Supporting information

Novel pyrazole containing compounds active against *Mycobacterium tuberculosis*

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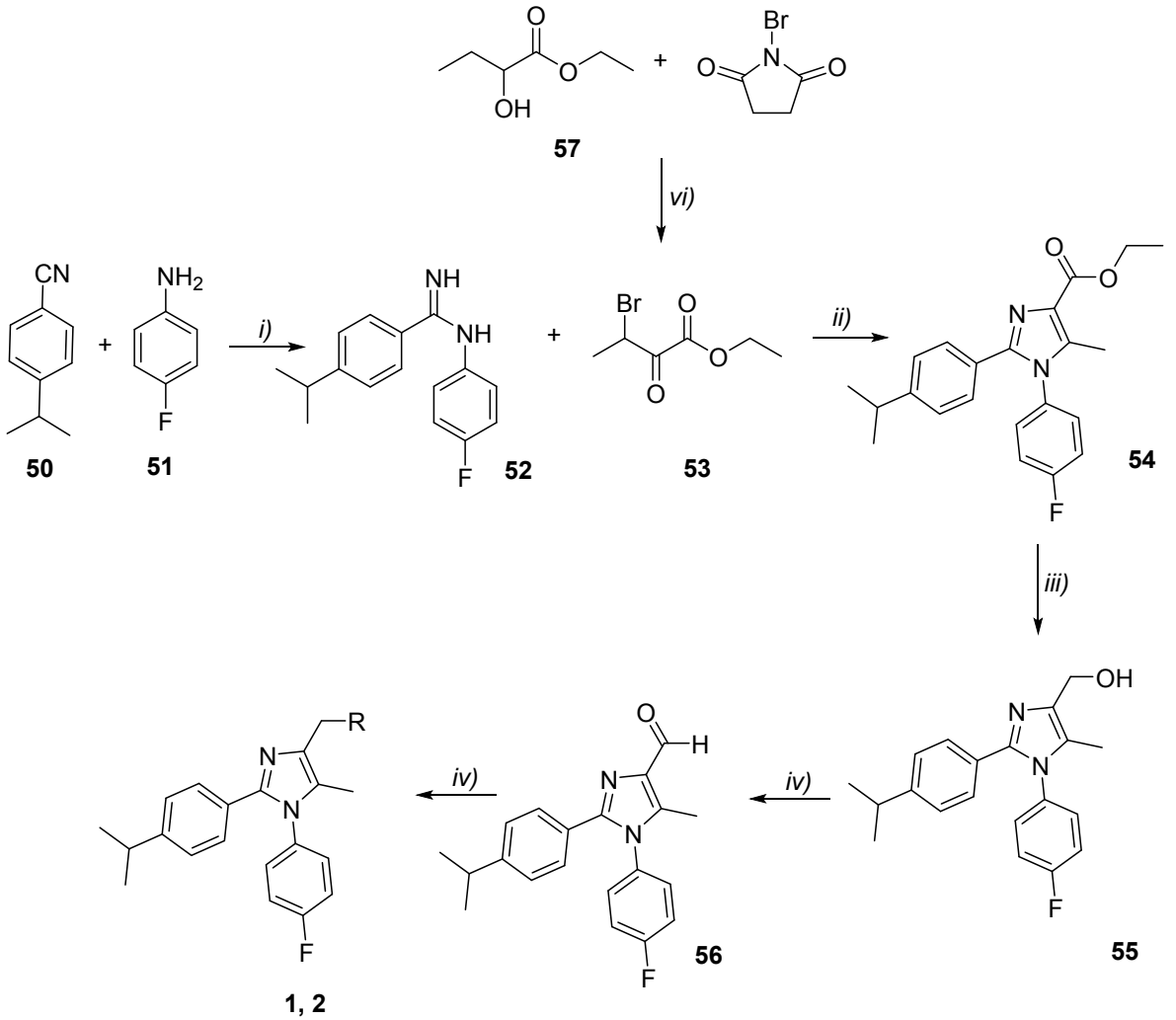
Chemistry

Reagents and solvents were obtained from commercial sources (Fluka, Sigma-Aldrich, Alfa Aesar). Analytical TLC was performed on Merck silica gel (60F254) precoated plates (0.25 mm). The compounds were visualized under UV light (254 nm) and/or stained with the relevant reagent. Flash column chromatography was performed on silica gel with pore size 60 Å, 230−400 mesh particle size, and 40−63 μm particle size, with the indicated solvents. The yields refer to the purified products, and they were not optimized. All the solid compounds were obtained as amorphous solids, and melting points were not measured. ^{1}H NMR spectra were recorded on a Bruker Avance III NMR spectrometer and in a Bruker DPX Avance 400 MHz instrument equipped with a QNP probe and are reported in ppm using tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded on a Bruker Avance

III NMR spectrometer at 295 K and are reported in ppm using solvent as internal standard (DMSO-d_6 at 39.5 ppm; CDCl3 at 77.0 ppm). Mass spectra data measurements were performed on a VG-Analytical Autospec Q mass spectrometer. Analytical purity was ≥95% unless stated otherwise. The purities of the final compounds were checked using a Waters ZQ2000 coupled with LC Waters 2795 and Waters 2996 PDA detector.

Imidazoles **1** and **2** were prepared according to the reaction pathway reported in **Scheme S1**. Briefly, the reaction between the 4-isopropylbenzonitrile **50** and the 4-fluoroaniline **51** using sodium bis(trimethylsilyl) amide as a strong non nucleophilic base, afforded the arylbenzamidine **52**. Microwave assisted condensation of **52** with ethyl 3-bromo-2-oxobutanoate **53** gave the intermediate ethyl-1,2-diaryl-1H-imidazole-4-carboxylate **54**. Ethyl ester **54** was converted into the corresponding imidazole-4-carbaldehyde **56** in two steps, LiAlH4 reduction and Dess-Martin periodinane oxidation. Finally, **56** underwent reductive amination with the appropriate amine in the presence of NaBH(CH3COO)3 to produce the desired final compounds **1** and **2**. Ethyl 3-bromo-2-oxobutanoate **53** was obtained by reacting ethyl 2-hydroxybutanoate **57** with NBS.

Scheme S1. Synthetic pathway for compounds **1** and **2**.

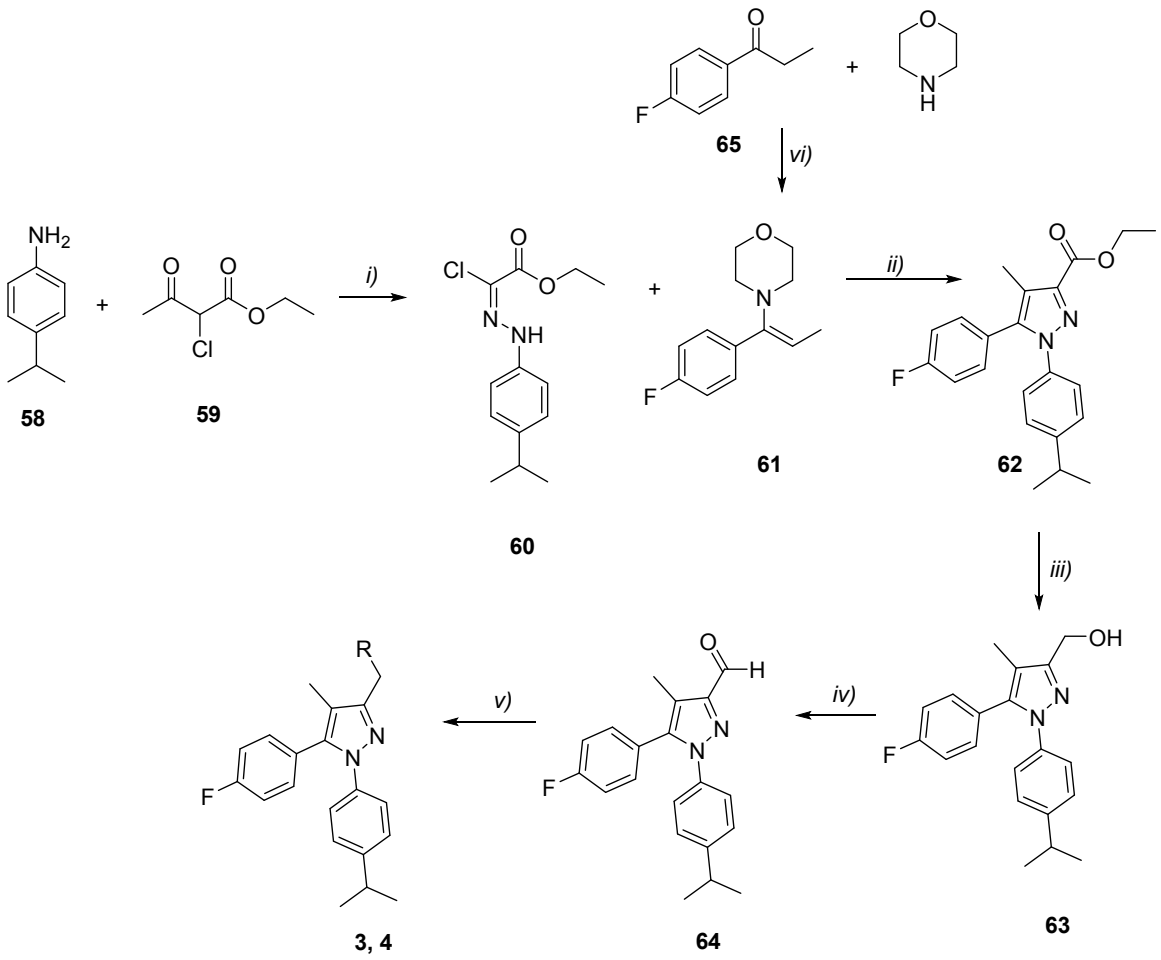


Reagents and conditions: i) $NaN(Si(CH_3)_3)_2$, THF, room temperature, 18 h; ii) $NaHCO_3$, CF_3COOH, EtOH, microwave, 20 min; iii) $LiAlH_4$, THF, 0 °C and then room temperature, 3h; iv) Dess-Martin periodinane, DCM, room temperature, 30 min; v) Amine, CH_3COOH, $NaBH(CH_3COO)_3$, DCE, room temperature, 2h; vi) CCl_4, 85 °C, 5h.

Compounds **3** and **4** were synthesized according to the synthetic pathway shown in **Scheme S2**. 4-Isopropylaniline **58** was first converted into the diazonium salt with HCl and NaNO2 and then treated with ethyl 2-chloroacetoacetate **59** to give the hydrazone **60**. 4'-Fluoropropiophenone **65** was converted into the corresponding enamine **61** with

morpholine, TiCl4 and DIPEA. Hydrazone **60** was then treated with the morpholine enamine **61** under basic conditions at room temperature to give the 1,5-diarylpyrazole **62**. Ethyl ester **62** was converted into the corresponding pyrazole-3-carbaldehyde **64** in two steps as seen for the imidazole-4-carbaldehyde **56** in **Scheme 1**. Finally, **64** underwent reductive amination with the appropriate amine in the presence of NaBH(CH3COO)3 to produce the desired final compounds **3** and **4**.

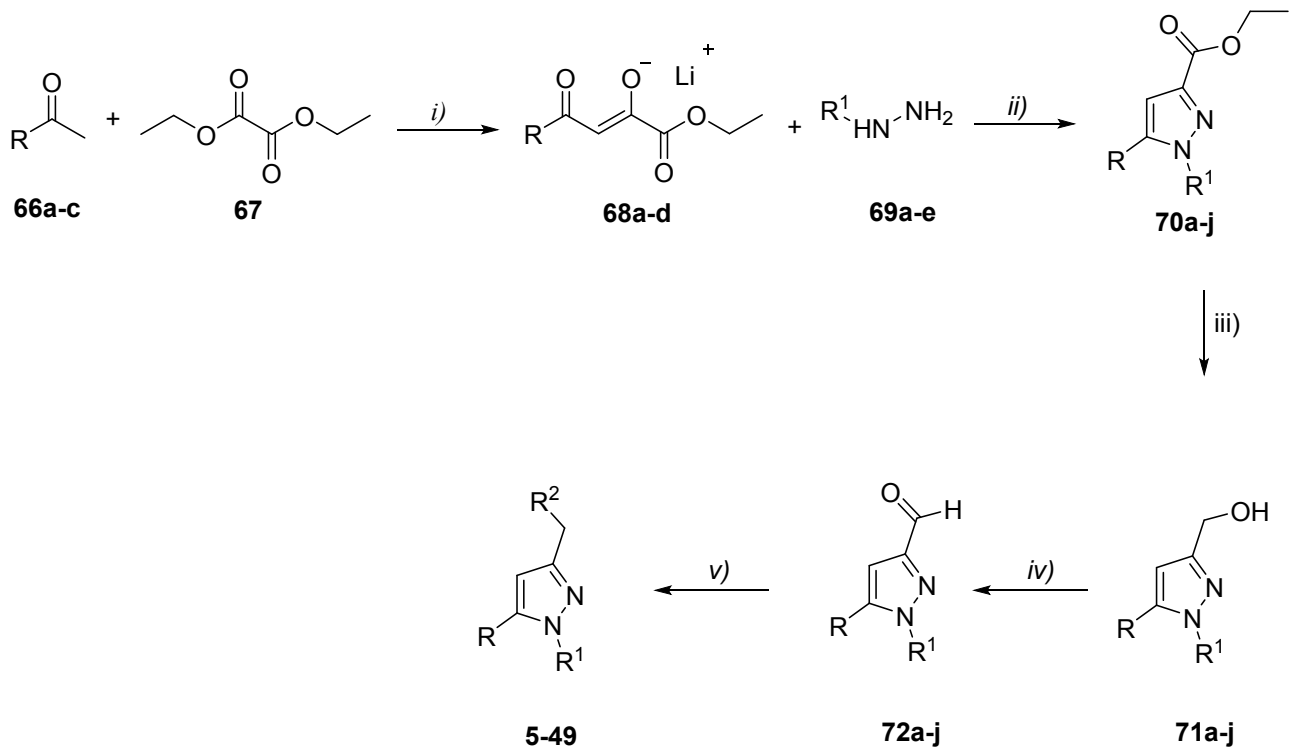
Scheme S2. Synthetic pathway for compounds **3** and **4**.



Reagents and conditions: i) 37% HCl, $NaNO_2$, AcONa, H_2O, EtOH, 0 °C and then room temperature, 22 h; ii) DIPEA, EtOH, room temperature, 18h; iii) $LiAlH_4$, THF, 0 °C and then room temperature, 3h; iv) Dess-Martin periodinane, DCM, room temperature, 30 min; v) Amine, CH_3COOH, $NaBH(CH_3COO)_3$, DCE, room temperature, 2h; vi) MgSO4, $TiCl_4$, DIPEA, toluene, room temperature and then 60 °C, 18 h.

Compounds **5-49** were prepared as shown in **Scheme S3**. The reaction between ketones **66a-c** and diethyloxalate **67** in the presence of lithium bis(trimethylsilyl)-amide gave the desired lithium salts **68a-d** that were in turn cyclized with the appropriate hydrazines **69a-e** to afford pyrazoles **70a-j**. Ethyl esters **70a-j** were converted into the corresponding pyrazole-3-carbaldehydes **72a-j** in two steps as seen for the imidazole-4-carbaldehyde **56** in **Scheme 1**. Finally, **72a-j** underwent reductive amination with the appropriate amine in the presence of NaBH(CH3COO)3 to produce the desired final compounds **5-49**.

Scheme S3. Synthetic pathway for compounds **5-49**.



Reagents and conditions: i) $LiN(Si(CH_3)_3)_2$, THF, -78 °C and then room temperature, 24 h; ii) EtOH, 90 °C, 5h; iii) $LiAlH_4$, THF, 0 °C and then room temperature, 3h; iv) Dess-Martin periodinane, DCM, room temperature, 30 min; v) Amine, CH3COOH, $NaBH(CH_3COO)_3$, DCE, room temperature, 2h.

General Procedures

***N*-(4-fluorophenyl)-4-isopropylbenzimidamide (52).** A solution of **51** (6.9 mmol) in anhydrous THF (1 ml) was added dropwise under N_2 to sodium hexamethyldisilazide (6.9 ml, 1 M in THF). The obtained mixture was stirred for 20 min, and then a solution of **50** (6.9 mmol) in anhydrous THF (2 ml) was slowly added. The resulting mixture was stirred for 18 h and at the end poured into ice-water (10 ml). The mixture was extracted with DCM, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Crystallization from cyclohexane gave **52** as white crystals in good yield (75%). ^{1}H NMR (400 MHz, DMSOd_6): δ ppm= 7.87 (d, 2H, *J*= 7.83 Hz), 7.28 (d, 2H, *J*= 7.83 Hz), 7.10 (m, 2H), 6.80 (m, 2H), 6.23 (s broad, 2H), 2.93 (sept, 1H, *J*= 7.10 Hz), 1.22 (d, 6H, *J*= 7.10 Hz).

Ethyl 3-bromo-2-oxobutanoate (53). To a solution of ethyl 2-hydroxybutanoate **57** (15 mmol) in 30 ml of CCl_4, NBS (30 mmol) was added under N_2. The reaction mixture was heated at 85 °C for 5 h. At the end, the reaction mixture was cooled down and the precipitated was filtered off. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* affording **53** as colorless oil (75%) that was used for the next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 5.18 (q, 1H), 4.40 (q, 2H Hz), 1.82 (d, 3H), 1.41 (t, 3H).

Ethyl 1-(4-fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-imidazole-4-carboxylate (54). 52 (0.4 mmol), **53** (0.6 mmol) and $NaHCO_3$ (0.6 mmol) were dissolved in ethanol (1 ml) in a sealed glass tube equipped with a stirring bar. The tube was heated in the cavity of the microwave reactor for 5 min (150W, internal temperature 170 °C, and internal pressure 100 psi). Afterwards, TFA (0.03 ml) was added and the reaction mixture was heated again in the cavity of the microwave reactor for 15 min (150W, internal temperature 150 °C, and internal pressure 100 psi). After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue suspended in DCM and then washed with H_2O and brine. The organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (cyclohexane/EtOAc) 6/1 (v/v)) to yield **54** as a pale yellow powder (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (d, 2H), 7.21 (m, 4H), 7.10 (d, 2H), 4.47 (q, 2H), 2.86 (sept, 1H), 2.42 (s, 3H), 1.46 (t, 3H), 1.21 (d, 6H).

Ethyl-2-chloro-2-(2-(4-isopropylphenyl)hydrazono)acetate (60). To an ice cooled solution of isopropylaniline **58** (7.4mmol) in ethanol (2 ml), 1 ml of 37% HCl was added. Afterwards, a chilled solution of sodium nitrite (8.1 mmol in 2.4 ml of H_2O) was added dropwise and the reaction mixture was stirred for 1 h checking that the temperature never rose above 10 °C. To this cooled solution, a chilled solution of ethyl chloroacetate **59** (7.4 mmol) and sodium acetate (11.1 mmol) in ethanol-water (9:1, 20 ml) was added dropwise**.** The reaction mixture was allowed to reach room temperature and stirred for 4 h. It was then poured into water and allowed to stand for 18 h. At the end, the mixture was filtered and the precipitate washed with water and concentrated *in vacuo* to give **60** as a white solid (yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.29 (s, 1H), 7.24-7.14 (m, 4H), 4.38 (q, 2H), 2.88 (sept, 1H), 1.40 (t, 3H), 1.24 (d, 6H).

4-(1-(4-Fluorophenyl)prop-1-en-1-yl)morpholine (61). To a solution of morpholine (40 mmol) in toluene (6 ml), $MgSO_4$ (0.44 g) was added and the resulting suspension was stirred at room temperature for 10 min. The suspension was ice cooled and $TiCl_4$ (5.17 mmol, 1M in toluene) was slowly added to give a dark green suspension. 4-Fluoro-propiophenone **65** (6.6 mmol) and DIPEA (33 mmol) were dissolved in 2.2 ml of toluene and this mixture was slowly added to the suspension. The resulting mixture was heated at 60 °C for 18 h. At the end, the reaction mixture was cooled to room temperature and the solid was filtered off. The filtrate was concentrated *in vacuo* to give the enamine **61** as a pale yellow oil (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.30 (m, 2H), 7.03 (m, 2H), 4.70 (q, 1H), 3.68 (m, 4H), 2.68 (m, 4H), 1.57 (d, 3H).

Ethyl 5-(4-fluorophenyl)-1-(4-isopropylphenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (62). To a stirred solution of **60** (9.72 mmol) and **61** (9.72 mmol) in 70 ml of ethanol, DIPEA (5.1 ml) was added. The reaction mixture was stirred for 18 h at room temperature and then concentrated *in vacuo*. The crude material was purified by column chromatography (cyclohexane/EtOAc) 20/1 (v/v)) to give **62** as a yellow pail powder (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.13 (m, 6H), 7.05 (t, 2H), 4.45 (q, 2H), 2.88 (sept, 1H), 2.30 (s, 3H), 1.42 (m, 3H), 1.21 (d, 6H).

General procedure for the preparation of lithium salts 68a-d. 2,4-Dioxovalerate **68b** was commercially available while lithium salts **68a,c-d** were prepared as follows. To a -70 °C cooled solution of lithium bis(trimethylsilyl)amide (12.3 mmol) in 30 ml of anhydrous THF, a solution of the appropriate acetophenone **66a-c** in 3 ml of anhydrous THF was added dropwise and the resulting solution was stirred for 1 h at -70 °C. Afterwards, diethyl oxalate **67** (150 mmol) was added over 5 min and the resulting dark orange solution was warmed to room temperature over 4 h and then left stirring for 18 h. At the end, the precipitate was filtered, washed with diethyl ether and dried *in vacuo* to give lithium salts **68a,c-d** in good yields (80-94%).

Lithium (*Z*)-1-ethoxy-4-(4-isopropylphenyl)-1,4-dioxobut-2-en-2-olate (68a). Pale yellow powder (yield 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.86 (d, 2H), 7.24 (d, 2H), 6.60 (s, 1H), 3.87 (q, 2H), 2.94 (sept, 1H), 1.27 (d, 6H), 0.98 (t, 3H).

Lithium (*Z*)-1-ethoxy-4-(6-methylpyridin-3-yl)-1,4-dioxobut-2-en-2-olate (68c). Pale yellow powder (yield 94%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.86 (d, 1H), 8.05 (dd,1H,), 7.29 (d, 1H), 6.40 (s, 1H), 4.16 (q, 2H), 2.50 (s, 3H), 1.26 (t, 3H).

Lithium (*Z*)-1-ethoxy-1,4-dioxo-4-(4-(trifluoromethyl)phenyl)but-2-en-2-olate (68d). Pale yellow powder (yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.95 (d, 2H), 7.62 (d, 2H), 6.59 (s, 1H), 4.11 (m, 2H), 1.19 (m, 3H).

General procedure for the preparation of carboxylates 70a-j. To solution of the appropriate lithium salt **68a,c-d** or dioxovalerate **68b** (2.12 mmol) in 12 ml of ethanol the appropriate hydrazine **69a-e** was added (2.12 mmol) and the reaction mixture was heated at 90 °C for 5h. At the end, the reaction mixture was cooled down to room temperature and the solvent was evaporated *in vacuo*. Water (10 ml) was added and the mixture was extracted with ethyl acetate. The organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by column chromatography (cyclohexane/EtOAc) 2/1 (v/v)) to yield carboxylates **70a-j** in good yields (35-90% yield).

Ethyl 1-(4-fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carboxylate (70a). Pale yellow solid (yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.36 (m, 2H), 7.20 (d, 2H), 7.14 (d, 2H), 7.08 (m, 2H), 7.04 (s, 1H), 4.48 (q, 2H), 2.93 (sept, 1H), 1.45 (t, 3H), 1.27 (d, 6H).

Ethyl 1-cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carboxylate (70b). Yellow oil (yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.36 (d, 2H), 7.30 (d, 2H), 6.76 (s, 1H), 4.44 (q, 2H), 4.15 (tt, 1H), 3.01 (sept,1H), 2.23-2.11 (m, 2H), 1.95-1.85 (m, 5H), 1.66 (m, 1H), 1.42 (t, 3H), 1.32 (m, 8H).

Ethyl 1-isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carboxylate (70c). White solid (yield 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (m, 4H), 6.74 (s, 1H), 4.62 (sept, 1H), 4.44 (q, 2H), 2.99 (sept, 1H), 1.53 (d, 6H), 1.42 (t, 3H), 1.30 (d, 6H).

Ethyl 1-cyclobutyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carboxylate (70d). Pale yellow oil (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.31 (m, 4H), 6.76 (s, 1H), 4.81 (m, 1H), 4.42 (q, 2H), 2.99 (m, 1H), 2.95-2.85 (m, 2H), 2.33 (m, 2H), 1.90 (m, 1H), 1.80-1.70 (m, 1H), 1.42 (t, 3H), 1.31 (d, 6H).

Ethyl 5-(4-isopropylphenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazole-3-carboxylate (70e). White solid (yield 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.34 (d, 2H), 7.28 (d, 2H), 6.76 (s, 1H), 4.43 (q, 2H), 3.99-3.87 (m, 3H), 3.49 (m, 1H), 2.99 (sept, 1H), 2.60-2.38 (m, 1H), 2.17-2.03 (m, 2H), 1.85-1.65 (m, 2H), 1.40 (t, 3H), 1.31 (d, 6H).

Ethyl 1-cyclohexyl-5-methyl-1*H*-pyrazole-3-carboxylate (70f). Colorless oil (yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 6.53 (s, 1H), 4.38 (q, 2H), 4.02 (tt, 1H), 2.31 (s, 3H), 2.12-1.97 (m, 2H), 1.92 (m, 4H), 1.72 (m, 1H), 1.48-1.23 (m, 6H).

Ethyl 1-cyclohexyl-5-(6-methylpyridin-3-yl)-1*H*-pyrazole-3-carboxylate (70g). White solid (yield 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.52 (d, 1H, *J*= 2.40 Hz), 7.58 (dd, 1H), 7.29 (d,

1H), 6.80 (s, 1H), 4.43 (q, 2H), 4.06 (tt, 1H), 2.65 (s, 3H), 2.20-2.07 (m, 2H), 1.89 (m, 4H), 1.66 (m, 2H), 1.40 (t, 3H), 1.33-1.21 (m, 2H).

Ethyl 1-(4-fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carboxylate (70h). Yellow solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.58 (d, 2H), 7.31 (m, 4H), 7.09 (m, 2H), 4.47 (q, 2H), 1.43 (t, 3H).

Ethyl 1-cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carboxylate (70i). White solid (yield 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.85 (d, 2H), 7.60 (d, 2H), 6.89 (s, 1H), 4.49 (q, 2H), 4.18 (tt, 1H), 2.25 (m, 2H), 2.00 (m, 4H), 1.73 (m, 2H), 1.50 (t, 3H), 1.36 (m, 2H).

Ethyl 1-isopropyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carboxylate (70j). White solid (yield 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.75 (d, 2H), 7.51 (d, 2H), 6.81 (s, 1H), 4.55 (sept, 1H), 4.43 (q, 2H), 1.53 (d, 6H), 1.41 (t, 3H).

General procedure for the preparation of alcohols 55, 63 and 71a-j. To an ice-cold solution of the appropriate carboxylate (**54, 62** and **70a-j**) (0.41 mmol) in anhydrous THF (5 ml) $LiAlH_4$ was added dropwise under N_2 (0.49 ml, 1 M in THF). The reaction mixture was stirred for 1 h at 0 °C and then for 2 h at room temperature. At the end, the reaction mixture was cooled down to 0 °C and diluted with 0.18 ml of EtOAc, 0.08 ml of H_2O and 0.1 ml of NaOH 2N and stirred for 30 min. The precipitate was filtered off and the filtrate was dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (cyclohexane/EtOAc) 1/1 (v/v)) to yield **55**, **63** and **71a-j** in good yields (38-94% yield).

(1-(4-Fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-imidazol-4-yl)methanol (55). White solid (yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.07-7.26 (m, 8H), 4.70 (s, 2H), 2.84 (sept, 1H), 2.16 (s broad, 1H), 2.08 (s, 3H), 1.19 (d, 6H).

(5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-4-methyl-1*H*-pyrazol-3-yl)methanol (63). White solid (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.13 (m, 6H), 7.05 (m, 2H), 4.75 (s, 2H), 3.05 (s broad, 1H), 2.88 (sept, 1H), 2.30 (s, 3H), 1.21 (d, 6H).

(1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methanol (71a). White solid (yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.28 (m, 2H), 7.17 (d, 2H), 7.12 (d, 2H), 7.04 (m, 2H), 6.49 (s, 1H), 4.79 (s, 2H), 2.90 (sept, 1H), 2.05 (s broad, 1H), 1.23 (d, 6H).

(1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methanol (71b). Colorless oil (yield 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.30 (m, 4H), 6.21 (s, 1H), 4.73 (s, 2H), 4.08 (m, 1H), 3.49 (m, 1H), 2.98 (sept, 1H), 2.33 (s broad, 1H), 2.03 (m, 2H), 1.87 (m, 5H), 1.27 (d, 6H), 1.22 (m, 2H).

(1-Isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methanol (71c). Colorless oil (yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.28 (m, 4H), 6.20 (s, 1H), 4.73 (s, 2H), 4.52 (sept, 1H), 2.96 (sept, 1H), 1.94 (s broad, 1H), 1.45 (d, 6H), 1.29 (d, 6H).

(1-Cyclobutyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methanol (71d). Colorless oil (yield 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.30 (m, 4H), 6.23 (s, 1H), 4.75 (s, 2H), 2.97 (m, 1H), 2.78 (m, 2H), 2.32 (m, 2H), 2.14 (s broad, 1H), 1.87 (m, 1H), 1.71 (m, 2H), 1.30 (d, 6H).

(5-(4-Isopropylphenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazol-3-yl)methanol (71e). White solid (yield 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.33 (d, 2H), 7.29 (d, 2H), 6.23 (s, 1H), 4.72 (s, 2H), 4.31 (tt, 1H), 3.97-3.87 (m, 2H), 3.81 (m, 1H), 3.46 (dt, 1H), 2.98 (sept, 1H), 2.41-2.27 (m, 1H), 2.13-2.03 (m, 1H), 1.82-1.72 (m, 2H), 1.31 (d, 6H).

(1-Cyclohexyl-5-methyl-1*H*-pyrazol-3-yl)methanol (71f). White crystals (yield 88.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 5.98 (s, 1H), 4.64 (s, 2H), 3.99-3.86 (m, 1H), 2.27 (s, 3H), 1.96-1.86 (m, 6H), 1.73 (m, 1H), 1.46-1.22 (m, 3H).

(1-Cyclohexyl-5-(6-methylpyridin-3-yl)-1*H*-pyrazol-3-yl)methanol (71g). White crystals (yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.51 (d, 1H), 7.57 (dd, 1H), 7.28 (d, 1H), 6.27 (s, 1H), 4.74 (s, 2H), 3.97 (tt, 1H), 2.65 (s, 3H), 2.10-1.94 (m, 2H), 1.93-1.79 (m, 4H), 1.65 (m, 2H), 1.35-1.16 (m, 2H).

(1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methanol (71h). White solid (yield 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.60 (d, 2H), 7.36 (d, 2H), 7.28 (m, 2H), 7.09 (m, 2H), 6.62 (s, 1H), 4.83 (s, 2H), 2.07 (s broad, 1H).

(1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methanol (71i). White solid (yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.87 (d, 2H), 7.65 (d, 2H), 6.69 (s, 1H), 4.77 (s, 2H), 4.18 (tt, 1H), 2.21 (m, 2H), 1.95 (m, 4H), 1.73 (m, 2H), 1.36 (m, 2H).

(1-Isopropyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methanol (71j). White solid (yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.73 (d, 2H), 7.49 (d, 2H), 6.29 (s, 1H), 4.76 (s, 2H), 4.50 (sept, 1H), 2.18 (s broad, 1H), 1.50 (d, 6H).

General procedure for the preparation of carbaldehydes 56, 64 and 72a-j. To a solution of the appropriate alcohol (**55**, **63** or **71a-j**) (0.31 mmol) in anhydrous DCM (5 ml) Dess-Martin periodinane was added under N_2 (0.4 mmol). The reaction mixture was stirred for 30 min at room temperature. At the end, the reaction mixture was diluted with 5.1 ml of sat $NaHCO_3$ and 5.1 ml of sat $Na_2S_2O_3$ and stirred for 30 min. The reaction mixture was extracted with DCM, the organic layers washed with sat $NaHCO_3$ and brine and dried over Na_2SO_4. After concentration *in vacuo* the crude product was purified by column chromatography (cyclohexane/EtOAc) 5/1 (v/v)) to give **56, 64** and **72a-j** in good yields (51-98% yield).

1-(4-Fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-imidazole-4-carbaldehyde (56). White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.08 (s, 1H), 7.36-7.10 (m, 8H), 2.85 (sept, 1H), 2.40 (s, 3H), 1.20 (d, 6H).

5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-4-methyl-1*H*-pyrazole-3-carbaldehyde (64). White solid (yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.15 (s, 1H), 7.17-7.04 (m, 8H), 2.90 (sept, 1H), 2.32 (s, 3H), 1.23 (d, 6H).

1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carbaldehyde (72a). White solid (yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.09 (s, 1H), 7.36 (m, 2H), 7.22 (d, 2H), 7.16 (d, 2H), 7.12 (m, 2H), 7.01 (s, 1H), 2.94 (sept, 1H), 1.25 (d, 6H).

1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carbaldehyde (72b). White solid (yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.02 (s, 1H), 7.37 (d, 2H), 7.30 (d, 2H), 6.77 (s, 1H), 4.23 (tt, 1H), 3.02 (sept, 1H), 2.06 (m, 2H), 2.05-1.90 (m, 4H),1.72 (m, 2H), 1.64 (m, 2H), 1.31 (d, 6H).

1-Isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carbaldehyde (72c). Pale yellow oil (yield 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.01 (s, 1H), 7.35 (d, 2H), 7.29 (d, 2H), 6.75 (s, 1H), 4.67 (sept, 1H), 3.01 (sept, 1H), 1.54 (d, 6H), 1.33 (d, 6H).

1-Cyclobutyl-5-(4-isopropylphenyl)-1*H*-pyrazole-3-carbaldehyde (72d). White solid (yield 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.96 (s, 1H), 7.20 (m, 4H), 6.69 (s, 1H), 4.79 (m, 1H), 2.91 (sept, 1H), 2.76 (m, 2H), 2.30 (m, 2H), 1.88 (m, 1H), 1.72 (m, 1H), 1.23 (d, 6H).

5-(4-Isopropylphenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazole-3-carbaldehyde (72e). White solid (yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.99 (s, 1H), 7.34 (d, 2H), 7.28 (d, 2H), 6.76 (s, 1H), 4.43 (tt, 1H), 4.02-3.91 (m, 2H), 3.84 (t, 1H), 3.49 (td, 1H), 2.99 (sept, 1H), 2.45-2.31 (m, 1H), 2.20-2.09 (m, 1H), 1.87-1.68 (m, 2H), 1.32 (d, 6H).

1-Cyclohexyl-5-methyl-1*H*-pyrazole-3-carbaldehyde (72f). Pale yellow solid (yield 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 9.91 (s, 1H), 6.54 (s, 1H), 4.12-3.96 (m, 1H), 2.33 (s, 3H), 2.01-1.91 (m, 6H), 1.76 (m, 1H), 1.51-1.24 (m, 3H).

1-Cyclohexyl-5-(6-methylpyridin-3-yl)-1*H*-pyrazole-3-carbaldehyde (72g). White crystals (yield 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.01 (s, 1H), 8.53 (d, 1H), 7.59 (dd, 1H), 7.32 (d, 1H), 6.80 (s, 1H), 4.10 (tt, 1H), 2.67 (s, 3H), 2.15-2.00 (m, 2H), 2.00-1.84 (m, 4H), 1.36-1.24 (m, 4H).

1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbaldehyde (72h). White solid (yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.08 (s, 1H), 7.61 (d, 2H), 7.33 (m, 4H), 7.13 (m, 2H), 7.08 (s, 1H).

1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbaldehyde (72i). White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.03 (s, 1H), 7.79 (d, 2H), 7.52 (d, 2H), 6.83 (s, 1H), 4.15 (m, 1H), 2.09 (m, 2H), 1.97 (m, 4H), 1.86 (m, 1H), 1.30 (m, 3H).

1-Isopropyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazole-3-carbaldehyde (72j). White solid (yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 10.01 (s, 1H), 7.75 (d, 2H), 7.50 (d, 2H), 6.82 (s, 1H), 4.57 (sept, 1H), 1.52 (d, 6H).

General procedure for the preparation of compounds 1-49. To a solution of the appropriate carbaldehyde (**56, 64** and **72a-j)** (0.26 mmol) in 5 ml of anhydrous DCE a drop of glacial acetic acid was added and the mixture was stirred for 10 min. Afterwards, the appropriate amine (0.26 mmol) and $NaBH(CH_3COO)_3$ (0.36 mmol) were added and the reaction mixture was stirred for 2 h. At the end, the mixture was quenched with sat $NaHCO_3$ (5 ml) and extracted with DCM. The organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (cyclohexane/EtOAc) 1/1 (v/v)) to yield compounds **1-49** in good yields (34-94%).

4-((1-(4-Fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-imidazol-4-yl)methyl)morpholine (1). White solid (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.23 (d, 2H), 7.15 (m, 4H), 7.06 (d, 2H), 3.82 (s broad, 4H), 3.65 (s broad, 2H), 2.82 (sept, 1H), 2.72 (s broad, 4H), 2.09 (s, 3H), 1.19 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 163.82, 161.23, 148.73, 146.44, 133.75, 129.85, 129.68, 128.21, 127.90, 126.19, 116.91, 116.71, 116.48, 66.75, 55.55, 53.56, 33.90, 24.07, 10.24. LRMS $(M + H)^+$(ESI$^+$) 394.22 $[M + H]^+$(calcd for $C_{24}H_{28}FN_3OH^+$ 394.23).

1-((1-(4-Fluorophenyl)-2-(4-isopropylphenyl)-5-methyl-1*H*-imidazol-4-yl)methyl)-4-methoxypiperidine (2). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.23 (d, 2H), 7.14 (m, 4H), 7.05 (d, 2H), 3.60 (s broad, 2H), 3.34 (s, 3H), 3.27 (s broad, 1H), 2.95 (s broad, 2H), 2.83 (m, 1H), 2.08 (s, 3H), 1.98 (s broad, 2H), 1.70 (m broad, 4H), 1.18 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 163.82, 161.23, 148.73, 146.44, 133.75, 129.85, 129.68, 128.21, 127.90, 126.19, 116.91, 116.71, 116.48, 55.55, 53.56, 51, 33.90, 30.63, 24.07, 10.24. LRMS $(M + H)^+$(ESI$^+$) 422.26 $[M + H]^+$(calcd for $C_{26}H_{32}FN_3OH^+$ 422.26).

4-((5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-4-methyl-1*H*-pyrazol-3-yl)methyl)morpholine (3). White solid (yield 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.17-7.01 (m, 8H), 3.77 (s broad, 4H), 3.66 (s broad, 2H), 2.87 (sept, 1H), 2.63 (s broad, 4H), 2.10 (s, 3H), 1.21 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 169.72, 161.52, 156.58, 154.62, 147.41, 139.57, 137.58, 131.72, 131.37,

126.73, 125.09, 115.92, 114.97, 66.85, 55.56, 50,98, 33.89, 24.35, 8.91. LRMS $(M + H)^+(ESI^+)$ 394.26 $[M + H]^+$(calcd for $C_{24}H_{28}FN_3OH^+$ 394.23).

1-((5-(4-Fluorophenyl)-1-(4-isopropylphenyl)-4-methyl-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (4). White solid (yield 50%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.17-7.01 (m, 8H), 3.66 (s broad, 2H), 3.34 (s, 3H), 3.26 (s broad, 1H), 2.87 (m, 3H), 2.33 (m, 2H), 2.09 (s, 3H), 1.98 (m, 2H), 1.21 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 169.72, 161.52, 156.58, 154.62, 147.41, 139.57, 137.58, 131.72, 131.37, 126.73, 125.09, 115.92, 114.97, 55.56, 50,98, 50.60, 33.89, 30.77, 24.35, 8.91. LRMS $(M + H)^+(ESI^+)$ 422.22 $[M + H]^+$(calcd for $C_{26}H_{32}FN_3OH^+$ 422.26).

4-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (5). White solid (yield 94%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.27 (m, 2H), 7.15 (m, 4H), 7.02 (m, 2H), 6.48 (s, 1H), 3.76 (m, 4H), 3.65 (s, 2H), 2.89 (sept, 1H), 2.61 (s broad, 4H), 1.24 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.82, 160.36, 149.26, 144.24, 136.30, 128.56, 127.54, 127.09, 127.01, 126.61, 115.92, 115.69, 107.83, 65.96, 55.69, 53.56, 33.84, 23.82. LRMS $(M + H)^+(ESI^+)$ 380.22 $[M + H]^+$(calcd for $C_{23}H_{26}FN_3OH^+$ 380.21).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (6). White solid (yield 70%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.21 (m, 2H), 7.07 (m, 4H), 6.96 (m, 2H), 6.41 (s broad, 1H), 3.58 (s broad, 2H), 3.29 (s, 3H), 3.17 (s broad, 1H), 2.81 (m, 3H), 2.22 (m, 2H), 1.87 (m, 2H), 1.59-1.47 (m, 2H), 1.17 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.75, 160.29, 149.14, 144, 136.34, 128.52, 127.68, 127.08, 127, 126.58, 15.85, 115.62, 107.80, 55.75, 55.56, 51, 33.83, 30.63, 23.82. LRMS $(M + H)^+(ESI^+)$ 408.23 $[M + H]^+$(calcd for $C_{25}H_{30}FN_3OH^+$ 408.24).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-3-methoxypiperidine (7). White solid (yield 34%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.29 (m, 2H), 7.18 (m, 4H), 7.05 (m, 2H), 6.52 (s, 1H), 3.76 (s, 2H), 3.43 (m, 4H), 3.22 (m, 1H), 2.95-2.71 (m, 2H), 2.33-2.11 (m, 2H), 2.08-1.93 (m, 2H), 1.83-1.74 (m, 1H), 1.72-1.60 (m, 1H), 1.13 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$):

δ ppm= 162.82, 160.36, 149.26, 144.24, 136.30, 128.56, 127.54, 127.09, 127.01, 126.61, 115.92, 115.69, 107.83, 65.96, 59.77, 55.69, 53.56, 33.84, 31.44, 23.82, 21.29. LRMS $(M + H)^+$(ESI$^+$) 408.25 $[M + H]^+$(calcd for $C_{25}H_{30}FN_3OH^+$ 408.24).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperidin-4-ol (8). White solid (yield 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.31 (m, 2H), 7.17 (m, 4H), 7.05 (m, 2H), 6.57 (s, 1H), 3.76 (m, 3H), 3.00 (m, 2H), 2.92 (sept, 1H), 2.47 (s broad, 2H), 2.08 (m, 2H), 1.90 (s broad, 1H), 1.74-1.62 (m, 2H), 1.27 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.75, 160.29, 149.14, 144, 136.34, 128.52, 127.68, 127.08, 127, 126.58, 115.85, 115.62, 107.80, 65.96, 55.75, 51, 33.83, 30.63, 23.82. LRMS $(M + H)^+$(ESI$^+$) 394.22 $[M + H]^+$(calcd for $C_{24}H_{29}FN_3OH^+$ 394.23).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperidin-3-ol (9). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.28 (m, 2H), 7.14 (m, 4H), 7.04 (m, 2H), 6.61 (s broad, 1H), 3.99 (s broad, 1H), 3.84 (s broad, 2H), 2.93-2.70 (m, 5H), 2.61 (s broad, 1H), 2.03 (s broad, 2H), 1.67 (m, 2H), 1.24 (d, 6H, *J*= 7.10 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.82, 160.36, 149.26, 144.24, 136.30, 128.56, 127.54, 127.09, 127.01, 126.61, 115.92, 115.69, 107.83, 65.96, 59.77, 55.69, 53.56, 33.84, 31.44, 23.82, 21.29. LRMS $(M + H)^+$(ESI$^+$) 394.22 $[M + H]^+$(calcd for $C_{24}H_{29}FN_3OH^+$ 394.23).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-methylpiperazine (10). White solid (yield 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.30 (m, 2H), 7.16 (m, 4H), 7.05 (m, 2H), 6.49 (s, 1H), 3.77 (s, 2H), 2.99-2.87 (m, 9 H), 2.52 (s, 3H), 1.27 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 161.76, 159.30, 148.19, 143.04, 135.26, 127.49, 126.59, 126.06, 125.98, 125.59, 114.86, 114.63, 106.69, 57.96, 54.83, 51.82, 45.98, 32.81, 22.79. LRMS $(M + H)^+$(ESI$^+$) 393.22 $[M + H]^+$(calcd for $C_{24}H_{29}FN_4H^+$ 393.24).

***Tert*-butyl 4-((1-(4-fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperazine-1-carboxylate (11).** White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.20 (m, 2H), 7.07 (m, 4H), 6.95 (m, 2H), 6.39 (s, 1H), 3.60 (s, 2H), 3.41 (m, 4H), 2.82 (sept, 1H), 2.48 (m, 4H), 1.39

(s, 9H), 1.17 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 161.76, 159.30, 153.77, 148.19, 143.04, 135.26, 127.49, 126.59, 126.06, 125.98, 125.59, 114.86, 114.63, 106.69, 78.60, 57.96, 54.83, 51.82, 32.81, 28.68, 27.41, 22.79. LRMS $(M + H)^+$(ESI$^+$) 479.27 $[M + H]^+$(calcd for $C_{28}H_{35}FN_4O_2H^+$ 479.28).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-(pyridin-2-yl)piperazine (12). White solid (yield 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.19 (dd, 1H), 7.47 (td, 1H), 7.30 (m, 2H), 7.15 (m, 4H), 7.03 (m, 2H), 6.63 (m, 2H), 6.54 (s, 1H), 3.77 (s broad, 2H), 3.64 (m, 4H), 2.89 (sept, 1H), 2.78 (m, 4H), 1.24 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.73, 160.43, 159.37, 149.26, 147.98, 144.12, 137.51, 136.32, 128.56, 127.12, 127.03, 126.63, 115.91, 115.68, 113.40, 107.96, 107.10, 55.67, 52.63, 44.93, 33.84, 23.75. LRMS $(M + H)^+$(ESI$^+$) 456.25 $[M + H]^+$(calcd for $C_{28}H_{30}FN_5H^+$ 456.26).

1-((1-(4-Fluorophenyl)-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4,4-dimethyl-1,4-azasilinane (13). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.29 (m, 2H), 7.15 (m, 4H), 7.04 (m, 2H), 6.52 (s, 1H), 3.74 (s, 2H), 2.90 (m, 5H), 1.25 (d, 6H), 0.84 (m, 4H), 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.82, 160.36, 149.26, 144.24, 136.30, 128.56, 127.54, 127.09, 127.01, 126.61, 115.92, 115.69, 107.83, 55.69, 53.56, 33.84, 23.82, 13.17, 3.22. LRMS $(M + H)^+$(ESI$^+$) 422.25 $[M + H]^+$(calcd for $C_{25}H_{32}FN_3SiH^+$ 422.24).

4-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (14). White solid (yield 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.29 (m, 4H), 6.19(s broad, 1H), 4.08 (m, 1H), 3.76 (m, 4H), 3.63 (s broad, 2H), 2.97 (sept, 1H), 2.59 (s broad, 4H), 2.04 (m, 2H), 1.86 (m, 4H), 1.29 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.10, 143.59, 128.85, 128.53, 126.75, 105.87, 66.78, 57.51, 56.25, 53.26, 33.93, 33.34, 25.64, 25.09, 23.92. LRMS $(M + H)^+$(ESI$^+$) 368.25 $[M + H]^+$(calcd for $C_{23}H_{33}N_3OH^+$ 368.27).

4-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)thiomorpholine (15). Pale yellow oil (yield 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.33 (m, 4H), 6.20 (s, 1H), 4.11 (m,

1H), 3.70 (s, 2H), 3.00 (sept, 1H), 2.87 (s broad, 4H), 2.76 (s broad, 4H), 2.07 (m, 2H), 1.89 (m, 4H), 1.67 (m, 4H), 1.33 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.11, 143.45, 129.06, 128.41, 126.76, 105.88, 57.37, 56.25, 53.26, 33.75, 33.18, 27, 25.64, 25.09, 23.77. LRMS $(M + H)^+(ESI^+)$ 384.28 $[M + H]^+$(calcd for $C_{23}H_{33}N_3SH^+$ 384.25).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (16). Pale yellow oil (yield 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (m, 4H), 6.19 (s, 1H), 4.10 (m, 1H), 3.61 (s, 2H), 3.36 (s, 3H), 3.23 (m, 1H), 2.99 (sept, 1H), 2.87 (m, 2H), 2.22 (m, 2H), 2.07 (m, 2H), 1.99-1.82 (m, 8H), 1.62 (m, 2H), 1.34 (d, 6H), 1.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.03, 147.45, 143.61, 128.81, 128.65, 126.82, 105.77, 57.69, 56.63, 53.64, 51, 34.02, 33.43, 30.63, 25.73, 25.31, 23.91. LRMS $(M + H)^+(ESI^+)$ 396.30 $[M + H]^+$(calcd for $C_{25}H_{37}N_3OH^+$ 396.30).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-3-methoxypiperidine (17). Pale yellow oil (yield 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.33 (m, 4H), 6.19 (s, 1H), 4.10 (m, 1H), 3.66 (s, 2H), 3.38 (s, 4H), 3.06-2.93 (m, 2H), 2.76 (m, 1H), 2.22-2.02 (m, 4H), 1.99-1.88 (m, 4H), 1.75 (m, 2H), 1.66 (m, 1H), 1.58 (m, 1H), 1.33 (d, 2H), 1.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.03, 147.45, 143.61, 128.81, 128.65, 126.82, 105.77, 65.96, 57.69, 56.63, 53.64, 34.02, 33.43, 31.44, 25.73, 25.31, 23.91, 21.29. LRMS $(M + H)^+(ESI^+)$ 396.28 $[M + H]^+$(calcd for $C_{25}H_{37}N_3OH^+$ 396.30).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperidin-4-ol (18). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (m, 4H), 6.21 (s, 1H), 4.10 (m, 1H), 3.74 (m, 1H), 3.65 (s, 2H), 2.99 (sept, 1H), 2.91 (m, 2H), 2.30 (m, 2H), 2.05-1.67 (m, 9H), 1.34 (d, 6H), 1.29 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.03, 147.45, 143.61, 128.81, 128.65, 126.82, 105.77, 57.69, 56.63, 53.64, 51.00, 34.02, 33.43, 30.63, 25.73, 25.31, 23.91. LRMS $(M + H)^+(ESI^+)$ 382.31 $[M + H]^+$(calcd for $C_{24}H_{35}N_3OH^+$ 382.29).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-methylpiperazine (19). White solid (yield 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.34 (m, 4H), 6.18 (s, 1H), 4.09 (m, 1H), 3.67 (s, 2H), 3.02 (s broad, 2H), 2.99 (sept, 1H), 2.71-2.58 (m, 8H), 2.36 (s, 3H), 2.03 (m, 3H), 1.87 (m, 4H), 1.66 (m, 1H), 1.33 (d, 6H), 1.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.10, 147.73, 143.58, 128.86, 128.57, 126.76, 105.71, 57.50, 56.02, 52.67, 45.98, 33.93, 33.34, 27.57, 25.65, 25.09, 23.92. LRMS $(M + H)^+$(ESI$^+$) 381.28 $[M + H]^+$(calcd for $C_{24}H_{36}N_4H^+$ 381.30).

***Tert*-butyl 4-((1-cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperazine-1-carboxylate (20).** White solid (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (m, 4H), 6.17 (s, 1H), 4.07 (m, 1H), 3.62 (s, 2H), 3.46 (s broad, 4H), 2.96 (sept, 1H), 2.50 (s broad, 4H), 2.05 (m, 2H), 1.89-1.65 (m, 6H), 1.43 (s, 9H), 1.30 (d, 6H), 1.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 154.76, 149.10, 147.73, 143.58, 128.86, 128.57, 126.76, 105.71, 79.49, 57.50, 56.02, 52.67, 33.93, 33.34, 28.44, 27.57, 25.65, 25.09, 23.92. LRMS $(M + H)^+$(ESI$^+$) 467.34 $[M + H]^+$(calcd for $C_{28}H_{42}N_4O_2H^+$ 467.34).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperazine (21). White solid (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.28 (m, 4H), 6.16 (s, 1H), 4.07 (m, 1H), 3.59 (s, 2H), 2.95 (m, 5H), 2.50 (s broad, 4H), 2.20 (s broad, 1H), 2.03 (m, 2H), 1.88 (m, 4H), 1.29 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.03, 147.45, 143.61, 128.81, 128.65, 126.82, 105.77, 57.69, 56.63, 53.64, 45.56, 34.02, 33.43, 25.73, 25.31, 23.91. LRMS $(M + H)^+$(ESI$^+$) 367.29 $[M + H]^+$(calcd for $C_{23}H_{34}N_4H^+$ 367.29).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-(pyridin-2-yl)piperazine (22). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.18 (dd, 1H), 7.46 (td, 1H), 7.29 (m, 4H), 6.60 (m, 2H), 6.20 (s, 1H), 4.08 (m, 1H), 3.68 (s, 2H), 3.58 (m, 4H), 2.96 (sept, 1H), 2.69 (m, 4H), 2.05 (m, 2H), 1.87 (m, 4H), 1.32 (d, 6H), 1.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 159.56, 149.06, 147.97, 147.26, 143.55, 137.41, 128.99, 128.71, 126.84, 113.19, 107.16,

105.81, 57.50, 55.96, 52.65, 45.09, 33.88, 33.35, 25.66, 25.10, 23.92. LRMS $(M + H)^+$(ESI$^+$) 444.30 $[M + H]^+$(calcd for $C_{28}H_{37}N_5H^+$ 444.31).

1-((1-Cyclohexyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4,4-dimethyl-1,4-azasilinane (23). White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.27 (m, 4H), 6.15 (s, 1H), 4.03 (m, 1H), 3.64 (s, 2H), 2.93 (sept, 1H), 2.74 (m, 4H), 1.99 (m, 2H), 1.86-1.72 (m, 6H), 1.28 (d, 6H), 1.23 (m, 2H), 0.80 (m, 4H), 0.00 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 148.99, 143.49, 128.84, 128.58, 126.89, 126.69, 105.83, 57.42, 55.82, 52.19, 33.88, 33.31, 25.61, 25.08, 23.88, 13.17, -3.22. LRMS $(M + H)^+$(ESI$^+$) 410.29 $[M + H]^+$(calcd for $C_{25}H_{39}N_3SiH^+$ 410.30).

4-((1-Isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (24). White solid (yield 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.31 (m, 4H), 6.16 (s, 1H), 4.50 (sept, 1H), 3.74 (m, 4H), 3.60 (s, 2H), 2.94 (sept, 1H), 2.55 (m, 4H), 1.45 (d, 6H), 1.29 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.16, 148.78, 143.63, 128.94, 128.57, 126.81, 105.79, 66.90, 56.36, 53.36, 49.76, 33.93, 23.92, 22.96. LRMS $(M + H)^+$(ESI$^+$) 328.22 $[M + H]^+$(calcd for $C_{20}H_{29}N_3OH^+$ 328.24).

1-((1-Isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (25). White solid (yield 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.29 (m, 4H), 6.20 (s, 1H), 4.52 (sept, 1H), 3.63 (s, 2H), 3.33 (s, 3H), 3.23 (m, 1H), 2.96 (sept, 1H), 2.88 (m, 2H), 2.28 (m, 2H), 1.95 (m, 2H), 1.66 (m, 2H), 1.44 (d, 6H), 1.29 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.16, 148.78, 143.63, 128.94, 128.57, 126.81, 105.79, 56.36, 53.36, 49.76, 33.93, 30.63, 23.92, 22.96. LRMS $(M + H)^+$(ESI$^+$) 356.26 $[M + H]^+$(calcd for $C_{22}H_{33}N_3OH^+$ 356.27).

1-((1-Isopropyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)piperidin-3-ol (26). White solid (yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.32 (m, 4H), 6.19 (s, 1H), 4.54 (sept, 1H), 3.89 (m, 1H), 3.67 (m, 2H), 2.99 (sept, 1H), 2.61 (m, 4H), 2.43 (m, 1H), 1.90 (m, 1H), 1.61 (m, 3H), 1.48 (d, 6H), 1.32 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.26, 144.24, 136.30, 128.56, 127.54, 126.61, 107.83, 65.96, 59.77, 55.69, 53.56, 49.76, 33.84, 31.44, 23.82, 22.96, 21.29. LRMS $(M + H)^+$(ESI$^+$) 342.27 $[M + H]^+$(calcd for $C_{21}H_{31}N_3OH^+$ 342.25).

4-((1-Cyclobutyl-5-(4-isopropylphenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (27). White solid (yield 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.21 (m, 4H), 6.13 (s, 1H), 4.68 (quin, 1H), 3.68 (m, 4H), 3.56 (s, 2H), 2.90 (sept, 1H), 2.70 (m, 2H), 2.52 (m, 4H), 2.24 (m, 2H), 1.79 (m, 1H), 1.63 (m, 1H), 1.29 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.21, 147.50, 143.88, 128.84, 128.38, 126.69, 105.90, 66.92, 56.38, 53.44, 52.48, 33.95, 30.73, 23.94, 14.59. LRMS $(M + H)^+$(ESI$^+$) 340.23 $[M + H]^+$(calcd for $C_{21}H_{29}N_3OH^+$ 340.24).

4-((5-(4-Isopropylphenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazol-3-yl)methyl)morpholine (28). White solid (yield 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.31 (m, 2H), 7.27 (m, 2H), 6.19 (s, 1H), 4.33 (m, 1H), 3.90 (m, 2H), 3.83 (m, 1H), 3.74 (m, 4H), 3.58 (s, 2H), 3.46 (m, 1H), 2.95 (sept, 1H), 2.54 (m, 4H), 2.35 (m, 1H), 2.09 (m, 1H), 1.75 (m, 2H), 1.31 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.10, 147.75, 144.07, 128.51, 127.66, 126.53, 105.58, 71, 67.27, 66.66, 56.02, 53.61, 53.18, 33.62, 29.72, 25.28, 23.56. LRMS $(M + H)^+$(ESI$^+$) 370.25 $[M + H]^+$(calcd for $C_{22}H_{31}N_3O_2H^+$ 370.25).

1-((5-(4-Isopropylphenyl)-1-(tetrahydro-2*H*-pyran-3-yl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (29). Colorless oil (yield 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm=7.30 (m, 4H), 6.20 (s, 1H), 4.30 (m, 1H), 3.89 (m, 2H), 3.83 (m, 1H), 3.57 (s, 2H), 3.46 (m, 1H), 3.34 (s, 3H), 3.21 (m, 1H), 2.97 (sept, 1H), 2.83 (m, 2H), 2.35 (m, 1H), 2.21 (m, 2H), 2.13 (m, 1H), 1.91 (m, 2H), 1.76-1.61 (m, 4H), 1.31 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 149.34, 148.85, 144.29, 128.83, 128.07, 126.82, 105.81, 71.33, 67.59, 55.95, 55.47, 53.90, 51.13, 33.93, 30.88, 30.03, 25.61, 23.88. LRMS $(M + H)^+$(ESI$^+$) 398.27 $[M + H]^+$(calcd for $C_{24}H_{35}N_3O_2H^+$ 398.28).

4-((1-Cyclohexyl-5-methyl-1*H*-pyrazol-3-yl)methyl)morpholine (30). Colorless oil (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 5.94 (s, 1H), 3.92 (m, 1H), 3.72 (m, 4H), 3.51 (s, 2H), 2.49 (m, 4H), 2.25 (s, 3H), 1.96-1.86 (m, 6H), 1.40-1.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 147.22, 143.22, 105.63, 65.96, 57.44, 56.36, 33.92, 33.33, 25.65, 25.09, 10.24. LRMS $(M + H)^+$(ESI$^+$) 264.20 $[M + H]^+$(calcd for $C_{15}H_{25}N_3OH^+$ 264.21).

1-((1-Cyclohexyl-5-methyl-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (31). Yellow oil (yield 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 5.93 (s, 1H), 3.89 (m, 1H), 3.50 (s, 2H), 3.32 (s, 3H), 3.18 (m, 1H), 2.80 (m, 2H), 2.24 (s, 3H), 2.15 (m, 2H), 1.92 (m, 8H), 1.71 (m, 1H), 1.58 (m, 2H), 1.39-1.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 145.62, 137.52, 104.91, 57.33, 55.98, 55.44, 51.04, 32.73, 30.90, 25.77, 25.16, 11.17. LRMS $(M + H)^+$(ESI$^+$) 292.25 $[M + H]^+$(calcd for $C_{17}H_{29}N_3OH^+$ 292.24).

4-((1-Cyclohexyl-5-(6-methylpyridin-3-yl)-1*H*-pyzazol-3-yl)methyl)morpholine (32). White solid (yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.51 (d, 1H), 7.56 (dd, 1H), 7.25 (d, 1H), 6.22 (s, 1H), 3.97 (m, 1H), 3.74 (m, 4H), 3.59 (s, 2H), 2.63 (s, 3H), 2.54 (m, 4H), 2.03 (m, 2H), 1.86 (m, 4H), 1.65 (m, 1H), 1.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 158.43, 148.77, 147.83, 139.96, 136.51, 124.34, 123.07, 106.23, 66.98, 57.83, 56.33, 53.49, 33.29, 25.56, 24.97, 24.32. LRMS $(M + H)^+$(ESI$^+$) 341.23 $[M + H]^+$(calcd for $C_{20}H_{28}N_4OH^+$ 341.23).

5-(1-Cyclohexyl-4-((4-methoxypiperidin-1-yl)methyl)-1*H*-pyrazol-2-yl)-2-methylpyridine (33). Colorless oil (yield 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.52 (d, 1H), 7.57 (dd, 1H), 7.25 (d, 1H), 6.23 (s, 1H), 3.96 (m, 1H), 3.58 (s, 2H), 3.34 (s, 3H), 3.21 (m, 1H), 2.85 (m, 2H), 2.63 (s, 3H), 2.21 (m, 2H), 2.05 (m, 2H), 1.89 (m, 6H), 1.64 (m, 3H), 1.25 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 158.35, 148.78, 139.88, 136.55, 124.45, 123.07, 106.15, 57.80, 55.96, 55.48, 51.15, 33.31, 30.91, 25.58, 24.99, 24.32. LRMS $(M + H)^+$(ESI$^+$) 369.22 $[M + H]^+$(calcd for $C_{22}H_{32}N_4OH^+$ 369.24).

4-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (34). White solid (yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.57 (d, 2H), 7.33 (d, 2H), 7.26 (m, 2H), 7.07 (m, 2H), 6.59 (s, 1H), 3.77 (m, 4H), 3.67 (s, 2H), 2.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 163.16, 160.58, 149.94, 142.52, 135.82, 133.88, 130.78, 130.51, 130.21, 130.01, 128.74, 127.07, 125.58, 125.19, 122.49, 116.28, 116, 108.81, 66.85, 56.09, 53.58. LRMS $(M + H)^+$(ESI$^+$) 406.15 $[M + H]^+$(calcd for $C_{21}H_{19}F_4N_3OH^+$ 406.15).

4-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)thiomorpholine (35). Yellow solid (yield 70%). ^{1}H NMR (400 MHz, $DMSOd_6$): δ ppm= 7.71 (d, 2H), 7.43 (d, 2H), 7.28 (m, 4H), 6.69 (s, 1H), 3.56 (s, 2H), 2.71 (m, 4H), 2.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.96, 160.49, 142.39, 135.75, 133.69, 130.43, 130.10, 128.77, 127.12, 127.04, 125.51, 125.16, 122.46, 116.22, 115.99, 108.59, 56.47, 54.82, 27.88. LRMS $(M + H)^+$(ESI^+) 422.15 $[M + H]^+$(calcd for $C_{21}H_{19}F_4N_3SH^+$ 422.13).

1-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (36). White solid (yield 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.59 (d, 2H), 7.36 (d, 2H), 7.28 (m, 2H), 7.08 (m, 2H), 6.62 (s, 1H), 3.69 (s, 2H), 3.37 (s, 3H), 3.28 (m, 1H), 2.93 (m, 2H), 2.35 (m, 2H), 1.97 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 163.16, 160.58, 149.94,142.52, 135.82, 133.88, 130.78, 130.51, 130.21, 130.01, 128.74, 127.07, 125.58, 125.19, 122.49, 116.28, 116, 108.81, 56.09, 53.58, 51, 30.63. LRMS $(M + H)^+$(ESI^+) 434.19 $[M + H]^+$(calcd for $C_{23}H_{23}F_4N_3OH^+$ 434.19).

1-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)piperidine (37). White solid (yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.56 (d, 2H), 7.33 (d, 2H), 7.26 (m, 2H), 7.05 (m, 2H), 6.58 (s, 1H), 3.62 (s, 2H), 2.53 (s broad, 4H), 1.63 (m, 4H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 163.15, 160.54, 142.53, 135.93, 133.85, 130.47, 130.03, 129.63, 128.80, 127.28, 127.16, 125.57, 125.22, 116.23, 115.96, 109.05, 108.79, 56.49, 54.53, 25.98, 24.09. LRMS $(M + H)^+$(ESI^+) 404.18 $[M + H]^+$(calcd for $C_{22}H_{21}F_4N_3H^+$ 404.18).

***Tert*-butyl 4-((1-(4-fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)piperazine-1-carboxylate (38).** White solid (yield 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.50 (d, 2H), 7.26 (d, 2H), 7.18 (m, 2H), 6.99 (m, 2H), 6.48 (s, 1H), 3.59 (s, 2H), 3.41 (t, 4H), 2.47 (t, 4H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.14, 159.58, 153.71, 141.49, 134.76, 132.78, 129.54, 129.39, 129.19, 127.80, 126.20, 126.05, 124.52, 115.23, 115.06, 107.71,

78.68, 54.63, 51.90, 51.72, 27.46. LRMS $(M + H)^+$(ESI$^+$) 505.22 $[M + H]^+$(calcd for $C_{26}H_{28}F_4N_4O_2H^+$ 505.22).

1-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4-(pyridin-2-yl)piperazine (39). White solid (yield 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 8.19 (dd, 1H), 7.57 (d, 2H), 7.47 (td, 1H), 7.34 (d, 2H), 7.27 (m, 2H), 7.06 (m, 2H), 6.63 (m, 3H), 3.73 (s, 2H), 3.60 (m, 4H), 2.72 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.96, 160.49, 159.37, 149.26, 144.12, 142.39, 135.75, 133.69, 130.43, 130.10, 128.77, 127.12, 127.04, 125.51, 125.16, 122.46, 116.22, 115.99, 113.40, 108.59, 107.96, 56.47, 54.82, 44.93. LRMS $(M + H)^+$(ESI$^+$) 482.19 $[M + H]^+$(calcd for $C_{26}H_{23}F_4N_5H^+$ 482.20).

1-((1-(4-Fluorophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4,4-dimethyl-1,4-azasilinane (40). White solid (yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.56 (d, 2H), 7.33 (d, 2H), 7.28 (m, 2H), 7.05 (m, 2H), 6.62 (s broad, 1H), 3.74 (s, 2H), 2.86 (m, 4H), 0.84 (m, 4H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 162.83, 160.61, 142.13, 133.89, 130.54, 130.23, 130.04, 129.76, 128.81, 127.14, 127.06, 125.59, 125.14, 116.07, 115.89, 108.72, 55.52, 52.43, 13.45, -3.07. LRMS $(M + H)^+$(ESI$^+$) 448.22 $[M + H]^+$(calcd for $C_{23}H_{25}F_4N_3SiH^+$ 448.18).

4-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (41). White solid (yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.72 (d, 2H), 7.47 (d, 2H), 6.30 (s broad, 1H), 4.00 (m, 1H), 3.78 (m, 4H), 3.66 (s broad, 2H), 2.61 (m, 4H), 2.04 (m, 2H), 1.86 (m, 4H), 1.27 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 141.95, 134.90, 130.51, 130.18, 129.23, 125.65, 106.31, 66.75, 57.91, 55.88, 55.53, 33.31, 25.62, 25.02. LRMS $(M + H)^+$(ESI$^+$) 394.21 $[M + H]^+$(calcd for $C_{21}H_{26}F_3N_3OH^+$ 394.21).

4-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)thiomorpholine (42). Yellow solid (yield 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.72 (d, 2H), 7.48 (d, 2H), 6.26 (s, 1H), 4.00 (m, 1H), 3.68 (s, 2H), 2.84-2.69 (m, 8H), 2.04 (m, 2H), 1.87 (m, 5H), 1.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 141.93, 134.89, 129.30, 125.64, 122.66, 120.49, 116.59, 106.56,

57.90, 56.55, 54.26, 33.32, 27.88, 25.56, 25.02. LRMS $(M + H)^+(ESI^+)$ 410.19 $[M + H]^+$(calcd for $C_{21}H_{26}F_3N_3SH^+$ 410.19).

1-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (43). White solid (yield 75%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.71 (d, 2H), 7.48 (d, 2H), 6.26 (s, 1H), 3.99 (m, 1H), 3.60 (s, 2H), 3.33 (s, 3H), 3.22 (m, 1H), 2.85 (m, 2H), 2.24 (m, 2H), 2.06-1.85 (m, 8H), 1.64 (m, 3H), 1.25 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 141.95, 134.90, 130.51, 130.18, 129.23, 125.65, 106.31, 57.91, 55.88, 55.53, 51.04, 33.31, 30.78, 29.71, 25.62, 25.02. LRMS $(M + H)^+(ESI^+)$ 422.25 $[M + H]^+$(calcd for $C_{23}H_{30}F_3N_3OH^+$ 422.24).

1-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)piperidine (44). White solid (yield 70%). ^1H NMR (400 MHz, $DMSOd_6$): δ ppm= 7.84 (d, 2H), 7.63 (d, 2H), 6.27 (s, 1H), 4.03 (m, 1H), 3.38 (s, 2H), 2.34 (m, 3H), 1.86 (m, 4H), 1.75 (m, 2H), 1.59 (m, 1H), 1.47 (m, 4H), 1.35 (m, 2H), 1.28-1.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 141.93, 134.89, 129.30, 125.64, 122.66, 120.49, 116.59, 106.56, 57.90, 56.55, 54.26, 33.32, 25.73, 25.56, 25.02, 24.17. LRMS $(M + H)^+(ESI^+)$ 392.25 $[M + H]^+$(calcd for $C_{22}H_{28}F_3N_3H^+$ 392.23).

***Tert*-butyl 4-((1-cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methyl)piperazine-1-carboxylate (45).** White solid (yield 86%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 7.71 (d, 2H), 7.48 (d, 2H), 6.24 (s, 1H), 3.99 (m, 1H), 3.61 (s, 2H), 3.46 (m, 4H), 2.49 (m, 4H), 2.04 (m, 2H), 1.87 (m, 4H), 1.65 (m, 1H), 1.45 (s, 9H), 1.27 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 154.82, 142.04, 134.79, 130.55, 130.22, 129.90, 129.23, 125.75, 125.72, 125.68, 125.64, 125.34, 122.63, 106.37, 79.59, 57.96, 55.94, 52.76, 33.32, 29.72, 28.44, 25.60, 25.01. LRMS $(M + H)^+(ESI^+)$ 493.27 $[M + H]^+$(calcd for $C_{26}H_{35}F_3N_4O_2H^+$ 493.28).

1-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methyl)-4-(pyridin-2-yl)piperazine (46). White solid (yield 87%). ^1H NMR (400 MHz, $CDCl_3$): δ ppm= 8.18 (d, 1H), 7.72 (d, 2H), 7.47 (m, 3H), 6.62 (m, 2H), 6.27 (s, 1H), 4.01 (m, 1H), 3.67 (s, 2H), 3.58 (t, 4H), 2.68 (t, 4H), 2.06 (m, 2H), 1.89 (m, 4H), 1.69 (m, 2H), 1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm=

159.56, 149.06, 147.97, 147.26, 143.55, 137.41, 130.52, 130.41, 128.99, 128.71, 122.66, 113.19, 107.16, 105.81, 57.50, 55.96, 52.65, 45.09, 33.88, 33.35, 25.66, 25.10, 23.92. LRMS $(M + H)^+(ESI^+)$ 470.27 $[M + H]^+$(calcd for $C_{26}H_{30}F_3N_5H^+$ 470.25).

1-((1-Cyclohexyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4,4-dimethyl-1,4-azasilinane (47). White solid (yield 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.71 (d, 2H), 7.48 (d, 2H), 6.28 (s, 1H), 3.99 (m, 1H), 3.68 (s, 2H), 2.80 (m, 4H), 2.06 (m, 2H), 1.87 (m, 4H), 1.27 (m, 4H), 0.85 (m, 4H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 148.91, 141.84, 134.98, 130.52, 130.41, 129.96, 129.18, 125.58, 122.66, 106.25, 57.87, 55.81, 52.36, 33.31, 25.62, 25.03, 13.56, -3.09. LRMS $(M + H)^+(ESI^+)$ 436.23 $[M + H]^+$(calcd for $C_{23}H_{32}F_3N_3SiH^+$ 436.24).

4-((1-Isopropyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)morpholine (48). White solid (yield 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.71 (d, 2H, *J*= 8.10 Hz), 7.48 (d, 2H), 6.25 (s, 1H), 4.45 (sept, 1H), 3.74 (m, 4H), 3.61 (s, 2H), 2.55 (m, 4H), 1.46 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 148.01, 141.98, 134.81, 130.59, 130.27, 129.28, 125.72, 125.69, 125.65, 125.61, 125.31, 122.61, 106.40, 66.98, 56.33, 53.48, 50.18, 22.92. LRMS $(M + H)^+(ESI^+)$ 354.18 $[M + H]^+$(calcd for $C_{18}H_{22}F_3N_3OH^+$ 354.18).

1-((1-Isopropyl-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-yl)methyl)-4-methoxypiperidine (49). White solid (yield 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm= 7.70 (d, 2H), 7.49 (d, 2H), 6.26 (s, 1H), 4.46 (sept, 1H), 3.61 (s, 2H), 3.33 (s, 3H), 3.23 (m, 1H), 2.86 (m, 2H), 2.25 (m, 2H), 1.95 (m, 2H), 1.63 (m, 2H), 1.46 (d, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm= 148.01, 141.98, 134.81, 130.59, 130.27, 129.28, 125.72, 125.69, 125.65, 125.61, 125.31, 122.61, 106.40, 57.90, 56.33, 53.48, 50.18, 30.63, 22.92. LRMS $(M + H)^+(ESI^+)$ 382.21 $[M + H]^+$(calcd for $C_{20}H_{26}F_3N_3OH^+$ 382.21).

UPLC-MS analysis

UPLC-MS involved the following: Waters Acquity UPLC system coupled to a Waters TQD ESI mass spectrometer and Waters TUV detector. A Waters Acquity UPLC BEH C18 1.7 μm, 3 mm × 50 mm column was used. Method involved the following: Acetate NH_4 25mM + 10% ACN at pH 6.6 /ACN, 0.0-0.2 min 99.9: 0.1, 0.2-1.0 min 10:90, 1.0-1.8 min 10:90, 1.9-2.0 min 99.9:0.1 at temperature 40ºC. The UV detection was an averaged signal from wavelength of 210 nm to 400 nm. The quasi-molecular ions $[M+H]^+$ were detected.

Biological assays

MIC determination. The measurement of the minimum inhibitory concentration (MIC) against *M. tuberculosis* strains for each tested compound was performed in 96-well flat-bottom, polystyrene microtiter plates in a final volume of 100 μl. Ten two-fold drug dilutions in neat DMSO starting at 50 μM were performed. Drug solutions were added to Middlebrook 7H9 medium (Difco). The inoculum was standardized to approximately $16e^7$ cfu/ml and diluted 1 in 100 in Middlebrook 7H9 broth (Difco). This inoculum (100 μl) was added to the entire plate but G-12 and H-12 wells were used as blank controls. All plates were placed in a sealed box

to prevent drying out of the peripheral wells and incubated at 37 °C without shaking for six days. A Resazurin solution was prepared by dissolving one tablet of Resazurin (Resazurin Tablets for Milk Testing; Ref 330884Y' VWR International Ltd) in 30 ml of sterile PBS (phosphate buffered saline). Of this solution, 25 µl were added to each well. Fluorescence was measured (Spectramax M5 Molecular Devices, Excitation 530 nm, Emission 590 nm) after 48 hours to determine the MIC value.

HepG2 cytotoxicity assay. HepG2 cells were cultured using Eagle's MEM supplemented with 10% heat-inactivated FBS, 1% NEAA and 1% penicillin/streptomycin. Prior to addition of the cell suspension, 250 nl of test compounds per well were pre-dispensed in TC-treated black clear-bottomed 384 well plates (Greiner, cat.# 781091) with an Echo 555 instrument. After that, 25 µl of HepG2 (ATCC HB-8065) cells (~3000 cells/well) grown to confluency in Eagle's MEM supplemented with 10% heat-inactivated FBS, 1% NEAA and 1% Penicillin/Streptomycin were added to each well with the reagent dispenser. Plates were allowed to incubate at 37 °C with 20% O2 and 5% CO2 for 48 h. After the incubation period (48h), the plates were equilibrated to room temperature before proceeding to develop the luminescent signal. ATP levels measured with CellTiter Glo kit (Promega) were used as cell viability read-out. 25 µl of CellTiter Glo substrate dissolved in the buffer was added to each

well. Plates were incubated at room temperature for 10 minutes for stabilization of luminescence signal and read on View Lux with excitation and emission filters of 613 and 655 nm, respectively.

Generation of spontaneous resistant mutants, genome sequencing and assembly. Mycobacterial strains were grown on 7H11 agar (Becton Dickinson) supplemented with 0.5% glycerol and 10% OADC. Mycobacterial cultures were usually grown at 37 °C without shaking for about three weeks. Compounds **6** and **22** were dissolved in dimethyl sulfoxide. *M. tuberculosis* resistant mutants to compounds **6** and **22** were isolated by plating about 10^{10} cells from late exponential wild-type cultures onto solid media containing different concentrations of each compound, ranging from 5 to 10-fold MIC for the wild-type strain. Plates were incubated at 37 °C for 4 weeks. The MIC of compounds **6** and **22** for the isolated resistant mutants was evaluated three times. DNA was extracted by the CTAB-lysozyme method.[1] Samples were sequenced on an Illumina HiSeq 4000 with a read length of 150 bp in paired-end mode. Genome sequences were assembled by a comparative-assembly method.[2] Reads were mapped to the genome sequence of *M. tuberculosis* H37Rv (NC_000962.2) as a reference genome using BWA.[3] Then, regions with indels or clusters of single nucleotide polymorphisms (SNPs) were identified and repaired by building local

contigs from overlapping reads spanning such regions. Genome sequences were aligned using MUMMER v3.[2,4] SNPs were extracted according to the following criteria: coverage ≥ 10x (covered by at least 10 reads) with purity ≥ 70% (conversion to non-reference nucleotide). SNPs in repetitive regions were filtered out (repetitive regions were defined as sites for which an overlapping 35 bp window matches elsewhere in the genome with at most 2 mismatches).

DMPK

Chrom log DpH7.4 determinations. 10 ml of 10 mM DMSO stock solutions were diluted to 750 ml with octanol saturated pH 7.4 phosphate buffer and 160 ml buffer saturated octanol

in a 96 well deep well block. Block were sealed and inverted for 3 sets of 50 inversions, then centrifuged at 300 g for 20 min. Both phases were then quantified using generic gradient UV-HPLC.

Artificial membrane permeability determinations. Membrane permeability was determined following published protocols.[5]

% of binding to human serum albumin (HSA). The assay uses an Agilent 1100 HPLC, a Chromtech HSA column 50x3.0mm 5 micron, 50mM ammonium acetate (pH7.4) as mobile phase A and 2-propanol as mobile phase B. 10 µl of 10mM DMSO stock solution of sample is diluted with 990 µl of 50:50 mobile phases A and B. The flow rate is 1.8mL/min at 30 °C with gradient of 0-3min 0-30%B, 3-5min 30%B, 5-5.1min 30-0% B, 5.1-6min 0% B. Injection volume 10 µl monitoring at 215 and 254nm. Retention time is then related to % HSA binding by relation to a set of 9 control standards with known binding affinities.

Kinetic solubility. 5ml of 10mM DMSO stock solution is diluted to 100µl with pH7.4 phosphate buffered saline, equilibrated for 1 hour at room temperature and filtered through Millipore Multiscreen HTS-PCF filter plates (MSSL BPC). The filtrate is quantified by suitably calibrated Charged Aerosol Detector.[6] The upper limit of the solubility is 500 µM when working from 10 mM DMSO stock solution.

Solubility determination in FaSSIF. Solids were processed in duplicate with 1 mg of material weighed into two separate vials (each receives 1mg + 20%). One set of vials was diluted with 1 ml of DMSO and sonicated by a Covaris acoustic mixer; this set was used as reference set. Second set of vials was diluted with 1 ml of FaSSIF buffer and mixed on a plate shaker for four hours at room temperature. At the four-hour time-point, DMSO and FaSSIF sample solutions were transferred from their vials to a Greiner V-bottom 96-well plate and a Millipore 96-well filter plate, respectively, by a disposable-tip liquid handler. The filter plate containing the FaSSIF samples was positioned over a separate Greiner V-bottom-96-well plate and centrifuged at 2000 rpm for 5-10 minutes to remove any remaining particulate from the solution. The plates were covered with a pierceable membrane and loaded onto a Water Acquity UPLC-MS. The samples were injected onto a Waters BEH C18 column (1.7 M, 2.1 x 50 mm) and subjected to mobile phase gradient (H2O/ACN buffered with formic acid) over 1.8 minutes. The sample components were measured by UV absoption via a photodiode array detector.

Human ether-a-go-go-related gene (hERG) activity determination. The hERG inhibition profile of compounds was determined as previously described.[7]

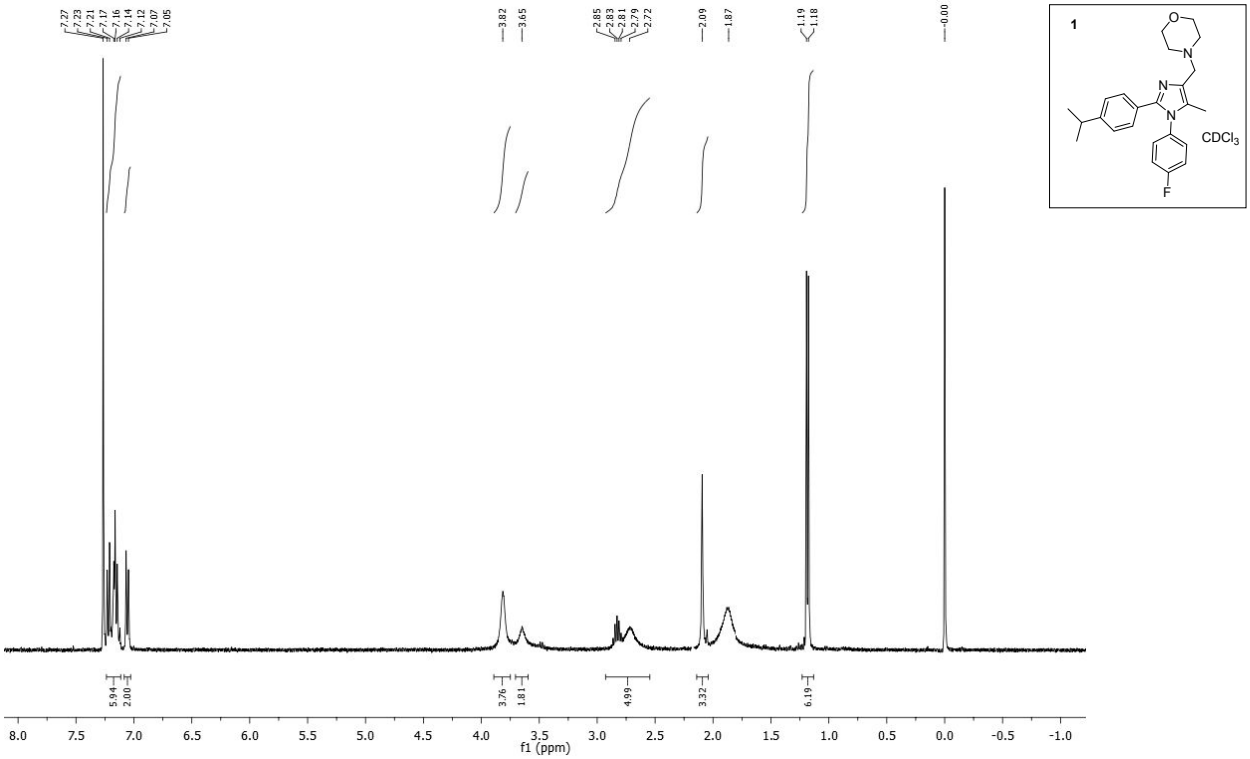
Intrinsic clearance (CLint) in microsomes. Test compound (0.5 μM) was incubated with male CD1 mouse and human liver microsomes (0.5 mg/mL 50 mM potassium phosphate buffer, pH7.4) and the reaction started with addition of excess NADPH). Immediately, at time zero, and serial times up to 30 minutes an aliquot of the incubation mixture was removed and mixed with acetonitrile to stop the reaction. Internal standard was added to all samples, the samples centrifuged to sediment precipitated protein and the plates then sealed prior to UPLCMSMS analysis. Metabolic stability expressed as a percentage of parent remaining is calculated using the peak area ratio (compound peak area/internal standard peak area) of the parent remaining after each incubation time (t=x) compared to time zero (t=0) of the incubation. Intrinsic clearance (Clint) was calculated from the half-life (t(1/2)) using the following equations: Clint (ml/min/g tissue) = (0.693/(t(1/2)) x (mL of incubation/mg microsomal protein) x (mg microsomal protein/gm liver).

In vivo studies.

Materials and Methods. All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare, and Treatment of Animals.

Specific pathogen-free, 8-10 week-old female C57BL/6 mice were purchased from Harlan Laboratories and were allowed to acclimate for one week. In brief, mice were intratracheally infected with 100.000 CFU/mouse (*M. tuberculosis* H37Rv strain). Products were administered for 4 consecutive days starting on day five after infection. Lungs were harvested on day nine (24 hours after the last administration). All lung lobes were aseptically removed, homogenized and frozen. Homogenates were plated in 10% OADC-7H11 medium for 14 days at 37 °C.

NMR Spectra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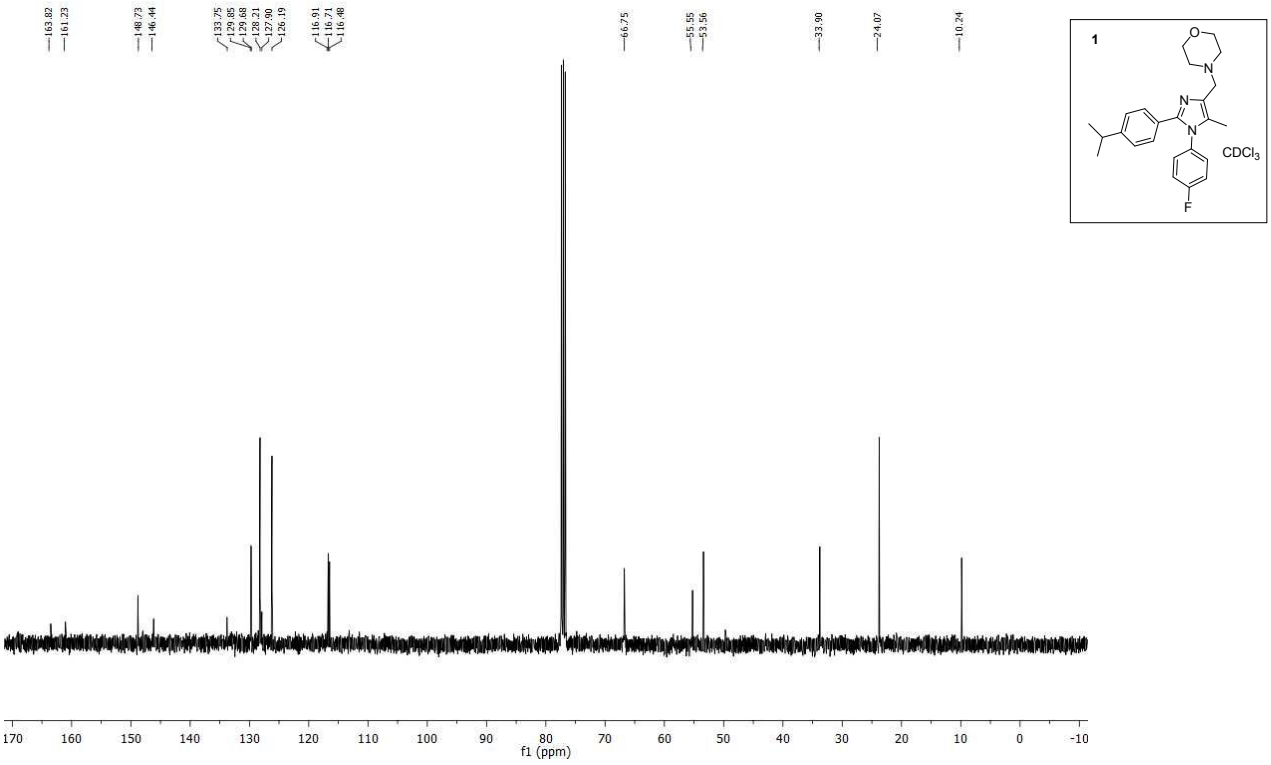
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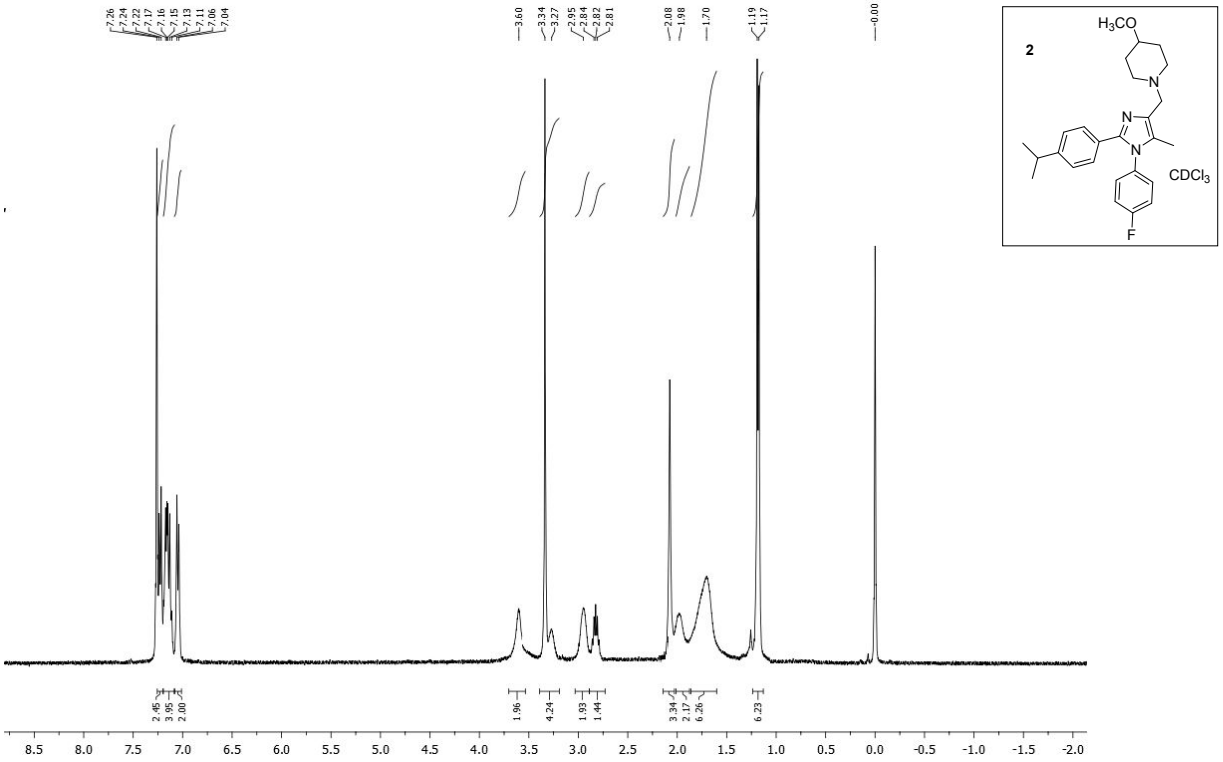
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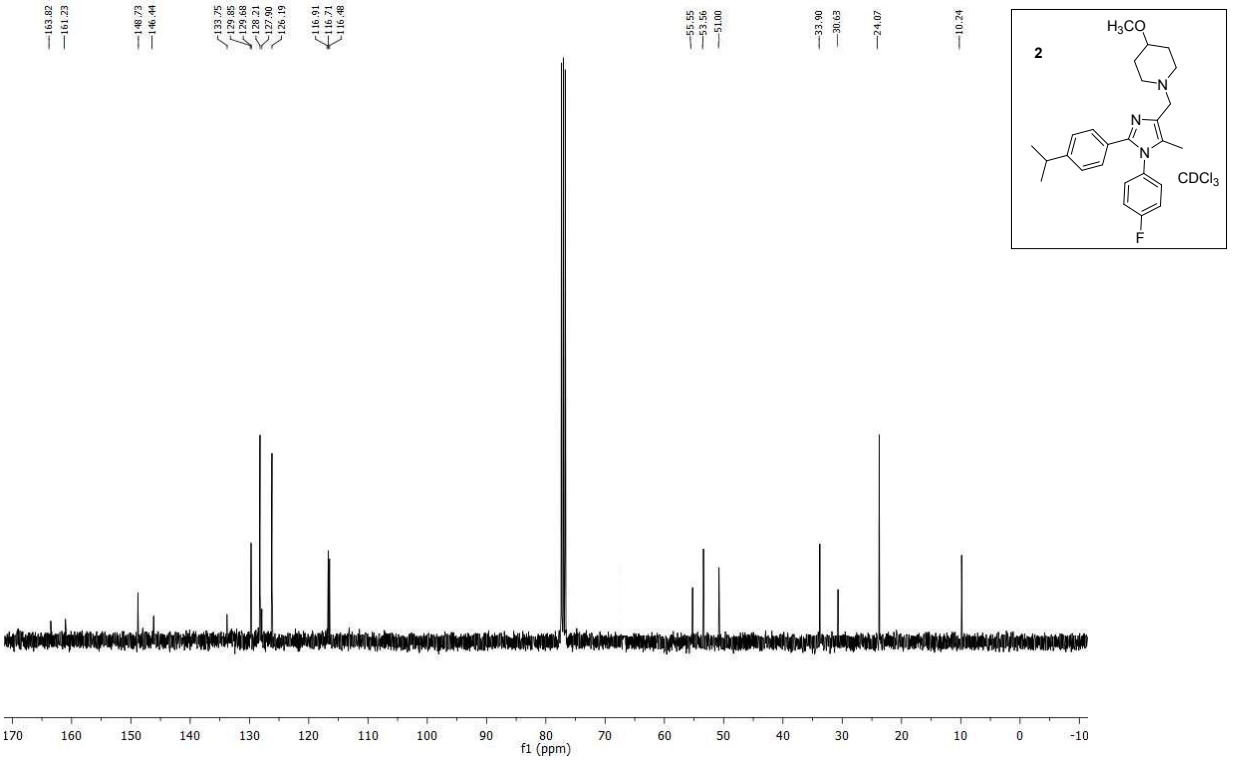
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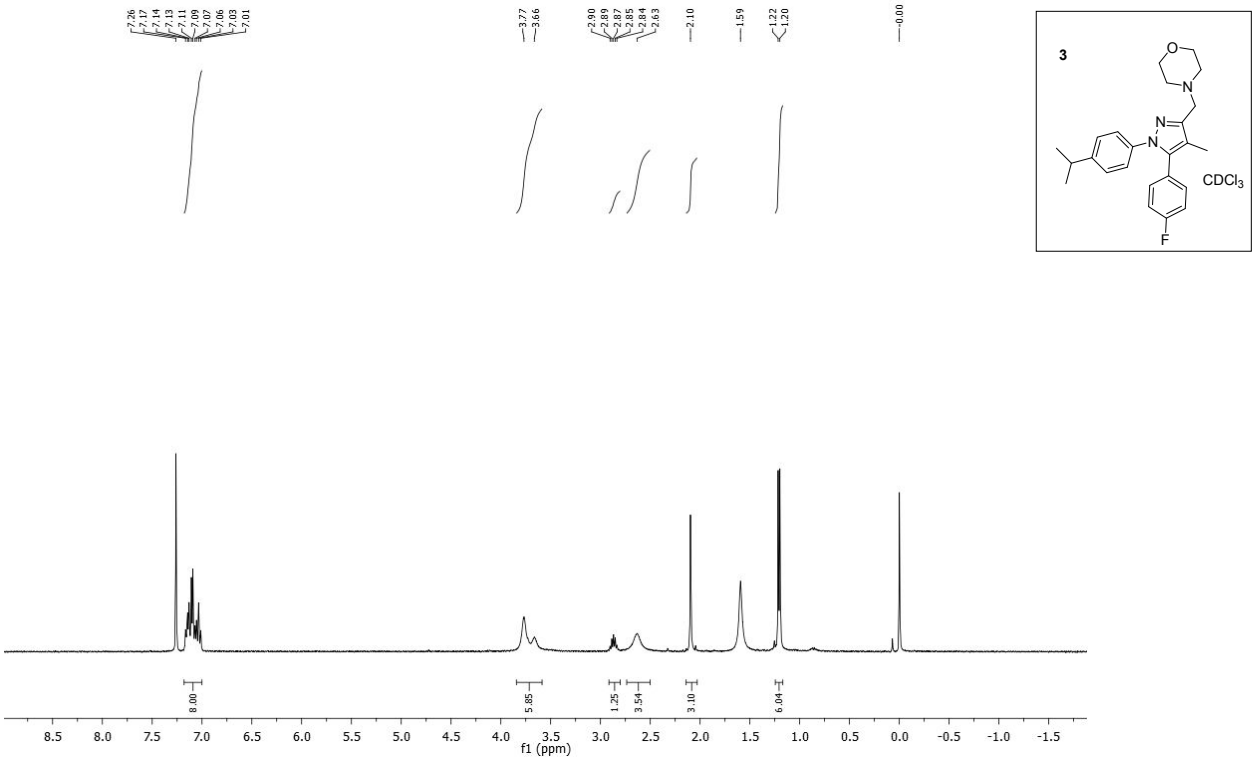
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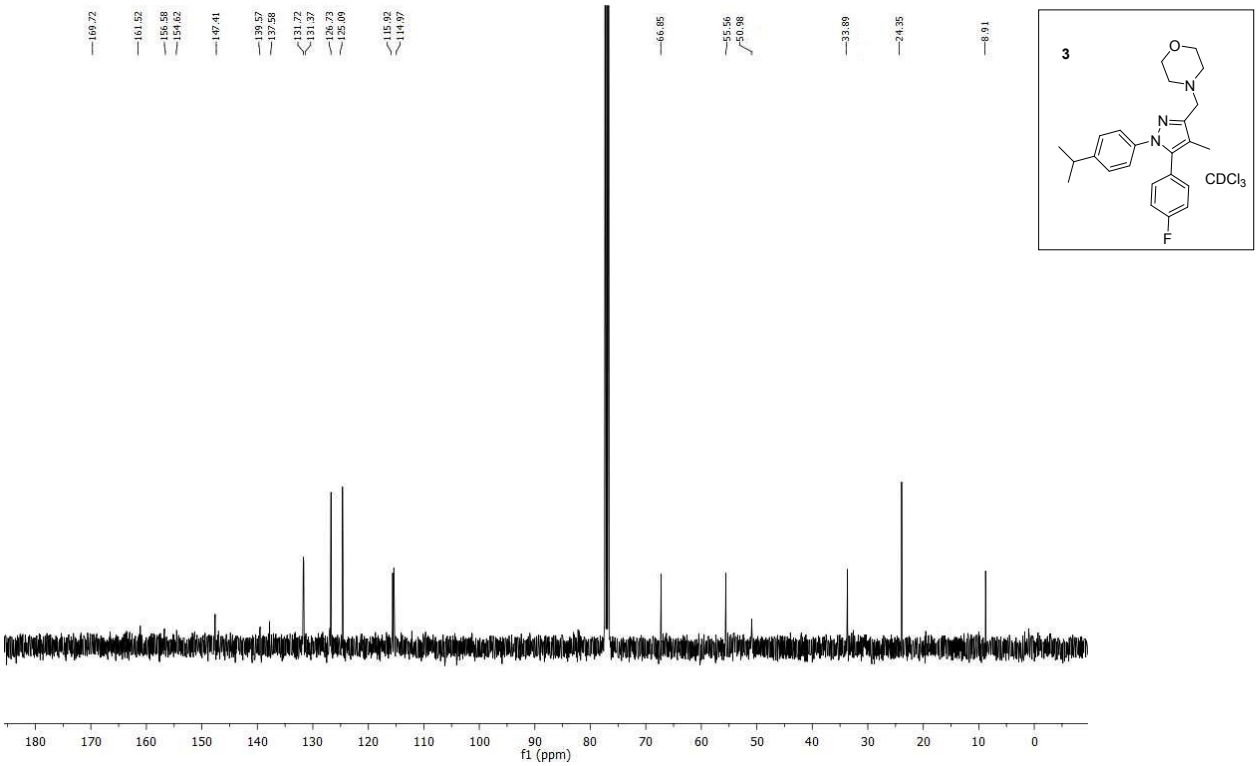
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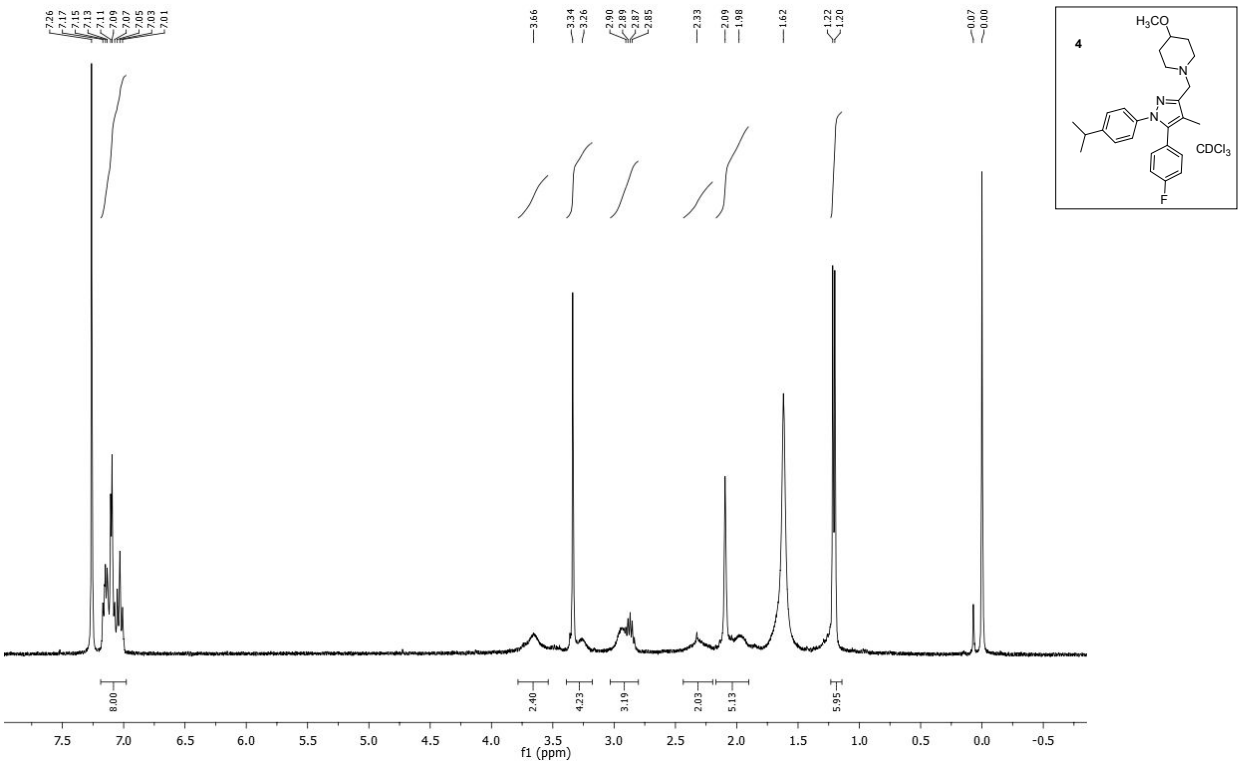
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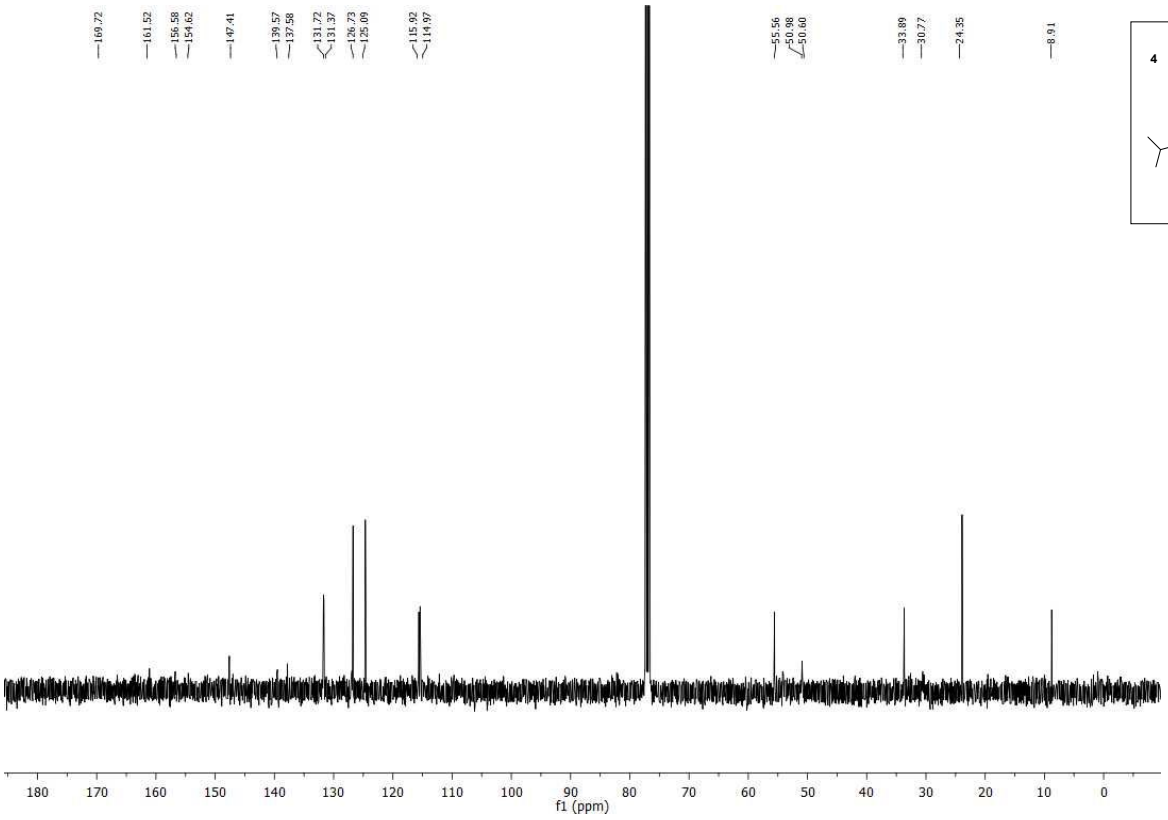
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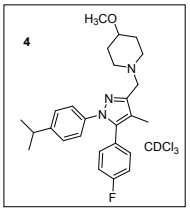
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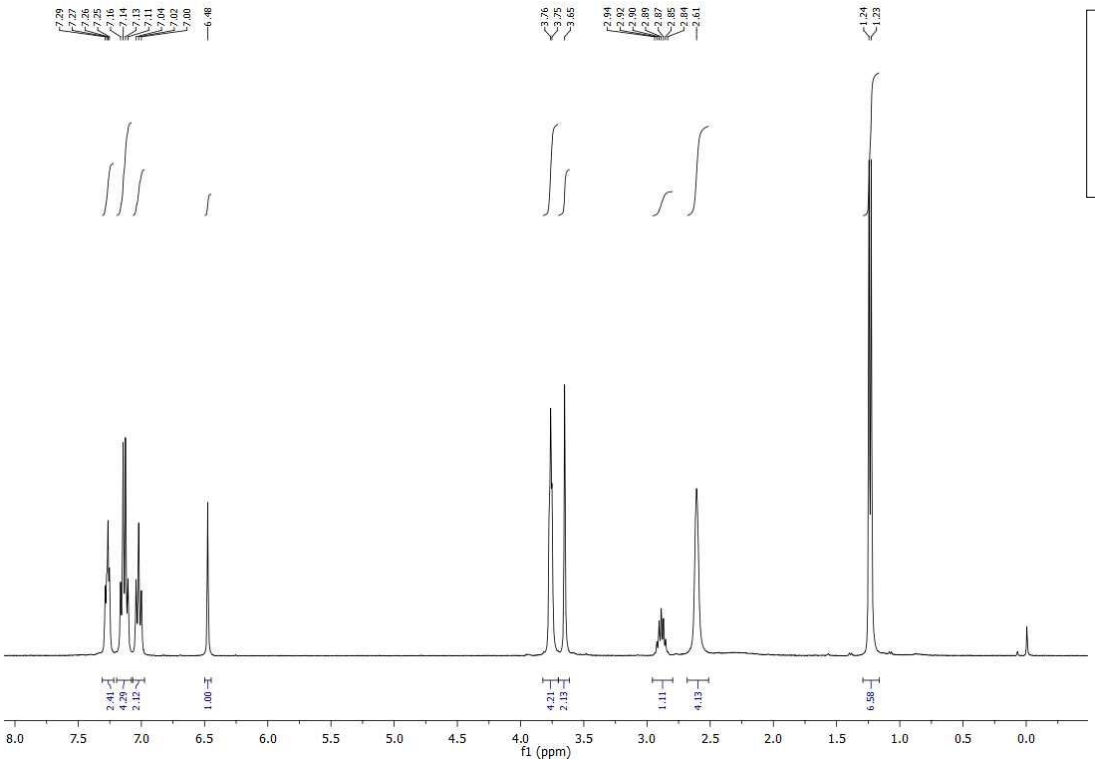
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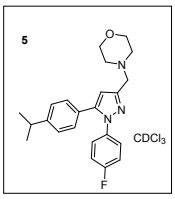
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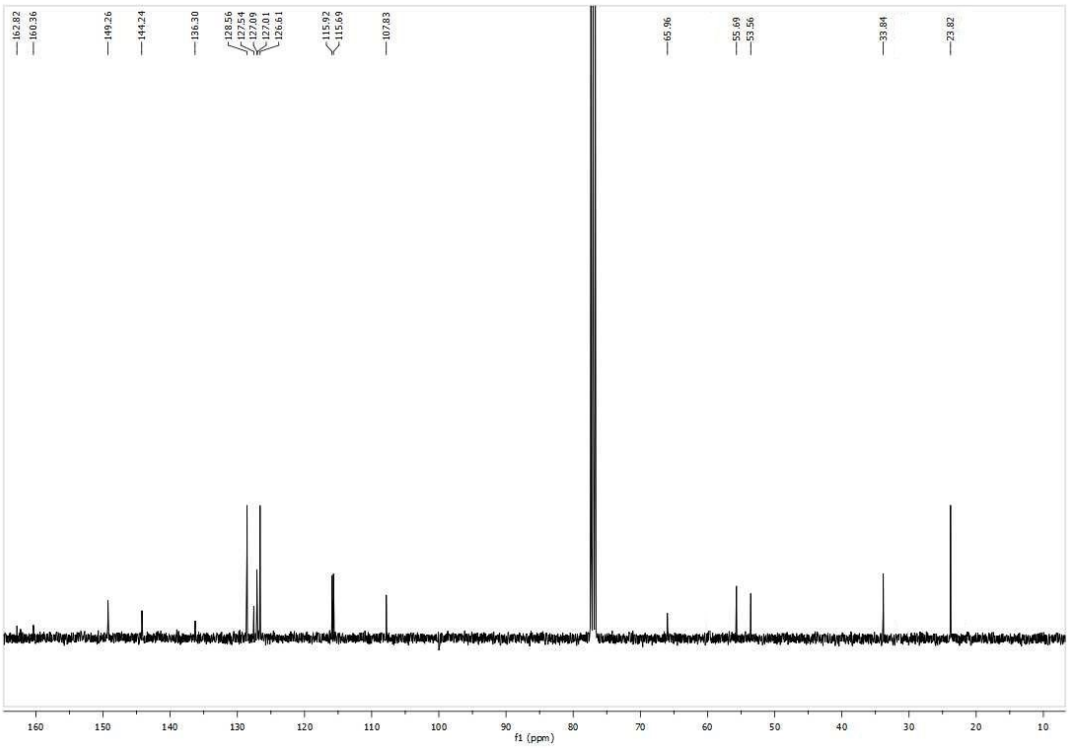
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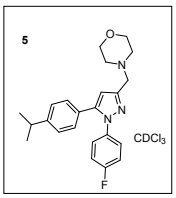
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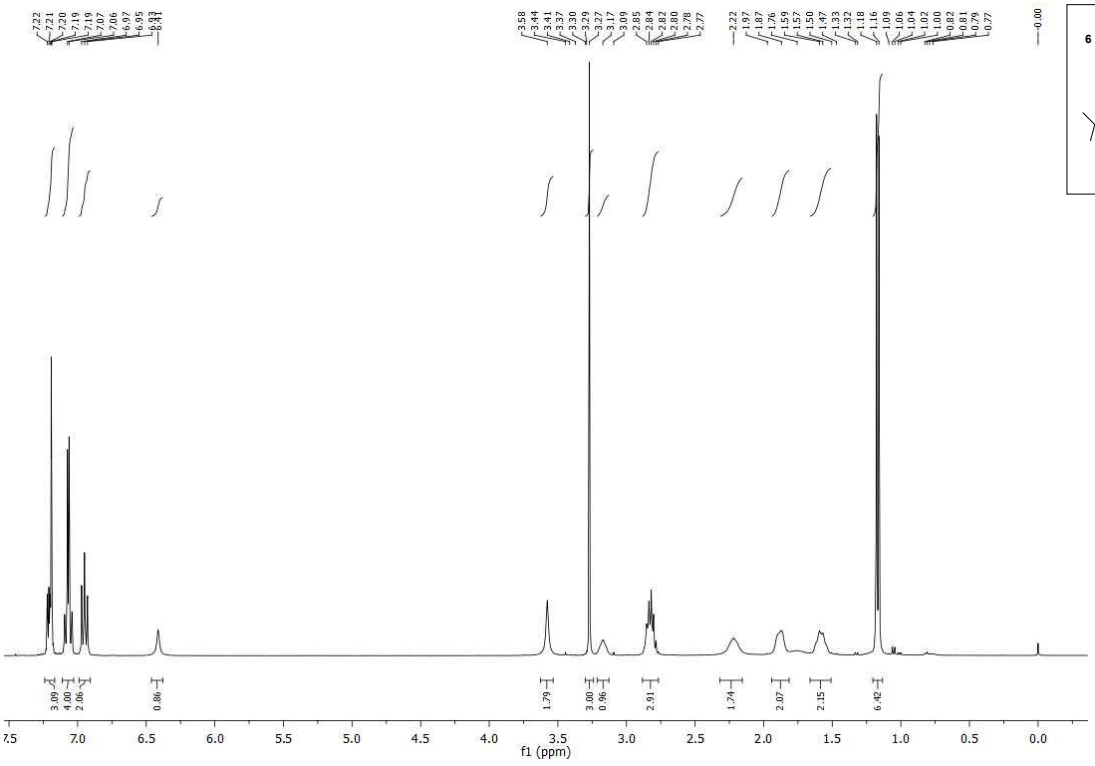
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7.06
6.97
6.95
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3.44
3.41
3.37
3.30
3.29
3.27
3.17
3.09
3.05
2.84
2.82
2.80
2.78
2.77
2.22
1.97
1.87
1.76
1.59
1.52
1.50
1.47
1.33
1.32
1.18
1.16
1.09
1.06
1.04
1.02
1.00
0.82
0.81
0.79
0.77
0.00
3.09
4.00
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1.79
3.00
0.96
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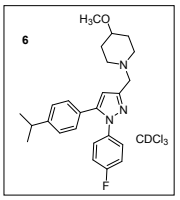
1.74
2.07
2.15
6.42
f1 (ppm)


6
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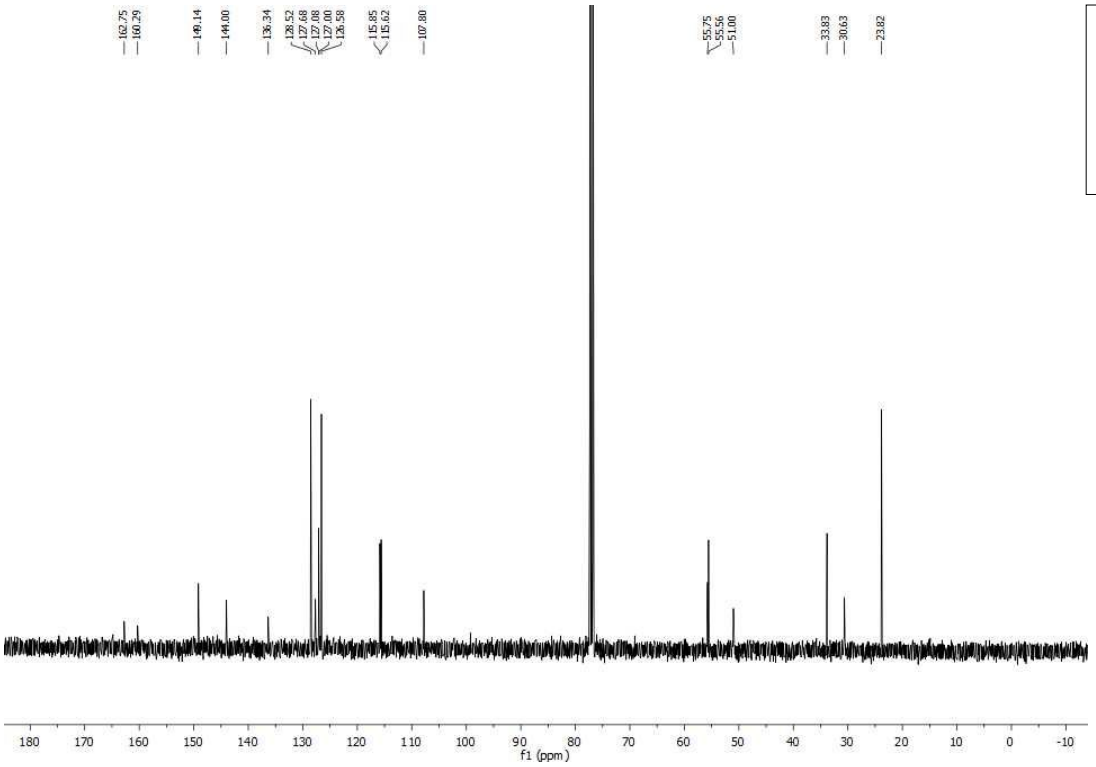
N
N
CDCl3
F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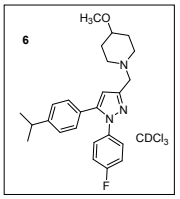
128.52
127.68
127.08
127.00
126.58
115.85
115.62
107.80
55.75
55.56
51.00
33.83
30.63
23.82
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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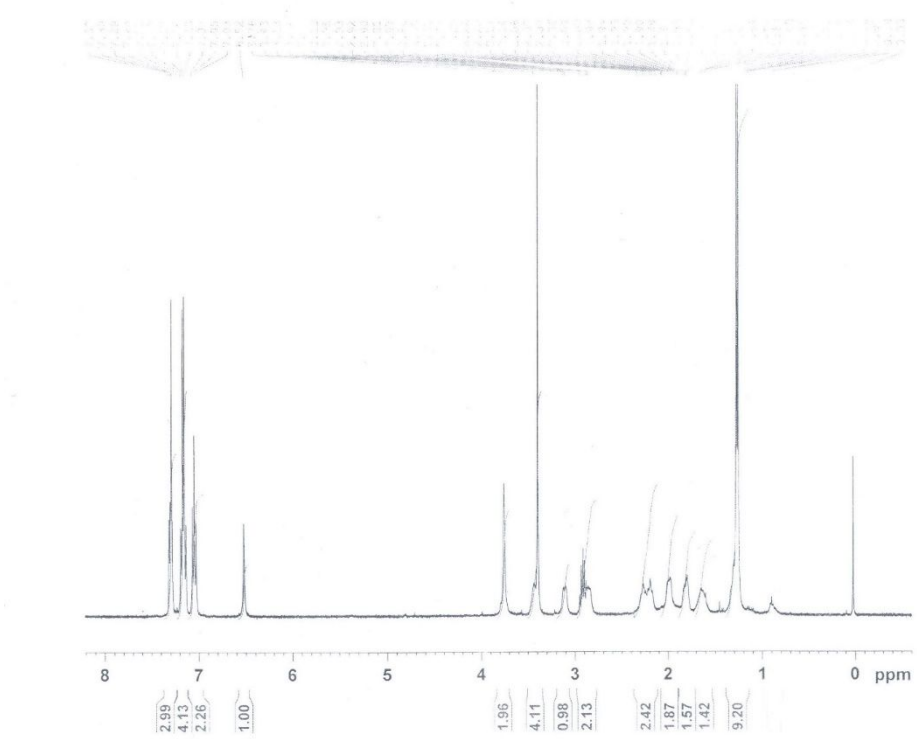
N
N
N
CDCl3
F


8 7 6 5 4 3 2 1 0 ppm
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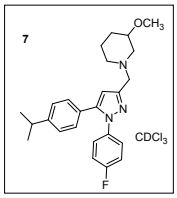
1.00
1.96
4.11
0.98
2.13
2.42
1.87
1.57
1.42
9.20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OCH3
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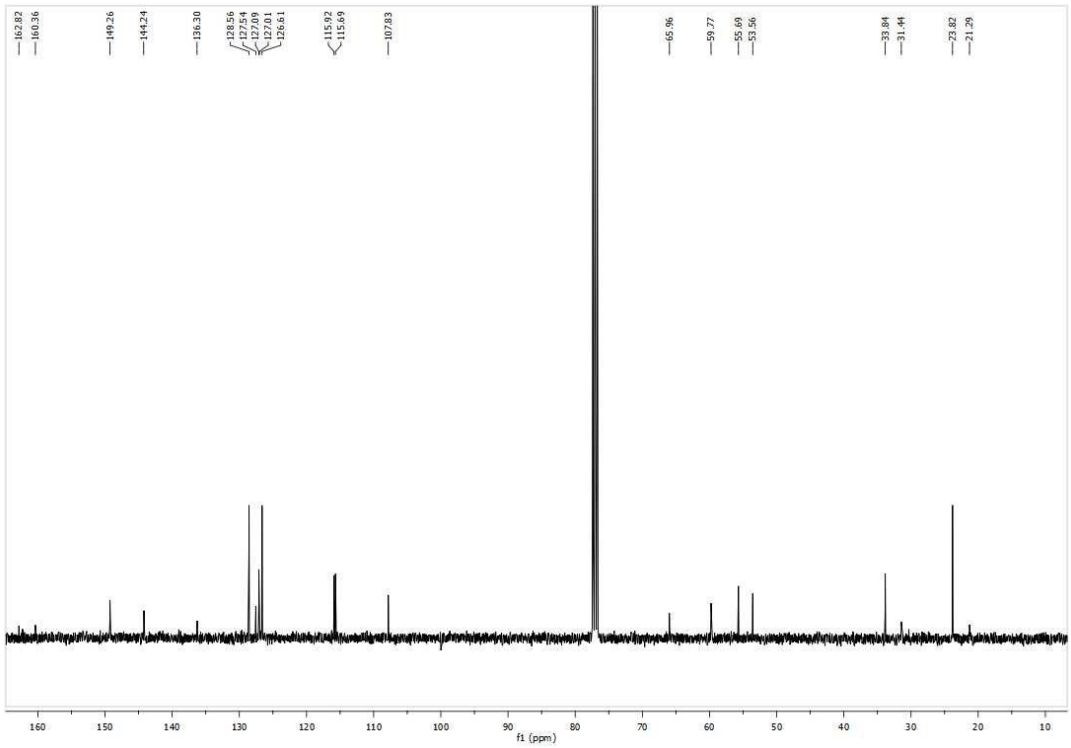
N
N
CDCl3
F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128.56
127.54
127.09
127.01
126.61
115.92
115.69
107.83
65.96
59.77
55.69
53.56
33.84
31.44
23.82
21.29
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140
130
120
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100
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80
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60
50
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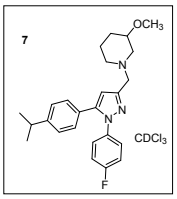
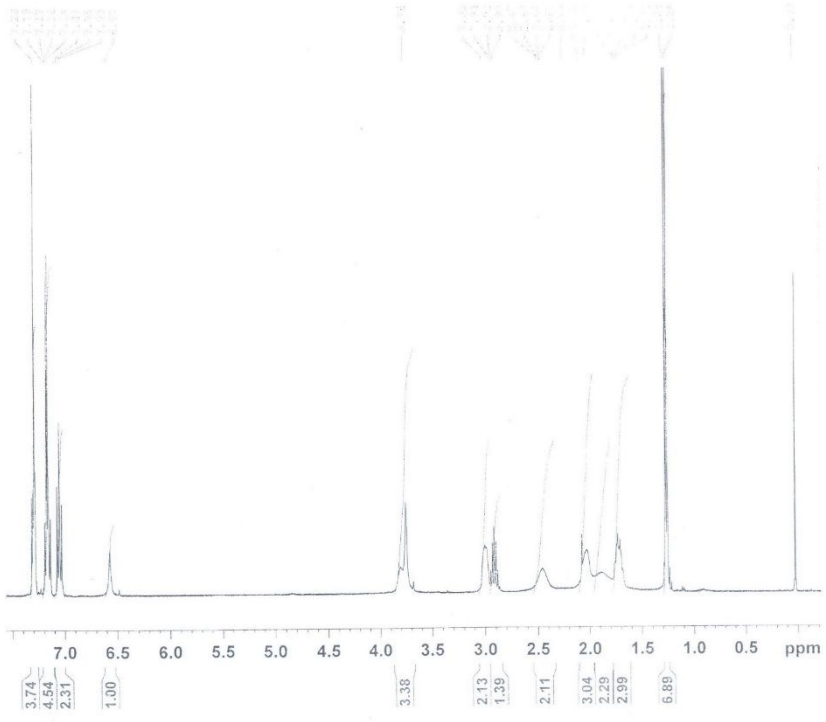
30
20
10
f1 (ppm)


7
OCH3
N
N
N
CDCl3
F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4.0
3.5
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2.5
2.0
1.5
1.0
0.5
ppm
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1.00
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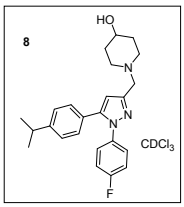
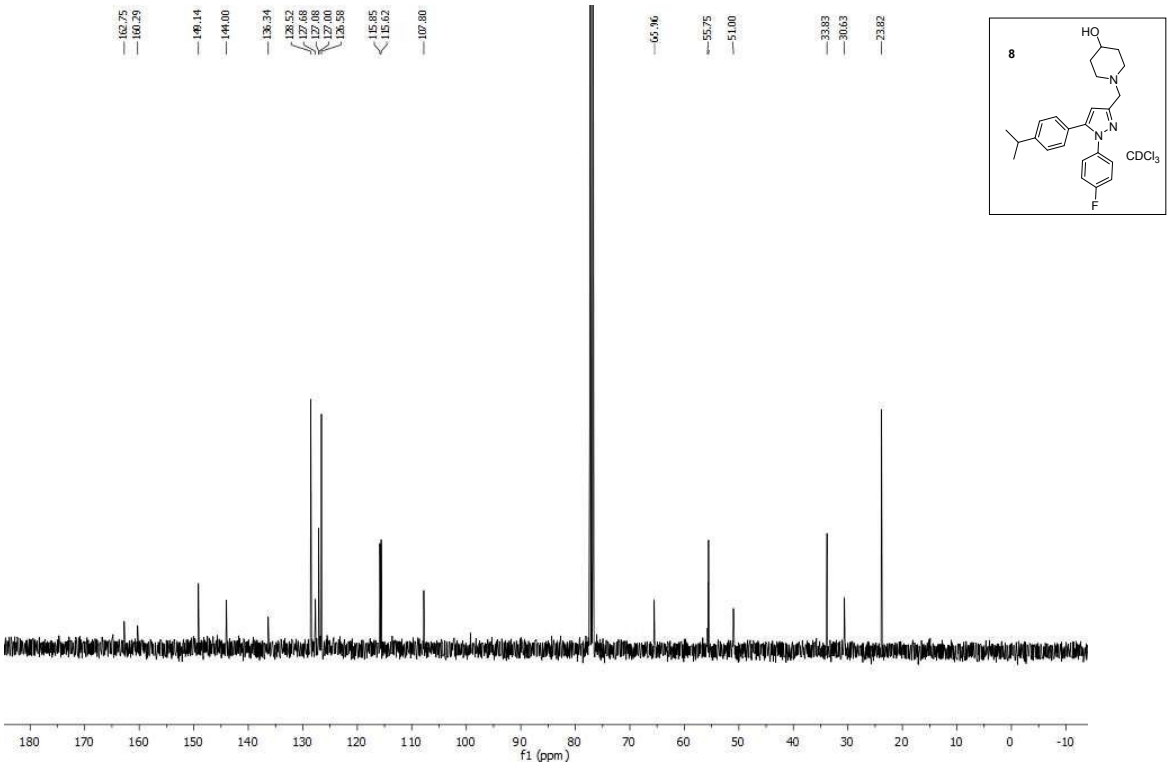
2.13
1.39
2.11
3.04
2.29
2.99
6.89


8
HO
N
N
N
CDCl3
F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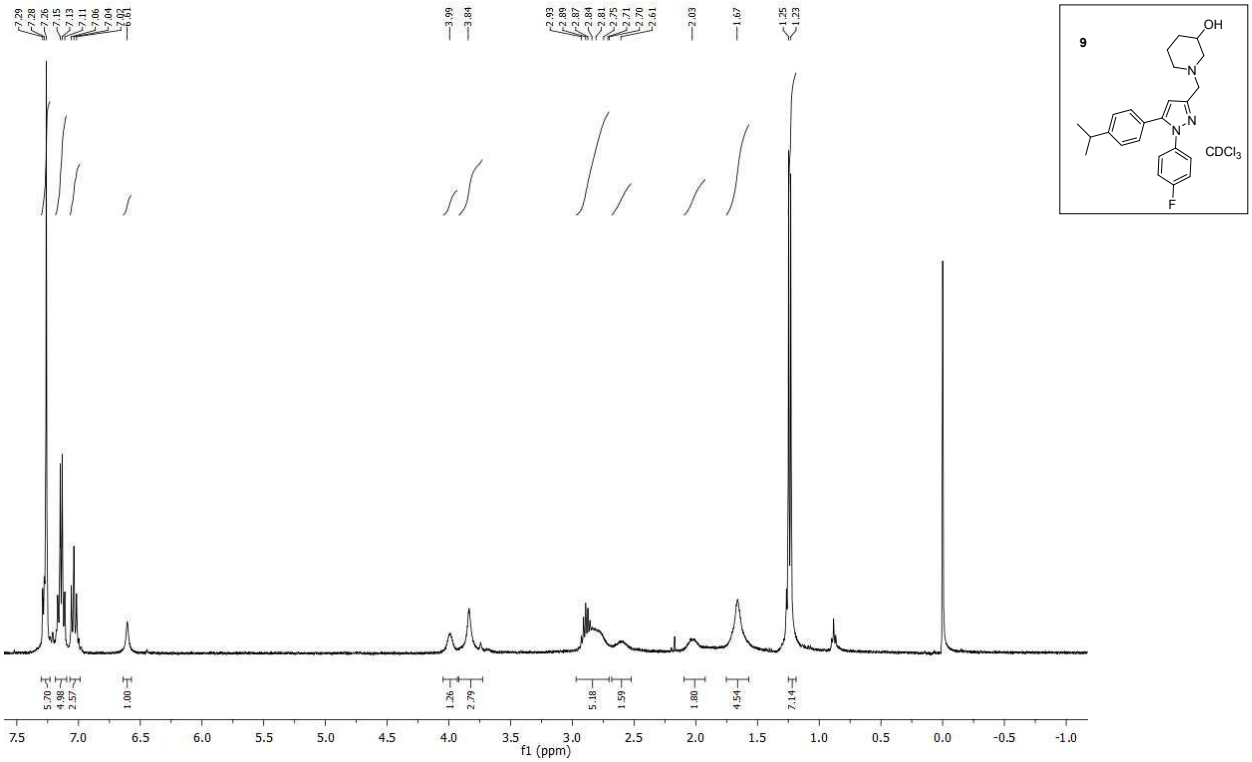
128.52
127.68
127.08
127.00
126.58
115.85
115.62
107.80
66.96
55.75
51.00
33.83
30.63
23.82
8
HO
N
N
N
CDCl3
F
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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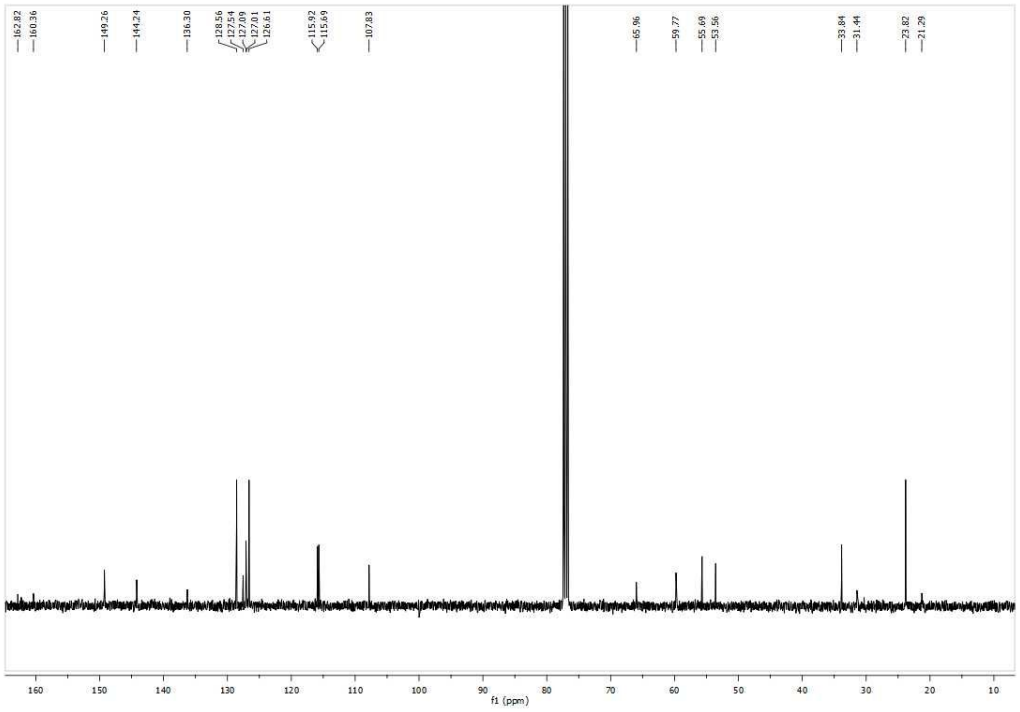
7.28
7.26
7.15
7.13
7.11
7.06
7.04
7.01
6.61
3.99
3.84
2.93
2.89
2.87
2.84
2.81
2.75
2.71
2.70
2.61
2.03
1.67
1.25
1.23
9
OH
N
N
N
CDCl3
F
5.70
4.98
2.57
1.00
1.26
2.79
5.18
1.59
1.80
4.54
7.14
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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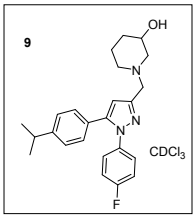
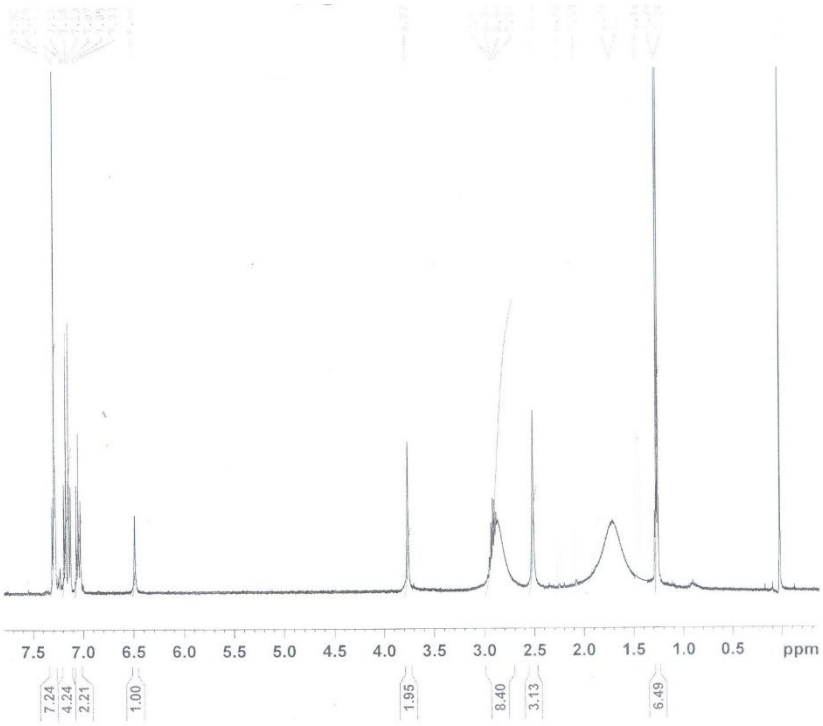
144.24
136.30
128.56
127.54
127.09
127.01
126.81
115.92
115.69
107.83
65.96
59.77
55.69
53.56
33.84
31.44
23.82
21.29
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


9
OH
N
N
N
CDCl3
F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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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1.00
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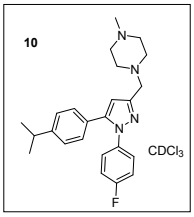
8.40
3.13
6.49


10
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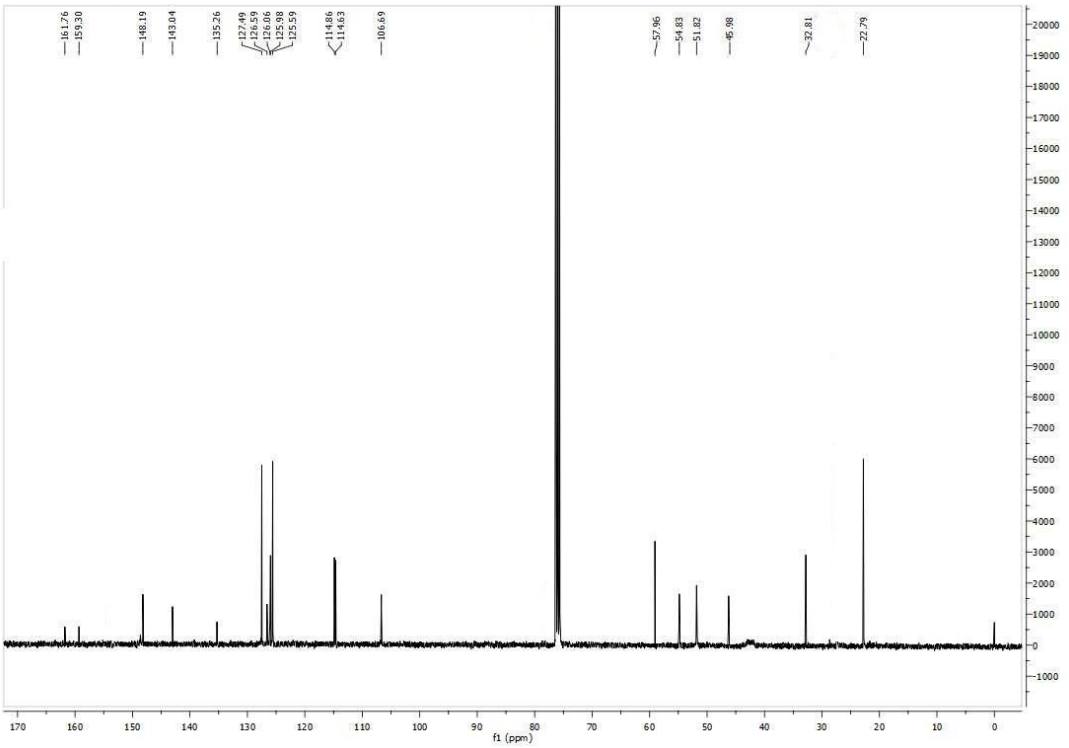
N
N
N
CDCl3
F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126.06
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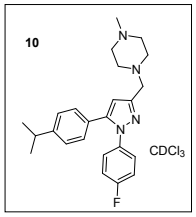
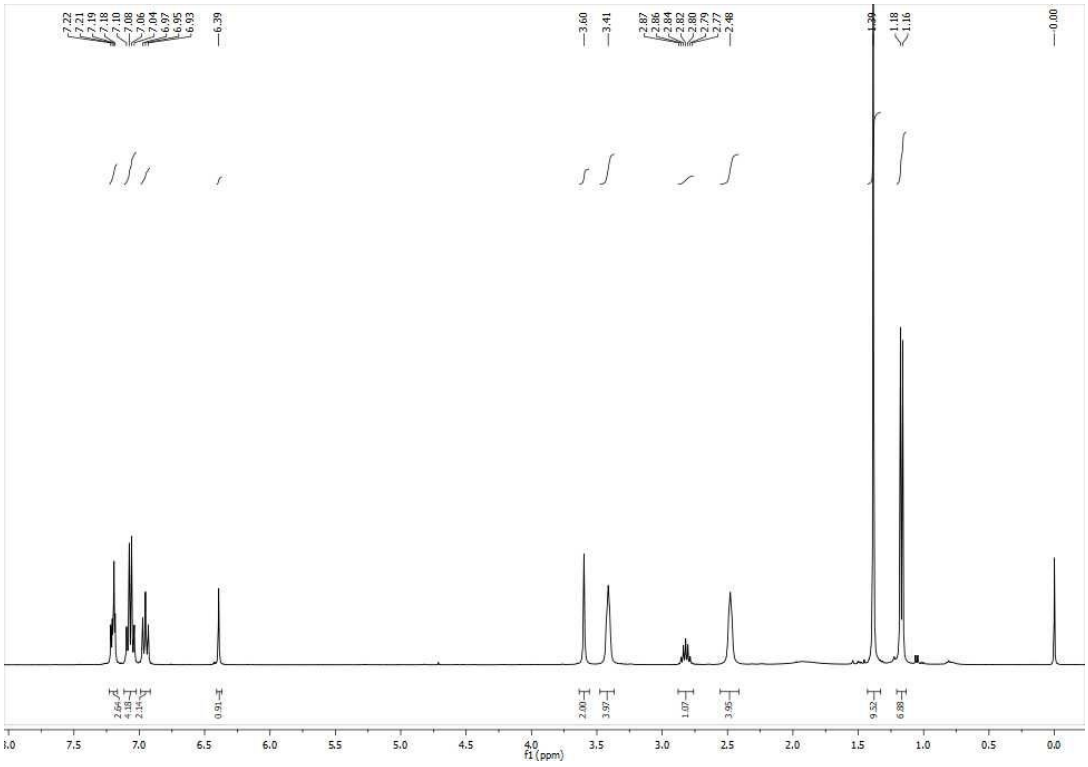
114.63
106.69
57.96
54.83
51.82
45.98
32.81
22.79
f1 (ppm)


10
CDCl3
F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7.21
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7.10
7.08
7.06
7.04
6.97
6.95
6.93
6.39
3.60
3.41
2.87
2.86
2.84
2.82
2.80
2.79
2.77
2.48
1.20
1.18
1.16
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2.14
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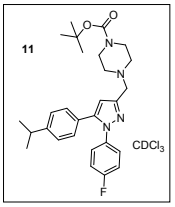
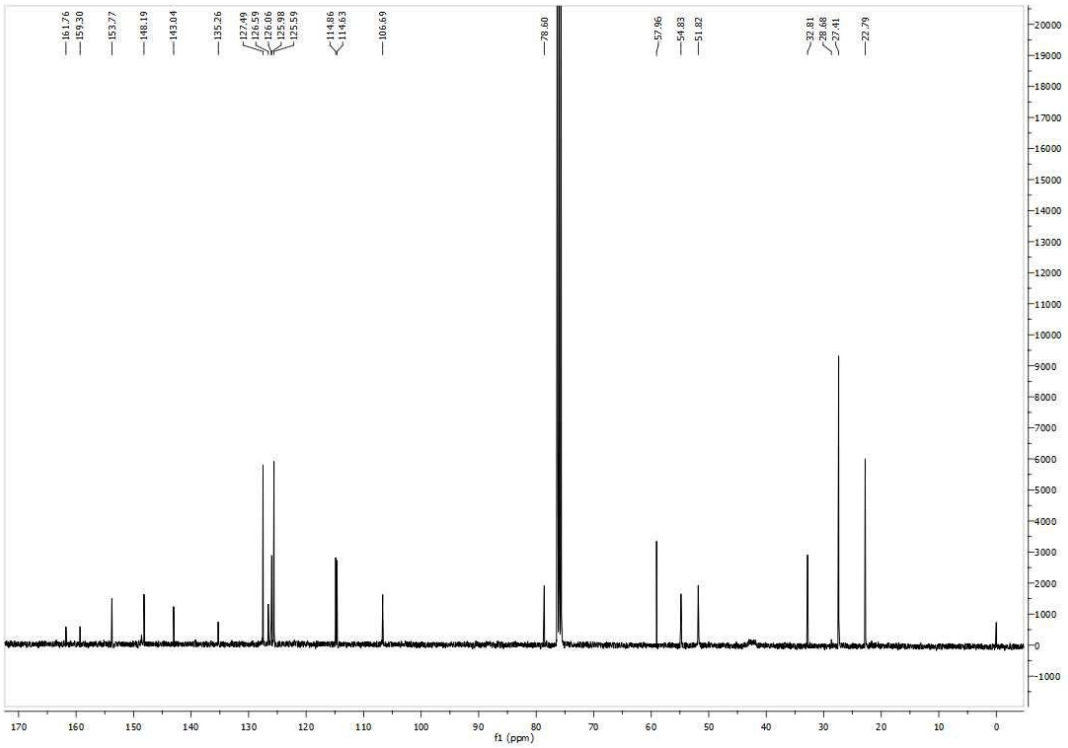
2.00
3.97
1.07
3.95
9.52
6.88
f1 (ppm)


11
CDCl3
F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159.30
153.77
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143.04
135.26
127.49
126.59
126.06
125.98
125.59
114.86
114.63
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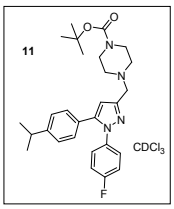
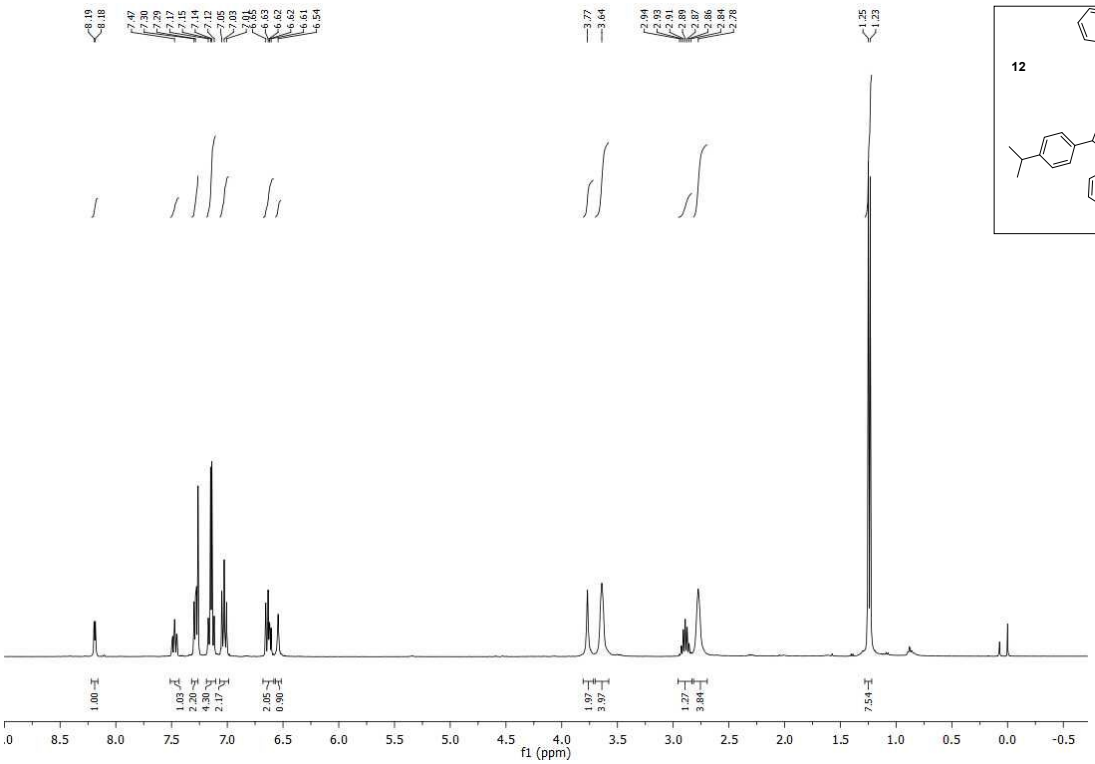
78.60
57.96
54.83
51.82
32.81
28.68
27.41
22.79
f1 (ppm)


11
CDCl3
F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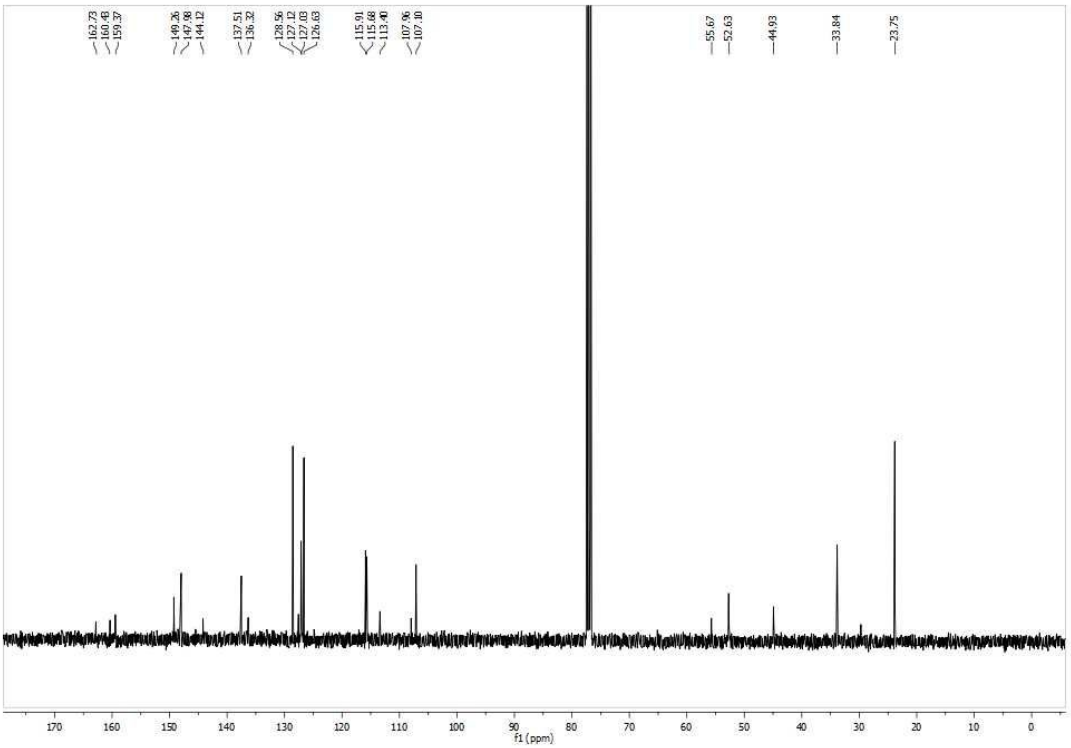
7.12
7.05
7.03
6.63
6.62
6.62
6.61
6.54
3.77
3.64
2.94
2.93
2.91
2.89
2.87
2.86
2.84
2.78
1.25
1.23
1.00
1.03
2.20
4.30
2.17
2.05
0.90
1.97
3.97
1.27
3.84
7.54
f1 (ppm)

12
CDCl3
F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136.32
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127.12
127.05
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113.40
107.96
107.10
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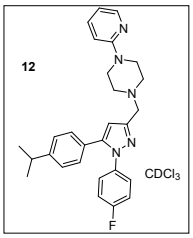
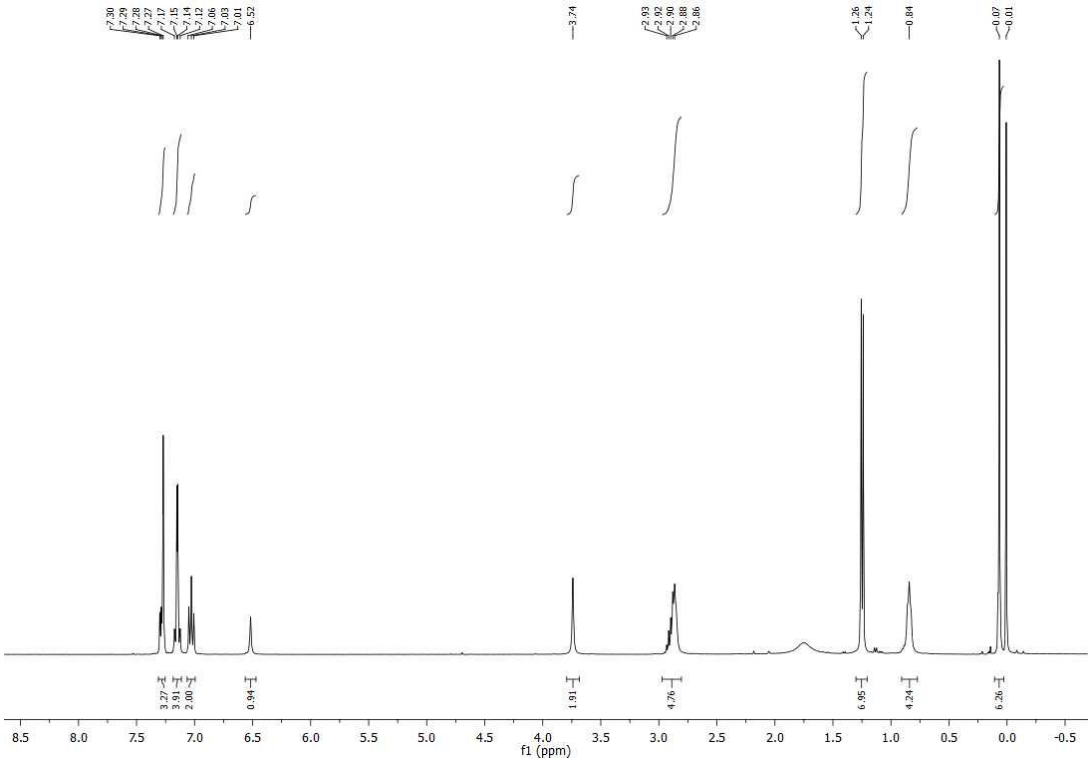
52.63
44.93
33.84
23.75
f1 (ppm)


12
CDCl3
F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7.29
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7.27
7.17
7.15
7.14
7.12
7.06
7.03
7.01
6.52
3.74
2.93
2.92
2.90
2.88
2.86
1.26
1.24
0.84
0.07
0.01
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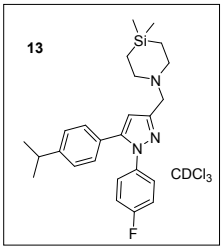
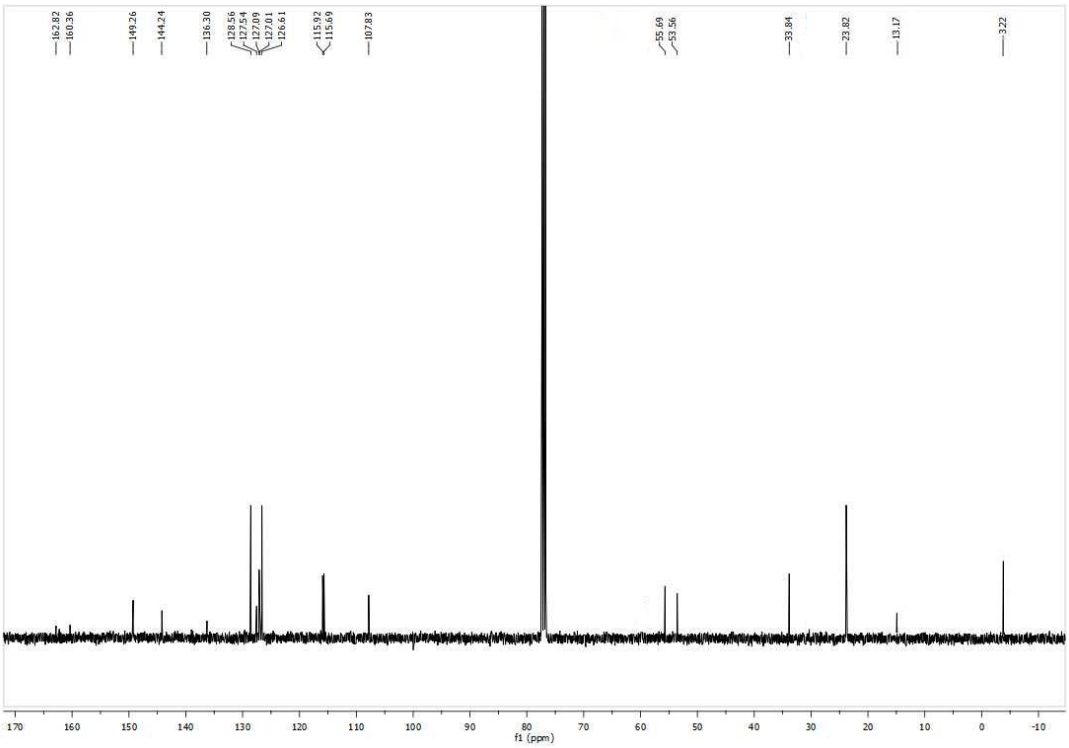
3.91
2.00
0.94
1.91
4.76
6.95
4.24
6.26
f1 (ppm)


13
Si
N
CDCl3
F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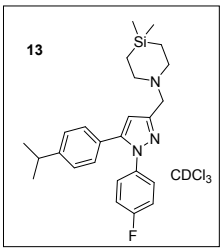
33.84
23.82
13.17
3.22
f1 (ppm)


13
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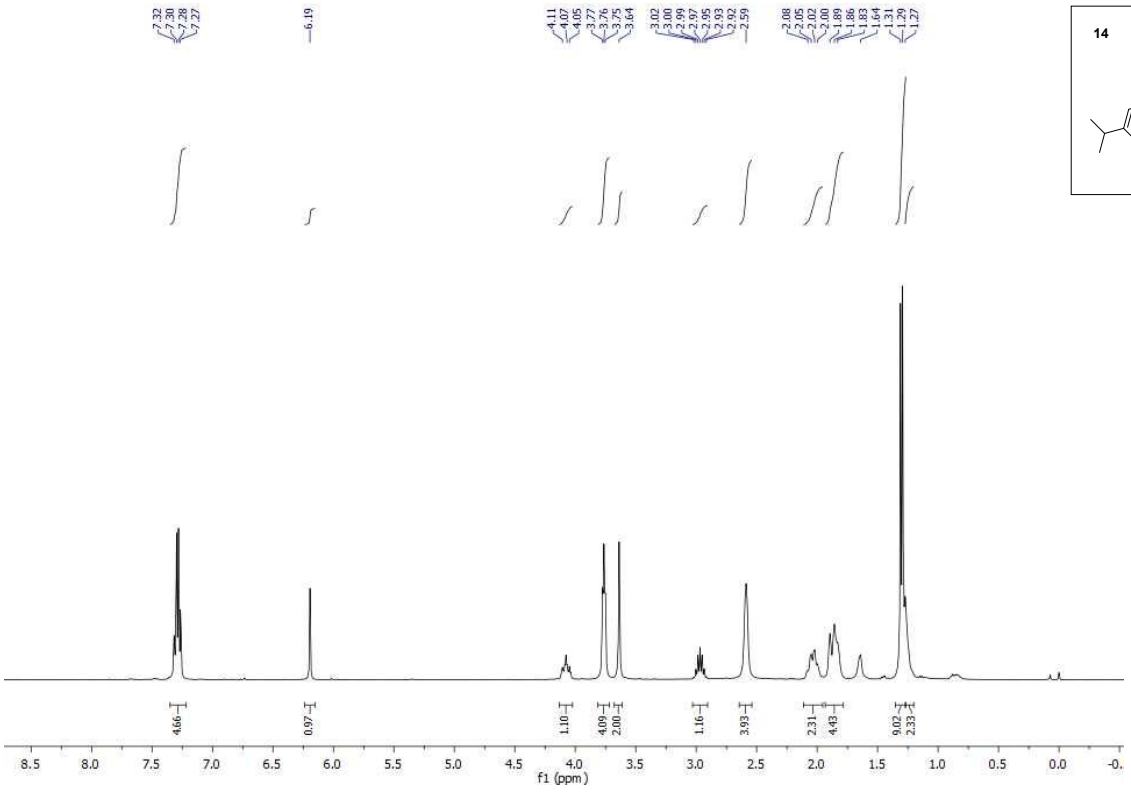
N
N
N
CDCl3
F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4.07
4.05
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3.76
3.75
3.64
3.02
3.00
2.99
2.97
2.95
2.93
2.92
2.59
2.08
2.05
2.02
2.00
1.89
1.86
1.83
1.64
1.31
1.29
1.27
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1.16
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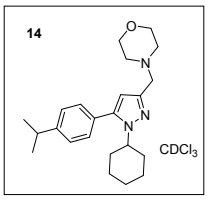
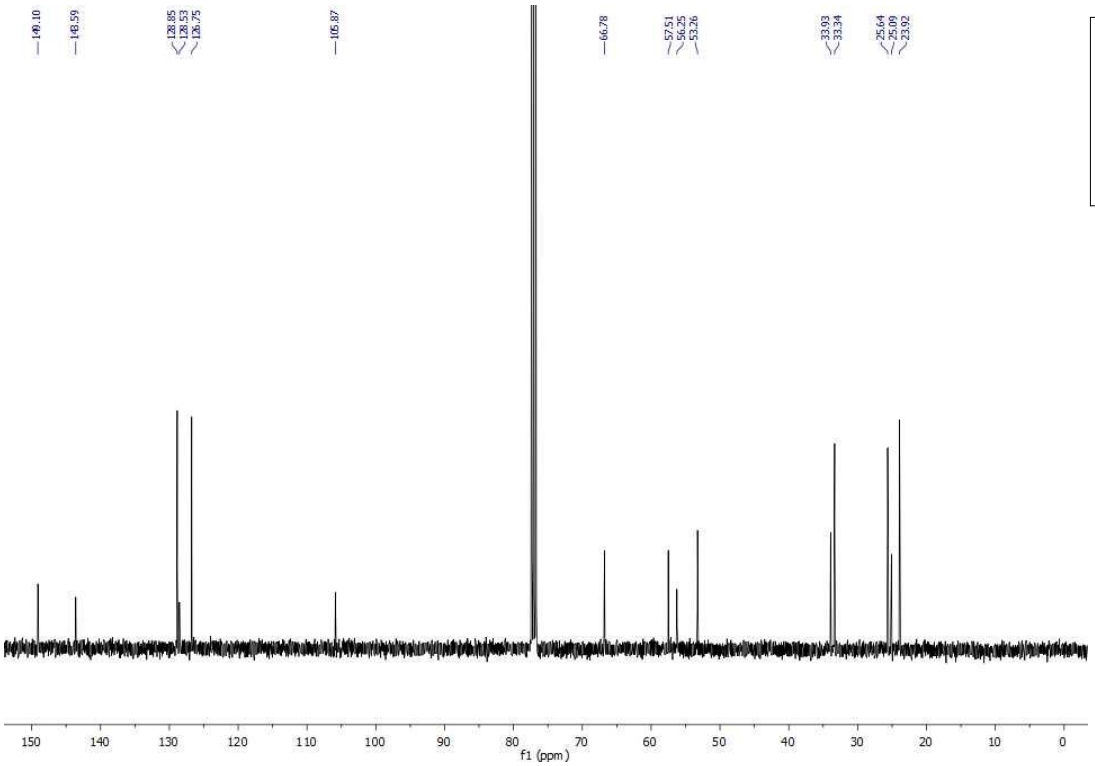
2.31
4.43
9.02
2.33
f1 (ppm)


14
O
N
N
N
CDCl3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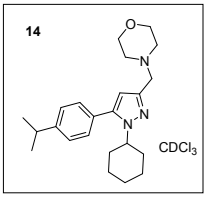
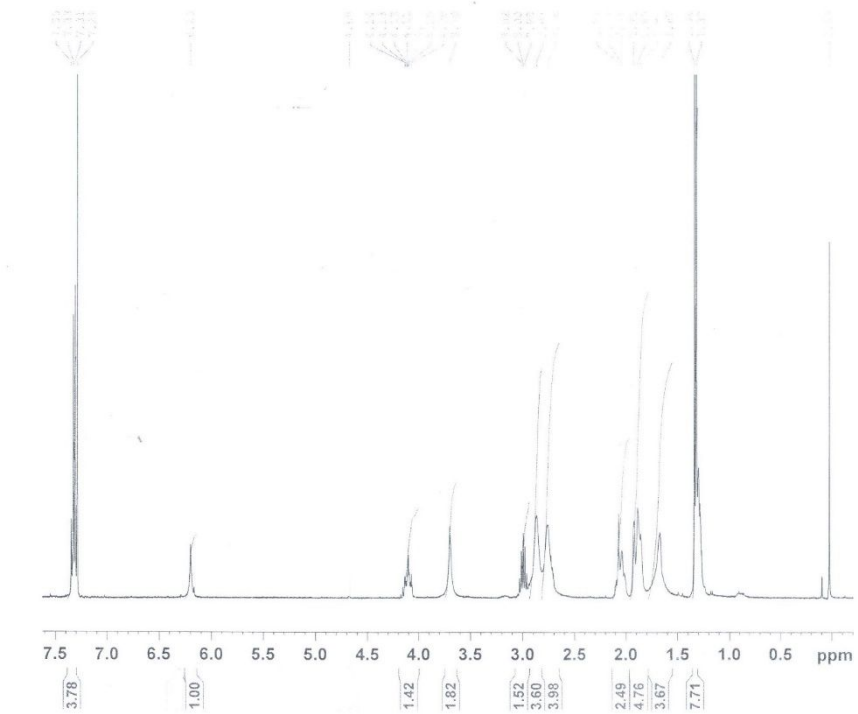
105.87
66.78
57.51
56.25
53.26
33.93
33.34
25.64
25.09
23.92
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


14
O
N
N
N
CDCl3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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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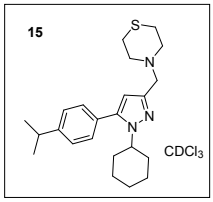
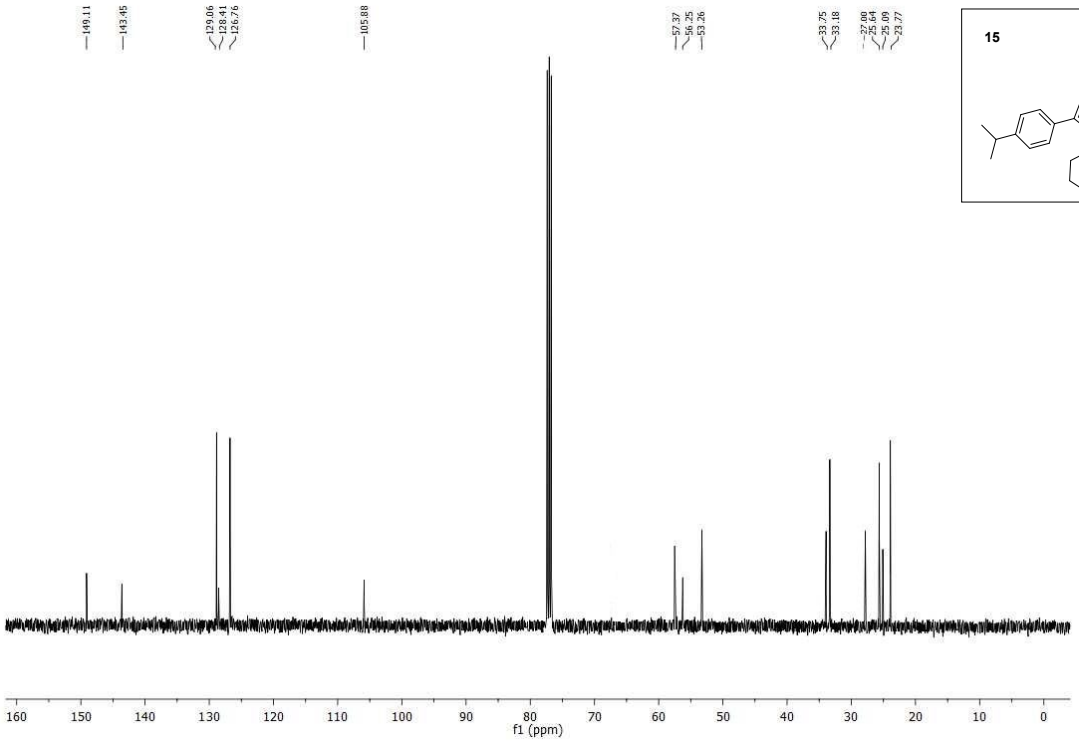
3.98
2.49
4.76
3.67
7.71


15
S
N
N
N
CDCl3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105.88
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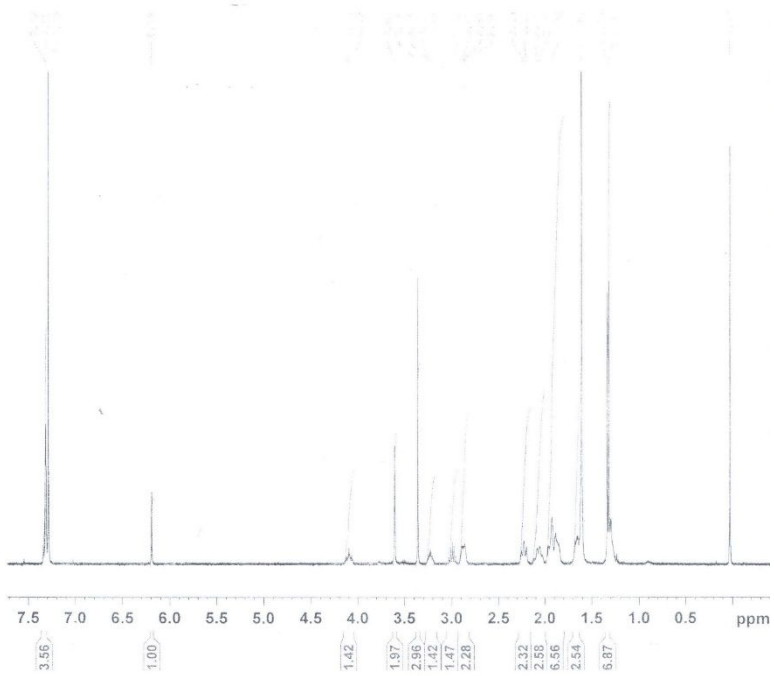
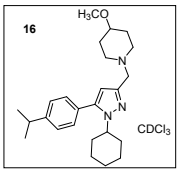
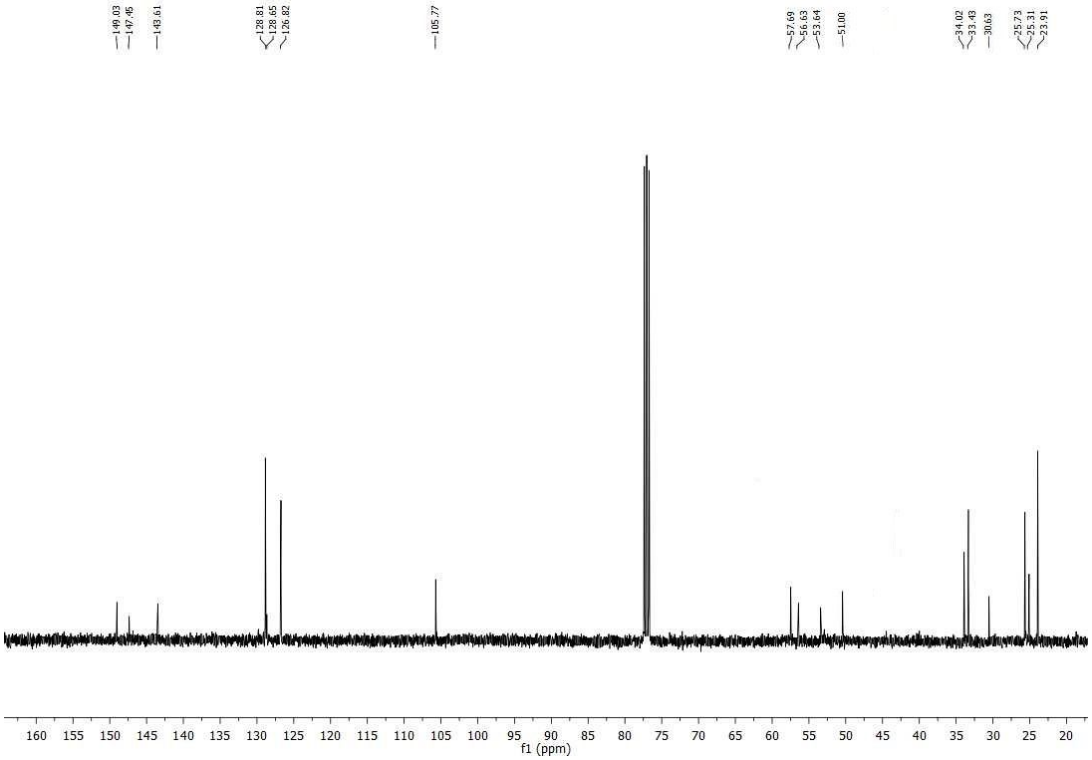
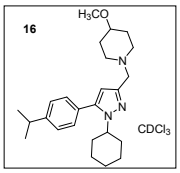
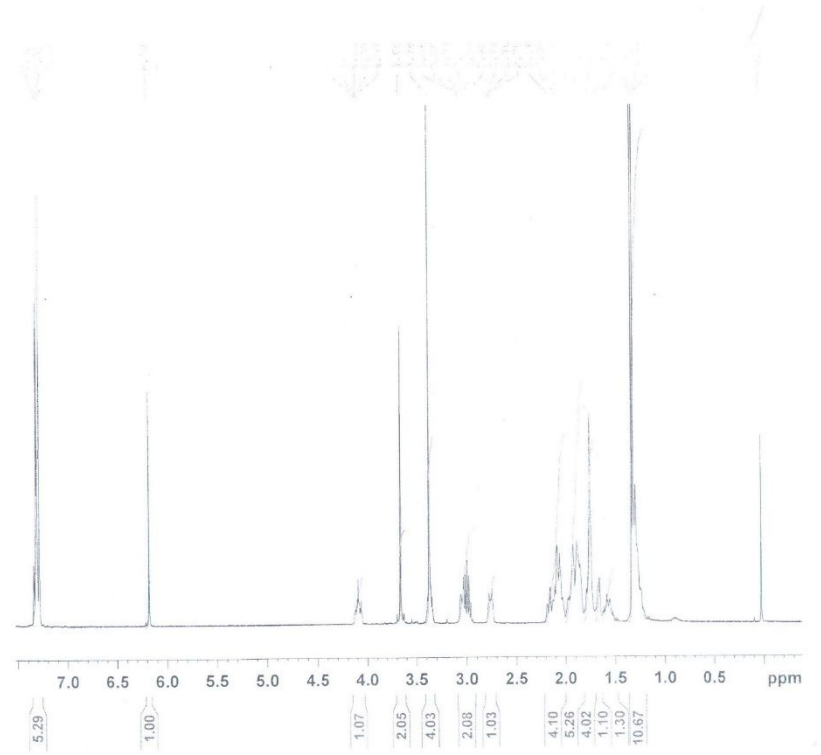
56.25
53.26
33.75
33.18
27.00
25.64
25.09
23.77
15
CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

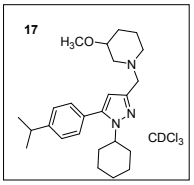

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.56
1.00
1.42
1.97
2.96
1.42
1.47
2.28
2.32
2.58
6.56
2.54
6.87

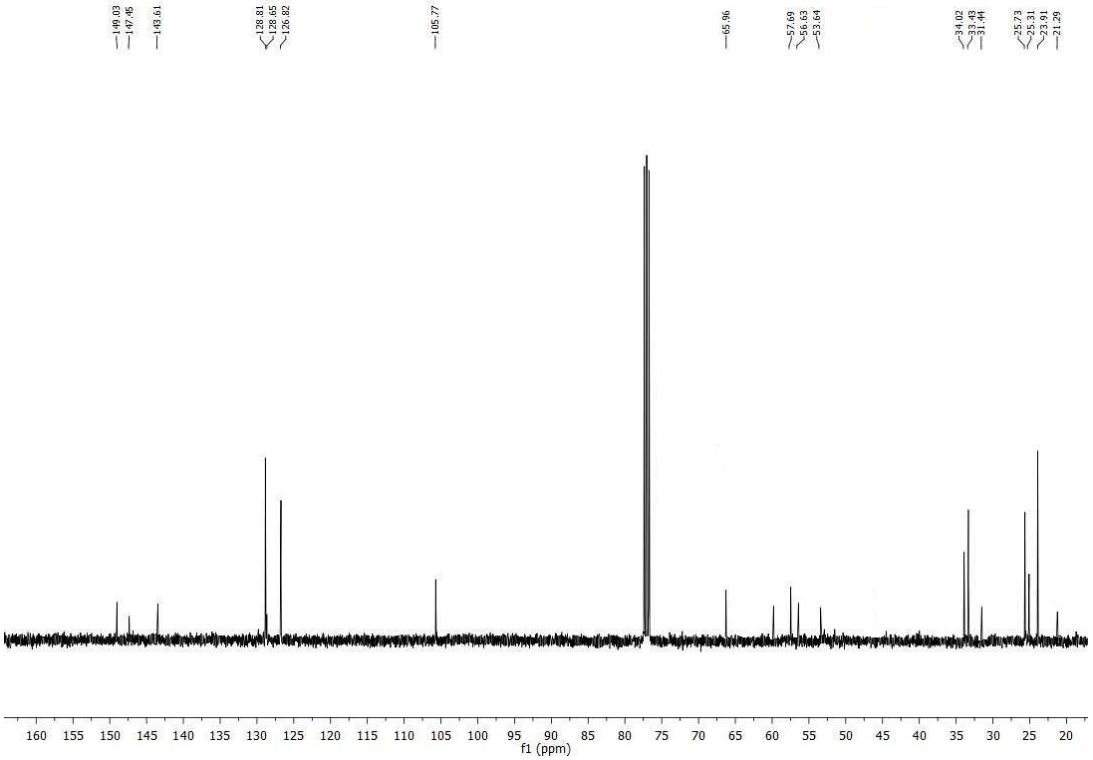

H3CO
16
CDCl3


149.03
147.45
143.61
128.81
128.65
126.82
105.77
67.69
56.63
53.64
51.00
34.02
33.49
30.63
25.73
25.31
23.91
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)


16
H3CO
N
N
N
CDCl3


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 ppm
5.29
1.00
1.07
2.05
4.03
2.08
1.03
4.10
5.26
4.02
1.10
1.30
10.67


17
H3CO
N
N
N
CDCl3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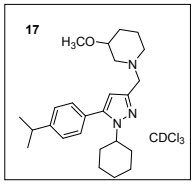
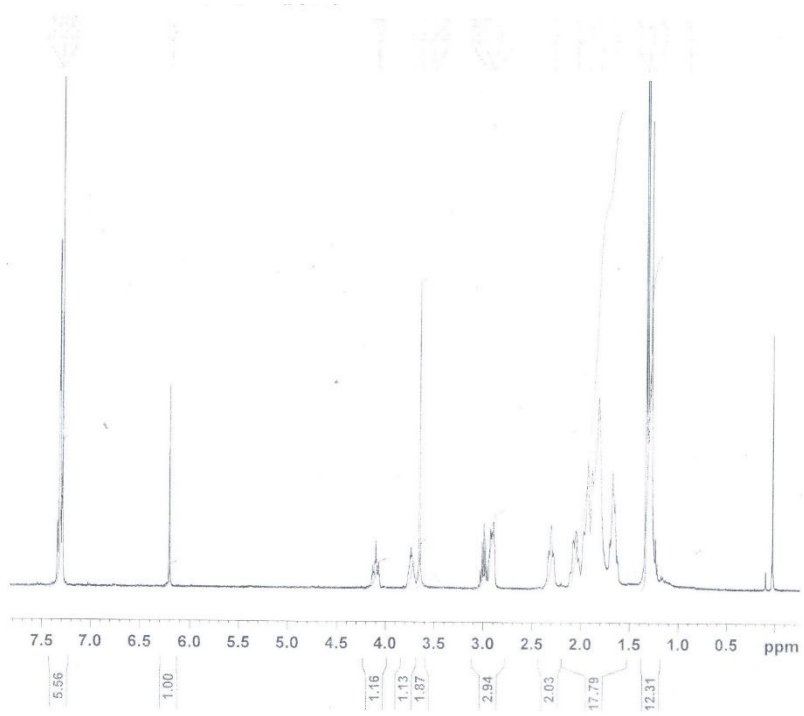
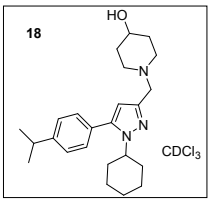
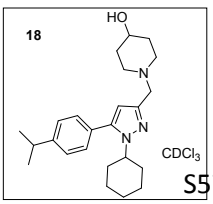
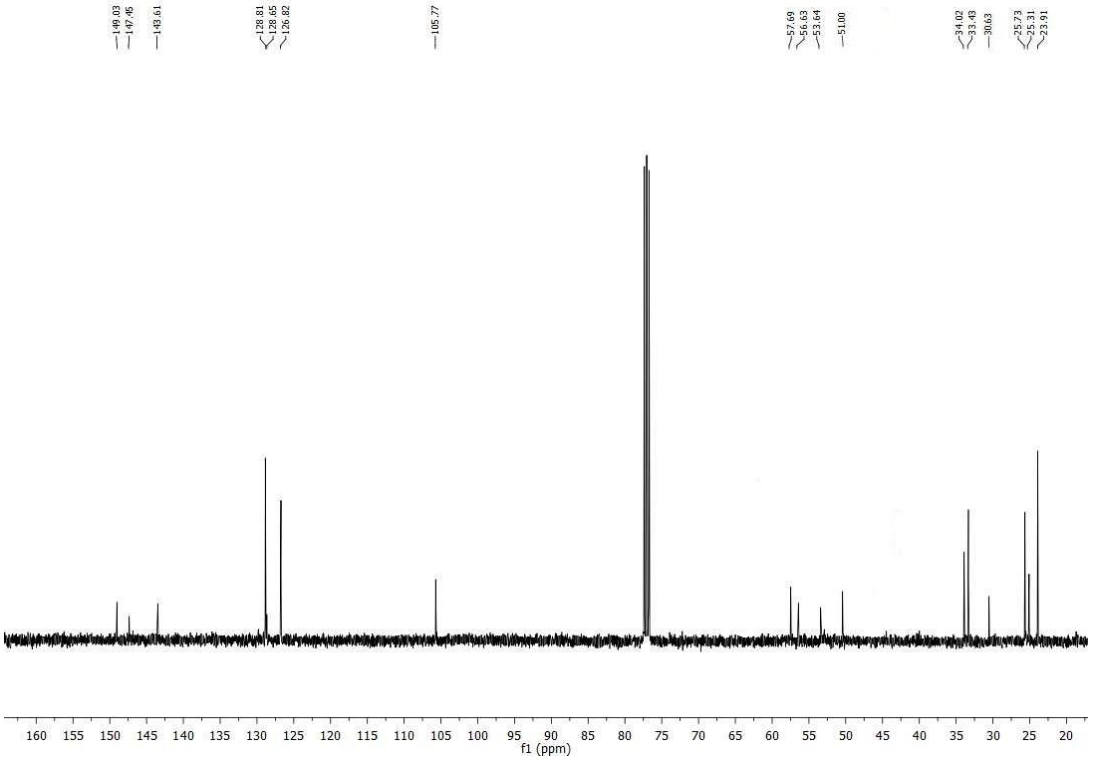
147.45
143.61
128.81
128.65
126.82
105.77
65.96
57.69
56.63
53.64
34.02
33.48
31.44
25.73
25.31
23.91
21.29
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

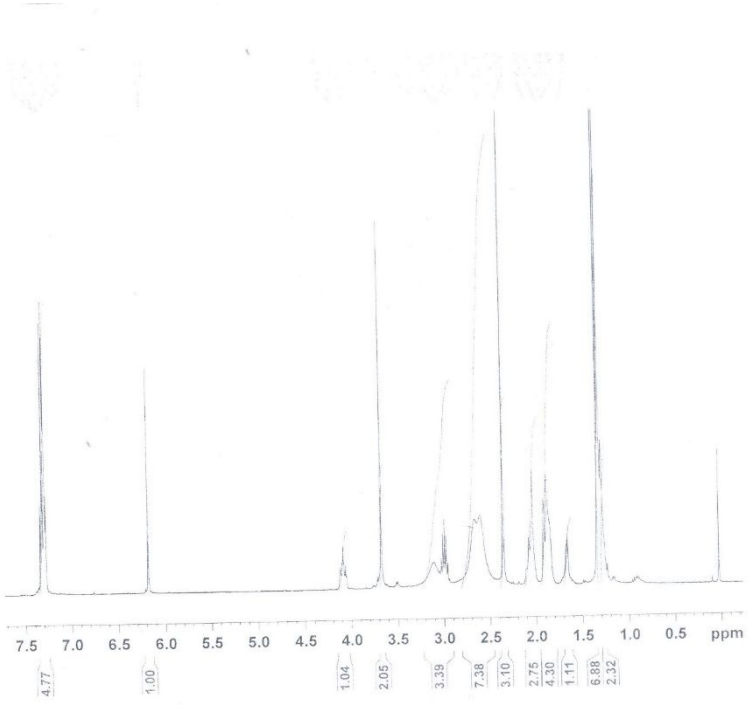

17
H_3CO
N
N
N
$CDCl_3$

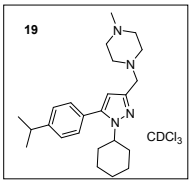

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.56
1.00
1.16
1.13
1.87
2.94
2.03
17.79
12.31

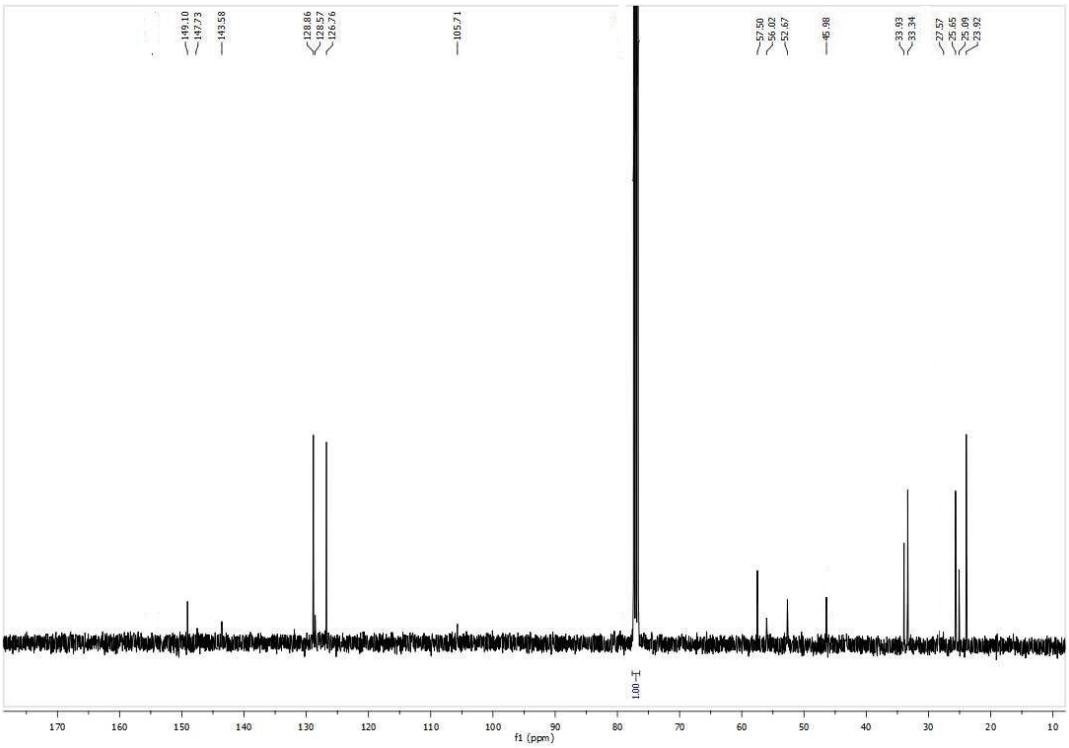

18
HO
N
N
N
$CDCl_3$

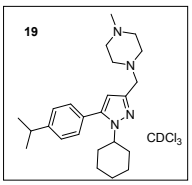

18
HO
N
N
N
$CDCl_3$

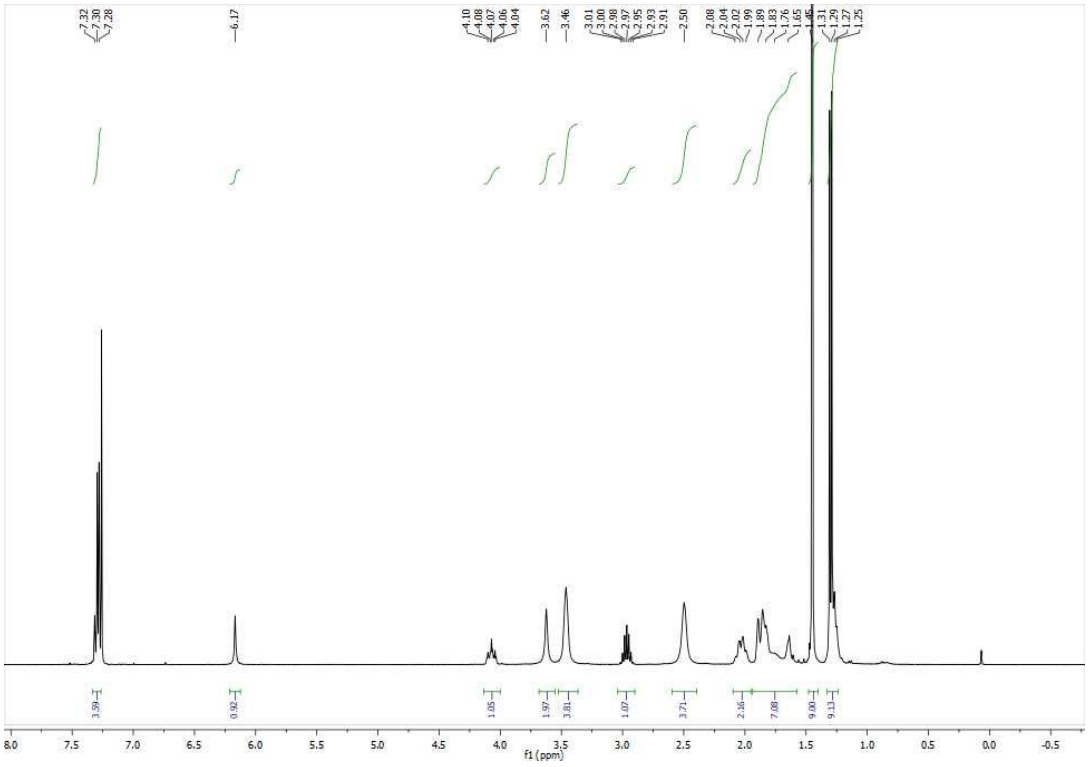

149.03
147.45
143.61
128.81
128.65
126.82
105.77
67.69
56.63
53.64
51.00
34.02
31.49
30.03
25.73
25.31
23.91
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

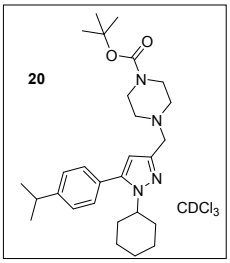

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.77
1.00
1.04
2.05
3.39
7.38
3.10
2.75
4.30
1.11
6.88
2.32

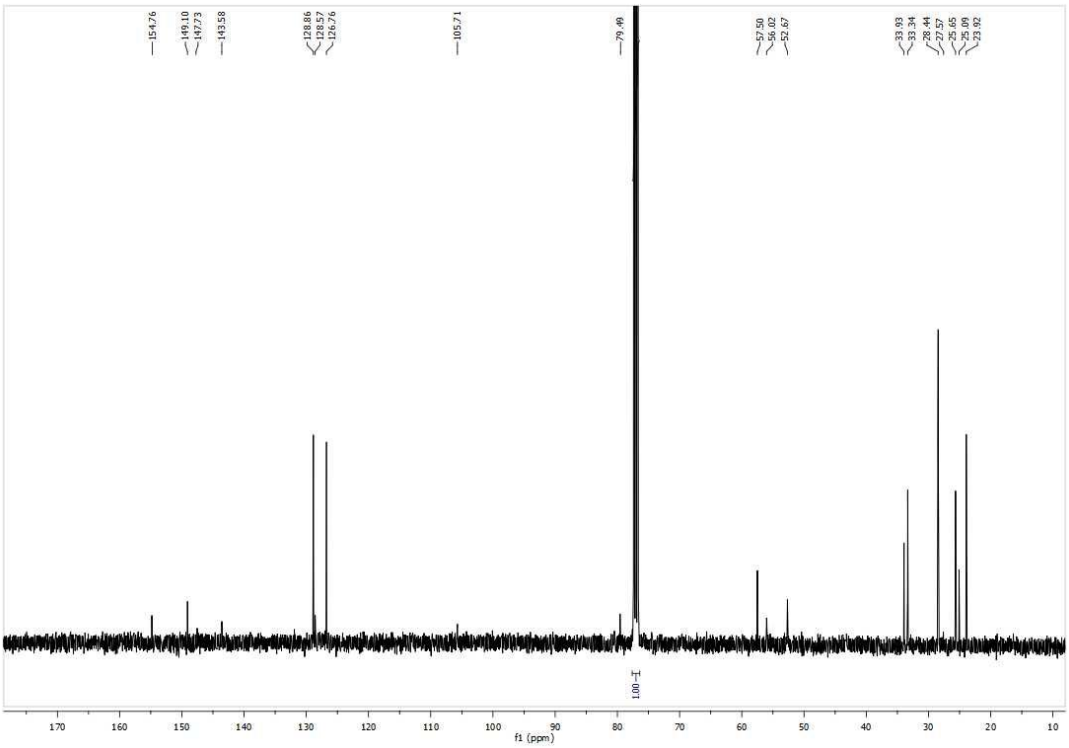

19
CDCl3

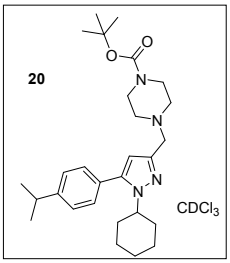

149.10
147.73
143.58
128.86
128.57
126.76
105.71
57.50
56.02
52.67
46.98
33.93
33.34
27.57
25.65
25.09
23.92
1.00
f1 (ppm)

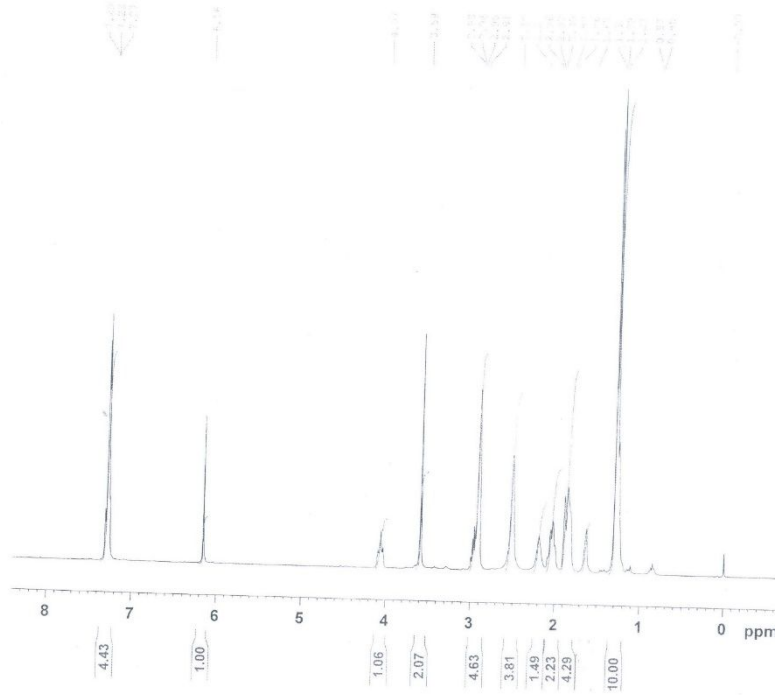

19
CDCl3

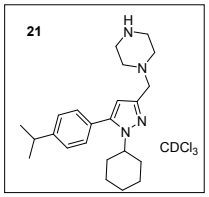

7.32
7.30
7.28
6.17
4.10
4.08
4.07
4.06
4.04
3.62
3.46
3.01
3.00
2.98
2.97
2.95
2.93
2.91
2.50
2.08
2.04
2.02
1.89
1.83
1.76
1.65
1.46
1.31
1.29
1.27
1.25
3.99
0.92
1.05
1.97
3.81
1.07
3.71
2.16
7.08
9.00
9.13
f1 (ppm)

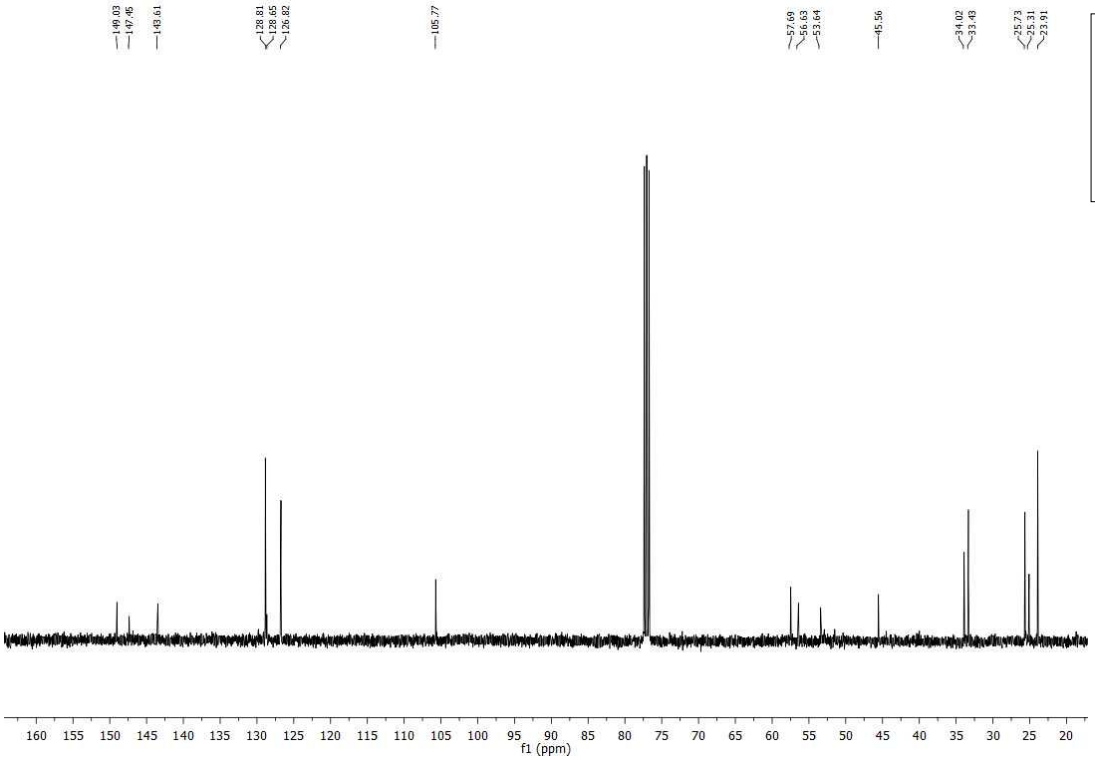

20
CDCl3

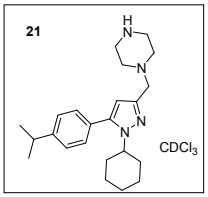

154.76
149.10
147.73
143.58
128.86
128.57
126.76
105.71
79.49
57.50
56.02
52.67
33.93
33.34
28.44
27.57
25.65
25.09
23.92
f1 (ppm)

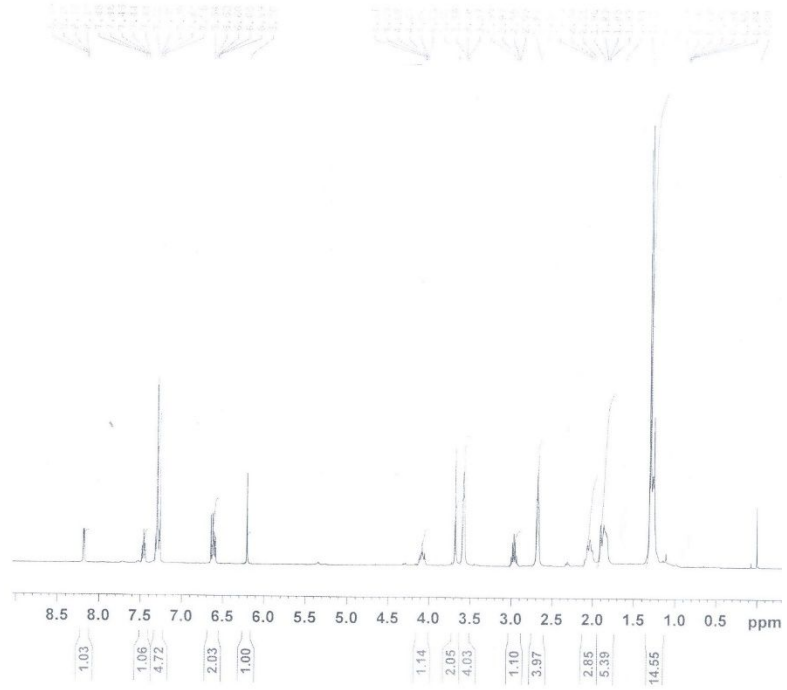

20
CDCl3

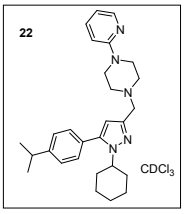

8
7
6
5
4
3
2
1
0
ppm
4.43
1.00
1.06
2.07
4.63
3.81
1.49
2.23
4.29
10.00

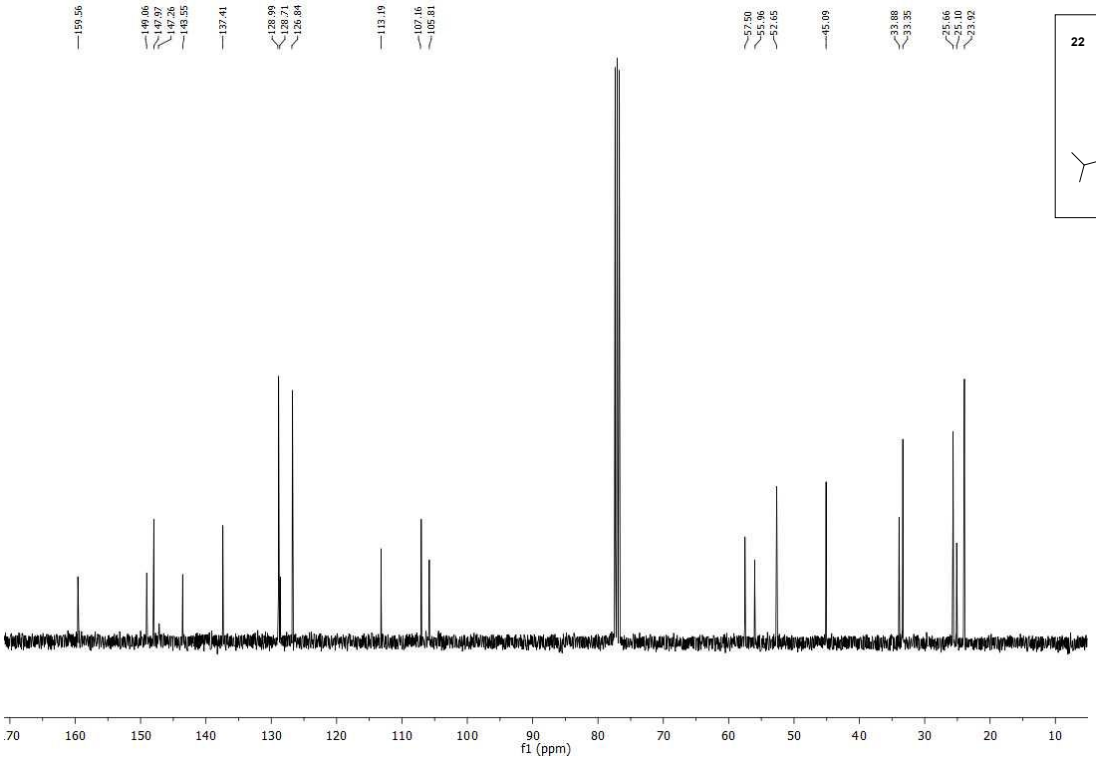

21
CDCl3

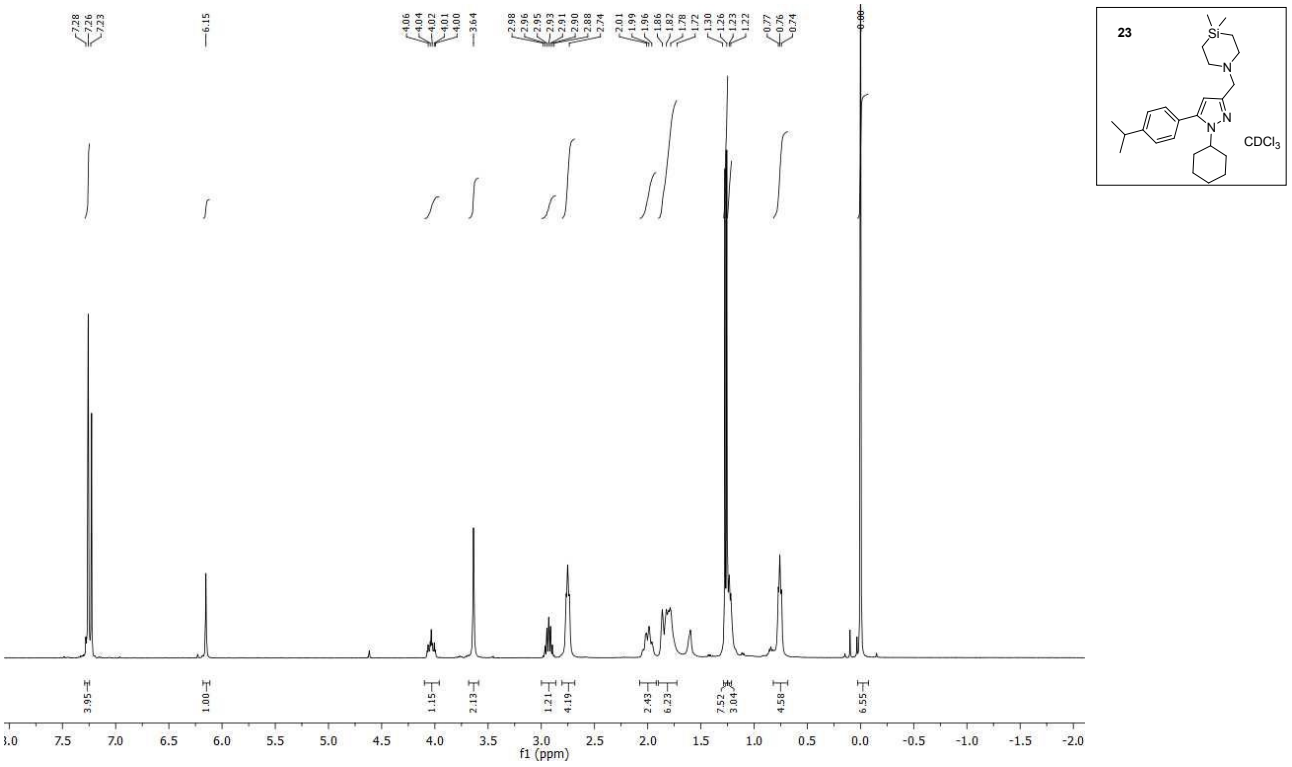

149.03
147.45
143.61
128.81
128.65
126.82
105.77
67.69
56.63
53.64
45.56
34.02
33.49
25.73
25.31
23.91
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

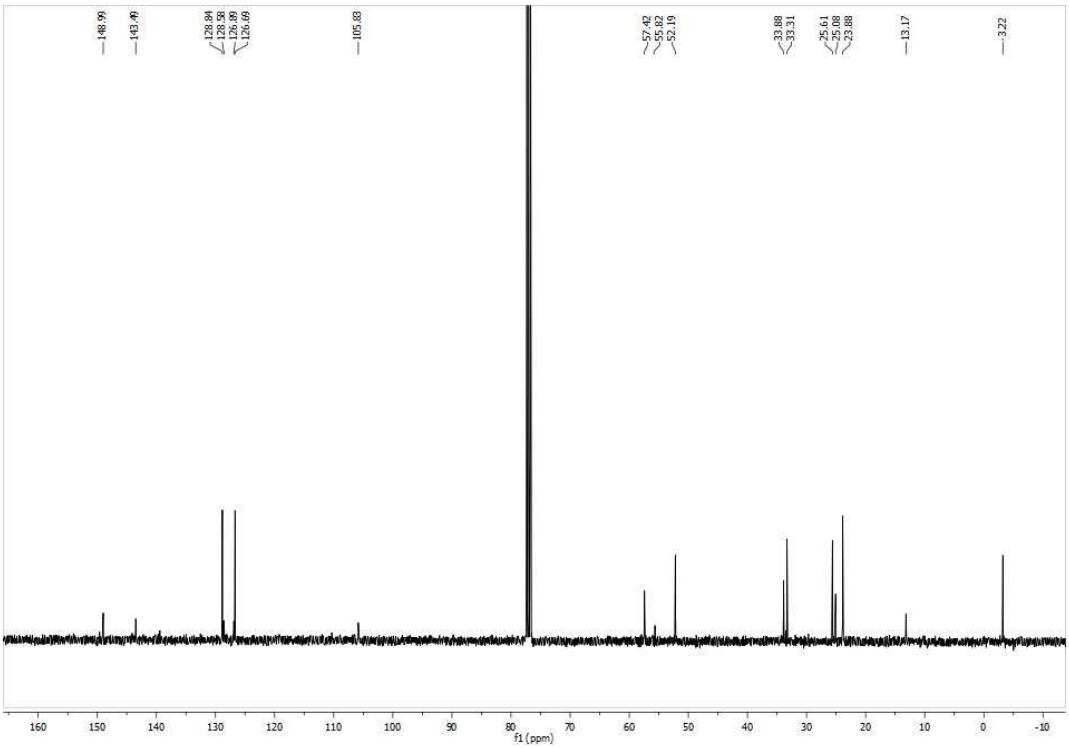

21
H
N
N
N
N
CDCl3

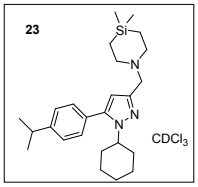

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.03
1.06
4.72
2.03
1.00
1.14
2.05
4.03
1.10
3.97
2.85
5.39
14.55

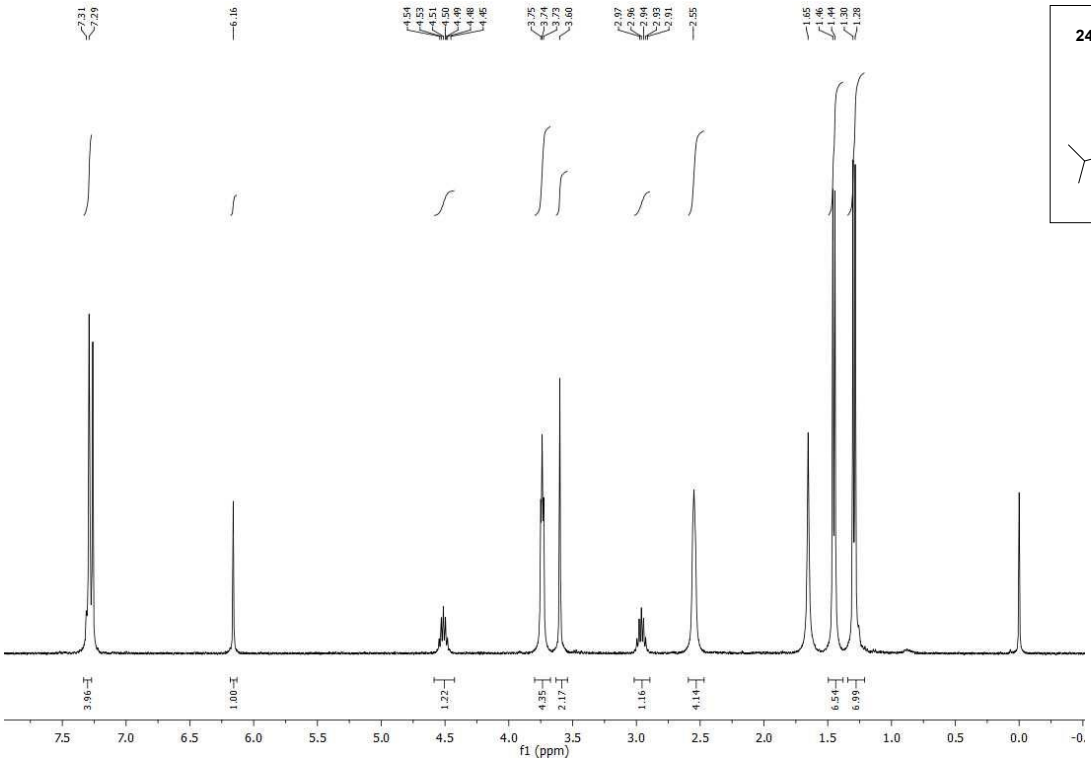

22
N
N
N
N
N
CDCl3


159.56
149.06
147.97
147.26
143.55
137.41
128.99
128.71
126.84
113.19
107.16
105.81
57.50
55.96
52.65
45.09
33.88
33.35
25.66
25.10
23.92
22
CDCl3
f1 (ppm)


7.28
7.26
7.23
6.15
4.06
4.04
4.02
4.01
4.00
3.64
2.98
2.96
2.95
2.93
2.91
2.90
2.88
2.74
2.01
1.99
1.96
1.86
1.82
1.78
1.72
1.30
1.26
1.23
1.22
0.77
0.76
0.74
0.00
23
CDCl3
3.95
1.00
1.15
2.13
1.21
4.19
2.43
6.23
7.52
3.04
4.58
6.55
f1 (ppm)


148.99
143.49
128.84
128.30
126.98
126.69
105.83
57.42
55.82
52.19
33.88
33.31
25.61
25.08
23.88
13.17
3.22
f1 (ppm)


23
Si
N
N
N
CDCl3


7.31
7.29
6.16
4.54
4.53
4.51
4.50
4.49
4.48
4.46
3.75
3.74
3.73
3.60
2.97
2.96
2.94
2.93
2.91
2.55
1.65
1.46
1.44
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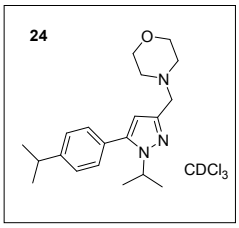
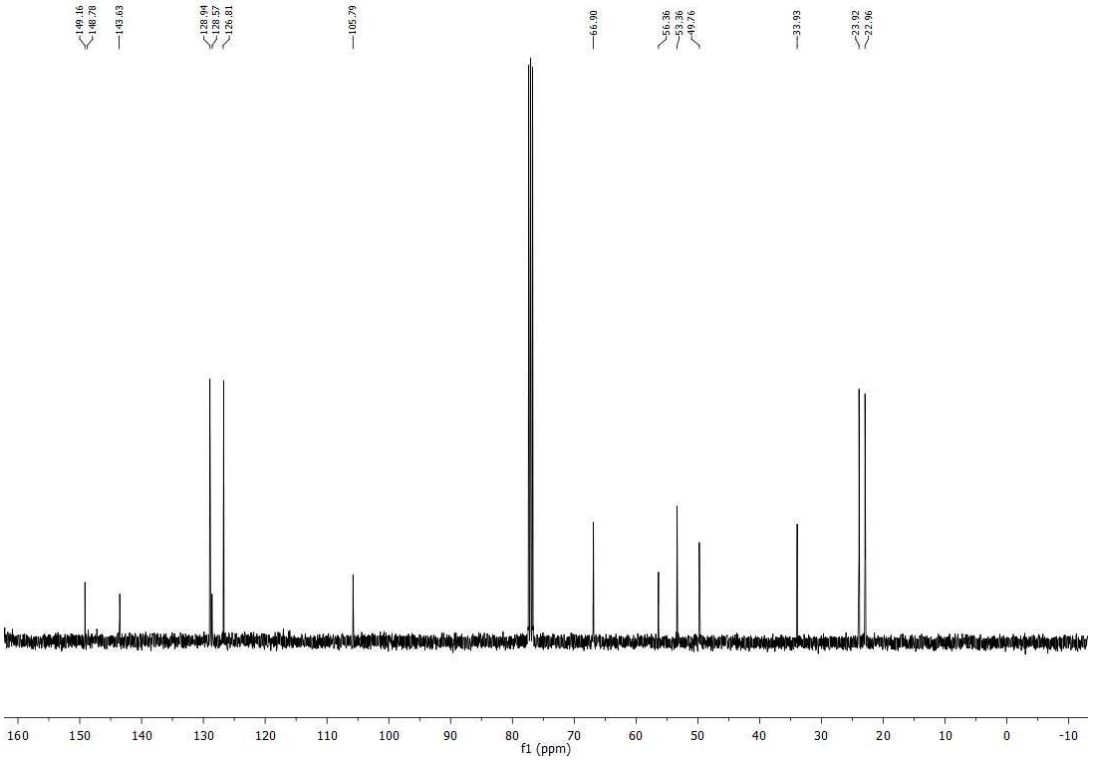
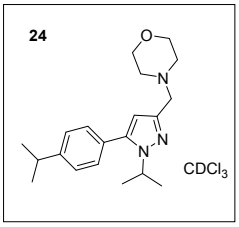
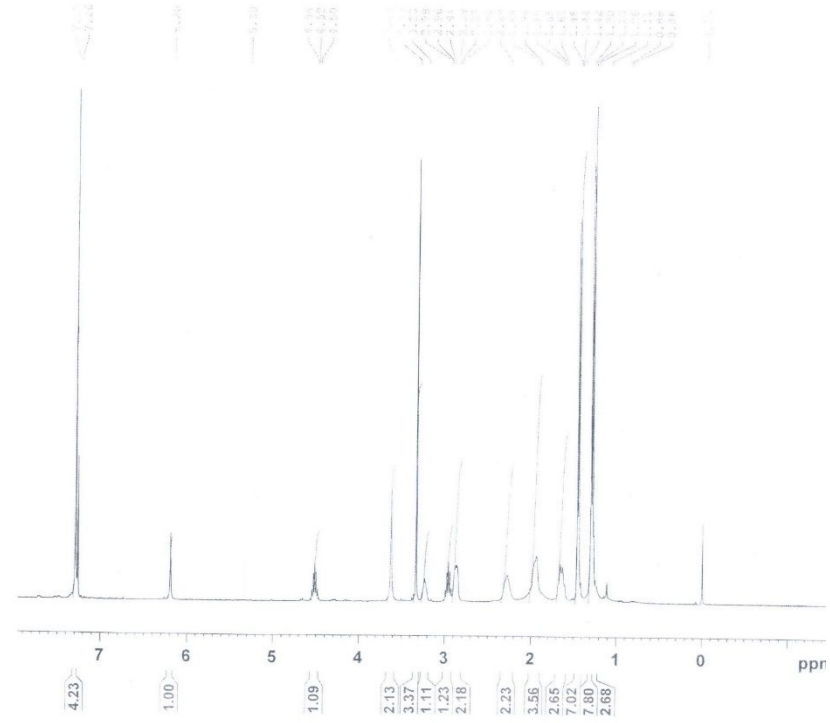
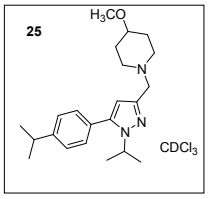
2.17
1.16
4.14
6.54
6.99
f1 (ppm)

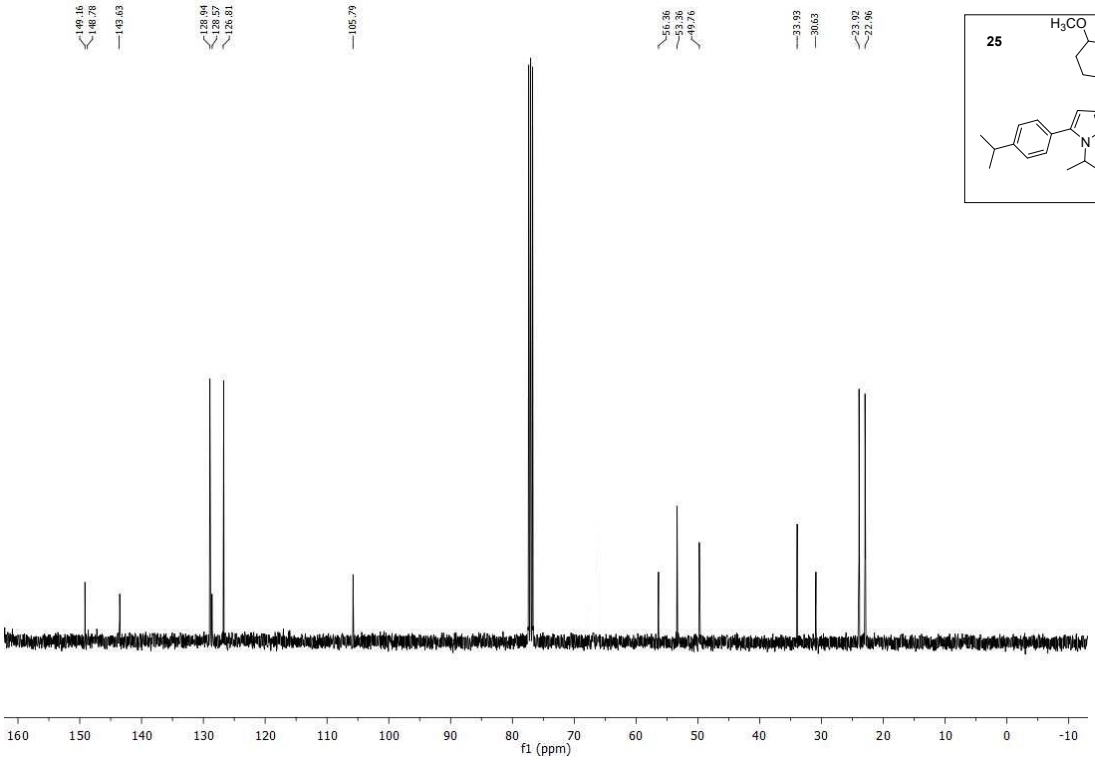

24
O
N
N
N
CDCl3


149.16
148.78
143.63
128.94
128.57
126.81
105.79
66.90
56.36
53.36
49.76
33.93
23.92
22.96
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

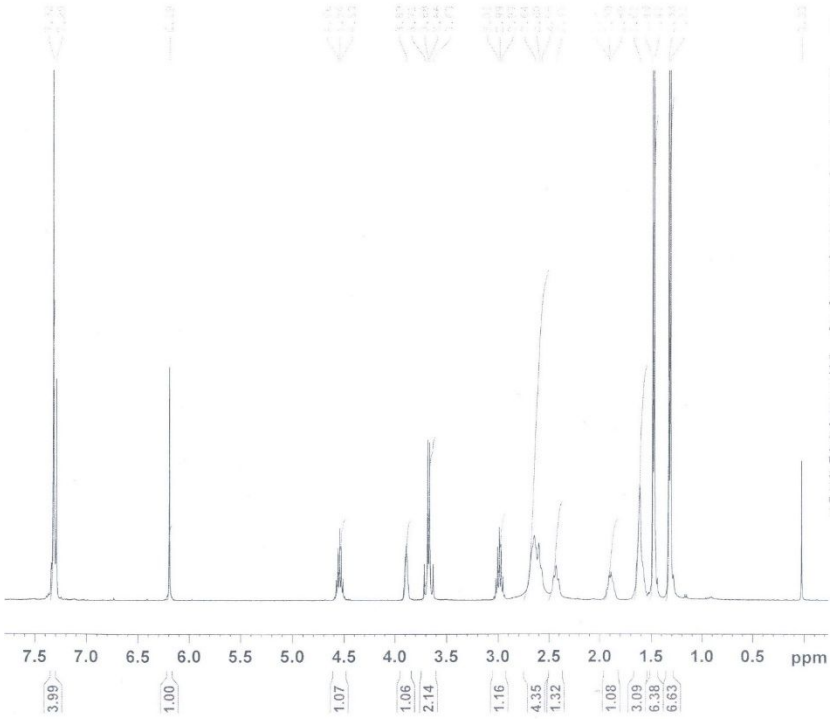

24
O
N
N
N
CDCl3

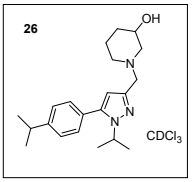

7
6
5
4
3
2
1
0
ppm
4.23
1.00
1.09
2.13
3.37
1.11
1.23
2.18
2.23
3.56
2.65
7.02
7.80
2.68

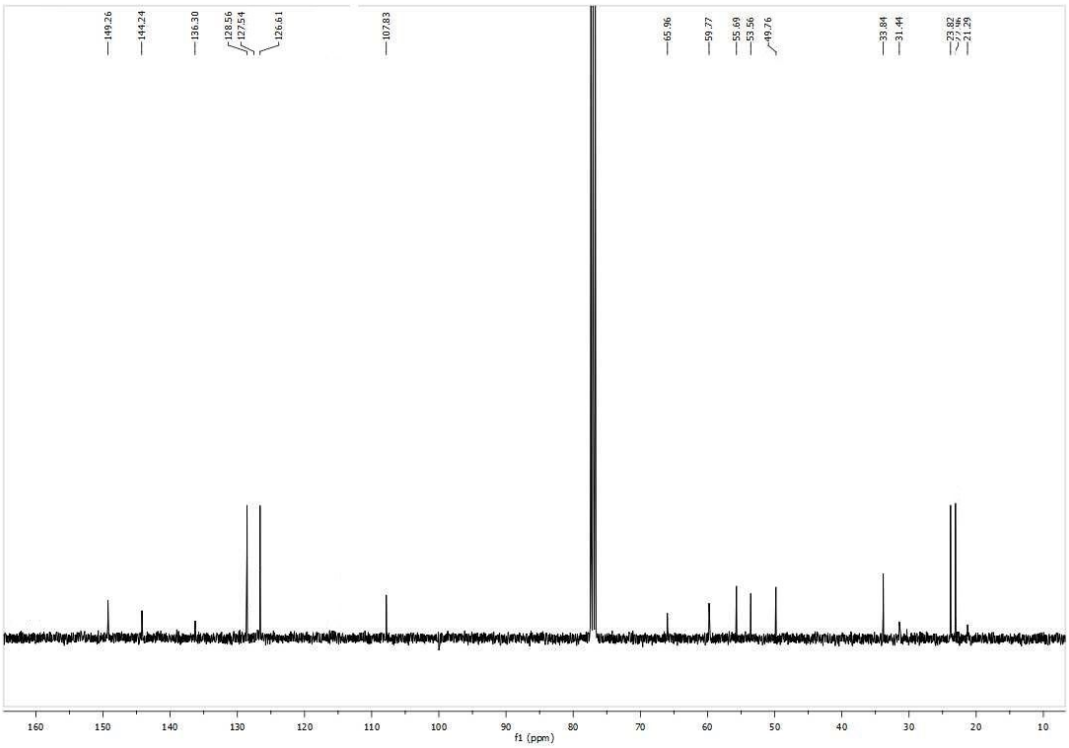

25
H3CO
N
N
N
CDCl3

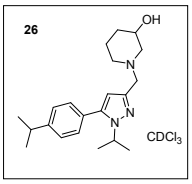

149.16
148.78
143.63
126.94
126.57
126.81
105.79
56.36
53.36
49.76
33.93
30.63
23.92
22.96
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

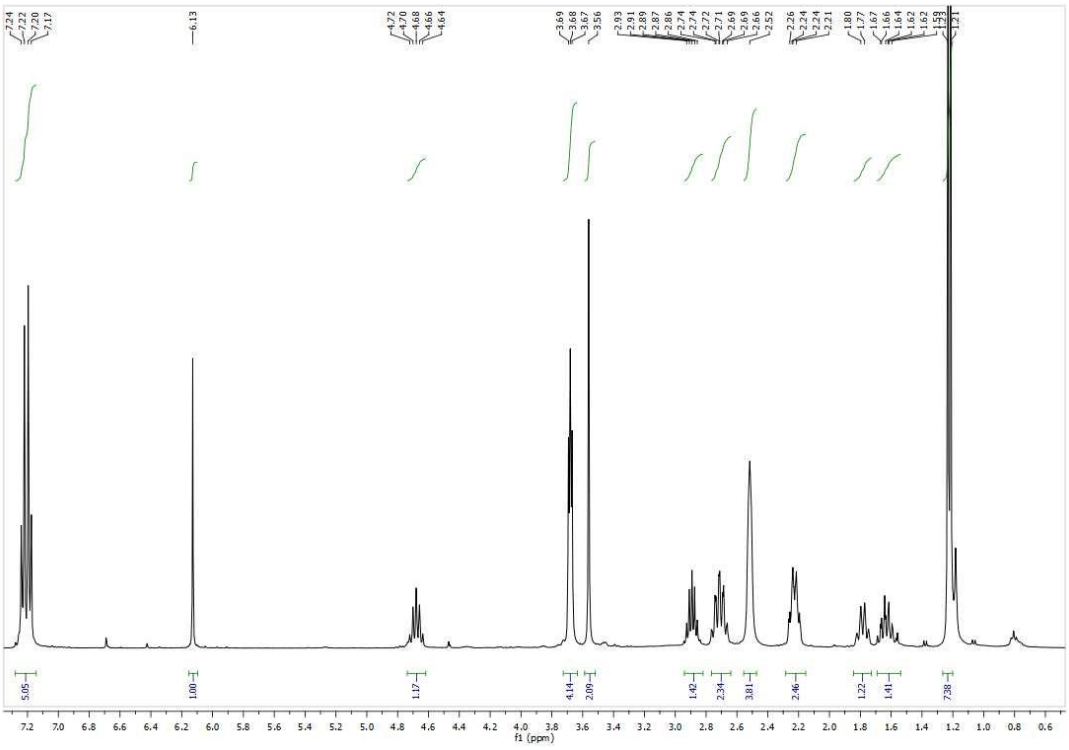
25
H3CO
N
N
N
CDCl3

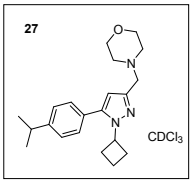

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.99
1.00
1.07
1.06
2.14
1.16
4.35
1.32
1.08
3.09
6.38
6.63

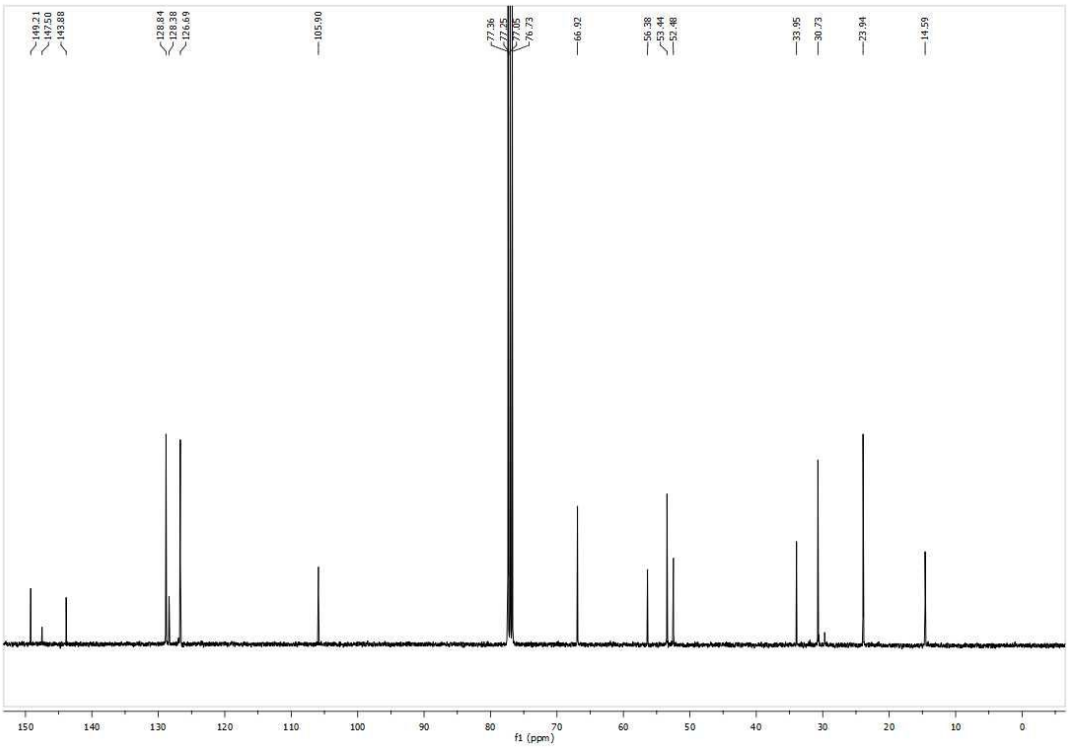

26
OH
N
N
N
CDCl3

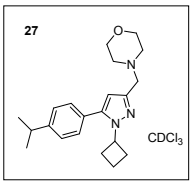

149.26
144.24
136.30
128.56
127.54
126.61
107.83
65.96
59.77
55.69
53.56
49.76
33.84
31.44
21.29
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

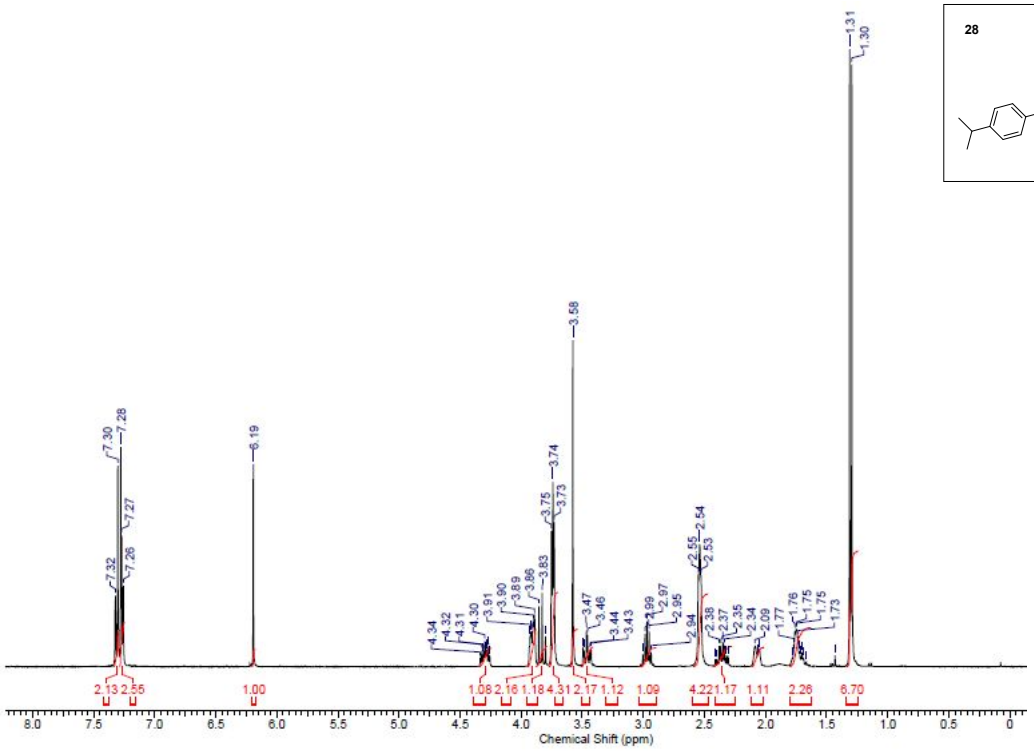

26
OH
N
N
N
CDCl3

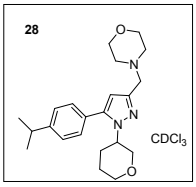

7.24
7.22
7.20
7.17
6.13
4.72
4.70
4.68
4.66
4.64
3.69
3.68
3.67
3.56
2.93
2.91
2.89
2.87
2.86
2.74
2.72
2.71
2.69
2.66
2.52
2.26
2.24
2.24
2.21
1.80
1.77
1.67
1.66
1.64
1.62
1.62
1.33
1.21
5.05
1.00
1.17
4.14
2.09
1.40
2.34
3.81
2.46
1.22
1.41
7.38
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
f1 (ppm)

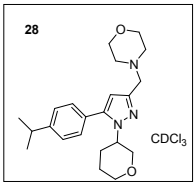

27
O
N
N
N
CDCl3

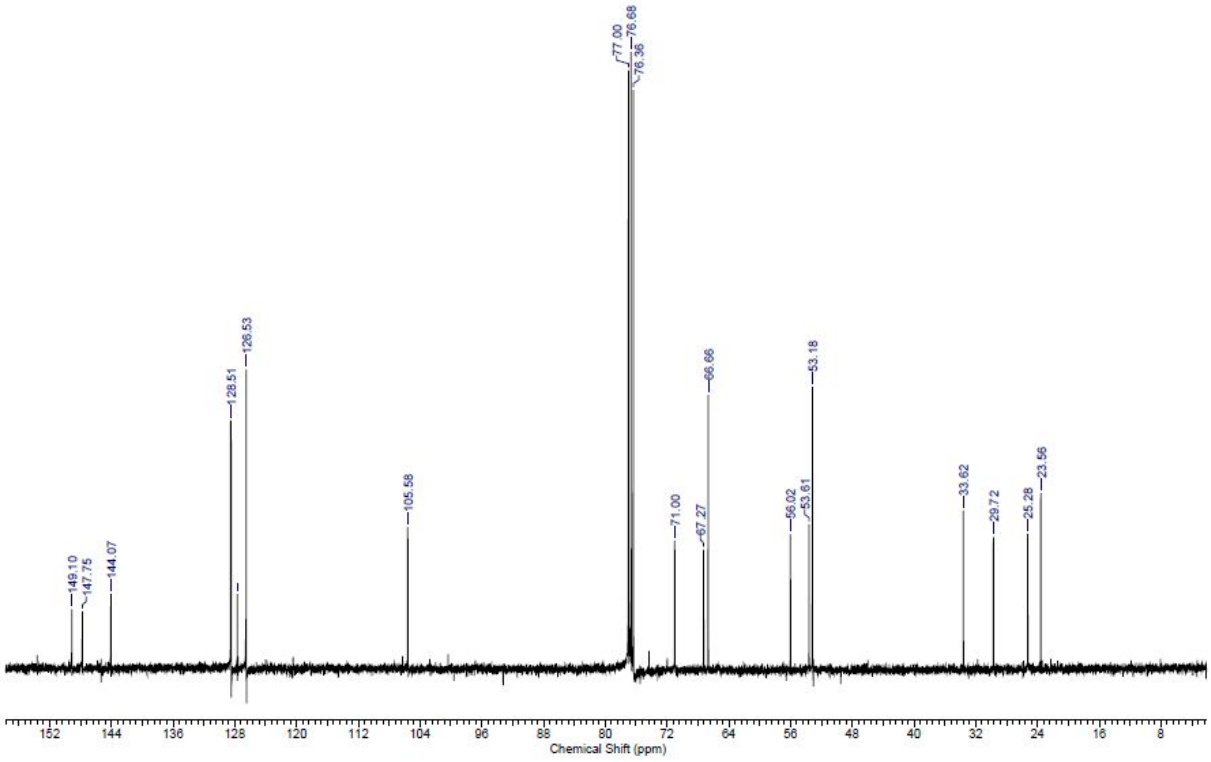

149.21
147.50
143.88
128.84
128.38
126.69
105.90
77.36
77.05
76.73
66.92
56.38
53.44
52.48
33.95
30.73
23.94
14.59
f1 (ppm)

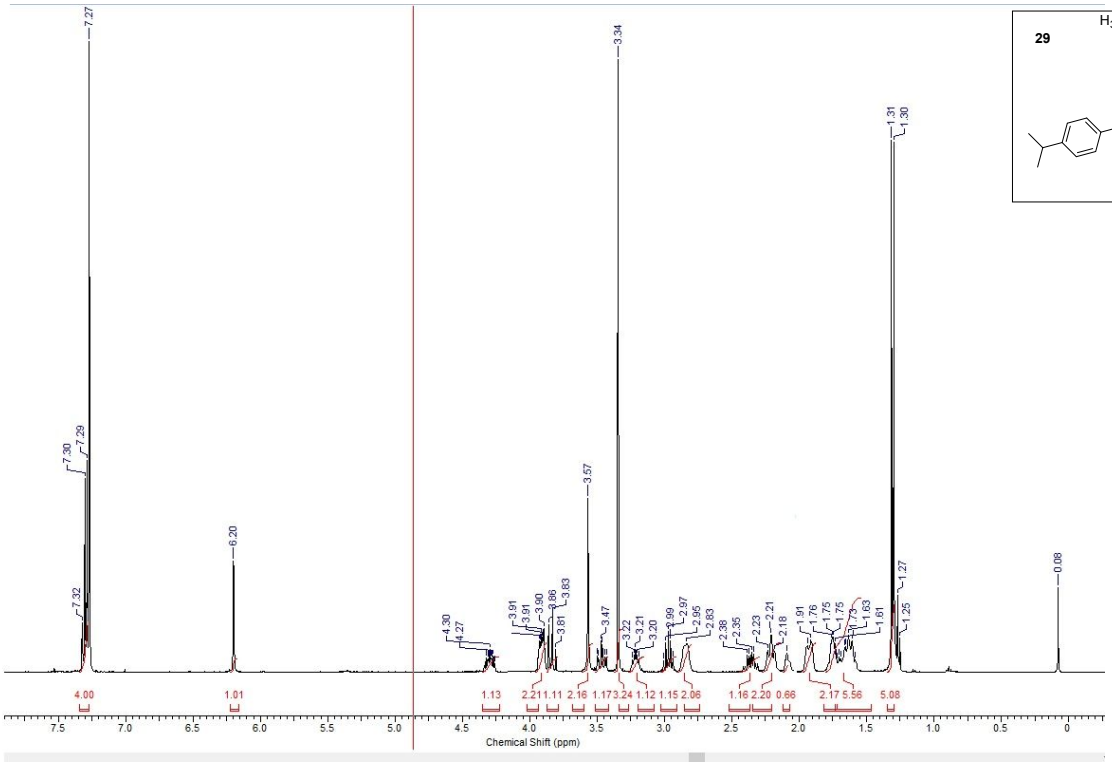

27
CDCl3

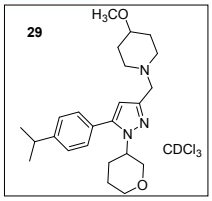

7.30
7.28
7.27
7.26
7.32
6.19
3.58
3.74
3.75
3.73
3.83
3.86
3.89
3.90
3.91
4.30
4.31
4.32
4.34
3.47
3.46
3.44
3.43
2.99
2.97
2.95
2.94
2.55
2.54
2.53
2.38
2.37
2.35
2.34
2.09
1.77
1.76
1.75
1.75
1.73
1.31
1.30
2.13
2.55
1.00
1.08
2.16
1.18
4.31
2.17
1.12
1.09
4.22
1.17
1.11
2.26
6.70
Chemical Shift (ppm)

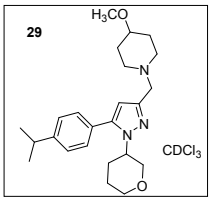

28
CDCl3

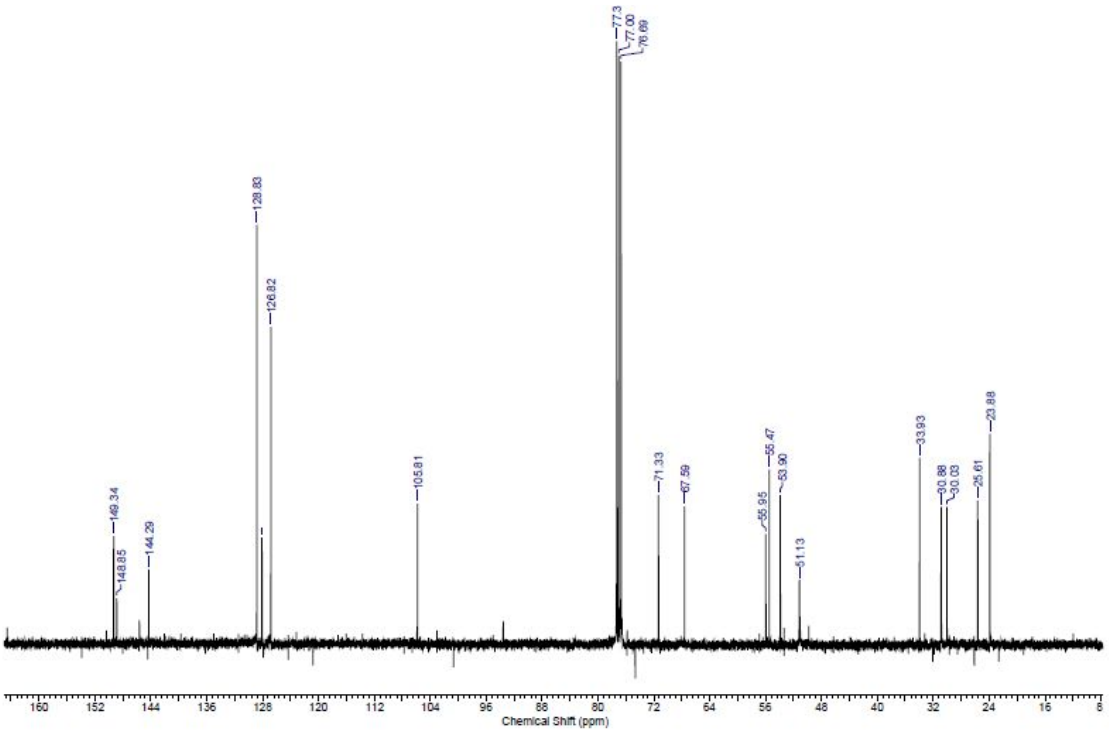

28
CDCl3

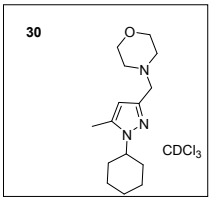

77.00
76.68
76.36
128.51
126.53
105.58
71.00
66.66
67.27
56.02
53.61
53.18
33.62
29.72
25.28
23.56
149.10
147.75
144.07
Chemical Shift (ppm)

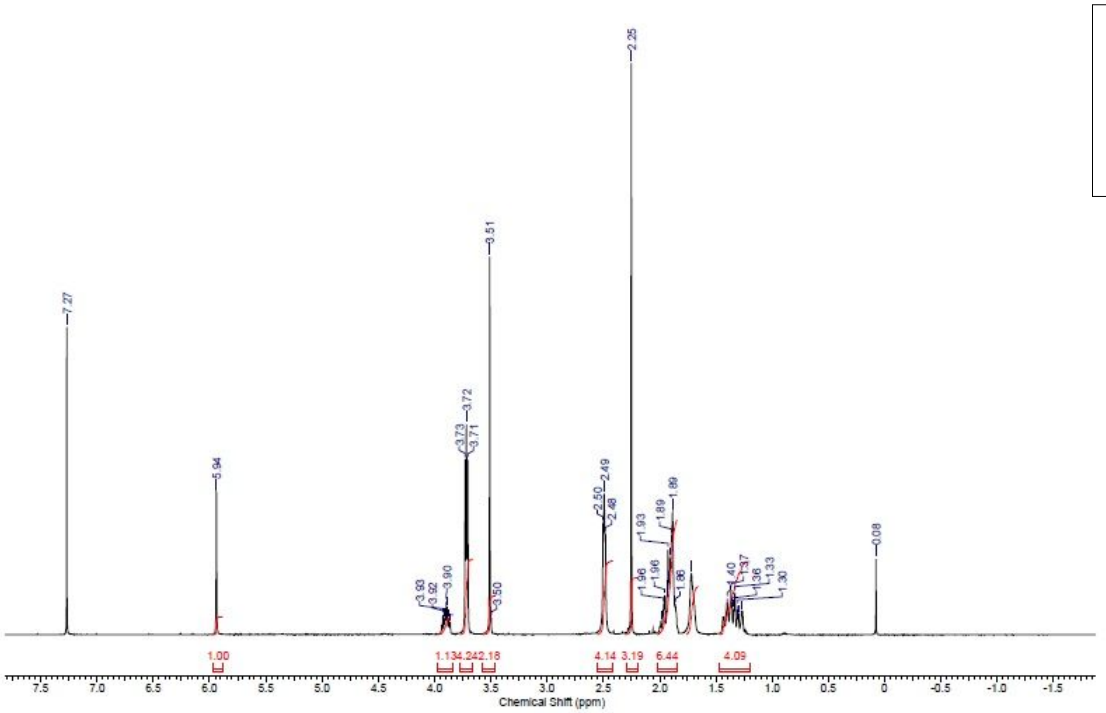

7.27
7.30
7.29
7.32
6.20
3.57
3.34
1.31
1.30
1.27
1.25
0.08
4.00
1.01
Chemical Shift (ppm)

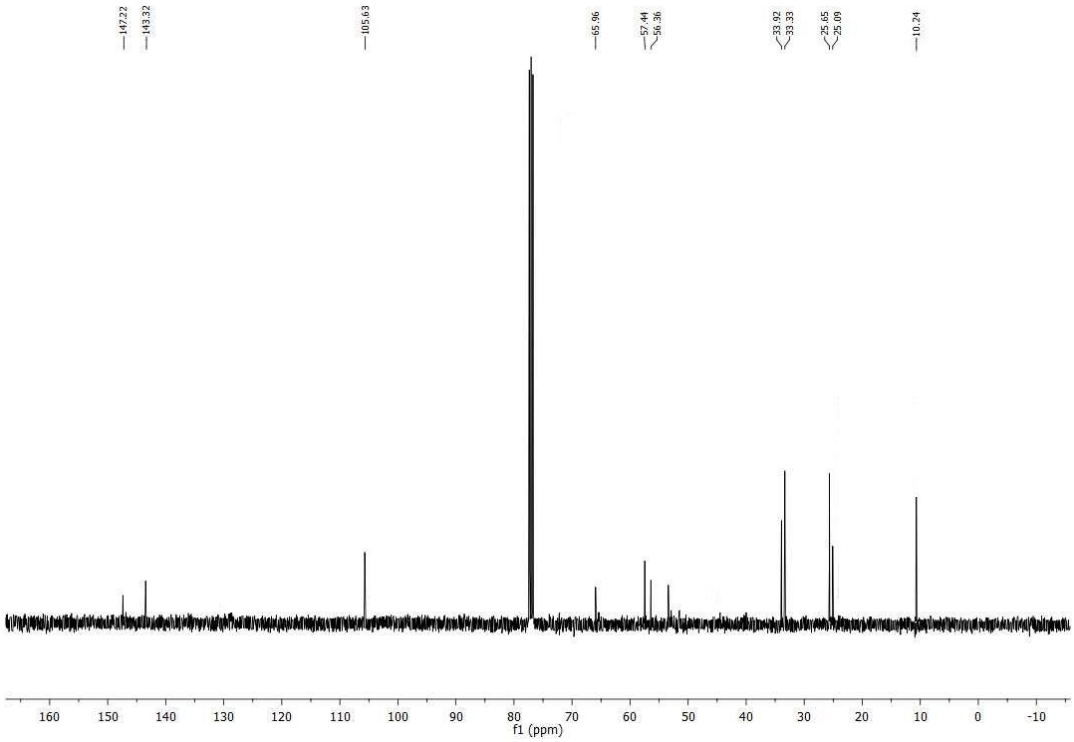

29
H3CO
N
N
N
O
CDCl3

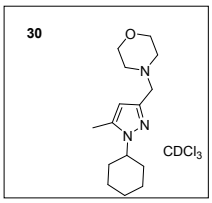

29
H3CO
N
N
N
O
CDCl3

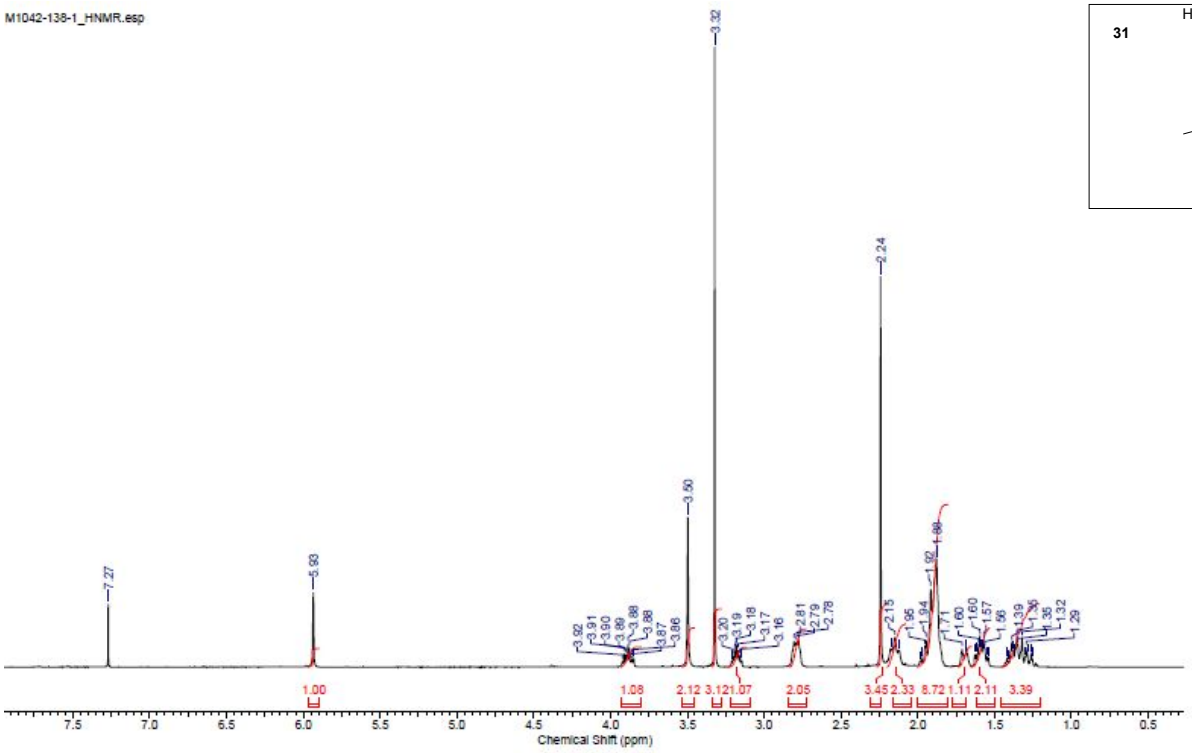

77.3
77.00
76.69
128.83
126.82
149.34
148.85
144.29
105.81
71.33
67.59
55.47
55.95
53.90
51.13
33.93
30.88
30.03
25.61
23.88
Chemical Shift (ppm)

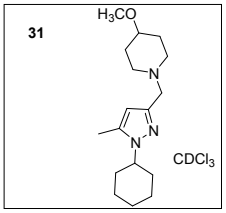

30
CDCl3

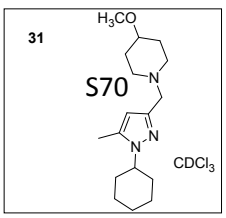

7.27
5.94
3.93
3.92
3.90
3.73
3.72
3.71
3.51
3.50
2.50
2.49
2.48
2.25
1.93
1.89
1.89
1.96
1.96
1.86
1.40
1.37
1.36
1.33
1.30
0.08
1.00
1.13
4.24
2.18
4.14
3.19
6.44
4.09
Chemical Shift (ppm)

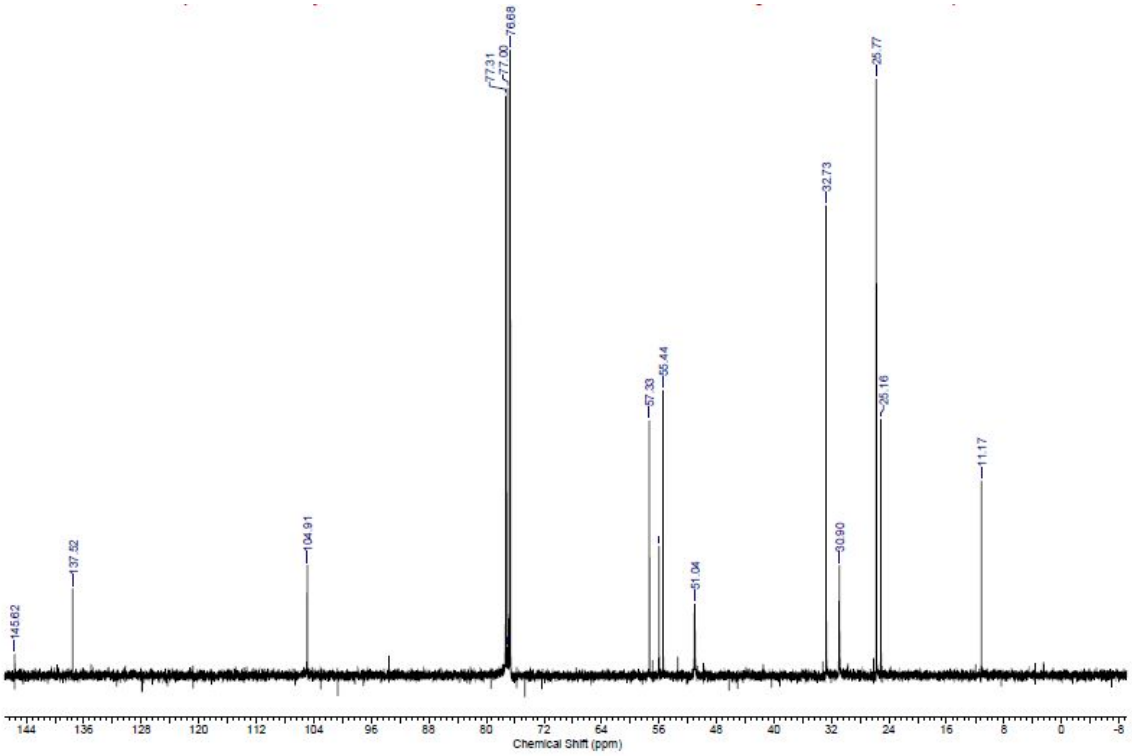

147.22
143.32
105.63
65.96
57.44
56.36
33.92
33.33
25.65
25.09
10.24
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

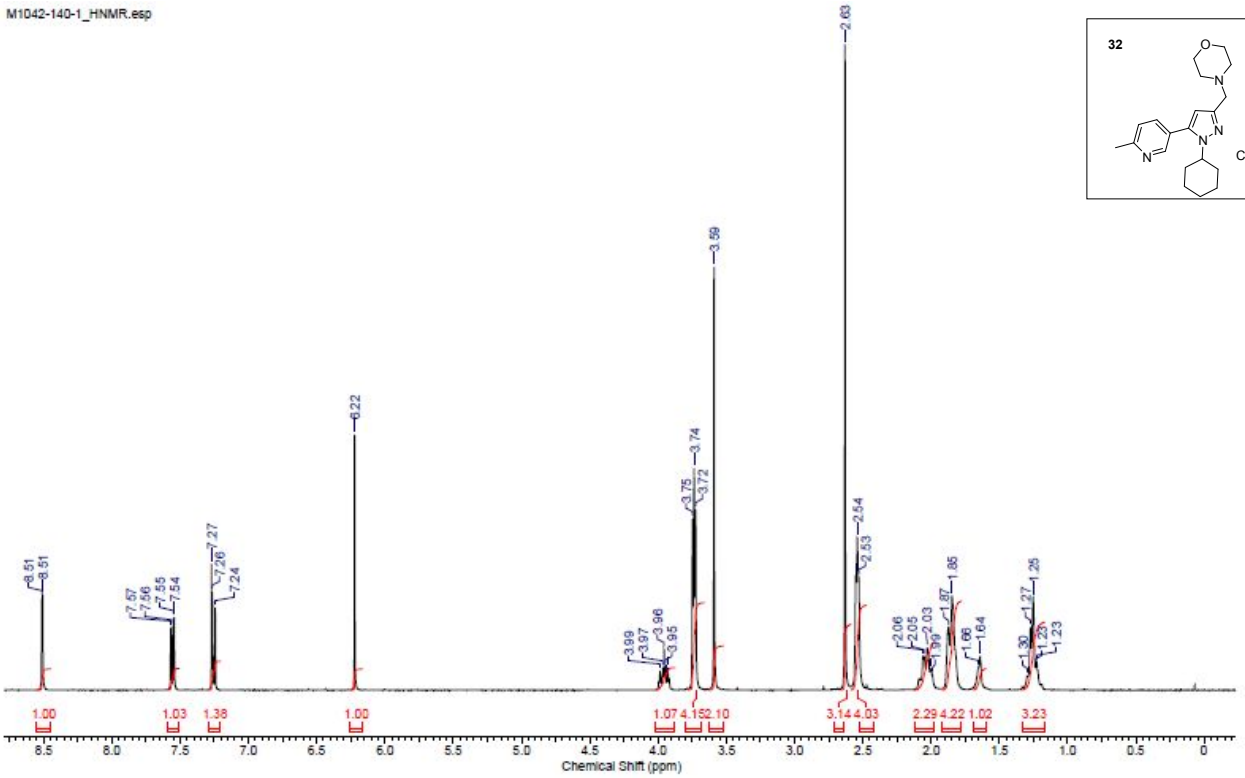

30
O
N
N
N
CDCl3


M1042-138-1_HNMR.esp
7.27
5.93
3.92
3.91
3.90
3.89
3.88
3.88
3.87
3.86
3.50
3.32
3.20
3.19
3.18
3.17
3.16
2.81
2.79
2.78
2.24
2.15
1.96
1.94
1.92
1.88
1.71
1.60
1.60
1.57
1.56
1.39
1.36
1.35
1.32
1.29
1.00
1.08
2.12
3.12
1.07
2.05
3.45
2.33
8.72
1.11
2.11
3.39
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
Chemical Shift (ppm)

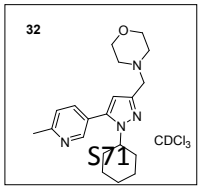

31
H3CO
N
N
N
CDCl3

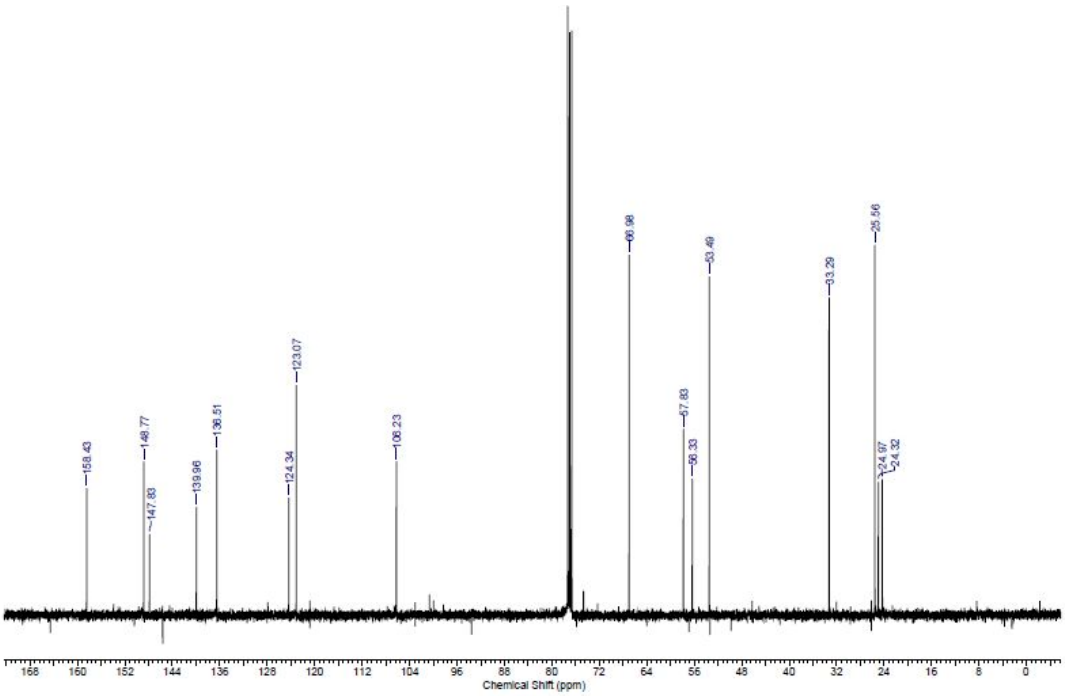

31
H3CO
N
N
N
CDCl3

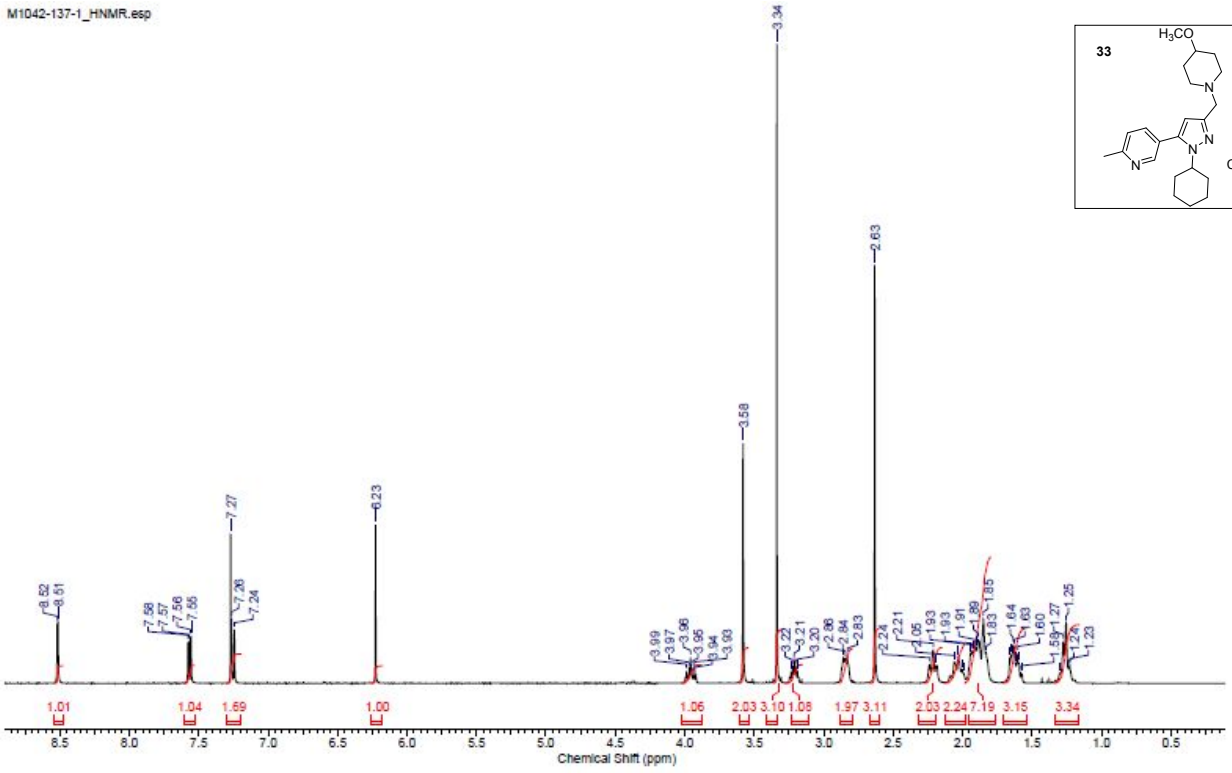

145.62
137.52
104.91
77.31
77.00
76.68
57.33
55.44
51.04
32.73
30.90
26.77
26.16
11.17
Chemical Shift (ppm)


M1042-140-1_HNMR.esp
8.51
8.51
7.57
7.56
7.55
7.54
7.27
7.26
7.24
6.22
3.99
3.97
3.96
3.95
3.75
3.74
3.72
3.59
2.63
2.54
2.53
2.06
2.05
2.03
1.99
1.87
1.86
1.66
1.64
1.30
1.27
1.26
1.23
1.00
1.03
1.38
1.00
1.07
4.15
2.10
3.14
4.03
2.29
4.22
1.02
3.23
Chemical Shift (ppm)

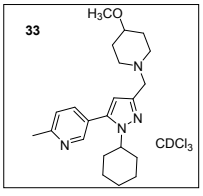
32
CDCl3

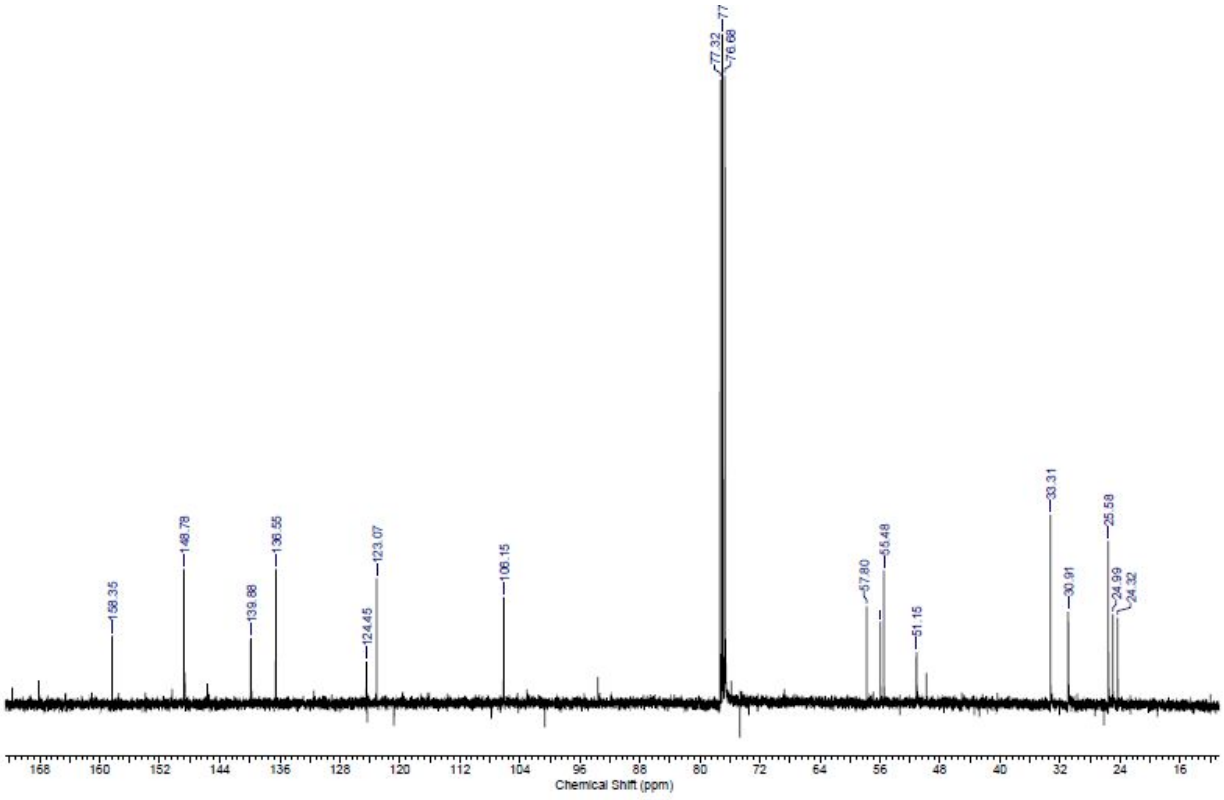

32
CDCl3

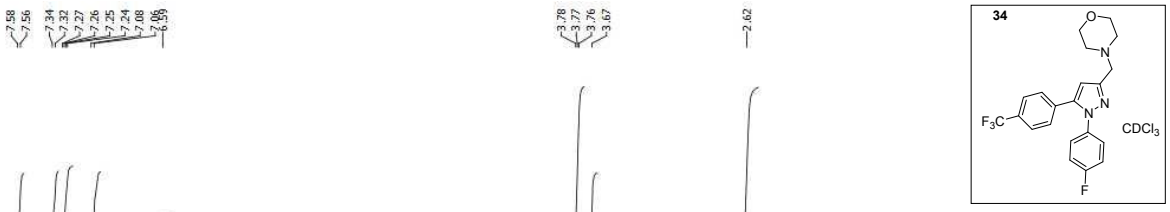

158.43
148.77
147.83
139.96
136.51
124.34
123.07
106.23
66.98
57.83
56.33
53.49
33.29
25.56
24.97
24.32
Chemical Shift (ppm)

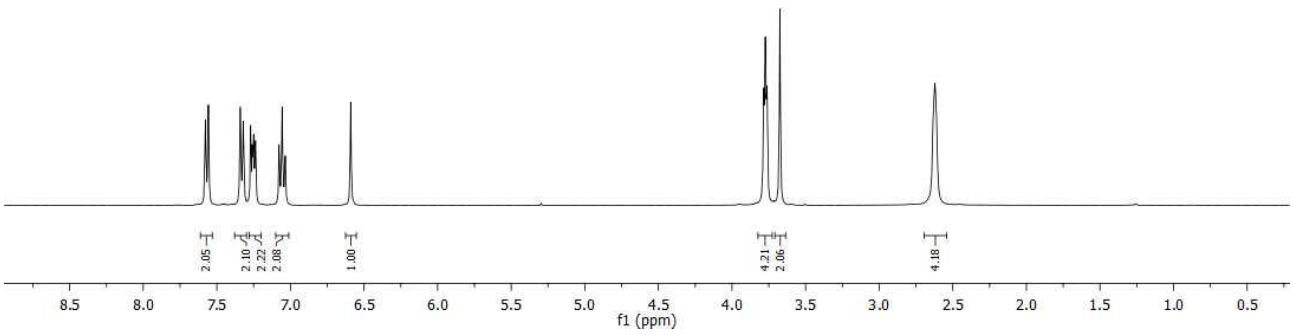

M1042-137-1_HNMR.esp
8.52
8.51
7.58
7.57
7.56
7.55
7.27
7.26
7.24
6.23
3.99
3.97
3.96
3.95
3.94
3.93
3.58
3.34
3.22
3.21
3.20
2.86
2.84
2.83
2.63
2.24
2.21
2.05
1.93
1.93
1.91
1.89
1.85
1.83
1.64
1.63
1.60
1.59
1.27
1.26
1.25
1.23
1.01
1.04
1.69
1.00
1.06
2.03
3.10
1.08
1.97
3.11
2.03
2.24
7.19
3.15
3.34
Chemical Shift (ppm)

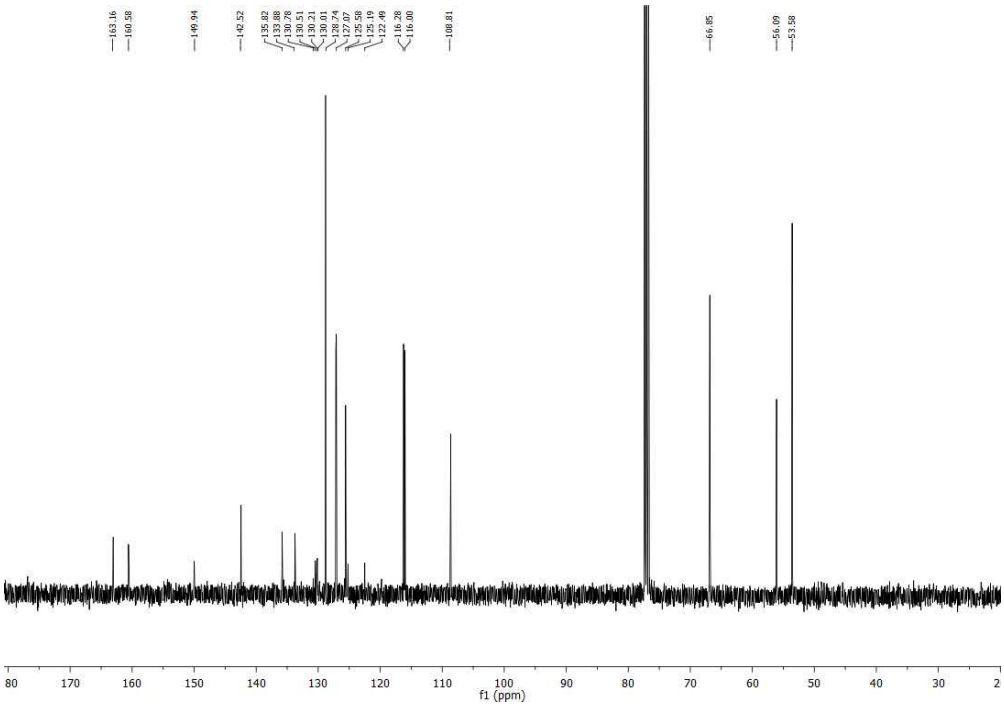
33
H3CO
N
N
N
CDCl3

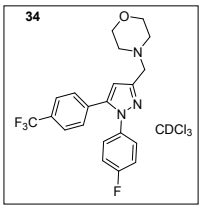

33
H3CO
N
N
N
CDCl3

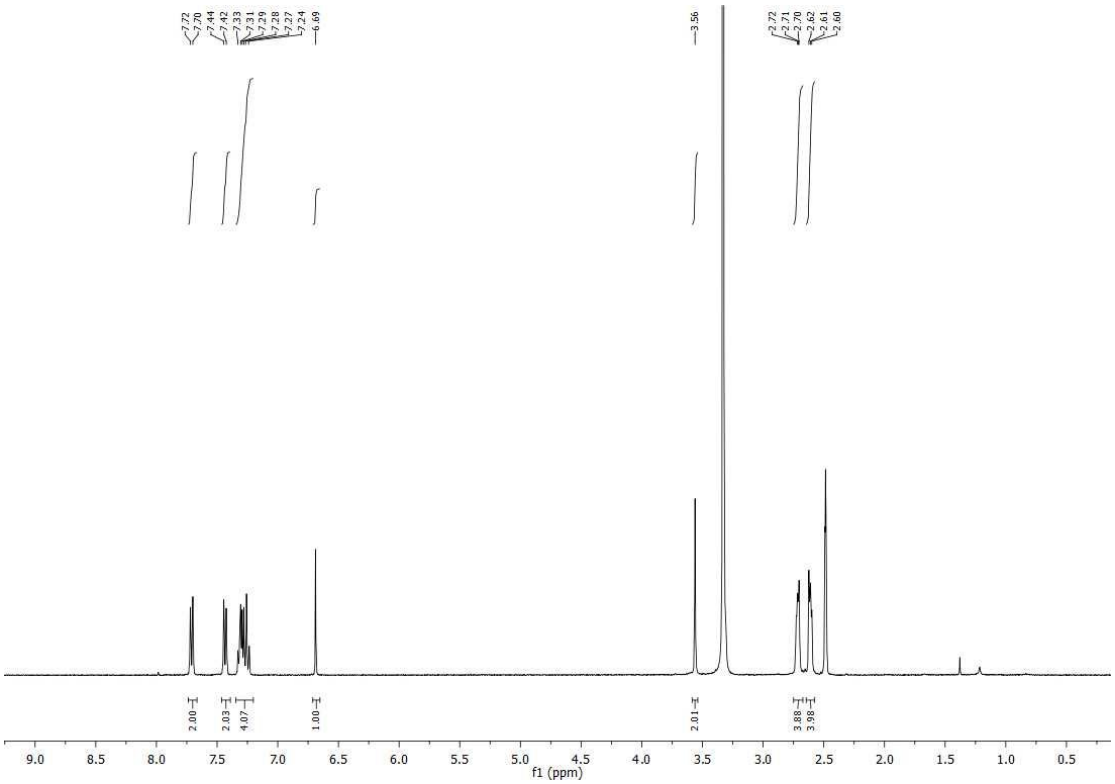

77.32
77
76.68
158.35
148.78
139.88
136.55
124.45
123.07
106.15
57.80
55.48
51.15
33.31
30.91
25.58
24.99
24.32
Chemical Shift (ppm)

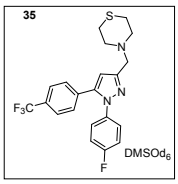

7.58
7.56
7.34
7.32
7.27
7.26
7.25
7.24
7.08
7.06
6.99
3.78
3.77
3.76
3.67
2.62
34
CDCl3

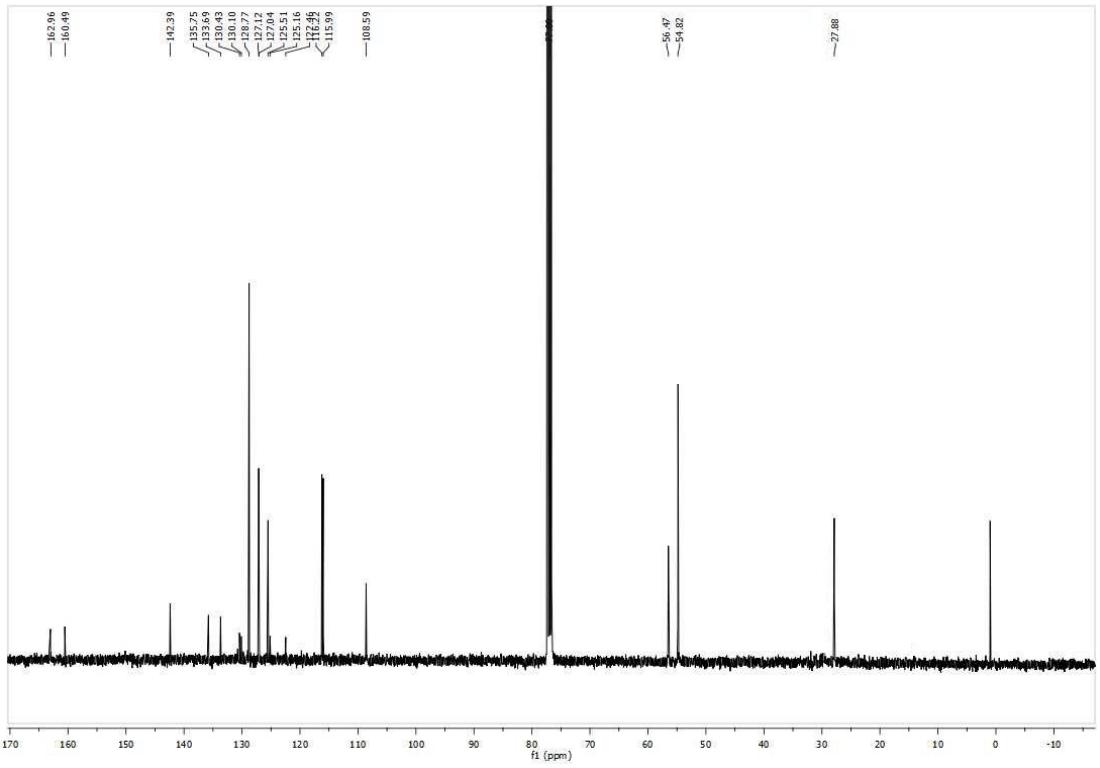

2.05
2.10
2.22
2.08
1.00
4.21
2.06
4.18
f1 (ppm)

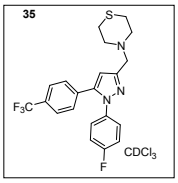

163.16
160.58
149.94
142.52
135.82
133.88
130.78
130.51
130.21
130.01
128.74
127.07
125.58
125.49
122.49
116.28
116.00
108.81
66.85
56.09
53.58
f1 (ppm)

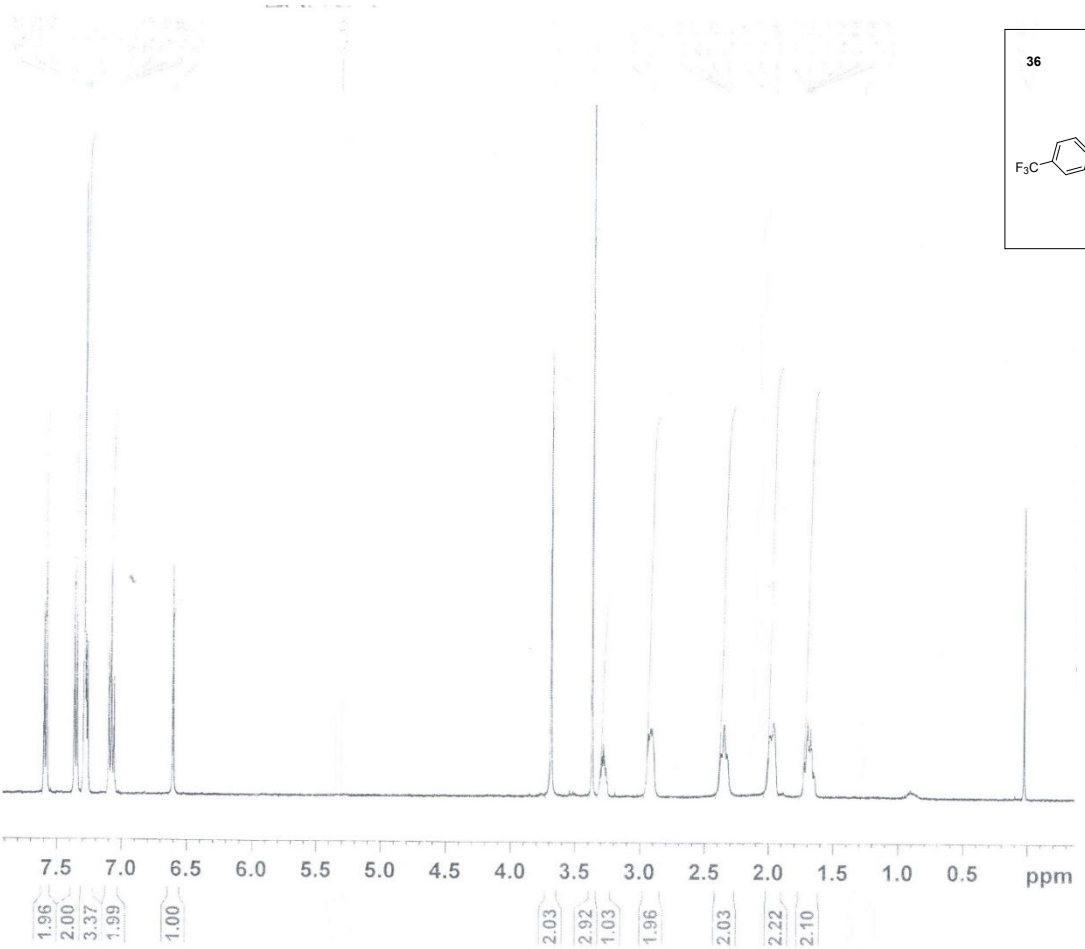

34
O
N
N
N
F3C
CDCl3
F

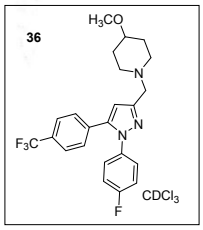

7.72
7.70
7.44
7.42
7.33
7.31
7.29
7.28
7.27
7.24
6.69
3.56
2.72
2.71
2.70
2.62
2.61
2.60
2.00
2.03
4.07
1.00
2.01
3.88
3.98
f1 (ppm)

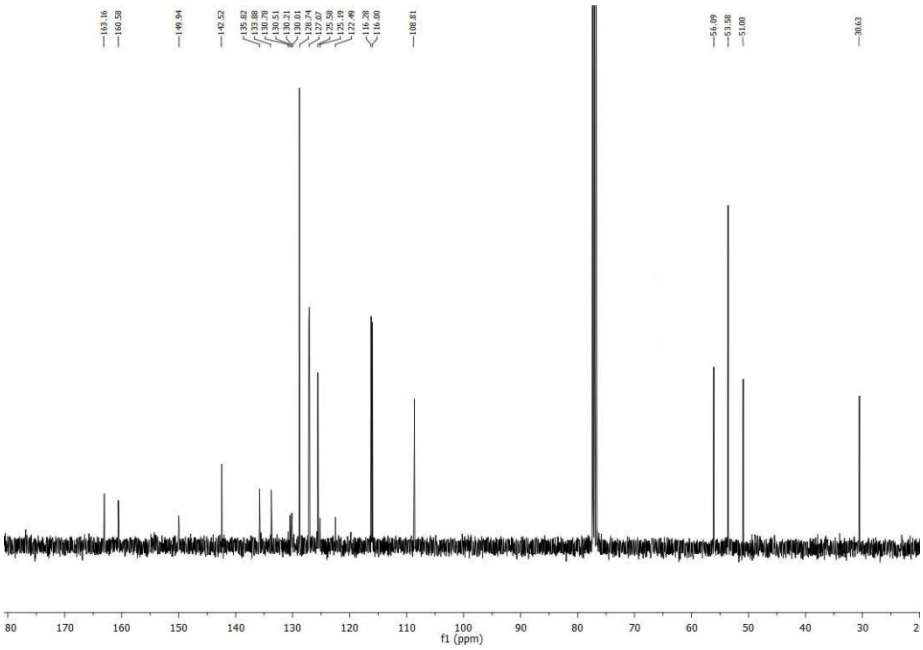

35
S
N
N
N
F3C
DMSOd6
F


162.96
160.49
142.39
135.75
133.69
130.43
130.10
128.77
127.12
127.04
125.51
125.16
116.35
115.99
108.59
56.47
54.82
27.88
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


35
S
N
N
N
F3C
CDCl3
F


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
ppm
1.96
2.00
3.37
1.99
1.00
2.03
2.92
1.03
1.96
2.03
2.22
2.10


36
H3CO
N
N
N
F3C
CDCl3
F


163.16
160.58
149.94
142.52
135.82
133.88
130.78
130.51
130.21
130.01
128.74
127.67
125.58
125.39
122.49
116.28
116.00
108.81
56.09
53.58
51.00
30.63
80
170
160
150
140
130
120
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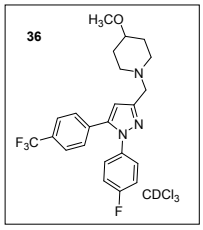
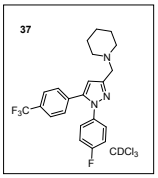
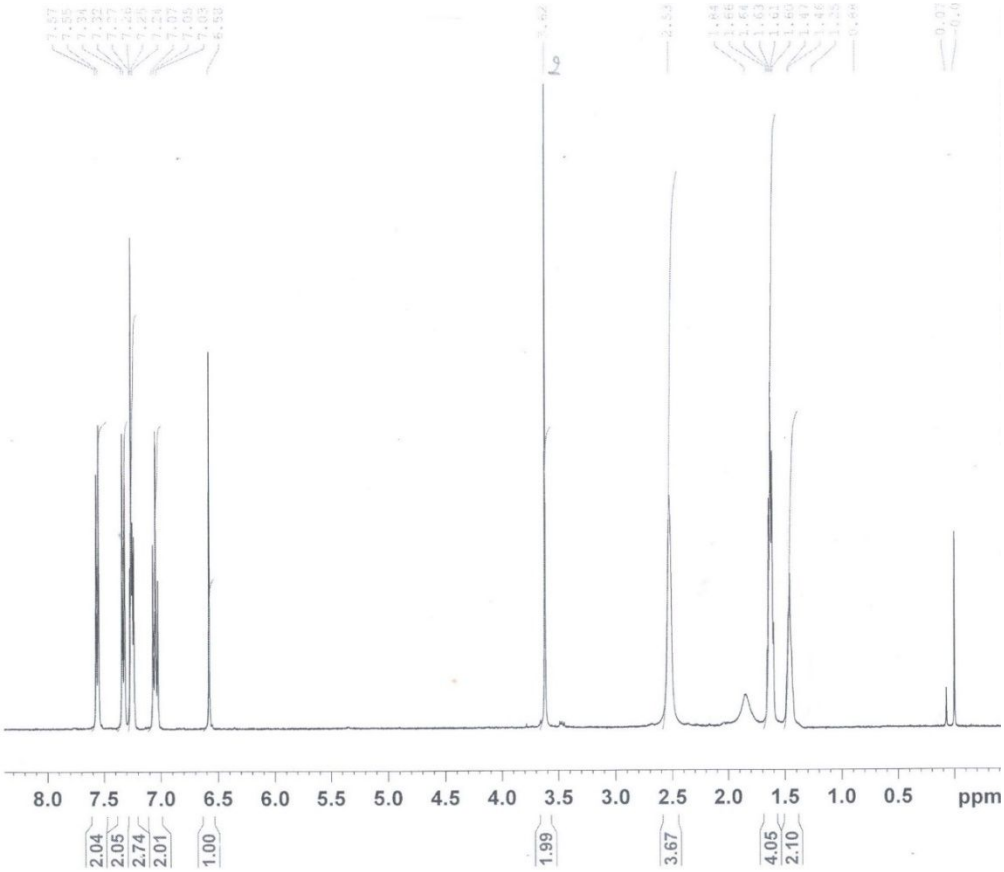
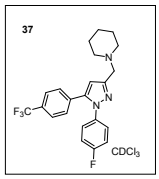
80
70
60
50
40
30
2
f1 (ppm)

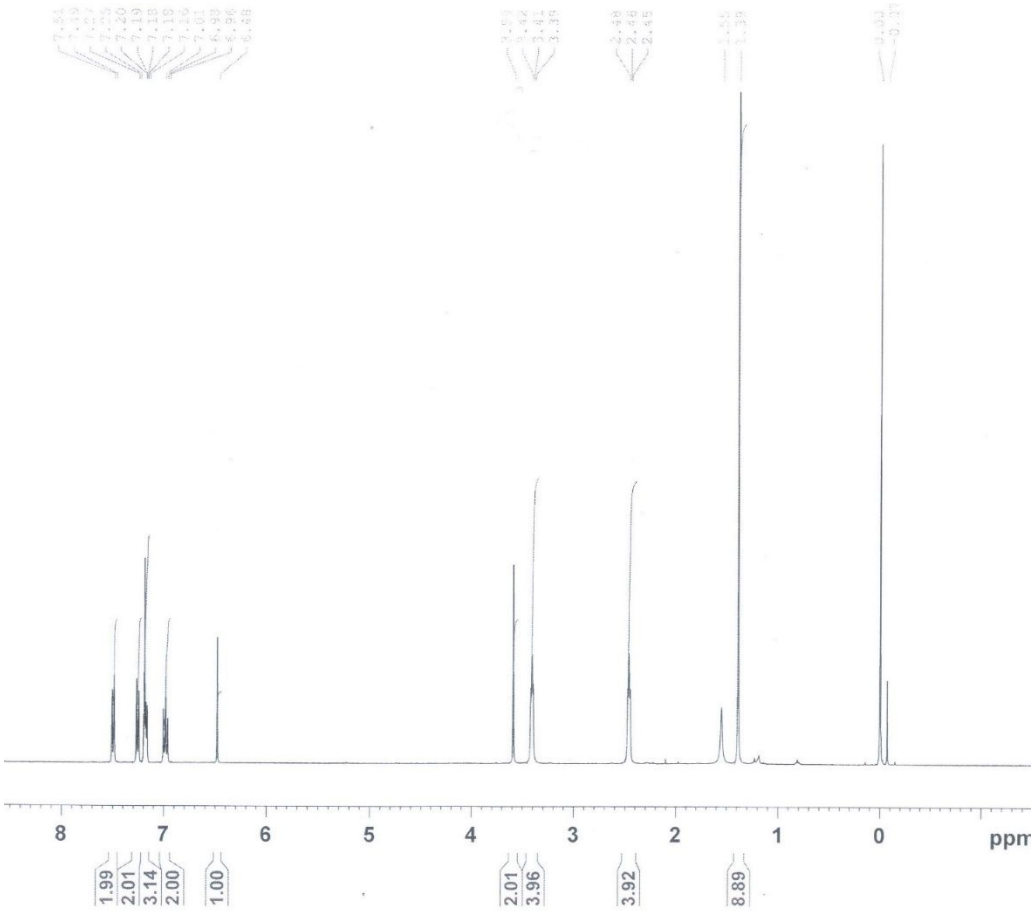

36
H3CO
N
N
N
F3C
CDCl3
F

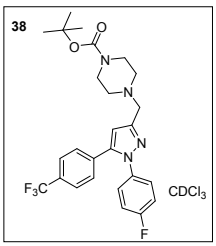

37
N
N
N
F3C
CDCl3
F

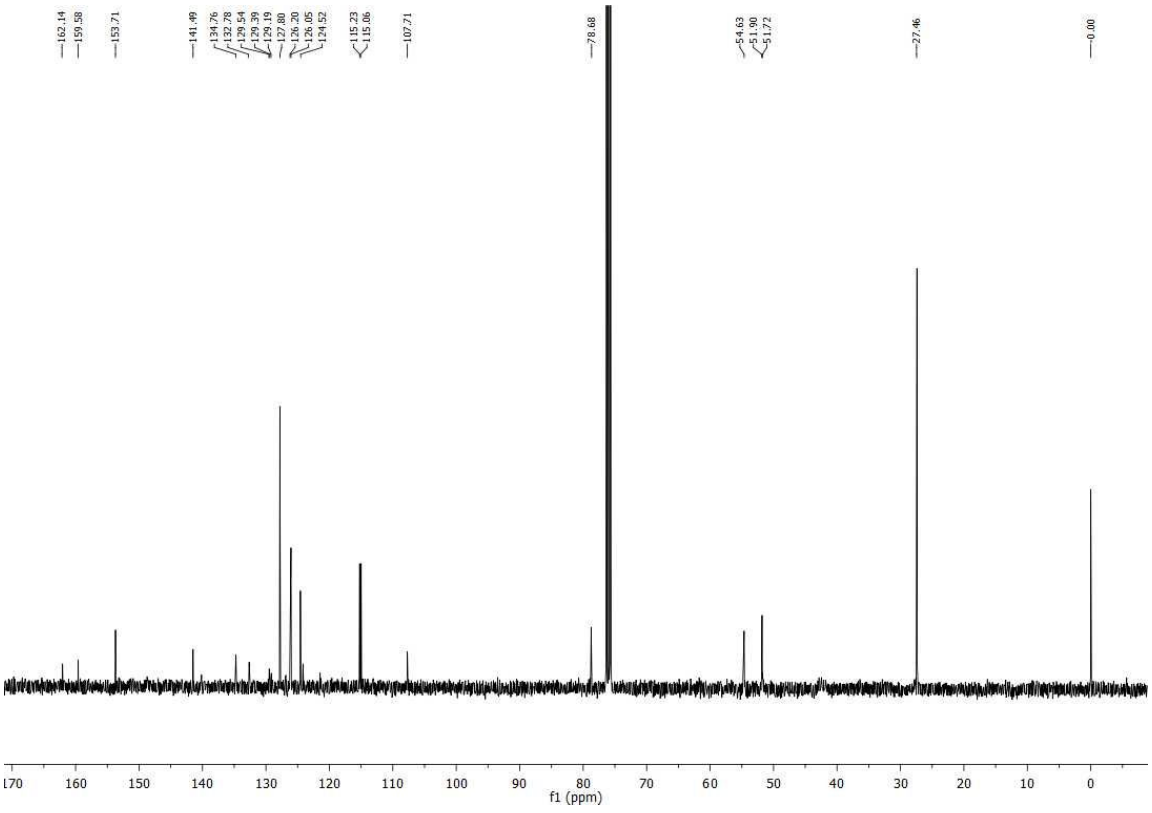

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.04
2.05
2.74
2.01
1.00
1.99
3.67
4.05
2.10

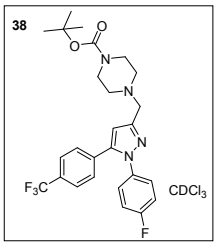

37
N
N
N
F3C
CDCl3
F

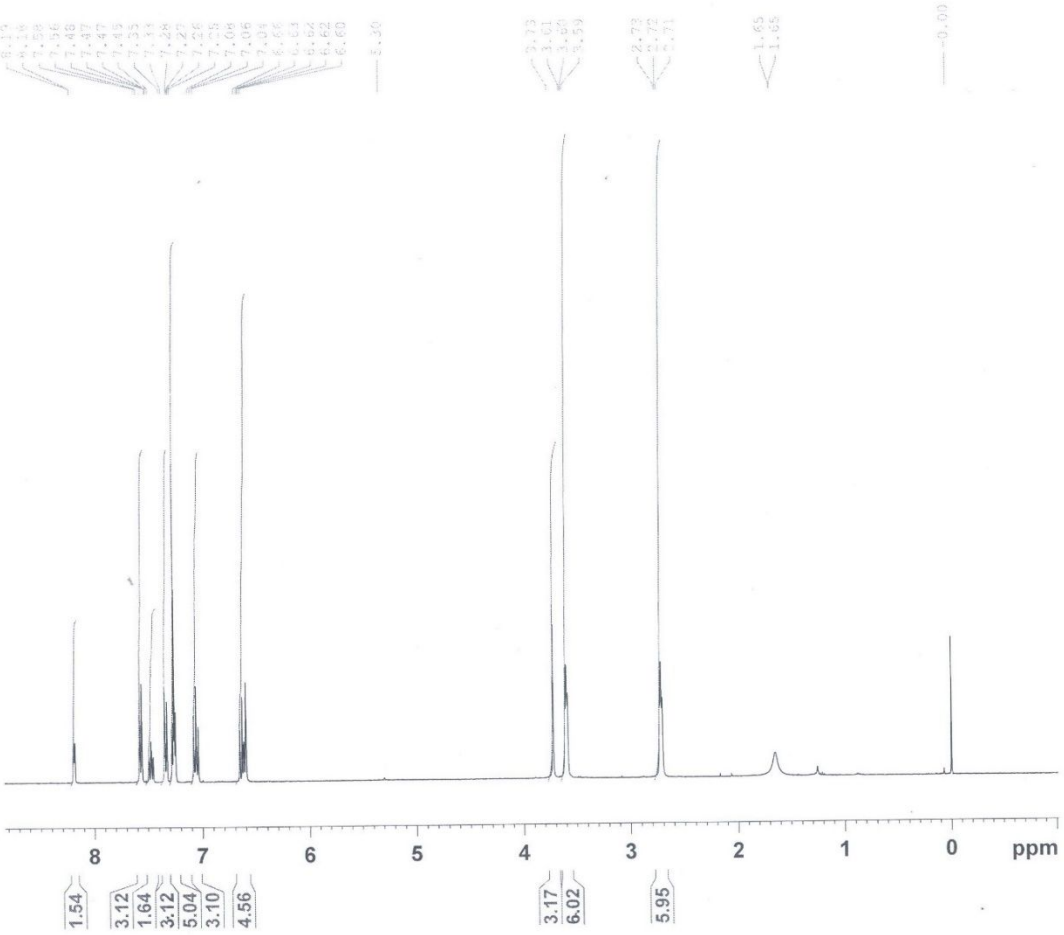
163.15
160.54
142.53
135.93
133.85
130.47
130.03
129.63
128.80
127.28
127.16
125.57
115.96
109.05
108.79
56.49
54.53
25.98
24.09
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

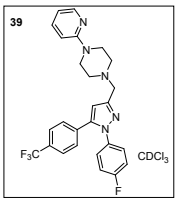

8
7
6
5
4
3
2
1
0
ppm
1.99
2.01
3.14
2.00
1.00
2.01
3.96
3.92
8.89

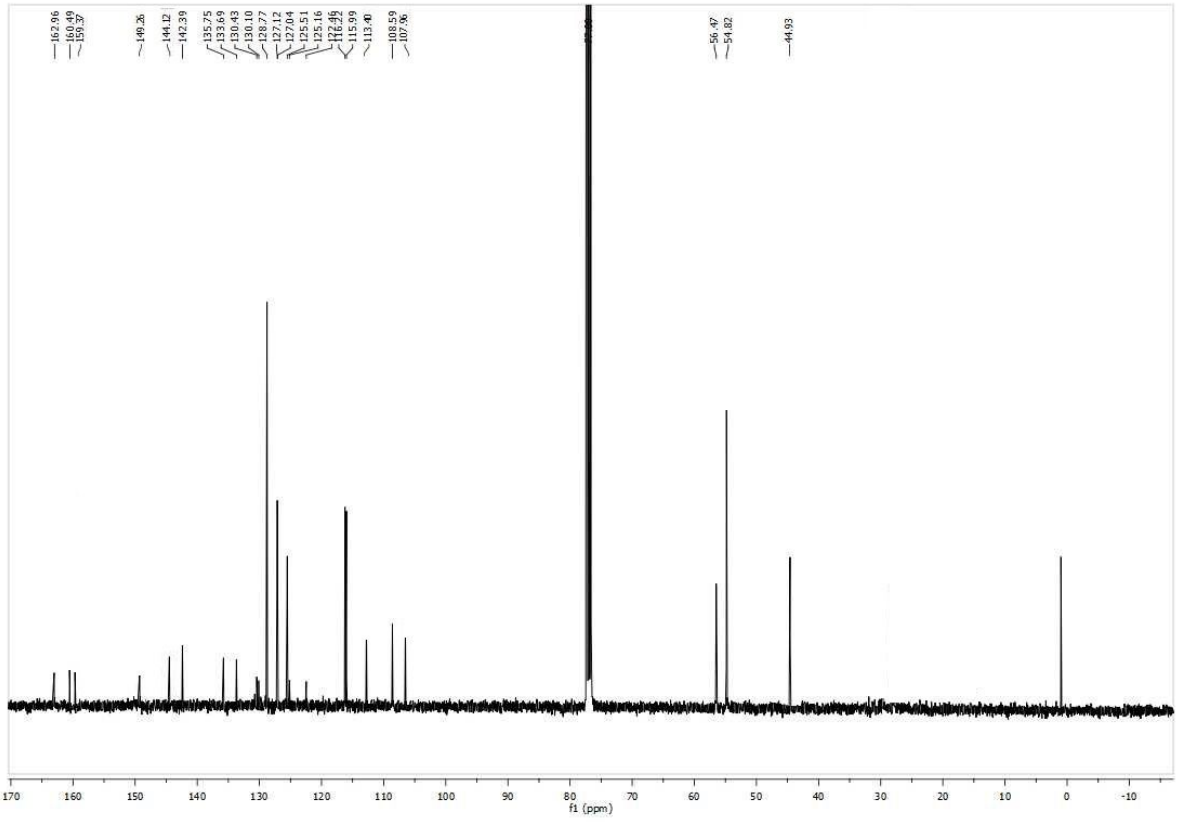

38
F3C
CDCl3
F


162.14
159.58
153.71
141.49
134.76
132.78
129.54
129.39
129.19
127.80
126.20
126.05
124.52
115.23
115.06
107.71
78.68
54.63
51.90
51.72
27.46
0.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


38
F3C
CDCl3
F


8.13
8.12
7.58
7.56
7.48
7.47
7.45
7.33
7.28
7.27
7.26
7.05
7.04
7.03
6.66
6.64
6.62
6.60
5.30
3.73
3.61
3.59
2.72
2.71
1.65
1.65
0.00
8
7
6
5
4
3
2
1
0
ppm
1.54
3.12
1.64
3.12
5.04
3.10
4.56
3.17
6.02
5.95


39
N
N
N
N
F3C
CDCl3
F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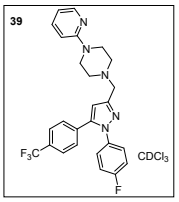
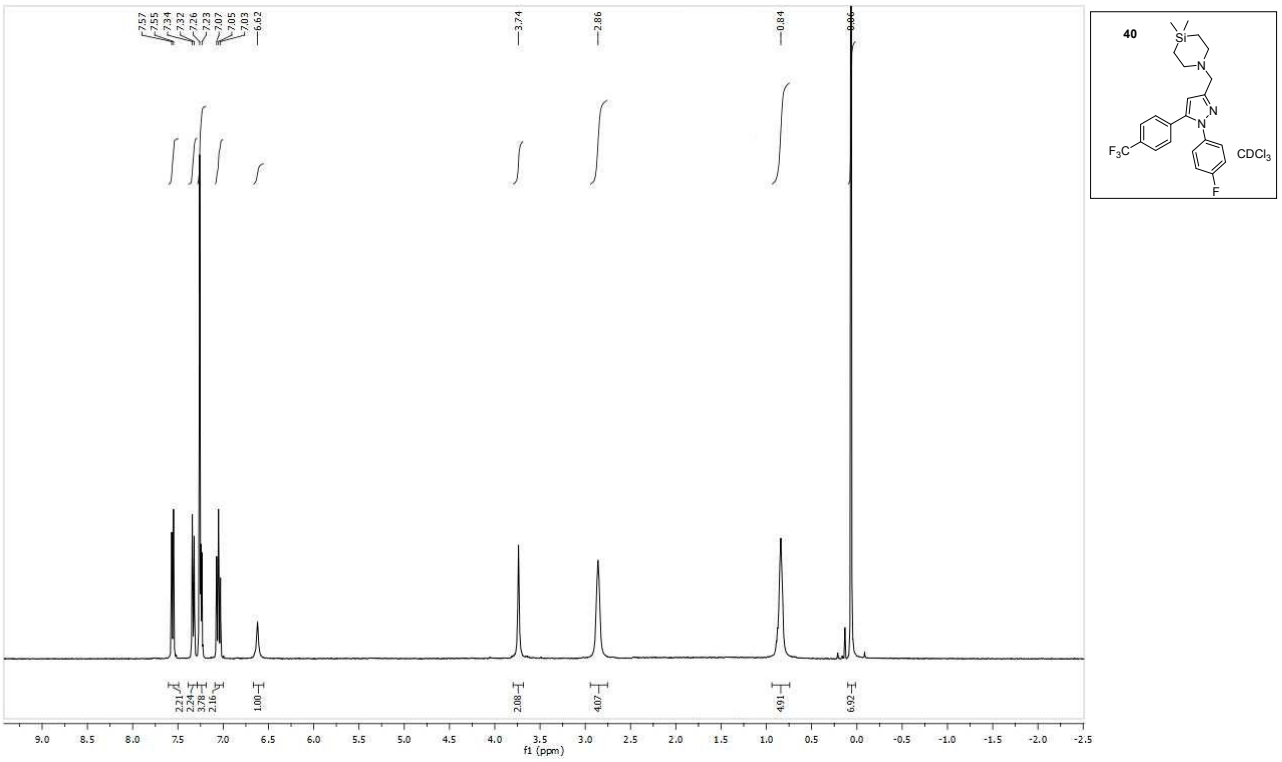
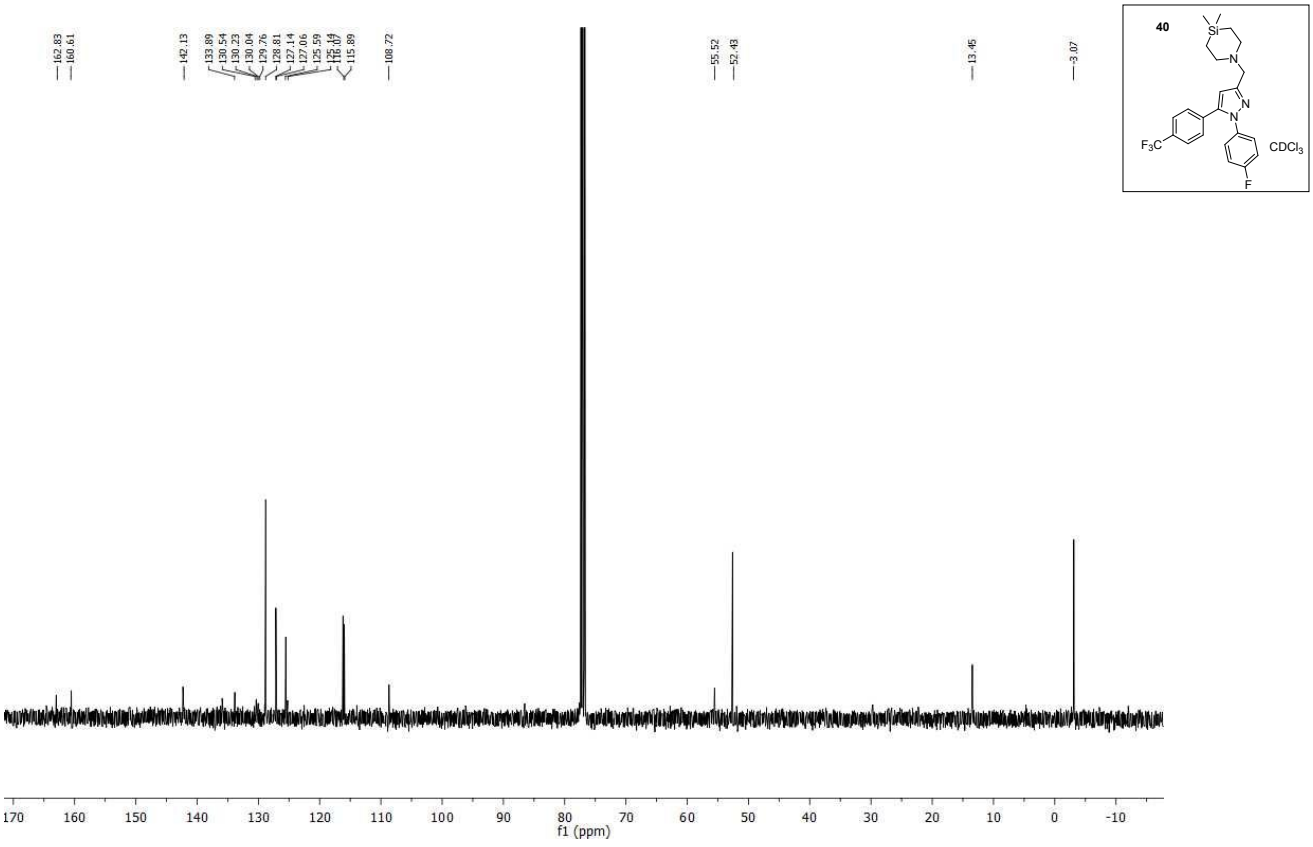
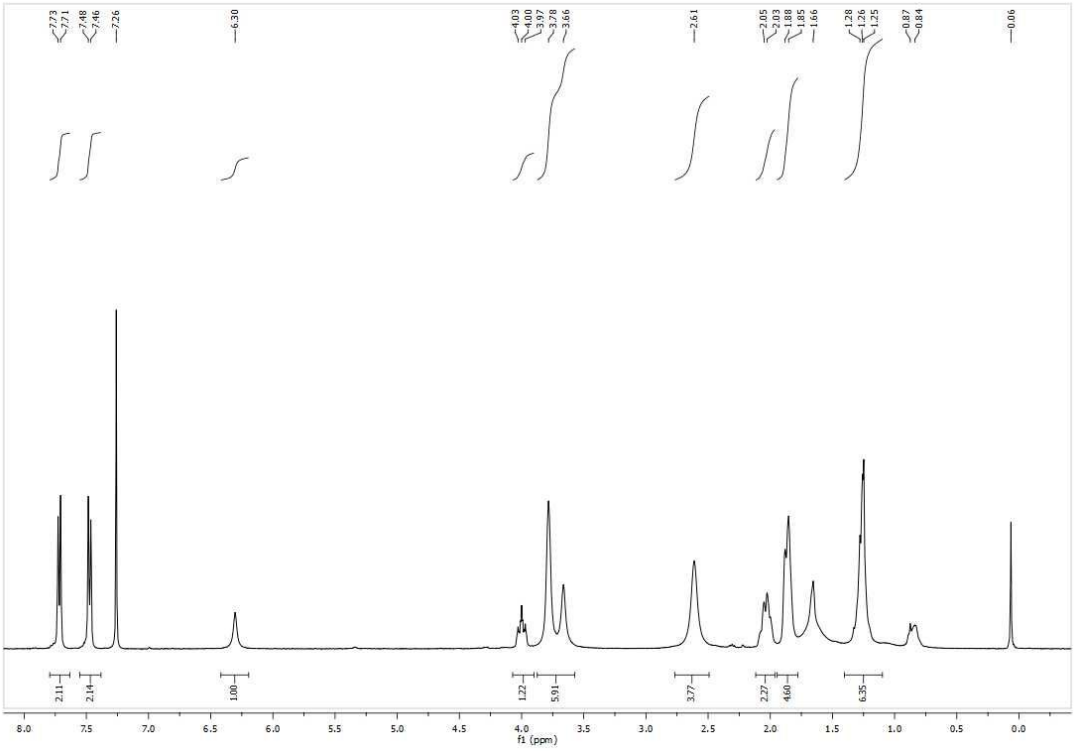
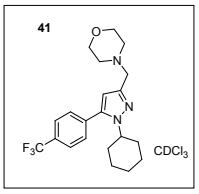
160.49
159.37
149.26
144.12
142.39
135.75
133.69
130.43
130.10
128.77
127.12
127.04
125.51
125.16
122.46
116.22
115.99
113.40
108.59
107.96
77.00
56.47
54.82
44.93
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

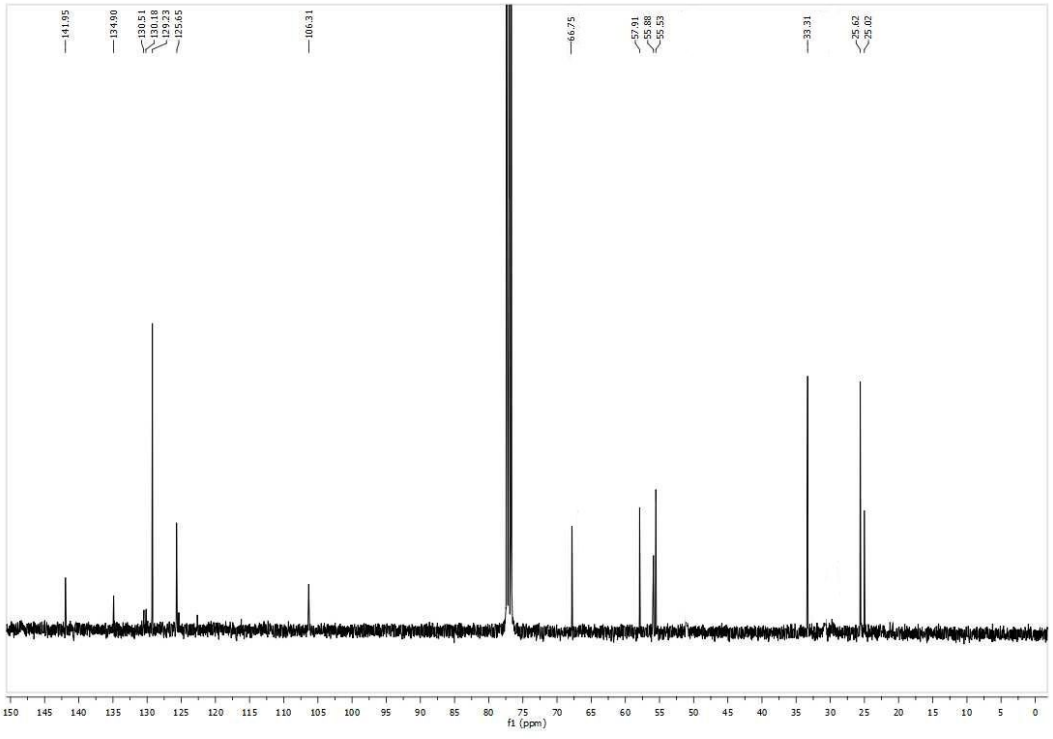

39
N
N
N
N
F3C
CDCl3
F

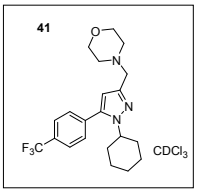

7.57
7.55
7.34
7.32
7.26
7.23
7.07
7.05
7.03
6.62
3.74
2.86
0.84
0.06
2.21
2.24
3.78
2.16
1.00
2.08
4.07
4.91
6.02
f1 (ppm)
40
Si
N
N
F3C
CDCl3
F

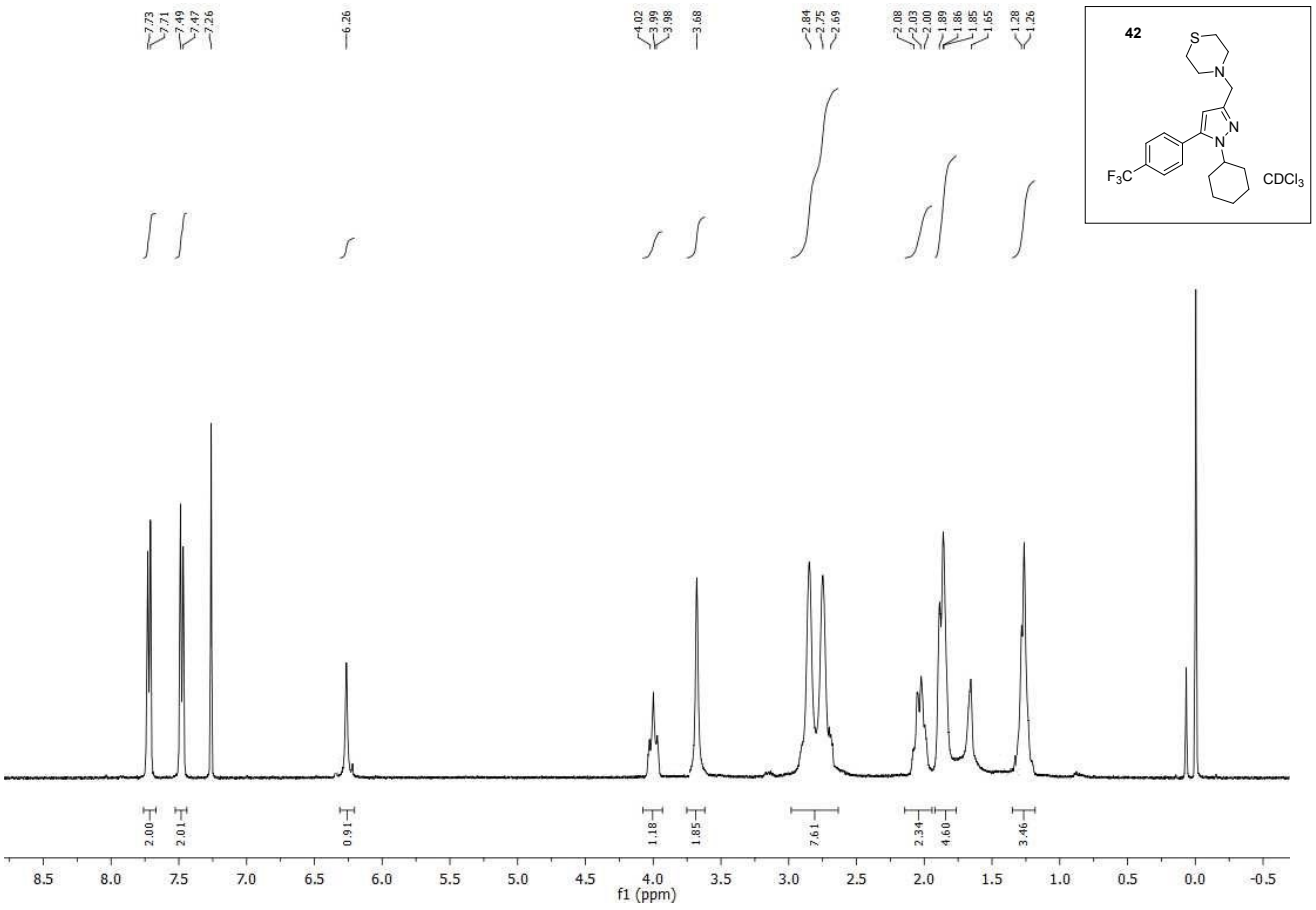

162.83
160.61
142.13
133.89
130.54
130.23
130.04
129.76
128.81
127.14
127.06
125.59
115.89
108.72
55.52
52.43
13.46
-3.07
f1 (ppm)
40
Si
N
N
F3C
CDCl3
F


7.73
7.71
7.48
7.46
7.26
6.30
4.03
4.00
3.97
3.78
3.66
2.61
2.05
2.03
1.88
1.85
1.66
1.28
1.26
1.25
0.87
0.84
0.06
2.11
2.14
1.00
1.22
5.91
3.77
2.27
4.60
6.35
f1 (ppm)

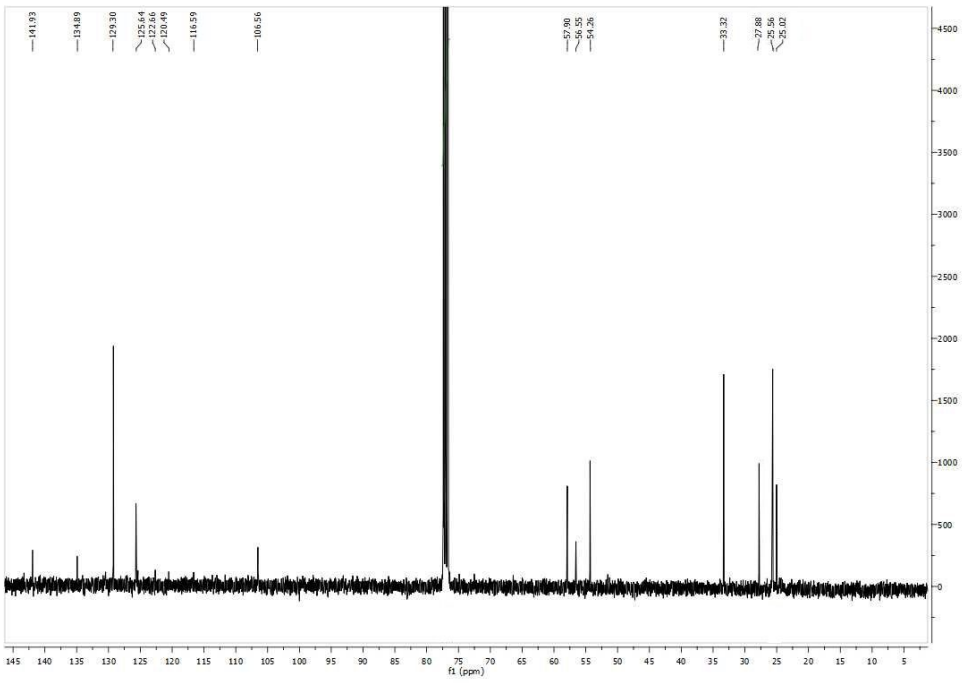

41
O
N
N
N
F3C
CDCl3

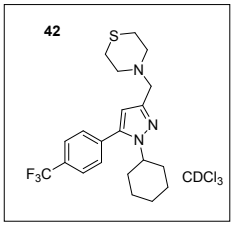

141.95
134.90
130.51
130.18
129.23
125.65
106.31
66.75
57.91
55.88
55.53
33.31
25.62
25.02
f1 (ppm)

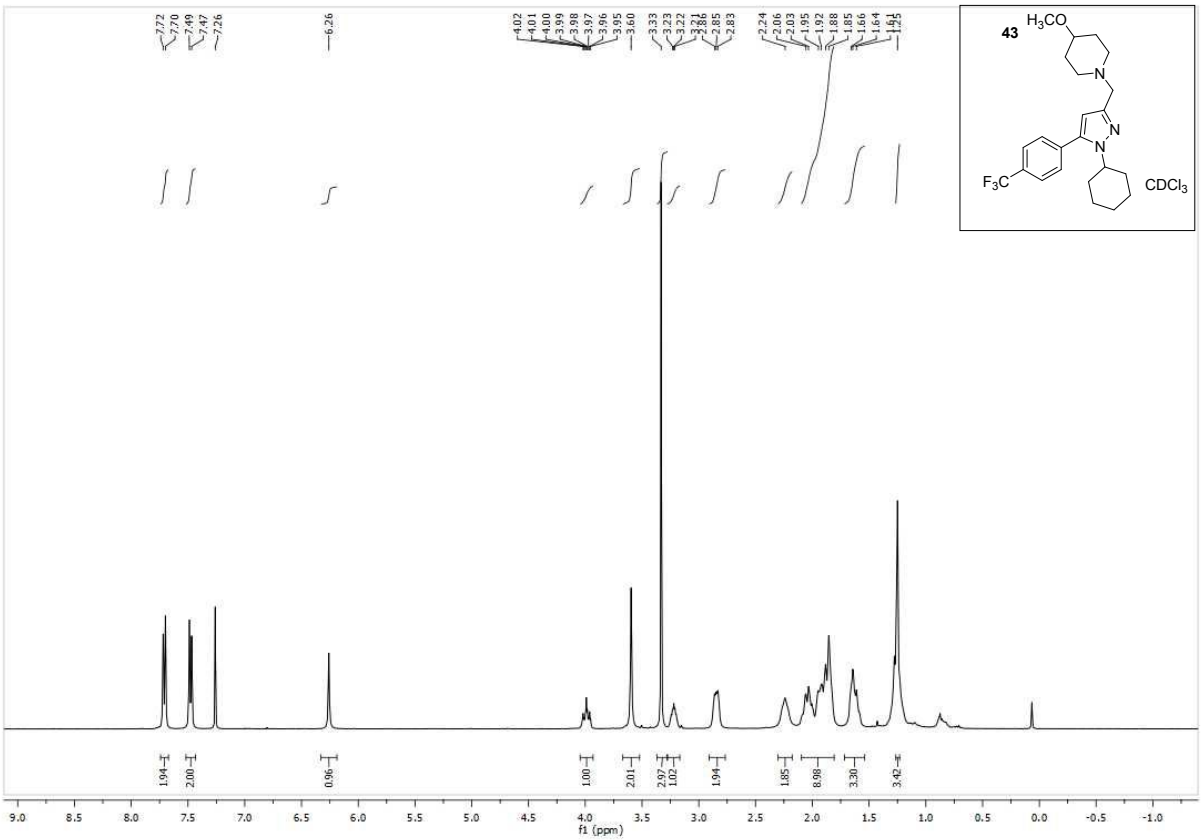

41
O
N
N
N
F3C
CDCl3


7.73
7.71
7.49
7.47
7.26
6.26
4.02
3.99
3.98
3.68
2.84
2.75
2.69
2.08
2.03
2.00
1.89
1.86
1.85
1.65
1.28
1.26
2.00
2.01
0.91
1.18
1.85
7.61
2.34
4.60
3.46
f1 (ppm)

42
S
N
N
N
F3C
CDCl3


141.93
134.89
129.30
125.64
123.56
120.49
116.59
106.56
57.90
56.55
54.26
33.32
27.88
25.56
25.02
f1 (ppm)


42
S
N
N
N
F3C
CDCl3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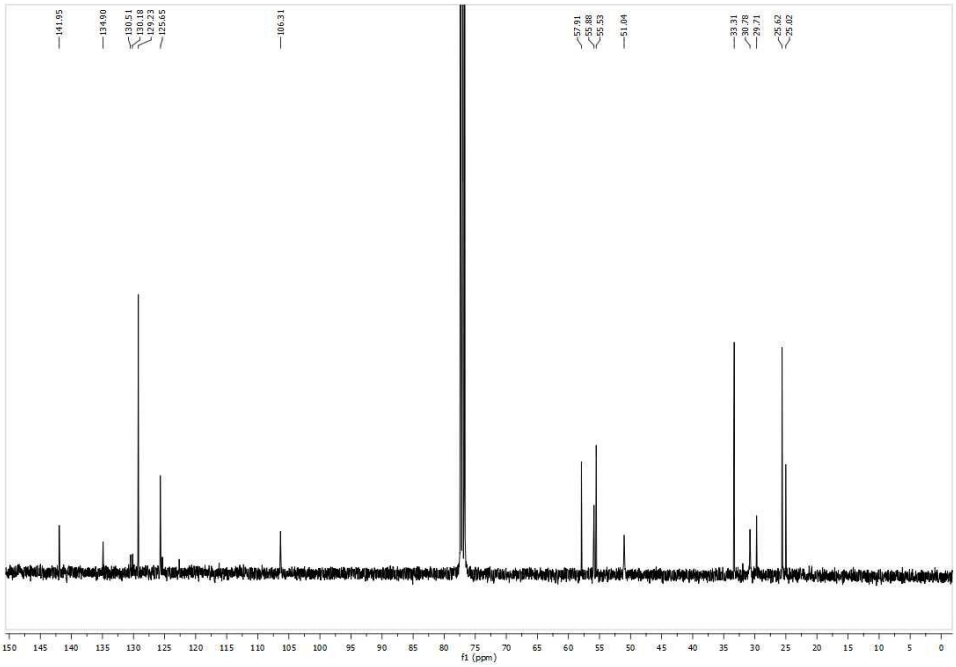
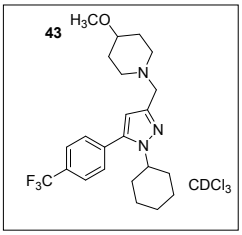
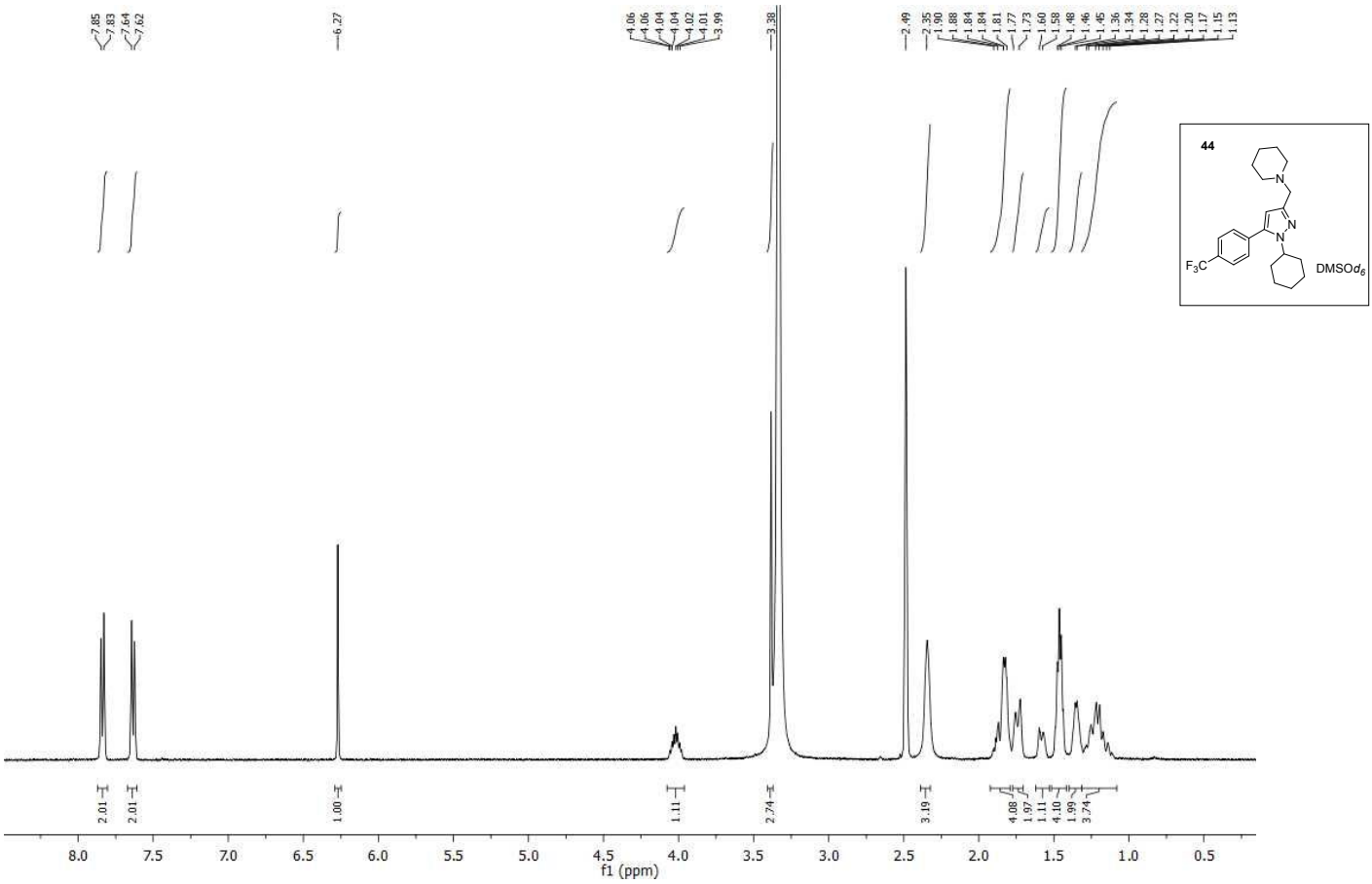
7.70
7.49
7.47
7.26
6.26
4.02
4.01
4.00
3.99
3.98
3.97
3.96
3.95
3.60
3.33
3.23
3.22
3.21
2.88
2.85
2.83
2.24
2.06
2.03
1.95
1.92
1.88
1.85
1.66
1.64
1.61
1.25
1.94
2.00
0.96
1.00
2.01
2.97
1.02
1.94
1.85
8.98
3.30
3.42
f1 (ppm)

43
H3CO
N
N
N
F3C
CDCl3


141.95
134.90
130.51
130.18
129.23
125.65
106.31
57.91
55.88
55.53
51.04
33.31
30.78
29.71
25.62
25.02
f1 (ppm)


43
H3CO
N
N
N
F3C
CDCl3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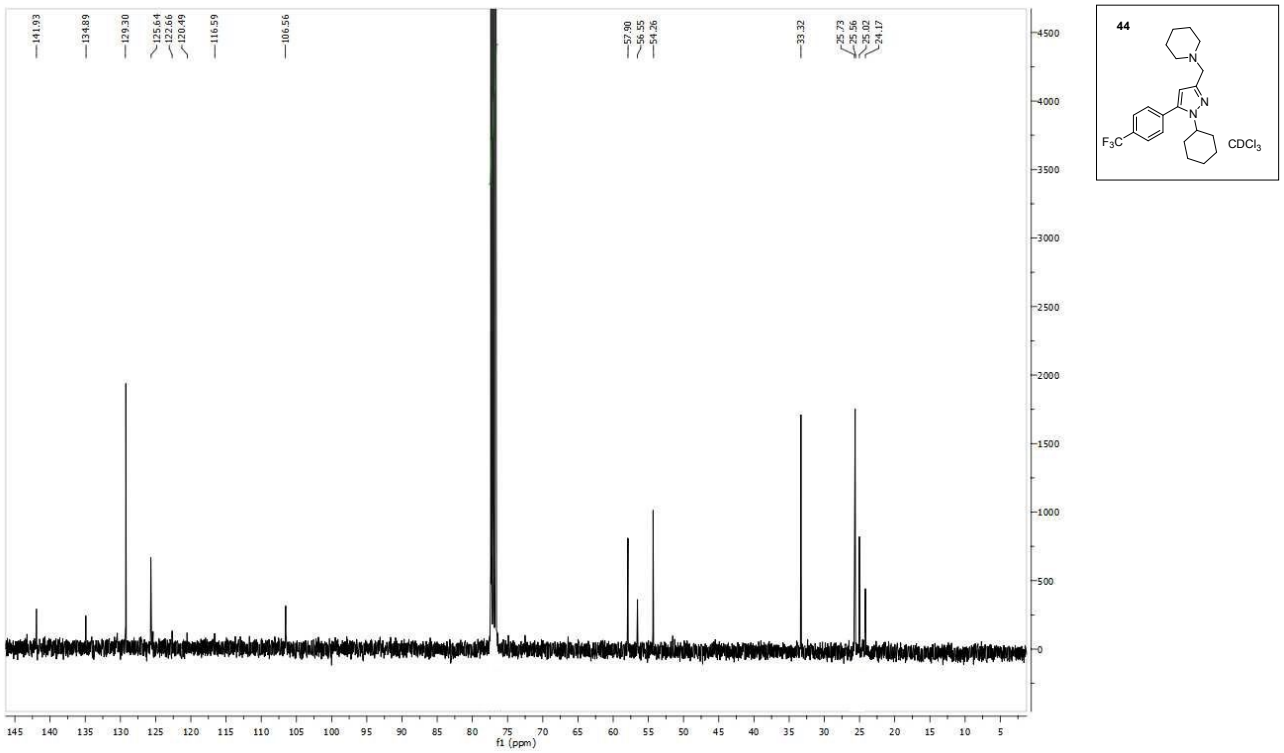
7.83
7.64
7.62
6.27
4.06
4.06
4.04
4.04
4.02
4.01
3.99
3.38
2.49
2.35
1.90
1.88
1.84
1.84
1.81
1.77
1.73
1.60
1.58
1.48
1.46
1.45
1.36
1.34
1.28
1.27
1.22
1.20
1.17
1.15
1.13
2.01
2.01
1.00
1.11
2.74
3.19
4.08
1.97
1.11
4.10
1.99
3.74
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
44
F3C
DMSOd6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134.89
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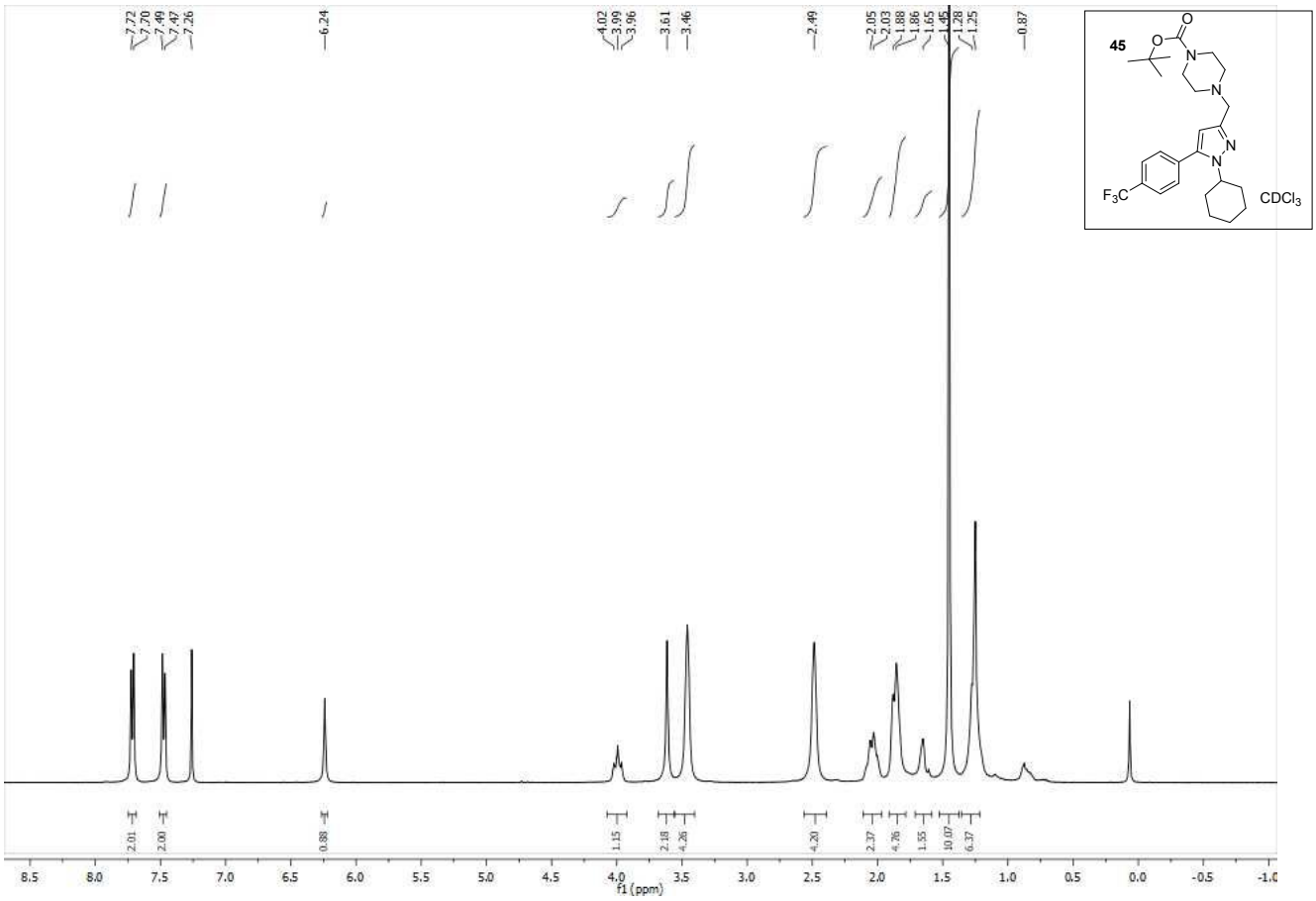
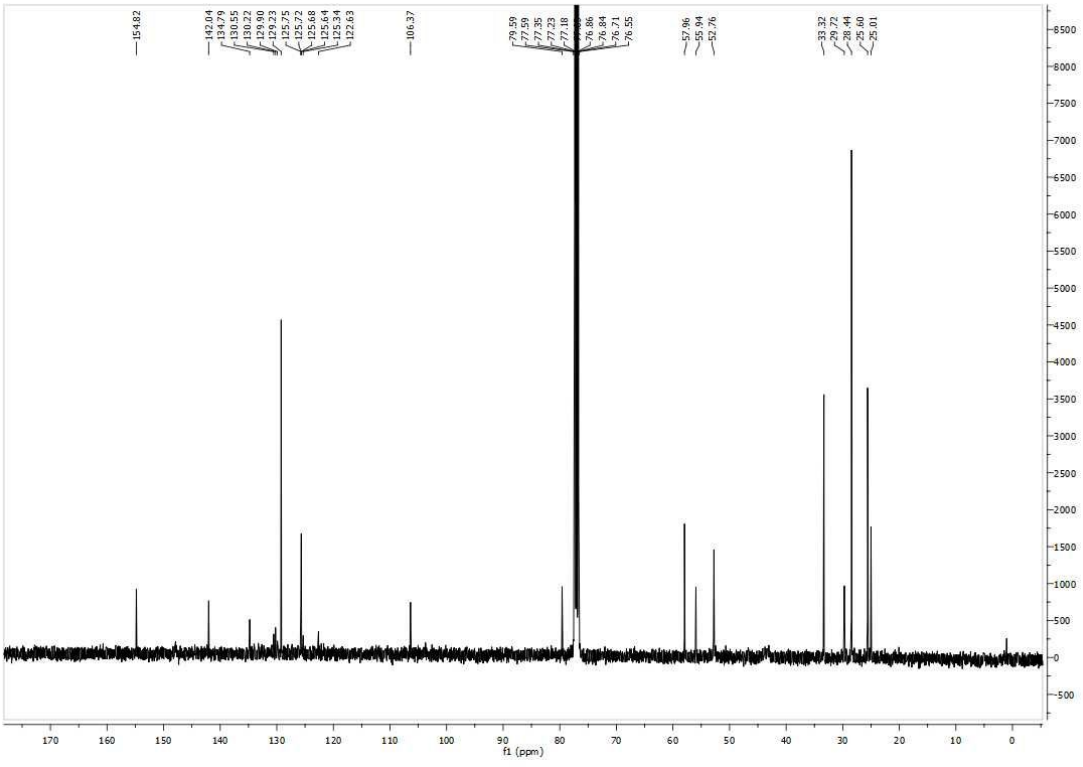
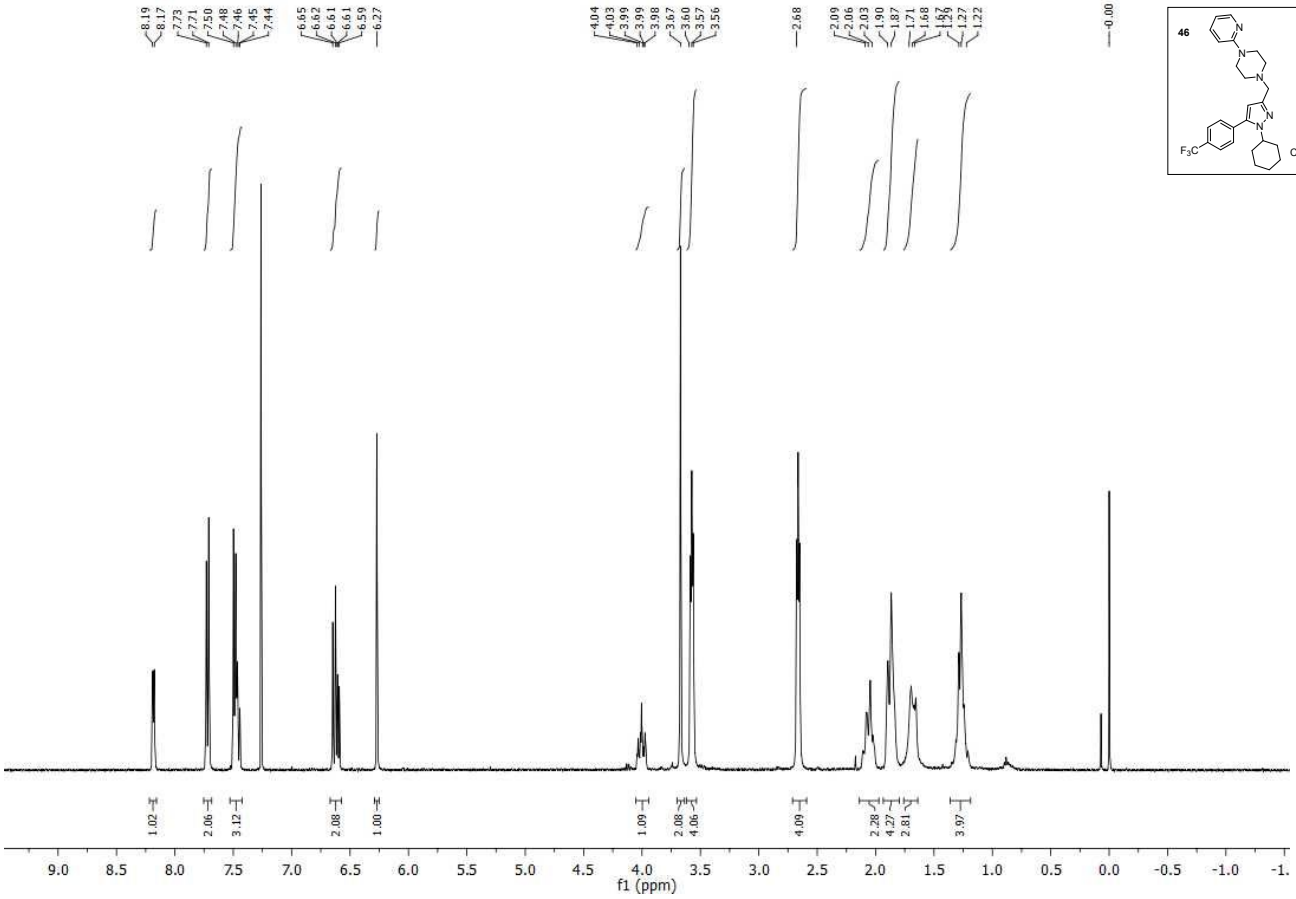
125.64
122.66
120.49
116.59
106.56
57.90
56.55
54.26
33.32
25.73
25.56
25.02
24.17
4500
4000
3500
3000
2500
2000
1500
1000
500
0
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
f1 (ppm)
44
F3C
CDCl3


7.72
7.70
7.49
7.47
7.26
6.24
4.02
3.99
3.96
3.61
3.46
2.49
2.05
2.03
1.88
1.86
1.65
1.45
1.28
1.25
0.87
2.01
2.00
0.88
1.15
2.18
4.26
4.20
2.37
4.76
1.55
10.07
6.37
f1 (ppm)
45
CDCl3


154.82
142.04
130.22
129.90
129.23
125.75
125.72
125.68
125.64
125.34
122.63
106.37
79.59
77.59
77.35
77.23
77.18
76.86
76.84
76.71
76.55
57.96
55.94
52.76
33.32
29.72
28.44
25.60
25.01
f1 (ppm)
45
CDCl3


8.19
8.17
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7.71
7.50
7.48
7.46
7.45
7.44
6.65
6.62
6.61
6.61
6.59
6.27
4.04
4.03
3.99
3.99
3.98
3.67
3.60
3.57
3.56
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2.06
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1.90
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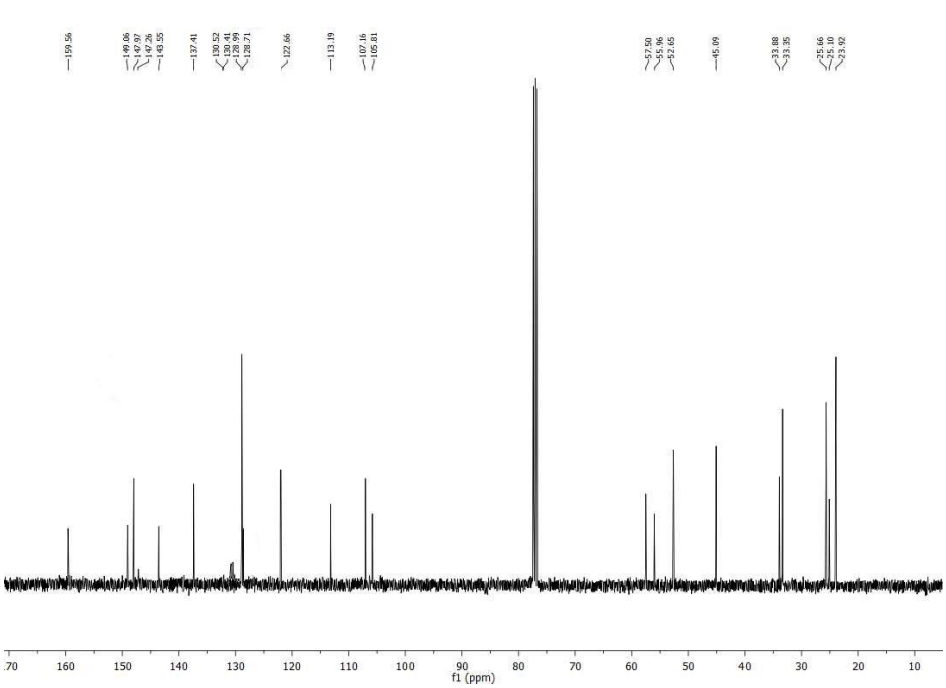
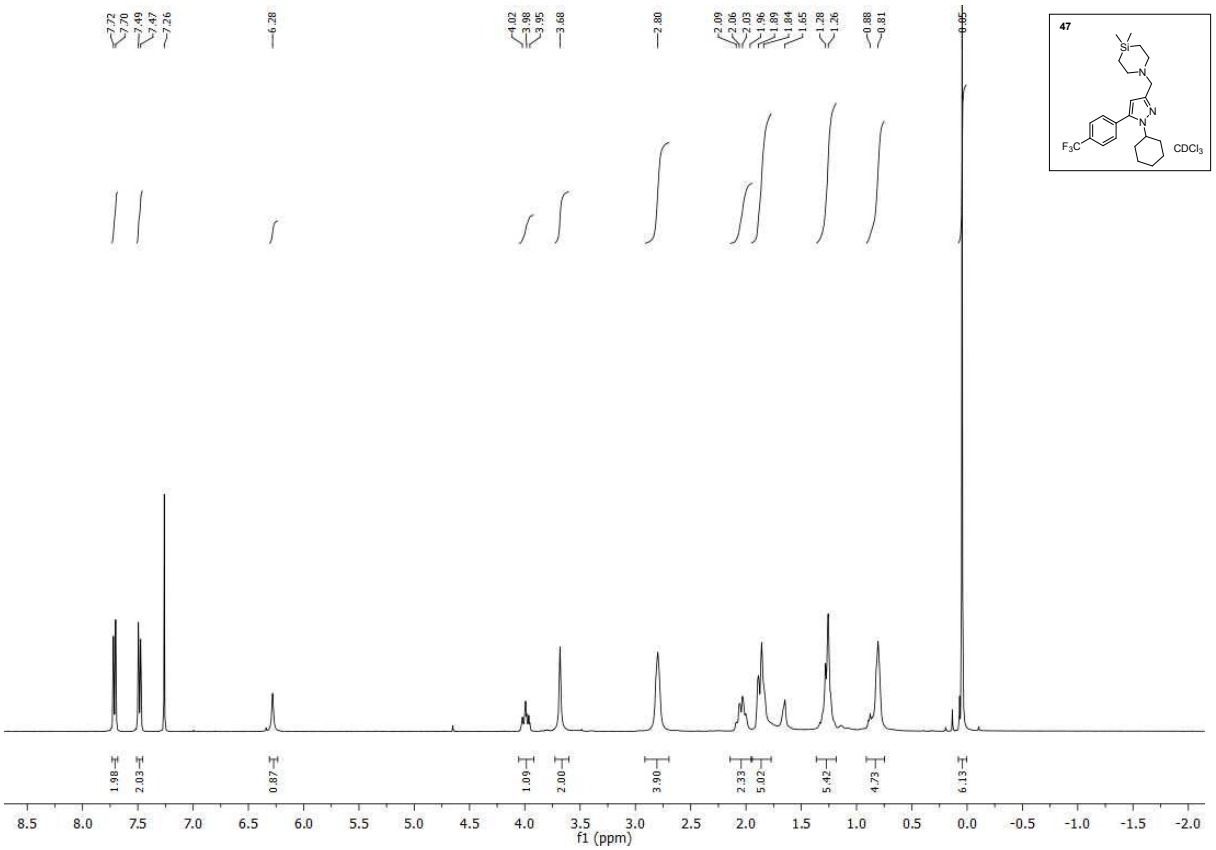
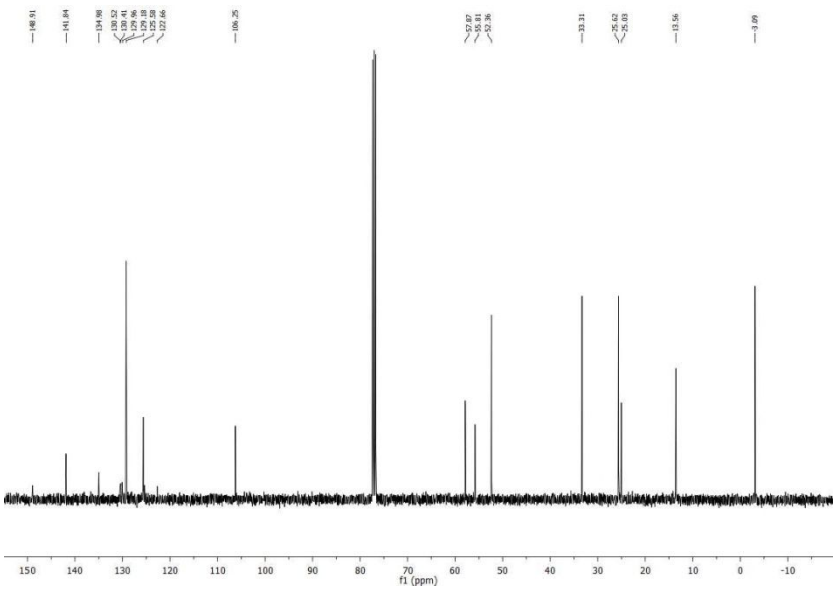
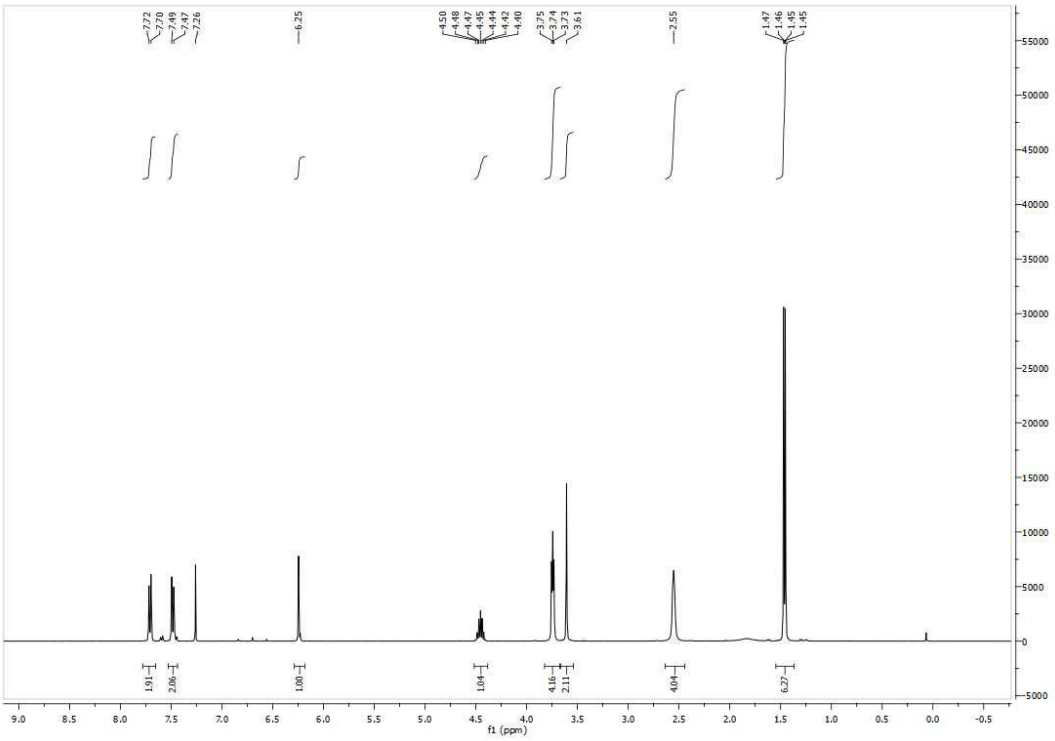
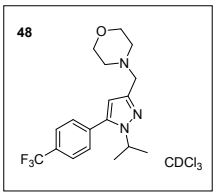
1.27
1.22
0.00
1.02
2.06
3.12
2.08
1.00
1.09
2.08
4.06
4.09
2.28
4.27
2.81
3.97
f1 (ppm)
46
CDCl3

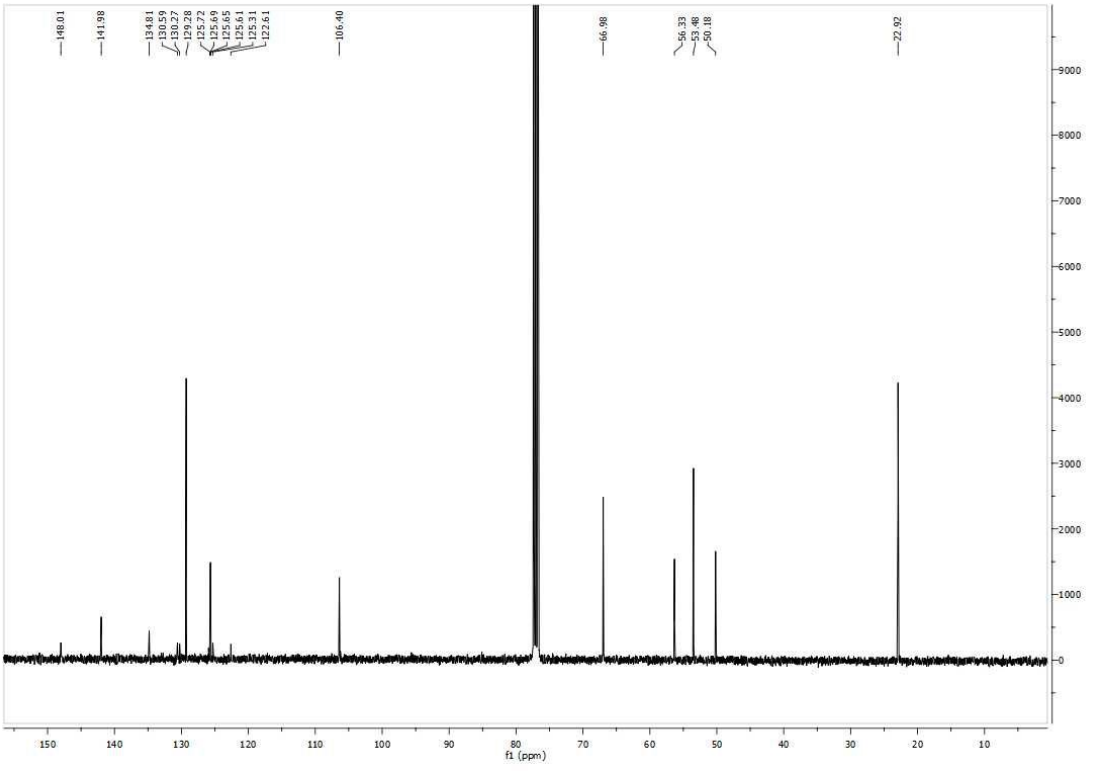

159.56
149.06
147.97
147.26
140.55
137.41
130.52
128.41
128.99
128.71
122.66
113.19
107.16
105.81
57.50
55.96
52.65
45.09
33.88
33.35
25.66
25.10
23.92
f1 (ppm)
46
CDCl3

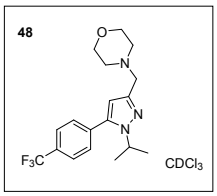

7.72
7.70
7.49
7.47
7.26
6.28
4.02
3.98
3.95
3.68
2.80
2.09
2.06
2.03
1.96
1.89
1.84
1.65
1.28
1.26
0.88
0.81
0.00
1.98
2.03
0.87
1.09
2.00
3.90
2.33
5.02
5.42
4.73
6.13
f1 (ppm)
47
CDCl3

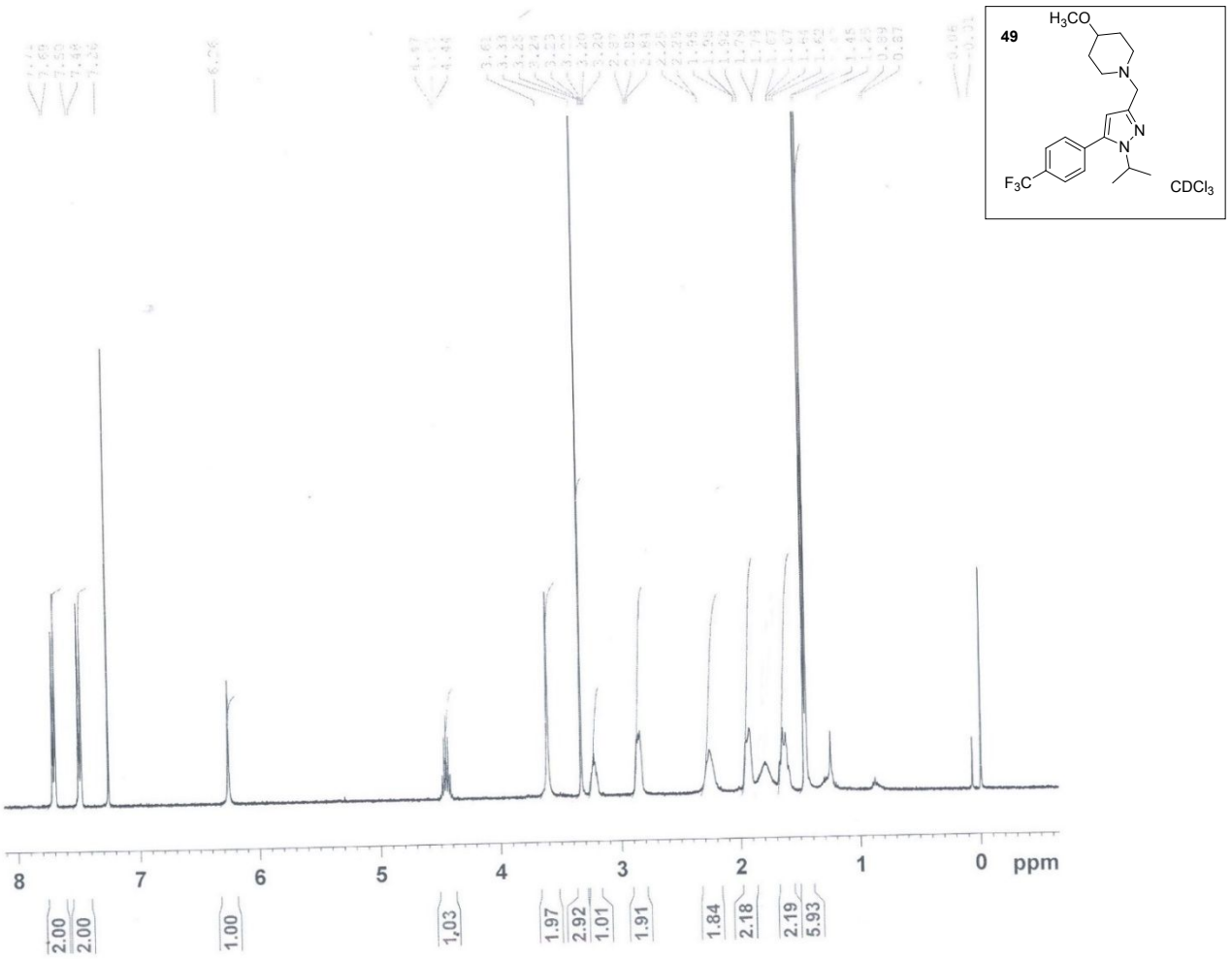

148.91
141.84
134.98
130.52
130.41
129.96
129.38
125.58
122.66
106.25
57.87
55.81
52.36
33.31
25.62
25.03
13.56
-3.09
f1 (ppm)
47
CDCl3

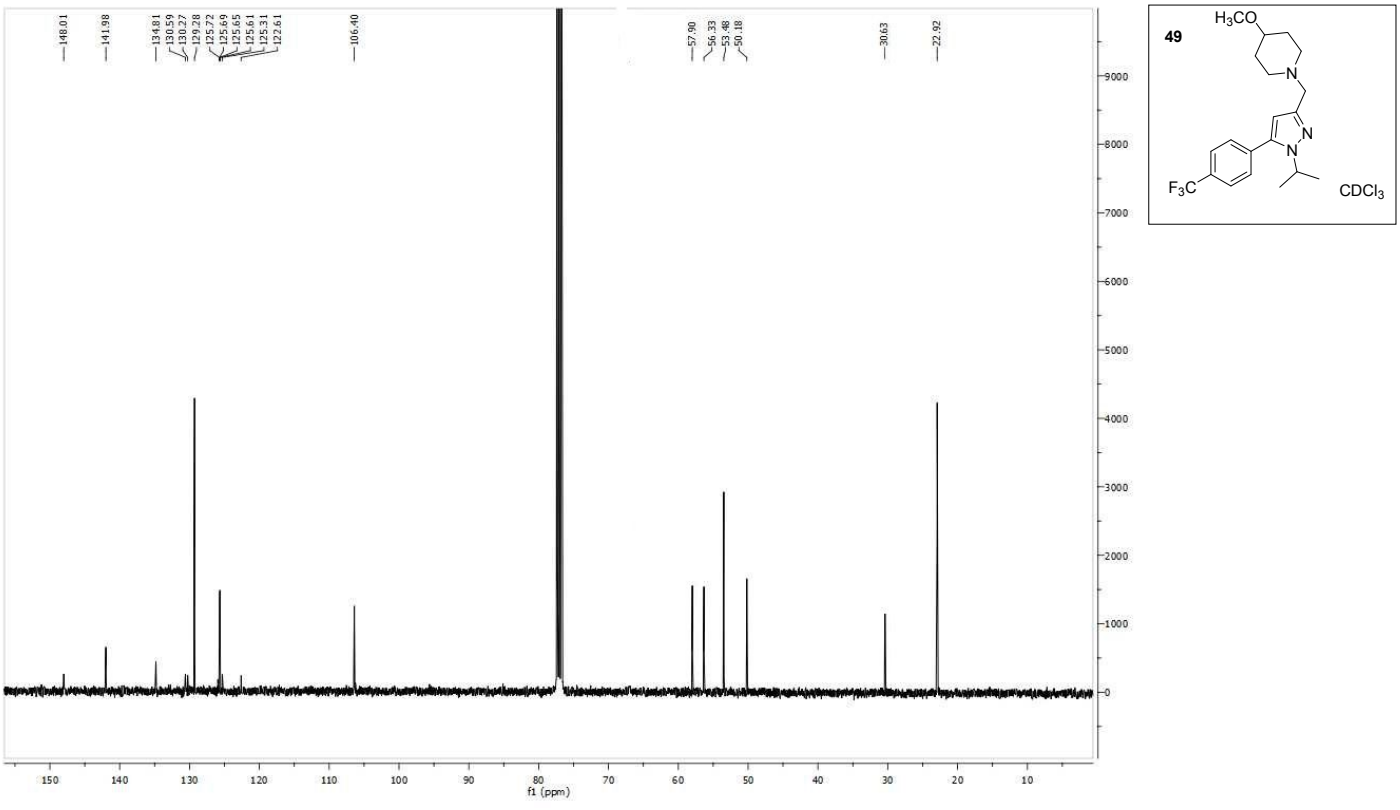

7.72
7.70
7.49
7.47
7.26
6.25
4.50
4.48
4.47
4.45
4.44
4.42
4.40
3.75
3.74
3.73
3.61
2.55
1.47
1.46
1.45
1.45
1.91
2.06
1.00
1.04
4.16
2.11
4.04
6.27
f1 (ppm)


48
F_3C
$CDCl_3$


148.01
141.98
134.81
130.59
130.27
129.28
125.72
125.69
125.65
125.61
125.31
122.61
106.40
66.98
56.33
53.48
50.18
22.92
f1 (ppm)


48
F_3C
$CDCl_3$


49
H_3CO
F_3C
$CDCl_3$
8
7
6
5
4
3
2
1
0
ppm
2.00
2.00
1.00
1,03
1.97
2.92
1.01
1.91
1.84
2.18
2.19
5.93


148.01
141.98
134.81
130.59
130.27
129.28
125.72
125.69
125.65
125.61
125.51
122.61
106.40
57.90
56.33
53.48
50.18
30.63
22.92
49
H_3CO
F_3C
$CDCl_3$
f1 (ppm)

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