Electronic Supporting Information for:

Synthesis, Computational Investigation and Biological Evaluation of α,α-Difluoromethyl Embodying Ketones Pyrazole and Isoxazole Nuclei as COX Inhibitors

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General Experimental Information

All reagents, as well as all solvents used for synthesis and deuterated solvents employed for NMR analysis, were purchased from Sigma-Aldrich/Fluka (Milano, Italia) and used without any further purification. NMR spectra were recorded by means of a Varian Gemini 500 MHz (^{1}H) e 125 MHz (^{13}C) instrument or, alternatively, a Brüker Avance III 400 MHz (^{1}H), using $CDCl_3$, acetone-d_6, and DMSO-d_6 as solvents depending on the solubility of the compounds; the chemical shifts (δ) were provided in ppm using TMS as internal standard and coupling constants (*J*) in Hertz (Hz). The patterns of splitting were described as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad singlet (bs). All new compounds were characterized by ^{1}HNMR, ^{13}CNMR and HRMS analysis. All known compounds are characterized by ^{1}HNMR and MS analysis. Melting points of the various synthetic intermediates and final compounds were determined using a "BUCHI Melting Point B-545 Apparatus" and are incorrect. Thin layer chromatography (TLC) was performed on Merck 60 F254 plates (Merck KGaA, Darmstadt, Germany). For the column chromatography Macherey-Nagel 60 M (0.040–0.063 mm) silica gel was used.

NIH/3T3 fibroblastic cell line was obtained from the American Type Culture Collection (Manassas, VA, USA). All reagents, for biological assays, were purchased from Sigma-Aldrich/Fluka (Milan, Italy). The evaluation of inhibition against cyclooxygenase (COX) activity was carried out using a COX inhibitor screening assay kit (Item. No. 701230, Cayman Chemical Company, Ann Arbor, MI, USA).

General Synthetic Procedures

General procedure 1 for the 1,3-dipolar cycloaddition of diazo compounds to alkynes. A 5 mL round-bottom flask equipped with a reflux condenser was charged with ethyl diazocarboxylate (1.2 equiv) and the corresponding alkyne (1 equiv) and was heated at 80 °C. After complete conversion of the starting material shown by TLC, the excess of reagent was evaporated under *vacuum*. The corresponding pure product was obtained after trituration of the crude with diethyl ether.

General procedure 2 for the synthesis of *N*-substituted pyrazoles. To a solution of 2,4-dioxovalerate (1 equiv) in ethanol (10 mL) and the corresponding hydrazine (1.1 equiv) was added catalytic amount of HCl 12 M and the reaction was left stirring under reflux for 3 h. The solvent was removed under reduced pressure, then the crude was taken up in ethyl acetate (10 mL) and washed with brine (3 × 5 mL mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and the resulting crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

General procedure 3 for the 1*H*-pyrazole methylation. To a solution of 1*H*-pyrazole (1 equiv) and potassium carbonate (2 equiv) in dry DMF (4 mL) was added iodomethane (2 equiv) at room temperature. The reaction mixture was stirred overnight at the same temperature and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

General procedure 4 for the 1,3-dipolar cycloaddition of nitrile oxide compounds to alkynes. To a solution of ethyl 2-chloro-2-(hydroxyimino)acetate (3 equiv) and the corresponding alkyne (1 equiv) in dry THF (10 mL) was added triethylamine (3.5 equiv) and the reaction was left stirring at rt overnight. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was washed with HCl 1 M (2 × 10 mL), brine (30 × 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

General procedure 5 for ethyl esters hydrolysis. To a solution of the pyrazole/isoxazole ethyl ester (1 equiv) in ethanol/water (1:1, v/v, 12 mL) was added LiOH (10 equiv) and the mixture was left stirring at rt overnight. The reaction was concentrated under reduced pressure, the residue was taken up in water and adjusted to pH 4 with 2 N HCl. The formed precipitate was filtered, washed with water and dried under *vacuum* to afford the corresponding carboxylic acid as a white solid.

General procedure 6 for the preparation of Weinreb amides. To a solution of carboxylic acid (1 equiv) in anhydrous CPME (5 mL) was added 1,1'-carbonyldiimidazole (1.2 equiv) in one portion and the resulting mixture was allowed to stir at rt for 1 h. Then, *N,O*-dimethylhydroxylamine hydrochloride (DMHA, 1.2 equiv) and 4-methylmorpholine (NMM, 1.5 equiv) were added to the mixture, turning the solution a cloudy white. The reaction mixture was stirred at rt overnight, then quenched with 3 mL of a saturated aq. solution of NH_4Cl. Then, the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with a saturated aq. solution of $NaHCO_3$ (3 × 5 mL) and brine (3 × 5 mL) then, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

General procedure for the preparation of α,α-Difluoroketones. To a solution of Weinreb amide (1 equiv) in dry THF (5 mL) cooled at 0 °C was added (difluoromethyl)trimethylsilane (2 equiv) under argon atmosphere. Then potassium *tert*-pentoxide 1.7 M in toluene (1.8 equiv) was added dropwise with good stirring at 0 °C during a period of 15 min. The reaction mixture was further stirred to reach rt within 4 h. After complete conversion of the starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with brine (3 × 5 mL), dried over anhydrous

Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified *via* column chromatography on silica gel to afford the corresponding pure compound.

Spectral and Characterization Data

Ethyl 5-phenyl-1*H*-pyrazole-3-carboxylate (7): by following the General Procedure 1, starting from phenylacetylene (1 equiv) and ethyl diazocarboxylate (1.2 equiv), the desired ethyl 5-phenyl-1*H*-pyrazole-3-carboxylate was obtained in 89% yield as white solid; mp = 136 - 137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.75 (d, 2H, *J* = 7.9 Hz, Ph H-2,6), 7.42 (t, 2H, *J* = 7.9 Hz, Ph H-3,5) 7.35 (t, 1H, *J* = 7.9 Hz, Ph H-4), 7.09 (s, 1H, Pyr H-4), 4.36 (q, 2H, *J* = 7.1 Hz, -C*H*$_2$CH$_3$), 1.36 (t, 3H, *J* = 7.1 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.66 (TLC: *n*-hexane/ethyl acetate 7:3). MS (ESI): 217.1 $[M+H]^+$. Spectral data match with those ones previously reported.[1]

5-phenyl-1*H*-pyrazole-3-carboxylic acid (8): by following the General Procedure 5, starting from **7** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-phenyl-1*H*-pyrazole-3-carboxylic acid was obtained in 94% yield as white solid; mp = 119 – 121 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 13.78 (bs, 1H, Pyr -NH), 13.02 (bs, 1H, -OH), 7.81 (d, 2H, *J* = 7.4 Hz, Ph H-2,6), 7.42 (t, 2H, *J* = 7.4 Hz, Ph H-3,5), 7.33 (t, 1H, *J* = 6.9 Hz, Ph H-4), 7.17 (s, 1H, Pyr H-4). R$_f$: 0.13 (TLC: 1% HCOOH in dichloromethane/methanol 95:5). MS (ESI): 189.0 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

Ethyl 5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate (9): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), phenylhydrazine (1.2 equiv) and catalytic HCl 12M in ethanol (10 mL), the desired ethyl 5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate was obtained in 43% yield as white solid; mp = 103 – 107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 – 7.39 (m, 5H, Ph H), 6.72 (s, 1H, Pyr H-4), 4.39 (q, 2H, *J* = 7.1 Hz, -C*H*$_2$CH$_3$), 2.31 (s, 3H, Pyr-CH$_3$), 1.37 (t, 3H, *J* = 7.1 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.48 (TLC: petroleum ether/ethyl acetate 8:2). MS (ESI): 231.1 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

Ethyl 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (10): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), 4-bromophenylhydrazine (1.2 equiv) and catalytic HCl 12M in ethanol (12 mL), the desired ethyl 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate was obtained in 45% yield as a white solid; mp = 103 – 107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53 (d, 2H, *J* = 8.8 Hz, Ph H-3,5), 7.28 (d, 2H, *J* = 8.8 Hz, Ph H-2,6), 6.64 (s, 1H, Pyr H-4), 4.33 (q, 2H, *J* = 7.3 Hz, -C*H*$_2$CH$_3$), 2.25 (s, 3H, Pyr-CH$_3$), 1.31 (t, 3H, *J* = 7.3 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.40 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 309.1 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

Ethyl 1-(4-cyanophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate (11): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), 4-cyanophenylhydrazine (1.2 equiv) and catalytic HCl 12M in ethanol (12 mL), the desired ethyl 1-(4-cyanophenyl)-5-methyl-1*H*-pyrazole-3-carboxylate was obtained in 44% yield as a white solid; mp = 110 - 114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, 2H, *J* = 8.8 Hz, Ph H-2,6) 7.60 (d, 2H, J = 8.8 Hz, Ph H-3,5), 6.70 (s, 1H, Pyr H-4), 4.33 (q, 2H, *J* = 7.4 Hz, -C*H*$_2$CH$_3$), 2.35 (s, 3H, Pyr-CH$_3$), 1.33 (t, 3H, *J* = 7.4 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.66 (TLC: petroleum ether/ethyl acetate 7:3). MS (ESI): 256.1 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

Ethyl 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylate (12): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), phenylhydrazine (1.2 equiv) and catalytic HCl 12M in ethanol (14 mL), the desired ethyl 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylate was obtained in 41% yield as a brownish-red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 – 7.38 (m, 5H, Ph H), 6.80 (s, 1H, Pyr H-4), 4.20 (q, 2H, *J* = 7.1 Hz, -C*H*$_2$CH$_3$), 2.35 (s, 3H, Pyr-CH$_3$), 1.21 (t, 3H, *J* = 7.1 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.74 (TLC: petroleum ether/ethyl acetate 8:2). MS (ESI): 231.1 $[M+H]^+$. Spectral data match with those ones previously reported.[3]

Ethyl 1-(4-bromophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (13): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), 4-bromophenylhydrazine (1.2 equiv) and catalytic HCl 12M in ethanol (10 mL), the desired ethyl 1-(4-bromophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate was obtained in 34% yield as whitish needles; mp = 137 - 138 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56 (d, 2H, *J* = 8.8 Hz, H-3,5), 7.39 (d, 2H, *J* = 8.8 Hz, H-2,6), 6.81 (s, 1H, Pyr H-4), 4.24 (q, 2H, *J* = 7.3 Hz, -C*H*$_2$CH$_3$), 2.35 (s, 3H, Pyr-CH$_3$), 1.26 (t, 3H, *J* = 7.3 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.75 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 309.1 $[M+H]^+$. Spectral data match with those ones previously reported.[4]

Ethyl 1-(4-cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate (14): by following the General Procedure 2, starting from 2,4-dioxovalerate (1 equiv), 4-cyanophenylhydrazine (1.2 equiv) and catalytic HCl 12 M in ethanol (12 mL), the desired ethyl ethyl 1-(4-cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylate was obtained in 33% yield as a white solid; mp = 41 - 43 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (d, 2H, *J* = 8.8 Hz, H-2,6), 7.55 (d, 2H, *J* = 8.8 Hz, H-3,5), 6.85 (s, 1H, Pyr H-4), 4.25 (q, 2H, *J* = 7.4 Hz, -C*H*$_2$CH$_3$), 2.34 (s, 3H, Pyr-C*H*$_3$), 1.28 (t, 3H, *J* = 7.4 Hz, -CH$_2$C*H*$_3$). R$_f$: 0.66 (TLC: petroleum ether/ethyl acetate 7:3). MS (ESI): 256.1 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylic acid (15): by following the General Procedure 5, starting from **9** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylic acid was obtained in 94% yield as whitish needle-shaped crystals; mp = 106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.45 – 7.41 (m, 5H, Ph H), 6.74 (s, 1H, Pyr H-4), 2.31 (s, 3H, CH$_3$). R$_f$: 0.18 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 1:1). MS (ESI): 203.1 $[M+H]^+$. Spectral data match with those ones previously reported.[5]

1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid (16): by following the General Procedure 5, starting from **10** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 1-(4-bromophenyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid was obtained in 95% yield as whitish crystals; mp = 184 - 186 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.42 (bs, 1H, -COOH), 7.62 (d, 2H, *J* = 8.8 Hz,

Ph H-3,5), 7.36 (d, 2H, *J* = 8.8 Hz, Ph H-2,6), 6.78 (s, 1H, Pyr H-4), 2.35 (s, 3H, CH_3). R_f: 0.39 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 7:3). MS (ESI): 281.0 $[M+H]^+$. Spectral data match with those ones previously reported.[6]

1-(4-cyanophenyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid (17): by following the General Procedure 5, starting from **11** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 1-(4-cyanophenyl)-5-methyl-1*H*-pyrazole-3-carboxylic acid was obtained in 93% yield as a white solid; mp = 230 - 232 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.91 (bs, 1H, -COOH), 8.03 (d, 2H, *J* = 8.8 Hz, Ph H-2,6), 7.81 (d, 2H, *J* = 8.8 Hz, Ph H-3,5), 6.74 (s, 1H, Pyr H-4), 3.30 (s, 3H, CH_3). R_f: 0.16 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 6:4). MS (ESI): 228.1 $[M+H]^+$. Spectral data match with those ones previously reported.[6]

3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylic acid (18): by following the General Procedure 5, starting from **12** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 3-methyl-1-phenyl-1*H*-pyrazole-5-carboxylic acid was obtained in 91% yield as a brownish powder; mp = 145 - 149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.34 (m, 5H, Ph H), 6.82 (s, 1H, Pyr H-4), 2.31 (s, 3H, CH_3). R_f: 0.15 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 1:1). MS (ESI): 203.1 $[M+H]^+$. Spectral data match with those ones previously reported.[2]

1-(4-bromophenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid (19): by following the General Procedure 5, starting from **13** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 1-(4-bromophenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid was obtained in 93% yield as a white solid; mp = 211 - 213 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.44 (bs, 1H, -COOH), 7.60 (d, 2H, *J* = 8.8 Hz, Ph H-3,5), 7.40 (d, 2H, *J* = 8.8 Hz, Ph H-2,6), 6.89 (s, 1H, Pyr H-4), 2.34 (s, 3H, CH_3). R_f: 0.29 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 7:3). MS (ESI): 281.0 $[M+H]^+$. Spectral data match with those ones previously reported.[6]

1-(4-cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid (20): by following the General Procedure 5, starting from **14** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 1-(4-cyanophenyl)-3-methyl-1*H*-pyrazole-5-carboxylic acid was obtained in 96% yield as a white powder; mp = 225 - 226 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ 7.90 (d, 2H, *J* = 8.3 Hz, H-2,6), 7.73 (d, 2H, *J* = 8.3 Hz, H-3,5), 6.94 (s, 1H, Pyr-H-4), 2.31 (s, 3H, CH_3). R_f: 0.26 (TLC: 2% HCOOH in petroleum ether/ethyl acetate 1:1). MS (ESI): 228.1 $[M+H]^+$. Spectral data match with those ones previously reported.[6]

Ethyl 5-phenylisoxazole-3-carboxylate (21): by following the General Procedure 4, starting from phenylacetylene (1 equiv), ethyl 2-chloro-2(hydroxymino)acetate (3 equiv) and triethylamine (3.5 equiv) in dry THF (10 mL), the desired ethyl 5-phenylisoxazole-3-carboxylate was obtained in 65% yield as a sticky clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 - 7.87 (m, 2H, Ph H), 7.58 - 7.55 (m, 3H, Ph H), 7.00 (s, 1H, Isox H-4), 4.55 (q, 2H, *J* = 7.3 Hz, -CH_2CH$_3$), 1.52 (t, 3H, *J* = 7.3 Hz, -CH$_2$CH_3). R_f: 0.64 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 218.0 $[M+H]^+$. Spectral data match with those ones previously reported.[7]

Ethyl 5-(*p*-tolyl)isoxazole-3-carboxylate (22): by following the General Procedure 4, starting from 4-ethynyltoluene (1 equiv), ethyl 2-chloro-2(hydroxymino)acetate (3 equiv) and triethylamine (3.5 equiv) in dry THF (10 mL), the desired ethyl 5-(*p*-tolyl)isoxazole-3-carboxylate was obtained in 66% yield as a sticky clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 7.4 Hz, Ph H), 7.35 (d, 2H, *J* = 7.5 Hz, Ph H), 6.93 (s, 1H, Isox H-4), 4.53 (q, 2H, *J* = 7.3 Hz, -CH_2CH$_3$), 2.48 (s, 3H, PhCH_3), 1.50 (t, 3H, *J* = 7.3 Hz, -CH$_2$CH_3). R_f: 0.76 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 232.1 $[M+H]^+$. Spectral data match with those ones previously reported.[8]

Ethyl 5-(4-methoxyphenyl)isoxazole-3-carboxylate (23): by following the General Procedure 4, starting from 4-ethynylanisole (1 equiv), ethyl 2-chloro-2(hydroxymino)acetate (3 equiv) and triethylamine (3.5 equiv) in dry THF (10 mL), the desired ethyl 5-(4-methoxyphenyl)isoxazole-3-carboxylate was obtained in 43% yield as a white solid; m.p. = 85 - 88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, 2H, *J* = 7.8 Hz, Ph H), 6.90 (d, 2H, *J* = 7.8 Hz, Ph H), 7.00 (s, 1H, Isox H-4), 4.53 (q, 2H, *J* = 7.3 Hz, -CH_2CH$_3$), 3.72 (s, 3H, OCH_3), 1.49 (t, 3H, *J* = 7.3 Hz, -CH$_2$CH_3). R_f: 0.52 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 248.4 $[M+H]^+$. Spectral data match with those ones previously reported.[9]

Ethyl 5-(4-chlorophenyl)isoxazole-3-carboxylate (24): by following the General Procedure 4, starting from 1-chloro-4-ethynylbenzene (1 equiv), ethyl 2-chloro-2(hydroxymino)acetate (3 equiv) and triethylamine (3.5 equiv) in dry THF (10 mL), the desired ethyl 5-(4-chlorophenyl)isoxazole-3-carboxylate was obtained in 59% yield as a white solid; m.p. = 126 - 129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, 2H, *J* = 7.8 Hz, Ph H), 7.65 (d, 2H, *J* = 7.8 Hz, Ph H), 6.99 (s, 1H, Isox H-4), 4.50 (q, 2H, *J* = 7.3 Hz, -CH_2CH$_3$), 1.39 (t, 3H, *J* = 7.3 Hz, -CH$_2$CH_3). R_f: 0.7 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 252.3 $[M+H]^+$. Spectral data match with those ones previously reported.[10]

Ethyl 5-(4-bromophenyl)isoxazole-3-carboxylate (25): by following the General Procedure 4, starting from 1-bromo-4-ethynylbenzene (1 equiv), ethyl 2-chloro-2(hydroxymino)acetate (3 equiv) and triethylamine (3.5 equiv) in dry THF (10 mL), the desired ethyl 5-(4-bromophenyl)isoxazole-3-carboxylate was obtained in 44% yield as a white powder; m.p. = 133 - 134 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2H, *J* = 7.8 Hz, Ph H), 7.58 (d, 2H, *J* = 7.8 Hz, Ph H), 6.94 (s, 1H, Isox H-4), 4.46 (q, 2H, *J* = 7.3 Hz, -CH_2CH$_3$), 1.54 (t, 3H, *J* = 7.3 Hz, -CH$_2$CH_3). R_f: 0.7 (TLC: petroleum ether/diethyl ether 7:3). MS (ESI): 296.0 $[M+H]^+$. Spectral data match with those ones previously reported.[11]

5-phenylisoxazole-3-carboxylic acid (26): by following the General Procedure 5, starting from **21** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-phenylisoxazole-3-carboxylic acid was obtained in 97% yield as a beige powder; m.p. = 136 - 138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 - 7.81 (m, 2H, Ph H), 7.52 – 7.49 (m, 3H, Ph H), 6.99 (s, 1H, Isox H-4). R_f: 0.42 (TLC: 2% HCOOH in *n*-hexane/ethyl acetate 1:1). MS (ESI): 191.0 $[M+H]^+$. Spectral data match with those ones previously reported.[12]

5-(*p*-tolyl)isoxazole-3-carboxylic acid (27): by following the General Procedure 5, starting from **22** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-(*p*-tolyl)isoxazole-3-carboxylic acid was obtained in 93% yield as a beige powder; m.p. = 155 - 159 °C. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.24 (bs, 1H, -COO*H*), 7. 78 (d, 2H, *J* = 8.4 Hz, Ph H), 7.33 (d, 2H, *J* = 8.4 Hz, Ph H), 7.10 (s, 1H, Isox H-4), 2.36 (s, 3H, -CH_3). R_f: 0.18 (TLC: 2% HCOOH in *n*-hexane/ethyl acetate 1:1). MS (ESI): 204.1 $[M+H]^+$. Spectral data match with those ones previously reported.[8]

5-(4-methoxyphenyl)isoxazole-3-carboxylic acid (28): by following the General Procedure 5, starting from **23** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-(4-methoxyphenyl)isoxazole-3-carboxylic acid was obtained in 95% yield as a white powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.30 (s, 1H, COOH), 7.00 (d, 2H, *J* = 7.8 Hz, Ph H), 6.91 (d, 2H, *J* = 7.8 Hz, Ph H), 6.98 (s, 1H, Isox H-4), 3.77 (s, 3H, OCH_3). R_f: 0.2 (TLC: 2% HCOOH in *n*-hexane/ethyl acetate 1:1). MS (ESI): 220.0 $[M+H]^+$. Spectral data match with those ones previously reported.[12]

5-(4-chlorophenyl)isoxazole-3-carboxylic acid (29): by following the General Procedure 5, starting from **24** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-(4-chlorophenyl)isoxazole-3-carboxylic acid was obtained in 97% yield as a white amorphous powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.50 (s, 1H, COOH), 7.89 (d, 2H, *J* = 8.0 Hz, Ph H), 7.67 (d, 2H, *J* = 8.0 Hz, Ph H), 7.30 (s, 1H, Isox H-4). R_f: 0.3 (TLC: 2% HCOOH in *n*-hexane/ethyl acetate 1:1). MS (ESI): 224.0 $[M+H]^+$. Spectral data match with those ones previously reported.[12]

5-(4-bromophenyl)isoxazole-3-carboxylic acid (30): by following the General Procedure 5, starting from **25** (1 equiv) and LiOH (10 equiv) in ethanol/water (1:1, v/v, 12 mL) the desired 5-(4-bromophenyl)isoxazole-3-carboxylic acid was obtained in 95% yield as a white non-crystalline powder. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.23 (s, 1H, COOH), 7.85 (d, 2H, *J* = 8.1 Hz, Ph H), 7.51 (d, 2H, *J* = 8.1 Hz, Ph H), 7.22 (s, 1H, Isox H-4). R_f: 0.3 (TLC: 2% HCOOH in *n*-hexane/ethyl acetate 1:1). MS (ESI): 269.9 $[M+H]^+$. Spectral data match with those ones previously reported.[8]

***N*-methoxy-*N*-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide (31)**: by following the General Procedure 6, starting from **8** (500 mg, 2.66 mmol, 1 equiv), 1,1′-carbonyldiimidazole (517 mg, 3.192 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (311 mg, 3.192 mmol, 1.2 equiv), 4-methylmorpholine (403 mg, 3.99 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-*N*-methyl-5-phenyl-1*H*-pyrazole-3-carboxamide was obtained in 91% yield (559 mg) as a yellow oil without any further purifications. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, Ph H-2,6), 7.38 (t, 2H, Ph H-3,5), 7.30 (t, 1H, Ph H-4), 7.10 (s, 1H, Pyr H-4), 7.04 (Pyr-NH), 3.76 (s, 3H, OCH_3), 3.39 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.0, 150.8, 135.2, 132.0, 128.7, 128.0, 125.7, 105.5, 61.5, 33.0. HRMS (ESI), *m/z*: calcd. for $C_{12}H_{14}N_3O_2^+$: 232.1081 $[M+H]^+$; found: 232.1086.

***N*-methoxy-*N*,1-dimethyl-5-phenyl-1*H*-pyrazole-3-carboxamide (32)**: by following the General Procedure 3, starting from **31** (105 mg, 0.45 mmol, 1 equiv), potassium carbonate (34 mg, 0.9 mmol, 2 equiv), iodomethane (127 mg, 0.9 mmol, 2 equiv), and dry DMF (4 mL), the desired *N*-methoxy-*N*,1-dimethyl-5-phenyl-1*H*-pyrazole-3-carboxamide was obtained in 90% yield (114 mg) as yellow oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4 (v/v) as eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81 (d, $^3J_{H,H}$ = 8.3 Hz, 2H, Ph H-2,6), 7.41 (t, 2H, Ph H-3,5), 7.32 (t, 1H, Ph H-4), 7.05 (s, 1H, Pyr H-4), 4.17 (s, 3H, Pyr NCH_3), 3.69 (s, 3H, OCH_3), 3.38 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.6, 141.7, 134.4, 132.0, 128.8, 128.1, 125.7, 104.5, 61.8, 40.0, 33.3. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{16}N_3O_2^+$: 246.1237 $[M+H]^+$; found: 246.1231.

***N*-methoxy-*N*,5-dimethyl-1-phenyl-1*H*-pyrazole-3-carboxamide (33)**: by following the General Procedure 6, starting from **15** (660 mg, 3.26 mmol, 1 equiv), 1,1′-carbonyldiimidazole (635 mg, 3.91 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (381 mg, 3.91 mmol, 1.2 equiv), 4-methylmorpholine (494 mg, 4.89 mmol, 0.5 mL) and CPME (5 mL), the desired *N*-methoxy-*N*,5-dimethyl-1-phenyl-1*H*-pyrazole-3-carboxamide was obtained in 94% yield (752 mg) as yellow oil without any further purifications. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 – 7.25 (m, 5H, Ph H-2,3,4,5,6), 6.96 (s, 1H, Pyr, H-4), 3.67 (s, 3H, OCH_3), 3.34 (s, 3H, NCH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.8, 144.9, 139.3, 139.1, 128.8, 127.9, 124.7, 109.0, 61.1, 34.3, 12.1. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{16}N_3O_2^+$: 246.1237 $[M+H]^+$; found: 246.1233.

1-(4-bromophenyl)-*N*-methoxy-*N*,5-dimethyl-1*H*-pyrazole-3-carboxamide (34): by following the General Procedure 6, starting from **16** (500 mg, 1.78 mmol, 1 equiv), 1,1′-carbonyldiimidazole (346 mg, 2.136 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (208 mg, 2.136 mmol, 1.2 equiv), 4-methylmorpholine (268 mg, 2.67 mmol, 0.3 mL) and CPME (5 mL), the desired 1-(4-bromophenyl)-*N*-methoxy-*N*,5-dimethyl-1*H*-pyrazole-3-carboxamide was obtained in 95% yield (548 mg) as yellow oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.59 (d, 2H, Ph H-3,5), 7.35 (d, 2H, Ph H-2,6), 6.67 (s, 1H, Pyr H-4), 3.78 (s, 3H, OCH_3), 3.44 (s, 3H, NCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.4, 145.8, 139.7, 138.5, 132.4, 126.6, 122.1, 109.8, 61.4, 33.6, 12.5. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{15}BrN_3O_2^+$: 324.0342 $[M+H]^+$; found: 324.0350.

1-(4-cyanophenyl)-*N*-methoxy-*N*,5-dimethyl-1*H*-pyrazole-3-carboxamide (35): by following the General Procedure 6, starting from **17** (500 mg, 2.2 mmol, 1 equiv), 1,1′-carbonyldiimidazole (428 mg, 2.64 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (257 mg, 2.64 mmol, 1.2 equiv), 4-methylmorpholine (386 mg, 3.3 mmol, 0.4 mL) and CPME (5 mL), the desired 1-(4-cyanophenyl)-*N*-methoxy-*N*,5-dimethyl-1*H*-pyrazole-3-carboxamide was obtained in 92% yield (550 mg) as yellow oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79 (d, 2H, Ph H-2,6), 7.64 (d, 2H, Ph H-3,5), 6.58 (s, 1H, Pyr H-4), 3.70 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 2.39 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.4, 144.0, 135.7, 130.5, 132.4, 121.6, 110.1, 118.6, 107.8, 63.4, 37.7, 12.5. HRMS (ESI), *m/z*: calcd. for $C_{14}H_{15}N_4O_2^+$: 271.1190 $[M+H]^+$; found: 271.1197.

1-(4-bromophenyl)-*N*-methoxy-*N*,3-dimethyl-1*H*-pyrazole-5-carboxamide (36): by following the General Procedure 6, starting from **19** (250 mg, 0.889 mmol, 1 equiv), 1,1′-carbonyldiimidazole (173 mg, 1.067 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (104 mg, 1.067 mmol, 1.2 equiv), 4-methylmorpholine (134 mg, 1.333 mmol, 0.15 mL) and CPME (5 mL), the desired 1-(4-bromophenyl)-*N*-methoxy-*N*,3-dimethyl-1*H*-pyrazole-5-carboxamide was obtained in 93% yield (241 mg) as yellow oil after column chromatography on silica gel (petroleum ether/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53 (d, J = 8.8, 2H, Ph H-3,5), 7.32 (d, J = 8.8, 2H, Ph H-2,6), 6.53 (s, 1H, Pyr H-4), 3.56 (s, 3H, OCH_3), 3.22 (s, 3H, NCH_3), 2.36 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.4, 146.3, 139.4, 138.1, 132.0, 126.2, 121.6, 109.4, 61.3, 33.6, 12.2. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{15}BrN_3O_2^+$: 324.0342 $[M+H]^+$; found: 324.0346.

***N*-methoxy-*N*-methyl-5-phenylisoxazole-3-carboxamide (37)**: by following the General Procedure 1, starting from **26** (500 mg, 2.64 mmol, 1 equiv), 1,1'-carbonyldiimidazole (513 mg, 3.17 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (309 mg, 3.17 mmol, 1.2 equiv), 4-methylmorpholine (400 mg, 3.96 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-*N*-methyl-5-phenylisoxazole-3-carboxamide was obtained in 57% yield (326 mg) as a white solid after column chromatography on silica gel (*n*-hexane/ethyl acetate 8:2). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (m, 2H, Ph H-2,6), 7.31 (m, 3H, Ph H-3,4,5), 6.72 (s, 1H, Isox H-4), 3.67 (s, 3H, OCH_3), 3.25 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 158.3, 149.7, 130.5, 129.0, 126.7, 125.8, 100.4, 62.3, 32.9. HRMS (ESI), *m/z*: calcd. for $C_{12}H_{13}N_2O_3^+$: 233.0921 $[M+H]^+$; found: 233.0915.

***N*-methoxy-*N*-methyl-5-(*p*-tolyl)isoxazole-3-carboxamide (38):** by following the General Procedure 6, starting from **27** (500 mg, 2.46 mmol, 1 equiv), 1,1'-carbonyldiimidazole (479 mg, 2.95 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (288 mg, 2.95 mmol, 1.2 equiv), 4-methylmorpholine (373 mg, 3.69 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-*N*-methyl-5-(*p*-tolyl)isoxazole-3-carboxamide was obtained in 82% (200 mg) as a white solid after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.58 (d, $^{3}J_{H,H}$ = 8.2 Hz, 2H, Ph H-2,6), 7.16 (d, $^{3}J_{H,H}$ = 8.2 Hz, 2H, Ph H-3,5), 6.72 (s, 1H, Isox H-4), 3.72 (s, 3H, OCH_3), 3.32 (s, 3H, NCH_3), 2.28 (s, 3H, Ph-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.3, 148.6, 133.7, 130.5, 126.9, 127.8, 124.6, 104.2, 61.9, 34.8, 21.5. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{15}N_2O_3^+$: 247.1077 $[M+H]^+$; found: 247.1085.

***N*-methoxy-5-(4-methoxyphenyl)-*N*-methylisoxazole-3-carboxamide (39)**: by following the General Procedure 6, starting from **28** (500 mg, 2.28 mmol, 1 equiv), 1,1'-carbonyldiimidazole (444 mg, 2.74 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (267 mg, 2.74 mmol, 1.2 equiv), 4-methylmorpholine (346 mg, 3.42 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-5-(4-methoxyphenyl)-*N*-methylisoxazole-3-carboxamide was obtained in 79% (471 mg) as a white solid after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.64 (d, $^{3}J_{H,H}$ = 8.8 Hz, 2H, Ph H-2,6), 6.89 (d, $^{3}J_{H,H}$ = 8.8 Hz, 2H, Ph H-3,5), 6.66 (s, 1H, Isox H-4), 3.76 (s, 3H, $PhOCH_3$), 3.75 (s, 3H, $NOCH_3$), 3.33 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 170.1, 161.3, 158.2, 127.4, 119.4, 114.4, 98.8, 62.5, 55.3, 32.7. HRMS (ESI), *m/z*: calcd. for $C_{13}H_{15}N_2O_4^+$: 263.1026 $[M+H]^+$; found: 263.1020.

5-(4-chlorophenyl)-*N*-methoxy-*N*-methylisoxazole-3-carboxamide (40): by following the General Procedure 6, starting from **29** (500 mg, 2.23 mmol, 1 equiv), 1,1'-carbonyldiimidazole (434 mg, 2.67 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (261 mg, 2.67 mmol, 1.2 equiv), 4-methylmorpholine (0.4 mL, 3.34 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-5-(4-chlorophenyl)-*N*-methylisoxazole-3-carboxamide was obtained in 84% (200 mg) as a white solid after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (d, $^{3}J_{H,H}$ = 8.2 Hz, 2H, Ph H-2,6), 7.41 (d, $^{3}J_{H,H}$ = 8.2 Hz, 2H, Ph H-3,5), 6.83 (s, 1H, Isox H-4), 3.80 (s, 3H, OCH_3), 3.37 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.1, 160.7, 158.3, 136.7, 129.5, 127.2, 125.3, 100.9, 62.5, 32.9. HRMS (ESI), *m/z*: calcd. for $C_{12}H_{12}ClN_2O_3^+$: 267.0531 $[M+H]^+$; found: 267.0536.

5-(4-bromophenyl)-*N*-methoxy-*N*-methylisoxazole-3-carboxamide (41): by following the General Procedure 6, starting from **30** (261 mg, 2.67 mmol, 1.2 equiv), 1,1'-carbonyldiimidazole (362 mg, 2.23 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (217 mg, 2.23 mmol, 1.2 equiv), 4-methylmorpholine (282 mg, 2.79 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-5-(4-bromophenyl)-*N*-methylisoxazole-3-carboxamide was obtained in 86% (250 mg) as a white solid after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (d, $^{3}J_{H,H}$ = 8.6 Hz, 2H, Ph H-2,6), 7.58 (d, $^{3}J_{H,H}$ = 8.6 Hz, 2H, Ph H-3,5), 6.84 (s, 1H, Isox H-4), 3.79 (s, 3H, OCH_3), 3.37 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 169.4, 160.7, 158.5, 135.1, 132.3, 127.4, 121.7 (Ph C-1), 100.8, 62.5, 33.0. HRMS (ESI), *m/z*: calcd. for $C_{12}H_{12}BrN_2O_3^+$: 311.0026 $[M+H]^+$; found: 311.0020.

5-isopropyl-*N*-methoxy-*N*-methylisoxazole-3-carboxamide (42): by following the General Procedure 6, starting from the commercially available 5-isopropylisoxazole-3-carboxylic acid (500 mg, 3.22 mmol, 1 equiv), 1,1'-carbonyldiimidazole (625 mg, 3.86 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (376 mg, 3.86 mmol, 1.2 equiv), 4-methylmorpholine (488 mg, 4.83 mmol, 0.5 mL) and CPME (5 mL), the desired 5-isopropyl-*N*-methoxy-*N*-methylisoxazole-3-carboxamide was obtained in 78% (347 mg) as a yellow oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.21 (s, 1H, Isox H-4), 3.69 (s, 3H, OCH_3), 3.28 (s, 3H, NCH_3), 3.02 (m, $^{3}J_{H,H}$ = 6.9 Hz, 1H, C*H*$(CH_3)_2$, 1.23 [d, $^{3}J_{H,H}$ = 6.9 Hz, 6H, CH(C*H*$_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.3, 135.1, 121.6, 99.8, 62.2, 32.7, 27.0, 20.6. HRMS (ESI), *m/z*: calcd. for $C_9H_{15}N_2O_3^+$: 199.1077 $[M+H]^+$; found: 199.1073.

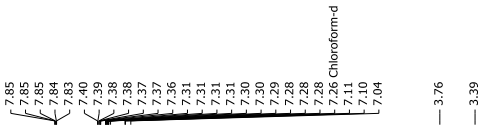
***N*-methoxy-*N*-methyl-3-phenylisoxazole-5-carboxamide (43)**: by following the General Procedure 6, starting from the commercially available 3-phenylisoxazole-5-carboxylic acid (500 mg, 2.64 mmol, 1 equiv), 1,1'-carbonyldiimidazole (514 mg, 3.16 mmol, 1.2 equiv), *N,O*-dimethylhydroxylamine hydrochloride (308 mg, 3.16 mmol, 1.2 equiv), 4-methylmorpholine (400 mg, 3.96 mmol, 0.4 mL) and CPME (5 mL), the desired *N*-methoxy-*N*-methyl-3-phenylisoxazole-5-carboxamide was obtained in 82% (400 mg) as a yellow oil after column chromatography on silica gel (*n*-hexane/ethyl acetate 6:4). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76 (m, 2H, Ph H-2,6), 7.37 (m, 3H, Ph H-3,4,5), 7.12 (s, 1H, Isox H-4), 3.76 (s, 3H, OCH_3), 3.31 (s, 3H, NCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 160.5, 162.2, 130.3, 128.9, 128.1, 126.7, 106.7, 62.0, 32.9. HRMS (ESI), *m/z*: calcd. for $C_{12}H_{13}N_2O_3^+$: 233.0921 $[M+H]^+$; found: 233.0915.

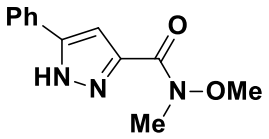
Table S1. For each ligand, the residues involved in the interaction and the binding affinity expressed in Kcal/mol are reported.

	COX-2		COX-1	
LIGANDS	**BINDING AFFINITIES[a]**	**INTERACTIONS[b]**	**BINDING AFFINITIES[a]**	**INTERACTIONS[b]**
XRAY		VAL116, VAL349, TYR385, ALA527, SER530, LEU531		ARG120, VAL349, LEU352, TY355, LEU384, TYR385, TRP387, MET522, ILE 523, ALA527, LEU531
CONTROL	-9.1	VAL349, LEU352, TYR385, VAL523, ALA527, SER530	-9.0	ARG120, VAL349 , TY355, LEU384, TYR385, TRP387, MET522, ILE 523, ALA527, LEU531
44	-7.6	VAL 349, LEU352, TYR385, VAL523, GLY526, ALA527	-8.1	ARG120, VAL349, LEU352, PHE518, ILE523, GLY526, ALA527
45	-6.9	VAL349, LEU352, TYR385, VAL523, GLY 526, ALA527, SER530, LEU531	-8.0	VAL349, LEU352, PHE518, ILE523, GLY526, ALA527
46	-6.4	HIS90, TYR355, VAL349, LEU352, TYR385, VAL523, GLY526, ALA527, SER530	-8.2	ARG120, LEU352, LEU384, TYR385, TRP387, ALA527
47	-6.8	HIS90, VAL349 LEU352, TYR385, VAL523, GLY526, ALA527, SER530	-8.3	VAL349, LEU352, TYR385 GLY526, ALA 527, SER530, LEU531
48	-7.6	VAL349, LEU385, ALA527, SER530, LEU531	-7.6	ARG120, TYR355, LEU352, SER353, LEU384, ILE523, GLY526, ALA527
49	-7.4	HIS90, VAL349, TYR355, TYR385, VAL523, GLY526, ALA527, SER530	-7.4	VAL116, VAL349, LEU352, TYR355, LEU359, GLY526, ALA527, SER530, LEU531
50	-7.8	VAL116, VAL349, TYR355, TYR385, ALA527, SER530, LEU531	-7.7	ARG120, LEU352, TYR355, TYR385, TRP387, ALA527
51	-7.3	VAL116, VAL349, TYR355, TYR385, ALA527, SER530, LEU531	-7.6	VAL116, VAL349, TYR355, LEU359, TYR385, GLY526, ALA527, LEU531
52	-7.4	VAL116, VAL349, LEU352, LEU359, TYR385, VAL523, ALA527, LEU531	-7.6	ARG120, VAL349, LEU352, TYR355, LEU384 TYR385, TRP387, GLY526, ALA527
53	-6.5	VAL349, LEU352, TYR385, VAL523, GLY526, ALA527, SER530	-6.0	VAL349, TYR385, GLY526, ALA527, SER530

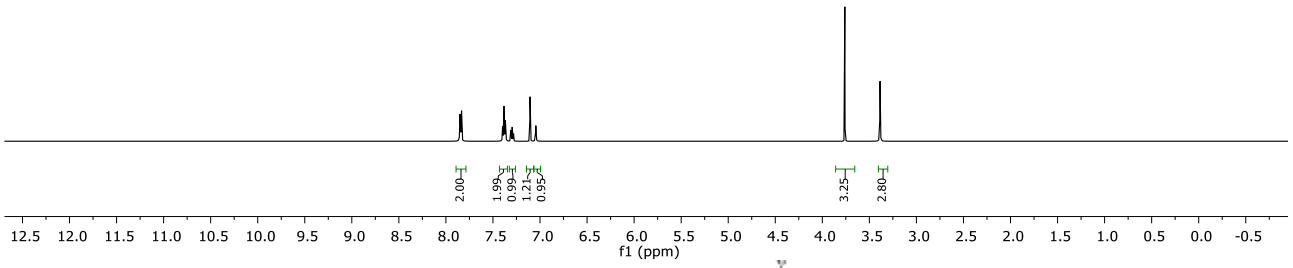
[a] (kcal/mol) [b] Amino acid residues

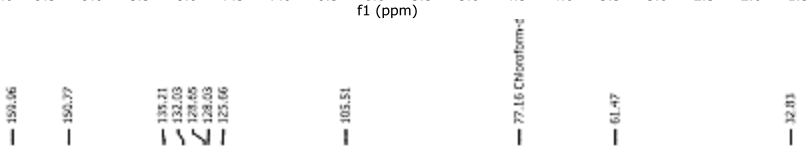
Copies of ^{1}H NMR and ^{13}C NMR of New Compounds

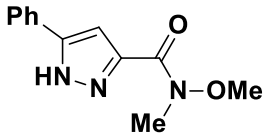




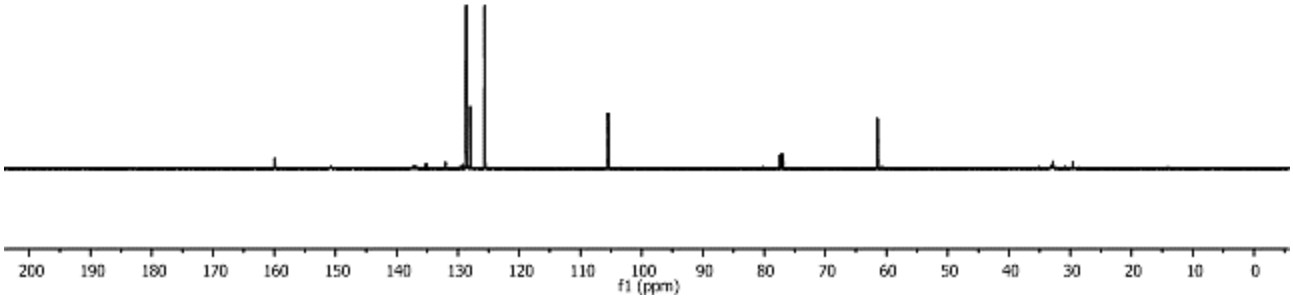
^{1}H NMR, 500 MHz, $CDCl_3$

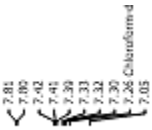


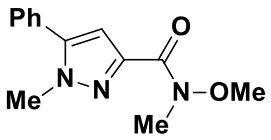




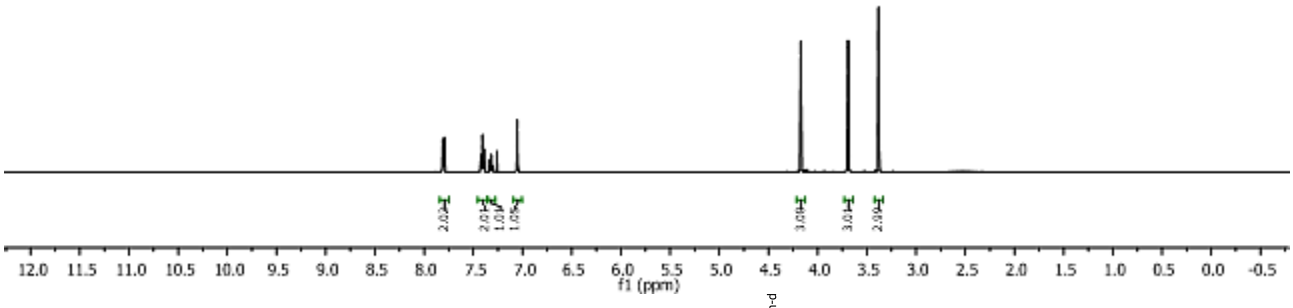
^{13}C NMR, 125 MHz, $CDCl_3$

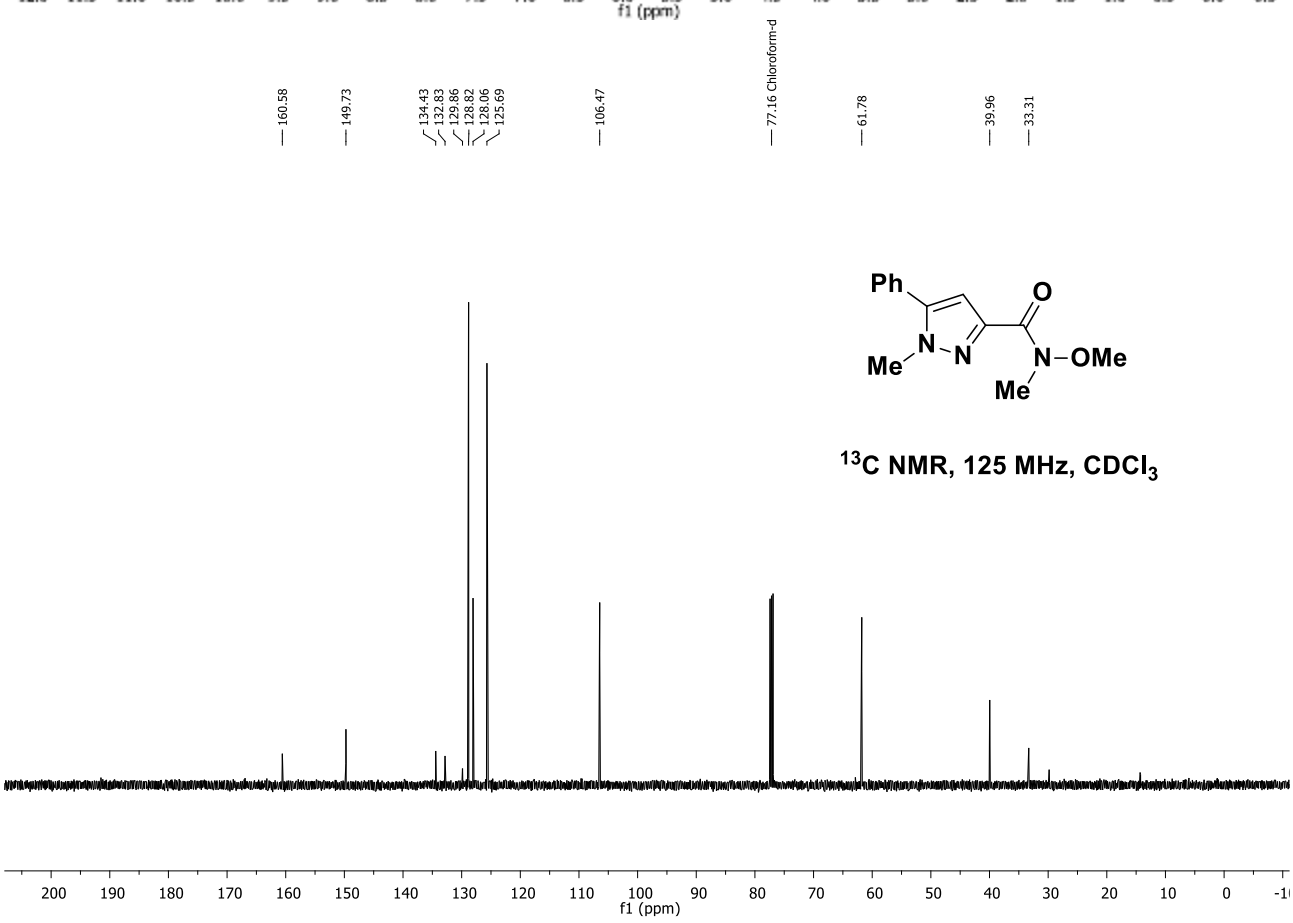




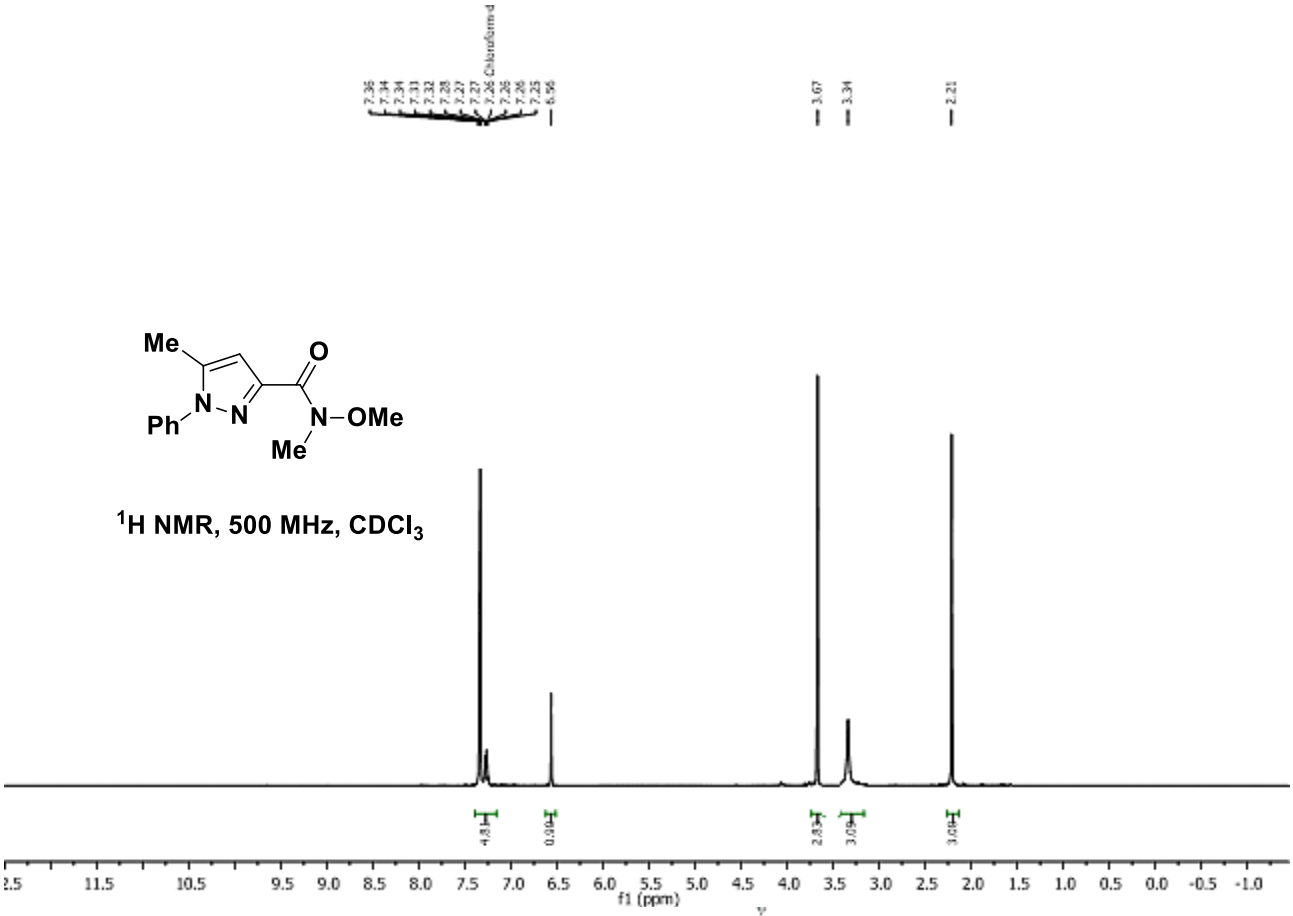


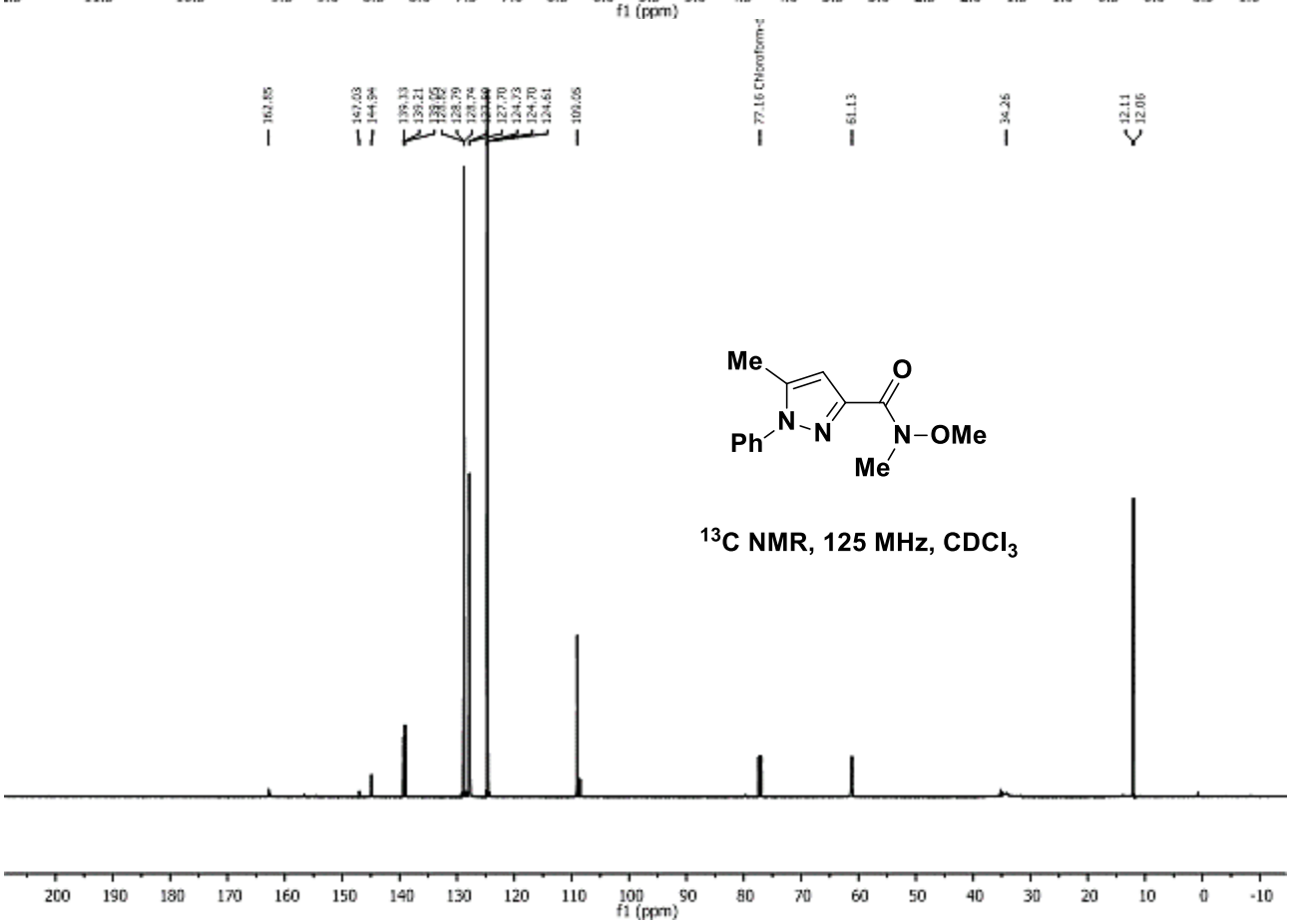
^{1}H NMR, 500 MHz, $CDCl_3$

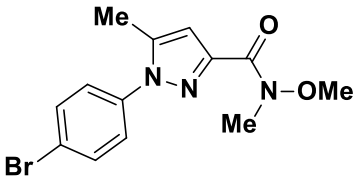




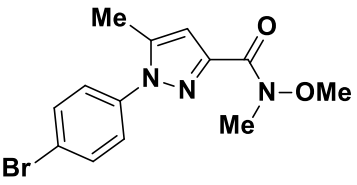
^{13}C NMR, 125 MHz, $CDCl_3$


Me
O
Ph
N
N
N–OMe
Me
1H NMR, 500 MHz, CDCl3
f1 (ppm)

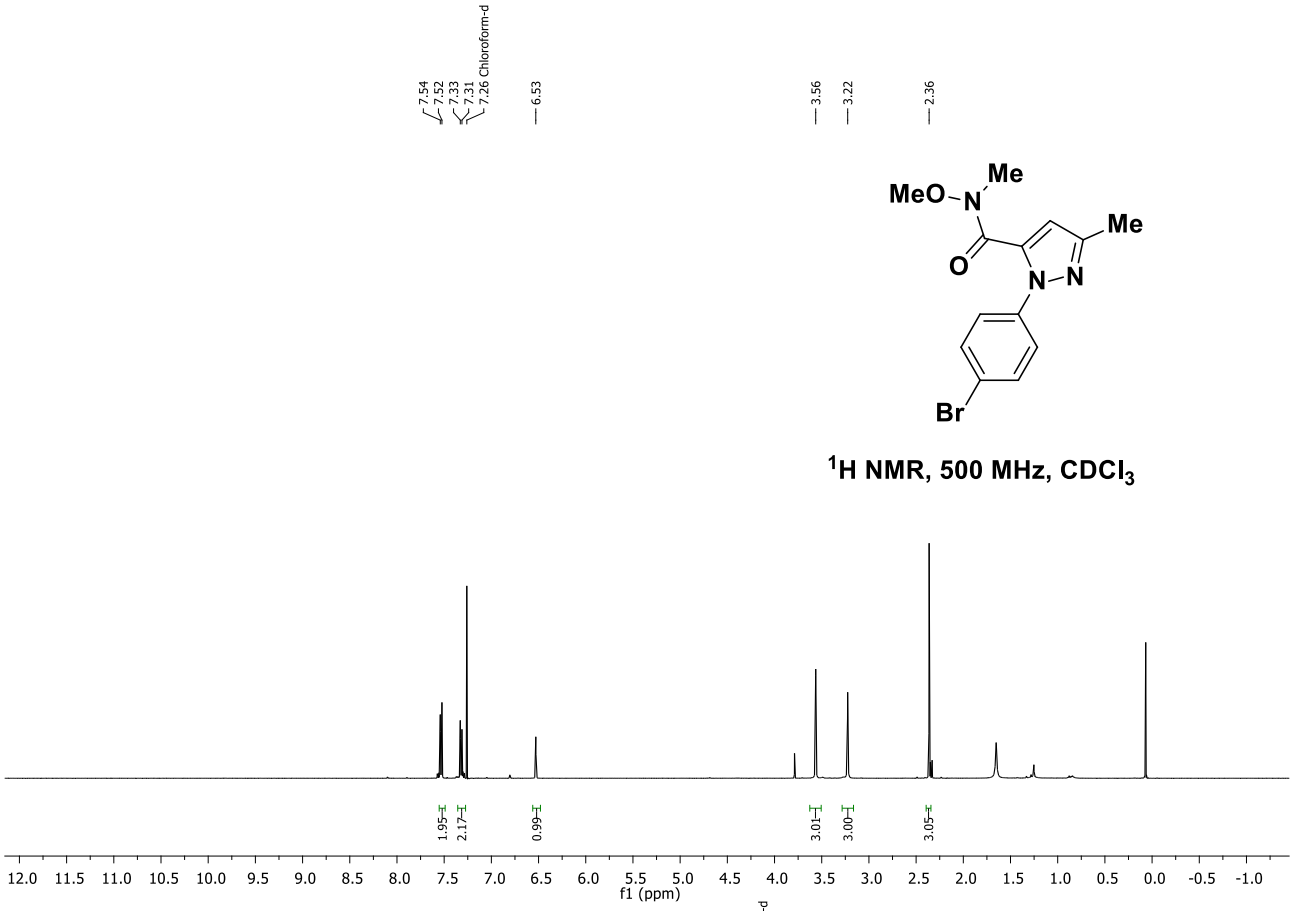

Me
O
Ph
N
N
N–OMe
Me
13C NMR, 125 MHz, CDCl3
f1 (ppm)



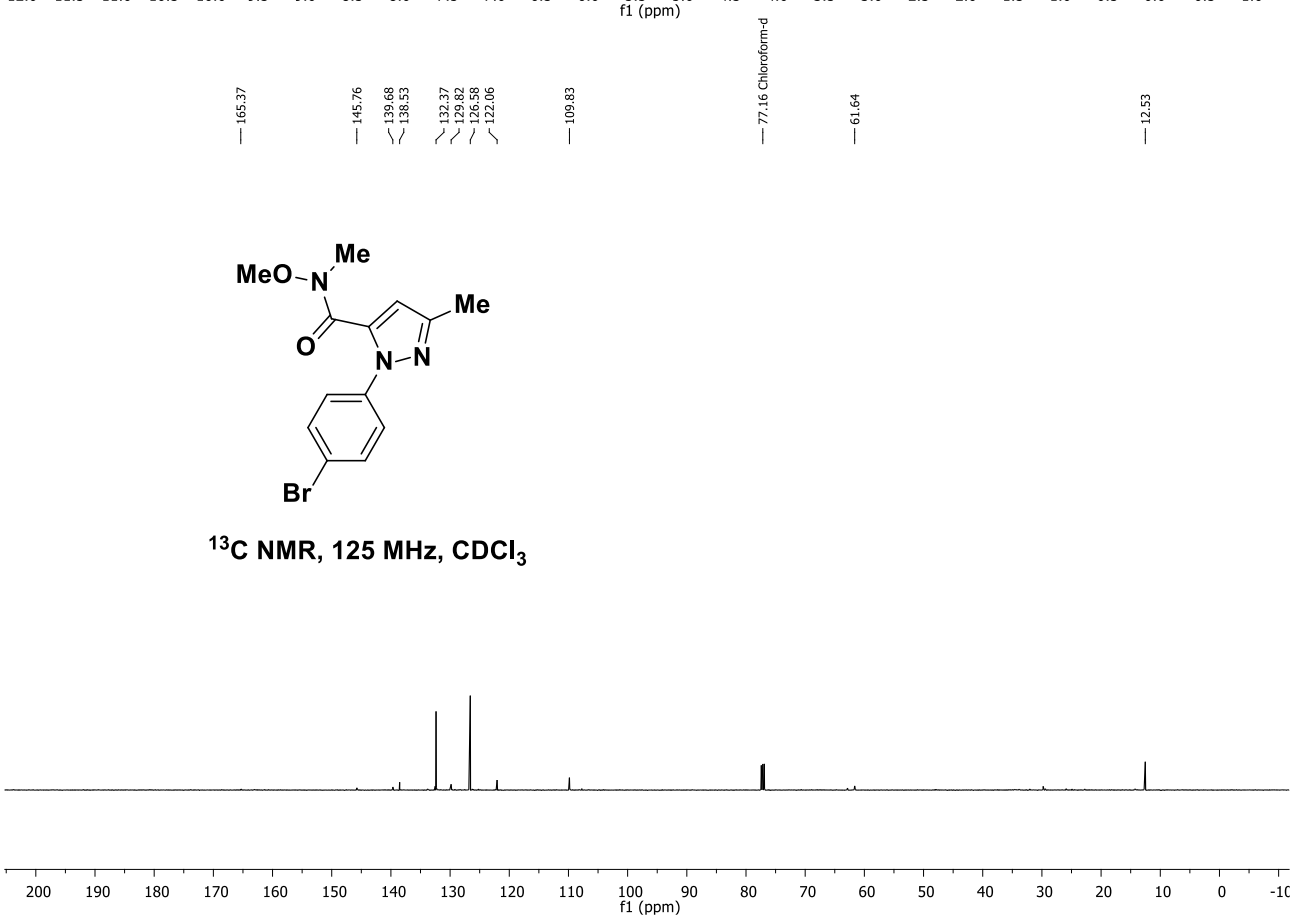
^{1}H NMR, 500 MHz, $CDCl_3$



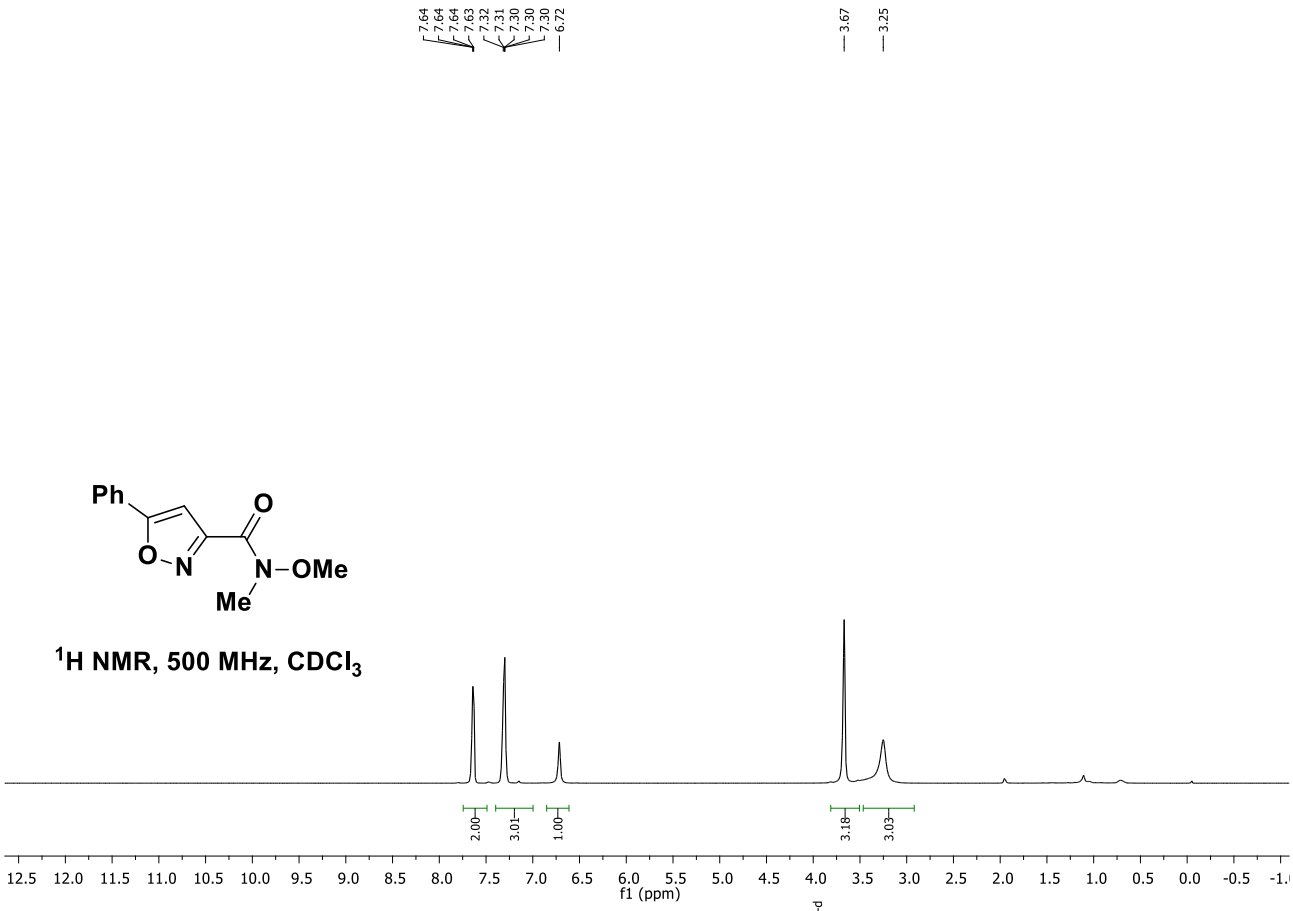
^{13}C NMR, 125 MHz, $CDCl_3$



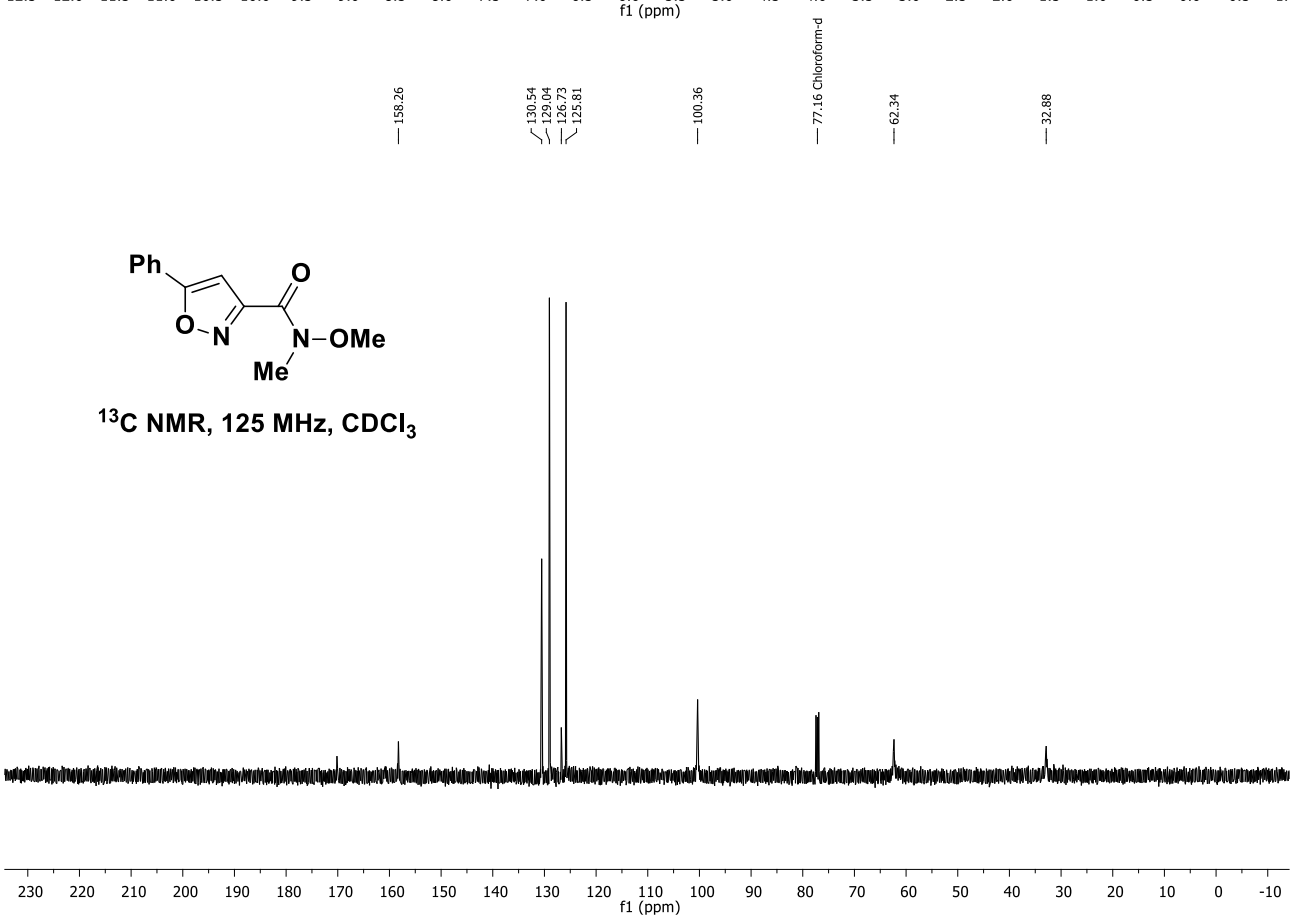
^{1}H NMR, 500 MHz, $CDCl_3$



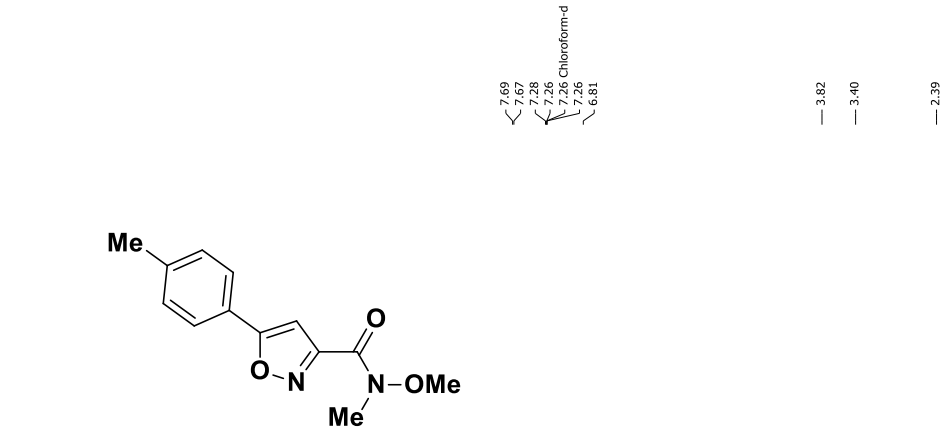
^{13}C NMR, 125 MHz, $CDCl_3$



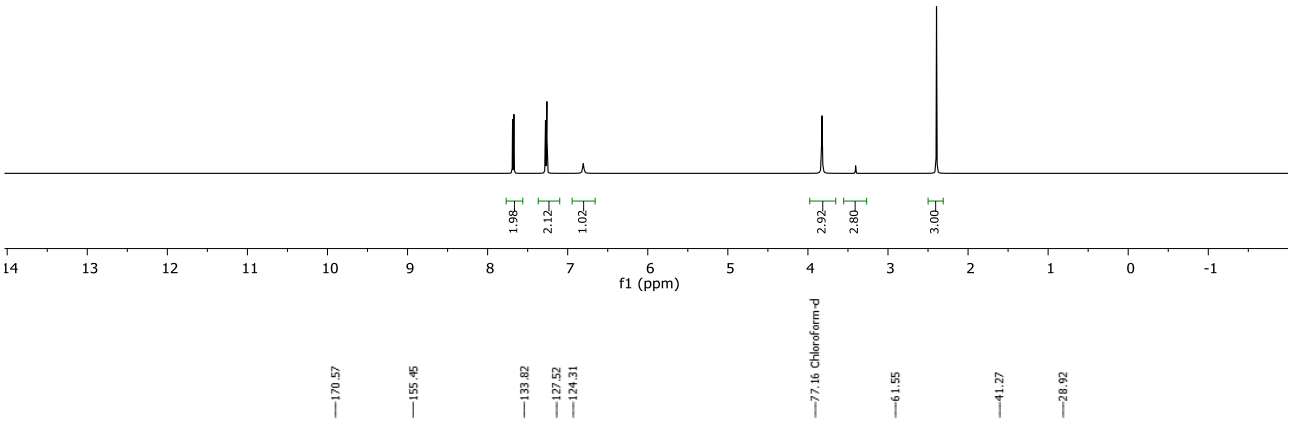
^{1}H NMR, 500 MHz, $CDCl_3$



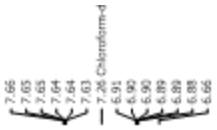
^{13}C NMR, 125 MHz, $CDCl_3$

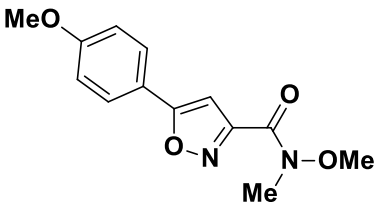


^{1}H NMR, 500 MHz, $CDCl_3$

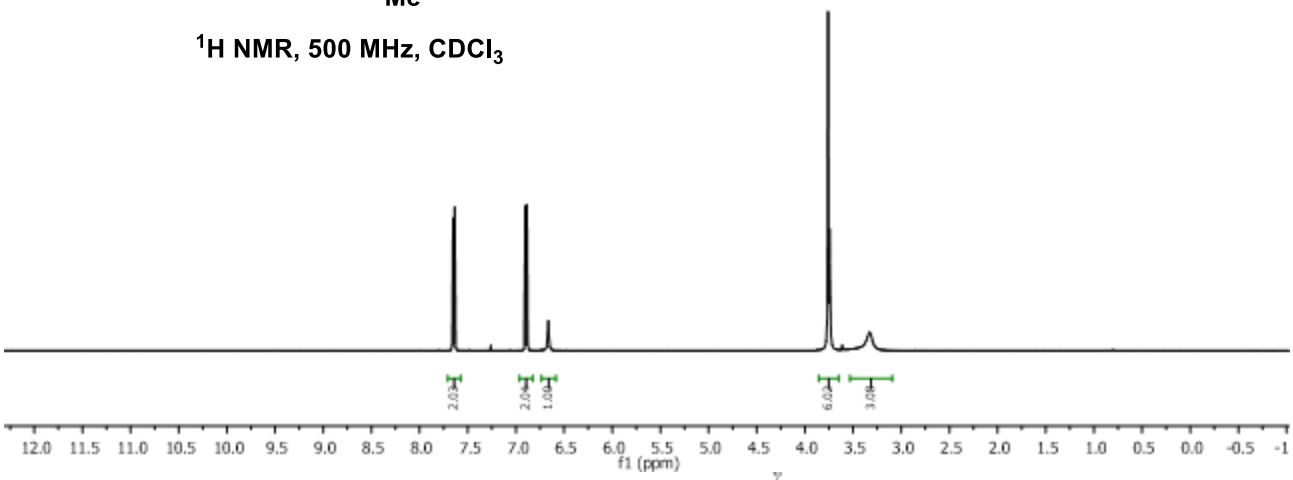


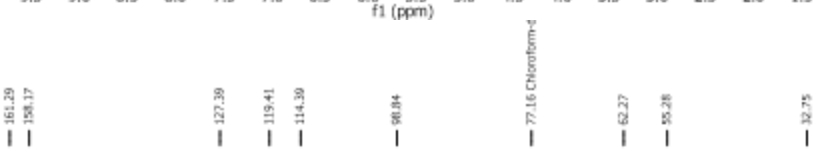
^{13}C NMR, 125 MHz, $CDCl_3$

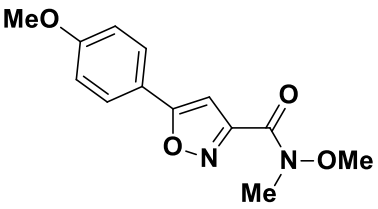




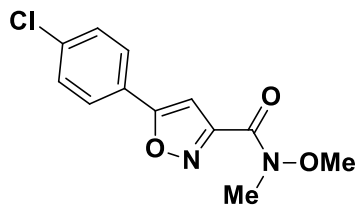
^{1}H NMR, 500 MHz, $CDCl_3$



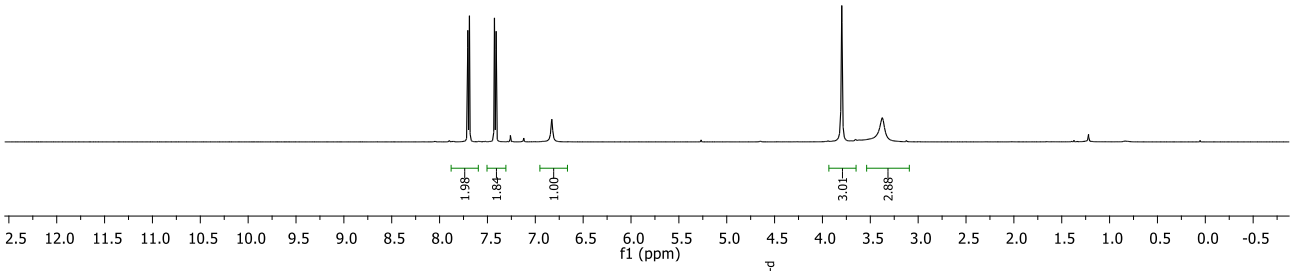


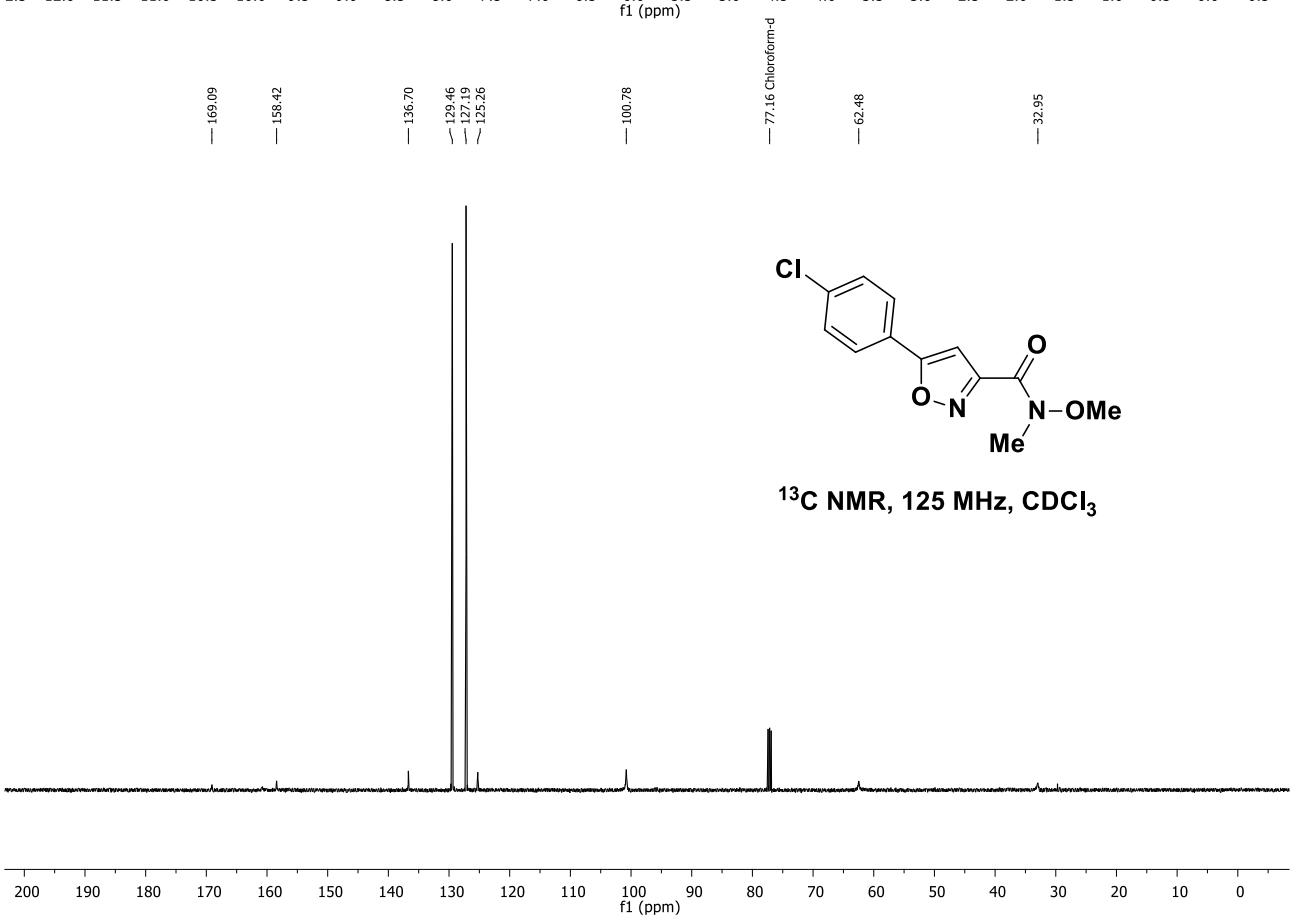


^{13}C NMR, 125 MHz, $CDCl_3$

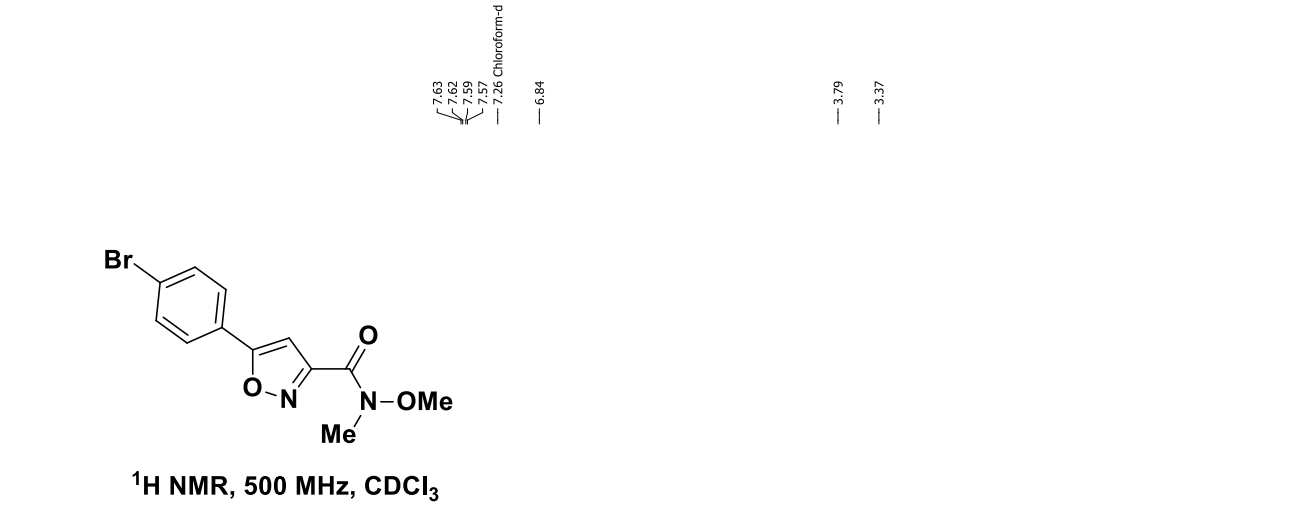


^{1}H NMR, 500 MHz, $CDCl_3$

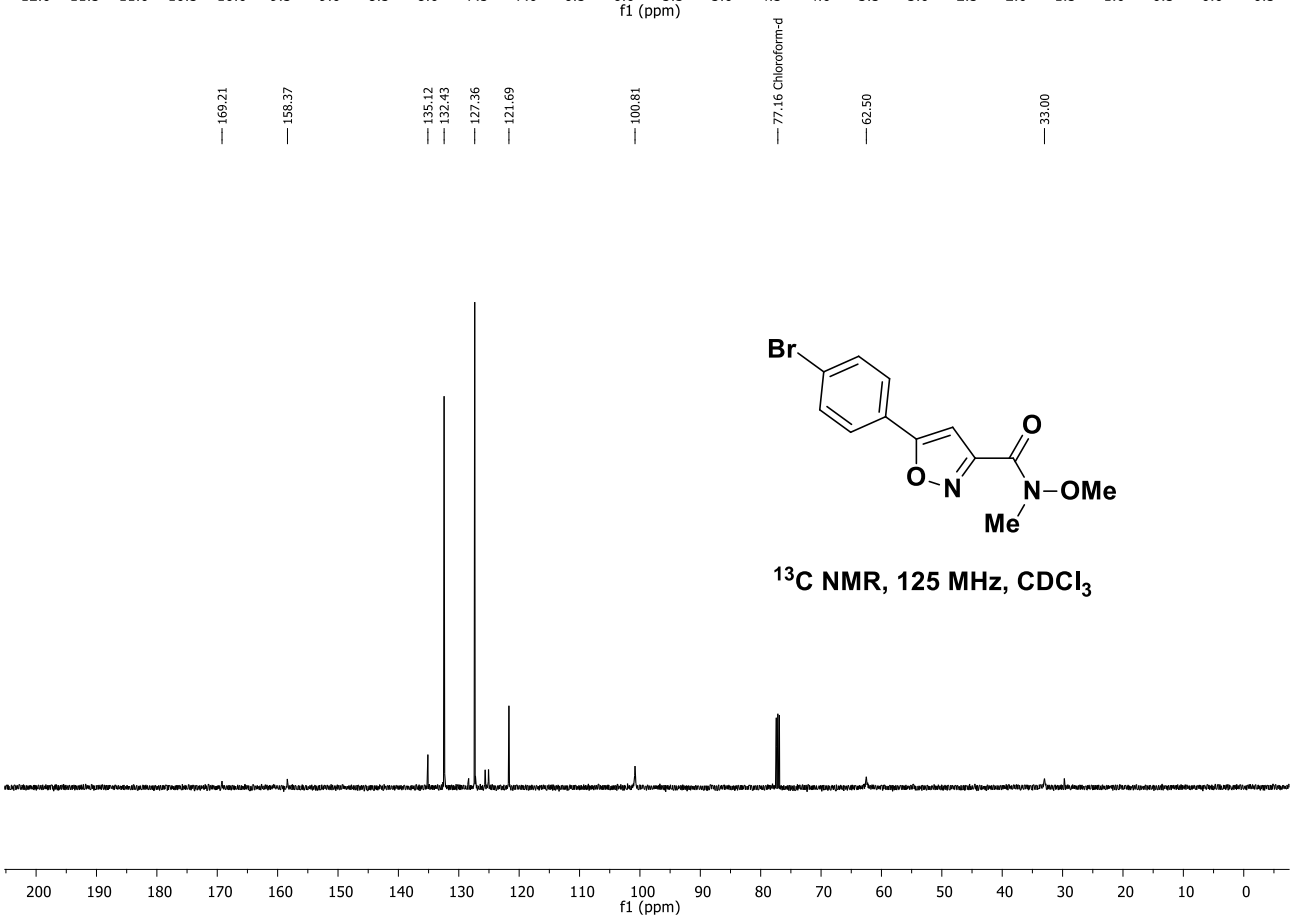




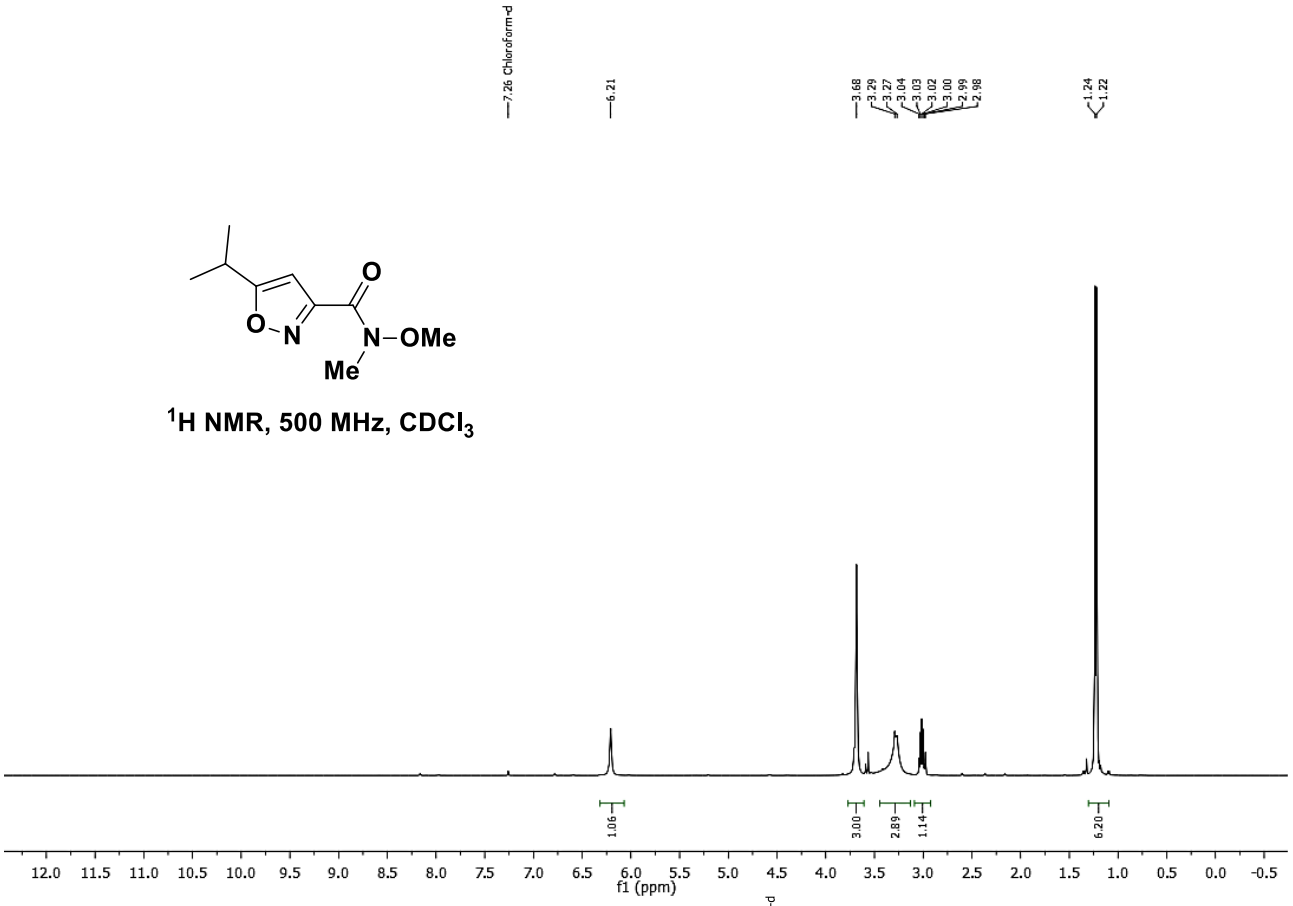
^{13}C NMR, 125 MHz, $CDCl_3$



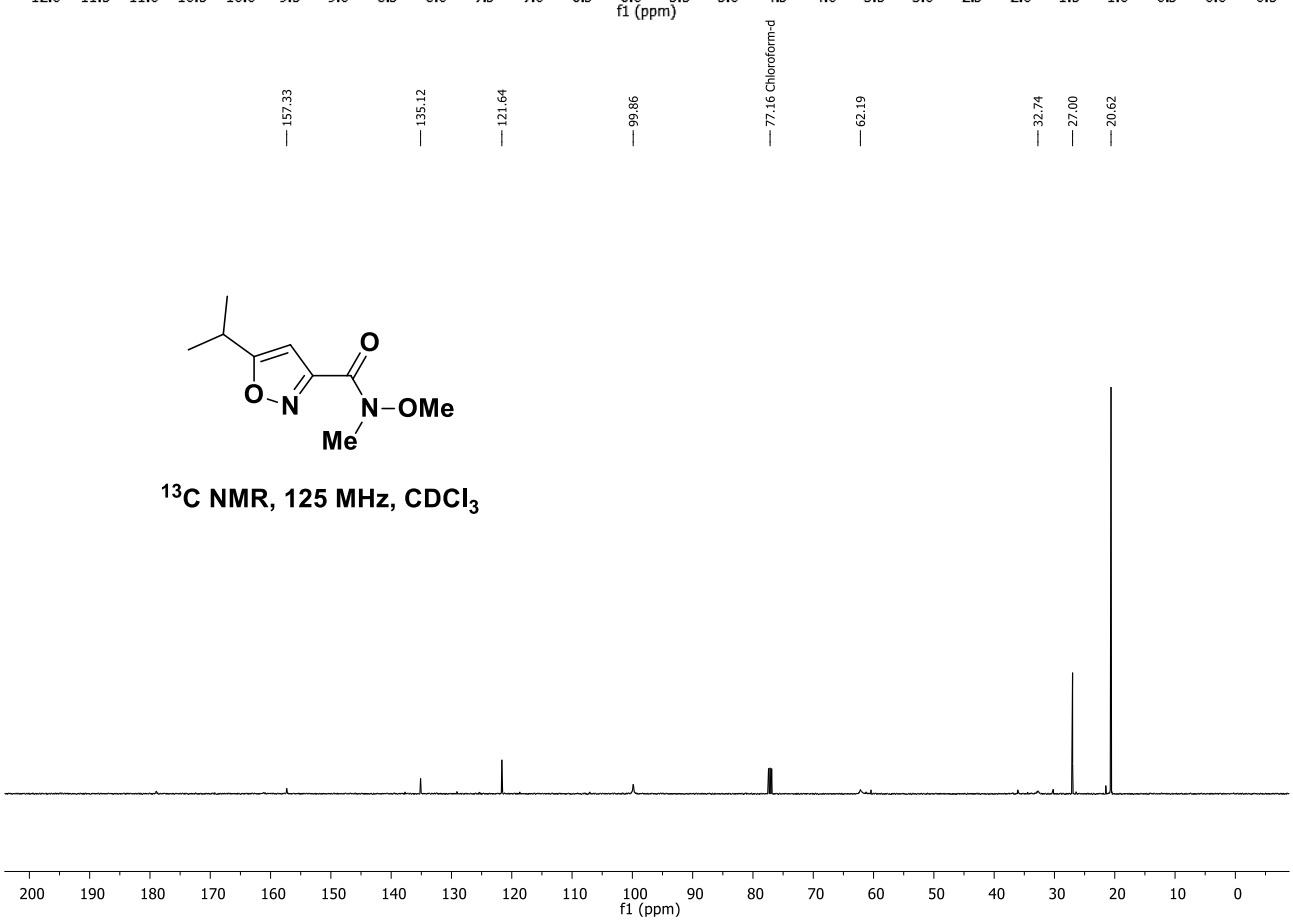
^{1}H NMR, 500 MHz, $CDCl_3$



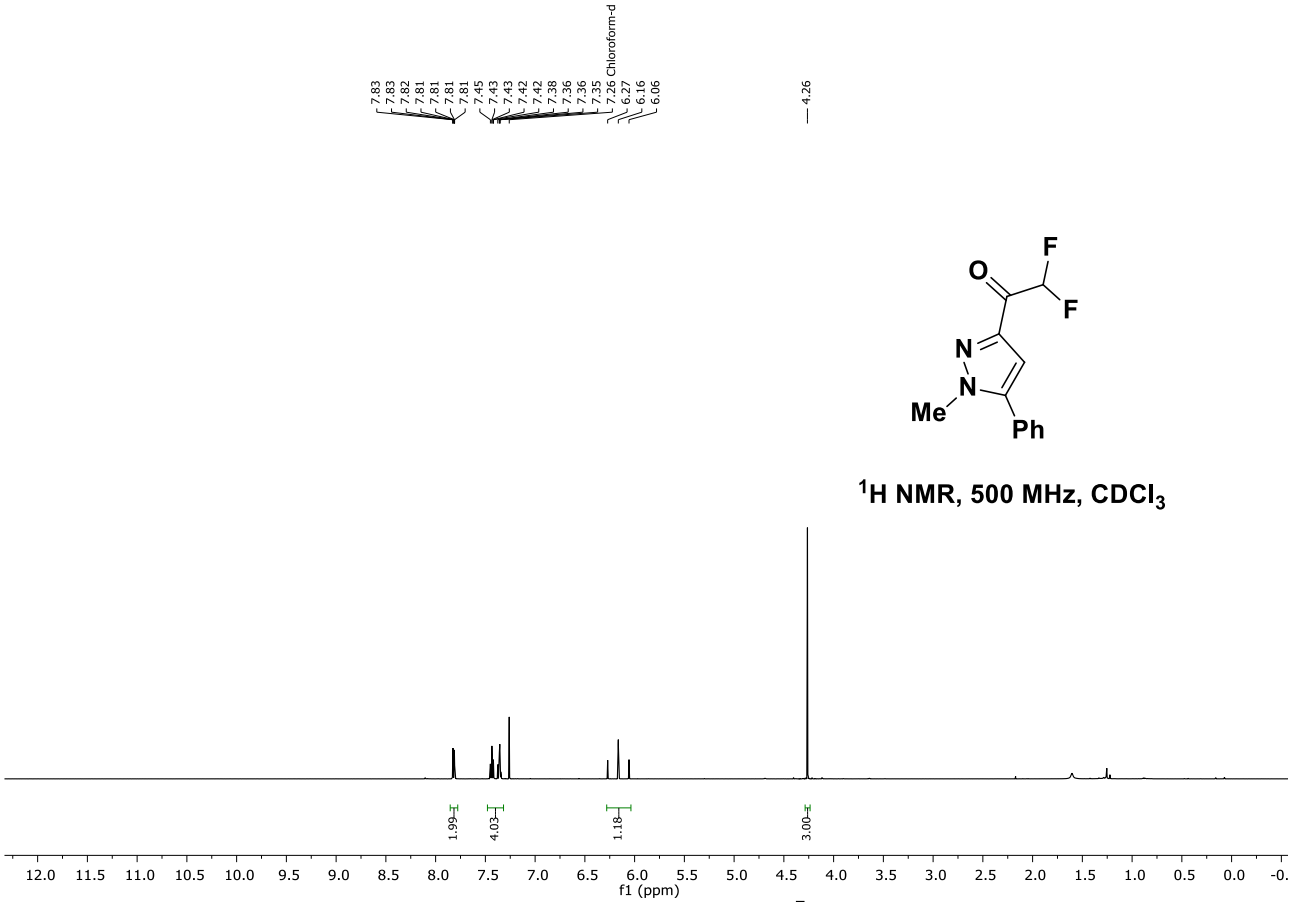
^{13}C NMR, 125 MHz, $CDCl_3$

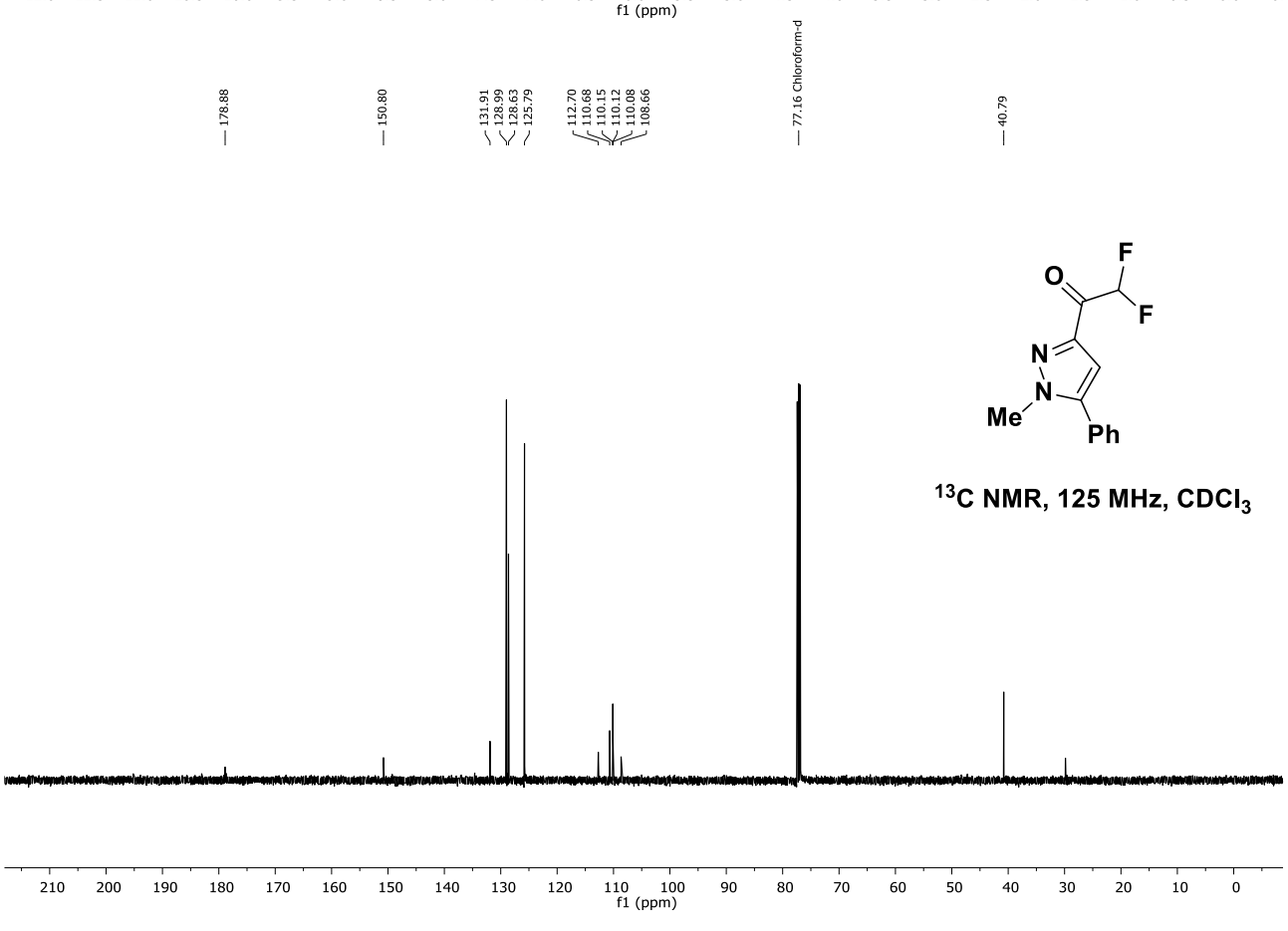


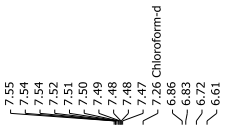
^{1}H NMR, 500 MHz, $CDCl_3$

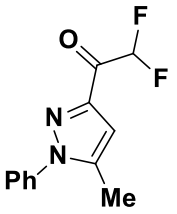


^{13}C NMR, 125 MHz, $CDCl_3$

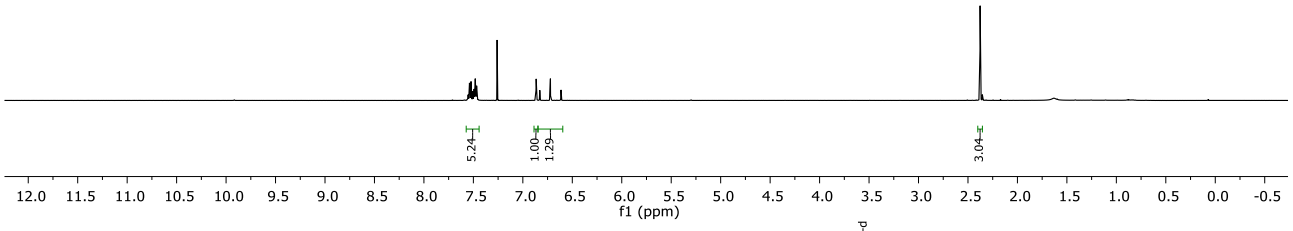

7.83
7.83
7.82
7.81
7.81
7.81
7.81
7.45
7.43
7.43
7.42
7.42
7.38
7.36
7.36
7.35
7.26 Chloroform-d
6.27
6.16
6.06
4.26
F
O
F
N
N
Me
Ph
1H NMR, 500 MHz, CDCl3
1.99
4.03
1.18
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

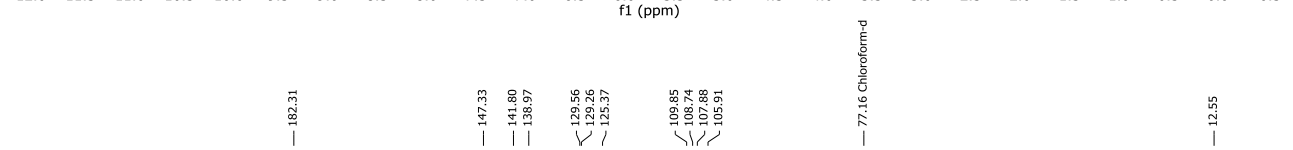

178.88
150.80
131.91
128.99
128.63
125.79
112.70
110.68
110.15
110.12
110.08
108.66
77.16 Chloroform-d
40.79
F
O
F
N
N
Me
Ph
13C NMR, 125 MHz, CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

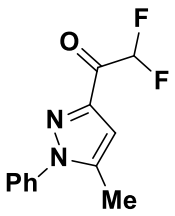




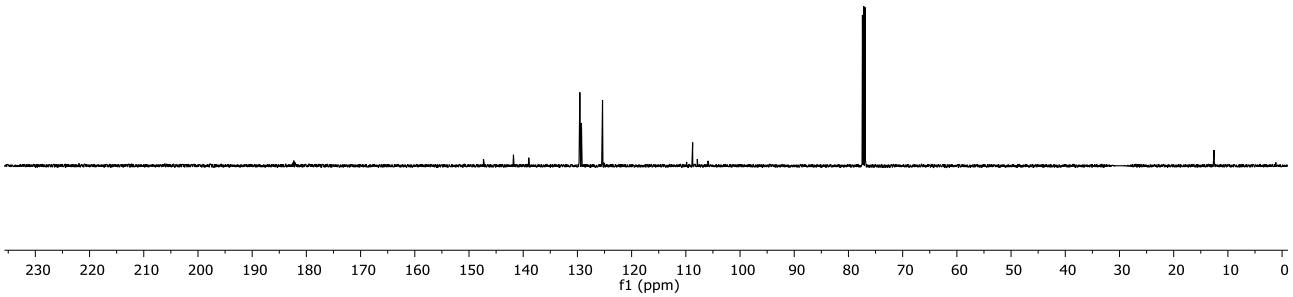
^{1}H NMR, 500 MHz, $CDCl_3$

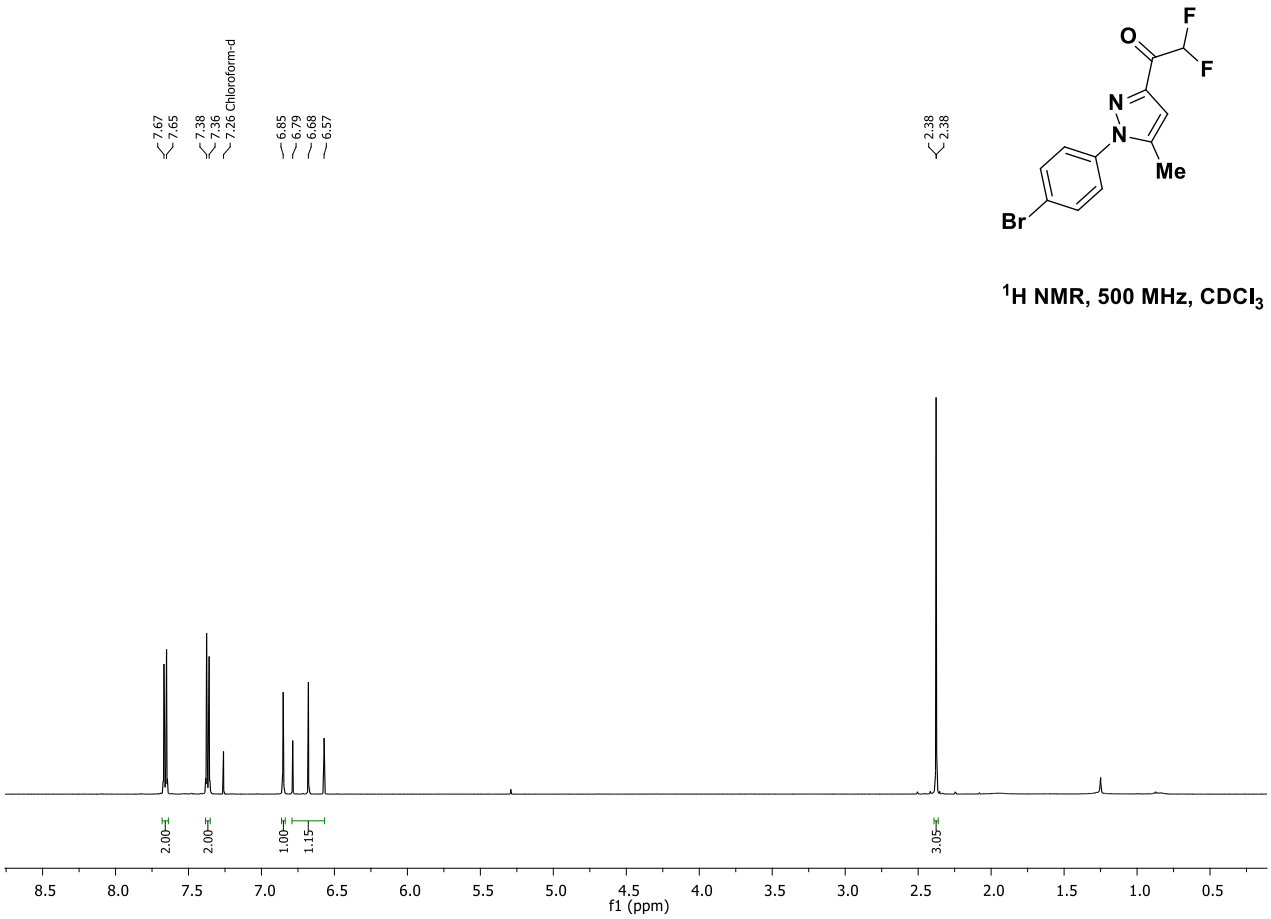




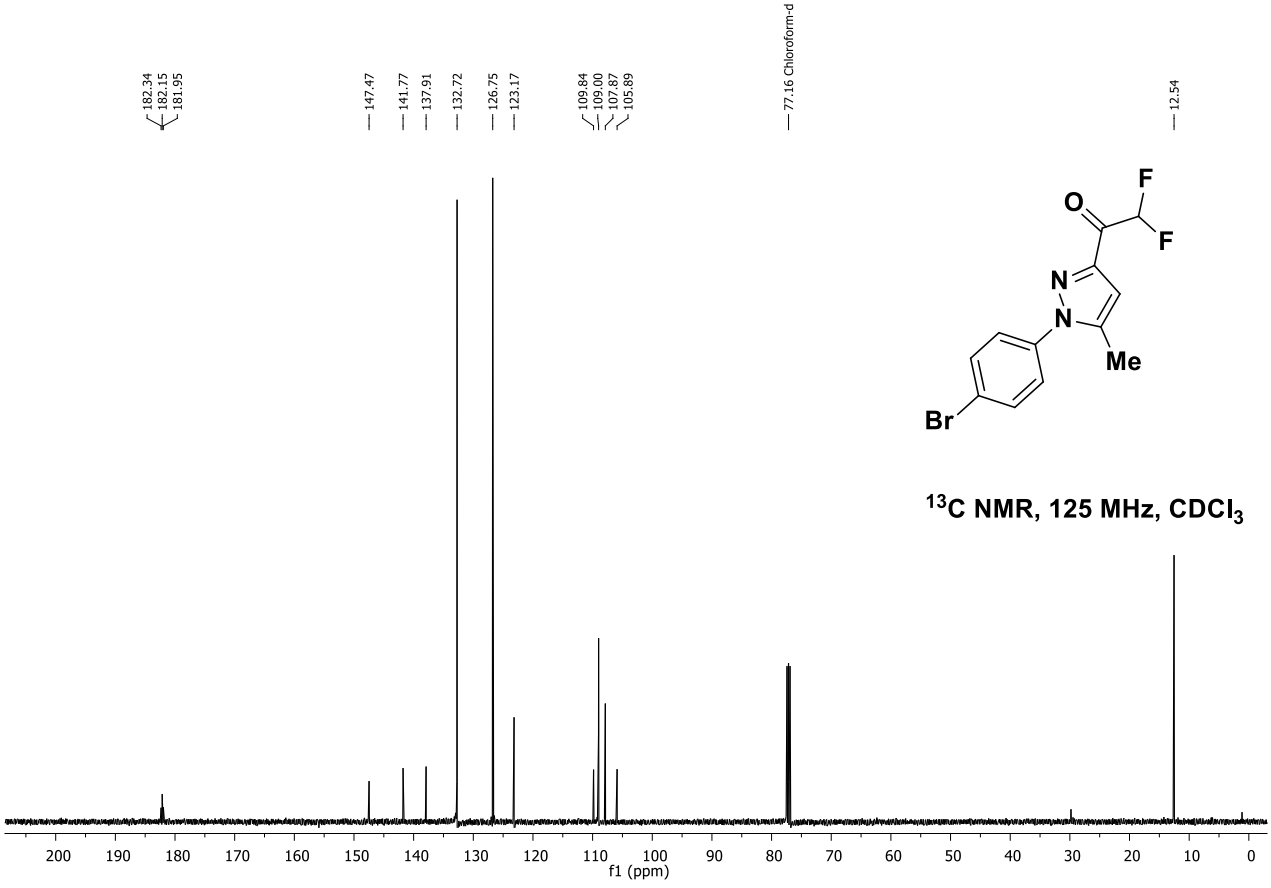


^{13}C NMR, 125 MHz, $CDCl_3$

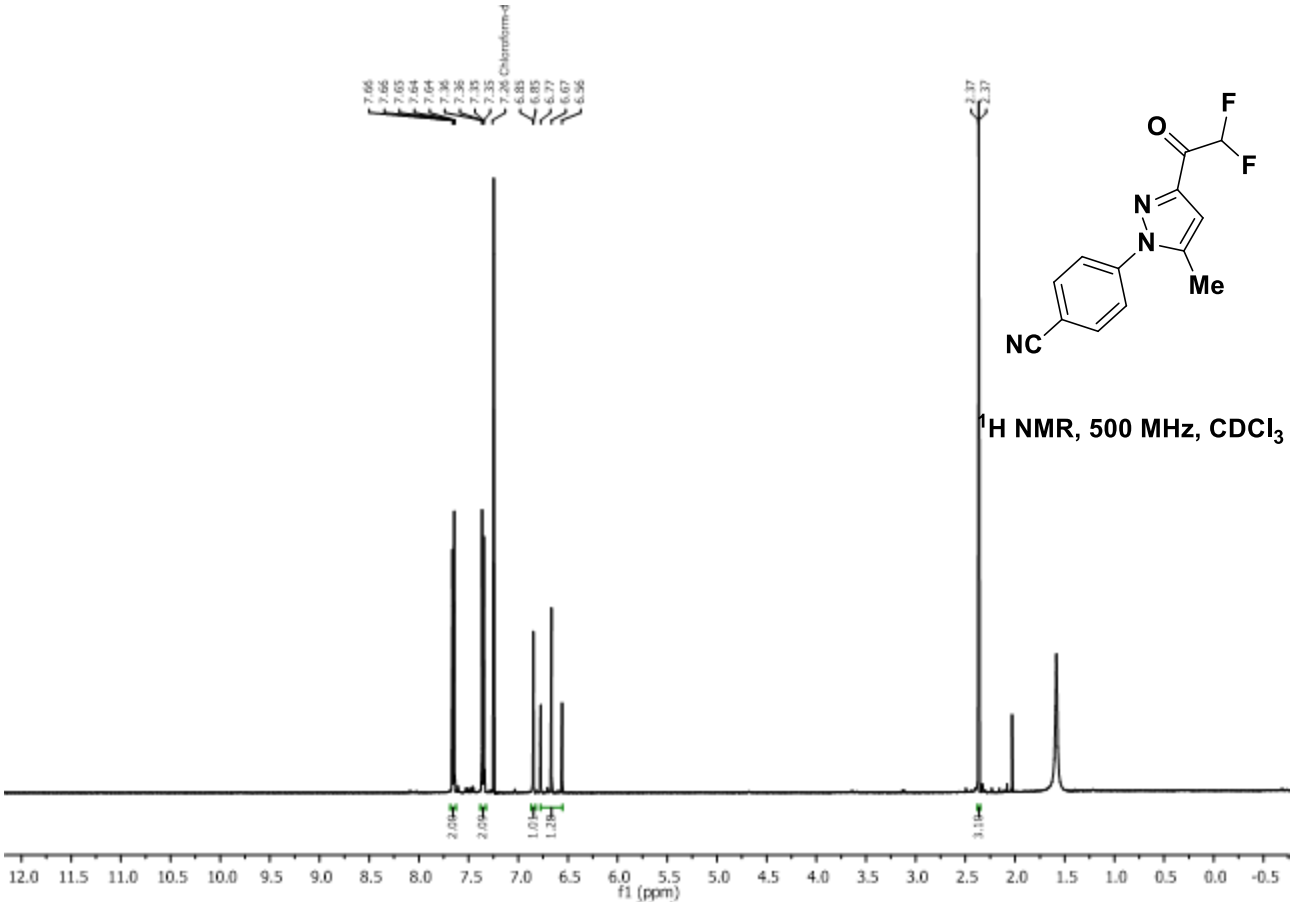


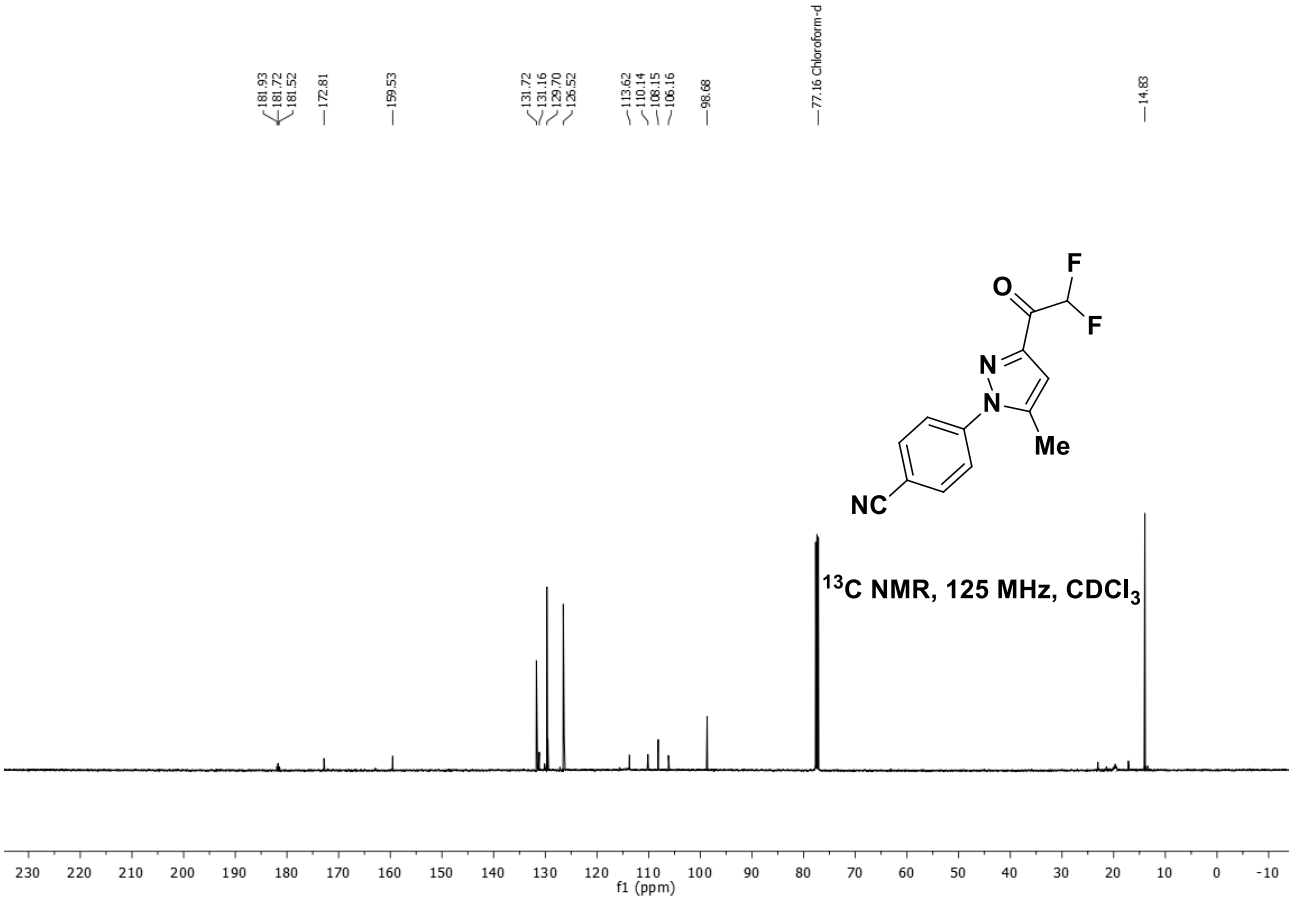


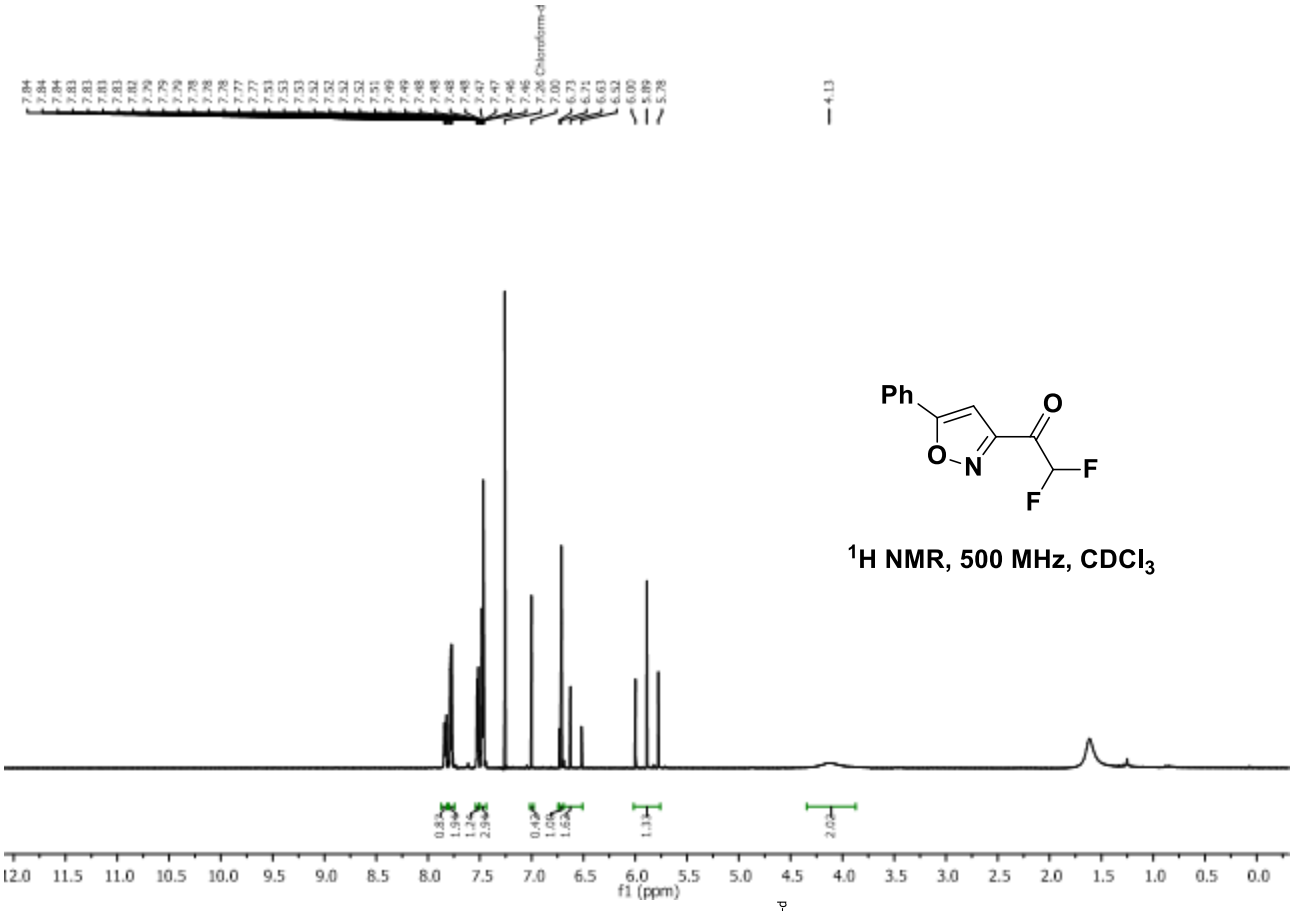
^{1}H NMR, 500 MHz, $CDCl_3$



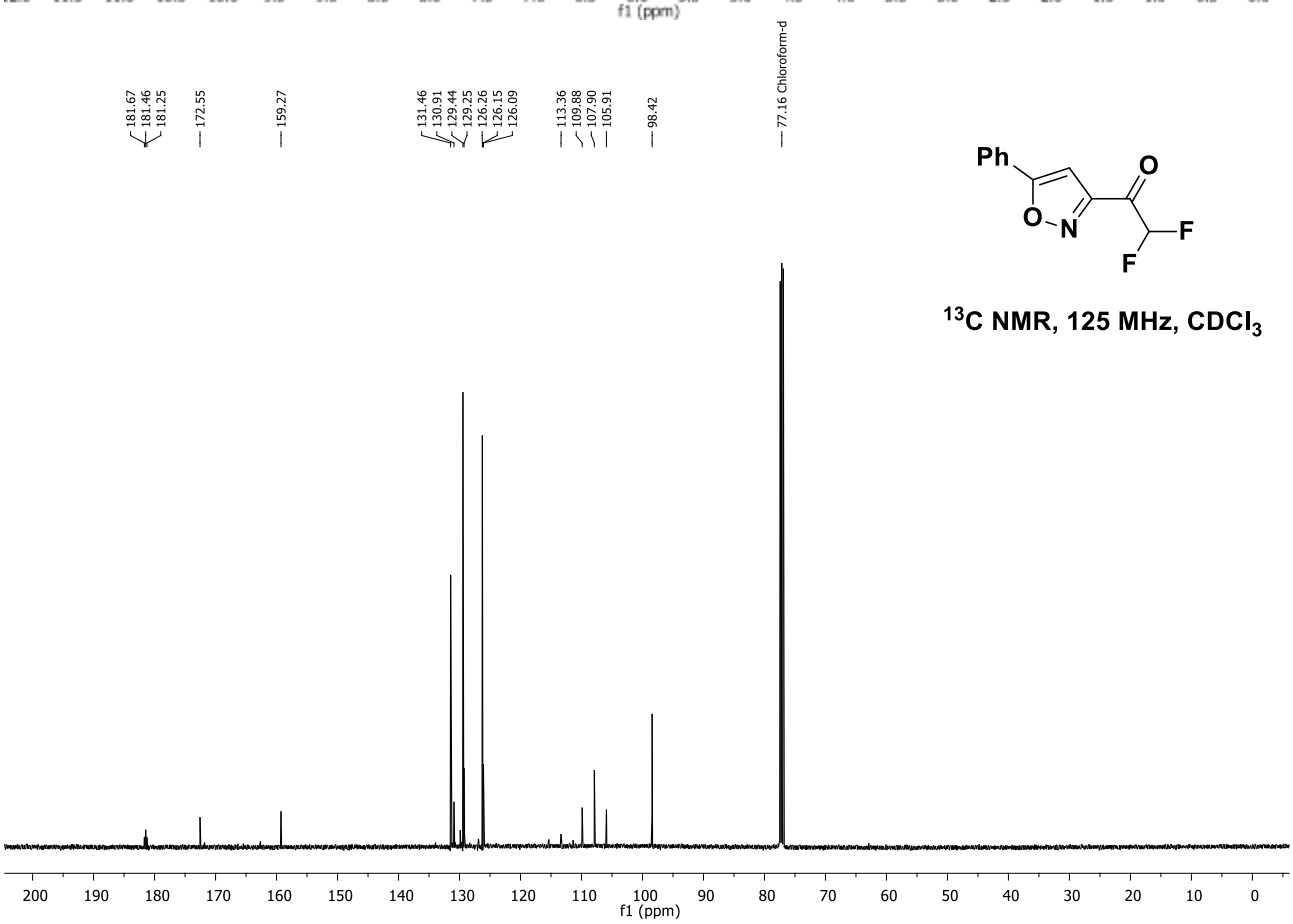
^{13}C NMR, 125 MHz, $CDCl_3$


F
O
F
N
N
Me
NC
^{1}H NMR, 500 MHz, CDCl$_3$
f1 (ppm)

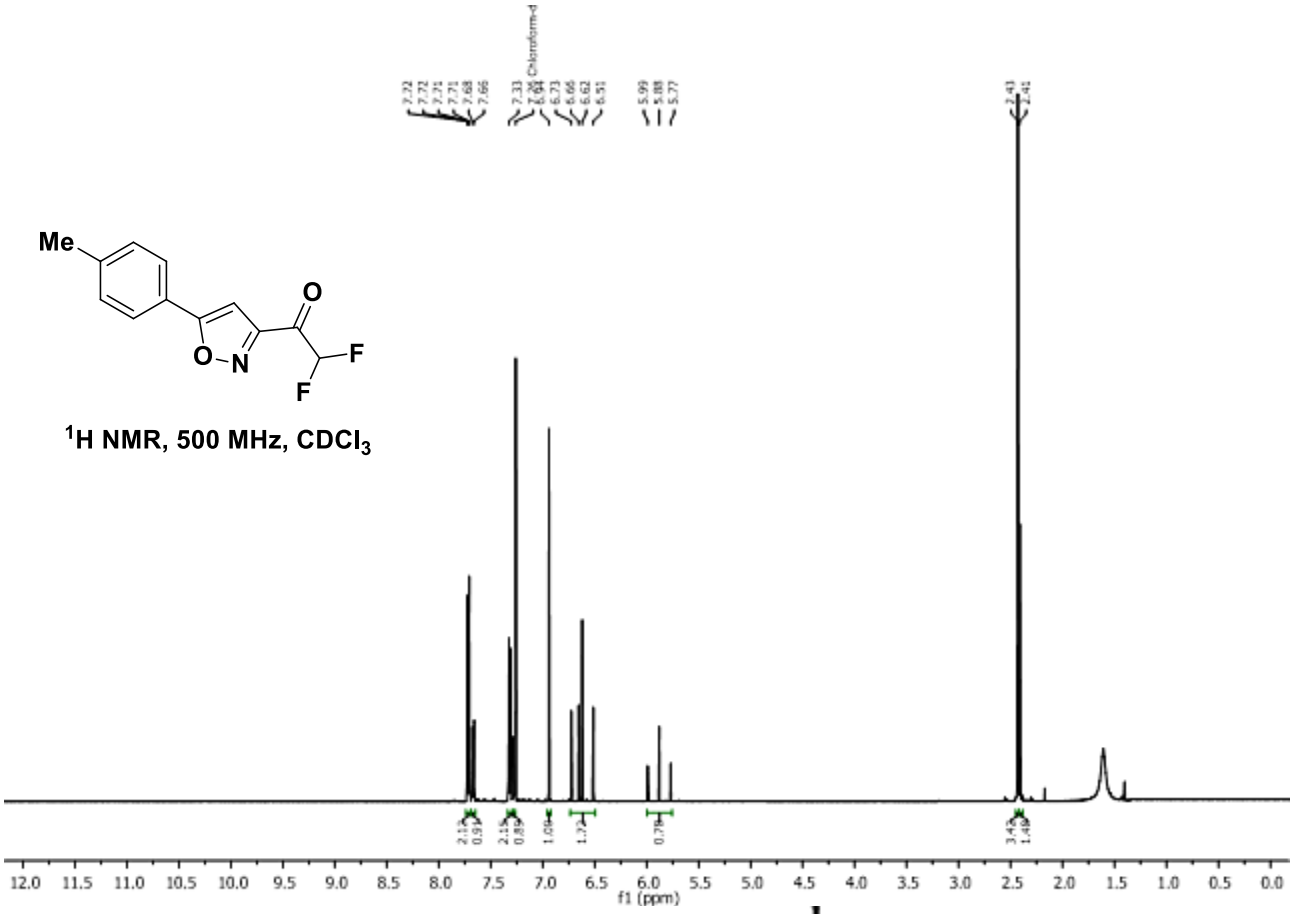

F
O
F
N
N
Me
NC
^{13}C NMR, 125 MHz, CDCl$_3$
f1 (ppm)

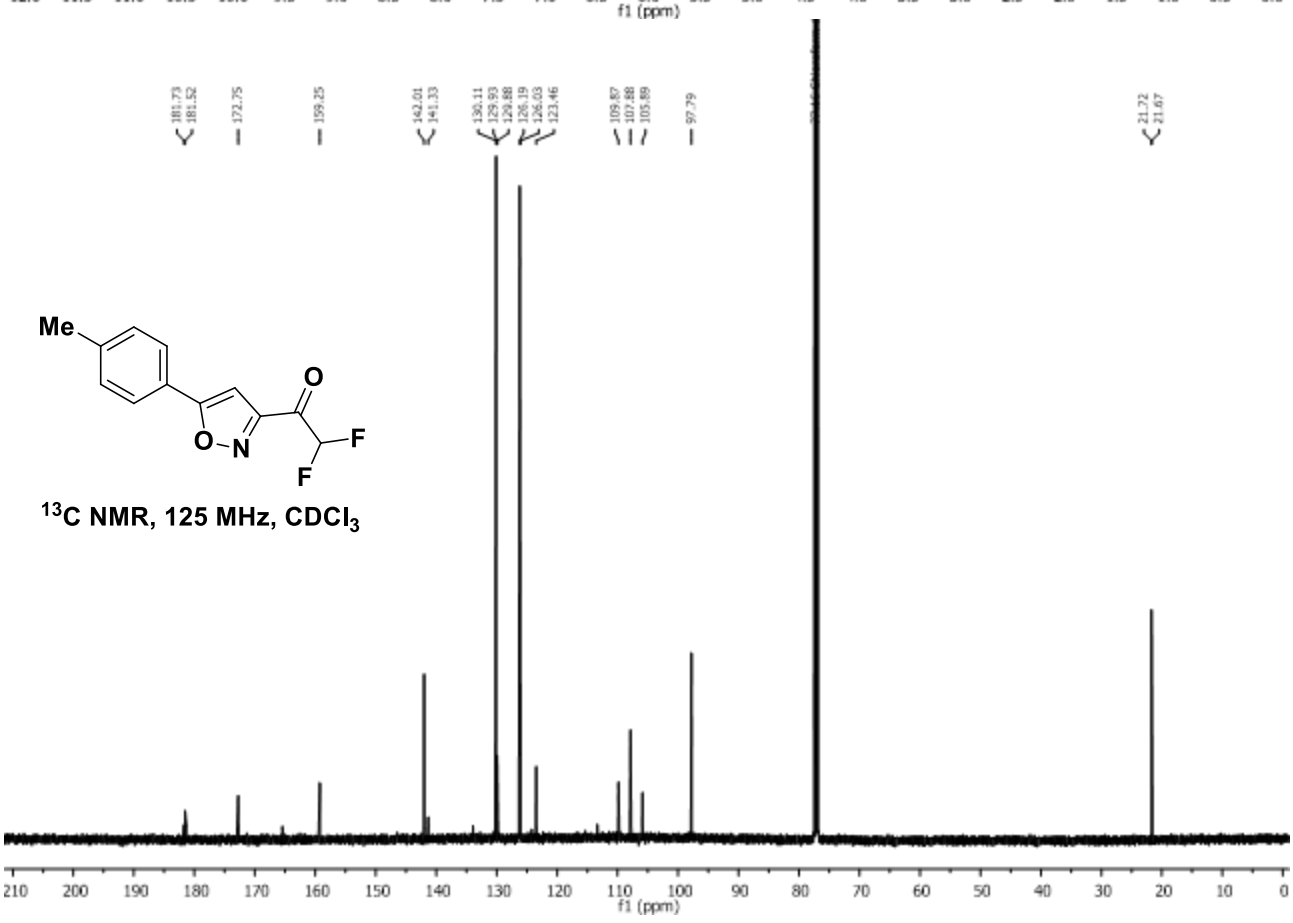


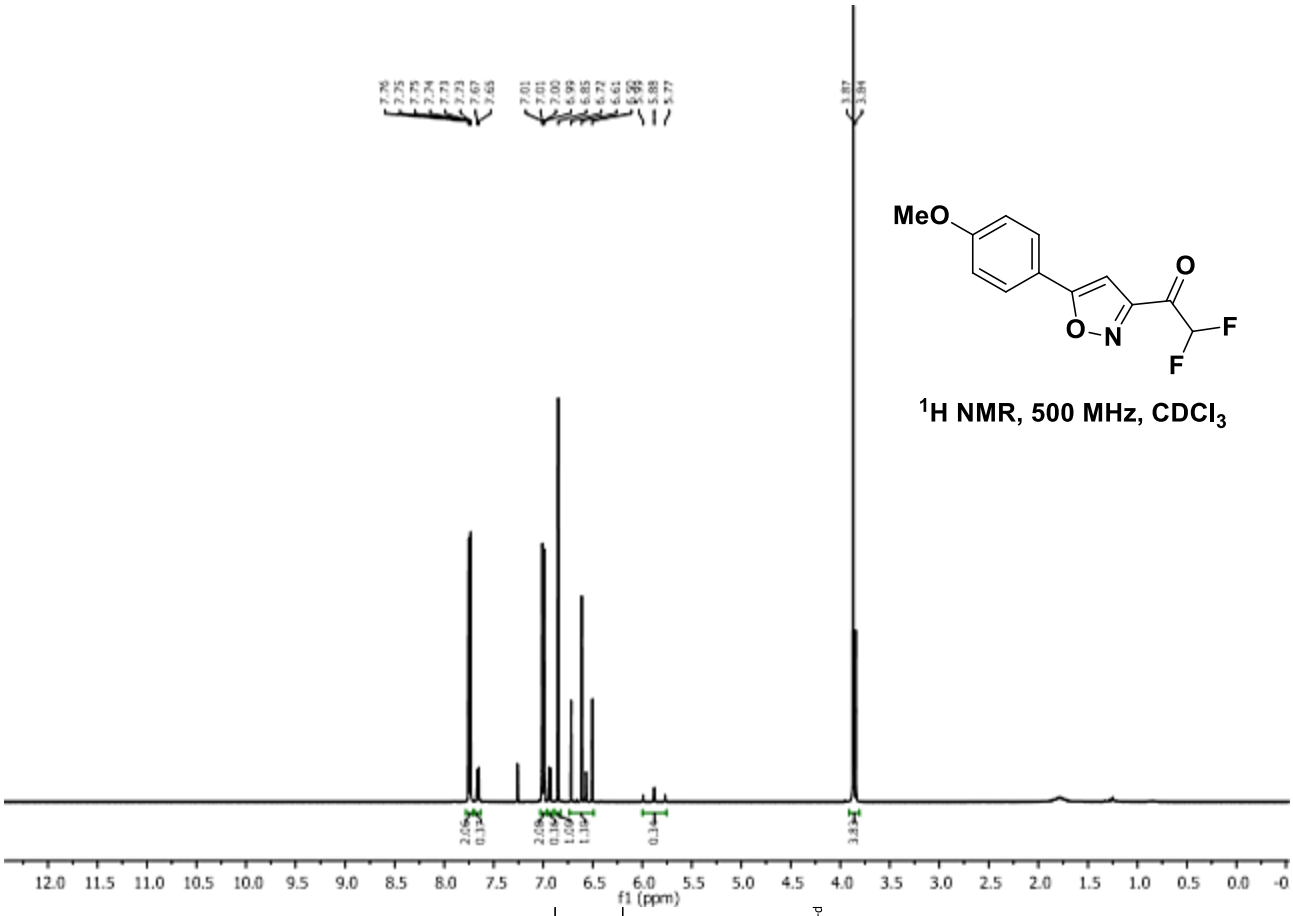
^{1}H NMR, 500 MHz, $CDCl_3$

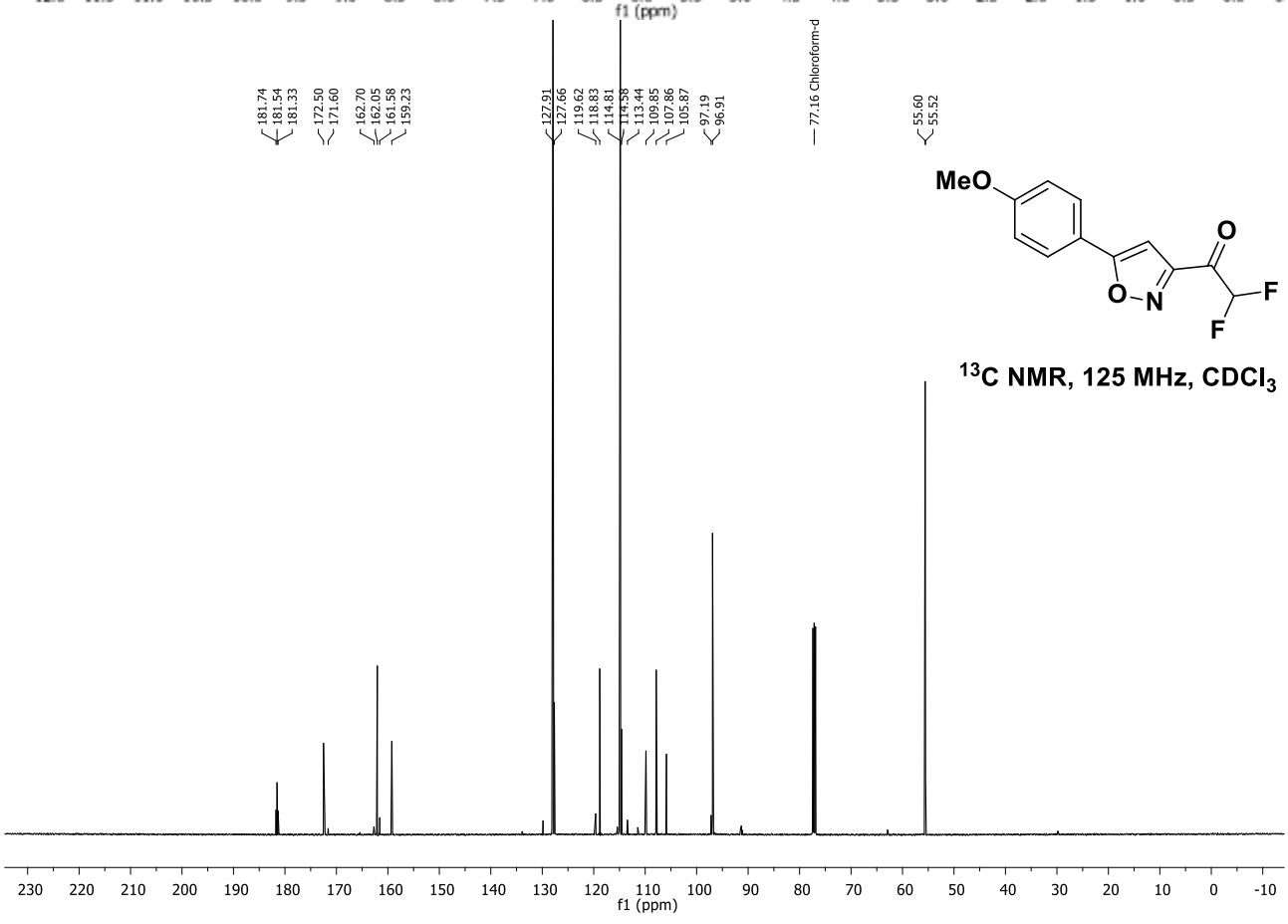


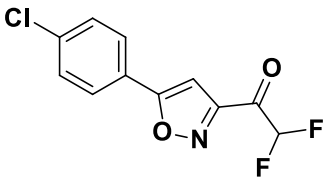
^{13}C NMR, 125 MHz, $CDCl_3$


Me
O
O
N
F
F
^{1}H NMR, 500 MHz, $CDCl_3$
f1 (ppm)

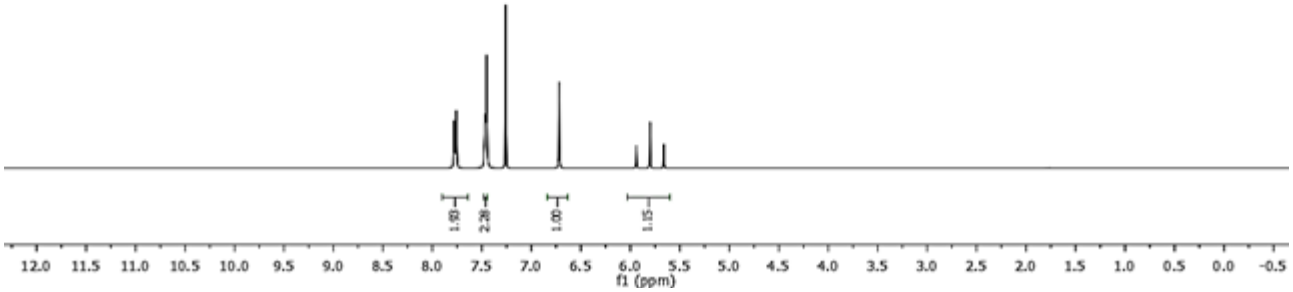

Me
O
O
N
F
F
^{13}C NMR, 125 MHz, $CDCl_3$
f1 (ppm)

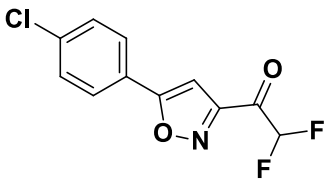

MeO
O
O
N
F
F
^{1}H NMR, 500 MHz, CDCl$_3$
f1 (ppm)


MeO
O
O
N
F
F
^{13}C NMR, 125 MHz, CDCl$_3$
77.16 Chloroform-d
f1 (ppm)

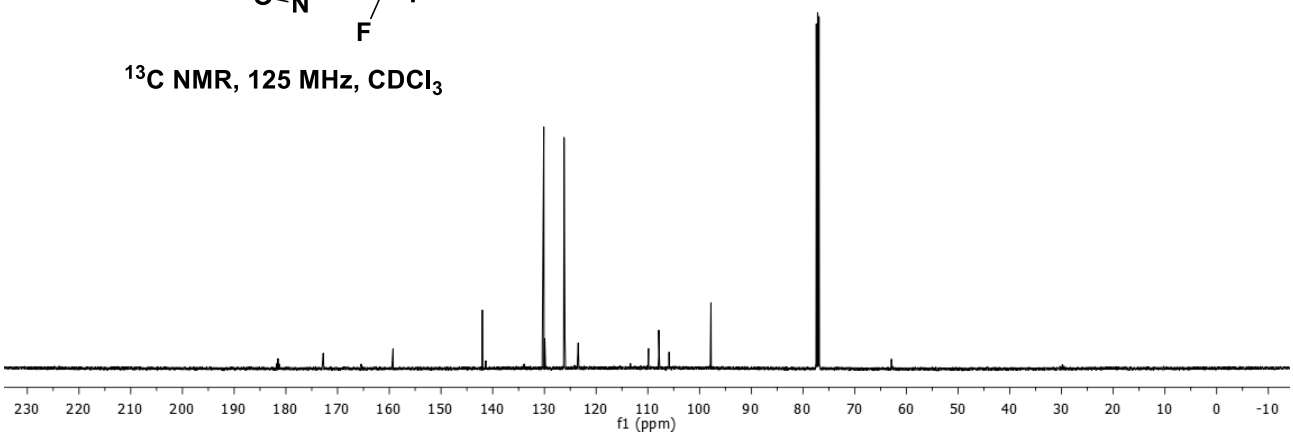


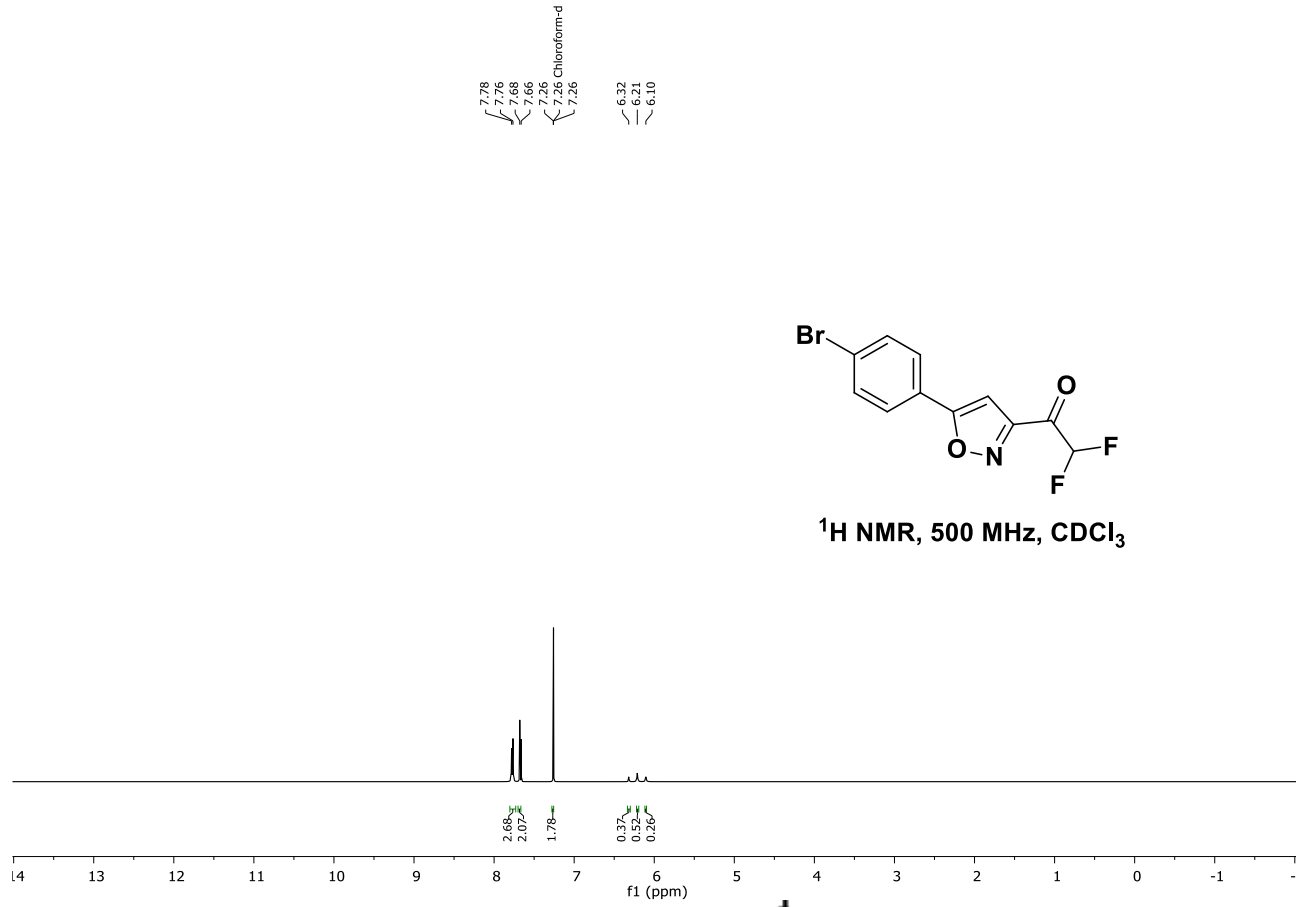
^{1}H NMR, 500 MHz, $CDCl_3$



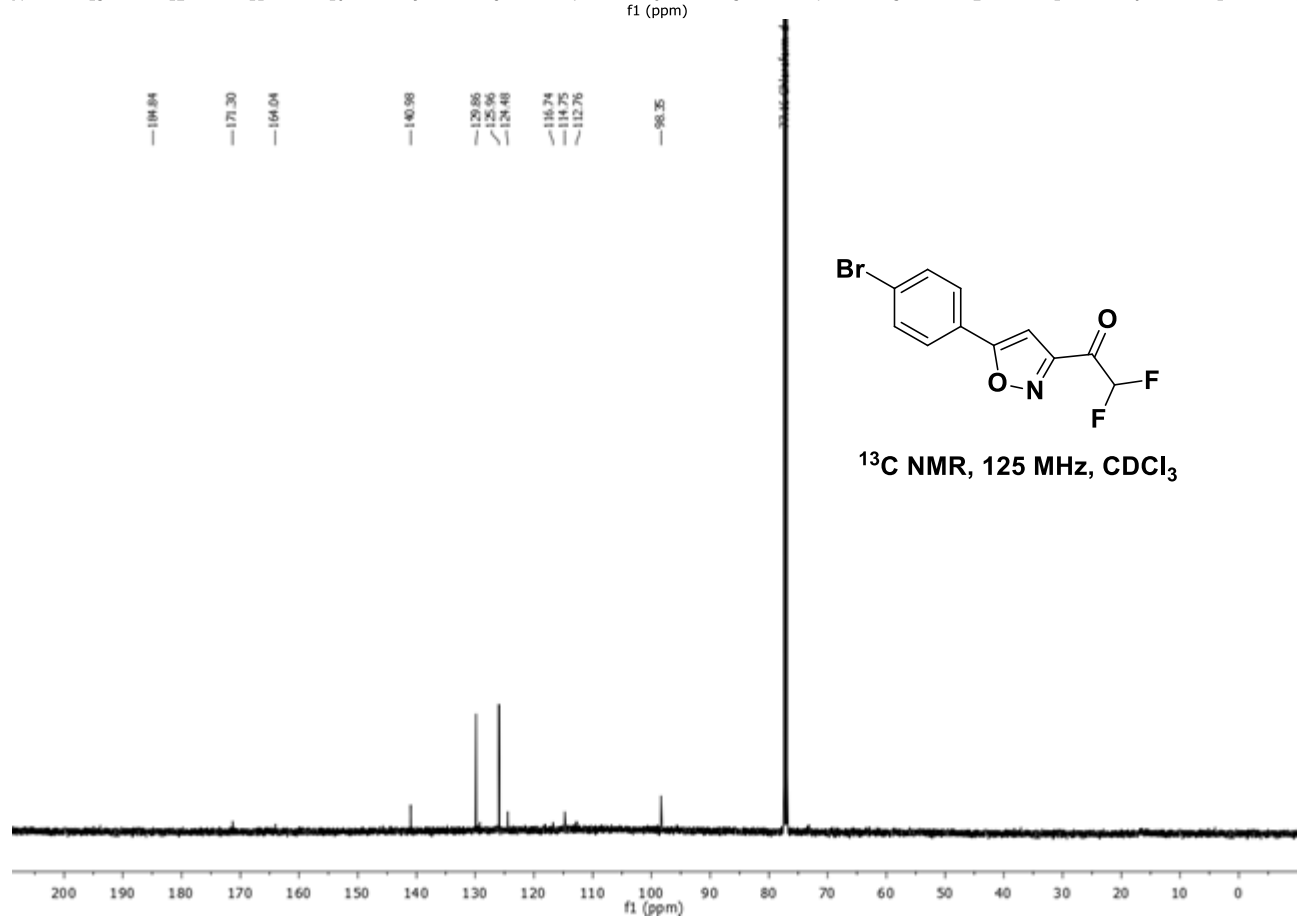


^{13}C NMR, 125 MHz, $CDCl_3$

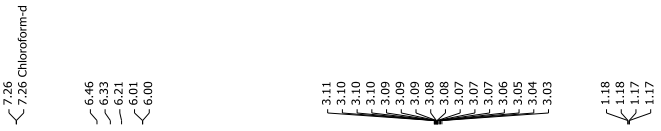


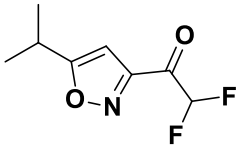


^{1}H NMR, 500 MHz, $CDCl_3$

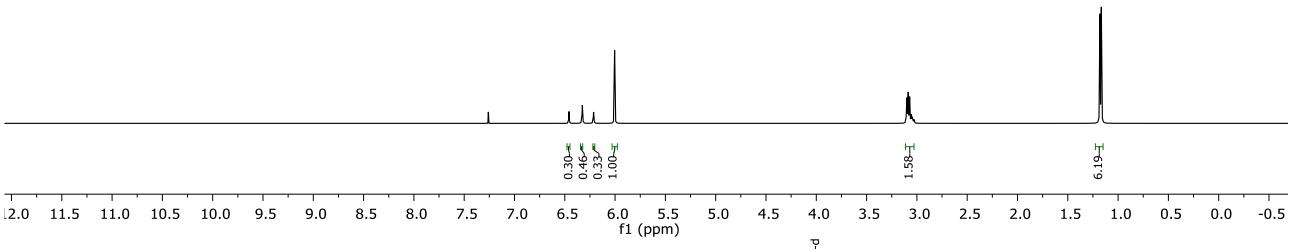


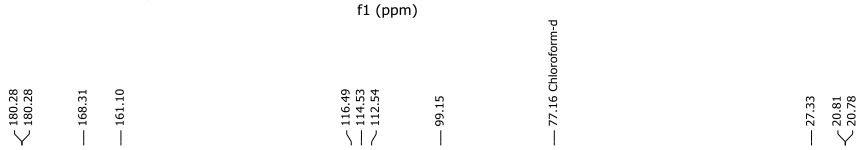
^{13}C NMR, 125 MHz, $CDCl_3$

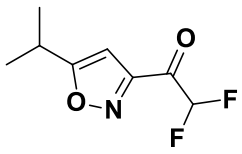




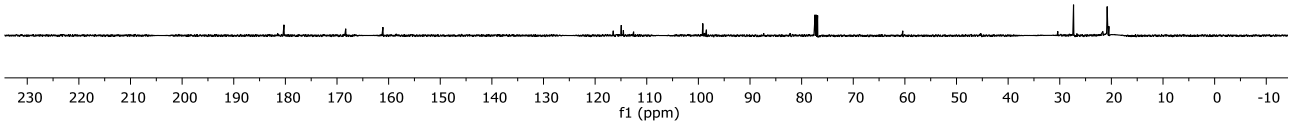
^{1}H NMR, 500 MHz, $CDCl_3$







^{13}C NMR, 125 MHz, $CDCl_3$



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