Supporting Information

2-(1-Methylhydrazinyl)pyridine-Directed C−H Functionalization/Spirocyclization Cascade: Facile Access to Spirosuccinimide Derivatives

Hua Zhao,[†] Xiaoru Shao,[†] Taimin Wang,[†] Shengxian Zhai,[‡] Shuxian Qiu,[†] Cheng Tao,[‡] Huifei Wang,[†] Hongbin Zhai*[,†,‡,⊥]

[†]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China

[‡]The State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China.

[⊥]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Email: zhaihb@pkusz.edu.cn

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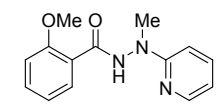
1. Materials and methods

All reactions were carried out under Argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF was distilled from sodium-benzophenone. Dichloromethane and was distilled from calcium hydride. Thin-layer chromatography (TLC) was conducted with 0.25 mm Tsingdao silica gel plates (60F-254) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Flash column chromatography was performed on Tsingdao silica gel (200-300 mesh) and neutral/basic aluminum oxide (200-300 mesh). ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400 or 500 MHz) and reported relative to deuterated solvent signals or tetramethylsilane internal standard signals. Data for ^{1}H NMR spectra were reported as follows: chemical shift (δ/ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.), coupling constant (*J*/Hz) and integration. ^{13}C NMR spectra were recorded on Bruker Spectrometers (100 or 125 MHz). Data for ^{13}C NMR spectra were reported in terms of chemical shift. ^{19}F NMR spectra were recorded on Bruker Spectrometers (376 MHz). High-resolution mass spectrometry (HRMS) was conducted on Bruker Apex IV RTMS. X-ray diffraction was performed on Rigaku Saturn 70 CCD diffractometer using graphite monochromated Cu-Kα radiation at a temperature of 100 ±1 K. Crystallographic data were obtained from Oxford diffraction single crystal X-ray diffractometer (Gemini S Ultra).

2. General procedure for the synthesis of starting materials



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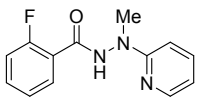

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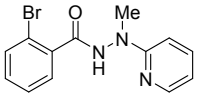

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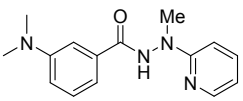

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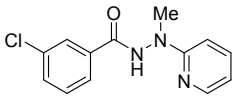

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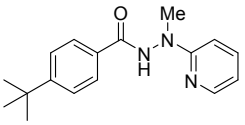

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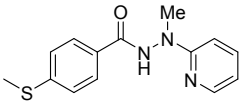

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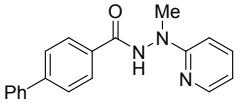

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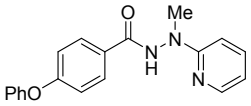

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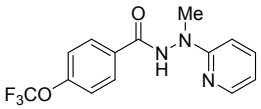

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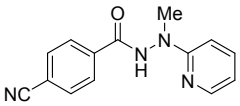

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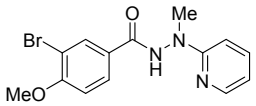

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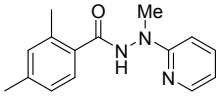

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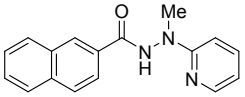
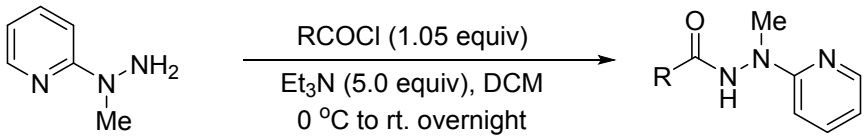


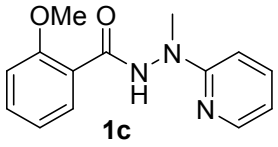
1w

Representative Method : (1c, 1d, 1f, 1g, 1h, 1j, 1l, 1m, 1n, 1s, 1t, 1u, 1v, 1w) [1]



To a stirred mixture of 2-(1-methylhydrazinyl)pyridine[1] (1.0 equiv, 5 mmol) and Et_3N (5.0 equiv) in dry CH_2Cl_2 (0.2 to 0.5 M) was added benzoyl chloride (1.05 equiv) dropwise under Ar atmosphere at 0 °C. Kept the reaction mixture stirred at 0 °C for about 0.5 h, then the resulting mixture was warmed to room temperature and stirred overnight at this temperature. Upon completion of the reaction indicated by TLC, The

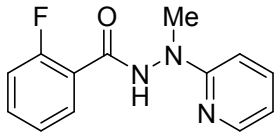
reaction mixture was washed with H_2O and extracted with CH_2Cl_2 (20 mL) for three times. The combined organic phases were washed with brine, dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product.



1c

2-methoxy-N'-methyl-N'-(pyridin-2-yl)benzohydrazide: [1]

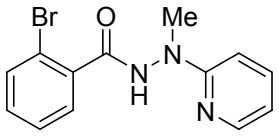
Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1c** (80% yield) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.98 (s, 1H), 8.55-8.53 (m, 1H), 8.52 (d, *J* = 1.6, 1H), 7.83 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 7.80 – 7.55 (m, 1H), 7.47 – 7.40 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.00 (ddd, *J* = 5.6, 4.8, 0.8 Hz, 1H), 4.34 (s, 3H), 3.79 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.0, 159.6, 157.5, 147.7, 137.5, 133.6, 132.6, 121.5, 120.0, 114.2, 111.4, 107.2, 56.1, 38.5. **HRMS** m/z ($[M+H]^+$) called for $C_{14}H_{16}N_3O_2$: 258.1243, found: 258.1240.



1d

2-fluoro-N'-methyl-N'-(pyridin-2-yl)benzohydrazide:

Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1d** (65% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.72 (d, *J* = 11.5 Hz, 1H), 8.19 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.05 (td, *J* = 8.0, 2.0 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.49 – 7.45 (m, 1H), 7.29 – 7.22 (m, 1H), 7.18 – 7.13 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.72 – 6.63 (m, 1H), 3.43 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 163.0 (d, J_{C-F} = 3.8 Hz), 161.6, 159.6, 159.2, 147.7, 137.6, 134.0 (d, J_{C-F} = 8.8 Hz), 132.2 (d, J_{C-F} = 2.5 Hz), 125.0 (d, J_{C-F} = 2.5 Hz), 119.7 (d, J_{C-F} = 12.5 Hz), 116.1 (d, J_{C-F} = 25.0 Hz), 114.7, 107.1, 38.6. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -110.4. **HRMS** m/z ($[M+Na]^+$) called for $C_{13}H_{12}FN_3NaO$: 268.0862, found: 268.0852.

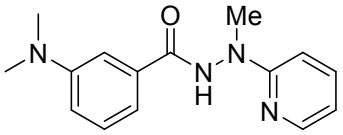


1f

2-bromo-N'-methyl-N'-(pyridin-2-yl)benzohydrazide:

Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1f** (80% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.28 (s, 1H), 8.21 – 8.11 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.35 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.29 (td, *J* = 7.5, 2.0 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.71

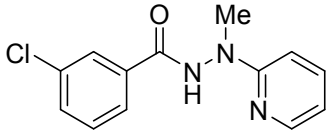
(dd, *J* = 6.5, 5.0 Hz, 1H), 3.42 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.7, 159.1, 147.6, 137.7, 135.8, 133.5, 131.8, 129.8, 127.6, 119.7, 114.9, 107.5, 38.5. **HRMS** m/z ($[M+H]^+$) called for $C_{13}H_{13}BrN_3O$: 306.0242, found: 306.0240.



1g

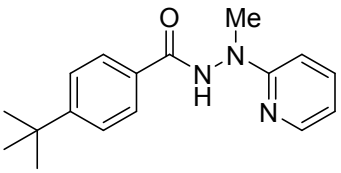
3-(dimethylamino)-N'-methyl-N'-(pyridin-2-yl)benzohydrazide:

Prepared according to the general method, purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1g** (60% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.45 (s, 1H), 8.20 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.51 – 7.41 (m, 1H), 7.29 (d, *J* =8.0 Hz, 1H), 7.24 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.87 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.69 (dd, *J* = 6.5, 5.0 Hz, 1H), 3.42 (s, 3H), 2.98 (s, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 167.3, 159.5, 150.8, 147.7, 137.6, 133.4, 129.3, 115.9, 114.6, 114.1, 111.4, 107.2, 40.4, 38.7. **HRMS** m/z ($[M+H]^+$) called for $C_{15}H_{19}N_4O$: 271.1559, found: 271.1553.



1h

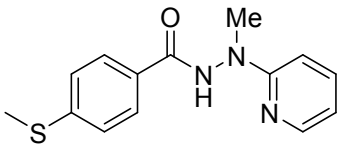
3-chloro-N'-methyl-N'-(pyridin-2-yl)benzohydrazide: Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1h** (85% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.69 (brs, 1H), 8.14 (d, *J* = 4.0 Hz, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 6.5, 5.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.28 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 165.5, 159.1, 147.3, 137.8, 134.8, 134.2, 132.0, 129.9, 127.8, 125.3, 114.8, 107.2, 38.8. **HRMS** m/z ($[M+H]^+$) called for $C_{13}H_{13}ClN_3O$: 262.0747, found: 262.0738.



1j

4-(tert-butyl)-N'-methyl-N'-(pyridin-2-yl)benzohydrazide: Prepared according to the general method, purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1j** (85% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.91 (s, 1H), 8.26 – 8.13 (m, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.47-7.43 (m, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.68 (dd, *J* = 7.0, 5.5 Hz, 1H), 3.38 (s, 3H), 1.33 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.5, 159.4, 155.7, 147.5, 137.6, 129.6, 127.2, 125.6, 114.6, 107.2, 38.8, 35.0, 31.1. **HRMS** m/z ($[M+H]^+$) called for

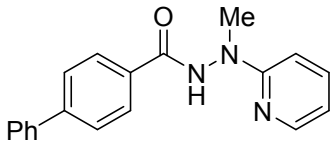
$C_{17}H_{22}N_3O$: 284.1763, found: 284.1759.



1l

N'-methyl-4-(methylthio)-N'-(pyridin-2-yl)benzohydrazide：

Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1l** (82% yield) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.97 (s, 1H), 8.23 – 8.10 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.51-7.47 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 3.6 Hz, 1H), 6.71 (d, *J* = 6.8 Hz, 1H), 3.39 (s, 3H), 2.50 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.1, 159.3, 147.5, 144.4, 137.8, 128.4, 127.6, 125.3, 114.7, 107.2, 39.0, 14.9. **HRMS** m/z ($[M+H]^+$) called for $C_{14}H_{16}N_3OS$: 274.1014, found: 274.1008.

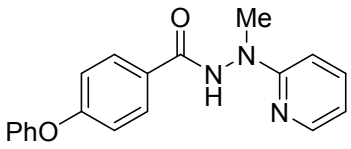


1m

N'-methyl-N'-(pyridin-2-yl)-[1,1'-biphenyl]-4-carbohydrazide：

Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1m** (85% yield) as a white solid. **^{1}H NMR (500**

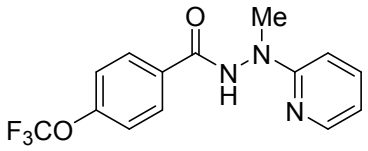
MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.20 (d, *J* = 4.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.62 – 7.58 (m, 4H), 7.52 – 7.43 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 6.74 – 6.66 (m, 1H), 3.42 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.4, 159.3, 147.6, 144.9, 139.9, 137.7, 131.2, 129.0, 128.1, 127.9, 127.3, 127.2, 114.7, 107.2, 38.9. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{18}N_3O$: 304.1450, found: 304.1446.



1n

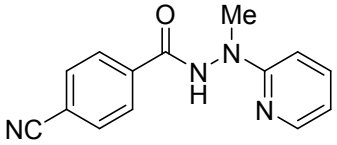
N'-methyl-4-phenoxy-N'-(pyridin-2-yl)benzohydrazide :

Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1n** (75% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.92 (s, 1H), 8.16 (d, *J* = 4.5 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.70-6.67 (m, 1H), 3.38 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.0, 161.1, 159.4, 155.8, 147.6, 137.7, 130.0, 129.3, 126.8, 124.4, 119.9, 117.8, 114.7, 107.2, 38.9. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{18}N_3O_2$: 320.1399, found: 320.1394.



1s

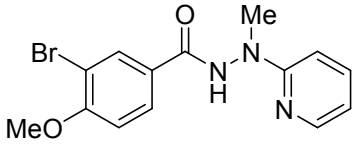
N'-methyl-N'-(pyridin-2-yl)-4-(trifluoromethoxy)benzohydrazide : Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1s** (80% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.61 (s, 1H), 8.17 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.55 – 7.44 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.73 (dd, *J* = 7.0, 5.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 3.36 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 165.4, 159.1, 151.8, 147.4, 137.9, 130.9, 129.3, 120.5, 120.3 (q, J_{C-F} = 256.3 Hz), 114.8, 107.2, 38.9. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -57.7. **HRMS** m/z ($[M+H]^+$) called for $C_{14}H_{13}F_3N_3O_2$: 312.0960, found: 312.0955.



1t

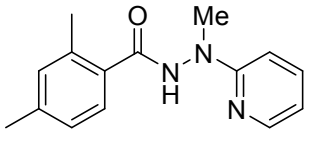
4-cyano-N'-methyl-N'-(pyridin-2-yl)benzohydrazide: Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1t** (82% yield) as a white solid. **^{1}H NMR (500 MHz, DMSO)** δ 11.02 (s, 1H), 8.14 (d, *J* = 4.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.0 Hz,

2H), 7.58 – 7.44 (m, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.71 (dd, *J* = 6.5, 5.5 Hz, 1H), 3.31 (s, 3H). **^{13}C NMR (125 MHz, DMSO)** δ 164.8, 159.8, 147.8, 138.0, 137.1, 133.1, 128.8, 118.7, 114.8, 114.4, 107.3, 38.1. **HRMS** m/z ([M+H]$^+$) called for $C_{14}H_{13}N_4O$: 253.1089, found: 253.1084.



1u

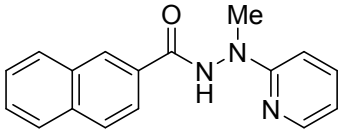
3-bromo-4-methoxy-N'-methyl-N'-(pyridin-2-yl)benzohydrazide： Prepared according to the general method , purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1u** (50% yield) as a white solid. **^{1}H NMR (500 MHz, DMSO)** δ 11.03 (brs, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.12 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.97 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.69 (brs, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 6.90 (brs, 1H), 6.81 (brs, 1H), 3.92 (s, 3H), 3.33 (s, 3H). **^{13}C NMR (100 MHz, DMSO)** δ 164.0, 158.3, 157.7, 144.5, 139.8, 132.3, 129.2, 125.6, 113.9, 112.3, 110.5, 108.1, 56.7, 38.3. **HRMS** m/z ([M+H]$^+$) called for $C_{14}H_{15}BrN_3O_2$: 336.0348, found: 336.0343.



1v

N',2,4-trimethyl-N'-(pyridin-2-yl)benzohydrazide： Prepared according to the general method, purified by column chromatography (*n*-

hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1v** (80% yield) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (ddd, *J* = 5.2, 2.0, 0.8 Hz, 1H), 7.98 (s, 1H), 7.50 (ddd, *J* = 8.8, 7.2, 2.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.71 (ddd, *J* = 7.2, 5.2, 0.8 Hz, 1H), 3.42 (s, 3H), 2.45 (s, 3H), 2.35 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.1, 159.3, 147.7, 140.8, 137.6, 137.2, 132.1, 130.7, 127.1, 126.4, 114.7, 107.1, 38.8, 21.3, 19.8. **HRMS** m/z ($[M+H]^+$) called for $C_{15}H_{18}N_3O$: 256.1450, found: 256.1447.



1w

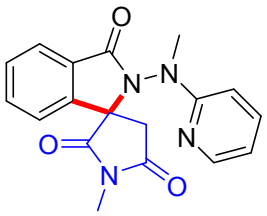
N'-methyl-N'-(pyridin-2-yl)-2-naphthohydrazide： Prepared according to the general method, purified by column chromatography (*n*-hexanes/EtOAc = 3:1 to 1:1) to afford the corresponding product **1w** (80% yield) as a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.21 (s, 1H), 8.35 (s, 1H), 8.20 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.87-7.77 (m, 4H), 7.58 – 7.45 (m, 3H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.42 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 159.3, 147.5, 137.8, 134.9, 132.5, 129.6, 129.0, 128.5, 128.1, 127.9, 127.7, 126.8, 123.6, 114.7, 107.3, 38.9. **HRMS** m/z ($[M+H]^+$) called for $C_{17}H_{16}N_3O$: 278.1293, found: 278.1292.

3. General procedure for cobalt-catalyzed C (*sp*^{2})-H C−H Functionalization/Spirocyclization Cascade:

Method A: A mixture of N'-methyl-N'-(pyridin-2-

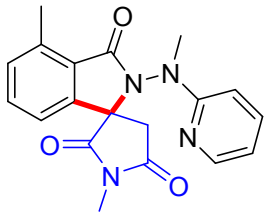
yl)benzohydrazide (0.20 mmol), maleimide (0.6 mmol), $Co(OAc)_2 \cdot 4H_2O$ (4.98 mg, 0.02 mmol), Ag_3PO_4 (125.6 mg, 0.3 mmol), NaOPiv (37.2 mg, 0.3 mmol) and DCE (2.0 mL) was added to a 25 mL sealed tube. The tube was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a plug of Celite, followed by washing with 70 mL of ethyl acetate. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography on to provide the product. The product gives two sets of NMR signals, owing to the presence of rotamers around the amide.

Method B: A mixture of N'-methyl-N'-(pyridin-2-yl)benzohydrazide (0.80 mmol), bismaleimide (0.2 mmol), $Co(OAc)_2 \cdot 4H_2O$ (9.96 mg, 0.04 mmol), Ag_3PO_4 (251 mg, 0.6 mmol), NaOPiv (74.4 mg, 0.6 mmol) and DCE (2.0 mL) was added to a 25 mL sealed tube. The tube was stirred at 140 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a plug of Celite, followed by washing with 70 mL of ethyl acetate. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography to provide the product. The product gives two sets of NMR signals, owing to the presence of rotamers around the amide.



3aa

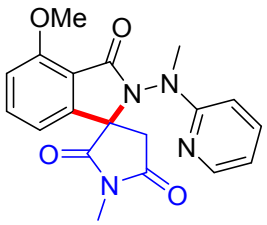
1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3aa** (64 mg, 95% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.63 (td, *J* = 7.5, 1.0 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.80 (dd, *J* = 7.0, 5.1 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 3.60 (d, *J* = 18.5 Hz, 1H), 3.49 (s, 3H), 3.15 (s, 3H), 3.10 (d, *J* = 19.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.2, 173.7, 165.7, 159.5, 148.1, 142.5, 138.1, 133.3, 129.9, 129.8, 124.7, 120.4, 116.4, 107.1, 69.4, 39.1, 36.8, 25.7. **HRMS** m/z ($[M+H]^+$) called for $C_{18}H_{17}N_4O_3$: 337.1301, found: 337.1293.



3ba

1',4-dimethyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-

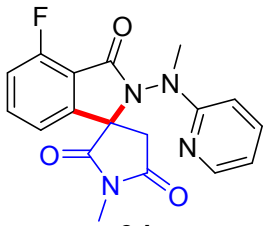
hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ba** (56 mg, 80% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.60 (d, *J* = 18.5 Hz, 1H), 3.48 (s, 3H), 3.15 (s, 3H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.70 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.5, 173.9, 166.5, 159.7, 148.1, 143.0, 139.2, 138.1, 132.8, 132.0, 126.8, 117.6, 116.3, 107.0, 68.8, 39.1, 37.1, 25.7, 17.1. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{19}N_4O_3$: 351.1457, found: 351.1453.



3ca

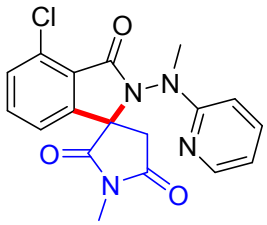
4-methoxy-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ca** (37 mg, 950% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.52 – 7.49 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.77 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 3.56 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.13 (s, 3H), 3.07 (d, *J* =

18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.2, 173.8, 164.5, 159.8 157.8, 148.1, 144.8, 138.0, 135.1, 116.9, 116.2, 112.3, 112.1, 107.1, 68.8, 56.0, 39.0, 37.1, 25.7. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{19}N_4O_4$: 367.1406, found: 367.1405.



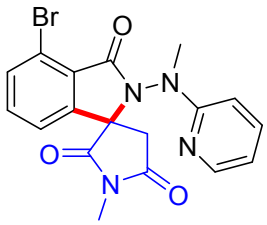
3da

4-fluoro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3da** (58 mg, 82% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 4.5 Hz, 1H), 7.61 (td, *J* = 8.0, 4.5 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.20 (t, *J* = 8.6 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.82 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.67 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.15 (s, 3H), 3.10 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.9, 173.7, 162.7, 160.1, 159.3, 157.5, 148.1, 144.6 (d, $J_{C\text{-}F}$ = 3.0 Hz), 138.2, 135.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 117.5 (d, $J_{C\text{-}F}$ = 19.0 Hz), 116.7, 116.6 (d, $J_{C\text{-}F}$ = 4.0 Hz), 107.2, 69.1, 39.2, 36.9, 25.9. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.7. **HRMS** m/z ($[M+H]^+$) called for $C_{18}H_{16}FN_4O_3$: 355.1206, found: 355.1199.



3ea

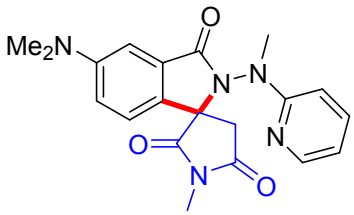
4-chloro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ea** (68 mg, 91% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.49 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.82 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 3.71 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.15 (s, 3H), 3.09 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.9, 173.7, 163.5, 159.3, 148.1, 144.7, 138.2, 134.0, 132.5, 131.7, 126.1, 119.1, 116.7, 107.2, 68.5, 39.2, 36.9, 25.9. **HRMS** m/z ($[M+H]^+$) called for $C_{18}H_{16}ClN_4O_3$: 371.0911, found: 371.0906.



3fa

4-bromo-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the

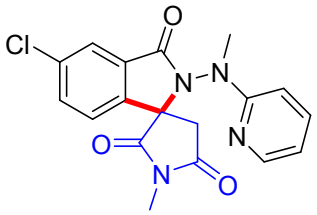
corresponding product **3fa** (50 mg, 60% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.70 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.58-7.54 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.5, 0.5 Hz, 1H), 6.83 – 6.81 (m, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 3.72 (d, *J* = 19.0 Hz, 1H), 3.46 (s, 3H), 3.15 (s, 3H), 3.09 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.8, 173.6, 163.8, 159.3, 148.1, 144.9, 138.2, 134.9, 134.0, 127.7, 120.1, 119.5, 116.7, 107.2, 68.3, 39.2, 36.9, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{18}H_{16}BrN_4O_3$: 415.0406, found: 415.0396.



3ga

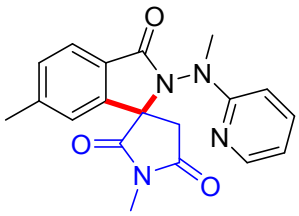
5-(dimethylamino)-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ga** (67 mg, 88% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.79 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 3.51 (d, *J* = 17.0 Hz, 1H), 3.50 (s, 3H), 3.15 (s, 3H), 3.05 (d, *J* = 16.0 Hz, 1H), 3.02 (s, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 175.0, 174.1, 166.7, 159.8,

151.8, 148.2, 138.0, 130.7, 129.4, 120.8, 117.0, 116.2, 107.1, 106.9, 69.0, 40.5, 38.9, 36.9, 25.6. **HRMS** m/z ([M+H]$^+$) called for $C_{20}H_{22}N_5O_3$: 380.1723, found: 380.1718.



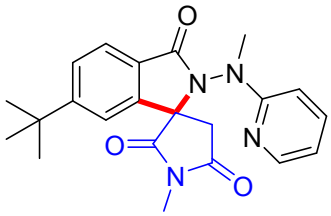
3ha

5-chloro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ha** (59mg, 80% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (ddd, *J* = 5.0, 1.8, 0.8 Hz, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.58-7.55 (m, 1H), 7.24 (d, *J* = 8.0 Hz 1H), 6.83 (ddd, *J* = 7.0, 5.0, 0.5 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.66 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.16 (s, 3H), 3.08 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.9, 173.6, 164.5, 159.2, 148.2, 140.6, 138.2, 136.5, 133.4, 131.8, 124.9, 121.8, 116.7, 107.1, 69.3, 39.2, 36.7, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{18}H_{16}ClN_4O_3$: 371.0911, found: 371.0914.



3ia

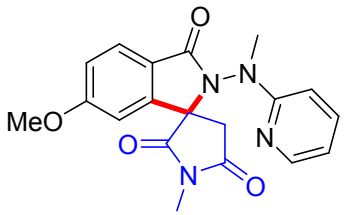
1',6-dimethyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ia** (64 mg, 91% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.53 (ddd, *J* = 8.9, 7.3, 1.9 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 6.80 (dd, *J* = 6.7, 4.8 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.57 (d, *J* = 18.5 Hz, 1H), 3.49 (s, 3H), 3.17 (s, 3H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.4, 173.9, 165.9, 159.6, 148.1, 144.5, 142.0, 138.0, 130.9, 127.2, 124.6, 120.8, 116.3, 107.0, 69.3, 39.1, 36.9, 25.7, 22.0. **HRMS** m/z ([M+H]$^+$) called for $C_{19}H_{19}N_4O_3$: 351.1457, found: 351.1451.



3ja

6-(tert-butyl)-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure, purified by silica gel column

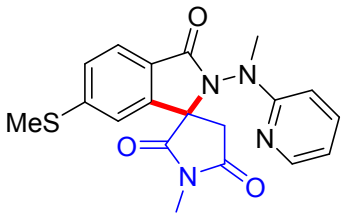
chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ja** (75 mg, 95% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.3, 1.5 Hz, 1H), 7.20 (d, *J* = 1.0 Hz, 1H), 6.79 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.59 (d, *J* = 18.5 Hz, 1H), 3.48 (s, 3H), 3.17 (s, 3H), 3.12 (d, *J* = 18.5 Hz, 1H), 1.34 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.5, 174.0, 165.8, 159.6, 157.8, 148.1, 142.6, 138.0, 127.5, 127.2, 124.3, 116.8, 116.3, 107.1, 69.4, 39.1, 36.8, 35.6, 31.3, 25.7. **HRMS** m/z ($[M+H]^+$) called for $C_{22}H_{25}N_4O_3$: 393.1927, found: 393.1921.



3ka

6-methoxy-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ka** (62 mg, 85% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (ddd, *J* = 5.0, 2.0, 1.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.54-7.50 (m, 1H), 7.06 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.80 – 6.78 (m, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.56 (d, *J* = 18.5 Hz, 1H), 3.47 (s, 3H), 3.15 (s, 3H), 3.08 (d, *J* = 18.5 Hz, 1H).

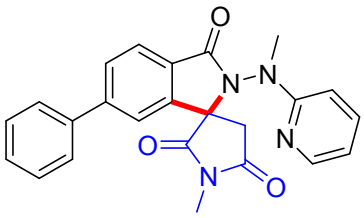
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 173.9, 165.6, 164.1, 159.7, 148.1, 144.6, 138.0, 126.3, 122.1, 116.30, 115.9, 107.0, 105.8, 69.1, 55.9, 39.1, 36.9, 25.7. HRMS m/z ($[M+H]^+$) called for $C_{19}H_{19}N_4O_4$: 367.1406, found: 367.1402.



3la

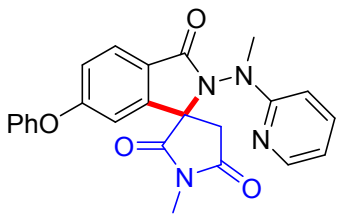
1'-methyl-2-(methyl(pyridin-2-yl)amino)-6-(methylthio)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione：

Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3la** (64 mg, 84% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.35 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.05 (d, *J* = 1.0 Hz, 1H), 6.78 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 3.57 (d, *J* = 19.0 Hz, 1H), 3.44 (s, 3H), 3.12 (s, 3H), 3.08 (d, *J* = 19.0 Hz, 1H), 2.48 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.2, 173.8, 165.6, 159.5, 148.1, 146.7, 143.1, 138.2, 126.7, 126.1, 124.8, 117.2, 116.5, 107.1, 69.1, 39.2, 36.7, 25.9, 15.2. HRMS m/z ($[M+H]^+$) called for $C_{19}H_{19}N_4O_3S$: 383.1178, found: 383.1157.



3ma

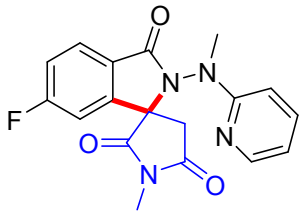
1'-methyl-2-(methyl(pyridin-2-yl)amino)-6-phenylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ma** (77 mg, 93% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.57-7.54 (m, 3H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.44 – 7.42 (m, 2H), 6.82 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 3.66 (d, *J* = 18.5 Hz, 1H), 3.51 (s, 3H), 3.19 (d, *J* = 18.5 Hz, 1H), 3.18 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.3, 173.8, 165.7, 159.6, 148.2, 147.1, 143.3, 139.7, 138.1, 129.2, 129.1, 128.6, 128.5, 127.5, 125.1, 119.1, 116.5, 107.1, 69.5, 39.2, 36.9, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{24}H_{21}N_4O_3$: 413.1614, found: 413.1601.



3na

1'-methyl-2-(methyl(pyridin-2-yl)amino)-6-phenoxyspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared

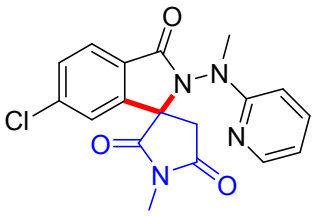
according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3na** (80 mg, 93% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.55-7.51 (m, 1H), 7.39 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.04 (m, 3H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.59 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.12 (s, 3H), 3.07 (d, *J* = 19.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.1, 173.6, 165.3, 162.4, 159.5, 155.1, 148.1, 144.5, 138.1, 130.2, 126.4, 124.9, 123.9, 120.0, 119.0, 116.4, 109.7, 107.0, 69.0, 39.1, 36.7, 25.7. **HRMS** m/z ([M+H]$^+$) called for $C_{24}H_{21}N_4O_4$: 429.1563, found: 429.1557.



3oa

6-fluoro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3oa** (67 mg, 95% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (ddd, *J* = 5.0, 1.5, 0.7 Hz, 1H), 7.89 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.57-7.54 (m, 1H), 7.26 (td, *J* = 9.0, 2.0 Hz, 1H), 7.00 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.67 (d, *J* = 8.5 Hz, 1H),

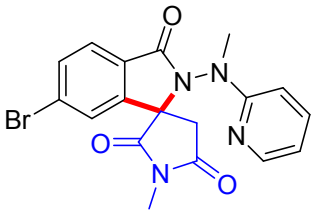
3.66 (d, J = 19.0 Hz, 1H), 3.46 (s, 3H), 3.16 (s, 3H), 3.10 (d, J = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 173.8, 173.4, 166.9, 164.8 (d, $J_{C\text{-}F}$ = 15.0 Hz), 159.3, 148.1, 144.7 (d, $J_{C\text{-}F}$ = 8.8 Hz), 138.1, 127.1 (d, $J_{C\text{-}F}$ = 8.8 Hz), 126.0, 117.7 (d, $J_{C\text{-}F}$ = 23.8 Hz), 116.6, 108.3 (d, $J_{C\text{-}F}$ = 2.5 Hz), 107.1, 69.2, 39.2, 36.7, 25.8. **^{19}F NMR (376 MHz, CDCl$_3$):** δ -57.6. HRMS m/z ([M+H]$^+$) called for $C_{18}H_{16}FN_4O_3$: 355.1206, found: 355.1202.



3pa

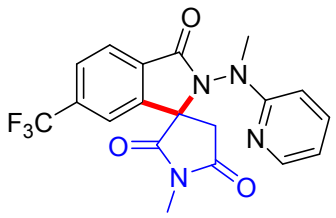
6-chloro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3pa** (69 mg, 93% yield) as a foam solid. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.14 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.57-7.53 (m, 2H), 7.28 (d, J = 1.5 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.67 (d, J = 8.5 Hz, 1H), 3.64 (d, J = 18.5 Hz, 1H), 3.45 (s, 3H), 3.16 (s, 3H), 3.10 (d, J = 19.0 Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 173.7, 173.5, 164.8, 159.2, 148.1, 143.9, 139.7, 138.2, 130.5, 128.4, 126.0,

121.1, 116.7, 107.1, 69.1, 39.2, 36.6, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{18}H_{16}ClN_4O_3$: 371.0911, found: 371.0909.



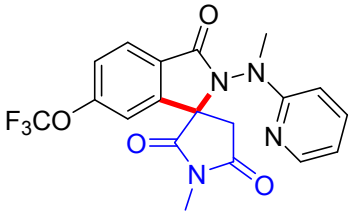
3qa

6-bromo-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3qa** (75 mg, 90% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.57 – 7.54 (m, 1H), 7.44 (d, *J* = 1.5 Hz, 1H), 6.82 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 3.65 (d, *J* = 18.5 Hz, 1H), 3.45 (s, 3H), 3.17 (s, 3H), 3.10 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.7, 173.4, 164.9, 159.2, 148.2, 144.1, 138.2, 133.4, 128.9, 127.9, 126.1, 124.0, 116.7, 107.1, 69.0, 39.2, 36.6, 25.9. **HRMS** m/z ([M+H]$^+$) called for $C_{18}H_{16}BrN_4O_3$: 415.0406, found: 415.0400.



3ra

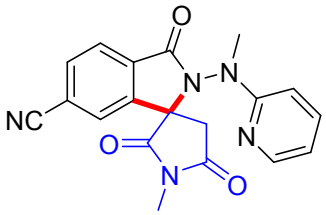
1'-methyl-2-(methyl(pyridin-2-yl)amino)-6-(trifluoromethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ra** (78 mg, 96% yield) as a foam solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.55 (s, 1H), 6.84 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 3.74 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.19 (s, 3H), 3.15 (d, *J* = 19.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.6, 173.4, 164.4, 159.1, 148.2, 142.9, 138.2, 135.4, (q, J_{C-F} = 32.5 Hz), 133.4, 127.2 (q, J_{C-F} = 271.3 Hz), 125.4, 122.3 (q, J_{C-F} = 21.3 Hz), 118.0 (q, J_{C-F} = 3.8 Hz), 116.9, 107.2, 69.50, 39.2, 36.6, 25.9. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -62.5. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{16}F_3N_4O_3$: 405.1175, found: 405.1168.



3sa

1'-methyl-2-(methyl(pyridin-2-yl)amino)-6-(trifluoromethoxy)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione:

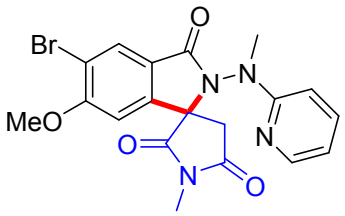
Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3sa** (80 mg, 95% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.57 (m, 1H), 7.43 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.12 (s, 1H), 6.83 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 3.71 (d, *J* = 18.5 Hz, 1H), 3.46 (s, 3H), 3.18 (s, 3H), 3.12 (d, *J* = 19.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.7, 173.5, 164.5, 159.2, 152.8 (q, J_{C-F} = 2.0 Hz), 148.2, 144.2, 138.2, 128.4, 126.6, 122.5, 120.2 (q, J_{C-F} = 258.0 Hz), 116.8, 113.41, 107.2, 69.2, 39.2, 36.6, 25.9. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -103.1. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{16}F_3N_4O_4$: 421.1124, found: 421.1118.



3ta

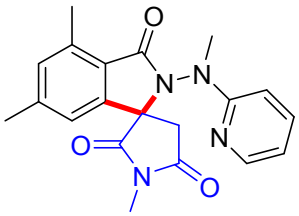
1'-methyl-2-(methyl(pyridin-2-yl)amino)-2',3,5'-trioxospiro[isoindoline-1,3'-pyrrolidine]-6-carbonitrile: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ta** (69 mg, 96% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.86 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.64 (s, 1H), 7.60 – 7.57 (m, 1H), 6.84 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.72 (d,

J = 8.5 Hz, 1H), 3.74 (d, J = 19.0 Hz, 1H), 3.43 (s, 3H), 3.18 (s, 3H), 3.12 (d, J = 19.0 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.3, 173.1, 163.9, 158.8, 148.1, 143.0, 138.3, 133.9, 133.8, 125.5, 124.7, 117.3, 117.0, 116.8, 107.2, 69.3, 39.2, 36.4, 25.9. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{16}N_5O_3$: 362.1253, found: 362.1246.



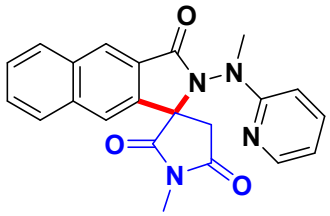
3ua

5-bromo-6-methoxy-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ua** (74 mg, 83% yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (dd, J = 5.0, 1.0 Hz, 1H), 8.05 (s, 1H), 7.56 – 7.52 (m, 1H), 6.81 (dd, J = 7.0, 5.0 Hz, 1H), 6.69 (s, 1H), 6.65 (d, J = 8.5 Hz, 1H), 3.93 (s, 3H), 3.65 (d, J = 19.0 Hz, 1H), 3.43 (s, 3H), 3.16 (s, 3H), 3.10 (d, J = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.9, 173.8, 164.5, 160.1, 159.4, 148.1, 143.3, 138.1, 129.6, 123.3, 116.6, 114.5, 107.1, 103.3, 69.0, 56.9, 39.2, 36.7, 25.9. **HRMS** m/z ($[M+H]^+$) called for $C_{19}H_{18}BrN_4O_4$: 445.0511, found: 445.0507.



3va

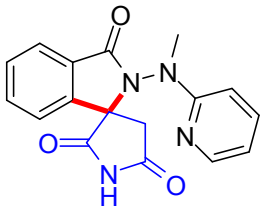
1',4,6-trimethyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3va** (65 mg, 89% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.11 (s, 1H), 6.86 (s, 1H), 6.79 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H), 3.55 (d, *J* = 18.5 Hz, 1H), 3.48 (s, 3H), 3.15 (s, 3H), 3.06 (d, *J* = 18.5 Hz, 1H), 2.65 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.7, 174.0, 166.6, 159.8, 148.1, 143.8, 143.3, 138.8, 138.0, 132.9, 124.1, 118.1, 116.2, 107.0, 68.6, 39.1, 37.1, 25.7, 21.8, 17.0. **HRMS** m/z ([M+H]$^+$) called for $C_{20}H_{21}N_4O_3$: 365.1614, found: 365.1610.



3wa

1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[benzo[f]isoindole-1,3'-pyrrolidine]-2',3,5'(2H)-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-

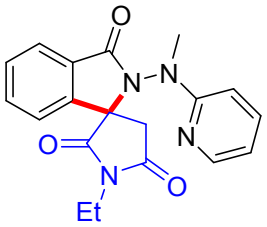
hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3wa** (63 mg, 82% yield) as a foam solid.**^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.44 (s, 1H), 8.21 – 8.16 (m, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 2H), 7.57-7.53 (m, 1H), 6.83 – 6.79 (m, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 3.66 (d, *J* = 18.5 Hz, 1H), 3.55 (s, 3H), 3.21 (s, 3H), 3.20 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.7, 174.1, 165.8, 159.5, 148.2, 138.2, 137.9, 135.6, 133.6, 129.8, 128.6, 128.3, 127.5, 126.8, 125.6, 119.9, 116.5, 107.2, 69.4, 39.3, 37.8, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{22}H_{19}N_4O_3$: 387.1457, found: 387.1451.



3ab

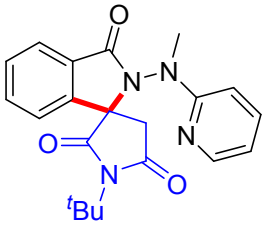
2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione：Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ab** (47 mg, 72% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.34 (brs, 1H), 8.17 – 8.16 (m, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.66 (td, *J* = 7.5, 1.0 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.39 (d, *J* = 7.5 Hz, 1H), 6.82 – 6.80(m, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.63 (d, *J* = 18.5 Hz, 1H), 3.52 (s, 3H), 3.10 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.1, 173.5, 165.8, 159.4, 148.1, 142.2,

138.1, 133.4, 130.0 129.7, 124.8, 120.4, 116.5, 107.1, 70.6, 39.2, 37.7. **HRMS** m/z ([M+H]$^+$) called for $C_{17}H_{15}N_4O_3$: 323.1144, found: 323.1138.



3ac

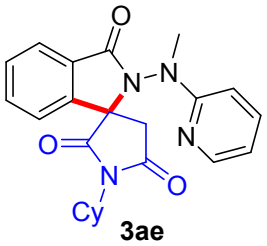
1'-ethyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (*n*-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ac** (65 mg, 93% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 4.8, 1.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 3.71 (q, *J* = 7.0 Hz, 2H), 3.57 (d, *J* = 18.5 Hz, 1H), 3.49 (s, 3H), 3.08 (d, *J* = 18.5 Hz, 1H), 1.25 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.0, 173.5, 165.8, 159.5, 148.1, 142.6, 138.1, 133.4, 129.9, 129.8, 124.7, 120.2, 116.4, 107.0, 69.2, 39.0, 36.7, 34.6, 13.0. **HRMS** m/z ([M+H]$^+$) called for $C_{19}H_{19}N_4O_3$: 351.1457, found: 351.1450.



3ad

1'-(tert-butyl)-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-

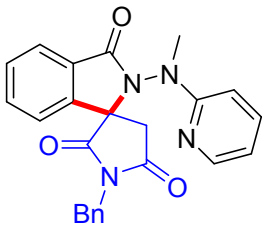
1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure, method A, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ad** (66 mg, 87% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.65 (td, *J* = 7.5, 1.0 Hz, 1H), 7.57 (td, *J* = 7.5, 1.0 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.81 – 6.78 (m, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 3.54 (s, 3H), 3.39 (d, *J* = 18.5 Hz, 1H), 2.97 (d, *J* = 18.0 Hz, 1H), 1.64 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.7, 174.5, 165.9, 159.6, 148.2, 143.0, 138.0, 133.3, 129.9, 129.8, 124.8, 119.9, 116.2, 107.0, 69.2, 59.8, 38.9, 37.0, 28.3. **HRMS** m/z ([M+H]$^+$) called for $C_{21}H_{23}N_4O_3$: 379.1770, found: 379.1765



3ae

1'-cyclohexyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ae** (74 mg, 92% yield) as a foam solid.**^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.63 (td, *J* = 7.5, 1.0 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.55 – 7.49 (m, 1H), 7.26 (d, *J* = 7.5 Hz, 1H),

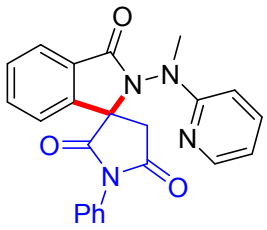
6.80 (dd, *J* = 6.8, 5.0 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 4.10 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.50 (s, 3H), 3.49 (d, *J* = 18.5 Hz, 1H), 3.03 (d, *J* = 18.5 Hz, 1H), 2.22 (qd, *J* = 12.5, 3.7 Hz, 1H), 2.12 (qd, *J* = 12.5, 3.7 Hz, 1H), 1.85 (dd, *J* = 13.5, 2.8 Hz, 2H), 1.71-1.66 (m, 3H), 1.38 – 1.27 (m, 2H), 1.24-1.18 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.1, 173.7, 165.8, 159.5, 148.2, 142.8, 138.0, 133.3, 129.9, 129.8, 124.7, 120.1, 116.3, 107.0, 68.9, 52.7, 38.9, 36.6, 29.0, 28.7, 25.6, 25.7, 24.9. **HRMS** m/z ($[M+H]^+$) called for $C_{23}H_{24}N_4O_3$: 405.1927, found: 405.1920.



3af

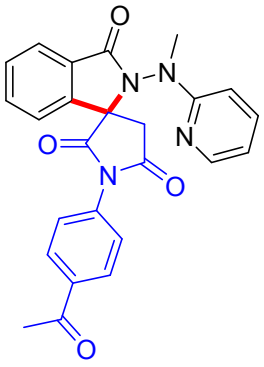
1'-benzyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3af** (77 mg, 93% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.16 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.56-7.54 (m, 3H), 7.39 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.34-7.32 (m, 3H), 7.06 (dd, *J* = 5.7, 2.8 Hz, 1H), 6.81 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 4.83 (d, *J* = 14.0 Hz, 1H), 4.78 (d, *J* = 14.0 Hz, 1H), 3.63 (d, *J* = 19.0 Hz, 1H), 3.37 (s, 3H), 3.09 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.0, 173.3, 165.7, 159.4, 148.2, 142.5, 138.1, 135.2, 133.3, 129.9,

128.8, 128.6, 128.3, 124.7, 120.3, 116.4, 107.0, 69.3, 43.3, 39.0, 36.8. **HRMS** m/z ([M+H]$^+$) called for $C_{24}H_{21}N_4O_3$: 413.1614, found: 413.1605.



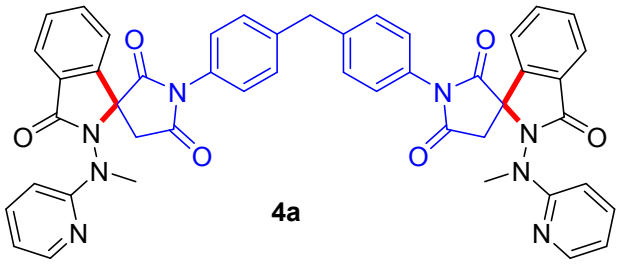
3ag

2-(methyl(pyridin-2-yl)amino)-1'-phenylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: Prepared according to the general procedure method A, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ag** (76 mg, 95% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.69 (td, *J* = 7.5, 1.0 Hz), 7.63 – 7.55 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.44 (dd, *J* = 7.5, 3.0 Hz, 2H), 7.37 – 7.35 (m, 2H), 6.84 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 3.80 (d, *J* = 18.5 Hz, 1H), 3.56 (s, 3H), 3.27 (d, *J* = 18.5 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.3, 172.6, 165.8, 159.5, 148.2, 142.5, 138.2, 133.5, 131.4, 130.1, 129.8, 129.3, 129.1, 126.1, 124.9, 120.2, 116.5, 107.1, 69.5, 39.2, 36.9. **HRMS** m/z ([M+H]$^+$) called for $C_{23}H_{19}N_4O_3$: 399.1457, found: 399.1452.



3ah

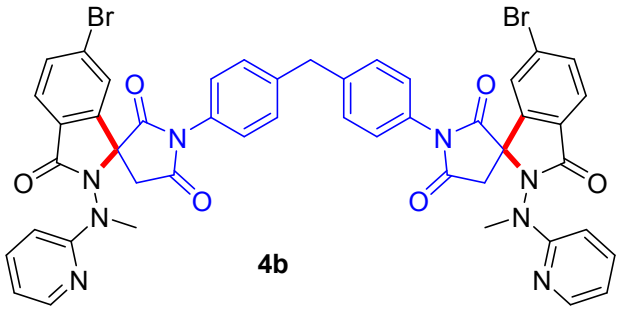
1'-(4-acetylphenyl)-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure method A, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **3ah** (81 mg, 92% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.68 (td, *J* = 7.5, 1.0 Hz, 1H), 7.58 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 1H), 6.83 (dd, *J* = 7.0, 5.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 3.83 (d, *J* = 18.5 Hz, 1H), 3.53 (s, 3H), 3.28 (d, *J* = 18.5 Hz, 1H), 2.60 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.6, 173.0, 172.1, 165.7, 159.4, 148.1, 142.3, 138.1, 137.1, 135.3, 133.5, 130.2, 129.8, 129.2, 126.0, 124.9, 120.3, 116.6, 107.1, 69.5, 39.3, 36.9, 26.5. **HRMS** m/z ($[M+H]^+$) called for $C_{25}H_{21}N_4O_4$: 441.1563, found: 441.1556.



4a

1',1'''-(methylenebis(4,1-phenylene))bis(2-(methyl(pyridin-2-

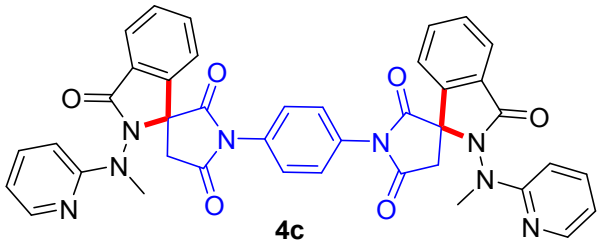
yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione)： Prepared according to the general procedure method B, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **4a** (148 mg, 92% yield) as a foam solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 4.0 Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 2H), 7.60 – 7.54 (m, 4H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.32 – 7.26 (m, 8H), 6.82 (dd, *J* = 6.8, 5.2 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.05 (s, 2H), 3.78 (d, *J* = 18.5 Hz, 2H), 3.54 (s, 6H), 3.25 (d, *J* = 18.5 Hz, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.3, 172.6, 165.8, 159.5, 148.2, 142.5, 141.3, 138.1, 133.5, 130.1, 129.9, 129.8, 129.7, 126.2, 124.8, 120.3, 116.5, 107.1, 69.5, 41.1, 39.2, 36.9. **HRMS** m/z ($[M+H]^+$) called for $C_{47}H_{37}N_8O_6$: 809.2836, found: 809.2835.



4b

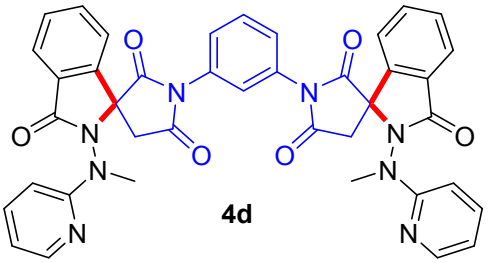
1',1'''-(methylenebis(4,1-phenylene))bis(6-bromo-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione): Prepared according to the general procedure method B, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **4b** (158 mg, 82% yield) as a foam solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 4.0 Hz, 2H), 7.74 (dd, *J* = 18.8, 8.0 Hz, 4H), 7.61 – 7.56 (m, 4H), 7.35 – 7.25 (m, 8H), 6.84 (dd, *J* = 6.4, 5.2 Hz,

2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.06 (s, 2H), 3.84 (d, *J* = 18.8 Hz, 2H), 3.50 (s, 6H), 3.21 (d, *J* = 18.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.9, 172.5, 165.0, 159.2, 148.2, 144.0, 141.5, 138.3, 133.6, 129.9, 129.6, 128.9, 128.1, 126.3, 126.3, 124.1, 116.9, 107.2, 69.1, 41.1, 39.4, 36.7. **HRMS** m/z ([M+H]$^+$) called for $C_{47}H_{35}Br_2N_8O_6$: 965.1046, found: 965.1039.



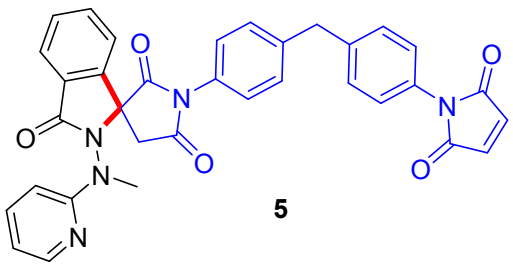
4c

1',1'''-(1,4-phenylene)bis(2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione)： Prepared according to the general procedure method B, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **4c** (118 mg, 82% yield) as a foam solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.20 (dd, *J* = 4.8, 1.2 Hz, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.72-7.68 (m, 2H), 7.65 – 7.58 (m, 4H), 7.57 (d, *J* = 2.8 Hz, 4H), 7.43 (d, *J* = 7.6 Hz, 2H), 6.85 (dd, *J* = 6.8, 4.8 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 3.85 (d, *J* = 18.4 Hz, 2H), 3.55 (s, 3H), 3.54 (s, 3H), 3.28 (d, *J* = 18.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.1, 172.3, 165.8, 159.4, 148.2, 142.3, 138.2, 133.6, 131.7, 130.3, 129.9, 126.8, 126.8, 125.0, 120.2, 116.7, 107.2, 69.5, 39.4, 37.0. **HRMS** m/z ([M+H]$^+$) called for $C_{40}H_{31}N_8O_6$: 719.2367, found: 719.2363.



4d

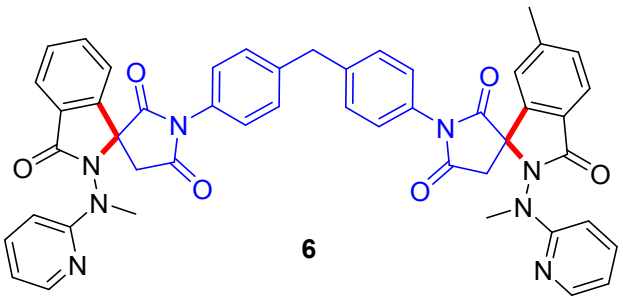
1',1'''-(1,3-phenylene)bis(2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione): Prepared according to the general procedure method B, purified by silica gel column chromatography (n-hexanes/EtOAc = 5:1 to 1:1) to afford the corresponding product **4d** (121 mg, 84% yield) as a foam solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 – 8.12 (m, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 6.4 Hz, 2H), 7.64-7.55 (m, 6H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 6.84 (t, *J* = 5.6 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.84 (d, *J* = 4.8 Hz, 1H), 3.79 (d, *J* = 5.2 Hz, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.26 (d, *J* = 18.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.1, 173.0, 172.3, 165.8, 159.5, 159.4, 148.2, 142.2, 138.3, 133.6, 132.2, 130.2, 129.9, 129.8, 126.2, 124.9, 123.3, 120.5, 116.7, 107.2, 69.5, 39.4, 36.9. **HRMS** m/z ([M+H]$^+$) called for $C_{40}H_{31}N_8O_6$: 719.2367, found: 719.2363.



5

1'-(4-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzyl)phenyl)-2-

(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: A mixture of N'-methyl-N'-(pyridin-2-yl)benzohydrazide (0.20 mmol), bismaleimide (0.4 mmol), $Co(OAc)_2 \cdot 4H_2O$ (4.98 mg, 0.02 mmol), Ag_3PO_4 (125.6 mg, 0.3 mmol), NaOPiv (37.2 mg, 0.3 mmol) and DCE (2.0 mL) was added to a 25 mL sealed tube. The tube was stirred at 110 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a plug of celite, followed by washing with 70 mL of ethyl acetate. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography to provide the product **5** (79 mg, 68% yield) as a foam solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.53 (d, *J* = 4.0 Hz, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 8.02 (td, *J* = 7.6, 0.8 Hz, 1H), 7.95-7.88 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.58 (m, 8H), 7.18 - 7.13 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.39 (s, 2H), 4.13 (d, *J* = 18.8 Hz, 1H), 3.89 (s, 3H), 3.59 (d, *J* = 18.4 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.3, 172.7, 169.5, 165.8, 159.4, 148.1, 142.4, 141.6, 140.0, 138.1, 134.1, 133.5, 130.1, 129.8, 129.8, 129.7, 129.6, 129.5, 129.4, 126.1, 124.8, 120.3, 116.5, 107.1, 69.4, 41.0, 39.2, 36.9. **HRMS** m/z ($[M+H]^+$) called for $C_{34}H_{26}N_5O_5$: 584.1934, found: 584.1927.



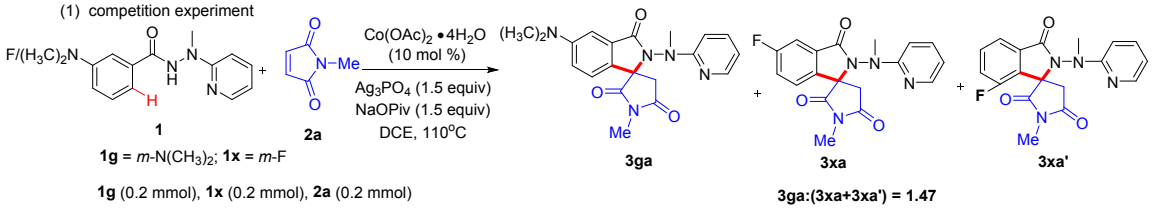
6

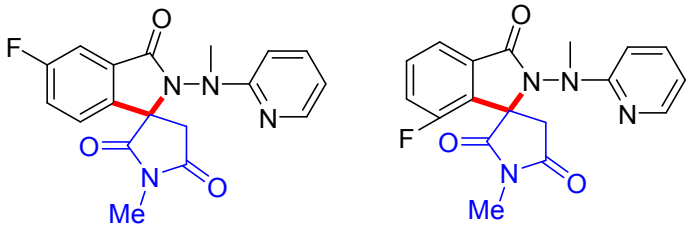
2-(methyl(pyridin-2-yl)amino)-1'-(4-(4-(6-methyl-2-(methyl(pyridin-2-yl)amino)-2',3,5'-trioxospiro[isoindoline-1,3'-pyrrolidin]-1'-yl)benzyl)phenyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: A mixture of **1i** (0.60 mmol), **5** (0.2 mmol), $Co(OAc)_2 \cdot 4H_2O$ (4.98 mg, 0.02 mmol), Ag_3PO_4 (125 mg, 0.3 mmol), NaOPiv (37.2 mg, 0.3 mmol) and DCE (2.0 mL) was added to a 25 mL sealed tube. The tube was stirred at 140 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a plug of celite, followed by washing with 70 mL of ethyl acetate. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography on to provide the product **6** (115 mg, 70% yield) as a foam solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 4.4, 0.8 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.26 (m, 8H), 7.22 (s, 1H), 6.84 – 6.79(m, 2H), 6.70 (t, *J* = 8.54Hz, 2H), 4.05 (s, 2H), 3.79 (d, *J* = 14.4 Hz, 1H), 3.74 (d, *J* = 14.0 Hz, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 3.26 (d, *J* = 8.8 Hz, 1H), 3.22 (d, *J* = 8.4

Hz, 1H), 2.47 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.5, 173.4, 172.9, 172.8, 166.0, 165.9, 159.6, 159.5, 148.2, 144.7, 142.8, 142.5, 141.5, 141.4, 138.3, 138.2, 133.6, 131.1, 130.2, 129.9, 129.84, 129.80, 129.7, 129.6, 127.2, 126.3, 124.9, 124.7, 120.8, 120.4, 116.6, 116.5, 107.2, 107.1, 69.5, 69.3, 41.1, 39.3, 37.0, 36.9, 22.1. **HRMS** m/z ($[M+H]^+$) called for $C_{48}H_{39}N_8O_6$: 823.2993, found: 823.2988.

4. Preliminary Mechanistic Experiments

1. competition experiment

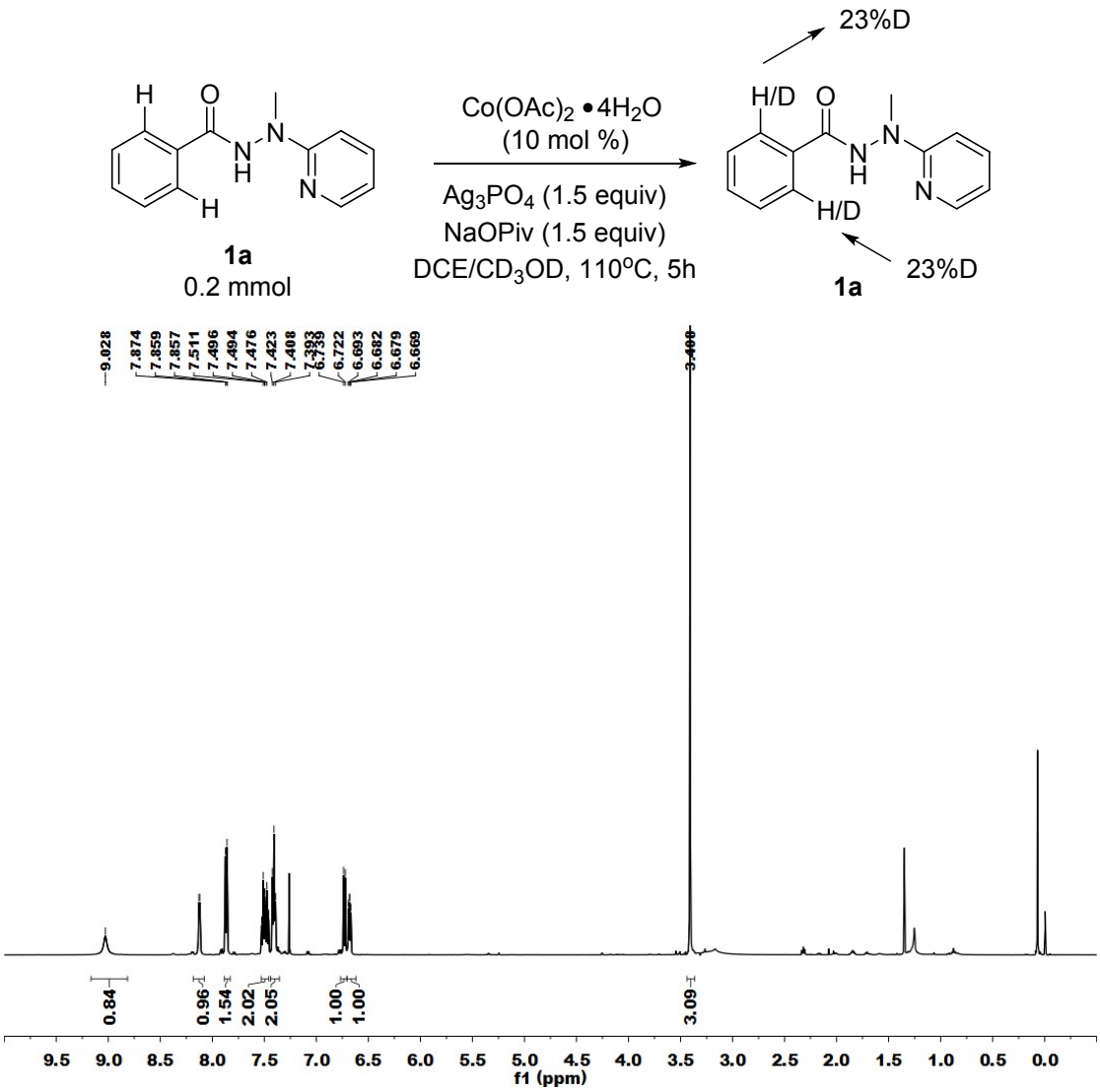




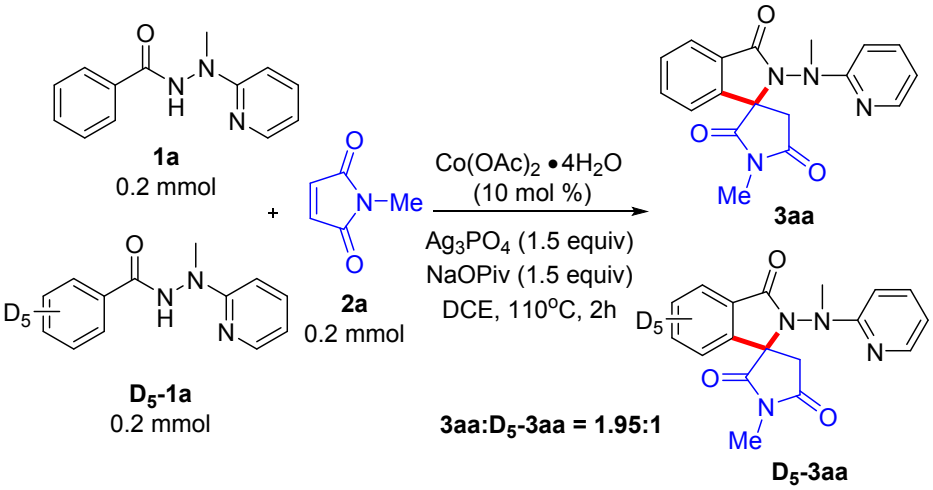
5-fluoro-1'-methyl-2-(methyl(pyridin-2-yl)amino)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione: A mixture of two regioisomers inseparable by silica gel column chromatography was generated. **^{1}H NMR (400 MHz, $CDCl_3$) (major)** δ 8.14 (d, *J* = 4.8 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.34 – 7.25 (m, 2H), 6.81 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.69 – 6.65 (m, 1H), 3.63 (d, *J* = 18.8 Hz, 1H), 3.44 (s, 3H), 3.14 (s, 3H), 3.08 (d, *J* = 18.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) (major)** δ 174.0, 173.7,

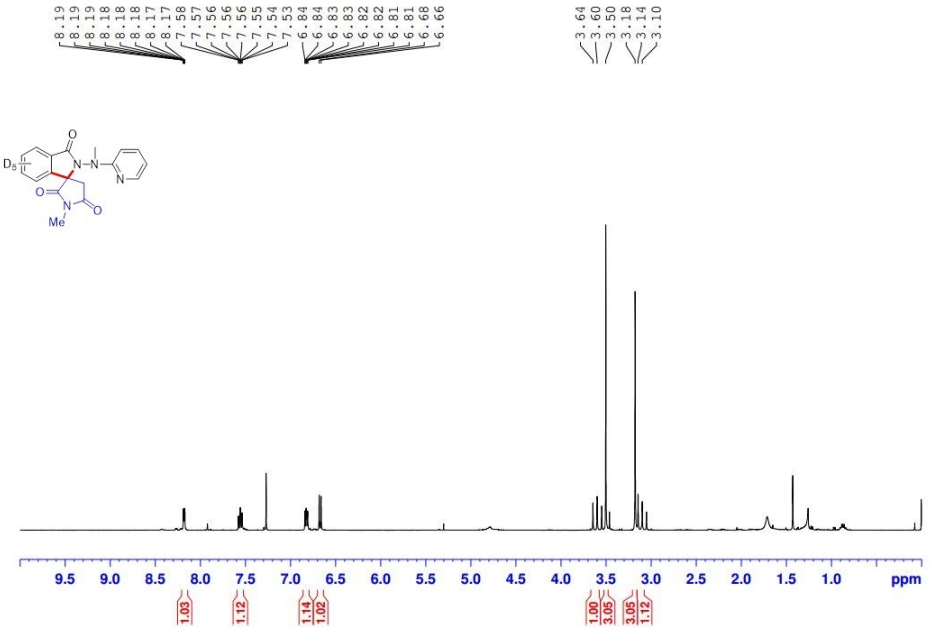
173.5, 159.2, 148.1, 138.2, 137.9 (d, J_{C-F} = 3.0 Hz), 132.2, 122.5 (d, d, J_{C-F} = 9.0 Hz), 120.8 (d, J_{C-F} = 24.0 Hz), 120.0 (d, J_{C-F} = 19.0 Hz), 116.7, 111.7(d, J_{C-F} = 24.0 Hz), 107.1, 69.2, 39.2, 36.6, 25.8. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -109.1, -120.7. **HRMS** m/z ($[M+H]^+$) called for $C_{18}H_{16}FN_4O_3$: 355.1206, found: 355.1200.

2. H/D scrambling

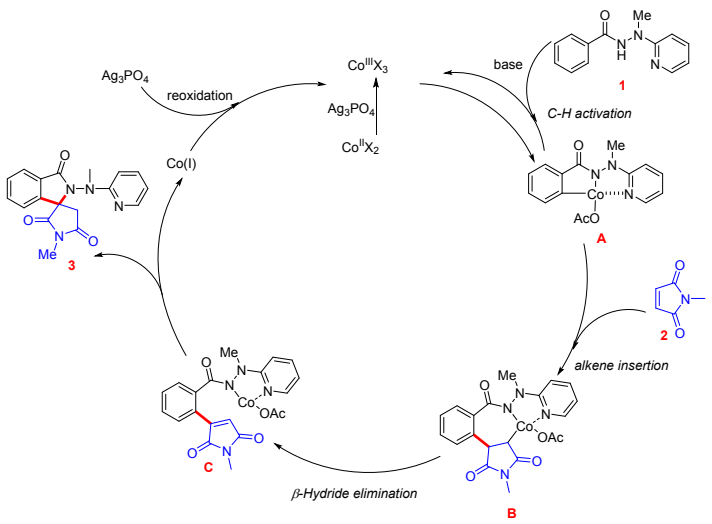


3. Competition reaction through two parallel reactions.





4. Proposed reaction mechanism

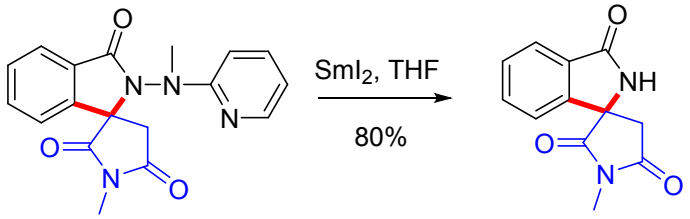


Based on our mechanistic studies and previous mechanistic insights[2], we propose the catalytic cycle. Co(II) is oxidized to Co(III) by Ag_3PO_4, then chelation of Co(III) to hydrazide **1** assisted by base and subsequent reversible C-H activation produces intermediate **A**. Subsequently, the migratory insertion into the maleimide to give intermediate **B**. *β*-Hydride elimination of intermediate **B** gives intermediate **C**. The intramolecular aza-Michael addition of alkenylated product **C** generates the spirocyclic compound **3** and cobalt species. Later, the active Co(III) species was regenerated through oxidation of Co(I) with Ag_3PO_4, and the regenerated Co(III) species enters the next catalytic cycle.

5. Reductive removal of the directing group

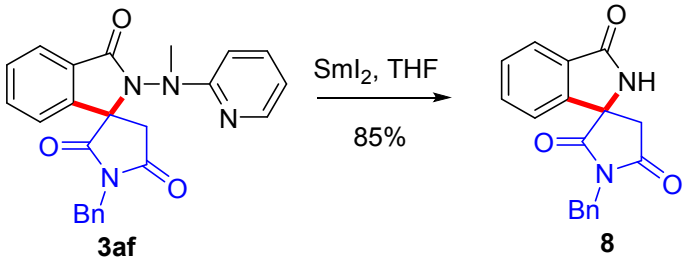
General experiment procedure: An oven-dried 25 mL two-neck round bottom flask was charged with **3** (0.1 mmol). After purging with Ar three times, 5 mL fresh distilled THF was added, followed by SmI_2 (0.1 M in THF, 20 equiv) was added dropwise at 0 °C. After 5 minutes, the mixture was warmed to 40 °C and stirred overnight. After that the

mixture was quenched with 5 mL saturated aqueous $Na_2S_2O_3$ and extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under reduced pressure and the product was obtained via column chromatography.[2]



3aa **7**

1'-methylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione： Prepared according to the general procedure, **7** was obtained in 80% yield. **^{1}H NMR (400 MHz, DMSO)** δ 9.07 (s, 1H), 8.05 – 7.99 (m, 2H), 7.96 (td, *J* = 7.2, 1.2 Hz, 1H), 7.89 (td, *J* = 7.2, 1.2 Hz, 1H), 3.73 (s, 3H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.44 (d, *J* = 18.0 Hz, 1H). **^{13}C NMR (100 MHz, DMSO)** δ 176.0, 174.6, 169.4, 145.8, 133.1, 132.1, 129.9, 123.5, 122.7, 64.4, 39.8, 25.8. **HRMS** m/z ([M+H]$^+$) called for $C_{12}H_{11}N_2O_3$: 231.0770, found: 231.0760.



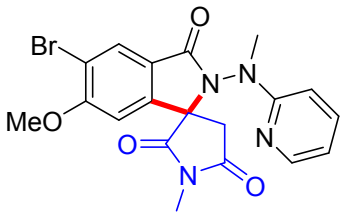
3af **8**

1'-benzylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione:

Prepared according to the general procedure, **8** was obtained in 85% yield. **^{1}H NMR (300 MHz, DMSO)** δ 8.89 (s, 1H), 7.74 – 7.55 (m, 4H), 7.39-

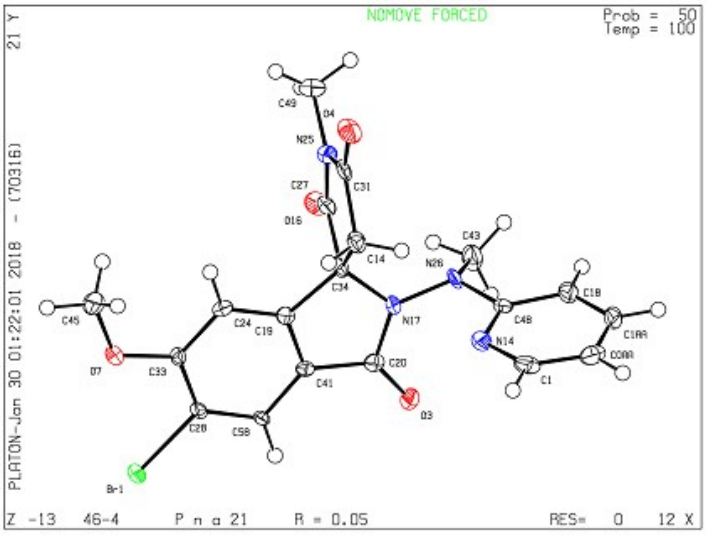
7.30 (m, 5H), 4.73 (d, J = 15.3 Hz, 1H), 4.67 (d, J = 15.3 Hz, 1H), 3.44 (d, J = 18.3 Hz, 1H), 3.22 (d, J = 18.6 Hz, 1H). **^{13}C NMR (125 MHz, DMSO)** δ 175.8, 174.2, 169.4, 145.8, 136.1, 133.2, 132.1, 130.0, 129.1, 128.1, 128.1, 123.7, 122.3, 64.4, 42.9, 39.6. **HRMS** m/z ([M+H]$^+$) called for $C_{18}H_{15}N_2O_3$: 307.1083, found: 307.1072.

6. X-ray Crystallographic Data of Compound 3ua



3ua

X-ray of 3aa (CCDC：1822031)



7. References

1. (a) Stadler, A.-M.; Lehn, J.-M. *J. Am. Chem. Soc.* **2014**, *136*, 3400. (b) Radunsky, C.; Kösters, J.; Letzel, M.; Yogendra, S.; Schwickert, C.; Manck, S.;

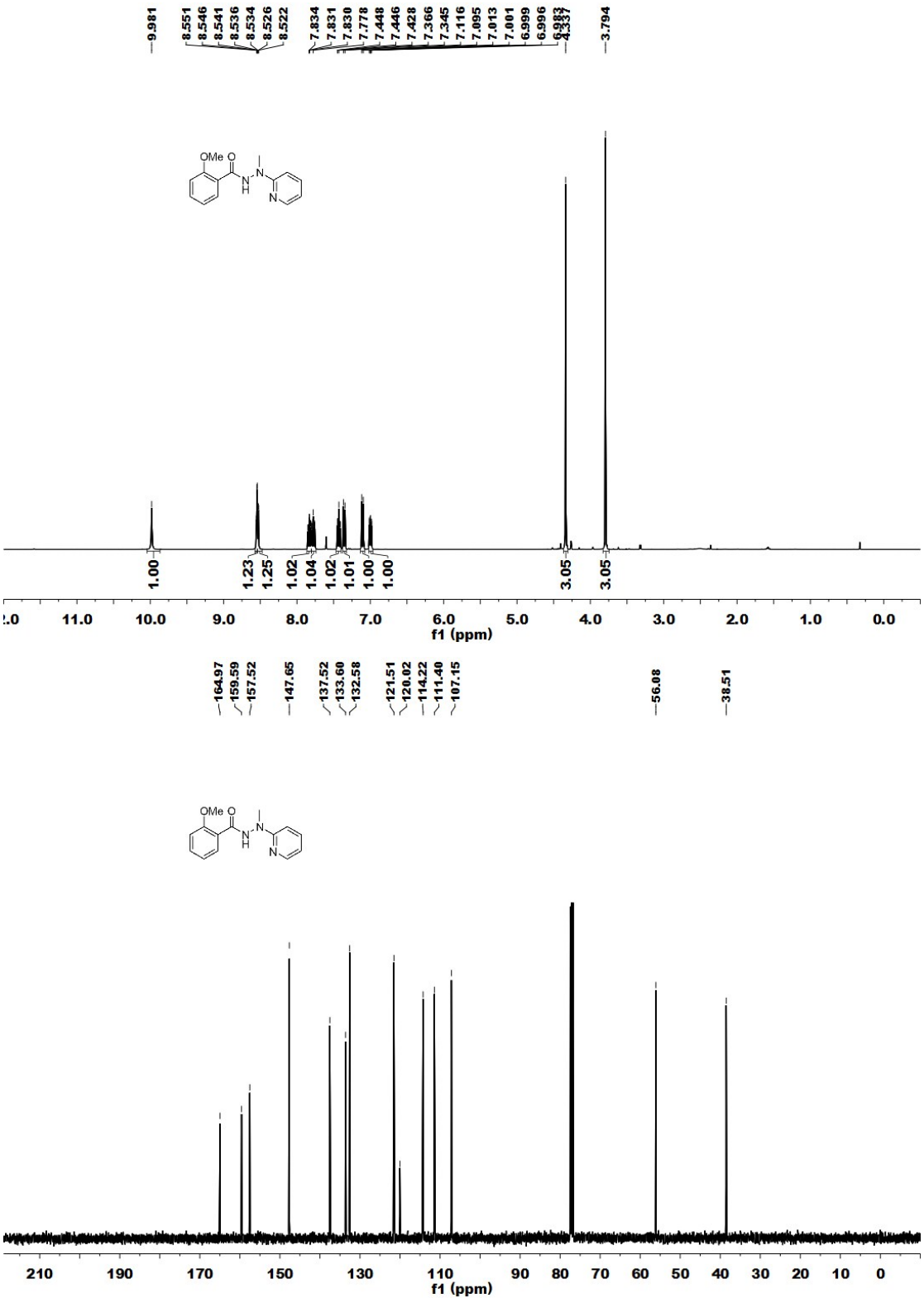
Sarkar, B.; Pöttgen, R.; Weigand, J.; Neugebauer, J.; Müller, J. *Eur. J. Inorg. Chem.* **2015,** *24***,** 4006. (c) Stadler, A.-M.; Karmazin, L.; Bailly, C. *Angew. Chem. Int. Ed.* **2015**, 54, 14570.

2. (a) Lv, N.; Liu, Y.; Xiong, C.; Liu, Z.; Zhang, Y. *Org. Lett.* **2017**, *19*, 4640. (b) Manoharan, R.; Jeganmohan, M. *Org. Lett.* **2017**, *19*, 5884.

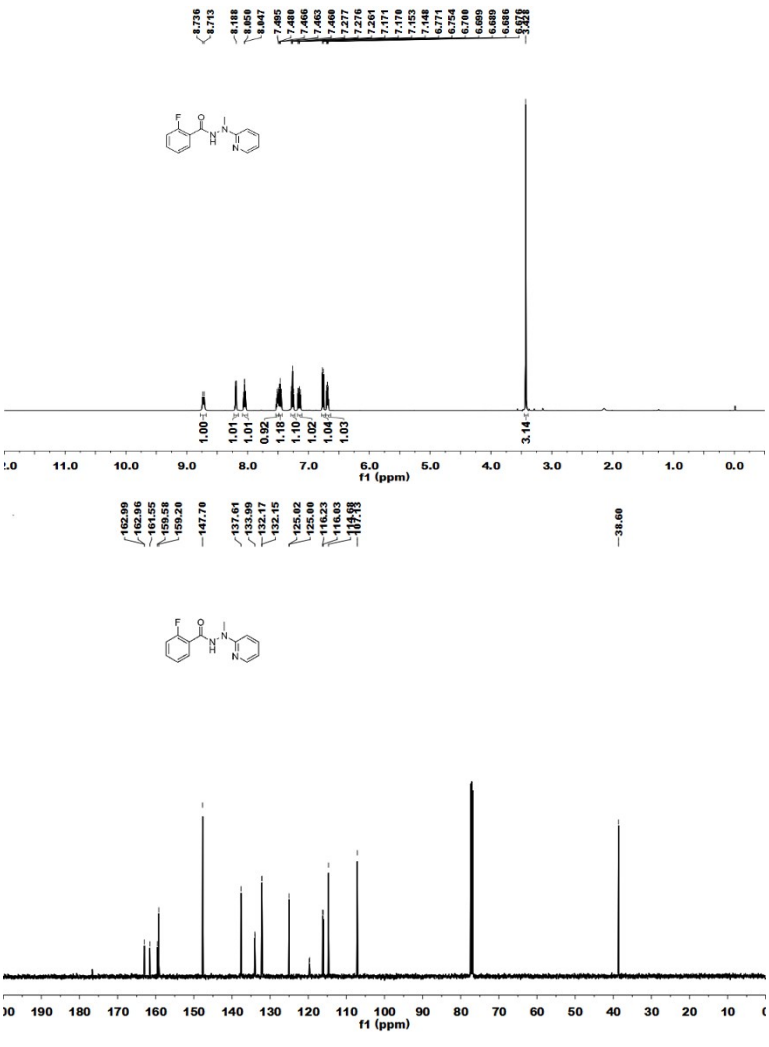
3. (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 4952.

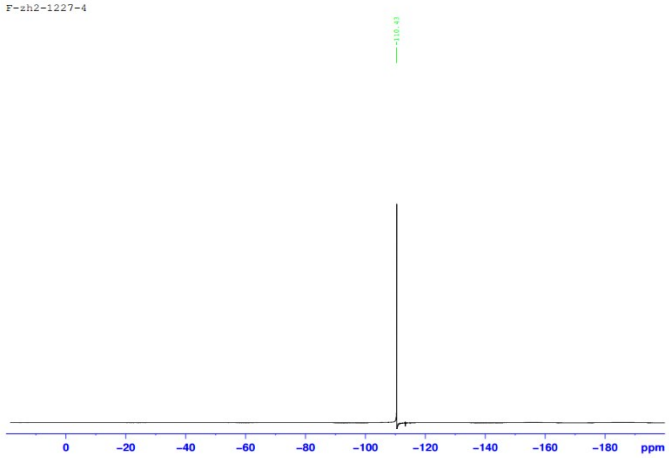
8. ^{1}H, ^{13}C and ^{19}F NMR Spectra

^{1}H, ^{13}C NMR spectra of compound 1c

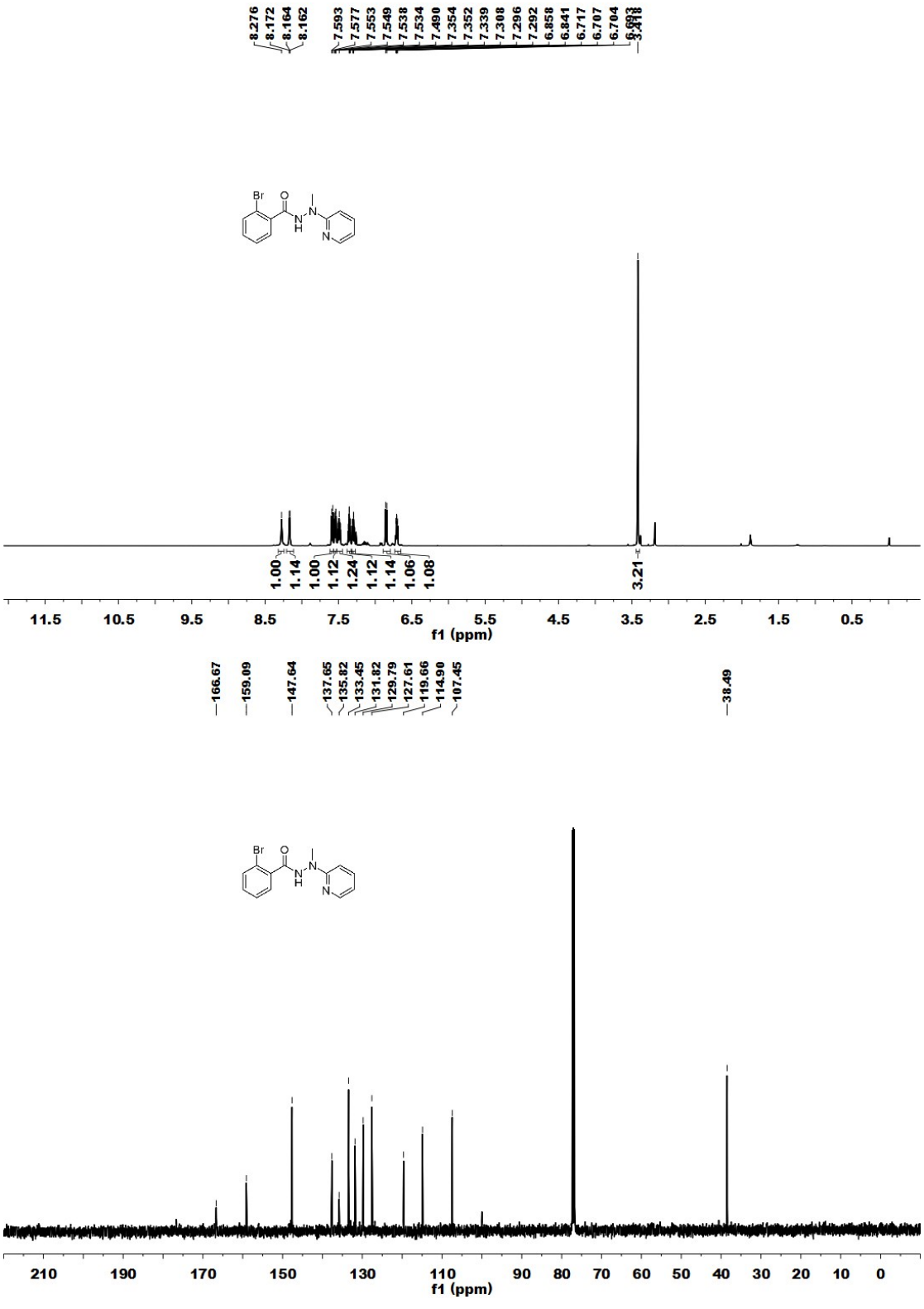


^{1}H, ^{13}C, ^{19}F NMR spectra of compound 1d

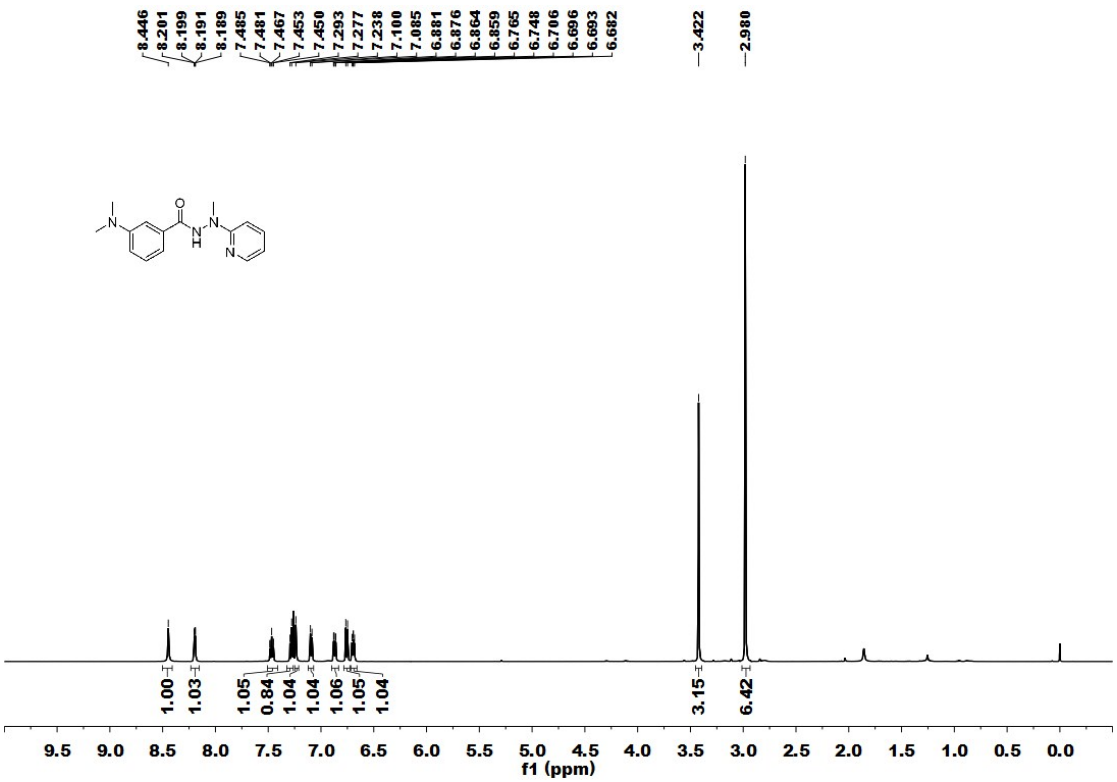


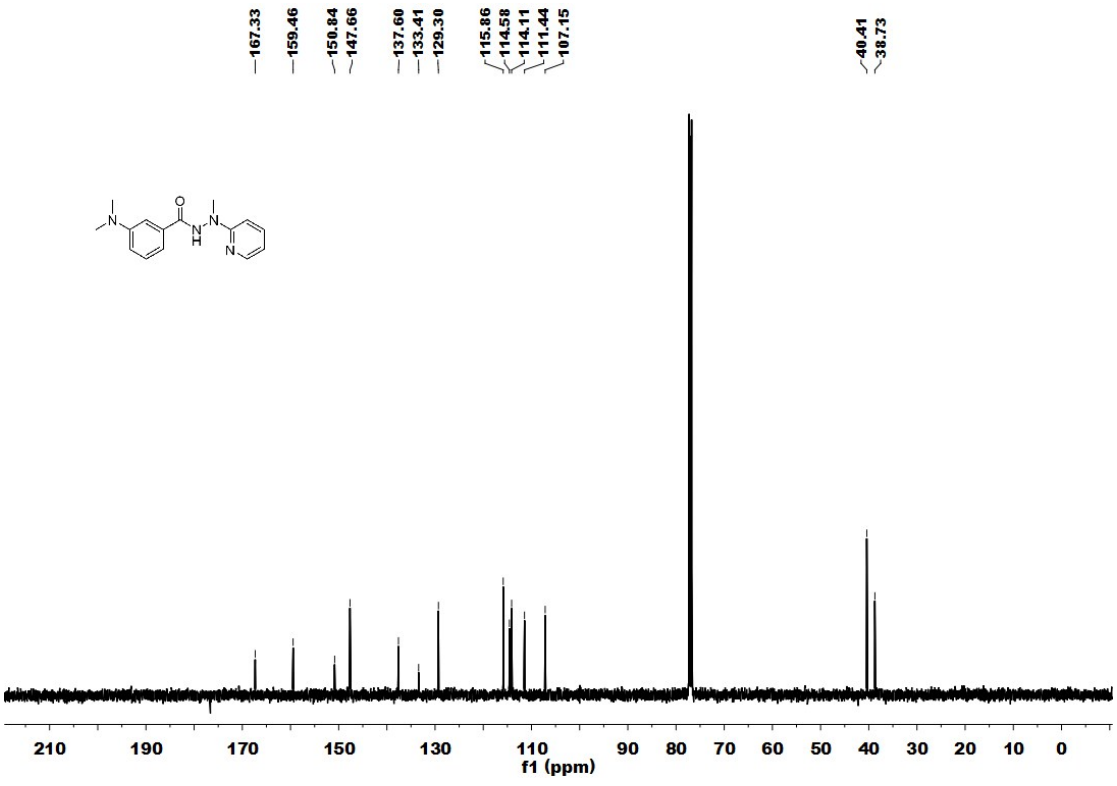


^{1}H, ^{13}C NMR spectra of compound 1f

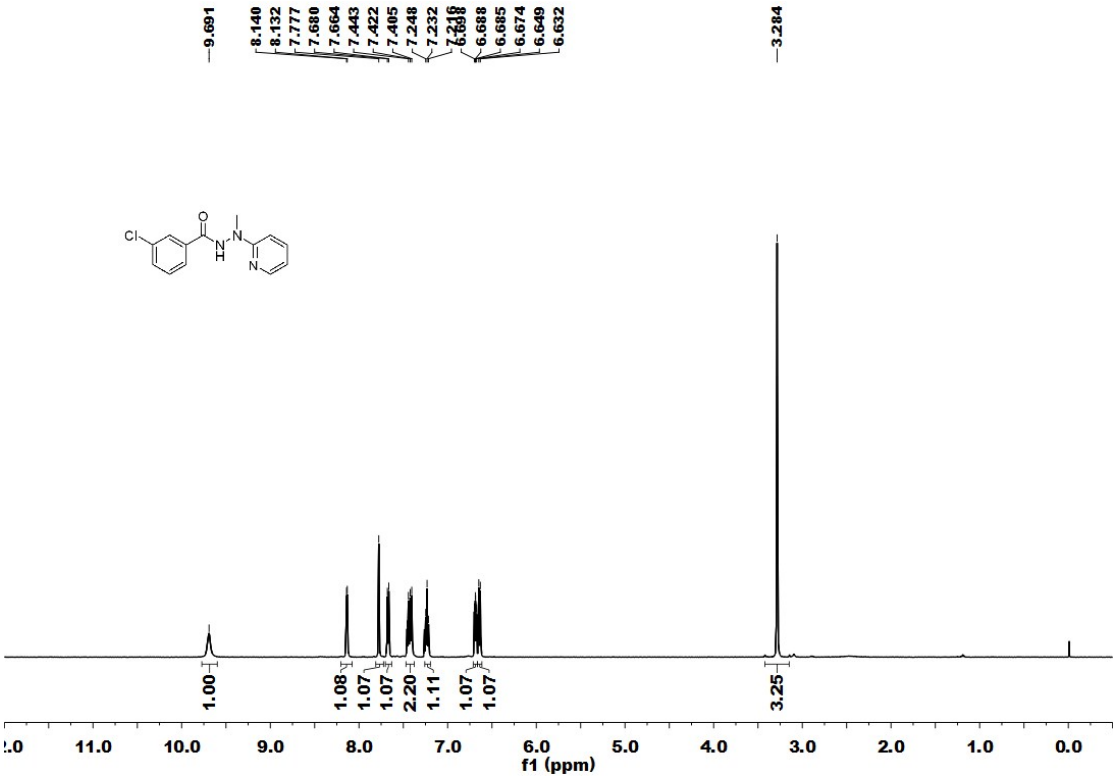


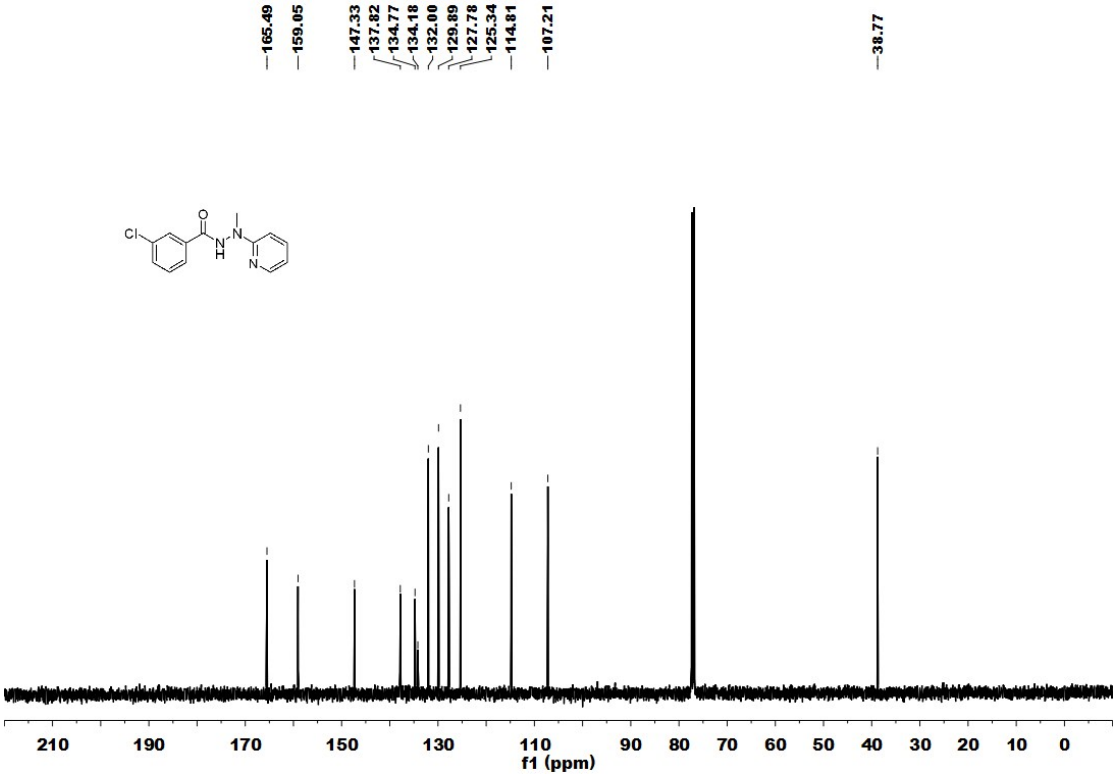
^{1}H, ^{13}C NMR spectra of compound 1g



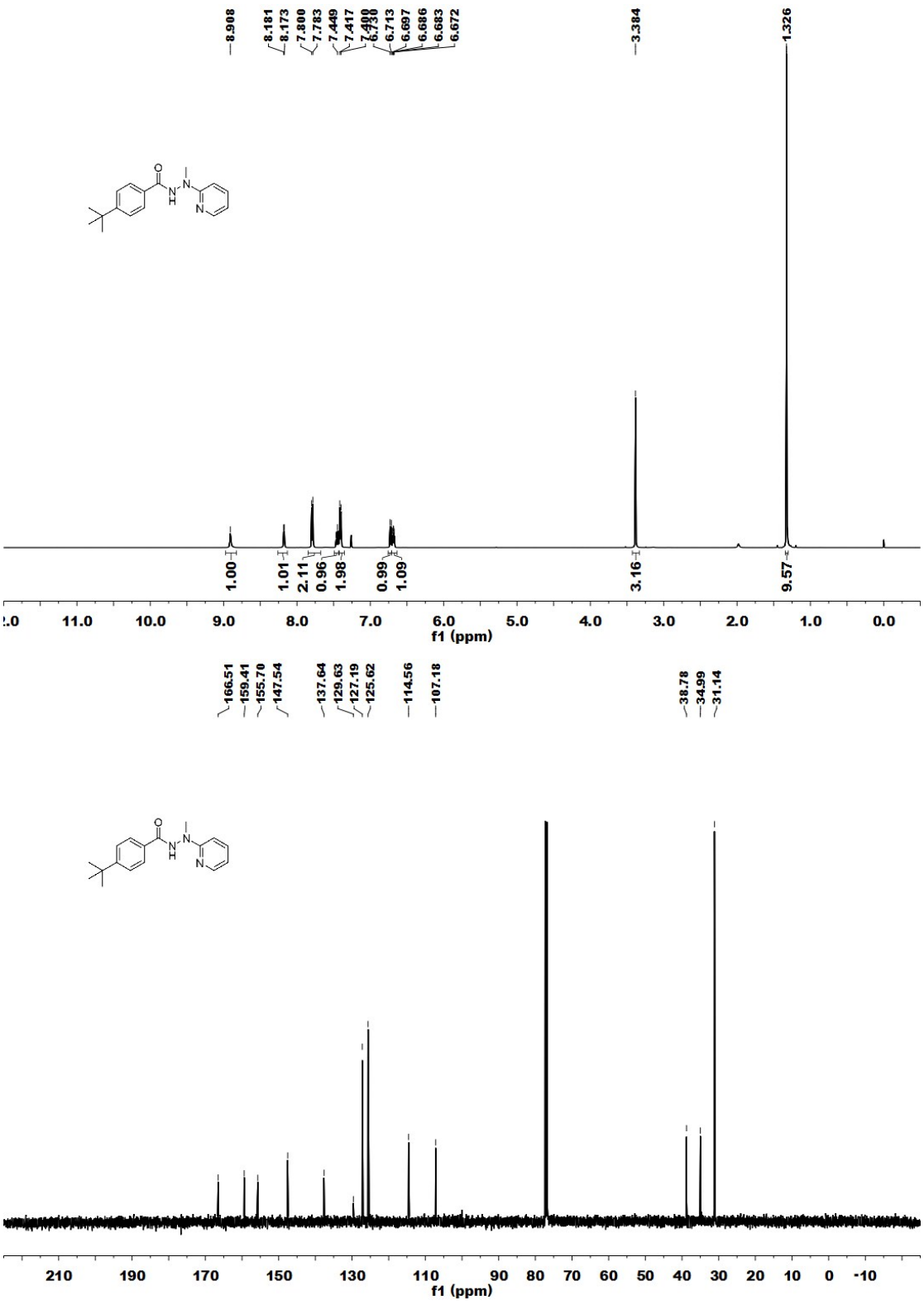


^{1}H, ^{13}C NMR spectra of compound 1h

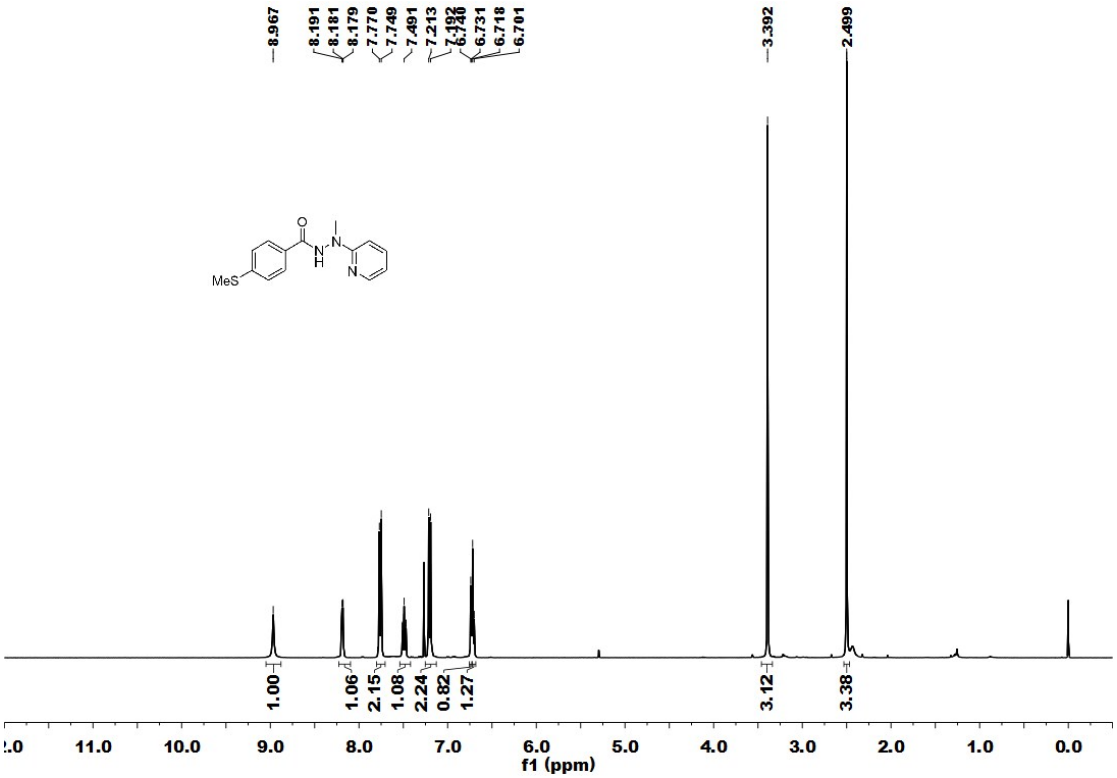


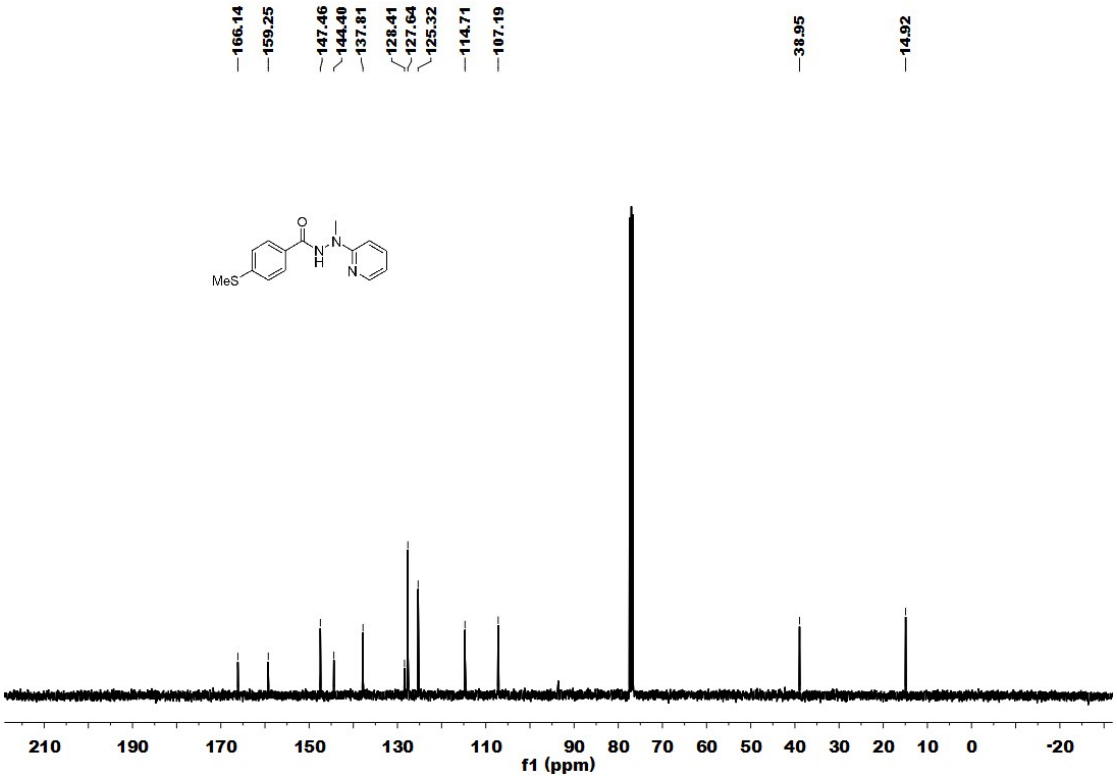


^{1}H, ^{13}C NMR spectra of compound 1j

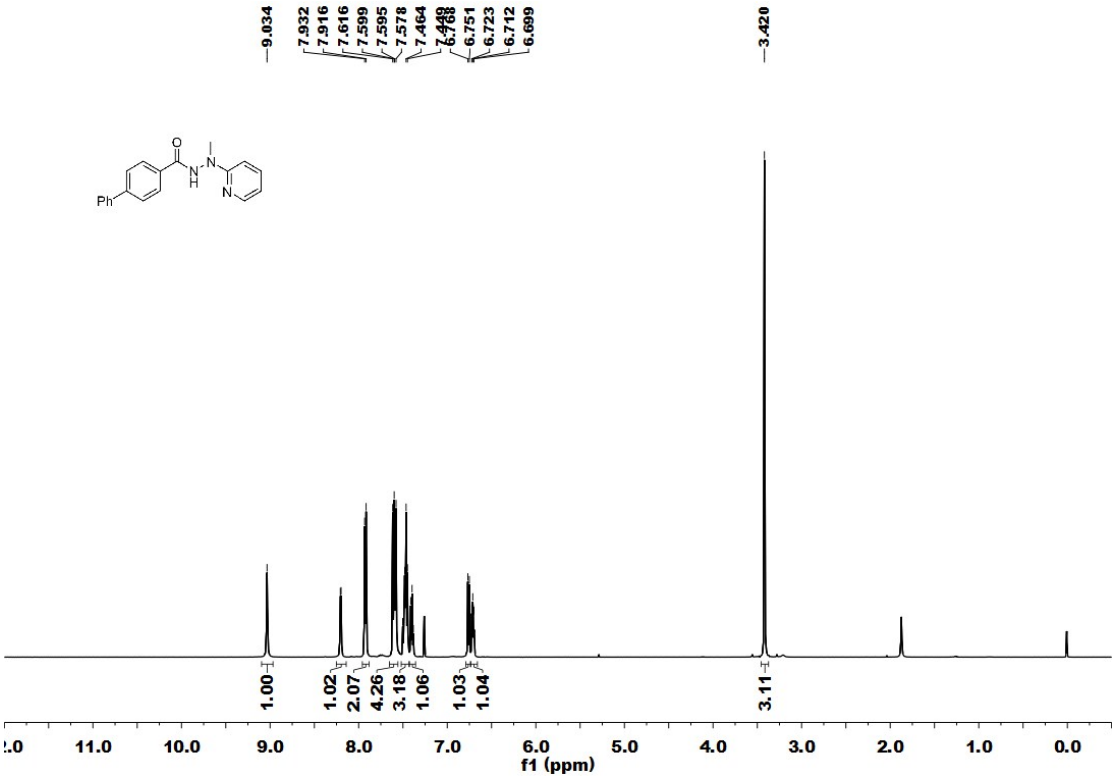


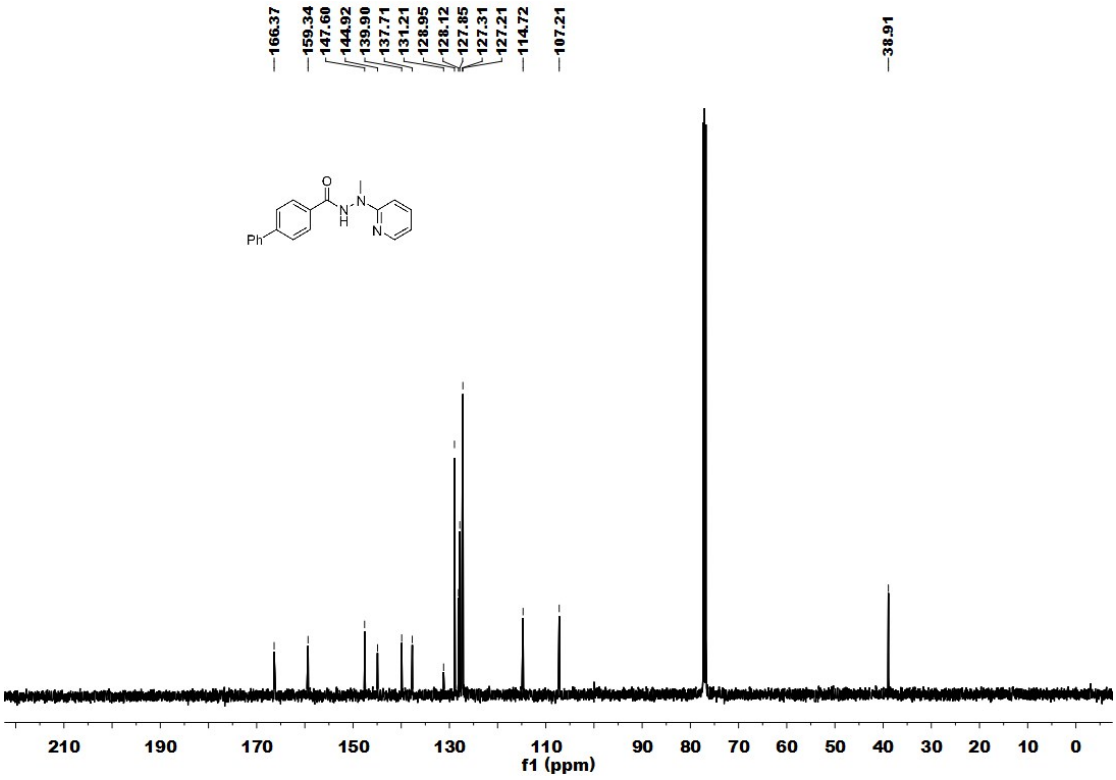
^{1}H, ^{13}C NMR spectra of compound 1l


8.967
8.191
8.181
8.179
7.770
7.749
7.491
7.213
6.731
6.718
6.701
3.392
2.499
MeS
1.00
1.06
2.15
1.08
2.24
0.82
1.27
3.12
3.38
f1 (ppm)

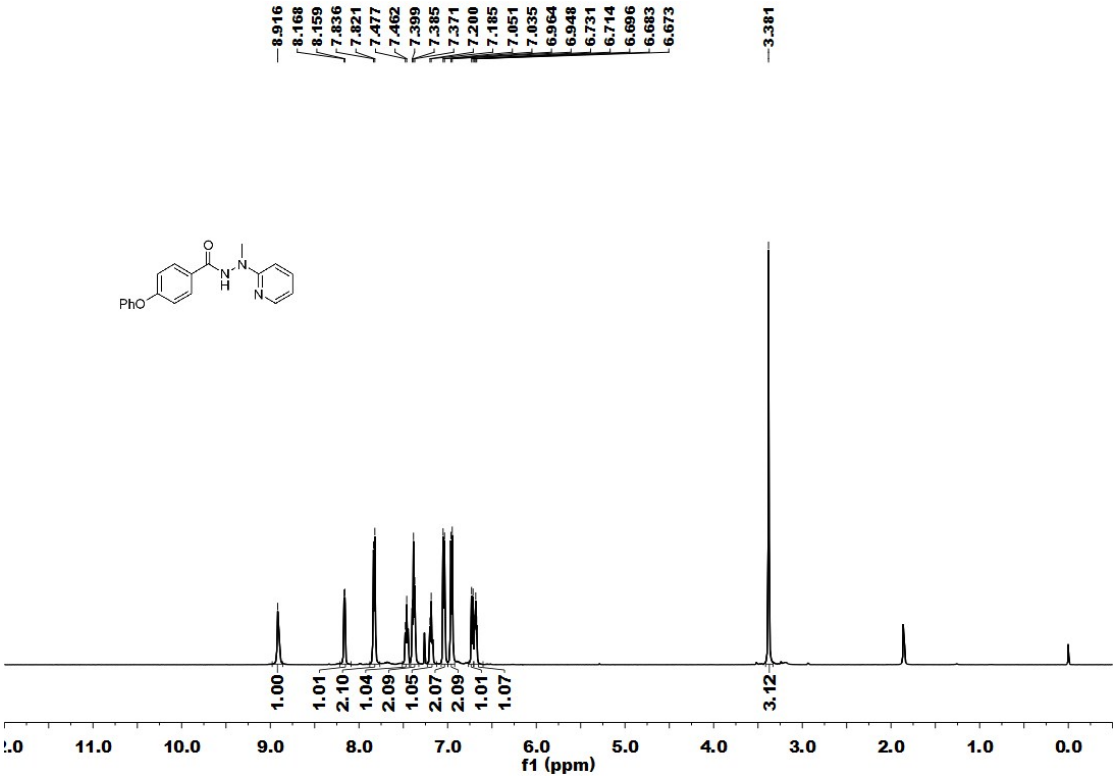

166.14
159.25
147.46
144.40
137.81
128.41
127.64
125.32
114.71
107.19
38.95
14.92
MeS
f1 (ppm)

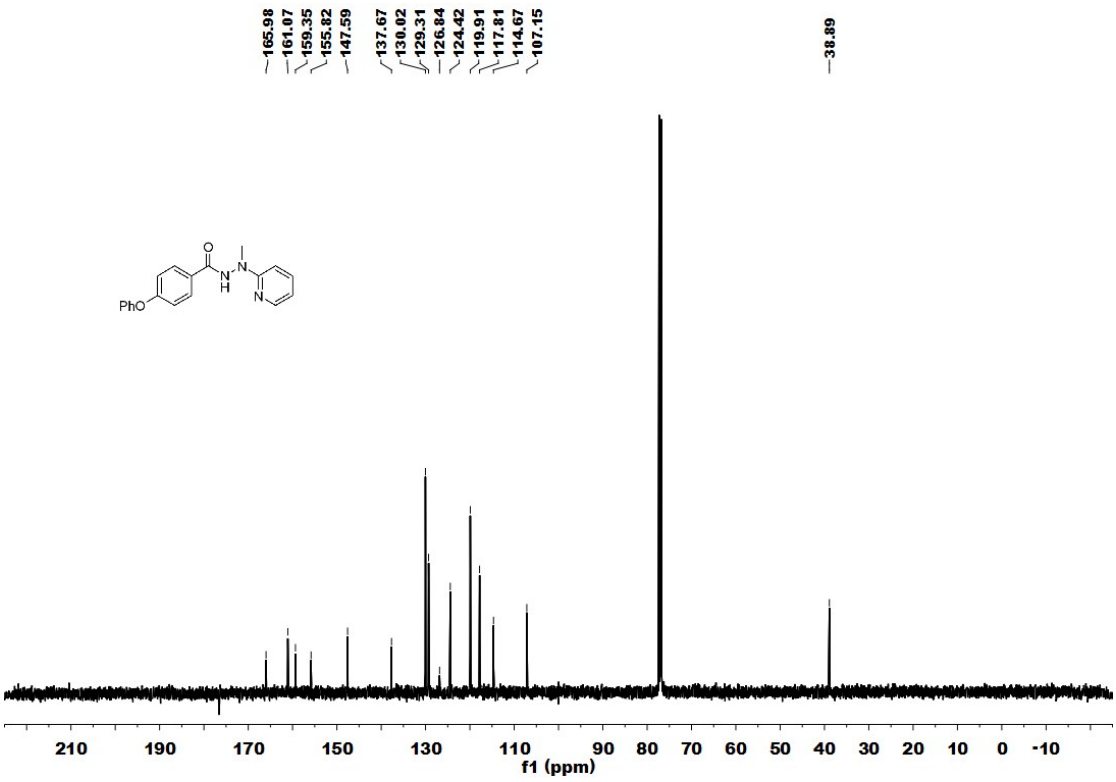
^{1}H, ^{13}C NMR spectra of compound 1m



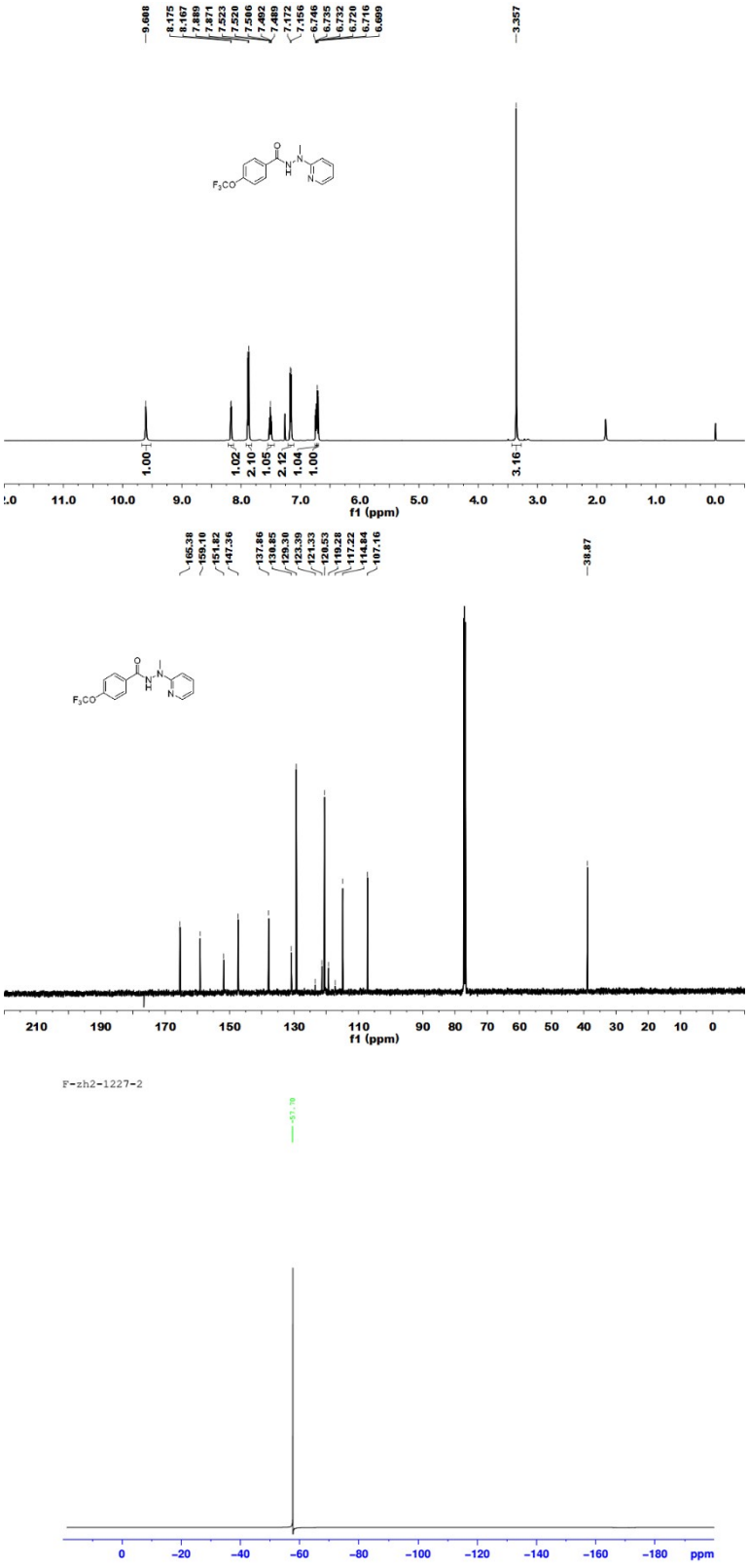


^{1}H, ^{13}C NMR spectra of compound 1n

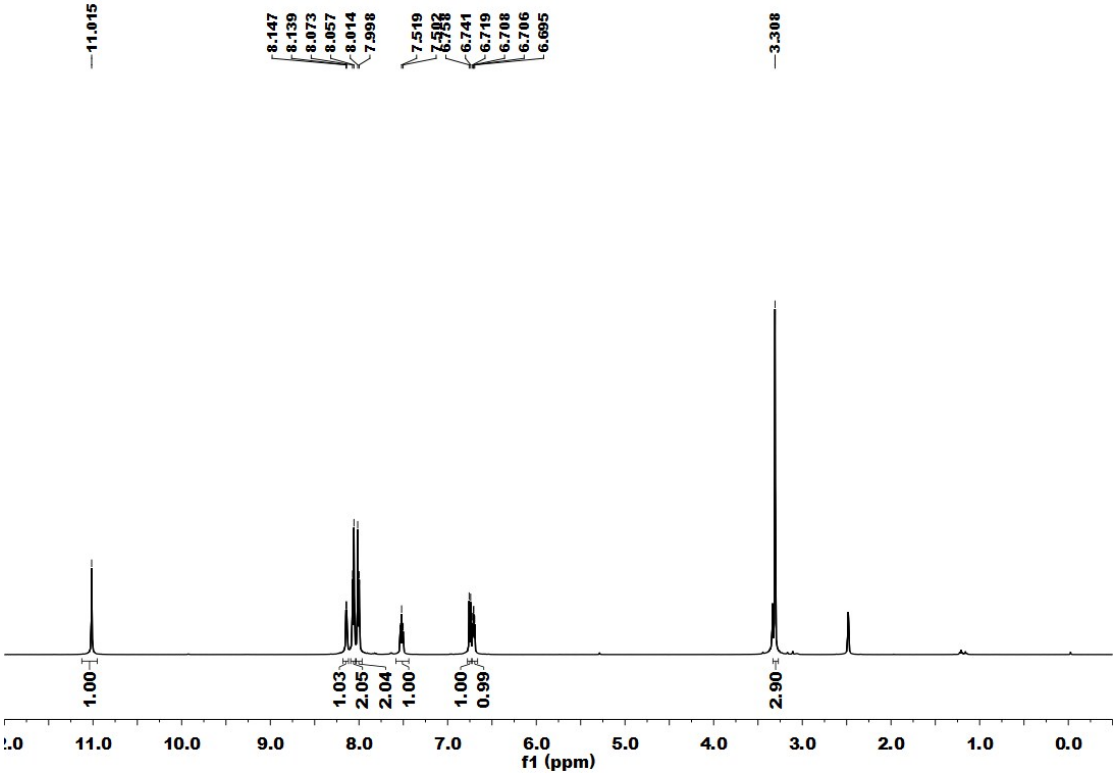


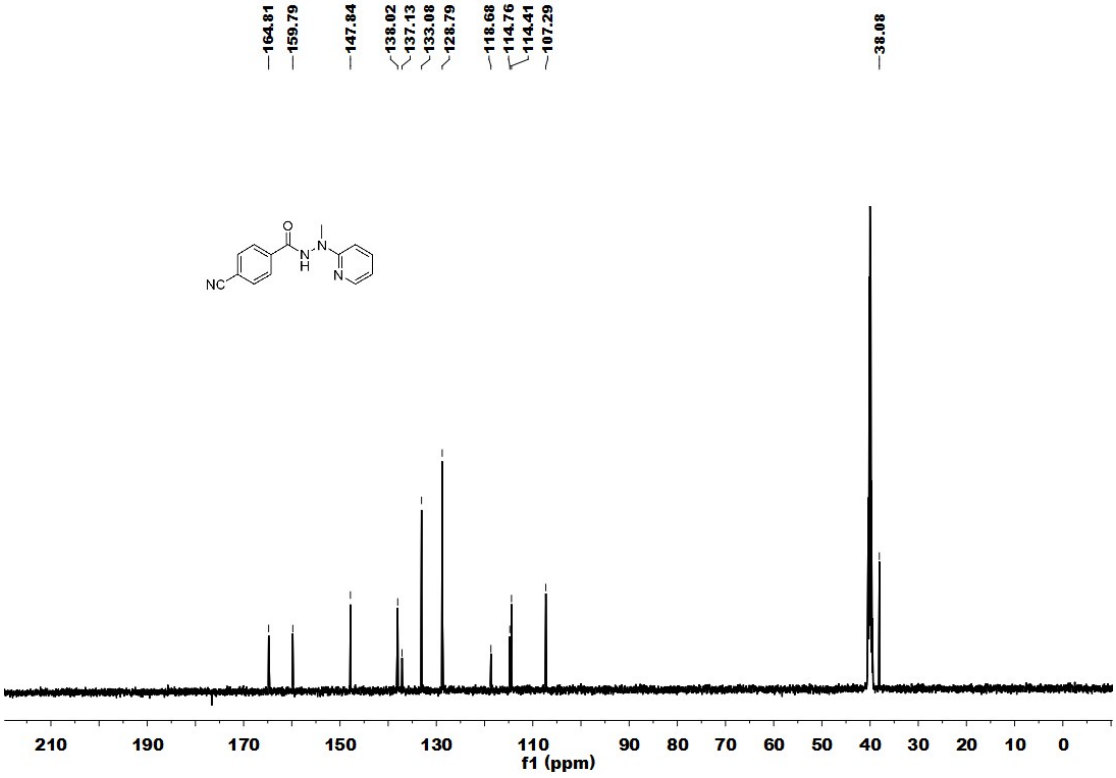


^{1}H, ^{13}C, ^{19}F NMR spectra of compound 1s

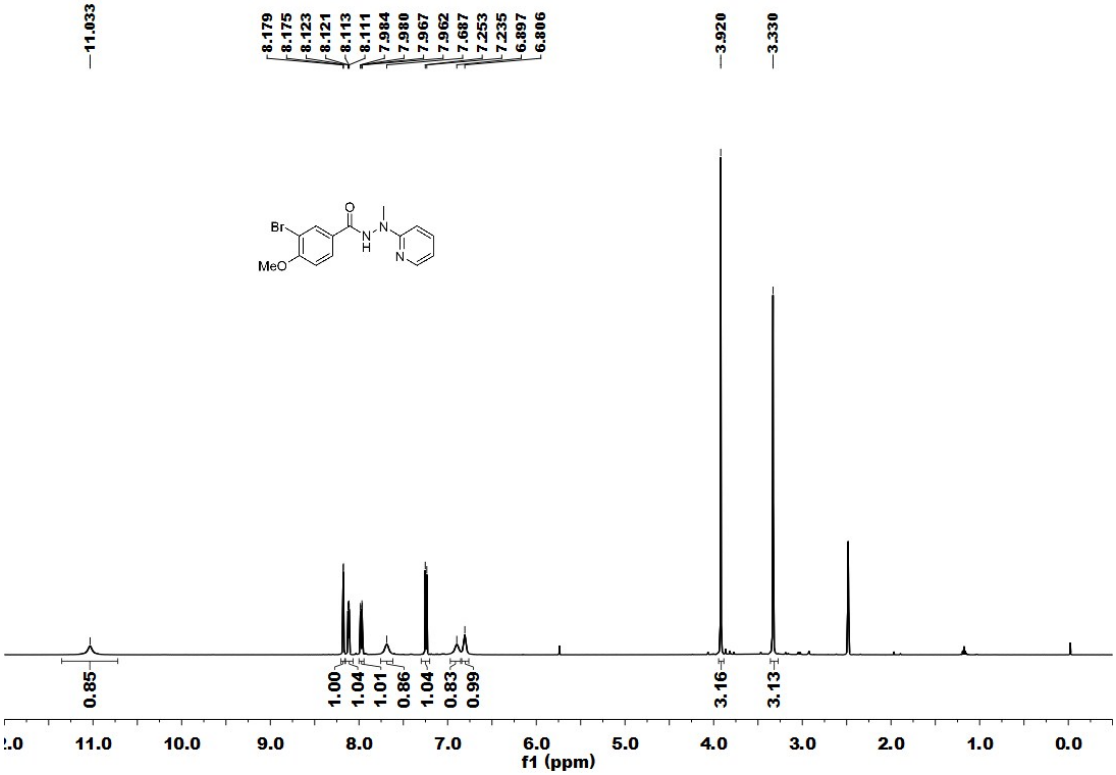


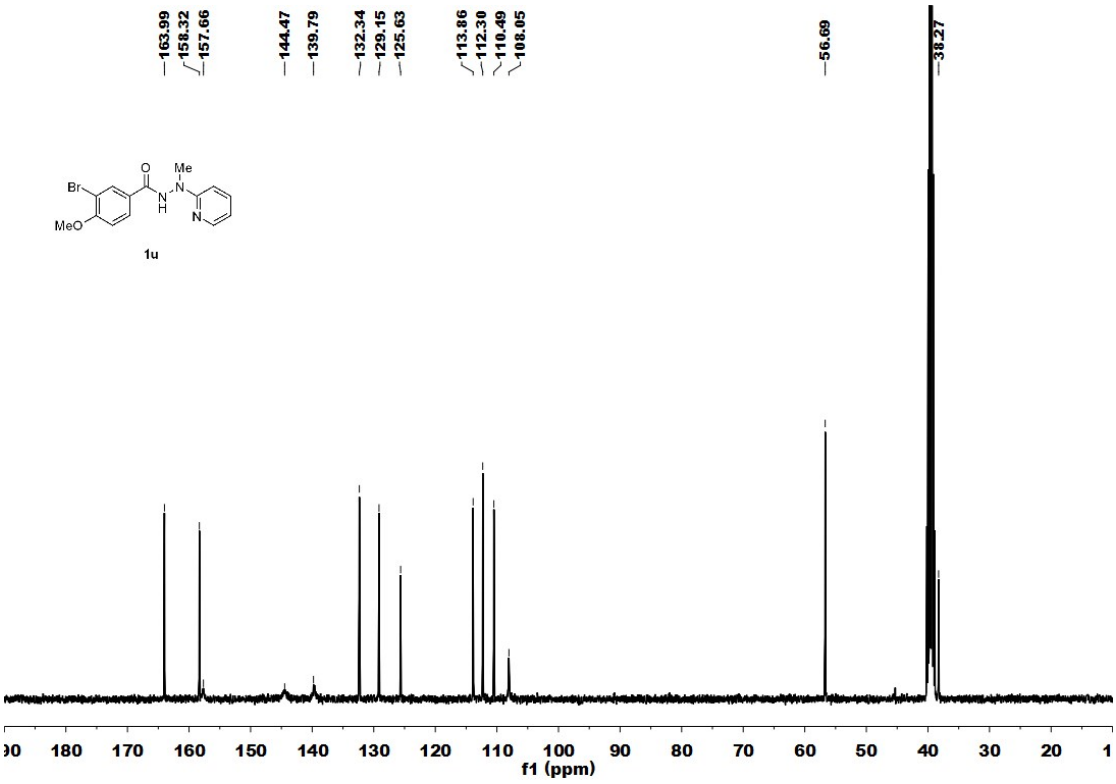
^{1}H, ^{13}C NMR spectra of compound 1t



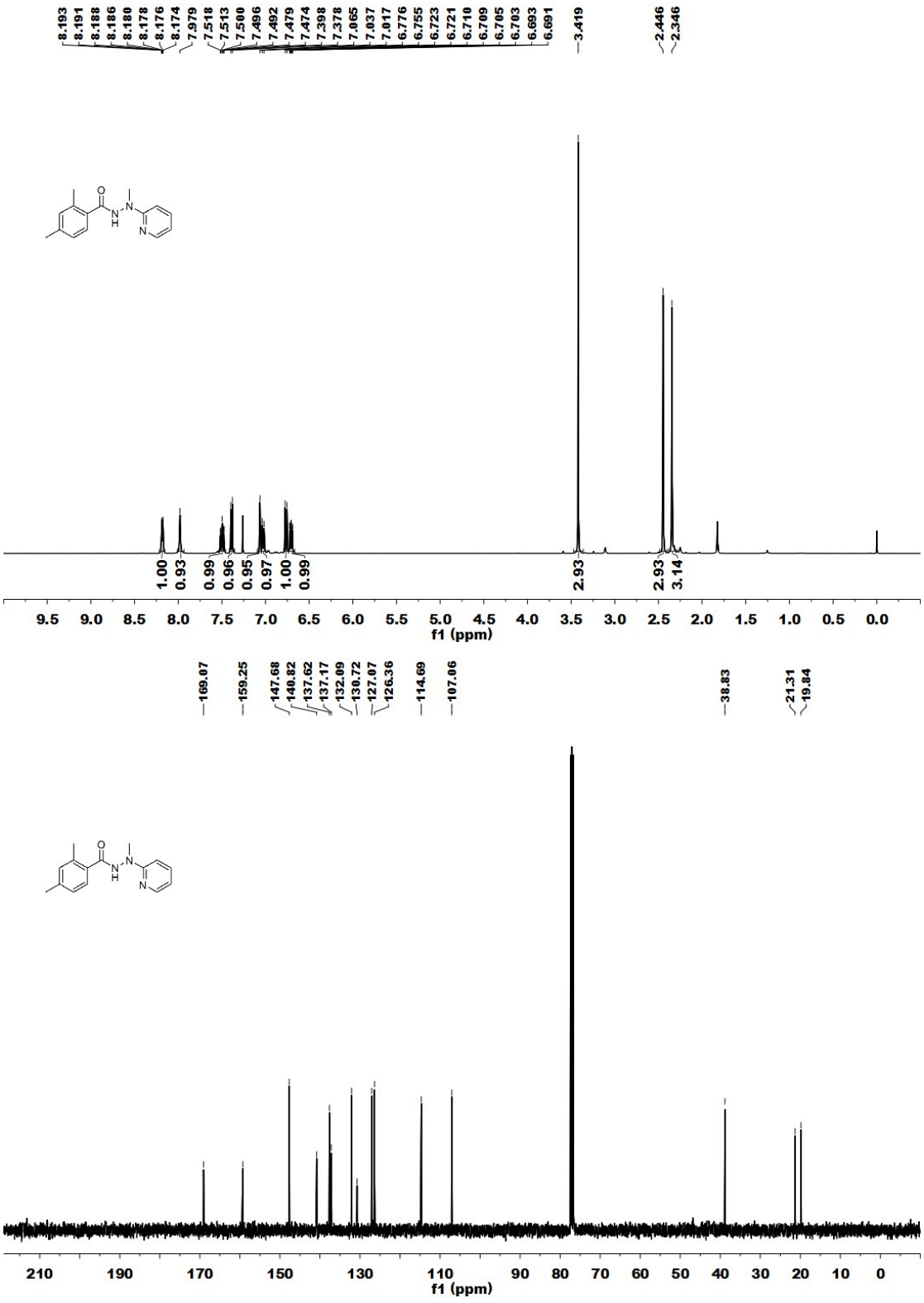


^{1}H, ^{13}C NMR spectra of compound 1u

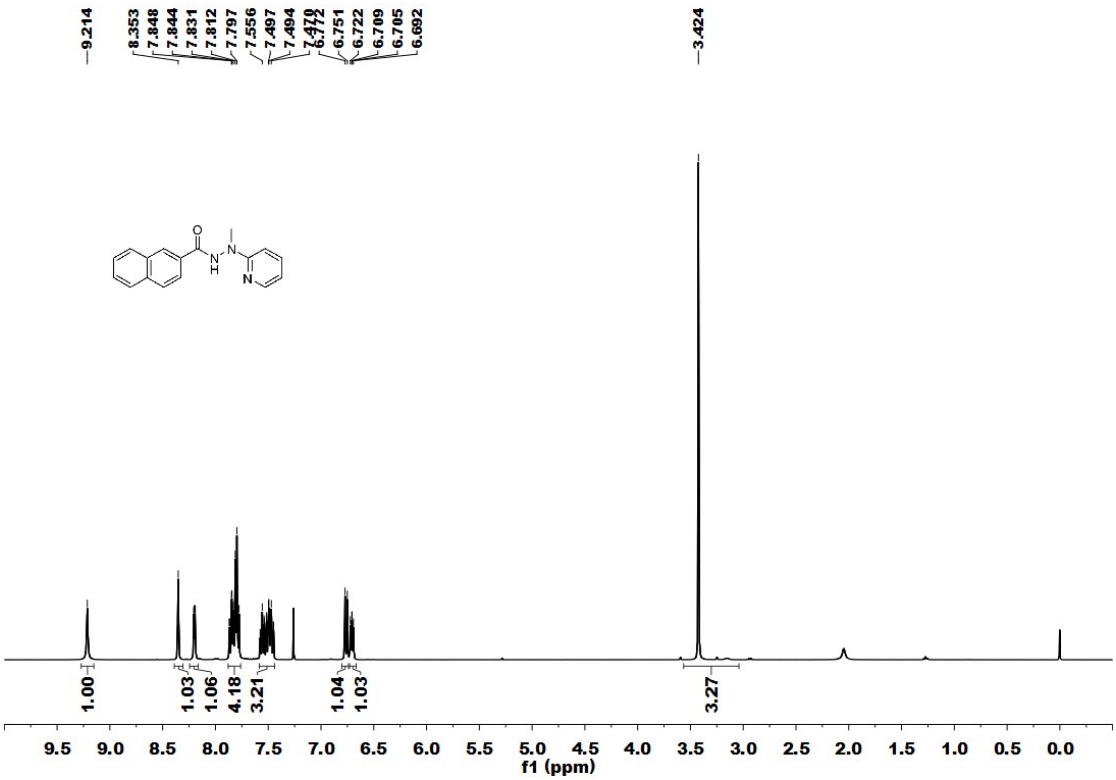


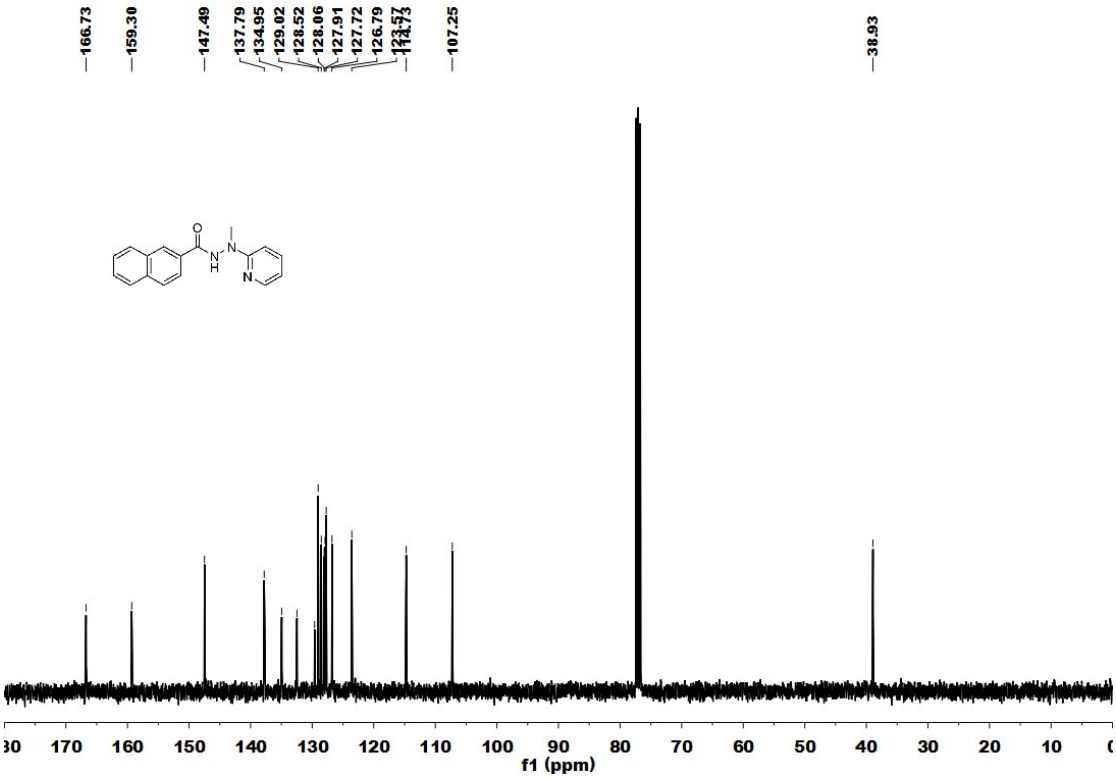


^{1}H, ^{13}C NMR spectra of compound 1v

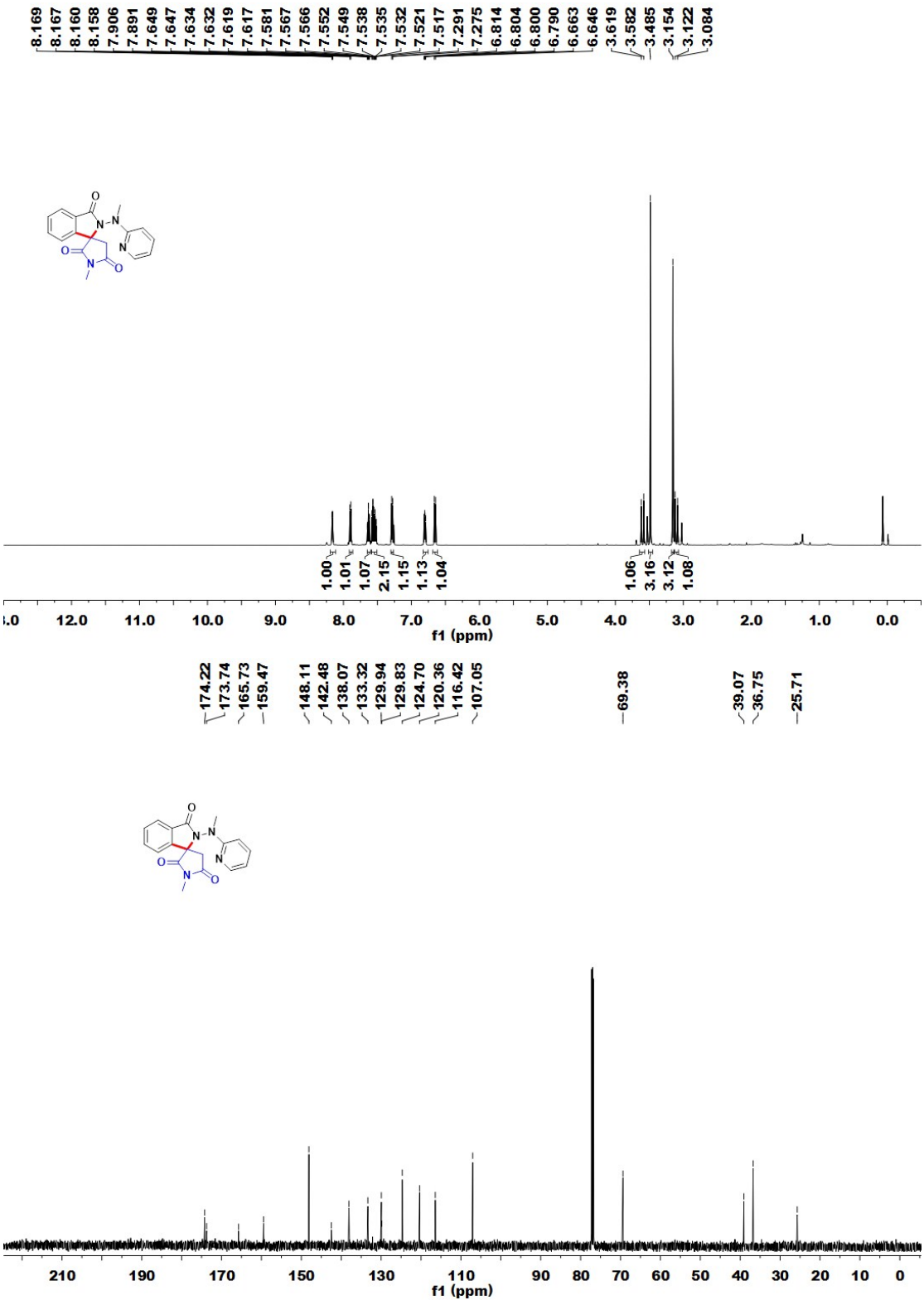


^{1}H, ^{13}C NMR spectra of compound 1w

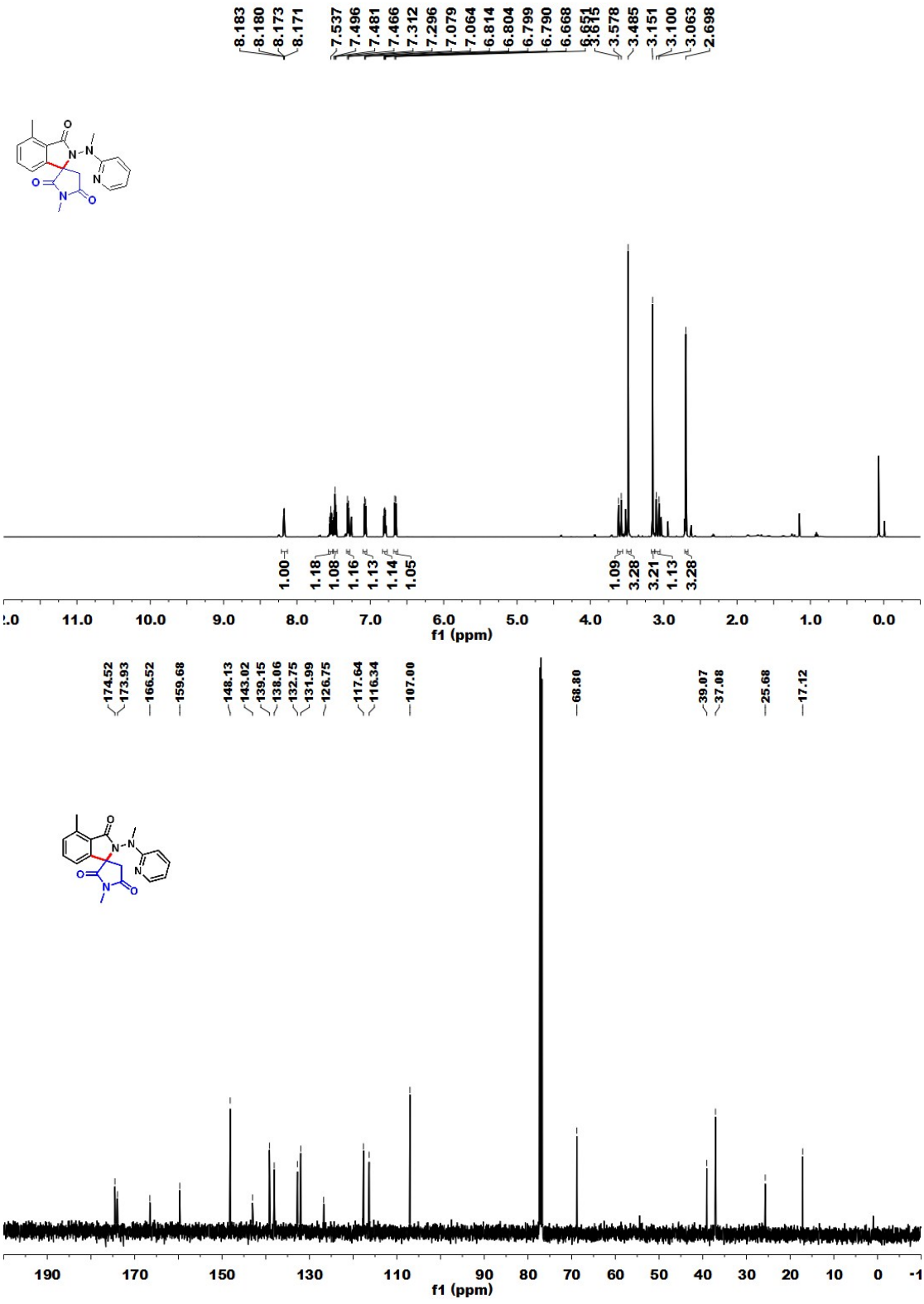




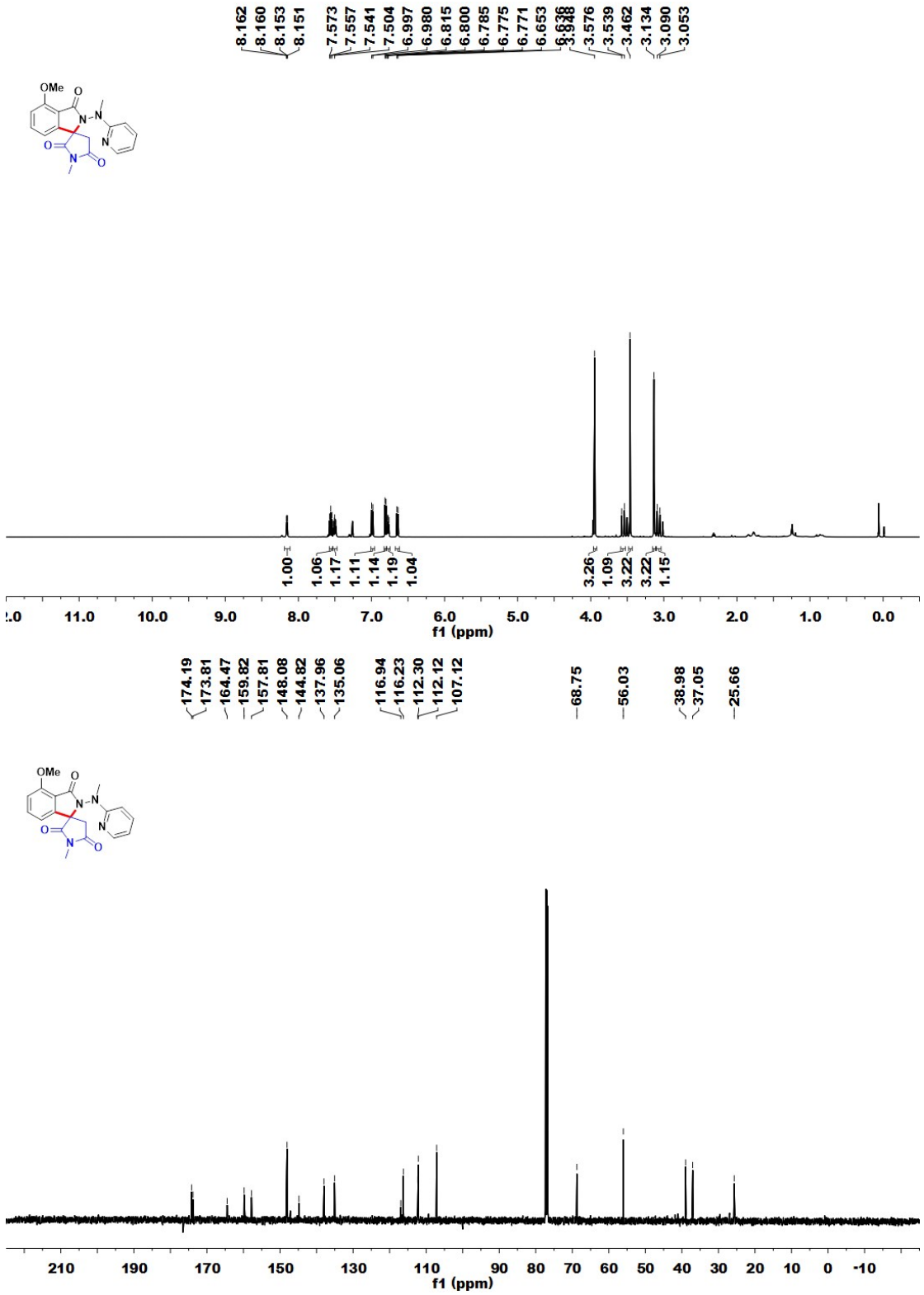
^{1}H, ^{13}C NMR spectra of compound 3aa



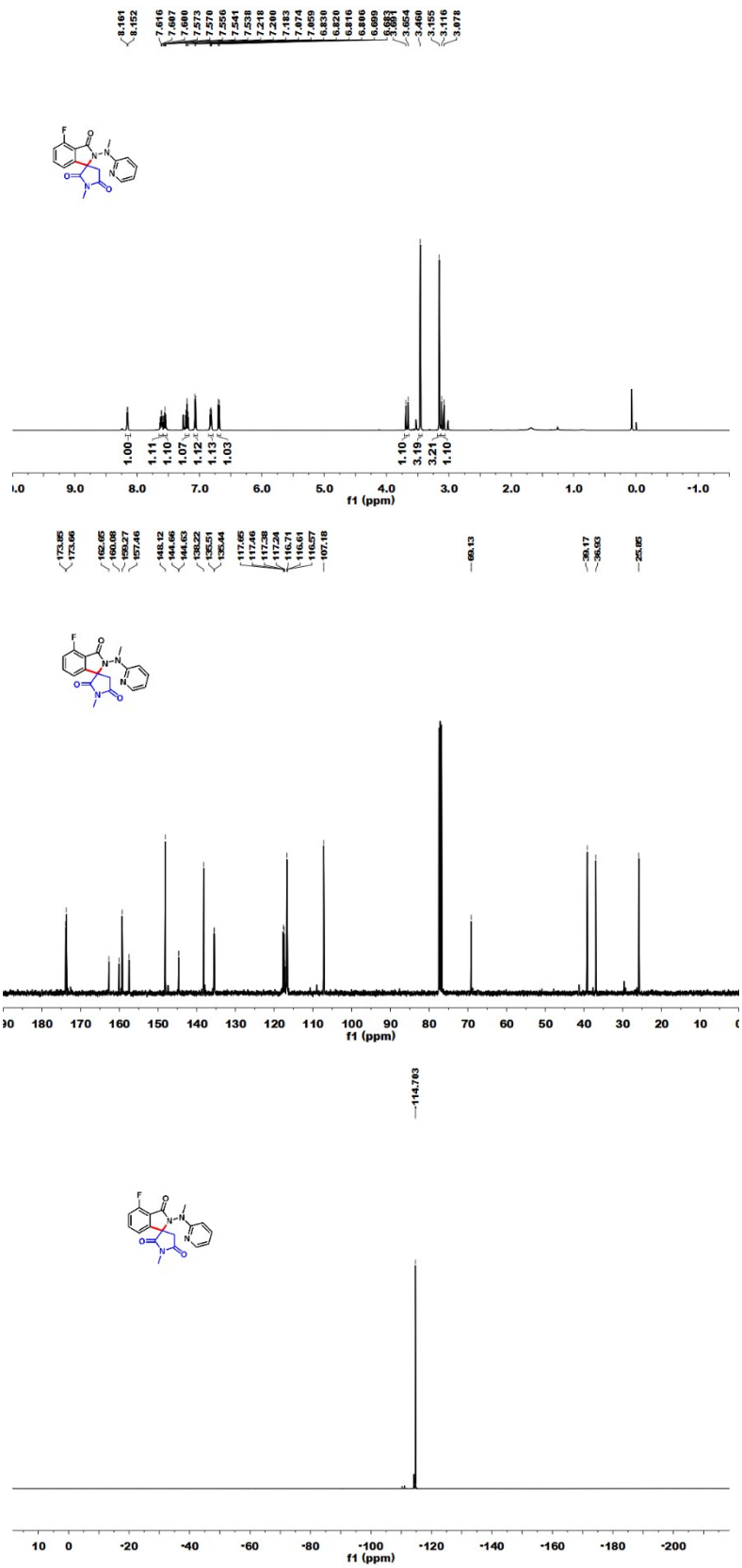
^{1}H, ^{13}C NMR spectra of compound 3ba



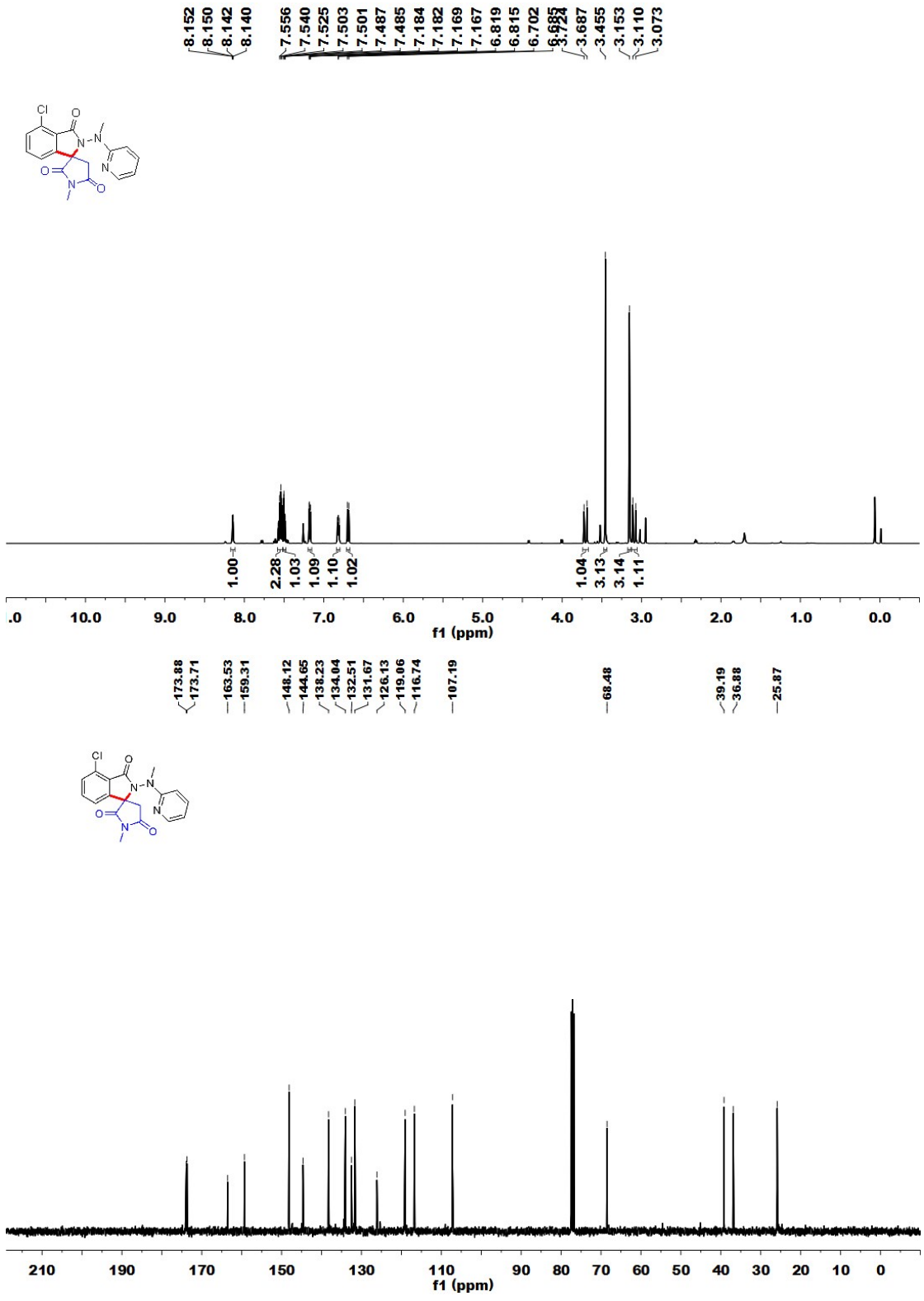
^{1}H, ^{13}C NMR spectra of compound 3ca



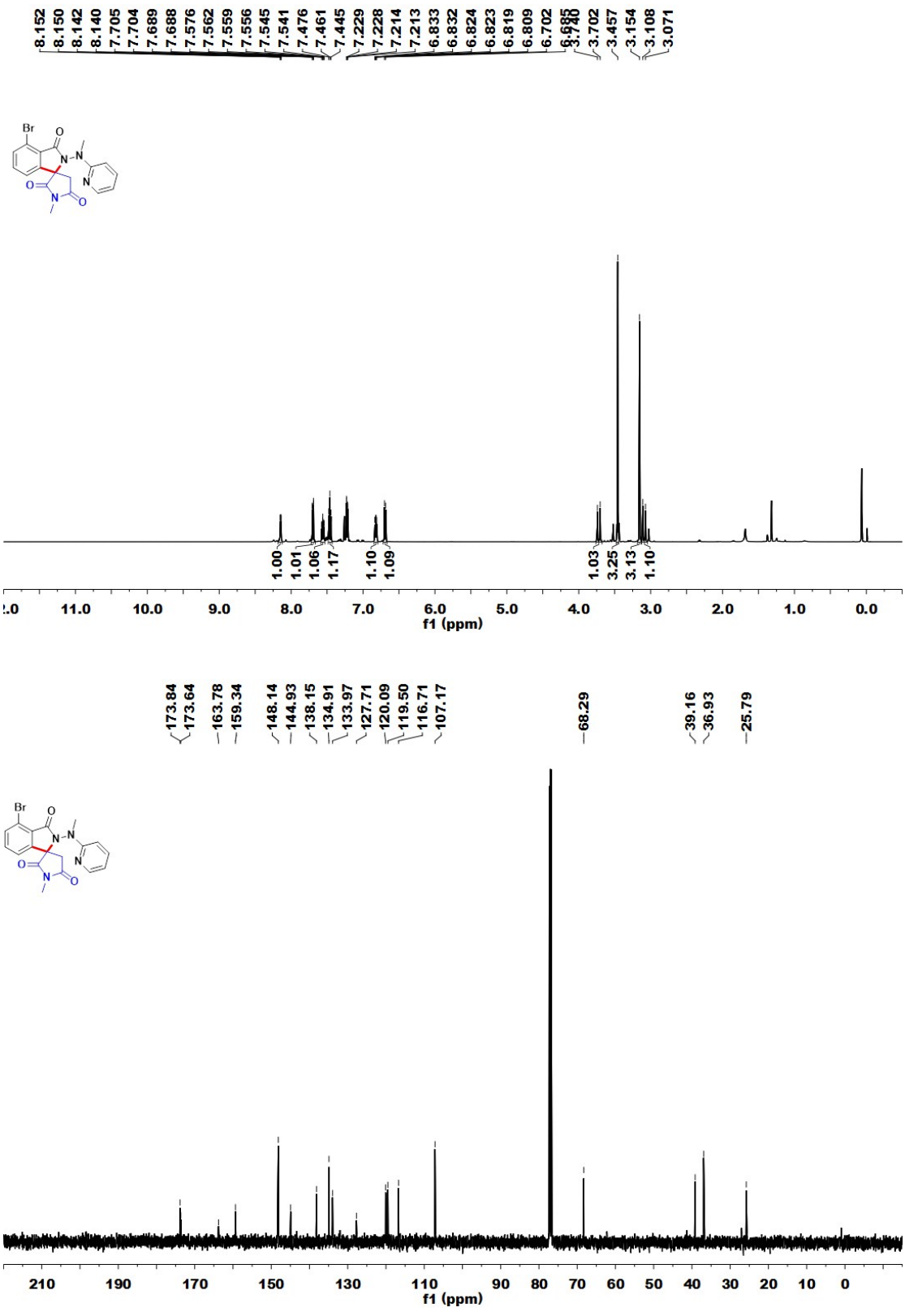
^{1}H, ^{13}C , ^{19}F NMR spectra of compound 3da



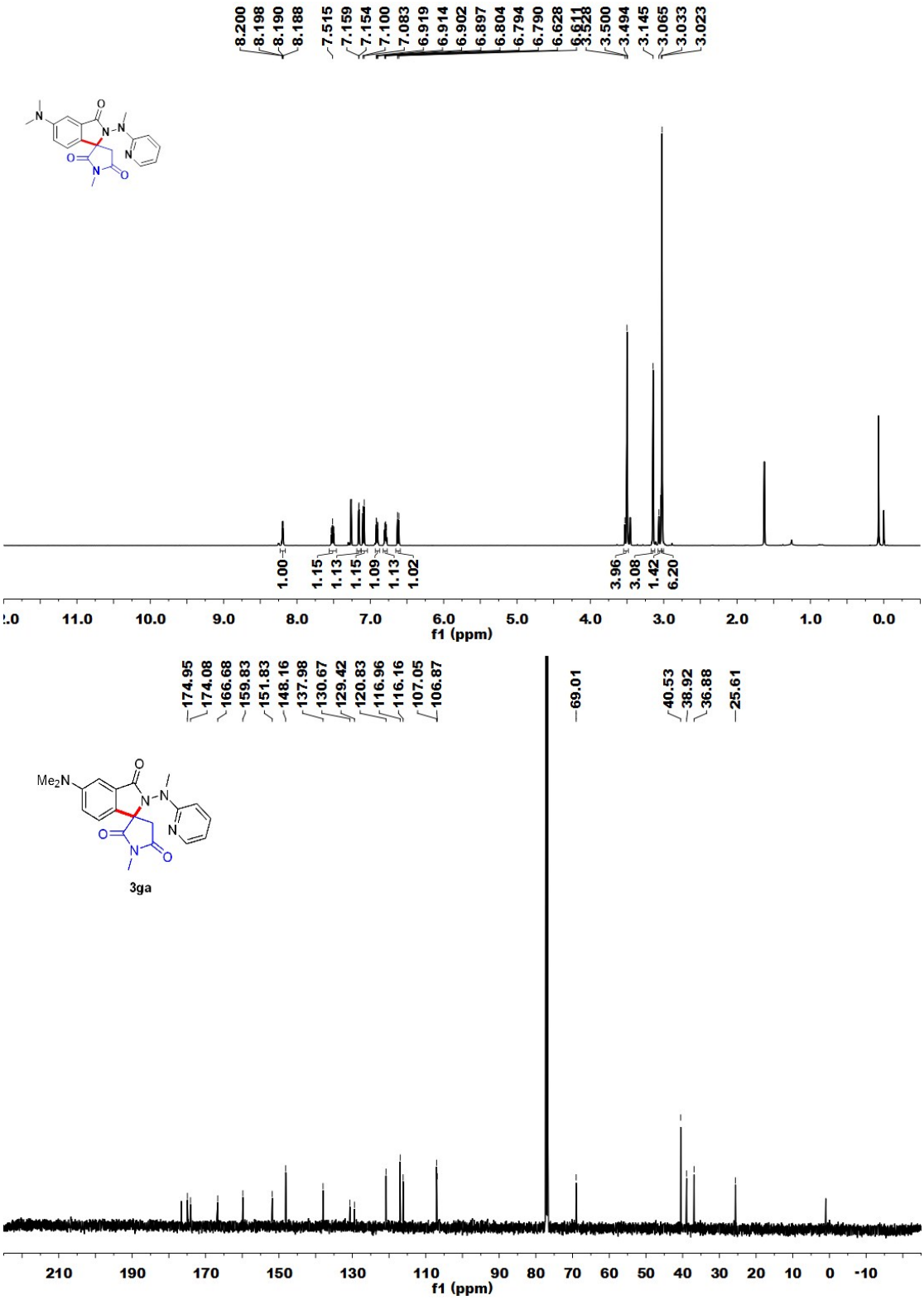
^{1}H, ^{13}C NMR spectra of compound 3ea



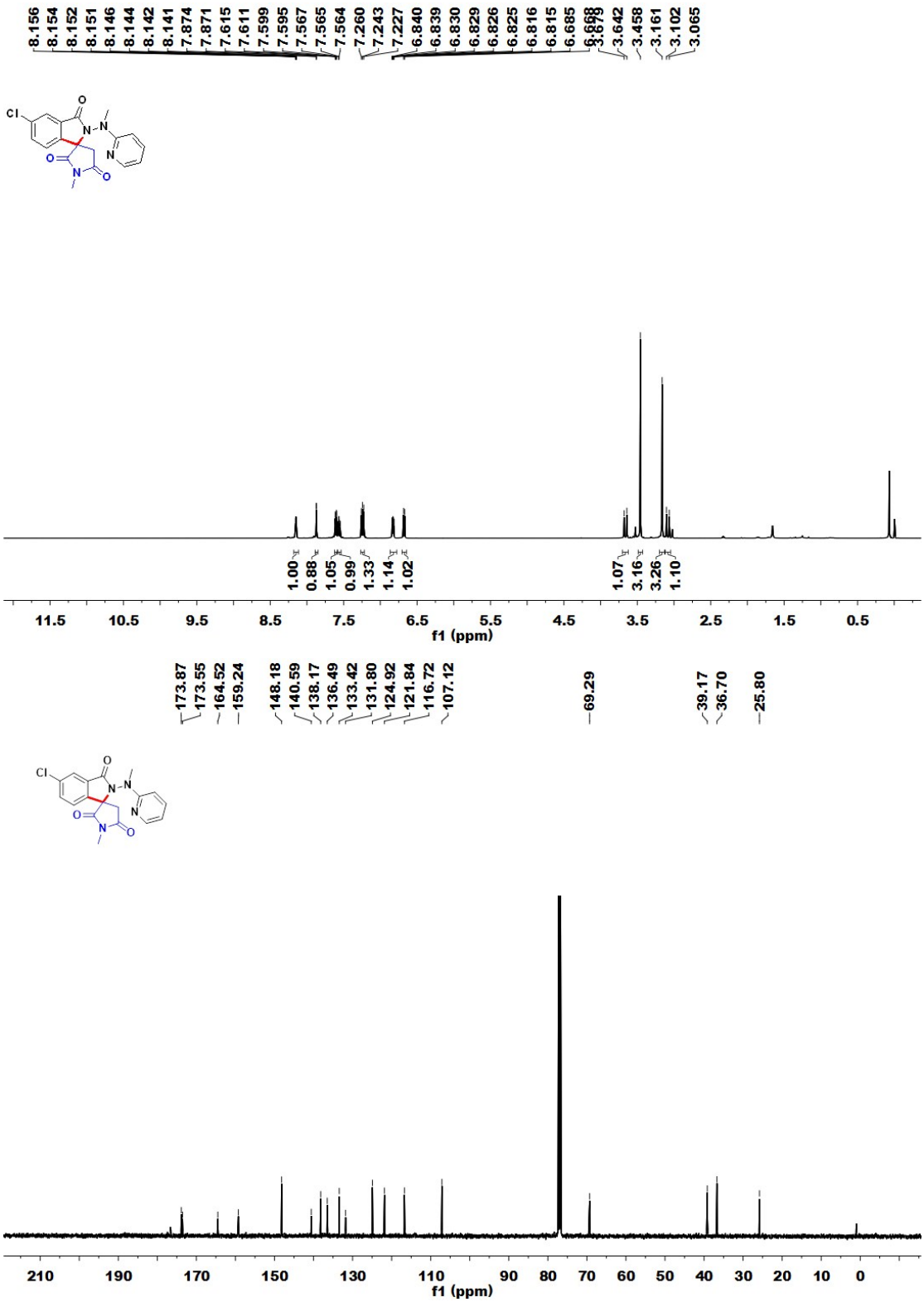
^{1}H, ^{13}C NMR spectra of compound 3fa



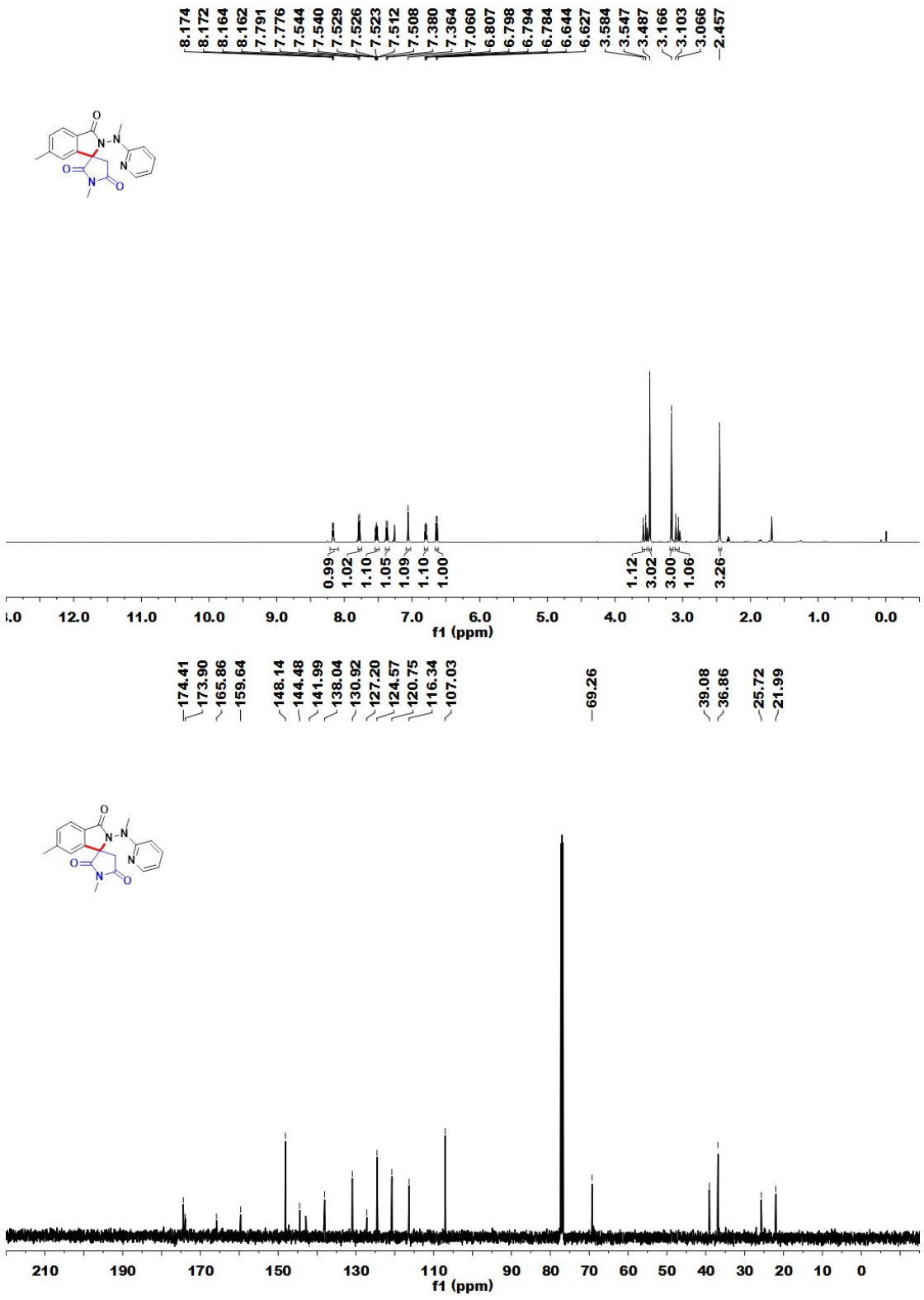
^{1}H, ^{13}C NMR spectra of compound 3ga



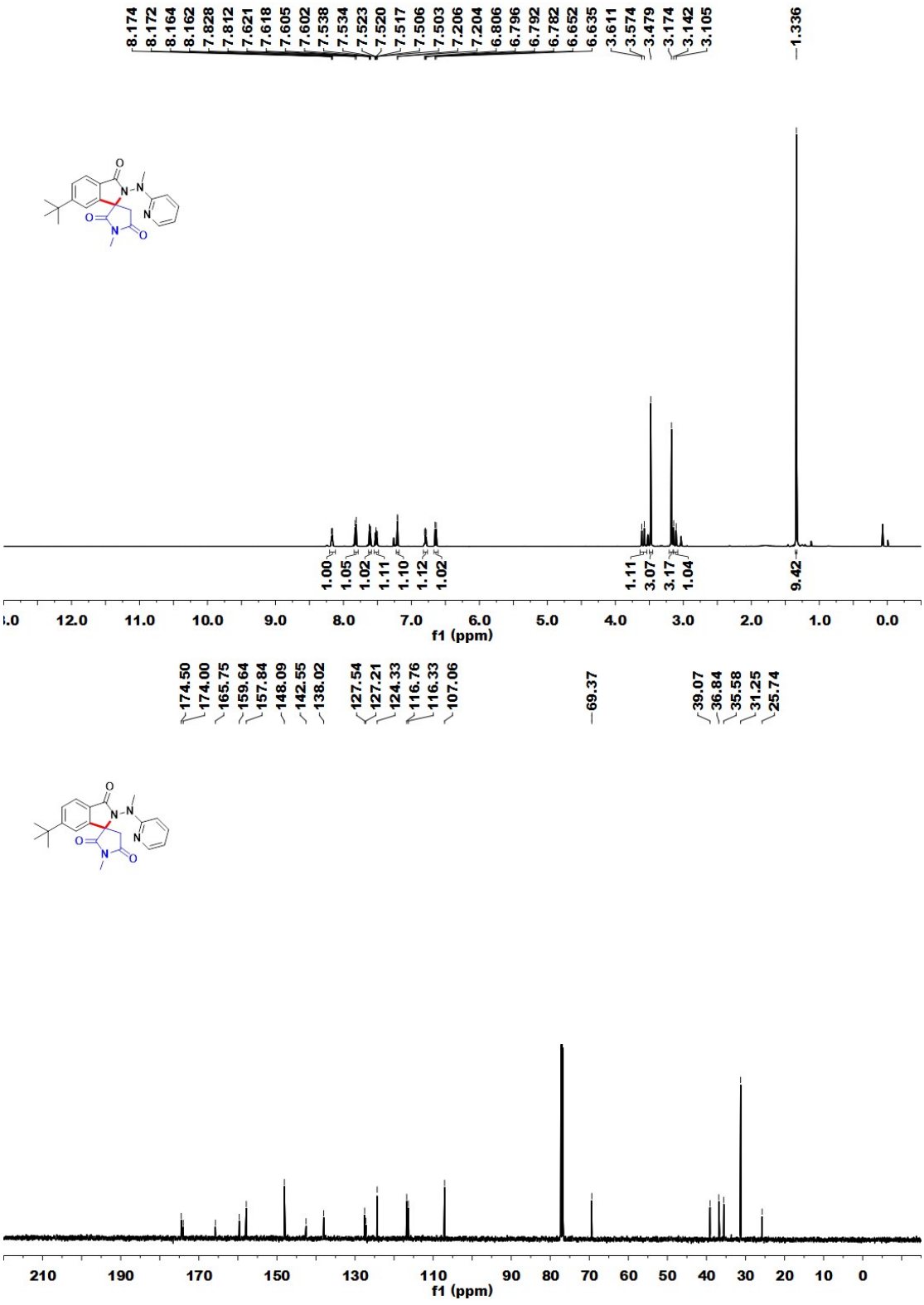
^{1}H, ^{13}C NMR spectra of compound 3ha



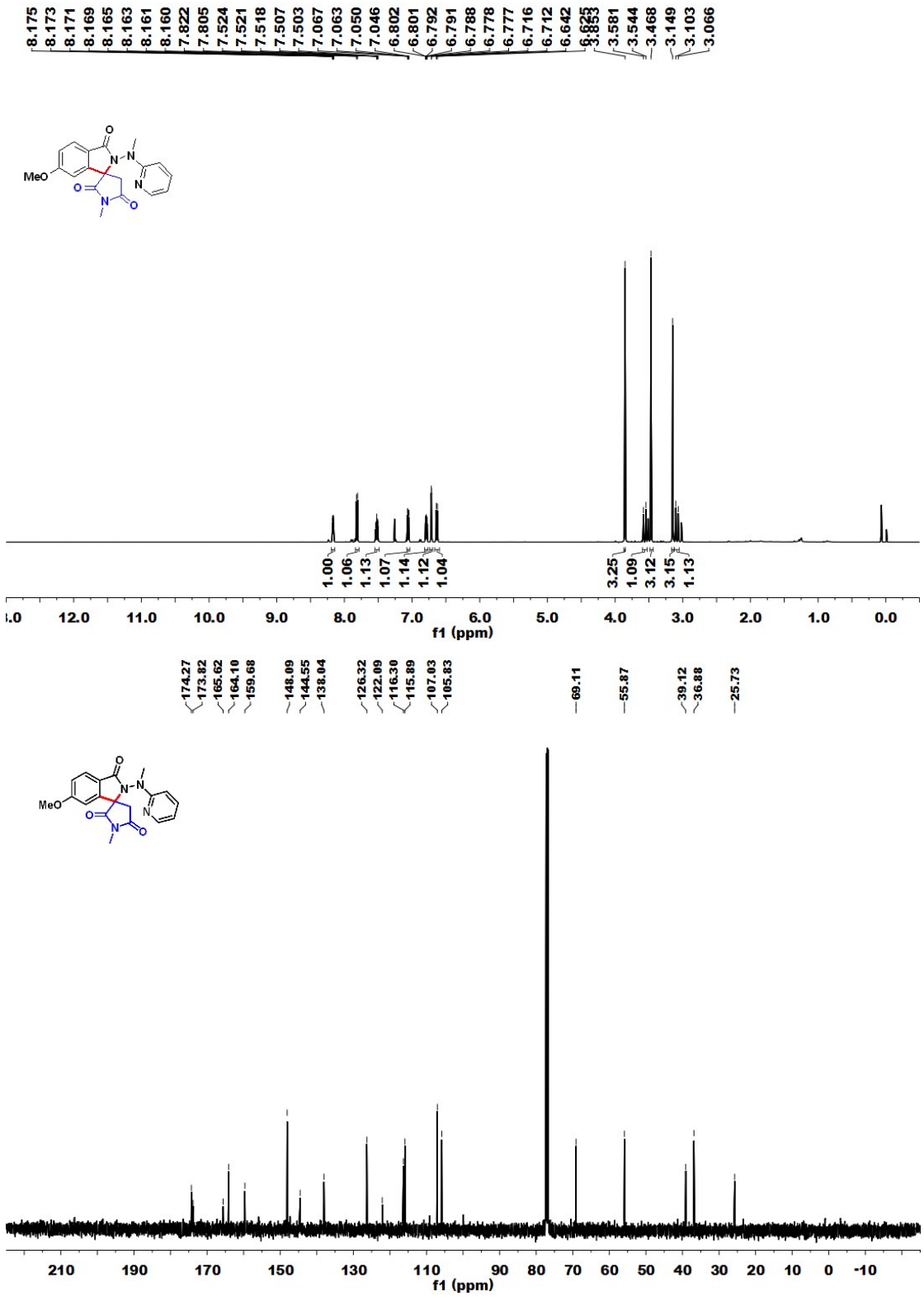
^{1}H, ^{13}C NMR spectra of compound 3ia



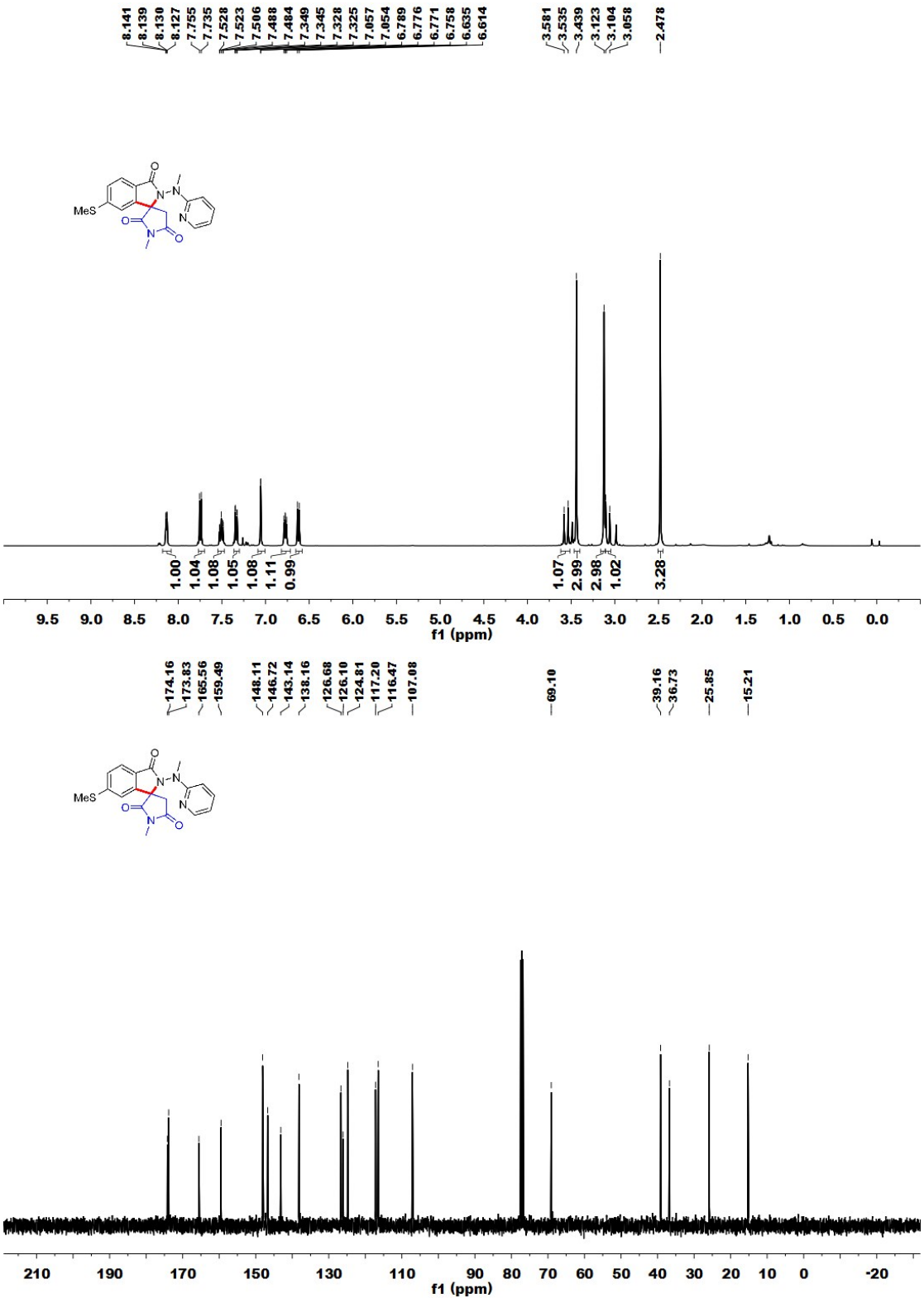
^{1}H, ^{13}C NMR spectra of compound 3ja



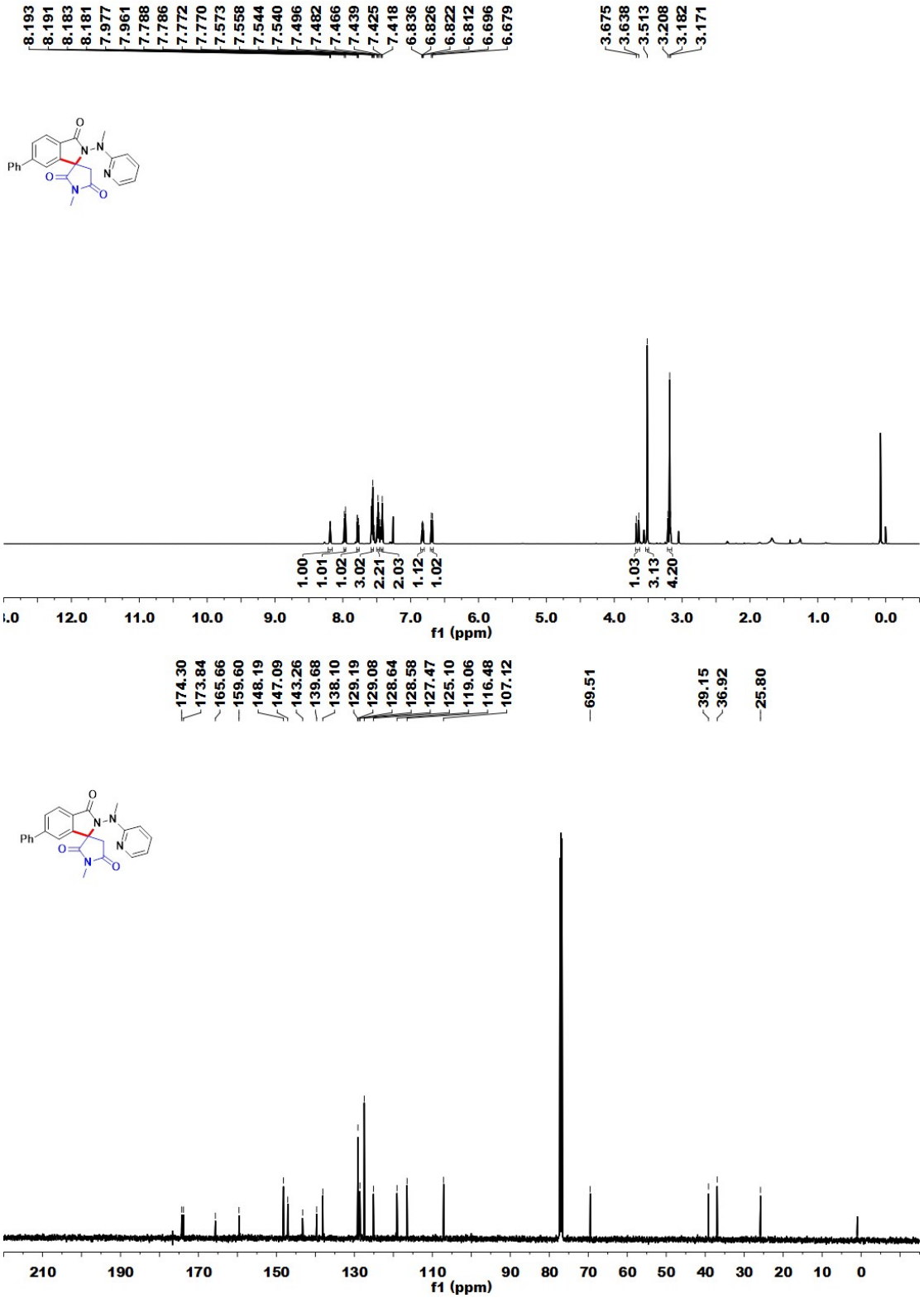
^{1}H, ^{13}C NMR spectra of compound 3ka



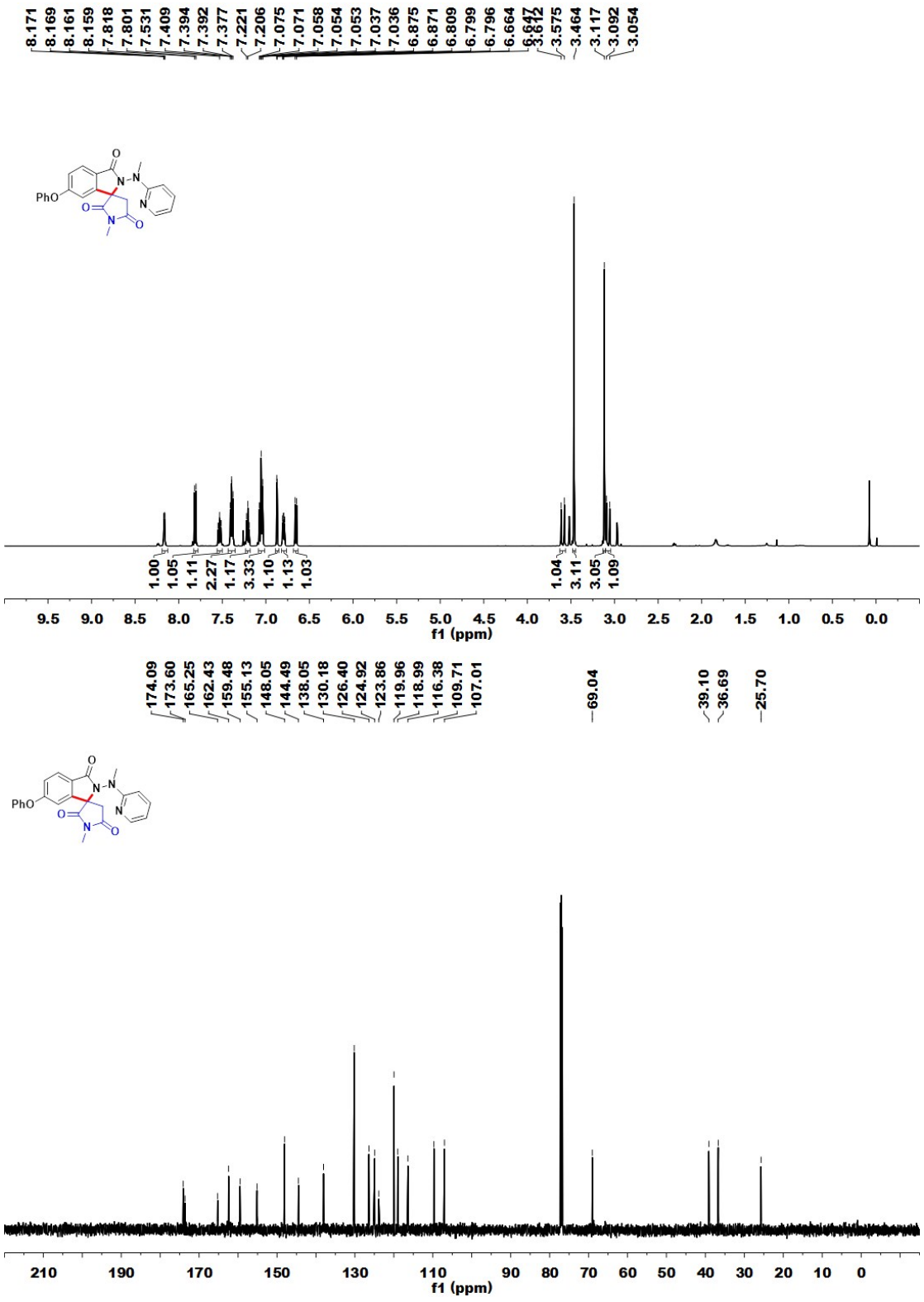
^{1}H, ^{13}C NMR spectra of compound 3la



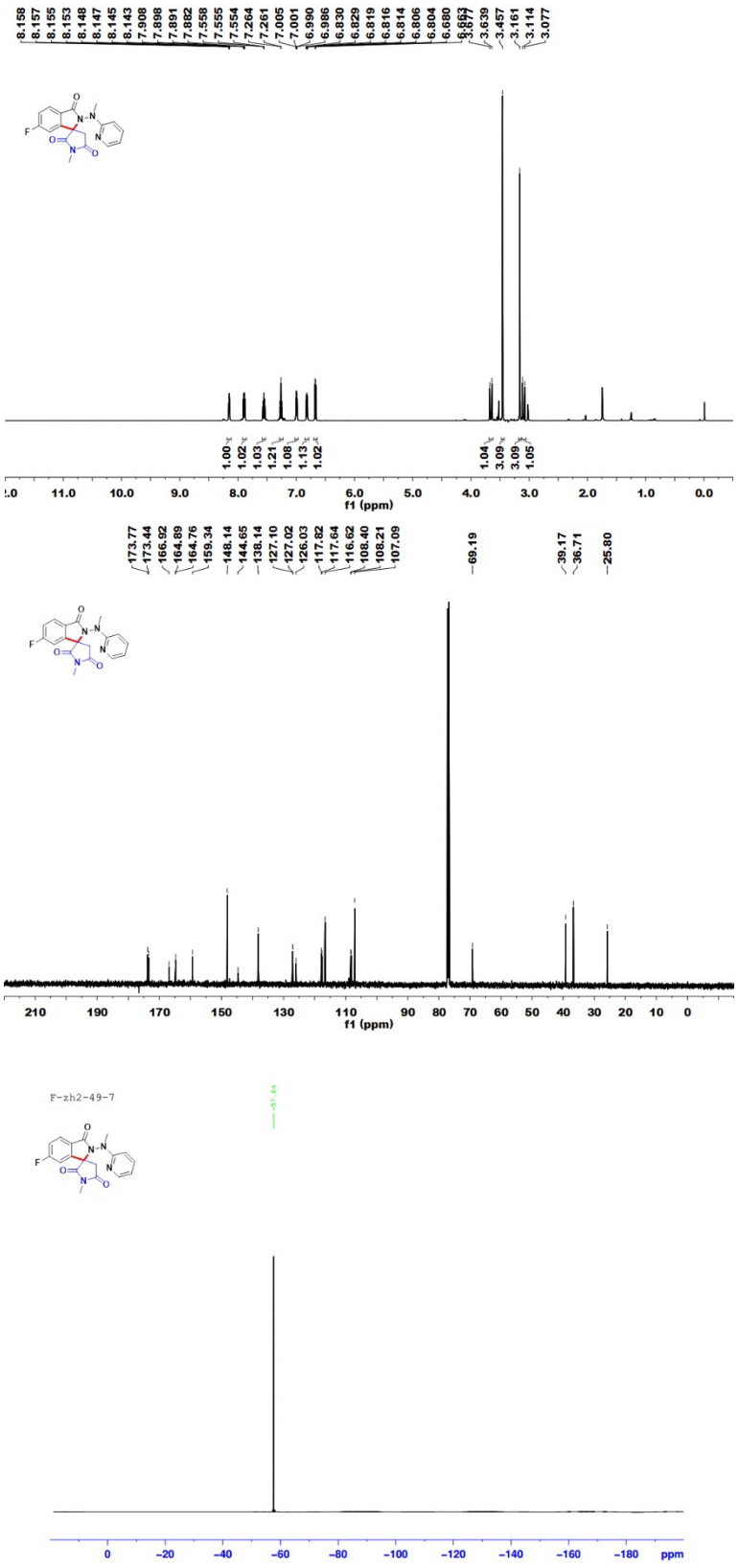
^{1}H, ^{13}C NMR spectra of compound 3ma



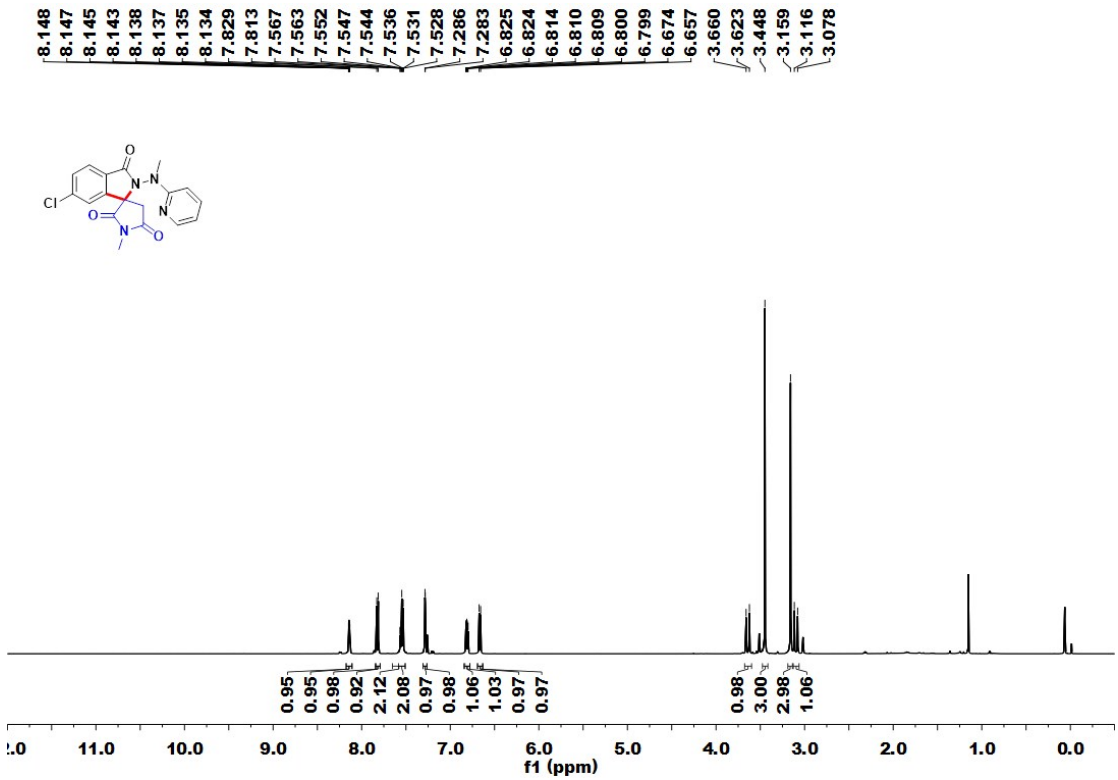
^{1}H, ^{13}C NMR spectra of compound 3na

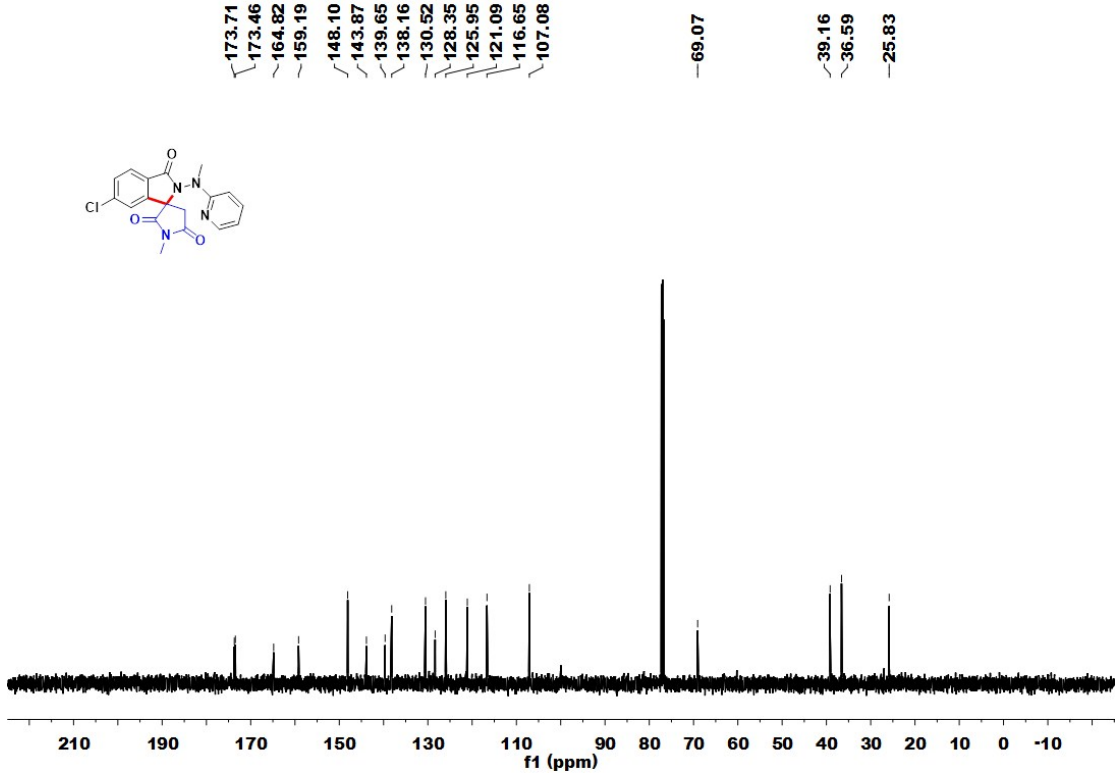


^{1}H, ^{13}C, ^{19}FNMR spectra of compound 3oa

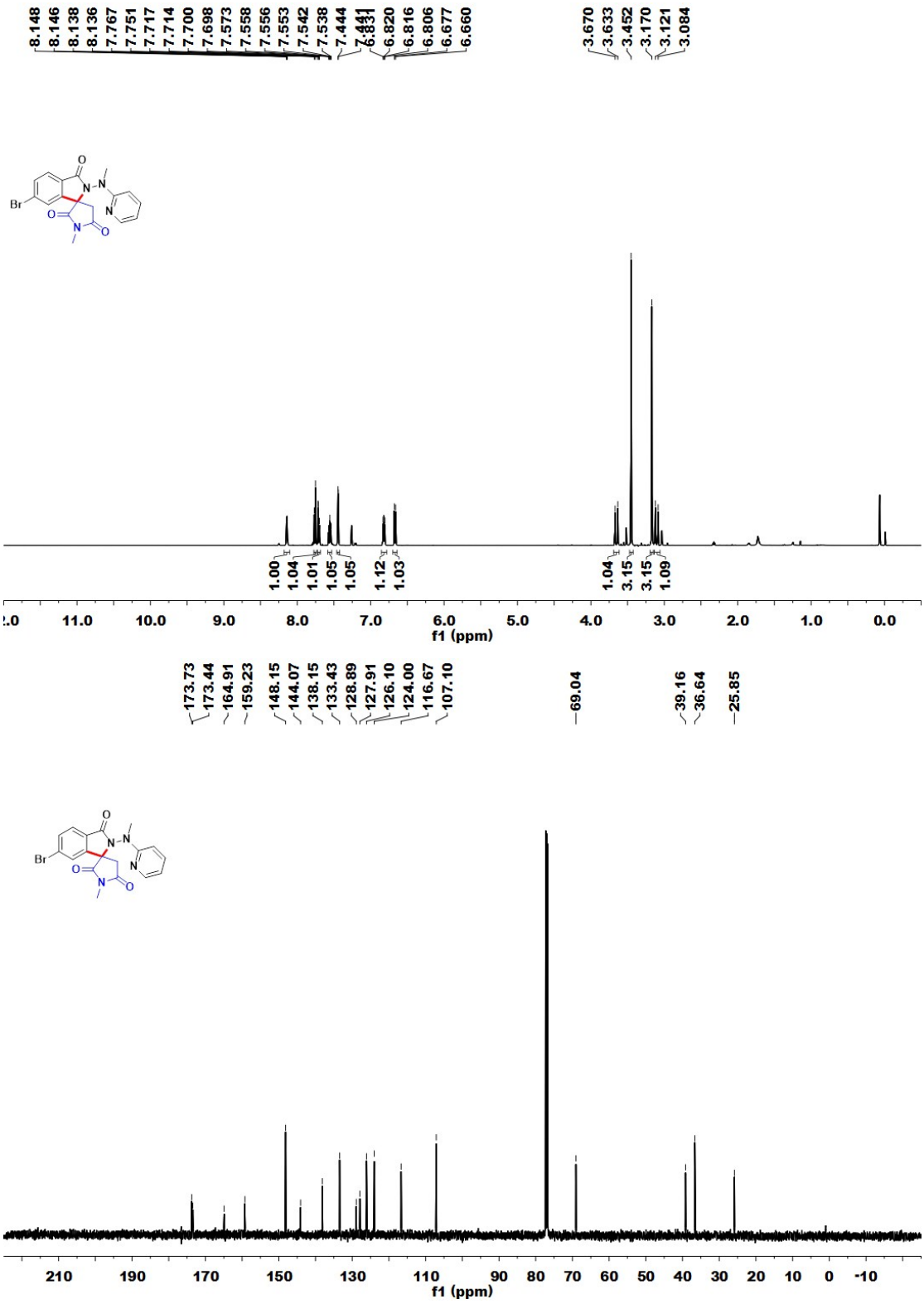


^{1}H, ^{13}C NMR spectra of compound 3pa

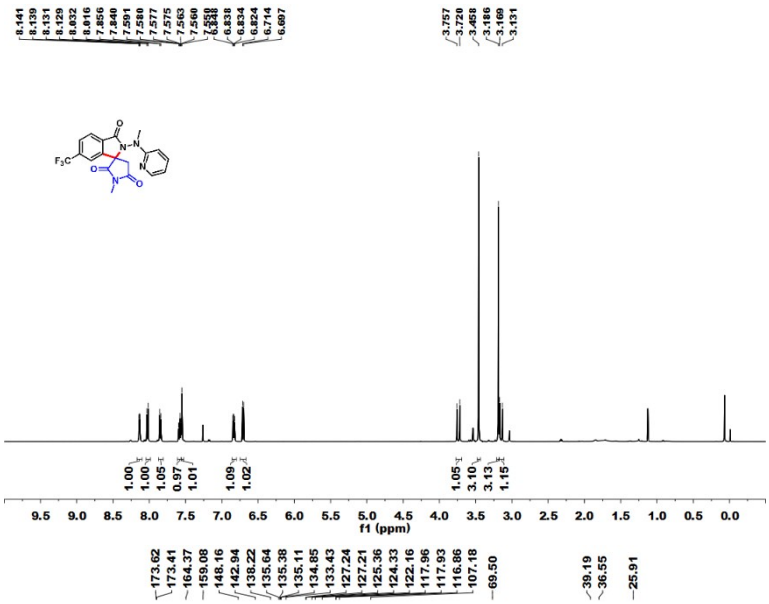

8.148
8.147
8.145
8.143
8.138
8.137
8.135
8.134
7.829
7.813
7.567
7.563
7.552
7.547
7.544
7.536
7.531
7.528
7.286
7.283
6.825
6.824
6.814
6.810
6.809
6.800
6.799
6.674
6.657
3.660
3.623
3.448
3.159
3.116
3.078
Cl
0.95
0.95
0.98
0.92
2.12
2.08
0.97
0.98
1.06
1.03
0.97
0.97
0.98
3.00
2.98
1.06
f1 (ppm)

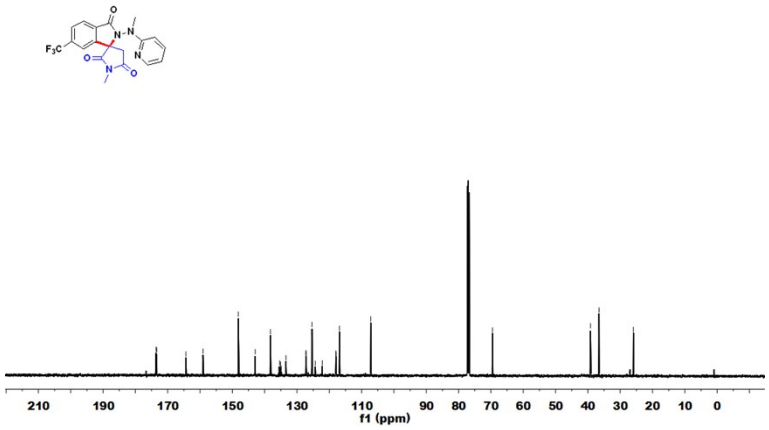

173.71
173.46
164.82
159.19
148.10
143.87
139.65
138.16
130.52
128.35
125.95
121.09
116.65
107.08
69.07
39.16
36.59
25.83
Cl
f1 (ppm)

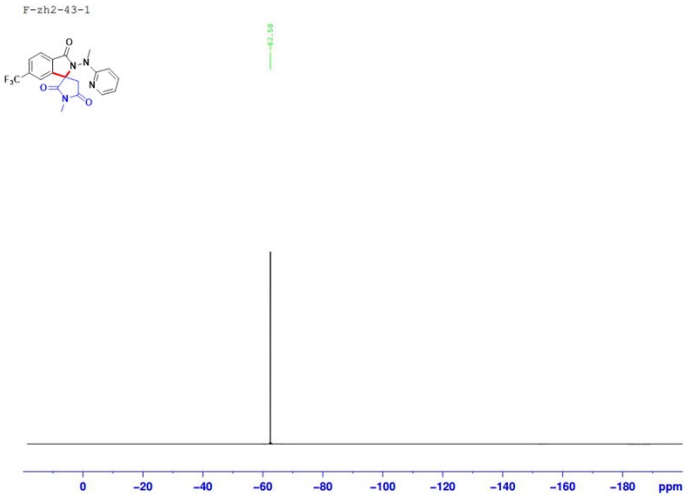
^{1}H, ^{13}C NMR spectra of compound 3qa



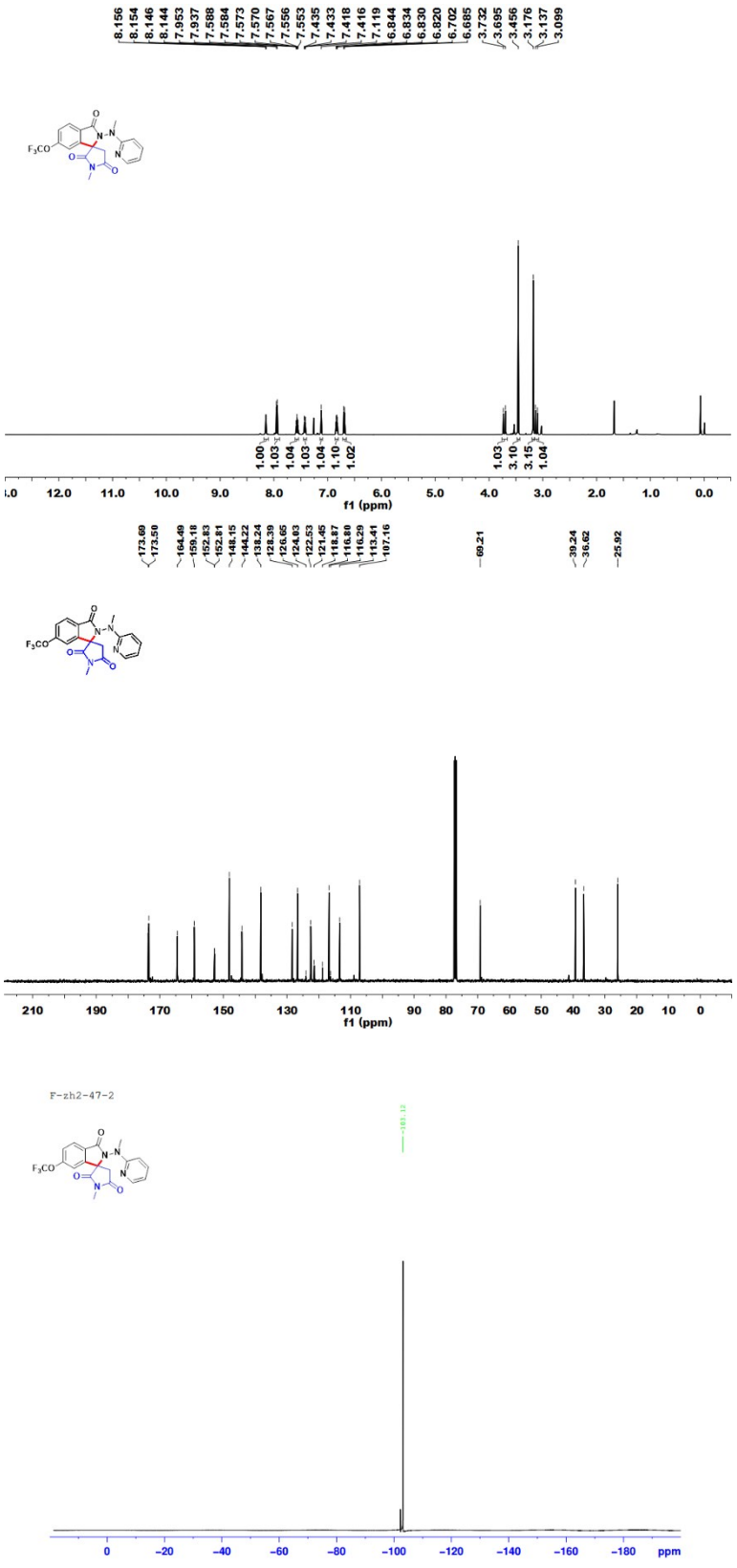
^{1}H, ^{13}C, ^{19}F NMR spectra of compound 3ra



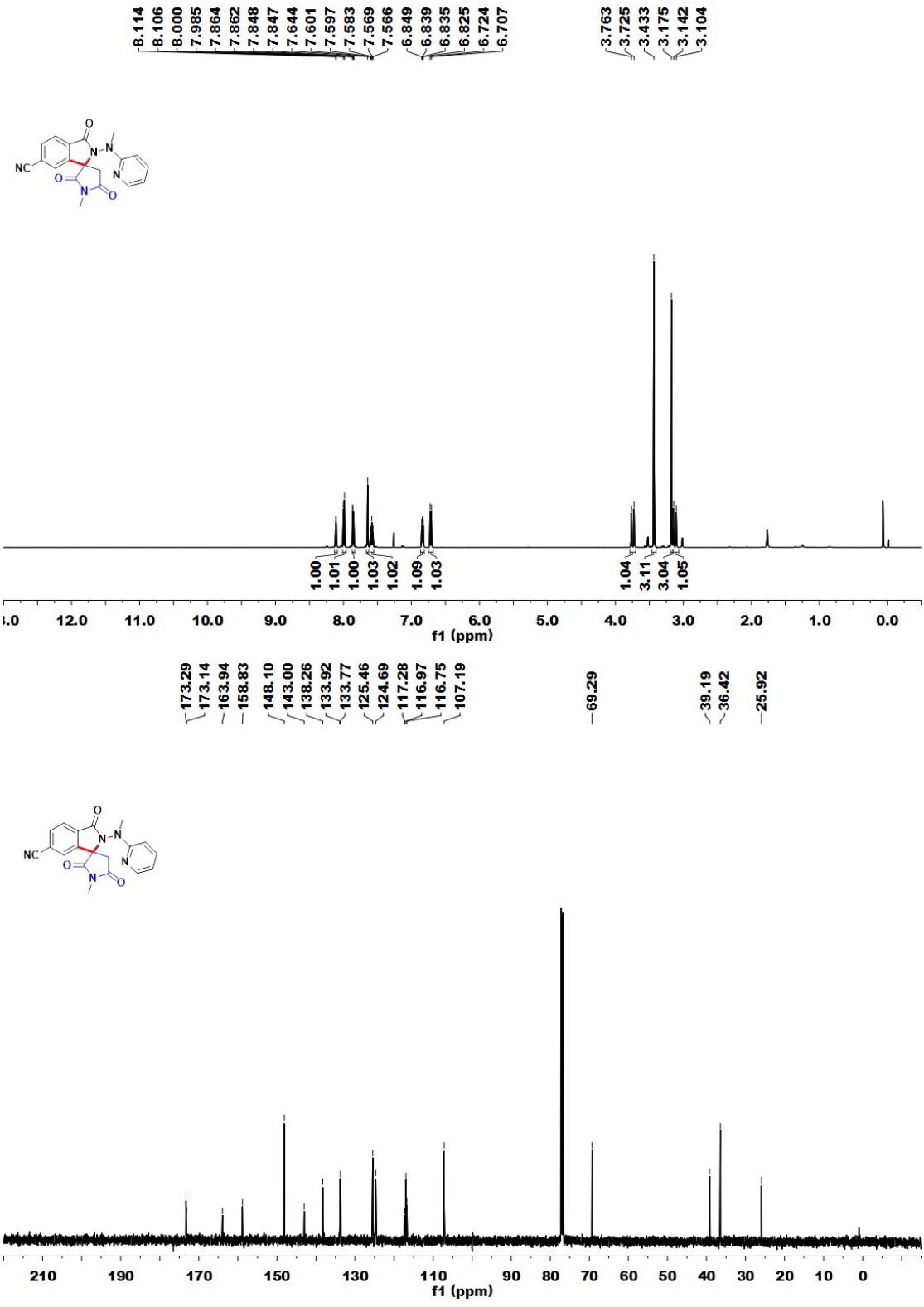




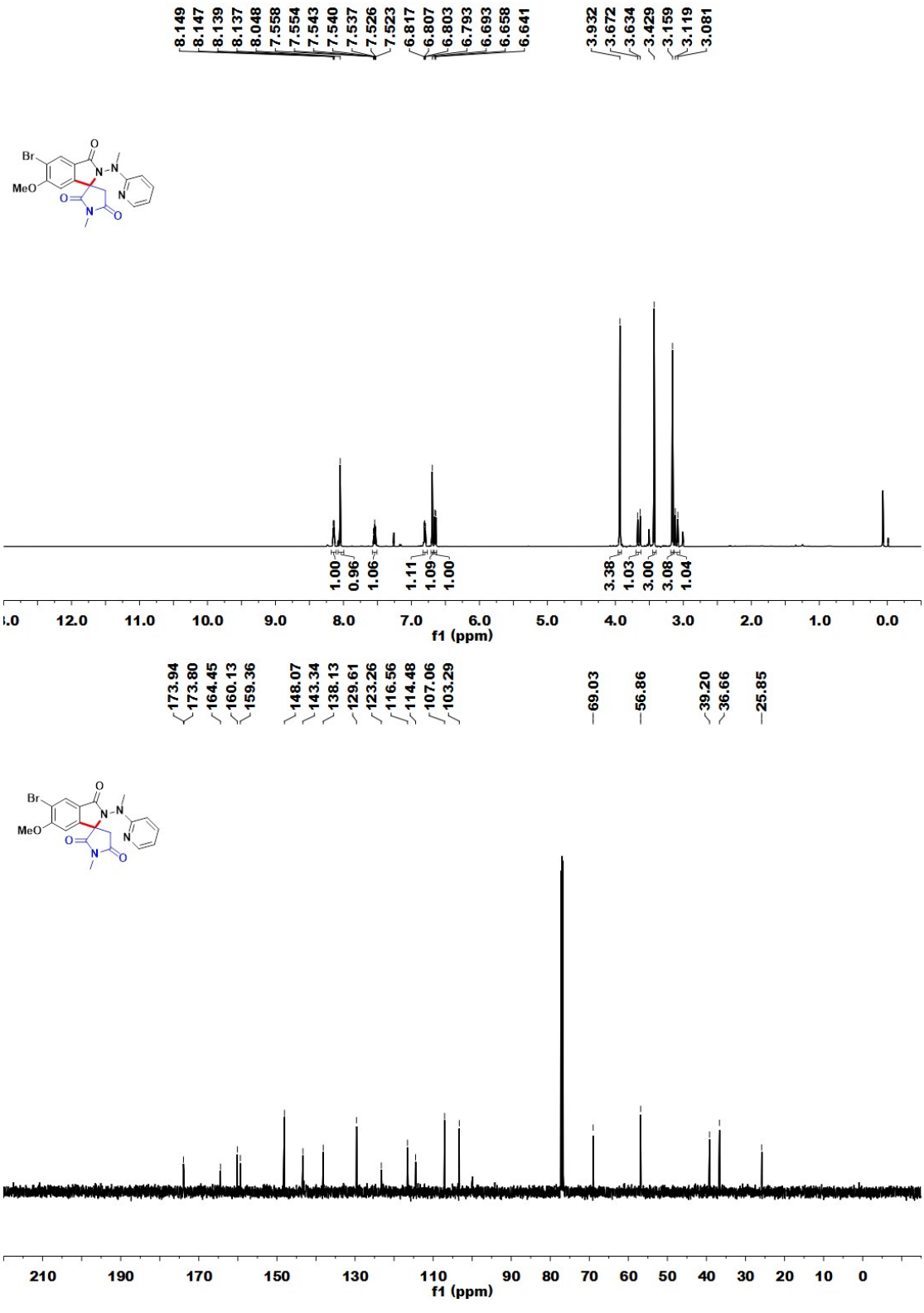
^{1}H, ^{13}C, ^{19}F NMR spectra of compound 3sa



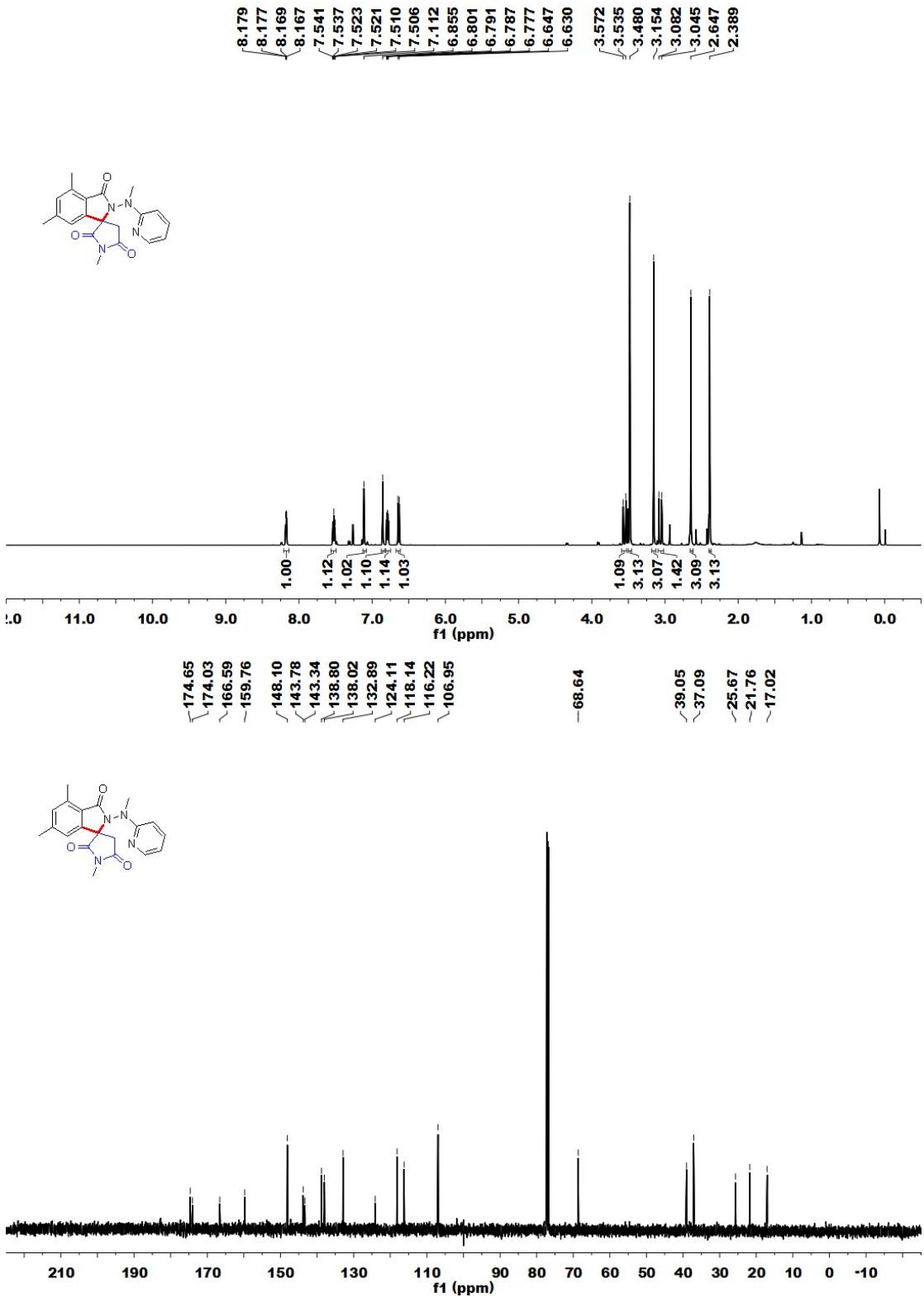
^{1}H, ^{13}C NMR spectra of compound 3ta



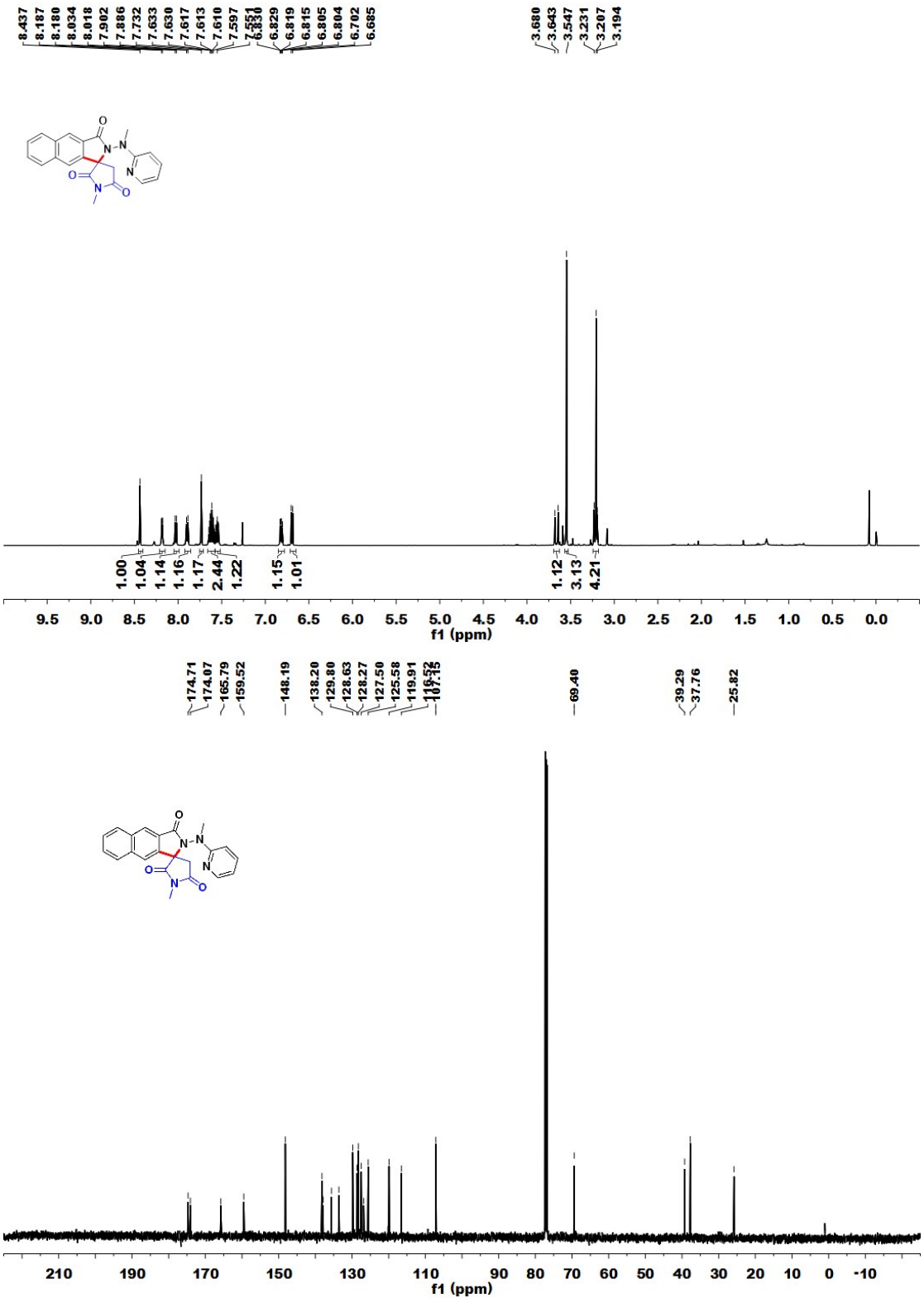
^{1}H, ^{13}C NMR spectra of compound 3ua



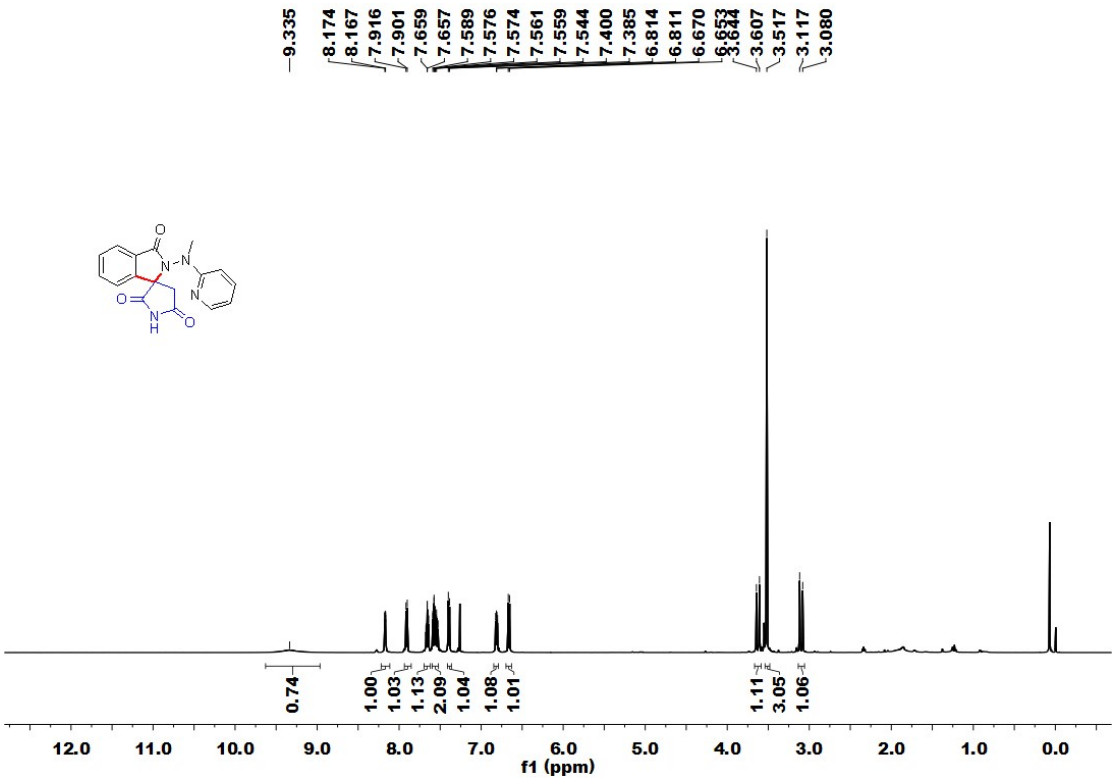
^{1}H, ^{13}C NMR spectra of compound 3va

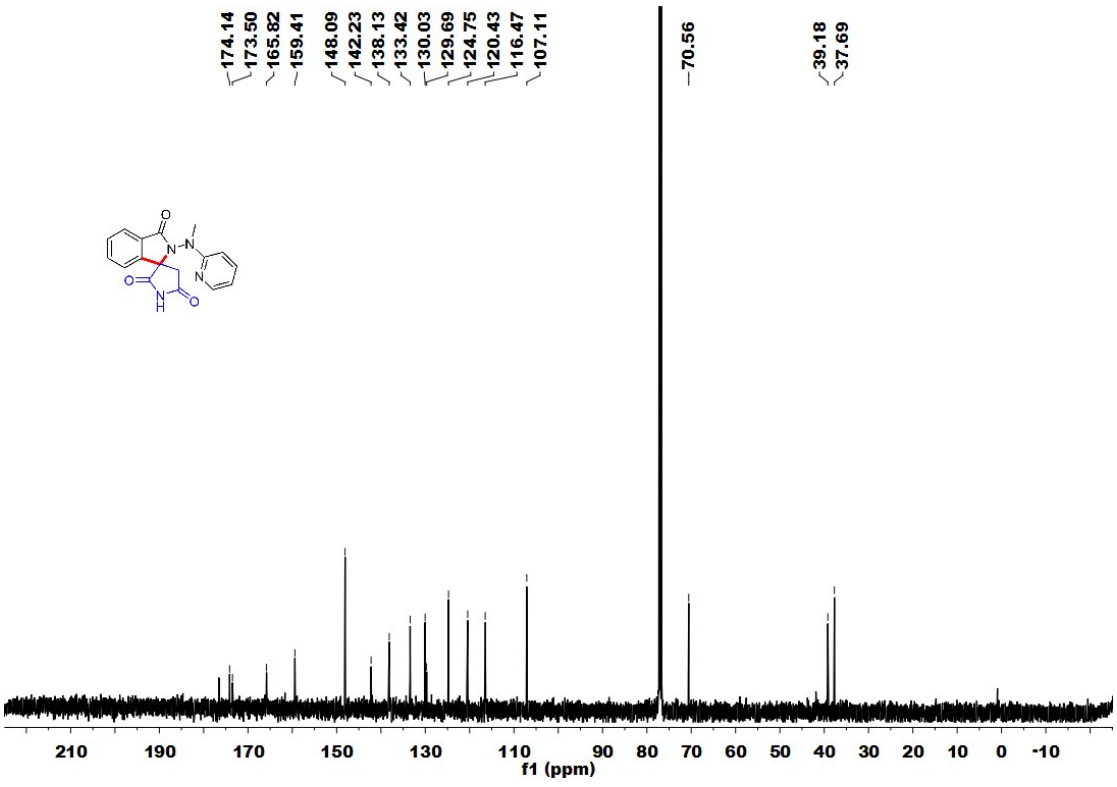


^{1}H, ^{13}C NMR spectra of compound 3wa

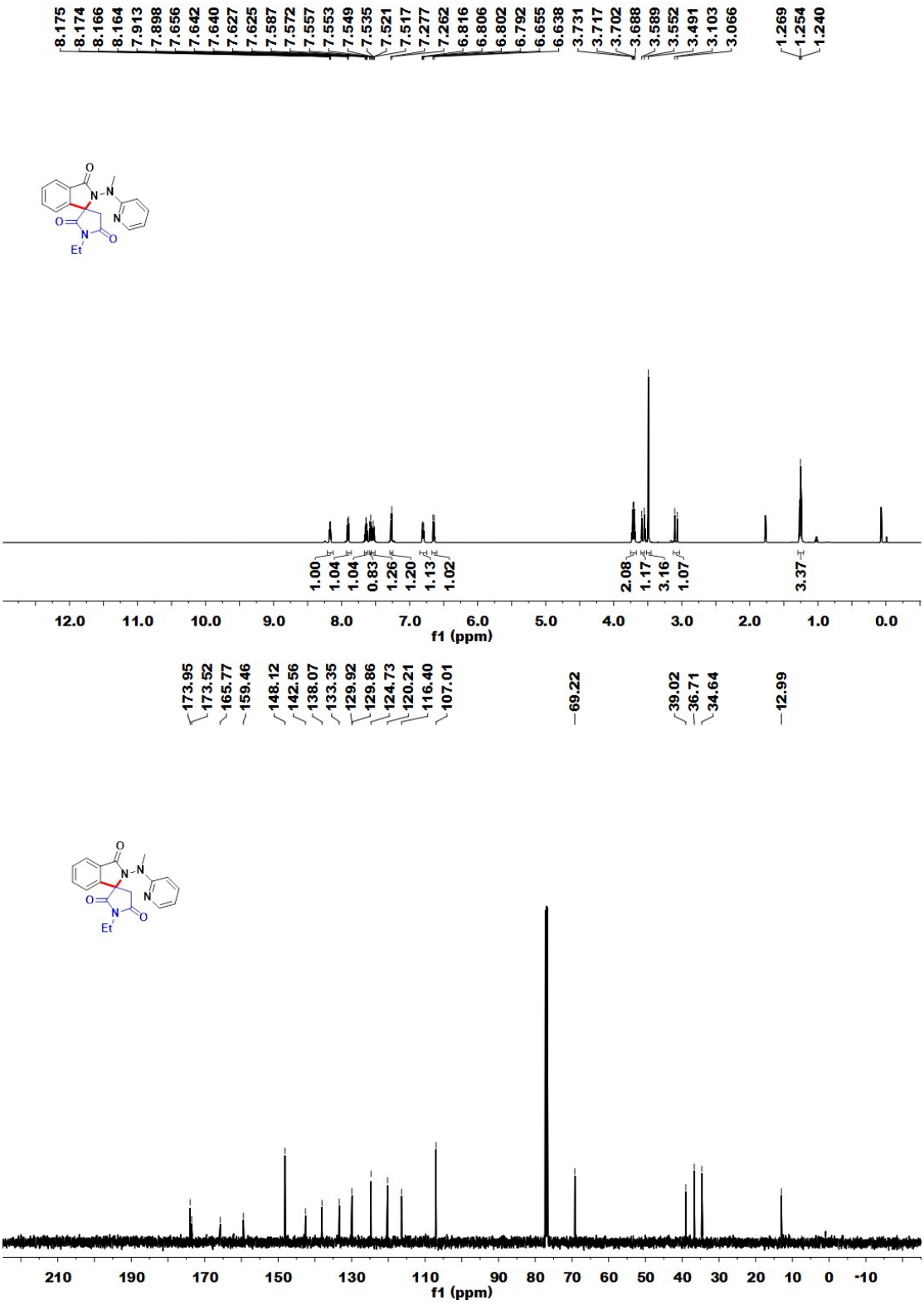


^{1}H, ^{13}C NMR spectra of compound 3ab

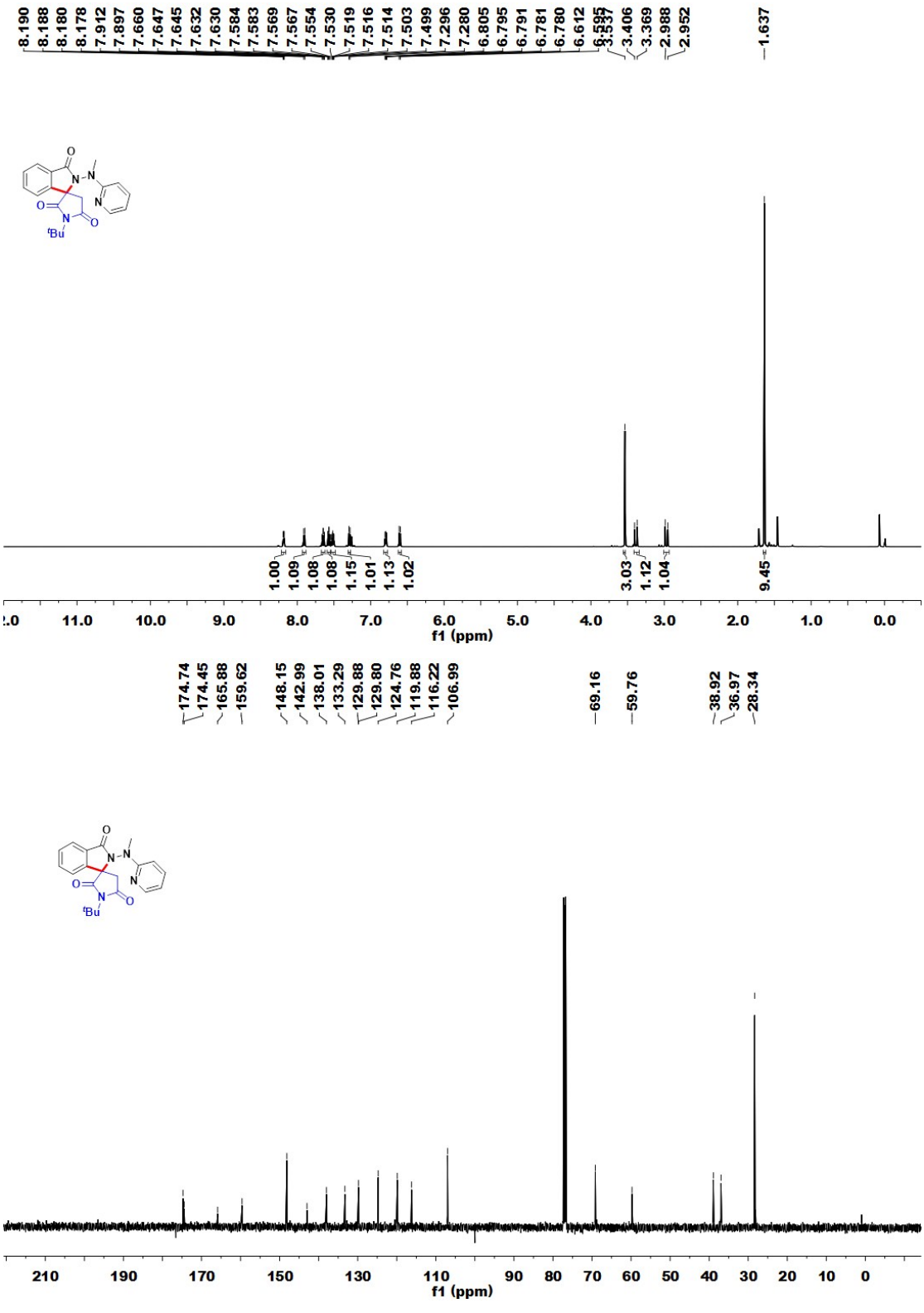

9.335
8.174
8.167
7.916
7.901
7.659
7.657
7.589
7.576
7.574
7.561
7.559
7.544
7.400
7.385
6.814
6.811
6.670
6.653
3.644
3.607
3.517
3.117
3.080
0.74
1.00
1.03
1.13
2.09
1.04
1.08
1.01
1.11
3.05
1.06
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)


174.14
173.50
165.82
159.41
148.09
142.23
138.13
133.42
130.03
129.69
124.75
120.43
116.47
107.11
70.56
39.18
37.69
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

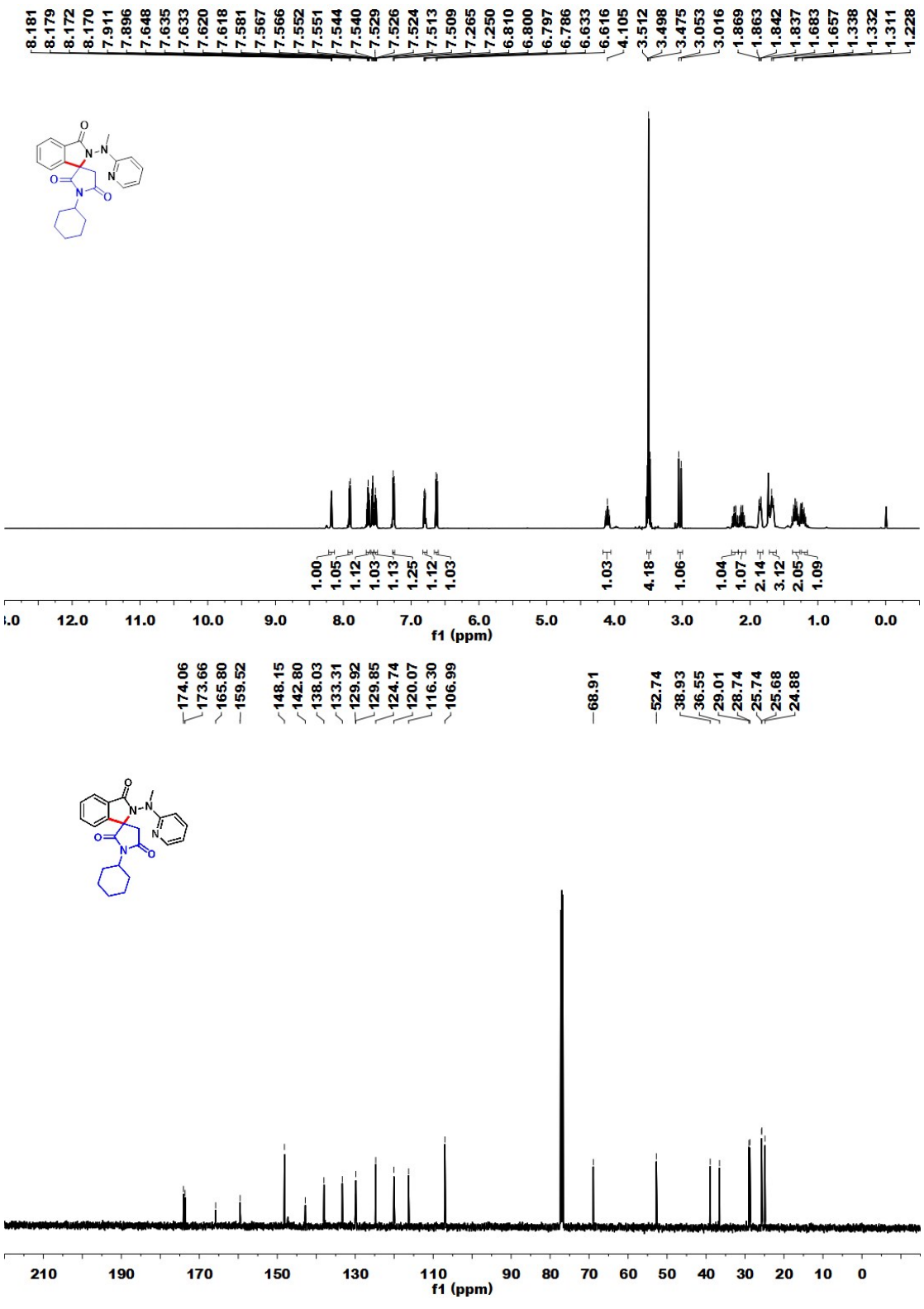
^{1}H, ^{13}C NMR spectra of compound 3ac



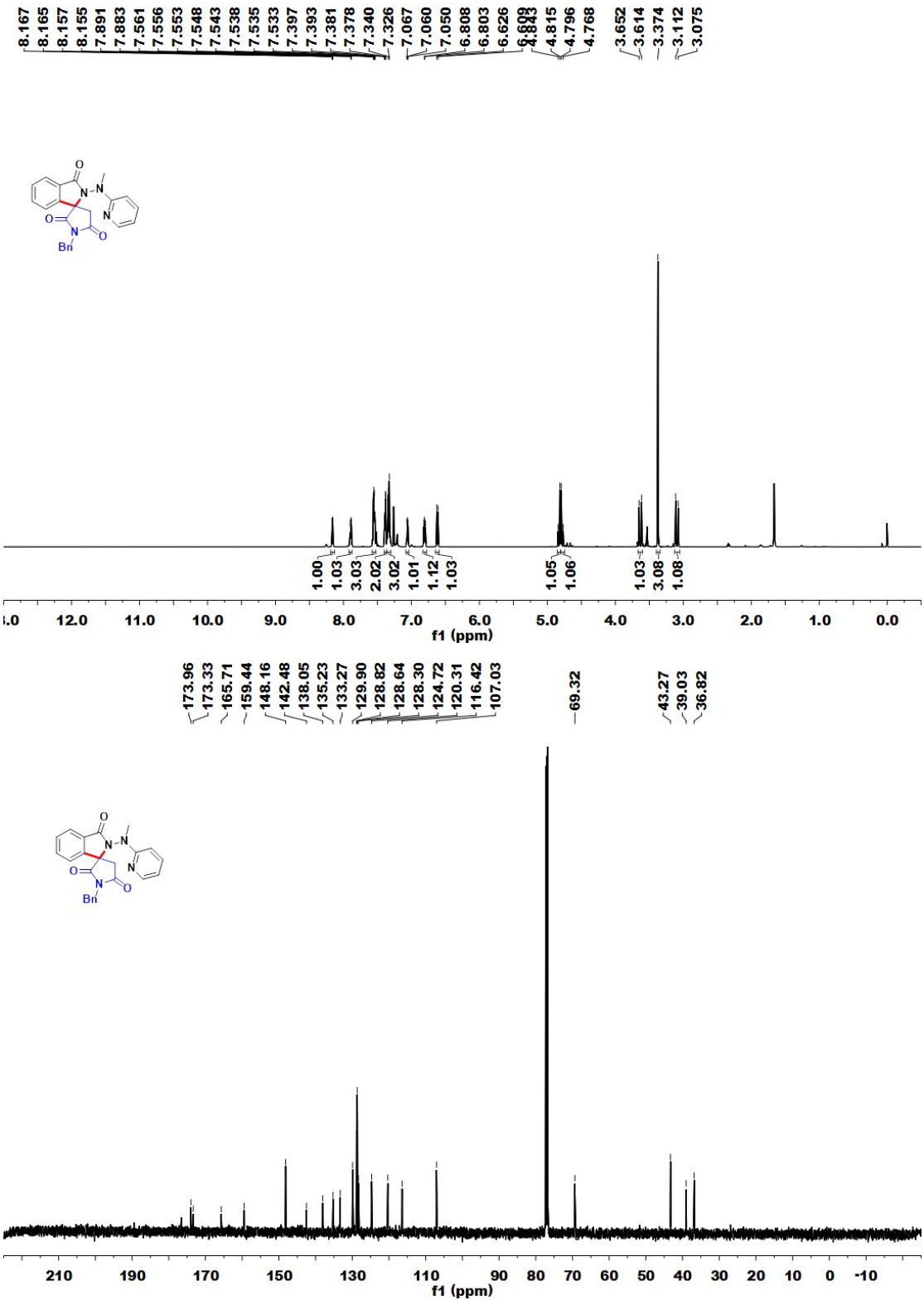
^{1}H, ^{13}C NMR spectra of compound 3ad



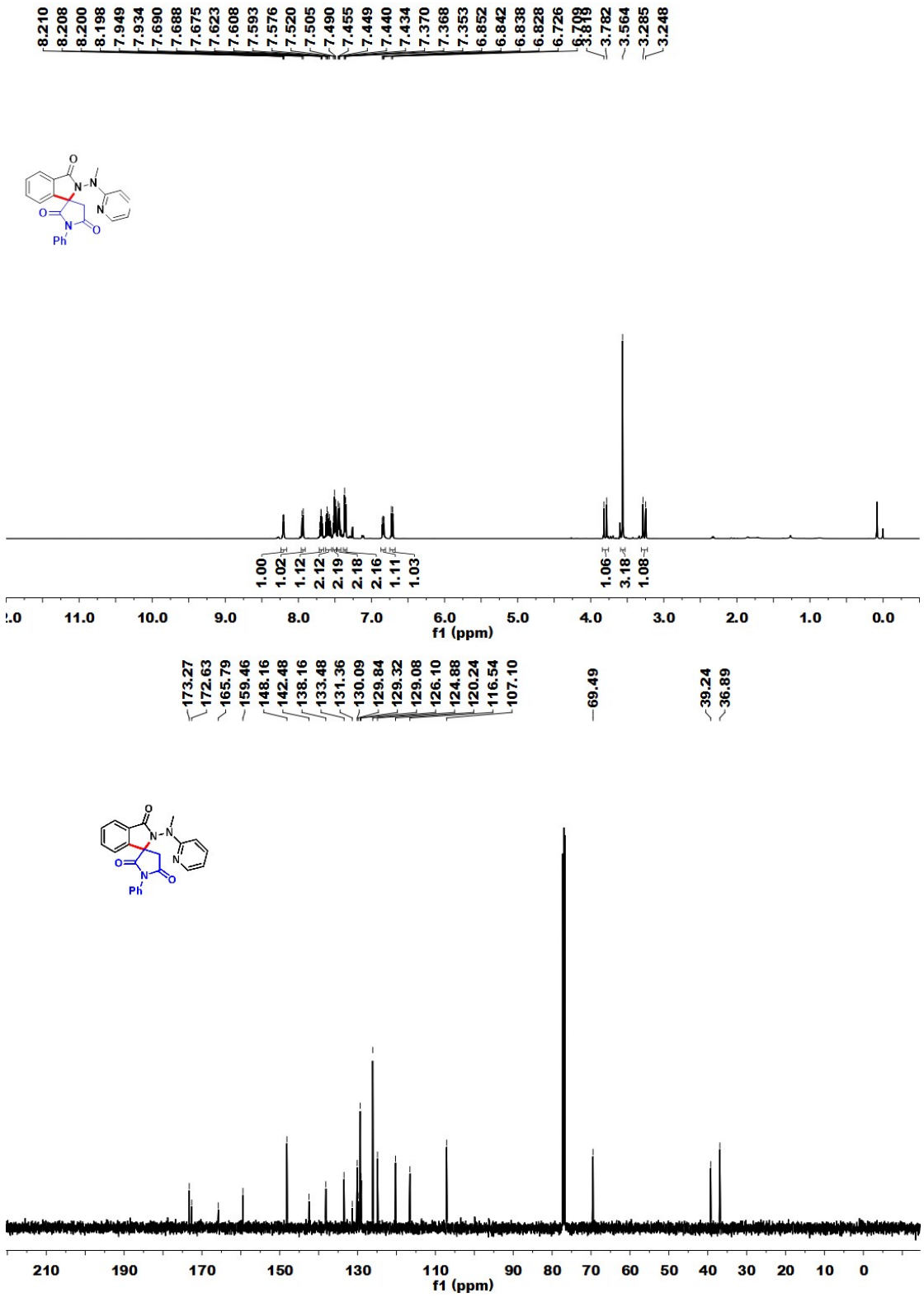
^{1}H, ^{13}C NMR spectra of compound 3ae



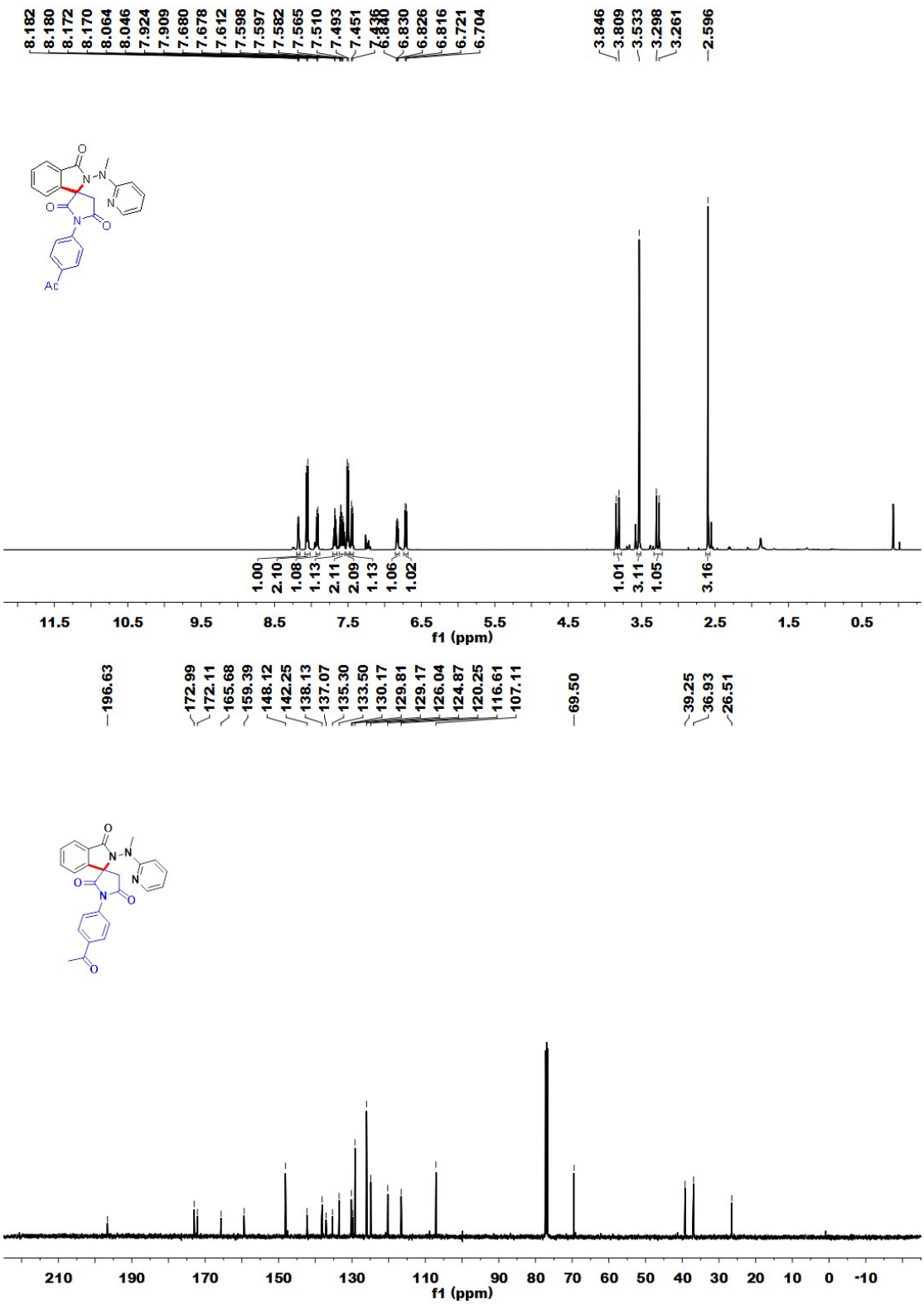
^{1}H, ^{13}C NMR spectra of compound 3af



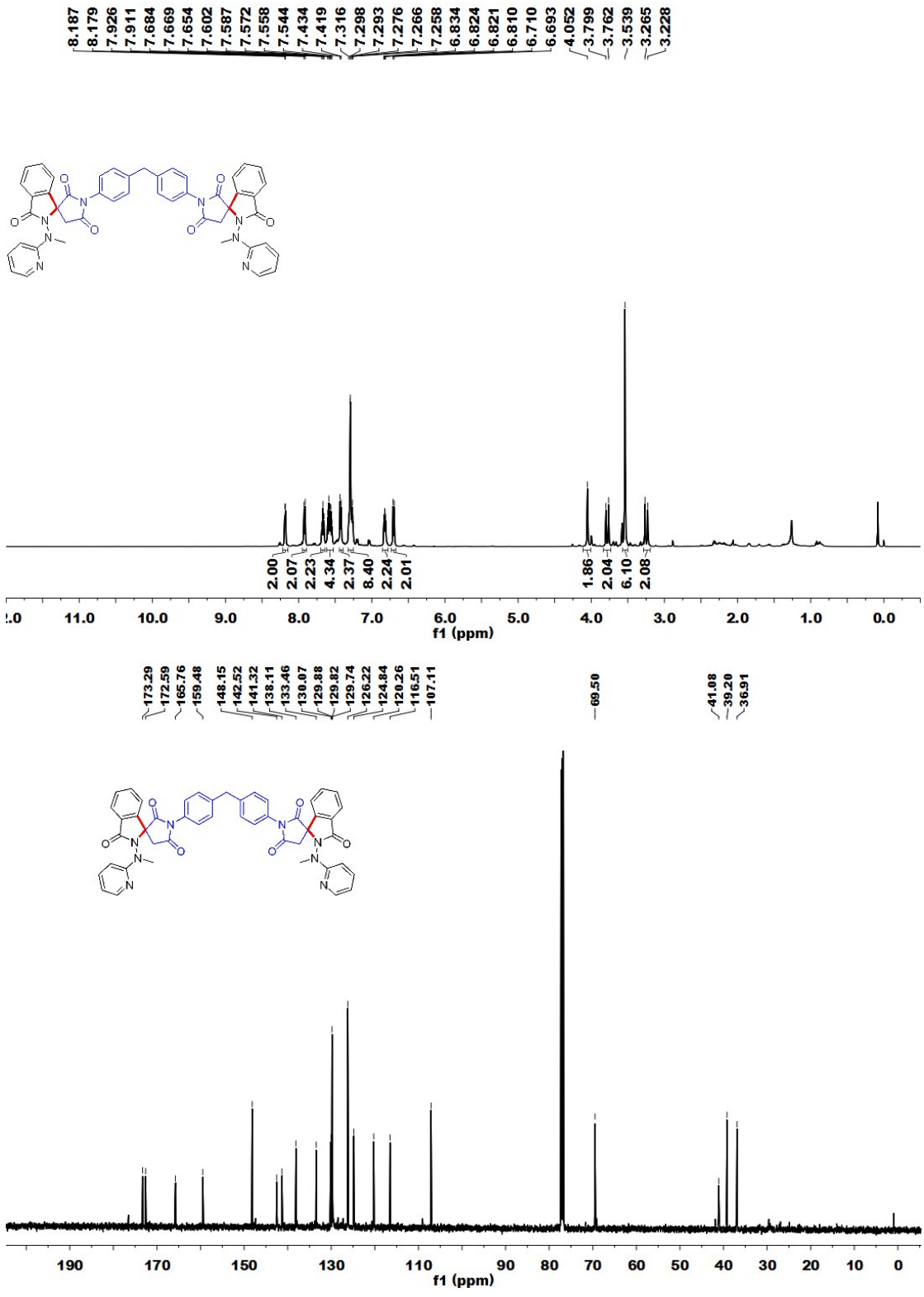
^{1}H, ^{13}C NMR spectra of compound 3ag



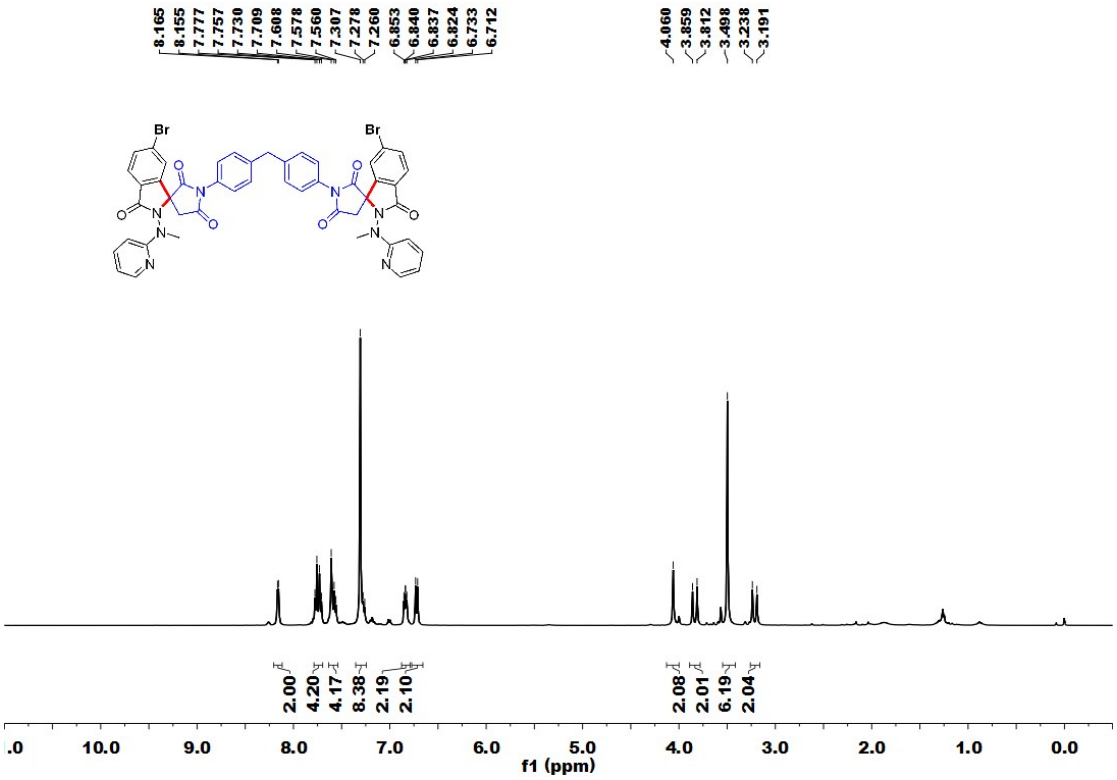
^{1}H, ^{13}C NMR spectra of compound 3ah

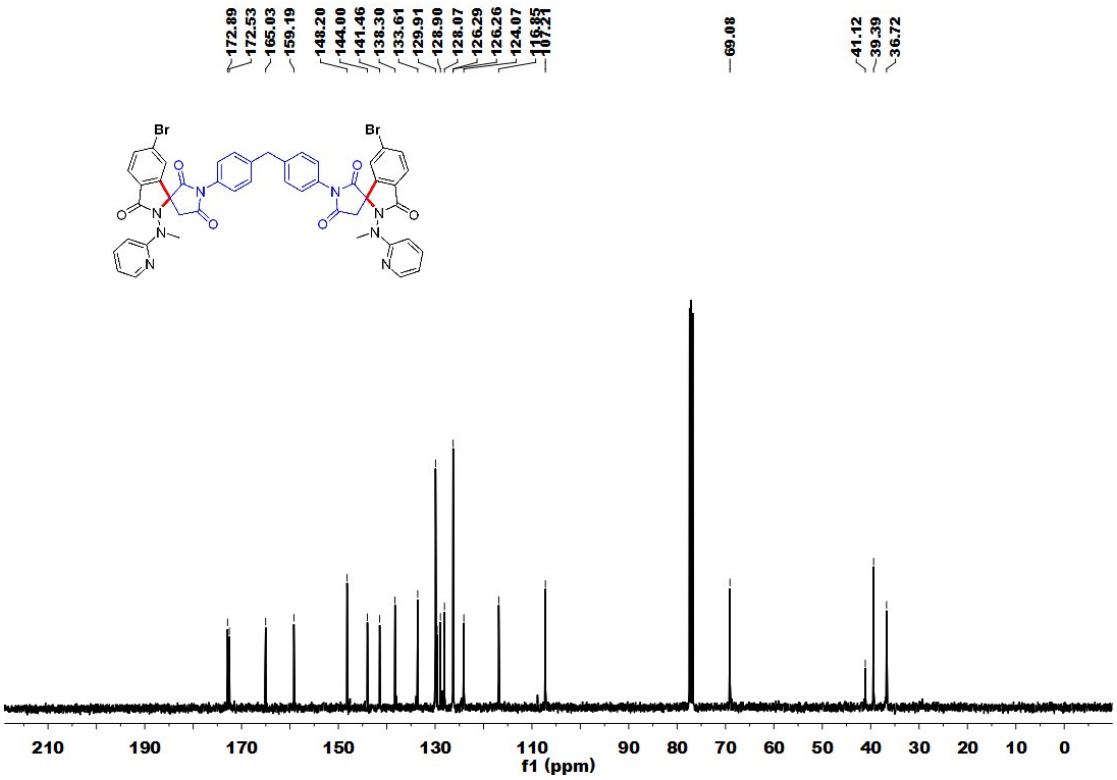


^{1}H, ^{13}C NMR spectra of compound 4a

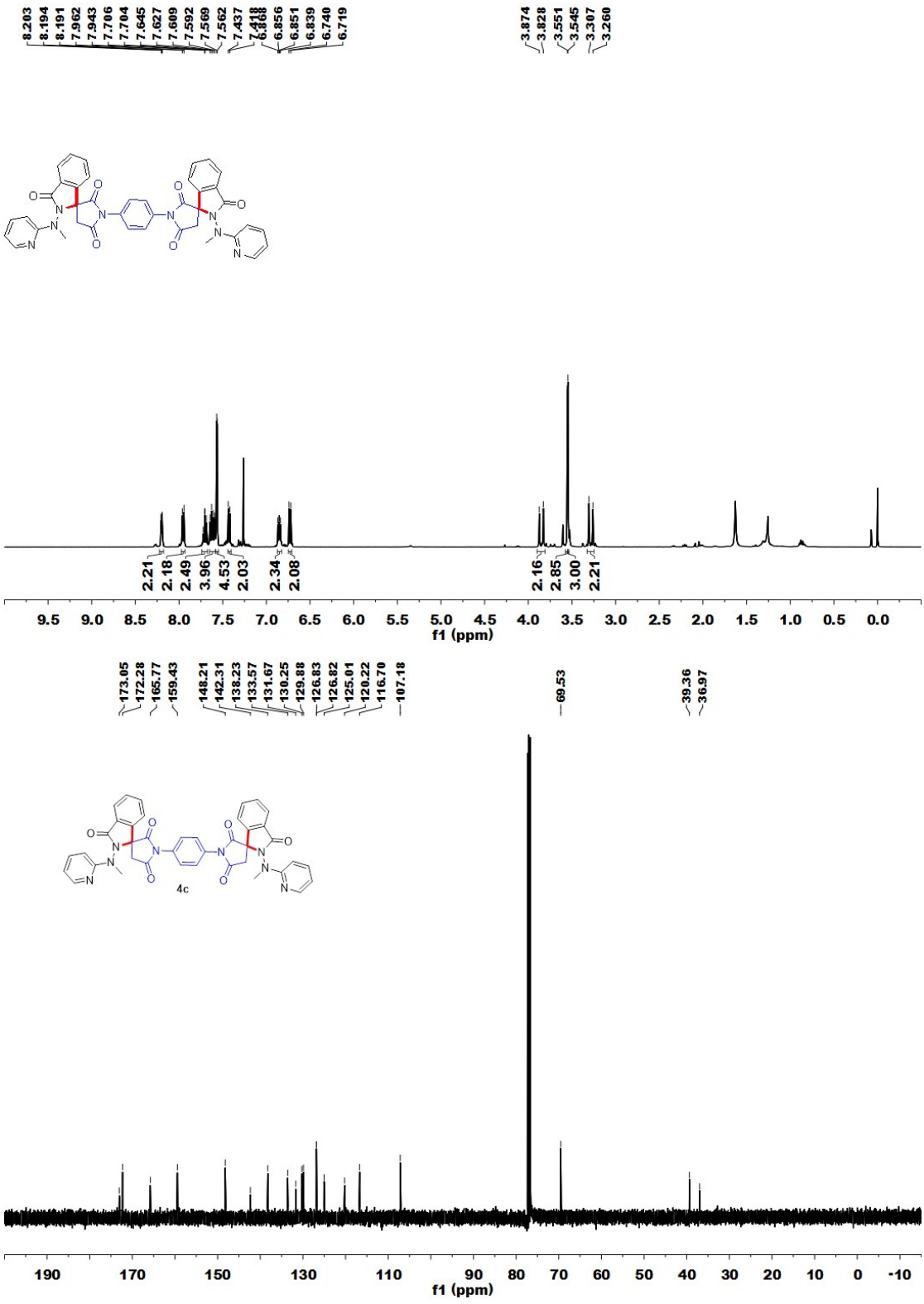


^{1}H, ^{13}C NMR spectra of compound 4b

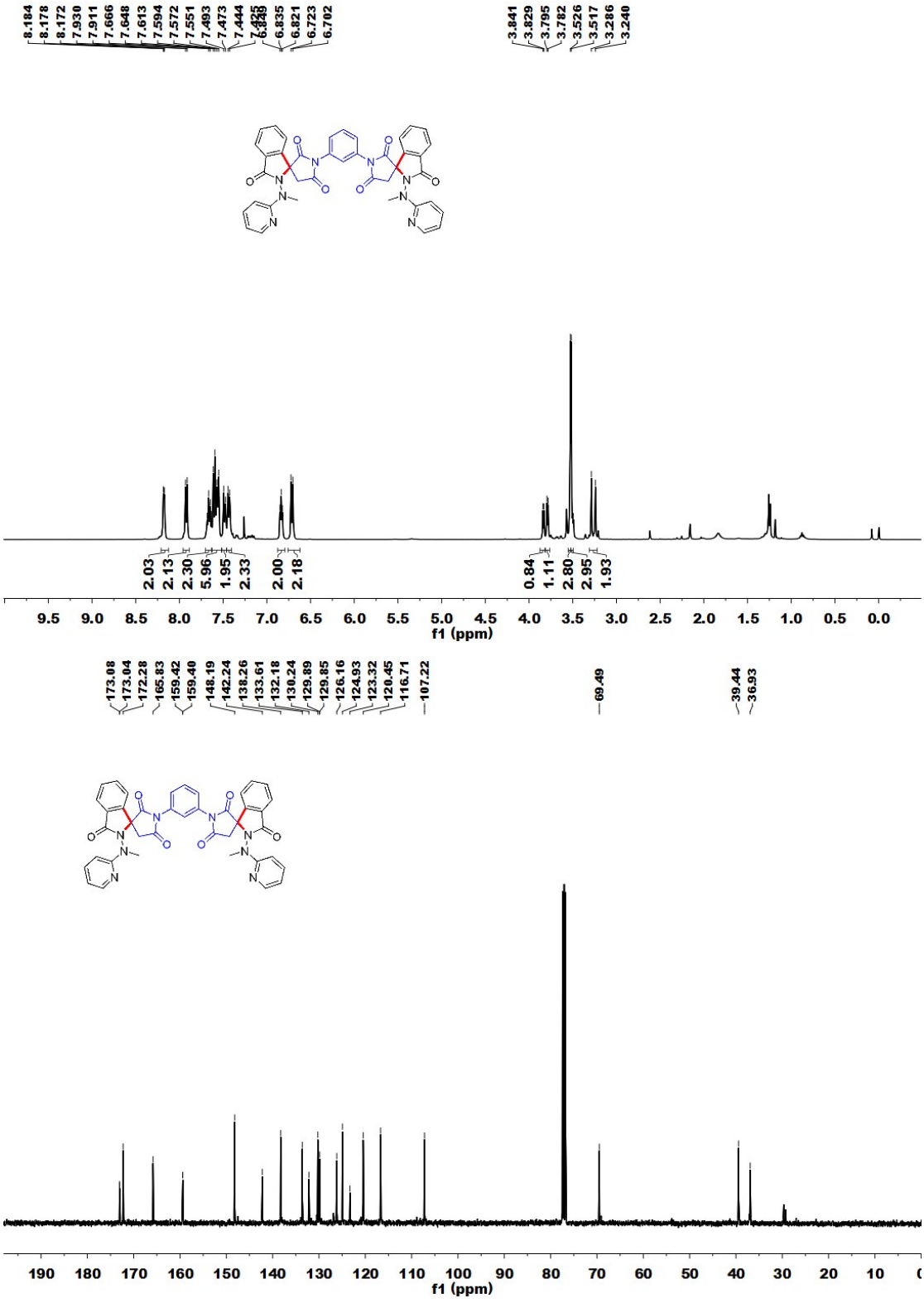




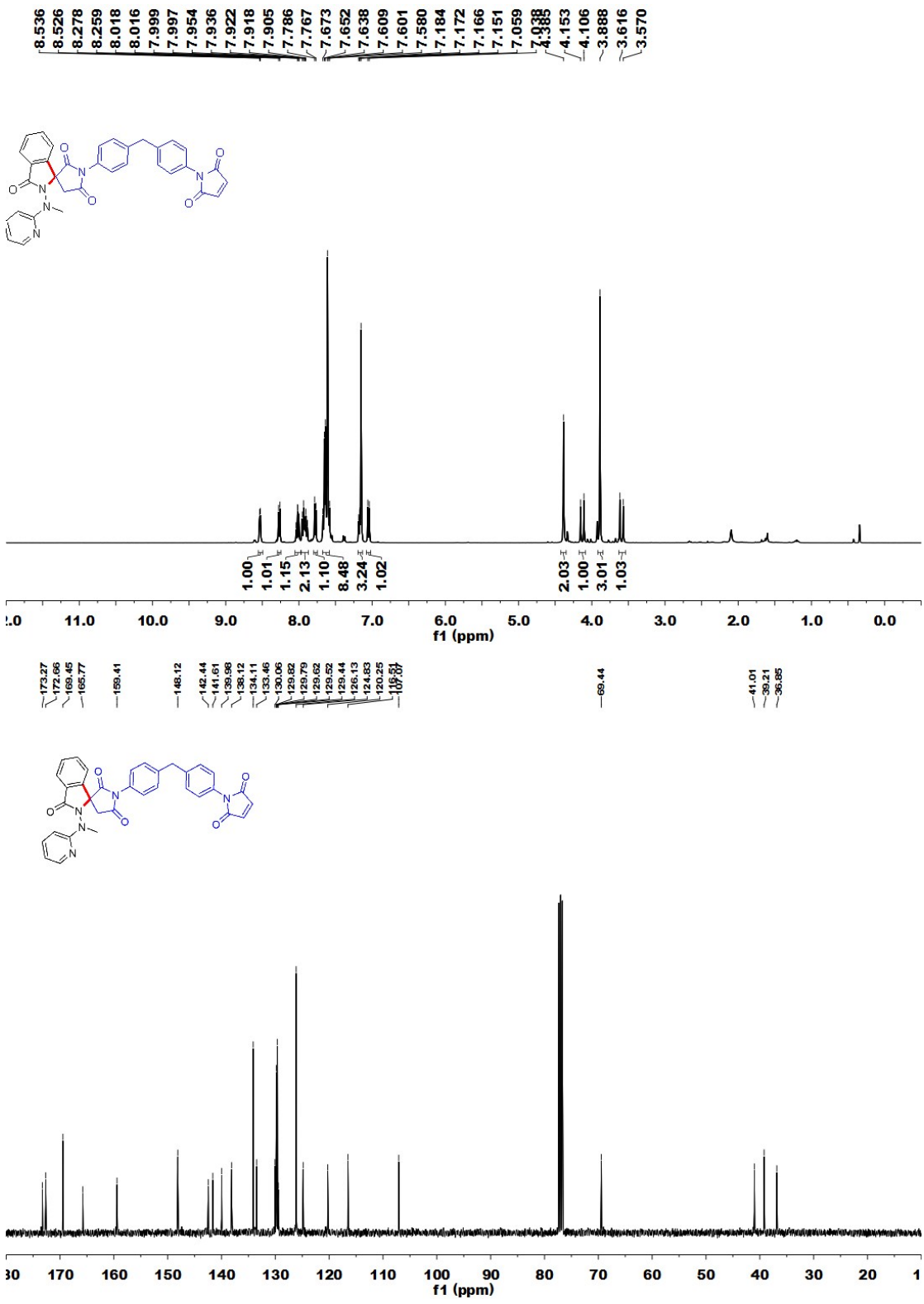
^{1}H, ^{13}C NMR spectra of compound 4c



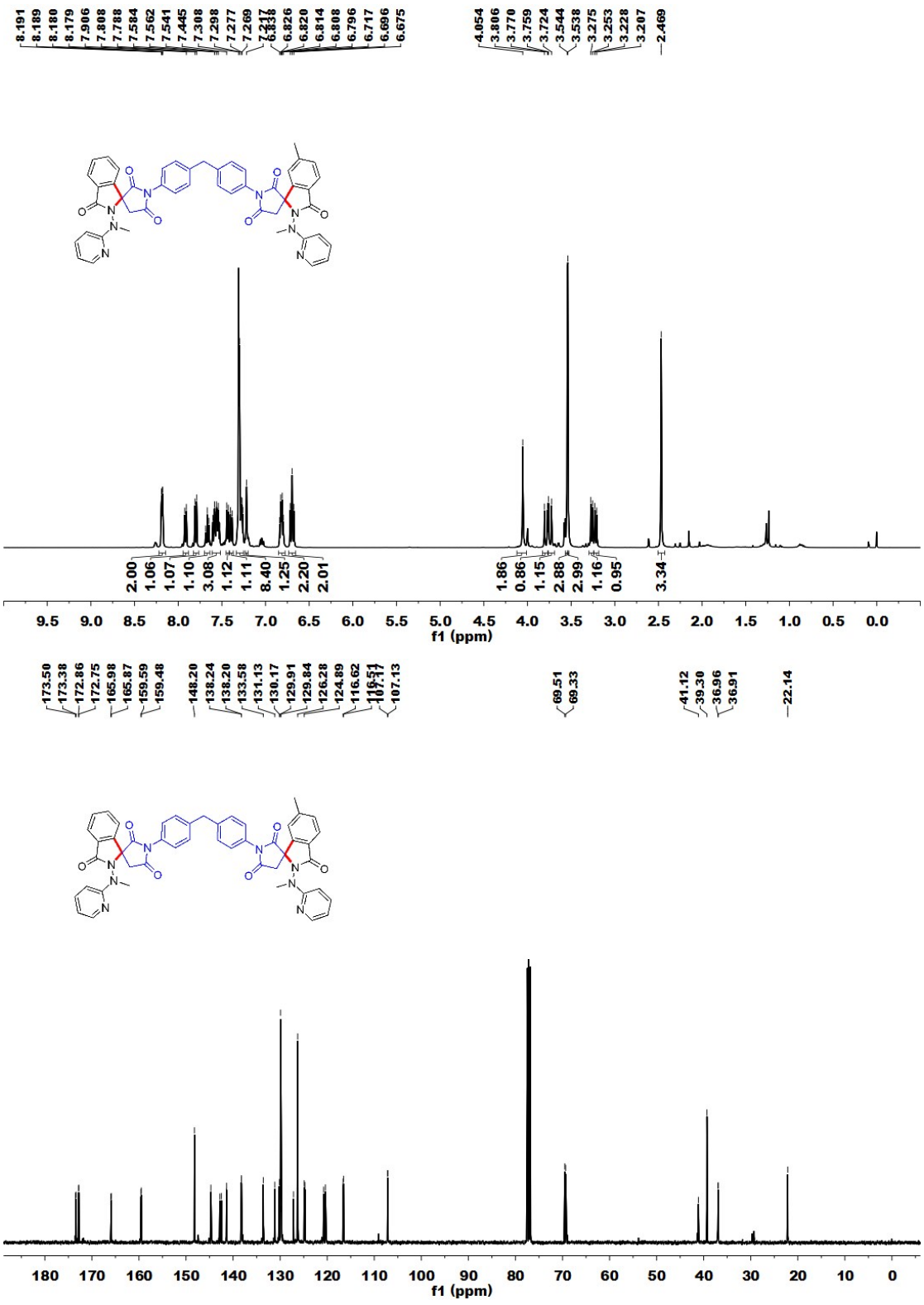
^{1}H, ^{13}C NMR spectra of compound 4d



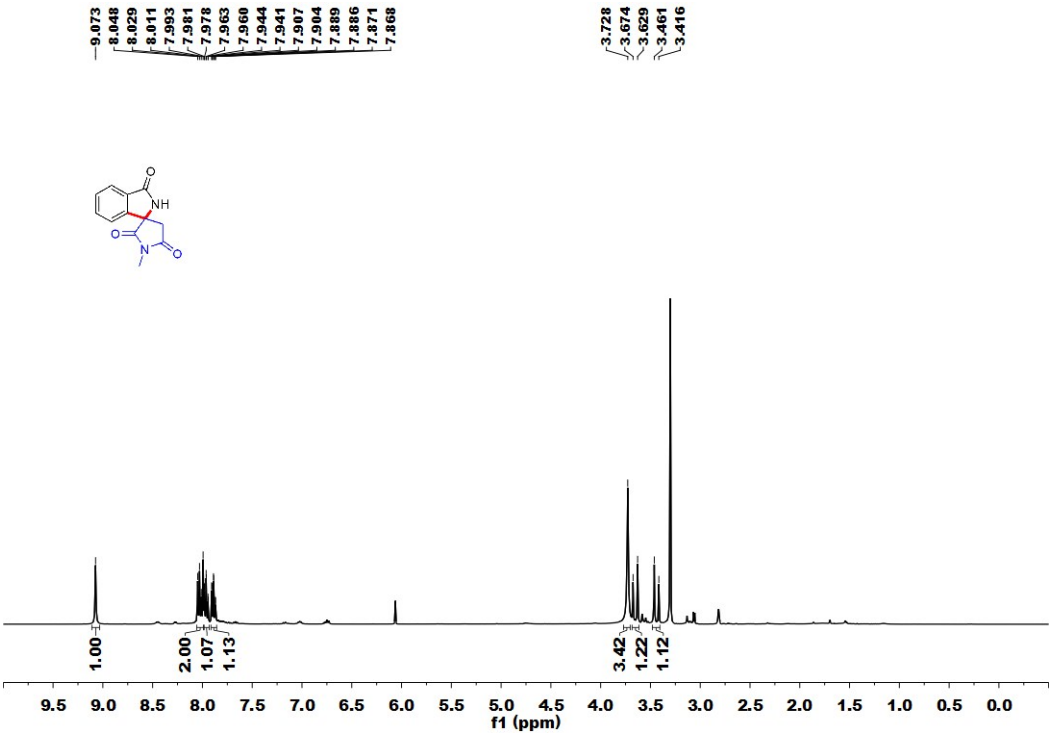
^{1}H, ^{13}C NMR spectra of compound 5

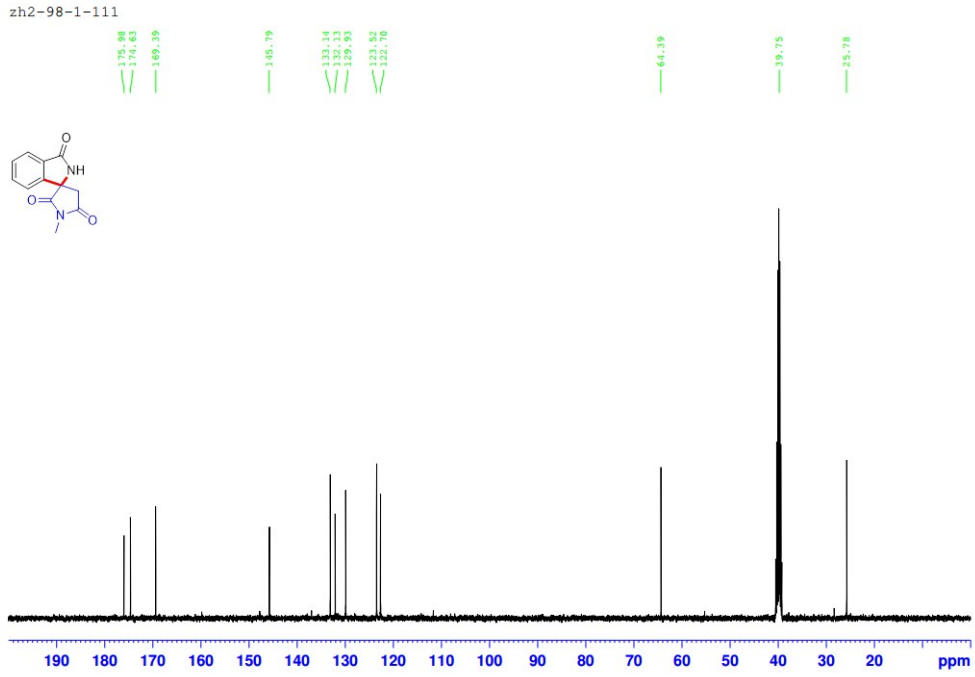


^{1}H, ^{13}C NMR spectra of compound 6

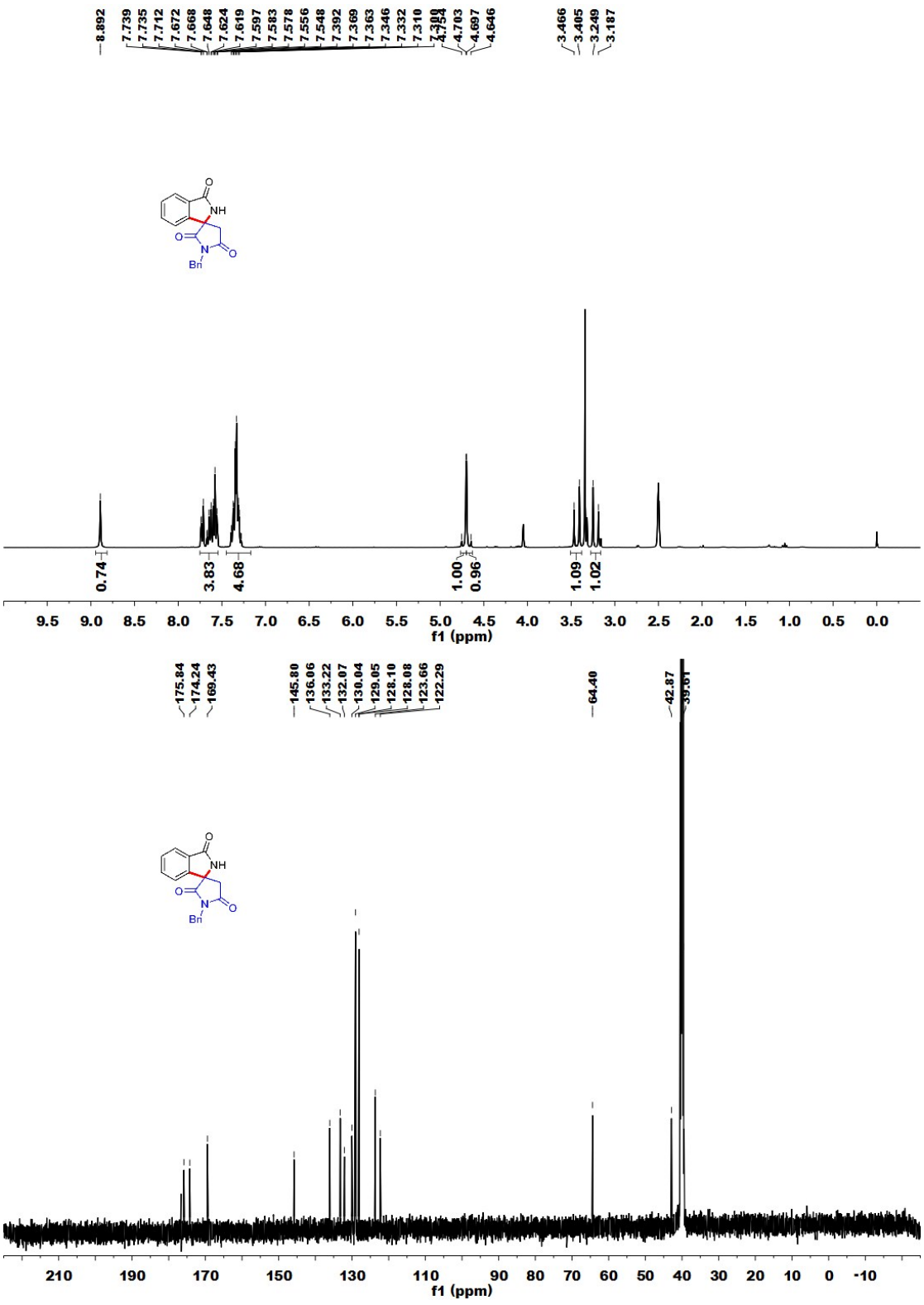


^{1}H, ^{13}C NMR spectra of compound 7

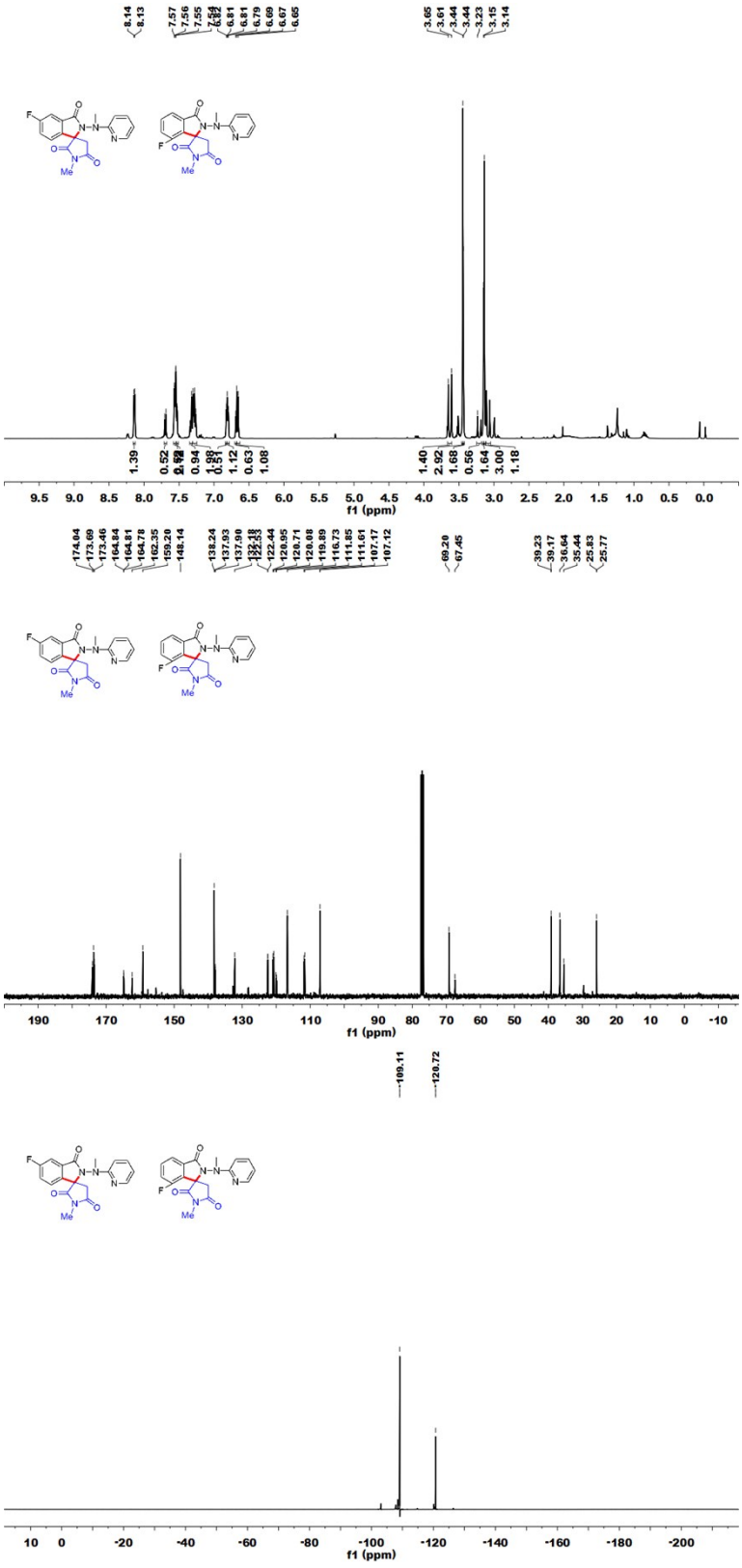




^{1}H, ^{13}C NMR spectra of compound 8



^{1}H, ^{13}C, ^{19}F NMR spectra of compound 3xa and 3xá'


8.14
8.13
7.57
7.56
7.55
6.81
6.81
6.79
6.69
6.67
6.65
3.65
3.61
3.44
3.44
3.23
3.15
3.14
1.39
0.52
0.94
1.12
0.63
1.08
1.40
2.92
1.68
0.56
1.64
3.00
1.18
f1 (ppm)
174.04
173.69
173.46
164.84
164.81
164.78
162.35
159.20
148.14
138.24
137.93
137.90
122.44
120.95
120.71
120.68
119.89
116.73
111.85
111.66
111.45
107.17
107.12
69.29
67.45
39.23
39.17
39.11
35.44
25.83
25.77
f1 (ppm)
-109.11
-120.72
f1 (ppm)