SUPPORTING INFORMATION

Novel Valdecoxib Derivatives by Ruthenium(II)-Promoted 1,3-Dipolar Cycloaddition of Nitrile Oxides with Alkynes - Synthesis and COX-2 Inhibition Activity.

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Contents

Experimental

Chemistry

All commercial reagents and solvents were used without further purification unless otherwise specified. All solvents were dried by standard methods and distilled under argon. The hydroximoyl chlorides **2a** and **2b** were synthesized according to the literature by the reaction of the corresponding benzaldoximes with N-chlorosuccinimide.[39]

Flash chromatography was conducted using silica gel (mesh size 40−63 μm). Thin-layer chromatography (TLC) was performed on silica gel F-254 aluminium plates. Visualization was carried out using UV (254 nm/366 nm). Analytical HPLC analysis were carried out on an Agilent 1200 system with a C18 column (250 × 4.6 mm, 5 μm) using an isocratic eluent (acetonitrile/water+0.1% TFA 70/30) by a gradient pump with a flow rate of 1 mL/min. The products were monitored by an UV detector at 254 nm. Mass spectrometry was performed with a XevoTQ-S© mass spectrometer by using the electrospray ionization (ESI) mode. Melting points were determined on a melting points apparatus (Galen III) and are uncorrected.

Nuclear magnetic resonance spectra (NMR) were recorded on a 400 MHz (Unity INOVA 400, Varian) or 600 MHz (VNMRS 600, Varian) spectrometer. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 101 MHz, and ^{19}F NMR spectra were recorded at 376 MHz, all of them in $CDCl_3$ $(CD_3)_2SO$ or $CO(CD_3)_2$ solution. NMR spectra were referenced to the residual solvent shifts for ^{1}H and ^{13}C, and to $CFCl_3$ for ^{19}F spectra as internal standards, δ-values are given in ppm.

4-Ethynyl-benzenesulfonamide (1a). To a solution of 4-[(trimethylsilyl)ethynyl]-benzenesulfonamide (**1j**) (70 mg, 0.28 mmol) in THF (2.4 mL), a solution of tetra-N-butylammonium fluoride (TBAF) 1M in THF was added (0.16 mL, 0.135 mmol) and the mixture was stirred for 1 h at r.t. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, PE:AcOEt 6:4) to provide the compound **1a** as a white solid (45 mg). Yield: 90%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.89 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 4.81 (s, 2H), 3.25 (s, 1H). ^{13}C NMR ($CDCl_3$, δ, ppm) 143.4, 132.6 (2C), 125.9, 125.7 (2C), 82.3, 81.4.

1-Ethynyl-4-(methylsulfonyl)benzene (1b). To a solution of trimethyl{[4-(methylsulfonyl)phenyl]ethynyl}silane (**1k**) (536.8 mg, 2.13 mmol) in THF (18.8 mL), was added a solution of TBAF 1M in THF (1.0 mL, 1.0 mmol) and the mixture was stirred for 1 h at r.t. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, PE:AcOEt 6:4) to provide the compound **1b** as a white solid (326 mg). Yield: 85%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.91 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 3.29 (s, 1H), 3.05 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 140.7, 133.3 (2C), 127.9 (2C), 127.7, 82.3, 81.4, 47.7.

4-(Prop-1-yn-1-yl)benzenesulfonamide (1c). Trimethylsilylacetylene (0.29 mL, 1.91 mmol) was dissolved in THF (0.8 mL) and cooled at -78°C. n-BuLi 2.5 M in hexane (0.83 mL, 2.10 mmol) was added dropwise and stirred for 30 min at -78°C. Methyl iodide (0.13 mL, 2.10 mmol) was added to the reaction dropwise. The resulting mixture was warmed to r.t. over 1 h. This solution was added over a mixture of 4-bromobenzenesulfonamide (300.0 mg, 1.27 mmol), CuI (72.6 mg, 0.38 mmol, 0.3 eq.), $Pd(PPh_3)_2Cl_2$ (89.2 mg, 0.13 mmol, 0.1 eq.), $Pd(PPh_3)_4$ (146.8 mg, 0.13 mmol, 0.1 eq.), TBAF 1M in THF (1.3 mL, 1.3 mmol) and Et_3N (5.8 mL) in DMF (27 mL) in a sealed tube. The reaction mixture was degassed, then heated at 65°C and allowed to stir at this temperature for 18 h. The reaction mixture was then cooled and passed through a plug of silica gel. Water was added and the layers were separated. The organic phase was washed with water (3 x 15mL), dried with Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (silica gel, PE:AcOEt 7:3) to provide the compound **1c** as a white solid (126 mg). Yield: 51%. ^{1}H NMR (DMSO-d_6, δ, ppm) 7.77 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.40 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 143.4, 132.6 (2C), 125.9, 125.7 (2C), 85.7, 79.8, 4.8.

1-(Methylsulfonyl)-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene (1d). To a suspension of Zn dust (295.6 mg) in anhydrous DMF (1 mL) under nitrogen atmosphere, a solution of 1,1,1-trichloro-2,2,2-trifluoroethane (947.9 mg, 5.06 mmol) in DMF (0.8 mL) was dropwise slowly added. The reaction mixture was stirred at 50°C for 2 h., then a solution of 4-methylthiobenzaldehyde (0.44 mL, 3.28 mmol) in DMF (1.2 mL) was added dropwise and the reaction mixture was allowed to react at 50°C overnight. Acetic anhydride (0.34 mL) and Zn dust (230 mg) were added and the mixture was stirred at 50°C for 4 h., then diluted with water, acidified with diluted HCl and extracted with dichloromethane. The organic phase was washed with water, dried with Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography (silica gel, PE:AcOEt 9:1) to provide the intermediate product *1-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-4-(methylsulfanyl)-benzene* as a colourless oil (364 mg). Yield: 44%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.66 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.22 (s, 1H, *E* isomer), 7.21 (s, 1H, *Z* isomer), 2.52 (s, 3H).^{19}F NMR ($CDCl_3$, δ, ppm) -61.49 (*Z* isomer), -68.56 (*E* isomer).

To a stirred solution of *1-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-4-(methylsulfanyl)benzene* (364 mg, 1.44 mmol) in DMSO (2 mL) was added finely powdered KOH (97.0 mg, 1.73 mmol). The mixture was stirred at r.t. overnight, then diluted with water, and extracted with Et_2O. The organic phase was washed with water and dried with Na_2SO_4. The solvent was evaporated and the crude mixture was purified via flash column chromatography (silica gel, PE) to provide *methyl-(4-[3,3,3-trifluoroprop-1-yn-1-yl]-phenyl)-sulfane* as a white solid (244 mg). Yield: 78%.

^{1}H NMR ($CDCl_3$, δ, ppm) 7.45 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 2.50 (s, 3H).^{19}F NMR ($CDCl_3$, δ, ppm) -49.66.

Methyl-(4-[3,3,3-trifluoroprop-1-yn-1-yl]phenyl)-sulfane (150 mg, 0.71 mmol) was dissolved in a mixture MeOH:H_2O 1:1 (4,2 mL) and water (1.9 mL). Oxone was added and the mixture was stirred at r.t. for 2 hours. After addition of water and extraction with AcOEt, the organic layer was passed through a silica gel plug. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, PE:AcOEt 7:3) to afford the compound ***1d*** as a white solid (167 mg). Yield: 95%. ^{1}H NMR ($CDCl_3$, δ, ppm) 8.00 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 3.08 (s, 3H).^{19}F NMR ($CDCl_3$, δ, ppm) -50.52. ^{13}C NMR ($CDCl_3$, δ, ppm) 140.7, 133.3 (2C), 127.9 (2C), 127.7, 108.4, 86.8, 80.9, 47.7.

1-(Chloroethynyl)-4-(methylsulfonyl)-benzene (1e). A dry reaction vial was charged with K_2CO_3 (88.6 mg, 0.64 mmol), NCS (342.3 mg, 2.56 mmol) and Ag_2CO_3 (35.3 mg, 0.13 mmol). The vial was sealed, evacuated and backfilled with argon. Then, n-BuOH (2.6 mL) and 1-ethynyl-4-(methylsulfonyl)-benzene (**1b**) (231.0 mg, 1.28 mmol) were added to the system and the mixture was stirred at 50°C for 4 hours. The mixture was allowed to cool to rt and then brine was added at 0°C. The resulting mixture was extracted with Et_2O (3 x 15 mL) and the combined organic phases were washed with a large amount of water and dried with Na_2SO_4. The solvent was removed under reduced pressure and purified by column chromatography on silica gel (PE:AcOEt 7:3) to give the product **1e** as a white solid (70.0 mg). Yield: 25%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.90 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 3.05 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 140.7, 133.3 (2C), 127.9 (2C), 127.7, 88.0, 83.7, 47.7.

3-[4-(Methylsulfonyl)phenyl]prop-2-ynal (1f). CuI (8.1 mg, 0.042 mmol, 0.05 eq.) was added to a mixture of $Pd(PPh_3)_2Cl_2$ (59.7 mg, 0.085 mmol, 0,1 eq.) and 1-bromo-4-(methylsulfonyl)benzene (200 mg, 0.85 mmol) in Et_2NH (5 mL) under a nitrogen atmosphere. Prop-2-yn-1-ol (0.4 mL, 8.5 mmol) was added and the reaction was stirred at 55°C for 5 h. Then, the mixture was cooled and passed through a plug of silica gel. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, PE:AcOEt 3:7) to afford the intermediate product *3-[4-(methylsulfonyl)phenyl]prop-2-yn-1-ol* as a white solid (125 mg). Yield: 70%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.89 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 4.27 (s, 2H), 3.05 (s, 3H).

To a solution of *3-[4-(methylsulfonyl)phenyl]prop-2-yn-1-ol* (786.0 mg, 3.74 mmol) and Et_3N (2.6 mL, 18.7 mmol) in DCM (19 mL) was added dropwise $TiCl_4$ (1.2 mL, 11.2 mmol) at 0°C. After stirring at 0°C for 1 hour, the mixture was quenched with 1M HCl aqueous solution and extracted with AcOEt (20 mL x 3). The organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography

(silica gel, PE:AcOEt 6:4) to afford the product **1f** as a white solid (324 mg). Yield: 42%. ^{1}H NMR ($CDCl_3$, δ, ppm) 9.45 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 3.08 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 175.0, 140.7, 133.3 (2C), 127.9 (2C), 127.7, 96.2, 88.2, 47.7.

Methyl 3-(4-(methylsulfonyl)phenyl)prop-2-ynoate (1g). To a mixture of *3-(4-(methylsulfonyl)phenyl)prop-2-yn-1-ol* (20.1 mg, 0.095 mmol), NaCN (4.7 mg, 0.095 mmol) and MnO_2 (124.0 mg, 1.43 mmol) stirring in THF (1 mL) was added MeOH (19 µL, 0.48 mmol). The reaction was heated to reflux and left to stir for 5 h. The resulting mixture was then filtered through Celite and the solvent removed under reduced pressure. The residue was purified by column chromatography (silica gel, PE:AcOEt 7:3) to afford **1g** as a white solid (10 mg). Yield: 44%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.97 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 3.87 (s, 3H), 3.07 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 153.9, 140.7, 133.3 (2C), 127.9 (2C), 127.7, 89.0, 86.1, 52.7, 47.7.

4-[4-(Methylsulfonyl)phenyl]but-3-yn-2-one (1h). $Pd(PPh_3)_2Cl_2$ (59.7 mg, 0.085 mmol, 0,05 eq.) and CuI (25.9 mg, 0.14 mmol, 0.08 eq.) were added to a solution of 1-bromo-4-(methylsulfonyl)benzene (400 mg, 1.7 mmol) and but-3-yn-2-ol (0.9 mL, 11.57 mmol) in a mix of TEA:DMF 1:1 (3.4 mL) and the batch was heated at 70°C for 18 h. The reaction mixture was poured into water (25 mL) and extracted with AcOEt (3 x 20 mL). The extracts were washed with brine (2 x 20 mL) and then dried. Volatile material was removed by evaporation and the residue was purified by chromatography on silica gel column eluting with PE:AcOE 3:7 to afford the intermediate product *4-[4-(methylsulfonyl)phenyl]but-3-yn-2-ol* as a white solid (368.5 mg). Yield: 97%. ^{1}H NMR ($CDCl_3$), δ, ppm) 7.89 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 4.78 (q, *J* = 6.5 Hz, 1H), 3.05 (s, 3H), 1.57 (d, *J* = 6.5 Hz, 3H).
4-[4-(Methylsulfonyl)phenyl]but-3-yn-2-ol (737.0 mg, 3.28 mmol) was added to a stirred solution of pyridinium dichlorochromate (1 g, 4.93 mmol) in dichloromethane (2 mL). After stirring overnight at r.t., Et_2O (30 mL) was added and the supernatant decanted from the black gum. The black gum was washed with Et_2O (3 x 15 mL). The combined organic portions were dried over Na_2SO_4, concentrated and the residue was purified by column chromatography (silica gel, PE:AcOEt 6:4) to afford the product **1h** as a white solid (354 mg). Yield: 48%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.97 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$, δ, ppm) 182.7, 140.7, 133.3 (2C), 127.9 (2C), 127.7, 91.2, 88.3, 47.7, 32.7.

3-[4-(Methylsulfonyl)phenyl]-1-phenylprop-2-yn-1-one (1i). To a solution of freshly dried THF (2.6 mL) under an Argon atmosphere were added benzoyl chloride (0.1 mL, 0.83 mmol) and 1-ethynyl-4-(methylsulfonyl)benzene **1b** (100 mg, 0.55 mmol). Then $Pd(PPh_3)_2Cl_2$ (19.5 mg, 0.028 mmol, 0,05 eq.) and CuI (5.3 mg, 0.028 mmol, 0.05 eq.) were added with stirring for 1-2

min. This was immediately followed by the addition of TEA (0.1 mL, 0.72 mmol). The reaction was allowed to proceed with stirring for 2 hours at 25°C, filtered, washed with AcOEt, and the solvent was removed *in vacuo*. The residue obtained was purified by silica gel column chromatography using PE:AcOE 7:3 as eluent to afford **1i** as a white solid (139.0 mg). Yield: 45%. ^{1}H NMR ($CDCl_3$, δ, ppm) 8.21 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 3.10 (s, 3H).

4-[(Trimethylsilyl)ethynyl]benzenesulfonamide (1j). To a solution of 4-bromobenzenesulfonamide (500 mg, 2.12 mmol) in 1,4-dioxane (4.2 mL) were added ethynyltrimethylsilane (0.6 mL, 4.24 mmol, 2 eq.), CuI (40.3 mg, 0.21 mmol, 0.1 eq.) and $Pd(PPh_3)_2Cl_2$ (148.6 mg, 0.21 mmol, 0,1 eq.) under a nitrogen atmosphere. Then Et_3N (3 mL, 21.18 mmol, 10 eq.) was added dropwise. After stirring overnight at 100°C, the mixture was cooled and passed through a plug of silica gel. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, PE:AcOEt 7:3) to afford **1j** as a white solid (318 mg). Yield: 71%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.85 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 4.90 (s, 2H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, δ, ppm) 143.4, 132.6 (2C), 125.9, 125.7 (2C), 98.9, 53.5, 3.4 (3C).

Trimethyl{[4-(methylsulfonyl)phenyl]ethynyl}silane (1k). To a solution of 1-bromo-4-(methylsulfonyl)benzene (500 mg, 2.13 mmol), CuI (40.5 mg, 0.21 mmol, 0.1 eq.) and $Pd(PPh_3)_2Cl_2$ (149.2 mg, 0.21 mmol, 0,1 eq.) in a mixture DCM:Et_3N 1:1 (15 mL) ethynyltrimethylsilane (0.59 mL, 4.15 mmol, 1.95 eq.), was added and the mixture was stirred overnight at r.t. Then, the mixture was passed through a plug of silica gel. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel, PE:AcOEt 7:3) to afford **1k** as a white solid (406 mg). Yield: 76%. ^{1}H NMR ($CDCl_3$, δ, ppm) 7.87 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.6 Hz, 2H), 3.05 (s, 3H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$, δ, ppm) 140.7, 133.3 (2C), 127.9 (2C), 127.7, 98.9, 53.5, 47.7, 3.4 (3C).

4-(3-(4-Fluorophenyl)isoxazol-4-yl)benzenesulfonamide (3a). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (76.6 mg, 0.44 mmol) and 4-ethynylbenzenesulfonamide **1a** (50.0 mg, 0.28 mmol). At r.t. 1,2-DCE (2.8 mL) was added followed by [Cp*RuCl(cod)] (15.7 mg, 15% mol) and Et_3N (62 µL, 0.44 mmol), and the vial was capped. After 5 min., the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (Petroleum Ether: AcOEt 6:4, R_f = 0.16). (**3a:4a** 99:1). The isoxazole **3a** was recrystallized from ether. white solid (m.p. 158-160ºC). Yield: 74% (65.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 9.38 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.38 (m, 6H), 7.33 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.0 (d, $^1J_{C,F}$ = 249 Hz), 159.11, 158.81, 143.48, 131.92, 130.82 (d, $^3J_{C,F}$ = 9.07 Hz),

128.88 (2C), 126.10 (2C), 124.37, 118.53, 116.08 (d, $^{2}J_{C,F}$ = 22.17 Hz). ^{19}F NMR (DMSO-d_6, δ, ppm)-111.32 ppm. Mass, calculated for $C_{15}H_{11}FN_2O_3S$: 318.21, found: 319.21 (M+H).

4-(3-Phenylisoxazol-4-yl)benzenesulfonamide (3b). A screw top vial purged with dry nitrogen was charged with 4-ethynylbenzenesulfonamide **1a** (50.0 mg, 0.28 mmol). At r.t. a solution of N-hydroxybenzimidoyl chloride **2b** (68.7 mg, 0.44 mmol) in dry 1,2-DCE (2.8 mL) was added followed by [Cp*RuCl(cod)] (15.7 mg, 15% mol) and Et_3N (62 µL, 0.44 mmol), and the vial was capped. After 5 min., the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (Petroleum Ether:AcOEt 6:4, Rf = 0.28). (**3b:4b** 98:2). The isoxazole **3b** was recrystallized from ether. white solid (m.p. 155-157ºC). Yield: 74% (61.3 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 9.37 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.38 (m, 9H) ppm. ^{13}C NMR (DMSO-d_6, δ, ppm) 159.61, 159.02, 143.42, 132.08, 129.95, 128.93 (2C), 128.85 (2C), 128.46 (2C), 127.92, 126.04 (2C), 118.53 ppm. Mass, calcd. for $C_{15}H_{12}N_2O_3S$: 300.33; found: 301.13 (M+H).

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)isoxazole (3c). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (76.9 mg, 0.44 mmol) and 1-ethynyl-4-(methylsulfonyl)benzene **1b** (50.0 mg, 0.28 mmol). At r.t., 1,2-DCE (2.8 mL) was added followed by [Cp*RuCl(cod)] (15.8 mg, 15% mol) and Et_3N (62 µL, 0.44 mmol), and the vial was capped. After 5 min., the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (Petroleum Ether:AcOEt 6:4, Rf = 0.14). (**3c:4c** 98:2). The isoxazole **3c** was recrystallized from ether. white solid (m.p. 136-138ºC). Yield: 65% (57.2 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 9.43 (s, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.52 (m, 4H), 7.34 (t, *J* = 8.5 Hz, 2H), 3.24 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.0 (d, $^{1}J_{C,F}$ = 249 Hz) 159.40, 158.82, 140.14, 133.77, 130.89 (d, $^{3}J_{C,F}$ = 9.07 Hz), 129.15 (2C), 127.44 (2C), 124.27, 118.32, 116.13 (d, $^{2}J_{C,F}$ = 22.17 Hz) 43.35. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.94. Mass, calcd. for $C_{16}H_{12}FNO_3S$: 317.33; found: 318.21 (M+H).

4-(4-(Methylsulfonyl)phenyl)-3-phenylisoxazole (3d). A screw top vial purged with dry nitrogen was charged with 1-ethynyl-4-(methylsulfonyl)benzene **1b** (50.0 mg, 0.28 mmol). At r.t. a solution of N-hydroxybenzimidoyl chloride **2b** (69.1 mg, 0.44 mmol) in 1,2-DCE (2.8 mL) was added followed by [Cp*RuCl(cod)] (15.8 mg, 15% mol) and Et_3N (62 µL, 0.44 mmol), and the vial was capped. After 10 min., the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (Petroleum Ether:AcOEt 6:4, Rf = 0.24). (**3d**:**4d** 99:1). The isoxazole **3d** was recrystallized from ether. white solid (m.p. 130-131ºC). Yield: 64% (53.2 mg). ^{1}H NMR (DMSO-

d_6, δ, ppm) 9.42 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.49 (m, 7H), 3.24 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 159.61, 159.33, 140.09, 133.92, 130.01, 129.10 (2C), 128.98 (2C), 128.51 (2C), 127.82, 127.37 (2C), 118.31, 43.34. Mass, calcd. for $C_{16}H_{13}NO_3S$: 299.34; found: 300.25 (M+H).

4-[3-(4-Fluorophenyl)-5-methylisoxazol-4-yl]benzenesulfonamide (3e) and 4-[3-(4-fluorophenyl)-4-methylisoxazol-5-yl]benzenesulfonamide (4e). *Thermal cycloaddition*: 4-(Prop-1-yn-1-yl)benzenesulfonamide **1c** (97.0 mg, 0.50 mmol) was dissolved in DME (5 mL) and heated to reflux (85ºC). 4-fluoro-N-hydroxybenzimidoyl chloride (431.1 mg, 2.48 mmol) **2a** and KF (144.3 mg, 2.48 mmol) were added in five portions at one hour intervals and the mixture was then refluxed overnight. After evaporation, the crude residue was purified by flash chromatography (silica gel, eluent petroleum ether:AcOEt 6:4, Rf = 0.32). (**3e**:**4e** 37:63). Regioisomers **3e**:**4e** were separated by semipreprative HPLC. **3e**: white solid. (m.p. 164-165ºC). Yield: 4% (7.3 mg). ^{1}H NMR (acetone-d_6, δ, ppm) 7.93 (d, J = 8.3 Hz, 2H), 7.49 – 7.40 (m, 4H), 7.18 (t, J = 8.8 Hz, 2H), 6.65 (bs, 2H), 2.50 (s, 3H).^{13}C NMR (acetone-d_6, δ, ppm) 168.52, 164.34 (d, $^1J_{C,F}$ =249 Hz) 160.91, 144.38, 134.96, 131.48 (d, $^3J_{C,F}$ = 9.07 Hz) 131.07 (2C), 127.44 (2C), 126.38, 116.52 (d, $^2J_{C,F}$ = 22.17 Hz) 115.36, 11.65. ^{19}F NMR (acetone-d_6, δ, ppm) -112.99. Mass, calcd. for $C_{16}H_{13}FN_2O_3S$: 332.34; found: 333.27 (M+H).

4e: white solid. (m.p. 200-206°C). Yield: 8% (15 mg). 1H NMR (acetone-d_6, δ, ppm) 8.10 (d, J = 8.1 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H), 7.82 – 7.78 (m, 2H), 7.35 (t, J = 8.8 Hz, 2H), 6.77 (s, 2H), 2.39 (s, 3H). ^{13}C-NMR (acetone-d_6, δ, ppm), 165.93, 165.41 (d, $^1J_{C,F}$ = 249 Hz), 164.89, 146.81, 133.19, 132.49 (d, $^3J_{C,F}$ = 9.09 Hz), 129.14, 128.70, 127.59, 117.70 (d, $^2J_{C,F}$ = 22.17 Hz), 112.37, 10.38. 19F NMR (acetone-d_6, δ, ppm) – 111.75. Mass, found: 333.27 (M+H).

3-(4-fluorophenyl)-4-[4-(methylsulfonyl)pheny]-5-(trifluoromethyl)isoxazole (3f). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (97.9 mg, 0.56 mmol) and 4-(3,3,3-trifluoroprop-1-yn-1-yl)benzenesulfonamide **1d** (70.0 mg, 0.28 mmol). At r.t., 1,2-DCE (1.4 mL) was added followed by [Cp*RuCl(cod)] (32.1 mg, 30% mol) and Et_3N (79 µL, 0.56 mmol), and the vial was capped. After 18 h., the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and a mixture of regioisomers **3f**:**4f** 40:60 was obtained. Regioisomers were separated by column chromatography (Petroleum Ether:AcOEt 7:3). **3f** (Rf = 0.31), white solid (m.p. 142-144ºC). Yield: 29% (31.3 mg). ^{1}H NMR DMSO-d_6, δ, ppm) 8.03 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.49 – 7.37 (m, 2H), 7.30 (t, J = 8.7 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.32 (d, $^1J_{C,F}$ = 249 Hz) 161.54, 153.47 (q, $^1J_{C,F}$ = 40.3 Hz 141.74, 130.99, 130.47 (d, $^3J_{C,F}$ = 9.07 Hz) 127.33, 122.66, 122.02, 119.76, 119.74, 119.32, 116.62, 116.2 (d, $^2J_{C,F}$ = 22.17 Hz) 113.92, 43.19. ^{19}F NMR (DMSO-d_6, δ, ppm) -60.98 (3F), -109.67 (1F). Mass, calcd. for $C_{17}H_{11}F_4NO_3S$: 385.33; found: 386.16 (M+H).

5-Chloro-3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)isoxazole (3g) and 4-chloro-3-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)isoxazole (4g). *Thermal cycloaddition:* To a stirred solution of 1-(chloroethynyl)-4-(methylsulfonyl)benzene **1e** (88.0 mg, 0.41 mmol) and oxime **2a** (213.4 mg, 1.23 mmol, 3 eq.) in toluene (2.1 mL) at 80°C was added a solution of Et_3N 1,5 M in toluene (4 eq.) dropwise over 5 hours. After 18 hours, the crude mixture was cooled to r.t., filtered, concentrated in vacuo and purified via flash chromatography over silica gel, eluting with PE:AcOEt 6:4 (Rf = 0.32) to give a mixture of regioisomers **3g**:**4g** 18:82. Regioisomers were separated by semipreprative HPLC. **3g**: white solid (m.p. 149-151ºC). Yield: 8% (11.5 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.01 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.32 (t, J = 8.9 Hz, 2H), 3.28 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.28, (d, $^2J_{C,F}$ = 249 Hz), 161.92, 152.51, 140.97, 132.03, 130.68 (d, $^3J_{C,F}$ = 9.07 Hz) 130.42 (2C), 127.59 (2C), 123.63, 116.21(d, $^2J_{C,F}$ = 22.17 Hz) 113.50, 43.26. ^{19}F NMR (DMSO-d_6, δ, ppm) -109.91. Mass, calcd. for $C_{16}H_{11}ClFNO_3S$: 351.01, found 352.17 (M+H).

4g: white solid (m.p. 148-149ºC). Yield: 37% (53.4 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.28 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.4 Hz, 2H), 7.93 (dd, J = 8.7, 5.5 Hz, 2H), 7.47 (t, J = 8.7 Hz, 2H), 3.32 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.5 (d, $^1J_{C,F}$ = 249 Hz) 159.85, 142.59, 130.6 (d, $^3J_{C,F}$ = 9.07 Hz) 129.67, 128.01 (2C), 127.25 (2C), 122.73, 122.70, 116.3 (d, $^2J_{C,F}$ = 22.17 Hz) 106.15, 43.26. ^{19}F NMR (DMSO-d_6, δ, ppm) -109.46. Mass, found: 352.17 (M+H).

3-(4-Fluorophenyl)-4-(4-(methylsulfonyl)phenyl)isoxazole-5-carbaldehyde (3h). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (66.7 mg, 0.38 mmol) and 3-(4-(methylsulfonyl)phenyl)propiolaldehyde **1f** (50.0 mg, 0.24 mmol). At r.t. 1,2-DCE (2,4 mL) was added followed by [Cp*RuCl(cod)] (13.7 mg, 15% mol) and Et_3N (54 μL, 0.38 mmol), and the vial was capped. After 1 hour, the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (petroleum ether:AcOEt 6:4, Rf = 0.26). (d.r. = 9:1). The isoxazole **3h** was recrystallized from ether. white solid (m.p. 159-161ºC). Yield: 57% (47.3 mg). ^{1}H NMR (acetone-d_6, δ, ppm) 9.44 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 8.11 (d, J = 8.6 Hz, 2H), 7.88 – 7.78 (m, 2H), 7.26 (t, J = 8.9 Hz, 2H), 3.20 (s, 3H). ^{13}C NMR (acetone-d_6, δ, ppm) 187.26, 166.46, 164.74 (d, $^1J_{C,F}$ = 249 Hz), 161.32, 145.95, 143.20, 132.38 (d, $^3J_{C,F}$ = 9,07 Hz), 130.93 (2C), 128.54 (2C), 125.13, 119.58, 116.24 (d, $^2J_{C,F}$ = 22.17 Hz), 44.06. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.30. Mass, calcd. for $C_{17}H_{12}FNO_4S$: 345.34; found 346.22 (M+H).

Methyl 3-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)isoxazole-5-carboxylate (3i). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (88.6 mg, 0.51 mmol) and methyl 3-(4-(methylsulfonyl)phenyl)propiolate **1g** (76.0

mg, 0.32 mmol). At r.t. 1,2-DCE (1,6 mL) was added followed by [Cp*RuCl(cod)] (18.2 mg, 15% mol) and Et_3N (71 µL, 0.51 mmol), and the vial was capped. After 1 hour, the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (petroleum ether:AcOEt 6:4, Rf = 0.26). (**3i**:**4i** 94:6). The isoxazole **3i** was recrystallized from ether. white solid (m.p. 164-165ºC). Yield: 59% (70.6 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.96 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.28 (t, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 163.11 (d, $^1J_{C,F}$ = 249 Hz), 161.41, 156.59, 155.95, 140.97, 133.05, 131.22 (2C), 130.82 (d, $^3J_{C,F}$ = 9.07 Hz), 126.75 (2C), 123.44, 122.19, 116.1 (d, $^2J_{C,F}$ = 22.17 Hz), 52.86, 43.29. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.25. Mass, calcd. for $C_{18}H_{14}FNO_5$: 375.37; found: 376.17 (M+H).

1-{3-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl}ethanone (3j). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (100.0 mg, 0.58 mmol) and 4-(4-(methylsulfonyl)phenyl)but-3-yn-2-one **1h** (80.0 mg, 0.36 mmol). At r.t. 1,2-DCE (1,8 mL) was added followed by [Cp*RuCl(cod)] (20.5 mg, 15% mol) and Et_3N (80 µL, 0.58 mmol), and the vial was capped. After 1 hour, the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated and the residue was purified by column chromatography (petroleum ether:AcOEt 6:4, Rf = 0.19). white solid (m.p. 166-167ºC). Yield: 63% (81.5 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.96 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.34 (m, 2H), 7.28 (t, *J* = 8.9 Hz, 2H), 3.28 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 187.23, 163.08 (d, $^1J_{C,F}$ = 249 Hz), 161.75, 161.45, 140.92, 133.42, 131.18 (2C), 130.79 (d, $^3J_{C,F}$ = 9.07 Hz), 126.86 (2C), 123.59, 119.82, 116.11 (d, $^2J_{C,F}$ = 22.17 Hz), 43.27, 28.27. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.36. Mass, calcd. for $C_{18}H_{14}FNO_4$: 359.37; found: 360.24 (M+H).

3-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]isoxazol-5-yl-(phenyl)methanone (3k). A screw top vial purged with dry nitrogen was charged with 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (85.5 mg, 0.49 mmol) and 3-[4-(methylsulfonyl)phenyl]-1-phenylprop-2-yn-1-one **1i** (70.0 mg, 0.25 mmol). At r.t. 1,2-DCE (1,2 mL) was added followed by [Cp*RuCl(cod)] (28.1 mg, 30% mol) and Et_3N (69 µL, 0.49 mmol), and the vial was capped. After 18 hour, the reaction mixture was passed through a plug of silica gel (AcOEt). The resulting solution was concentrated. Regioisomers (**3k**:**4k** 65:35) were separated by column chromatography (petroleum ether:AcOEt 6:4). **3k**: (Rf = 0.37). white solid (m.p. 182-184ºC). Yield: 58% (60.2 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.93 (d, *J* = 7.5 Hz, 2H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.56 (m, 4H), 7.46 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.31 (t, *J* = 8.8 Hz, 2H), 3.24 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 182.53, 163.13 (d, $^1J_{C,F}$ = 249 Hz) 162.26, 161.03, 140.77, 135.20, 134.37, 133.36, 131.09

(2C), 130.93 (d, $^{3}J_{C,F}$ = 9.07 Hz), 129.76 (2C), 128.78 (2C), 126.91 (2C), 123.51, 121.93, 116.14 (d, $^{2}J_{C,F}$ = 22.17 Hz), 43.30.^{19}F NMR (DMSO-d_6, δ, ppm) -110.28. Mass, calcd. for $C_{23}H_{16}FNO_4S$: 421.44, found: 422.28 (M+H).

4-[3-(4-Fluorophenyl)-5-(trimethylsilyl)isoxazol-4-yl]benzenesulfonamide (3l) and 4-[3-(4-fluorophenyl)-4-(trimethylsilyl)isoxazol-5-yl]benzenesulfonamide (4l). ***Thermal cycloaddition:*** Alkyne **1j** (100 mg, 0.39 mmol) was dissolved in DME (3.9 mL) and heated to reflux (85ºC). 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (171.2 mg, 0.987 mmol) and KF (68.8 mg, 1.184 mmol) were added in five portions at one hour intervals and the mixture was then refluxed overnight. After evaporation, the regioisomers (**3l**:**4l** 17:83) were separated by flash chromatography (silica gel, eluent petroleum ether:AcOEt 6:4). **3l**: (Rf = 0.32). white solid (205-208ºC). Yield: 11% (17.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.85 (d, *J* = 8.4 Hz, 2H), 7.49 – 7.43 (m, 4H), 7.38 (dd, *J* = 8.9, 5.5 Hz, 2H), 7.24 (t, *J* = 8.9 Hz, 2H), 0.19 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 175.21, 162.74 (d, $^{1}J_{C,F}$ = 249 Hz), 158.62, 143.96, 133.57, 130.83 (2C), 130.53 (d, $^{3}J_{C,F}$ = 9.07 Hz), 127.21, 125.77 (2C), 124.58, 115.84 (d, $^{2}J_{C,F}$ = 22.17 Hz), -1.34 (3C). ^{19}F NMR (DMSO-d_6, δ, ppm) -111.42. Mass, calcd. for $C_{18}H_{19}FN_2O_3SSi$: 390.50; found 391.23 (M+H).
4l: (Rf = 0.20). White solid (205-207ºC). Yield: 59% (90.9 mg). ^{1}H NMR DMSO-d_6, δ, ppm) 8.01 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.60 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.56 (s, 2H), 7.40 (t, *J* = 8.4 Hz, 2H), -0.04 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 174.08, 166.95, 162.94 (d, $^{1}J_{C,F}$ = 249 Hz), 145.86, 131.75, 131.17 (d, $^{3}J_{C,F}$ = 9.07 Hz), 129.70 (2C), 127.22, 126.01 (2C), 115.70 (d, $^{2}J_{C,F}$ = 22.17 Hz), 109.65, 0.04 (3C). ^{19}F NMR (DMSO-d_6, δ, ppm) -111.63. Mass, found: 391.23 (M+H).

3-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-5-(trimethylsilyl)isoxazole (3m) and 3-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-(trimethylsilyl)isoxazole (4m). *Thermal cycloaddition***:** Alkyne **1k** (100 mg, 0.40 mmol) was dissolved in DME (4.0 mL) and heated to reflux (85ºC). 4-fluoro-N-hydroxybenzimidoyl chloride **2a** (171.9 mg, 0.99 mmol) and KF (69.0 mg, 1.198 mmol) were added in five portions at one hour intervals and the mixture was then refluxed overnight. After evaporation, the crude residue was purified by flash-chromatography (silica gel, eluent petroleum ether/AcOEt 4:6, Rf=0.47). Regioisomers (**3m**:**4m** 22:78) were separated by semi-preparative HPLC. **3m**: (Rf = 0.35). White solid (m.p. 185-187ºC). Yield: 7% (10.8 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.98 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.38 (dd, *J* = 8.3, 5.7 Hz, 2H), 7.23 (t, *J* = 8.3 Hz, 2H), 3.27 (s, 3H), 0.20 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 175.39, 162.74 (d, $^{1}J_{C,F}$ = 249 Hz), 158.58, 140.65, 135.49, 131.22 (2C), 130.57 (d, $^{3}J_{C,F}$ = 9.07 Hz), 127.06 (2C), 126.98, 124.44, 115.87 (d, $^{2}J_{C,F}$ = 22.17 Hz), 43.33, -1.82 (3C). ^{19}F NMR (DMSO-d_6, δ, ppm) -111.38 ppm. Mass, calcd. for $C_{19}H_{20}FNO_3SSi$: 389.51; found: 390.22 (M+H).

4m (Rf = 0.33). White solid (m.p. 185-187ºC). Yield: 66% (101.7 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.13 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.66 – 7.56 (m, 2H), 7.40 (t, *J* = 8.7 Hz, 2H), 3.33 (s, 3H), -0.04 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 173.68, 166.96, 162.94 (d, $^{1}J_{C,F}$ = 249 Hz), 142.55, 133.38, 131.17 (d, $^{3}J_{C,F}$ = 9.07 Hz), 130.01 (2C), 127.36 (2C), 127.12, 115.70 (d, $^{2}J_{C,F}$ = 22.17 Hz), 110.09, 43.25, 0.01 (3C). ^{19}F NMR (DMSO-d_6, δ, ppm) -111.57 ppm. Mass, found: 390.22 (M+H).

4-[3-Phenyl-5-(trimethylsilyl)isoxazol-4-yl]benzenesulfonamide (3n) and 4-[3-phenyl-4-(trimethylsilyl)isoxazol-5-yl]benzenesulfonamide (4n). *Thermal cycloaddition:* Alkyne **1j** (100 mg, 0.39 mmol) was dissolved in DME (3.9 mL) and heated to reflux (85ºC). N-hydroxybenzimidoyl chloride **2b** (153.5 mg, 0.987 mmol) and KF (68.8 mg, 1.184 mmol) were added in five portions at one hour intervals and the mixture was then refluxed overnight. After evaporation, the crude residue was purified by flash chromatography (silica gel, eluent petroleum Ether:AcOEt 6:4, Rf = 0.47). Regioisomers (**3n**:**4n** 16:84) were separated by semi-preparative HPLC. **3n**: white solid (m.p. 202-203ºC). Yield: 5% (7.4 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 7.84 (d, *J* = 8.0 Hz, 2H), 7.39 (m, 9H), 0.20 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 175.07, 159.42, 143.89, 133.78, 130.84 (2C), 129.55, 128.71 (2C), 128.26 (2C), 128.10, 127.28, 125.71 (2C), -1.31 (3C). Mass, calcd. for $C_{18}H_{20}N_2O_3SSi$: 372.51; found: 373.27 (M+H).
4n: White solid (m.p. 202-203ºC). Yield: 65% (95.6 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.01 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.55 (s, 7H), -0.05 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 198.59, 173.97, 167.78, 145.81, 131.82, 130.77, 129.70 (2C), 128.84 (2C), 128.58 (2C), 125.97 (2C), 109.58, 0.03 (3C). Mass, found: 373.27 (M+H).

4-[4-(Methylsulfonyl)phenyl]-3-phenyl-5-(trimethylsilyl)isoxazole (3o) and 5-[4-(methylsulfonyl)phenyl]-3-phenyl-4-(trimethylsilyl)isoxazole (4o). *Thermal cycloaddition:* Alkyne **1k** (100 mg, 0.40 mmol) was dissolved in DME (4.0 mL) and heated to reflux (85ºC). N-hydroxybenzimidoyl chloride **2b** (171.9 mg, 0.99 mmol) and KF (69.0 mg, 1.198 mmol) were added in five portions at one hour intervals and the mixture was then refluxed overnight. After evaporation, the crude residue was purified by flash chromatography (silica gel, eluent petroleum ether:AcOEt 6:4, Rf = 0.22). Regioisomers **3o**:**4o** 11:89 were separated by semipreprative HPLC. **3o**: white solid (m.p. 182-183ºC). Yield: 4% (6 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.13 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.56 (s, 5H), 3.32 (s, 3H), -0.05 (s, 9H). ^{13}C NMR (DMSO-d_6, δ, ppm) 175.19, 159.29, 140.50, 135.59, 131.41, 129.50 (2C), 128.66, 128.20 (2C), 127.88 (2C), 126.95, 126.91 (2C), 43.22, 0.01 (3C). Mass, calcd. for $C_{19}H_{21}NO_3SSi$: 371.52; found: 372.20 (M+H).
4o: White solid (m.p. 182-183ºC). Yield: 70% (103.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.13 (d, J = 8.2 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 7.56 (s, 5H), 3.33 (s, 3H), -0.20 (s, 9H). ^{13}C NMR

(DMSO-d_6, δ, ppm) 173.59, 167.81, 142.51, 133.47, 130.69 (2C), 130.02, 129.71, 128.85 (2C), 128.60 (2C), 127.34 (2C), 110.03, 43.26, 0.01 (3C). Mass, found: 372.20 (M+1).

4-[3-(4-Fluorophenyl)isoxazol-5-yl]benzenesulfonamide (4a). Isoxazole **4l** (160 mg, 0.41 mmol) was added to a stirred suspension of CsF (124.5 mg, 0.82 mmol) in MeCN:EtOH 10:1 (2.2 mL). The mixture was heated at reflux under N_2 for 15 minutes, then cooled to r.t. The reaction was quenched by the addition of distillated water (10 mL) and extracted into AcOEt (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (petroleum ether:AcOEt 6:4 ratio, Rf = 0.21). white solid (m.p. 160-161ºC). Yield: 84% (109.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.11 (d, J = 8.2 Hz, 2H), 8.05 – 7.94 (m, 4H), 7.77 (s, 1H), 7.53 (s, 2H), 7.41 (t, J = 8.7 Hz, 2H). ^{13}C NMR (DMSO-d_6, δ, ppm) 168.42, 163.30 (d, $^1J_{C,F}$ = 249 Hz), 161.92, 145.44, 129.41, 128.94 (d, $^3J_{C,F}$ = 9.07 Hz), 126.63 (2C), 126.11 (2C), 124.86, 116.28 (d, $^2J_{C,F}$ = 22.17 Hz), 100.28. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.31. Mass, calcd. for $C_{15}H_{11}FN_2O_3S$: 318.32; found: 319.21 (M+H).

4-(3-Phenylisoxazole-5-yl)benzenesulfonamide (4b). Isoxazole **4n** (30 mg, 0.08 mmol) was added to a stirred suspension of CsF (24.5 mg, 0.16 mmol) in MeCN:EtOH 10:1 (1.1 mL). The mixture was heated at reflux under N_2 for 15 minutes, then cooled to r.t. The reaction was quenched by the addition of distillated water (10 mL) and extracted into AcOEt (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. The isoxazole was recrystallized from acetone. white solid (m.p.155-157ºC). Yield: 90% (21.8 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.12 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.96 – 7.91 (m, 2H), 7.78 (s, 1H), 7.62 – 7.46 (m, 5H). ^{13}C NMR (DMSO-d_6, δ, ppm) 168.33, 162.80, 145.39, 130.46, 129.48, 129.21 (2C), 128.26, 126.62 (2C), 126.60 (2C), 126.11 (2C), 100.30. Mass, calcd. for $C_{15}H_{12}N_2O_3S$: 300.33; found: 301.26 (M+H).

3-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]isoxazole (4c). Isoxazole **4m** (205 mg, 0.51 mmol) was added to a stirred suspension of CsF (156.0 mg, 1.02 mmol) in MeCN:EtOH 10:1 (3.3 mL). The mixture was heated at reflux under N_2 for 15 minutes, then cooled to r.t. The reaction was quenched by the addition of distillated water (10 mL) and extracted into AcOEt (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. The isoxazole was recrystallized from acetone. white solid (m.p. 135-136ºC). Yield: 76% (124.0 mg). ^{1}H NMR (d^6-DMSO, 400 MHz): δ 8.15 (q, J = 8.6 Hz, 4H), 8.06 – 7.94 (m, 2H), 7.86 (s, 1H), 7.42 (t, J = 8.9 Hz, 2H), 3.30 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 167.99, 163.37 (d, $^1J_{C,F}$ = 249 Hz) 161.89, 141.94, 130.83, 128.87 (d, $^3J_{C,F}$ = 9.07 Hz), 127.95 (2C), 126.27 (2C), 124.68, 116.21 (d, $^2J_{C,F}$ = 22.17 Hz), 100.81, 43.21. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.20. Mass, calcd. for $C_{16}H_{12}FNO_3S$: 317.33, found: 318.21 (M+H).

5-[4-(Methylsulfonyl)phenyl]-3-phenylisoxazole (4d). Isoxazol **4o** (59 mg, 0.16 mmol) was added to a stirred suspension of CsF (48.2 mg, 0.32 mmol) in MeCN:EtOH 10:1 (2.2 mL). The mixture was heated at reflux under N_2 for 15 minutes, then cooled to r.t. The reaction was quenched by the addition of distillated water (10 mL) and extracted into AcOEt (3 x 10 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash column chromatography (petroleum ether:AcOEt 6:4 ratio, Rf = 0.24). white solid (m.p. 131-133ºC). Yield: 74% (35.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.19 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 2H), 7.99 – 7.91 (m, 2H), 7.86 (s, 1H), 7.57 (m, 3H), 3.30 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 167.99, 162.86, 142.00, 130.99, 130.50, 129.21 (2C), 128.17, 128.02 (2C), 126.60 (2C), 126.37 (2C), 100.91, 43.31. Mass, calcd. for $C_{16}H_{13}NO_3S$: 299.34, found: 300.25 (M+H).

3-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)isoxazole (4f). *Thermal cycloaddition*: To a stirred solution of 1-(methylsulfonyl)-4-(3,3,3-trifluoroprop-1-yn-1-yl)benzene **1d** (30.0 mg, 0.12 mmol) and oxime **2a** (62.9 mg, 0.43 mmol, 3 eq.) in toluene (0.6 mL) at 80°C was added a solution of Et_3N 1,5 M in toluene (4 eq.) dropwise over 5 hours. After 18 hours, the crude mixture was cooled to r.t., filtered, concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with petroleum ether:AcOEt 7:3 (Rf = 0.32) to give the compound **4f** exclusively. white solid (m.p.141-143ºC). Yield: 62% (29.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.20 (d, *J* = 8.5 Hz, 2H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.74 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.47 (t, *J* = 8.6 Hz, 2H), 3.35 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 169.62, 163.51 (d, $^1J_{C,F}$ = 249 Hz), 160.26, 143.70, 131.12 (d, $^3J_{C,F}$ = 9.07 Hz), 129.96, 129.60, 127.67 (4C), 122.97, 119.86, 116.20 (d. $^2J_{C,F}$ = 9.07 Hz), 107.08 (q, $^1J_{C,F}$ = 38.28 Hz), 43.12. ^{19}F NMR (DMSO-d_6, δ, ppm) -53.25 (3F), -109.77 (1F). Mass, calcd. for $C_{17}H_{11}F_4NO_3S$: 385.33; found: 386.16 (M+H).

3-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]isoxazole-4-carbaldehyde (4h). *Thermal cycloaddition:* To a stirred solution of 3-[4-(methylsulfonyl)phenyl]propiolaldehyde **1f** (30.0 mg, 0.14 mmol) and oxime **2a** (27.5 mg, 0.16 mmol, 1.1 eq.) in toluene (0.5 mL) was added Et_3N (24 µL, 0.17 mmol) dropwise. The mixture was stirred for 5 hours. Then, solvents were removed by vacuum evaporation. The resultant crude product was purified by column chromatography on silica gel eluting by PE:AcOEt 6:4 (Rf = 0.25) to give the compound **4h** exclusively white solid (m.p. 158-159ºC). Yield: 45% (22.5 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 9.95 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 2H), 8.20 (d, *J* = 8.5 Hz, 2H), 8.01 – 7.77 (m, 2H), 7.43 (t, *J* = 8.9 Hz, 2H), 3.35 (s, 3H). 13C NMR (DMSO-d_6, δ, ppm) 184.16, 172.09, 163.37 (d, $^1J_{C,F}$ = 249 Hz), 161.59,143,58, 131.64 (d, $^3J_{C,F}$ = 9.07 Hz), 129.91, 129.66, 127.61, 123.24, 115.71 (d, $^2J_{C,F}$ = 22.17 Hz), 115.29, 43.06. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.18 ppm. Mass, calcd. for $C_{17}H_{12}FNO_4S$: 345.34; found 346.22 (M+H).

3-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]isoxazol-4-yl(phenyl)methanone (4k). *Thermal cycloaddition:* To a stirred solution of 3-[4-(methylsulfonyl)phenyl]-1-phenylprop-2-yn-1-one **1i** (41.0 mg, 0.14 mmol) and oxime **2a** (75.1 mg, 0.43 mmol, 3 eq.) in toluene (0.5 mL) at 80°C was added a solution of Et_3N 1,5 M in toluene (4 eq.) dropwise over 5 hours. After 18 hours, the crude mixture was cooled to r.t., filtered, concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with PE:AcOEt 7:3 (Rf = 0.18) to give the compound **4k** exclusively. white solid (m.p.184-186ºC). yield: 85% (52.0 mg). ^{1}H NMR (DMSO-d_6, δ, ppm) 8.02 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.84 – 7.79 (m, 2H), 7.60 – 7.54 (m, 3H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 8.9 Hz, 2H), 3.25 (s, 3H). ^{13}C NMR (DMSO-d_6, δ, ppm) 189.65, 167.32, 163.15 (d, $^1J_{C,F}$ = 249 Hz), 161.02, 142.77, 135.97, 134.69, 130.42 (d, $^3J_{C,F}$ = 9.07 Hz), 130.17, 129.65 (2C), 129.02 (2C), 128.34 (2C), 127.78 (2C), 123.77, 116.12 (d, $^2J_{C,F}$ = 22.17 Hz) 115.57, 43.12. ^{19}F NMR (DMSO-d_6, δ, ppm) -110.14. Mass, calcd. for $C_{23}H_{16}FNO_4S$: 421.44; found: 422.28 (M+H).

Table S1. Crystal structure parameters of compound 3l

Formula	$C_{18}H_{19}FN_2O_3SSi$
Fw (g mol^{-1})	390.50
T (K)	123
Cryst. syst.	triclinic
Space group	$P\bar{1}$ (no. 2)
Z	2
a (Å)	9.705(6)
b (Å)	9.854(6)
c (Å)	11.726(8)
α (°)	65.43(3)
$\exists$ (°)	68.51(3)
γ (°)	76.92(2)
V (Å^3)	945(1)
$\rho_{calc.}$ (g cm^{-3})	1.372
μ (mm^{-1})	0.26
λ (Å)	0.71073
θ_{max}	39.5
No. of parameters	246
GOF on F^2	1.05
R indices [$I > 2\sigma(I)$][a]	R_1 = 0.049
	wR_2 = 0.127
Weighting *A*/*B*[a]	0.0487 / 0.5381

[a] $R1 = \sum\left\|F_o\right| - \left|F_c\right\| / \sum\left|F_c\right|$; $wR2 = \sqrt{\left[\sum\{w(F_o^2 - F_c^2)^2\} / \sum\{w(F_o^2)2\}\right]}$;
$w = 1/[(\sigma^2(F_o^2) + (A \cdot P)^2 + B \cdot P]$; $P = (F_o^2 + 2F_c^2)/3$

Figure S1. View of the molecular structure of 3l

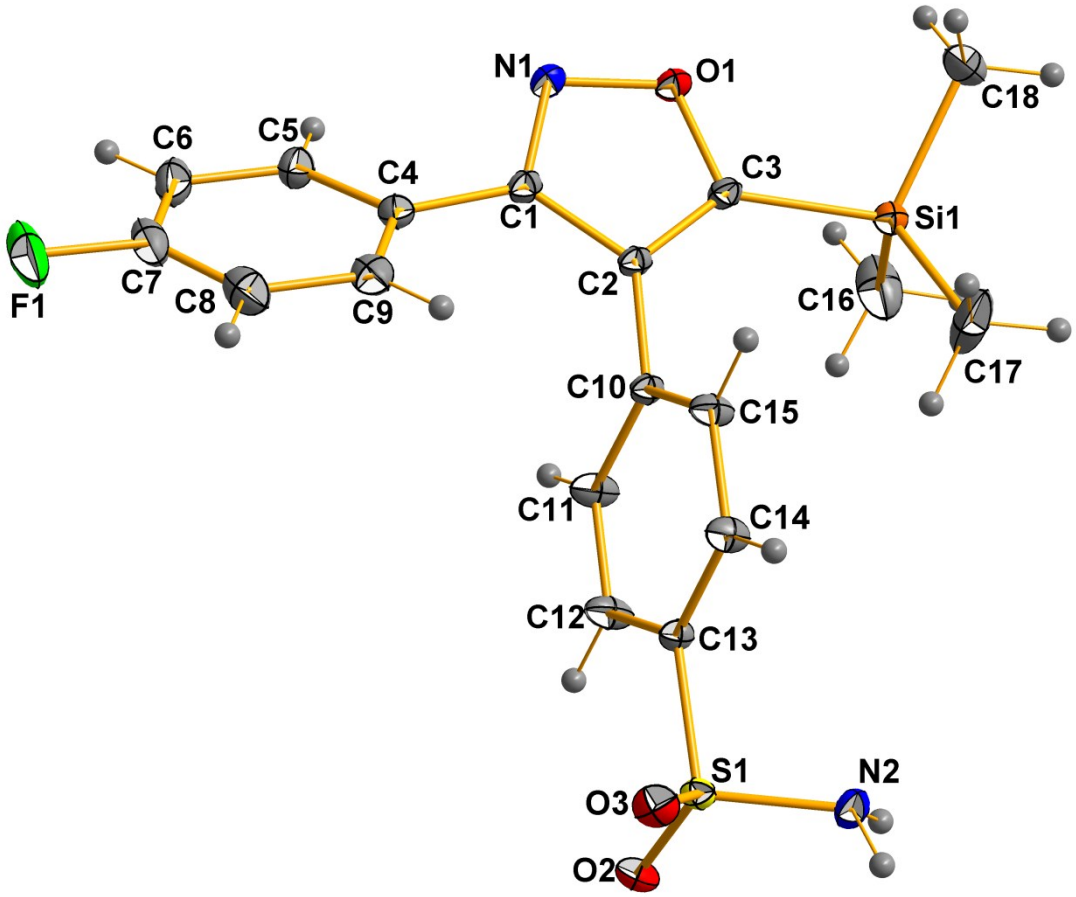


Figure S2. View of the packing of molecules of 3l

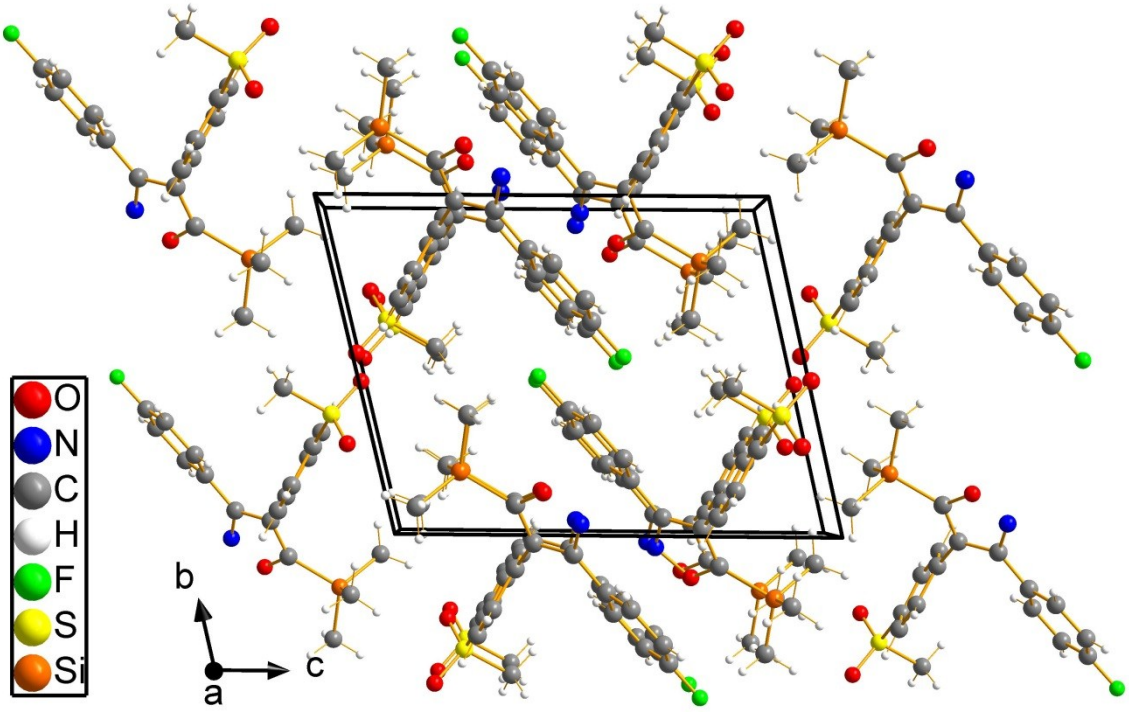


Table S2. Crystal structure parameters of compound 3m

Formula	$C_{19}H_{20}FN_2O_3SSi$
Fw (g mol^{-1})	389.51
T (K)	123
Cryst. syst.	triclinic
Space group	$P\bar{1}$ (no. 2)
Z	2
a (Å)	7.6192(5)
b (Å)	10.3601(7)
c (Å)	13.1271(9)
α (°)	102.578(4)
$\exists$ (°)	92.847(4)
γ (°)	101.855(4)
V (Å^3)	984.9(1)
$\rho_{calc.}$ (g cm^{-3})	1.313
μ (mm^{-1})	0.25
λ (Å)	0.71073
θ_{max}	32.8
No. of parameters	240
GOF on F^2	0.95
R indices [$I > 2\sigma(I)$][a]	R_1 = 0.058
	wR_2 = 0.139
Weighting *A*/*B*[a]	0.0549 / 0.0

[a] $R1 = \Sigma\left\|\|F_o\| - |F_c|\right\| / \Sigma|F_c|$; $wR2 = \sqrt{\left[\Sigma\{(F_o^2 - F_c^2)^2\} / \Sigma\{w(F_o^2)^2\}\right]}$;
$w = 1/[(\sigma^2(F_o^2) + (A \cdot P)^2 + B \cdot P]$; $P = (F_o^2 + 2F_c^2)/3$

Figure S3. View of the molecular structure of 3m

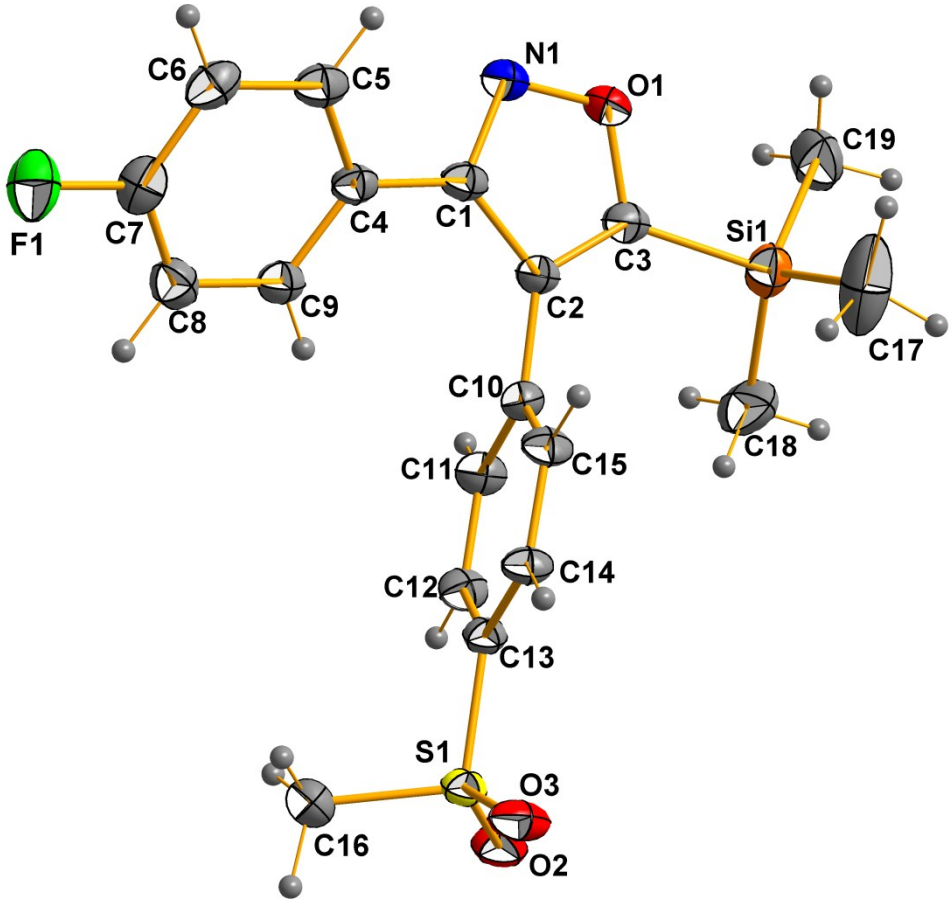


Figure S4. View of the packing of molecules of 3m

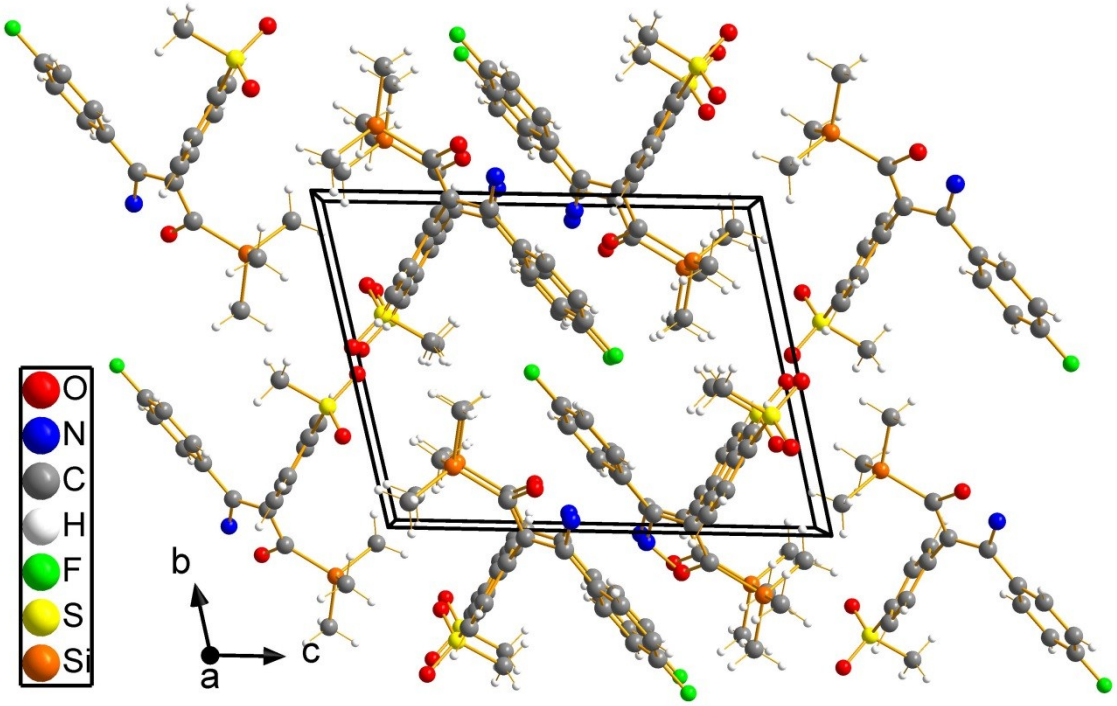
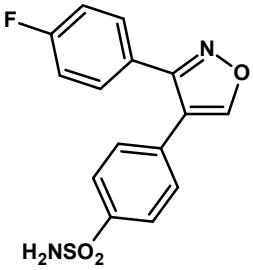


Figure S5. ^{1}H NMR spectrum of 3a

(**3a**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



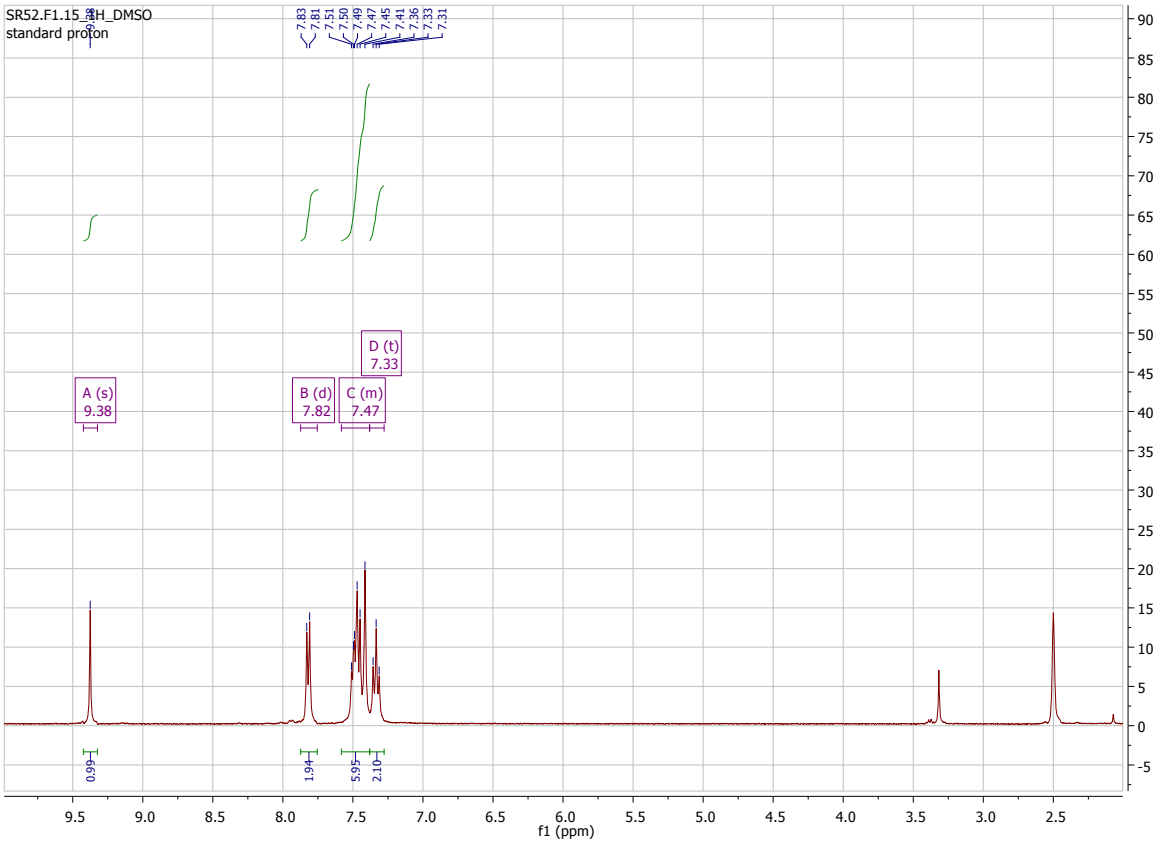
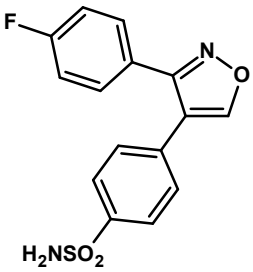


Figure S6. ^{13}C NMR spectrum of 3a

(**3a**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



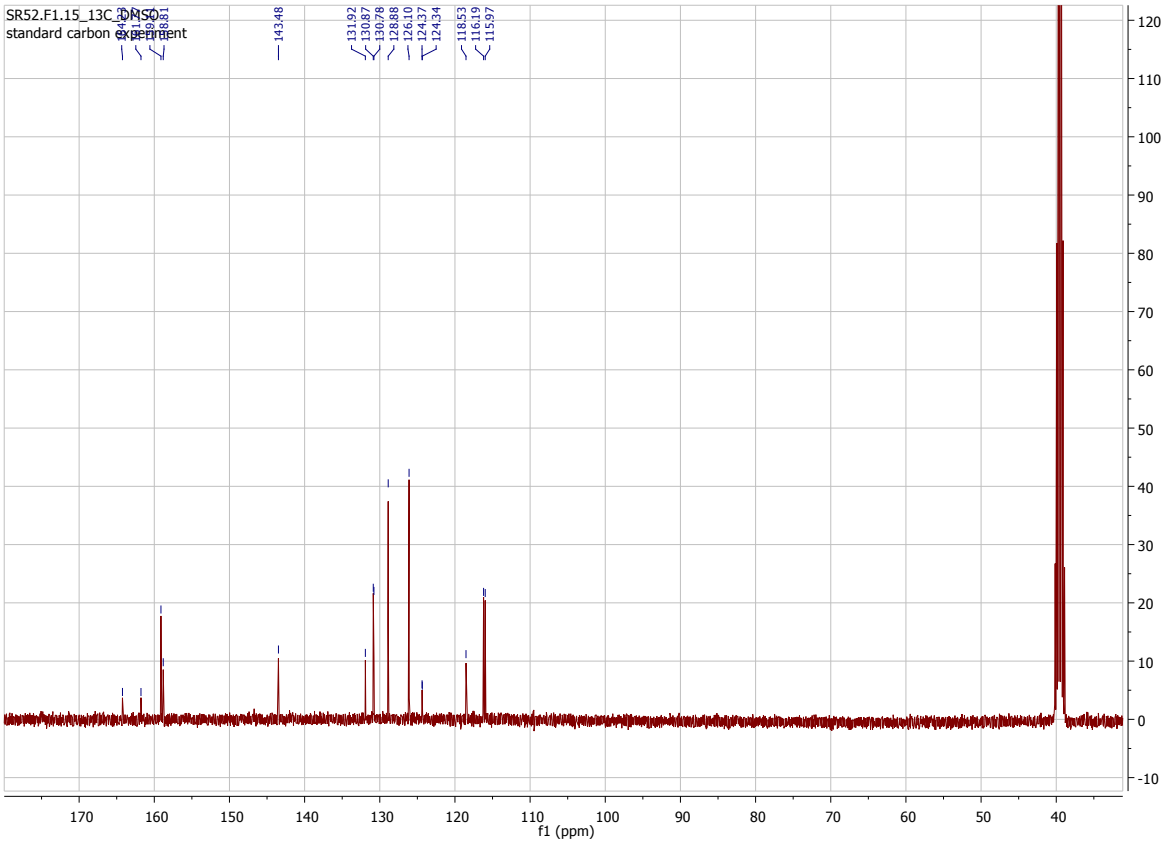
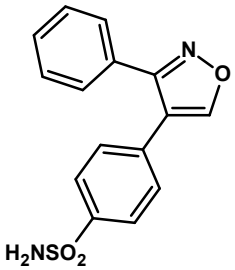


Figure S7. ^{1}H NMR spectrum of 3b

(**3b**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



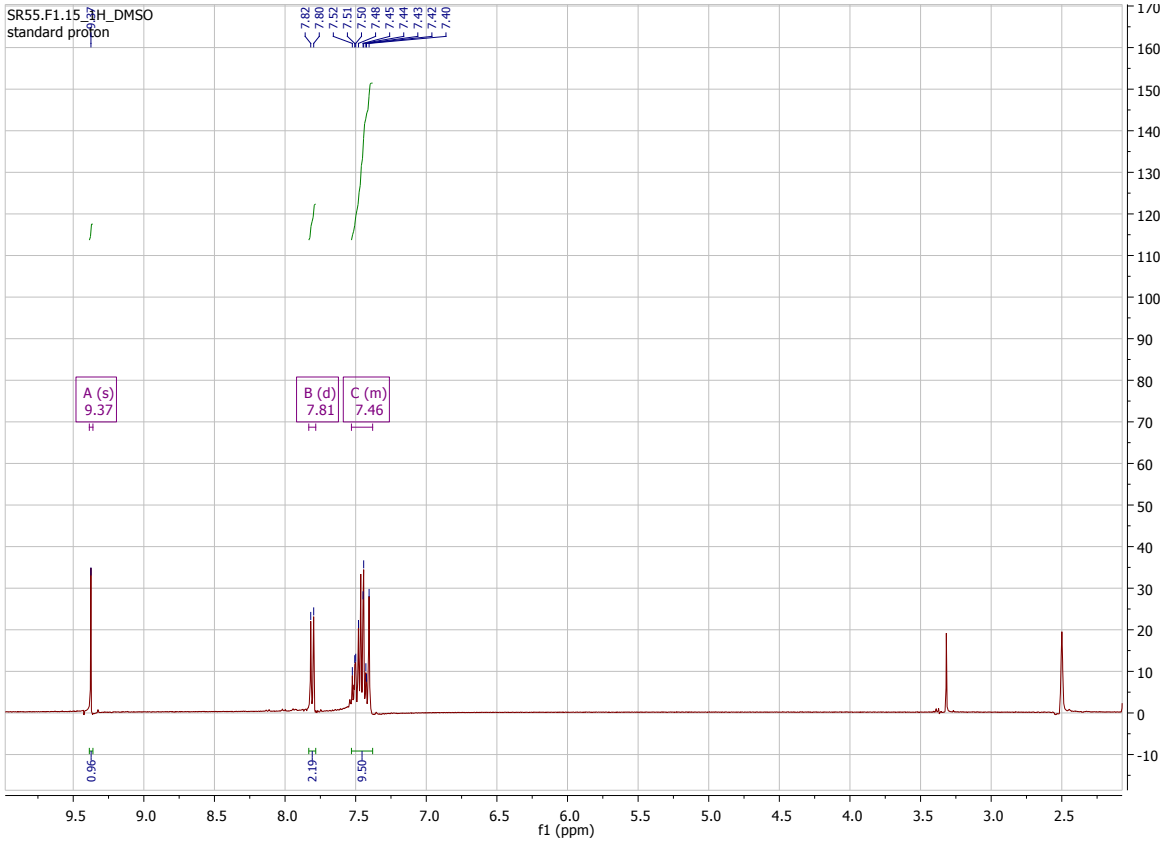
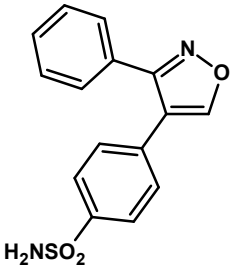


Figure S8. ^{13}C NMR spectrum of 3b

(**3b**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



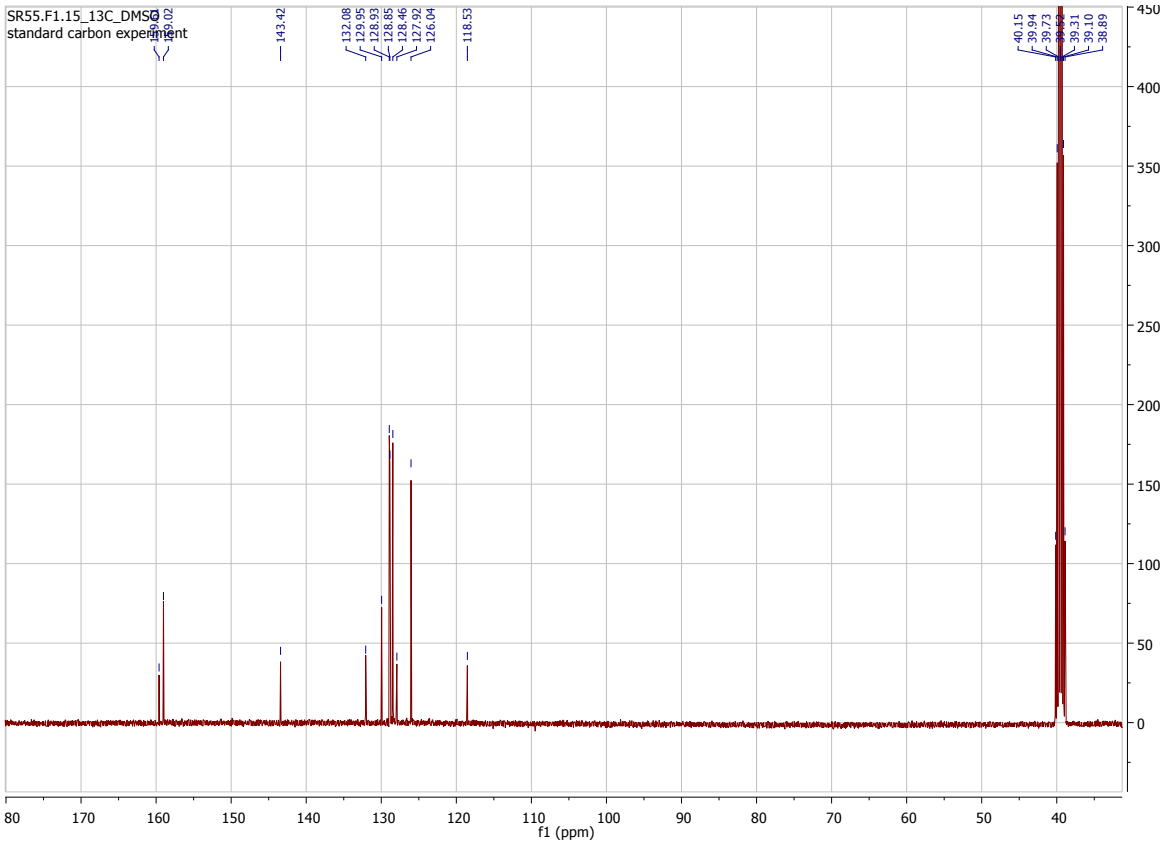
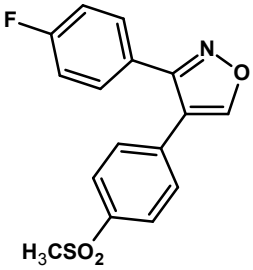


Figure S9. ^{1}H NMR spectrum of 3c

(**3c**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



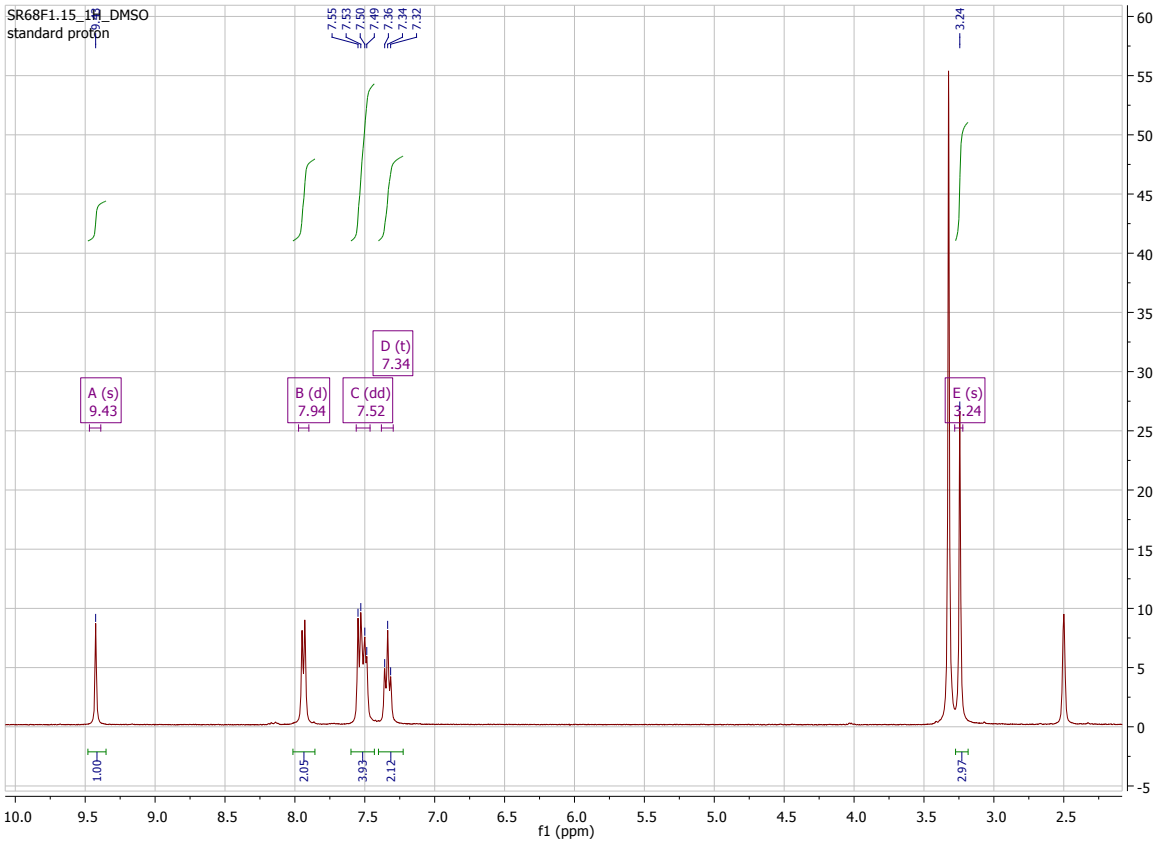
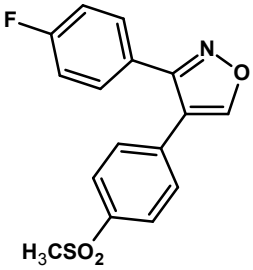


Figure S10. ^{13}C NMR spectrum of 3c

(**3c**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



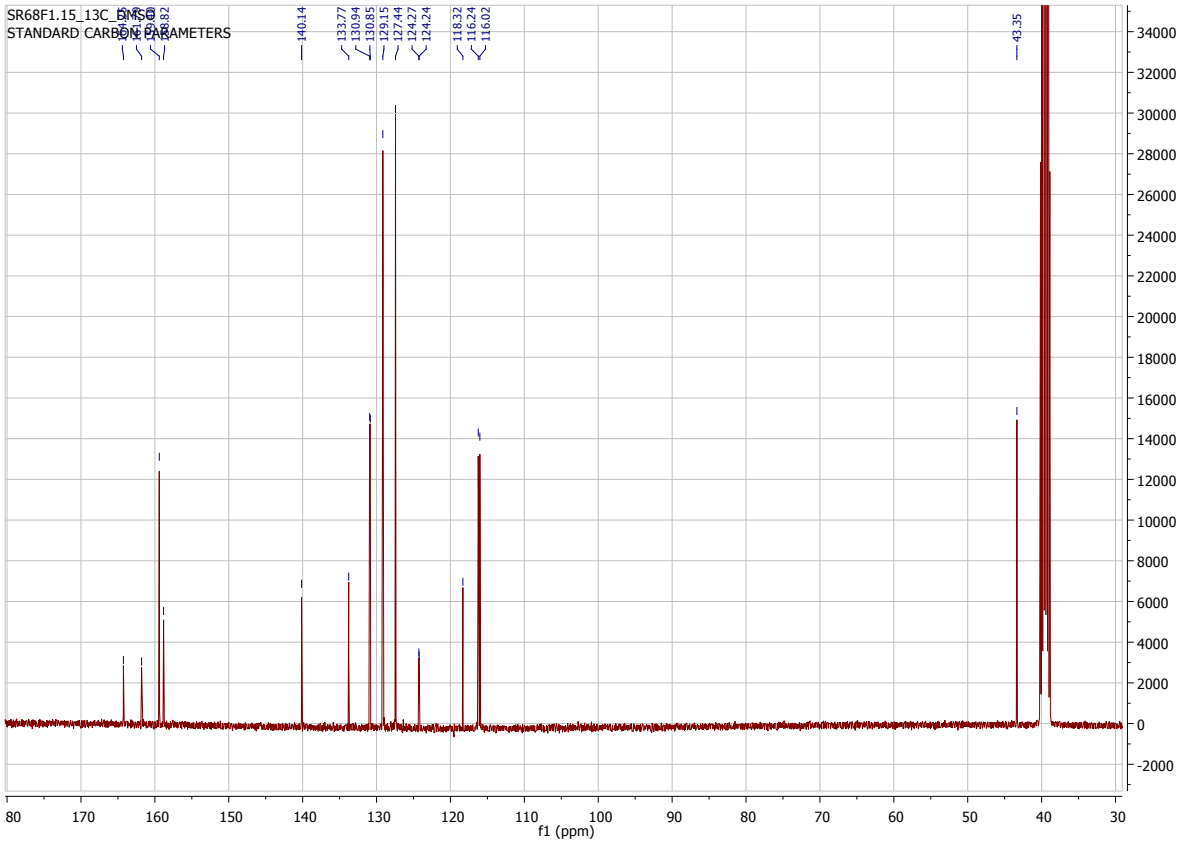
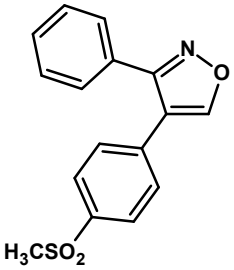


Figure S11. ^{1}H NMR spectrum of 3d

(**3d**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



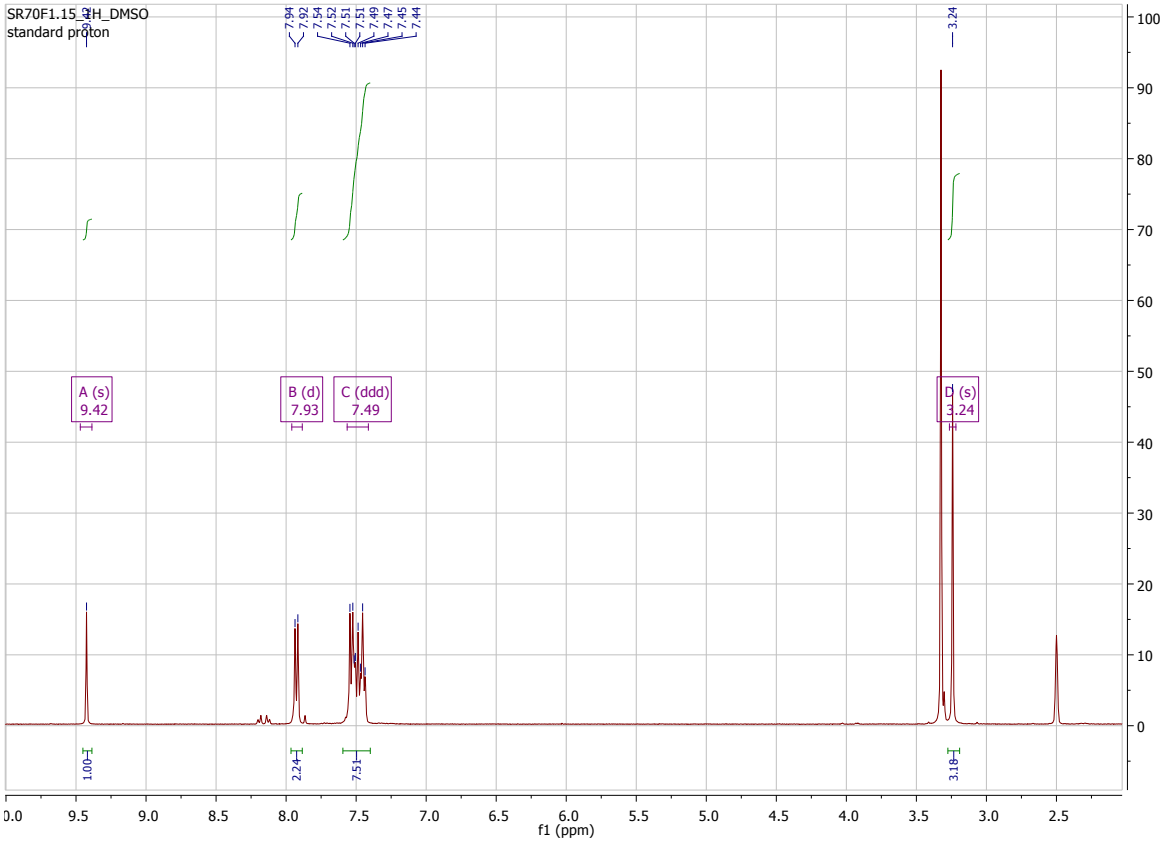
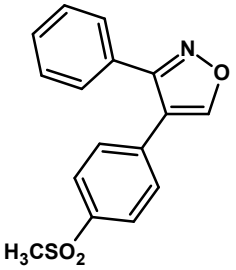


Figure S12. ^{13}C NMR spectrum of 3d

(**3d**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



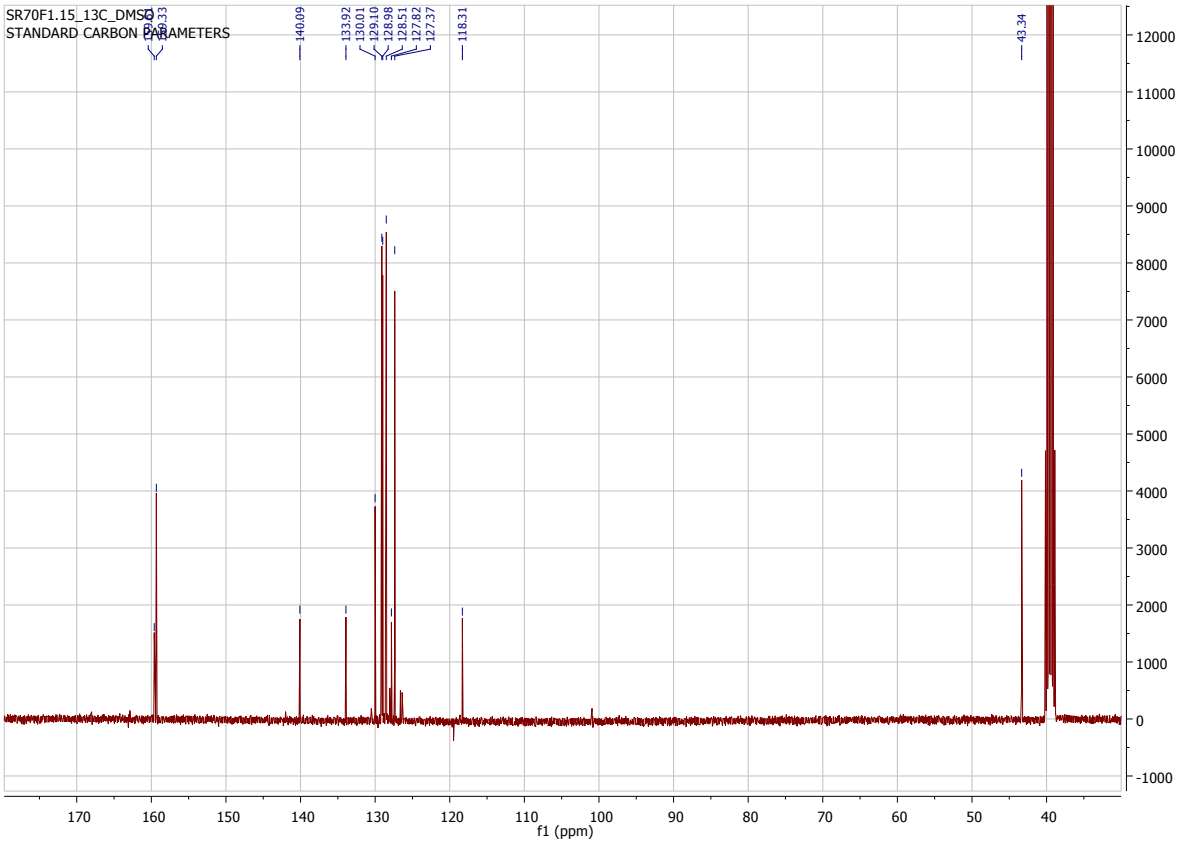
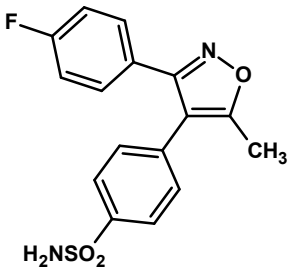


Figure S13. ^{1}H NMR spectrum of 3e

(**3e**) **^{1}H NMR** (acetone d6, 400 MHz)



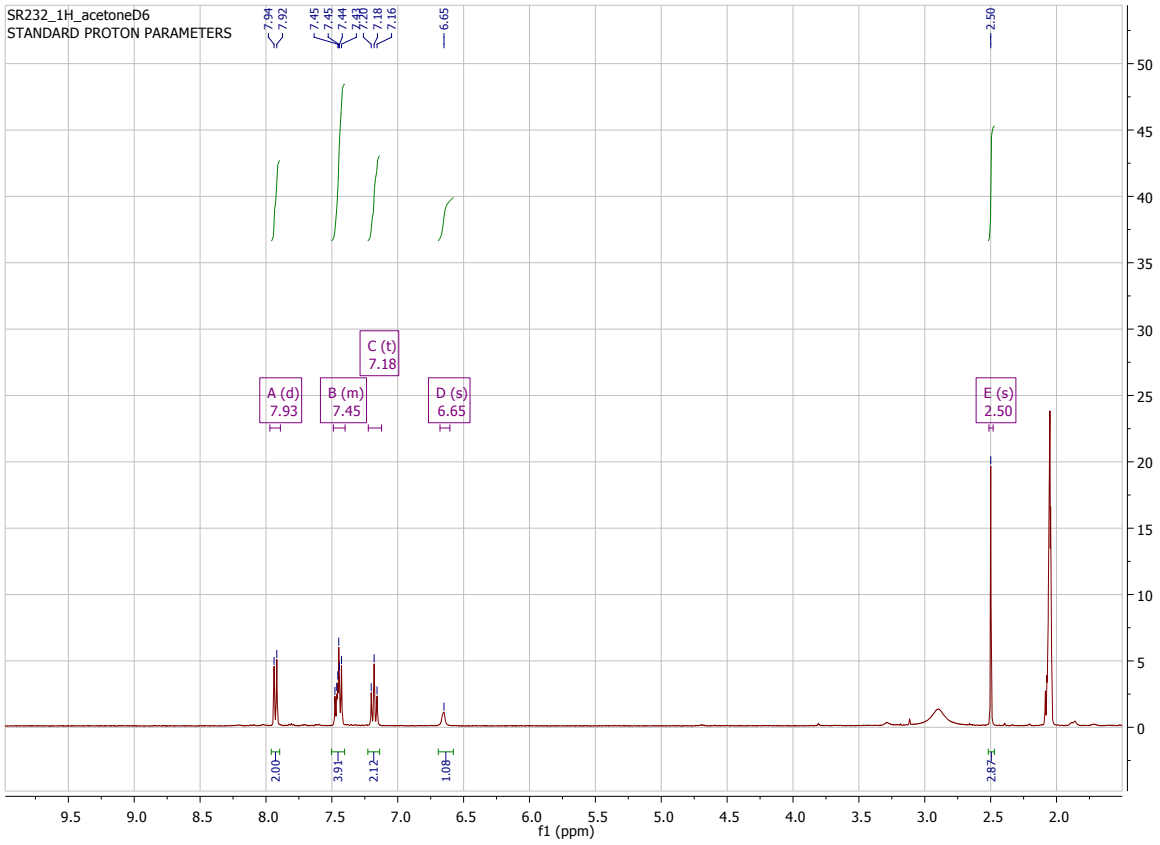
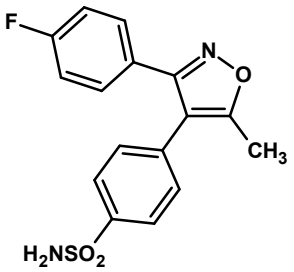


Figure S14. ^{13}C NMR spectrum of 3e

(**3e**) **^{13}C NMR** (acetone d6, 101 MHz)



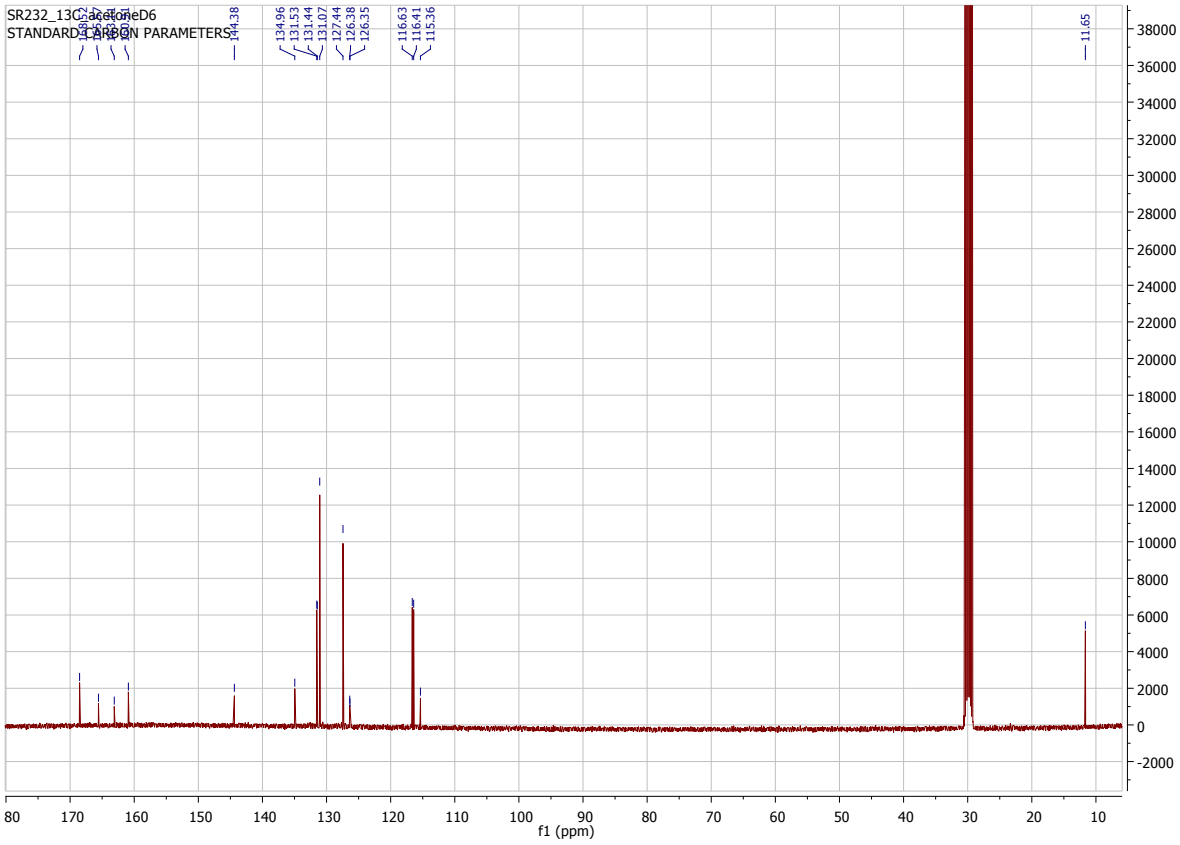
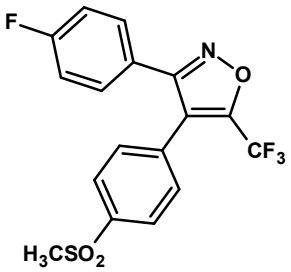


Figure S15. ^{1}H NMR spectrum of 3f

(**3f**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



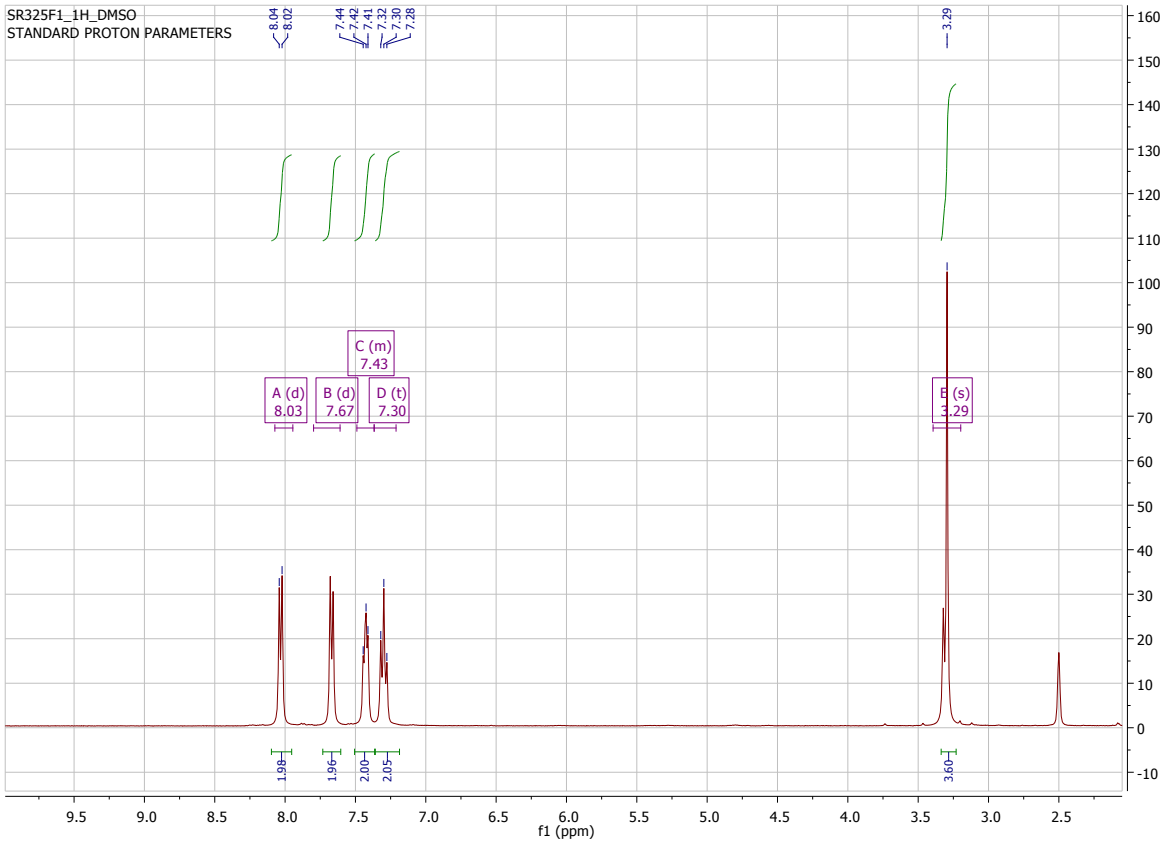
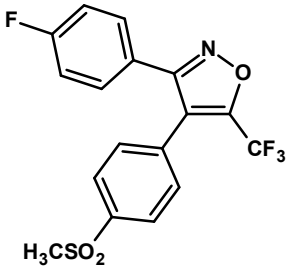


Figure S16. ^{13}C NMR spectrum of 3f

(**3f**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



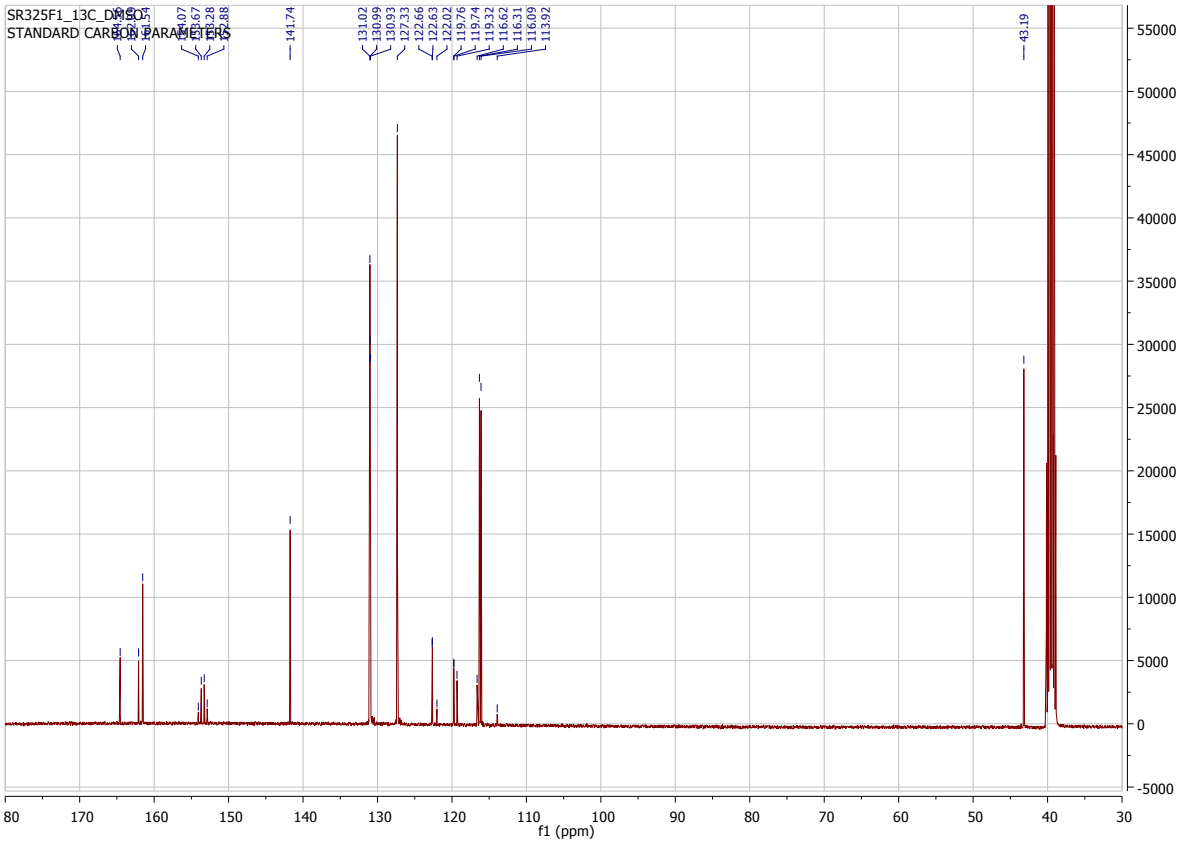
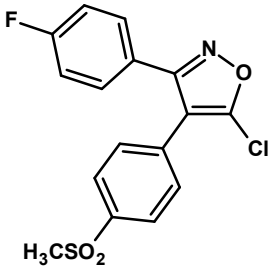


Figure S17. ^{1}H NMR spectrum of 3g

(**3g**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



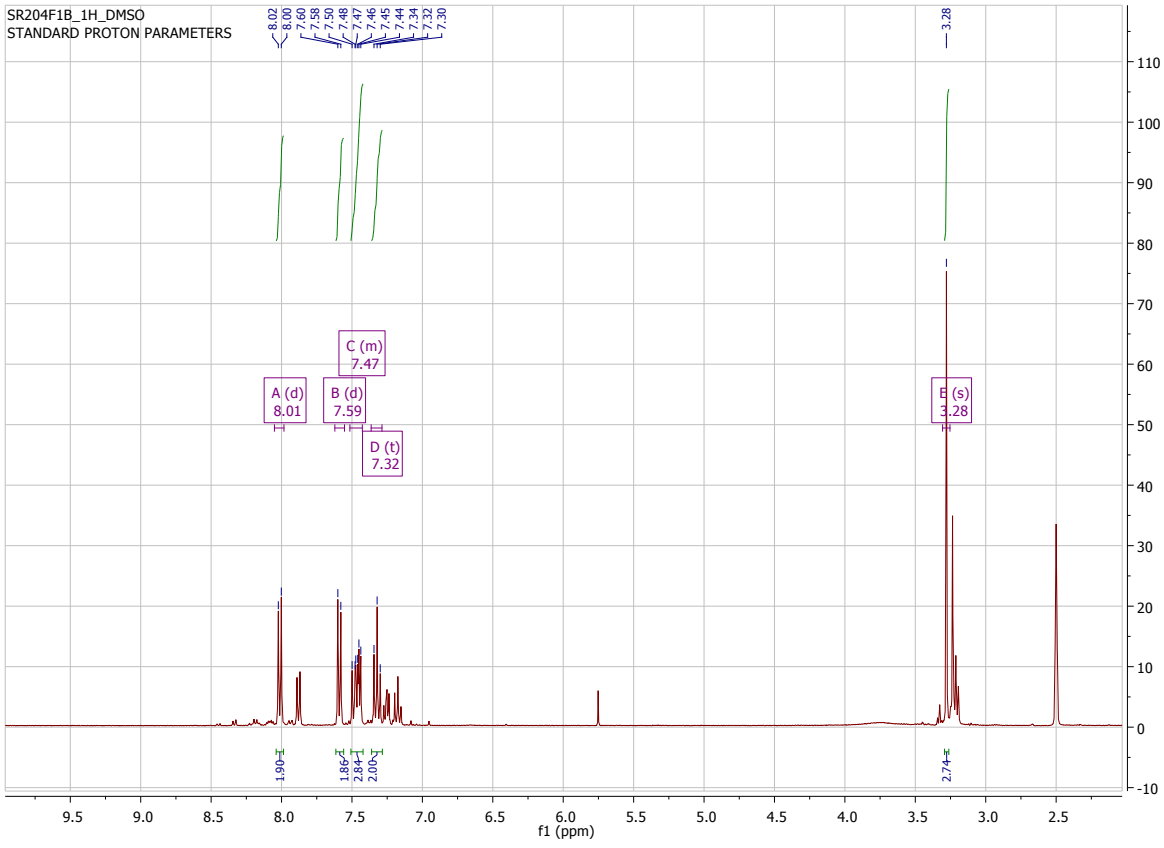
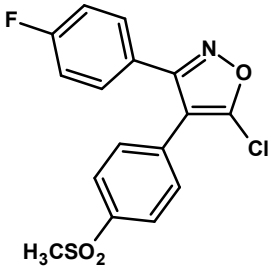


Figure S18. ^{13}C NMR spectrum of 3g

(**3g**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



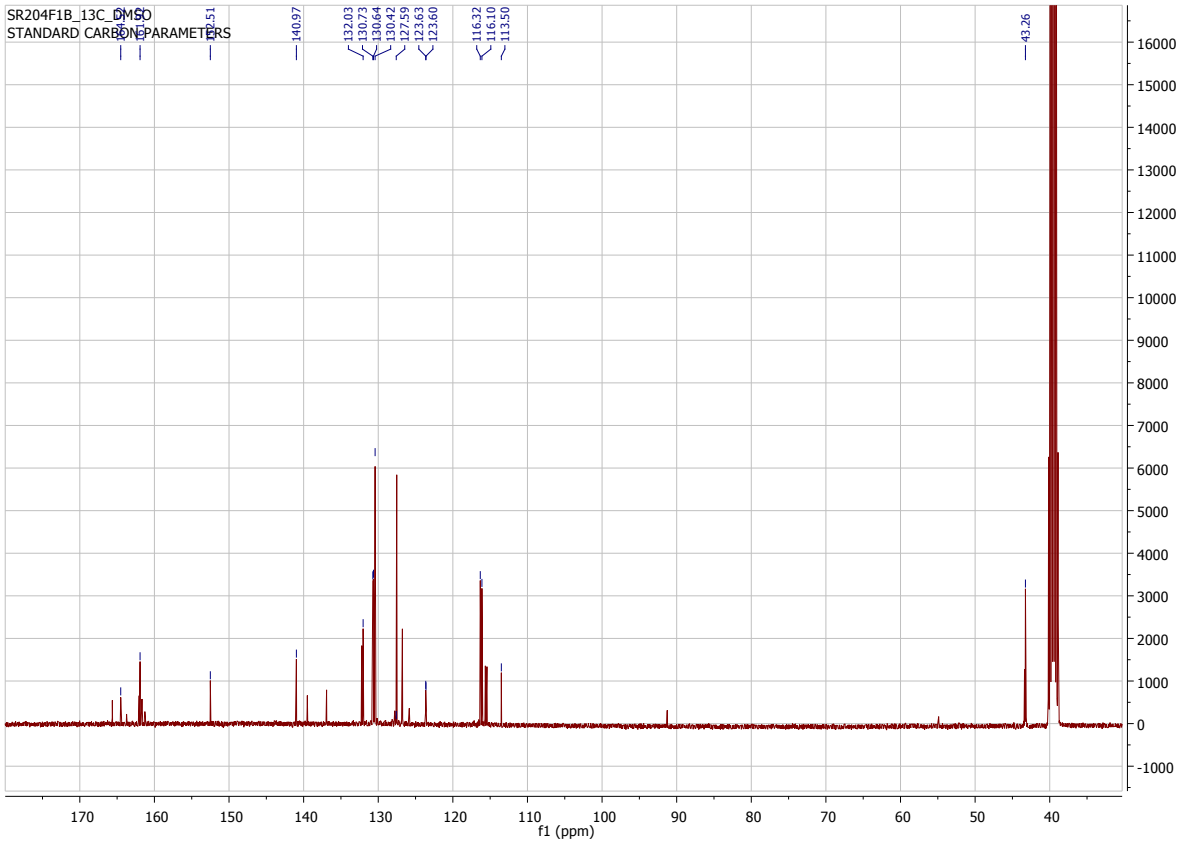
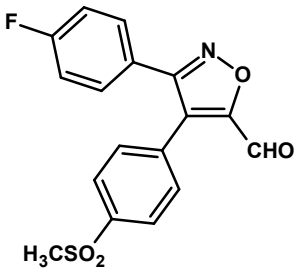


Figure S19. ^{1}H NMR spectrum of 3h

(**3h**) **^{1}H NMR** (acetone d6, 400 MHz)



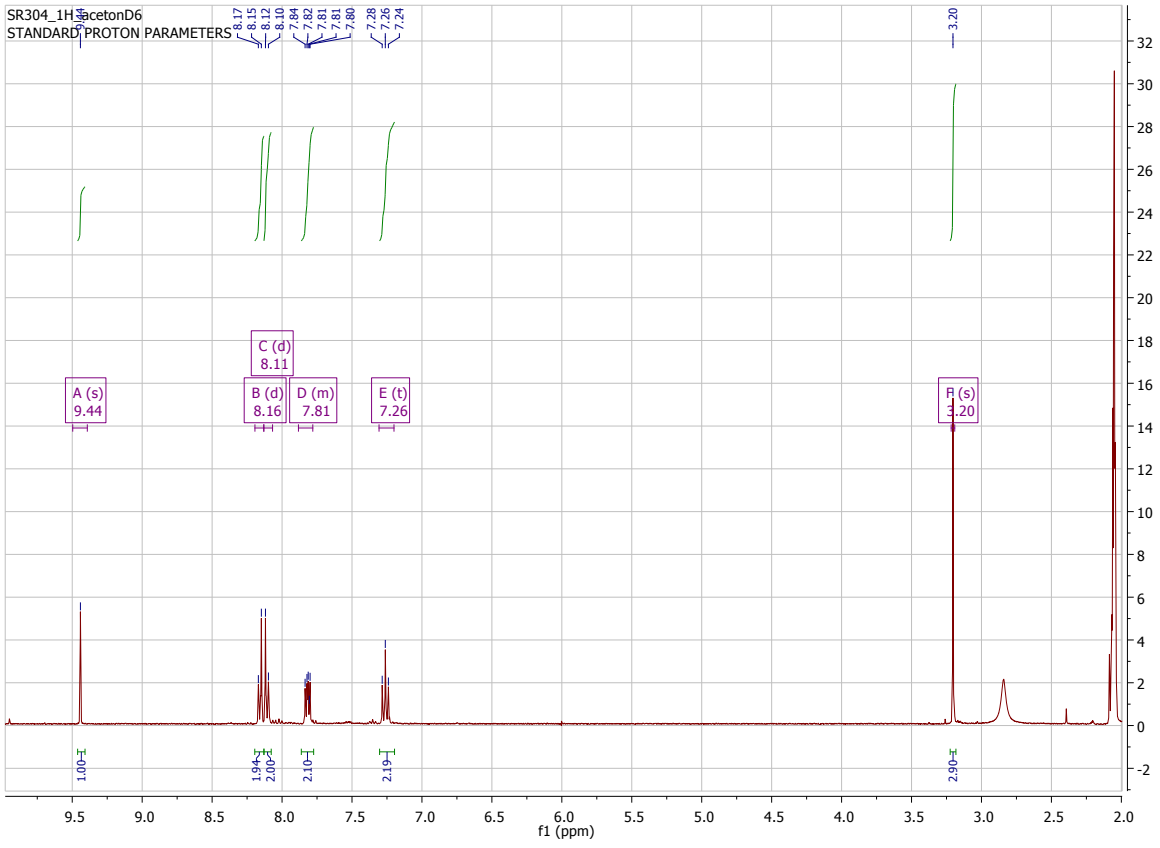
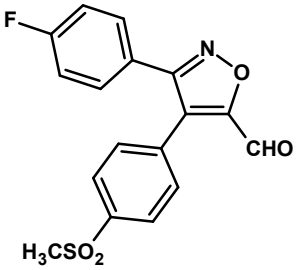


Figure S20. ^{13}C NMR spectrum of 3h

(**3h**) **^{13}C NMR** (acetone d6, 101 MHz)



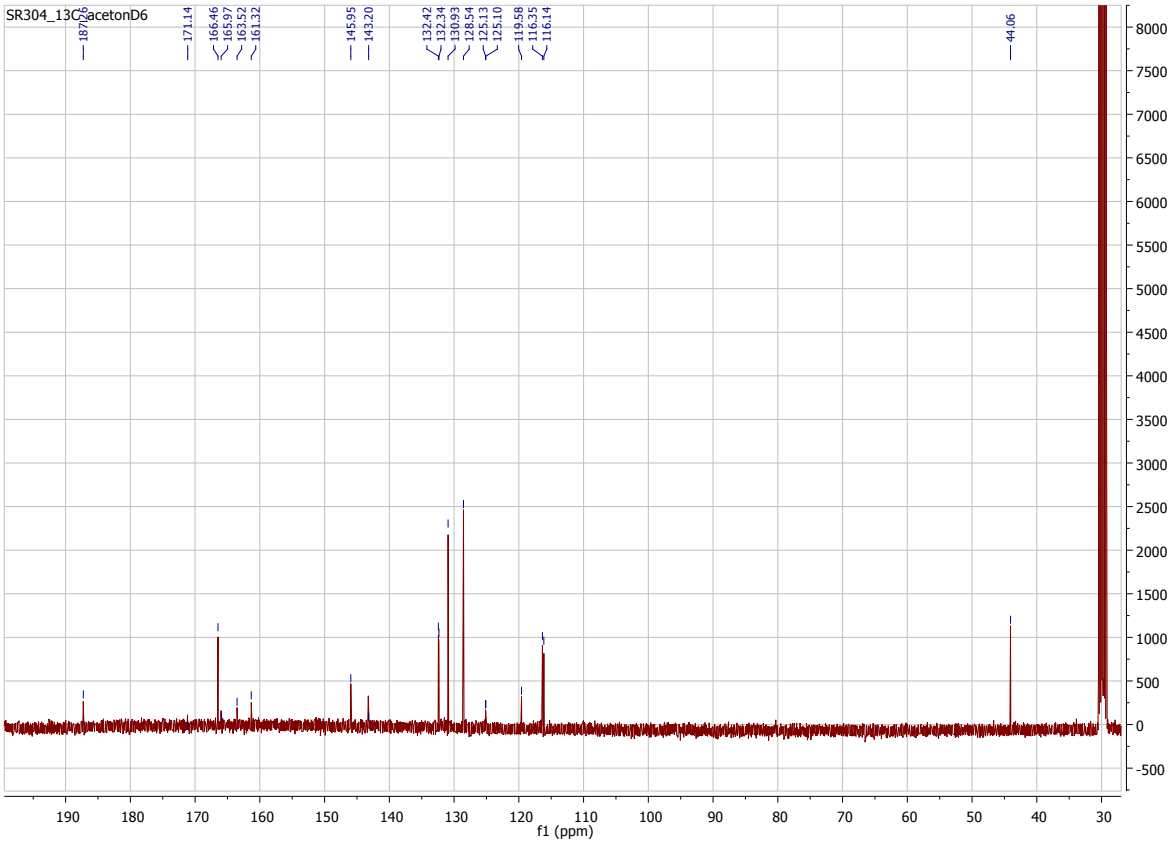
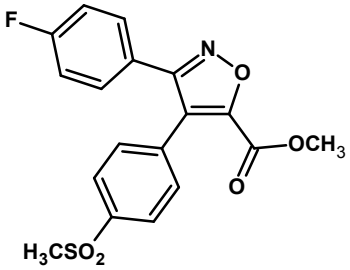


Figure S21. ^{1}H NMR spectrum of 3i

(**3i**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



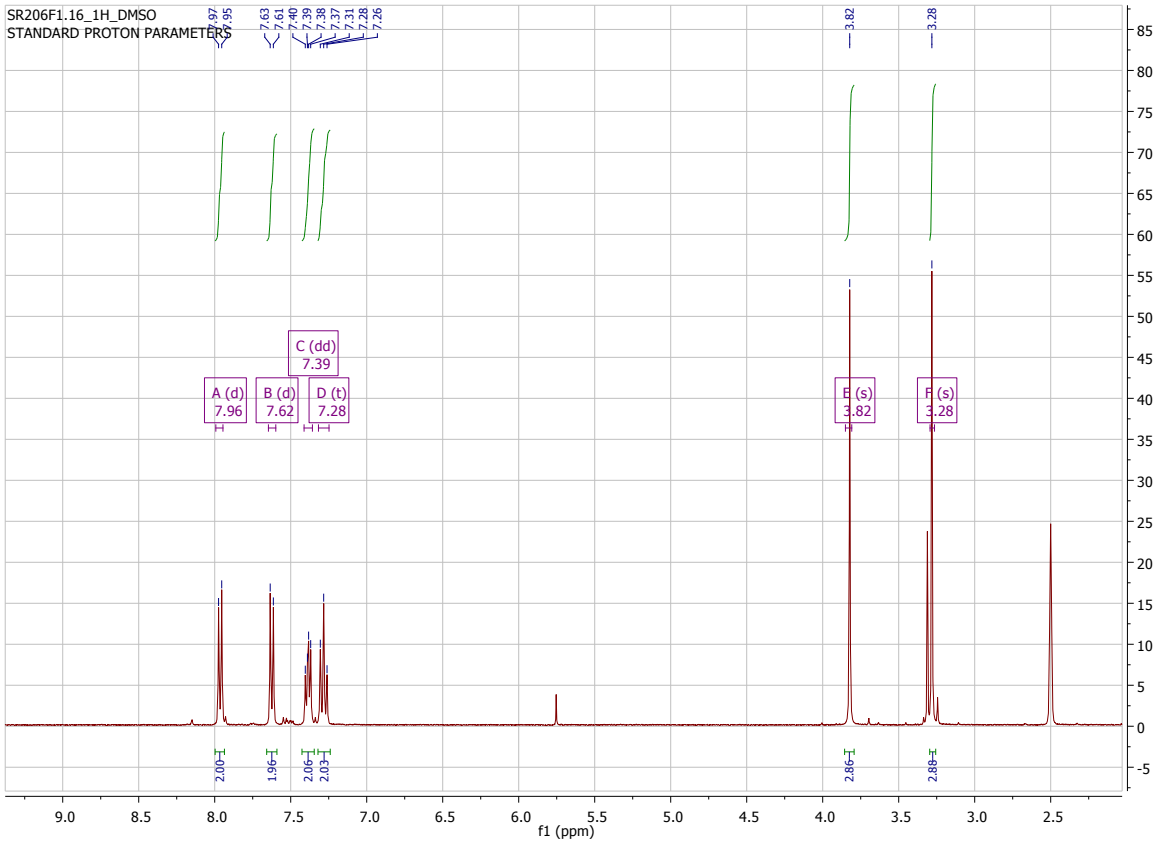
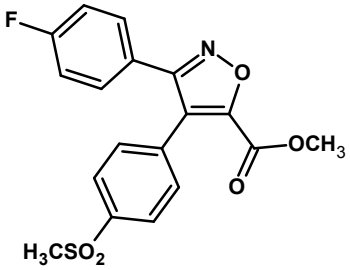


Figure S22. ^{13}C NMR spectrum of 3i

(**3i**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



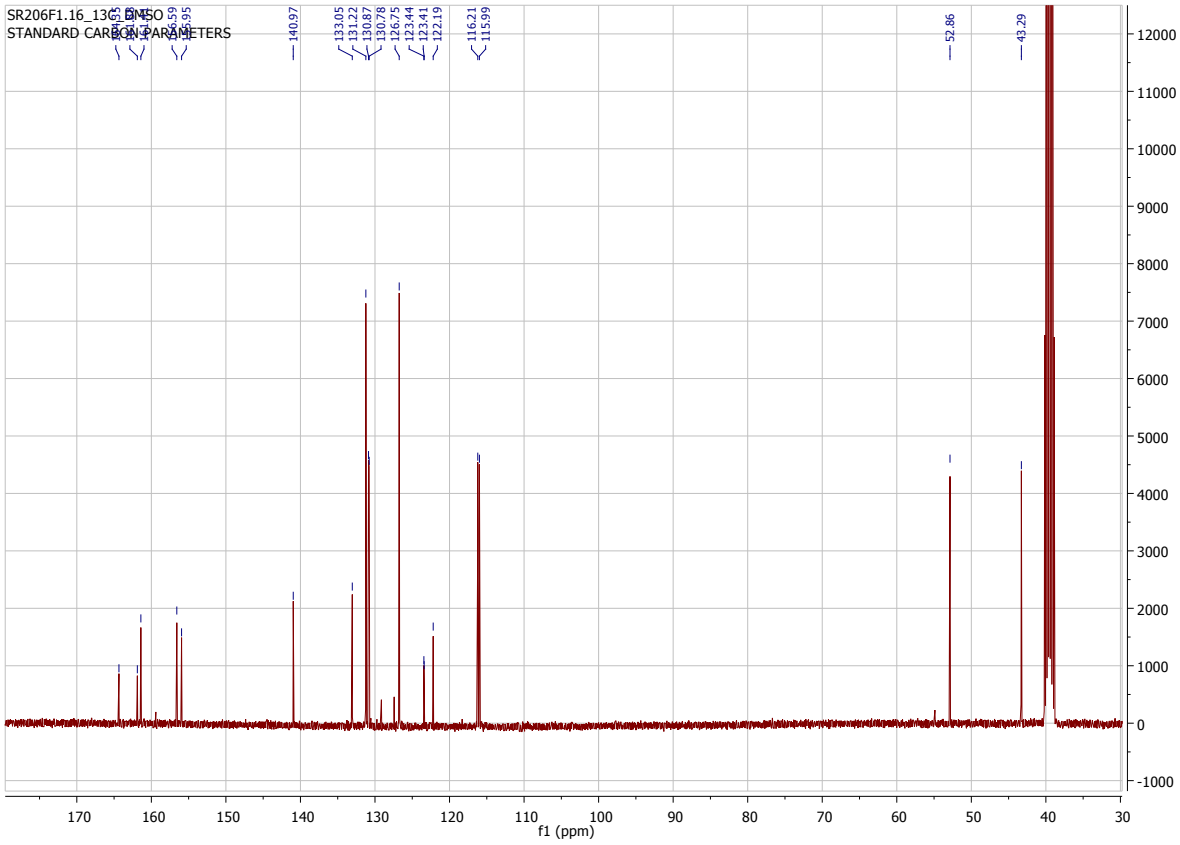
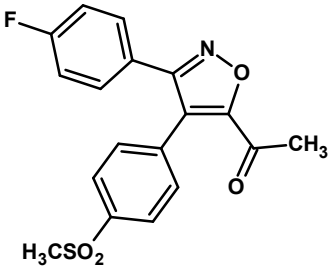


Figure S23. ^{1}H NMR spectrum of 3j

(**3j**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



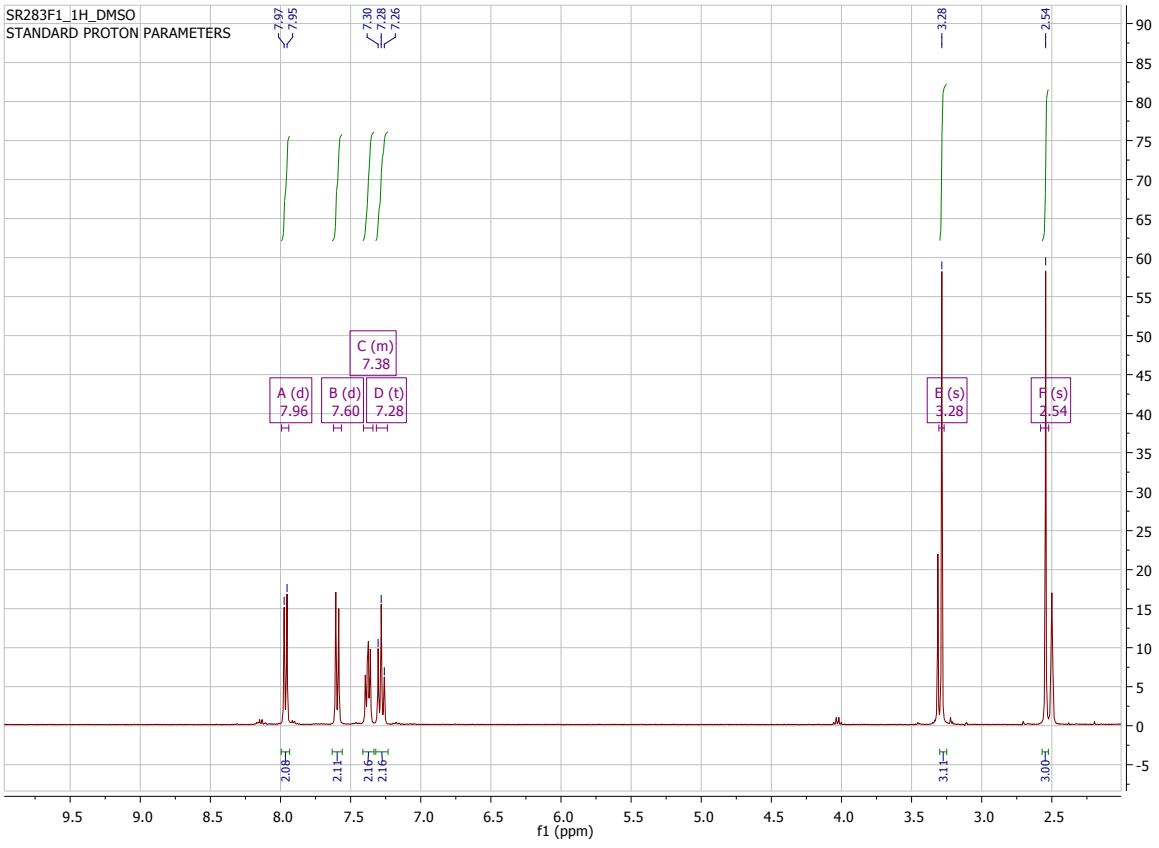
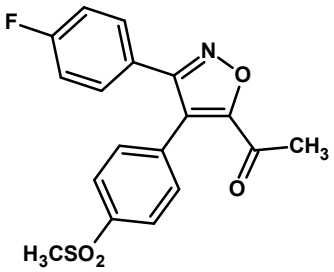


Figure S24. ^{13}C NMR spectrum of 3j

(**3j**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



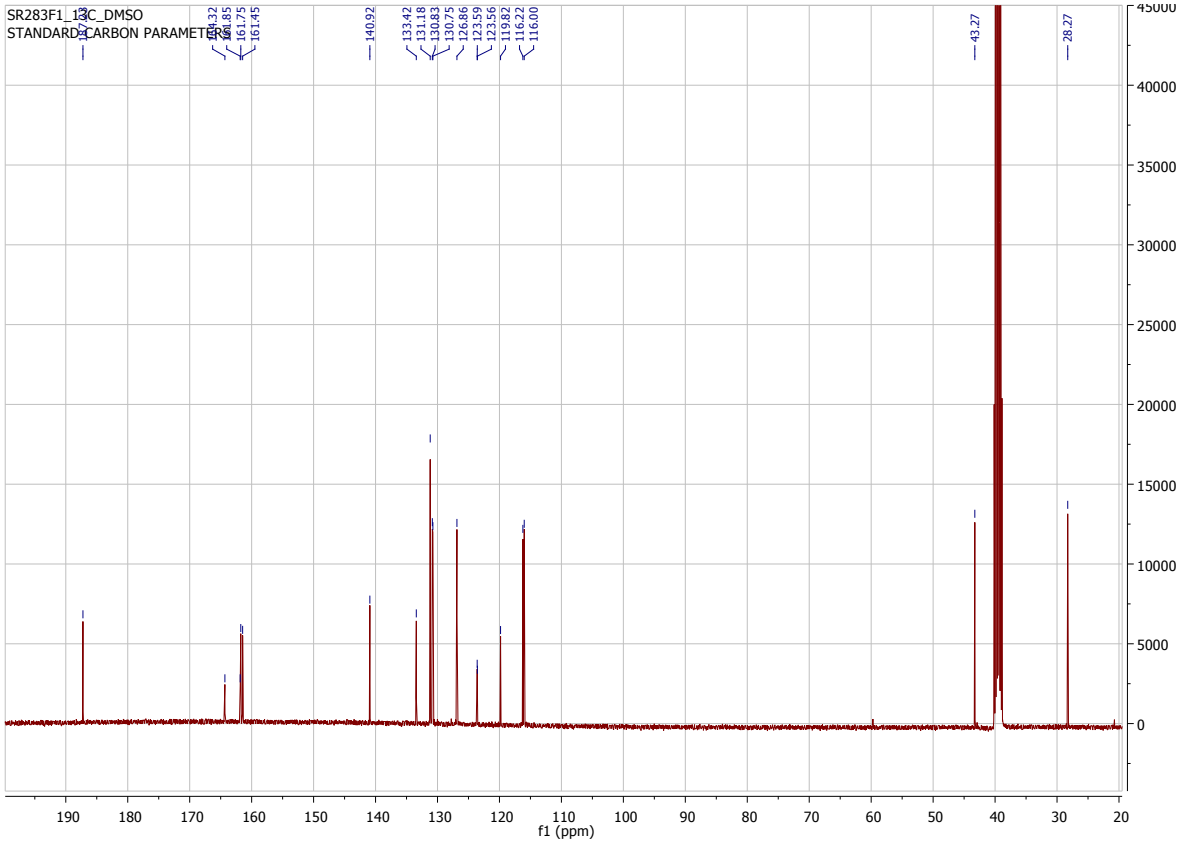
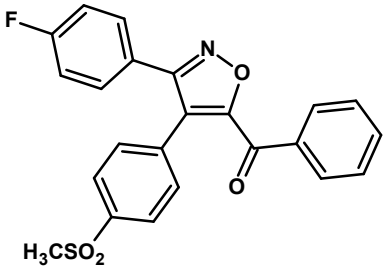


Figure S25. ^{1}H NMR spectrum of 3k

(**3k**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



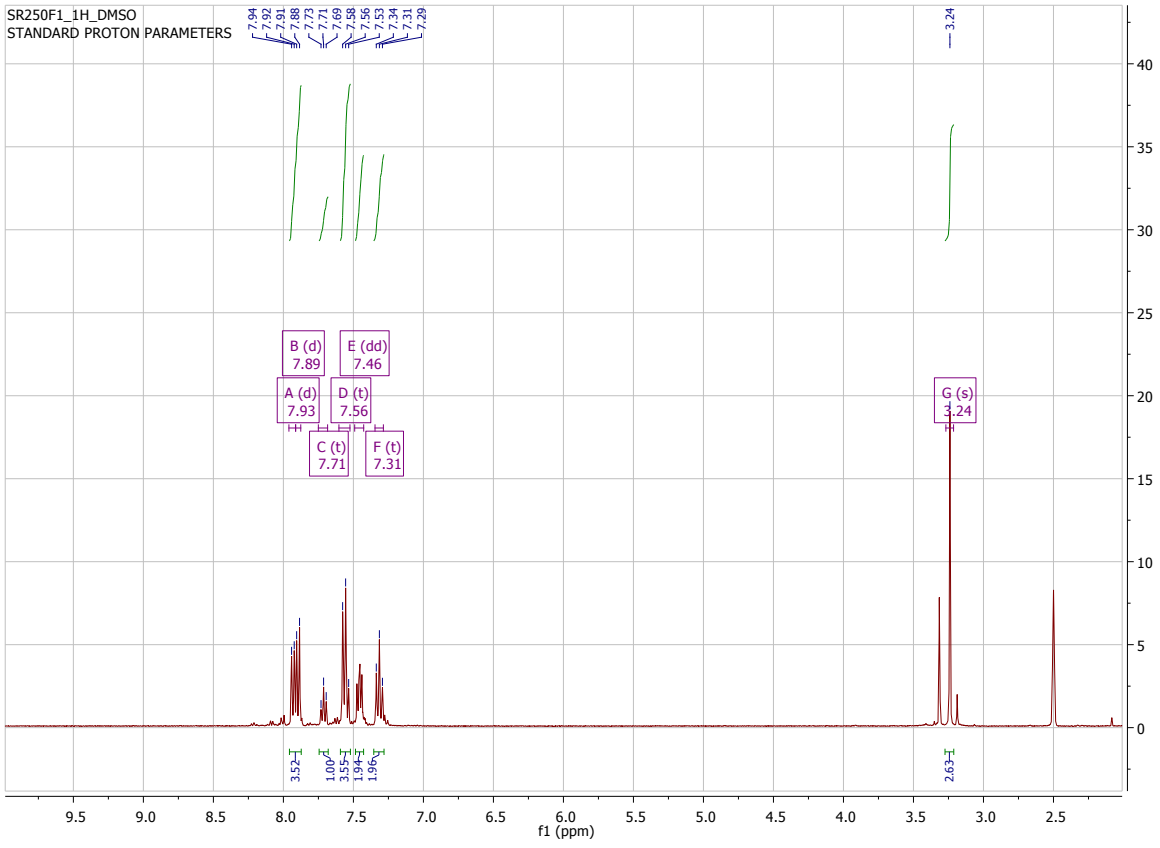
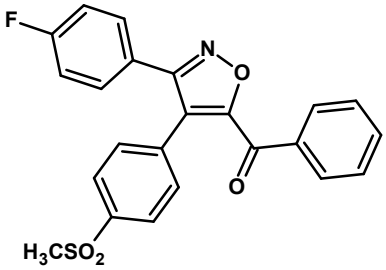


Figure S26. ^{13}C NMR spectrum of 3k

(**3k**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



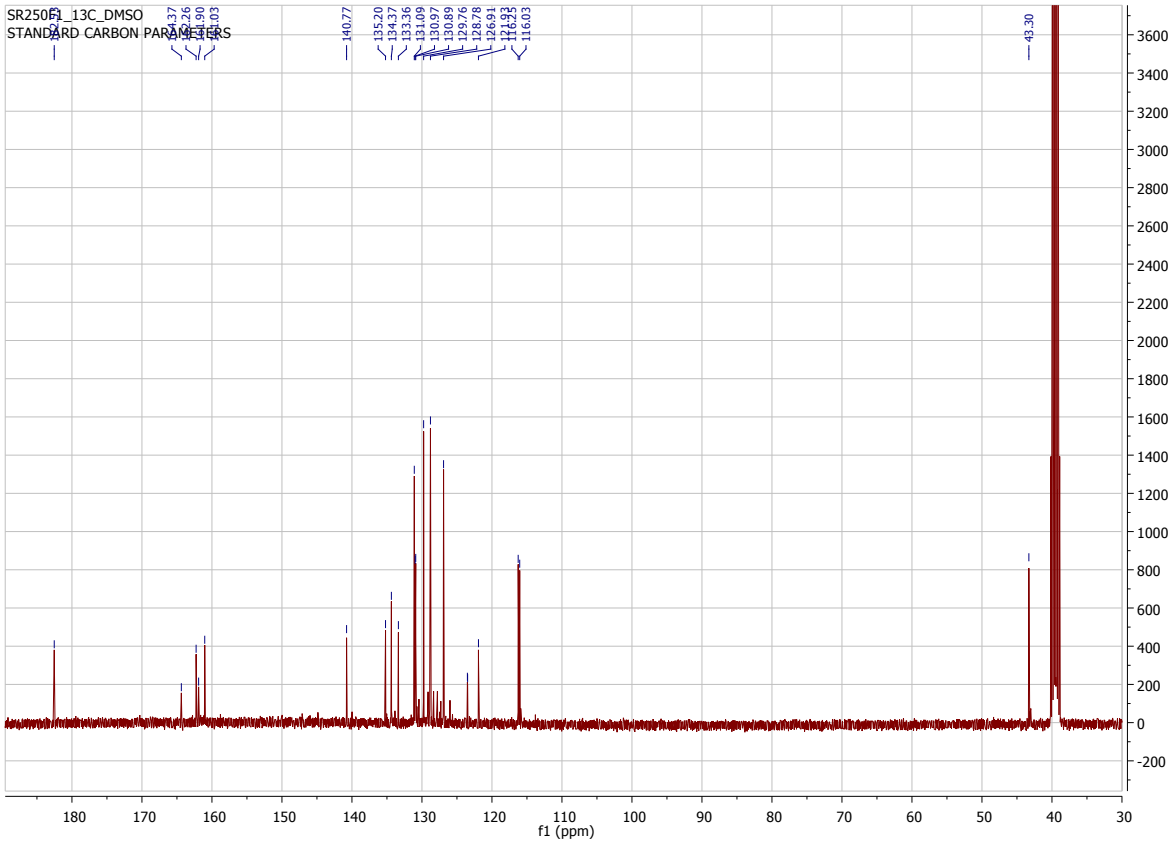
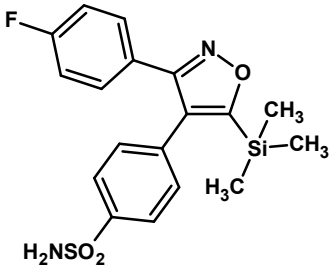


Figure S27. ^{1}H NMR spectrum of 3l

(**3l**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



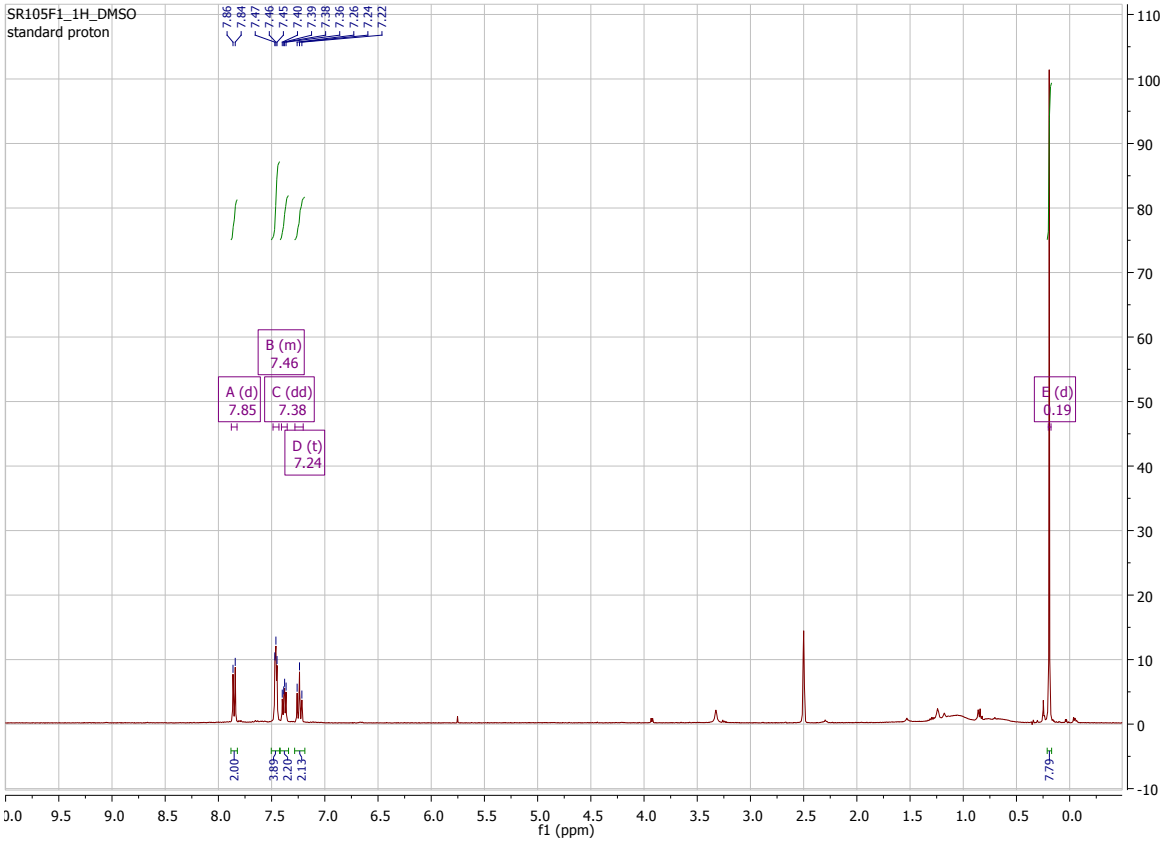
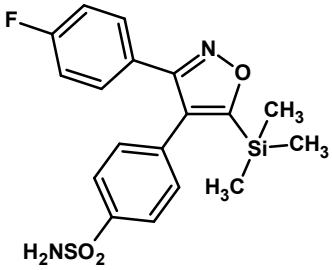


Figure S28. ^{13}C NMR spectrum of 3l

(**3l**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



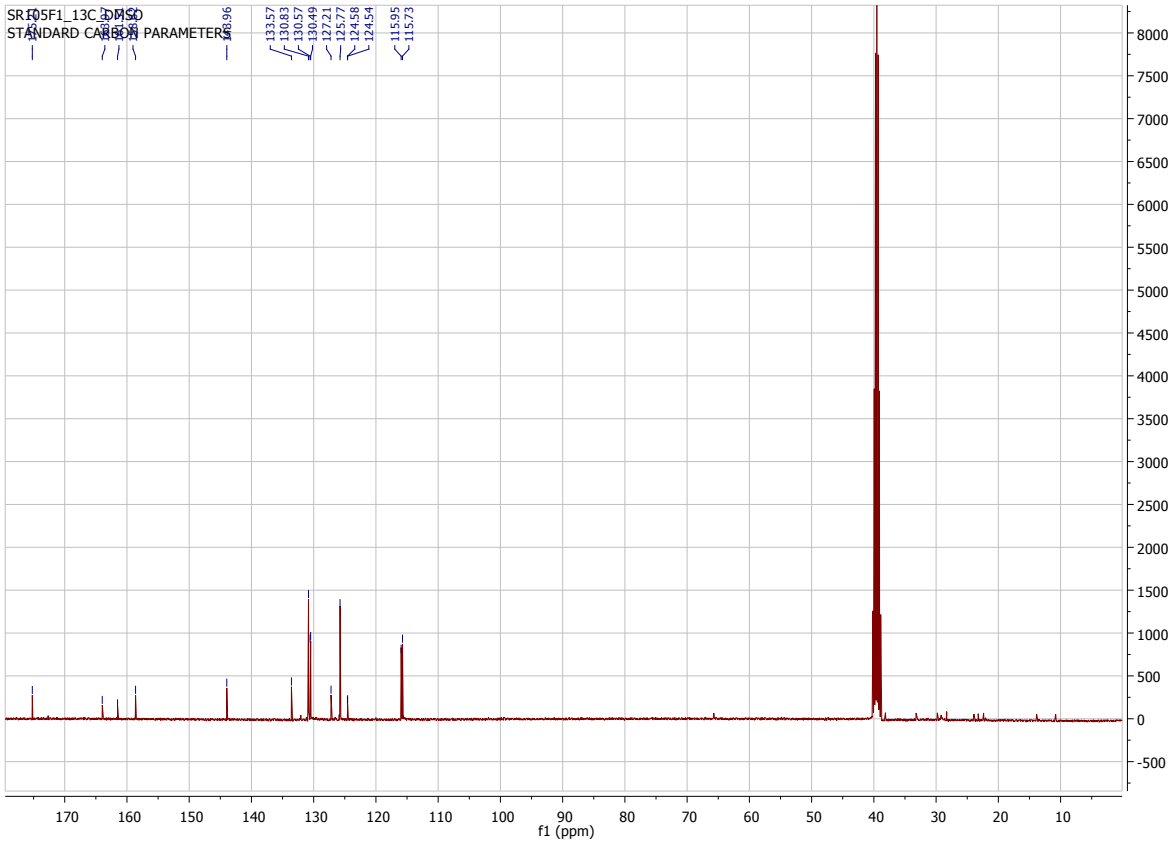
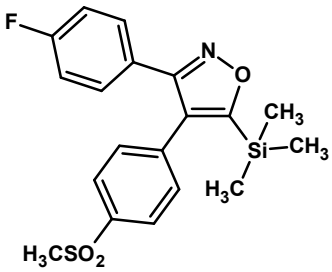


Figure S29. ^{1}H NMR spectrum of 3m

(**3m**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



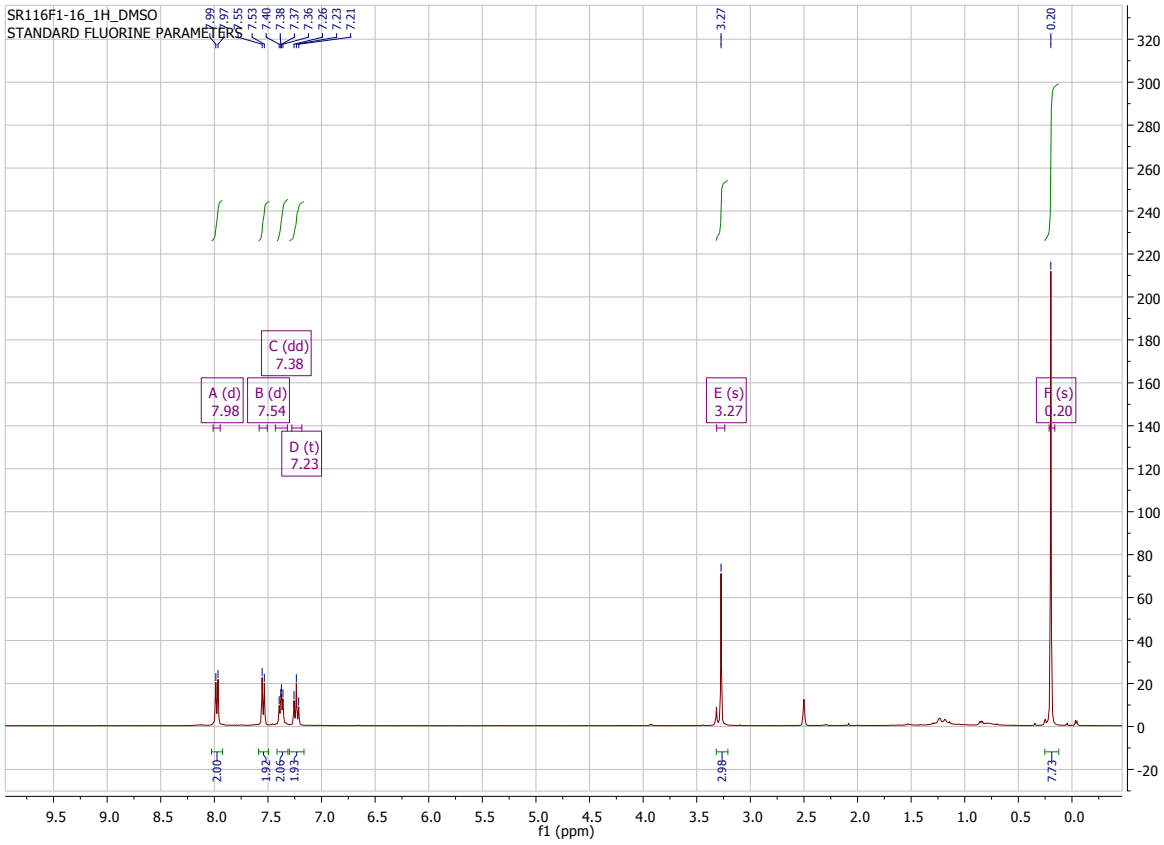
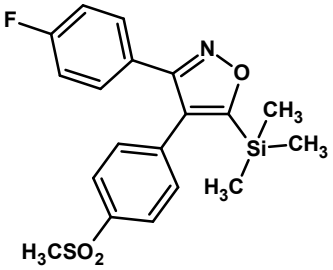


Figure S30. ^{13}C NMR spectrum of 3m

(**3m**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



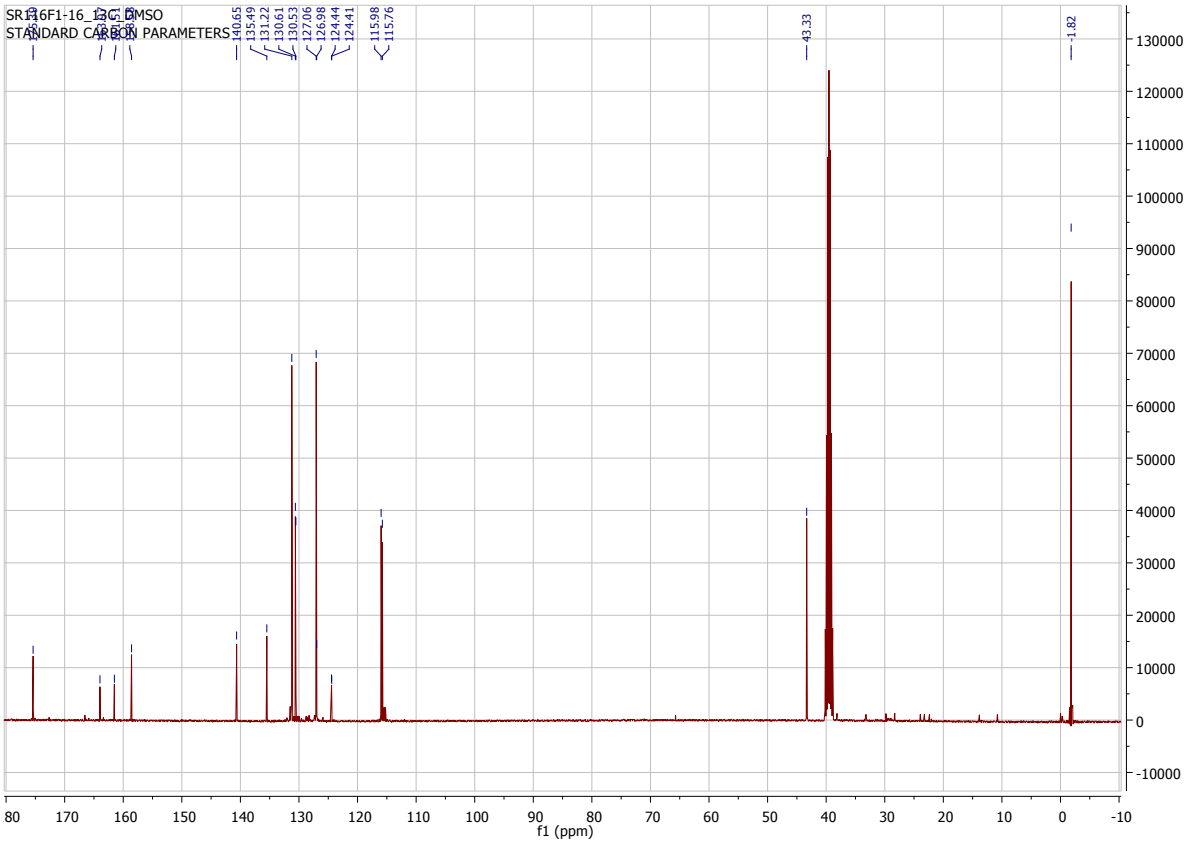
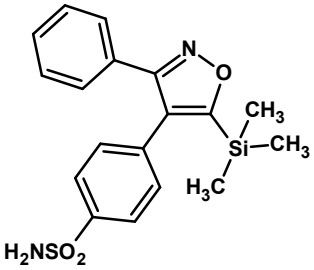


Figure S31. ^{1}H NMR spectrum of 3n

(**3n**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



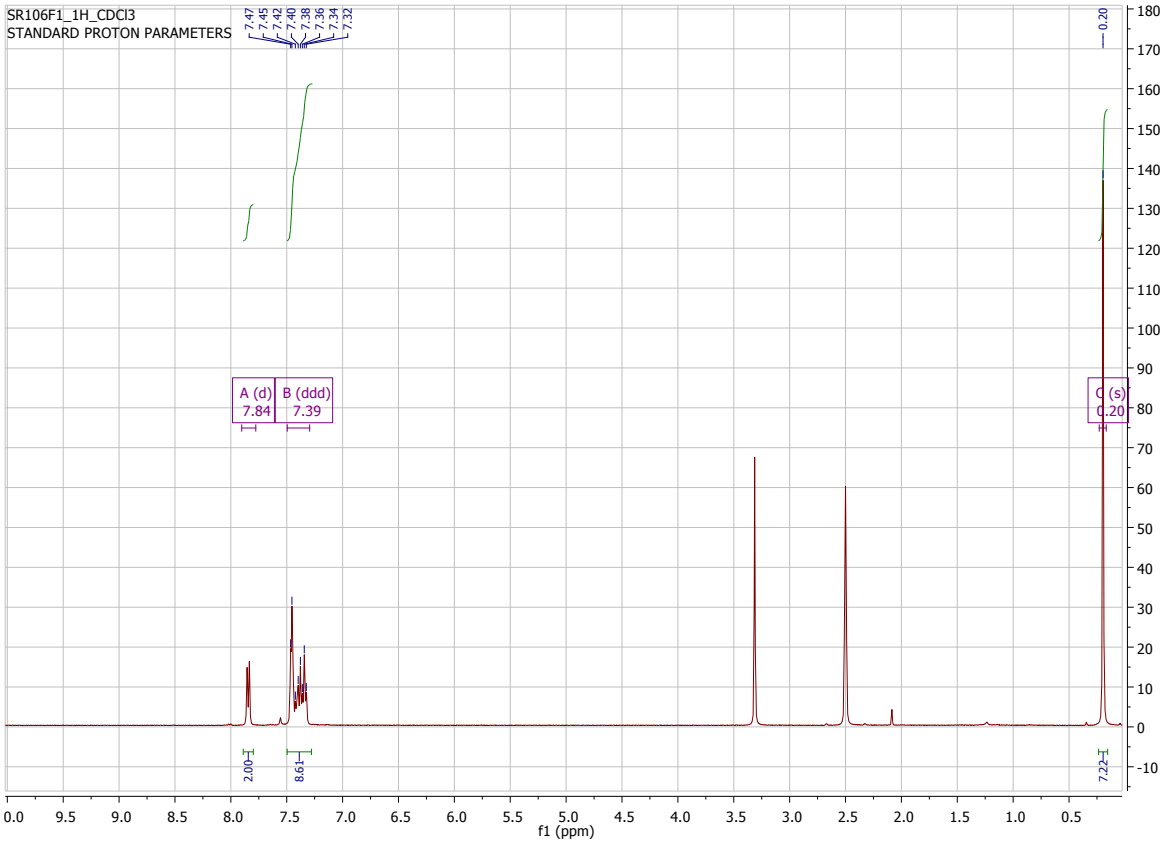
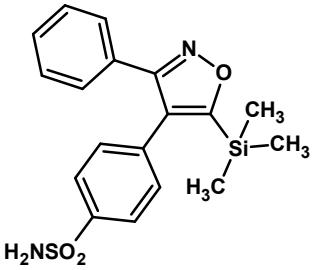


Figure S32. ^{13}C NMR spectrum of 3n

(**3n**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



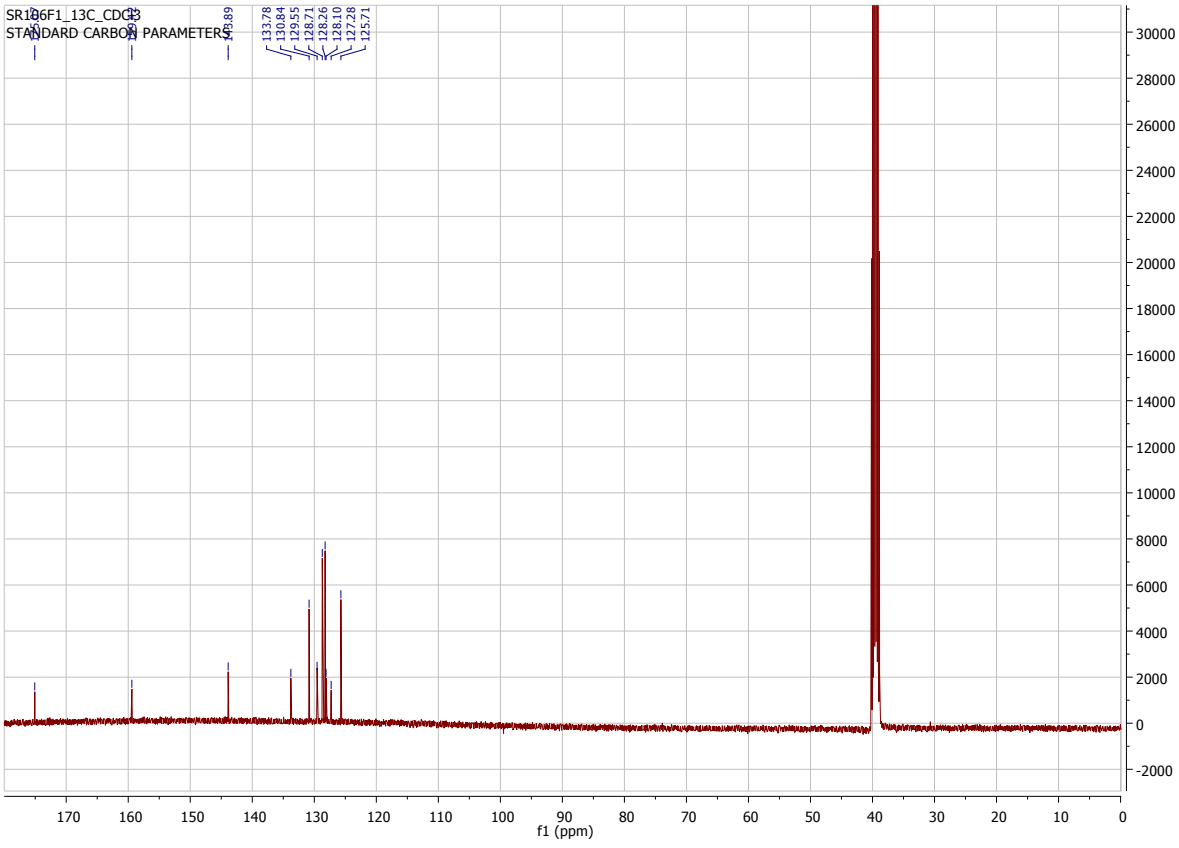
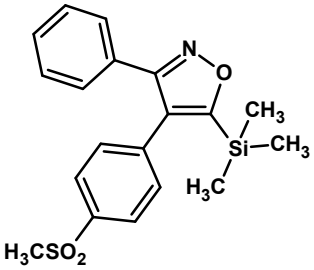


Figure S33. ^{1}H NMR spectrum of 3o

(**3o**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



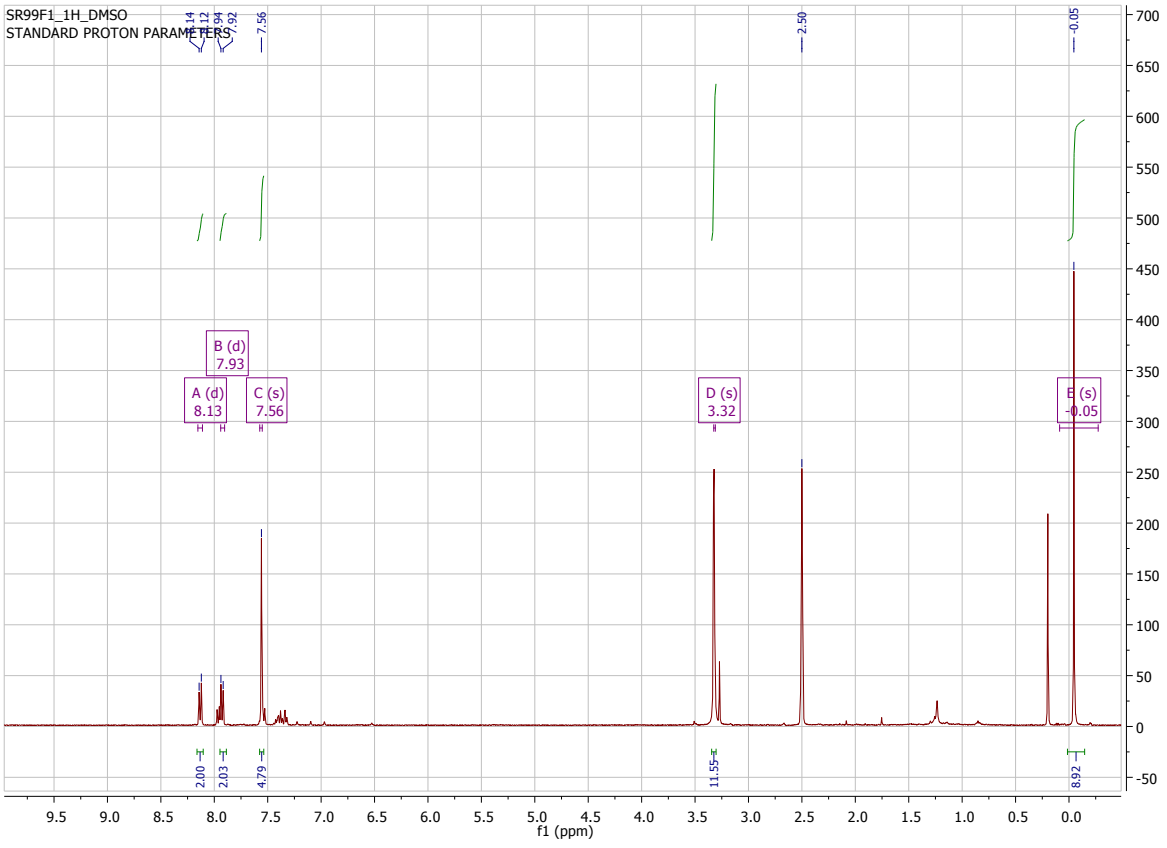
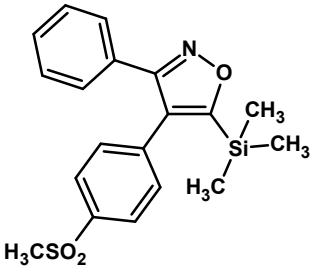


Figure S34. ^{13}C NMR spectrum of 3o

(**3o**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



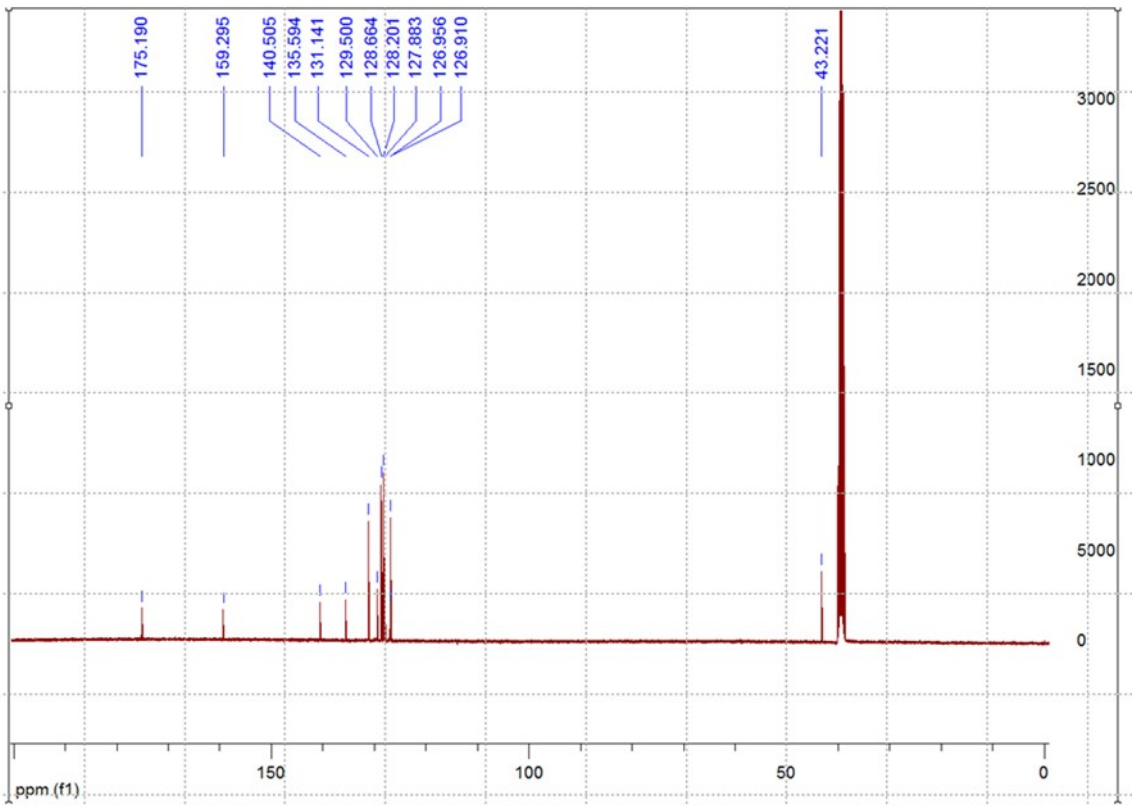
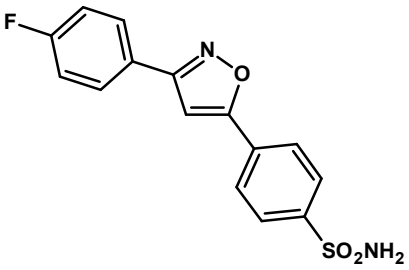


Figure S35. ^{1}H NMR spectrum of 4a

(**4a**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



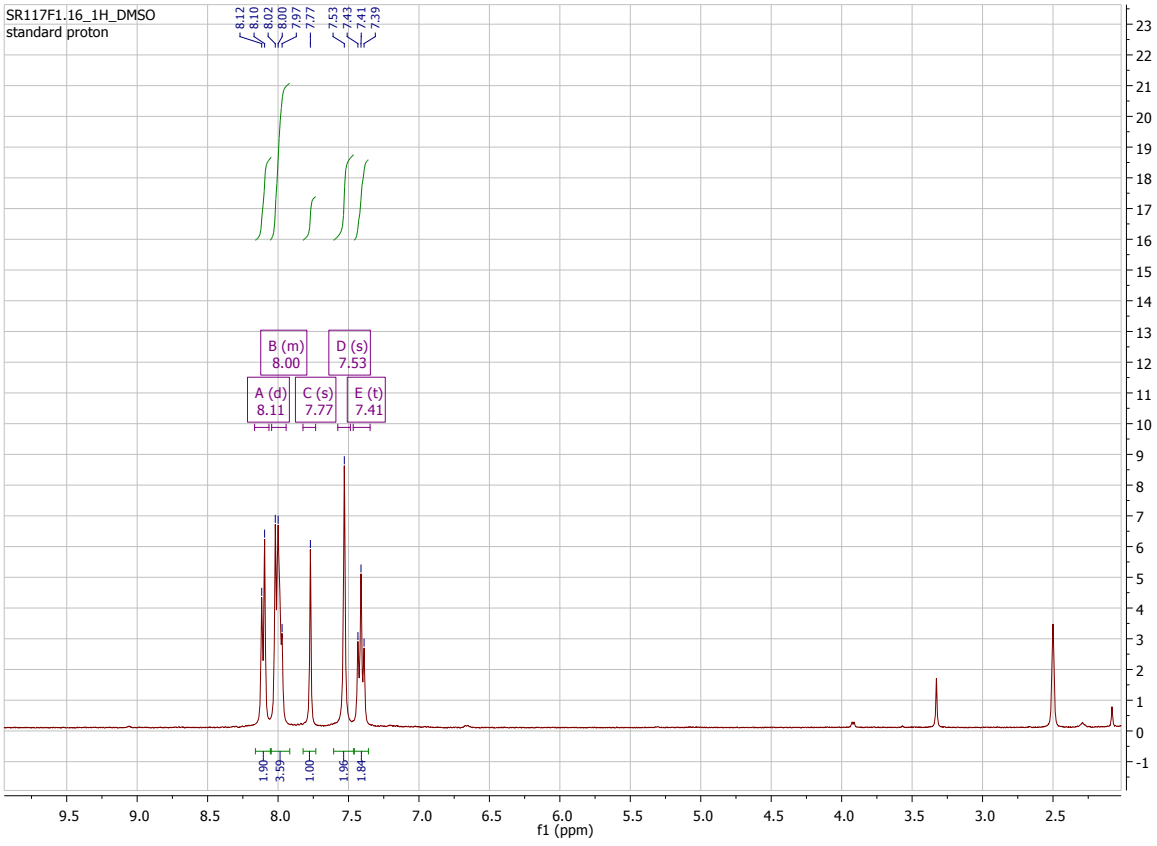
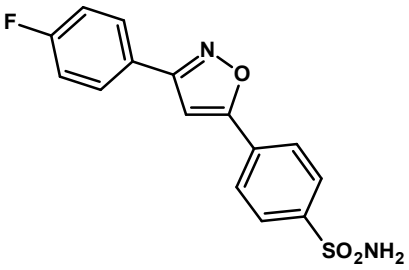


Figure S36. ^{13}C NMR spectrum of 4a

(**4a**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



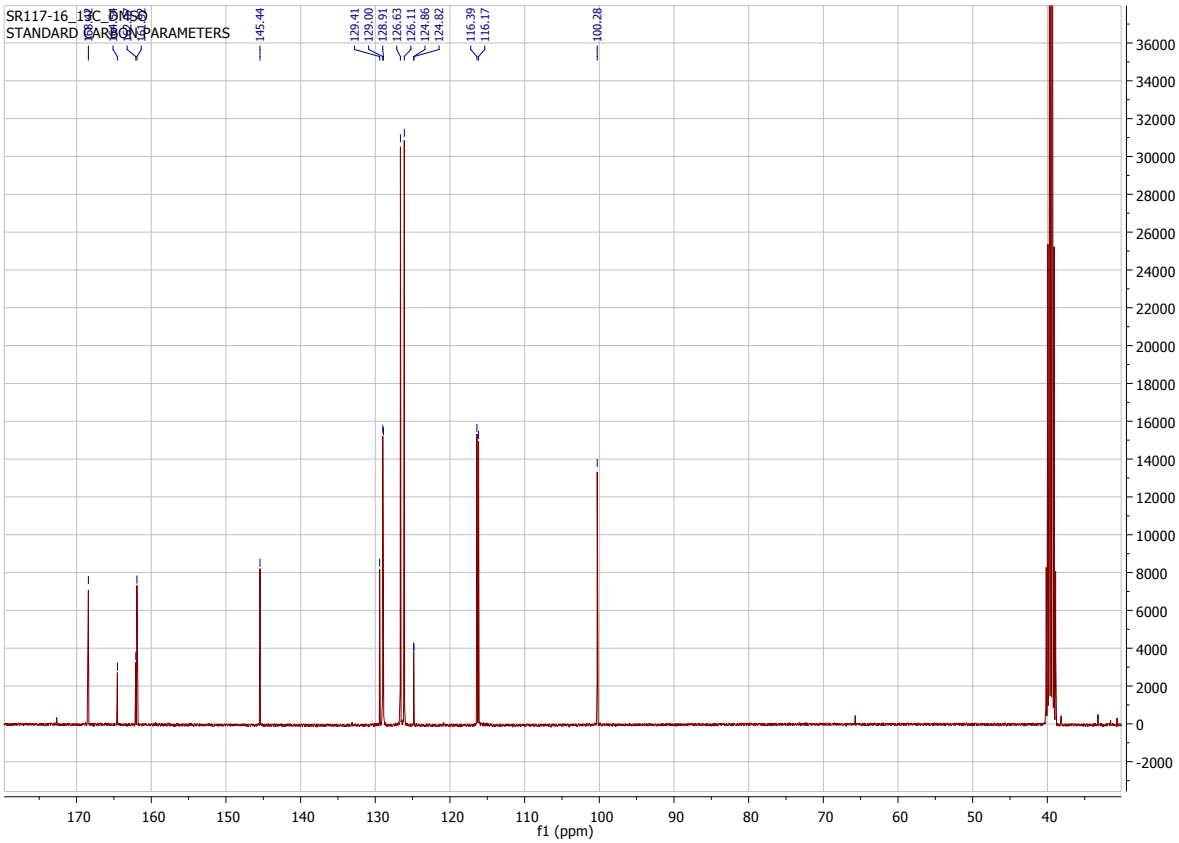


Figure S37. ^{1}H NMR spectrum of 4b

(**4b**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)

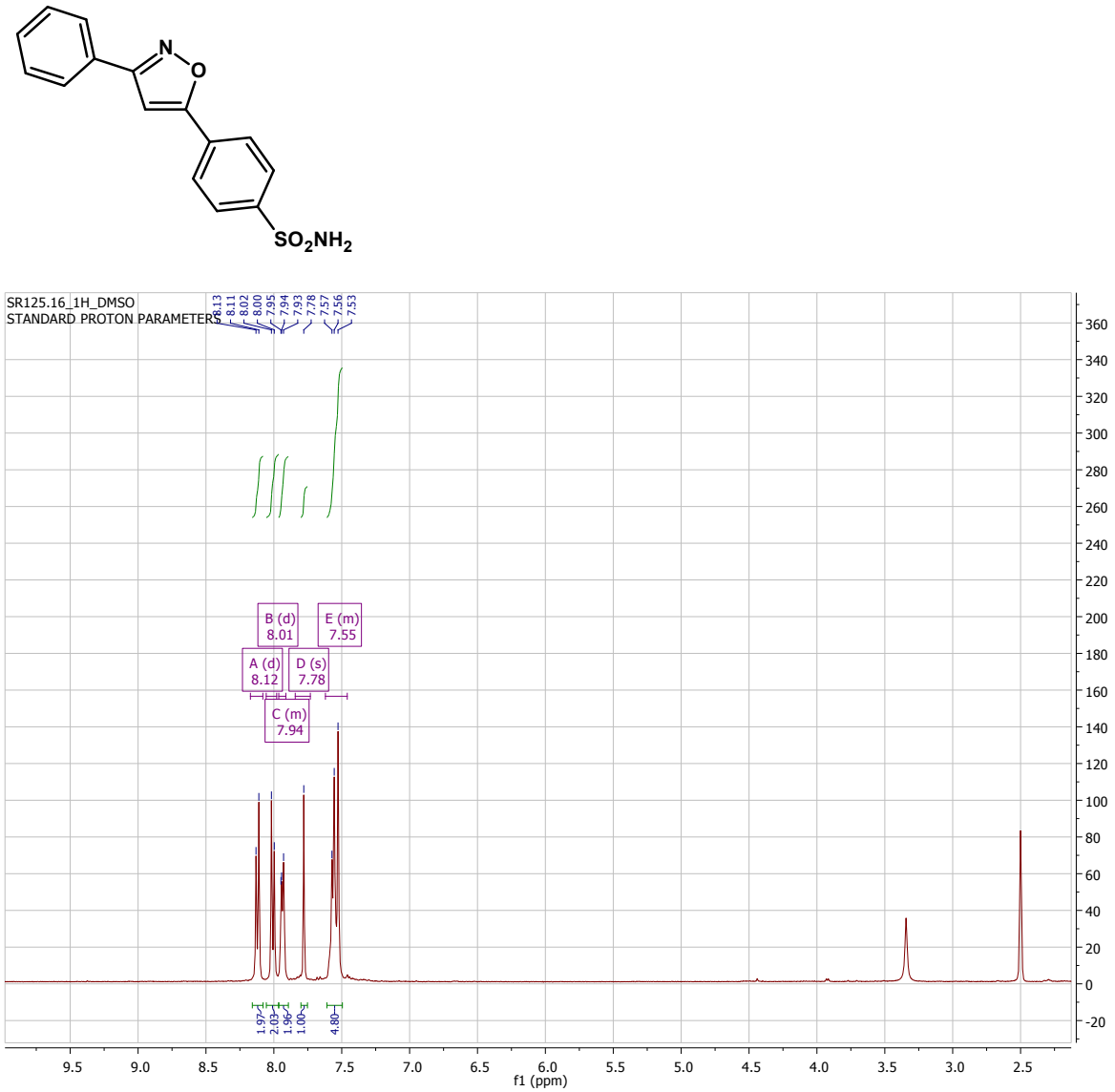
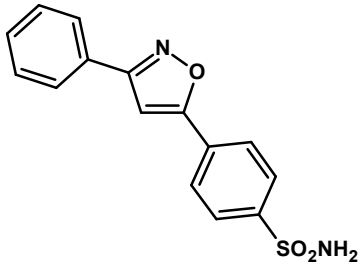


Figure S38. ^{13}C NMR spectrum of 4b

(**4b**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



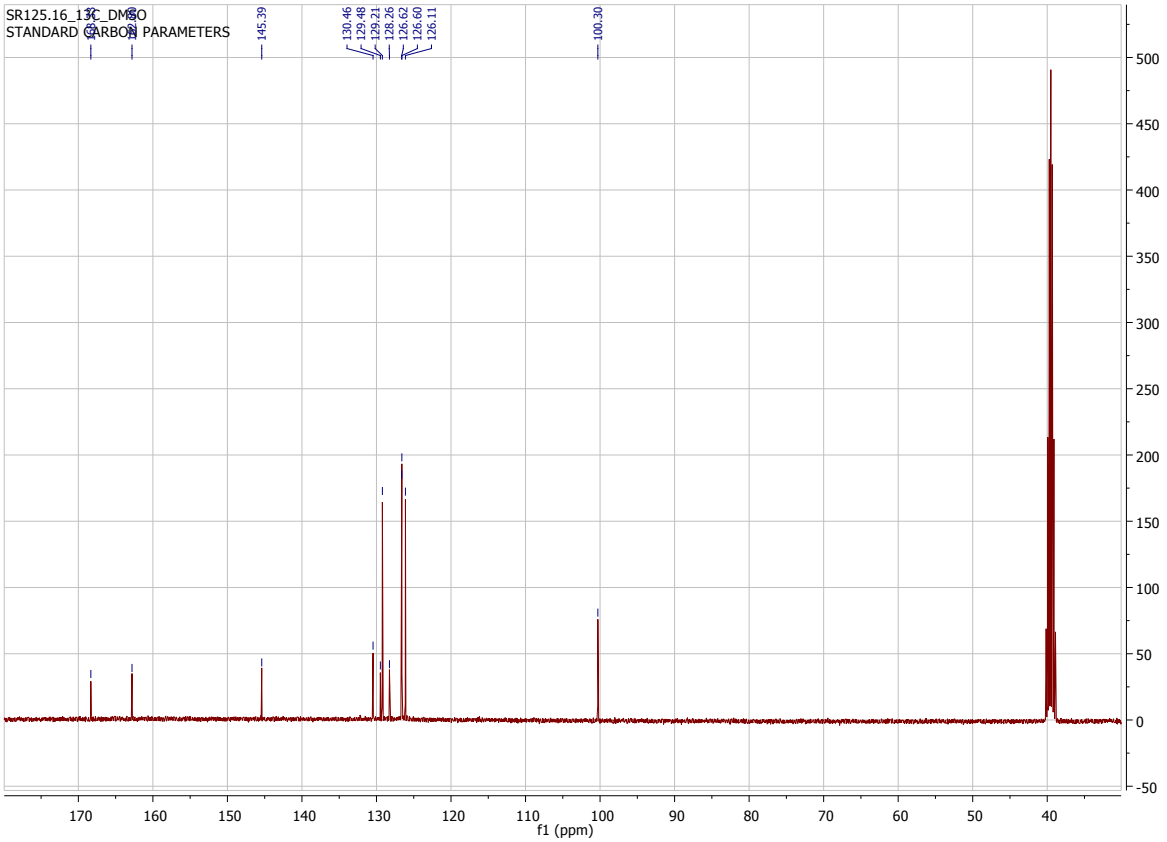
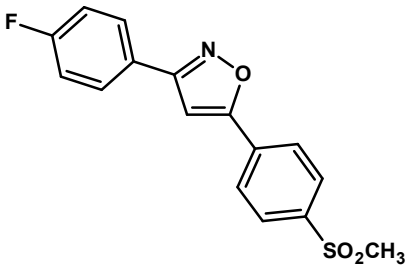


Figure S39. ^{1}H NMR spectrum of 4c

(**4c**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



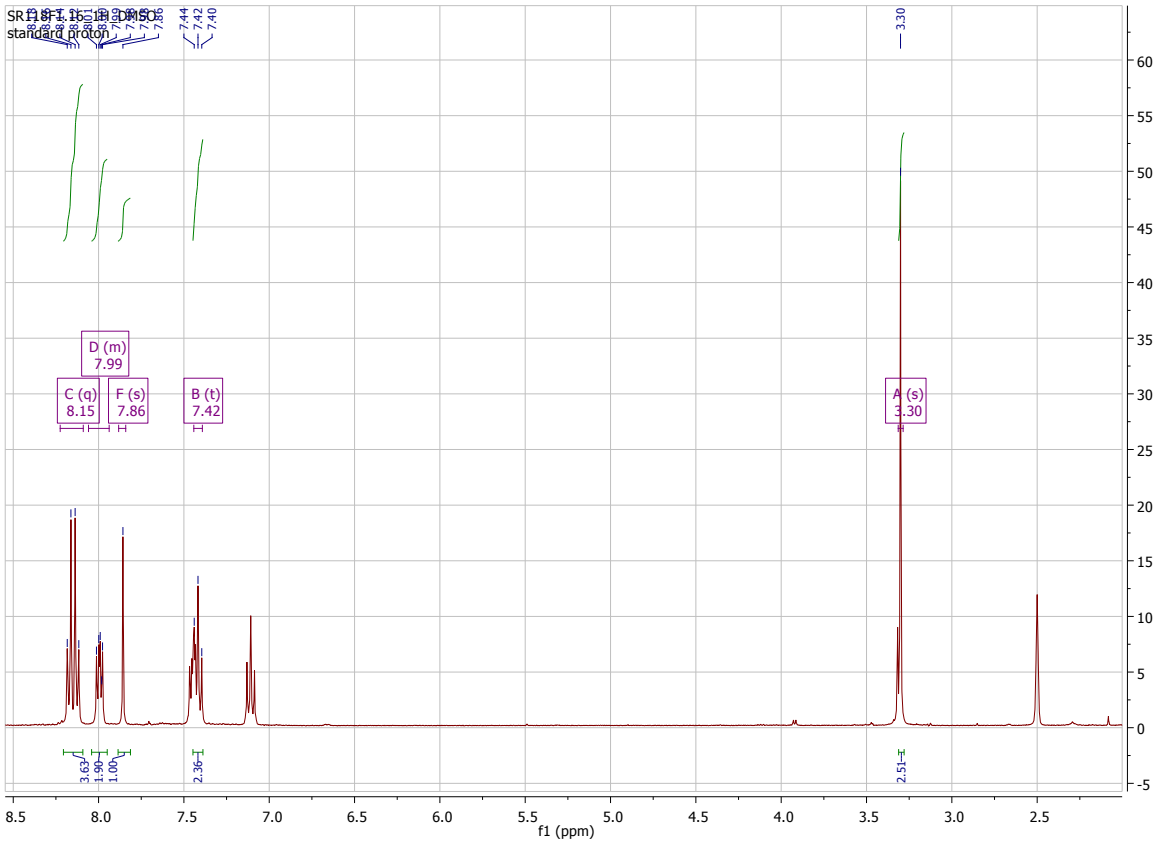
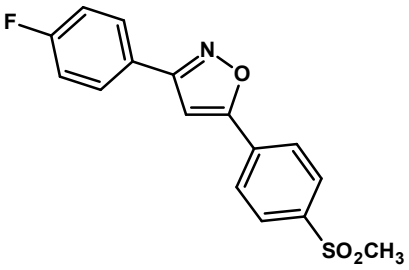


Figure S40. ^{13}C NMR spectrum of 4c

(**4c**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



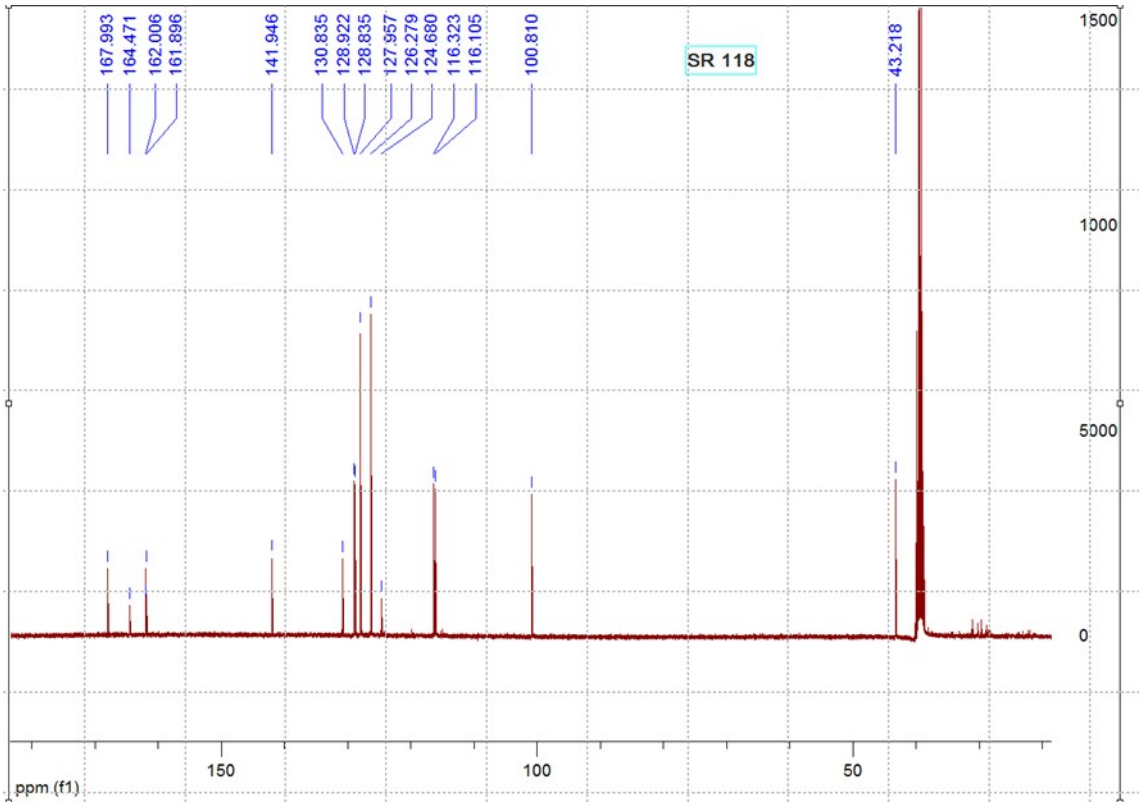


Figure S41. ^{1}H NMR spectrum of 4d

(**4d**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)

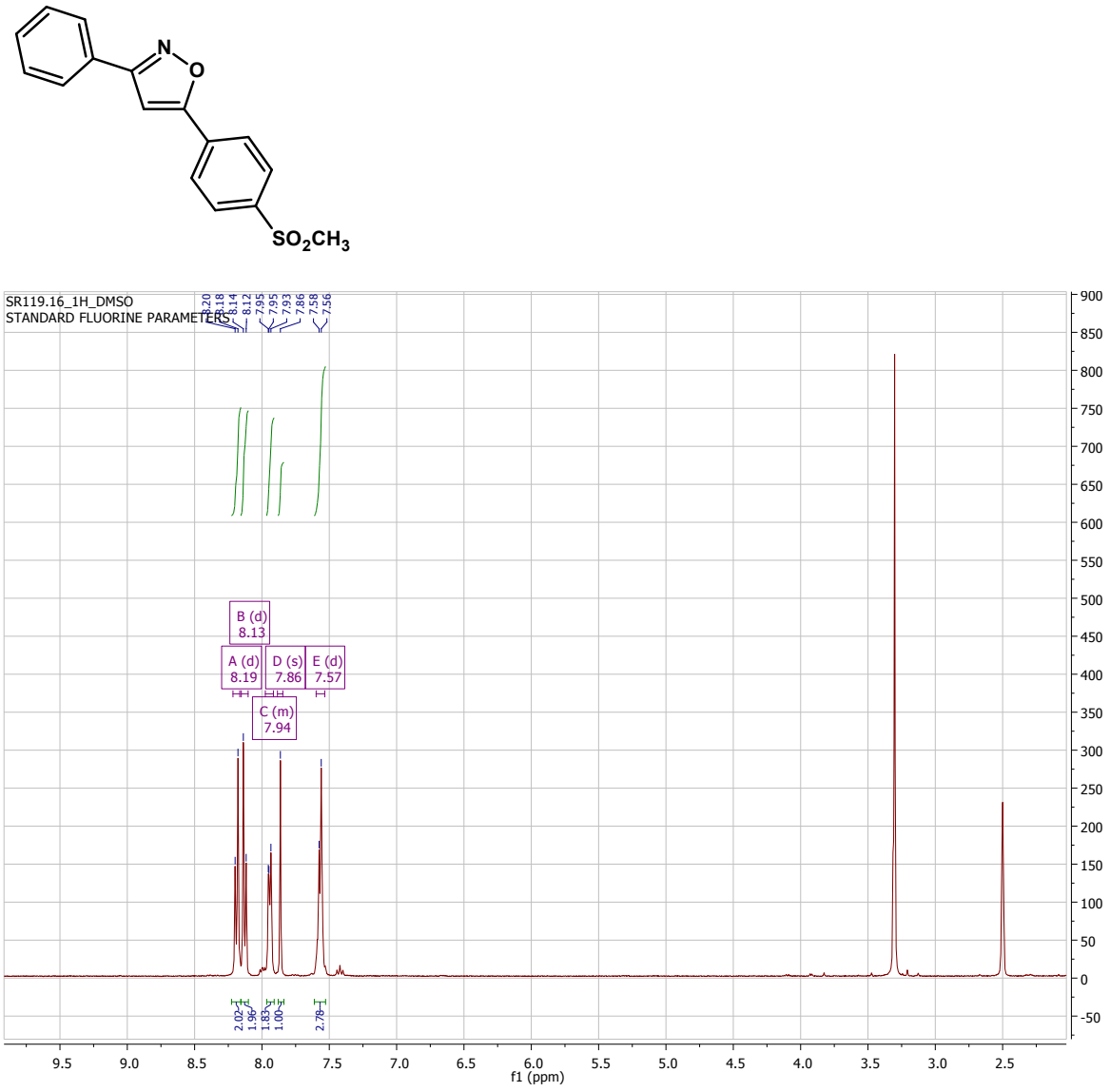


Figure S42. ^{13}C NMR spectrum of 4d

(**4d**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)

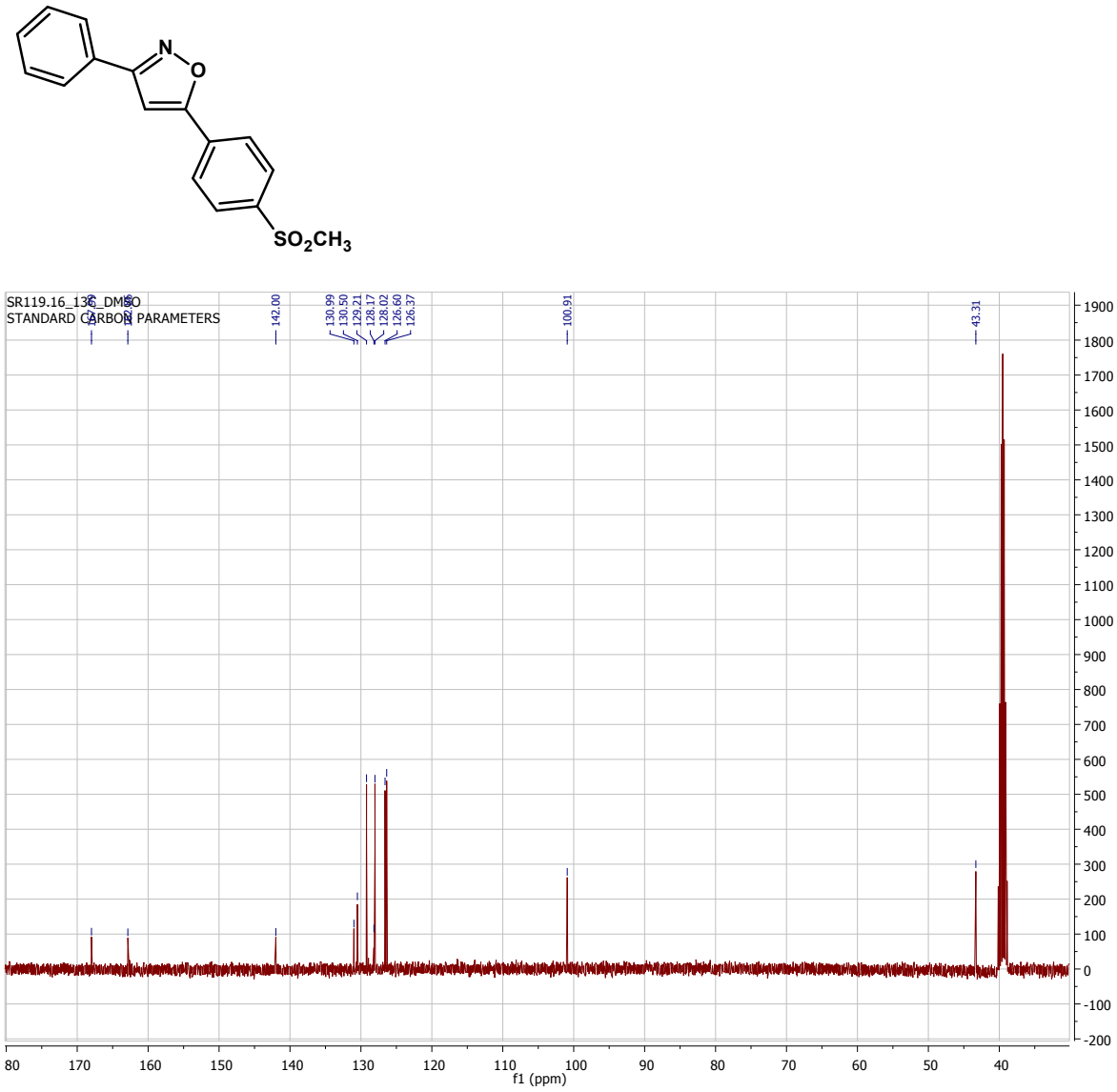
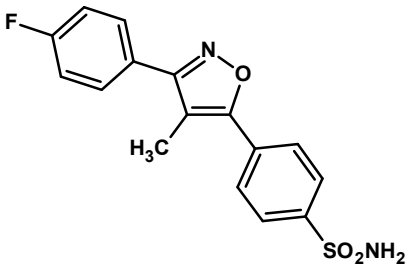


Figure S43. ^{1}H NMR spectrum of 4e

(**4e**) ^{1}H-NMR (acetone-d_6, 400 MHz)



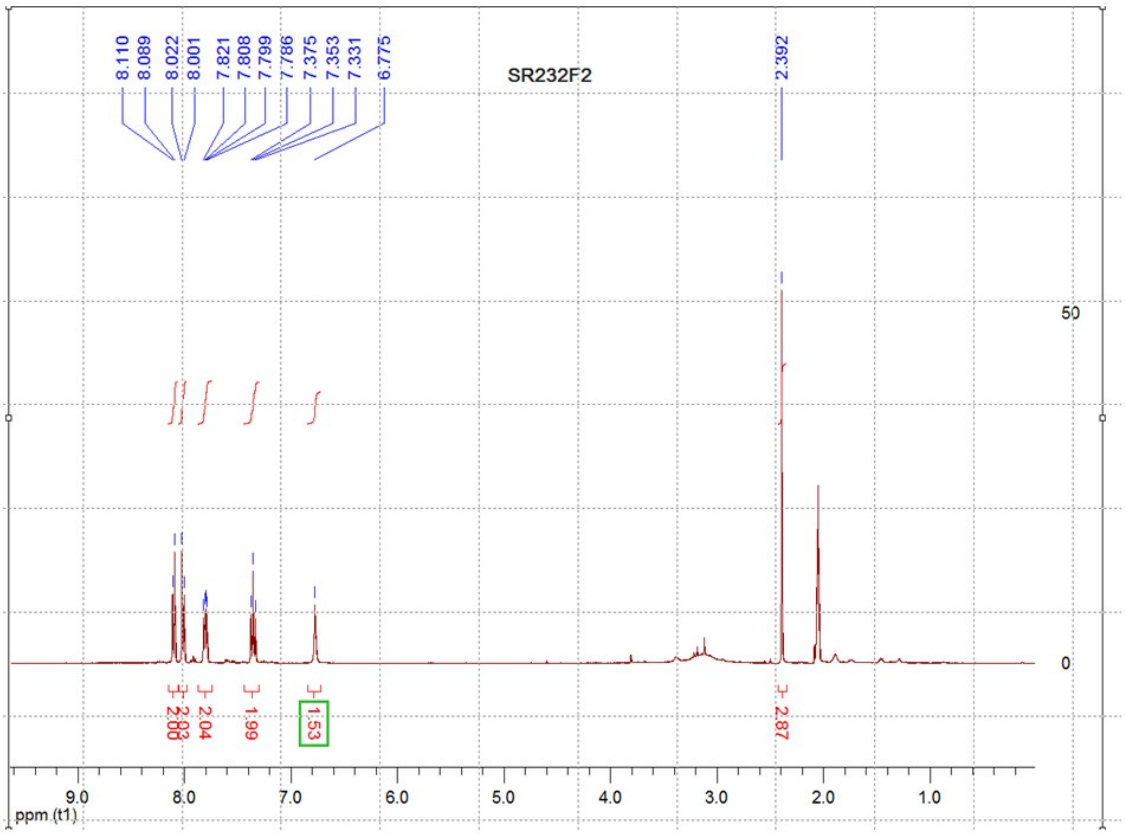
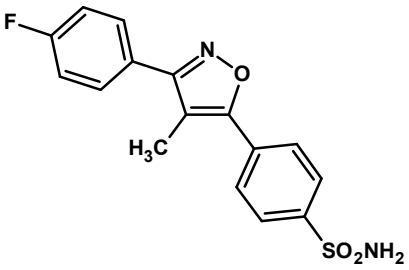


Figure S44. ^{13}C NMR spectrum of 4e

(**4e**) ^{13}C NMR (acetone-d6, 101 MHz)



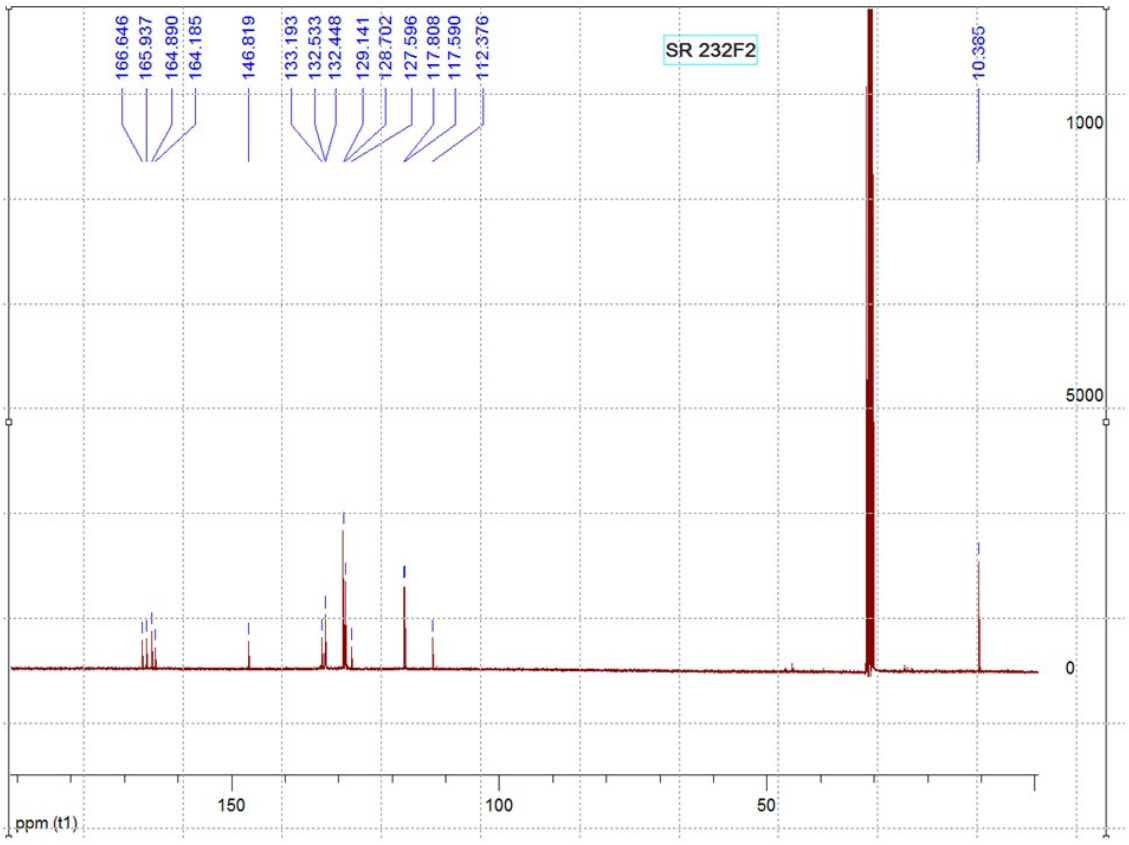
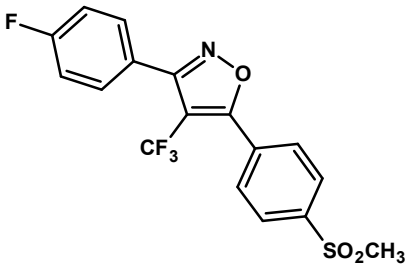


Figure S45. ^{1}H NMR spectrum of 4f

(**4f**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



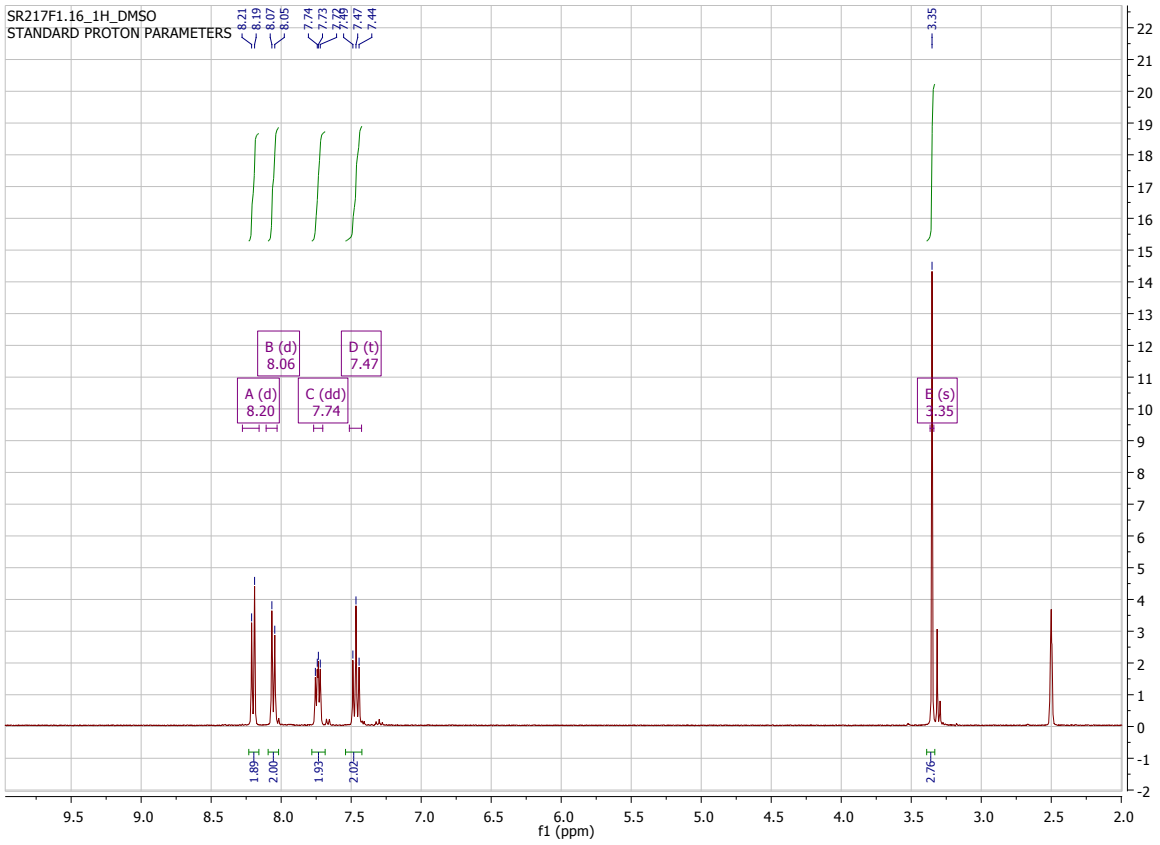
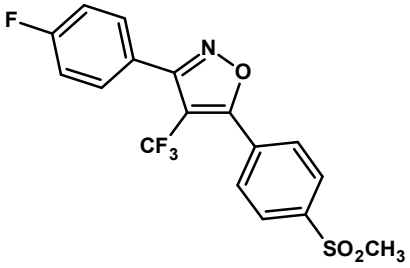


Figure S46. ^{13}C NMR spectrum of 4f

(**4f**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



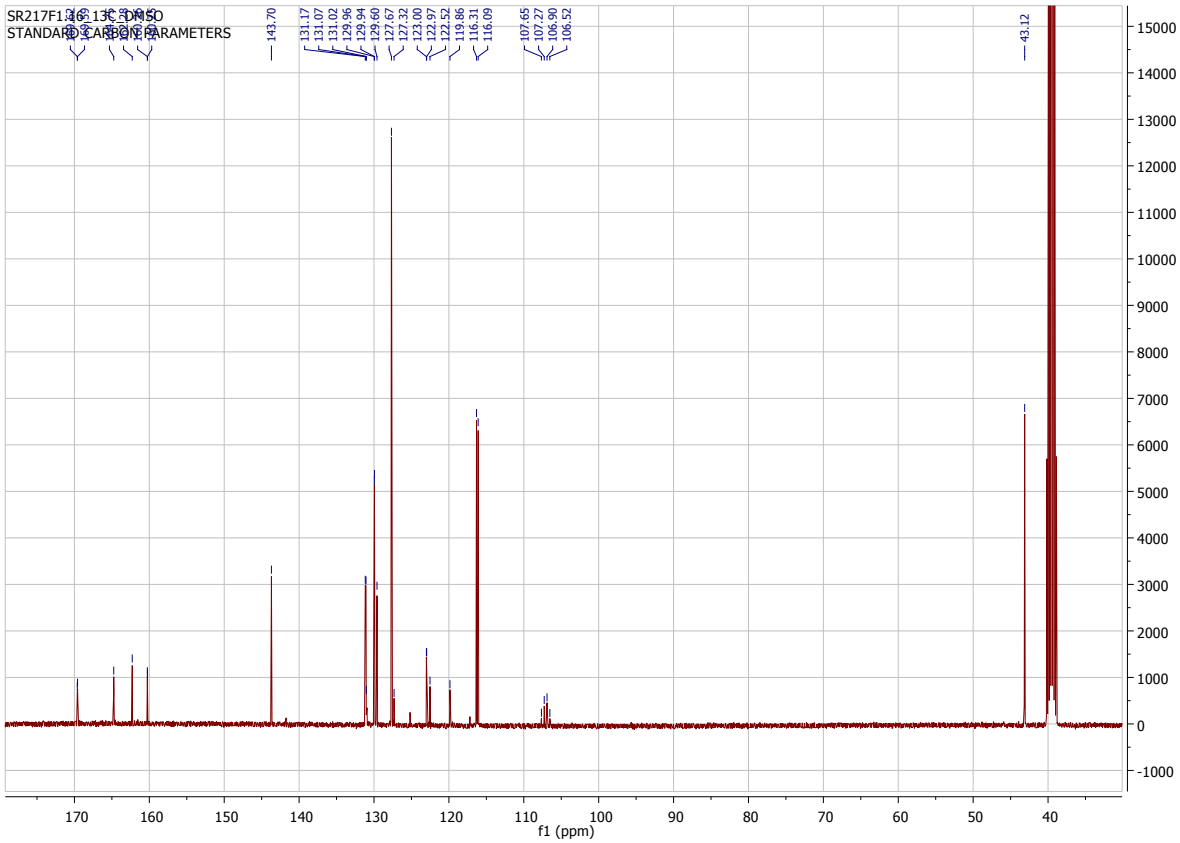
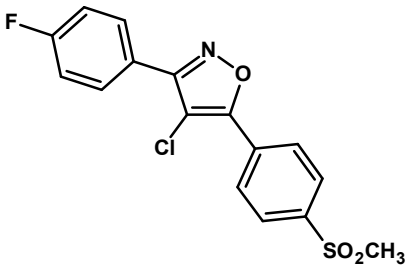


Figure S47. ^{1}H NMR spectrum of 4g

(**4g**) **^{1}H-NMR** (d^{6}-DMSO, 400 MHz)



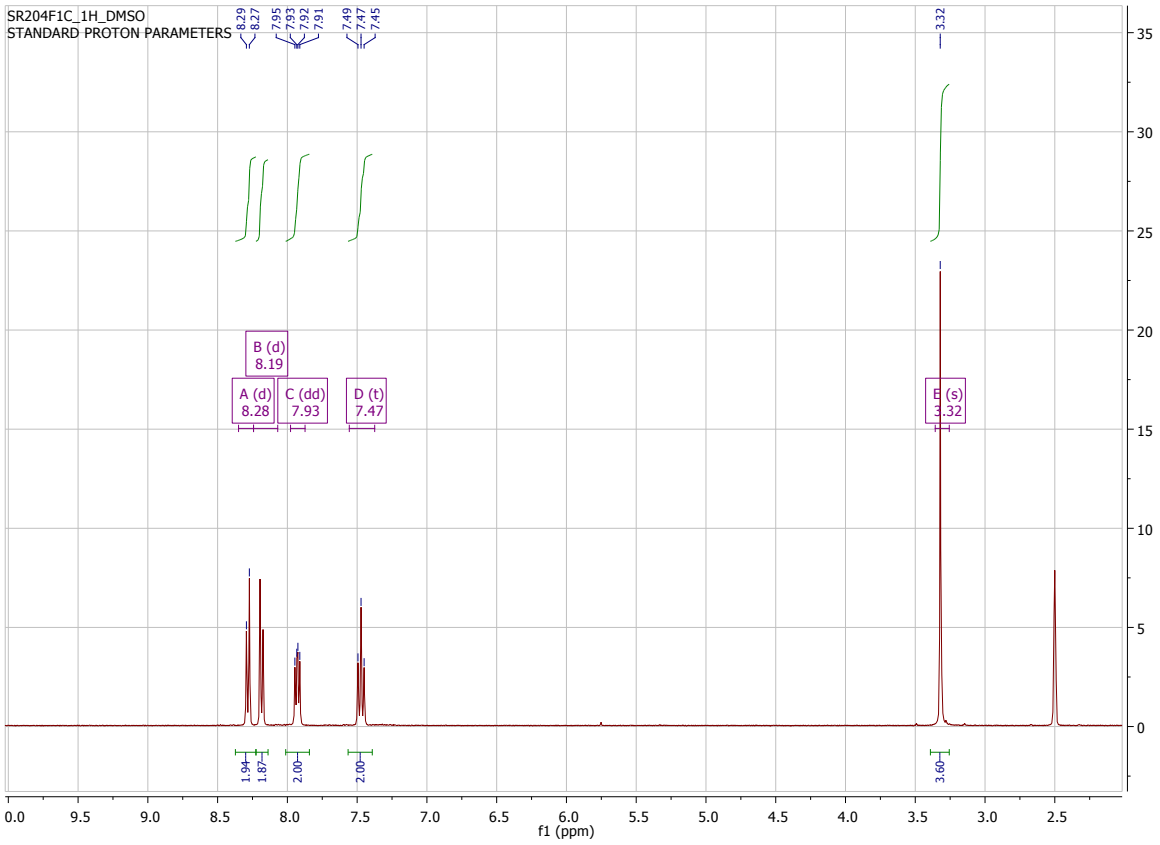
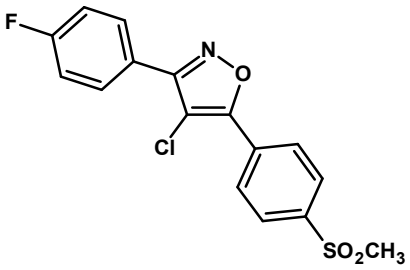


Figure S48. ^{13}C NMR spectrum of 4g

(**4g**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



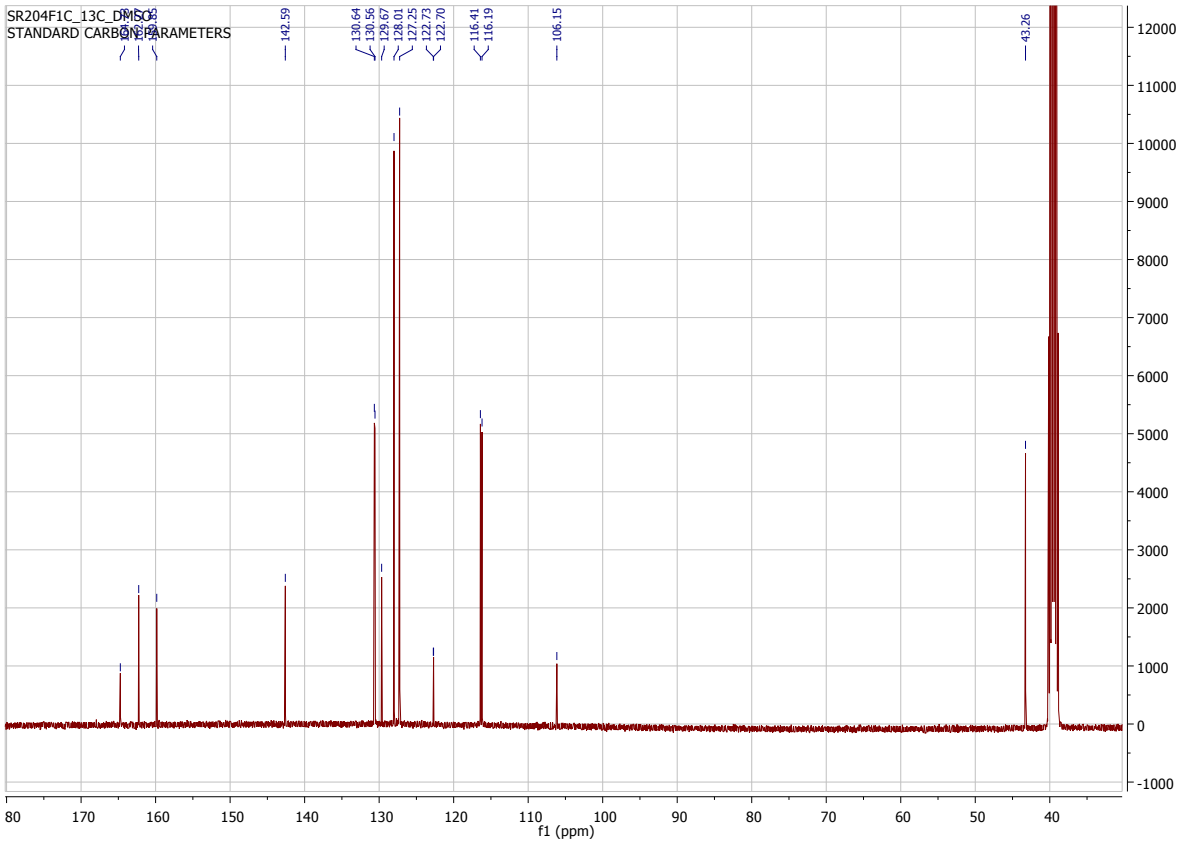
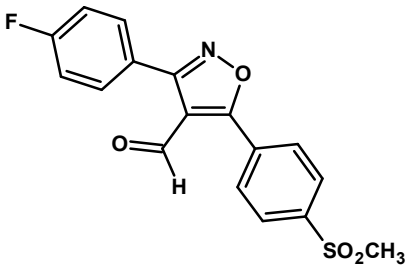


Figure S49. ^{1}H NMR spectrum of 4h

(**4h**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



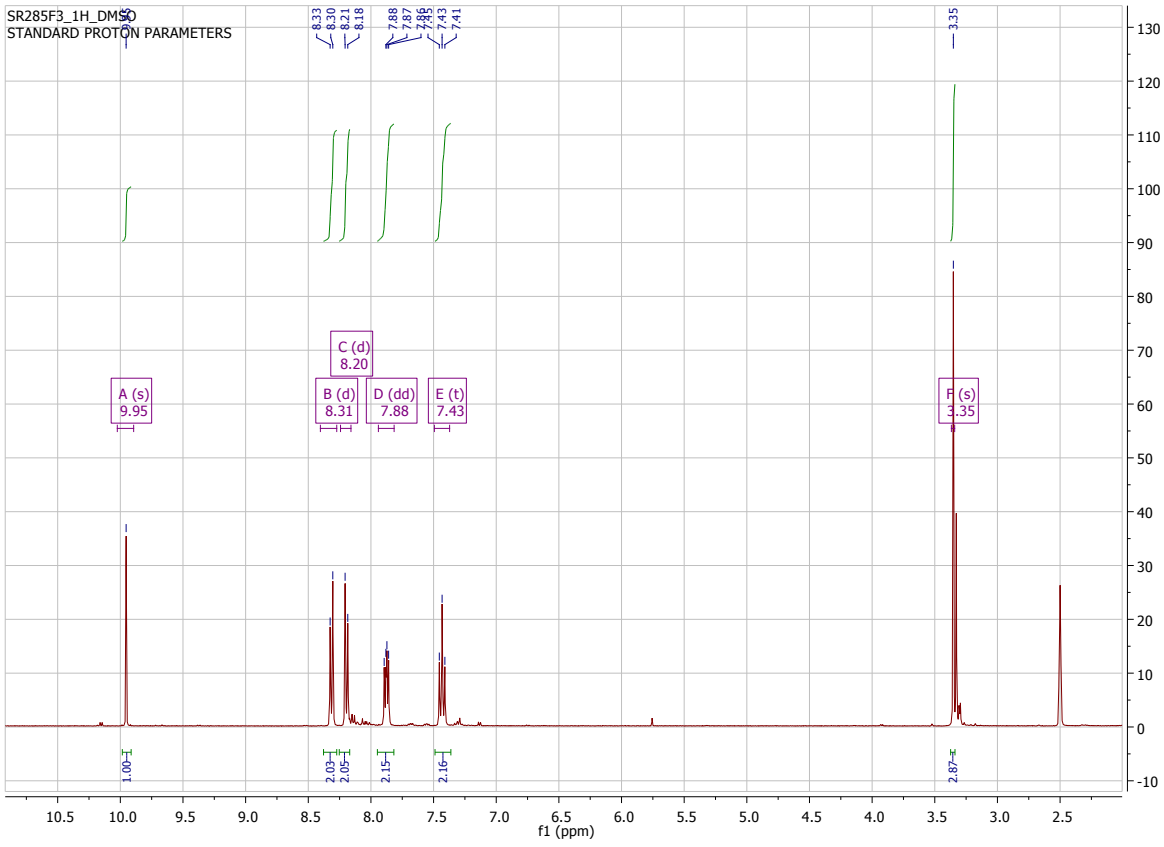
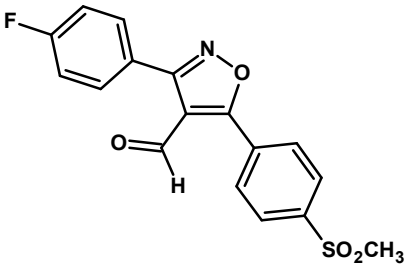


Figure S50. ^{13}C NMR spectrum of 4h

(**4h**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



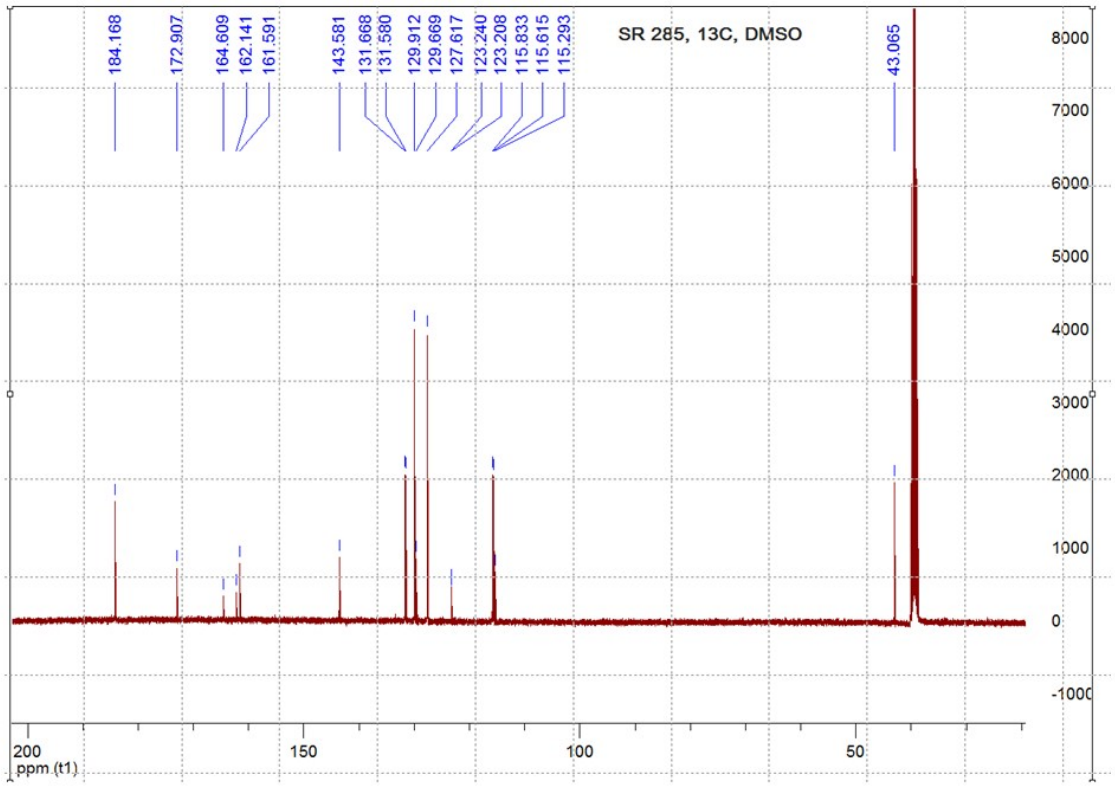
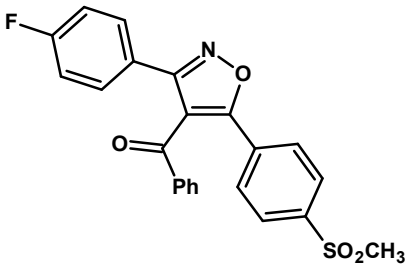


Figure S51. ^{1}H NMR spectrum of 4k

(**4k**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



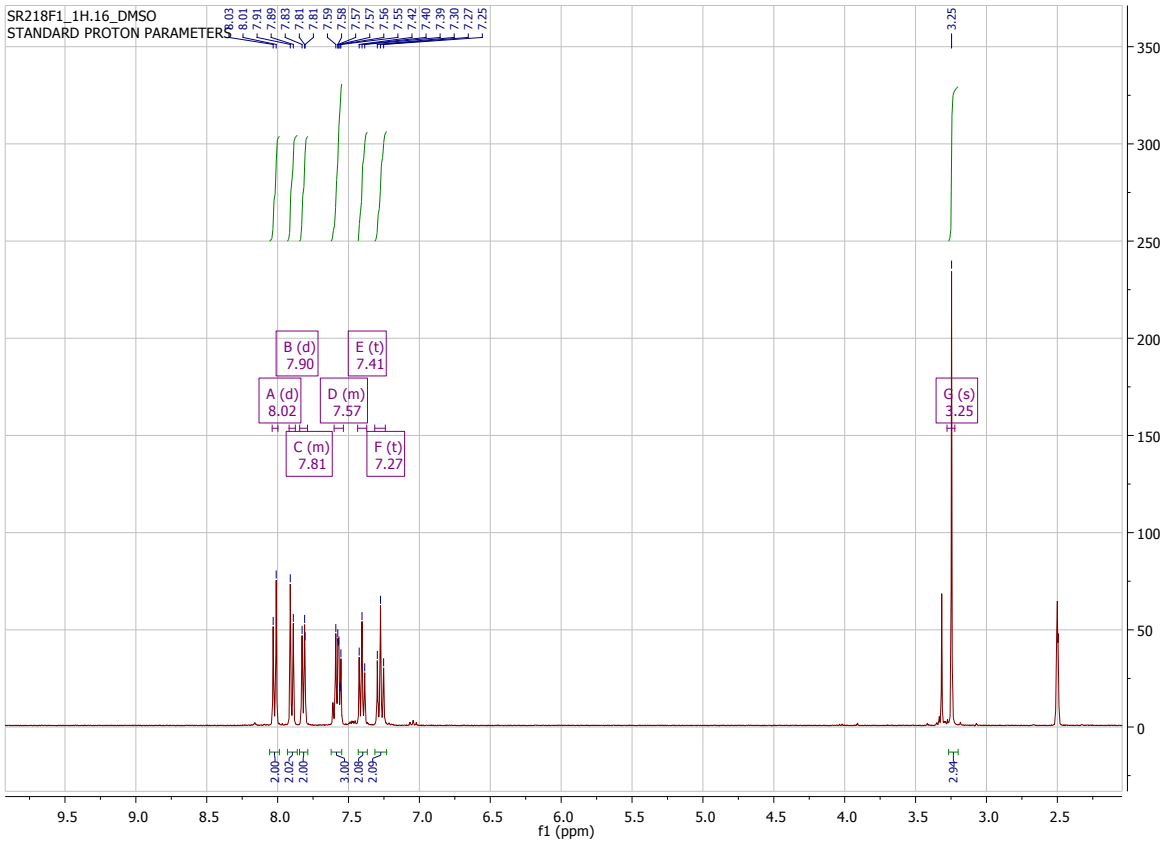
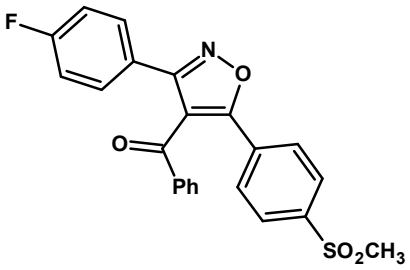


Figure S52. ^{13}C NMR spectrum of 4k

(**4k**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



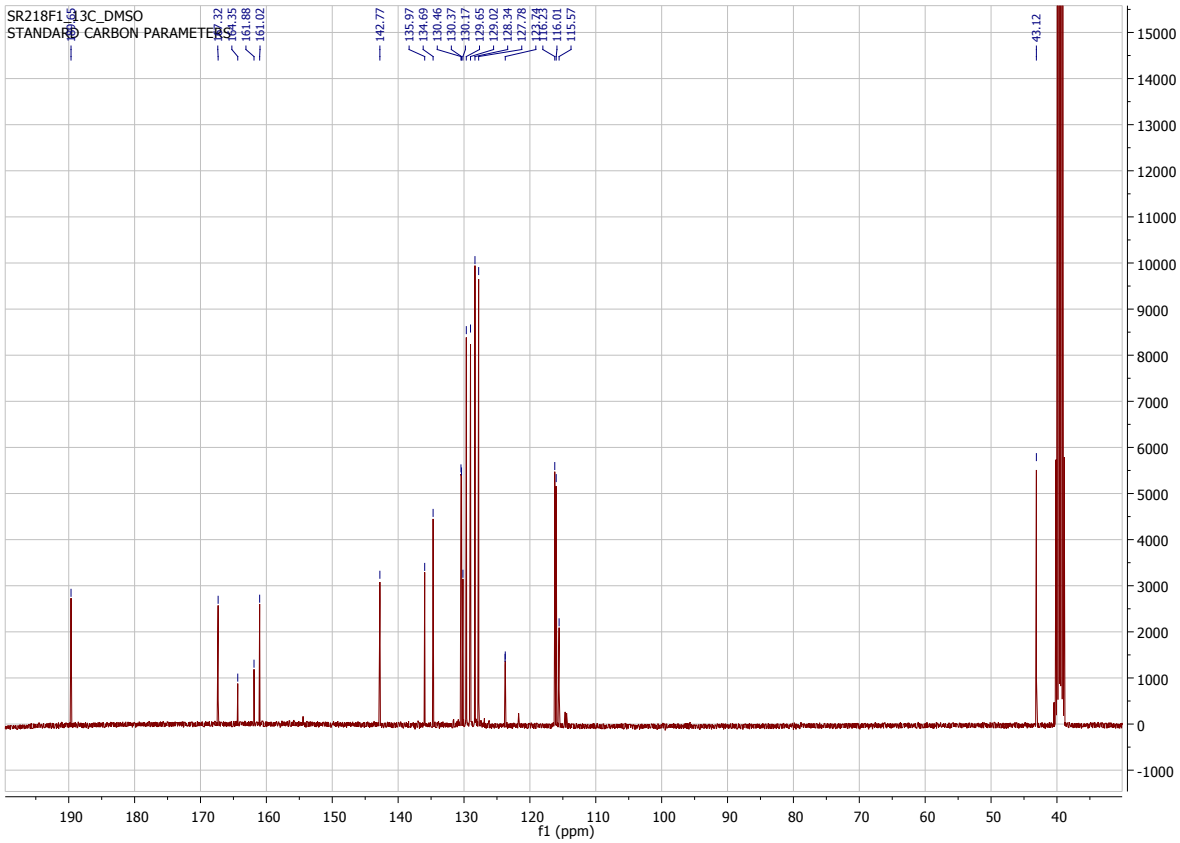
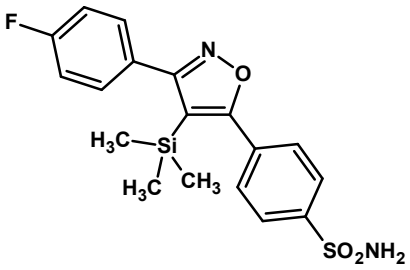


Figure S53. ^{1}H NMR spectrum of 4l

(**4l**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



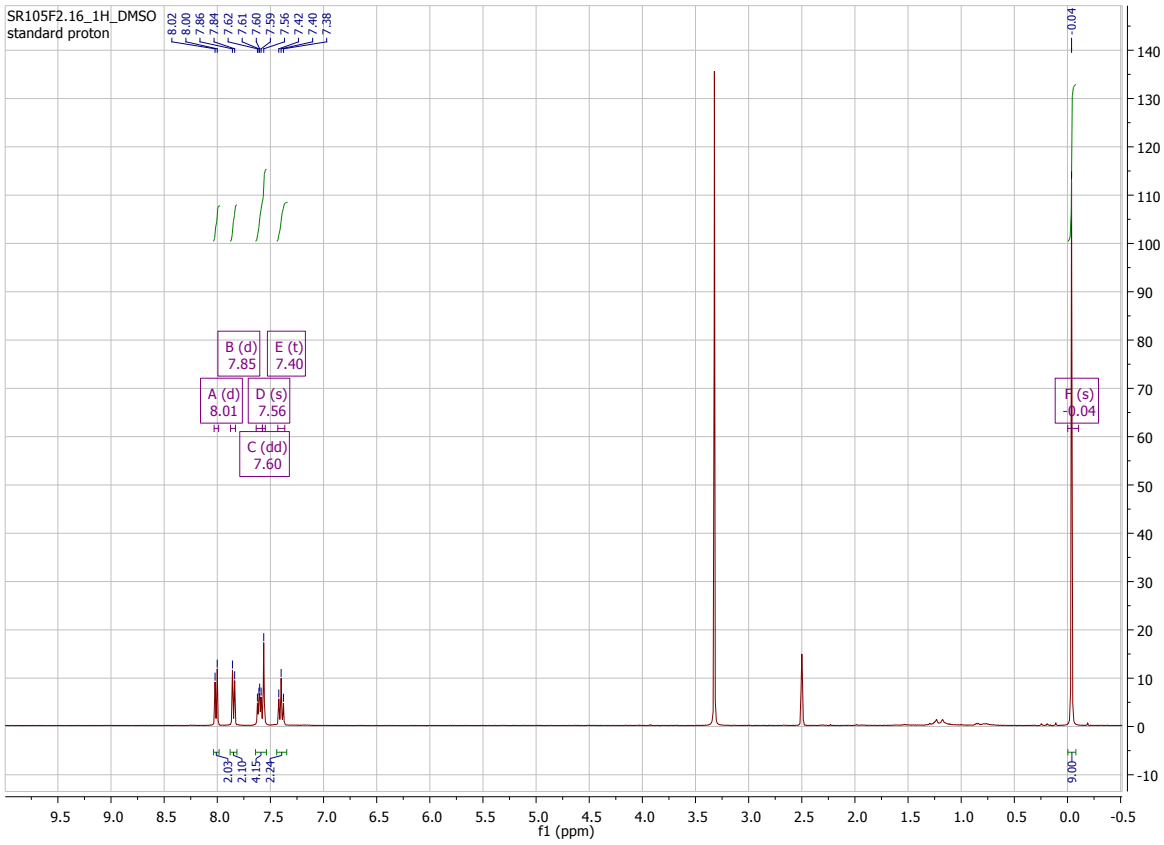
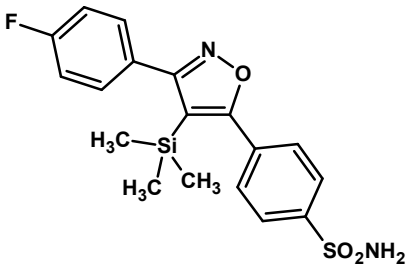


Figure S54. ^{13}C NMR spectrum of 4l

(**4l**) **^{13}C NMR** (d^6-DMSO, 101 MHz)



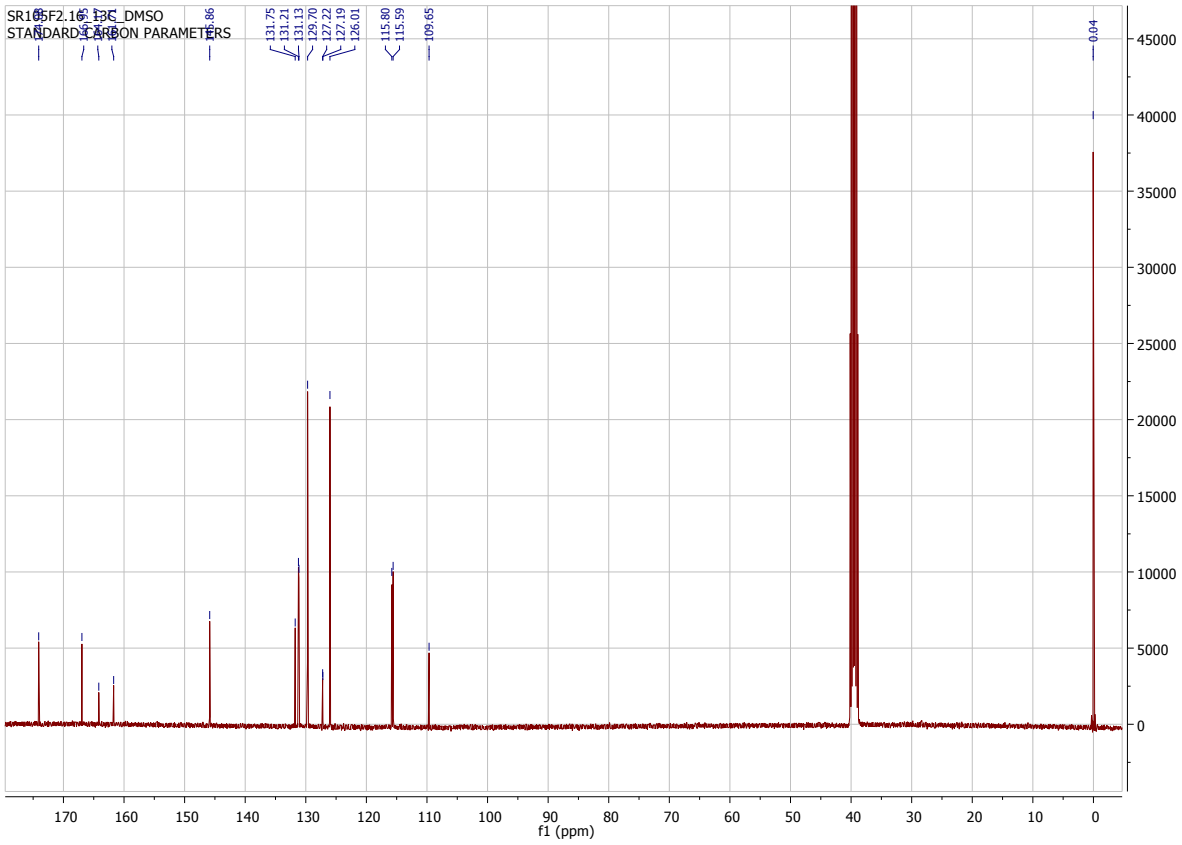
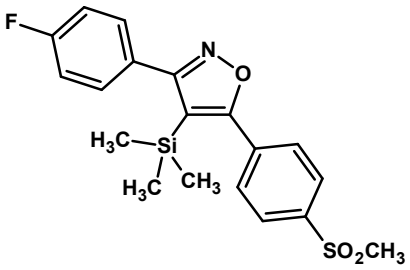


Figure S55. ^{1}H NMR spectrum of 4m

(**4m**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)



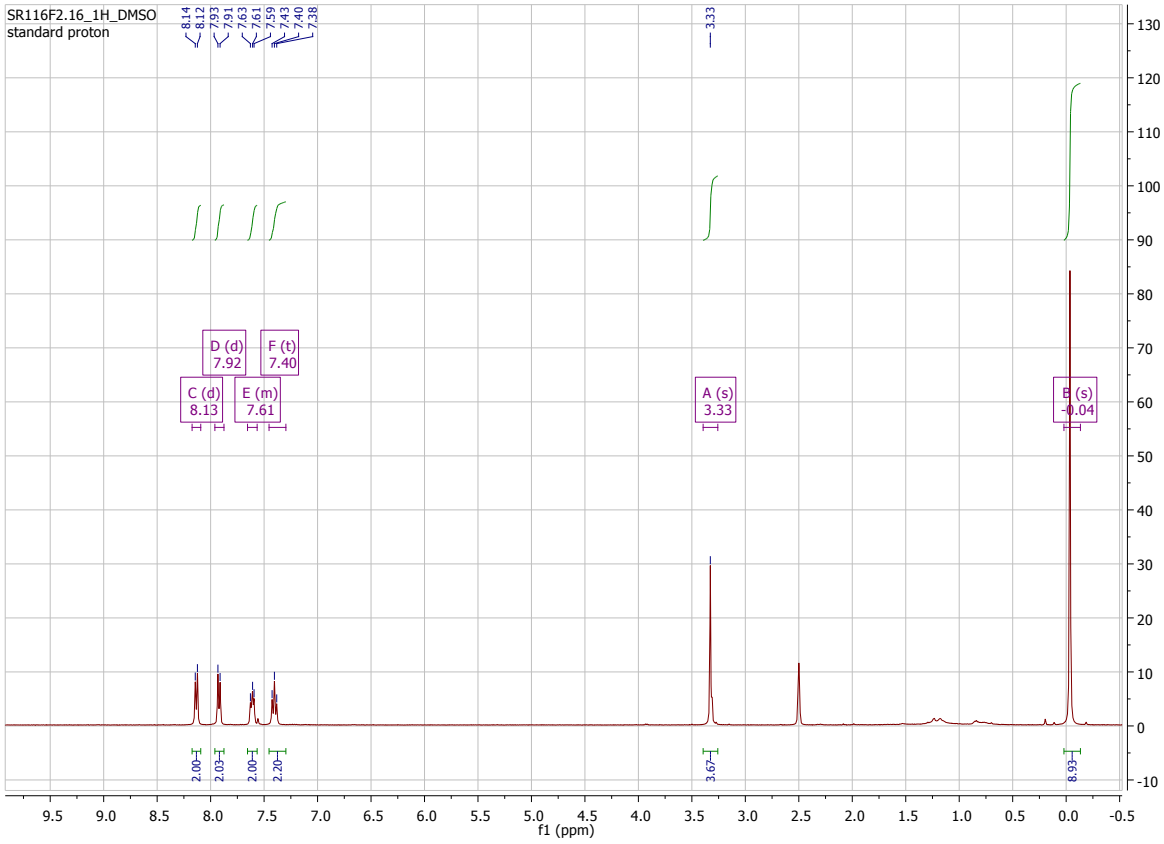
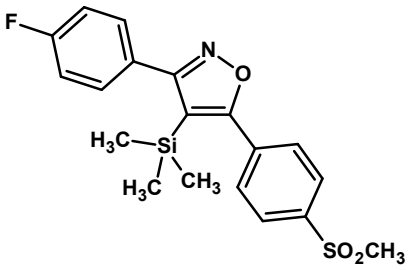


Figure S56. ^{13}C NMR spectrum of 4m

(**4m**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



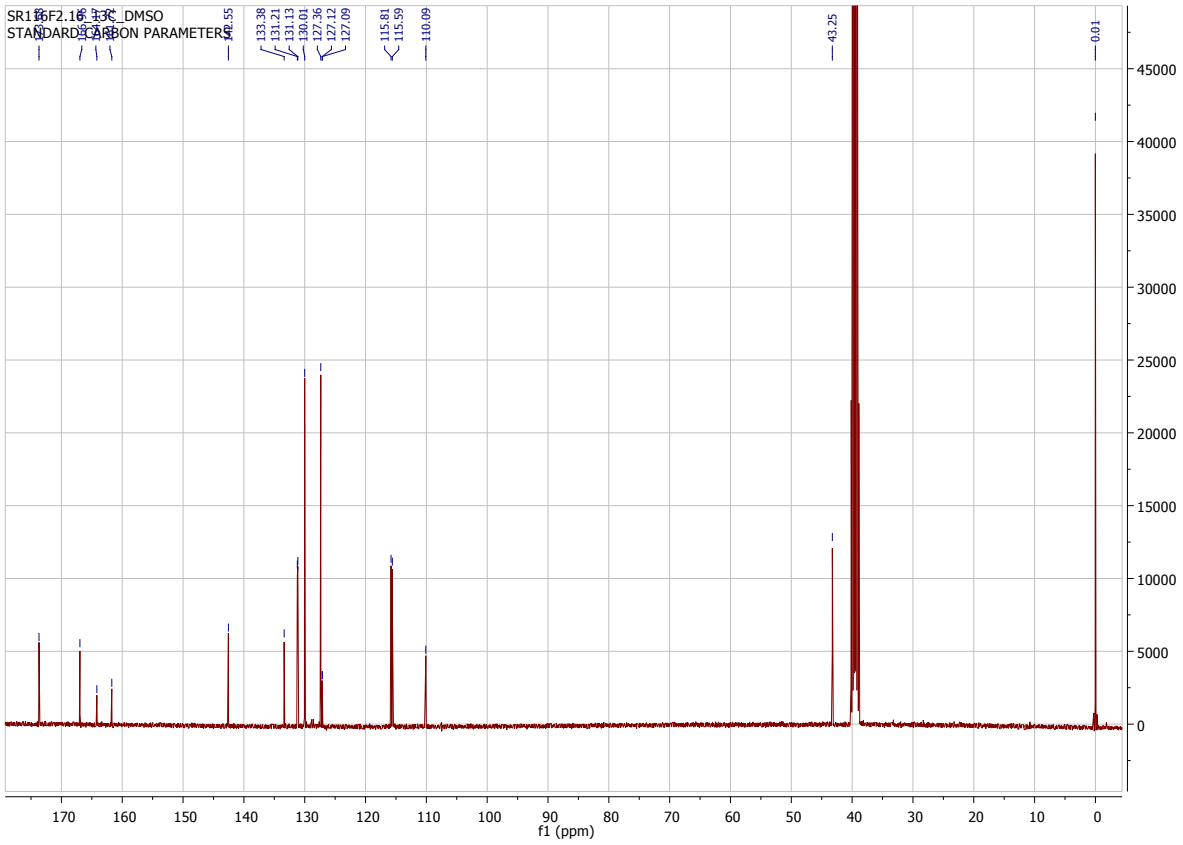


Figure S57. ^{1}H NMR spectrum of 4n

(**4n**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)

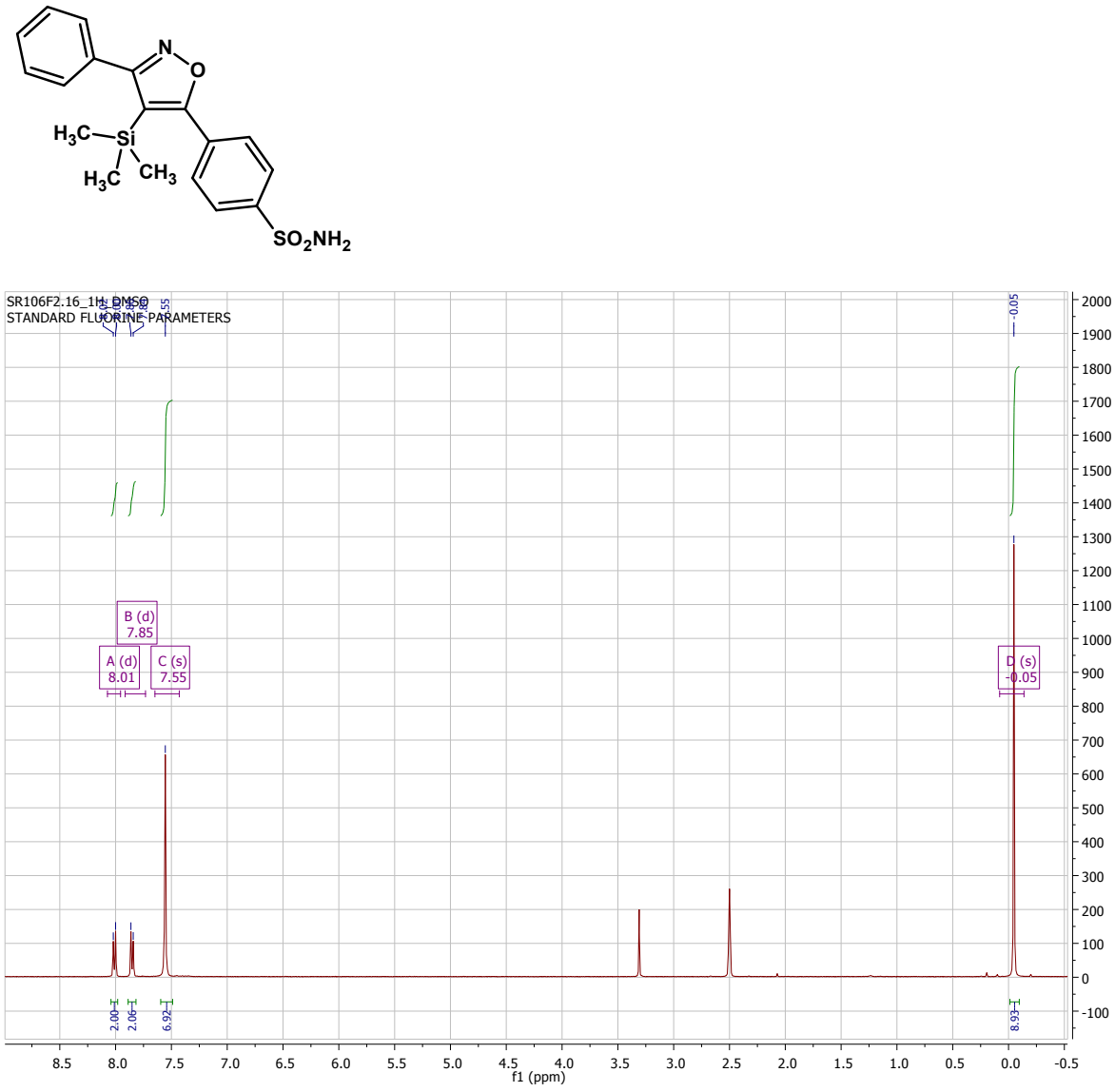


Figure S58. ^{13}C NMR spectrum of 4n

(**4n**) **^{13}C NMR** (d^6-DMSO, 101 MHz)

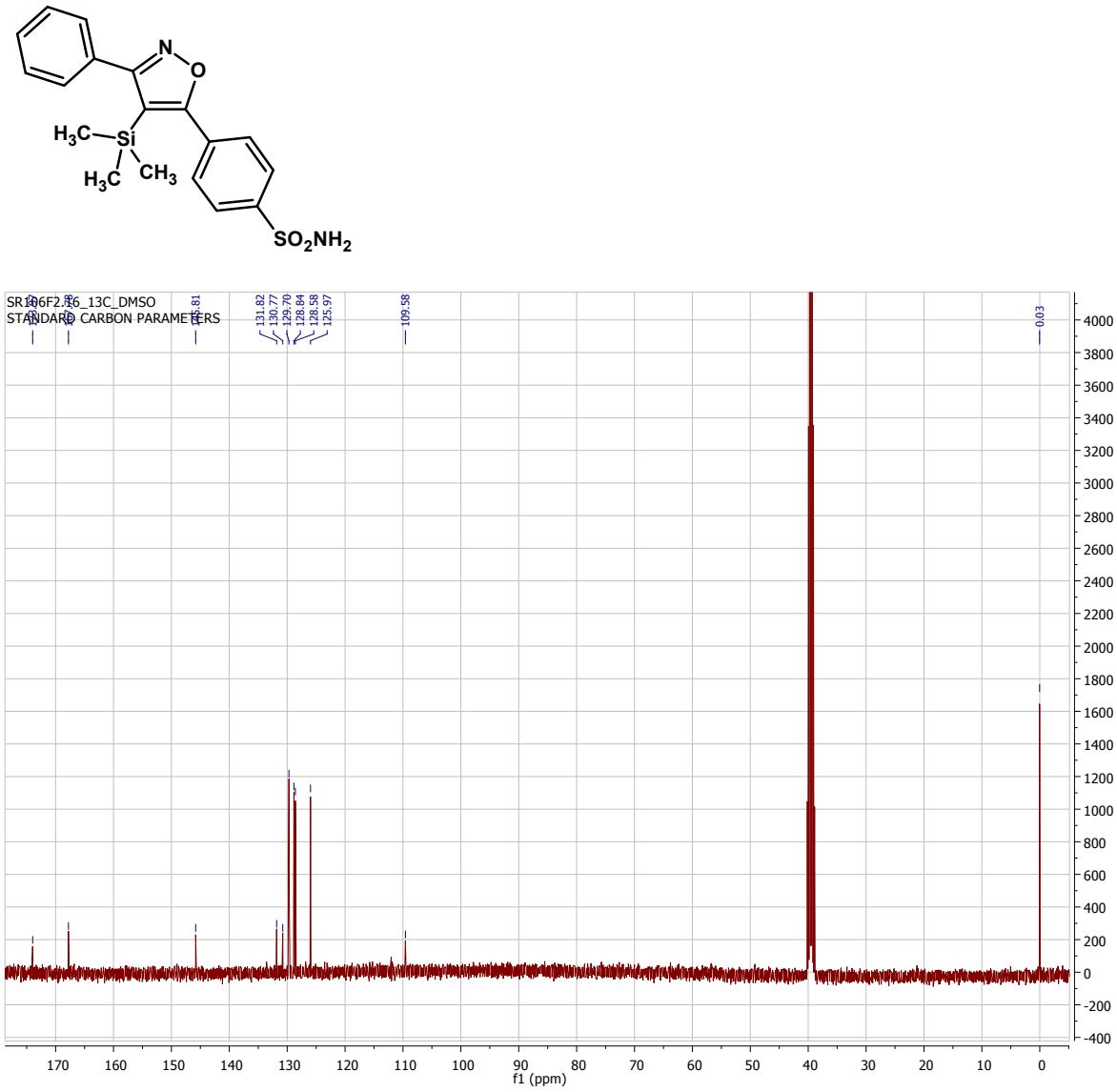


Figure S59. ^{1}H NMR spectrum of 4o

(**4o**) **^{1}H NMR** (d^{6}-DMSO, 400 MHz)

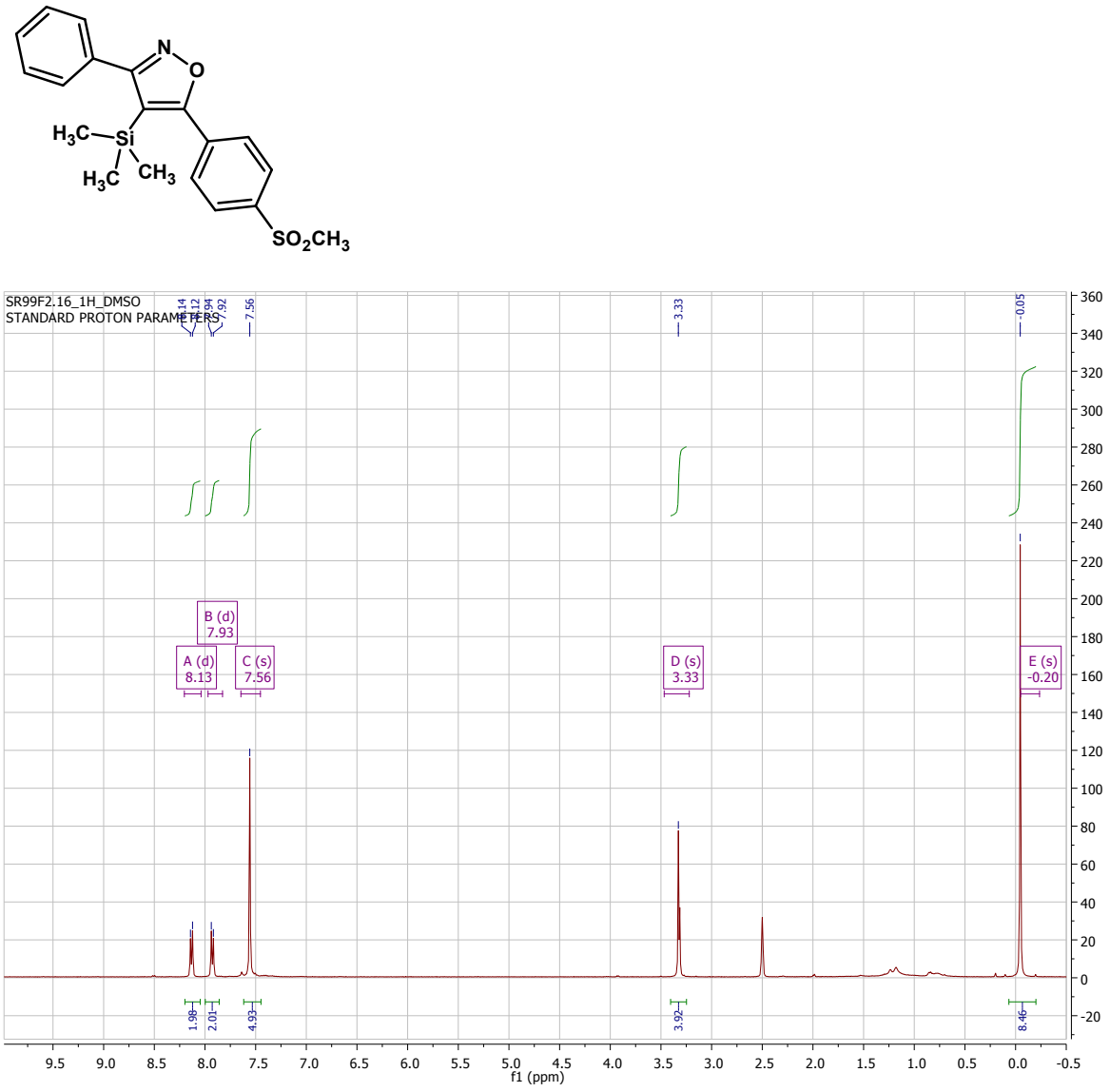
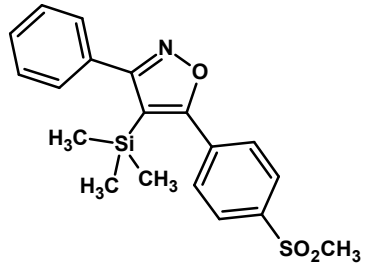


Figure S60. ^{13}C NMR spectrum of 4o

(**4o**) **^{13}C NMR** (d^{6}-DMSO, 101 MHz)



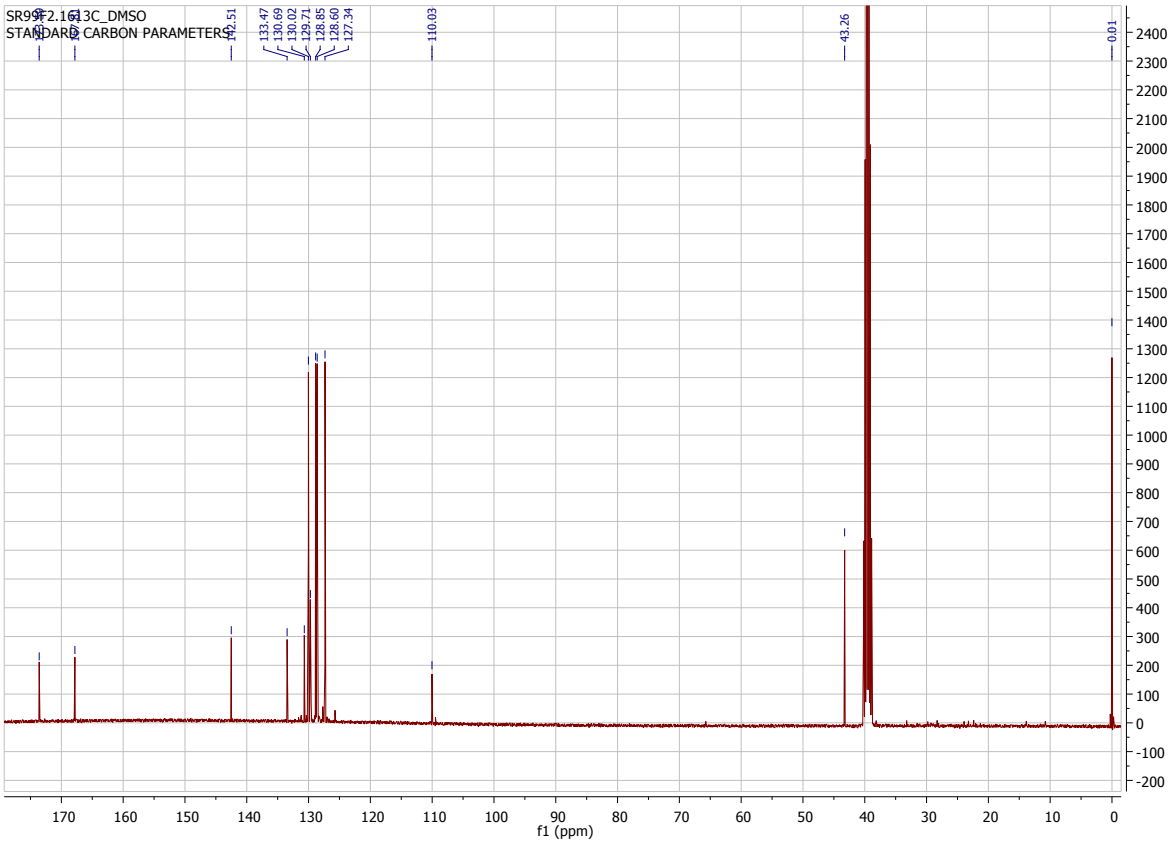


Figure S61. Shift of the signal of isoxazole proton in ^{1}H NMR observed for 3a and 4a.

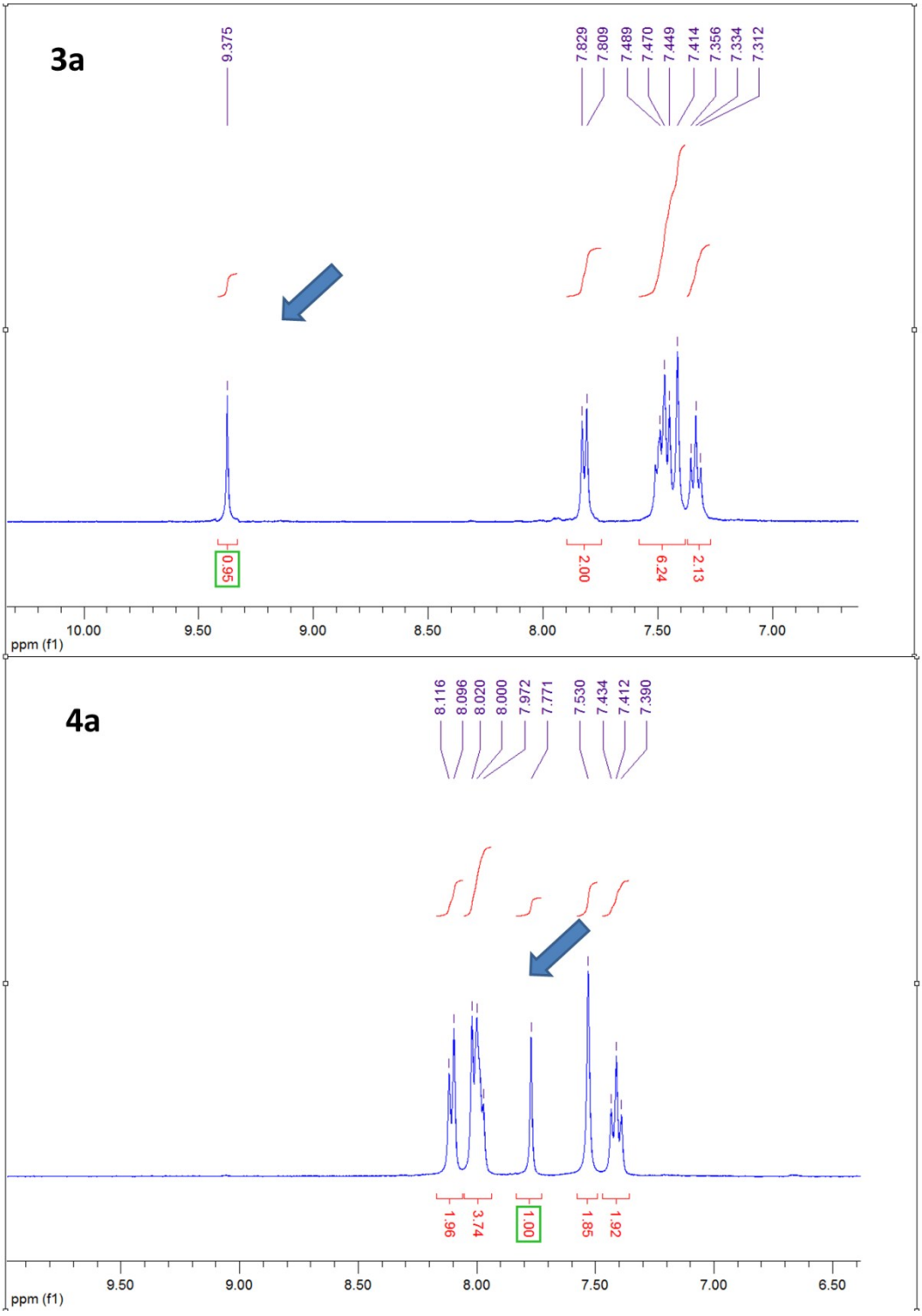


Figure S62. Shift of the signal of the trifluoromethyl group in ^{13}C NMR observed for 3f and 4f

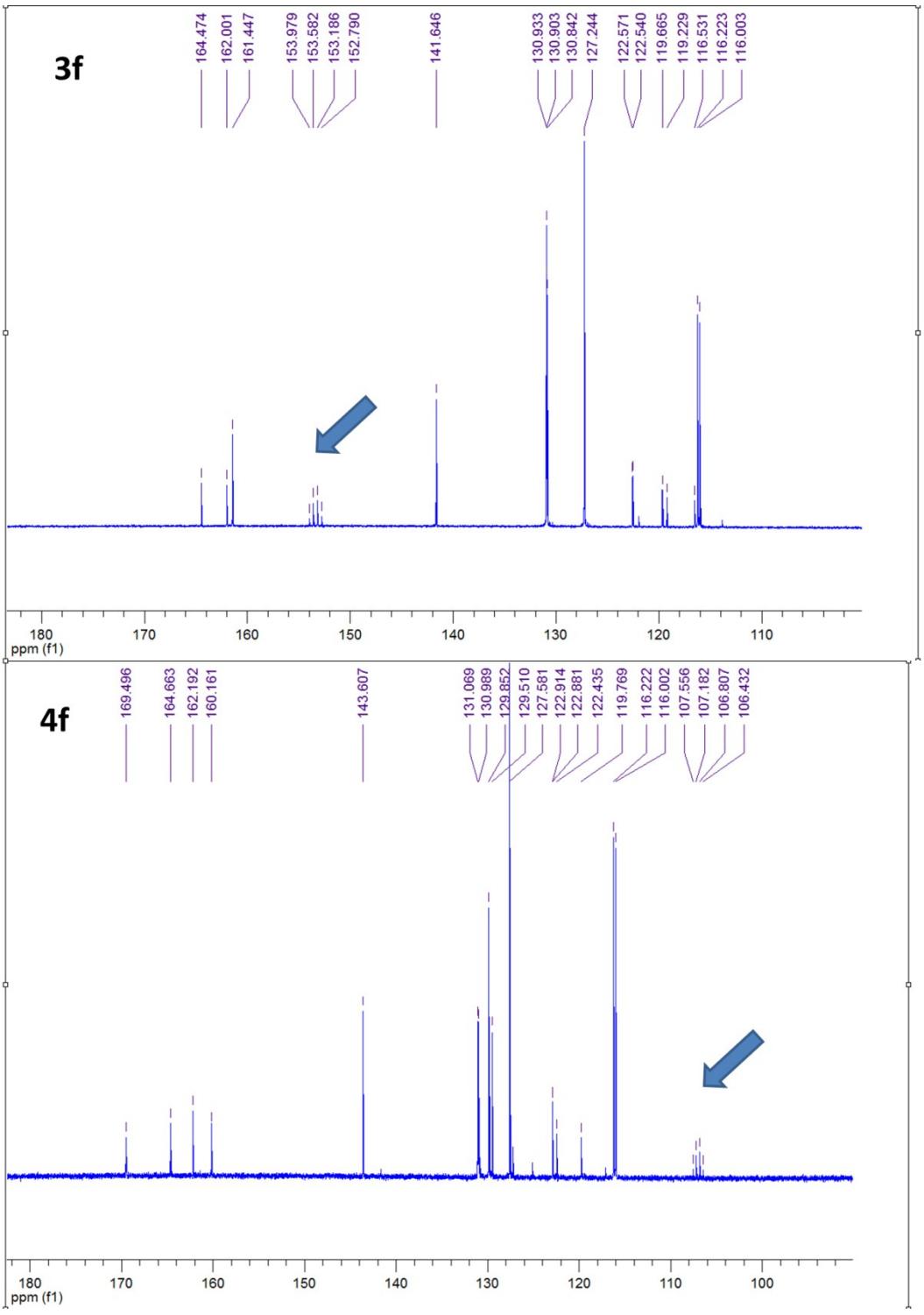


Figure S63. Dose response curves of each single determination of COX-2 inhibition and of the logistic fit determined by Origin software for 3a (A, B) and for valdecoxib (C, D). IC_{50} values were calculated from the curve. The coefficient of determination (R^2) illustrates the quality of the fit.