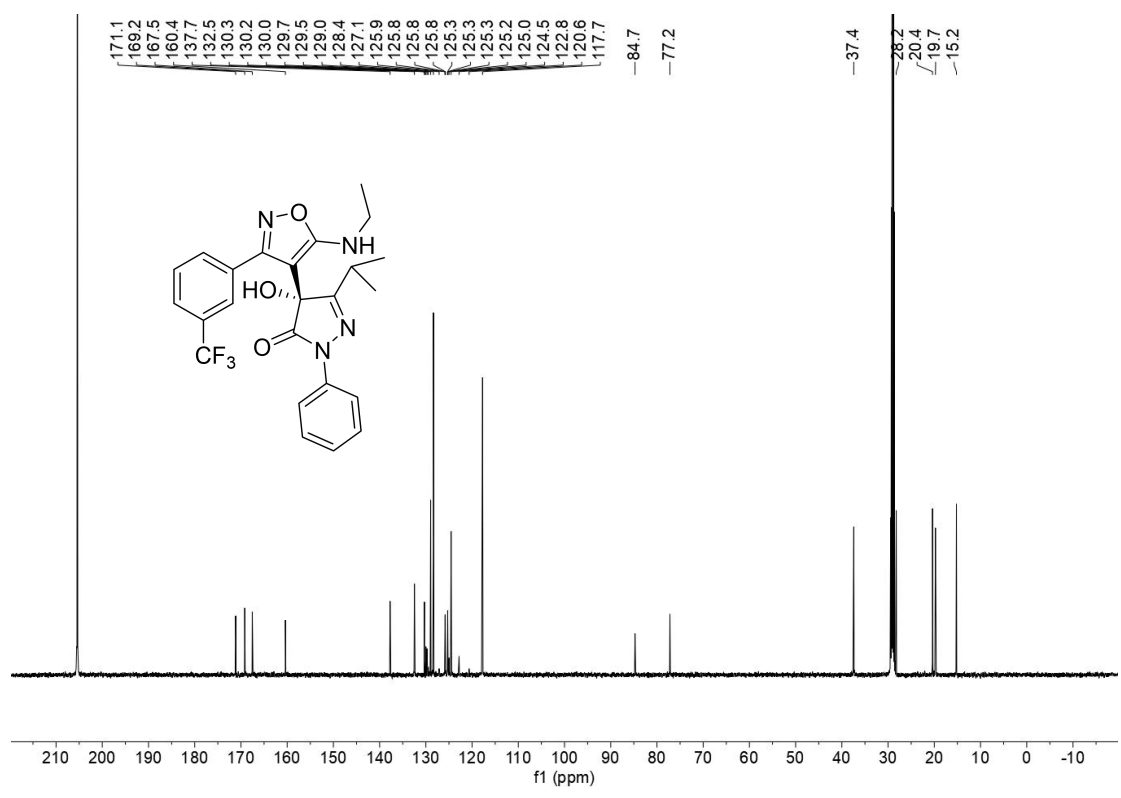
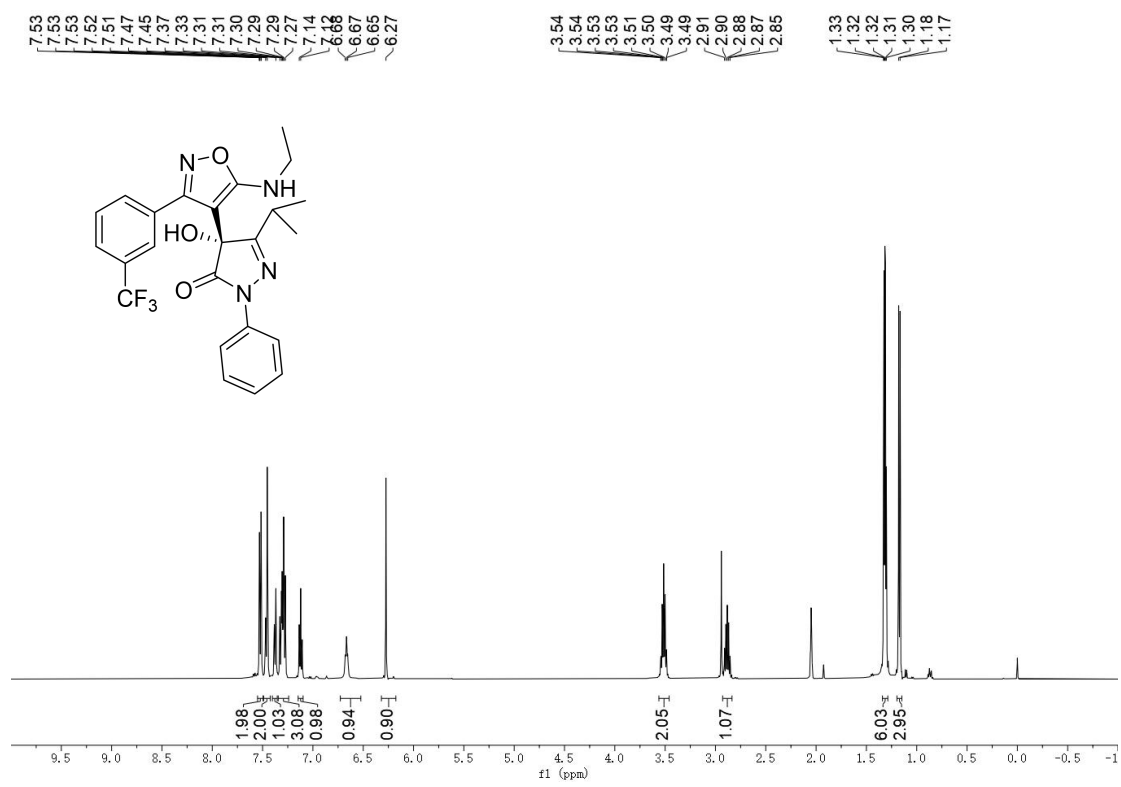


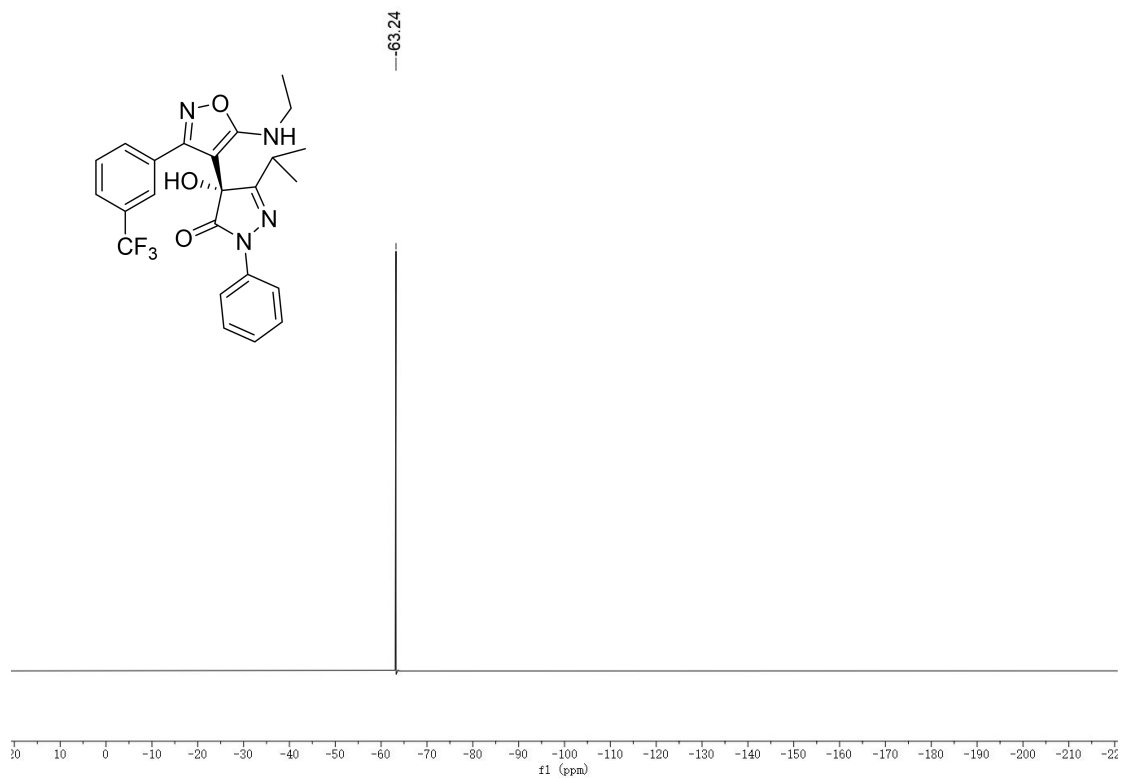
¹H NMR and ¹³C NMR of **3ak**



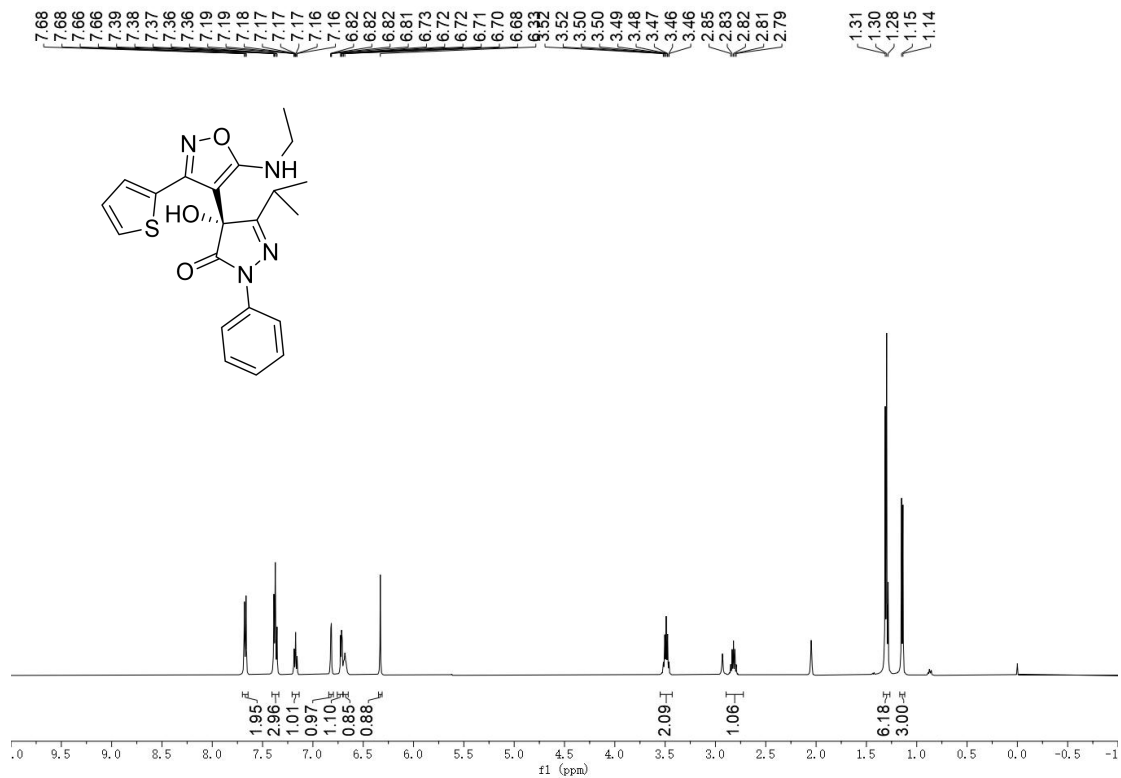


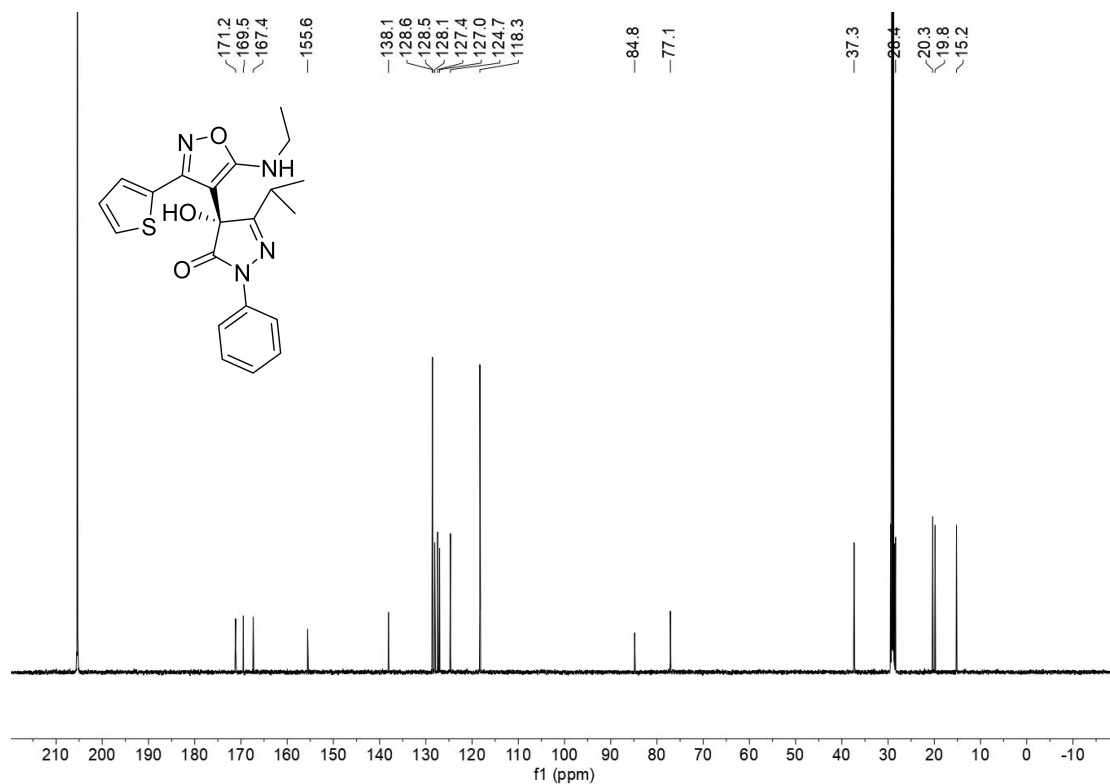
^1H NMR, ^{13}C NMR and ^{19}F NMR of **3al**



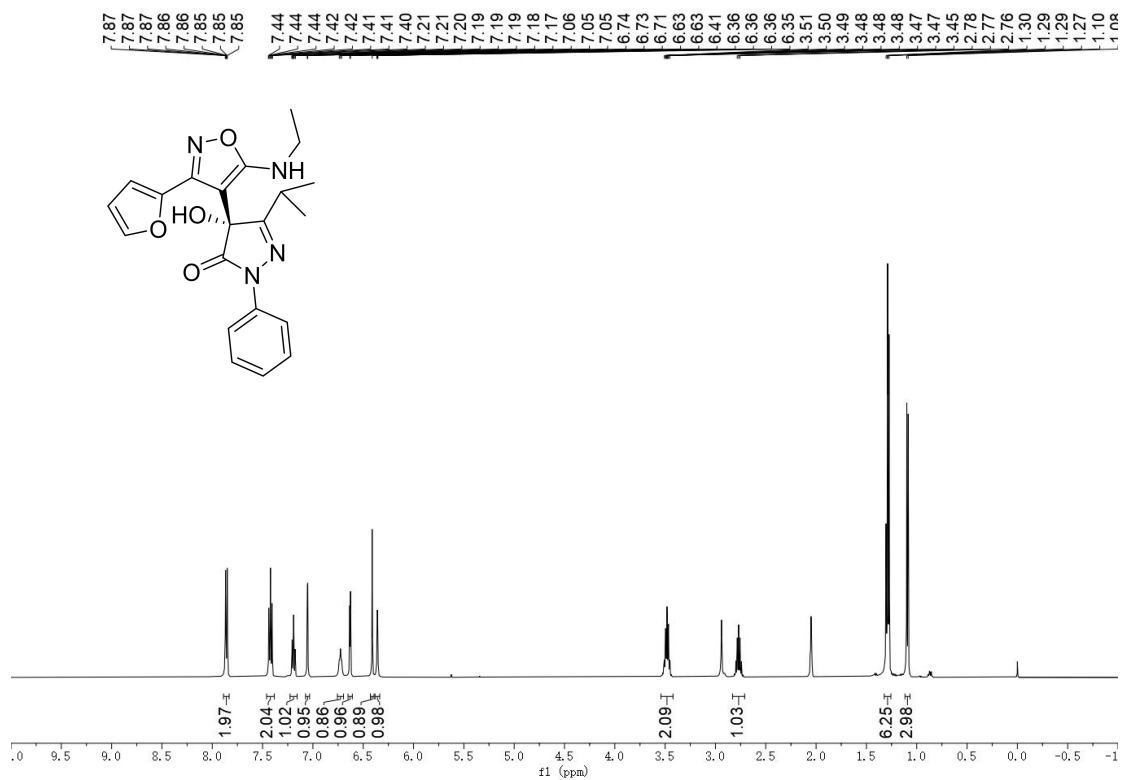


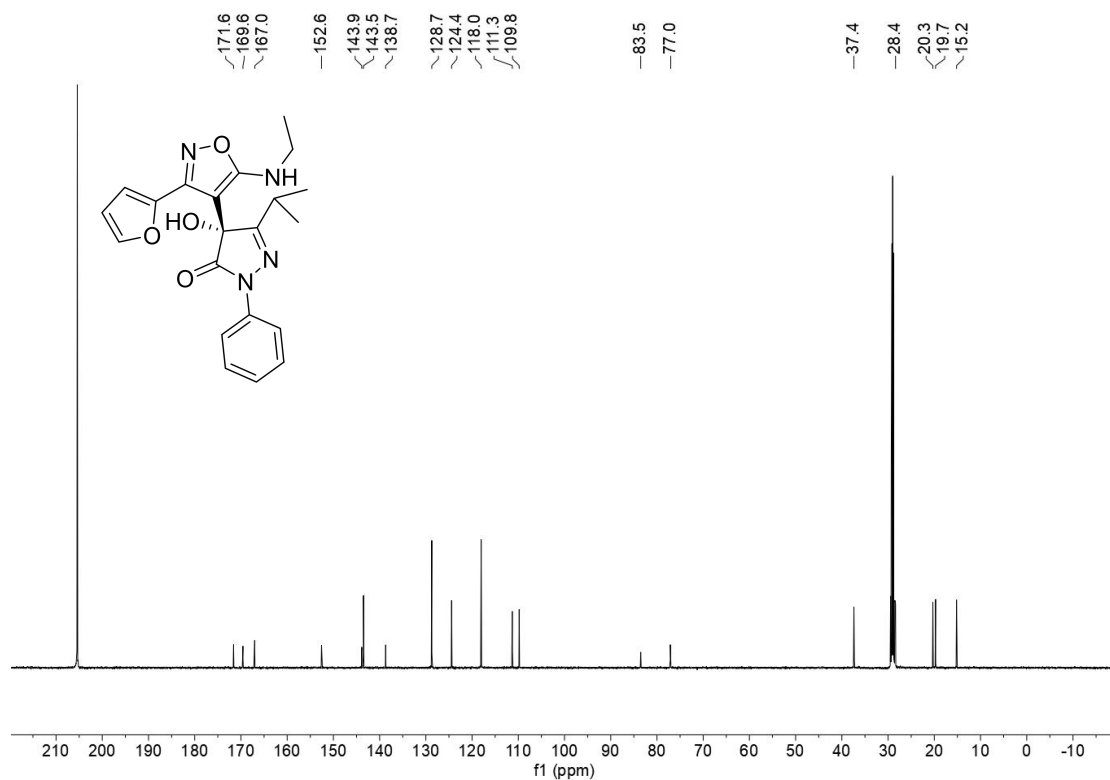
¹H NMR and ¹³C NMR of 3am



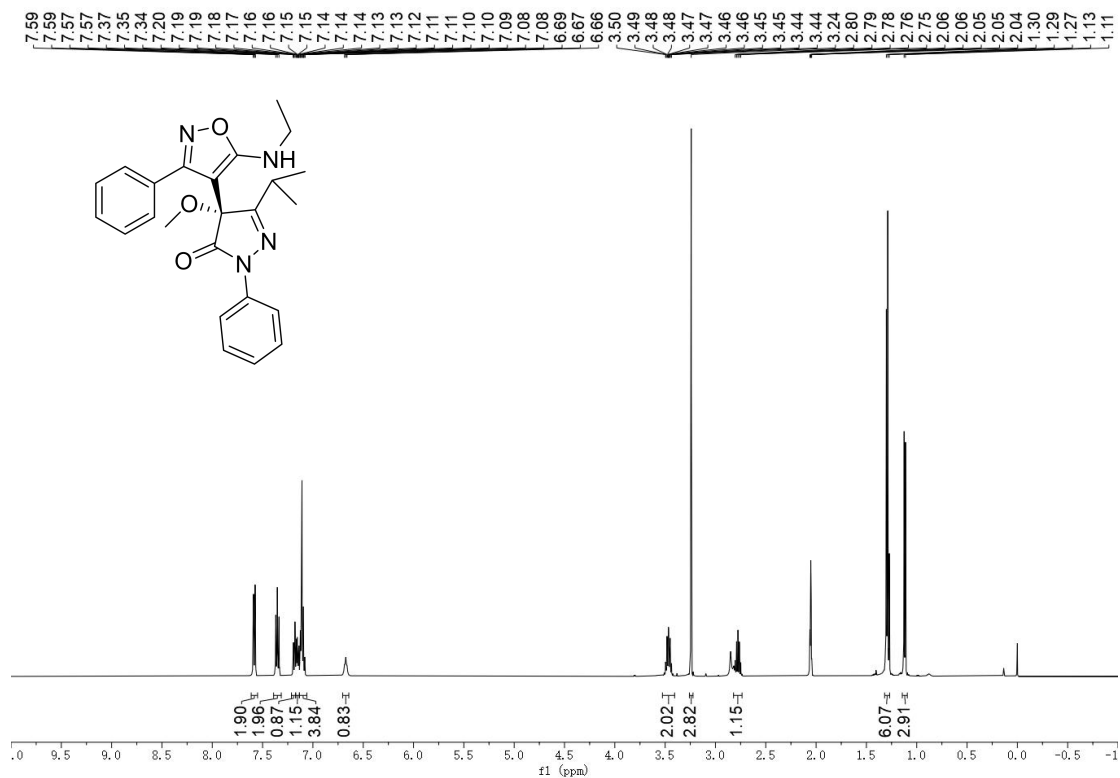


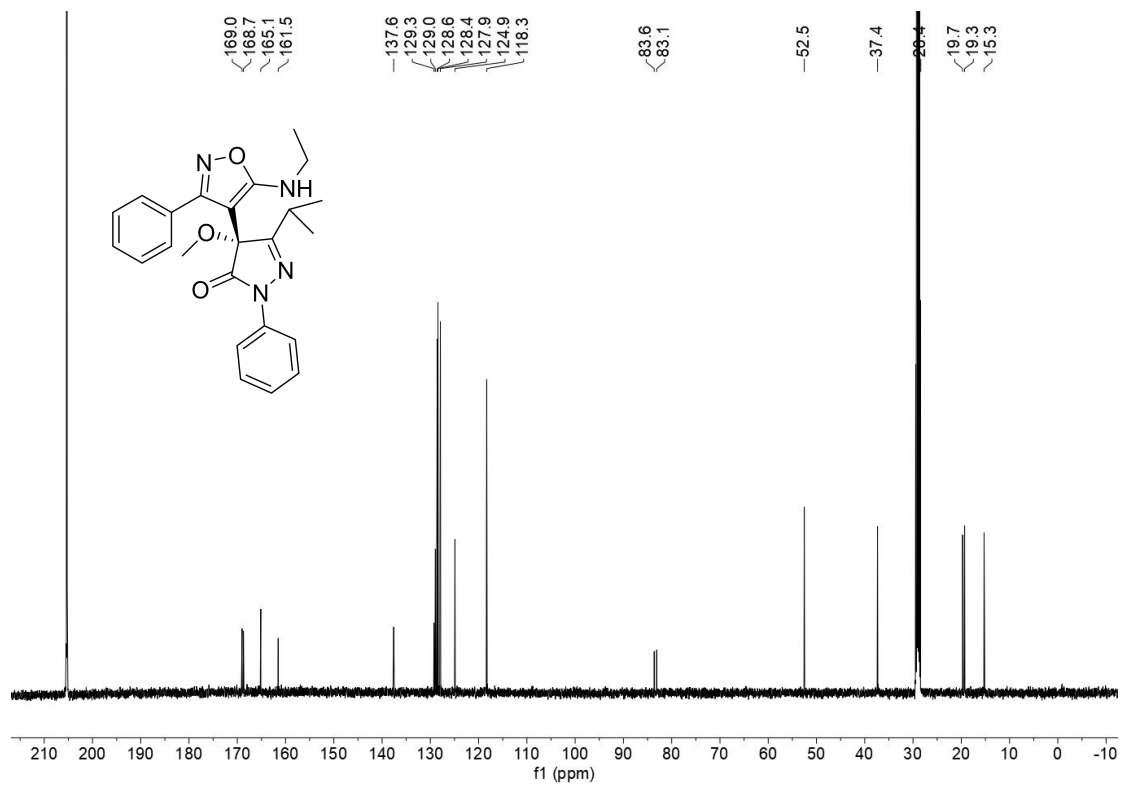
¹H NMR and ¹³C NMR of **3an**



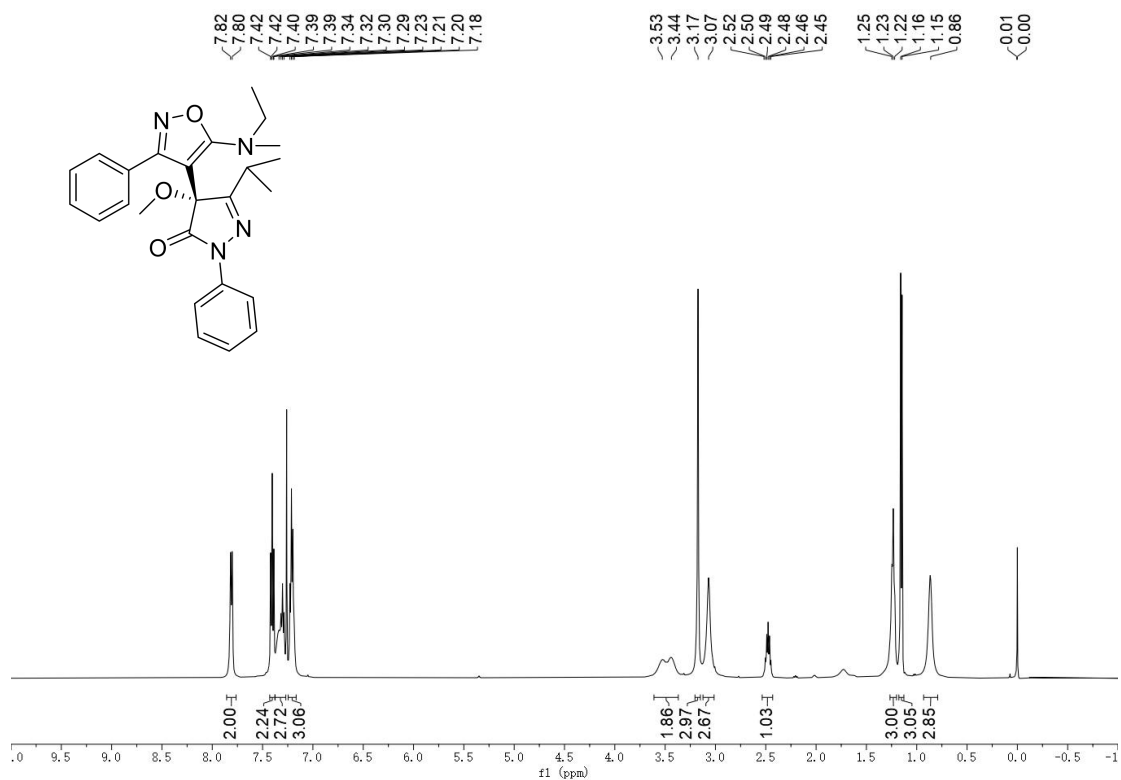


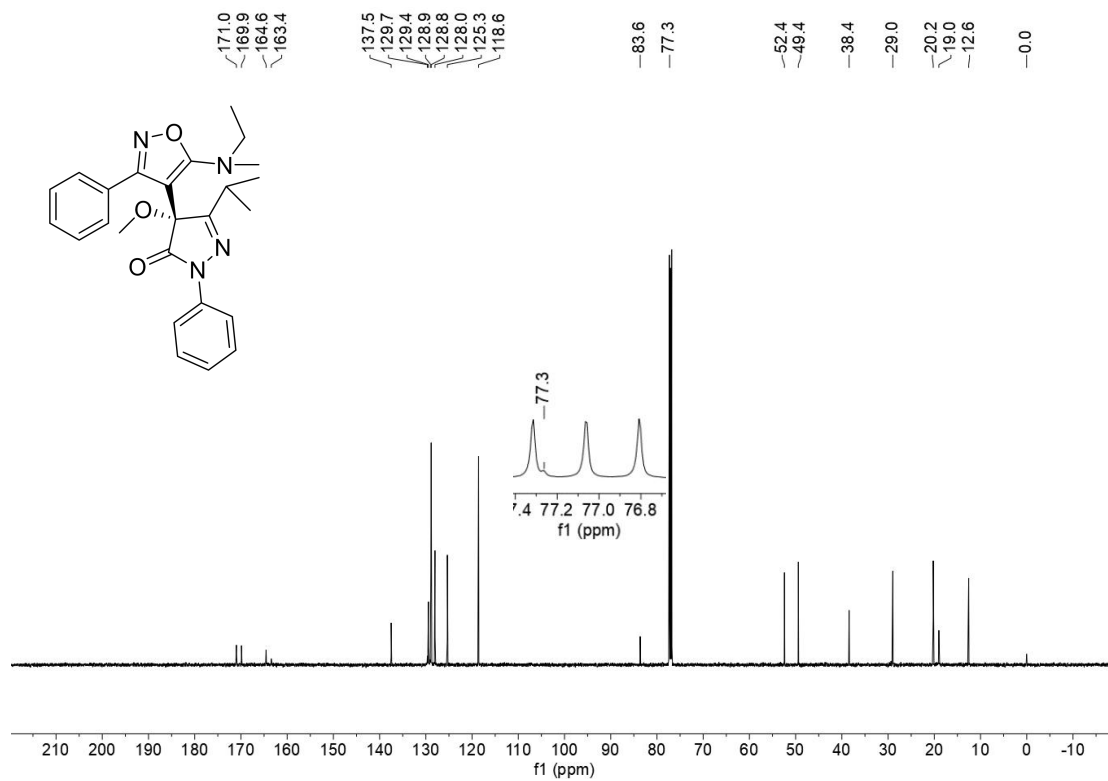
¹H NMR and ¹³C NMR of 4aa





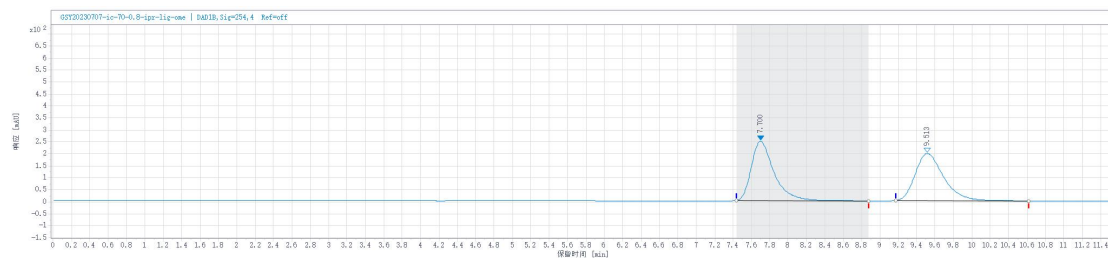
¹H NMR and ¹³C NMR of **5aa**





Part III HPLC Spectra

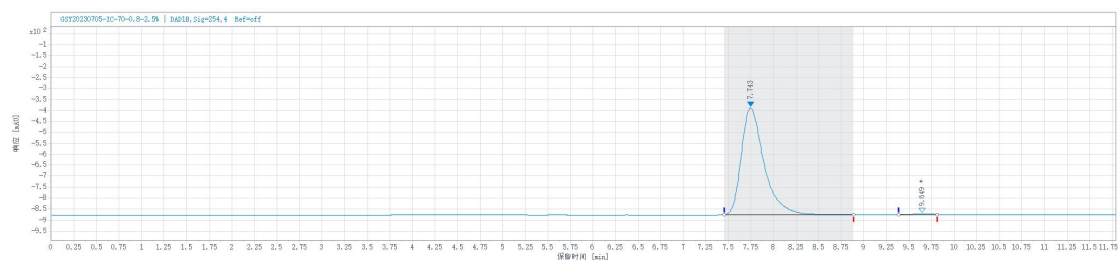
3aa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Azer [mAU*s]	Height [mAU]	Area%
7.70	1.44	4241.65	247.41	50.26
9.51	1.45	4197.59	196.27	49.74

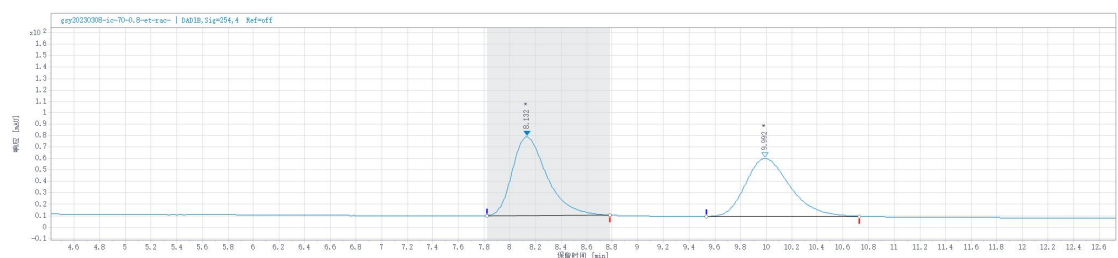
3aa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
7.74	1.43	8510.05	487.34	99.54
9.65	0.43	39.69	2.78	0.46

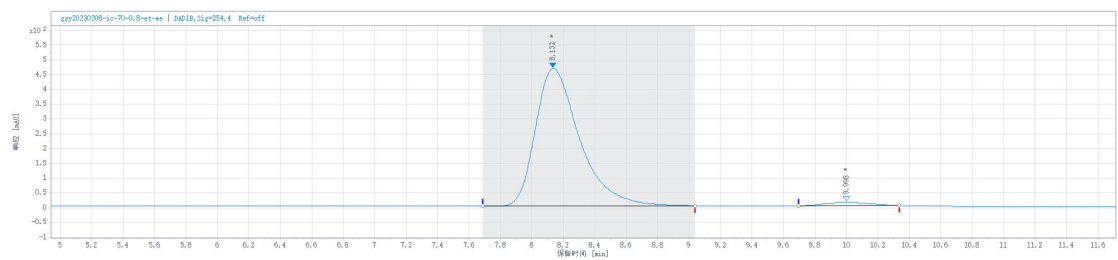
3ba racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.13	0.96	1286.19	68.54	51.44
9.99	1.19	1214.00	50.64	48.56

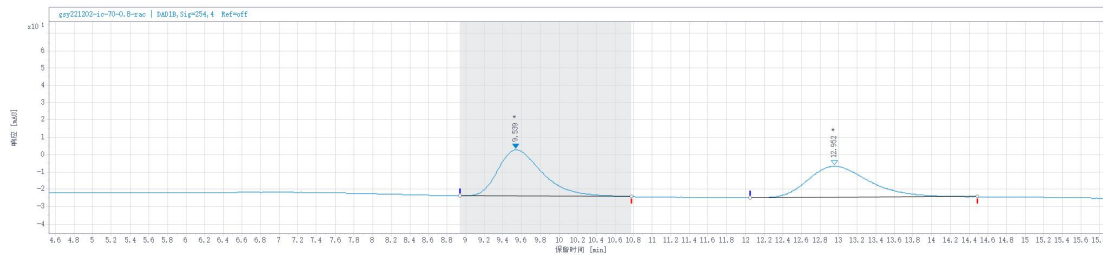
3ba



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.13	1.35	9068.29	465.37	97.47
10.00	0.65	235.61	11.68	2.53

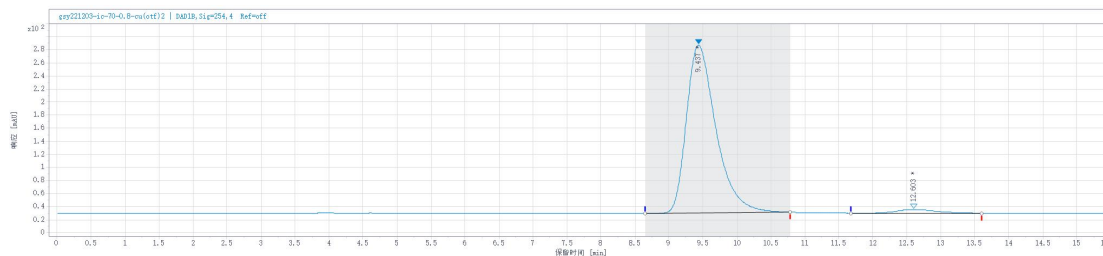
3ca racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
9.54	1.84	880.42	26.65	51.79
13.0	2.44	819.59	17.97	48.21

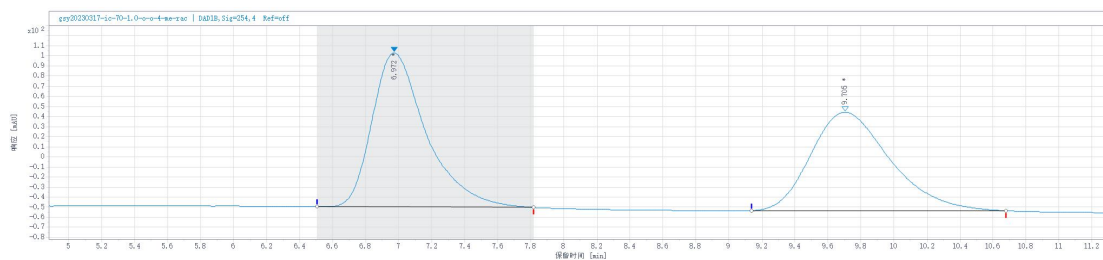
3ca



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
9.44	2.14	7774.57	257.05	97.22
12.6	1.93	222.72	5.58	2.78

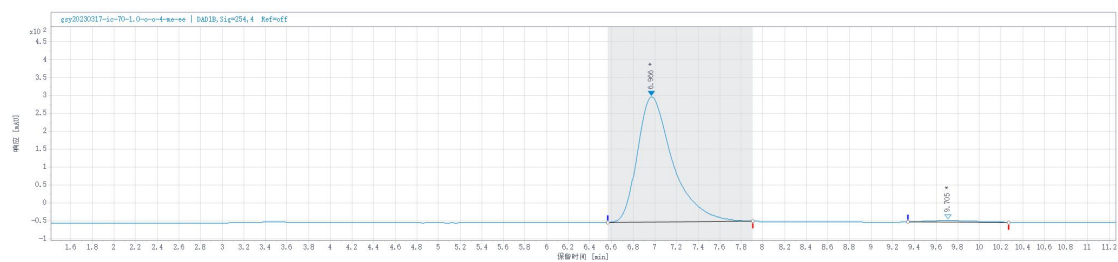
3da racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
6.97	1.32	3491.75	153.25	51.64
9.70	1.54	3269.36	97.91	48.36

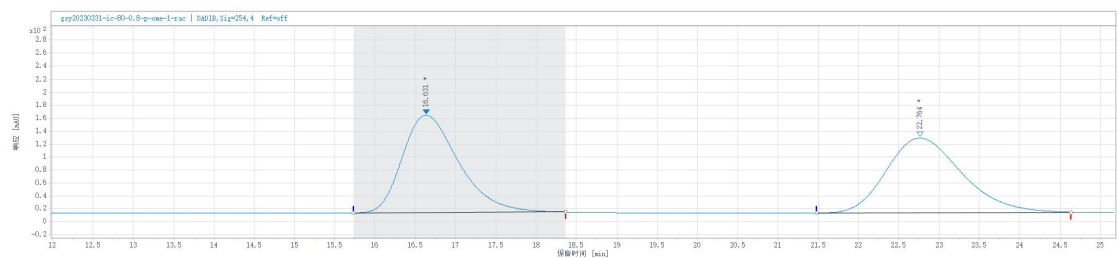
3da



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
6.97	1.34	7958.30	349.25	98.49
9.71	0.93	121.61	4.26	1.51

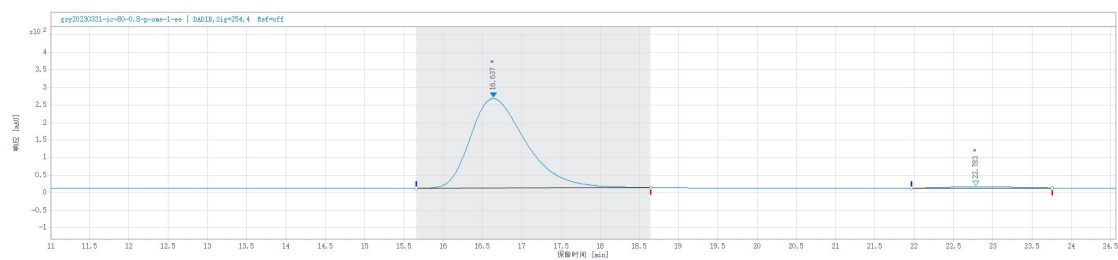
3ea racemic mixture:



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
16.6	2.63	7309.58	150.27	49.44
22.8	3.16	7476.24	115.02	50.56

3ea



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
16.6	2.98	12521.45	254.86	98.30
22.8	1.80	216.09	3.94	1.70

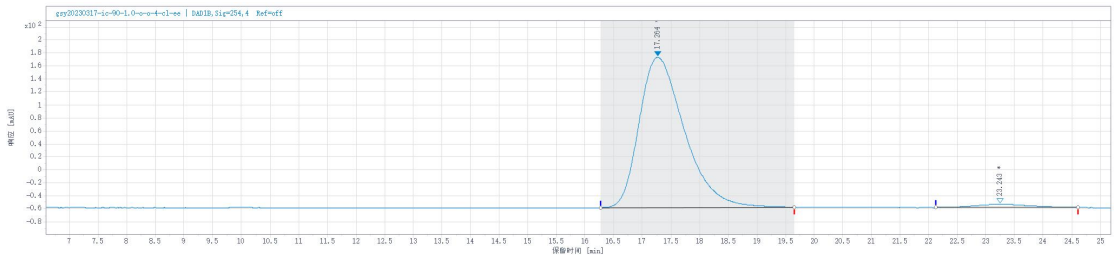
3fa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
17.3	2.97	1345.23	24.88	50.23
23.2	3.69	1332.76	18.71	49.77

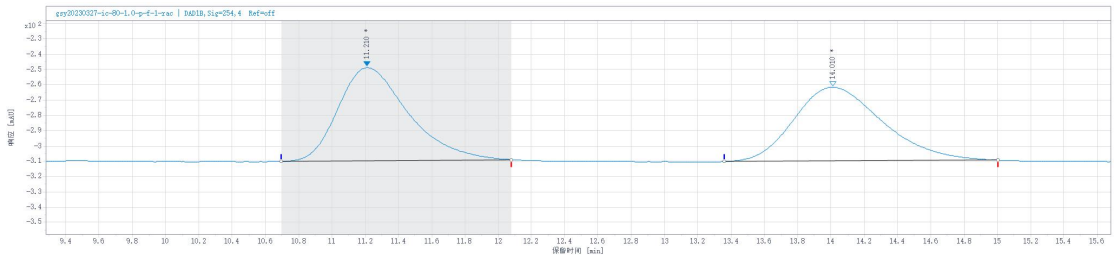
3fa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
17.3	3.38	12639.41	231.01	97.55
23.2	2.47	317.20	4.80	2.45

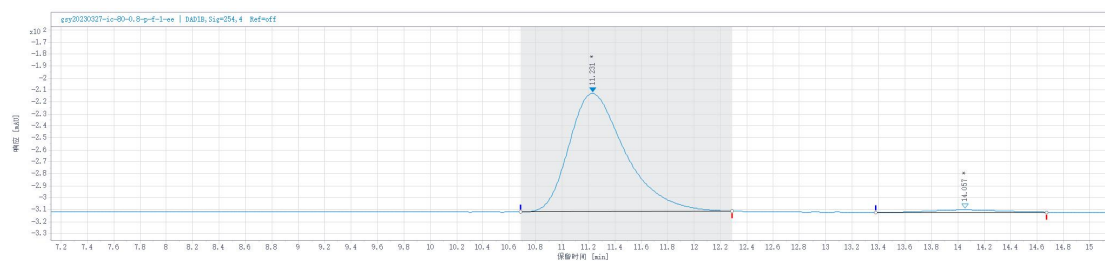
3ga racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
11.2	1.38	1785.62	60.88	49.97
14.0	1.65	1787.73	48.19	50.03

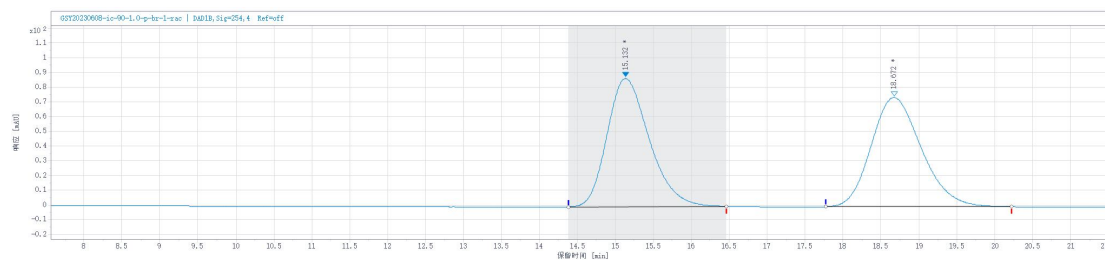
3ga



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.2	1.60	2936.35	99.03	97.81
14.1	1.30	65.87	1.98	2.19

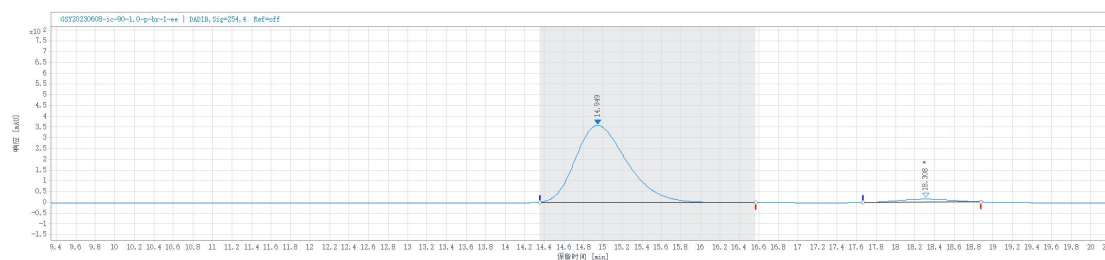
3ha racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
15.1	2.08	3367.34	87.16	49.66
18.7	2.45	3414.11	74.21	50.34

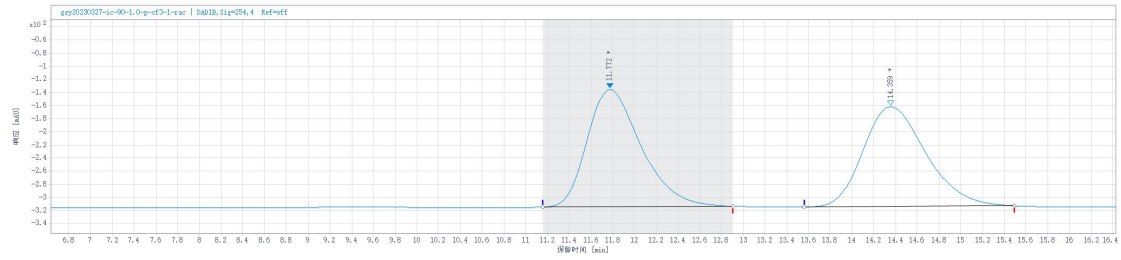
3ha



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
14.9	2.21	13055.25	356.25	95.92
18.3	1.22	555.57	14.57	4.08

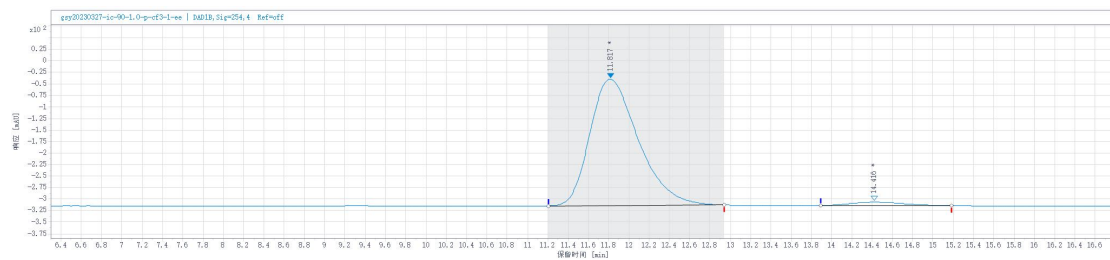
3ia racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.8	1.75	6154.34	178.72	50.20
14.4	1.93	6104.53	152.01	49.80

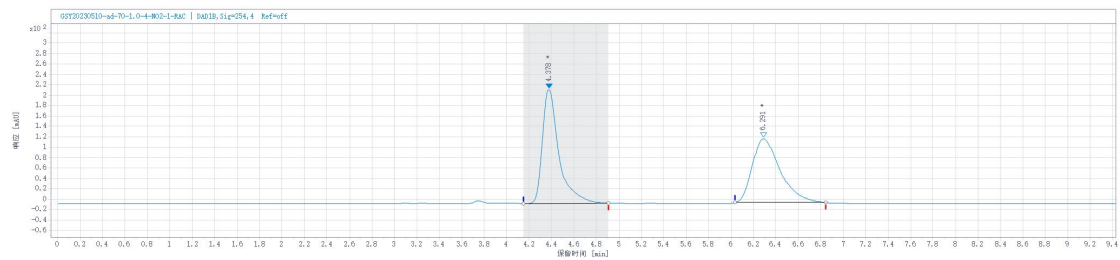
3ia



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.8	1.73	9110.24	274.40	97.08
14.4	1.29	273.62	7.47	2.92

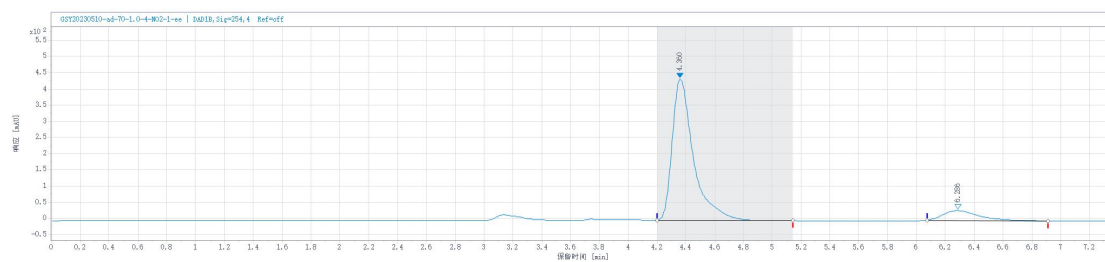
3ja racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
4.38	0.76	2222.76	218.93	51.08
6.29	0.80	2128.86	122.78	48.92

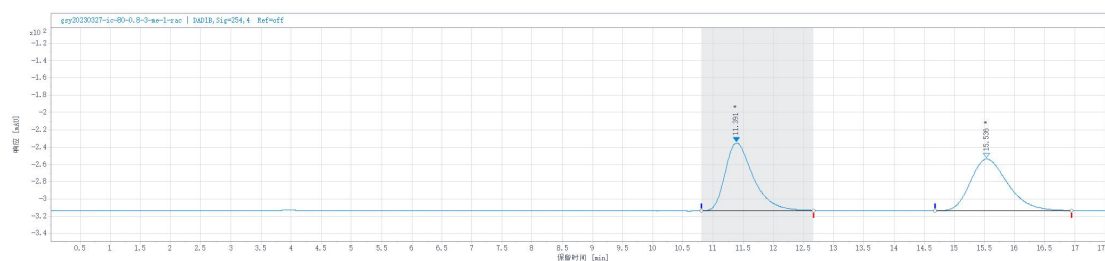
3ja



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
4.36	0.94	4452.73	435.58	89.81
6.29	0.84	505.14	30.06	10.19

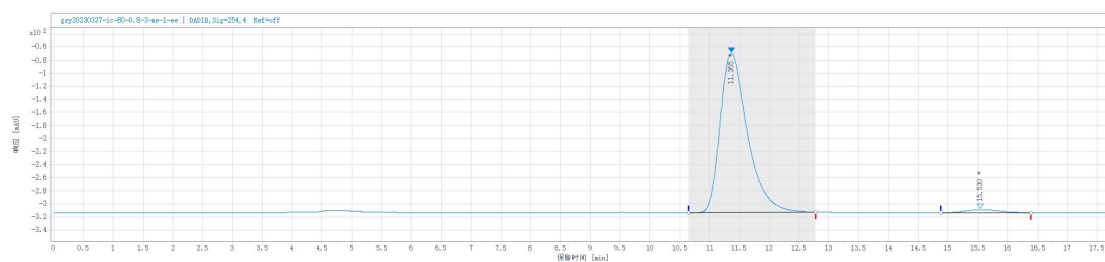
3ka racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
11.4	1.86	2529.70	78.29	49.70
15.5	2.25	2560.18	59.60	50.30

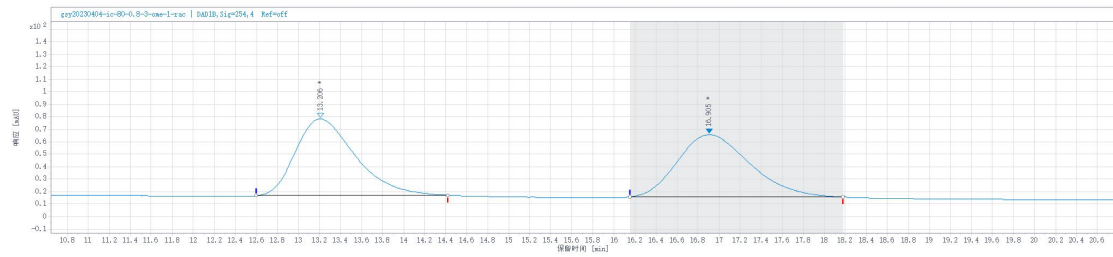
3ka



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
11.4	2.13	7757.06	244.30	97.66
15.5	1.51	185.50	4.68	2.34

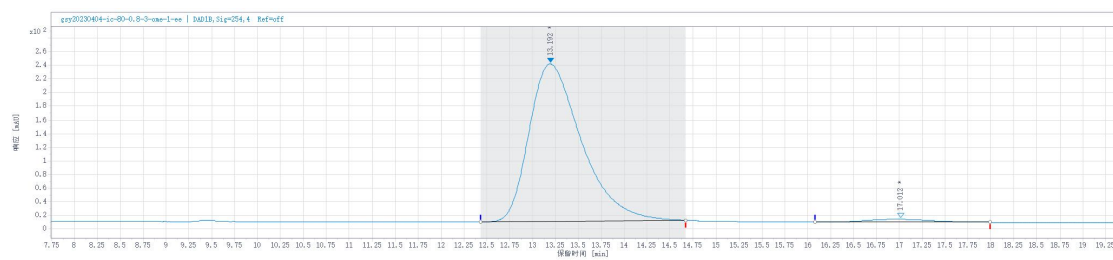
3la racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
13.2	1.82	2415.88	61.38	50.30
16.9	2.03	2387.02	49.84	49.70

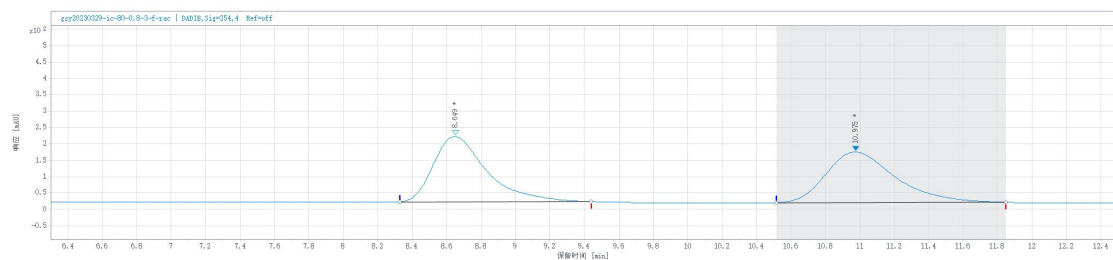
3la



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
13.2	2.24	9154.73	230.50	97.82
17.0	1.91	203.69	4.29	2.18

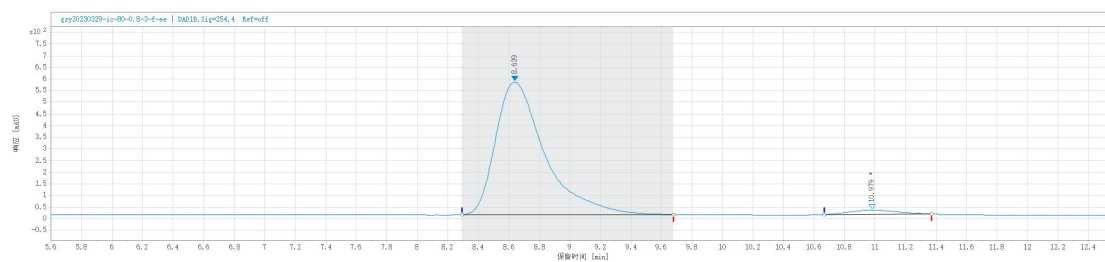
3ma racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.65	1.11	4276.33	199.29	49.82
11.0	1.33	4307.03	154.11	50.18

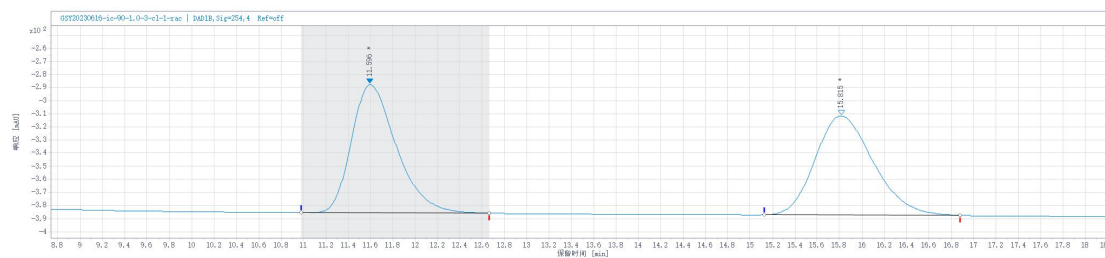
3ma



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
8.64	1.39	12722.70	568.76	97.08
11.0	0.71	382.95	17.28	2.92

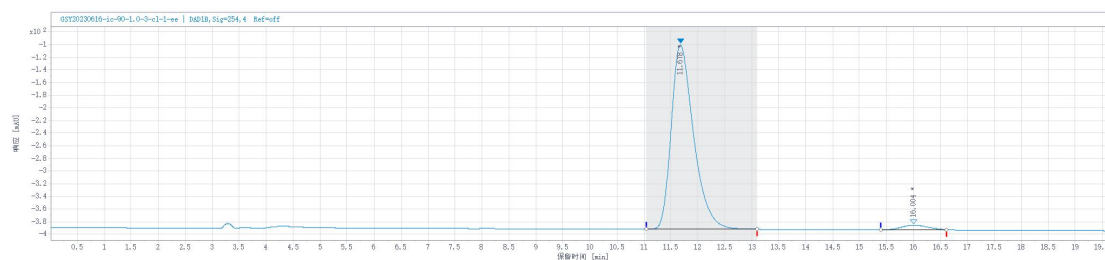
3na racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.6	1.68	2750.18	98.06	50.08
15.8	1.75	2741.09	75.77	49.92

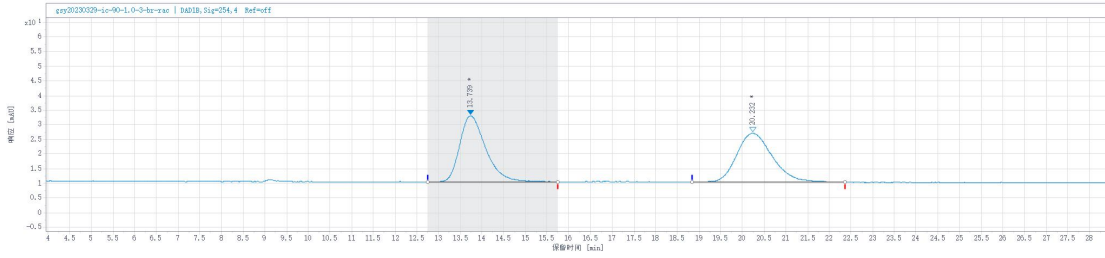
3na



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.7	2.06	8435.20	291.65	97.16
16.0	1.22	246.89	7.31	2.84

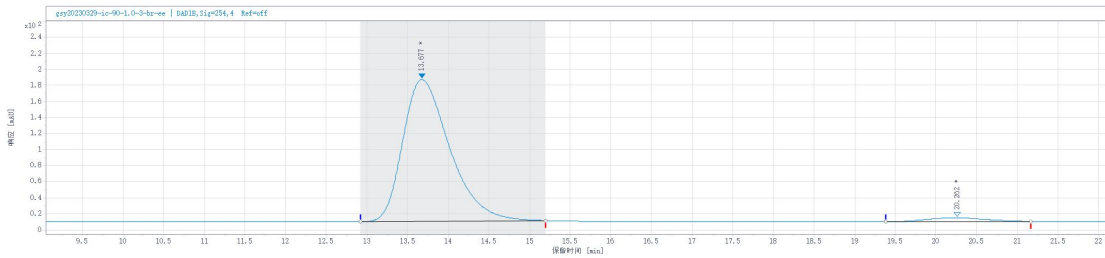
3oa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
13.7	3.00	941.58	22.57	50.07
20.2	3.51	938.81	16.63	49.93

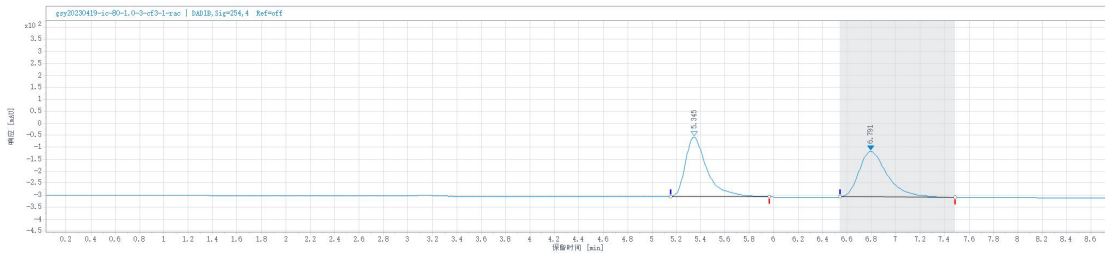
30a



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
13.7	2.27	7098.35	176.77	96.82
20.3	1.78	232.81	4.58	3.18

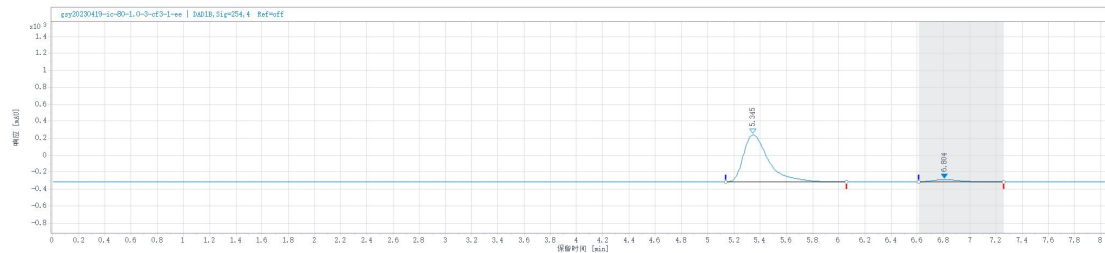
3pa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
5.34	0.81	3057.53	247.47	50.03
6.79	0.94	3053.77	189.70	49.97

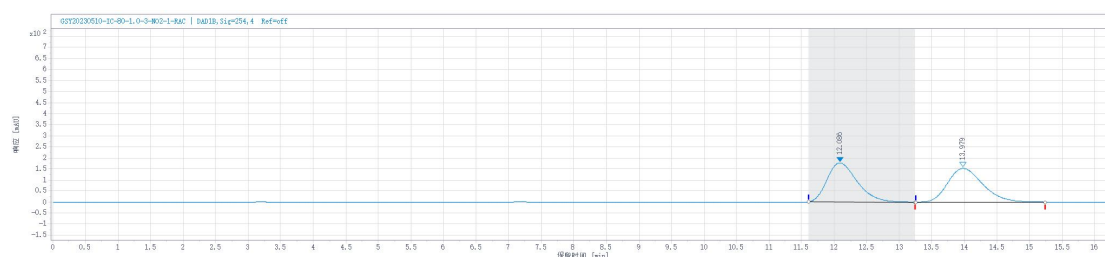
3pa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
5.34	0.92	7393.46	554.57	94.65
6.80	0.65	418.30	28.29	5.35

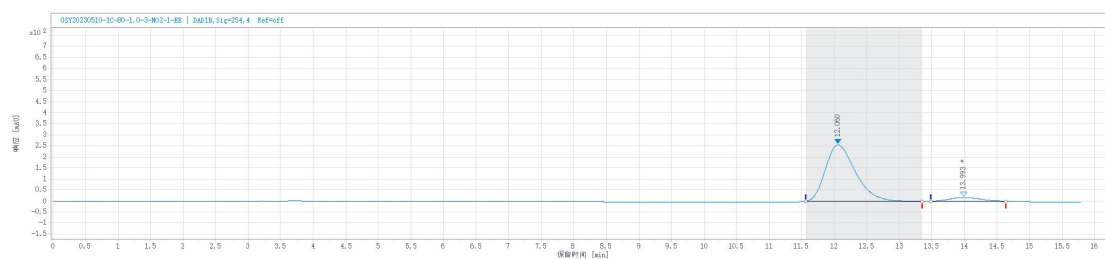
3qa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
12.1	1.64	5689.30	177.31	49.75
14.0	1.99	5746.86	152.93	50.25

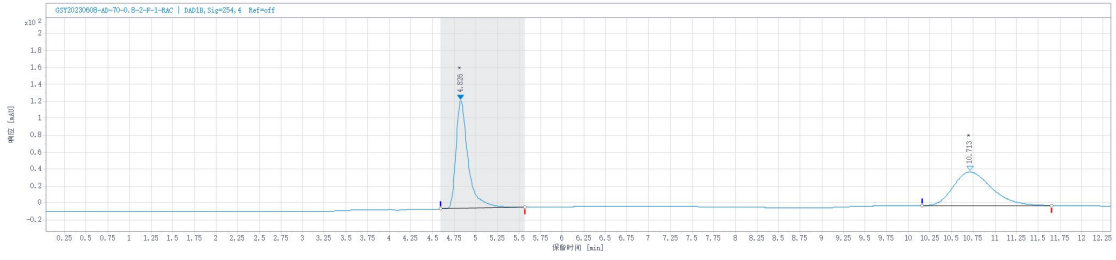
3qa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
12.1	1.79	8180.31	254.83	93.29
14.0	1.15	588.75	17.40	6.71

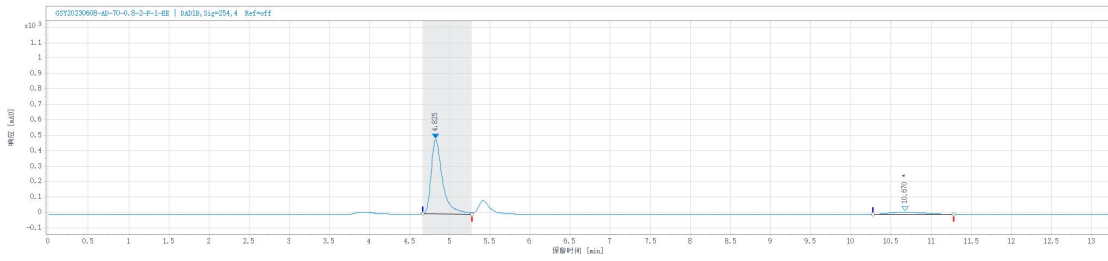
3ra racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
4.83	0.97	1256.17	127.32	50.60
10.7	1.49	1226.44	39.67	49.40

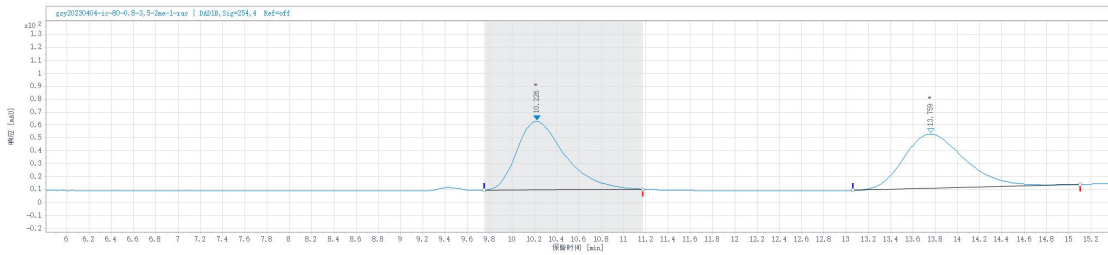
3ra



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
4.83	0.61	4765.74	483.49	92.06
10.7	1.00	410.79	14.59	7.94

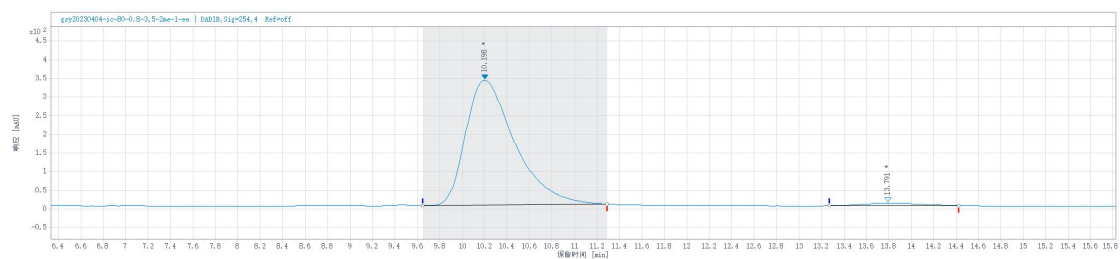
3sa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
10.2	1.42	1595.44	53.09	50.01
13.8	2.04	1594.69	42.01	49.99

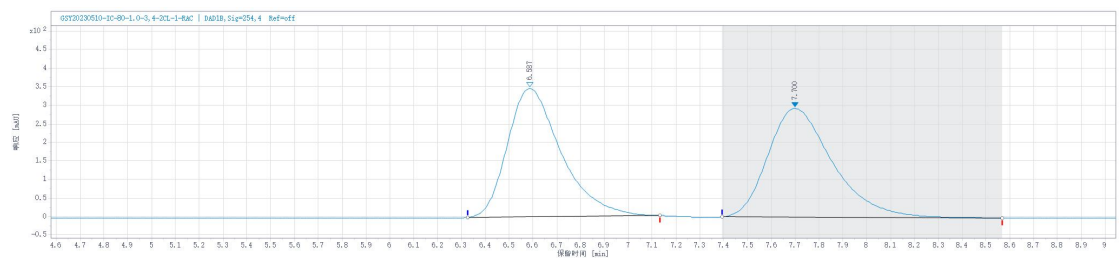
3sa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
10.2	1.65	10155.99	334.31	97.67
13.8	1.15	242.29	7.21	2.33

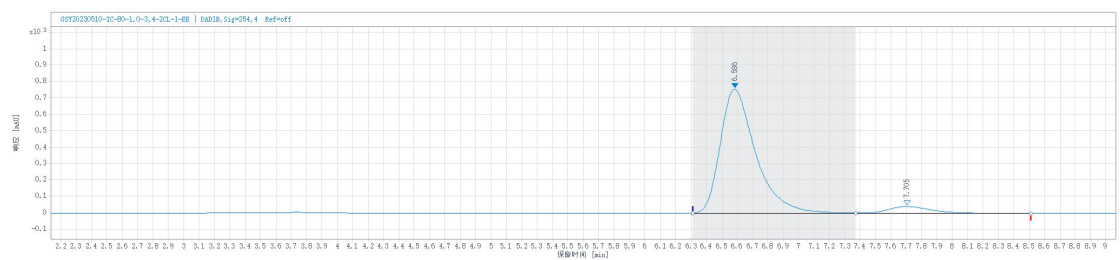
3ta racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
6.59	0.81	5416.84	346.29	49.52
7.70	1.17	5521.42	293.29	50.48

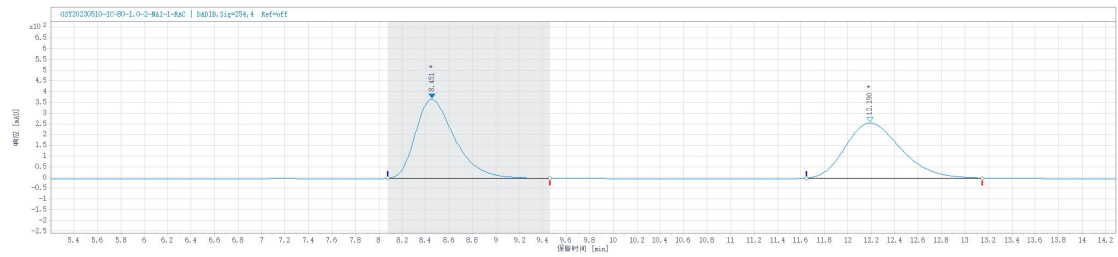
3ta



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
6.59	1.06	12099.60	756.51	93.80
7.71	1.14	800.36	41.50	6.20

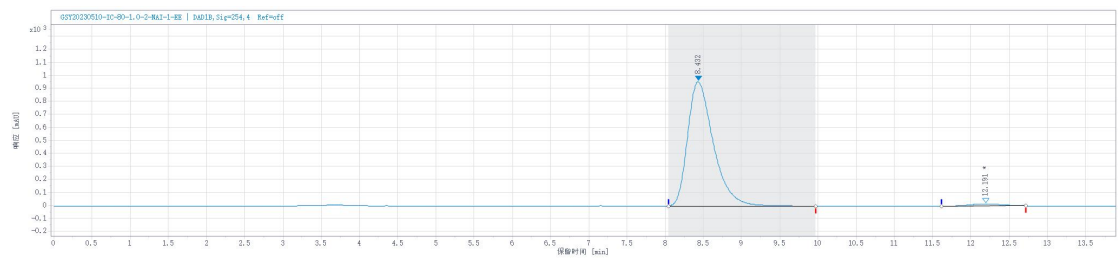
3ua racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.45	1.38	8580.44	368.03	50.45
12.2	1.49	8427.87	257.00	49.55

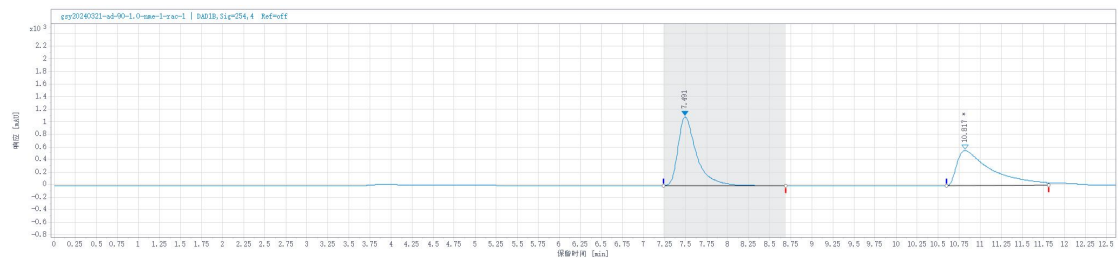
3ua



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.43	1.93	22340.54	954.86	97.84
12.2	1.10	492.13	16.45	2.16

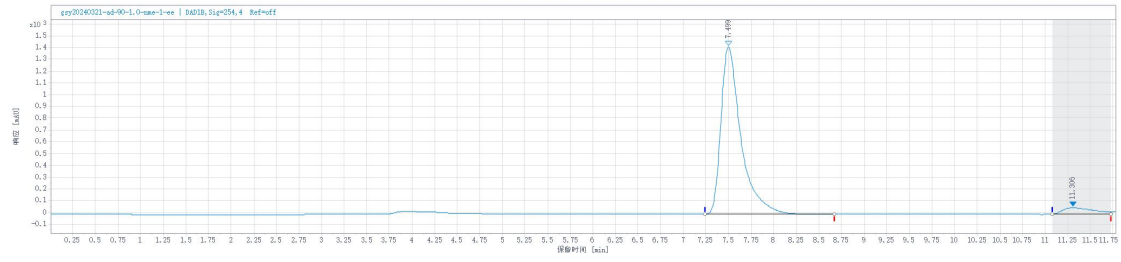
3va racemic mixture:



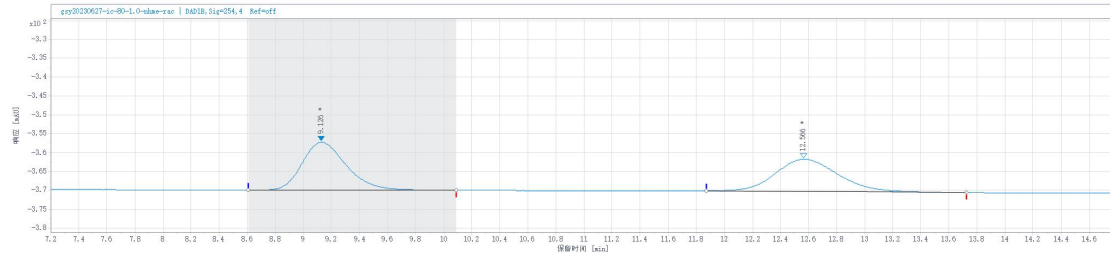
Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
7.49	1.45	16535.91	1089.95	51.30
10.8	1.22	15696.56	553.73	48.70

3va



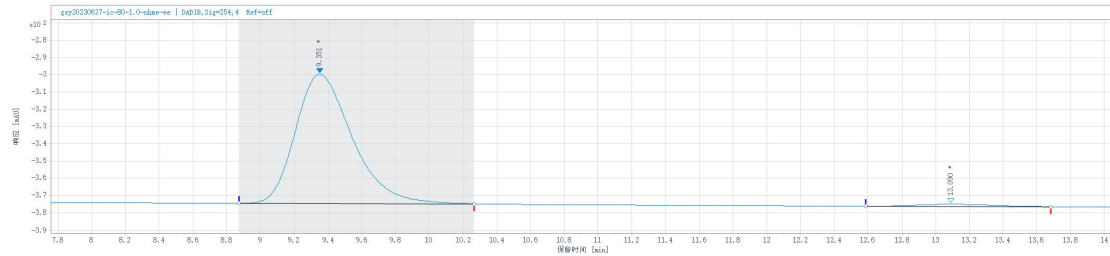
3ab racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
9.13	1.48	279.94	12.71	50.93
12.6	1.85	269.77	8.59	49.07

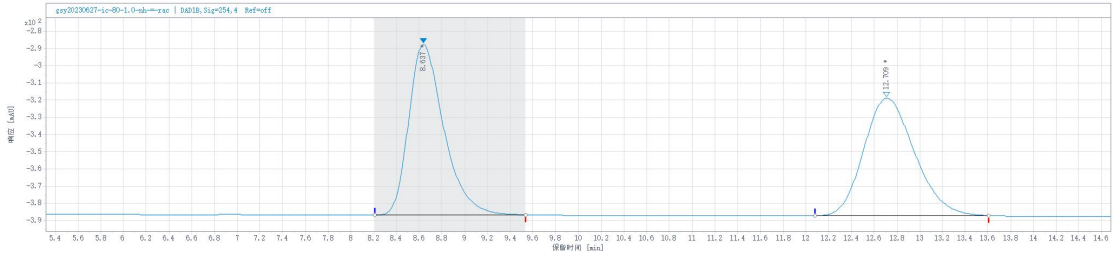
3ab



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
9.35	1.39	1752.19	74.91	97.91
13.1	1.10	37.45	1.22	2.09

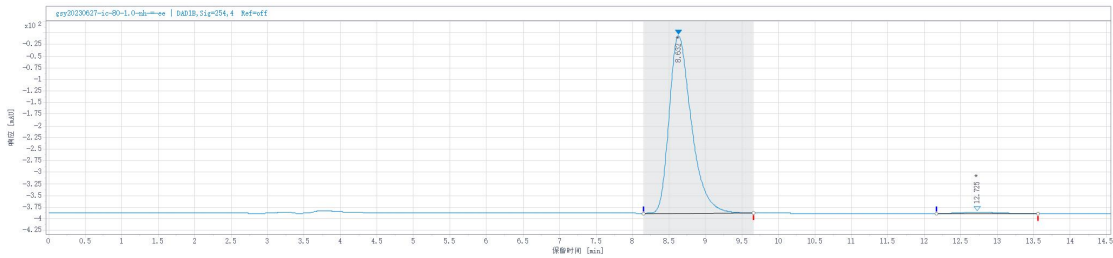
3ac racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.64	1.33	2130.84	99.28	50.08
12.7	1.53	2123.98	68.41	49.92

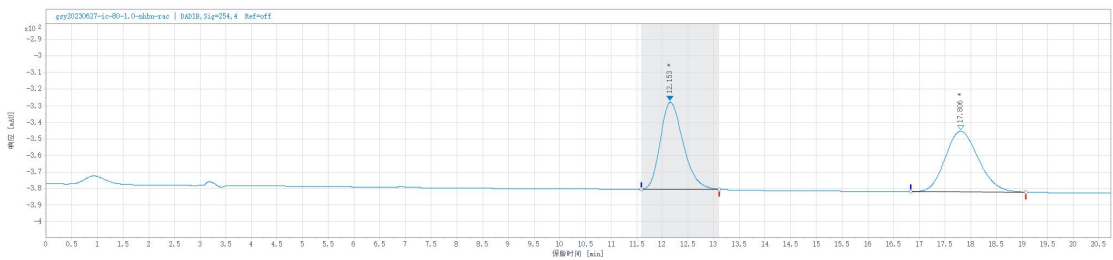
3ac



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.63	1.51	8094.62	381.98	98.81
12.7	1.39	97.47	3.17	1.19

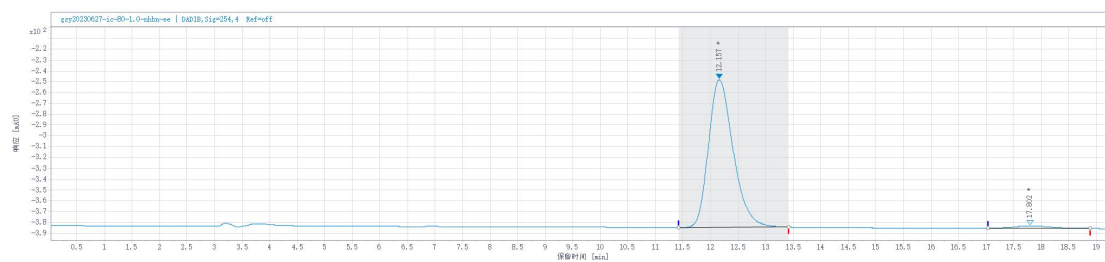
3ad racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
12.2	1.53	1630.54	52.57	49.71
17.8	2.24	1649.28	36.63	50.29

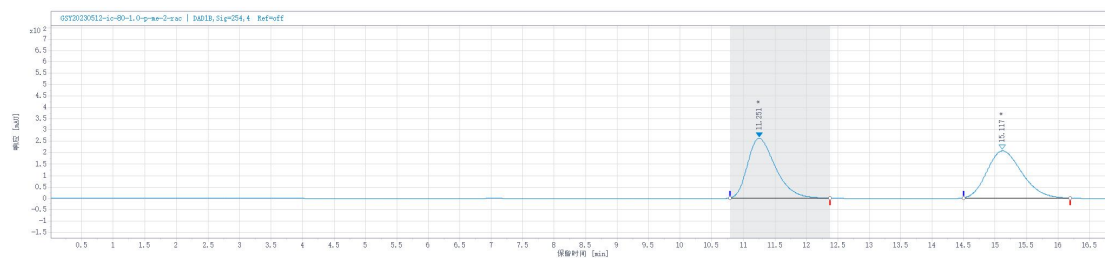
3ad



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
12.2	2.00	4240.58	136.18	97.57
17.8	1.85	105.56	2.37	2.43

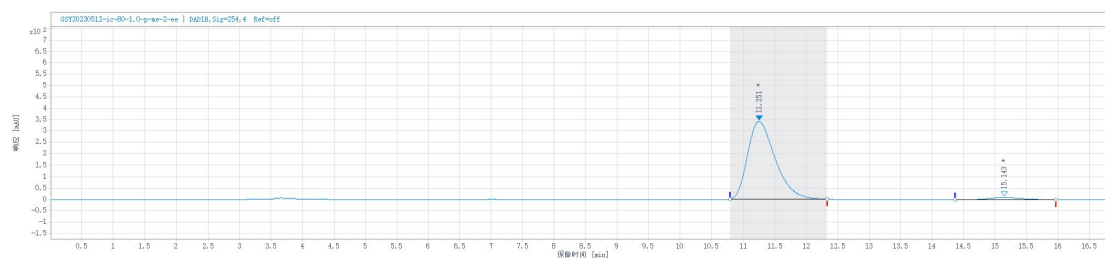
3ae racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.3	1.58	8037.74	262.58	50.34
15.1	1.69	7928.36	206.51	49.66

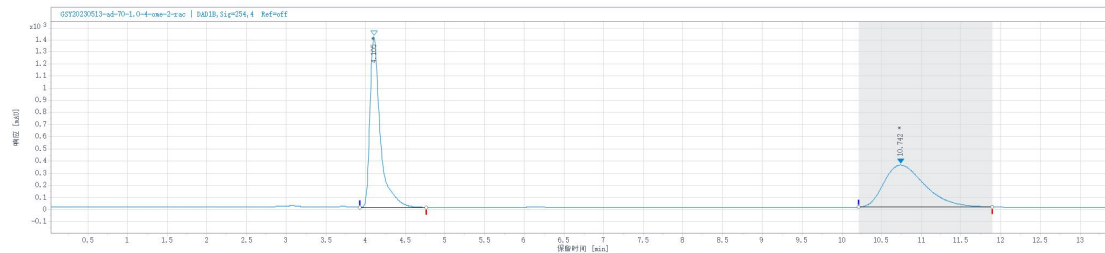
3ae



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
11.3	1.55	10401.98	341.86	96.68
15.1	1.60	357.19	9.45	3.32

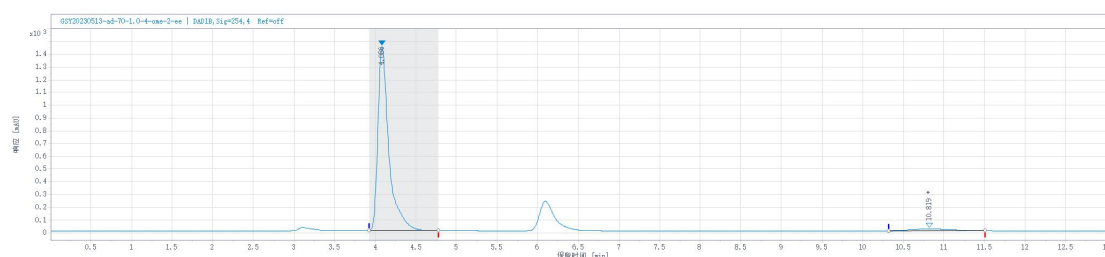
3af racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
4.10	0.83	12682.65	1406.65	50.39
10.7	1.68	12487.55	347.77	49.61

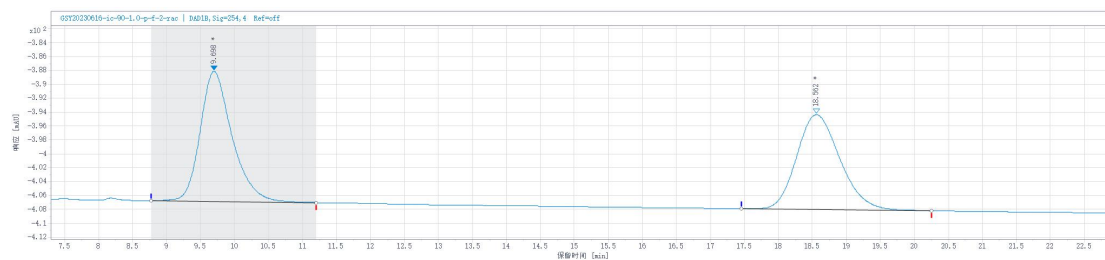
3af



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
4.09	0.85	13567.88	1438.70	96.87
10.8	1.18	438.27	13.22	3.13

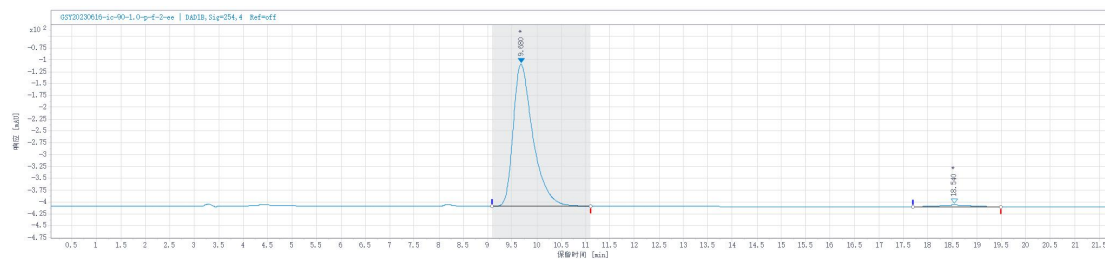
3ag racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
9.70	2.43	613.29	18.73	50.40
18.6	2.80	603.67	13.65	49.60

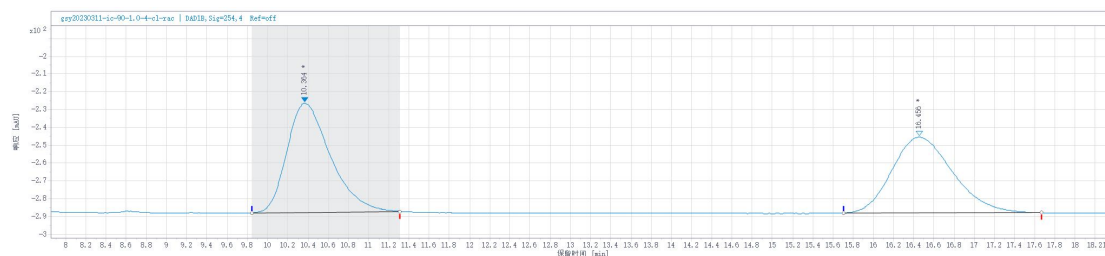
3ag



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
9.68	2.02	8387.63	299.49	98.26
18.5	1.80	148.56	3.42	1.74

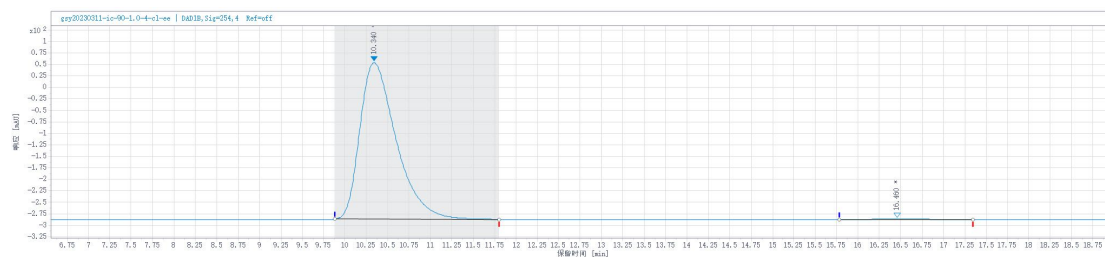
3ah racemic mixture:



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
10.4	1.46	1835.10	61.27	50.78
16.5	1.96	1778.53	42.49	49.22

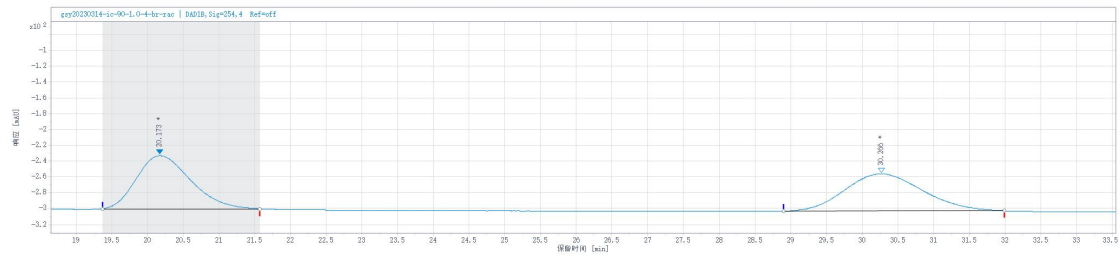
3ah



Signal: DAD1B, Sig=254,4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
10.3	1.92	10047.43	340.29	98.92
16.5	1.56	109.37	2.66	1.08

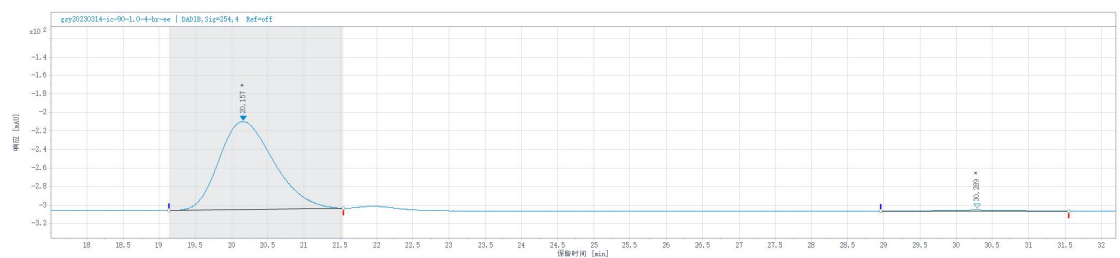
3ai racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
20.2	2.20	3522.17	67.11	49.85
30.3	3.08	3543.22	46.84	50.15

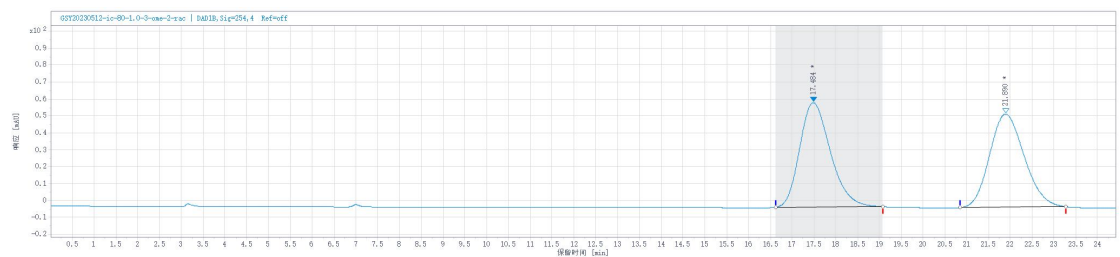
3ai



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
20.2	2.40	4985.51	95.16	98.27
30.3	2.60	87.84	1.33	1.73

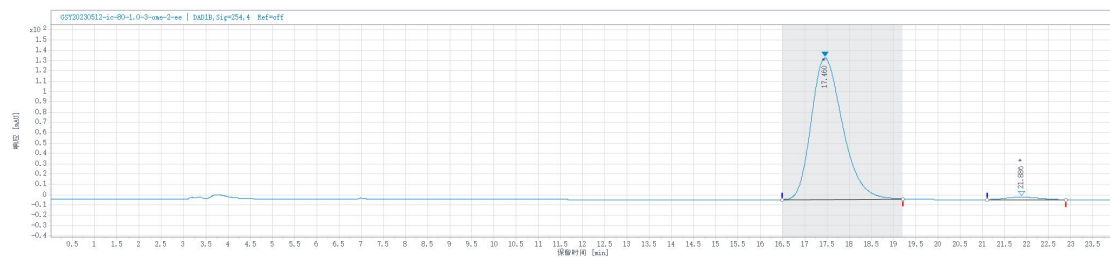
3aj racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
17.5	2.45	3023.17	61.69	49.98
21.9	2.42	3025.90	55.01	50.02

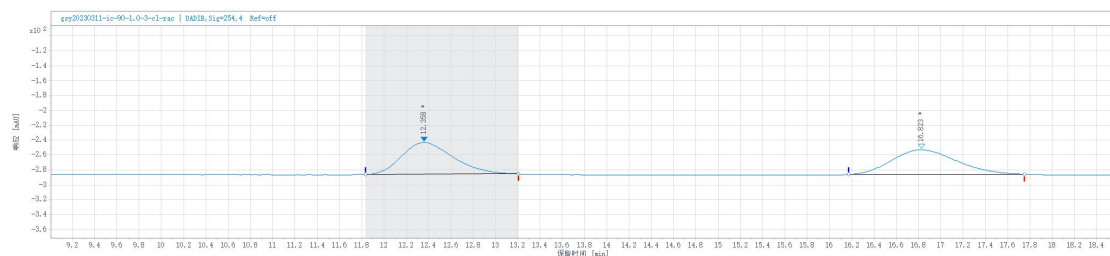
3aj



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
17.5	2.72	6708.98	137.02	98.10
21.9	1.76	129.69	2.54	1.90

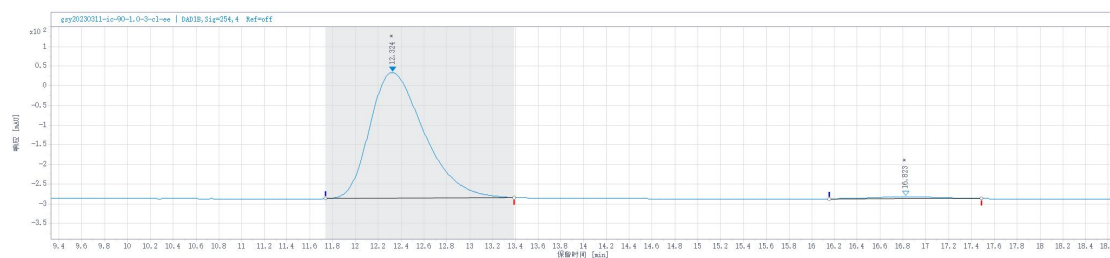
3ak racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
12.4	1.37	1371.00	42.50	50.69
16.8	1.58	1333.70	32.94	49.31

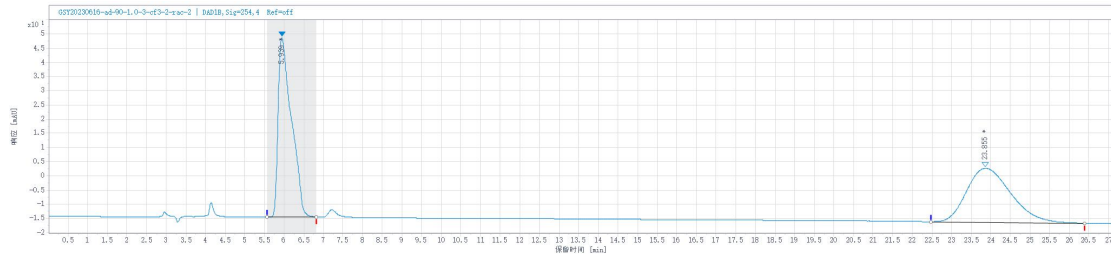
3ak



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
12.3	1.65	10557.91	319.87	98.21
16.8	1.34	191.96	5.08	1.79

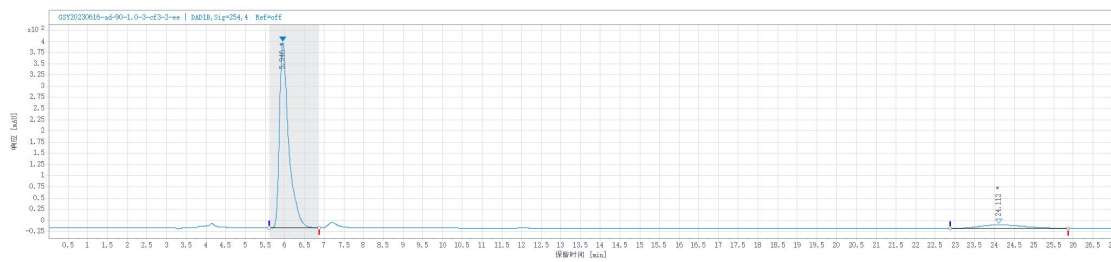
3al racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
5.94	1.26	1490.19	63.21	49.96
23.9	3.91	1492.37	19.03	50.04

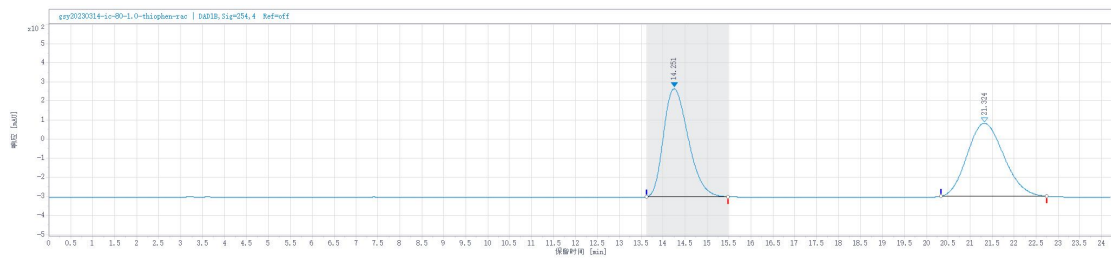
3al



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
5.95	1.28	6740.55	413.54	91.65
24.1	2.99	614.24	8.03	8.35

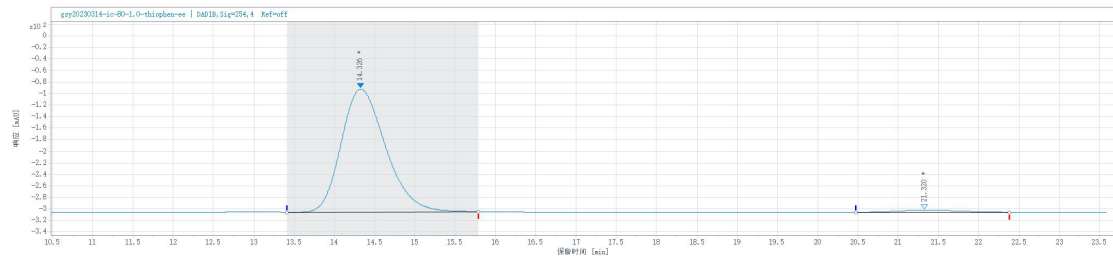
3am racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
14.3	1.86	22191.77	566.55	49.96
21.3	2.41	22230.57	382.69	50.04

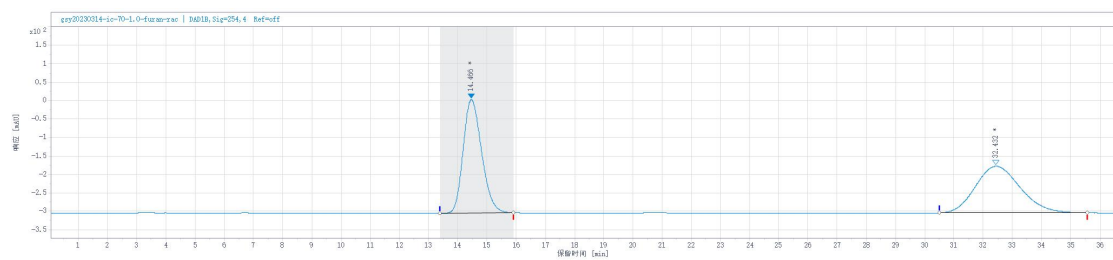
3am



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
14.3	2.37	8190.48	213.45	97.62
21.3	1.91	199.89	3.67	2.38

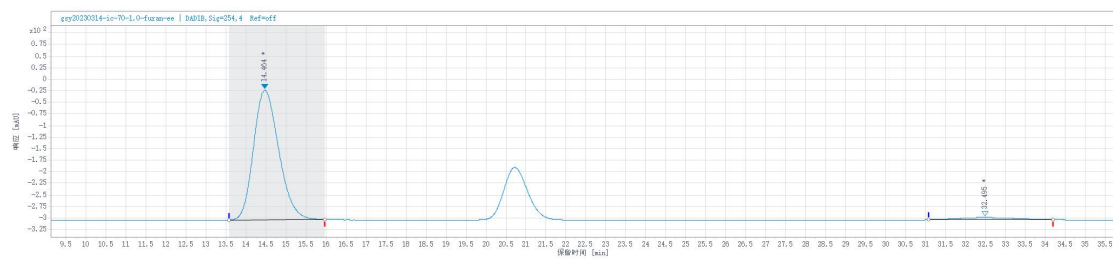
3an racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
14.5	2.52	13481.13	306.91	49.94
32.4	5.07	13514.97	126.01	50.06

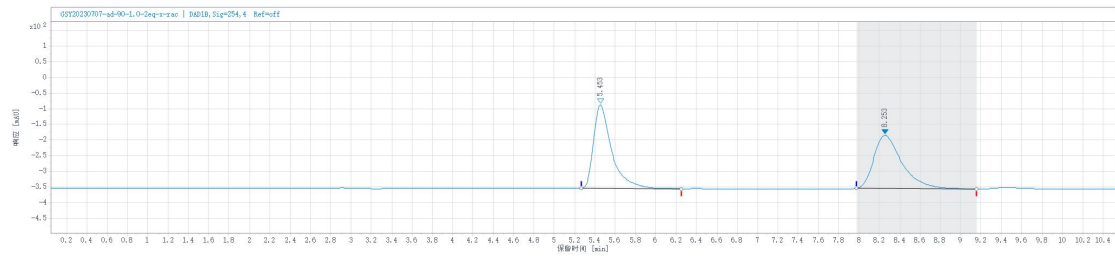
3an



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
14.5	2.40	12274.57	279.87	96.52
32.5	3.11	442.53	4.73	3.48

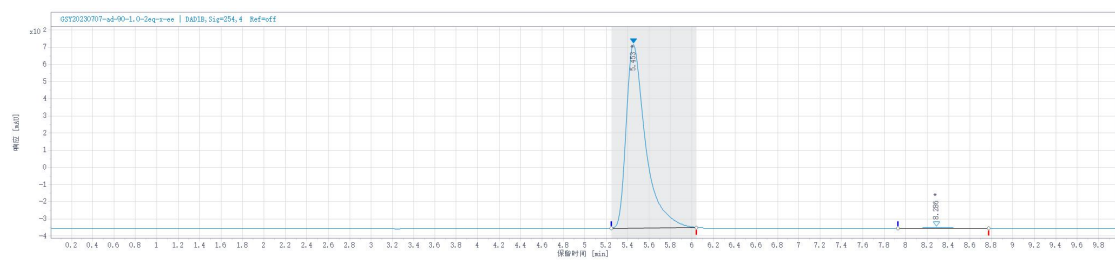
4aa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
5.45	0.99	3293.22	266.90	50.30
8.25	1.18	3253.44	169.28	49.70

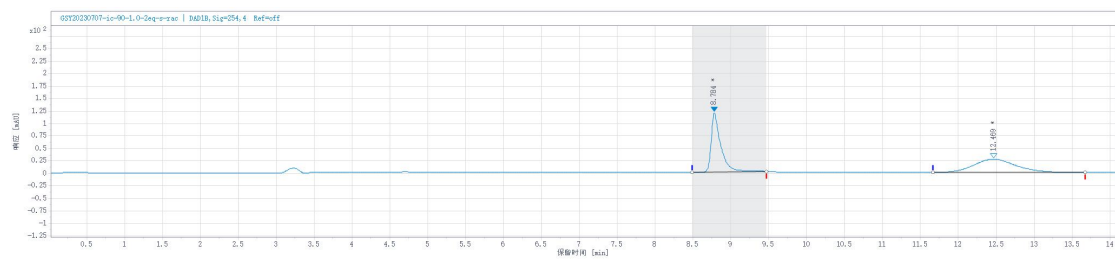
4aa



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
5.45	0.80	13438.68	1068.52	99.22
8.29	0.85	105.44	5.63	0.78

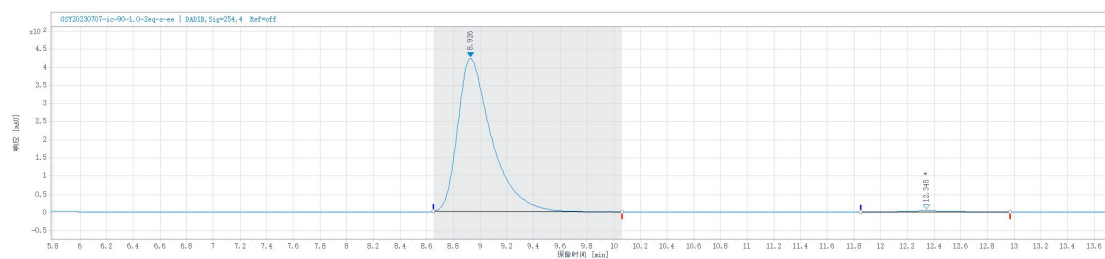
5aa racemic mixture:



Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Arer [mAU*s]	Height [mAU]	Area%
8.78	0.97	1039.07	118.52	49.67
12.5	2.01	1053.01	27.02	50.33

5aa

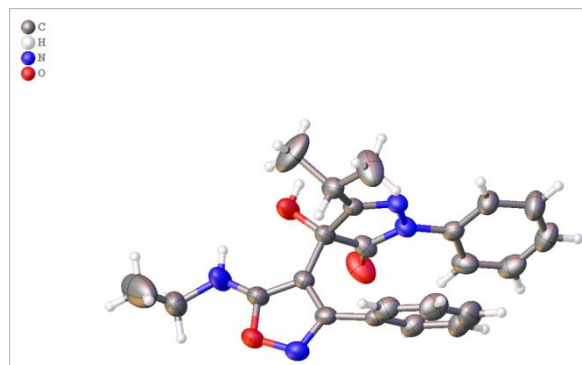
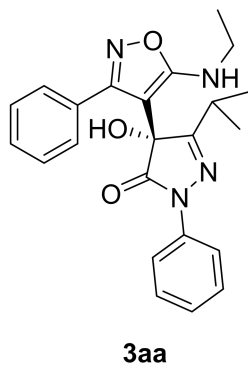


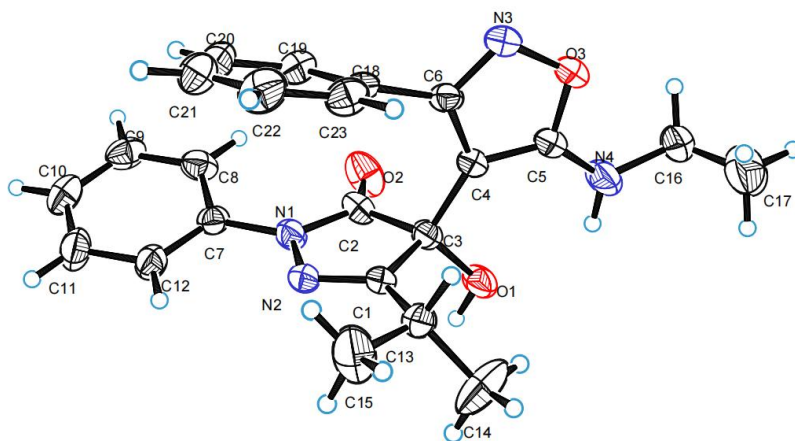
Signal: DAD1B, Sig=254, 4 Ref=off

RetTime [min]	width [min]	Area [mAU*s]	Height [mAU]	Area%
8.93	1.41	7451.70	421.62	99.03
12.3	1.12	73.02	3.08	0.97

Part IV Crystal data

(*R*)-**3aa** (25mg): single crystals are formed in THF (0.7ml) at room temperature about 5 days.





CCDC:2335999

Identification code	SCD-GSY2023-0706_auto
Empirical formula	C ₂₃ H ₂₄ N ₄ O ₃
Formula weight	404.46
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	8.99824(7)
b/Å	13.13119(9)
c/Å	17.79770(13)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2102.93(3)
Z	4
ρ _{calc} /cm ³	1.277
μ/mm ⁻¹	0.701
F(000)	856.0
Crystal size/mm ³	0.22 × 0.19 × 0.18
Radiation	Cu Kα (λ = 1.54184)
2θ range for data collection/°	8.368 to 145.812
Index ranges	-9 ≤ h ≤ 11, -16 ≤ k ≤ 16, -21 ≤ l ≤ 22
Reflections collected	15262
Independent reflections	4132 [R _{int} = 0.0284, R _{sigma} = 0.0172]
Data/restraints/parameters	4132/0/276

Goodness-of-fit on F^2	1.079
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0434$, $wR_2 = 0.1143$
Final R indexes [all data]	$R_1 = 0.0439$, $wR_2 = 0.1151$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.32/-0.23
Flack parameter	0.04(6)