Supporting Information for
"Rapid synthesis of 1,3,5-substituted 1,2,4-triazoles from carboxylic acids, amidines and hydrazines"

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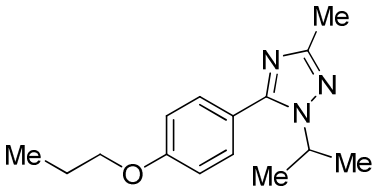
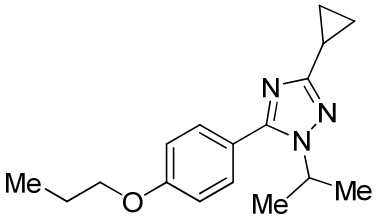
Table of Contents

General Procedure for Triazole Synthesis: DMF (10 mL) and DIPEA (1.45 mL, 8.3 mmol) were added to 4-propyloxybenzoic acid **1** (0.500 g, 2.8 mmol, 1.0 eq), benzamidine **2** (500 mg, 4.2 mmol, 1.5 eq) and HATU (1.16 g, 3.1 mmol, 1.1 eq) in a flask. The reaction was stirred at room temperature and monitored by LC-MS for consumption of acid **1** and formation of acylamidine intermediate **3**. After 3 hours, isopropylhydrazine hydrochloride (0.460 g, 4.2 mmol, 1.5 eq) then acetic acid (1.58 mL, 27.7 mmol, 10 eq) were added and the reaction mixture was heated to 80 °C and monitored for consumption of acylamidine intermediate. After 3 hours, the reaction was cooled to room temperature diluted with 200 mL EtOAc and extracted once with a saturated $NaHCO_3$ (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash column chromatography (0-100% EtOAc in heptanes) to afford pure compound **7** as a colorless crystalline solid (68% yield).



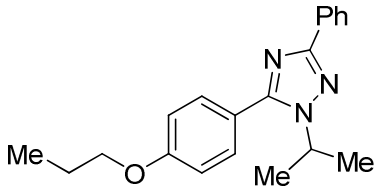
1-isopropyl-3-methyl-5-(4-propoxyphenyl)-1H-1,2,4-triazole (5). Following the general procedure, 4-propoxybenzoic acid was reacted with acetamidine hydrochloride and HATU for 2 hours at room temperature then isopropylhydrazine hydrochloride and acetic acid for 2 hours at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a light yellow oil (422 mg, 59% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 4.61 – 4.53 (m, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H), 1.75 (dt, *J* = 14.0, 7.0 Hz, 2H), 1.39 (d, *J* = 6.6 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 159.7, 158.5, 153.2, 130.0, 120.4, 114.7, 69.1, 49.6, 22.5, 21.9, 13.8, 10.3. HREIMS calc'd for $C_{15}H_{22}N_3O$: 260.1763, found 260.1922**.**



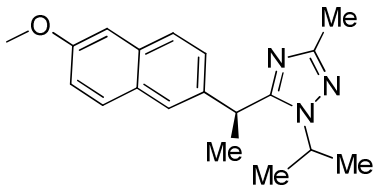
3-cyclopropyl-1-isopropyl-5-(4-propoxyphenyl)-1H-1,2,4-triazole (6). Following the general procedure, 4-propoxybenzoic acid was reacted with cyclopropanecarboxamidine hydrochloride and HATU for 2 hours at room temperature then isopropylhydrazine hydrochloride and acetic acid for 2 hours at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a white solid (661 mg, 84% yield).

^{1}H NMR (500 MHz, DMSO) δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.06 (d, *J* =8.5 Hz, 2H), 4.55 – 4.49 (m, 1H), 3.99 (t, *J* = 6.5 Hz, 2H), 2.01 – 1.95 (m, 1H), 1.80 – 1.71 (m, 2H), 1.38 (d, *J* = 6.5 Hz, 6H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.92 – 0.79 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 164.0, 160.2, 153.5, 130.6, 120.8, 115.2, 69.6, 50.2, 23.0, 22.4, 10.9, 9.4, 7.9. HREIMS calc'd for $C_{17}H_{24}N_3O$: 286.1919, found 286.2050.



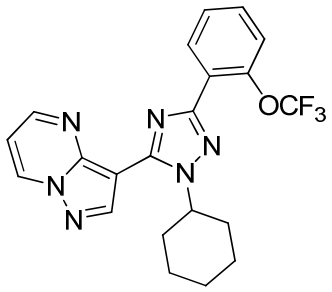
1-isopropyl-3-phenyl-5-(4-propoxyphenyl)-1H-1,2,4-triazole (7). Following the general procedure, 4-propoxybenzoic acid was reacted with benzamidine and HATU for 2 hours at room temperature then isopropylhydrazine hydrochloride and acetic acid for 2 hours at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a white solid (607 mg, 68% yield).

^{1}H NMR (500 MHz, DMSO) δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.51 – 7.40 (m, 3H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.68 (dt, *J* = 13.1, 6.5 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.73 (m, 2H), 1.48 (d, *J* = 6.6 Hz, 6H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 159.9, 159.8, 154.2, 131.2, 130.3, 129.0, 128.7, 125.7, 120.0, 114.8, 69.1, 50.3, 22.6, 21.9, 10.4. HREIMS calc'd for $C_{20}H_{24}N_3O$: 322.1919, found 322.2159.



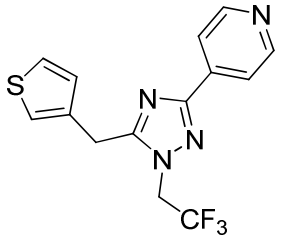
1-isopropyl-5-(1-(6-methoxynaphthalen-2-yl)ethyl)-3-methyl-1H-1,2,4-triazole (8). Following the general procedure, (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid was reacted with acetamidine and HATU for 2 hours at room temperature then isopropylhydrazine hydrochloride and acetic acid for 2 hours at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a pale yellow crystalline solid (343 mg, 51% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.76 (dd, *J* = 8.7, 3.3 Hz, 2H), 7.67 (s, 1H), 7.32 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.14 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.59 – 4.44 (m, 2H), 3.86 (s, 3H), 2.26 (s, 3H), 1.65 (d, *J* = 7.0 Hz, 3H), 1.33 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 157.9, 157.1, 156.5, 138.2, 133.1, 129.0, 128.4, 127.2, 126.0, 125.1, 118.7, 105.8, 55.1, 48.4, 35.6, 22.2, 21.8, 21.5, 13.9. HREIMS calc'd for $C_{19}H_{24}N_3O$: 310.1919, found 310.1988.



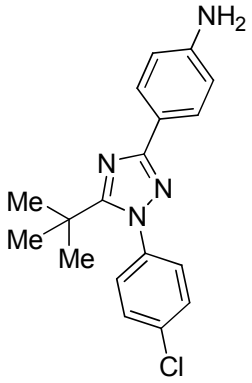
3-(1-cyclohexyl-3-(2-(trifluoromethoxy)phenyl)-1H-1,2,4-triazol-5-yl)pyrazolo[1,5-a]pyrimidine (9). Following the general procedure, pyrazolo[1,5-a]pyrimidine-3-carboxylic acid was reacted with 2-(trifluoromethoxy)benzene-1-carboximidamide hydrochloride and HATU for 4 hours at room temperature then cyclohexylhydrazine hydrochloride and acetic acid overnight at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) then reverse-phase HPLC (40-80% NH_4OH/MeCN) to give the titled compound as a pale yellow crystalline solid (322 mg, 41% yield).

^{1}H NMR (400 MHz, DMSO) δ 9.30 (dd, *J* = 7.0, 1.5 Hz, 1H), 8.76 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.63 (s, 1H), 8.17 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.61 – 7.47 (m, 3H), 7.25 (dd, *J* = 7.0, 4.1 Hz, 1H), 4.60 (tt, *J* = 11.3, 3.7 Hz, 1H), 2.07 (d, *J* = 10.4 Hz, 2H), 1.98 – 1.77 (m, 4H), 1.64 (d, *J* = 12.1 Hz, 1H), 1.38-1.14 (m, 3H). . ^{13}C NMR (126 MHz, DMSO) δ 157.6, 152.5, 147.3, 145.9, 145.5, 137.5, 131.0, 130.7, 128.4, 125.7, 123.2, 120.8 (q, *J* = 255.78), 110.3, 98.6, 58.3, 33.2, 25.3. HREIMS calc'd for $C_{21}H_{20}F_3N_6O$: 429.1651, found 429.1750.



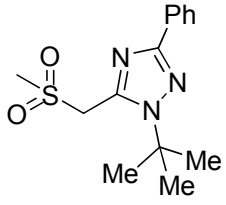
4-(5-(thiophen-3-ylmethyl)-1-(2,2,2-trifluoroethyl)-1H-1,2,4-triazol-3-yl)pyridine (10). Following the general procedure, 2-(thiophen-3-yl)acetic acid was reacted with 4-amidinopyridinium hydrochloride and HATU for 4 hours at room temperature then 2,2,2-trifluoroethylhydrazine and acetic acid overnight at 80°C. The crude product was purified by flash column chromatography (0-80% EtOAc in hexanes) to give the titled compound as a pale yellow solid (389 mg, 34% yield).

^{1}H NMR (400 MHz, DMSO) δ 8.70 (d, *J* = 6.0 Hz, 2H), 7.90 (d, *J* = 6.0 Hz, 2H), 7.43 (d, *J* = 5.1 Hz, 1H), 7.08 (d, *J* = 3.2 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.45 (q, *J* = 8.9 Hz, 2H), 4.60 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 158.9, 157.5, 150.5, 137.2, 137.2, 126.8, 126.7, 125.5, 123.2 (q, *J* = 279.8 Hz), 120.0, 48.5 (q, *J* = 34.3 Hz), 25.4. Structure was also confirmed by 2D HMBC data. HREIMS calc'd for $C_{14}H_{12}F_3N_4S$: 325.0735, found 325.0936.



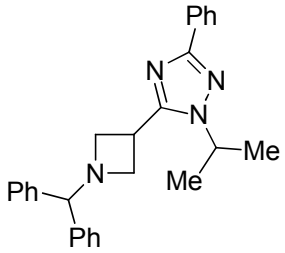
4-(5-tert-butyl-1-(4-chlorophenyl)-1H-1,2,4-triazol-3-yl)aniline (11). Following the general procedure, pivalic acid was reacted with 4-aminobenzamidine dihydrochloride and HATU overnight at room temperature then (p-chlorophenyl)hydrazine hydrochloride and acetic acid for 6 hours at 80°C. The crude product was purified by reverse-phase HPLC (30-70% NH_4OH/MeCN) to give the titled compound as a yellow solid (683 mg, 43% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.67 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 23.2, 8.7 Hz, 4H), 6.60 (d, *J* = 8.5 Hz, 2H), 5.34 (s, 2H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 163.0, 159.6, 149.7, 138.6, 134.3, 130.0, 129.1, 126.9, 118.2, 113.5, 33.0, 29.7. HREIMS calc'd for $C_{18}H_{20}ClN_4$: 327.1376, found 327.1462.



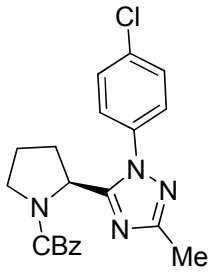
1-tert-butyl-5-(methylsulfonylmethyl)-3-phenyl-1H-1,2,4-triazole (12). Following the general procedure, 2-(methylsulfonyl)acetic acid was reacted with benzamidine hydrochloride and HATU overnight at room temperature then tert-butylhydrazine hydrochloride and acetic acid for 6 hours at 80°C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a white solid (261 mg, 25% yield).

^{1}H NMR (400 MHz, DMSO) δ 8.00 (d, *J* = 6.8 Hz, 2H), 7.51 – 7.40 (m, 3H), 5.04 (s, 2H), 3.30 (s, 3H), 1.71 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 158.3, 145.4, 130.6, 129.1, 128.7, 125.7, 61.5, 53.0, 41.1, 30.0. HREIMS calc'd for $C_{14}H_{20}N_3O_2S$: 294.1276, found 294.1482.



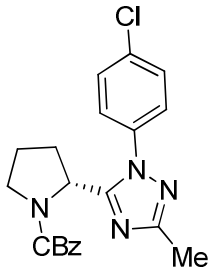
5-(1-Benzhydryl-azetidin-3-yl)-1-isopropyl-3-phenyl-1H-[1,2,4]triazole (13). Following the general procedure, 1-benzhydryl-azetidin-3-carboxylic acid was reacted with benzamidine and HATU overnight at room temperature then isopropylhydrazine hydrochloride and acetic acid for 1 h at 80˚C. The crude product was purified by flash column chromatography (10-100% EtOAc in hexanes) to give the titled compound as a colorless solid (404 mg, 53% yield).

^{1}H NMR (400 MHz, DMSO) δ 8.00 – 7.95 (m, 2H), 7.50 – 7.36 (m, 7H), 7.30 (t, *J* = 7.5 Hz, 4H), 7.19 (t, *J* = 7.3 Hz, 2H), 4.57 – 4.46 (m, 2H), 4.03 – 3.93 (m, 1H), 3.61 (t, *J* = 7.5 Hz, 2H), 3.30 (m, 2H), 1.36 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, DMSO) δ 159.8, 155.9, 142.7, 131.8, 129.3, 129.1, 128.9, 127.7, 127.5, 126.1, 77.2, 57.7, 49.7, 25.6, 22.9. HREIMS calcd for $C_{27}H_{29}N_4$: 409.2392, found: 409.2392.



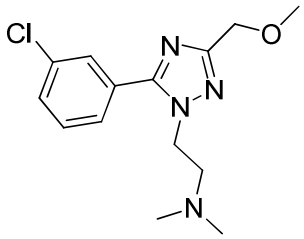
2-{(S)-2-[2-(4-Chloro-phenyl)-5-methyl-2H-[1,2,4]triazol-3-yl]-pyrrolidin-1-yl}-1-phenyl-ethanone (14). Following the General Procedure, N-carbobenzyloxy-L-proline was reacted with acetamidine hydrochloride and HATU (839 mg, 1.1 equiv) for 5 hours at room temperature then 4-chlorophenylhydrazine hydrochloride and acetic acid for 2 h at 80˚C. The crude product was purified by reverse-phase HPLC (30-70% NH_4OH/MeCN) then flash column chromatography (0-10% MeOH in DCM) gave the titled compound as a foam (309 mg, 39% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.61 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.39 – 7.19 (m, 5H), 6.90 (m, 1H), 5.01 (q, *J* = 12.8 Hz, 1H), 4.91 – 4.72 (m, 2H), 3.56 – 3.38 (m, 2H), 2.34– 1.82 (m, 4H), 2.28 (s, 3H). A mixture of rotamers was evident by ^{13}C NMR: ^{13}C NMR (126 MHz, DMSO) δ 160.1, 160.0, 157.8, 157.7, 154.3, 153.5, 137.2, 137.0, 136.3, 136.0, 133.9, 133.8, 129.9, 129.85, 128.86, 128.7, 128.3, 128.26, 127.9, 127.8, 127.7, 127.3, 66.5, 66.3, 53.0, 52.2, 47.4, 46.9, 33.1, 32.2, 24.3, 23.4, 14.1, 14.0 (rotomers evident). HREIMS calc'd for $C_{21}H_{22}ClN_4O_2$: 397.1431, found: 397.1522.



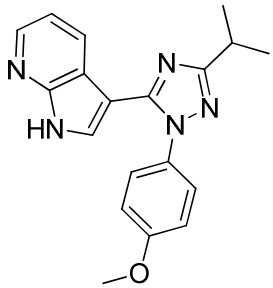
2-{(R)-2-[2-(4-Chloro-phenyl)-5-methyl-2H-[1,2,4]triazol-3-yl]-pyrrolidin-1-yl}-1-phenyl-ethanone (15). Following the General Procedure, N-carbobenzyloxy-D-proline was reacted with acetamidine hydrochloride and HATU for 5 hours at room then 4-chlorophenylhydrazine hydrochloride and acetic acid for 2 h at 80˚C. The crude product was purified by reverse-phase HPLC (30-70% NH_4OH/MeCN) then flash column chromatography (0-10% MeOH in DCM) gave the titled compound as a foam (285 mg, 36% yield). ^{1}H NMR data consistent/identical with **13**.

A mixture of **14** and **15** were resolved by analytical SFC to determine the extent of racemization. Analytical samples were determined to be >98% ee (Phenomenex Lux Cellulose-2, 10/90 MeOH/CO2 ramped to 55/45, 5mL/min, 40 ˚C, R_t (min) = 1.01 (R), 1.09 (S)).



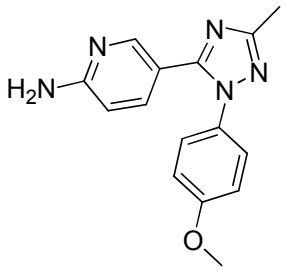
2-(5-(3-chlorophenyl)-3-(methoxymethyl)-1*H*-1,2,4-triazol-1-yl)-N,N-dimethylethanamine (16). Following the General Procedure, 3-chlorobenzoic acid was reacted with 2-methoxyacetimidamide hydrochloride and HATU for 3 hours at room temperature then 2-hydrazinyl-N,N-dimethylethanamine dihydrochloride salt and acetic acid for 3 hours at 80˚C. The crude product was purified by flash column chromatography (0-20% MeOH in DCM) then reverse phase HPLC (30-70% NH_4OH/MeCN) to give the titled compound as yellow oil (540 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J*=1.6, 1H), 7.59 (d, *J*=7.4, 1H), 7.50 – 7.39 (m, 2H), 4.57 (s, 2H), 4.23 (t, *J*=6.6, 2H), 3.50 (s, 3H), 2.81 (t, *J*=6.6, 2H), 2.20 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 159.5, 153.7, 133.5, 130.8, 130.0, 129.9, 128.5, 127.4, 66.7, 57.9, 57.7, 47.2, 45.1. Structure was also confirmed by 2D HMBC data. HREIMS calcd for $C_{14}H_{20}ClN_4O$: 295.1326, found: 295.1487.



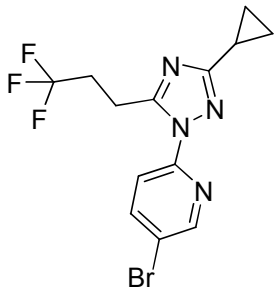
3-(3-isopropyl-1-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5-yl)-1H-pyrrolo[2,3-b]pyridine (17). Following the general procedure, 1H-pyrrolo[2,3-b]pyridine-3-carboxylic acid was reacted with isobutyrimidamide hydrochloride and HATU for 18 hours at room temperature then (4-methoxyphenyl)hydrazine hydrochloride and acetic acid for 3 h at 80˚C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a solid (333 mg, 30% yield).

^{1}H NMR (400 MHz, DMSO) δ = 11.98 (s, 1H), 8.41 (d, *J*=7.9, 1H), 8.30 (d, *J*=4.6, 1H), 7.44 (d, *J*=8.6, 2H), 7.19 (dd, *J*=7.9, 4.7, 1H), 7.10 (d, *J*=8.6, 2H), 6.90 (s, 1H), 3.84 (s, 3H), 3.07 (dt, *J*=13.8, 6.9, 1H), 1.36 (d, *J*=6.9, 6H). ^{13}C NMR (126 MHz, DMSO) δ 167.7, 159.7, 150.0, 148.0, 144.0, 131.1, 129.4, 127.9, 125.7, 117.8, 116.8, 114.8, 102.0, 55.5, 27.6, 21.6. HREIMS calcd for $C_{19}H_{20}N_5O$: 334.1668, found: 334.1858.



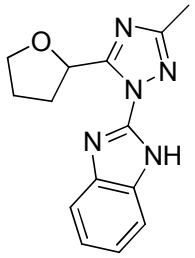
5-(1-(4-methoxyphenyl)-3-methyl-1*H*-1,2,4-triazol-5-yl)pyridin-2-amine (18). Following the General Procedure, 6-aminonicotinic acid was reacted with acetamidine hydrochloride and HATU for 18 hours at room temperature then (4-methoxyphenyl)hydrazine hydrochloride and acetic acid for 3 hours at 80˚C. The crude product was purified by flash column chromatography (0-20% MeOH in DCM) to give the titled compound as a solid (615 mg, 60% yield).

^{1}H NMR (500 MHz, DMSO) δ = 7.93 (d, *J*=2.3, 1H), 7.40 – 7.21 (m, 3H), 7.11 – 6.94 (m, 2H), 6.45 – 6.30 (m, 3H), 3.81 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 160.1, 159.2, 159.2, 152.5, 148.0, 136.5, 131.1, 127.2, 114.5, 111.8, 107.2, 55.4, 13.5. HREIMS calcd for $C_{15}H_{16}N_5O$: 282.1355, found: 282.1522.



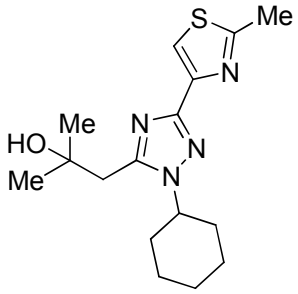
5-bromo-2-(3-cyclopropyl-5-(3,3,3-trifluoropropyl)-1*H*-1,2,4-triazol-1-yl)pyridine (19). Following the general procedure, 4,4,4-trifluorobutanoic acid was reacted with cyclopropanecarboximidamide hydrochloride and HATU for 3 hours at room temperature then 5-bromo-2-hydrazinylpyridine hydrochloride and acetic acid for 3 h at 80˚C. The crude product was purified by flash column chromatography (0-100% EtOAc in hexanes) to give the titled compound as a colorless solid (635 mg, 50% yield).

^{1}H NMR (400 MHz, DMSO) δ = 8.68 (d, *J*=2.4, 1H), 8.26 (dd, *J*=8.7, 2.4, 1H), 7.78 (d, *J*=8.8, 1H), 3.43 – 3.37 (m, 2H), 2.84 – 2.69 (m, 2H), 2.08 – 1.98 (m, 1H), 1.01 – 0.93 (m, 2H), 0.93 – 0.85 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.5, 154.4, 149.1, 148.6, 142.2, 127.1 (q, *J* = 276.8), 117.9, 117.3, 30.4 (q, *J* = 28.3), 21.6 (q, *J* = 3.3), 8.5, 7.6. HREIMS calcd for $C_{13}H_{13}BrF_3N_4$: 361.0276, found: 361.0331.



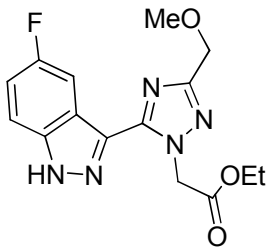
2-[3-Methyl-5-(tetrahydro-furan-2-yl)-[1,2,4]triazol-1-yl]-1H-benzoimidazole (20). Following the General Procedure, (±)-tetrahydrofuran-2-carboxylic acid (0.096 mL, 1.00 mmol) was reacted with acetamidine hydrochloride and HATU overnight at room temperature then 2-hydrazinyl-1H-benzo[d]imidazole and acetic acid for 2 h at 80˚C. The crude product was purified by flash column chromatography (80% EtOAc in hexanes) to give the title compound as a grey solid (140 mg, 52 % yield).

^{1}H NMR (400 MHz, DMSO) δ 13.17 (br, 1H), 7.57 (br, 2H), 7.31 – 7.18 (m, 2H), 6.01 (dd, *J* = 7.7, 5.4 Hz, 1H), 3.96 – 3.88 (m, 1H), 3.87 – 3.80 (m, 1H), 2.40 (s, 3H), 2.39 – 2.32 (m, 1H), 2.30 – 2.19 (m, 1H), 2.18 – 2.03 (m, 1H), 2.03 – 1.86 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 158.3, 143.3, 142.0, 131.9, 123.6, 122.9 119.9, 110.8, 72.5, 69.4, 30.8, 26.0, 13.8. HREIMS calc'd for $C_{14}H_{16}N_5O$: 270.1355, found: 270.1500.



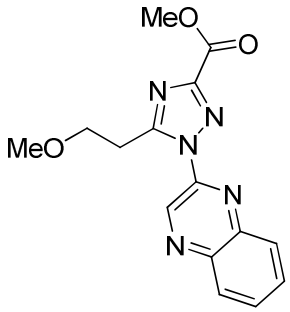
1-(1-cyclohexyl-3-(2-methylthiazol-4-yl)-1H-1,2,4-triazol-5-yl)-2-methylpropan-2-ol (21). Following the general procedure, 3-hydroxy-3-methylbutanoic acid was reacted with 2-methyl-1,3-thiazole-4-carboximidamide hydrochloride and HATU overnight at room temperature then cyclohexylhydrazine hydrochloride and acetic acid for 6 hours at 80°C. The crude product was purified by flash column chromatography (0-100% ethyl acetate in hexanes) then reverse-phase HPLC (20-60% NH_4OH/MeCN) to give the titled compound as a yellow crystalline solid (378 mg, 63% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.82 (s, 1H), 4.68 (s, 1H), 4.42 (td, *J* = 10.8, 5.4 Hz, 1H), 2.90 (s, 2H), 2.71 (s, 3H), 1.94 – 1.74 (m, 6H), 1.68 (d, *J* = 12.7 Hz, 1H), 1.51 – 1.23 (m, 3H), 1.21 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 165.6, 155.8, 152.7, 147.2, 117.0, 69.2, 56.3, 38.6, 32.5, 29.4, 24.9, 24.9, 18.8. HREIMS calc'd for $C_{16}H_{25}N_4OS$: 321.1749, found 321.1889.

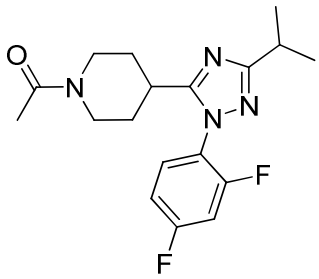


ethyl 2-(5-(5-fluoro-1H-indazol-3-yl)-3-(methoxymethyl)-1H-1,2,4-triazol-1-yl)acetate (22)
This compound was prepared following the general procedure.

^{1}H NMR (500 MHz, DMSO) δ 13.94 (s, 1H), 7.99 (dd, J = 9.0, 2.4 Hz, 1H), 7.72 (dd, J = 9.1, 4.2 Hz, 1H), 7.41 (td, J = 9.1, 2.5 Hz, 1H), 5.56 (s, 2H), 4.52 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.38 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H).. ^{13}C NMR (126 MHz, DMSO) δ 167.9, 160.2, 158.4 (d, J = 237.8 Hz), 149.4, 138.04, 133.8, 121.7 (d, J = 11.0 Hz), 117.4 (d, J = 27.6 Hz), 113.1 (d, J = 10.0 Hz), 105.8 (d, J = 24.6 Hz), 67.1, 61.7, 58.2, 52.2, 14.5. HREIMS calc'd for $C_{15}H_{17}FN_5O_3$: 334.1315, found 334.1315.

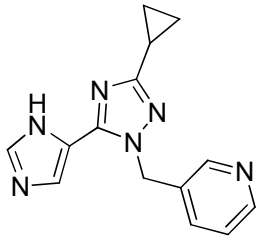


methyl 5-(2-methoxyethyl)-1-(quinoxalin-2-yl)-1H-1,2,4-triazole-3-carboxylate (23)
This compound was prepared following the general procedure.
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.30 – 8.17 (m, 1H), 8.13 – 8.04 (m, 1H), 7.96 – 7.79 (m, 2H), 4.08 (s, 3H), 3.97 (t, J = 6.8 Hz, 2H), 3.80 (t, J = 6.8 Hz, 2H), 3.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 157.6, 154.2, 144.3, 141.7, 139.7, 139.3, 131.6, 130.8, 129.5, 128.9, 69.6, 58.9, 53.2, 29.4. HREIMS calc'd for $C_{15}H_{16}N_5O_3$: 314.1253, found 314.1436.



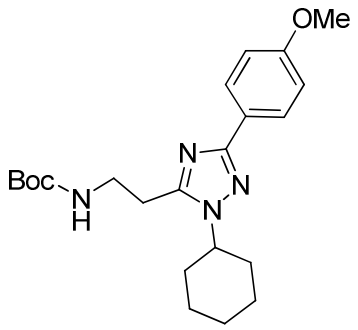
1-{4-[2-(2,4-Difluoro-phenyl)-5-isopropyl-2H-[1,2,4]triazol-3-yl]-piperidin-1-yl}-ethanone (24). Following the General Procedure, 1-acetylpiperidine-4-carboxylic acid (342 mg, 2.00 mmol) was reacted with 2-methylpropionamidine hydrochloride and HATU for 5 h at room temperature then (2,4-difluorophenyl)hydrazine hydrochloride and acetic acid for 2 h at 80˚C. The crude product was purified by flash column chromatography (50 - 100% EtOAc in hexanes) to give the title compound as a yellow oil (392 mg, 56 % yield).

^{1}H NMR (400 MHz, DMSO) δ 7.74 (td, *J* = 8.8, 6.0 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.36 – 7.26 (m, 1H), 4.32 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 13.7 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.96 (sept, *J* = 7.0 Hz, 1H), 2.86 – 2.74 (m, 1H), 2.57 (td, *J* = 12.7, 2.3 Hz, 1H), 1.99 (s, 3H), 1.80 – 1.61 (m, 3H), 1.52 (qd, *J* = 12.4, 4.2 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 168.1, 167.9, 162.6 (dd, *J* = 250.4, 11.7 Hz), 159.7, 156.8 (dd, *J* = 252.6, 13.2 Hz), 130.8 (d, *J* = 10.5 Hz), 121.4 (dd, *J* = 12.5, 3.6 Hz), 112.6 (dd, *J* = 22.7, 3.5 Hz), 105.5 (dd, *J* = 27.0, 24.2 Hz), 45.0, 32.3, 30.5, 29.9, 27.6, 21.2. HREIMS calc'd for $C_{18}H_{23}F_2N_4O$: 349.1840, found: 349.1949.



3-[3-Cyclopropyl-5-(3H-imidazol-4-yl)-[1,2,4]triazol-1-ylmethyl]-pyridine (25). Following the General Procedure, using potassium carbonate instead of diisopropylethylamine, 1H-imidazole-5-carboxylic acid (112 mg, 1.00 mmol) was reacted with cyclopropanecarboxamidine hydrochloride and HATU overnight at room temperature then 3-(hydrazinylmethyl)pyridine and acetic acid for 2 h at 80˚C. The crude product was purified by flash column chromatography (80% EtOAc in hexanes) to give the title compound as an off-white solid (136 mg, 51 % yield).

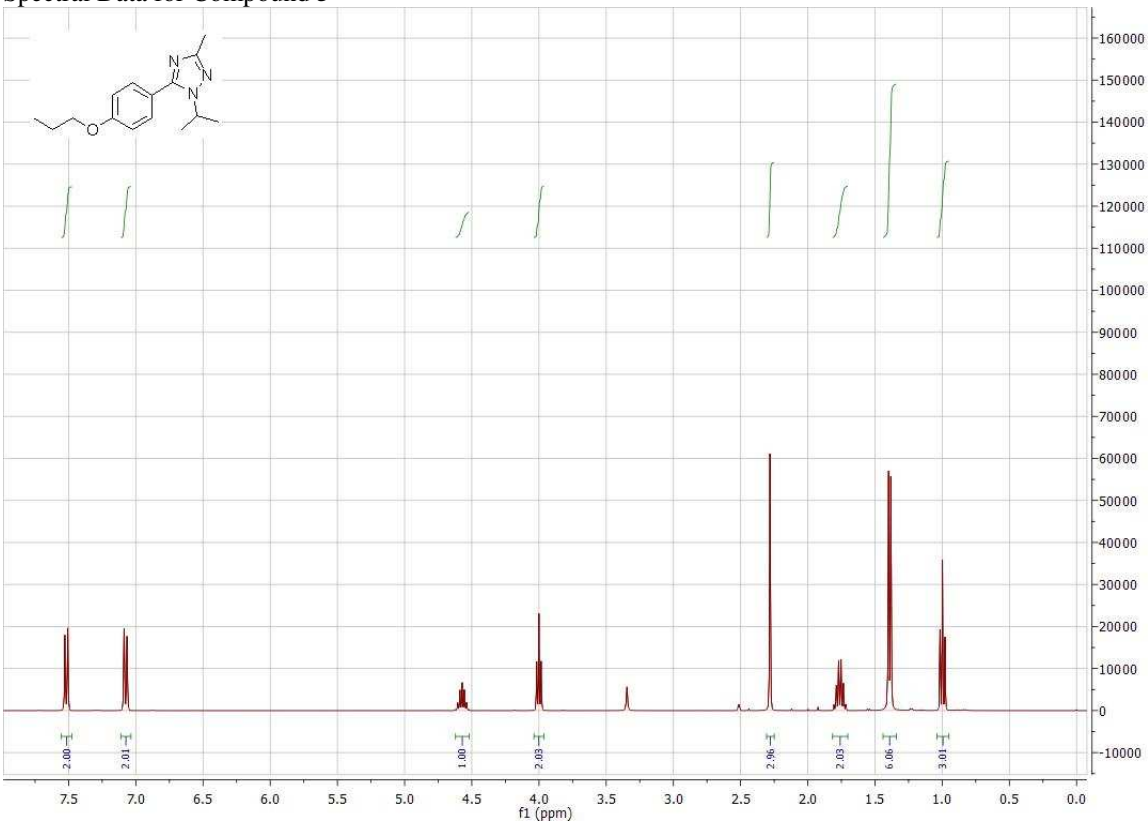
^{1}H NMR (400 MHz, DMSO) δ 12.60 (br, 1H), 8.51 (d, *J* = 1.8 Hz, 1H), 8.47 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (d, *J* = 0.7 Hz, 1H), 7.73 (s, 1H), 7.66 – 7.61 (m, 1H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.92 (s, 2H), 2.06 – 1.83 (m, 1H), 0.92 – 0.84 (m, 2H), 0.84 – 0.77 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 164.1, 149.0, 148.8, 148.7, 136.5, 135.3, 133.0, 130.0, 123.6, 118.2, 49.4, 8.6, 7.3. HREIMS calc'd for $C_{14}H_{15}N_6$: 267.1358, found: 267.1576.

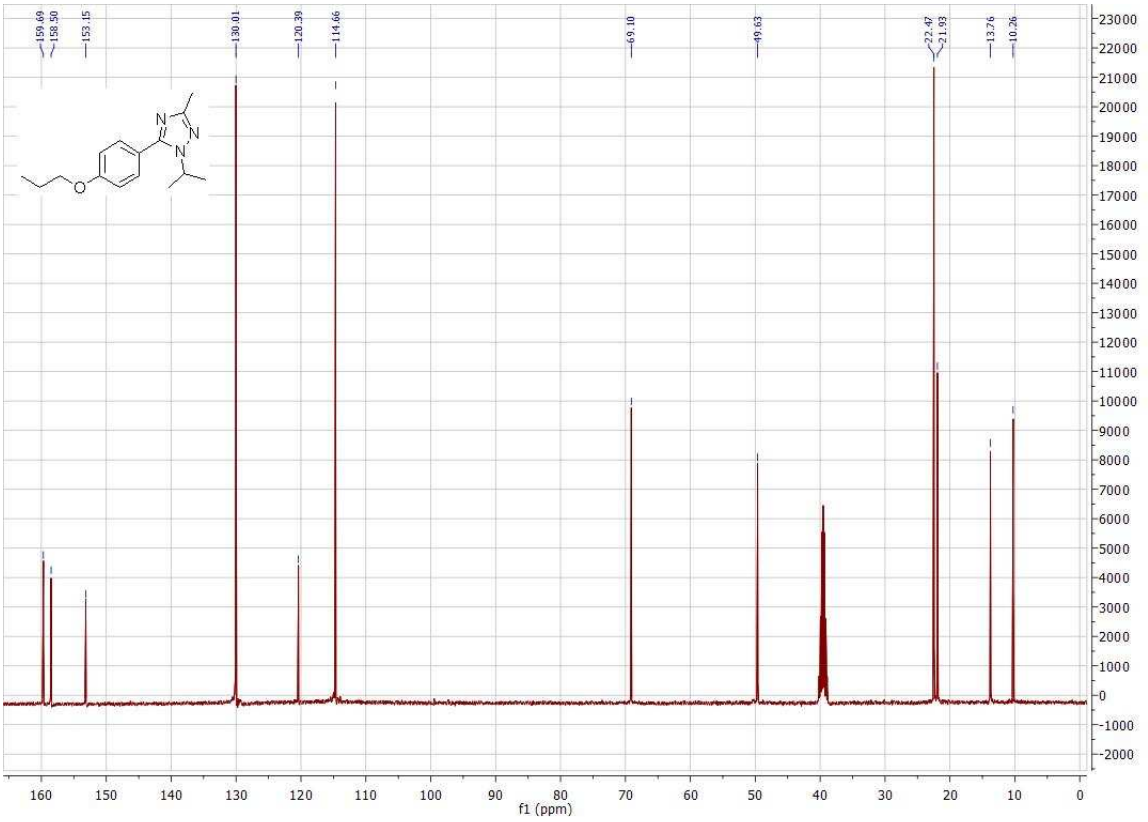


***tert*-butyl 2-(1-cyclohexyl-3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)ethylcarbamate (26).** Following the general procedure, N-(tert-butoxycarbonyl)-β-alanine was reacted with 4-methoxybenzamidine hydrochloride and HATU overnight at room temperature then cyclohexylhydrazine hydrochloride and acetic acid for 6 hours at 80°C. The crude product was purified by flash column chromatography then reverse-phase HPLC (40-80% NH_4OH/MeCN) to give the titled compound as a light yellow crystalline solid (277 mg, 26% yield).

^{1}H NMR (400 MHz, DMSO) δ 7.89 (d, *J* = 8.6 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 6.93 (t, *J* = 5.1 Hz, 1H), 4.25 – 4.15 (m, 1H), 3.80 (s, 3H), 3.35 – 3.27 (m, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 1.95-1.15 (m, 10H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 159.6, 159.2, 155.5, 153.1, 127.0, 124.1, 113.9, 77.7, 56.1, 55.1, 38.6, 32.5, 28.2, 25.8, 24.9, 24.8. HREIMS calc'd for $C_{22}H_{33}N_4O_3$: 401.2553, found 401.2603.

Spectral Data for Compound **5**





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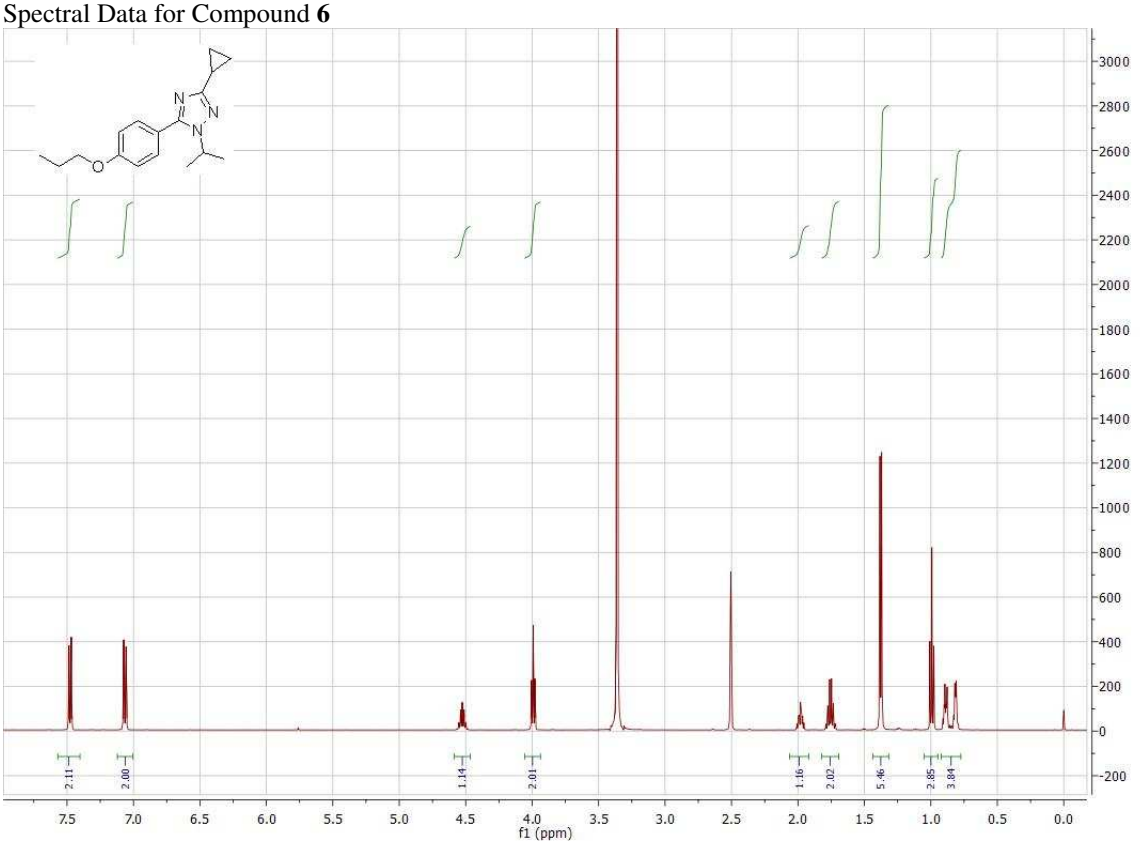

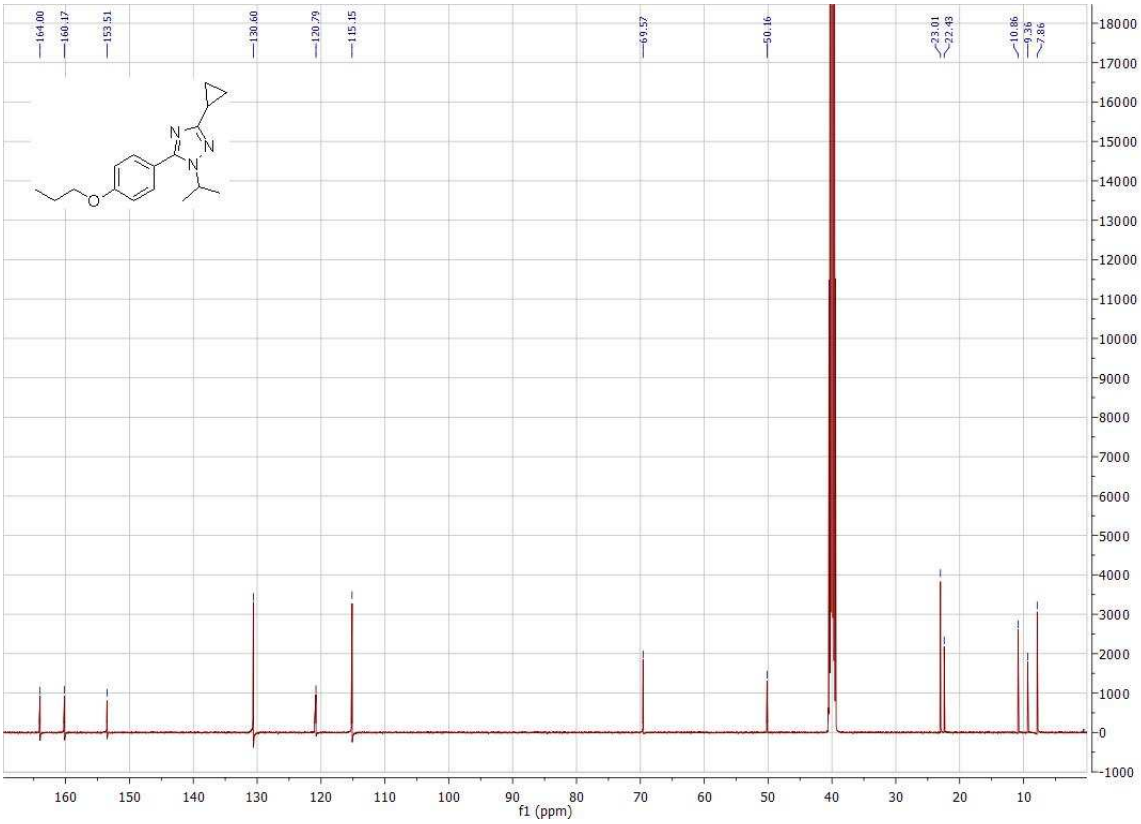

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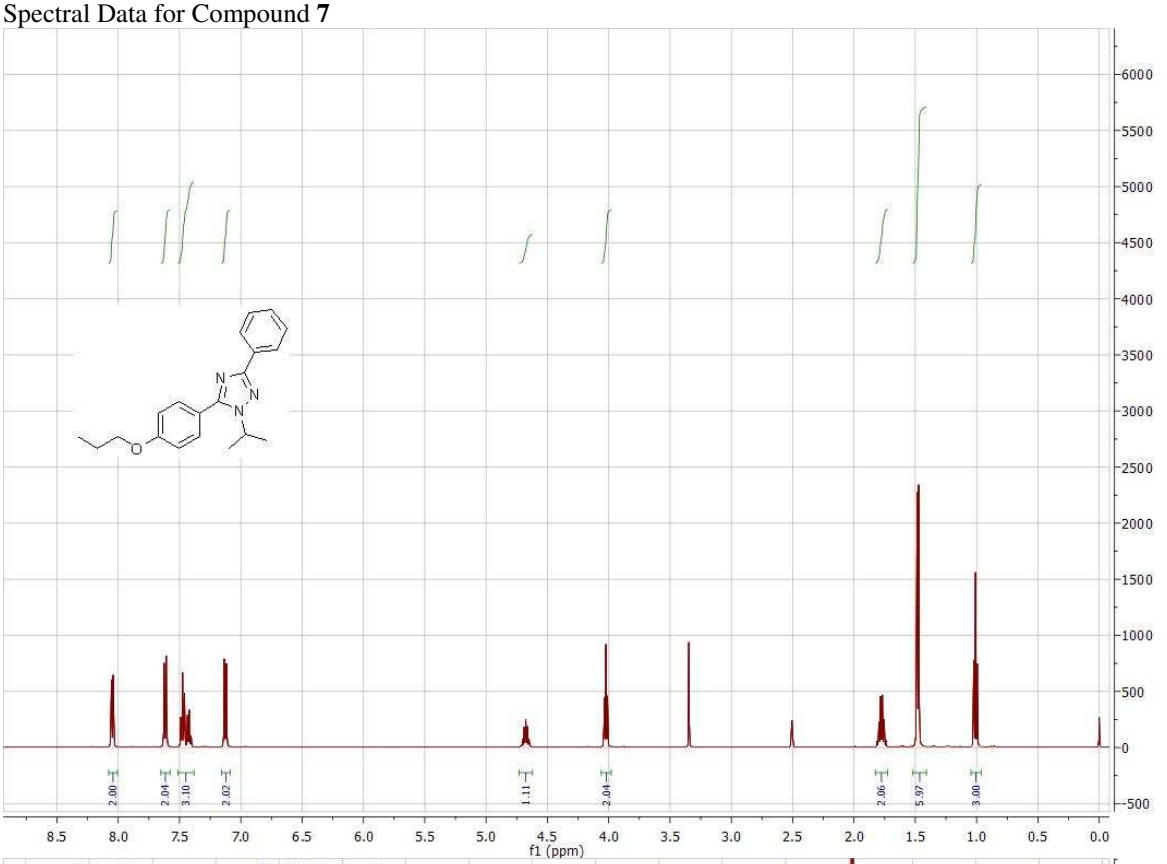

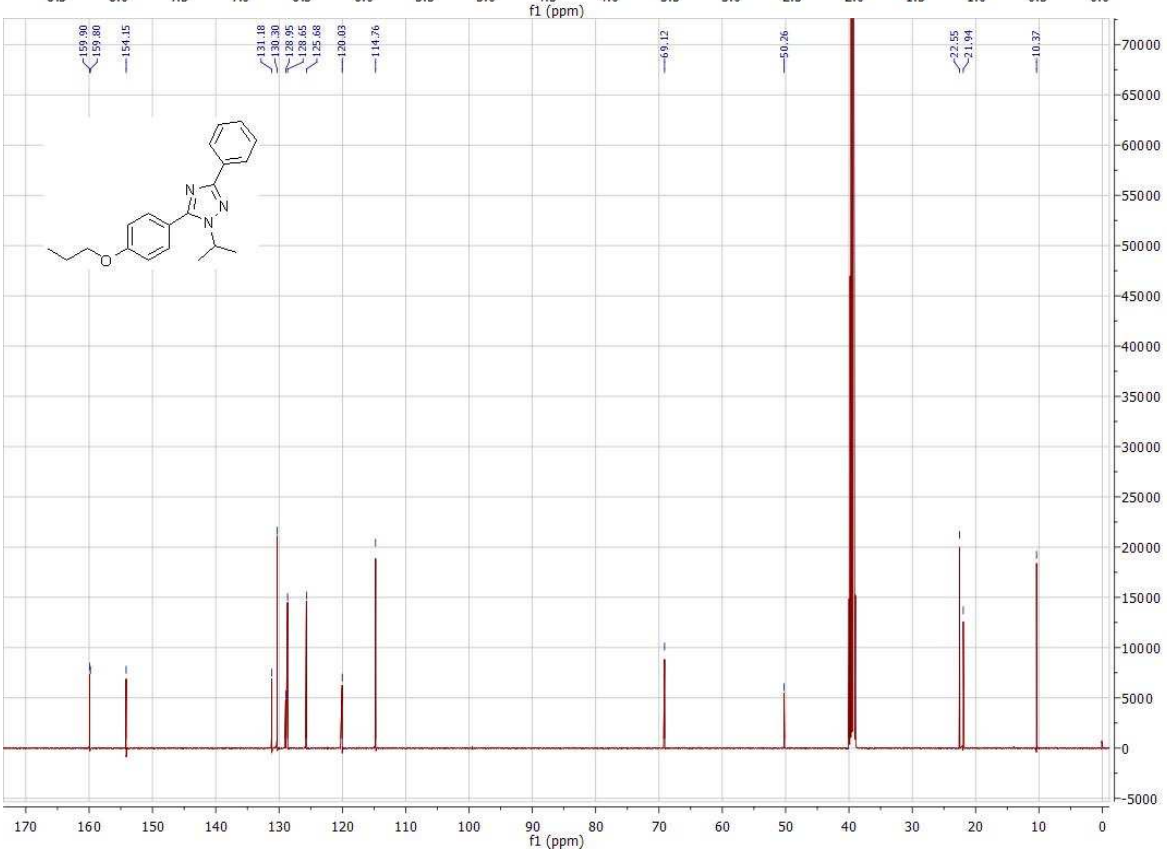

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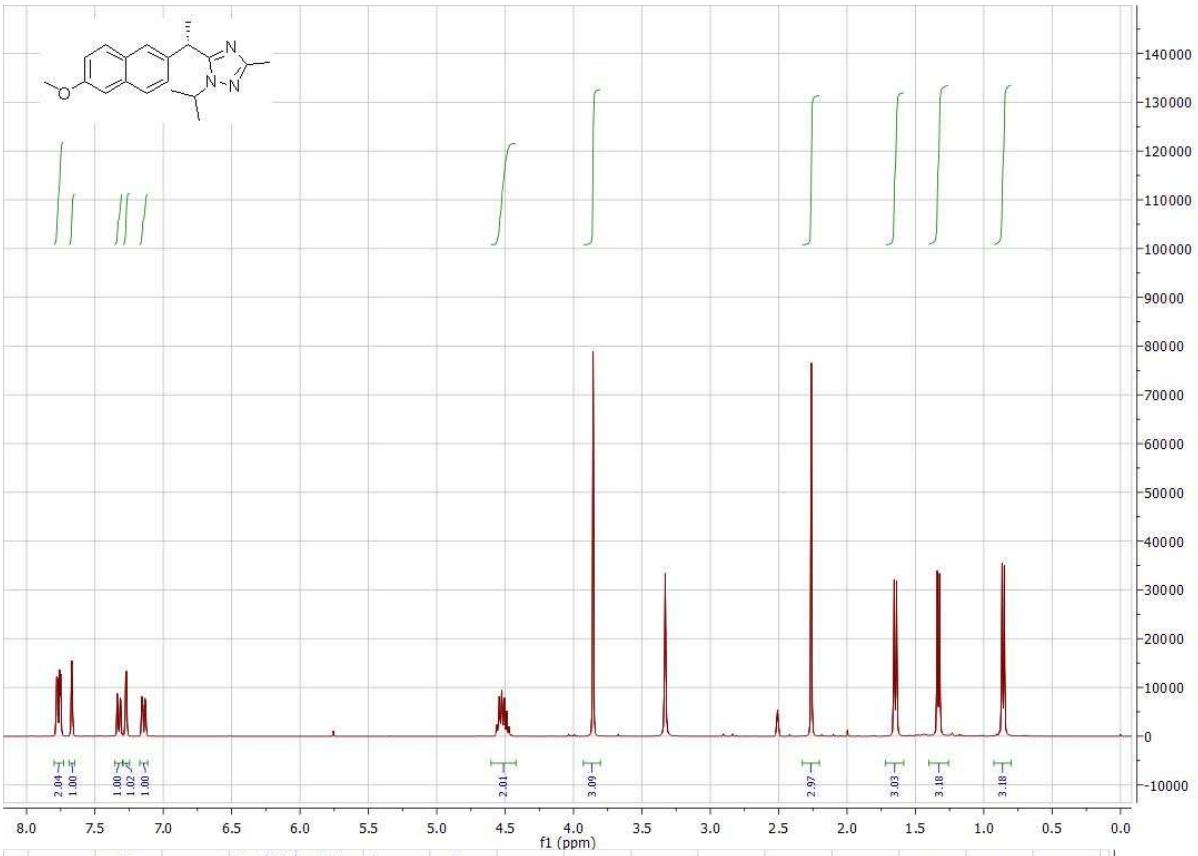

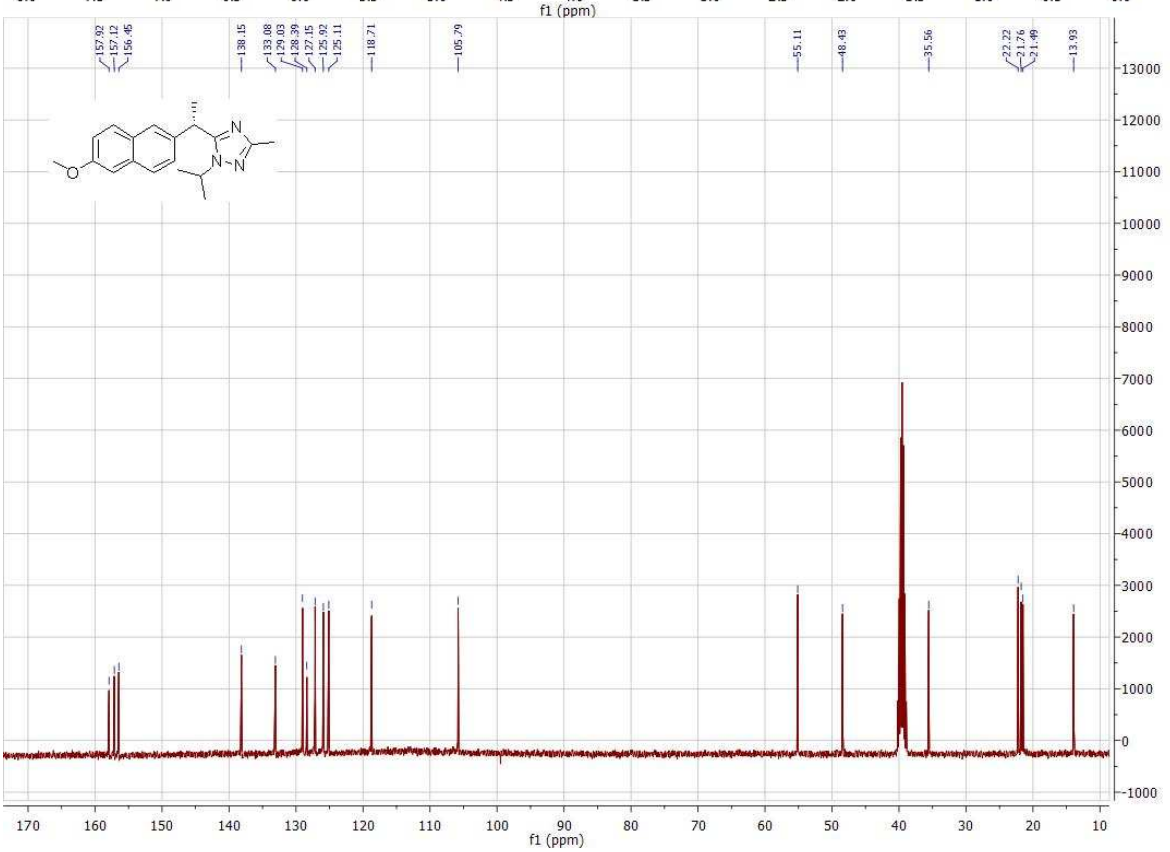

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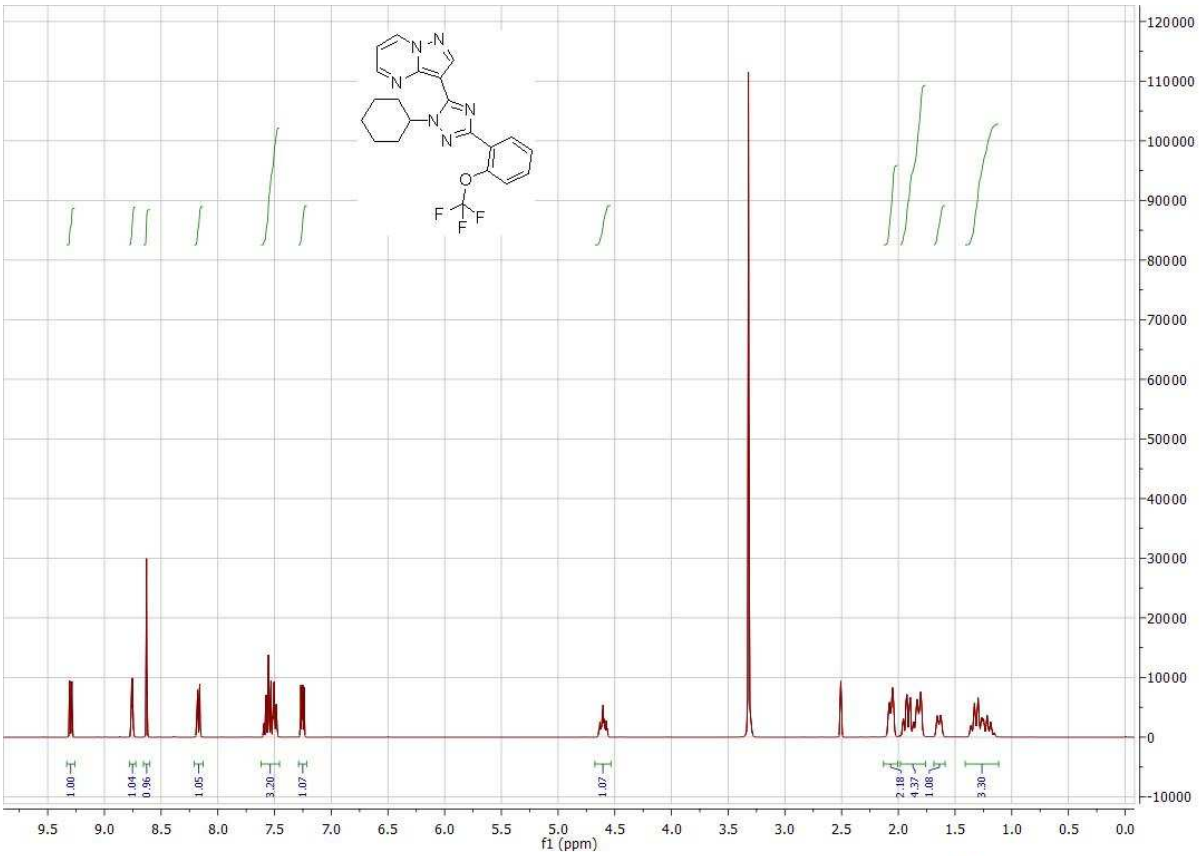

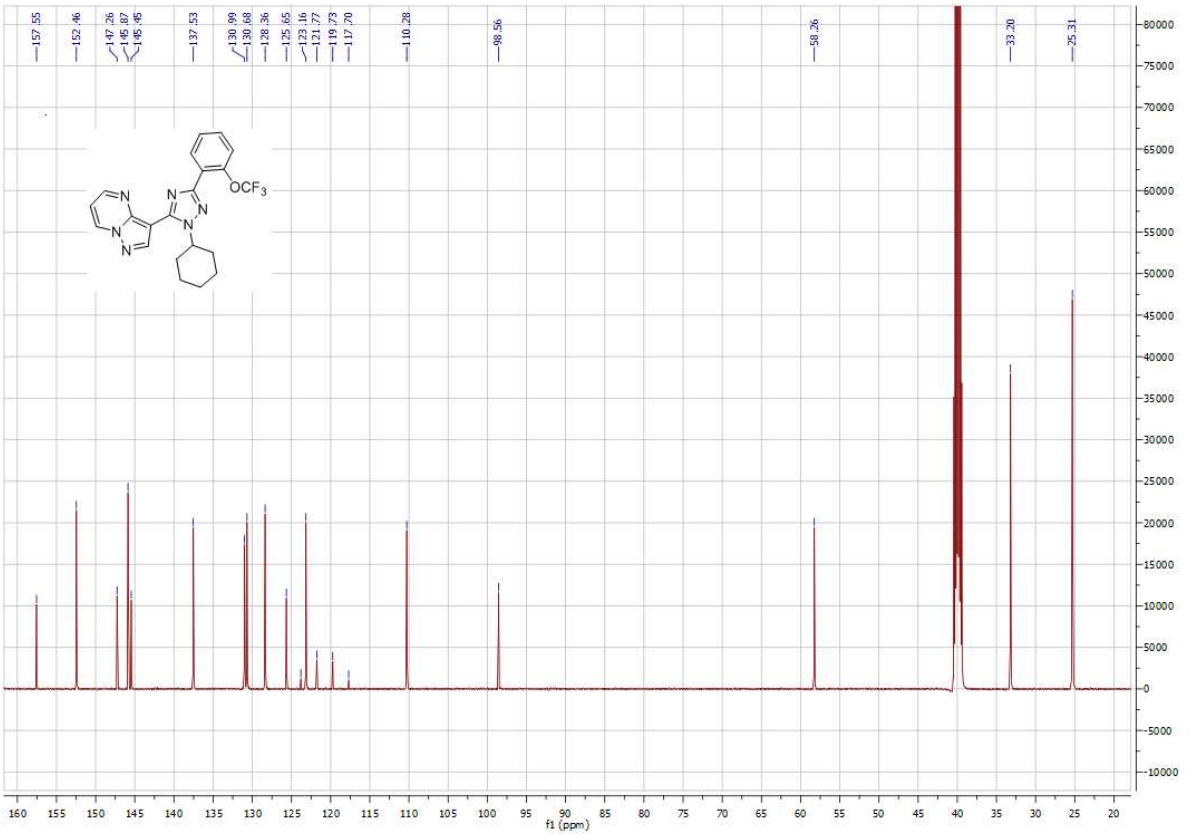

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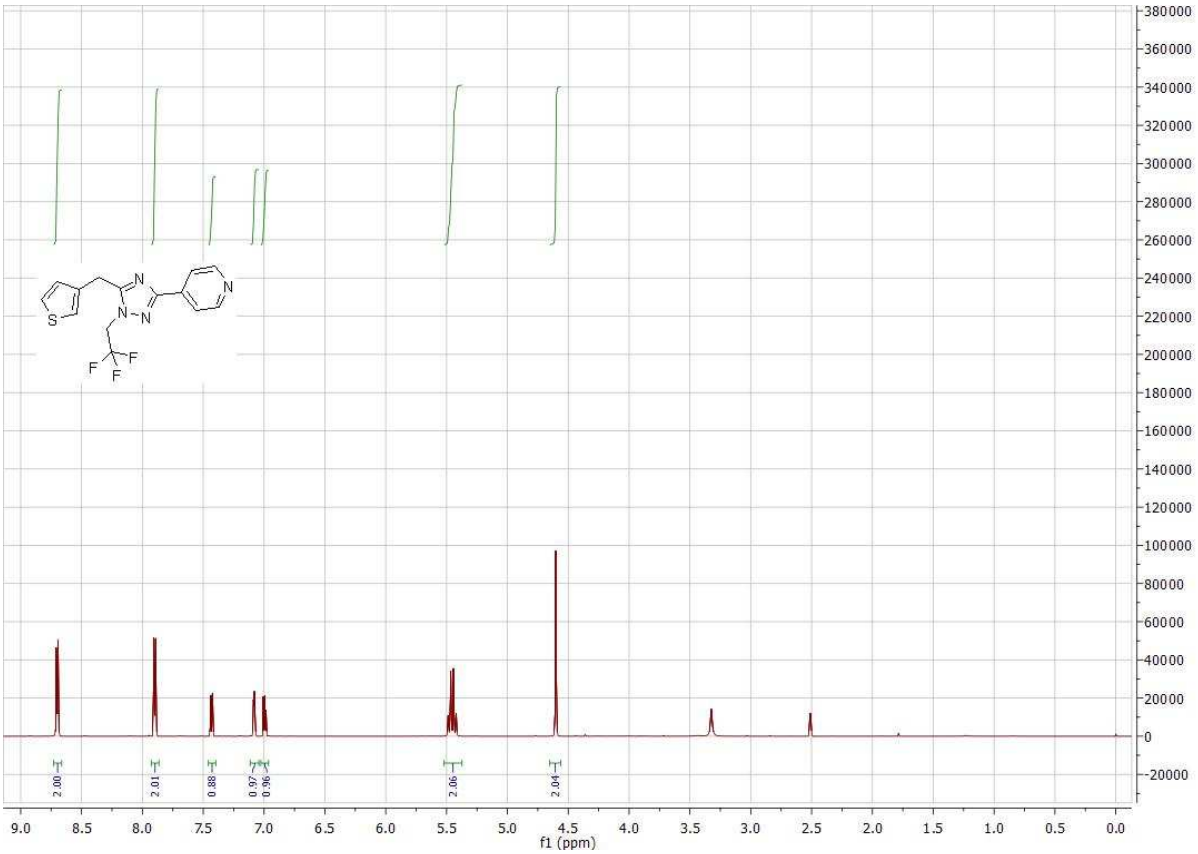

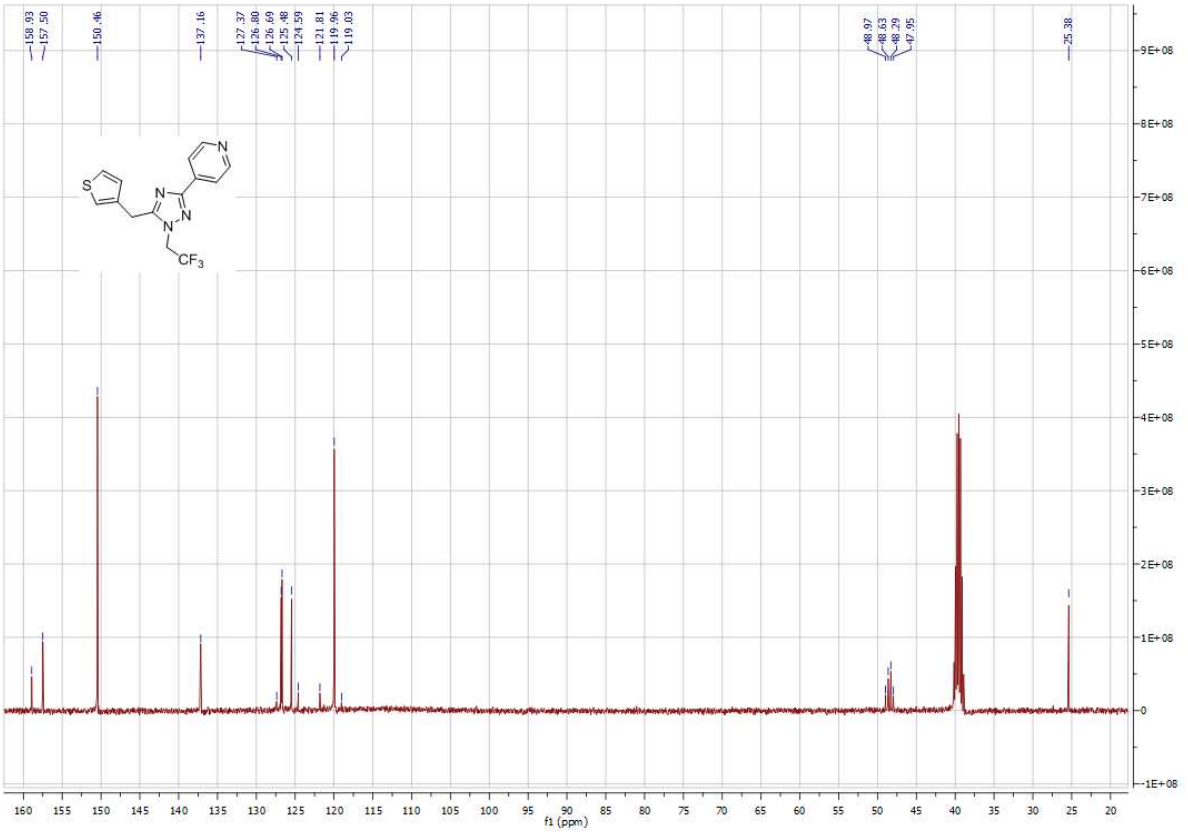

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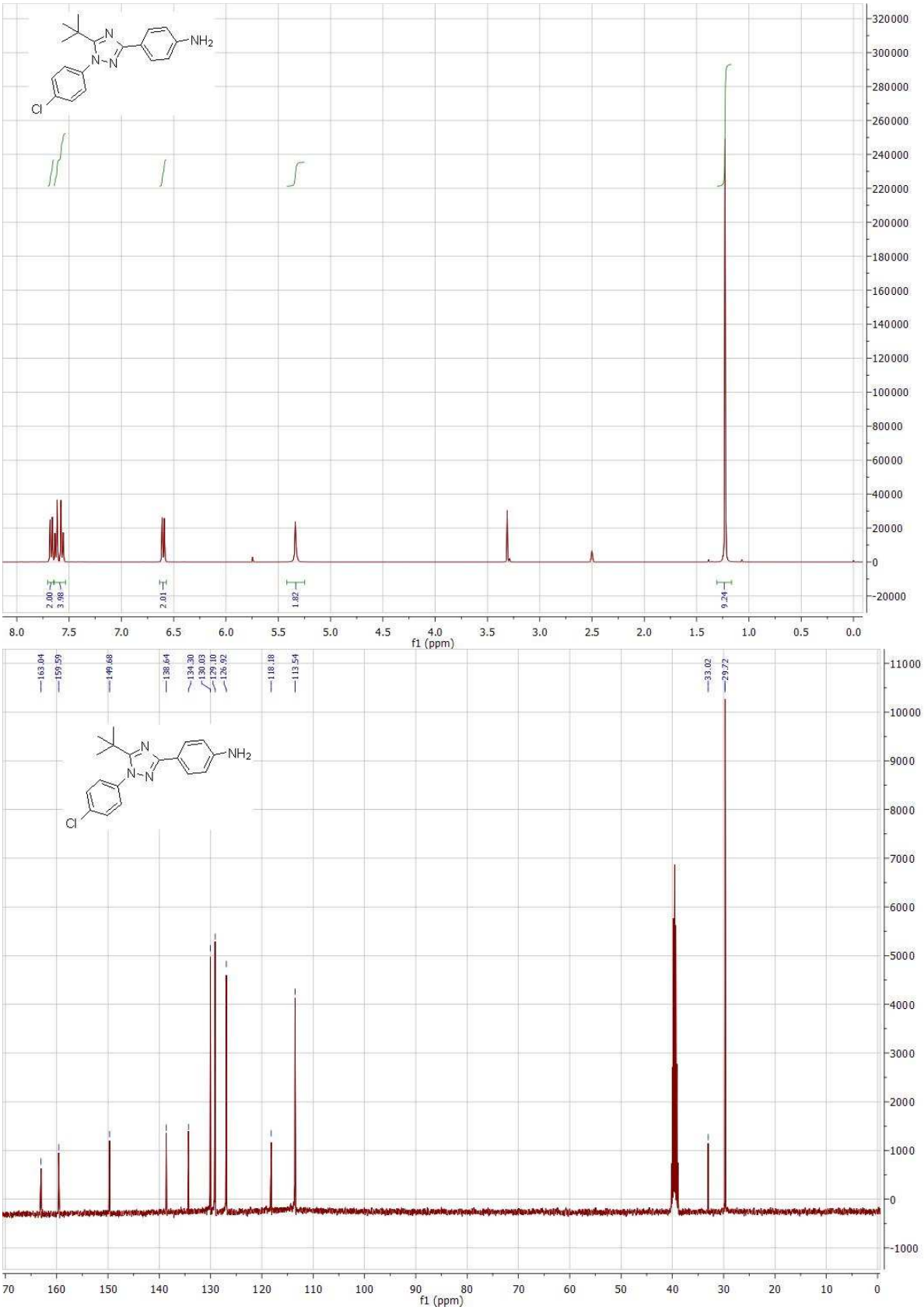

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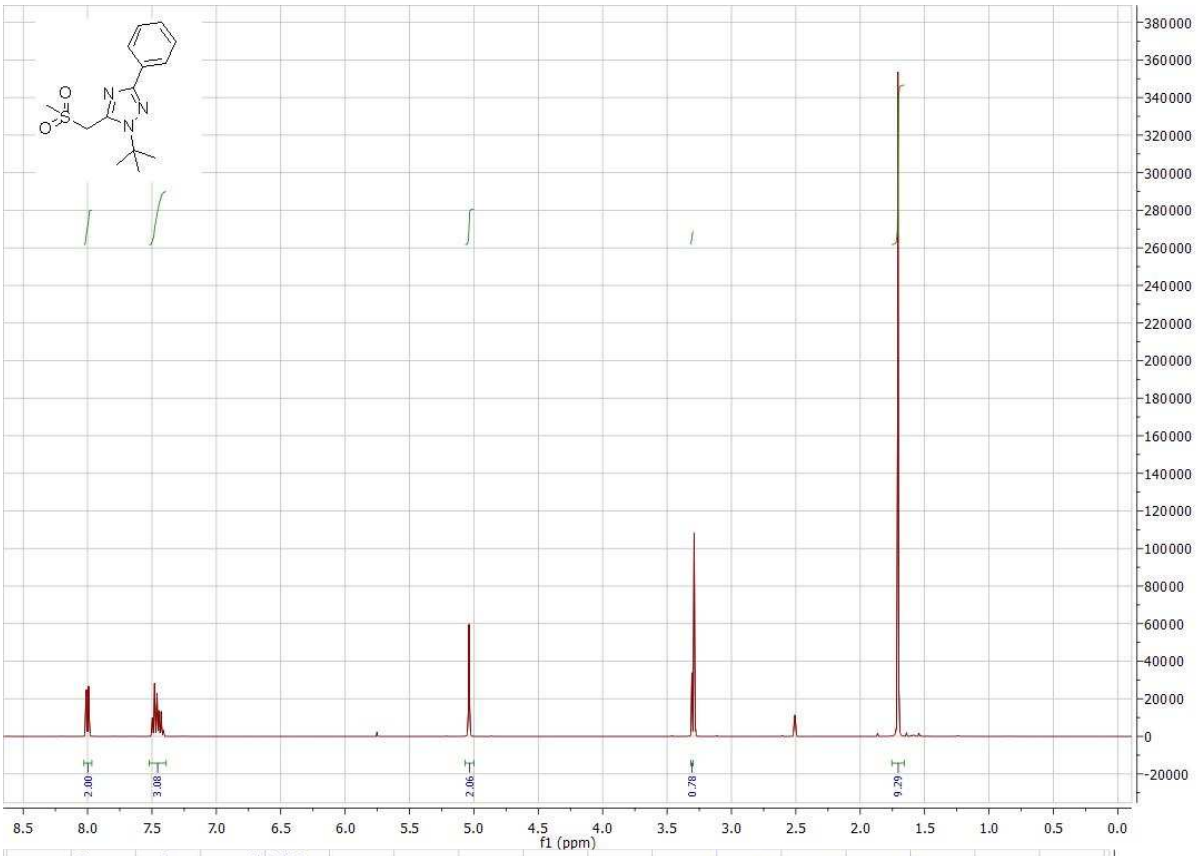

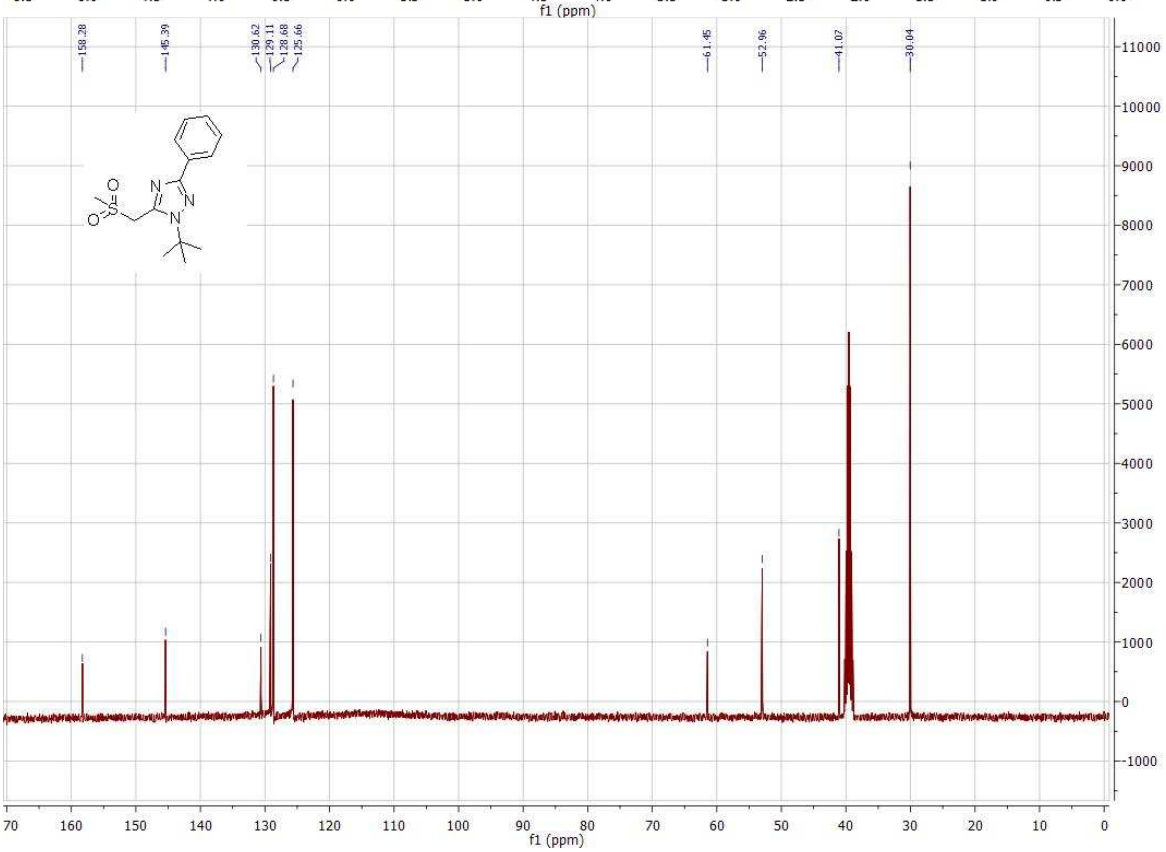

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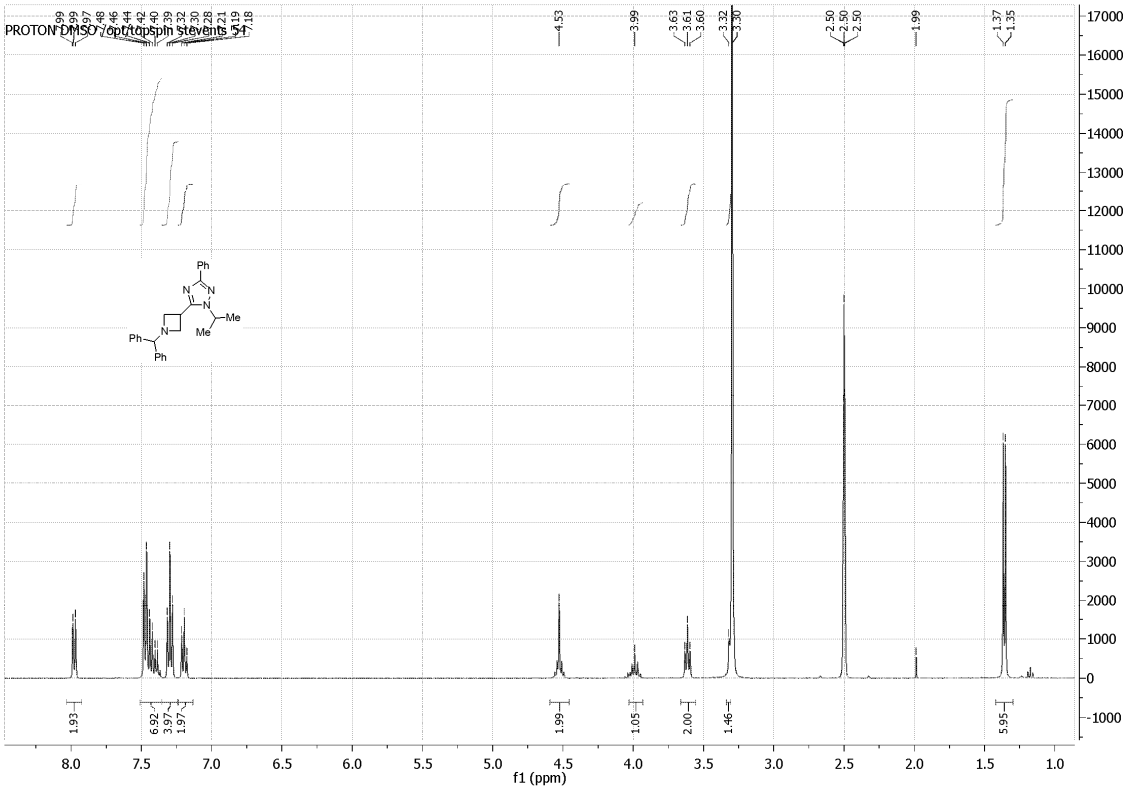

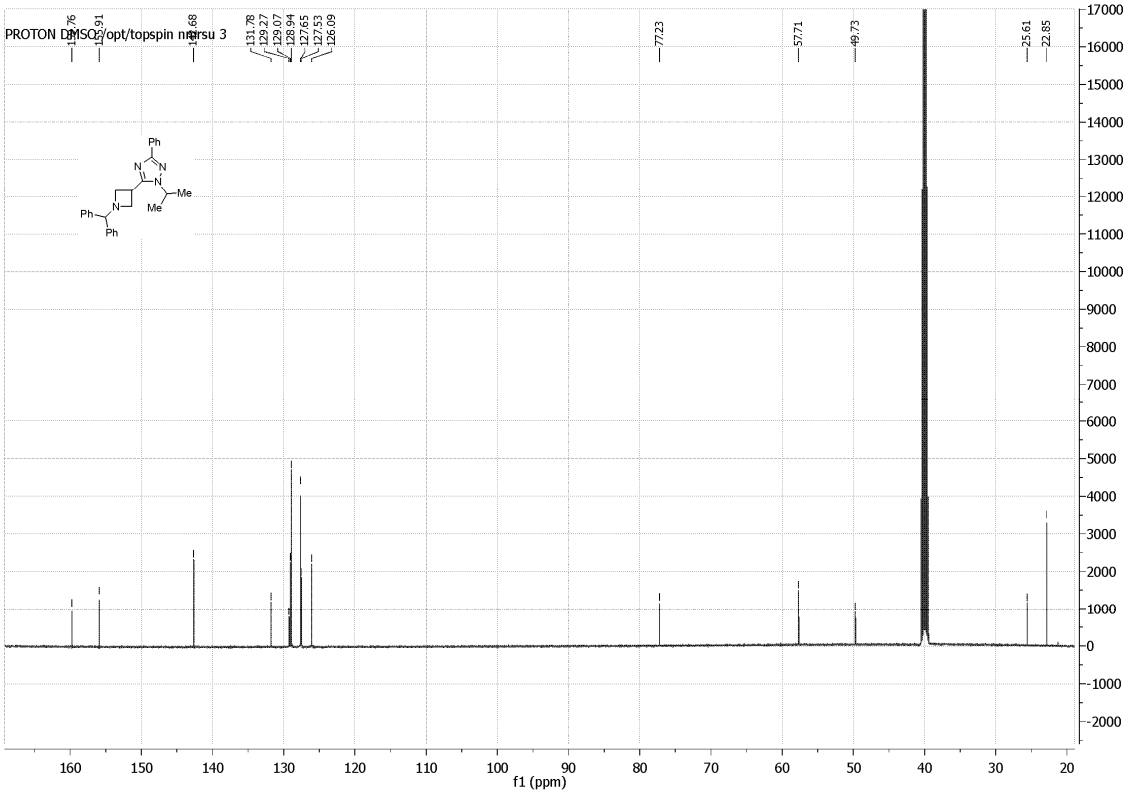

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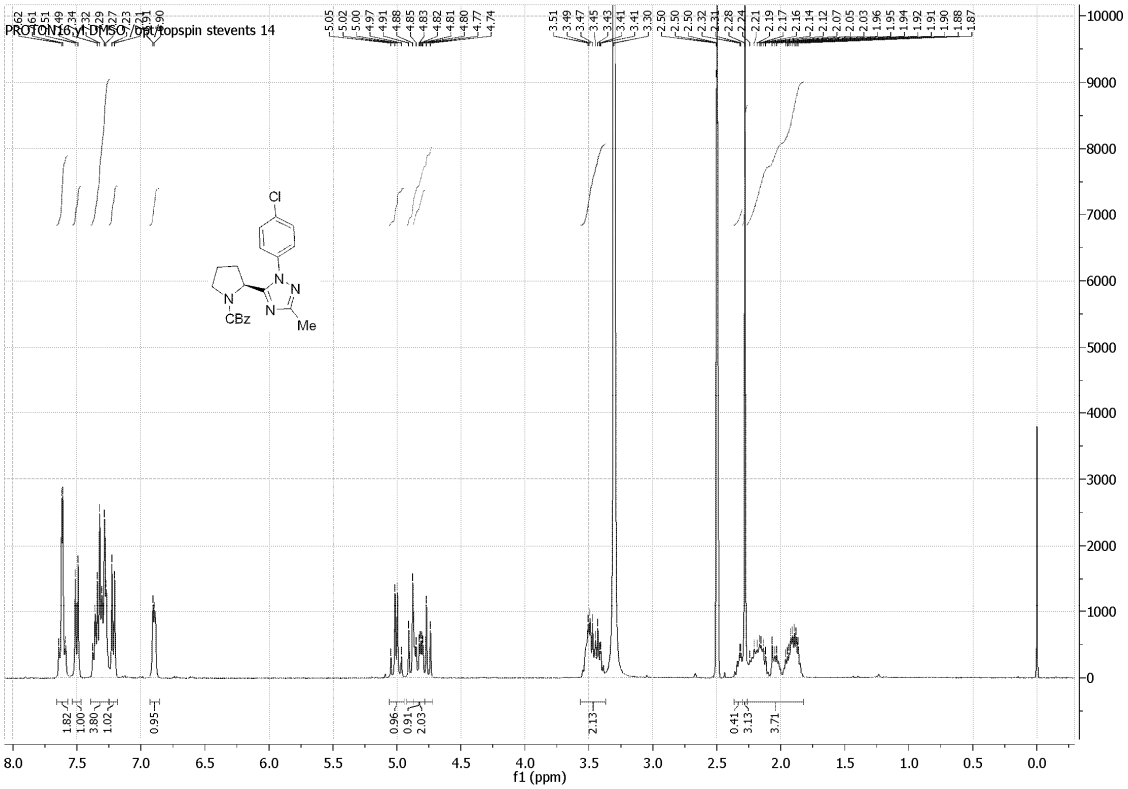

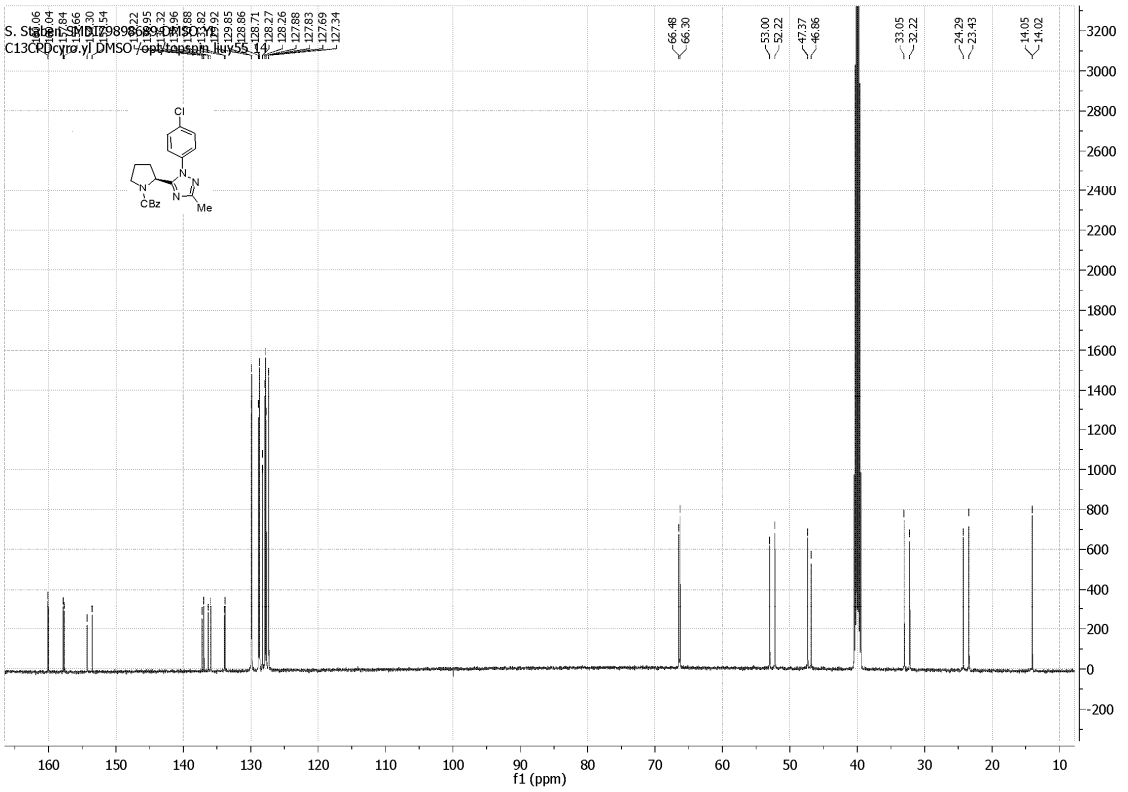

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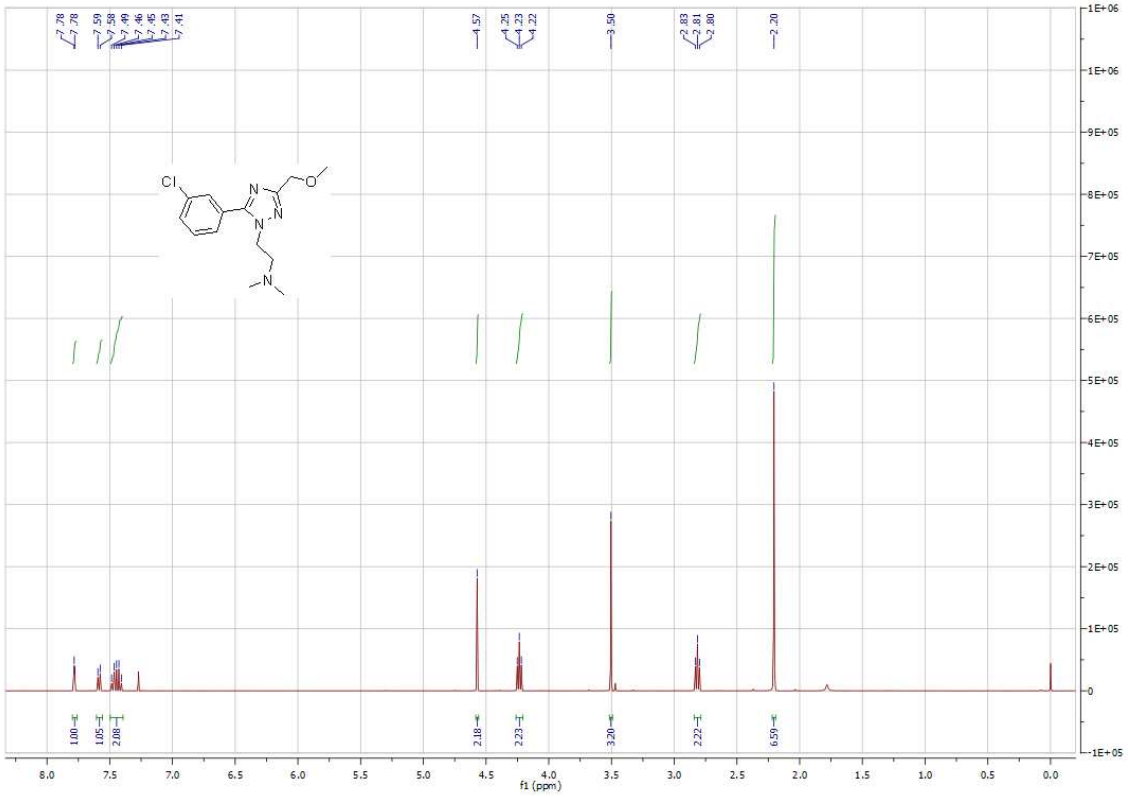

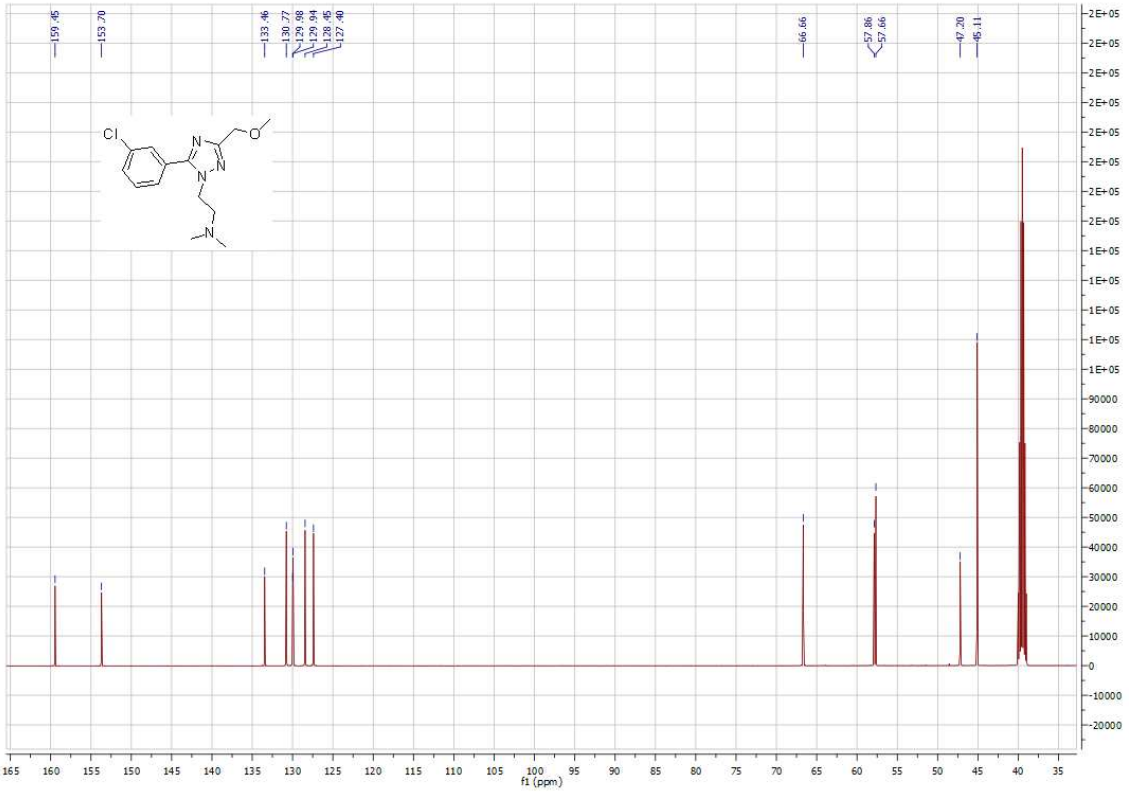

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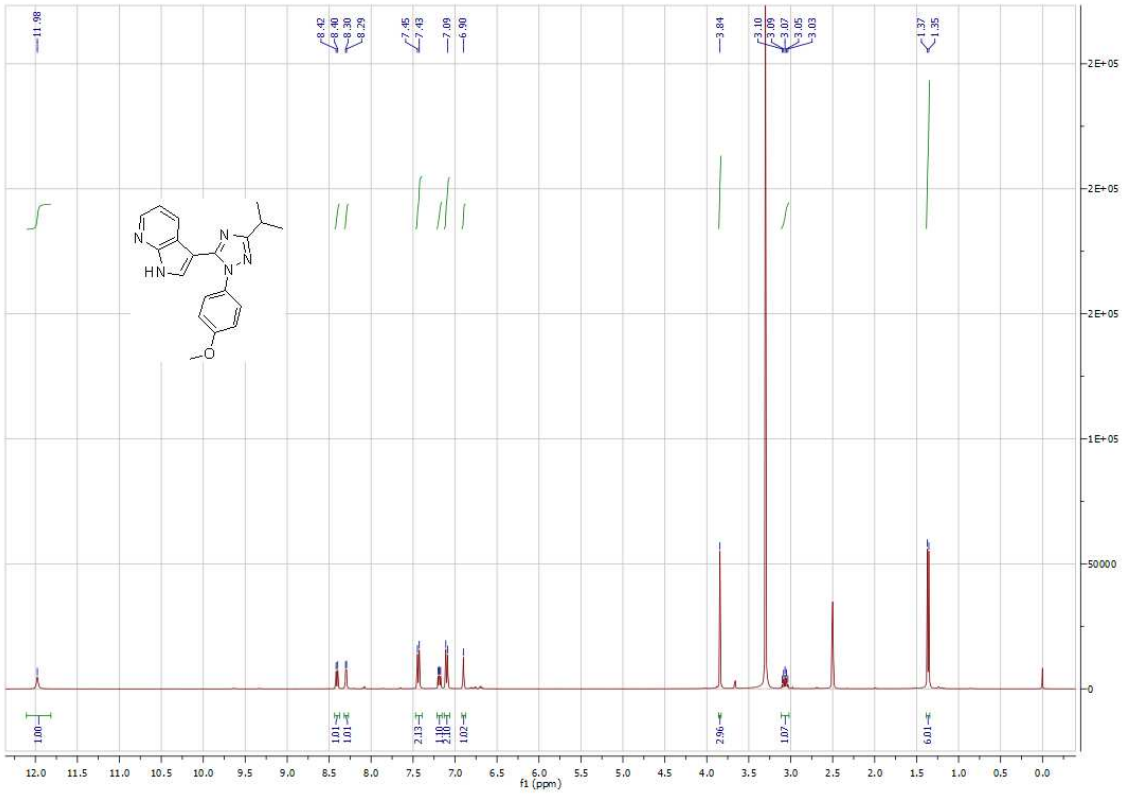

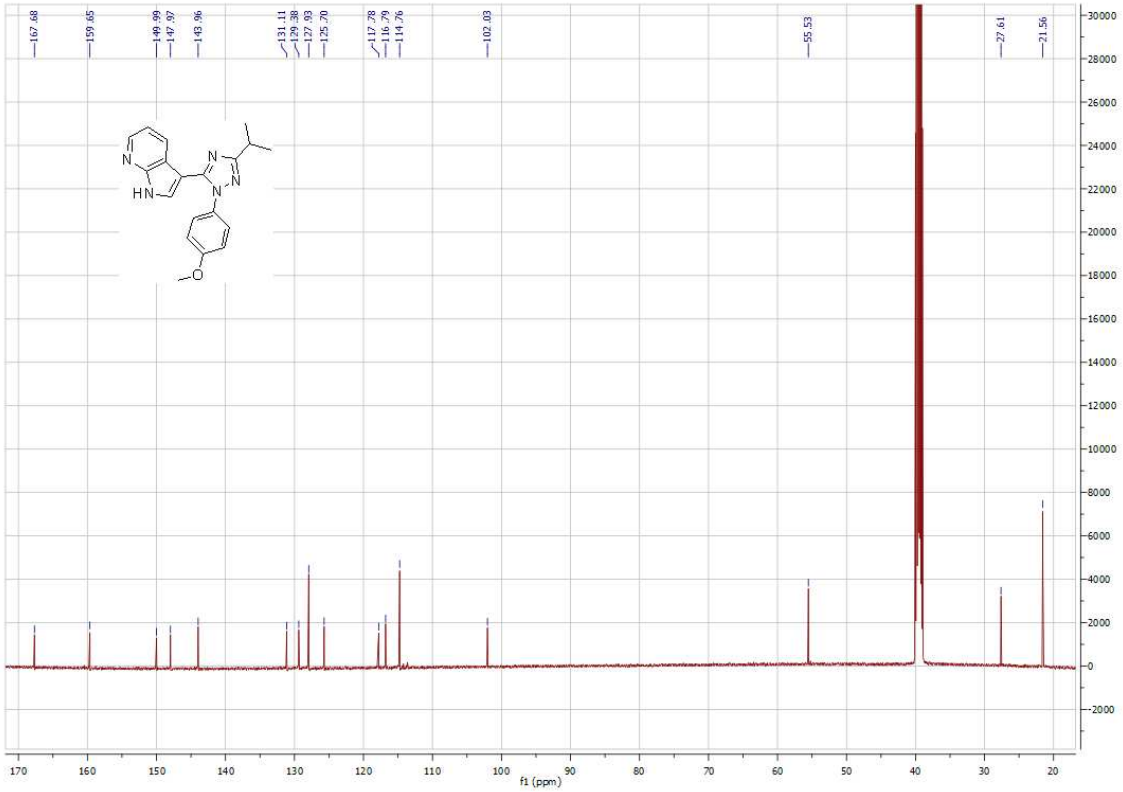

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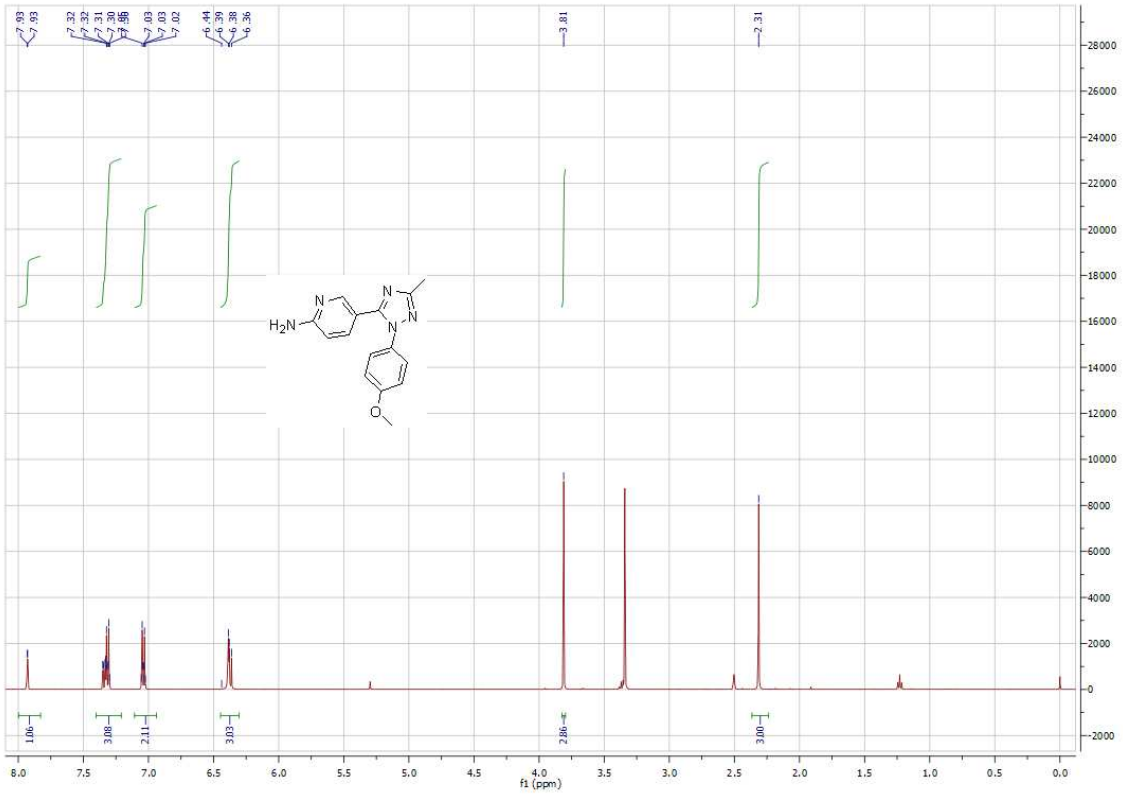

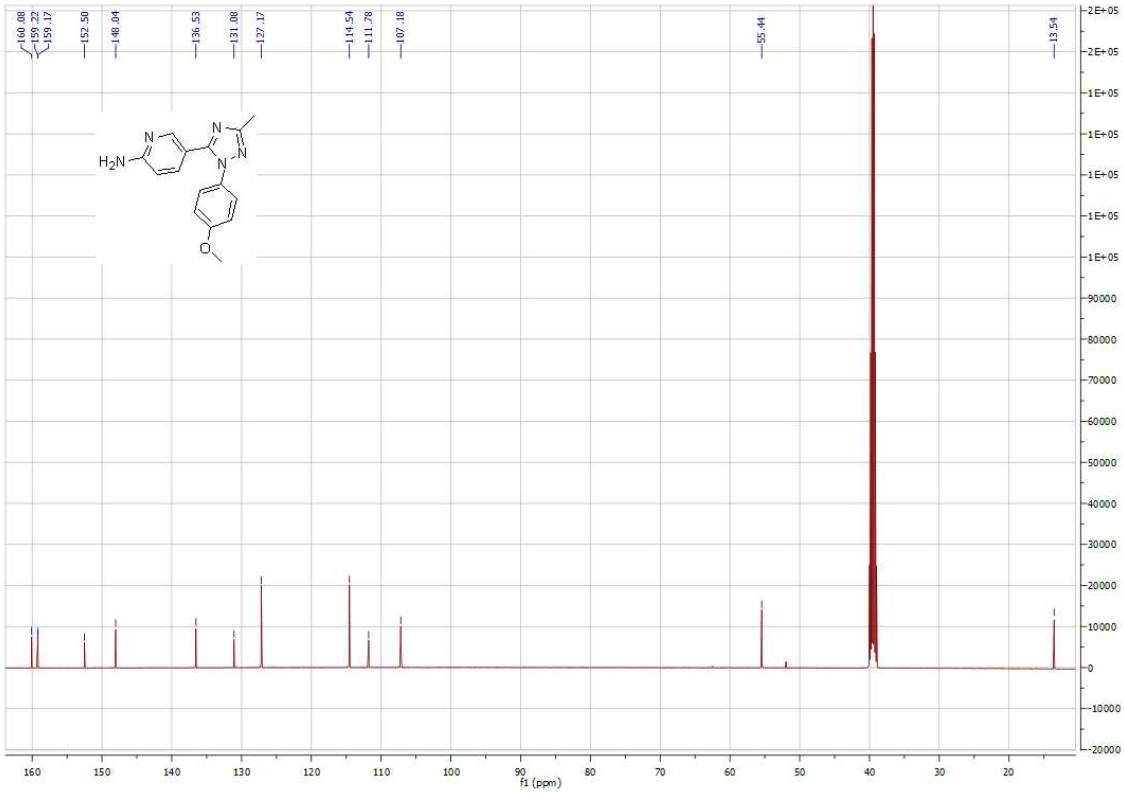

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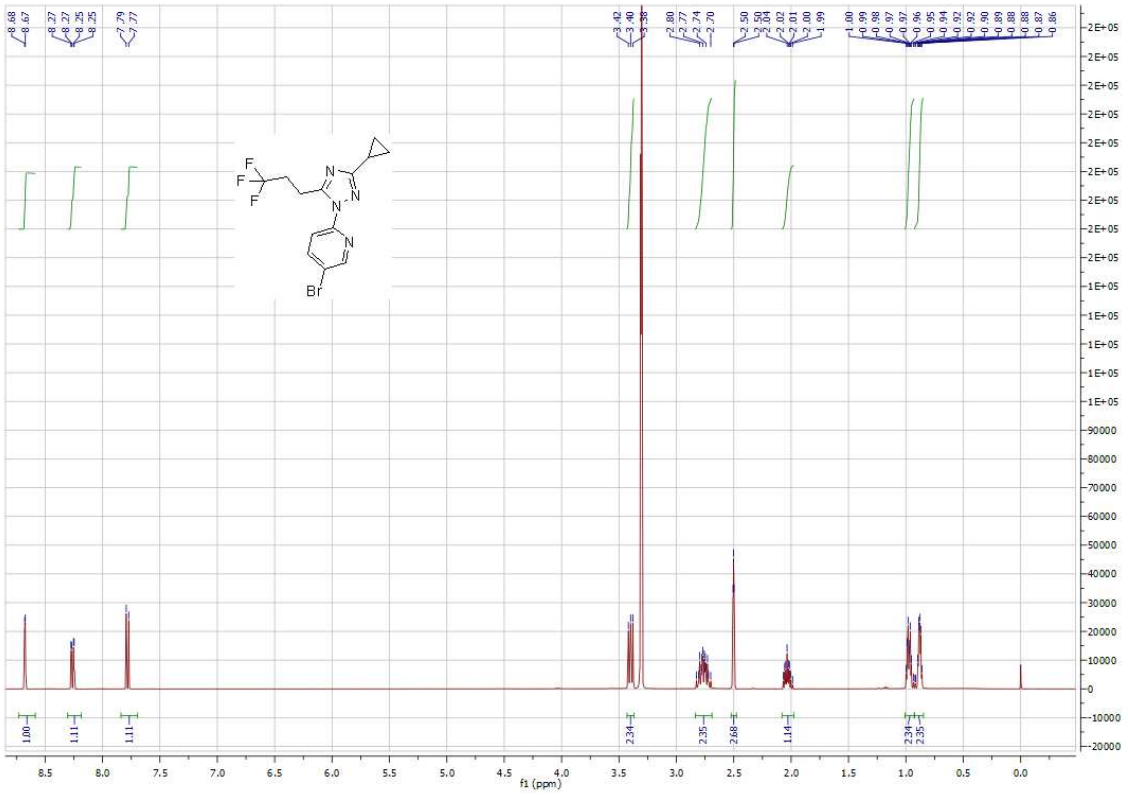
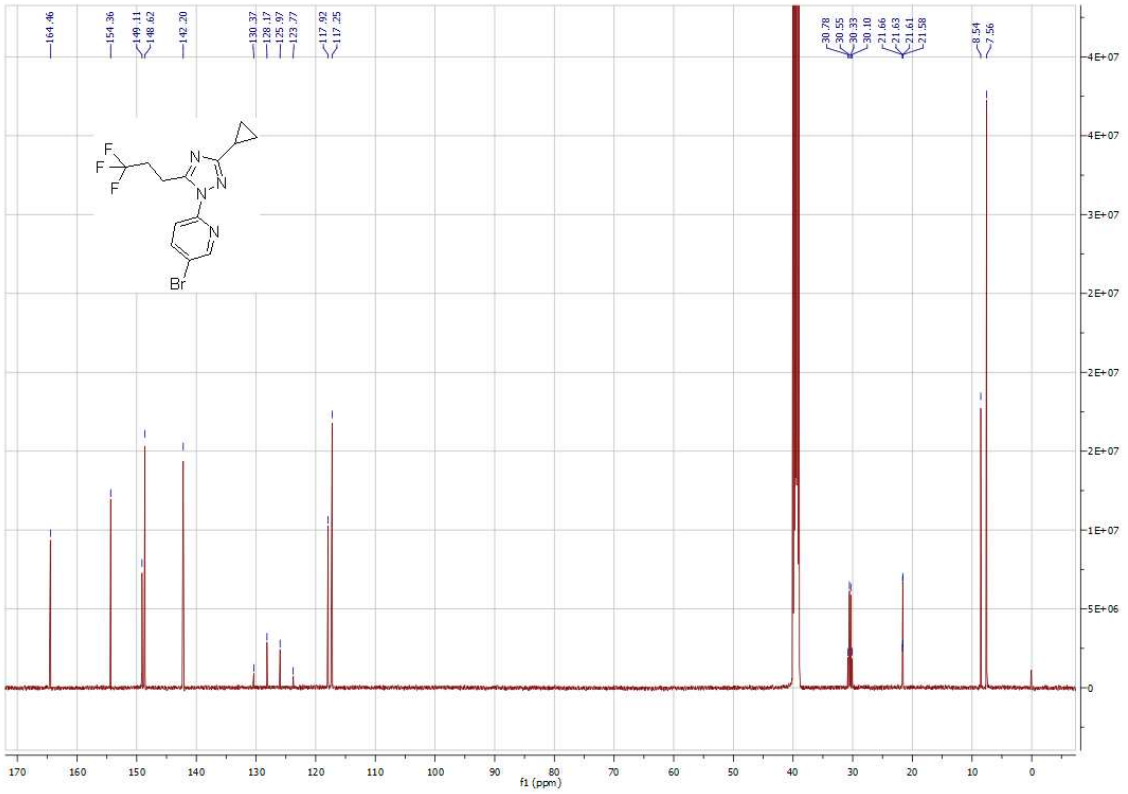
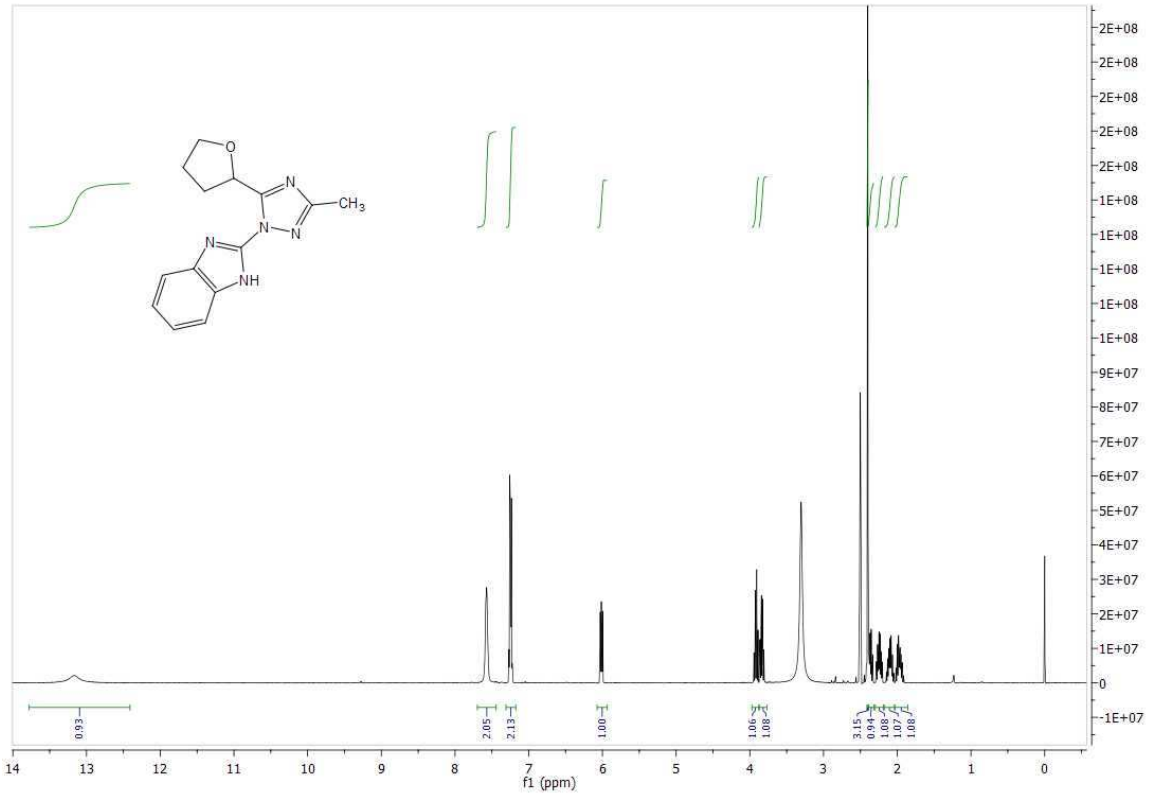
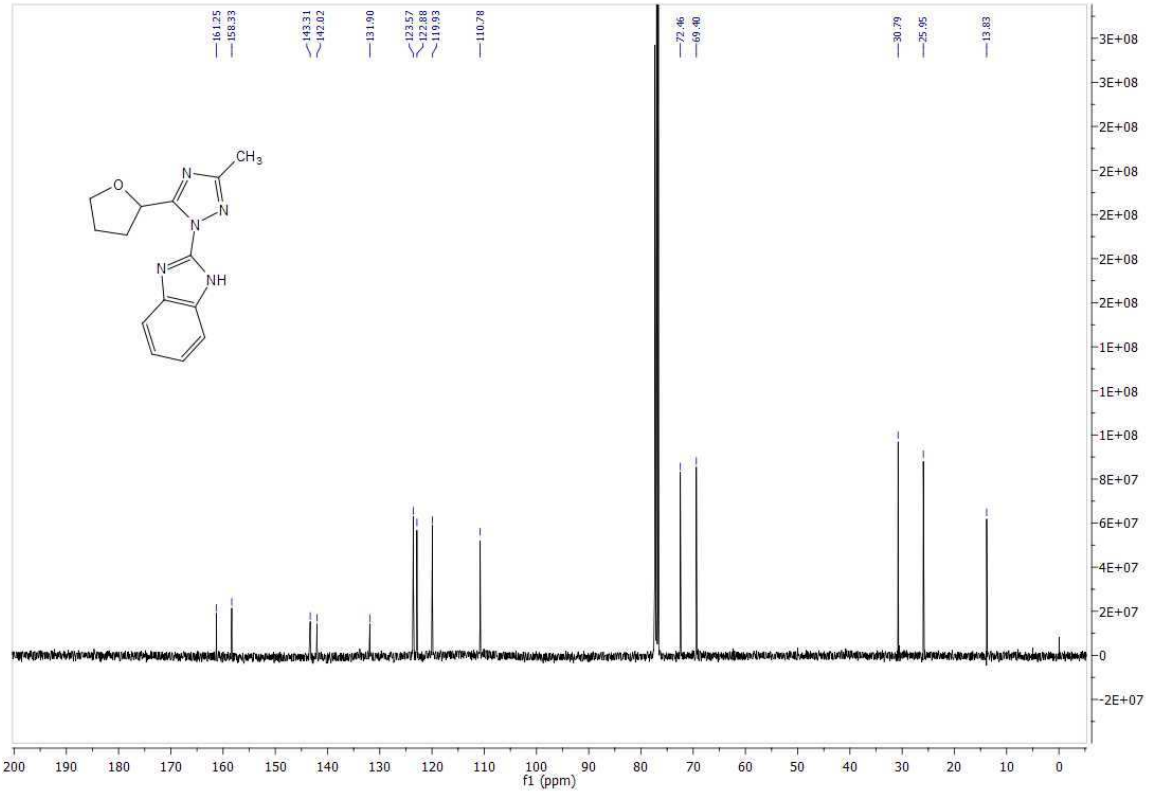


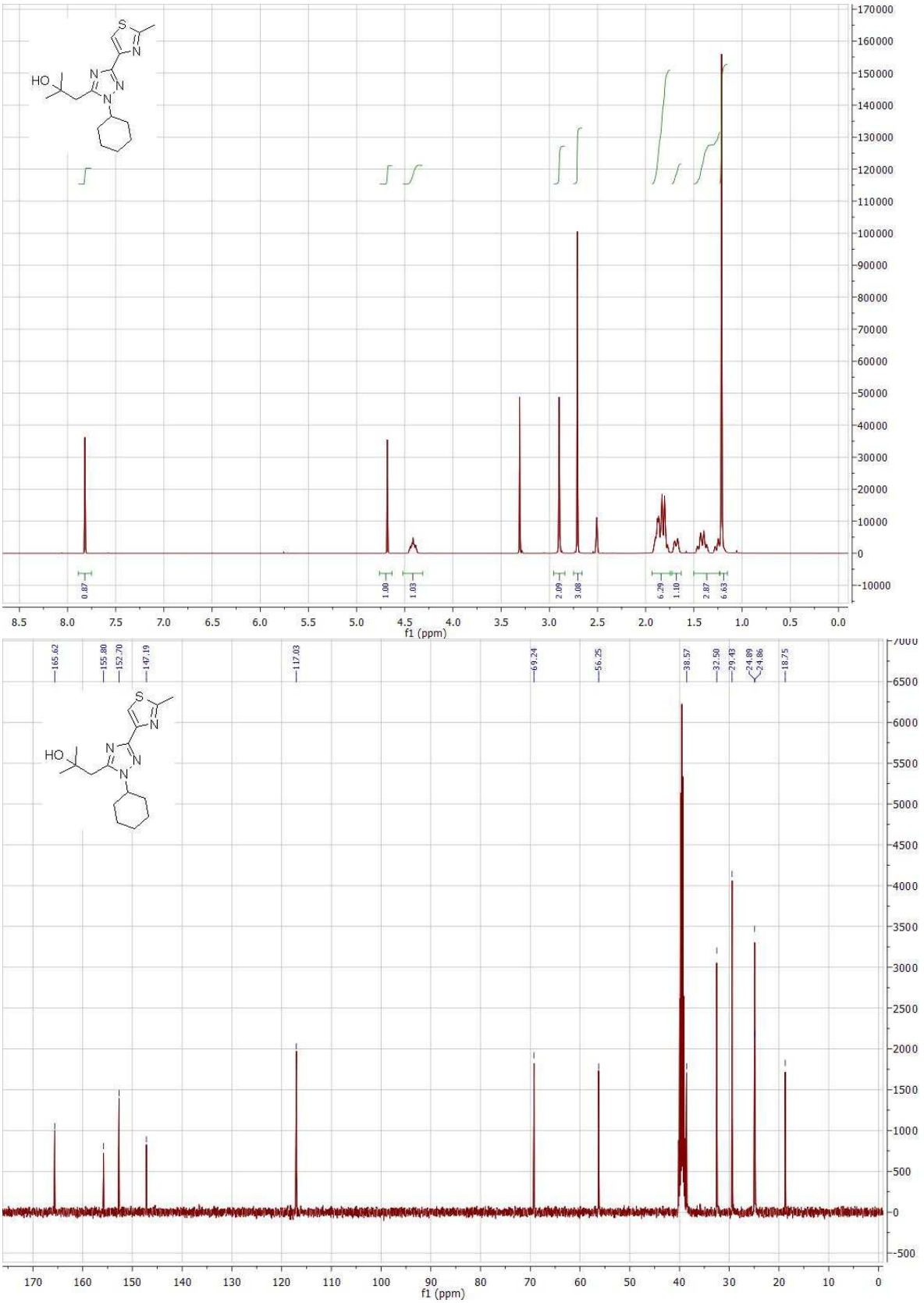


Spectral Data for Compound **20**

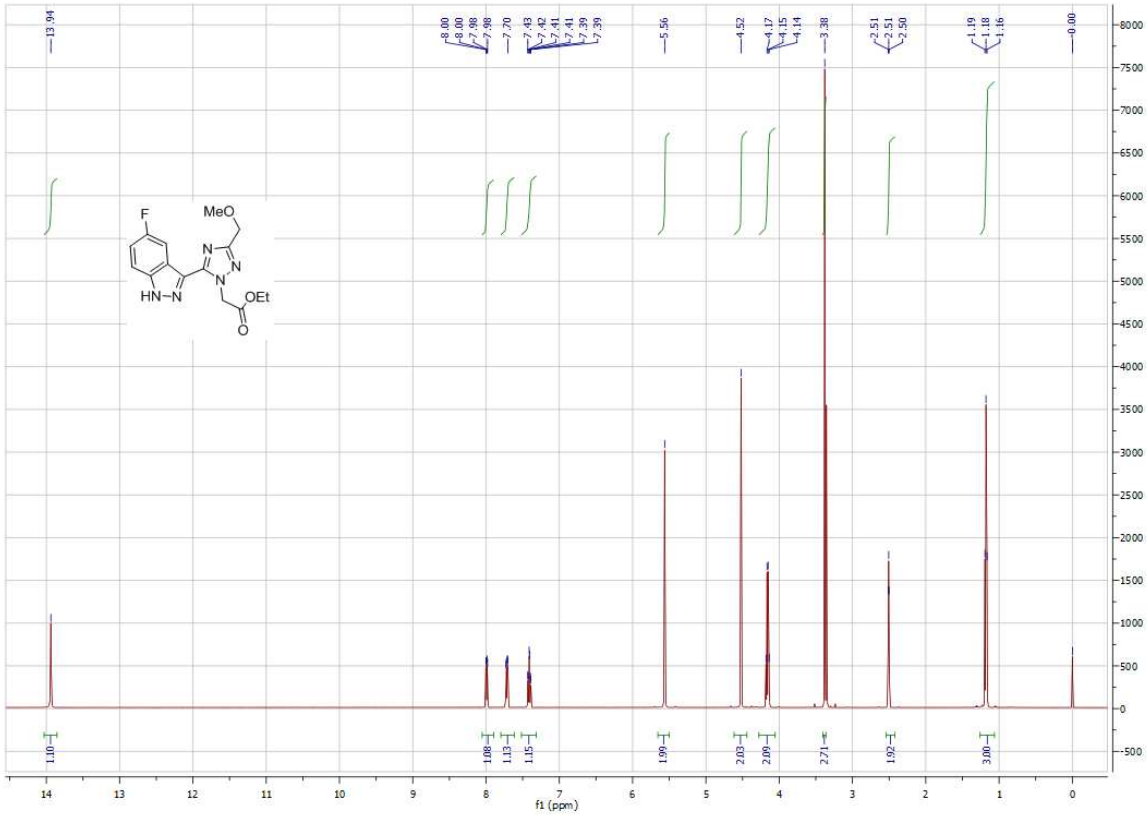


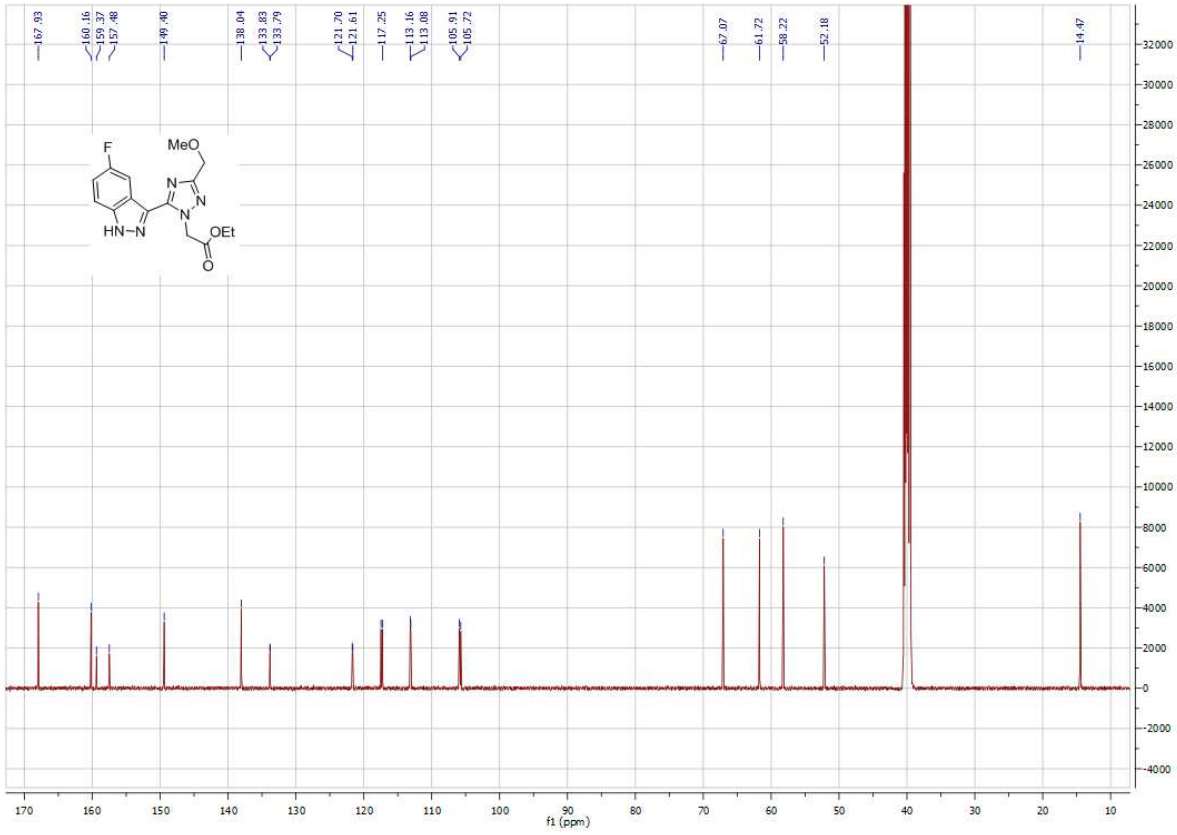


Spectral Data for Compound **21**

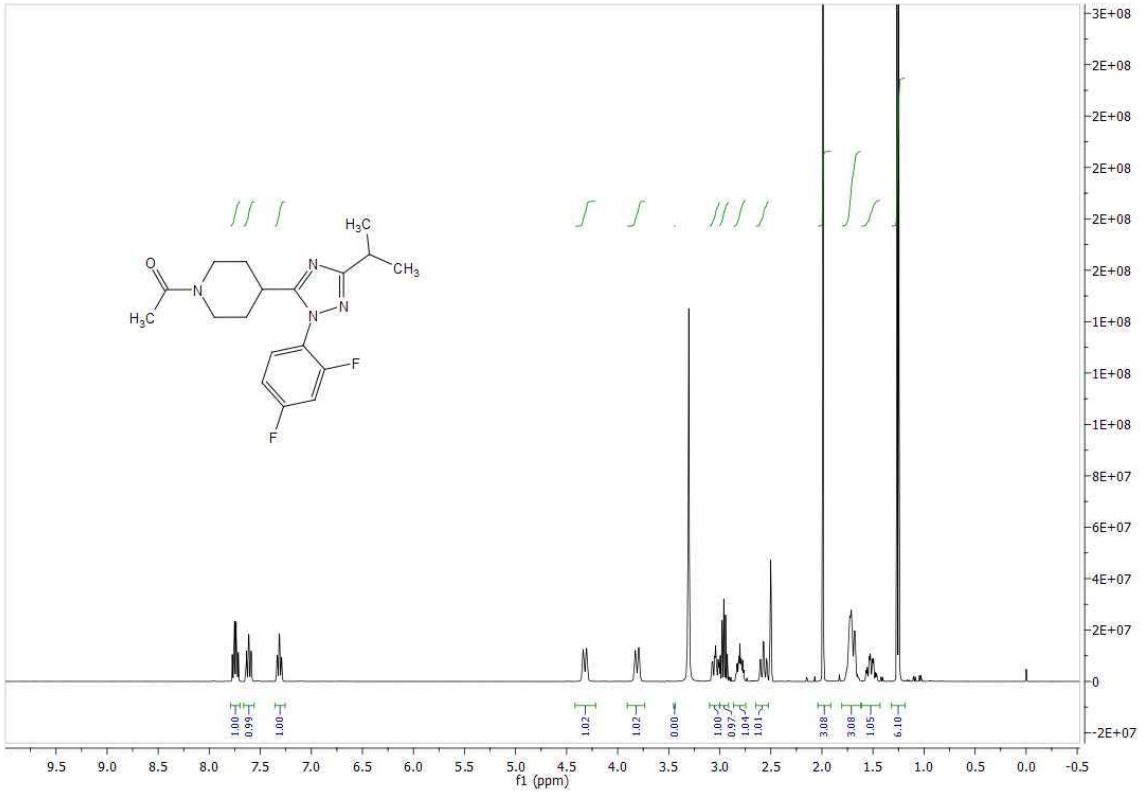


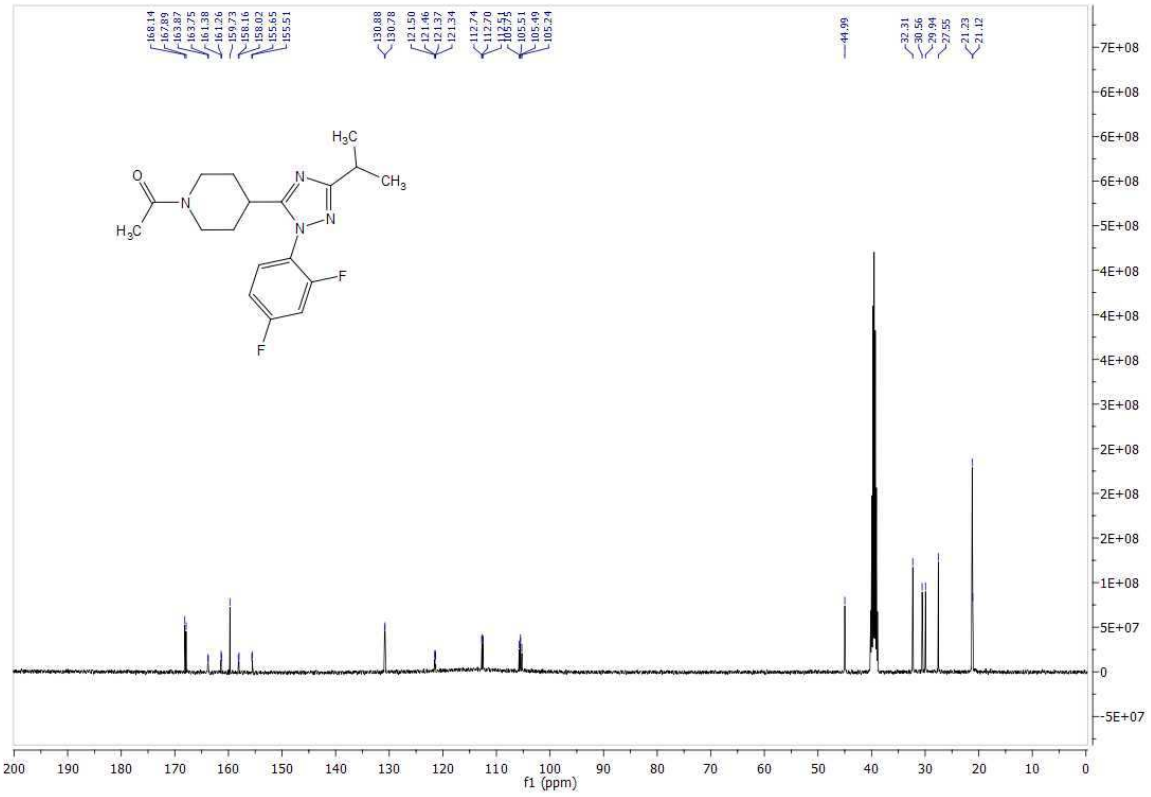
Spectral Data for Compound **22**


F
MeO
N
N
N
HN–N
OEt
O
f1 (ppm)

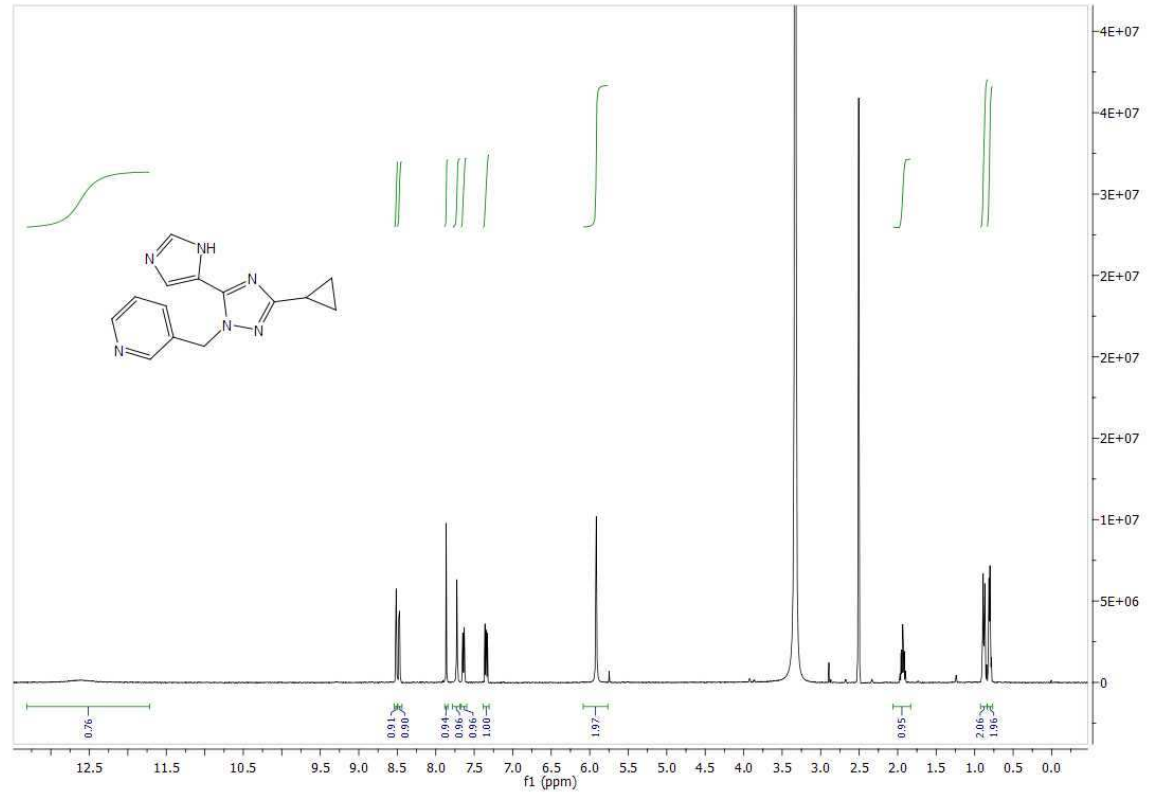

F
MeO
N
N
N
HN–N
OEt
O
f1 (ppm)

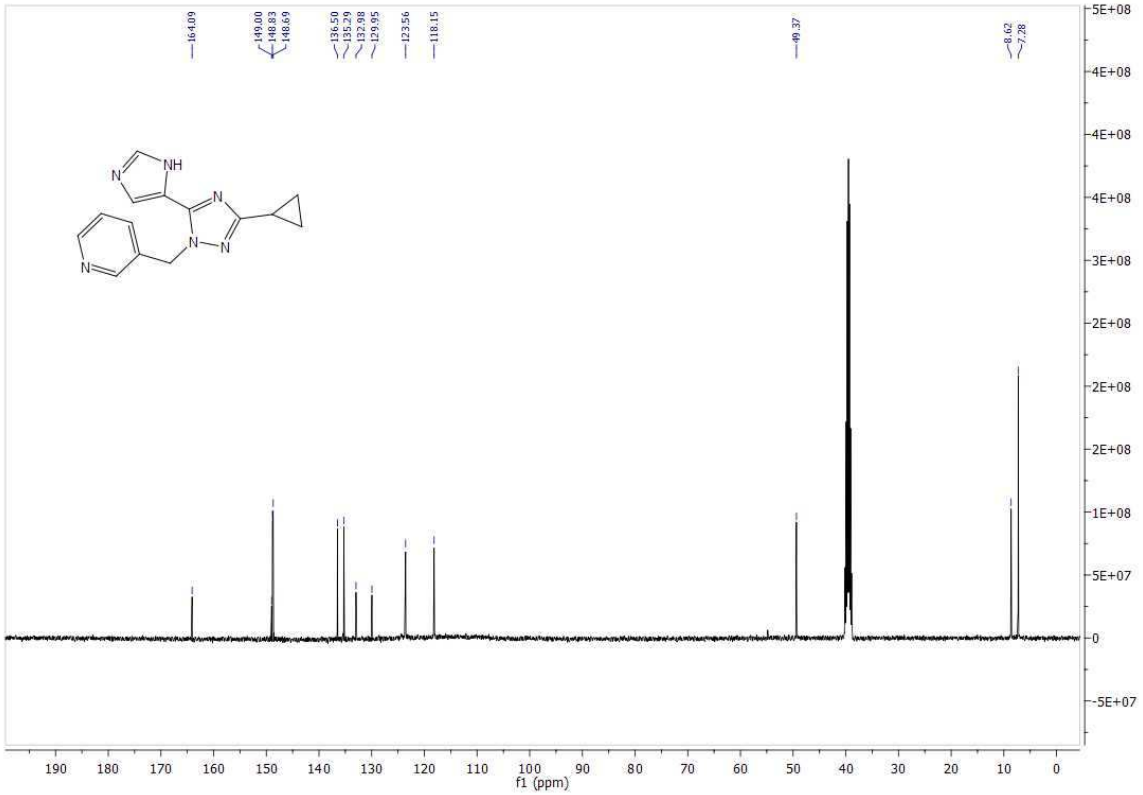
Spectral Data for Compound **24**



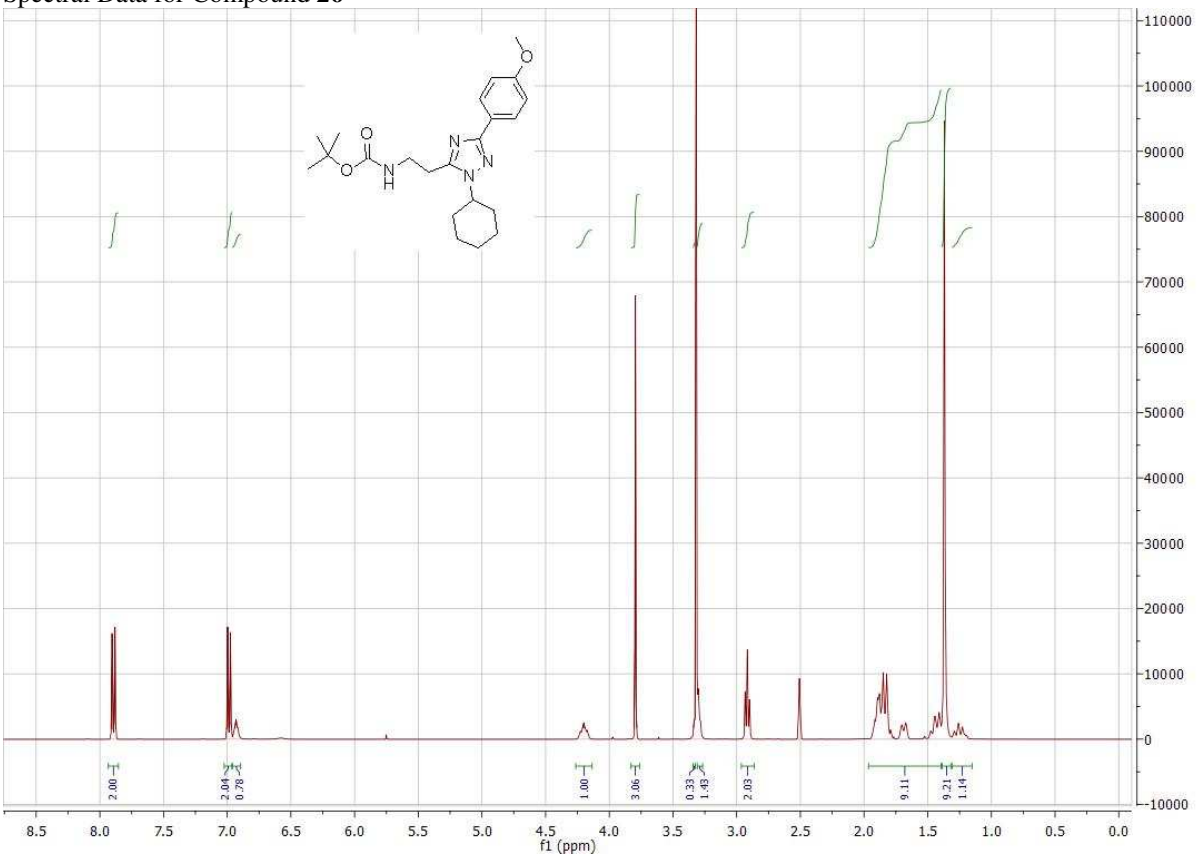


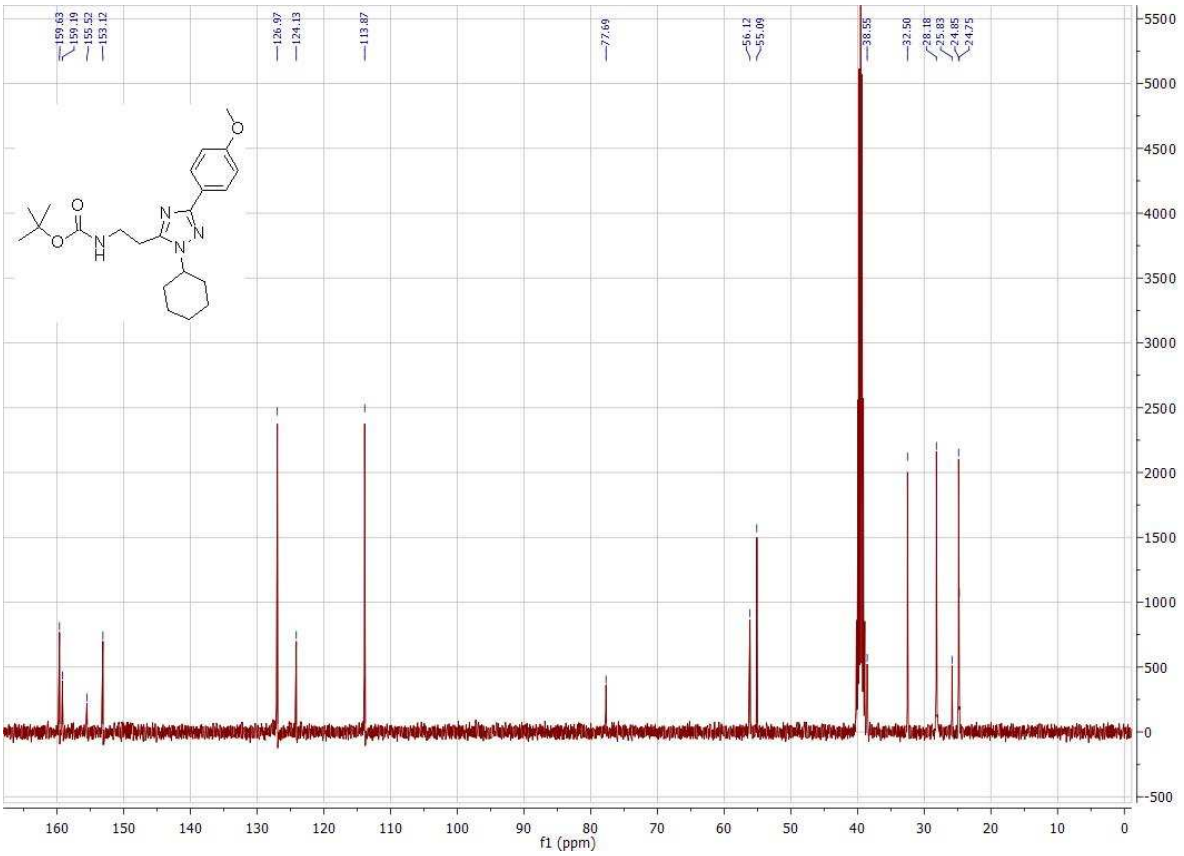
Spectral Data for Compound **25**



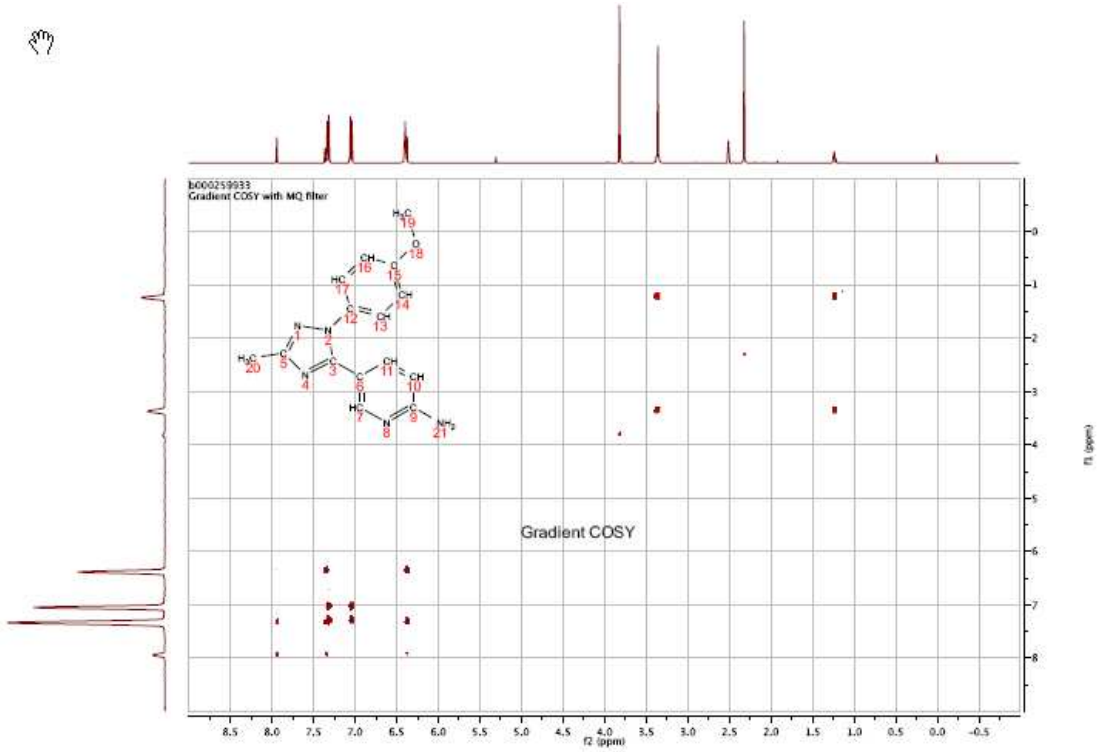


Spectral Data for Compound **26**

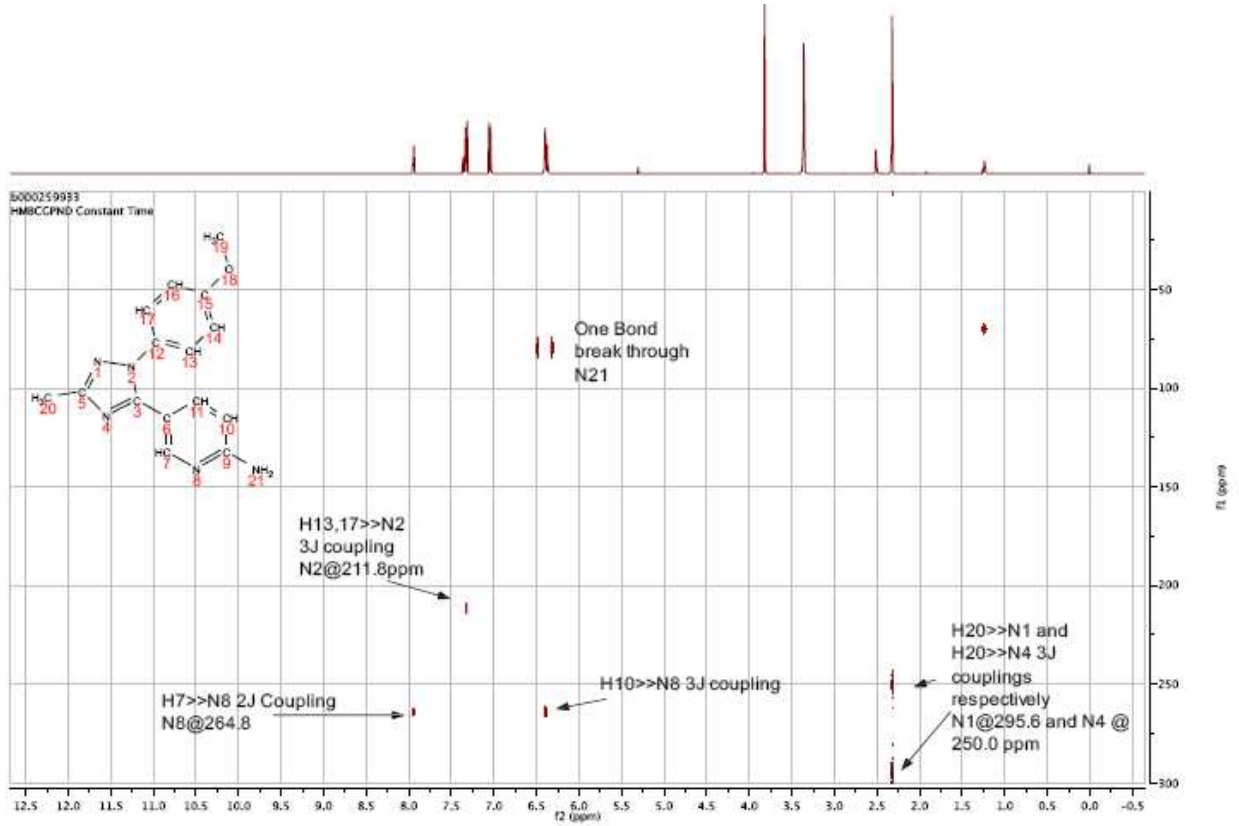




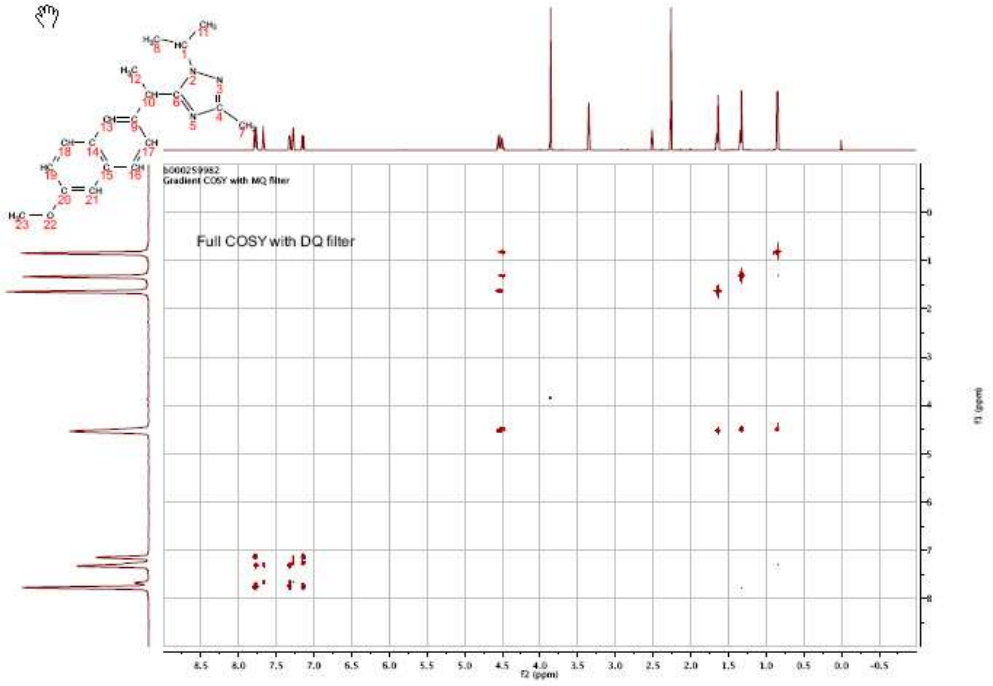
Gradient COSY data for 18.



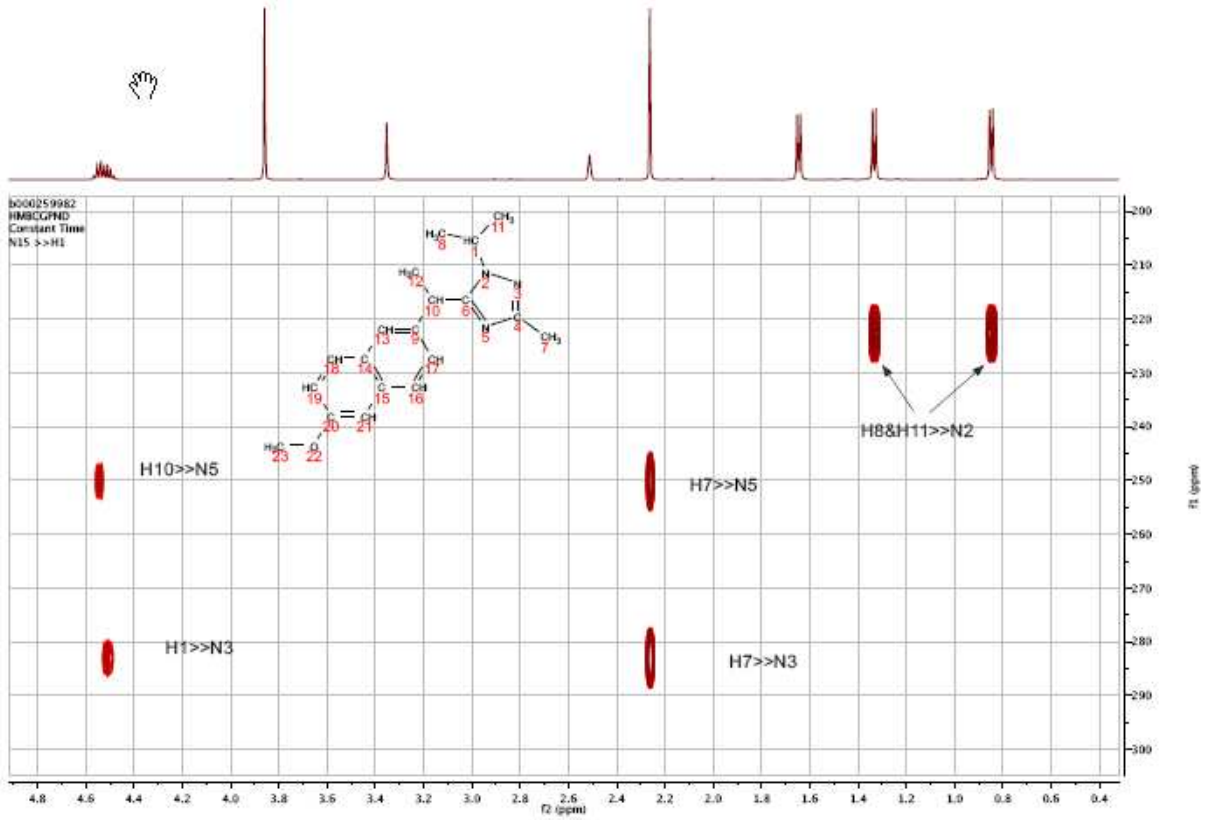
^{15}N HMBC data for 18.



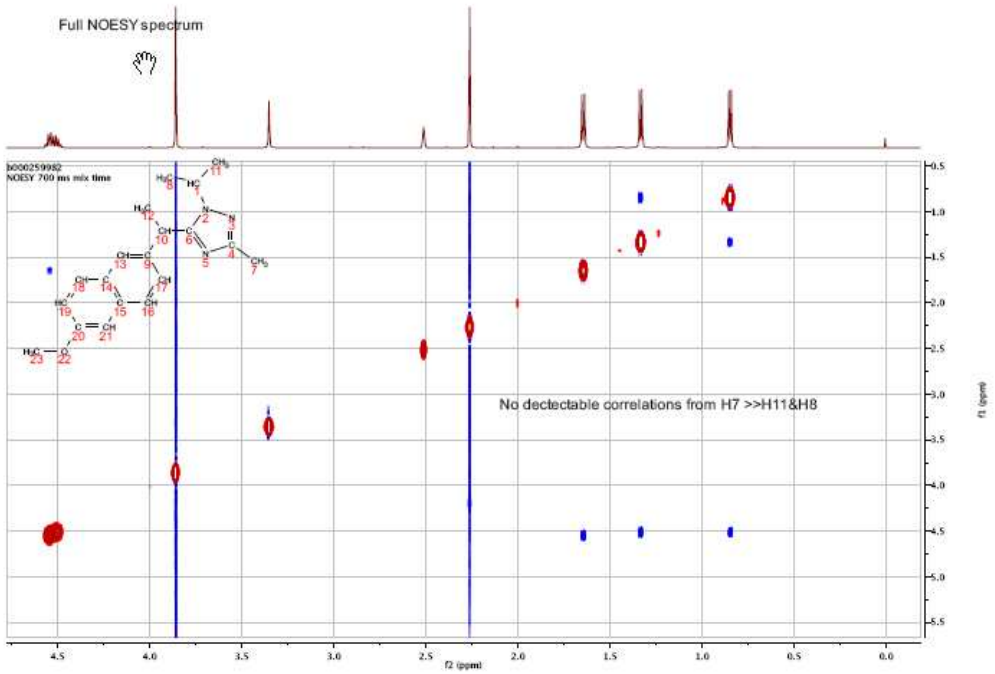
Gradient COSY data for 8.



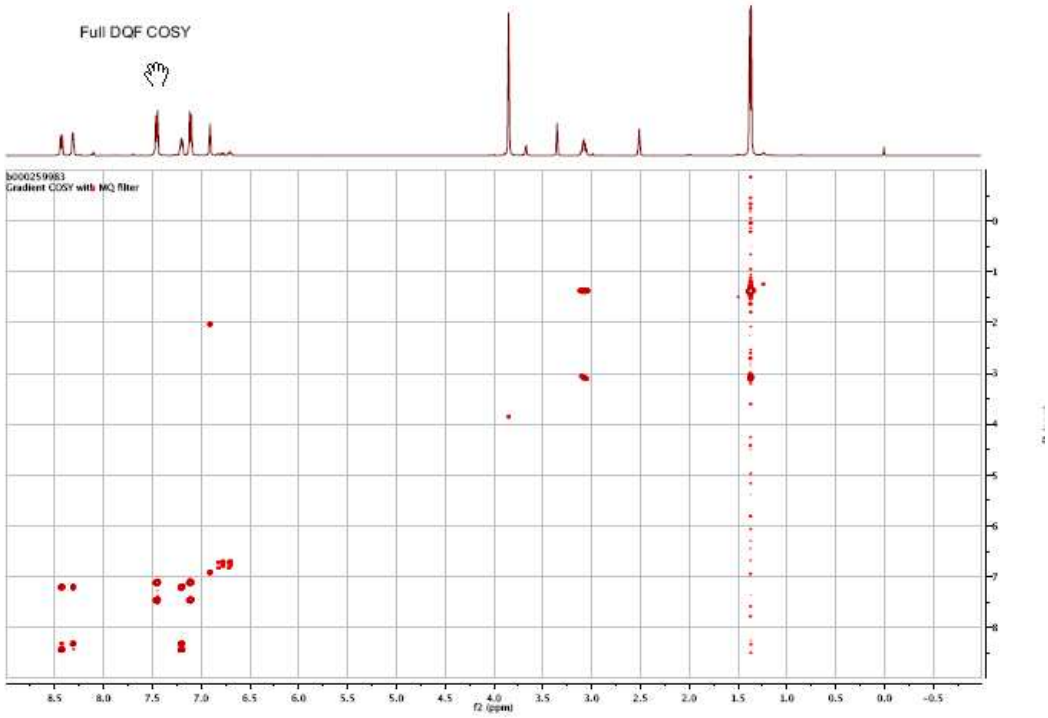
^{15}N HMBC data for 8.



^{1}H nOe data for 8.



Gradient COSY for 17.



^{1}H nOe data for 17.