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Synthesis of a library of 2-aryl-2H-tetrazole-5-carboxamides for photoaffinity labeling of aminergic G-protein coupled receptors

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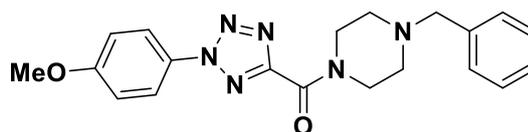
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Experimental procedures and characterization data

General considerations. All reagents were obtained from commercial sources and used without further purification. Tetrahydrofuran and dimethylformamide were distilled over suitable drying agents. Mass spectra were recorded with a Bruker Maxis HRMS-ESI-qTOF spectrometer (electrospray ionization mode). NMR data were recorded with Bruker Avance 400 spectrometer (400.13 MHz for ^1H and 100.61 MHz for ^{13}C) in CDCl_3 and were referenced to residual solvent proton peaks ($\delta_{\text{H}} = 7.28$) and solvent carbon peaks ($\delta_{\text{C}} = 77.0$). Melting points were determined with a Stuart SMP50 instrument in open capillary tubes.

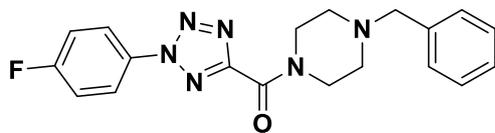
General procedure for the preparation of tetrazoles 5a-o

A mixture of appropriate *N*-substituted piperazine **1** (0.5 mmol) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **2** (Meldrum's acid, 0.5 mmol) in *o*-xylene (3 ml) was refluxed for 1 h, and the solvent was removed under reduced pressure. To the residue of intermediate **3** redissolved in acetonitrile (4 ml), a pre-stirred (30 min) mixture of 3-(chlorosulfonyl)benzoic acid (146 mg, 0.67 mmol) with sodium azide (49 mg, 0.75 mmol) and potassium carbonate (138 mg, 1 mmol) in water (4 ml) was added. The resulting emulsion was stirred at room temperature for 2 h, and then the diazotransfer product was extracted with chloroform (2×5 ml). The solution was evaporated to dryness, and the residue was dissolved in acetonitrile (10 ml). To this solution, KOH (70 mg, 2.5 mmol) in water (2 ml) was added. The resulting mixture was stirred at room temperature for 3 h, extracted with chloroform (2×5 ml), and the solvent was removed under reduced pressure. The dry residue of crude diazoacetamide **4** was dissolved in 10:1 THF-DMF mixture (3.3 ml). To this solution, AgNO_3 (9 mg, 0.05 mmol) and DABCO (62 mg, 0.55 mmol) were added at 0 °C followed by the addition of the corresponding arenediazonium tosylate $\text{ArN}_2^+\text{TsO}^-$ (0.75 mmol). The resulting mixture was stirred at room temperature overnight, diluted with water (5 ml) and extracted with chloroform (2×5 ml). The combined organic phases were washed with water (2×5 ml) and brine (5 ml). The solvent was evaporated, and the residue was purified by column chromatography on silica gel using *n*-hexane – ethyl acetate 2:1 as eluent.

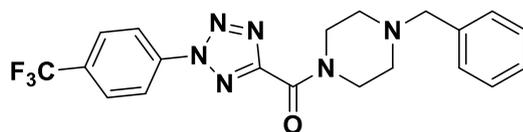


(4-Benzylpiperazin-1-yl)[2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl]methanone (5a). Yield 100 mg, 54%. Brown oil. ^1H NMR (400 MHz, CDCl_3) δ 8.16 – 7.93 (m, 2H), 7.38 – 7.31 (m, 4H), 7.30 – 7.21 (m, 1H), 7.08 – 6.98 (m, 2H), 4.10 – 3.80 (m, 7H), 3.57 (s, 2H), 2.59 (t, $J = 5.2$ Hz, 2H), 2.54 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.0, 159.9, 157.5, 137.5, 129.9,

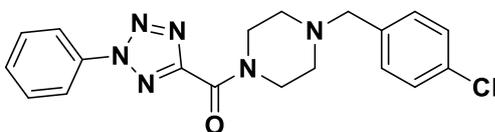
129.1, 128.4, 127.3, 121.7, 114.8, 62.8, 55.7, 53.3, 52.6, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[M+H]^+$ Calcd for $C_{20}H_{22}N_6O_2$ 379.1877; Found 379.1876.



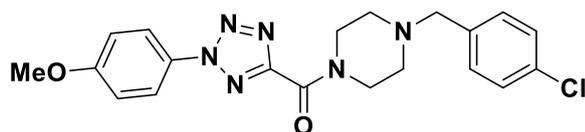
(4-Benzylpiperazin-1-yl)[2-(4-fluorophenyl)-2H-tetrazol-5-yl]methanone (5b). Yield 60 mg, 34%. Orange amorphous solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.10 (m, 2H), 7.55 – 7.32 (m, 4H), 7.32 – 7.23 (m, 3H), 3.91 (t, $J = 5.2$ Hz, 2H), 3.88 – 3.84 (m, 2H), 3.58 (s, 2H), 2.61 (t, $J = 5.2$ Hz, 2H), 2.59 – 2.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (d, $J = 251.6$ Hz), 160.2, 157.2, 137.5, 132.7 (d, $J = 3.5$ Hz), 129.1, 128.4, 127.4, 122.2 (d, $J = 8.9$ Hz), 116.9 (d, $J = 23.5$ Hz), 62.8, 53.3, 52.5, 47.2, 42.8. HRMS (ESI/Q-TOF) m/z : $[M+H]^+$ Calcd for $C_{19}H_{19}FN_6O$ 367.1677; Found 367.1676.



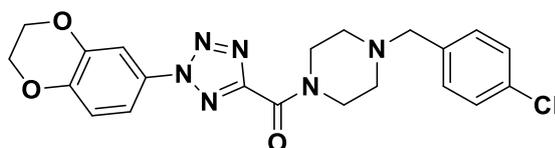
(4-Benzylpiperazin-1-yl)[2-(4-trifluoromethylphenyl)-2H-tetrazol-5-yl]methanone (5c). Yield 58 mg, 28%. Orange oil. 1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, $J = 8.5$ Hz, 2H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.52 – 7.24 (m, 5H), 3.97 – 3.89 (m, 2H), 3.89 – 3.84 (m, 2H), 3.60 (s, 2H), 2.63 (t, $J = 5.2$ Hz, 2H), 2.58 (t, $J = 5.1$ Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 157.0, 138.6, 137.2, 132.3 (q, $J = 33.3$ Hz), 129.2, 128.4, 127.5, 127.2 (q, $J = 3.7$ Hz), 123.3 (q, $J = 272.5$ Hz), 120.4, 62.7, 53.2, 52.5, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[M+H]^+$ Calcd for $C_{20}H_{19}F_3N_6O$ 417.1645; Found 417.1662.



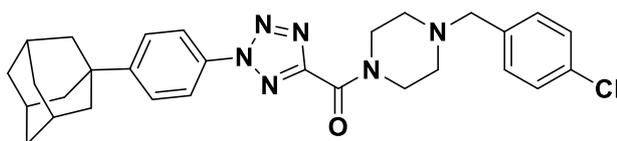
[4-(4-Chlorobenzyl)piperazin-1-yl](2-phenyl-2H-tetrazol-5-yl)methanone (5d). Yield 46 mg, 24%. Orange amorphous solid. 1H NMR (400 MHz, $CDCl_3$) δ 8.37 – 7.98 (m, 2H), 7.65 – 7.46 (m, 3H), 7.36 – 7.22 (m, 4H), 4.03 – 3.83 (m, 4H), 3.55 (s, 2H), 2.60 (t, $J = 5.1$ Hz, 2H), 2.55 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 157.4, 136.4, 135.9, 133.1, 130.4, 129.8, 128.6, 128.5, 120.2, 61.9, 53.2, 52.5, 47.0, 42.6. HRMS (ESI/Q-TOF) m/z : $[M+H]^+$ Calcd for $C_{19}H_{19}ClN_6O$ 383.1382; Found 383.1373.



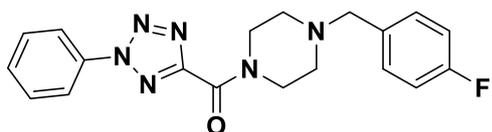
[4-(4-Chlorobenzyl)piperazin-1-yl][2-(4-methoxyphenyl)-2H-tetrazol-5-yl]methanone (5e). Yield 68 mg, 34%. Orange amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.21 – 8.03 (m, 2H), 7.46 – 7.21 (m, 4H), 7.15 – 6.96 (m, 2H), 3.94 – 3.75 (m, 7H), 3.53 (s, 2H), 2.58 (t, $J = 5.2$ Hz, 2H), 2.53 (t, $J = 5.1$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.0, 159.8, 157.5, 136.1, 133.0, 130.3, 129.9, 128.5, 121.7, 114.8, 62.0, 55.7, 53.2, 52.5, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{21}\text{ClN}_6\text{O}_2$ 413.1487; Found 413.1497.



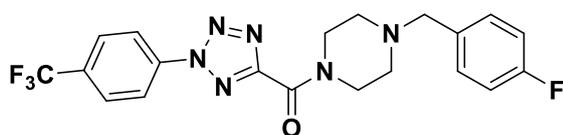
[4-(4-Chlorobenzyl)piperazin-1-yl][2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2H-tetrazol-5-yl]methanone (5f). Yield 128 mg, 58%. Orange solid, mp 134.0-135.3 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.67 (d, $J = 2.6$ Hz, 1H), 7.62 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.32 – 7.23 (m, 4H), 6.99 (d, $J = 8.8$ Hz, 1H), 4.32 (s, 4H), 4.03 – 3.72 (m, 4H), 3.51 (s, 2H), 2.56 (t, $J = 5.1$ Hz, 2H), 2.51 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.8, 157.4, 145.4, 144.1, 136.2, 133.0, 130.3, 130.1, 128.5, 118.1, 113.4, 109.8, 64.4, 64.4, 61.9, 53.2, 52.5, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{21}\text{ClN}_6\text{O}_3$ 441.1436; Found 441.1439.



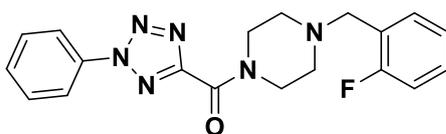
{2-[4-(Adamantan-1-yl)phenyl]-2H-tetrazol-5-yl}[4-(4-chlorobenzyl)piperazin-1-yl]methanone (5g). Yield 42 mg, 15%. Orange solid, mp 166.5-166.7 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.18 – 8.02 (m, 2H), 7.66 – 7.51 (m, 2H), 7.37 – 7.24 (m, 4H), 3.93 – 3.89 (m, 2H), 3.89 – 3.85 (m, 2H), 3.54 (s, 2H), 2.59 (t, $J = 5.1$ Hz, 2H), 2.57 – 2.50 (m, 2H), 2.15 (q, $J = 3.2$ Hz, 3H), 1.97 (d, $J = 2.9$ Hz, 6H), 1.91 – 1.62 (m, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 159.9, 157.5, 154.1, 136.1, 134.0, 133.1, 130.3, 128.5, 126.3, 119.9, 62.0, 53.2, 52.5, 47.1, 43.0, 42.7, 36.6, 36.5, 28.8. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{29}\text{H}_{33}\text{ClN}_6\text{O}$ 517.2477; Found 517.2465.



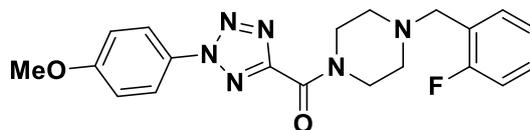
[4-(4-Fluorobenzyl)piperazin-1-yl][2-phenyl-2H-tetrazol-5-yl]methanone (6h). Yield 86 mg, 48%. Orange amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.33 – 8.00 (m, 2H), 7.71 – 7.46 (m, 3H), 7.37 – 7.24 (m, 2H), 7.15 – 6.96 (m, 2H), 3.90 (t, $J = 5.2$ Hz, 2H), 3.88 – 3.83 (m, 2H), 3.54 (s, 2H), 2.59 (t, $J = 5.2$ Hz, 2H), 2.54 (t, $J = 5.1$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.1 (d, $J = 245.3$ Hz), 160.1, 157.4, 136.4, 133.3 (d, $J = 3.1$ Hz), 130.6 (d, $J = 7.8$ Hz), 130.4, 129.8, 120.2, 115.2 (d, $J = 21.3$ Hz), 61.9, 53.2, 52.5, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_6\text{O}$ 367.1677; Found 367.1676.



[4-(4-Fluorobenzyl)piperazin-1-yl][2-(4-fluorophenyl)-2H-tetrazol-5-yl]methanone (5i). Yield 68 mg, 32%. Yellow amorphous solid. ^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, $J = 8.5$ Hz, 2H), 7.87 (d, $J = 8.6$ Hz, 2H), 7.50 – 7.24 (m, 2H), 7.13 – 6.83 (m, 2H), 3.97 – 3.89 (m, 2H), 3.88 – 3.83 (m, 2H), 3.55 (s, 2H), 2.61 (t, $J = 5.2$ Hz, 2H), 2.55 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.2 (d, $J = 245.6$ Hz), 160.5, 157.0, 138.6, 133.1 (d, $J = 2.5$ Hz), 132.3 (q, $J = 33.3$ Hz), 130.6 (d, $J = 8.0$ Hz), 127.2 (q, $J = 3.8$ Hz), 123.3 (q, $J = 272.5$ Hz), 120.4, 115.2 (d, $J = 21.2$ Hz), 61.9, 53.1, 52.4, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{18}\text{F}_4\text{N}_6\text{O}$ 435.1551; Found 435.1391.

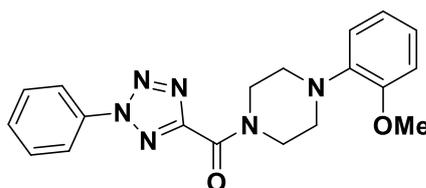


[4-(2-Fluorobenzyl)piperazin-1-yl](2-phenyl-2H-tetrazol-5-yl)methanone (5j). Yield 58 mg, 34%. Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 8.26 – 8.11 (m, 2H), 7.77 – 7.51 (m, 3H), 7.40 (td, $J = 7.5, 1.9$ Hz, 1H), 7.33 – 7.24 (m, 1H), 7.15 (td, $J = 7.5, 1.3$ Hz, 1H), 7.07 (ddd, $J = 9.6, 8.2, 1.2$ Hz, 1H), 3.95 – 3.90 (m, 2H), 3.90 – 3.86 (m, 2H), 3.68 (d, $J = 1.4$ Hz, 2H), 2.72 – 2.63 (m, 2H), 2.63 – 2.56 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.4 (d, $J = 246.5$ Hz), 160.1, 157.4, 136.5, 131.5 (d, $J = 4.4$ Hz), 130.4, 129.8, 129.2 (d, $J = 8.2$ Hz), 124.0 (d, $J = 14.6$ Hz), 124.0 (d, $J = 3.6$ Hz), 120.2, 115.4 (d, $J = 22.3$ Hz), 55.1 (d, $J = 2.0$ Hz), 53.0, 52.3, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{19}\text{FN}_6\text{O}$ 367.1677; Found 367.1675.



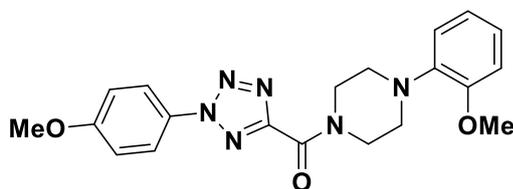
[4-(2-Fluorobenzyl)piperazin-1-yl][2-(4-methoxyphenyl)-2H-tetrazol-5-yl]methanone (5k).

Yield 76 mg, 38%. Brown oil. ^1H NMR (400 MHz, CDCl_3) δ 8.11 – 7.96 (m, 2H), 7.38 (td, $J = 7.5, 1.7$ Hz, 1H), 7.27 – 7.21 (m, 1H), 7.12 (td, $J = 7.5, 1.3$ Hz, 1H), 7.08 – 6.99 (m, 3H), 4.01 – 3.83 (m, 7H), 3.65 (s, 2H), 2.63 (t, $J = 5.1$ Hz, 2H), 2.58 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.4 (d, $J = 246.5$ Hz), 161.0, 159.9, 157.5, 131.5 (d, $J = 4.4$ Hz), 129.9, 129.1 (d, $J = 8.3$ Hz), 124.0 (d, $J = 14.7$ Hz), 124.0 (d, $J = 3.6$ Hz), 121.7, 115.4 (d, $J = 22.1$ Hz), 114.8, 55.7, 55.1 (d, $J = 2.0$ Hz), 53.0, 52.3, 47.1, 42.7. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{21}\text{FN}_6\text{O}_2$ 397.1783; Found 397.1783.



[4-(2-Methoxyphenyl)piperazin-1-yl](2-phenyl-2H-tetrazol-5-yl)methanone (5l).

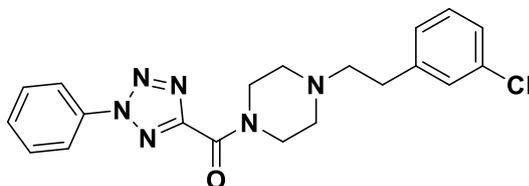
Yield 104 mg, 58%. Orange oil. ^1H NMR (400 MHz, CDCl_3) δ 8.23 – 8.17 (m, 2H), 7.65 – 7.50 (m, 3H), 7.05 (dt, $J = 8.0, 4.5$ Hz, 1H), 6.97 – 6.93 (m, 2H), 6.91 (d, $J = 8.0$ Hz, 1H), 4.16 – 3.98 (m, 4H), 3.90 (s, 3H), 3.23 – 3.19 (m, 2H), 3.19 – 3.15 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 160.1, 157.5, 152.3, 140.5, 136.5, 130.4, 129.8, 123.7, 121.1, 120.2, 118.6, 111.4, 55.5, 51.1, 50.5, 47.4, 43.0. HRMS (ESI/Q-TOF) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_6\text{O}_2$ 387.1540; Found 387.1538.



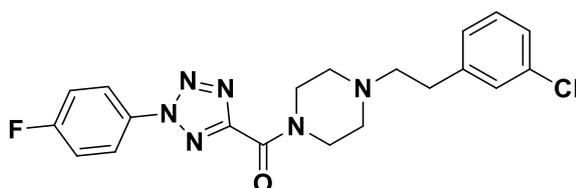
[2-(4-Methoxyphenyl)-2H-tetrazol-5-yl][4-(2-methoxyphenyl)piperazin-1-yl]methanone

(5m). Yield 130 mg, 66%. Beige solid, mp 136.2-137.2 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.18 – 7.99 (m, 2H), 7.15 – 7.00 (m, 3H), 6.94 (d, $J = 4.2$ Hz, 2H), 6.90 (d, $J = 8.0$ Hz, 1H), 4.18 – 3.98 (m, 4H), 3.93 – 3.83 (m, 6H), 3.20 (t, $J = 5.1$ Hz, 2H), 3.16 (t, $J = 5.0$ Hz, 2H). ^{13}C NMR

(101 MHz, CDCl₃) δ 161.0, 159.9, 157.6, 152.3, 140.5, 129.9, 123.7, 121.7, 121.1, 118.6, 114.8, 111.4, 55.7, 55.5, 51.1, 50.5, 47.4, 42.9. HRMS (ESI/Q-TOF) m/z : [M+Na]⁺ Calcd for C₂₀H₂₂N₆O₃ 417.1646; Found 417.1638.



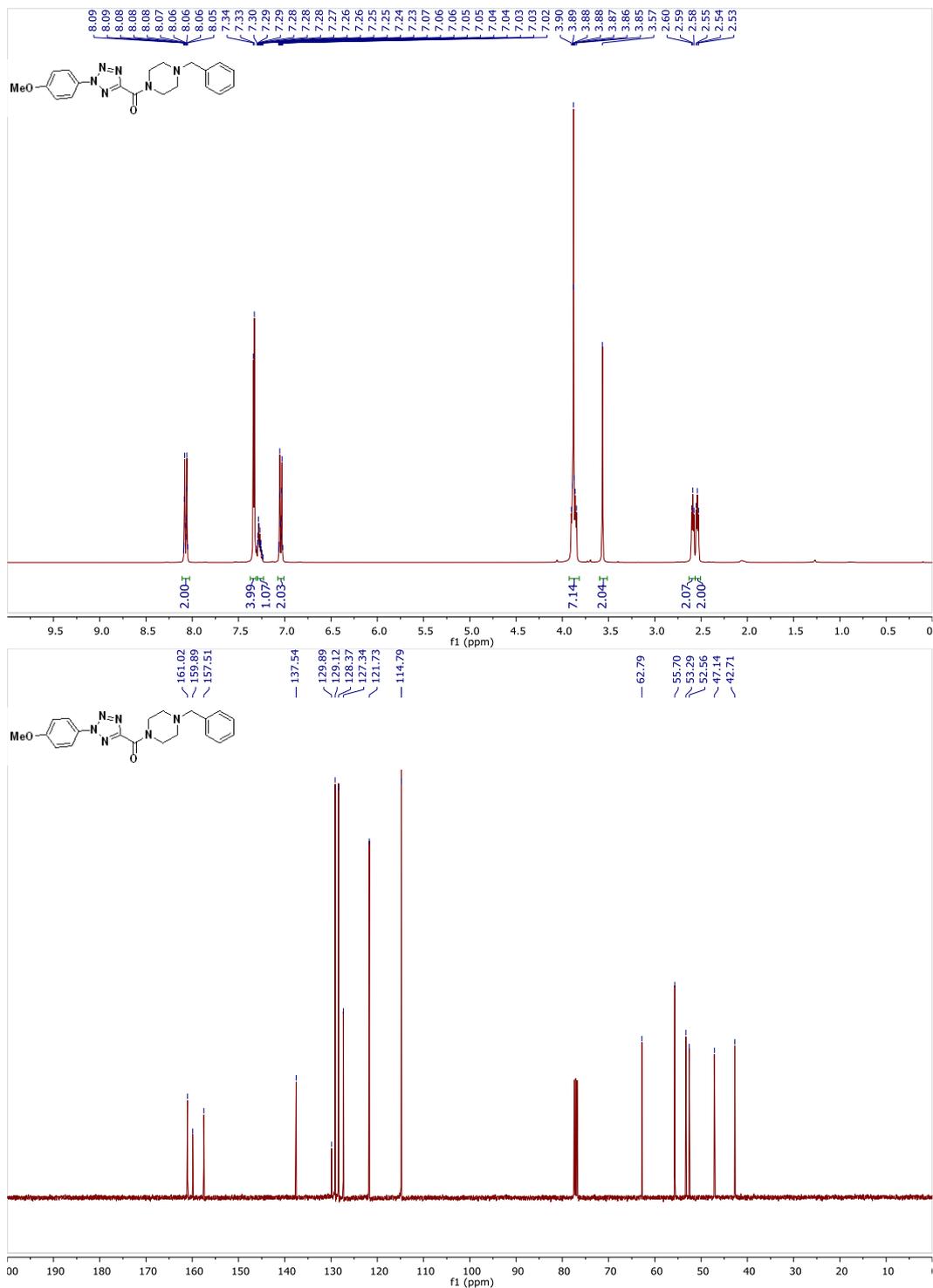
[4-(3-Chlorophenethyl)piperazin-1-yl](2-phenyl-2H-tetrazol-5-yl)methanone (5n). Yield 118 mg, 58%. Orange oil. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (dd, J = 8.2, 1.8 Hz, 2H), 7.72 – 7.45 (m, 3H), 7.26 – 7.17 (m, 3H), 7.15 – 6.98 (m, 1H), 3.92 (t, J = 5.1 Hz, 2H), 3.89 (t, J = 5.1 Hz, 2H), 2.81 (dd, J = 9.5, 6.1 Hz, 2H), 2.70 – 2.64 (m, 4H), 2.61 (t, J = 5.1 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 160.1, 157.4, 142.0, 136.4, 134.1, 130.4, 129.8, 129.7, 128.8, 126.9, 126.4, 120.2, 59.6, 53.4, 52.6, 47.1, 42.7, 33.1. HRMS (ESI/Q-TOF) m/z : [M+H]⁺ Calcd for C₂₀H₂₁ClN₆O 397.1538; Found 397.1541.



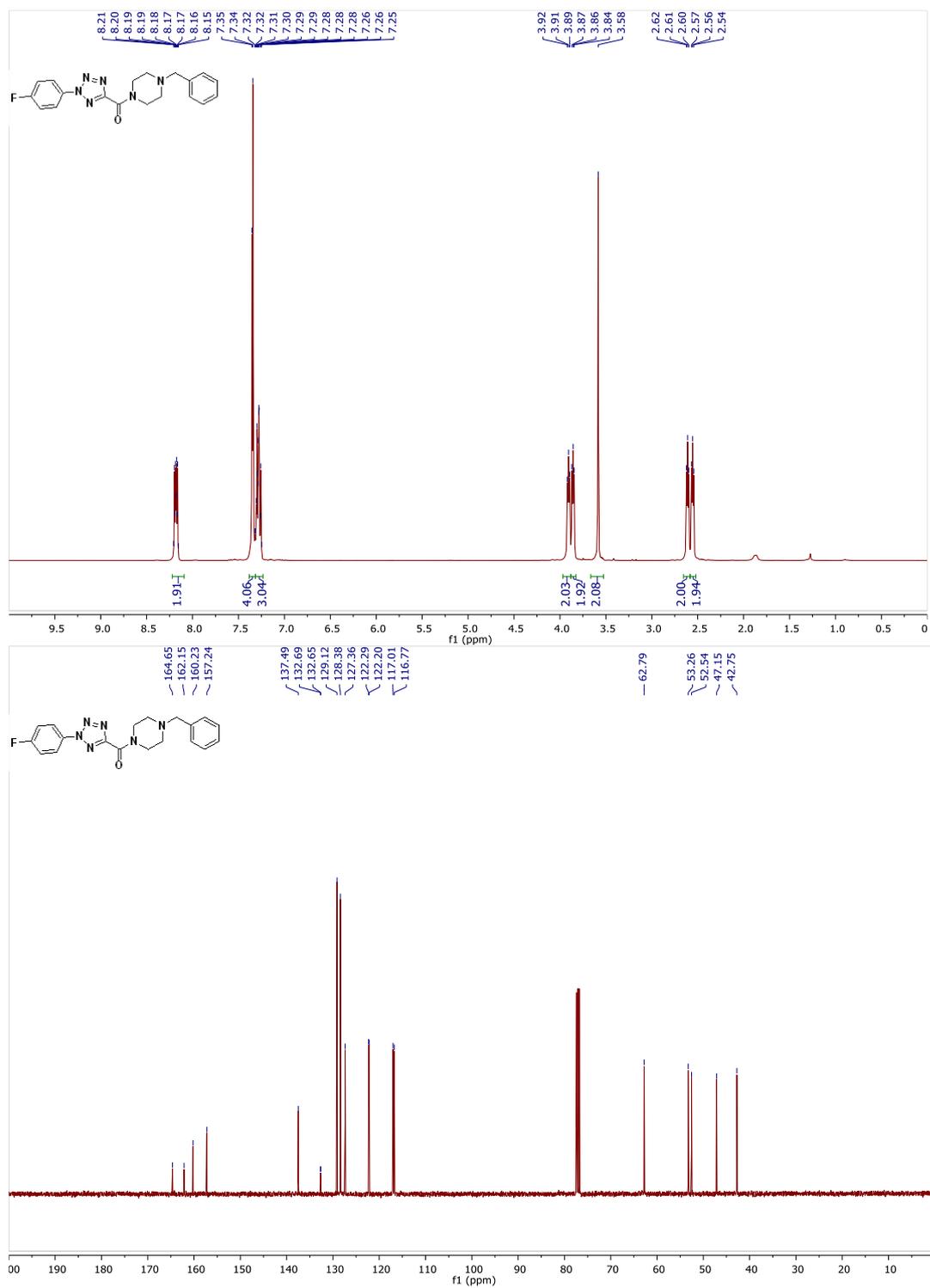
[4-(3-Chlorophenethyl)piperazin-1-yl][2-(4-fluorophenyl)-2H-tetrazol-5-yl]methanone (5o). Yield 25 mg, 15%. Yellow amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 8.26 – 8.13 (m, 2H), 7.39 – 7.27 (m, 2H), 7.27 – 7.19 (m, 3H), 7.11 (dt, J = 7.1, 1.7 Hz, 1H), 3.94 (t, J = 5.0 Hz, 2H), 3.90 (t, J = 5.0 Hz, 2H), 2.82 (dd, J = 9.6, 6.1 Hz, 2H), 2.68 (t, J = 7.6 Hz, 4H), 2.62 (t, J = 5.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 163.4 (d, J = 251.6 Hz), 160.2, 157.2, 142.0, 134.2, 132.7 (d, J = 3.2 Hz), 129.7, 128.8, 126.9, 126.4, 122.3 (d, J = 8.6 Hz), 116.9 (d, J = 23.5 Hz), 59.6, 53.4, 52.6, 47.1, 42.7, 33.2. HRMS (ESI/Q-TOF) m/z : [M+H]⁺ Calcd for C₂₀H₂₀ClFN₆O 415.1444; Found 415.1447.

Copies of ^1H and ^{13}C NMR spectra

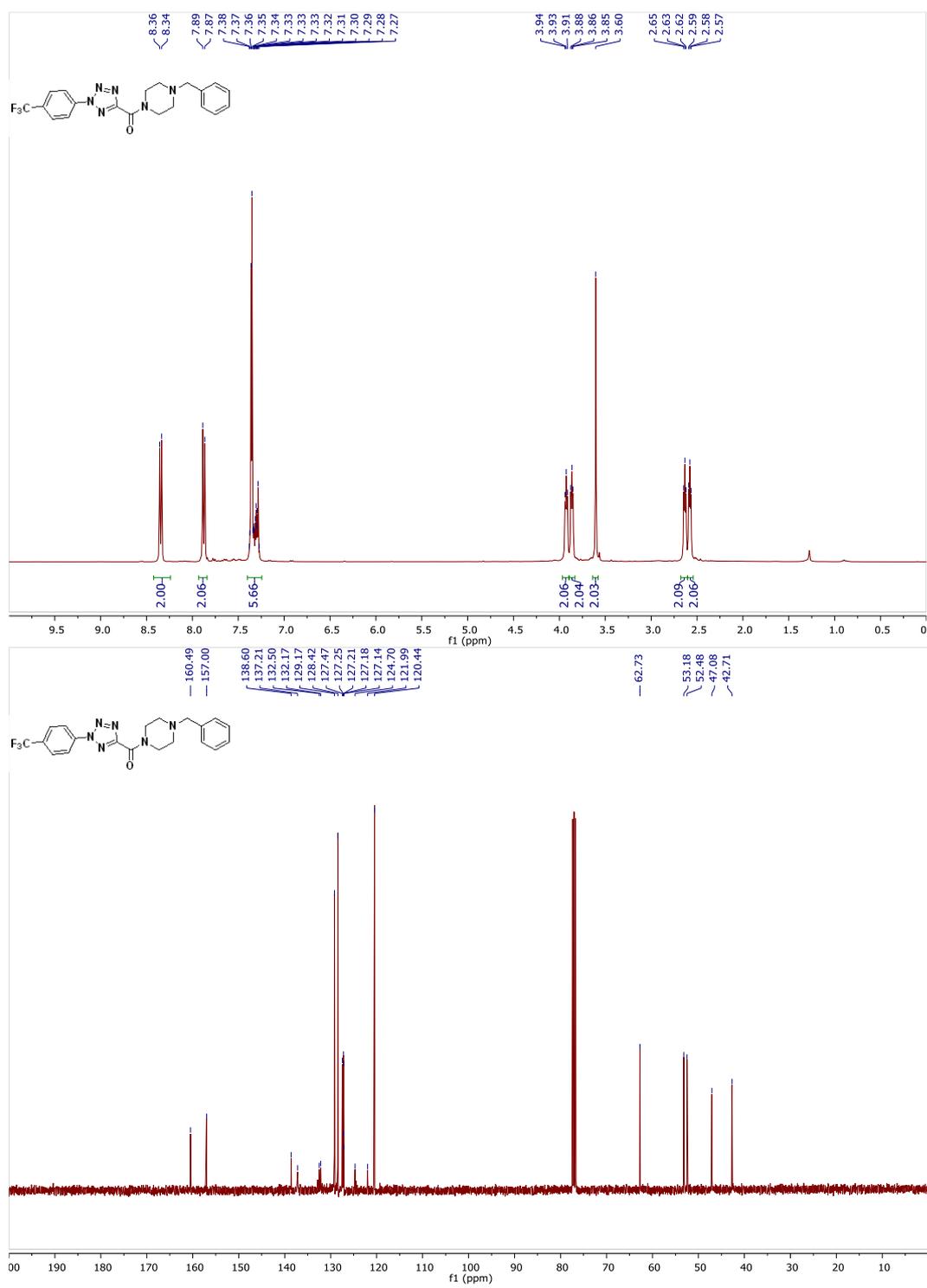
^1H and ^{13}C NMR spectra of compound **5a**



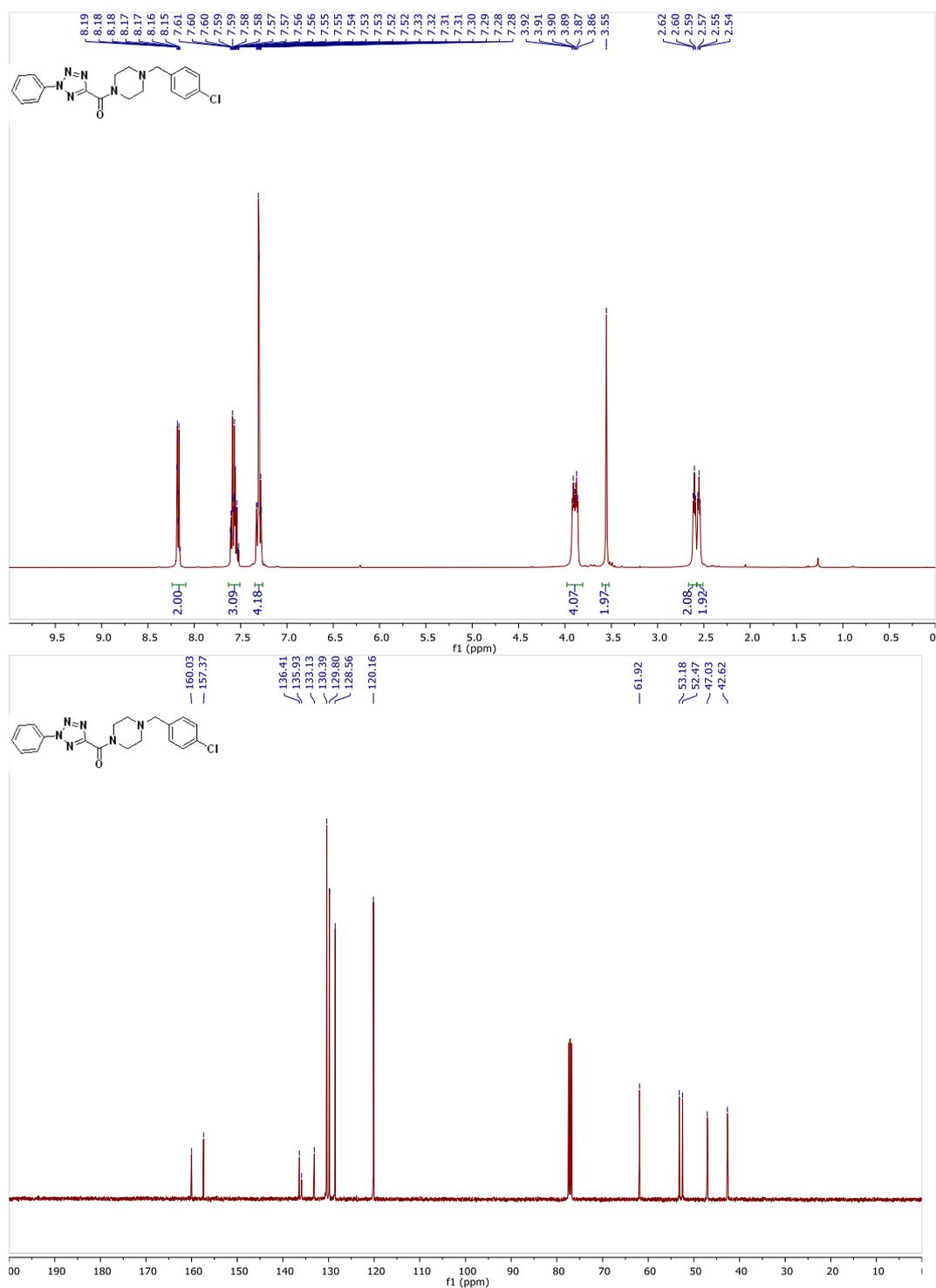
¹H and ¹³C NMR spectra of compound **5b**



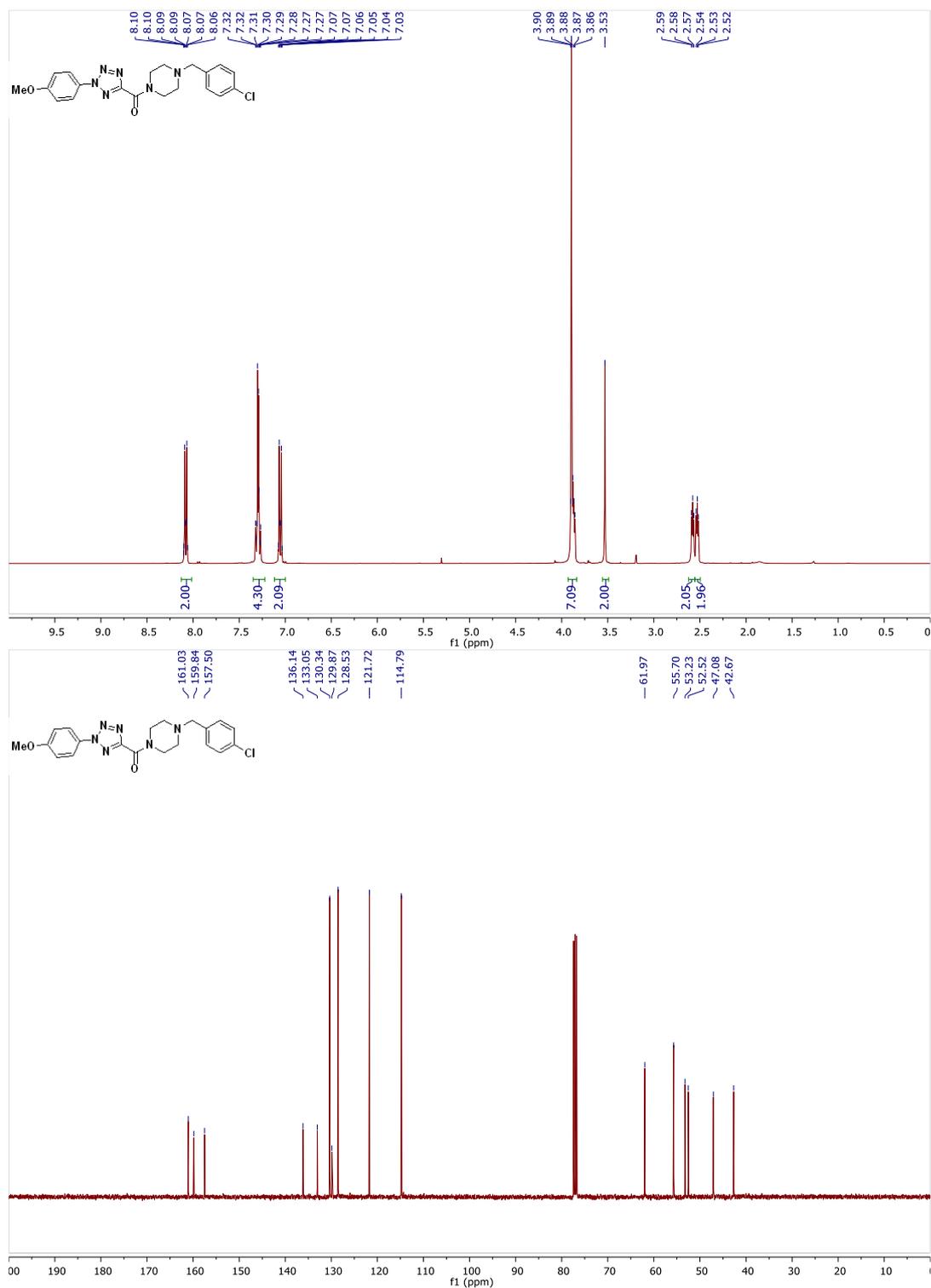
^1H and ^{13}C NMR spectra of compound **5c**



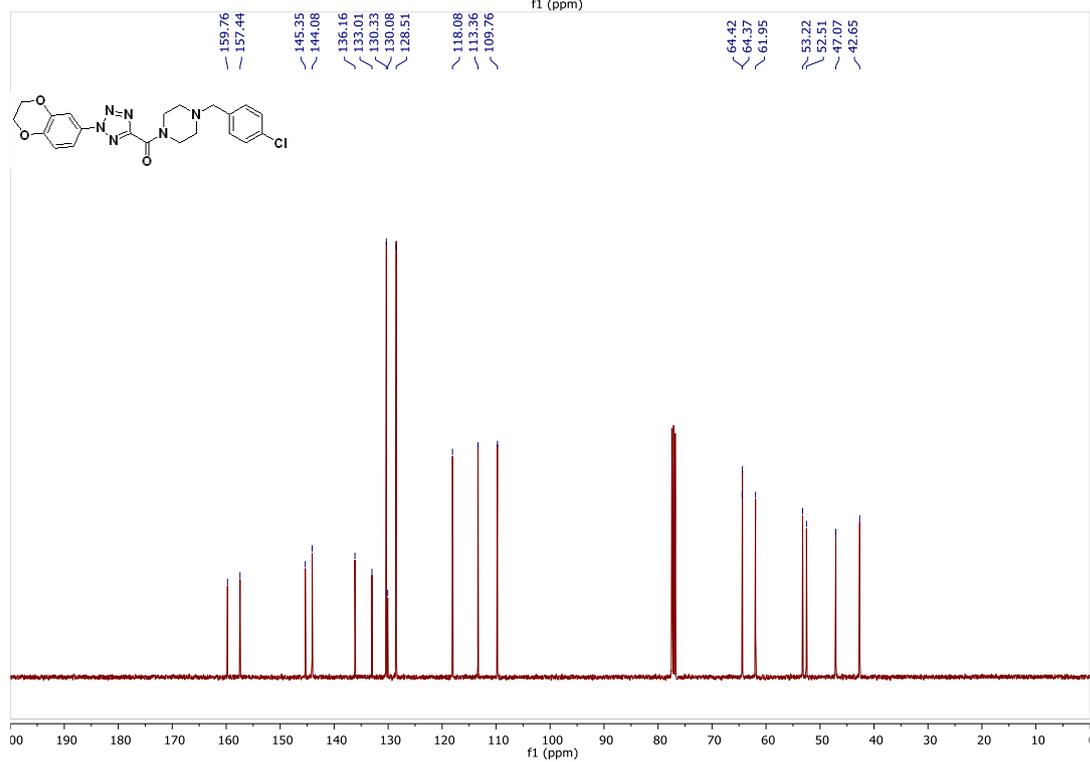
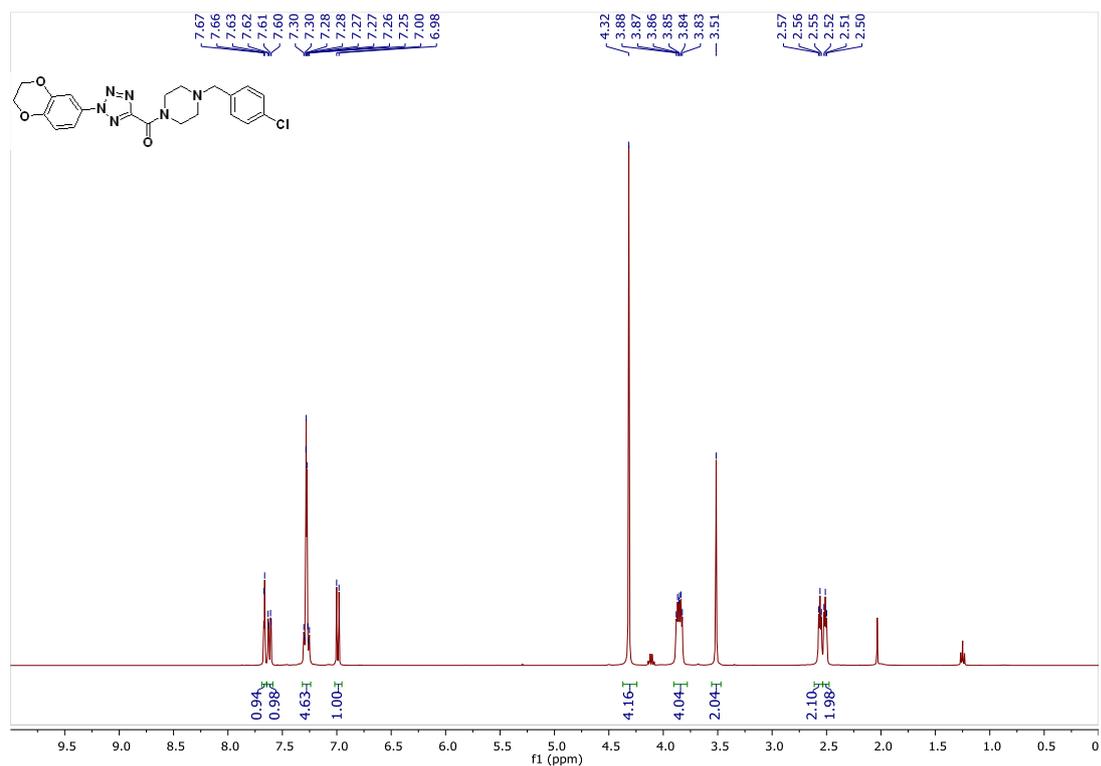
^1H and ^{13}C NMR spectra of compound **5d**



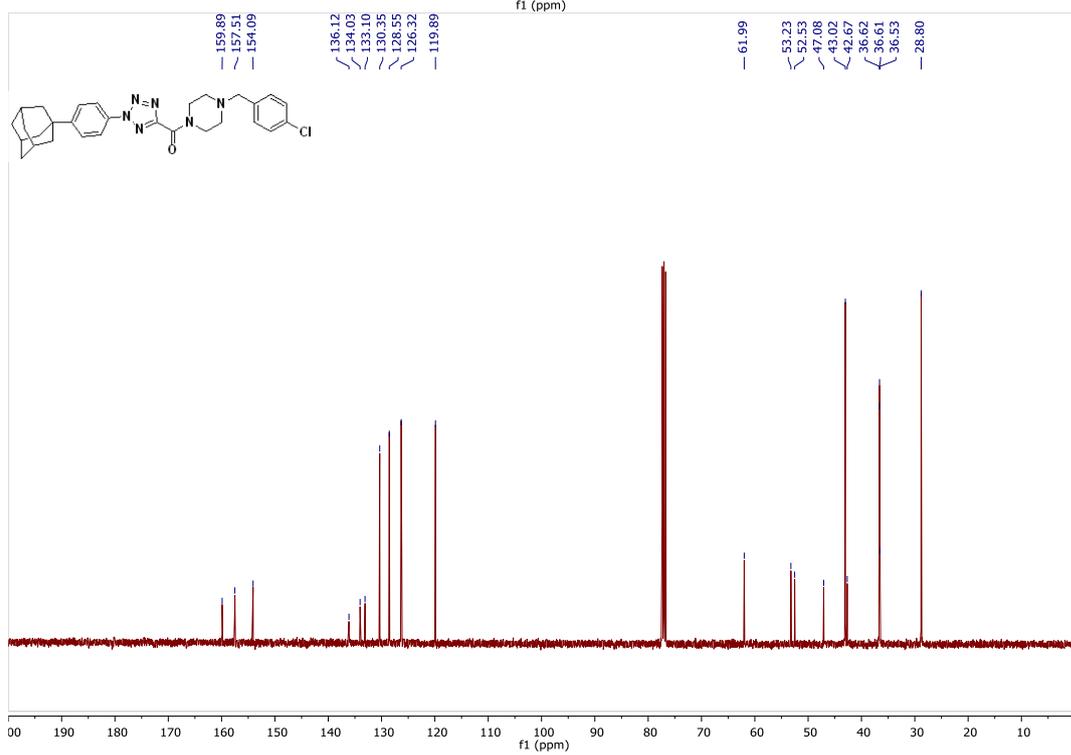
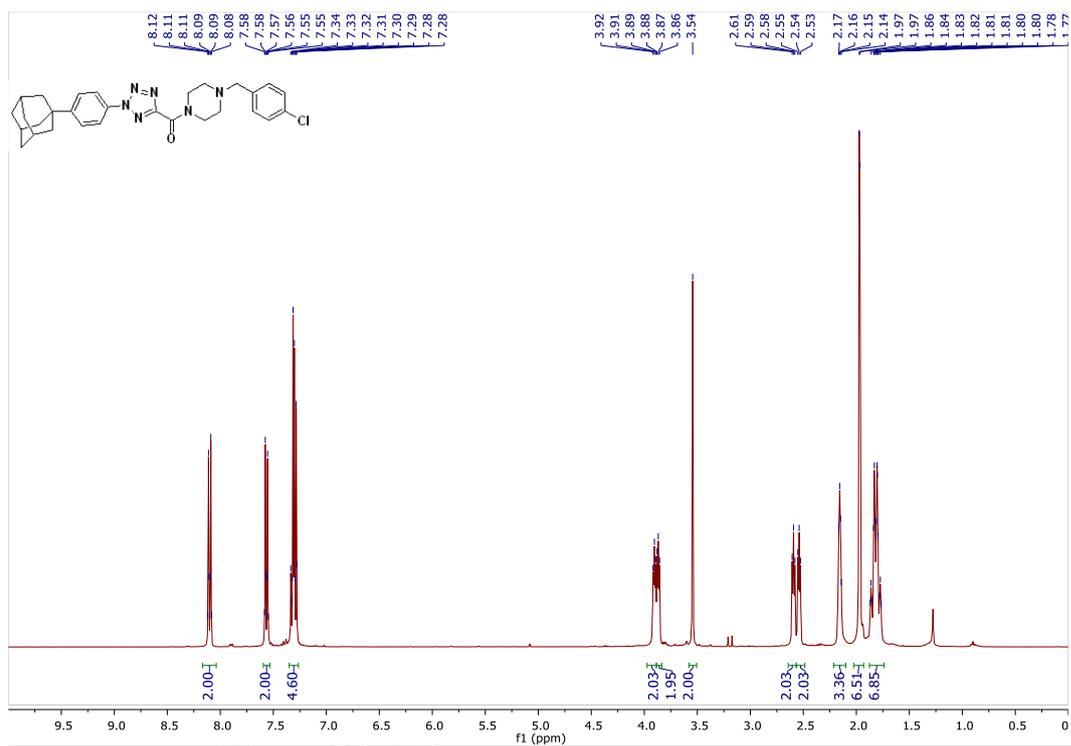
^1H and ^{13}C NMR spectra of compound **5e**



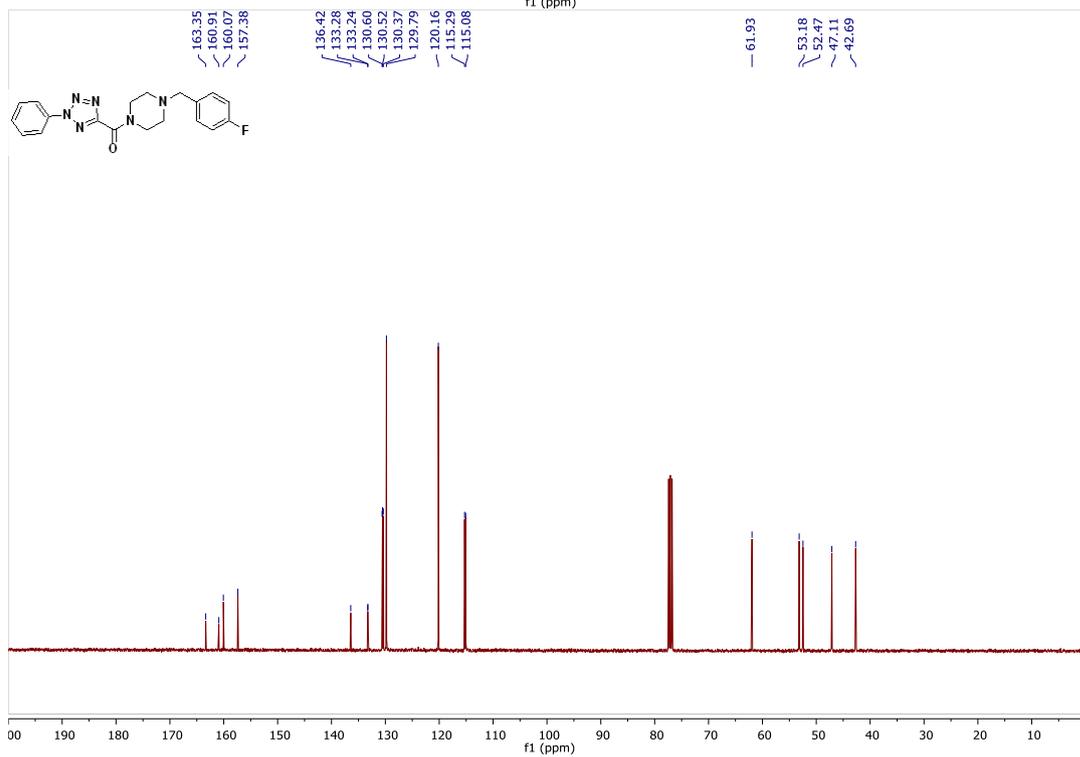
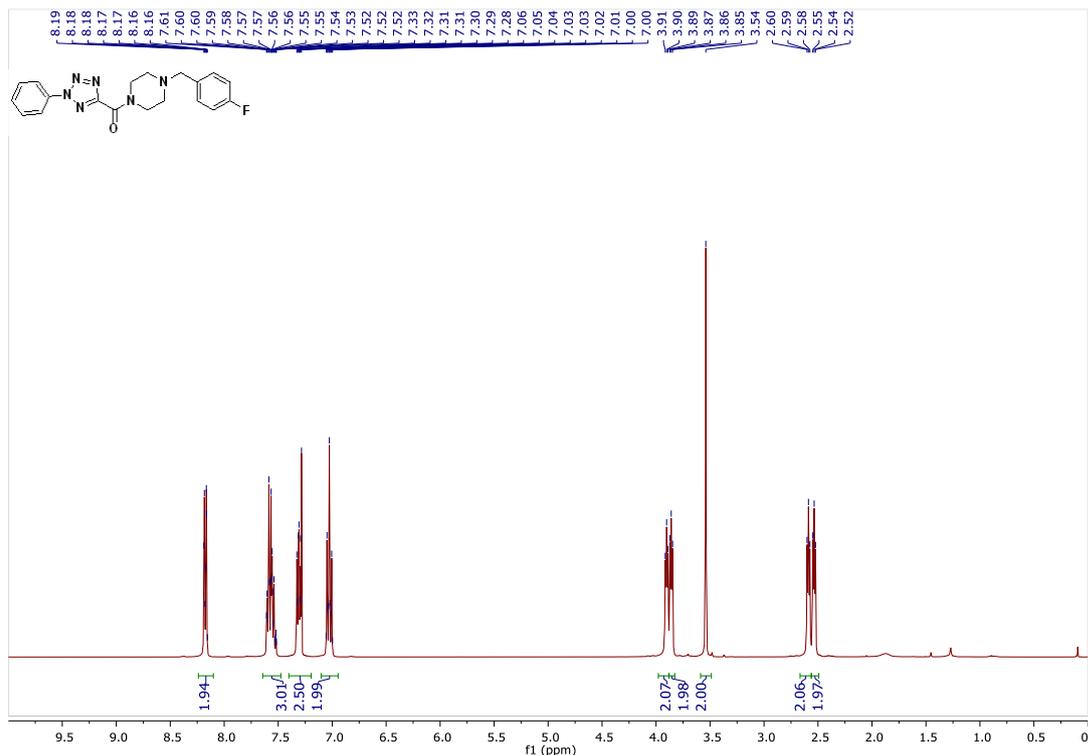
¹H and ¹³C NMR spectra of compound 5f



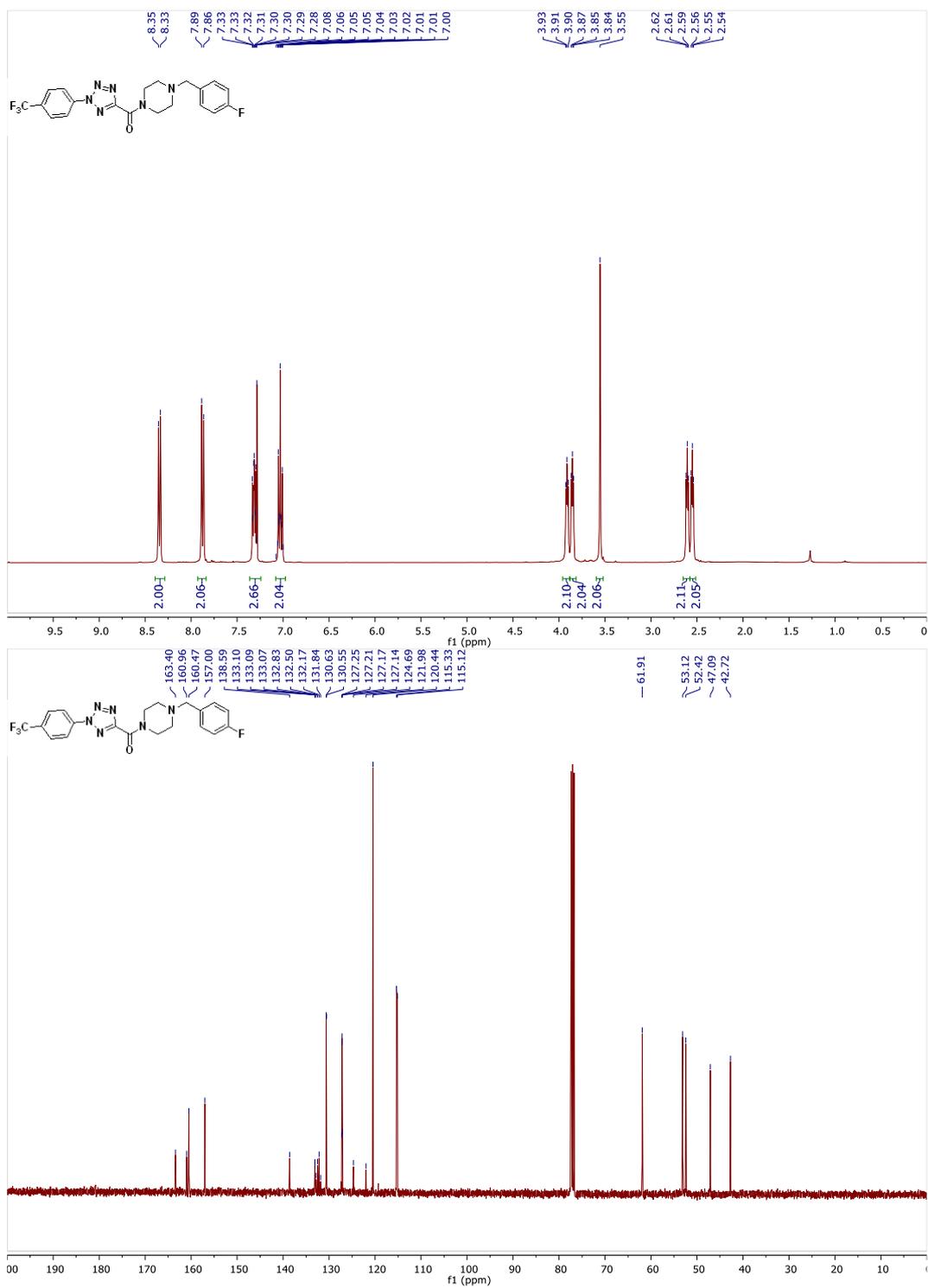
¹H and ¹³C NMR spectra of compound **5g**



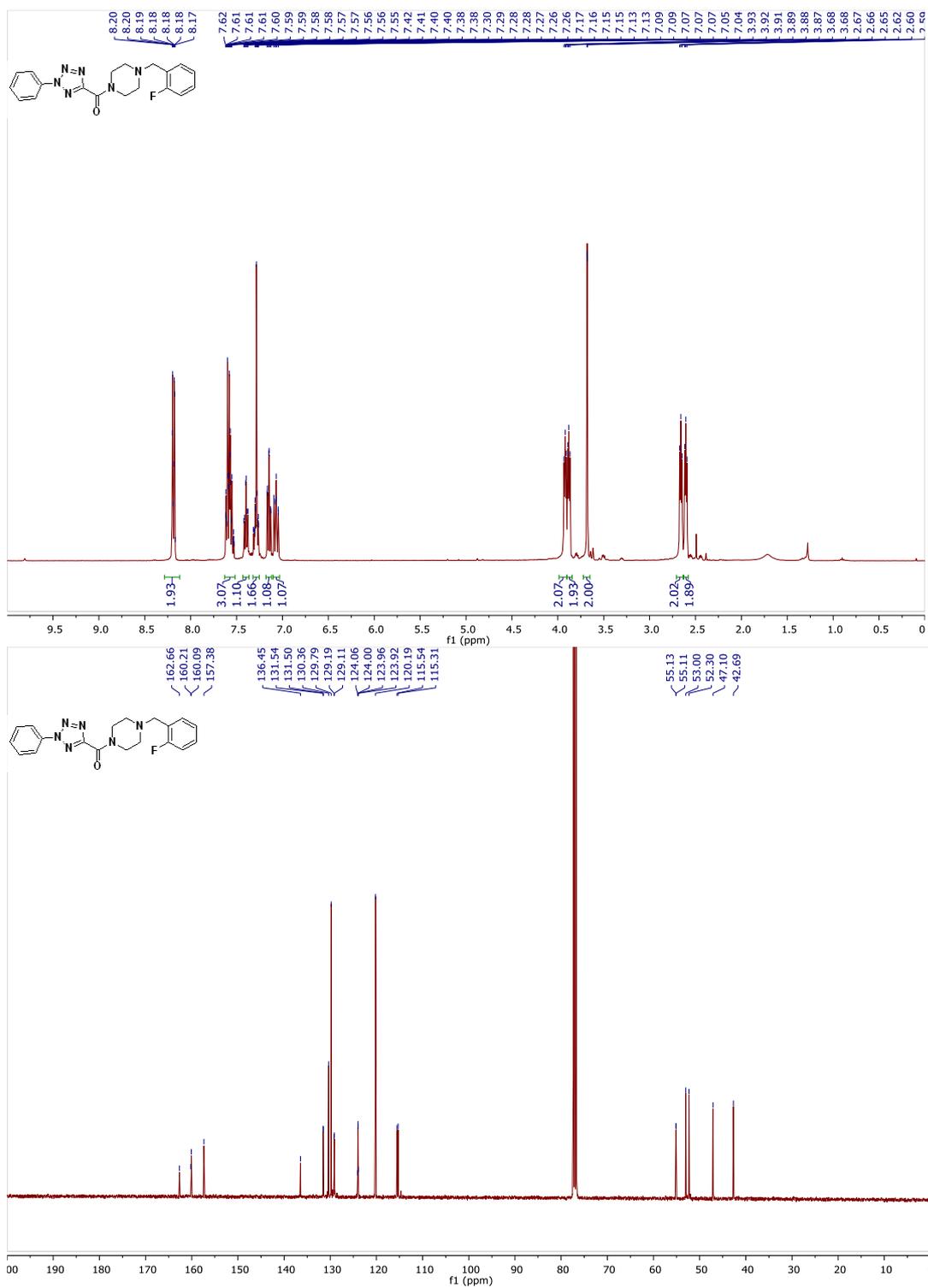
^1H and ^{13}C NMR spectra of compound **5h**



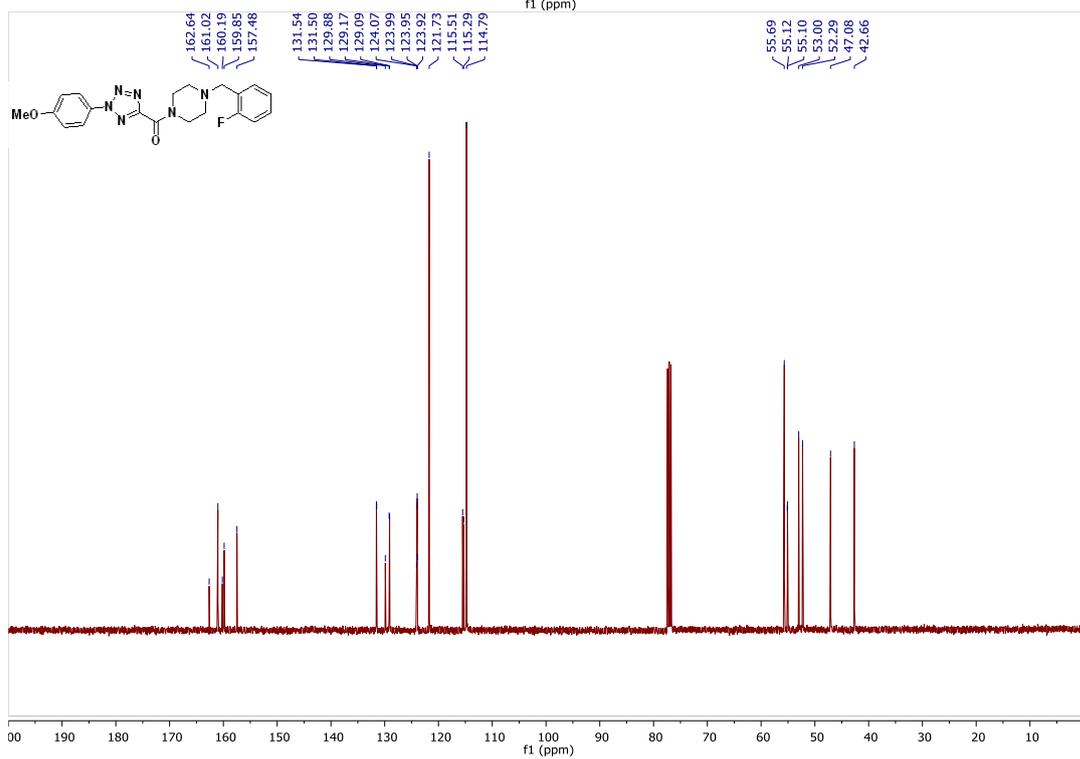
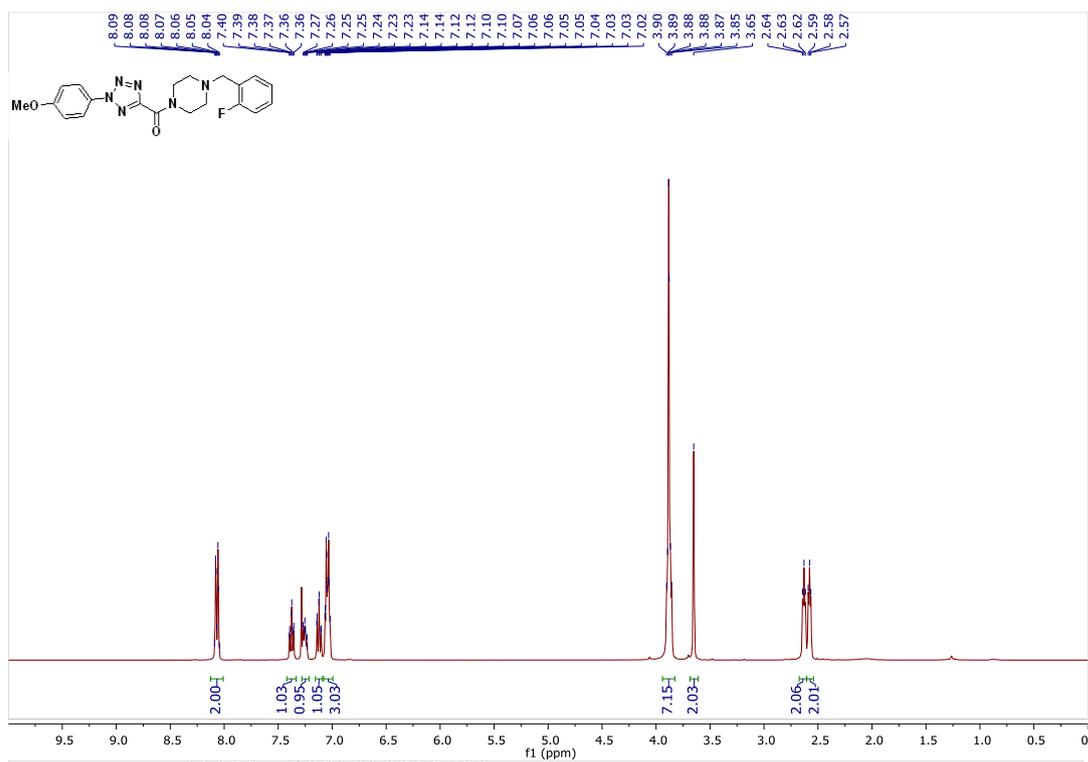
¹H and ¹³C NMR spectra of compound 5i



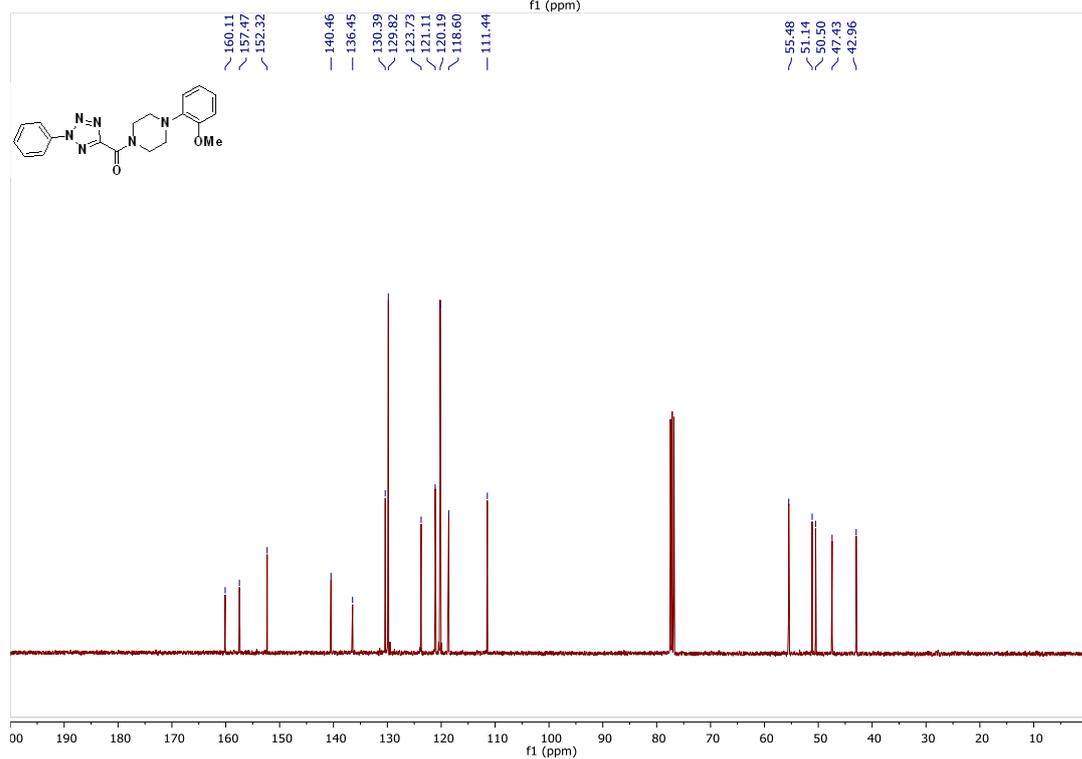
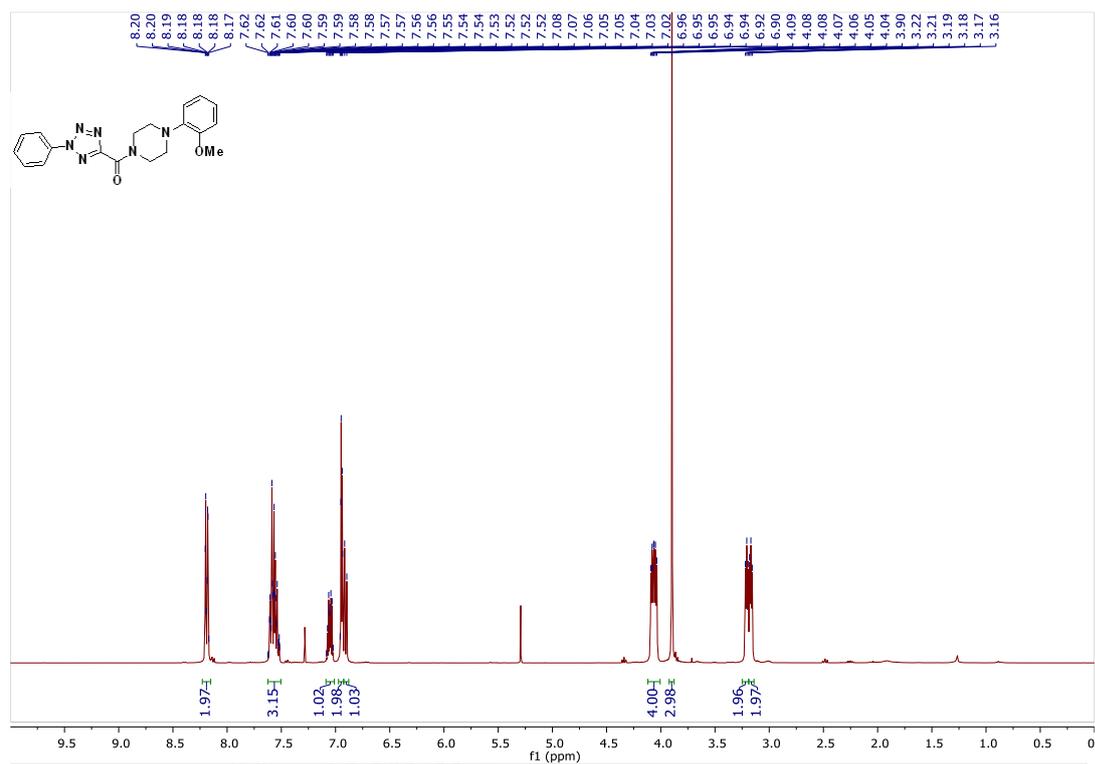
¹H and ¹³C NMR spectra of compound 5j



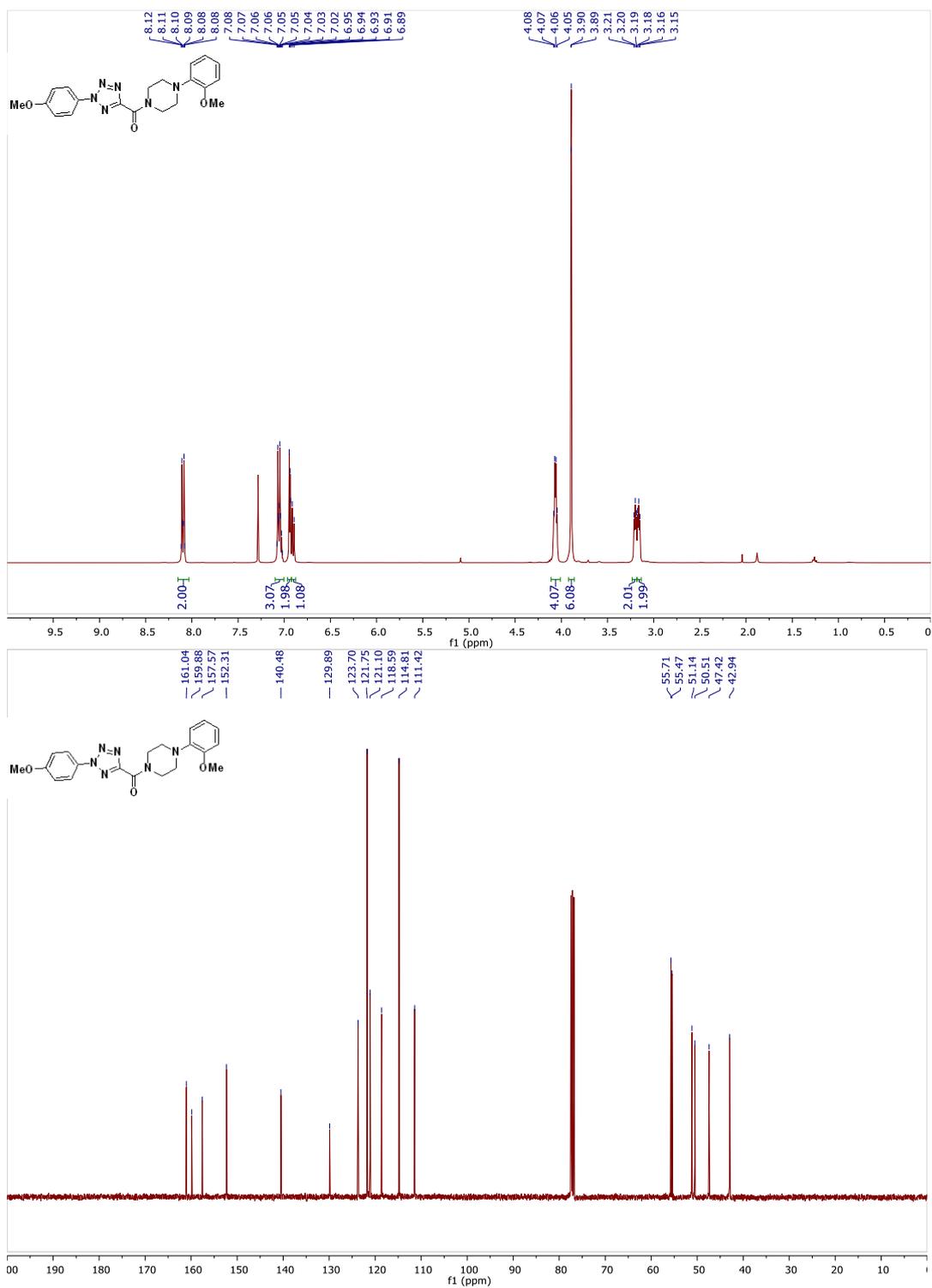
¹H and ¹³C NMR spectra of compound 5k



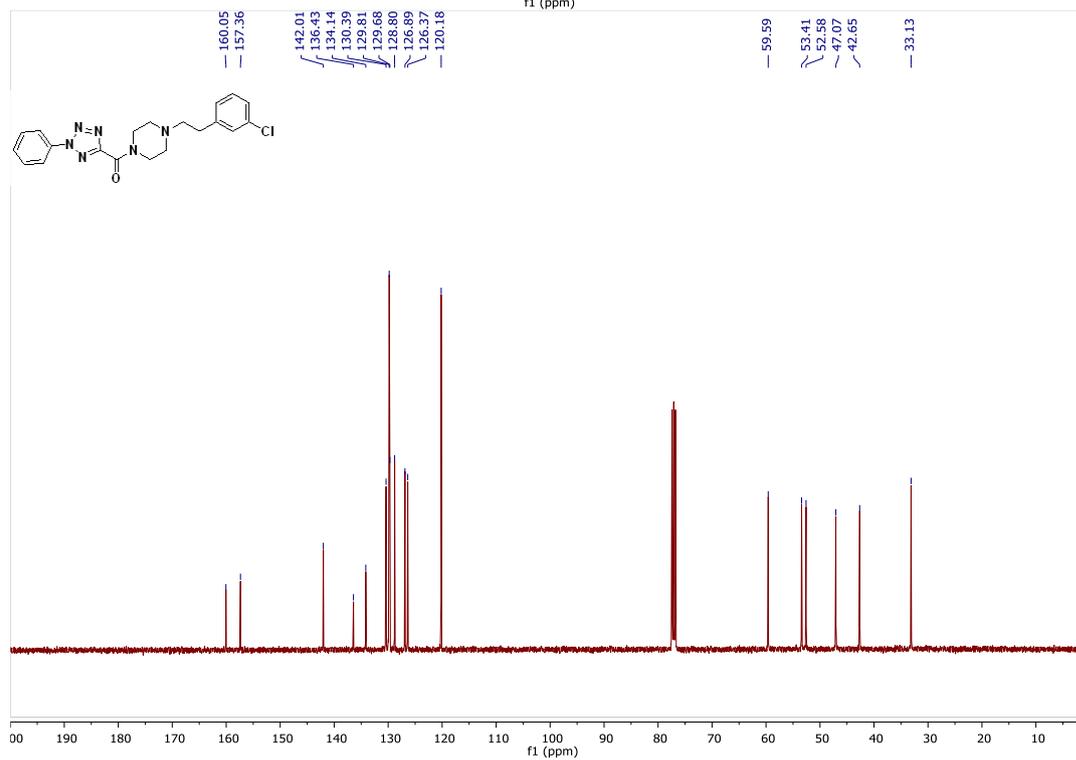
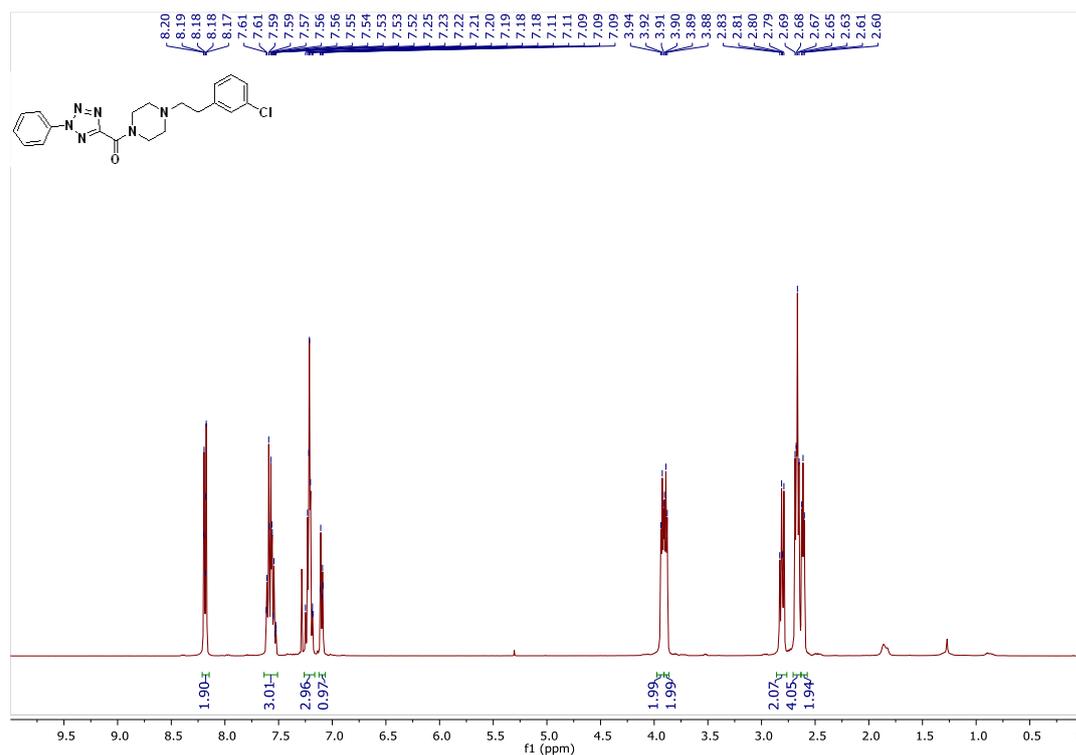
^1H and ^{13}C NMR spectra of compound **5I**



^1H and ^{13}C NMR spectra of compound **5m**



^1H and ^{13}C NMR spectra of compound **5n**



¹H and ¹³C NMR spectra of compound **5o**

