Discovery and structure-activity relationship study of novel isoxazole-based small molecules targeting Zika virus infections

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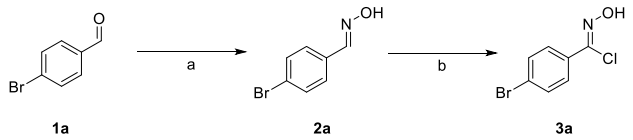
Contents

1. General Synthetic procedures

All solvents and reagents were purchased from commercial suppliers and used without further purification. All solvents, including dimethyl sulfoxide, dimethylformamide (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), acetonitrile, dichloromethane (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), ethanol (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), methanol (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), ethyl acetate (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), hexanes (Samchun Chemical Co., Ltd. Seoul, Republic of Korea), *tert*-butanol (Samchun Chemical Co., Ltd. Seoul, Republic of Korea),, isopropanol (Samchun Chemical Co., Ltd. Seoul, Republic of Korea),, and tetrahydrofuran (Samchun Chemical Co., Ltd. Seoul, Republic of Korea) were dried before use. Merck silica gel 60 F254 glass plates (Merck, KGaA, Darmstadt, Germany) were used for analytical thin-layer chromatography (TLC). Purification using column chromatography was performed on RediSep silica-cartridges (Teledyne ISCO, Lincoln, USA) with a medium-pressure liquid chromatography (LC) system. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using Bruker instruments (BRUKER, San Jose, USA) (300, 400, and 500 MHz for ^{1}H NMR and 101 and 126 MHz for ^{13}C NMR). Chemical shifts were quoted in parts per million (ppm) and referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, and m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). High-resolution mass spectra (HR-MS) were obtained using the electron impact (EI) ionization mode at 70 eV and Fast Atom Bombardment ionization mode at 5 keV. InChI codes for the examined compounds, along with certain bioassay results, are provided in the Supporting Information.

Synthetic scheme for intermediate 3a



Reaction conditions: (a) H_2NOH•HCl (1.20 eq), pyridine (2.40 eq), ethanol (0.50 M), rt, 1 h; (b) *N*-Chlorosuccinimide (1.0 eq), DMF (0.50 M), rt, 4 h.

Preparation of (*E*)-4-bromobenzaldehyde oxime (2a)

To a stirred solution of 4-bromobenzaldehyde (**1a**, 1.00 g, 5.40 mmol) in ethanol (10.8 mL, 0.50 M) was added hydroxylamine hydrochloride (0.45 g, 6.48 mmol) and pyridine (1.04 mL, 13.0 mmol) at room temperature. The mixture was stirred for 1 h at room temperature, and oxime formation was confirmed by TLC. The reaction mixture was quenched with a solution of hydrochloric acid (1.0 M) and extracted twice with EtOAc. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to get the desired product, (*E*)-4-bromobenzaldehyde oxime (**2a**, 0.92 g, 85%) as white solid.

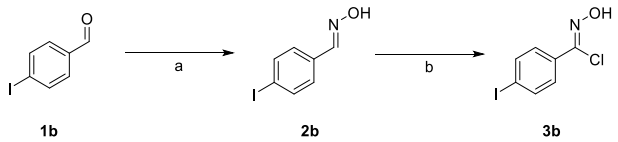
^{1}H NMR (300 MHz, DMSO-d_6): δ 11.39 (s, 1H), 8.14 (s, 1H), 7.75 (m, 4H).

(*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (3a)

To a stirred solution of (*E*)-4-bromobenzaldehyde oxime (**2a**, 0.91 g, 4.55 mmol) in DMF (9.10 mL, 0.50 M) was added *N*-chlorosuccinimide (0.61 g, 4.55 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature and the formation of the product was confirmed by TLC. The reaction mixture was quenched with water and extracted twice with EtOAc. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude was purified by column chromatography to afford the desired product, (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.93 g, 87%) as white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (s, 1H), 7.79–7.60 (m, 4H).

Synthetic scheme for intermediate 3b



Reaction conditions: (a) H_2NOH•HCl (1.20 eq), methanol: water (0.30 M), rt, 1 h; (b) *N*-Chlorosuccinimide (1.0 eq), DMF (0.50 M), rt, 4 h.

Preparation of (*E*)-4-iodobenzaldehyde oxime (2b)

To a stirred solution of 4-iodobenzaldehyde (**1b**, 2.00 g, 8.60 mmol) in methanol: water (1:1, 30 mL, 0.30 M) was added hydroxylamine hydrochloride (0.71 g, 10.3 mmol) at room temperature. The mixture was stirred for 1 h at room temperature, and oxime formation was confirmed by TLC. The reaction mixture was quenched with a solution of hydrochloric acid (1.0 M) and extracted twice with EtOAc. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to get the desired product, (*E*)-4-iodobenzaldehyde oxime (**2b**, 1.85 g, 87%) as white solid.

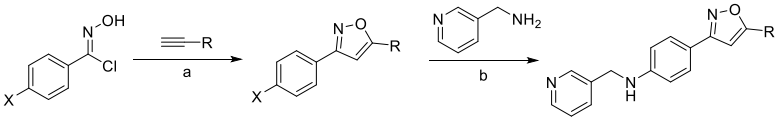
^{1}H NMR (500 MHz, DMSO) δ 11.38 (s, 1H), 8.11 (s, 1H), 7.87–7.65 (m, 2H), 7.54–7.24 (m, 2H).

(*Z*)-4-iodo-*N*-hydroxybenzimidoyl chloride (3b)

To a stirred solution of (*E*)-4-iodobenzaldehyde oxime (**2b**, 1.85 g, 7.4 mmol) in DMF (10 mL, 0.70 M) was added *N*-chlorosuccinimide (0.61 g, 7.4 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature and the formation of the product was confirmed by TLC. The reaction mixture was quenched with water and extracted twice with EtOAc. Combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude was purified by column chromatography to afford the desired product, (*Z*)-4-iodo-*N*-hydroxybenzimidoyl chloride (**3b**, 1.3 g, 61%) as white solid.

^{1}H NMR (300 MHz, DMSO) δ 12.53 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.6 Hz, 2H).

Synthetic scheme for compounds 6d, 7a–7r, and 8a–8m



3a (X= Br)
3b (X= I)

4a–4s
5a–5m

6d, **7a–7r**
8a–8m

Reaction conditions: (a) CuI (0.07 eq), *t*-butanol/THF (3:1, 0.30 M), rt, 10 min, $KHCO_3$ (1.0 eq), rt, 24 h; (b) CuI (0.10 eq), *L*-proline (0.20 eq), K_2CO_3 (3.0 eq), DMSO (0.50 M), 80 ^oC, 14 h.

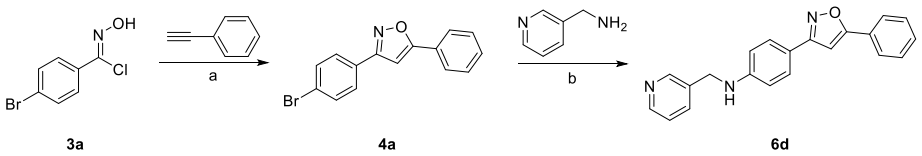
General procedure A

To a solution of (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 1.0 eq) and alkyne (1.0 eq) in *t*-butanol/THF (3:1, 0.30 M), copper (I) iodide (CuI) (0.07 eq) was added to the reaction mixture at room temperature and stirred for 10 min. Then $KHCO_3$ (1.0 eq) was added to the solution and stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the crude solid mixture was precipitated from isopropanol. The resulting crystalline solid was then filtered off and washed with a minimum amount of isopropanol to obtain the desired product.

General procedure B

To a solution of pyridine-3-methenamine (3.0 eq) in DMSO (0.50 M) were added isoxazole derivatives (**4a**–**4s**, 1.0 eq), copper (I) iodide (0.10 eq), *L*-proline (0.20 eq), and K_2CO_3 (3.0 eq). The reaction mixture was stirred at 80 ^oC for 14 h, then the reaction mixture was allowed to cool to room temperature, quenched with water, and extracted twice with EtOAc. The combined organic layers were washed with a brine solution, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography to obtain the desired product.

Synthesis of compound 6d



3a 4a 6d

Preparation of 3-(4-bromophenyl)-5-phenylisoxazole (4a)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol), and ethynylbenzene (0.09 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-phenylisoxazole (**4a**, 174 mg, 68%) as an off yellow solid.

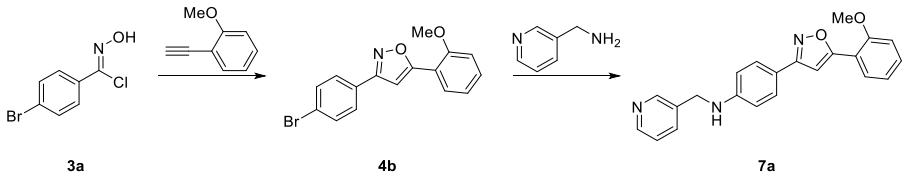
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.82 (m, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.56–7.46 (m, 3H), 6.83 (s, 1H).

Preparation of 4-(5-phenylisoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (6d)

The title compound was prepared from 3-(4-bromophenyl)-5-phenylisoxazole (**4a**, 0.17 g, 0.56 mmol) and pyridine-3-ylmethanamine (0.18 g, 1.68 mmol) in the manner described above general procedure **B** to obtain desired product, 4-(5-phenylisoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**6d**, 91.0 mg, 49%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (s, 1H), 8.48 (s, 1H), 7.89 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.59–7.50 (m, 3H), 7.41 (s, 1H), 7.39–7.35 (m, 1H), 6.83–6.79 (m, 1H), 6.73 (d, *J* = 8.7 Hz, 2H), 4.39 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.30, 163.09, 150.47, 149.40, 148.57, 135.51, 130.72, 129.71, 128.14, 127.60, 125.94, 116.44, 112.84, 98.45, 44.17. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{18}N_3O^+$ $[M+H]^+$: 328.1444 found 328.1448.

Synthesis of compound 7a



Preparation of 3-(4-bromophenyl)-5-(2-methoxyphenyl)isoxazole (4b)

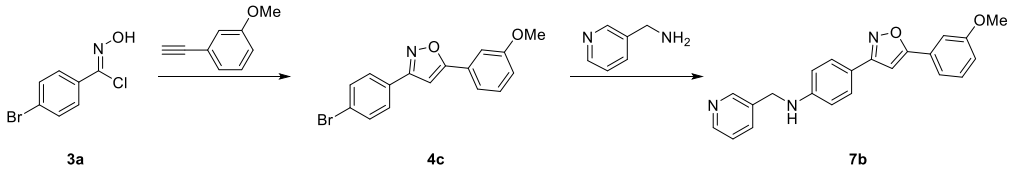
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol), and 1-ethynyl-2-methoxybenzene (0.11 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(2-methoxyphenyl)isoxazole (**4b**, 235 mg). The crude product was used for the next reaction wit hout further purification.

Preparation of 4-(5-(2-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7a)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-methoxyphenyl)isoxazole (**4b**, 0.07 g, 0.21 mmol) and pyridine-3-ylmethanamine (0.07 g, 0.63 mmol) in the manner described above general procedure **B** to obtain desired product, 4-(5-(2-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7a**, 5.40 mg, 2%, two step yield).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.47–8.46 (m, 1H), 7.86 (dd, J = 7.8, 1.8 Hz, 1H), 7.79–7.75 (m, 1H), 7.66–7.64 (m, 2H), 7.53–7.47 (m, 1H), 7.39–7.35 (m, 1H), 7.25–7.19 (m, 2H), 7.14–7.09 (m, 1H), 6.79 (t, J = 6.3 Hz, 1H), 6.73–6.70 (m, 2H), 4.39 (d, J = 5.7 Hz, 2H), 3.98 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 165.54, 162.91, 156.42, 150.36, 149.40, 148.57, 135.67, 135.53, 132.08, 128.17, 127.41, 123.97, 121.24, 116.66, 116.12, 112.83, 112.59, 101.56, 56.22, 44.18. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{20}N_3O_2^+$ $[M+H]^+$: 358.1550 found 358.1563.

Synthesis of compound 7b



Preparation of 3-(4-bromophenyl)-5-(3-methoxyphenyl)isoxazole (4c)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.10 g, 0.43 mmol) and 1-ethynyl-3-methoxybenzene (0.06 g, 0.43 mmol) in the manner described above general procedure **A** to obtain desired product, 3-(4-bromophenyl)-5-(3-methoxyphenyl)isoxazole (**4c**, 86.0 mg, 61%).

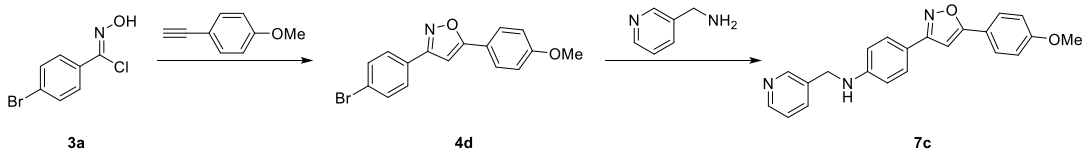
^{1}H NMR (300 MHz, DMSO-d_6): 7.93–7.68 (m, 5H), 7.53–7.43 (m, 3H), 7.12 (s, 1H), 3.86 (s, 3H).

Preparation of 4-(5-(3-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7b)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-methoxyphenyl)isoxazole (**4c**, 0.07 g, 0.21 mmol) and pyridine-3-ylmethanamine (0.07 g, 0.63 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(3-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7b**, 7.0 mg, 9%).

^{1}H NMR (300 MHz, CD_3OD): δ 8.58 (s, 1H), 8.43 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 9.0 Hz, 2H), 7.42–7.37 (m, 4H), 7.06–7.00 (m, 2H), 6.70 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 3.86 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.17, 163.09, 160.17, 150.47, 149.38, 148.56, 135.64, 135.54, 130.94, 128.80, 128.13, 123.99, 118.22, 116.60, 116.42, 112.84, 111.06, 98.79, 55.82, 44.15. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{20}N_3O_2^+$ $[M+H]^+$: 358.1550 found 358.1554.

Synthesis of compound 7c



3a **4d** **7c**

Preparation of 3-(4-bromophenyl)-5-(4-methoxyphenyl)isoxazole (4d)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-3-methoxybenzene (0.11 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(4-methoxyphenyl)isoxazole (**4d**, 184 mg, 66%).

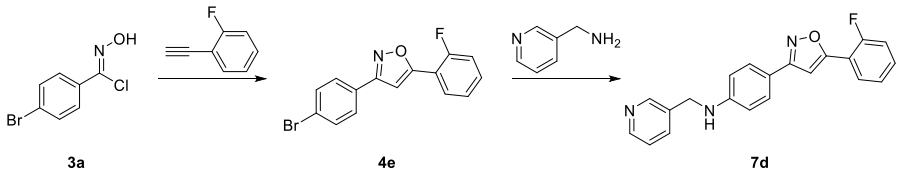
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (dd, J = 8.6, 3.4 Hz, 4H), 7.77 (d, J = 8.3 Hz, 2H), 7.51 (s, 1H), 7.13 (d, J = 8.5 Hz, 2H), 3.85 (s, 3H).

Preparation of 4-(5-(4-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7c)

The title compound was prepared from 3-(4-bromophenyl)-5-(4-methoxyphenyl)isoxazole (**4d**, 0.09 g, 0.27 mmol) and pyridine-3-ylmethanamine (0.09 g, 0.81 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(4-methoxyphenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7c**, 26.0 mg, 27%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.62 (d, J = 2.4 Hz, 1H), 8.46 (dd, J = 4.5, 1.5 Hz, 1H), 7.83–7.76 (m, 3H), 7.61 (d, J = 8.4 Hz, 2H), 7.39–7.34 (m, 1H), 7.24 (s, 1H), 7.10 (d, J = 9 Hz, 2H), 6.79 (t, J = 6 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 4.39 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.34, 162.99, 161.17, 150.39, 149.39, 148.56, 135.65, 135.53, 128.09, 127.62, 123.96, 120.32, 116.62, 115.11, 112.81, 96.93, 55.84, 44.16. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{20}N_3O_2^+$ $[M+H]^+$: 358.1550 found 358.1565.

Synthesis of compound 7d



Preparation of 3-(4-bromophenyl)-5-(2-fluorophenyl)isoxazole (4e)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-2-flurobenzene (0.10 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(2-fluorophenyl)isoxazole (**4e**, 0.20 g, 74%).

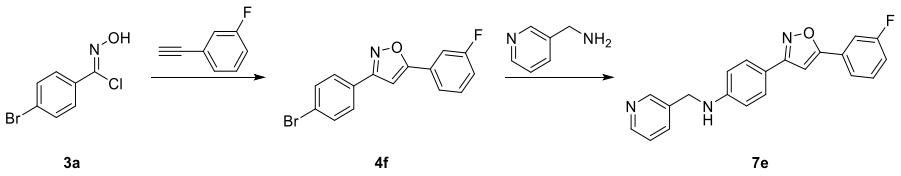
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05–7.88 (m, 3H), 7.76 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 7.2 Hz, 1H), 7.59–7.38 (m, 3H).

Preparation of 4-(5-(2-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7d)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-fluorophenyl)isoxazole (**4e**, 0.20 g, 0.63 mmol) and pyridine-3-ylmethanamine (0.20 g, 1.89 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(2-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7d**, 30.0 mg, 14%).

^{1}H NMR (500 MHz, CD_3OD): δ 8.59 (s, 1H), 8.44 (d, J = 5 Hz, 1H), 7.99–7.96 (m, 1H), 7.90–7.88 (m, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.55–7.52 (m, 1H), 7.44–7.42 (m, 1H), 7.39–7.31 (m, 2H), 7.08 (d, J = 3.5 Hz, 1H), 6.74 (d, J = 8.5 Hz, 2H), 4.49 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 163.57 (d, J = 2.6 Hz), 163.16, 150.84 (d, J = 253.0 Hz), 150.54, 149.37, 148.56, 135.63, 135.52, 132.83 (d, J = 8.6 Hz), 128.29, 128.15 (d, J = 2.0 Hz), 125.77 (d, J = 3.4 Hz), 123.98, 117.10 (d, J = 21.2 Hz), 116.12, 115.64 (d, J = 12.22 Hz) 112.84, 101.71 (d, J = 8.9 Hz), 44.14. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{17}FN_3O^+$ $[M+H]^+$: 346.1350 found 346.1355.

Synthesis of compound 7e



3a 4f 7e

Preparation of (4-bromophenyl)-5-(3-fluorophenyl)isoxazole (4f)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.10 g, 0.43 mmol) and 1-ethynyl-3-flurobenzene (0.15 g, 1.29 mmol, 3.0 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-fluorophenyl)isoxazole (**4f**, 0.10 g, 74%).

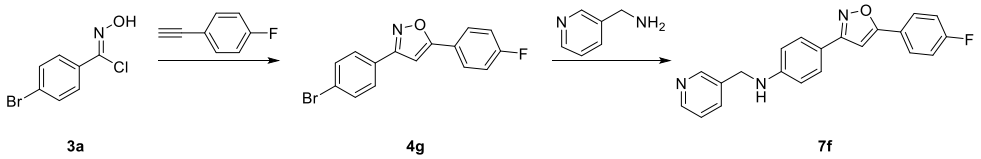
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.65 (dd, *J* = 8.2, 1.7 Hz, 3H), 7.58–7.44 (m, 2H), 7.24–7.13 (m, 1H), 6.85 (s, 1H).

Preparation of 4-(5-(3-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7e)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-fluorophenyl)isoxazole (**4f**, 0.05 g, 0.16 mmol) and pyridine-3-ylmethanamine (0.05 g, 0.48 mmol, 3.0 eq) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(3-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7e**, 20.0 mg, 37%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.49 (s, 1H), 7.79–7.72 (m, 3H), 7.63–7.59 (m, 3H), 7.51 (s, 1H), 7.39–7.35 (m, 2H), 6.85–6.82 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 4.40 (d, *J* = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 168.00 (d, *J* = 2.9 Hz), 163.19, 162.89 (d, *J* = 245.4 Hz), 150.56, 149.41, 148.58, 135.49, 132.00 (d, *J* = 8.6 Hz), 129.61 (d, *J* = 8.6 Hz), 128.13, 122.08 (d, *J* = 2.8 Hz), 117.55 (d, *J* = 21.0 Hz), 116.18, 112.90, 112.85, 112.67, 99.57, 44.15. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{17}FN_3O^+$ $[M+H]^+$: 346.1350 found 346.1360.

Synthesis of compound 7f



3a 4g 7f

Preparation of 3-(4-bromophenyl)-5-(4-fluorophenyl)isoxazole (4g)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-4-flurobenzene (0.10 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(4-fluorophenyl) isoxazole (**4g**, 200 mg, 74%).

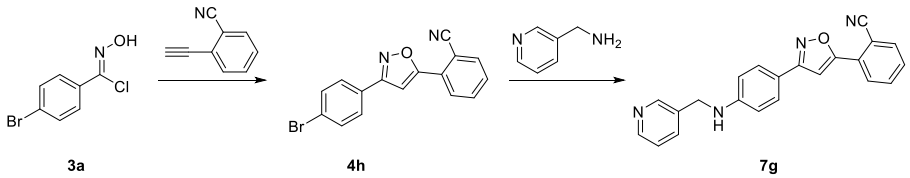
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97 (d, J = 7.1 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.65 (s, 1H), 7.45 (t, J = 8.6 Hz, 2H).

Preparation of 4-(5-(4-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7f)

The title compound was prepared from 3-(4-bromophenyl)-5-(4-fluorophenyl)isoxazole (**4g**, 0.20 g, 0.63 mmol) and pyridine-3-ylmethanamine (0.20 g, 1.89 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(4-fluorophenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7f**, 30.0 mg, 14%).

^{1}H NMR (500 MHz, CD_3OD): δ 8.60 (s, 1H), 8.45 (s, 1H), 7.94–7.88 (m, 3H), 7.65 (d, J = 8.0 Hz, 2H), 7.44–7.42 (m, 1H), 7.28 (t, J = 8.5 Hz, 2H), 7.09 (s, 1H), 6.73 (d, J = 8.5 Hz, 2H), 4.49 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 168.38, 163.50 (d, J = 249.0 Hz), 163.15, 150.49, 149.38, 148.56, 135.64, 135.53, 128.41 (d, J = 8.9 Hz), 128.13, 124.30 (d, J = 3.3 Hz), 123.99, 116.84 (d, J = 22.4 Hz), 116.33, 112.83, 98.39, 44.12, 39.96. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{17}FN_3O^+$ $[M+H]^+$: 346.1350 found 346.1357.

Synthesis of compound 7g



Preparation of 2-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (4h)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 2-ethynylbenzonitrile (0.13 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product 2-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4h**, 210 mg, 76%).

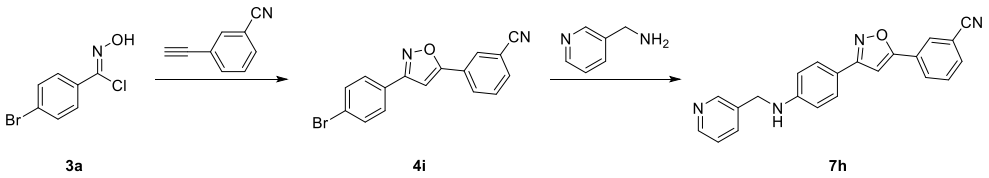
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25–8.06 (m, 1H), 7.90–7.74 (m, 3H), 7.71–7.53 (m, 4H), 7.49 (s, 1H).

Preparation of 2-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (7g)

The title compound was prepared from 2-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4h**, 0.20 g, 0.62 mmol) and pyridine-3-ylmethanamine (0.20 g, 1.86 mmol) in the manner described above general procedure **B** to obtain the desired product, 2-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (**7g**, 50.0 mg, 23%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.60 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.79–7.73 (m, 4H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.47 (s, 2H), 4.43–4.41 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 166.10, 163.13, 150.69, 149.40, 148.57, 135.51, 135.21, 134.40, 131.27, 129.58, 128.82, 128.27, 124.06, 118.18, 115.78, 112.89, 108.83, 101.85, 44.15. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}N_4O^+$ $[M+H]^+$: 353.1397 found 353.1400.

Synthesis of compound 7h



Preparation of 3-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (4i)

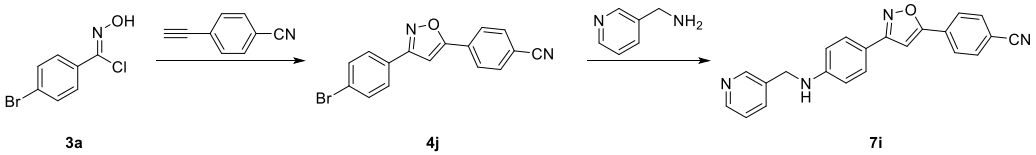
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.10 g, 0.43 mmol) and 3-ethynylbenzonitrile (0.08 g, 0.65 mmol, 1.5 eq) in the manner described above general procedure **A** to obtain the desired product 3-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4i**, 150 mg). The crude product was used for the next reaction without further purification.

Preparation of 3-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (7h)

The title compound was prepared from 3-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4i**, 0.15 g, 0.46 mmol) and pyridine-3-ylmethanamine (0.15 g, 1.38 mmol) in the manner described above general procedure **B** to obtain the desired product, 3-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (**7h**, 20.0 mg, 13%, two step yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.58 (d, *J* = 4.8 Hz, 1H), 8.12 (s, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.75–7.70 (m, 4H), 7.64 (t, *J* = 8 Hz, 1H), 7.34–7.30 (m, 1H), 6.85 (s, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.48–4.47 (m, 2H), 4.43 (d, *J* = 6.0 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 167.27, 163.27, 150.62, 149.39, 148.58, 135.60, 135.53, 134.04, 131.07, 130.26, 129.62, 128.62, 128.14, 123.98, 118.63, 116.03, 112.96, 112.88, 100.09, 44.11. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}N_4O^+$ $[M+H]^+$: 353.1397 found 353.1397.

Synthesis of compound 7i



3a 4j 7i

Preparation of 4-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (4j)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 4-ethynylbenzonitrile (0.13 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product, 4-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4j**, 0.20 g, 72%).

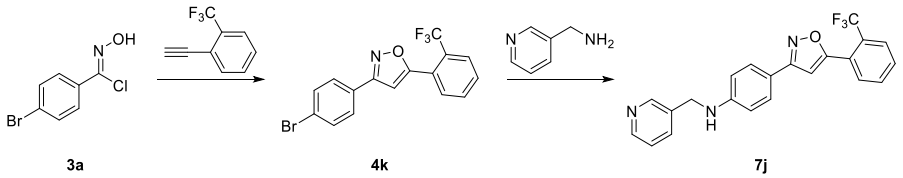
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 6.97 (s, 1H).

Preparation of 4-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (7i)

The title compound was prepared from 4-(3-(4-bromophenyl)isoxazol-5-yl)benzonitrile (**4j**, 0.20 g, 0.62 mmol) and pyridine-3-ylmethanamine (0. 20 g, 1.86 mmol) in the manner described above general procedure **B**, purified by preparatory HPLC to obtain the desired product, 4-(3-(4-((pyridin-3-ylmethyl)amino)phenyl)isoxazol-5-yl)benzonitrile (**7i**, 25.0 mg, 12%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.60 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.79–7.73 (m, 4H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.42 (s, 1H), 7.33 (s, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 4.48–4.46 (m, 2H), 4.43–4.41 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-*d*$_6$): δ 167.45, 163.34, 150.64, 149.40, 148.58, 135.59, 135.53, 133.74, 131.35, 128.18, 126.60, 123.99, 118.87, 115.94, 112.85, 100.92, 44.10. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}N_4O^+$ $[M+H]^+$: 353.1397 found 353.1399.

Synthesis of compound 7j



Preparation of 3-(4-bromophenyl)-5-(2-(trifluoromethyl)phenyl)isoxazole (4k)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.12 g, 0.51 mmol) and 1-ethynyl-2-(trifluoromethyl)benzene (0.10 g, 0.61 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(2-(trifluoromethyl)phenyl)isoxazole (**4k**, 150 mg, 80%).

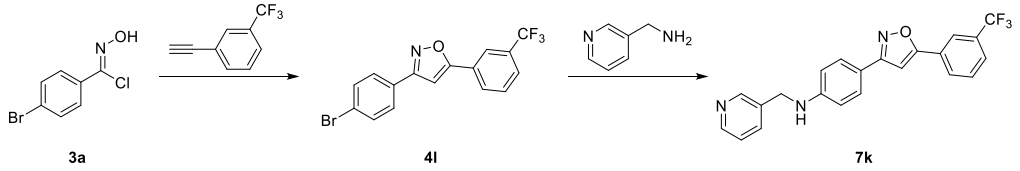
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.75 (m, 4H), 7.75–7.57 (m, 4H), 6.86 (s, 1H).

Preparation of 4-(5-(2-(trifluoromethyl)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (7j)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-(trifluoromethyl)phenyl)isoxazole (**4k**, 0.15 g, 0.41 mmol) and pyridine-3-ylmethanamine (0.13 g, 1.23 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(2-(trifluoromethyl)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (**7j**, 30.0 mg, 19%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.83 (d, *J* = 9 Hz, 2H), 7.72–7.66 (m, 4H), 7.60 (t, *J* = 8 Hz, 1H), 7.30–7.28 (m, 1H), 6.78 (s, 1H), 6.73–6.70 (m, 2H), 4.54 (t, *J* = 6 Hz, 1H), 4.45–4.44 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.86, 162.68, 149.12, 148.90, 135.05, 134.37, 132.02, 130.94, 130.04, 128.41, 128.18, 127.94 (q, *J* = 31.4 Hz), 126.84, 126.68 (q, *J* = 5.8 Hz), 126.58, 123.64, 123.57 (q, *J* = 274.1 Hz), 118.22, 112.92, 102.05 (q, *J* = 3.5 Hz), 45.43. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}F_3N_3O^+$ $[M+H]^+$: 396.1318 found 396.1324.

Synthesis of compound 7k



3a **4l** **7k**

Preparation of 3-(4-bromophenyl)-5-(3-(trifluoromethyl)phenyl)isoxazole (4l)

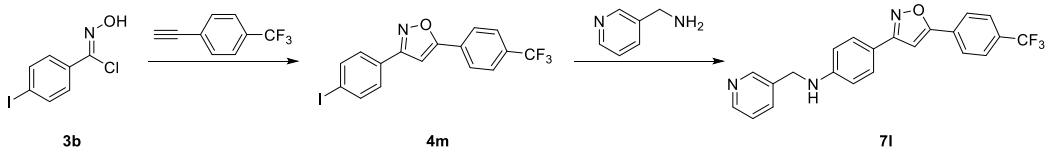
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-3-(trifluoromethyl)benzene (0.17 g, 1.02 mmol, 1.20 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-(trifluoromethyl)phenyl)isoxazole (**4l**, 250 mg, 80%).

Preparation of N-(pyridin-3-ylmethyl)-4-(5-(3-(trifluoromethyl)phenyl)isoxazol-3-yl)aniline (7k)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-(trifluoromethyl)phenyl)isoxazole (**4l**, 0.15 g, 0.41 mmol) and pyridine-3-ylmethanamine (0.13 g, 1.23 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(3-(trifluoromethyl)phenyl)isoxazol-3-yl)aniline (**7k**, 20.0 mg, 12%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.48–8.46 (m, 1H), 8.21 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.83–7.73 (m, 2H), 7.66 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.37 (dd, J = 8.0, 4.8 Hz, 1H), 6.83 (t, J = 6.4 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 167.65, 163.29, 150.60, 149.40, 148.58, 135.61, 135.53, 131.05, 130.53 (q, J = 32.9 Hz), 129.70, 128.50, 128.16, 127.13 (d, J = 3.9), 124.32 (q, J = 273.81 Hz), 123.97, 122.52 (q, J = 3.4 Hz), 116.12, 112.86, 99.96, 44.12. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{17}F_3N_3O^+$ $[M+H]^+$: 396.1318 found 396.1326.

Synthesis of compound 7l



3b 4m 7l

Preparation of 3-(4-iodophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (4m)

The title compound was prepared from (*Z*)-*N*-hydroxy-4-iodobenzimidoyl chloride (**3b**, 0.20 g, 0.71 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (0.14 g, 0.85 mmol, 1.20 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-iodophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (**4m**, 250 mg, 85%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (d, J = 8.0 Hz, 2H), 8.04–7.91 (m, 4H), 7.87 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H).

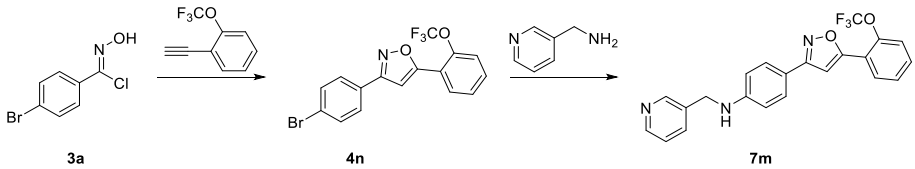
Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(4-(trifluoromethyl)phenyl)isoxazol-3-yl)aniline (7l)

The title compound was prepared from 3-(4-iodophenyl)-5-(4-(trifluoromethyl)phenyl)isoxazole (**4m**, 0.20 g, 0.48 mmol) and pyridine-3-ylmethanamine (0.16 g, 1.44 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(4-(trifluoromethyl)phenyl)isoxazol-3-yl)aniline (**7l**, 30.0 mg, 16%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.47 (d, J = 4.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.78–7.76 (m, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.37 (dd, J = 7.6, 4.4 Hz, 1H), 6.84 (t, J = 6.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 167.70, 163.31, 150.61, 149.40, 148.58, 135.59, 135.52, 131.13, 130.46 (q, J = 32.3 Hz), 128.19, 126.72, 126.67, 124.39 (q, J = 273.5 Hz), 123.96, 116.08, 112.85, 100.35, 44.13. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}F_3N_3O^+$ $[M+H]^+$: 396.1318 found 396.1326.

Synthesis of compound 7m



Preparation of 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)phenyl)isoxazole (4n)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-2-(trifluoromethoxy)benzene (0.19 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A**, to obtain the desired product, 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)phenyl)isoxazole (**4n**, 250 mg, 76%).

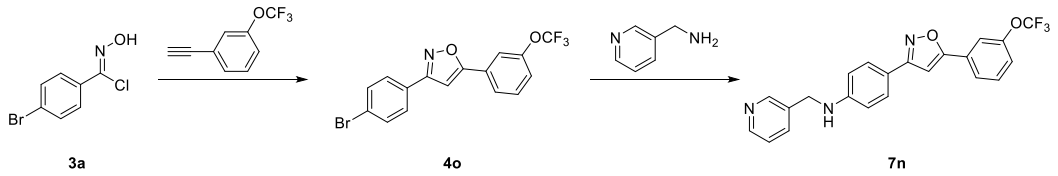
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.59–7.38 (m, 3H), 7.02 (s, 1H).

Preparation of 4-(5-(2-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7m)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)phenyl)isoxazole (**4n**, 0.20 g, 0.52 mmol) and pyridine-3-ylmethanamine (0.17 g, 1.56 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(4-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7m**, 25.0 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.58 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 3H), 7.52–7.41 (m, 3H), 7.33–7.29 (m, 1H), 6.96 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.47–4.42 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.02, 163.08, 149.14, 149.10, 148.94, 145.48, 135.02, 134.37, 131.04, 128.60, 128.18, 127.17, 123.66, 120.97, 120.68, 120.52 (q, *J* = 260 MHz), 118.37, 112.92, 101.63, 45.48. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}F_3N_3O_2^+$ $[M+H]^+$: 412.1267 found 412.1274.

Synthesis of compound 7n



Preparation of 3-(4-bromophenyl)-5-(3-(trifluoromethoxy)phenyl)isoxazole (4o)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-3-(trifluoromethoxy)benzene (0.19 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-(trifluoromethoxy)phenyl)isoxazole (**4o**, 0.25 g, 76%).

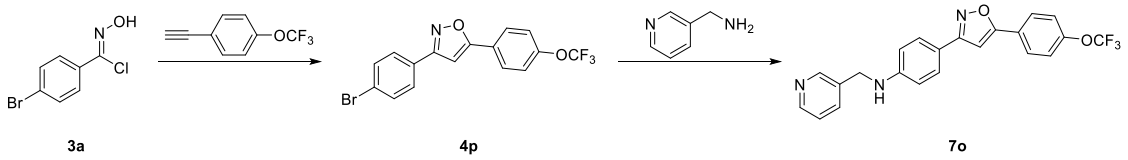
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81–7.74 (m, 3H), 7.71–7.64 (m, 3H), 7.57 (t, *J* = 8.1 Hz, 1H), 7.37–7.33 (m, 1H), 6.88 (s, 1H).

Preparation of 4-(5-(3-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (7n)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-(trifluoromethoxy)phenyl)isoxazole (**4o**, 0.20 g, 0.52 mmol) and pyridine-3-ylmethanamine (0.17 g, 1.56 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(3-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (**7n**, 70.0 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.58 (d, *J* = 4.8 Hz, 1H), 7.79–7.69 (m, 5H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.33–7.29 (m, 2H), 6.80 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.47–4.46 (m, 2H), 4.41–4.40 (m, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 167.59, 163.26, 150.58, 149.39, 149.33, 148.56, 135.60, 135.52, 131.96, 129.59, 128.16, 124.92, 123.96, 123.01, 120.52 (q, *J* = 257.5 Hz), 118.46, 116.14, 112.84, 99.84, 44.13. **HRMS** (FAB^+) *m/z* calcd. for $C_{22}H_{17}F_3N_3O_2^+$ $[M+H]^+$: 412.1267 found 412.1271.

Synthesis of compound 7o



3a 4p 7o

Preparation of 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)phenyl)isoxazole (4p)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-ethynyl-4-(trifluoromethoxy)benzene (0.19 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)phenyl)isoxazole (**4p**, 0.25 g, 76%).

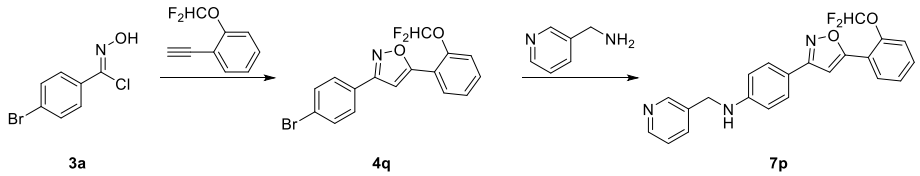
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.1 Hz, 2H), 7.81–7.72 (m, 3H), 7.60 (d, J = 8.3 Hz, 2H).

Preparation of 4-(5-(4-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (7o)

The title compound was prepared from 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)phenyl)isoxazole (**4p**, 0.20 g, 0.52 mmol) and pyridine-3-ylmethanamine (0.17 g, 1.56 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(4-(trifluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (**7o**, 50.0 mg, 23%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.49 (s, 1H), 8.01 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.47 (s, 1H), 7.38–7.36 (m , 1H), 6.84 (t, J = 6.0 Hz, 1H), 6.74 (d, J = 8.5 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 167.93, 163.22, 150.55, 149.77, 149.40, 148.56, 135.50, 128.16, 128.07, 126.77, 124.04, 122.20, 120.47 9 (q, 257.7 Hz), 116.23, 112.83, 99.22, 44.16. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{17}F_3N_3O_2^+$ $[M+H]^+$: 412.1267 found 412.1271.

Synthesis of compound 7p



Preparation of 3-(4-bromophenyl)-5-(2-(difluoromethoxy)phenyl)isoxazole (4q)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-(difluoromethoxy)-2-ethynylbenzene (0.17 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A**, to obtain the desired product, 3-(4-bromophenyl)-5-(2-(difluoromethoxy)phenyl)isoxazole (**4q**, 250 mg, 80%).

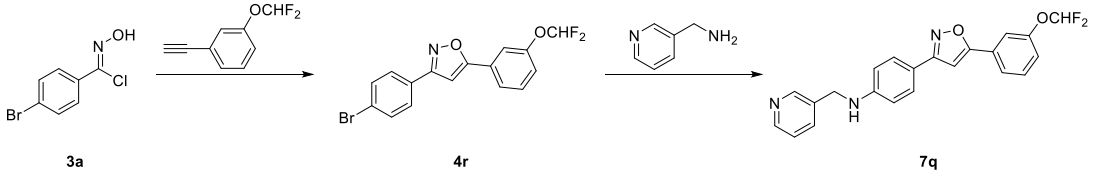
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.01 (dd, J = 7.8, 1.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.85–7.69 (m, 3H), 7.67–7.60 (m, 1H), 7.50–7.42 (m, 2H), 7.39 (s, 1H).

Preparation of 4-(5-(2-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7p)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-(difluoromethoxy)phenyl)isoxazole (**4q**, 0.24 g, 0.66 mmol) and pyridine-3-ylmethanamine (0.21 g, 1.98 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(2-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7p**, 50.0 mg, 19%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.58 (s, 1H), 8.10–8.07 (m, 1H), 7.73 (d, J = 8.8 Hz, 3H), 7.49–7.45 (m, 1H), 7.39–7.36 (m, 1H), 7.33–7.30 (m, 1H), 7.28–7.24 (m, 1H), 7.04 (s, 1H), 6.82–6.45 (m, 3H), 4.46 (s, 2H), 4.40 (s, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 164.70, 163.03, 150.53, 149.39, 148.56, 147.80, 135.51, 133.87, 132.21, 128.65, 128.18, 126.26, 123.99, 119.69, 119.28, 116.91 (t, J = 260.3 MHz), 116.24, 112.89, 101.93, 44.18. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{18}F_2N_3O_2^+$ $[M+H]^+$: 394.1362 found 394.1371.

Synthesis of compound 7q



Preparation of 3-(4-bromophenyl)-5-(3-(difluoromethoxy)phenyl)isoxazole (4r)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.11 g, 0.47 mmol) and 1-(difluoromethoxy)-3-ethynylbenzene (0.09 g, 0.56 mmol, 1.2 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-(difluoromethoxy)phenyl)isoxazole (**4r**, 60.0 mg, 35%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.88 (d, J = 8.5 Hz, 2H), 7.83–7.76 (m, 4H), 7.73 (s, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.57–7.23 (m, 2H).

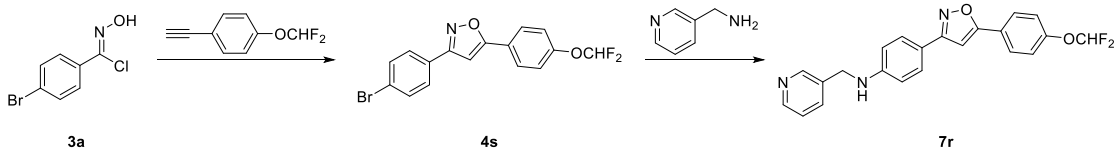
Preparation of 4-(5-(3-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7q)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-(difluoromethoxy)phenyl)isoxazole (**4r**, 0.10 g, 0.27 mmol) and pyridine-3-ylmethanamine (0.09 g, 0.81 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(3-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7q**, 24.0 mg, 22%).

^{1}H NMR (500 MHz, CD_3OD): δ 8.58 (s, 1H), 8.43 (s, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 6.0 Hz, 3H), 7.58–7.52 (m, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.17 (s, 1H), 6.95 (t, J = 74 Hz, 1H), 6.71 (d, J = 8.5 Hz, 2H), 4.47 (s, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 168.12, 163.20, 151.97 (t, J = 3.3 Hz), 150.55, 150.49, 149.40, 148.57, 135.61, 135.53, 131.64, 129.28, 128.15, 123.97, 122.66, 120.83, 116.77 (t, J = 258.9 Hz), 116.19, 115.99, 112.84, 99.47, 44.12. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{18}F_2N_3O_2^+$ $[M+H]^+$: 394.1362 found 394.1363.

Synthesis of compound 7r



3a **4s** **7r**

Preparation of 3-(4-bromophenyl)-5-(4-(difluoromethoxy)phenyl)isoxazole (4s)

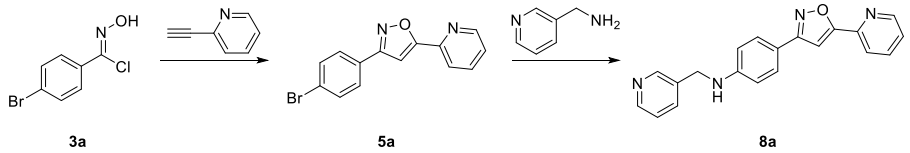
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 1-(difluoromethoxy)-4-ethynylbenzene (0.17 g, 1.02 mmol, 1.2 eq) in the manner described above general procedure **A**, to obtain the desired product, 3-(4-bromophenyl)-5-(4-(difluoromethoxy)phenyl)isoxazole (**4s**, 300 mg). The crude product was used for the next reaction without further purification.

Preparation of 4-(5-(4-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (7r)

The title compound was prepared from 3-(4-bromophenyl)-5-(4-(difluoromethoxy)phenyl)isoxazole (**4s**, 0.30 g, 0.82 mmol) and pyridine-3-ylmethanamine (0.27 g, 2.46 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(4-(difluoromethoxy)phenyl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**7r**, 25.0 mg, 8%, two step yield).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.63 (s, 1H), 8.48 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.53–7.24 (m, 5H), 6.83 (t, J = 6.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 168.41, 163.15, 152.64 (t, J = 3.3 Hz), 150.49, 149.36, 148.55, 135.70, 135.54, 128.14, 127.93, 124.52, 124.04, 119.61, 116.58 (t, J = 259.3 Hz), 116.33, 112.84, 98.44, 44.14. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{22}H_{18}F_2N_3O_2^+$ $[M+H]^+$: 394.1362 found 394.1361.

Synthesis of compound 8a



3a 5a 8a

Preparation of 3-(4-bromophenyl)-5-(pyridin-2-yl) isoxazole (5a)

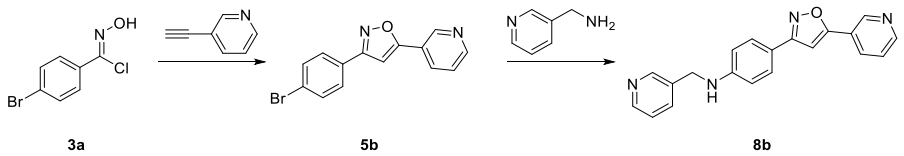
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 2-ethynylpyridine (0.09 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(pyridin-2-yl) isoxazole (**5a**, 234 mg). The crude product was used for the next reaction without further purification.

Preparation of 4-(5-(pyridin-2-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (8a)

The title compound was prepared from compounds 3-(4-bromophenyl)-5-(pyridin-2-yl) isoxazole (**5a**, 98.0 mg, 0.33 mmol) and pyridine-3-ylmethanamine (0.11 g, 0.99 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(pyridin-2-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**8a**, 18.0 mg, 17%).

^{1}H NMR (300 MHz, CD_3OD): δ 8.68 (dt, *J* = 5.1, 1.5 Hz, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 8.00–7.99 (m, 2H), 7.88 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.69–7.64 (m, 2H), 7.53–7.46 (m, 1H), 7.42 (dd, *J* = 7.8, 5.1 Hz, 1H), 7.30 (s, 1H), 6.76–6.71 (m, 2H), 4.48 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.02, 163.19, 150.60, 150.54, 149.38, 148.57, 146.35, 138.14, 135.63, 135.51, 128.28, 125.37, 123.97, 121.28, 116.18, 112.84, 100.62, 44.13. **HRMS** (FAB^+) *m/z* calcd. for $C_{20}H_{17}N_4O^+$ $[M+H]^+$: 329.1397 found 329.1407.

Synthesis of compound 8b



3a **5b** **8b**

Preparation of 3-(4-bromophenyl)-5-(pyridin-3-yl) isoxazole (5b)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.15 g, 0.64 mmol), and 3-ethynylpyridine (0.07 g, 0.64 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(pyridin-3-yl) isoxazole (**5b**, 0.15 g, 78%) as an off-yellow solid.

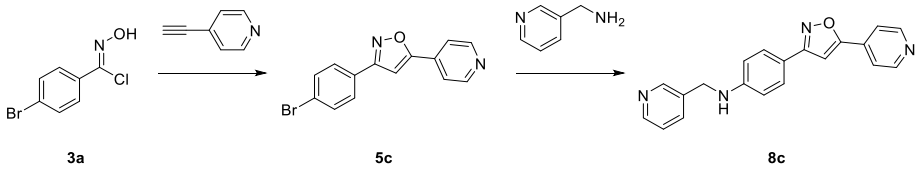
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.77 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (s, 1H), 6.94 (s, 1H).

Preparation of 4-(5-(pyridin-3-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (8b)

The title compound was prepared from 3-(4-bromophenyl)-5-(pyridin-3-yl) isoxazole (**5b**, 0.05 g, 0.17 mmol) and pyridine-3-ylmethanamine (0.05 g, 0.51 mmol) in the manner described above general procedure **B** to obtain the desired product, 4-(5-(pyridin-3-yl) isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl) aniline (**8b**, 20.0 mg, 37%).

^{1}H NMR (300 MHz, CD_3OD): δ 9.07 (d, *J* = 1.2 Hz, 1H), 8.64 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.59 (s, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 8.33–8.29 (m, 1H), 7.88 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.69–7.64 (m, 2H), 7.60 (ddd, *J* = 8.1, 5.1, 0.9 Hz, 1H), 7.43 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.30 (s, 1H), 6.76–6.71 (m, 2H), 4.48 (s, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 166.86, 163.16, 151.37, 150.59, 149.37, 148.56, 146.95, 135.61, 135.54, 133.28, 128.18, 124.70, 123.97, 123.77, 116.08, 112.86, 99.64, 44.12. **HRMS** (FAB^+) *m/z* calcd. for $C_{20}H_{17}N_4O^+$ $[M+H]^+$: 329.1397 found 329.1406.

Synthesis of compound 8c



3a 5c 8c

Preparation of 3-(4-bromophenyl)-5-(pyridin-4-yl)isoxazole (5c)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3c**, 0.15 g, 0.64 mmol) and 4-ethynylpyridine (0.07 g, 0.64 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(pyridin-4-yl)isoxazole (**5c**, 55.0 mg, 29%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.6 Hz, 3H), 7.73 (d, *J* = 4.9 Hz, 2H), 7.68–7.64 (m, 3H), 7.03 (s, 1H).

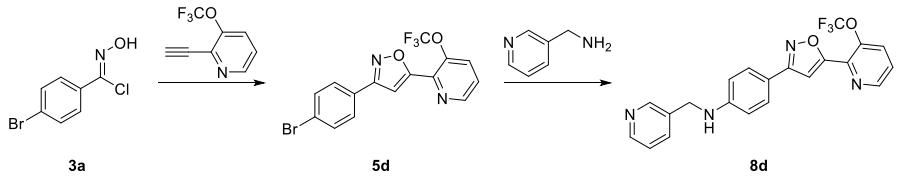
Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(pyridin-4-yl)isoxazol-3-yl)aniline (8c)

The title compound was prepared from 3-(4-bromophenyl)-5-(pyridin-4-yl)isoxazole (**5c**, 0.05 g, 0.15 mmol) and pyridine-3-ylmethanamine (0.05 g, 0.45 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(pyridin-4-yl)isoxazol-3-yl)aniline (**8c**, 10.0 mg, 19%).

^{1}H NMR (300 MHz, CD_3OD): δ 8.73–8.70 (m, 2H), 8.59 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 7.90–7.88 (m, 3H), 7.69–7.66 (m, 2H), 7.45–7.41 (m, 2H), 6.76–6.72 (m, 2H), 4.49 (s, 2H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 166.93, 163.35, 151.24, 150.67, 149.38, 148.58, 135.59, 135.54, 134.09, 128.21, 123.98, 119.79, 115.88, 112.87, 101.43, 44.11. **HRMS** (FAB^+) *m/z* calcd. for $C_{20}H_{17}N_4O^+$ $[M+H]^+$: 329.1397 found 329.1405.

Synthesis of compound 8d



Preparation of 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazole (5d)

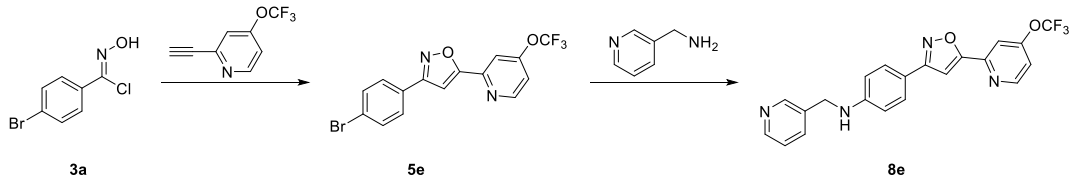
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 2-ethynyl-3-(trifluoromethoxy)pyridine (0.16 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5d**, 186 mg). The crude product was used for the next reaction without further purification.

Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(3-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (8d)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5d**, 0.05 g, 0.13 mmol) and pyridine-3-ylmethanamine (0.04 g, 0.39 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(3-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (**8d**, 12.0 mg, 23%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 7.75–7.65 (m, 4H), 7.42 (dd, *J* = 8.4, 4.5 Hz, 1H), 7.23 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.14 (s, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 4.76 (t, *J* = 5.7 Hz, 1H), 4.40 (d, *J* = 5.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.86, 162.73, 149.34, 149.00, 148.71, 148.05, 142.91, 142.89 (d, *J* = 2.0 Hz), 139.72, 135.02, 134.49, 132.09, 129.24, 128.15, 125.16, 123.62, 120.49 (q, *J* = 261.9 Hz), 117.72, 117.68, 112.86, 103.58, 45.28. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{16}F_3N_4O_2^+$ $[M+H]^+$: 413.1220 found 413.1219.

Synthesis of compound 8e



3a 5e 8e

Preparation of 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazole (5e)

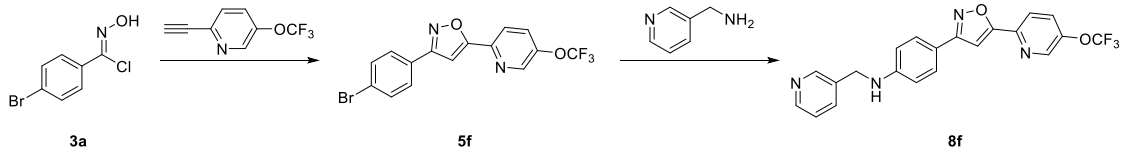
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 2-ethynyl-4-(trifluoromethoxy)pyridine (0.16 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5e**, 217 mg). The crude product was used for the next reaction without further purification.

Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (8e)

The title compound was prepared from 3-(4-bromophenyl)-5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5e**, 0.05 g, 0.13 mmol) and pyridin-3-ylmethanamine (0.04 g, 0.39 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(4-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (**8e**, 7.5 mg, 14%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.79 (dd, J = 4.5, 1.2 Hz, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.47 (dd, J = 4.8, 1.8 Hz, 1H), 8.15–8.11 (m, 1H), 7.79–7.67 (m, 4H), 7.47 (s, 1H), 7.37 (dd, J = 7.8, 4.5 Hz, 1H), 6.86 (t, J = 6.0 Hz, 1H), 6.75–6.70 (m, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.16, 163.19, 158.52, 151.91, 149.17, 149.15, 148.99, 148.93, 135.02, 134.27, 128.23, 123.65, 118.12, 114.79, 113.56, 112.93, 110.33, 100.73, 45.48. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{21}H_{16}F_3N_4O_2^+$ $[M+H]^+$: 413.1220 found 413.1307.

Synthesis of compound 8f



3a 5f 8f

Preparation of 3-(4-bromophenyl)-5-(5-(trifluoromethoxy)pyridin-2-yl)isoxazole (5f)

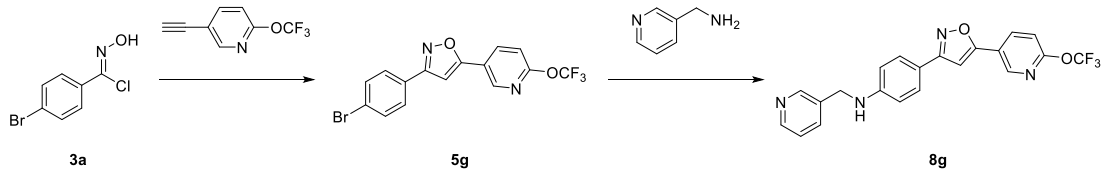
The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 2-ethynyl-5-(trifluoromethoxy)pyridine (0.16 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(5-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5f**, 224 mg). The crude product was used for the next reaction without further purification.

Preparation of N-(pyridin-3-ylmethyl)-4-(5-(5-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (8f)

The title compound was prepared from 3-(4-bromophenyl)-5-(5-(trifluoromethoxy)pyridin-2-yl)isoxazole (**5f**, 0.05 g, 0.13 mmol) and pyridin-3-ylmethanamine (0.04 g, 0.39 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(5-(trifluoromethoxy)pyridin-2-yl)isoxazol-3-yl)aniline (**8f**, 28.0 mg, 53%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.83 (s, 1H), 8.62 (d, J = 2.4 Hz, 1H), 8.46 (dd, J = 4.8, 1.5 Hz, 1H), 8.12 (d, J = 1.5 Hz, 2H), 7.77 (dt, J = 7.8, 2.1 Hz, 1H), 7.70–7.67 (m, 2H), 7.55 (s, 1H), 7.37 (dd, J = 7.8, 4.8 Hz, 1H), 6.85 (t, J = 6.0 Hz, 1H), 6.74–6.71 (m, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 167.71, 163.33, 150.62, 149.38, 148.57, 145.96 (d, J = 2.0 Hz), 145.31, 143.75, 135.61, 135.50, 130.72, 128.30, 123.97, 122.77, 120.43 (q, J = 259.5), 115.94, 112.83, 101.42, 44.11. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{21}H_{16}F_3N_4O_2^+$ $[M+H]^+$: 413.1220 found 413.1224.

Synthesis of compound 8g



Preparation of 3-(4-bromophenyl)-5-(6-(trifluoromethoxy)pyridin-3-yl)isoxazole (5g)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 5-ethynyl-2-(trifluoromethoxy)pyridine (0.16 g, 0.85) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(6-(trifluoromethoxy)pyridin-3-yl)isoxazole (**5g**, 158 mg, 48%).

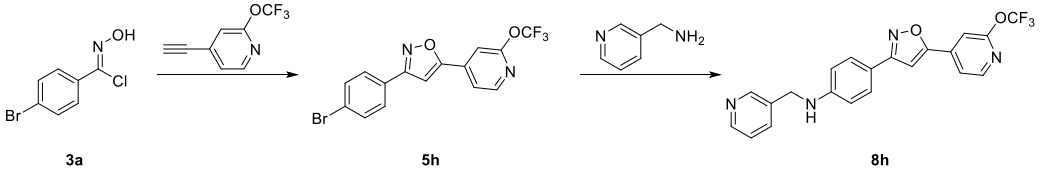
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (d, J = 2.4 Hz, 1H), 8.52 (dd, J = 8.7, 2.5 Hz, 1H), 7.94–7.71 (m, 5H), 7.54 (d, J = 8.6 Hz, 1H).

Preparation of N-(pyridin-3-ylmethyl)-4-(5-(6-(trifluoromethoxy)pyridin-3-yl)isoxazol-3-yl)aniline (8g)

The title compound was prepared from compounds 3-(4-bromophenyl)-5-(6-(trifluoromethoxy)pyridin-3-yl)isoxazole (**5g**, 0.05 g, 0.13 mmol) and pyridin-3-ylmethanamine (0.04 g, 0.39 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(6-(trifluoromethoxy)pyridin-3-yl)isoxazol-3-yl)aniline (**8g**, 8.0 mg, 15%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59–8.55 (m, 2H), 8.47–8.46 (m, 1H), 7.88–7.72 (m, 8H), 7.38–7.34 (m, 2H), 6.70 (d, J = 9.0 Hz, 1H), 4.60 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 169.65, 161.91, 159.67, 149.38, 148.50, 146.46, 135.89, 135.58, 134.36, 132.69, 132.63, 128.98, 128.44, 124.04, 123.96, 112.36, 109.11, 96.16, 42.20. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{21}H_{16}F_3N_4O_2^+$ $[M+H]^+$: 413.1220 found 413.1232.

Synthesis of compound 8h



Preparation of 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)pyridin-4-yl)isoxazole (5h)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 4-ethynyl-2-(trifluoromethoxy)pyridine (0.16 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)pyridin-4-yl)isoxazole (**5h**, 218 mg, 66%).

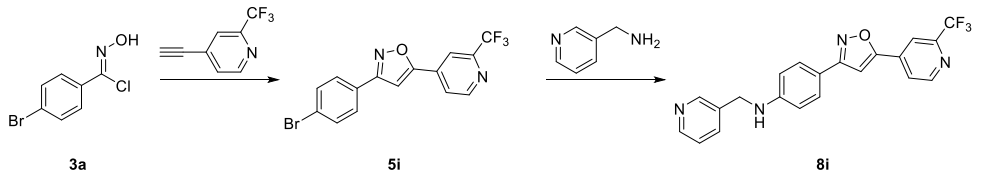
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (d, J = 5.2 Hz, 1H), 8.09 (s, 1H), 8.01–7.58 (m, 6H).

Preparation of N-(pyridin-3-ylmethyl)-4-(5-(2-(trifluoromethoxy)pyridin-4-yl)isoxazol-3-yl)aniline (8h)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-(trifluoromethoxy)pyridin-4-yl)isoxazole (**5h**, 0.05 g, 0.13 mmol) and pyridin-3-ylmethanamine (0.04 g, 0.39 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(2-(trifluoromethoxy)pyridin-4-yl)isoxazol-3-yl)aniline (**8h**, 17.0 mg, 32%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.56 (d, J = 5.1 Hz, 1H), 8.47 (d, J = 4.8 Hz, 1H), 7.87 (dd, J = 5.4, 1.5 Hz, 1H), 7.82 (s, 1H), 7.79–7.74 (m, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.37 (dd, J = 8.1, 4.8 Hz, 1H), 6.89 (t, J = 6.3 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 165.63, 163.43, 157.25 (d, J = 1.5 Hz), 150.77, 149.73, 149.39, 148.59, 138.93, 135.52, 128.20, 123.98, 120.18 (q, J = 261.3 Hz), 118.95, 115.62, 112.89, 109.22, 102.75, 44.09. **HRMS** (FAB$^+$) *m/z* calcd. for $C_{21}H_{16}F_3N_4O_2^+$ $[M+H]^+$: 413.1220 found 413.1223.

Synthesis of compound 8i



3a 5i 8i

Preparation of 3-(4-bromophenyl)-5-(2-(trifluoromethyl)pyridin-4-yl)isoxazole (5i)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.15 g, 0.64 mmol) and 4-ethynyl-2-(trifluoromethyl)pyridine (0.13 g, 0.77 mmol, 1.20 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(2-(trifluoromethyl)pyridin-4-yl)isoxazole (**5i**, 150 mg, 64%).

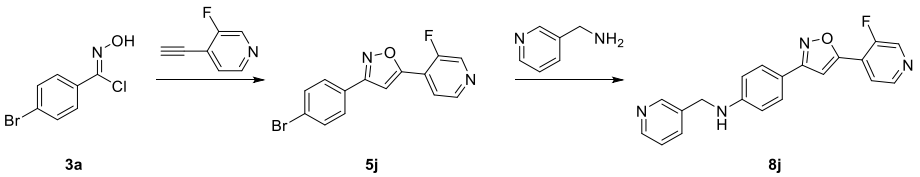
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.00 (d, *J* = 5.0 Hz, 1H), 8.37 (s, 1H), 8.19 (s, 2H), 7.98–7.65 (m, 4H).

Preparation of N-(pyridin-3-ylmethyl)-4-(5-(2-(trifluoromethyl)pyridin-4-yl)isoxazol-3-yl)aniline (8i)

The title compound was prepared from 3-(4-bromophenyl)-5-(2-(trifluoromethyl)pyridin-4-yl)isoxazole (**5i**, 0.15 g, 0.41 mmol) and pyridine-3-ylmethanamine (0.13 g, 1.23 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(2-(trifluoromethyl)pyridin-4-yl)isoxazol-3-yl)aniline (**8i**, 15.0 mg, 9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (d, *J* = 5.2 Hz, 1H), 8.68 (s, 1H), 8.59 (d, *J* = 4.8 Hz, 1H), 8.07 (s, 1H), 7.91 (d, *J* = 4.4 Hz, 1H), 7.74–7.71 (m, 3H), 7.32 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.05 (s, 1H), 6.75–6.72 (m, 2H), 4.48–4.45 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 165.73, 163.23, 151.06, 149.62, 149.37, 149.27, 149.00, 135.99, 135.03, 128.24, 122.62, 121.99, 119.90, 117.51, 116.48 (q, *J* = 2.8 Hz), 112.97, 100.79, 45.47. **HRMS** (FAB^+) *m/z* calcd. for $C_{21}H_{16}F_3N_4O^+$ $[M+H]^+$: 397.1271 found 397.1275.

Synthesis of compound 8j



3a 5j 8j

Preparation of 3-(4-bromophenyl)-5-(3-fluoropyridin-4-yl)isoxazole (5j)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol) and 4-ethynyl-3-fluoropyridine (0.10 g, 0.85) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(3-fluoropyridin-4-yl)isoxazole (**5j**, 236 mg, 87%).

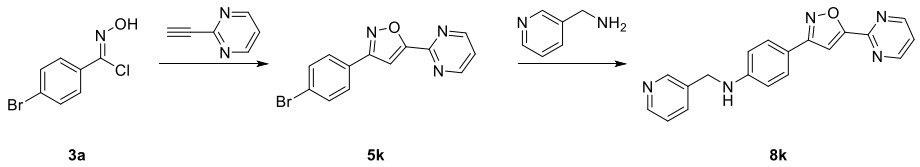
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.77 (d, J = 64.2 Hz, 2H), 7.99 –7.77 (m, 6H).

Preparation of 4-(5-(3-fluoropyridin-4-yl)isoxazol-3-yl)-N-(pyridin-3-ylmethyl)aniline (8j)

The title compound was prepared from 3-(4-bromophenyl)-5-(3-fluoropyridin-4-yl)isoxazole (**5j**, 0.05 g, 0.16 mmol) and pyridin-3-ylmethanamine (0.05 g, 0.48 mmol) in the manner described above general procedure **B**, to obtain the desired product, 4-(5-(3-fluoropyridin-4-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**8j**, 7.5 mg, 14%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, J = 2.1 Hz, 2H), 8.59 (dd, J = 5.1, 1.2 Hz, 2H), 7.90 (dd, J = 6.0, 4.8 Hz, 1H), 7.76–7.71 (m, 3H), 7.32 (dd, J = 7.8, 4.8 Hz, 1H), 7.13 (d, J = 3.3 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 4.46 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.32, 160.96 (d, J = 2.9 Hz), 154.86 (d, J = 263.4 Hz), 149.28, 149.16, 149.03, 146.44 (d, J = 5.3 Hz), 139.24 (d, J = 23.9 Hz), 135.02, 134.23, 128.27, 123.69, 122.39 (d, J = 10.0 Hz), 120.42, 117.76, 112.95, 104.25 (d, J = 10.4 Hz), 45.48. **HRMS** (FAB^+) *m/z* calcd. for $C_{20}H_{16}FN_4O^+$ $[M+H]^+$: 347.1303 found 347.1313.

Synthesis of compound 8k



3a 5k 8k

Preparation of 3-(4-bromophenyl)-5-(pyrimidin-2-yl)isoxazole (5k)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.15 g, 0.64 mmol) and 2-ethynylpyrimidine (0.08 g, 0.77 mmol, 1.20 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(pyrimidin-2-yl)isoxazole (**5k**, 0.15 g, 78%).

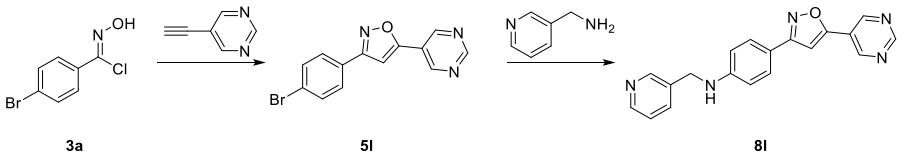
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (d, *J* = 4.9 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.92 (s, 1H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.65 (t, *J* = 4.9 Hz, 1H)

Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(pyrimidin-2-yl)isoxazol-3-yl)aniline (8k)

The title compound was prepared from 3-(4-bromophenyl)-5-(pyrimidin-2-yl)isoxazole (**5k**, 0.15 g, 0.50 mmol) and pyridine-3-ylmethanamine (0.16 g, 1.50 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(pyrimidin-2-yl)isoxazol-3-yl)aniline (**8k**, 20.0 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, *J* = 5.2 Hz, 2H), 8.64 (s, 1H), 8.54 (d, *J* = 4.8 Hz, 1H), 7.73–7.69 (m, 3H), 7.34–7.32 (m, 2H), 7.30–7.27 (m, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.54–4.52 (m, 1H), 4.44–4.43 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.37, 163.07, 157.66, 156.08, 149.20, 149.05, 148.85, 135.08, 134.38, 128.23, 123.66, 120.75, 117.98, 112.92, 112.90, 103.67, 45.40. **HRMS** (FAB^+) *m/z* calcd. for $C_{19}H_{16}N_5O^+$ $[M+H]^+$: 330.1349 found 330.1346.

Synthesis of compound 8l



3a 5l 8l

Preparation of 3-(4-bromophenyl)-5-(pyrimidin-5-yl)isoxazole (5l)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.15 g, 0.64 mmol) and 5-ethynylpyrimidine (0.08 g, 0.77 mmol, 1.20 eq) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(pyrimidin-5-yl)isoxazole (**5l**, 150 mg, 78%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.34 (s, 3H), 7.92 (s. 1H), 7.89–7.80 (m, 4H)

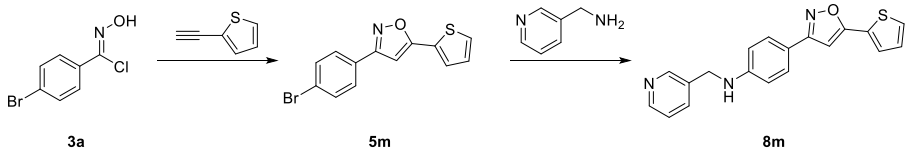
Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(pyrimidin-5-yl)isoxazol-3-yl)aniline (8l)

The title compound was prepared from 3-(4-bromophenyl)-5-(pyrimidin-5-yl)isoxazole (**5l**, 0.15 g, 0.50 mmol) and pyridine-3-ylmethanamine (0.16 g, 1.50 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(pyrimidin-5-yl)isoxazol-3-yl)aniline (**8l**, 20.0 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 9.18 (s, 2H), 8.67 (s, 1H), 8.58 (dd, J = 4.8, 1.6 Hz, 1H), 7.74–7.69 (m, 3H), 7.33–7.30 (m, 1H), 6.94 (s, 1H), 6.75–6.71 (m, 2H), 4.47 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 164.27, 163.18, 159.50, 154.11, 150.71, 149.39, 148.58, 135.53, 128.21, 123.98, 122.31, 115.77, 112.89, 100.90, 44.12. **HRMS** (FAB^+) *m/z* calcd. for $C_{19}H_{16}N_5O^+$ $[M+H]^+$: 330.1349 found 330.1345.

Synthesis of compound 8m



3a **5m** **8m**

Preparation of 3-(4-bromophenyl)-5-(thiophen-2-yl)isoxazole (5m)

The title compound was prepared from (*Z*)-4-bromo-*N*-hydroxybenzimidoyl chloride (**3a**, 0.20 g, 0.85 mmol), and 2-ethynylthiophene (0.09 g, 0.85 mmol) in the manner described above general procedure **A** to obtain the desired product, 3-(4-bromophenyl)-5-(thiophen-2-yl)isoxazole (**5m**, 178 mg, 68%).

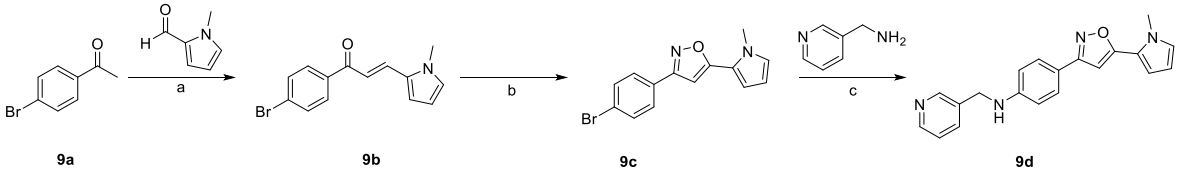
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.87 (d, J = 8.2 Hz, 3H), 7.79–7.71 (m, 3H), 7.49 (s, 1H), 7.28 (t, J = 4.4 Hz, 1H).

Preparation of *N*-(pyridin-3-ylmethyl)-4-(5-(thiophen-2-yl)isoxazol-3-yl)aniline (8m)

The title compound was prepared from 3-(4-bromophenyl)-5-(thiophen-2-yl)isoxazole (**5m**, 0.10 g, 0.33 mmol) and pyridine-3-ylmethanamine (0.11 g, 0.99 mmol) in the manner described above general procedure **B** to obtain the desired product, *N*-(pyridin-3-ylmethyl)-4-(5-(thiophen-2-yl)isoxazol-3-yl)aniline (**8m**, 6.5 mg, 6%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.84–7.77 (m, 3H), 7.68 (d, J = 3.6 Hz, 1H), 7.61 (d, J = 8.1 Hz, 3H), 7.27–7.23 (m, 3H), 6.84–6.80 (m, 1H), 6.71 (d, J = 8.1 Hz, 2H), 4.40 (d, J = 6.0 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6): δ 164.56 (d, J =7.8 Hz), 163.11 (d, J = 7.9 Hz), 150.55 (d, J = 8.2 Hz), 149.46, 148.60, 135.42, 129.66 (d, J = 8.1Hz),129.14, 129.06 (d, J = 7.3 Hz),128.22 (d, J = 7.8 Hz),127.96 (d, J = 7.4 Hz), 116.13 (d, J = 8.2 Hz), 112.83 (d, J = 7.7 Hz), 97.88 (d, J = 8.2 Hz), 44.20 (d, J = 7.2 Hz). **HRMS** (FAB$^+$) *m/z* calcd. for $C_{19}H_{16}N_3OS^+$ $[M+H]^+$: 334.1009 found 334.1009.

Synthesis of compound 9d



Reaction conditions: (a) aq. NaOH (40%), EtOH (0.30 M), 0 °C to 50 °C, 12 h; (b) NH_2OH • HCl (1.50 eq), NaOAc (3.0 eq), AcOH (2.0 eq), EtOH (0.10 M), reflux for 8 h; (c) CuI (0.10 eq), L-proline (0.20 eq), K_2CO_3 (3.0 eq), DMSO (0.50 M), 80 °C, 14 h.

Preparation of (*E*)-1-(4-bromophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (9b)

To a solution of 1-(4-bromophenyl)ethan-1-one (**9a**, 1.0 g, 5.02 mmol) and 1-methyl-1*H*-pyrrole-2-carbaldehyde (0.55 g, 5.02 mmol) in ethanol (16.7 mL, 0.30 M) was added 40% sodium hydroxide solution (1.3 mL) at room temperature. The reaction mixture was stirred at 50 °C for 12 h. The solid formed was filtered off under a vacuum and residue was washed with water to obtain the desired product, (*E*)-1-(4-bromophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (**9b**, 0.90 g, 62%) as yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6: δ 8.04 (d, J = 8.6 Hz, 2H), 7.81–7.63 (m, 3H), 7.52 (d, J = 15.2 Hz, 1H), 7.19–7.00 (m, 2H), 6.25–6.06 (m, 1H), 3.78 (s, 3H).

Preparation of 3-(4-bromophenyl)-5-(1-methyl-1*H*-pyrrol-2-yl)isoxazole (9c)

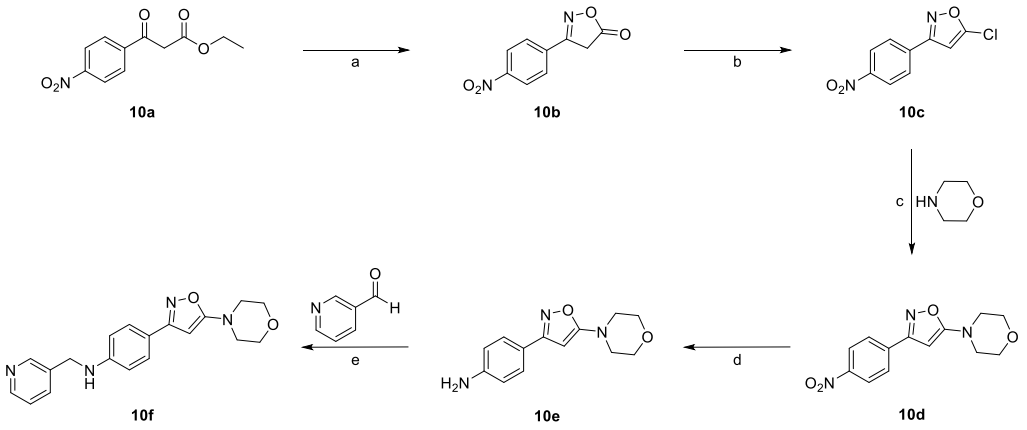
A solution sodium acetate (0.68 g, 8.28 mmol) in hot acetic acid (0.32 mL, 5.52 mmol) was added to a solution of hydroxylamine hydrochloride (0.58 g, 8.28 mmol) in ethanol (0.5 mL) at room temperature then a mixture was added to stirred solution of (*E*)-1-(4-bromophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)prop-2-en-1-one (**9b**, 0.80 g, 2.76 mmol) in ethanol (27.6 mL, 0.10 M). The resulted mixture was heated to reflux at 80 °C for 8 h. The mixture was cooled and concentrated under reduced pressure and neutralized with sodium hydroxide (0.1 N). The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was purified by silca-gel chromatography to obtain the desired product, 3-(4-bromophenyl)-5-(1-methyl-1*H*-pyrrol-2-yl)isoxazole (**9c**, 0.25 g, 30%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.33 (s, 1H), 6.50 (t, J = 2.2 Hz, 1H), 5.98 (dd, J = 3.6, 1.8 Hz, 1H), 5.81 (dd, J = 3.6, 2.7 Hz, 1H), 3.41 (s, 3H).

Preparation of 4-(5-(1-methyl-1*H*-pyrrol-2-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (9d)

The title compound was prepared from 3-(4-bromophenyl)-5-(1-methyl-1H-pyrrol-2-yl)isoxazole (**9c**, 0.16 g, 0.53 mmol) and pyridine-3-ylmethanamine **(**0.17 g, 1.59 mmol) in the manner described above general procedure **B**, to obtain the desired product, 4-(5-(1-methyl-1*H*-pyrrol-2-yl)isoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**9d**, 15.0 mg, 9%). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.47 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 6.5 Hz, 2H), 7.39–7.36 (m, 1H), 6.97–6.94 (m, 3H), 6.73 (d, J = 6.0 Hz, 2H), 6.65–6.64 (m, 1H), 6.14–6.13 (m, 1H), 4.40 (d, J = 6.0 Hz, 2H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.14, 156.98, 149.12, 149.02, 148.97, 135.04, 134.17, 127.41, 126.40, 123.66, 122.71, 117.34, 112.80, 112.10, 108.18, 96.10, 45.44, 37.18. **HRMS** (FAB^+) *m/z* calcd. for $C_{20}H_{19}N_4O^+$ $[M+H]^+$: 331.1553 found 331.1568.

Synthesis of compound 10f



Reaction conditions: (a) NH_2OH•HCl (2.0 eq), K_2CO_3 (1.50 eq), EtOH (0.50 M), rt to 78 °C, 4 h; (b) $POCl_3$ (7.0 eq), Et_3N (1.0 eq), 0 °C to 100 °C, 16 h; (c) K_2CO_3 (2.50 eq), DMF (0.50 M), 80 °C, 12 h; (d) $B_2(OH)_4$ (3.0 eq), 4,4'-bipyridine (0.05 eq), DMF (0.10 M), 5 min; (e) $NaCNBH_3$ (3.0 eq), TFA (1.50 eq), DMF (0.20 M), 0 °C to rt, 12 h.

Preparation of 3-(4-nitrophenyl)isoxazol-5(4*H*)-one (10b)

To a solution of ethyl-3-(4-nitrophenyl)-3-oxopropanoate (**10a**, 2.0 g, 8.43 mmol), hydroxylamine hydrochloride (1.17 g, 16.86 mmol) in ethanol:water (1:10, 16.9 mL, 0.50 M) was added K_2CO_3 (1.16 g, 8.43 mmol) at room temperature and stirred at 78 °C for 4 h. The mixture was cooled and concentrated under reduced pressure. Then residue was diluted with water and extracted twice with EtOAc. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate and concentrated in vacuo to obtain the desired product, 3-(4-nitrophenyl)isoxazol-5(4*H*)-one (**10b**, 1.06 g, 60%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H).

Preparation of 5-chloro-3-(4-nitrophenyl)isoxazole (10c)

To a solution of 3-(4-nitrophenyl)isoxazol-5(4*H*)-one (**10b**, 1.0 g, 4.85 mmol) was dissolved in phosphorus oxychloride (3.20 mL, 34.0 mmol) at 0 °C. To the reaction mixture triethylamine (0.68 mL, 4.85 mmol) was added dropwise at the same temperature. Then, the reaction was warmed up to room temperature and heated to reflux at 100 °C for 24 h. The reaction mixture

was cooled to room temperature. The reaction mixture was poured to ice and the pH was adjusted to 8 using an aqueous sodium hydroxide (2.0 M) solution, then extracted twice with dichloromethane, dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silca-gel chromatography to afford the desired product, 5-chloro-3-(4-nitrophenyl)isoxazole (**10c**, 0.30 g, 28%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), 6.60 (s, 1H).

Preparation of 4-(3-(4-nitrophenyl)isoxazol-5-yl)morpholine (10d)

To a solution of 5-chloro-3-(4-nitrophenyl)isoxazole (**10c**, 0.10 g, 0.45 mmol) in *N*,*N*-dimethylformamide (2.0 mL, 0.22 M) was added K_2CO_3 (0.12 g, 0.90 mmol) and morpholine (0.12 g, 1.35 mmol) at room temperature. The reaction mixture was heated at 80 °C for 12 h. Then, the reaction mixture was cooled to room temperature, quenched with water, extracted twice with EtOAc, washed by brine, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the desired product, 4-(3-(4-nitrophenyl)isoxazol-5-yl)morpholine (**10d**, 0.10 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43–8.18 (m, 2H), 8.02–7.79 (m, 2H), 5.42 (d, *J* = 1.9 Hz, 1H), 4.00–3.69 (m, 4H), 3.58–3.29 (m, 4H).

Preparation of 4-(5-morpholinoisoxazol-3-yl)aniline (10e)

To the solution of 4-(3-(4-nitrophenyl)isoxazol-5-yl)morpholine (**10d**, 0.10 g, 0.36 mmol) in *N*,*N*-dimethylformamide (3.60 mL, 0.10 M) was added tetrahydroxydiboron (0.10 g, 1.08 mmol) at room temperature. Then a solution of 4,4′-bipyridine (3.0 mg, 0.02 mmol) in 0.50 mL of DMF was added dropwise to the stirred solution. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with water, extracted twice with EtOAc. The organic layer was washed with brine, dried with anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure to get the desired product, 4-(5-morpholinoisoxazol-3-yl)aniline (**10e**, 120 mg). The crude product was taken for the next reaction without purification.

Preparation of 4-(5-morpholinoisoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (10f)

To a solution of 4-(5-morpholinoisoxazol-3-yl)aniline (**10e**, 0.12 g, 0.49 mmol) in dry tetrahydrofuran (2.5 mL, 0.20 M) was added trifluoroacetic acid (0.06 mL, 0.74 mmol) and was added nicotinaldehyde (0.08 g, 0.74 mmol) at room temperature. Sodium cyanoborohydride (0.09 g, 1.47 mmol) was added to the reaction mixture portion wise at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then stirred at room temperature for 12 h. The reaction mixture was diluted with water and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by Prep-HPLC to afford the desired product, 4-(5-morpholinoisoxazol-3-yl)-*N*-(pyridin-3-ylmethyl)aniline (**10f**, 10.0 mg, 6%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.46–8.45 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.47–7.44 (m, 2H), 7.36 (t, J = 6.5 Hz, 1H), 6.73–6.70 (m, 1H), 6.65 (d, J = 7.0 Hz, 2H), 5.69 (s, 1H), 4.36 (d, J = 6.0 Hz, 2H), 3.72–3.70 (m, 4H), 3.28–3.26 (m, 4H). **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.14, 163.21, 150.12, 149.38, 148.54, 135.70, 135.51, 127.75, 123.94, 117.45, 112.64, 77.02, 65.70, 46.89, 44.17. **HRMS** (FAB^{+}) *m/z* calcd. for $C_{19}H_{21}N_4O_2^{+}$ $[M+H]^{+}$: 337.1659 found 337.1660.

2. Biological Assays

Cells and viruses

Vero CCL-81 (ATCC® CCL-81, African green monkey kidney epithelial cell line) obtained from the American Type Culture Collection (ATCC®, Manassas, VA, USA) were maintained in Dulbecco's modified Eagle's medium (DMEM; HyClone™, Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS, Atlas Biologicals, Fort, Collins, CO, USA), 100 μg/mL streptomycin, and 100 IU/mL penicillin (Gibco, Invitrogen, Waltham, MA, USA) at 37 ℃ in a 5% CO_2 incubator. The ZIKV PRVABC59 (ATCC® VR-1843) strains were purchased form the American Type Culture Collection (ATCC®, Manassas, VA, USA). Subsequently, the virus stock was amplified, and viral titer were determined through plaque assay. The aliquots were stored at –80 ℃ until further use.

Antiviral assay

An immunofluorescence assay was used to evaluate the antiviral activities of compound. The compounds were dissolved in a 20 mM stock in 100% DMSO. Briefly, Vero cells were seeded in 96-well plates at a density of 2×10^4 cells per well. Following overnight incubations, equal volumes of the ZIKV PRVABC59 strain at a multiplicity of infections (MOI) of 0.01 added in the presence of various concentrations of compounds. At 48 h post-infection (p.i.), fixed cells were exposed to incubation with flavivirus E protein antibody 4G2 (ATCC® HB-112™, Manassas, VA, USA) for 1 h at room temperature. Then, the cells were further incubated with an AF488-conjugated goat anti-mouse IgG antibody (Invitrogen) for an additional 1 h at room temperature. Nuclei were counterstained using mounting media containing 4', 6'-diamidino-2-phenylindole (DAPI; Vector Laboratories, Burlingame, CA, USA). Image analysis was conducted using an Operetta high-content imaging system (PerkinElmer, Waltham, MA, USA). The percentage of DAPI-stained and infected cells were calculated using Harmony High-Content analysis software (PerkinElmer). The 50% effective concentration (EC_{50}) and the compound specific toxicity 50% cytotoxicity concentration (CC_{50}) were calculated using GraphPad prism 8 (GraphPad Software, San Diego, CA, USA) through the non-linear regression formula: log (inhibitor) versus normalized response -variable slope model. The selectivity index (SI) of each compound was determined by calculating the ratio of the CC_{50} to EC_{50}.

CYP inhibition assay (IC_{50}, μM)

Cyprotex's cytochrome P450 inhibition assay examined five primary isoforms: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The compound under testing was combined with human liver microsomes and diluted with potassium phosphate buffer (pH 7.4), followed by an incubation period at 37 °C for 5 minutes. Phenacetin, Tolbutamide, S-Mephenytoin, Dextromethorphan, Sorafenib were selected as a substrate for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, respectively. Following the addition of each substrate into a mixture containing NADPH solution, the combined mixture underwent a reaction at 37 ℃ for an additional 20 minutes. The samples were quenched by mixing with cold acetonitrile containing internal standard to cease the reaction. Subsequently, the mixture was centrifuged at 4,000 rpm at 4 °C for 15 minutes. The supernatant was then subjected to detection using LC-MS/MS (AB Sciex Qtrap 4000) coupled with HPLC (Agilent 1260), covering a range of test compound concentrations from 0.01 to 100 μM. The system's reliability was confirmed by utilizing ketoconazole, a known reference compound for its inhibition of CYP3A4. [1,2]

Cytotoxicity assay

Cytotoxicity assays used five different types of mammalian cells: VERO, HFL-1, L929, NIH 3T3, CHO-K1. The frozen cells were thawed and then cultured in either DMEM or RPMI1640 medium supplemented with 10% FBS (fetal bovine serum). Once the cell density reached 80-90%, sub culturing was performed at 2-3 days intervals. For the experimental setup, cells were detached using Trypsin EDTA and then distributed into 96-well plates at a density of 20,000 cells per well. The plates were subsequently placed in a 37 °C CO_2 incubator and incubated for 24 h.

A compound stock solution was prepared at concentrations of 10, 1, 0.1, 0.01, and 0.001 mM using DMSO (dimethyl sulfoxide). The compound was further diluted by factor of 1/100 by adding 1 μL of DMSO or each prepared stock solution to the respective wells. Incubation continued for an additional 24 h in a 37°C CO_2 incubator. Next, 10 μL of the EZ-CYTOX cell viability assay kit was added to each well and incubated in a 37°C CO_2 incubator for a duration ranging from 1 to 4 h. After the designed incubation period, the absorbance at 450 nm was measured using a TECAN plate reader (Infinite M1000 pro). The data were analyzed by calculating the percentage of the measured values compared to DMSO. Graphical

representation of the data was performed using GraphPad Prism 9, and the IC_{50} value was calculated from the resulting dose-response curve. [3]

hERG K^+ channel binding assay

The hERG tracer and membrane fraction were allowed to melt at room temperature before usage. The tracer and hERG assay buffer was diluted at a ratio of 1:62.5. Test compounds, such as astemizole, E-4031, along with the negative control (DMSO), were prepared using assay buffer and then further diluted with a solution four times. Following preparation, 5 μL of each diluted solution was dispensed into a 384-well black round-bottom plate. Additionally, 10 μL of the membrane fraction and 5 μL of hERG tracer were dispensed into each well alongside the previously added diluted solutions. The plate was then covered to block light and incubated at 25°C for 2 h. Following the incubation period, polarized light measurements were taken using a TECAN plate reader (Infinite M1000 pro) to obtain the reported results. [4]

Liver microsomal stability assay

To predict the extent of compounds metabolism in the liver, a crucial organ where compound metabolism primarily occurs, the metabolic stability of the compound was evaluated using rat or human liver microsomes. After incubating liver microsomes diluted with potassium phosphate buffer (pH 7.4) at 37 °C for 5 minutes, a mixture of test compound and NADPH solution was added, and the reaction was allowed to proceed at 37 °C for 30 minutes. The final concentration of the test compound was 1 μM, while the final concentration of microsome was 0.5 μM.

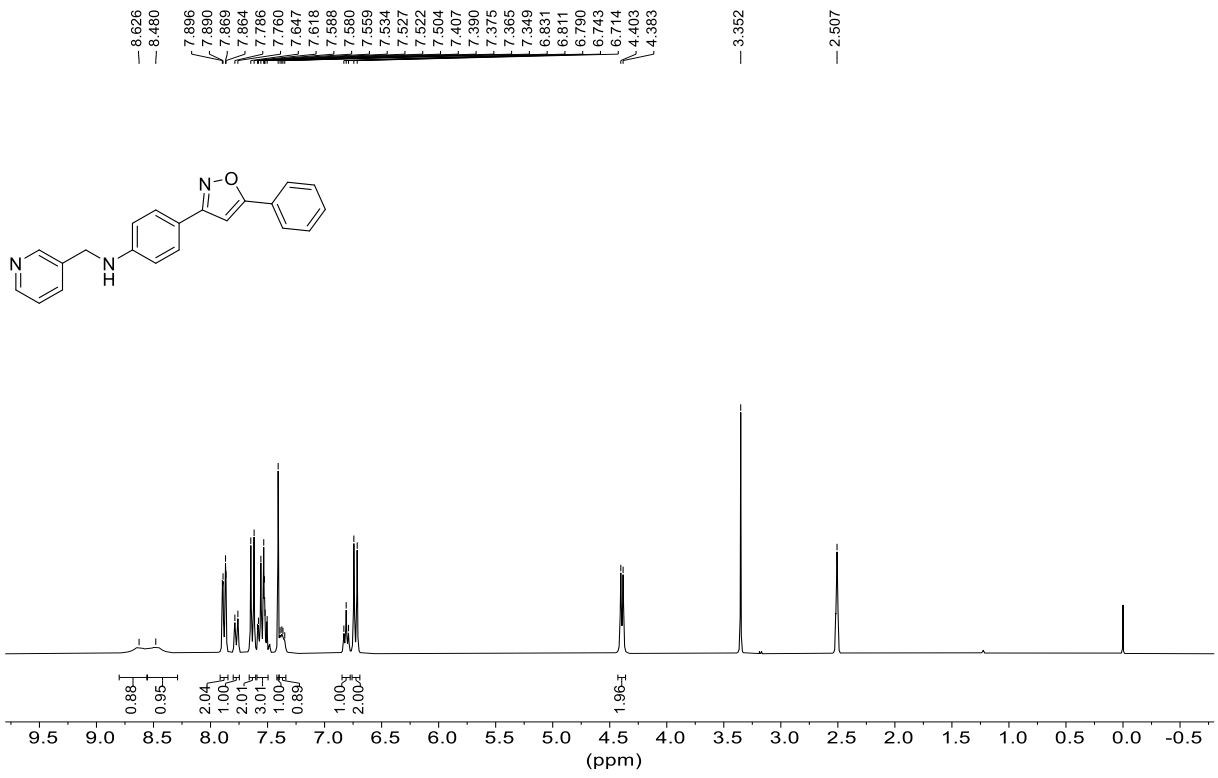
Samples were ultimately quenched with cold acetonitrile containing an internal standard to halt the reaction. After centrifugation at 4,000 rpm at 4 ℃ for 15 minutes, the supernatant was then analyzed using LC-MS/MS (Agilent 6460) coupled with HPLC (Agilent 1260). The peak areas for all components were automatically integrated using the Agilent 6460 quantitative analysis processing software. The system's reliability was confirmed using buspirone as a reference compound. [5,6]

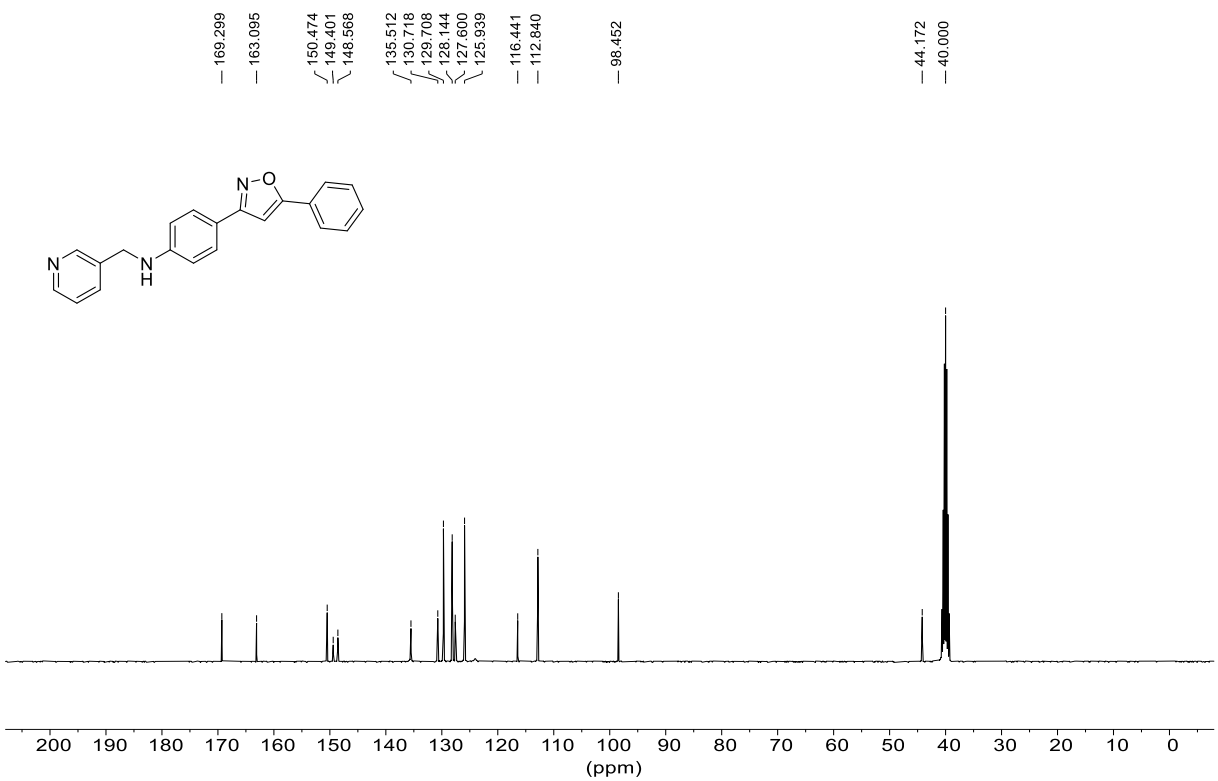
Plasma stability assay

Compound stock solution (10 mM in DMSO) was spiked onto the animal plasma (from innovative research) to prepare at a final compound concentration of 5 μM. PBS (from Thermo Fisher Scientific) was added to the RED plate chamber, the membrane was mounted, and then the plasma containing the compound was added. The mixture was then subjected to shaking incubation at 37 °C for 4 h. Samples were ultimately quenched with cold acetonitrile containing an internal standard to terminate the reaction and then protein was removed. After centrifugation at 4,000 rpm at 4 °C for 10 minutes, the supernatant was then utilized to detect compounds by LC-MS/MS (Agilent 6460) coupled with HPLC (Agilent 1260). The peak areas for all components were automatically integrated using Agilent 6460 quantitative analysis processing software. The plasma stability (%) was calculated by comparing the amount of compound remaining in the test sample to the amount present in the compared to the 0-hour response sample. The system was validated using propranolol and atenolol as reference compounds. [7,8]

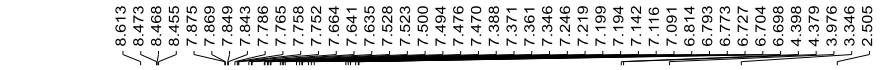
3. Spectra Copies of ^{1}H, ^{13}C NMR of Compounds

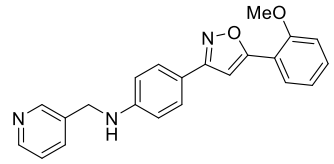
^{1}H NMR and ^{13}C NMR Spectra of Compound 6d

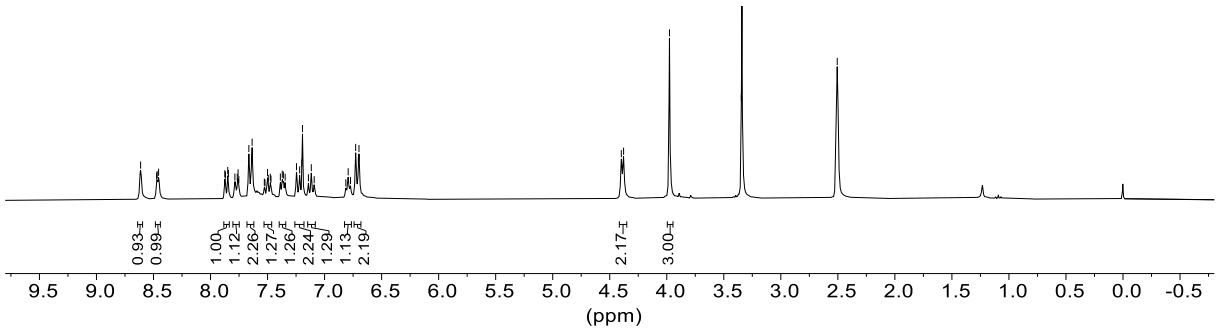


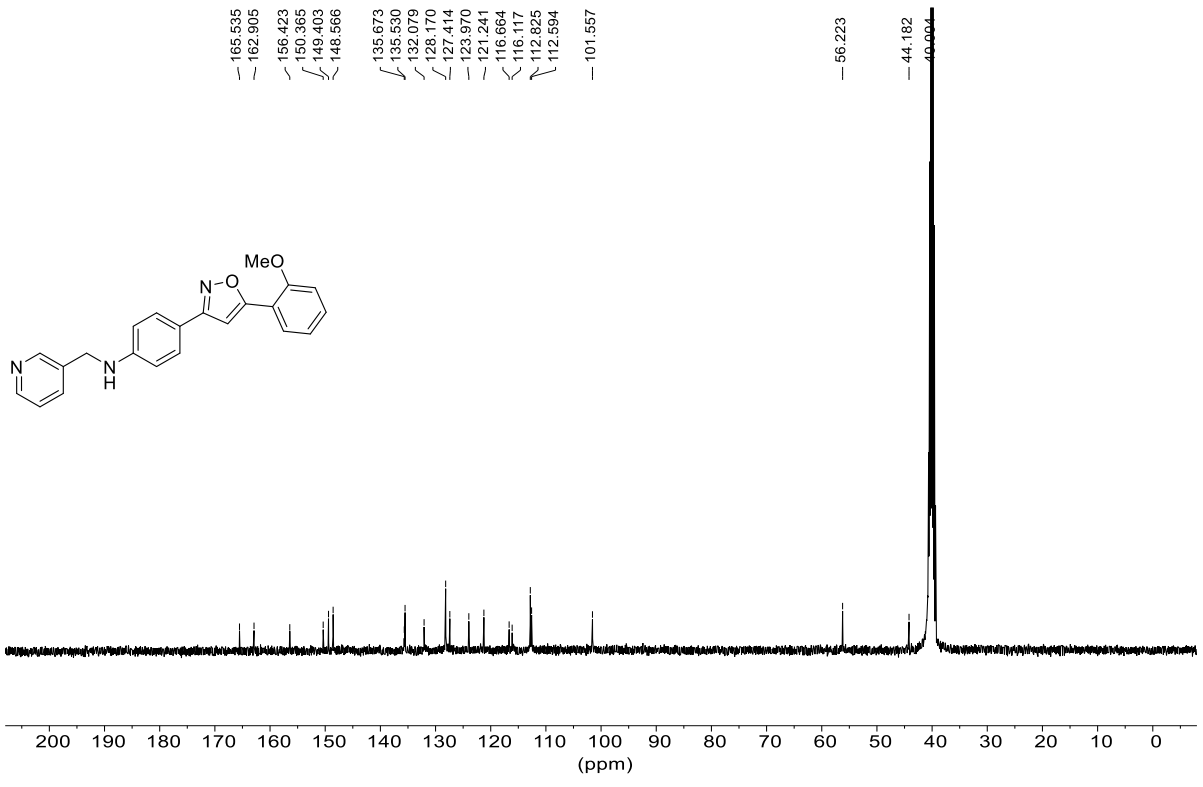


^{1}H NMR and ^{13}C NMR Spectra of Compound 7a

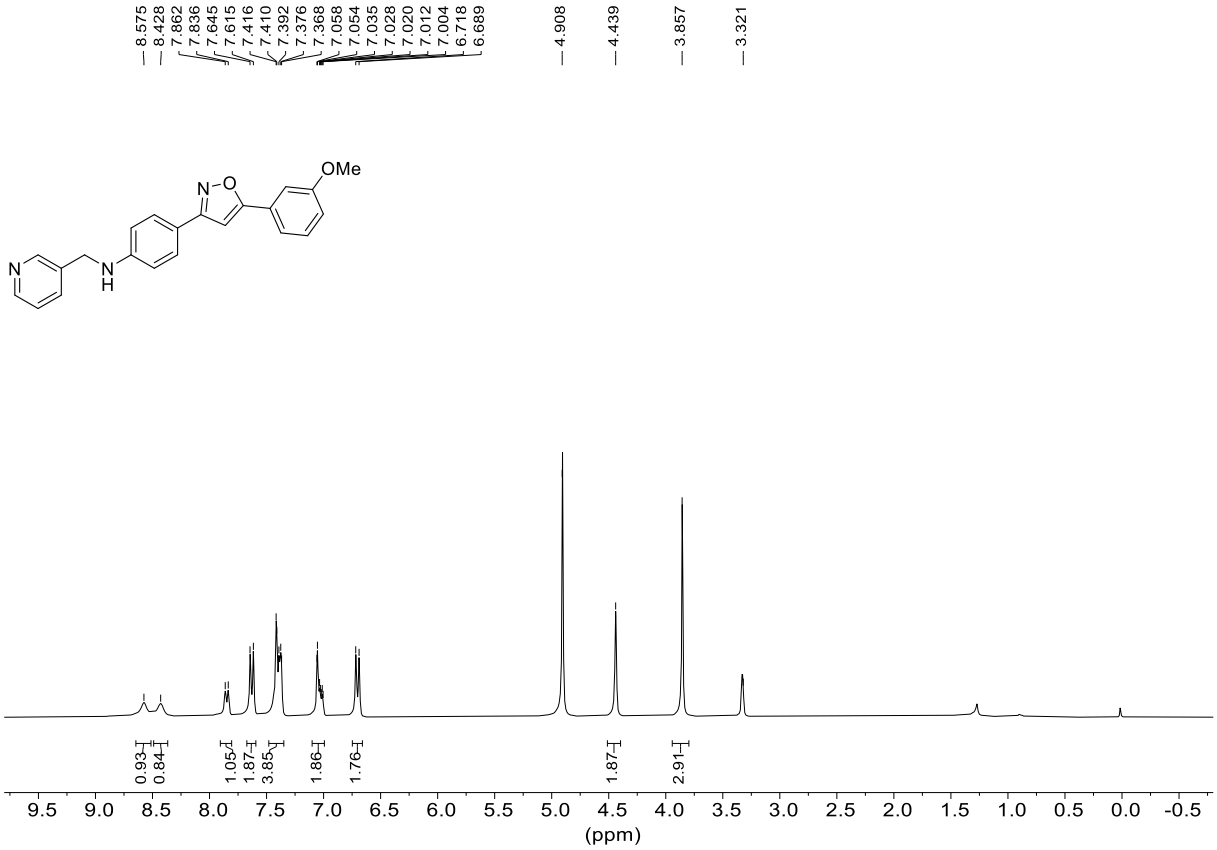


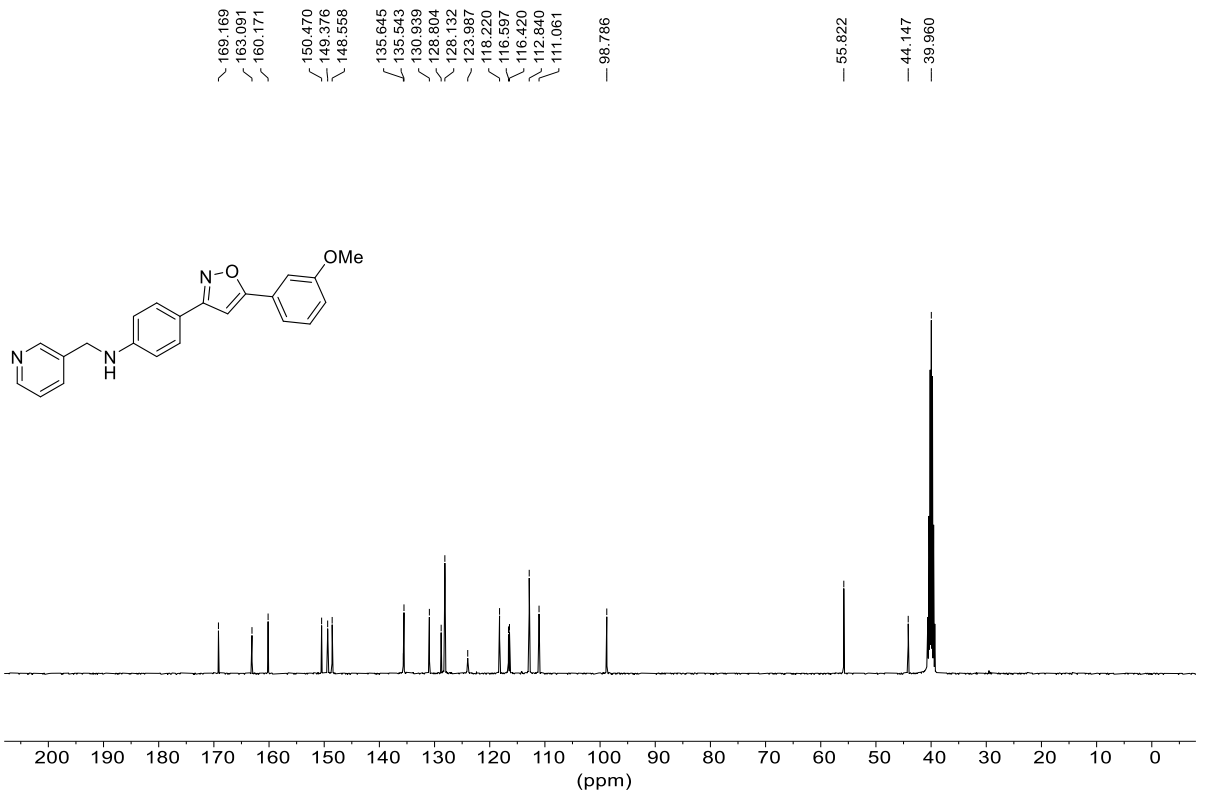




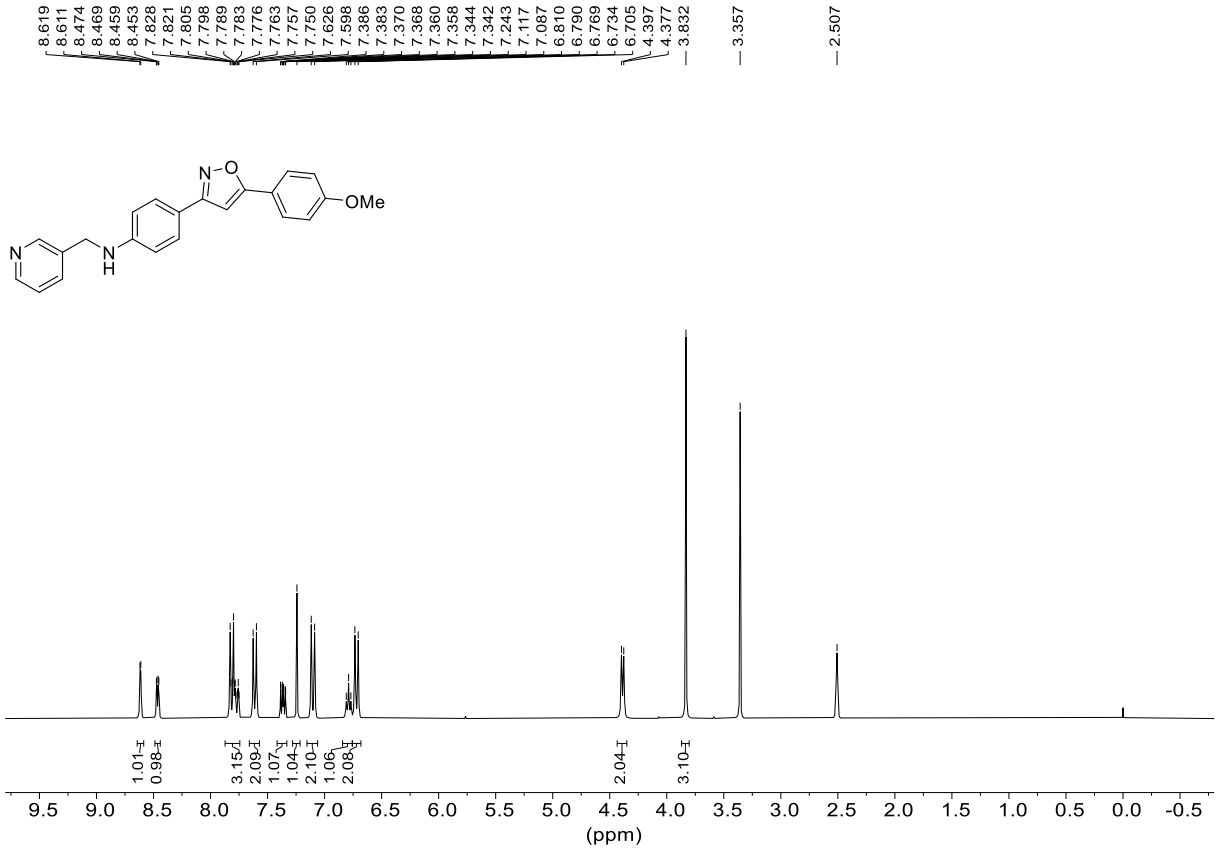


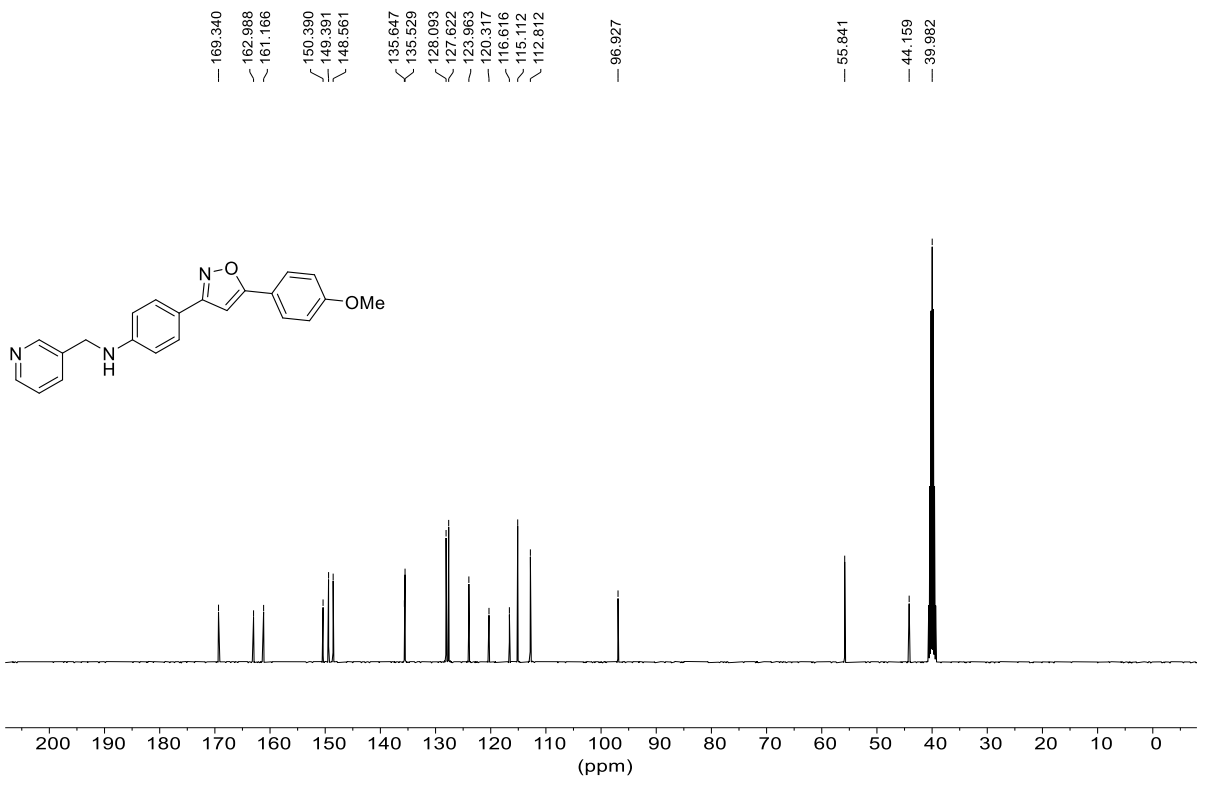
^{1}H NMR and ^{13}C NMR Spectra of Compound 7b



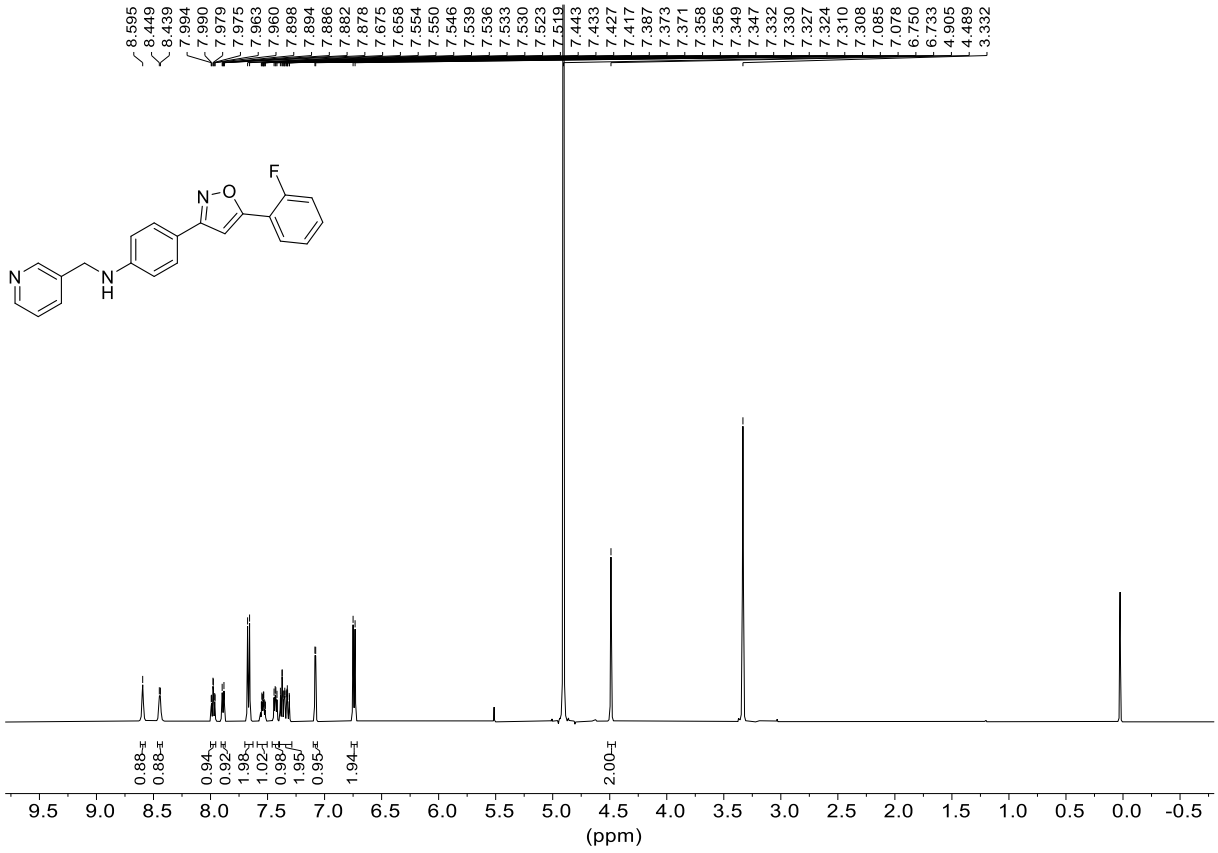


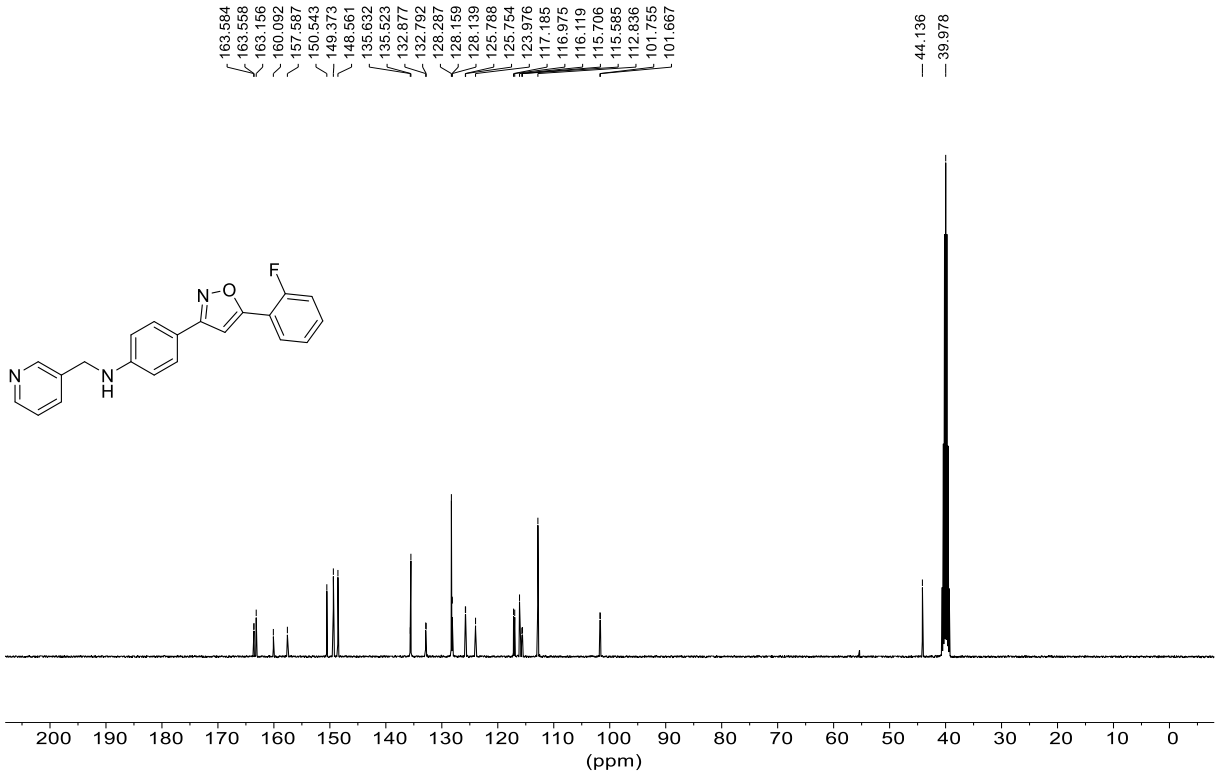
^{1}H NMR and ^{13}C NMR Spectra of Compound 7c



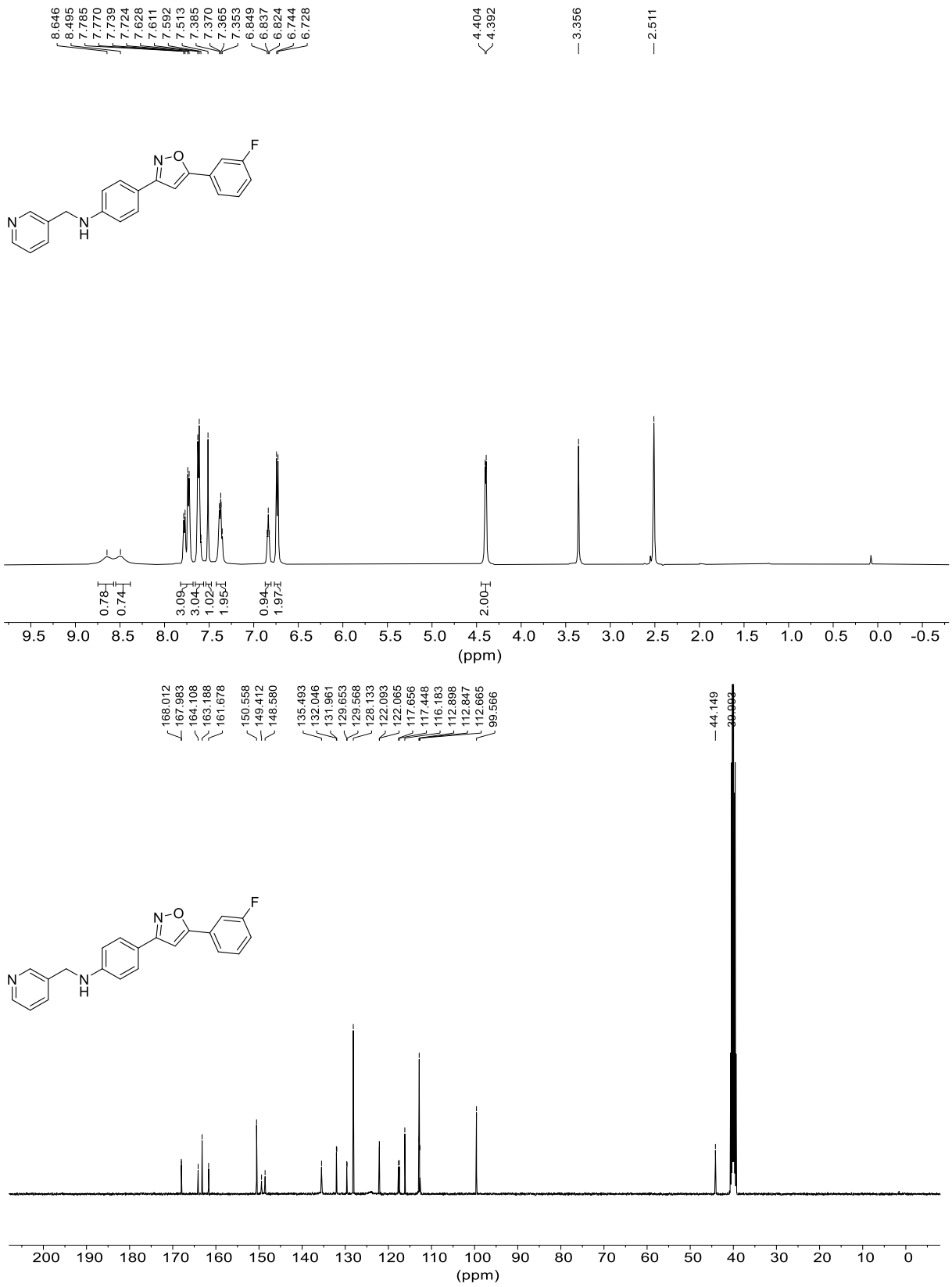


^{1}H NMR and ^{13}C NMR Spectra of Compound 7d

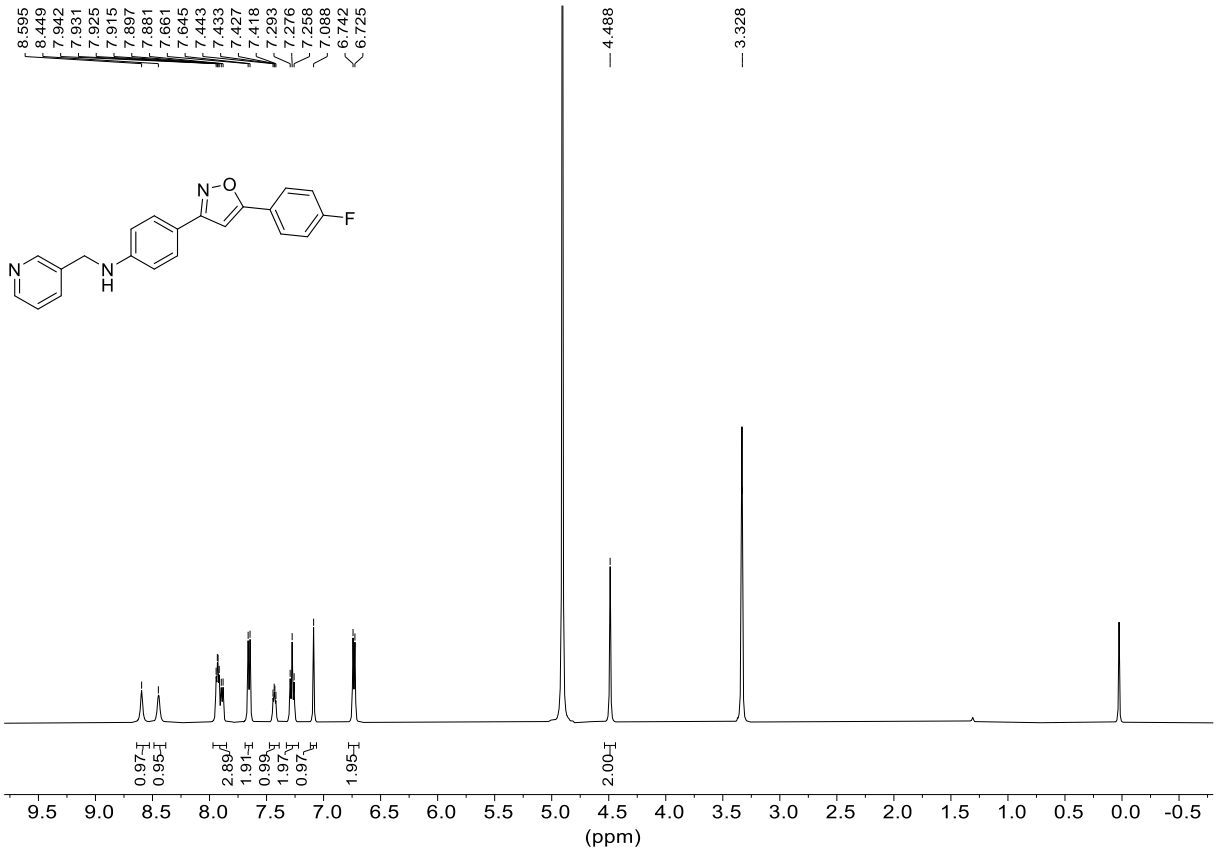


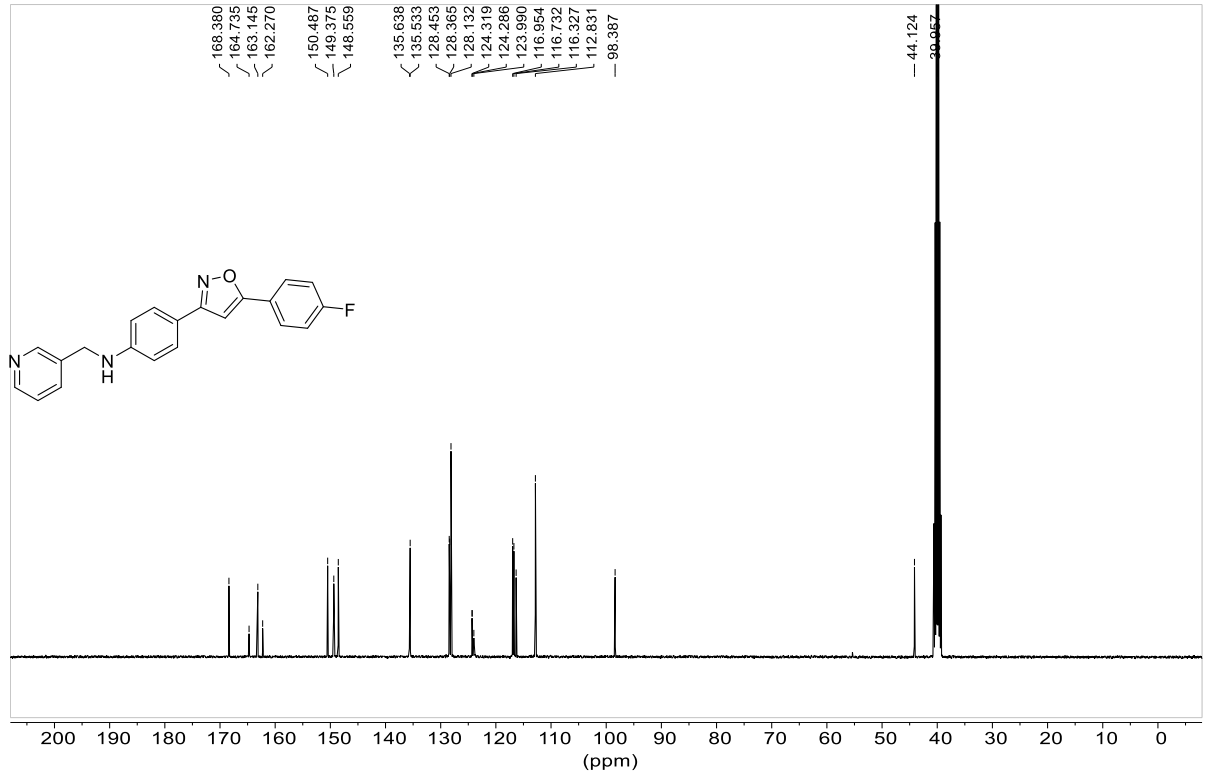


^{1}H NMR and ^{13}C NMR Spectra of Compound 7e

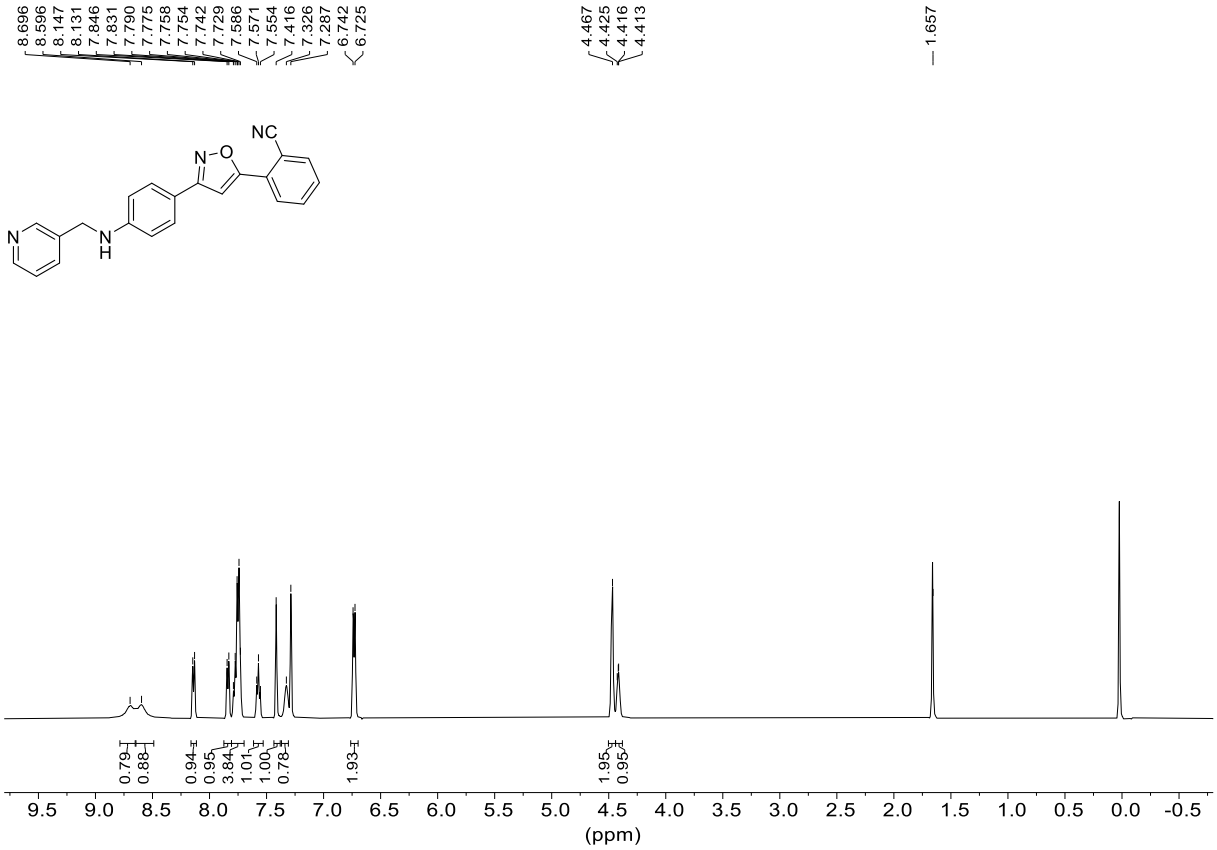


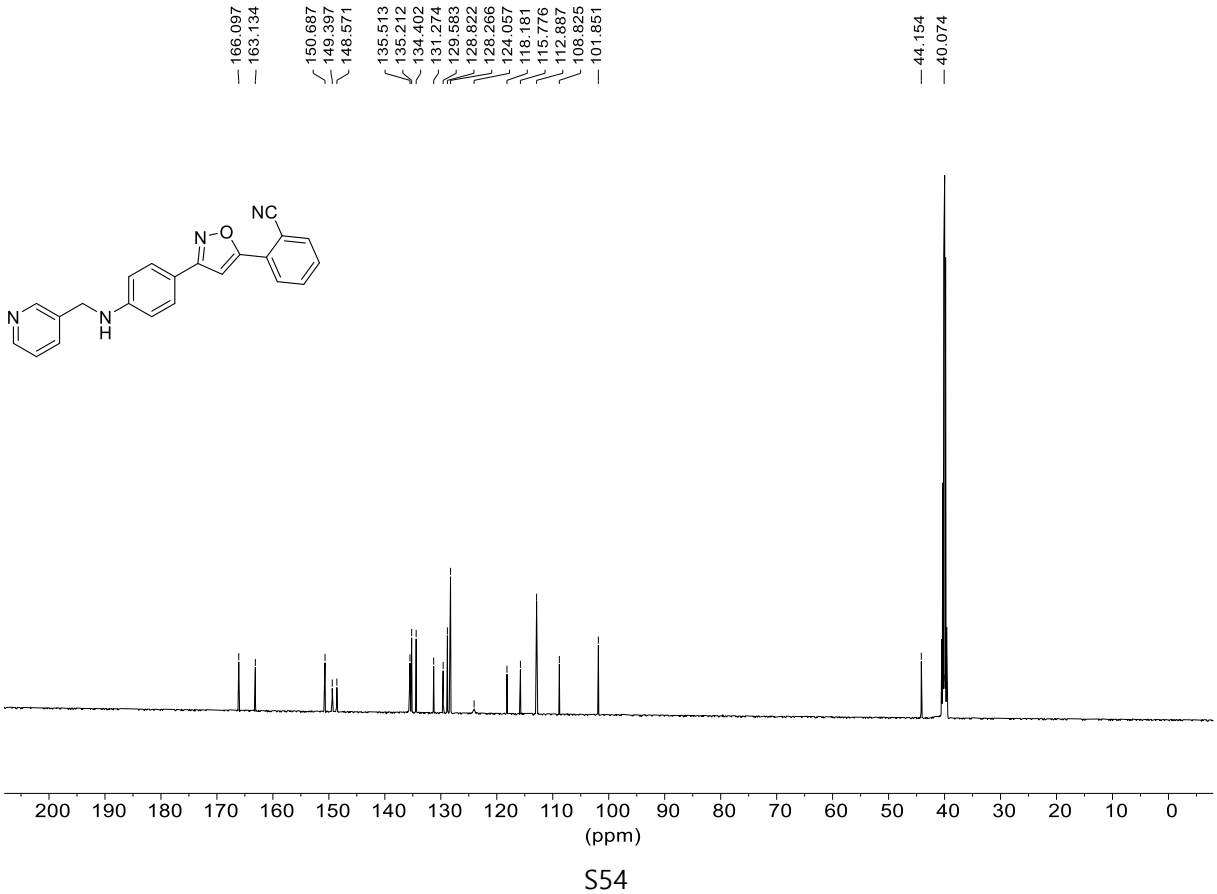
^{1}H NMR and ^{13}C NMR Spectra of Compound 7f



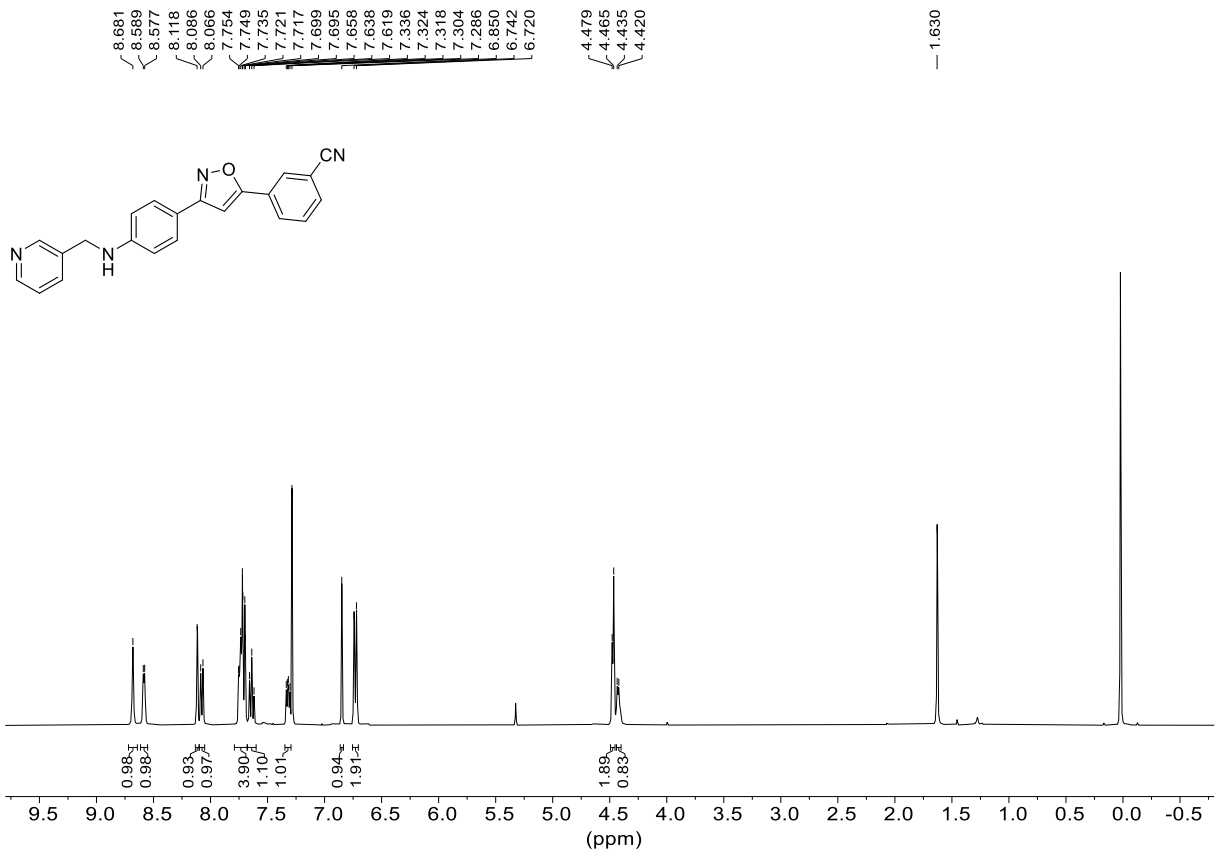


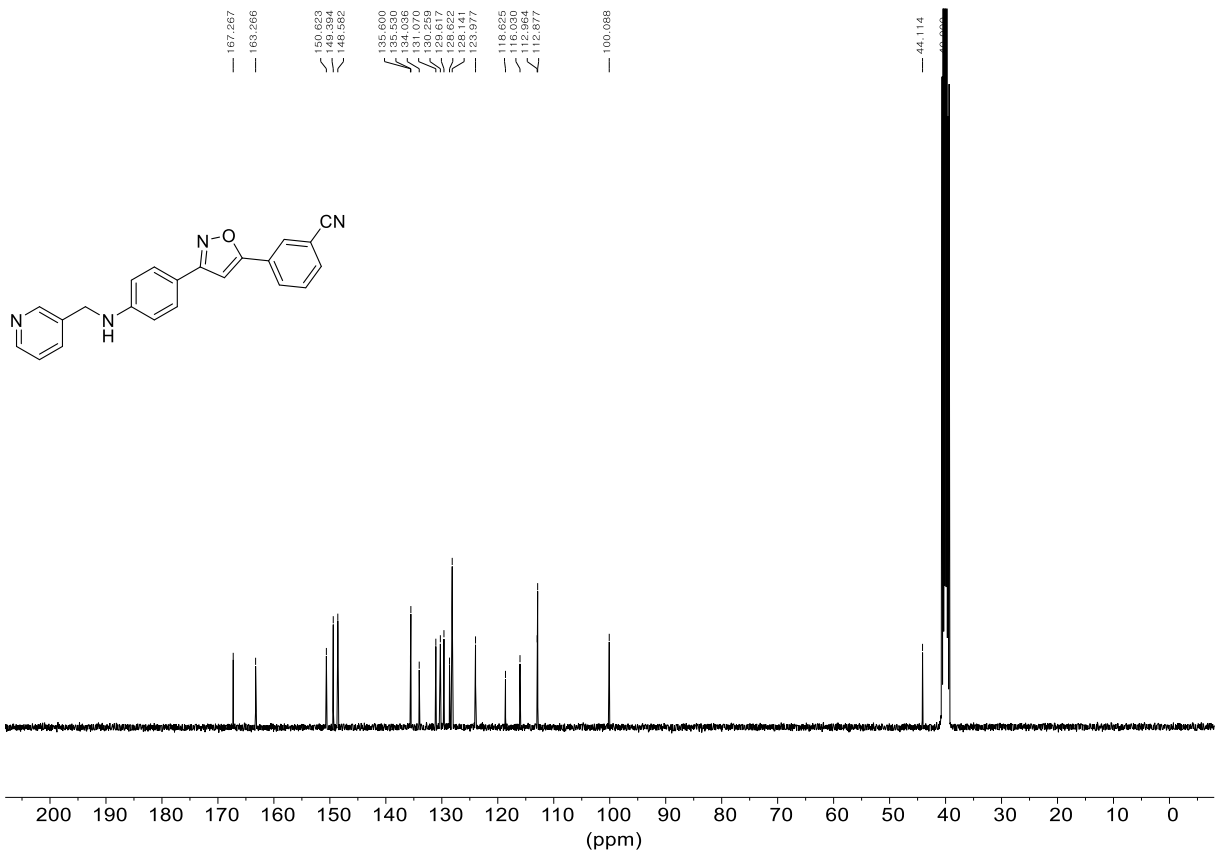
^{1}H NMR and ^{13}C NMR Spectra of Compound 7g



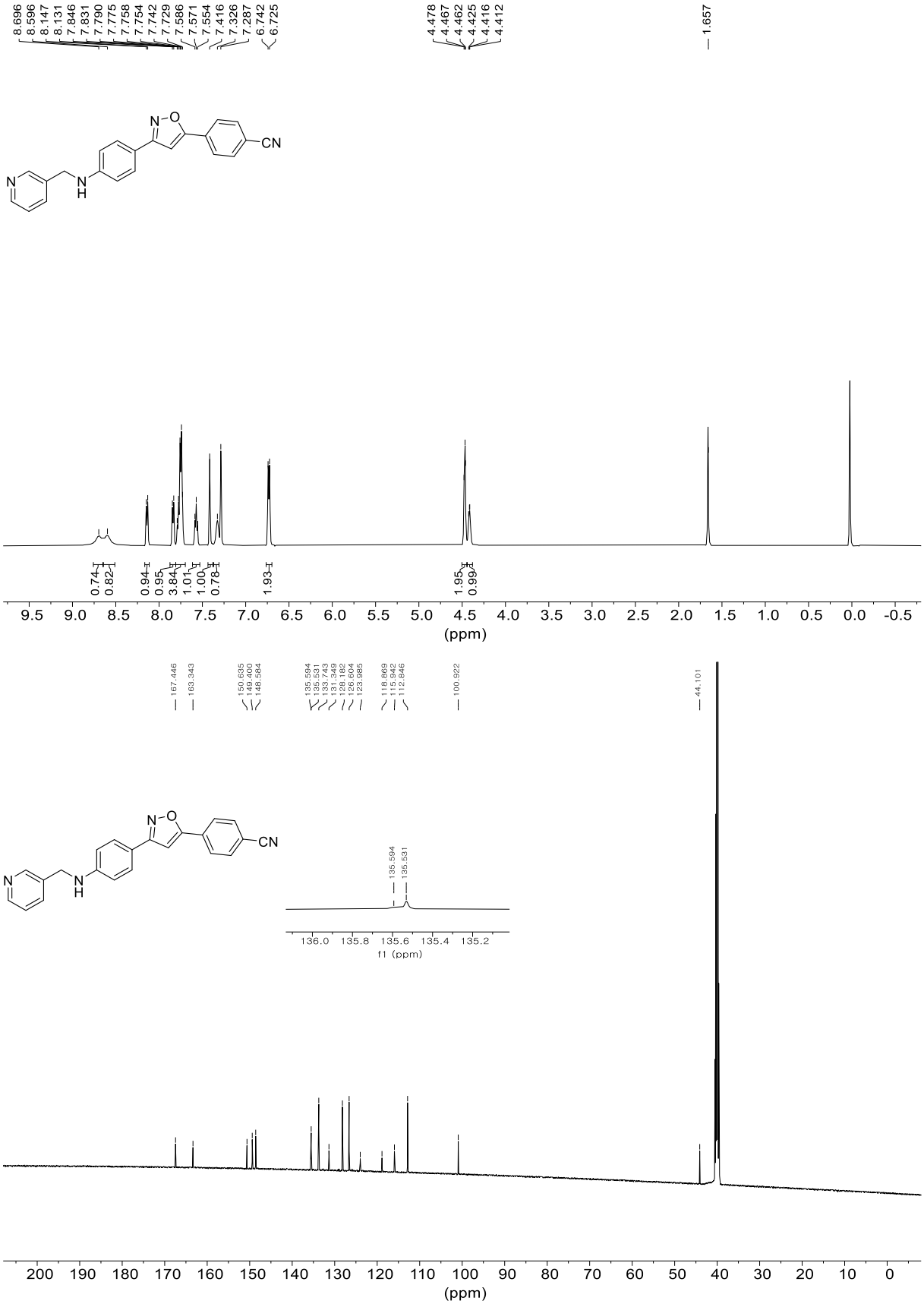


^{1}H NMR and ^{13}C NMR Spectra of Compound 7h

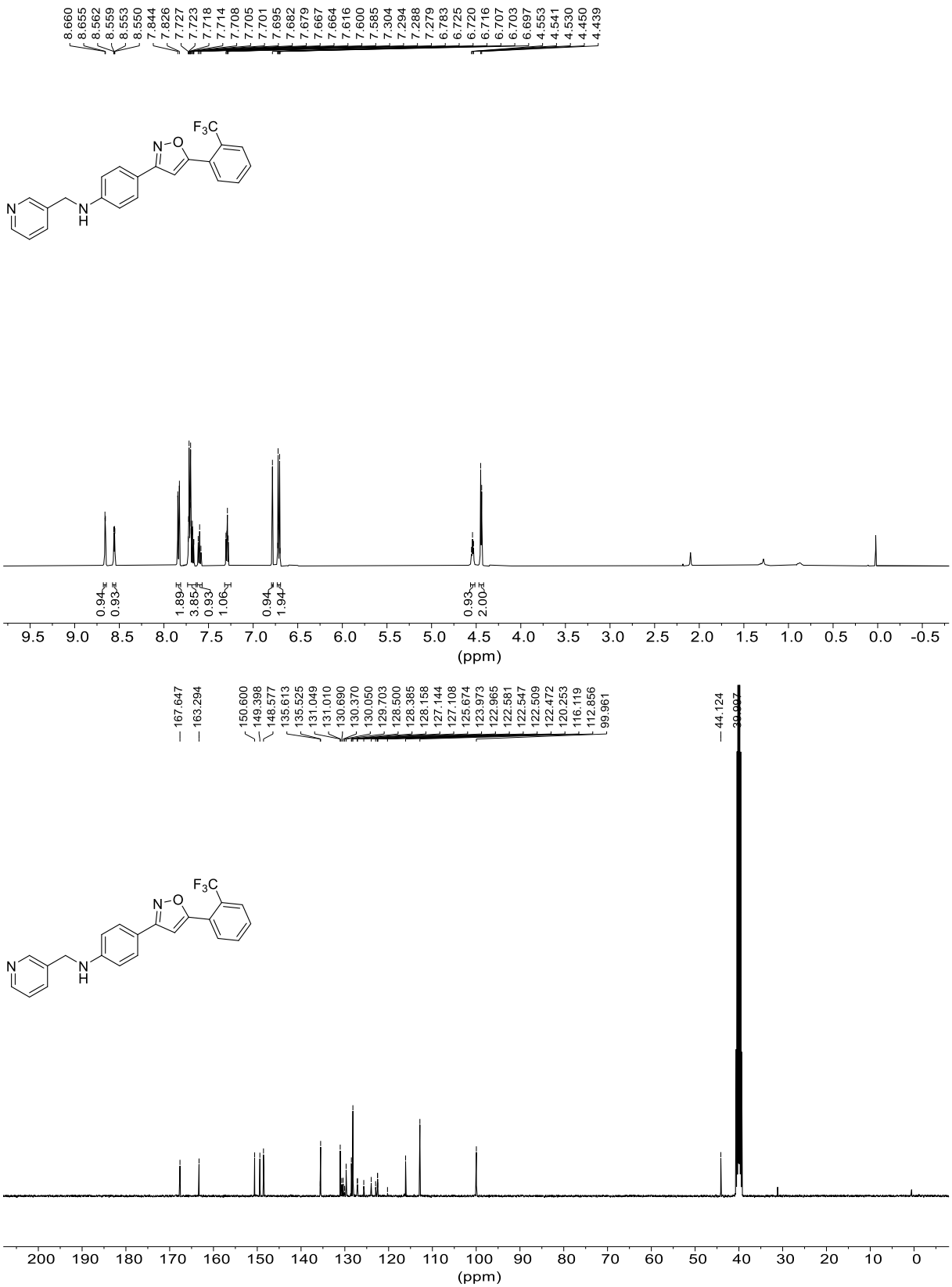




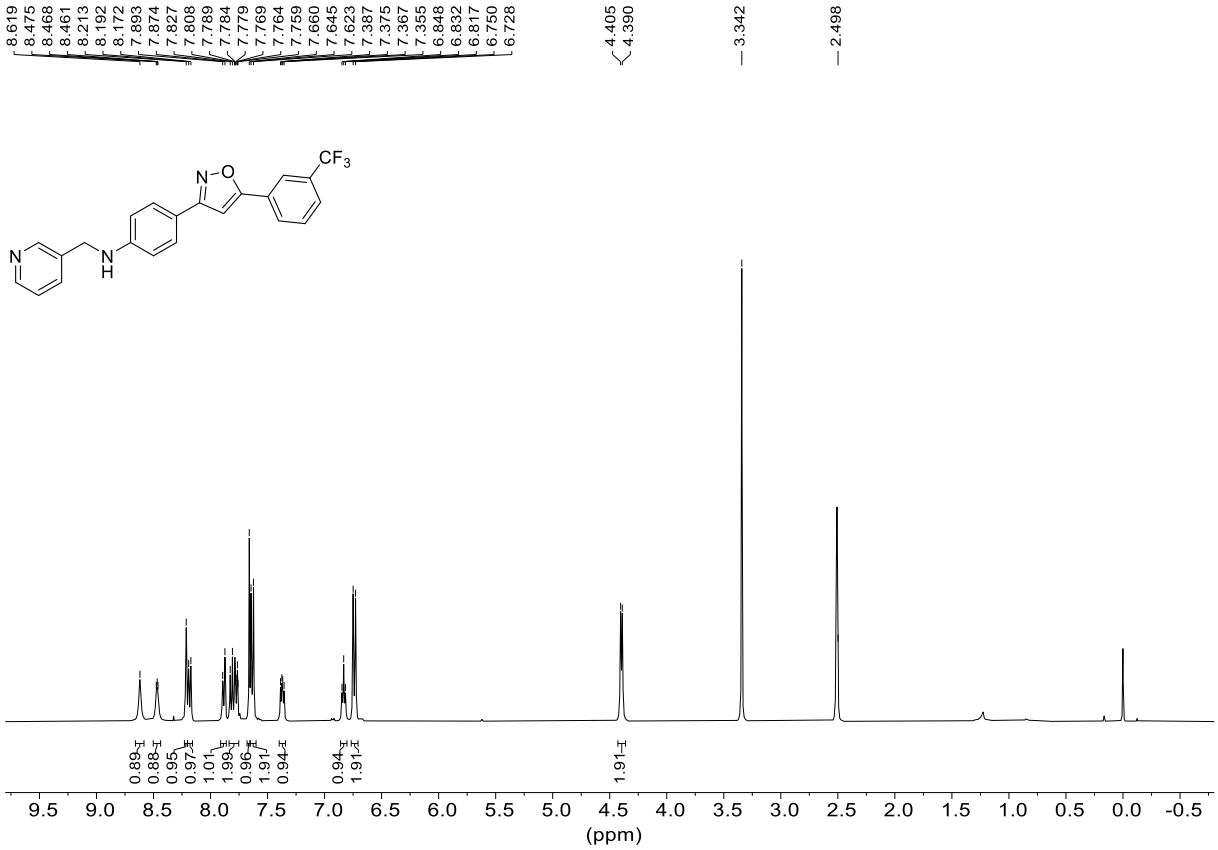
^{1}H NMR and ^{13}C NMR Spectra of Compound 7i

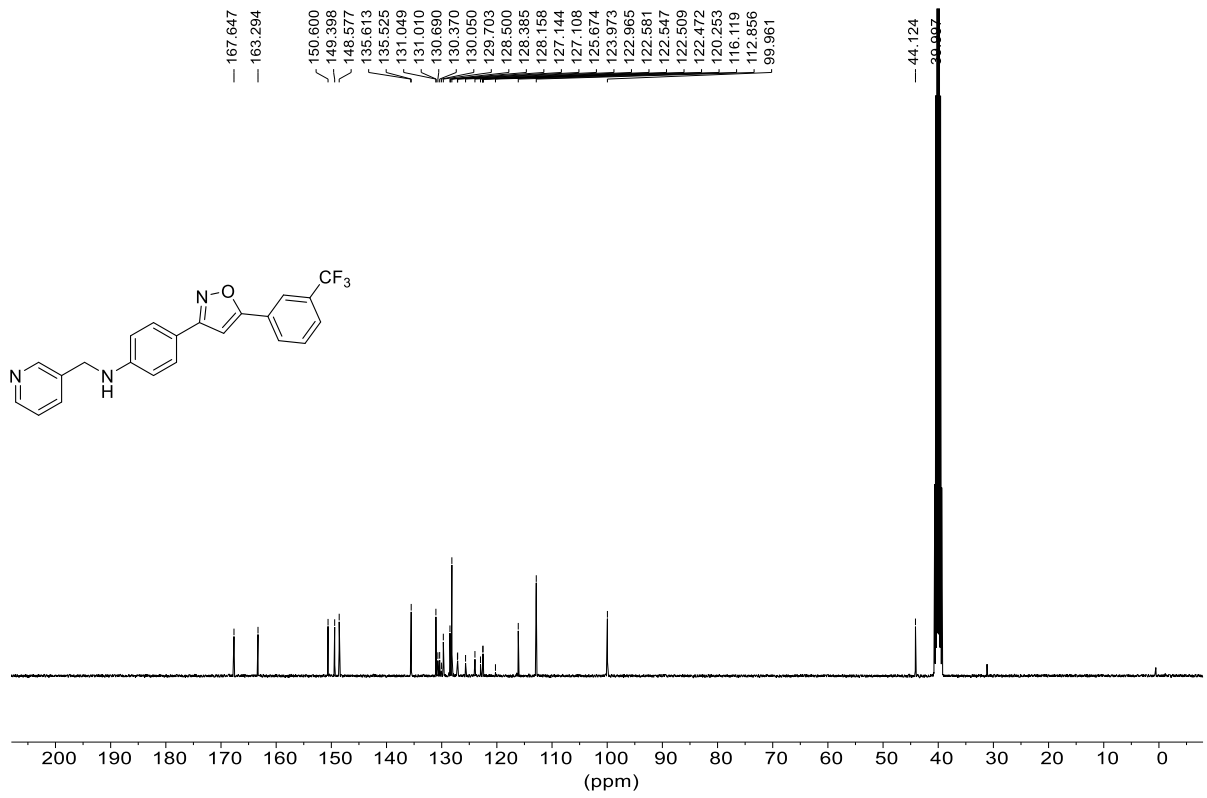


^{1}H NMR and ^{13}C NMR Spectra of Compound 7j

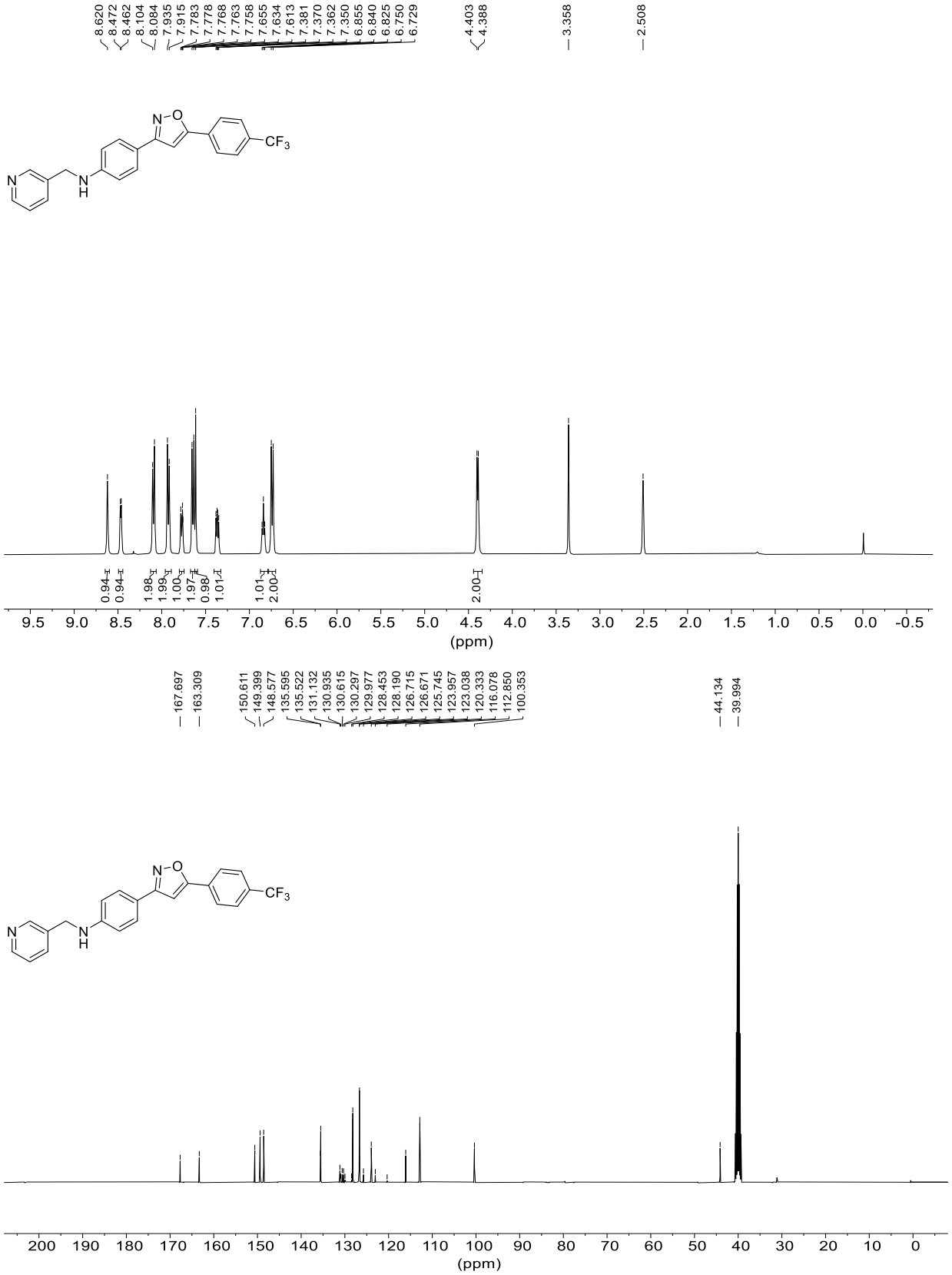


^{1}H NMR and ^{13}C NMR Spectra of Compound 7k

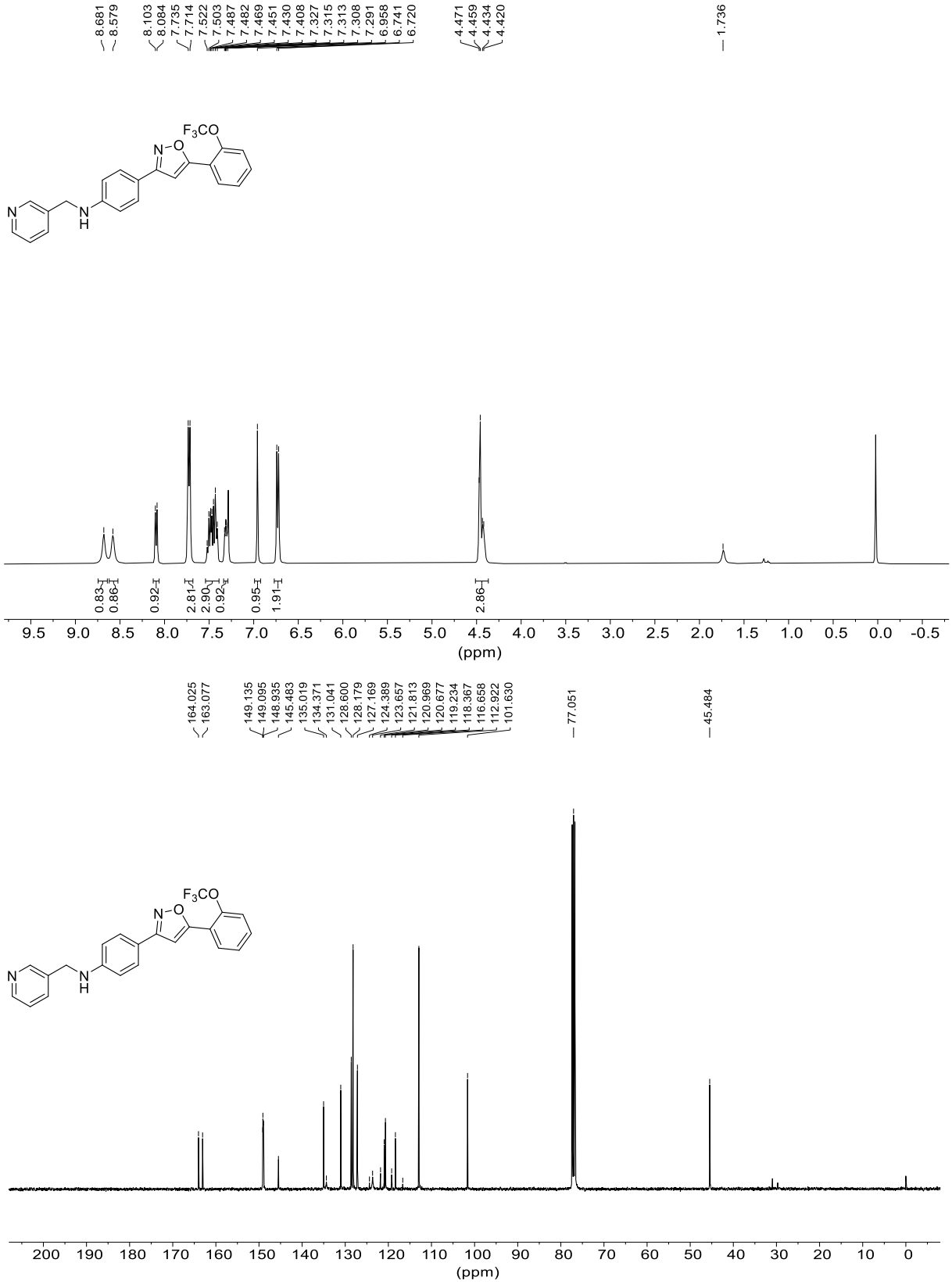




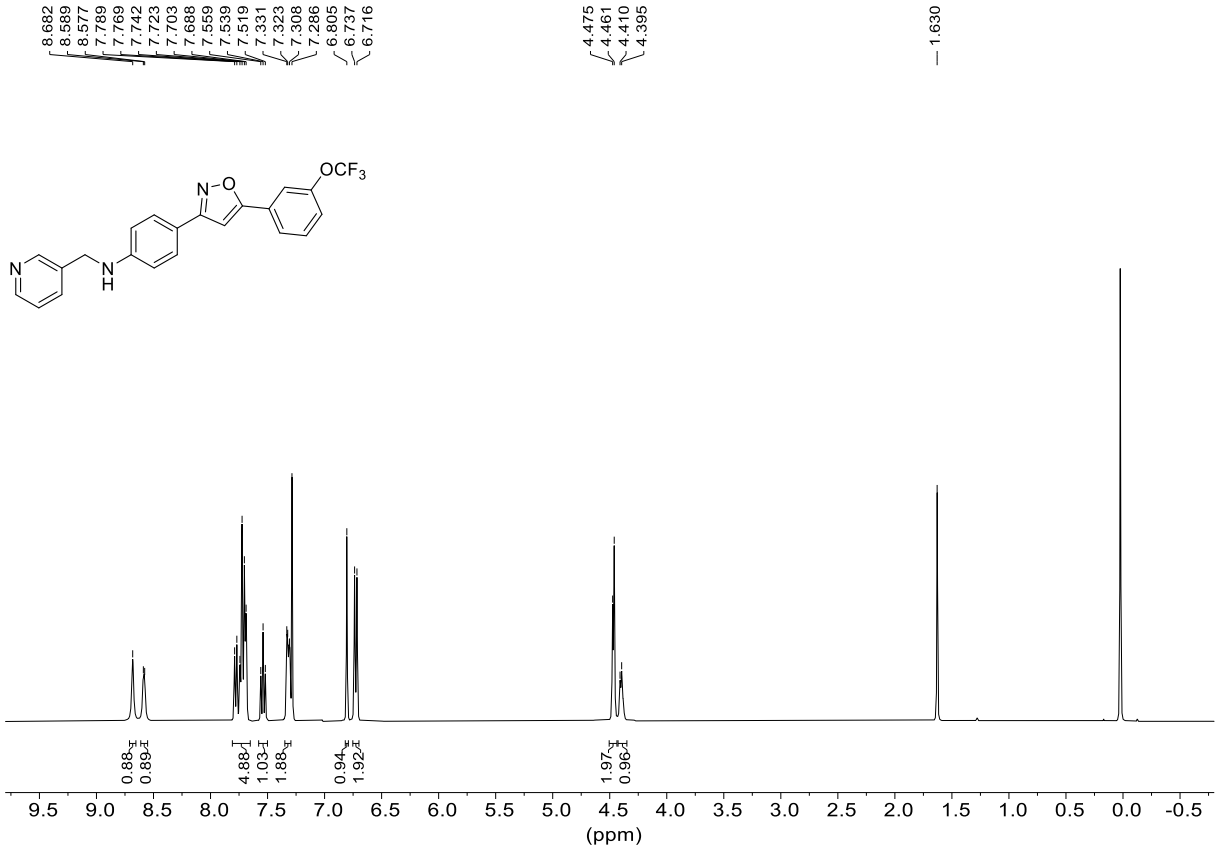
^{1}H NMR and ^{13}C NMR Spectra of Compound 7l

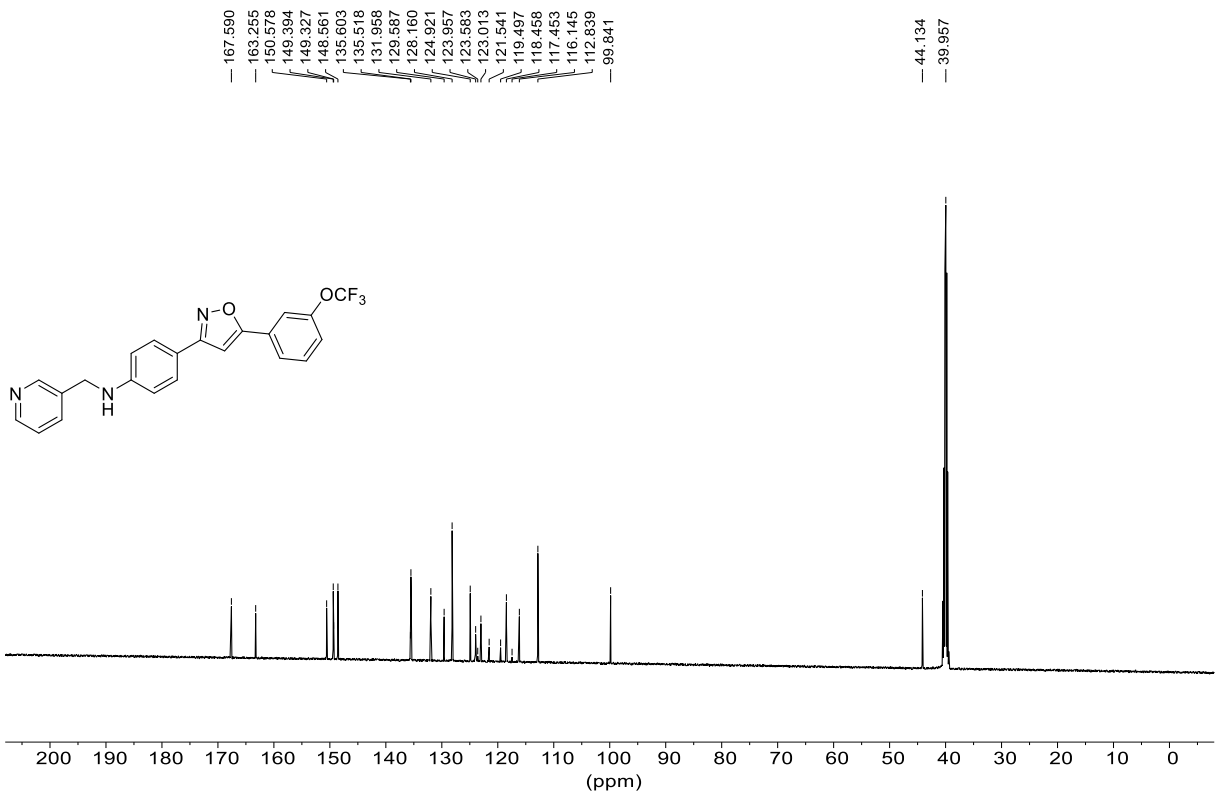


^{1}H NMR and ^{13}C NMR Spectra of Compound 7m

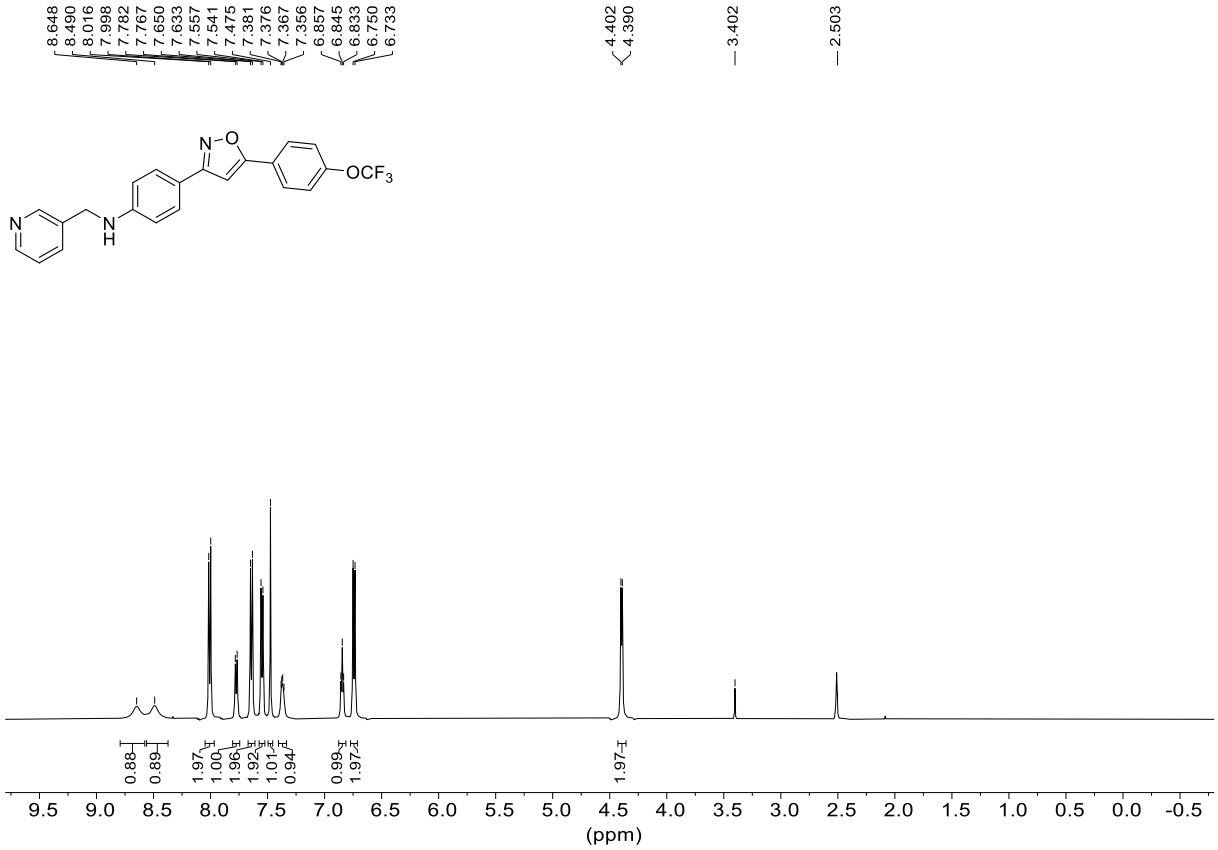


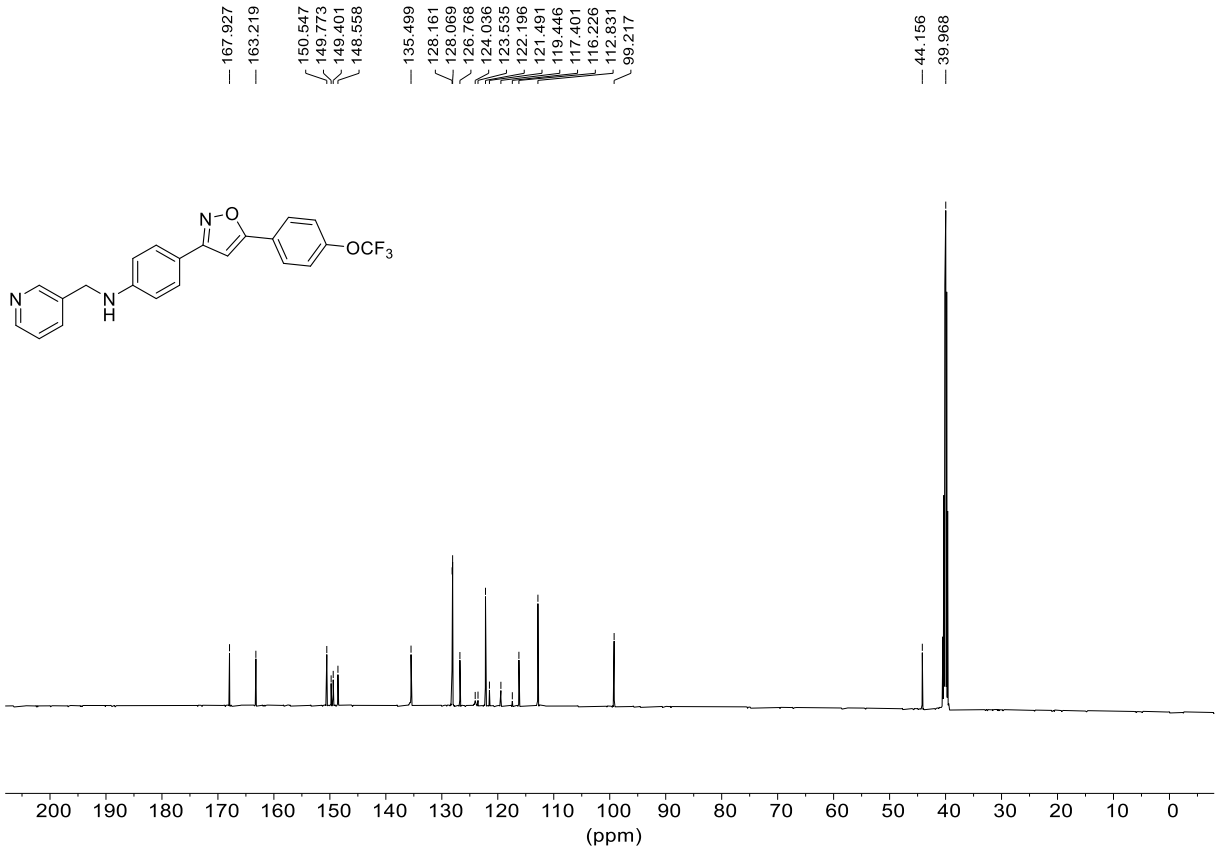
^{1}H NMR and ^{13}C NMR Spectra of Compound 7n



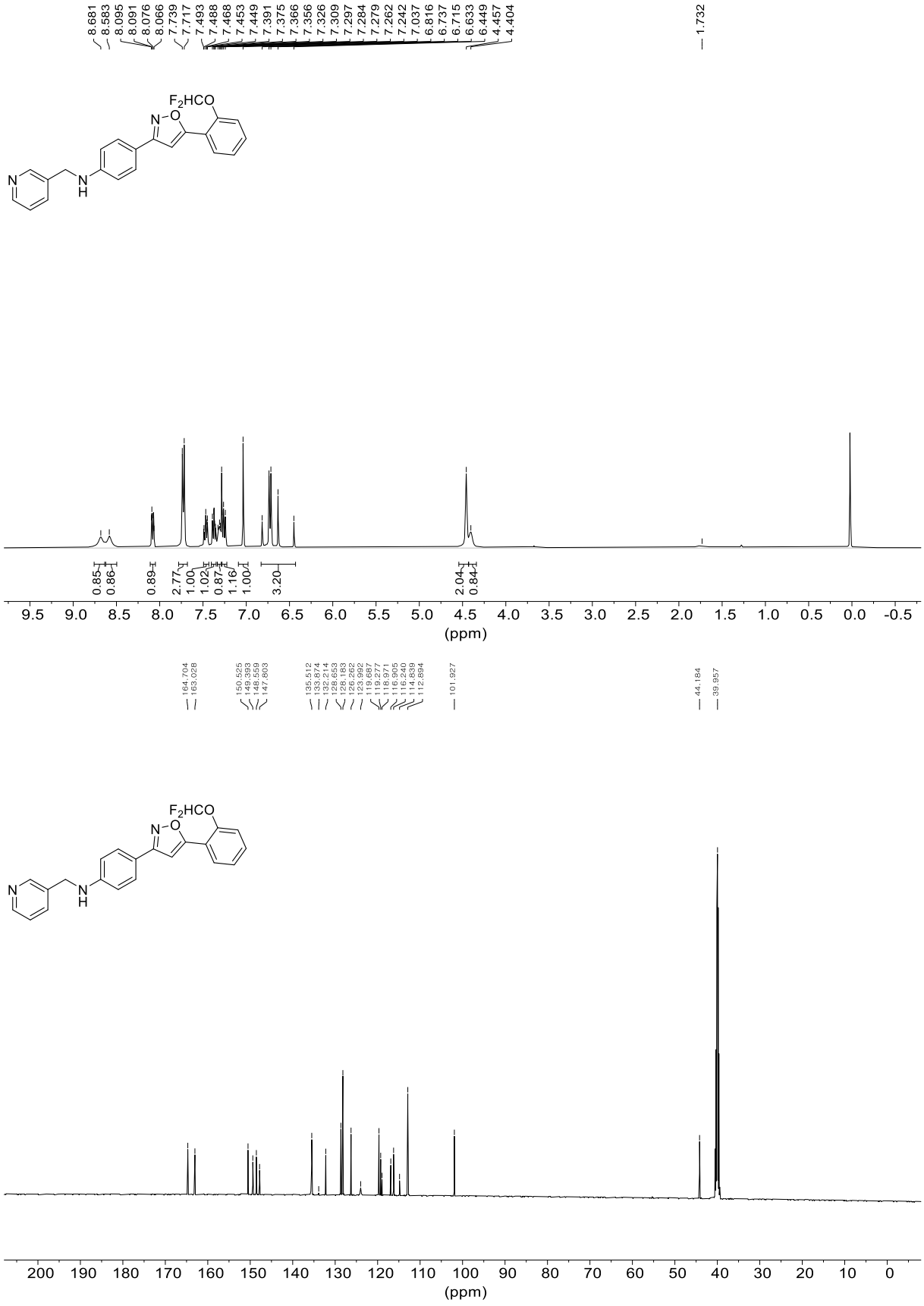


^{1}H NMR and ^{13}C NMR Spectra of Compound 7o

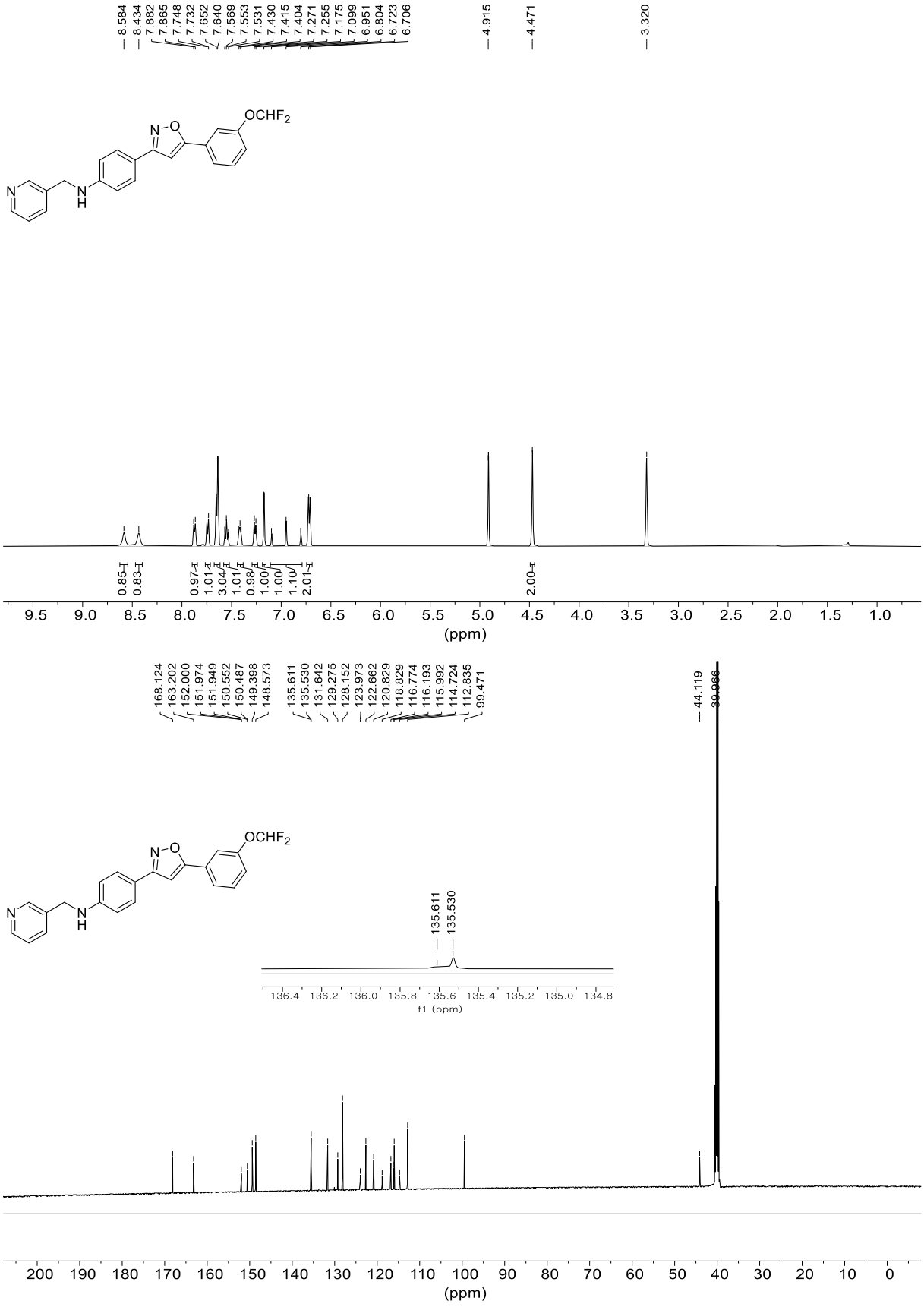




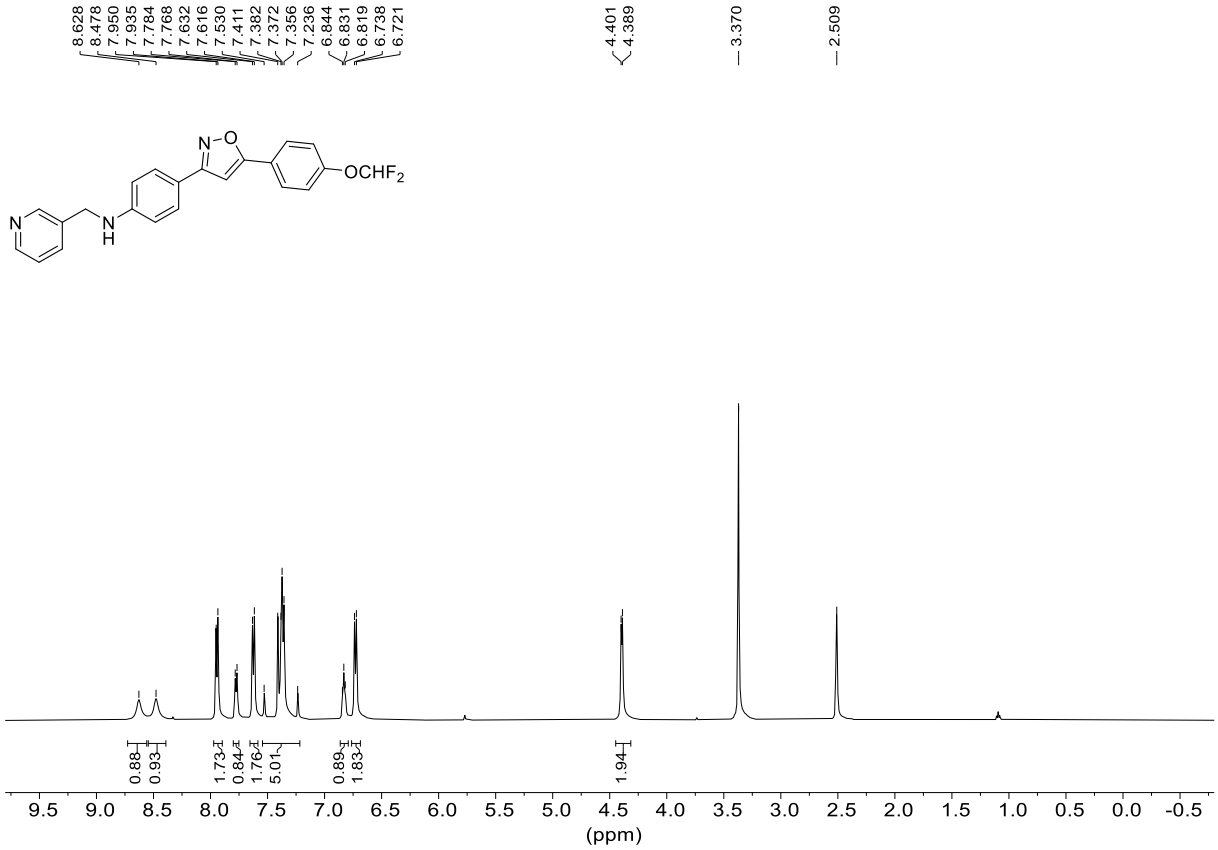
^{1}H NMR and ^{13}C NMR Spectra of Compound 7p

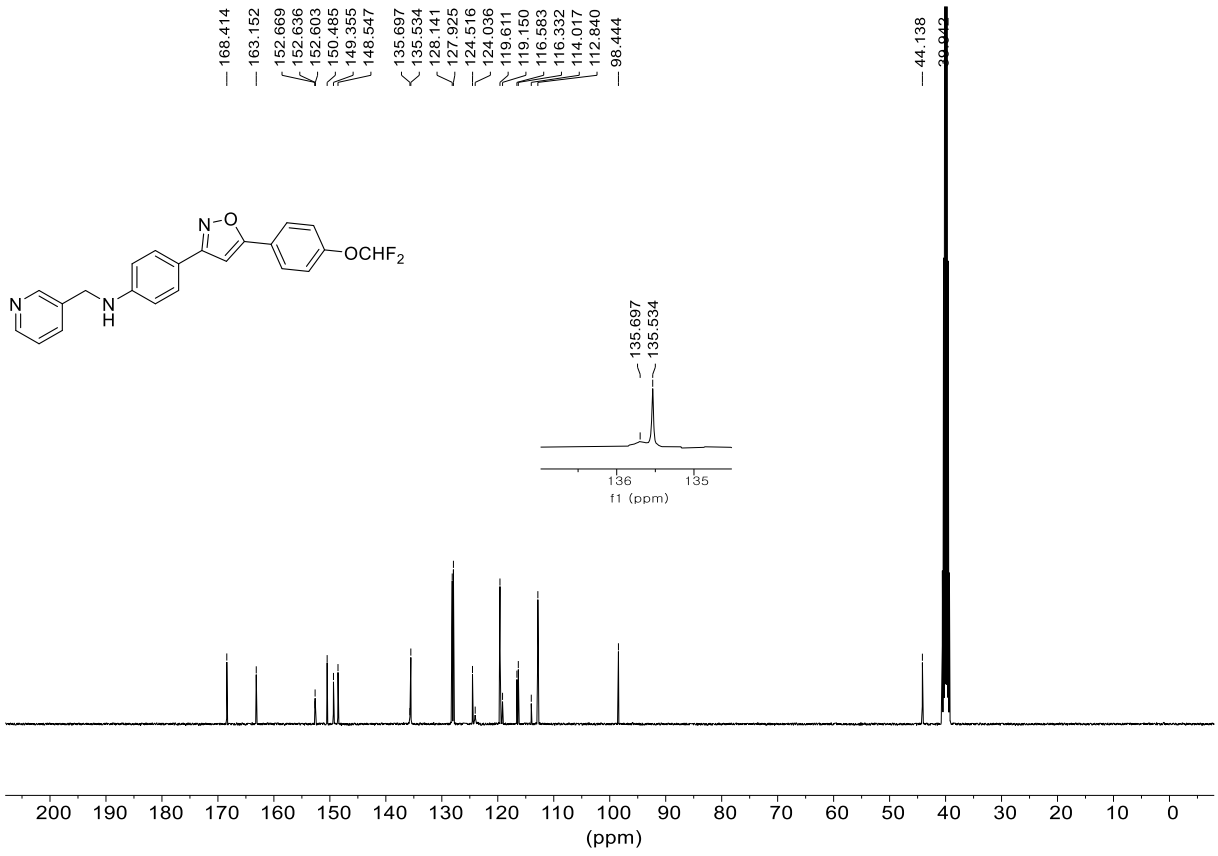


^{1}H NMR and ^{13}C NMR Spectra of Compound 7q

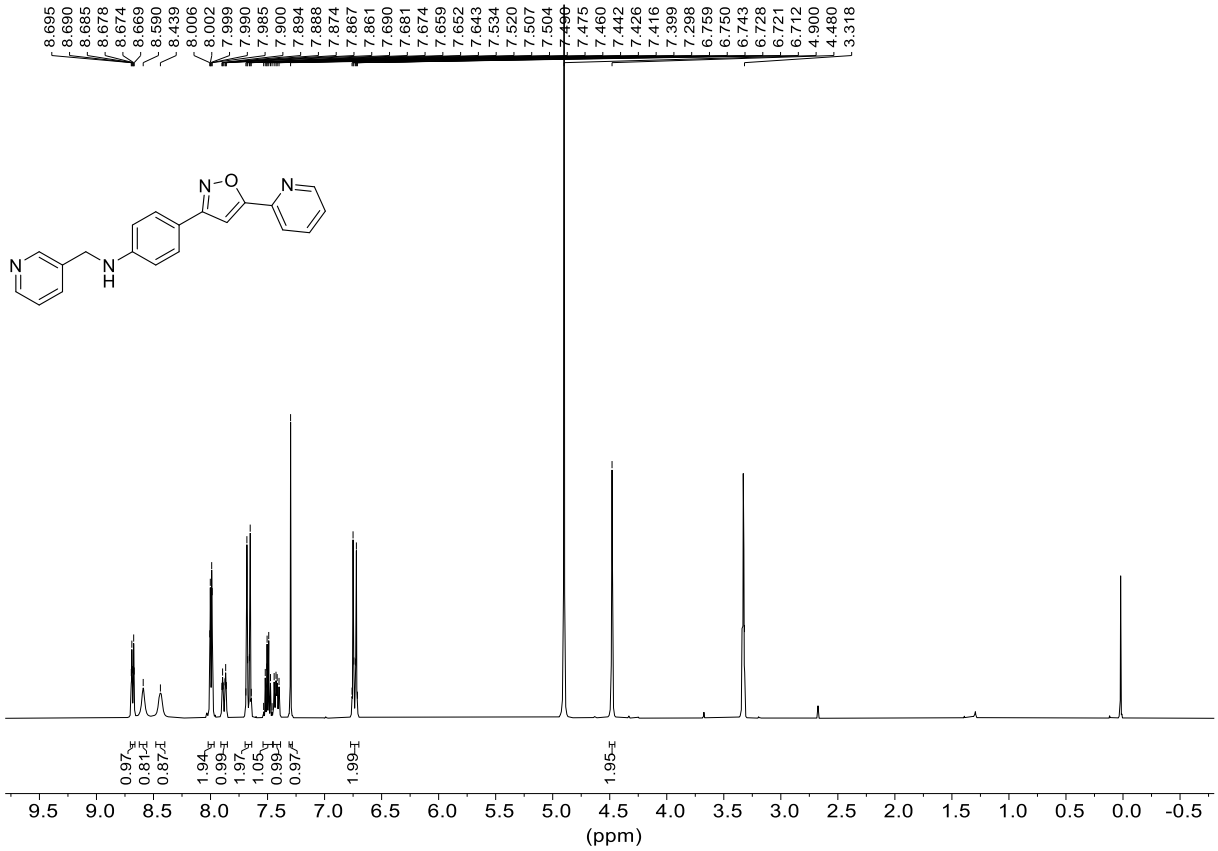


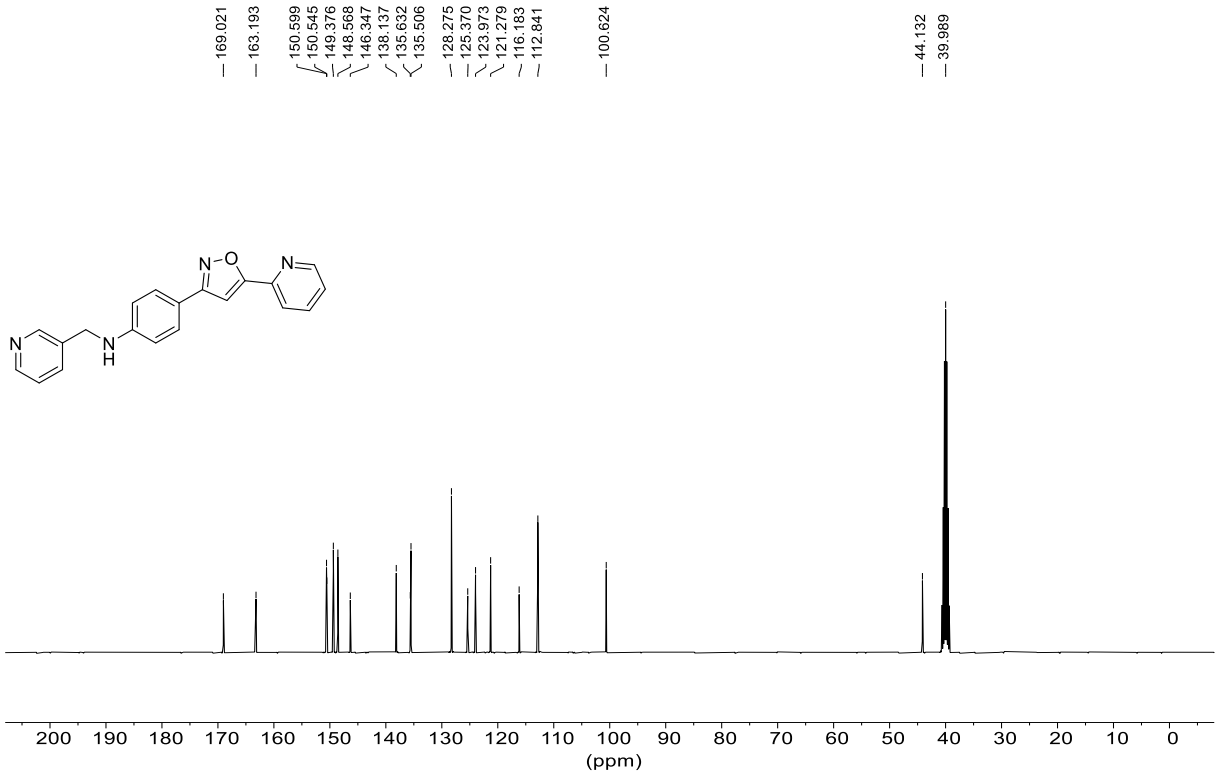
^{1}H NMR and ^{13}C NMR Spectra of Compound 7r



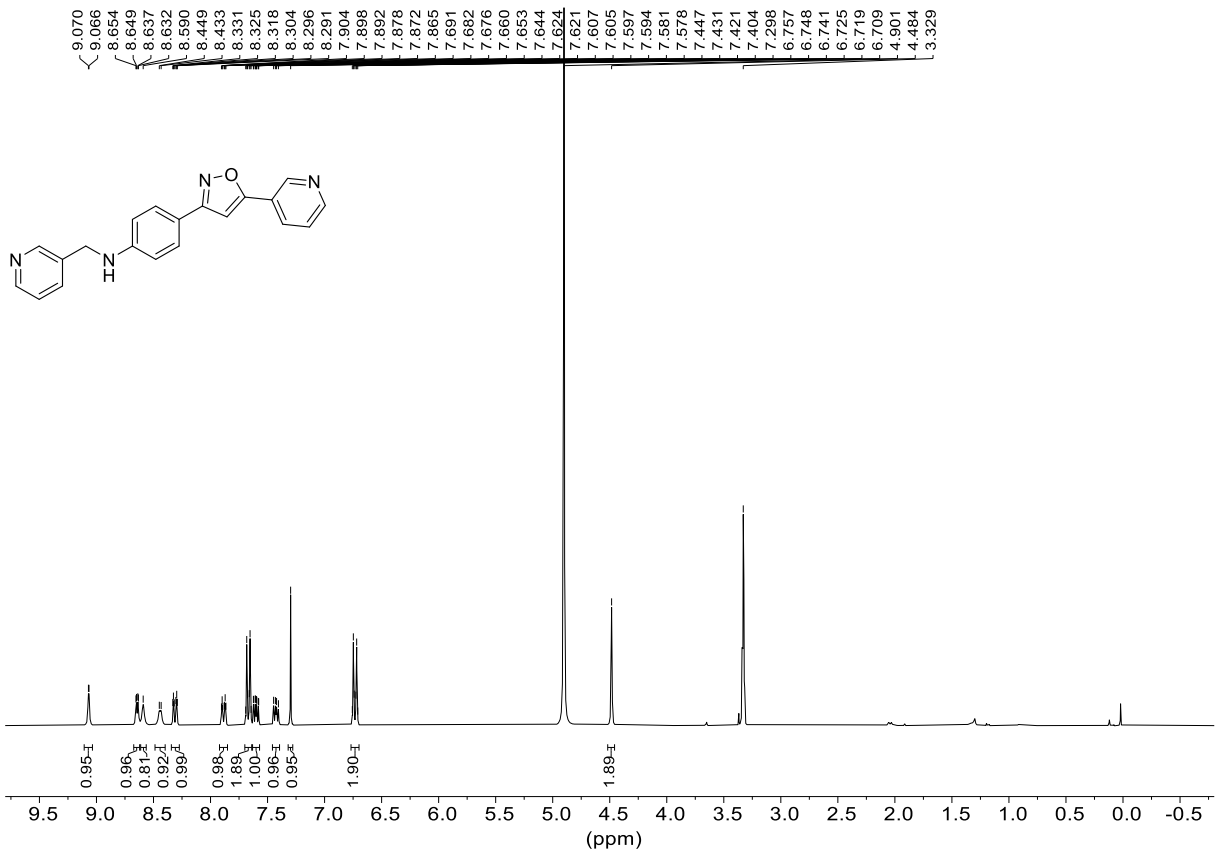


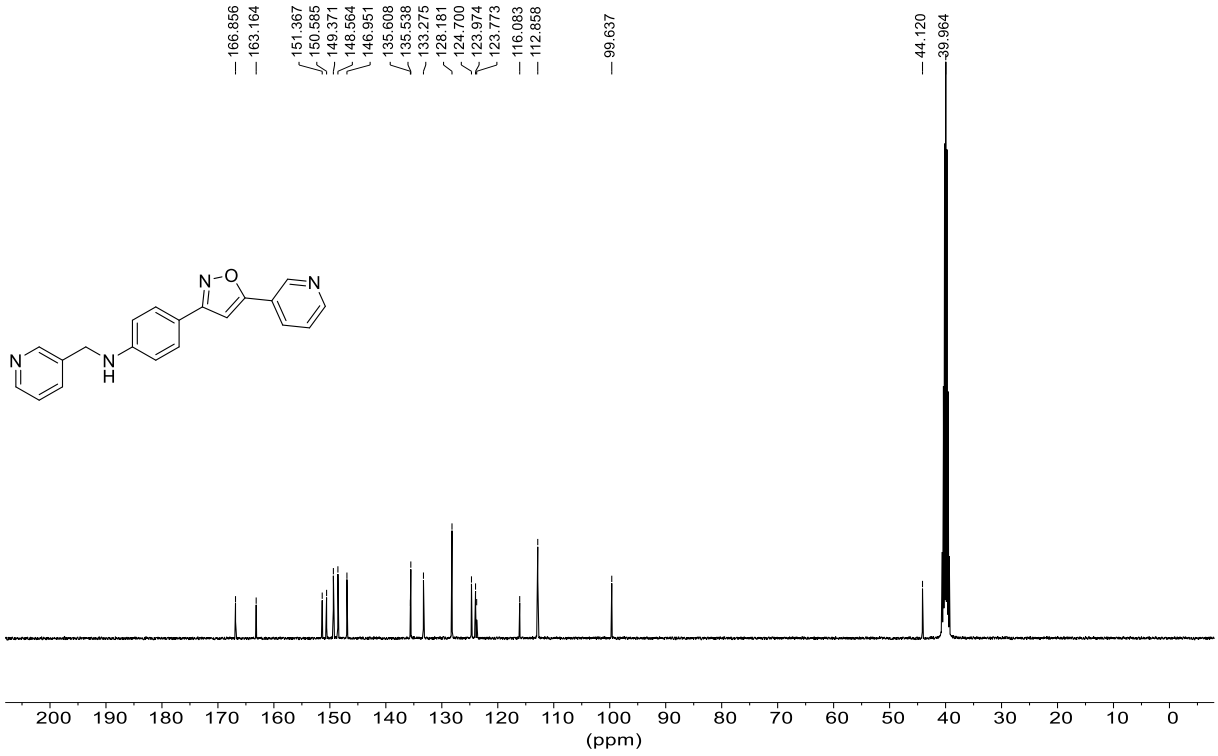
^{1}H NMR and ^{13}C NMR Spectra of Compound 8a



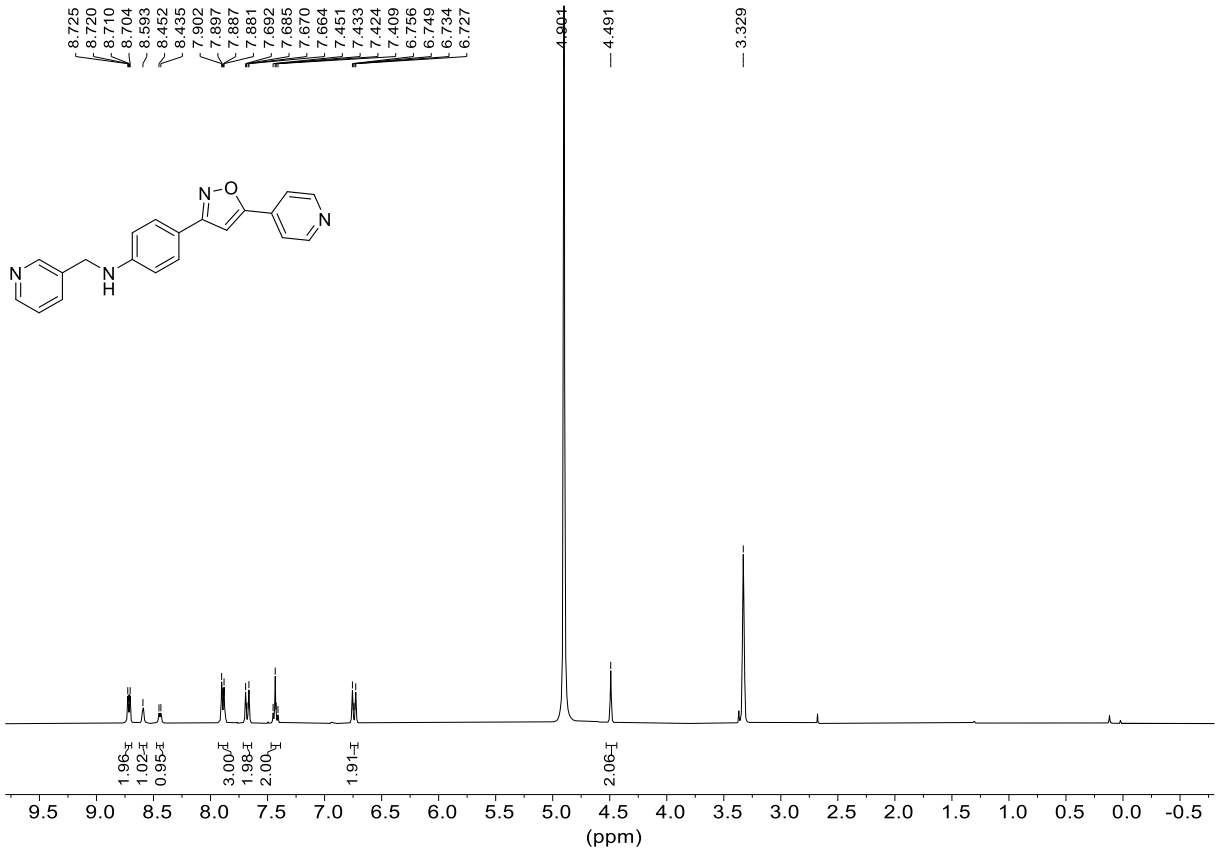


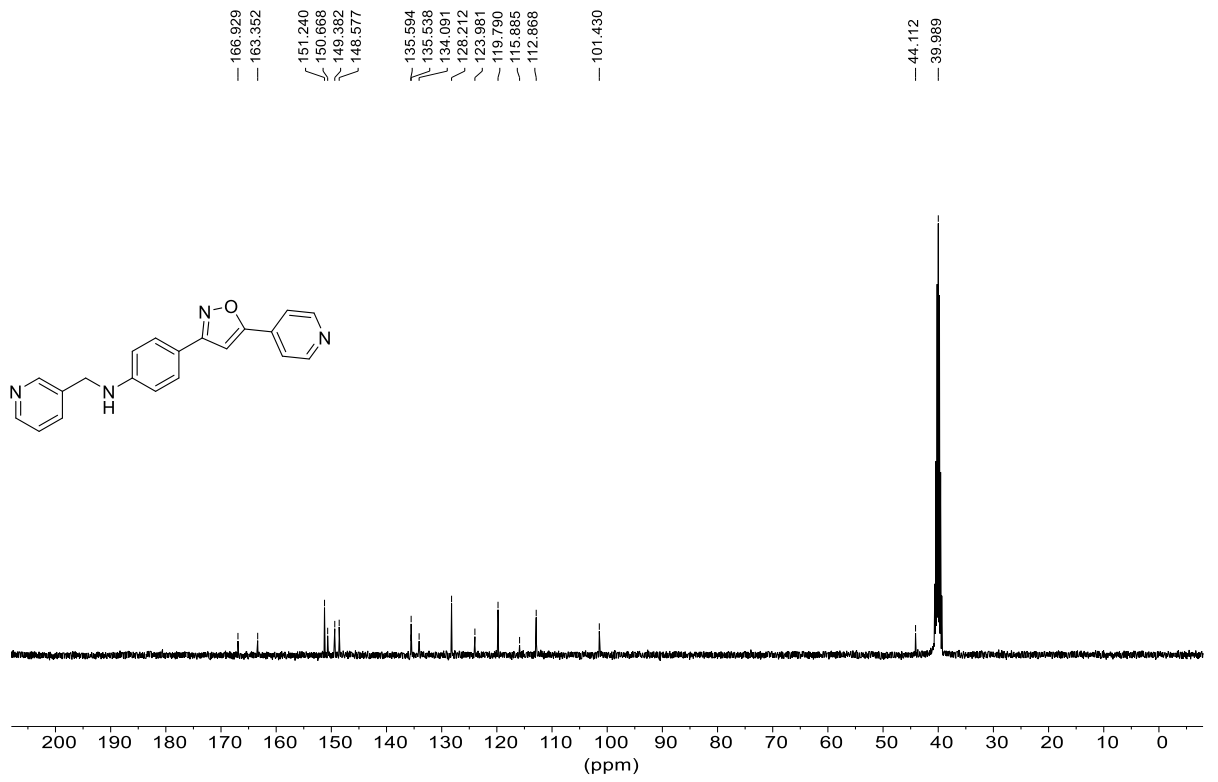
^{1}H NMR and ^{13}C NMR Spectra of Compound 8b



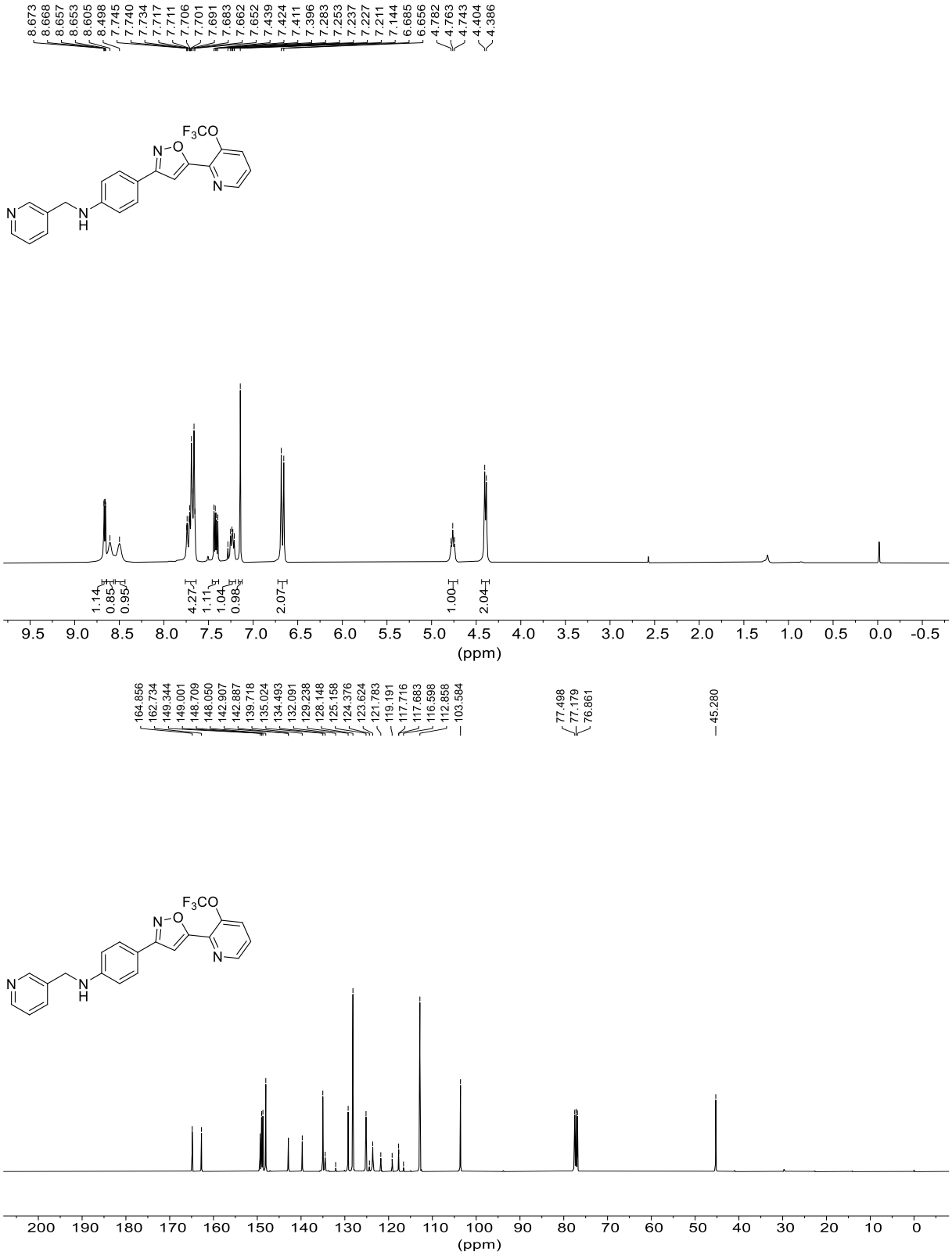


^{1}H NMR and ^{13}C NMR Spectra of Compound 8c

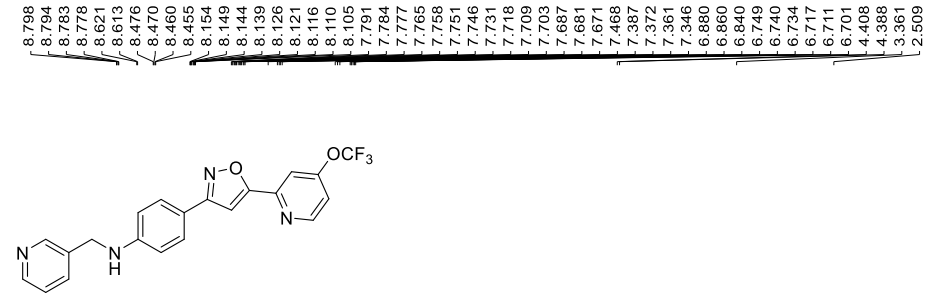


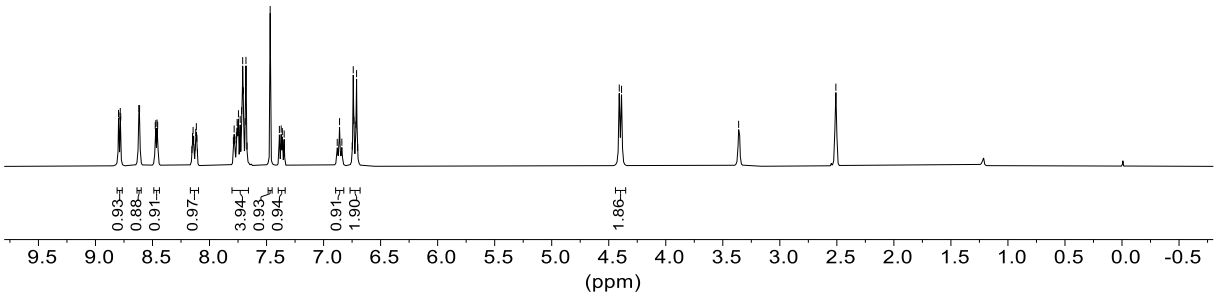


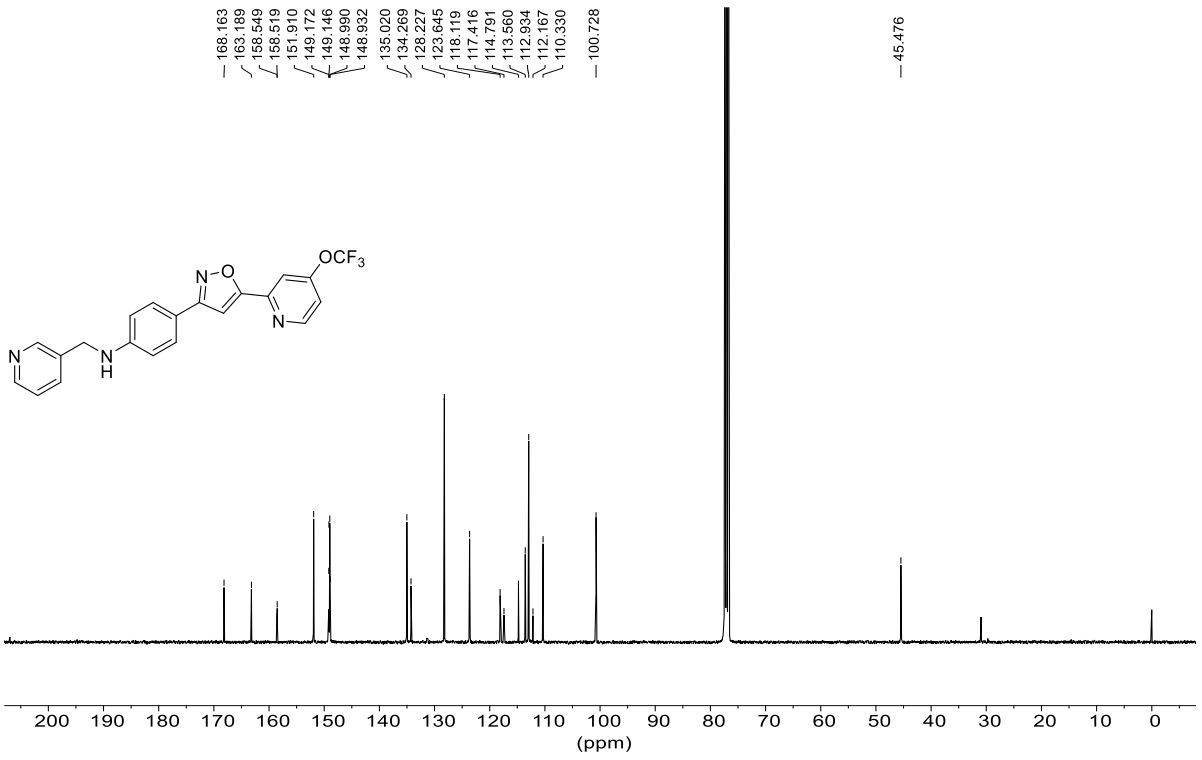
^{1}H NMR and ^{13}C NMR Spectra of Compound 8d



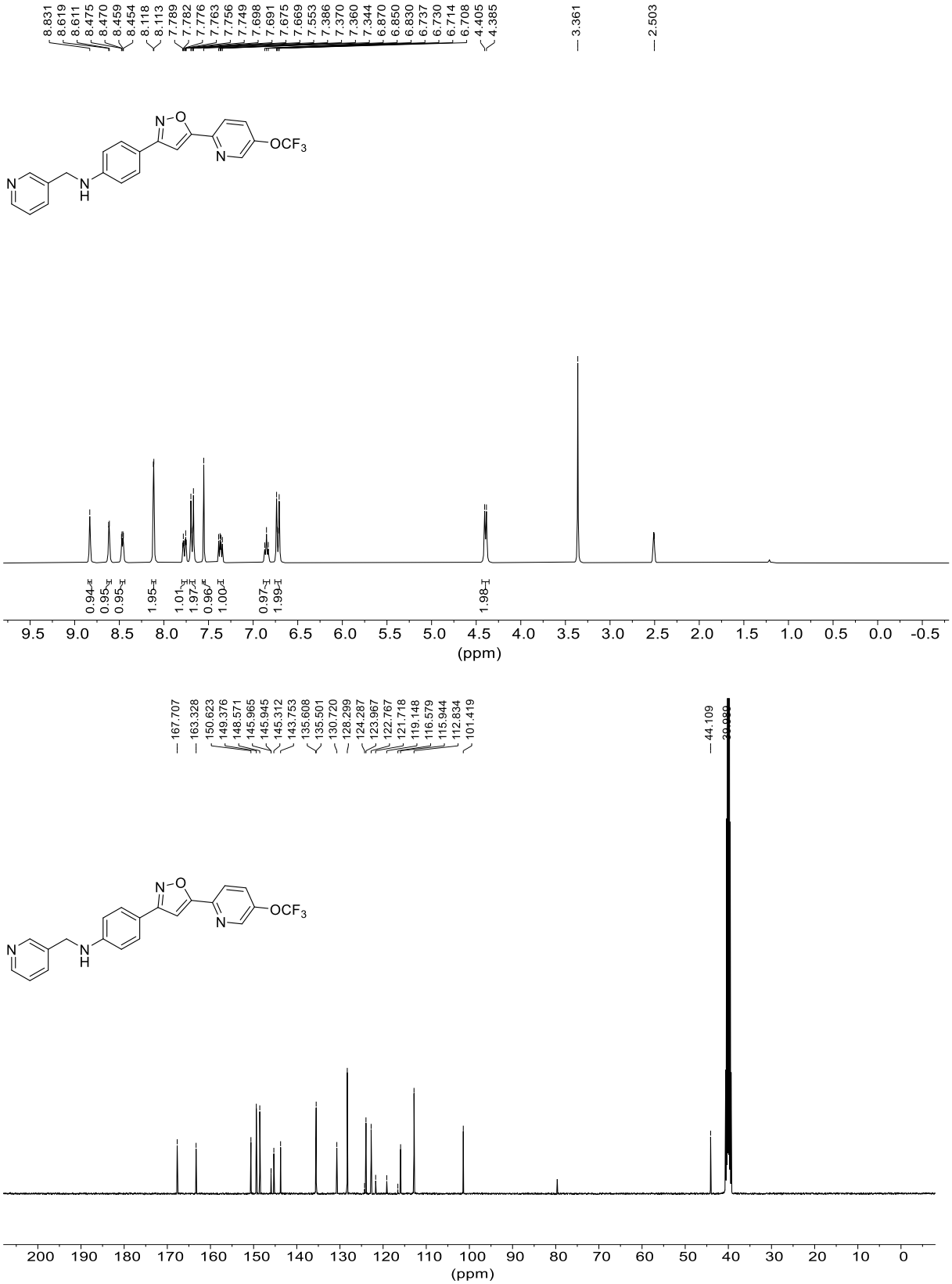
^{1}H NMR and ^{13}C NMR Spectra of Compound 8e



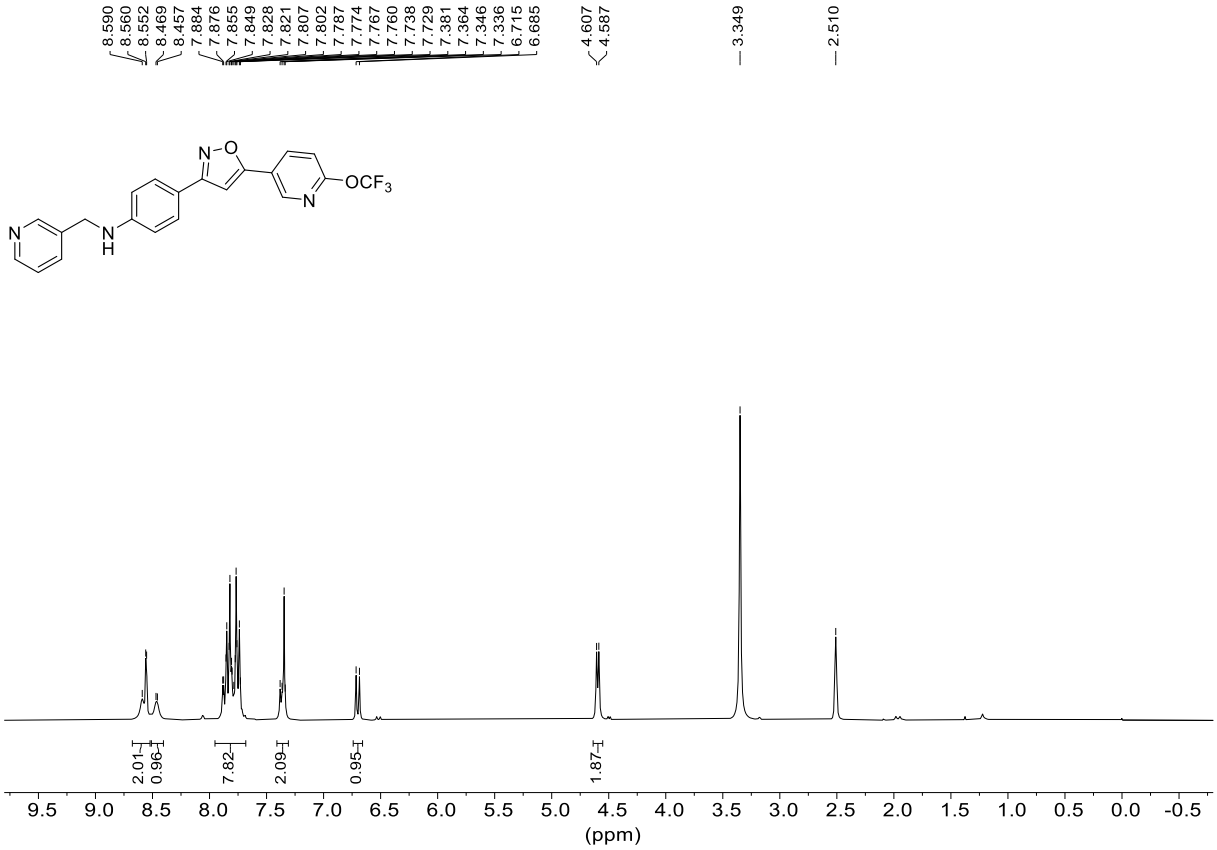


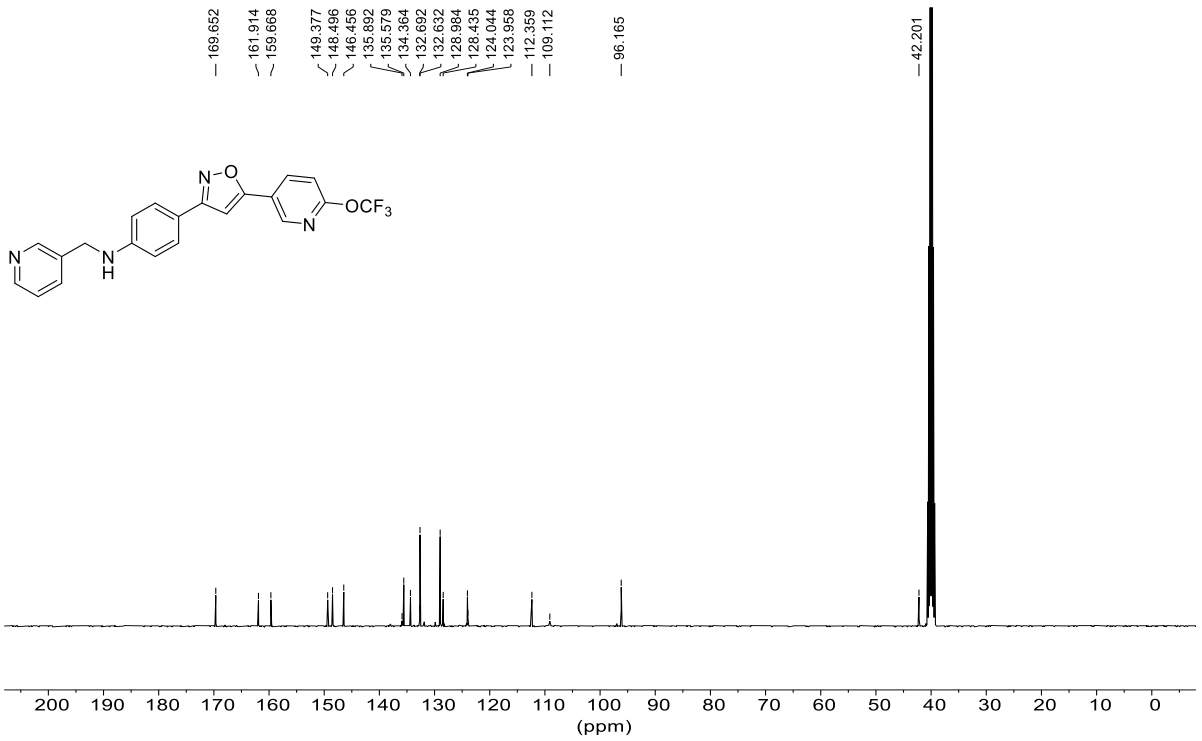


^{1}H NMR and ^{13}C NMR Spectra of Compound 8f

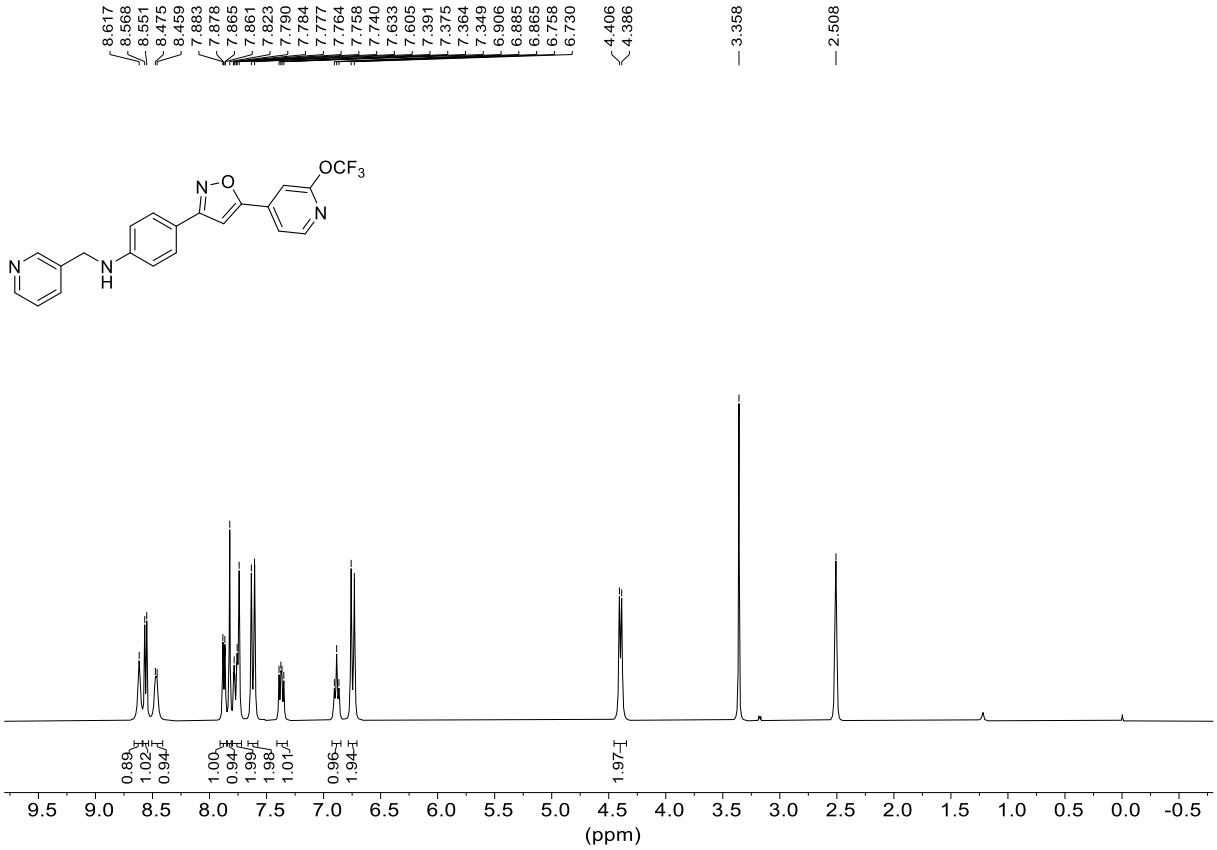


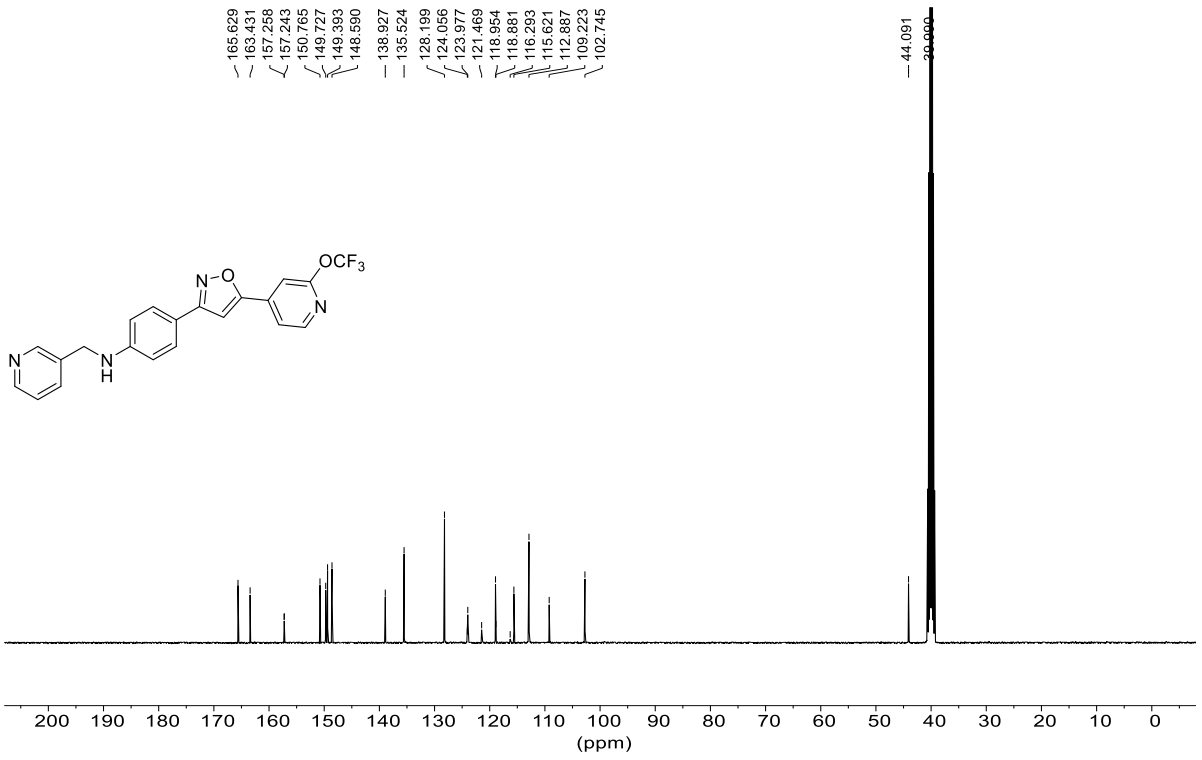
^{1}H NMR and ^{13}C NMR Spectra of Compound 8g



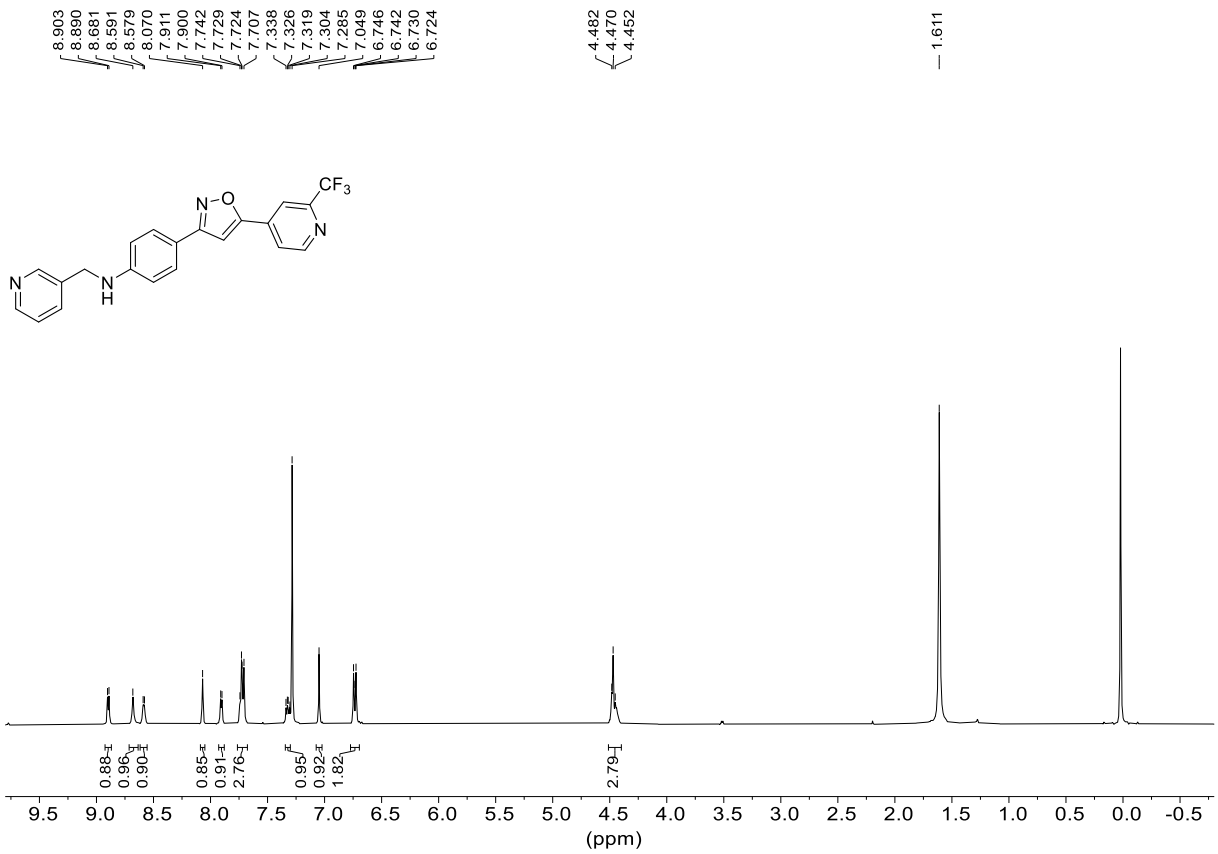


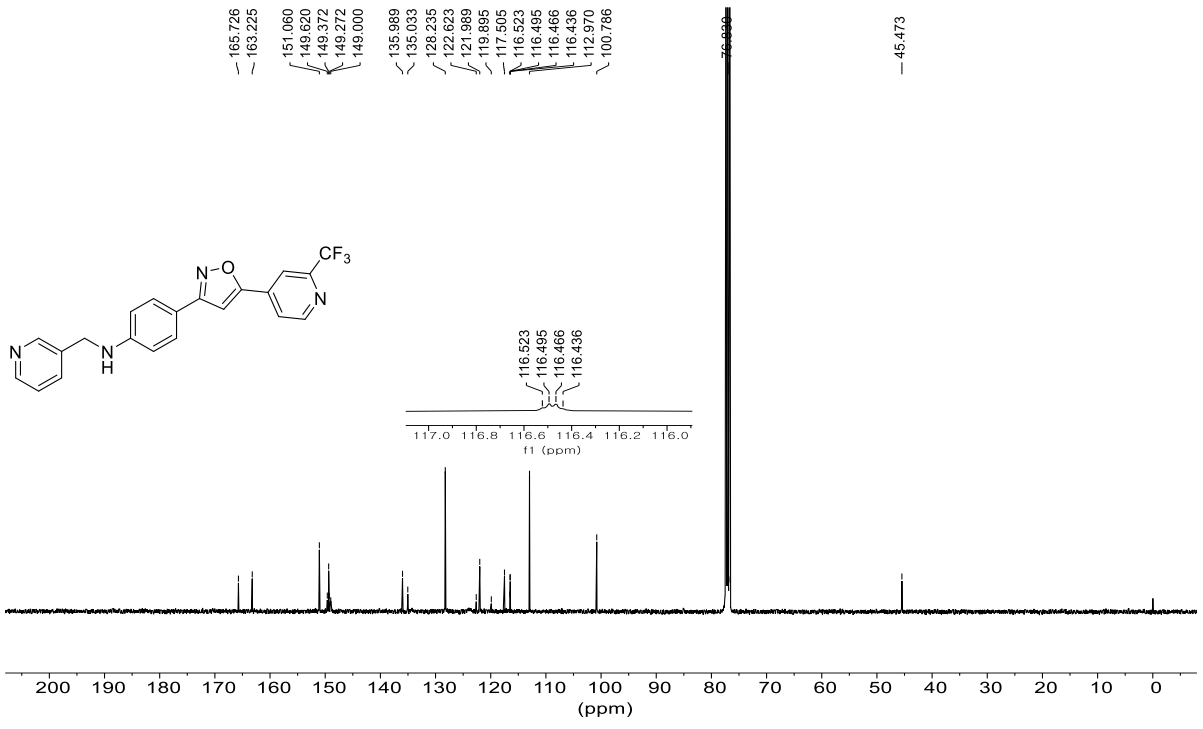
^{1}H NMR and ^{13}C NMR Spectra of Compound 8h



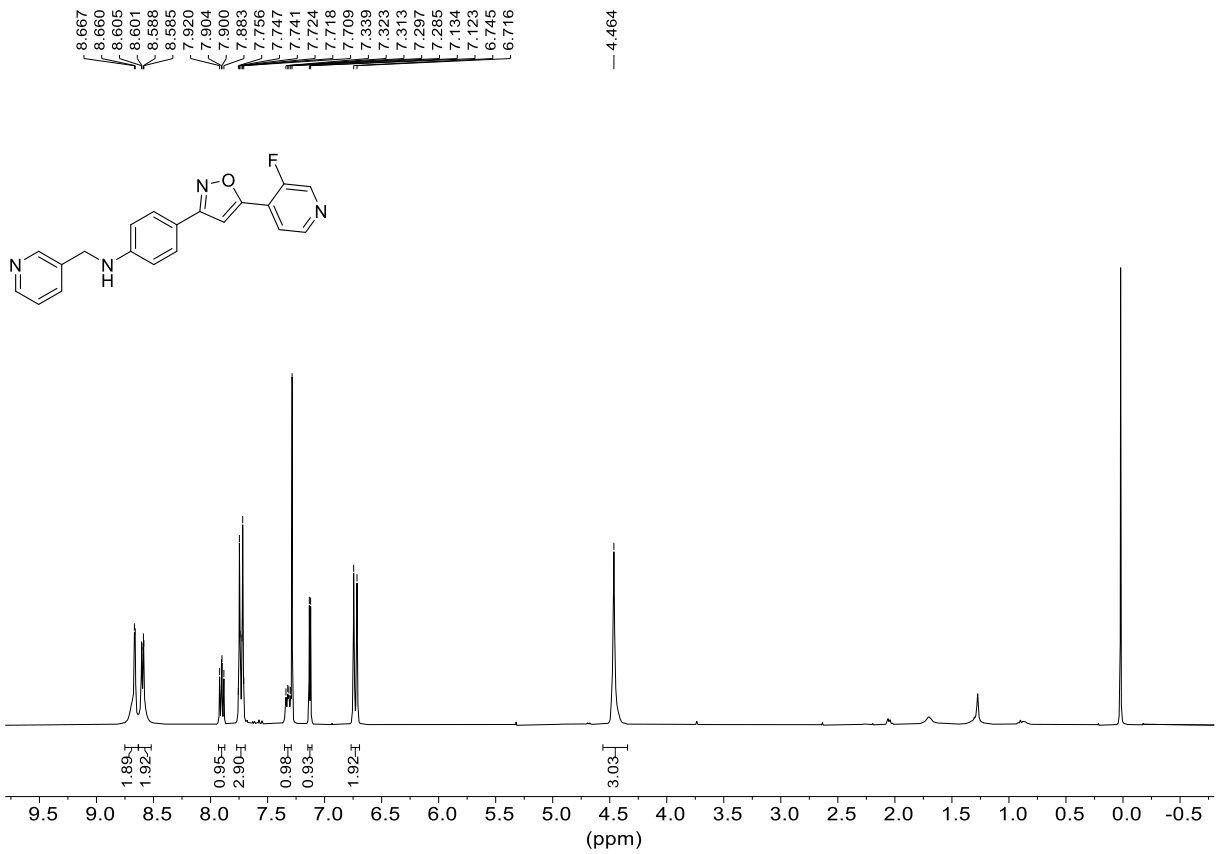


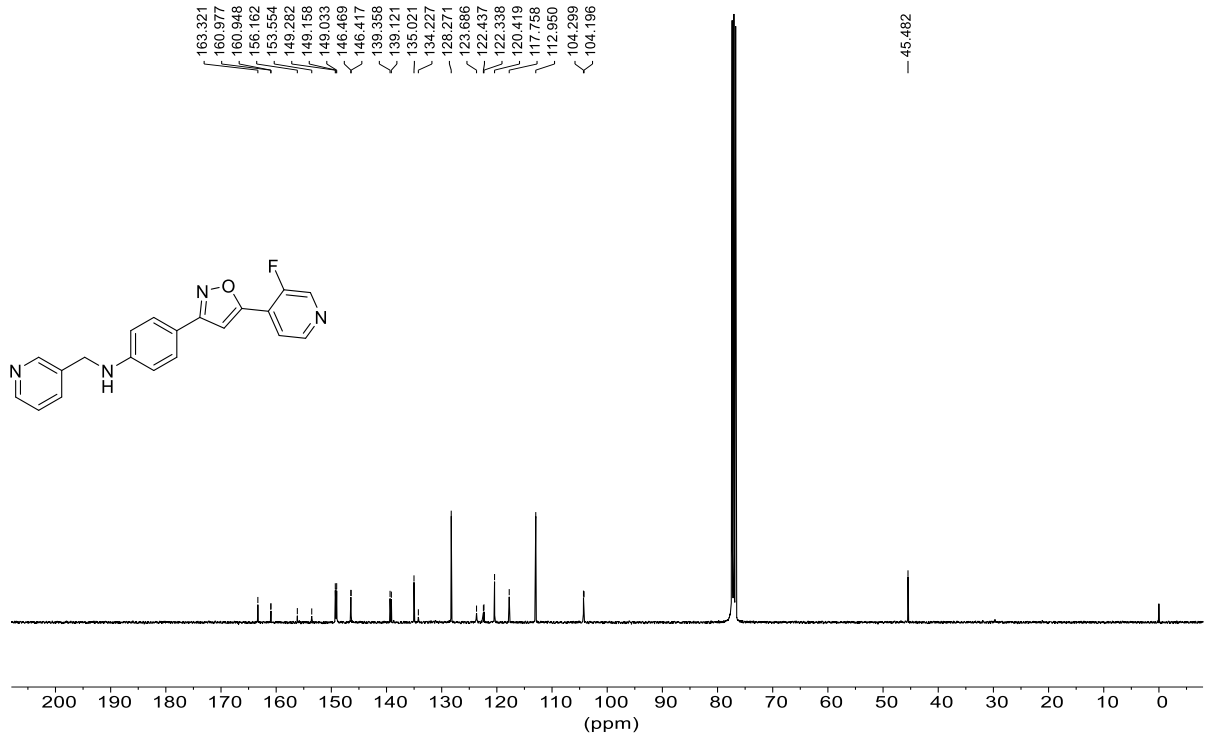
^{1}H NMR and ^{13}C NMR Spectra of Compound 8i



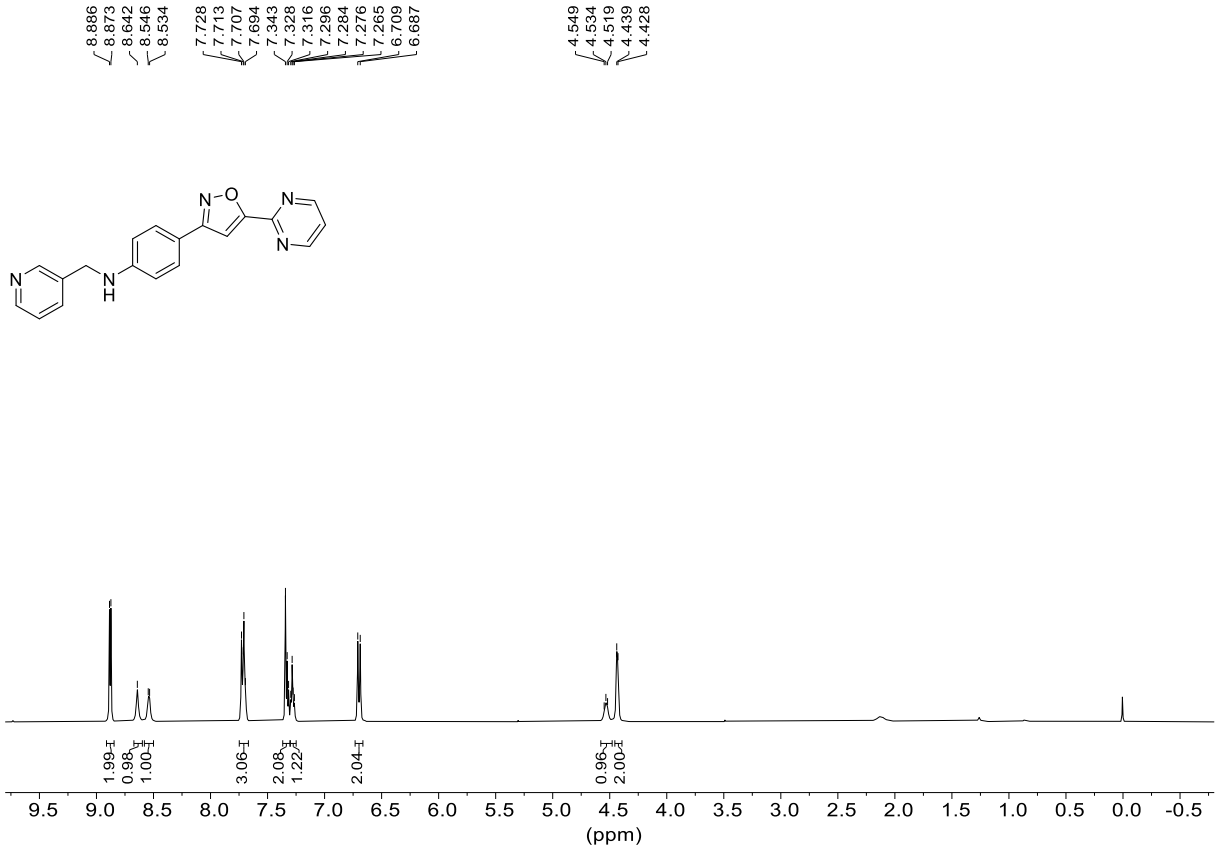


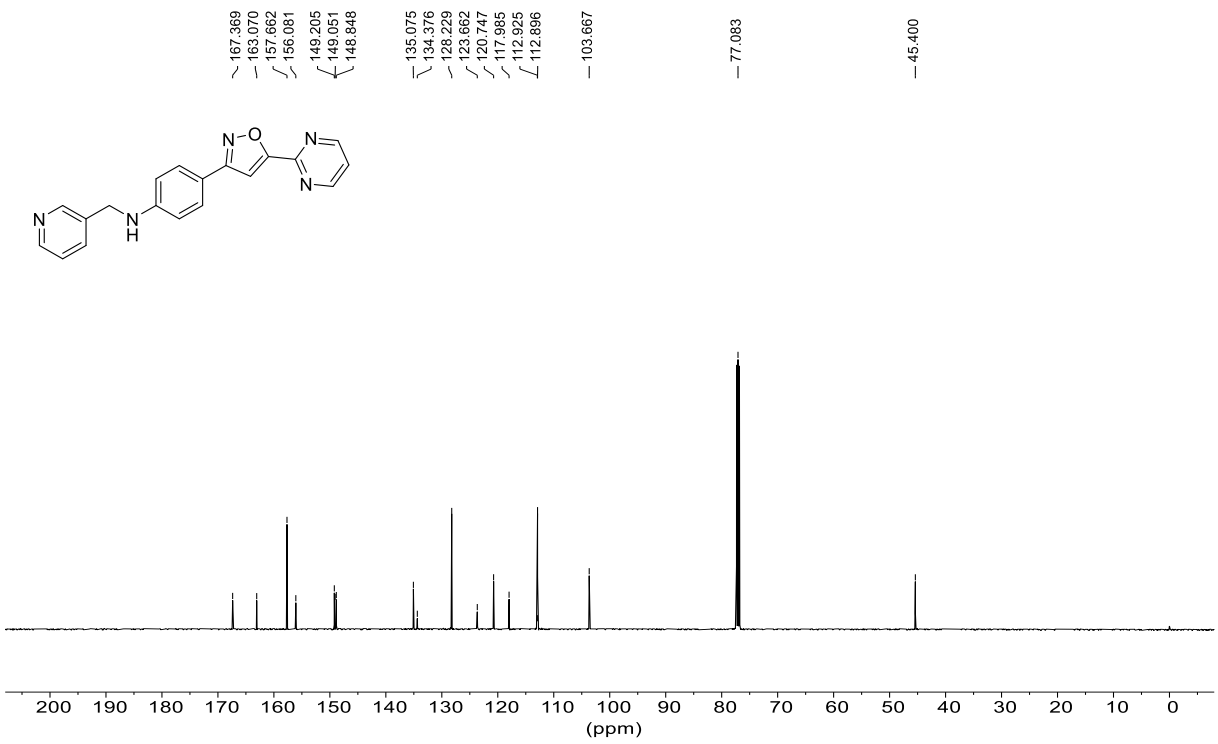
^{1}H NMR and ^{13}C NMR Spectra of Compound 8j



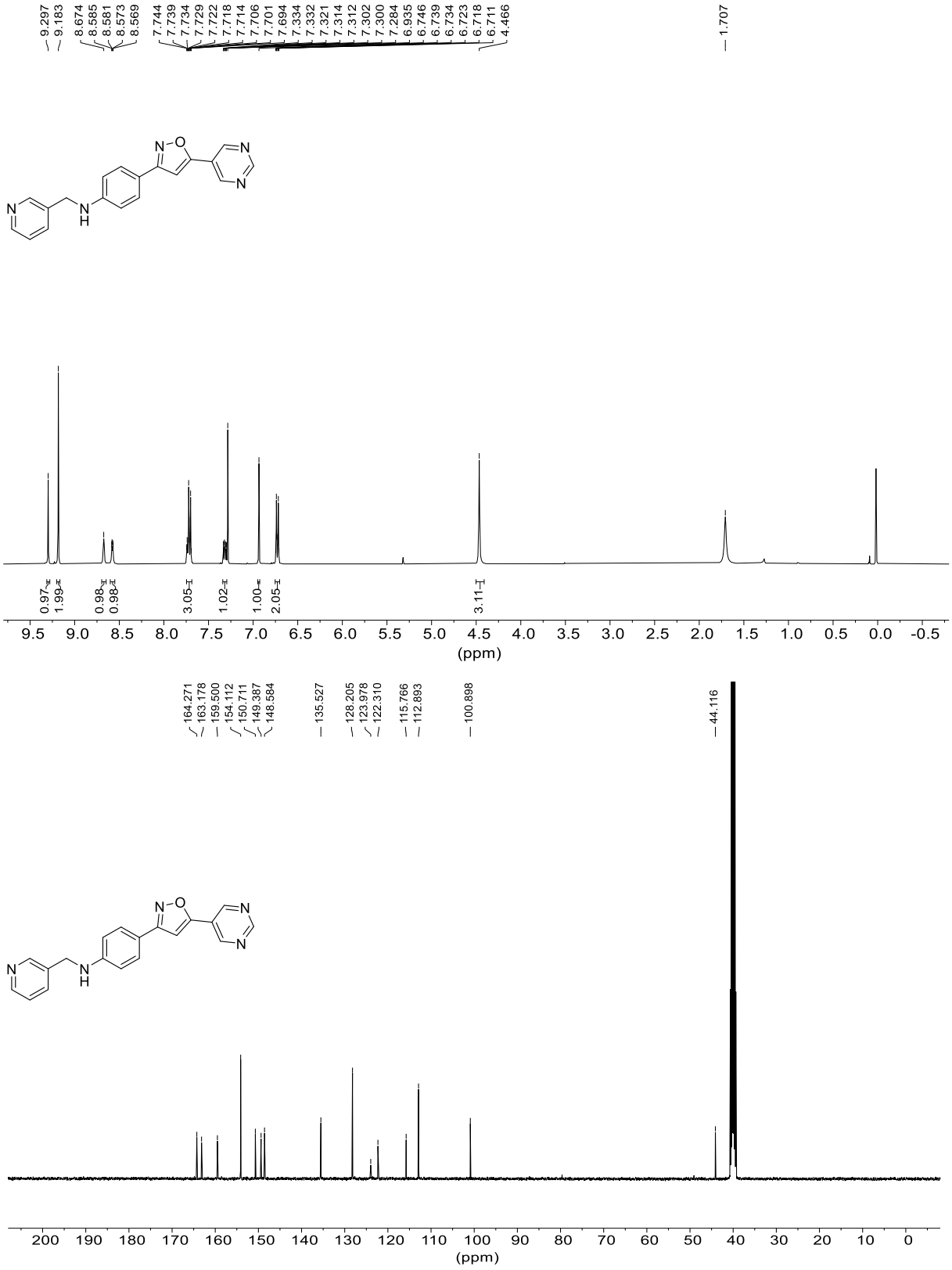


^{1}H NMR and ^{13}C NMR Spectra of Compound 8k

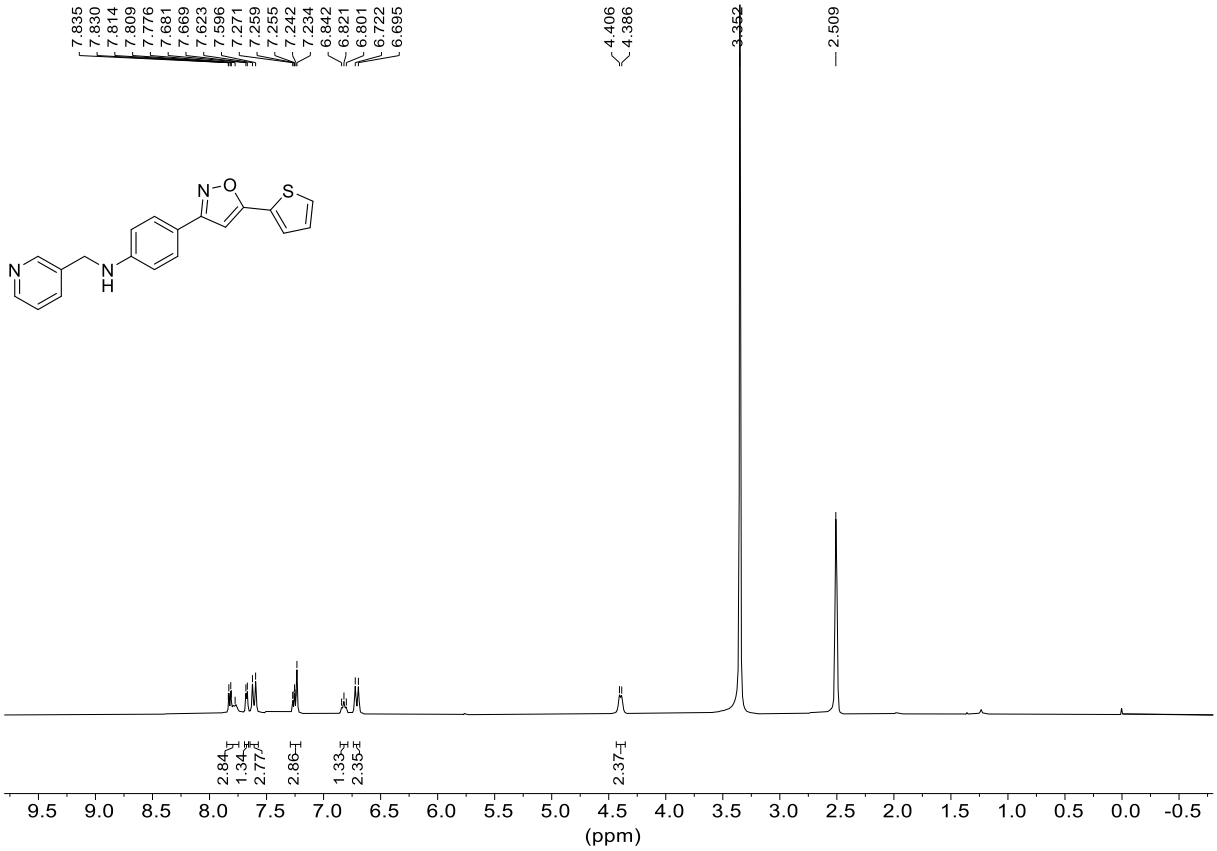


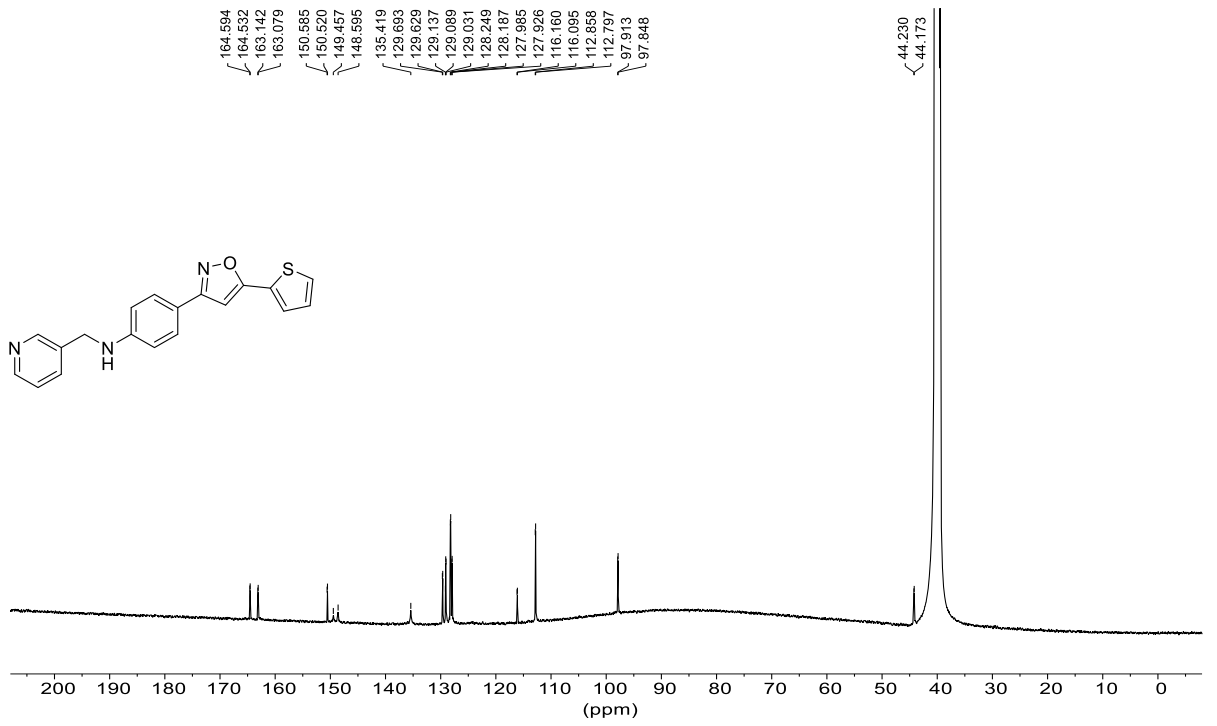


^{1}H NMR and ^{13}C NMR Spectra of Compound 8l

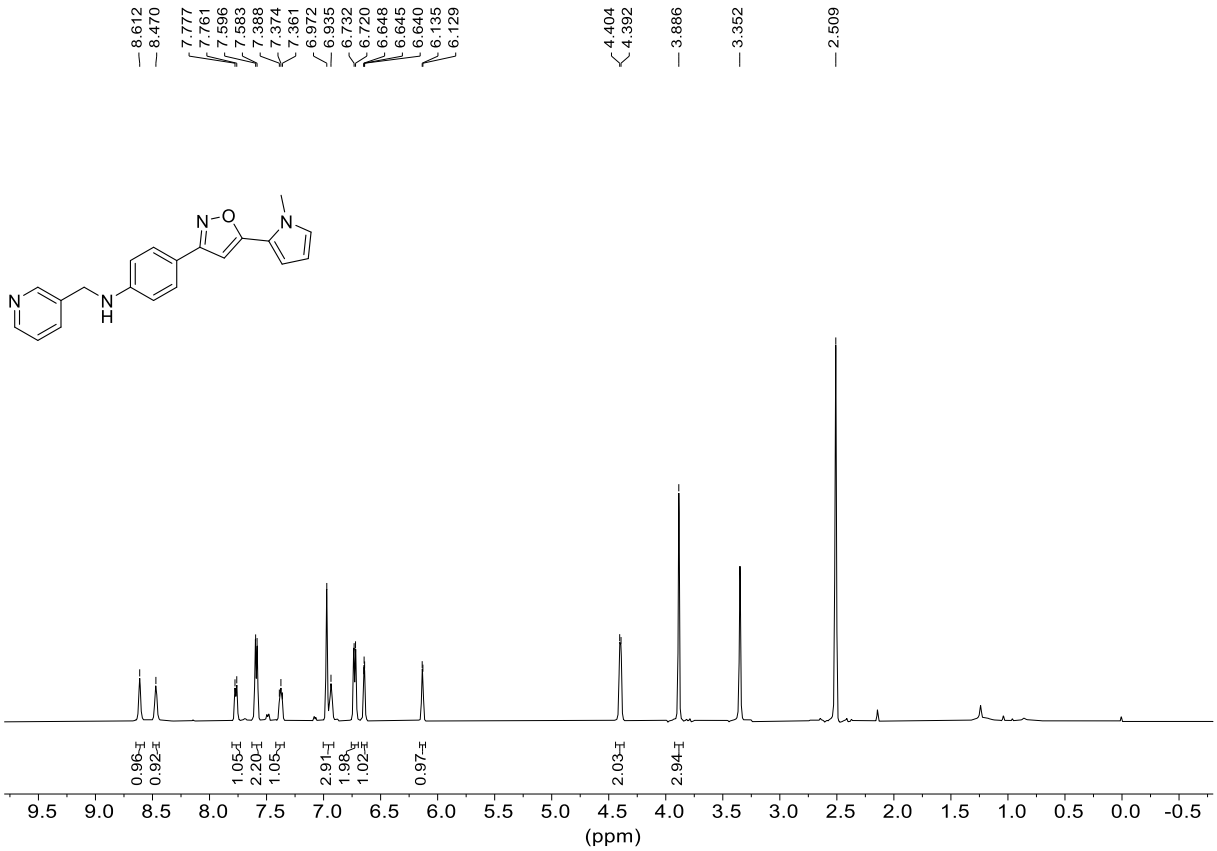


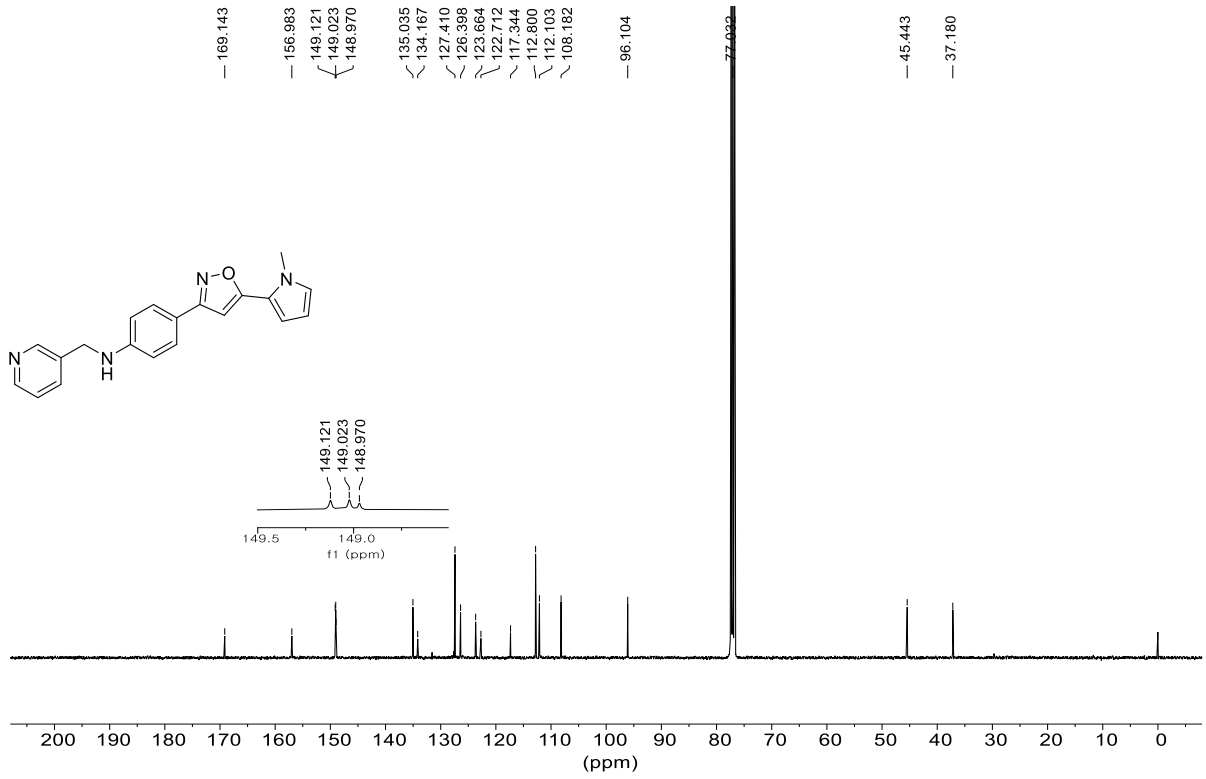
^{1}H NMR and ^{13}C NMR Spectra of Compound 8m



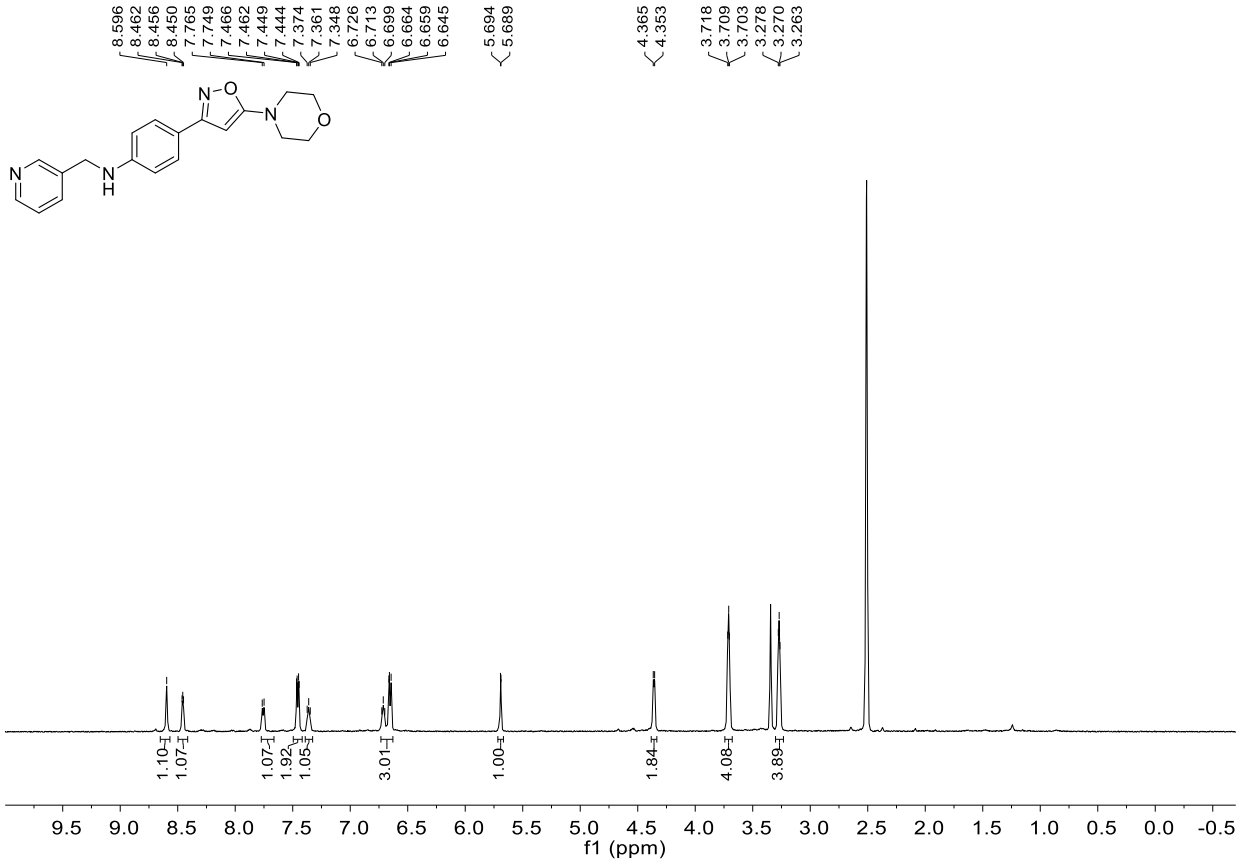


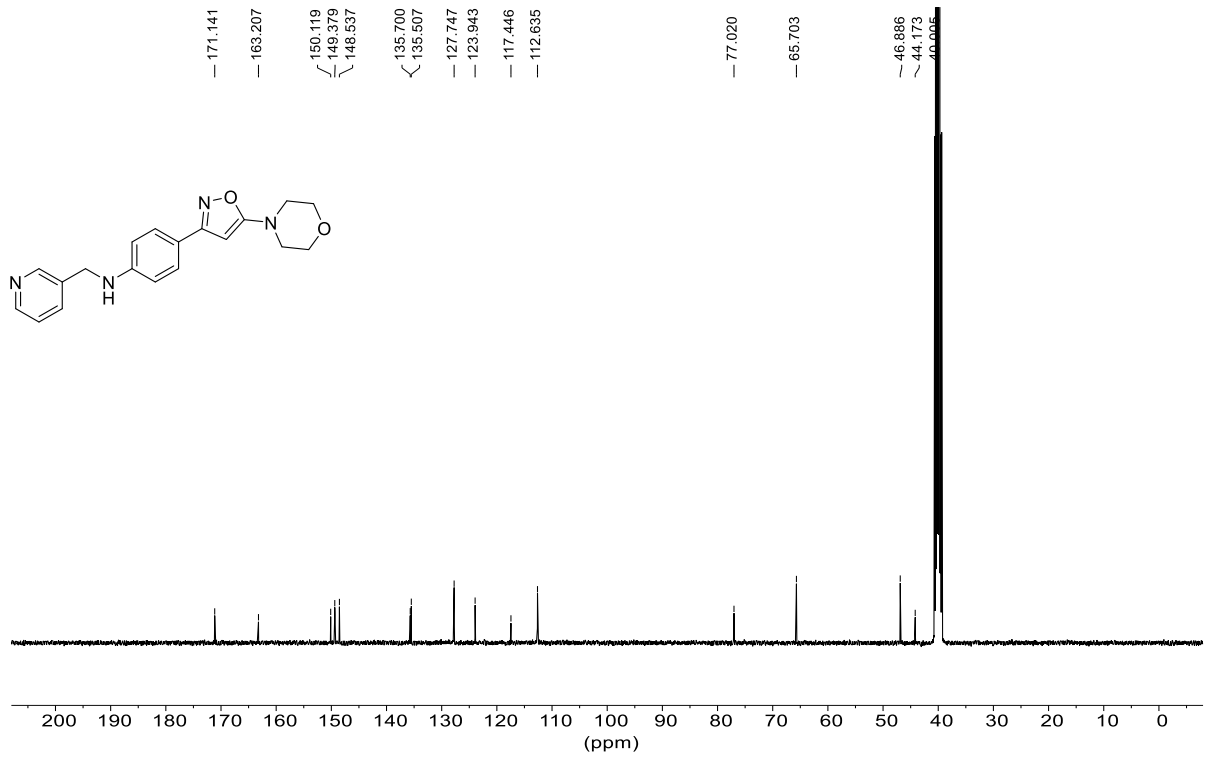
^{1}H NMR and ^{13}C NMR Spectra of Compound 9d





^{1}H NMR and ^{13}C NMR Spectra of Compound 10f





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