**SUPPORTING INFORMATION**

# Synthesis, biological evaluation and computational studies of pyrazole derivatives as *Mycobacterium tuberculosis* CYP121A1 inhibitors

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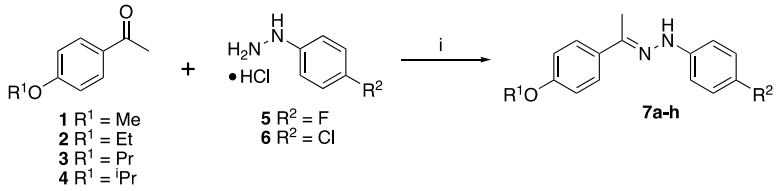
**Contents**

**General method for the synthesis of hydrazine derivatives (7)**. To a solution of phenylhydrazine hydrochloride (**5** or **6**) (1-2 equiv.) in dry EtOH (1 mL/mmol) was added $Et_3N$ (2 equiv.) and the reaction stirred at room temperature for 30 min. A solution of acetophenone (**1**-**4**) (1 equiv.) in dry EtOH (1 mL/mmol) and acetic acid (0.2 mL/mmol) was then added to the reaction, which was heated at 83 °C for 1 h. The solvent was then evaporated under reduced pressure and ice-$H_2O$ added to the remaining residue. The resulting precipitate was collected by filtration, dried, and used in the next reaction without further purification.




**1** $R^1$ = Me
**2** $R^1$ = Et
**3** $R^1$ = Pr
**4** $R^1$ = $^i$Pr

**5** $R^2$ = F
**6** $R^2$ = Cl

*(E)-1-(4-Fluorophenyl)-2-(1-(4-methoxyphenyl)ethylidene)hydrazine* (**7a**, $R^1$=$CH_3$, $R^2$=F). Prepared from 4-methoxyacetophenone (**1**) (0.32 g, 2.15 mmol) and 4-fluorophenylhydrazine hydrochloride (**5**) (0.7 g, 4.30 mmol). Yield 0.55 g (100%) as an orange solid. m.p: 90 - 92° C, $R_f$: 0.80 (petroleum ether - EtOAc 1:2 v/v). $^1$H NMR (DMSO-$d_6$): 9.12 (s,1H, NH), 7.72 (d, *J* = 9.0 Hz, 2H, Ar), 7.20 (m, 2H, Ar), 7.05 (m, 2H, Ar), 6.94 (d, *J* = 9.0 Hz, 2H, Ar), 3.78 (s, 3H, $OCH_3$), 2.22 (s, 3H, $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -126.54 (F - Ar)

*(E)-1-(4-Chlorophenyl)-2-(1-(4-methoxyphenyl)ethylidene)hydrazine* (**7b**, $R^1$=$CH_3$, $R^2$=Cl). Prepared from 4-methoxyacetophenone (**1**) (0.75 g, 5 mmol) and 4-chlorophenylhydrazine hydrochloride (**6**) (1.8 g, 10 mmol). Yield 1.374 g (100%) as an orange solid. m.p: 112 - 114° C (lit. mp[1] 128 - 130° C), $R_f$: 0.89 (petroleum ether-EtOAc 1:2 v/v). $^1$H NMR (DMSO-$d_6$): 9.27 (s,1H, NH), 7.73 (d, *J* = 9.0 Hz, 2H, Ar), 7.22 (m, 4H, Ar), 6.95 (d, *J* = 9.0 Hz, 2H, Ar), 3.07 (s, 3H, $OCH_3$), 2.23 (s, 3H, $CH_3$).

*(E)-1-(1-(4-Ethoxyphenyl)ethylidene)-2-(4-fluorophenyl)hydrazine* (**7c**, $R^1$=$CH_2H_3$, $R^2$=F). Prepared from 4-ethoxyacetophenone (**2**) (2.46 g, 15 mmol) and 4-fluorophenylhydrazine hydrochloride (**5**) (2.44 g, 15 mmol). Yield 3.85 g (94%) as a pale yellow solid. m.p: 76 - 78° C, $R_f$: 0.53 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.11 (s, 1H, NH), 7.70 (d, *J* = 8.9 Hz, 2H, Ar), 7.20 (m, 2H, Ar), 7.04 (m, 2H, Ar), 6.92 (d, *J* = 8.9 Hz, 2H, Ar), 4.05 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 2.21 (s, 3H, $CH_3$), 1.34 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -116.52 (F - Ar)

*(E)-1-(4-Chlorophenyl)-2-(1-(4-ethoxyphenyl)ethylidene)hydrazine* (**7d**, $R^1$=$CH_2H_3$, $R^2$=CL). Prepared from 4-ethoxyacetophenone (**2**) (0.821 g, 5 mmol) and 4-chlorophenylhydrazine hydrochloride (**6**) (0.895 g, 5 mmol). Yield 1.134 g (79%) as light brown solid. m.p: 133 - 136° C, $R_f$: 0.47 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): 9.26 (s,1H, NH), 7.71 (d, *J* = 8.9 Hz, 2H, Ar), 7.22(m, 4H, Ar), 6.93 (d, *J* = 8.9 Hz, 2H, Ar), 4.05 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 2.22 (s, 3H, $CH_3$), 1.34 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$).

*(E)-1-(4-Fluorophenyl)-2-(1-(4-propoxyphenyl)ethylidene)hydrazine* (**7e**, $R^1$= $CH_2CH_2CH_3$, $R^2$=F). Variation to method – stirred at room temperature. Prepared from 4-propoxyacetophenone (**3**) (0.8 g, 4.5 mmol) and 4-fluorophenylhydrazine hydrochloride (**5**) (1.46 g, 9 mmol). Yield 1.28 g (100%) as an orange semisolid. $R_f$: 0.90 (petroleum ether - EtOAc 2:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.11 (s,1H, NH), 7.71 (d, *J* = 9.0 Hz, 2H, Ar), 7.19 (m, 2H, Ar), 7.05 (t, *J* = 9.0 Hz, 2H, Ar), 6.94 (d, *J* = 9.0 Hz, 2H, Ar), 3.94 (t, *J* = 7.0 Hz, 2H, $OCH_2$), 2.21 (s, 3H, $CH_3$), 1.75 (m, 2H, $CH_3CH_2$), 0.99 (d, *J* = 7.50 Hz, 3H, $CH_2CH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -126.56 (F-Ar)

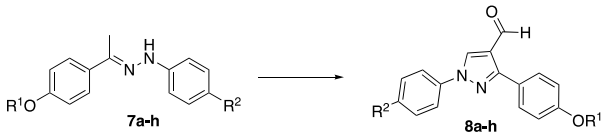
*(E)-1-(4-Chlorophenyl)-2-(1-(4-propoxyphenyl)ethylidene)hydrazine* (**7f**, $R^1$=$CH_2CH_2CH_3$, $R^2$=Cl). Prepared from 4-propoxyacetophenone (**3**) (0.8 g, 4.5 mmol) and 4-fluorophenylhydrazine hydrochloride (**6**) (1.60 g, 9 mmol). Yield 1.36 g (100%) as a light brown solid. m.p: 130 - 132° C, $R_f$: 0.90 (petroleum ether - EtOAc 2:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.27 (s, 1H, NH), 7.72 (d, *J* = 9.0 Hz, 2H, Ar), 7.23 (m, 4H, Ar), 6.94 (d, *J* = 8.50 Hz, 2H, Ar), 3.95 (t, *J* = 6.50 Hz, 2H, $OCH_2$), 2.22 (s, 3H, $CH_3$), 1.75 (m, 2H, $CH_3CH_2$), 0.99 (d, *J* = 7.50 Hz, 3H, $CH_2CH_3$).

*(E)-1-(4-Fluorophenyl)-2-(1-(4-isopropoxyphenyl)ethylidene)hydrazine* (**7g**, $R^1$=$CH(CH_3)_2$, $R^2$=F). Variation to method – stirred at room temperature. Prepared from 4-isopropoxyacetophenone (**4**) (0.3 g, 1.7 mmol) and 4-fluorophenylhydrazine hydrochloride (**5**) (0.54 g, 3.3 mmol). Yield 1.10 g (98%) as an orange semisolid. $R_f$: 0.72 (petroleum ether - EtOAc 2:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.11 (s, 1H, NH), 7.70 (d, *J* = 9.0 Hz, 2H, Ar), 7.19 (m, 2H, Ar), 7.04 (t, *J* = 9.0 Hz, 2H, Ar), 6.92 (d, *J* = 9.0 Hz, 2H, Ar), 4.63 (m, 1H, CH), 2.21 (s, 3H, $CH_3$), 1.28 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$).

*(E)-1-(4-Chlorophenyl)-2-(1-(4-isopropoxyphenyl)ethylidene)hydrazine* (**7h**, $R^1$=$CH(CH_3)_2$, $R^2$=Cl). Prepared from 4-isopropoxyacetophenone (**4**) (0.7 g, 3.9 mmol) and 4-chlorophenylhydrazine hydrochloride (**6**) (1.4 g, 7.8 mmol). Yield 1.18 g (100%) as a yellow solid. m.p: 84 - 86° C, $R_f$: 0.70 (petroleum ether - EtOAc 2:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.26 (s, 1H, NH), 7.71 (d, *J* = 8.9 Hz, 2H, Ar), 7.22 (m, 4H, Ar), 6.93 (d, *J* = 8.9 Hz, 2H, Ar), 4.64 (m, 1H, CH), 2.22 (s, 3H, $CH_3$), 1.28 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$).

**General method for the synthesis of aldehyde derivatives (8)**. To a mixture of dry DMF (3 equiv.) and $POCl_3$ (3 equiv.) was cooled at 0° C for 5 min, then stirred at room temperature where a solution of hydrazine (**7**) (1 equiv.) in dry DMF (0.5

mL/mmol) was added dropwise to the Vilsmeier-Haack reagent, allowed to warm to room temperature, and then heated at 60° C for 3 h. The reaction was brought to pH 8.0 with cold saturated $K_2CO_3$ solution and the precipitate collected by filtration, washed with water, dried, and used immediately in subsequent reactions without further purification.




*1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8a** $R^1$=$CH_3$, $R^2$=F). Prepared from (*E*)-1-(4-fluorophenyl)-2-(1-(4-methoxyphenyl)ethylidene)hydrazine (**7a**) (0.56 g, 2.17 mmol). Yield 0.61 g (95%) as an off-white solid. m.p: 144 - 146° C, $R_f$: 0.45 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.28 (s, 1H, pyrazole), 8.03 (m, 2H, Ar), 7.90 (d, *J* = 8.5 Hz, 2H, Ar), 7.43 (m, 2H, Ar), 7.07 (d, *J* = 9.0 Hz, 2H, Ar), 3.83 (s, 3H, $OCH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -114.66 (F - Ar). $^{13}$C NMR (DMSO-$d_6$): δ 185.07 (C, aldehyde), 162.49 (C, Ar), 160.55 and 162.49 (d, $^1J_{CF}$ = 244.0 Hz, C-F, Ar), 160.54 (C, Ar), 152.97 (C, pyrazole), 135.68 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 135.57 (CH, pyrazole), 130.53 (2 x CH, Ar), 124.01 (C, Ar), 122.44 (C, pyrazole), 121.84 and 121.91 (d, $^3J_{CF}$ = 8.8 Hz, 2 x CH, Ar), 116.87 and 117.05 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 114.46 (2 x CH, Ar), 55.73 ($CH_3$).

*1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8b** $R^1$=$CH_3$, $R^2$=Cl). Prepared from (*E*)-1-(4-chlorophenyl)-2-(1-(4-methoxyphenyl)ethylidene)hydrazine (**7b**) (1.3 g, 4.7 mmol). Yield 0.959 g (65%) as a buff solid. m.p: 142 - 144° C (lit. mp[1] 142-143[1]), $R_f$: 0.52 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.33 (s, 1H, pyrazole), 8.03 (d, *J* = 9.0 Hz, 2H, Ar), 7.90 (d, *J* = 9.0 Hz, 2H, Ar), 7.64 (d, *J* = 9.0 Hz, 2H, Ar), 7.07 (d, *J* = 9.0 Hz, 2H, Ar), 3.83 (s, 3H, $OCH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 185.07 (C, aldehyde), 160.60 (C-O, Ar), 153.07 (C, pyrazole), 137.92 (C, Ar), 135.68 (CH, pyrazole), 132.27 (C-Cl, Ar), 130.55 (2 x CH, Ar), 130.11 (2 x CH, Ar), 123.92 (C, pyrazole), 122.62 (C, Ar), 121.30 (2 x CH, Ar), 114.46 (2 x CH, Ar), 55.73 ($CH_3$).

*3-(4-Ethoxyphenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde* (**8c** $R^1$=$CH_2CH_3$, $R^2$=F). Prepared from (*E*)-1-(1-(4-ethoxyphenyl)ethylidene)-2-(4-fluorophenyl)hydrazine (**7c**) (3.0 g, 11 mmol). Yield 3.065 g (90%) as a white solid. m.p: 162 - 164° C, $R_f$: 0.39 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.28 (s, 1H, pyrazole), 8.03 (m, 2H, Ar), 7.89 (d, *J* = 9.0 Hz, 2H, Ar), 7.43 (m, 2H, Ar), 7.05 (d, *J* = 9.0 Hz, 2H, Ar), 4.10 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 1.37 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -114.68 (F - Ar). $^{13}$C NMR (DMSO-$d_6$): δ 185.07 (C, aldehyde), 160.55 and 162.49 (d, $^1J_{CF}$ = 244.0 Hz, C-F, Ar), 159.84 (C, Ar), 152.99 (C, pyrazole), 135.69 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 135.58 (CH, pyrazole), 130.53 (2 x CH, Ar), 123.87 (C, Ar), 122.43 (C, pyrazole), 121.83 and 121.89 (d, $^3J_{CF}$ = 7.5 Hz, 2x CH, Ar), 116.87 and 117.05 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 114.88 (2 x CH, Ar), 63.65 ($CH_2$), 15.10 ($CH_3$).

*1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8d** $R^1$=$CH_2CH_3$, $R^2$=Cl). Prepared from (*E*)-1-(4-chlorophenyl)-2-(1-(4-ethoxyphenyl)ethylidene)hydrazine (**7d**) (0.5 g, 1.7 mmol). Yield 0.525 g (93%) as a white solid. m.p: 138 - 140° C, $R_f$: 0.39 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.32 (s, 1H, pyrazole), 8.01 (d, *J* =9.0 Hz, 2H, Ar), 7.89 (d, *J* = 9.0 Hz, 2H, Ar), 7.64 (d, *J* = 9.0 Hz, 2H, Ar), 7.05 (d, *J* = 9.0 Hz, 2H, Ar), 4.10 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 1.37 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$).

*1-(4-Fluorophenyl)-3-(4-propoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8e** $R^1$=$CH_2CH_2CH_3$, $R^2$=F). Prepared from (*E*)-1-(4-fluorophenyl)-2-(1-(4-propoxyphenyl)ethylidene)hydrazine (**7e**) (1.2 g, 4.2 mmol). Yield 1.31 g (96%) as a yellow solid. m.p: 140 - 142° C, $R_f$: 0.41 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.27 (s, 1H, pyrazole), 8.04 (m, 2H, Ar), 7.90 (d, *J* = 9.0 Hz, 2H, Ar), 7.43 (t, *J* = 8.50 Hz, 2H, Ar), 7.07 (d, *J* =9.0 Hz, 2H, Ar), 4.0 (t, *J* = 6.5 Hz, 2H, $OCH_2$), 1.77 (m, 2H, $CH_3CH_2$), 1.01 (d, *J* = 7.50 Hz, 3H, $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): δ -114.67 (F-Ar). $^{13}$C NMR (DMSO-$d_6$): δ 185.07 (C, aldehyde), 162.49 and 160.54 (d, $^1J_{CF}$ = 245.3 Hz, C-F, Ar), 160.0 (C, Ar), 152.99 (C, pyrazole), 135.69 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 135.56 (CH, pyrazole), 130.52 (2 x CH, Ar), 123.86 (C, pyrazole), 122.43 (C, Ar), 121.89 and 121.82 (d, $^3J_{CF}$ = 8.80 Hz, 2 x CH, Ar), 117.05 and 116.86 (d, $^2J_{CF}$ = 23.90 Hz, 2 x CH, Ar), 114.92 (2 x CH, Ar), 69.52 ($OCH_2$), 22.48 ($CH_2CH_3$), 10.87 ($CH_3$).

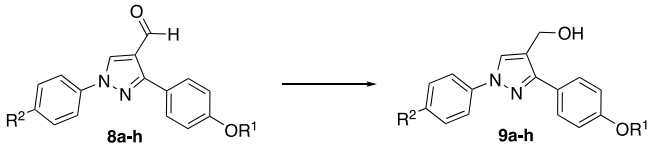
*1-(4-Chlorophenyl)-3-(4-propoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8f** $R^1$=$CH_2CH_2CH_3$, $R^2$=Cl). Prepared from (*E*)-1-(4-chlorophenyl)-2-(1-(4-propoxyphenyl)ethylidene)hydrazine (**7f**) (1.3 g, 4.3 mmol). Yield 1.47 g (100%) as a yellow solid. m.p: 132 - 134° C, $R_f$: 0.46 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.33 (s, 1H, pyrazole), 8.03 (d, *J* = 9.0 Hz, 2H, Ar), 7.90 (d, *J* = 9.0 Hz, 2H, Ar), 7.65 (d, *J* = 9.0 Hz, 2H, Ar), 7.06 (d, *J* = 9.0 Hz, 2H, Ar), 4.0 (t, *J* = 6.50 Hz, 2H, $OCH_2$), 1.77 (m, 2H, $CH_3CH_2$), 1.0 (d, *J* = 7.50 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 185.06 (C, aldehyde), 160.05 (C-O, Ar), 153.08 (C, pyrazole), 137.92 (C, Ar), 135.69 (CH, pyrazole), 132.26 (C-Cl, Ar), 130.53 (2 x CH, Ar), 130.10 (2 x CH, Ar), 123.77 (C, pyrazole), 122.61 (C, Ar), 121.29 (2 x CH, Ar), 114.92 (2 x CH, Ar), 69.53 ($OCH_2$), 22.48 ($CH_2CH_3$), 10.86 ($CH_3$).

*1-(4-Fluorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8g**, $R^1$=$CH(CH_3)_2$, $R^2$=F). Variation from method – reaction stirred at room temperature overnight. Prepared from (*E*)-1-(4-fluorophenyl)-2-(1-(4-isopropoxyphenyl)ethylidene)hydrazine (**7g**) (1.5 g, 5.2 mmol). Yield 1.65 g (98%) as a yellow solid. m.p: 137 - 139° C, $R_f$: 0.40 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.27 (s, 1H, pyrazole), 8.04 (m, 2H, Ar), 7.88 (d, *J*

= 9.0 Hz, 2H, Ar), 7.42 (t, *J* = 9.0 Hz, 2H, Ar), 7.05 (d, *J* =8.50 Hz, 2H, Ar), 4.71 (m, 1H, CH), 1.31 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{19}F$ NMR: (DMSO-$d_6$): δ -114.68 (F-Ar). $^{13}C$ NMR (DMSO-$d_6$): δ 185.08 (C, aldehyde), 162.49 and 160.54 (d, $^1J_{CF}$ = 245.3 Hz, C-F, Ar), 158.81 (C, Ar), 153.01 (C, pyrazole), 135.70 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 135.54 (CH, pyrazole), 130.57 (2 x CH, Ar), 123.69 (C, pyrazole), 122.42 (C, Ar), 121.88 and 121.82 (d, $^3J_{CF}$ = 7.55 Hz, 2 x CH, Ar), 117.05 and 116.87 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 115.91 (2 x CH, Ar), 69.73 (CH), 22.28 (2 x $CH_3$).

*1-(4-Chlorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazole-4-carbaldehyde* (**8h**, $R^1$=$CH(CH_3)_2$, $R^2$=Cl). Prepared from (*E*)-1-(4-chlorophenyl)-2-(1-(4-isopropoxyphenyl)ethylidene)hydrazine (**7h**) (1.18 g, 3.8 mmol). Yield 1.14 g (88%) as a yellow solid. m.p: 144 - 146° C, $R_f$: 0.52 (petroleum ether - EtOAc 4:1 v/v). $^1H$ NMR (DMSO-$d_6$): δ 9.97 (s, 1H, CHO), 9.32 (s, 1H, pyrazole), 8.03 (d, *J* = 9.0 Hz, 2H, Ar), 7.89 (d, *J* = 9.0 Hz, 2H, Ar), 7.65 (d, *J* = 9.0 Hz, 2H, Ar), 7.05 (d, *J* = 9.0 Hz, 2H, Ar), 4.71 (m, 1H, CH), 1.32 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{13}C$ NMR (DMSO-$d_6$): δ 185.08 (C, aldehyde), 158.85 (C-O, Ar), 153.10 (C, pyrazole), 137.93 (C, Ar), 135.67 (CH, pyrazole), 132.26 (C-Cl, Ar), 130.58 (2 x CH, Ar), 130.11 (2 x CH, Ar), 123.59 (C, pyrazole), 122.60 (C, Ar), 121.29 (2 x CH, Ar), 115.91 (2 x CH, Ar), 69.74 (CH), 22.29 (2x $CH_3$).

**General method for the synthesis of alcohol derivatives (9)**. To an ice-cooled solution of aldehyde (**8**) (1 equiv.) in dry EtOH (3 mL/mmol) was added $NaBH_4$ (1 equiv.) in portions, and then the reaction was stirred at room temperature for 1 h. The solvent was evaporated and $H_2O$ (7 mL/mmol) was added slowly and the reaction stirred for 30 min [2]. The reaction mixture was extracted with EtOAc (2 x 10 mL/mmol), then the combined organic layers washed with $H_2O$ (3 x 10 mL/mmol), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alcohol (**9**).




*(1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9a** $R^1$=$CH_3$, $R^2$=F). Prepared from 1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8a**) (0.6 g, 2 mmol). Yield 0.537 g (90%) as a light orange solid. m.p: 142 - 144° C, $R_f$: 0.08 (petroleum ether - EtOAc 4:1 v/v). $^1H$ NMR (DMSO-$d_6$): δ 8.45 (s, 1H, pyrazole), 7.90 (m, 2H, Ar), 7.82 (d, *J* = 9.0 Hz, 2H, Ar), 7.35 (m, 2H, Ar), 7.02 (d, *J* = 9.0 Hz, 2H, Ar), 5.19 (t, *J* = 5.0 Hz, 1H, OH), 4.52 (d, *J* = 5.0 Hz, 2H, $CH_2OH$), 3.81 (s, 3H, $OCH_3$). $^{19}F$ NMR: (DMSO-$d_6$): δ -117.13 (F - Ar). $^{13}C$ NMR (DMSO-$d_6$): δ 159.56 and 161.49 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 159.58 (C, Ar), 150.78 (C, pyrazole), 135.67 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 129.24 (CH, pyrazole), 129.11 (2 x CH, Ar), 125.88 (C, Ar), 122.02 (C, pyrazole), 120.34 and 120.41 (d, $^3J_{CF}$ = 8.8 Hz, 2 x CH, Ar), 116.62 and 116.80 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 114.46 (2 x CH, Ar), 55.61 ($OCH_3$), 54.57 ($CH_2OH$).

*(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9b** $R^1$=$CH_3$, $R^2$=Cl). Prepared from 1-(4-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8b**) (0.95 g, 3 mmol). Yield 0.88 g (93%) as an orange solid. m.p: 112 - 114° C, $R_f$: 0.06 (petroleum ether - EtOAc 4:1 v/v). $^1H$ NMR (DMSO-$d_6$): δ 8.51 (s, 1H, pyrazole), 7.93 (d, *J* = 9.0 Hz, 2H, Ar), 7.83 (d, *J* =9.0 Hz, 2H, Ar), 7.57 (d, *J* = 9.0 Hz, 2H, Ar), 7.05 (d, *J* = 9.0 Hz, 2H, Ar), 5.20 (t, *J* = 5.0 Hz, 1H, OH), 4.53 (d, *J* = 5.0 Hz, 2H, $CH_2OH$), 3.81 (s, 3H, $OCH_3$). $^{13}C$ NMR (DMSO-$d_6$): δ 159.66 (C, Ar), 151.05 (C, pyrazole), 138.86 (C, Ar), 130.36 (C, Ar), 129.91 (2 x CH, Ar), 129.22 (CH, pyrazole), 129.14 (2 x CH, Ar), 125.74 (C, Ar), 122.37 (C, pyrazole), 119.97 (2 x CH, Ar), 114.48 (2 x CH, Ar), 55.62 ($OCH_3$), 54.57 ($CH_2$).

*(3-(4-Ethoxyphenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)methanol* (**9c** $R^1$=$CH_2CH_3$, $R^2$=F). Variation to method - The crude product was purified by gradient column chromatography and the pure compound eluted with $CH_2Cl_2$ – MeOH 99:1 v/v. Prepared from 3-(4-ethoxyphenyl)-1-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde (**8c**) (2.5 g, 8 mmol). Yield 1.687 g (68%) as a light brown solid. m.p: 106 - 108° C, $R_f$: 0.09 (petroleum ether - EtOAc 4:1 v/v). $^1H$ NMR (DMSO-$d_6$): δ 8.46 (s, 1H, pyrazole), 7.91 (m, 2H, Ar), 7.81 (d, *J* = 9.0 Hz, 2H, Ar), 7.35 (m, 2H, Ar), 7.02 (d, *J* = 9.0 Hz, 2H, Ar), 5.18 (t, *J* = 5.0 Hz, 1H, OH), 4.53 (d, *J* = 5.0 Hz, 2H, $CH_2OH$), 4.08 (q, *J* = 6.50 Hz, 2H, $CH_2CH_3$), 1.36 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{19}F$ NMR: (DMSO-$d_6$): -117.16 (F – Ar). $^{13}C$ NMR (DMSO-$d_6$): δ 159.55 and 161.48 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 158.85 (C, Ar), 150.79 (C, pyrazole), 135.67 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 129.24 (CH, pyrazole), 129.10 (2x CH, Ar), 125.75 (C, Ar), 122.0 (C, pyrazole), 120.32 and 120.39 (d, $^3J_{CF}$ = 8.8 Hz, 2 x CH, Ar), 116.61 and 116.79 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 114.90 (2 x CH, Ar), 63.51 ($CH_2$), 54.57 ($CH_2OH$), 15.10 ($CH_3$).

*(1-(4-Chlorophenyl)-3-(4-ethoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9d** $R^1$=$CH_2CH_3$, $R^2$=Cl). Prepared from 1-(4-chlorophenyl)-3-(4-ethoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8d**) (0.327 g, 1 mmol). Yield 0.296 g (90%) as a white crystalline solid. m.p: 128 - 130° C, $R_f$: 0.1 (petroleum ether - EtOAc 4:1 v/v). $^1H$ NMR (DMSO-$d_6$): δ 8.50 (s, 1H, pyrazole), 7.92 (d, *J* = 9.0 Hz, 2H, Ar), 7.81 (d, *J* = 9.0 Hz, 2H, Ar), 7.56 (d, *J* = 9.0 Hz, 2H, Ar), 7.02 (d, *J* = 9.0 Hz, 2H, Ar), 5.20 (t, *J* = 4.95 Hz, 1H, OH), 4.51 (d, *J* = 4.9 Hz, 2H, $CH_2OH$ ), 4.08 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 1.36 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{13}C$ NMR (DMSO-

$d_6$): δ 158.93 (C, Ar), 151.06 (C, pyrazole), 138.86 (C, Ar), 130.35 (C, Ar), 129.91 (2 x CH, Ar), 129.22 (2 x CH, Ar), 129.14 (CH, pyrazole), 125.61 (C, Ar), 122.35 (C, pyrazole), 119.95 (2 x CH, Ar), 114.91 (2 x CH, Ar), 63.53 ($CH_2$), 54.57 ($CH_2$), 15.13 ($CH_3$).

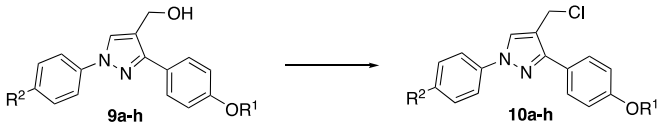
*(1-(4-Fluorophenyl)-3-(4-propoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9e** $R^1$=$CH_2CH_2CH_3$, $R^2$=F). Prepared from 1-(4-fluorophenyl)-3-(4-propoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8e**) (0.90 g, 2.77 mmol). Yield 0.80 g (89%) as an orange solid. m.p: 110 - 112° C, $R_f$: 0.1 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.45 (s, 1H, pyrazole), 7.92 (m, 2H, Ar), 7.81 (d, *J* = 9.0 Hz, 2H, Ar), 7.35 (t, *J* = 9.0 Hz, 2H, Ar), 7.03 (d, *J* = 9.0 Hz, 2H, Ar), 5.18 (t, *J* = 5.0 Hz, 1H, OH), 4.53 (d, *J* = 5.0 Hz, 2H, $CH_2$OH), 3.98 (t, *J* = 6.5 Hz, 2H, $OCH_2$), 1.76 (m, 2H, $CH_3CH_2$), 1.0 (d, *J* = 7.5 Hz, 3H, $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): -117.16 (F-Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.55 and 161.48 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 159.02 (C, Ar), 150.79 (C, pyrazole), 136.68 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 129.23 (CH, pyrazole), 129.10 (2x CH, Ar), 125.75 (C, Ar), 122.01 (C, pyrazole), 120.33 and 120.39 (d, $^3J_{CF}$ = 7.6 Hz, 2 x CH, Ar), 116.61 and 116.79 (d, $^2J_{CF}$ = 22.60 Hz, 2 x CH, Ar), 114.94 (2x CH, Ar), 69.42 ($OCH_2$), 54.58 ($CH_2$), 22.53 ($CH_2CH_3$), 10.89 ($CH_3$).

*(1-(4-Chlorophenyl)-3-(4-propoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9f** $R^1$=$CH_2CH_2CH_3$, $R^2$=Cl). Prepared from 1-(4-chlorophenyl)-3-(4-propoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8f**) (0.90 g, 2.77 mmol). Yield 0.64 g (80%) as a light brown solid. m.p: 100 - 102° C, $R_f$: 0.08 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.51 (s, 1H, pyrazole), 7.93 (d, *J* = 9.0 Hz, 2H, Ar), 7.82 (d, *J* = 9.0 Hz, 2H, Ar), 7.57 (d, *J* = 9.0 Hz, 2H, Ar), 7.03 (d, *J* = 9.0 Hz, 2H, Ar), 5.20 (t, *J* = 5.0 Hz, 1H, OH), 4.53 (d, *J* = 4.50 Hz, 2H, $CH_2$OH), 3.98 (t, *J* = 7.0 Hz, 2H, $OCH_2$), 1.77 (m, 2H, $CH_3CH_2$), 1.0 (d, *J* = 7.50 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 159.10 (C, Ar), 151.06 (C, pyrazole), 138.86 (C, Ar), 130.35 (C, Ar), 129.91 (2 x CH, Ar), 129.21 (CH, pyrazole), 129.13 (2 x CH, Ar), 125.60 (C, Ar), 122.35 (C, pyrazole), 119.95 (2 x CH, Ar), 114.96 (2 x CH, Ar), 69.43 ($OCH_2$), 54.58 ($CH_2$), 22.53 ($CH_2CH_3$), 10.90 ($CH_3$).

*(1-(4-Fluorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9g** $R^1$=$CH(CH_3)_2$, $R^2$=F). Prepared from 1-(4-fluorophenyl)-3-(4-isopropoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8g**) (0.80 g, 2.45 mmol). Yield 0.65 g (81%) as a buff solid. m.p: 110 - 112° C, $R_f$: 0.1 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.45 (s, 1H, pyrazole), 7.91 (m, 2H, Ar), 7.80 (d, *J* = 9.0 Hz, 2H, Ar), 7.35 (m, 2H, Ar), 7.0 (d, *J* = 9.0 Hz, 2H, Ar), 5.18 (t, *J* = 5.0 Hz, 1H, OH), 4.67 (m, 1H, CH), 4.52 (d, *J* = 4.5 Hz, 2H, $CH_2$OH), 1.30 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): -117.16 (F – Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.55 and 161.48 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 157.79 (C, Ar), 150.81 (C, pyrazole), 136.69 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 129.22 (CH, pyrazole), 129.15 (2 x CH, Ar), 125.60 (C, Ar), 121.99 (C, pyrazole), 120.31 and 120.38 (d, $^3J_{CF}$ = 8.8 Hz, 2 x CH, Ar), 116.61 and 116.80 (d, $^2J_{CF}$ = 23.9 Hz, 2 x CH, Ar), 116.0 (2 x CH, Ar), 69.60 (CH), 54.57 ($CH_2$), 22.32 (2x $CH_3$).

*(1-(4-Chlorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazol-4-yl)methanol* (**9h** $R^1$= $CH(CH_3)_2$, $R^2$=Cl). Prepared from 1-(4-chlorophenyl)-3-(4-isopropoxyphenyl)-1*H*-pyrazole-4-carbaldehyde (**8h**) (0.80 g, 2.3 mmol). Yield 0.77 g (98%) as a brown solid. m.p: 116 - 118° C, $R_f$: 0.09 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.51 (s, 1H, pyrazole), 7.91 (d, *J* = 9.0 Hz, 2H, Ar), 7.80 (d, *J* = 8.5 Hz, 2H, Ar), 7.56 (d, *J* = 9.0 Hz, 2H, Ar), 7.0 (d, *J* = 9.0 Hz, 2H, Ar), 5.19 (t, *J* = 5.0 Hz, 1H, OH), 4.68 (m, 1H, CH ), 4.52 (d, *J* = 5.0 Hz, 2H, $CH_2$OH), 1.30 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 157.87 (C, Ar), 151.08 (C, pyrazole), 138.87 (C, Ar), 130.34 (C, Ar), 129.91 (2 x CH, Ar), 129.21 (CH, pyrazole), 129.18 (2 x CH, Ar), 125.46 (C, Ar), 122.34 (C, pyrazole), 119.94 (2 x CH, Ar), 116.01 (2 x CH, Ar), 69.61 (CH), 54.57 ($CH_2$), 22.32 (2x $CH_3$).

**General method for the synthesis of chloride derivatives (10)**. To an ice-cooled solution of alcohol (**9**) (1 equiv.) in dry $CH_2Cl_2$ (2 mL/mmol) was added thionyl chloride ($SOCl_2$) (10 equiv.) dropwise. The reaction was stirred at 40° C for 4 h. The solvent was evaporated under reduced pressure and then while cooling in an ice-bath, carefully quenched with saturated aqueous $NaHCO_3$ in portions until slightly basic (pH 8.0). The product was extracted with EtOAc (3 x 10 mL/mmol), and the combined organic layers washed with brine (3 x 4 mL/mmol), $H_2O$ (2 x 4 mL/mmol), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude chloride (**10**), which was used immediately in subsequent reactions without further purification.




*4-(Chloromethyl)-1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole* (**10a** $R^1$=$CH_3$, $R^2$=F). Prepared from (1-(4-fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methanol carbaldehyde (**9a**) (0.50 g, 1.7 mmol). Yield 0.504 g (94%) as a brown solid. m.p: 116 - 118° C, $R_f$: 0.67 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.69 (s, 1H, pyrazole), 7.91 (m, 2H, Ar), 7.78 (d, *J* = 8.5 Hz, 2H, Ar), 7.38 (m, 2H, Ar), 7.08 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2$Cl), 3.82 (s, 3H, $OCH_3$). $^{19}$F NMR: (DMSO-$d_6$): -116.25 (F – Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.89 and 161.83 (d, $^1J_{CF}$ = 244 Hz, C-F, Ar), 159.90 (C, Ar), 150.89 (C, pyrazole), 136.26 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 130.78 (CH, pyrazole), 129.17 (2 x CH, Ar), 125.01 (C, Ar), 120.86 and 120.79 (d, $^3J_{CF}$ = 8.8 Hz, 2x CH, Ar), 117.67 (C, pyrazole), 116.91 and 116.72 (d, $^2J_{CF}$ = 23.8 Hz, 2 x CH, Ar), 114.70 (2 x CH, Ar), 55.67 ($OCH_3$), 38.40 ($CH_2$Cl).

*4-(Chloromethyl)-1-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazole* (**10b** $R^1$=$CH_3$, $R^2$=Cl). Prepared from (1-(4-chlorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methanol carbaldehyde (**9b**) (0.80 g, 2.5 mmol). Yield 0.825 g (99%) as a brown oil. $R_f$: 0.67 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.74 (s, 1H, pyrazole), 7.91 (d, *J* = 8.5 Hz, 2H, Ar), 7.78 (d, *J* = 9.0 Hz, 2H, Ar), 7.59 (d, *J* = 9.0 Hz, 2H, Ar), 7.08 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 3.82 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 159.95 (C, Ar), 151.12 (C, pyrazole), 138.46 (C, Ar), 131.04 (C, Ar), 130.76 (CH, pyrazole), 130.0 (2 x CH, Ar), 129.20 (2 x CH, Ar), 124.88 (C, Ar), 120.34 (2 x CH, Ar), 118.0 (C, pyrazole), 114.72 (2 x CH, Ar), 55.68 ($CH_3$), 38.30 ($CH_2Cl$).

*4-(Chloromethyl)-3-(4-ethoxyphenyl)-1-(4-fluorophenyl)-1H-pyrazole* (**10c** $R^1$=$CH_2CH_3$, $R^2$=F). Prepared from (3-(4-Ethoxyphenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)methanol (**9c**) (0.30 g, 1.0 mmol). Yield 0.295 g (98%) as a brown oil. $R_f$: 0.64 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.69 (s, 1H, pyrazole), 7.91 (m, 2H, Ar), 7.76 (d, *J* = 9.0 Hz, 2H, Ar), 7.38 (m, 2H, Ar), 7.06 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 4.09 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 1.36 (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{19}$F NMR: (DMSO-$d_6$): -116.27 (F – Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.89 and 161.83 (d, $^1J_{CF}$ = 244.0 Hz, C-F, Ar), 159.17 (C, Ar), 150.90 (C, pyrazole), 136.27 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 130.78 (CH, pyrazole), 129.16 (2 x CH, Ar), 124.87 (C, Ar), 120.85 and 120.78 (d, $^3J_{CF}$ = 8.8 Hz, 2 x CH, Ar), 117.65 (C, pyrazole), 116.91 and 116.73 (d, $^2J_{CF}$ = 22.6 Hz, 2 x CH, Ar), 115.13 (2 x CH, Ar), 63.59 ($CH_2$), 38.42 ($CH_2Cl$), 15.12 ($CH_3$).

*4-(Chloromethyl)-1-(4-chlorophenyl)-3-(4-ethoxyphenyl)-1H-pyrazole* (**10d** $R^1$=$CH_2CH_3$, $R^2$=Cl). Prepared from (1-(4-chlorophenyl)-3-(4-ethoxyphenyl)-1*H*-pyrazol-4-yl)methanol carbaldehyde (**9d**) (0.99 g, 3 mmol). Yield 0.97 g (93%) as a brown solid. m.p: 90 - 92° C, $R_f$: 0.65 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.75 (s, 1H, pyrazole), 7.92 (d, *J* = 9.0 Hz, 2H, Ar), 7.77 (d, *J* = 9.0 Hz, 2H, Ar), 7.59 (d, *J* = 9.0 Hz, 2H, Ar), 7.07 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 4.10 (q, *J* = 7.0 Hz, 2H, $CH_2CH_3$), 1.36(t, *J* = 7.0 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 159.24 (C, Ar), 151.12 (C, pyrazole), 138.47 (C, Ar), 131.02 (C, Ar), 130.77 (CH, pyrazole), 130.01 (2 x CH, Ar), 129.19 (2 x CH, Ar), 124.74 (C, Ar), 120.33 (2 x CH, Ar), 117.98 (C, pyrazole), 115.14 (2 x CH, Ar), 63.60 ($CH_2CH_3$), 38.32 ($CH_2Cl$), 15.12 ($CH_2CH_3$).

*4-(Chloromethyl)-1-(4-fluorophenyl)-3-(4-propoxyphenyl)-1H-pyrazole* (**10e** $R^1$=$CH_2CH_2CH_3$, $R^2$=F). Prepared from (1-(4-fluorophenyl)-3-(4-propoxyphenyl)-1*H*-pyrazol-4-yl)methanol (**9e**) (0.75 g, 2.3 mmol). Yield 0.79 g (100%) as a brown semisolid. $R_f$: 0.68 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.69 (s, 1H, pyrazole), 7.92 (m, 2H, Ar), 7.77 (d, *J* = 9.0 Hz, 2H, Ar), 7.37 (t, *J* = 9.0 Hz, 2H, Ar), 7.06 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 3.99 (t, *J* = 7.0 Hz, 2H, $OCH_2$), 1.77 (m, 2H, $CH_3CH_2$), 1.0 (d, *J* = 7.50 Hz, 3H, $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): -116.91 (F-Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.89 and 161.82 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 159.33 (C, Ar), 150.90 (C, pyrazole), 136.28 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 130.77 (CH, pyrazole), 129.16 (2 x CH, Ar), 124.87 (C, Ar), 120.84 and 120.77 (d, $^3J_{CF}$ = 8.80 Hz, 2 x CH, Ar), 117.65 (C, pyrazole), 116.90 and 116.72 (d, $^2J_{CF}$ = 22.64 Hz, 2 x CH, Ar), 115.17 (2 x CH, Ar), 69.48 ($OCH_2$), 38.41 ($CH_2Cl$), 22.50 ($CH_2CH_3$), 10.88 ($CH_3$).

*4-(Chloromethyl)-1-(4-chlorophenyl)-3-(4-propoxyphenyl)-1H-pyrazole* (**10f** $R^1$=$CH_2CH_2CH_3$, $R^2$=Cl). Prepared from (1-(4-chlorophenyl)-3-(4-propoxyphenyl)-1*H*-pyrazol-4-yl)methanol (**9f**) (0.64 g, 1.87 mmol). Yield 0.66 g (98%) as a brown semisolid. $R_f$: 0.67 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.75 (s, 1H, pyrazole), 7.90 (d, *J* = 9.0 Hz, 2H, Ar), 7.76 (d, *J* = 9.0 Hz, 2H, Ar), 7.60 (d, *J* = 9.0 Hz, 2H, Ar), 7.08 (d, *J* = 9.0 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 4.0 (t, *J* = 6.50 Hz, 2H, $OCH_2$), 1.77 (m, 2H, $CH_3CH_2$), 1.0 (d, *J* = 7.50 Hz, 3H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 159.40 (C, Ar), 151.13 (C, pyrazole), 138.47 (C, Ar), 131.02 (C, Ar), 130.76 (CH, pyrazole), 130.0 (2 x CH, Ar), 129.18 (2 x CH, Ar), 124.74 (C, Ar), 120.33 (2 x CH, Ar), 117.98 (C, pyrazole), 115.18 (2 x CH, Ar), 69.49 ($OCH_2$), 38.32 ($CH_2Cl$), 22.50 ($CH_2CH_3$), 10.88 ($CH_3$).

*4-(Chloromethyl)-1-(4-fluorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazole* (**10g** $R^1$= $CH(CH_3)_2$, $R^2$=F). Prepared from (1-(4-fluorophenyl)-3-(4-isopropoxyphenyl)-1*H*-pyrazol-4-yl)methanol (**9g**) (0.6 g, 1.8 mmol). Yield 0.58 g (94%) as a brown oil. $R_f$: 0.67 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.69 (s, 1H, pyrazole), 7.91 (m, 2H, Ar), 7.76 (d, *J* = 8.5 Hz, 2H, Ar), 7.38 (t, *J* = 9.0 Hz, 2H, Ar), 7.06 (d, *J* = 8.50 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 4.69 (m, 1H, CH), 1.31 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{19}$F NMR: (DMSO-$d_6$): -116.95 (F-Ar). $^{13}$C NMR (DMSO-$d_6$): δ 159.89 and 161.82 (d, $^1J_{CF}$ = 242.7 Hz, C-F, Ar), 158.12 (C, Ar), 150.91 (C, pyrazole), 136.28 (d, $^4J_{CF}$ = 2.5 Hz, C, Ar), 130.77 (CH, pyrazole), 129.20 (2 x CH, Ar), 124.70 (C, Ar), 120.82 and 120.76 (d, $^3J_{CF}$ = 7.6 Hz, 2 x CH, Ar), 117.64 (C, pyrazole), 116.91 and 116.72 (d, $^2J_{CF}$ = 23.8 Hz, 2 x CH, Ar), 116.18 (2 x CH, Ar), 69.68 (CH), 38.43 ($CH_2Cl$), 22.30 (2 x $CH_3$).

*4-(Chloromethyl)-1-(4-chlorophenyl)-3-(4-isopropoxyphenyl)-1H-pyrazole* (**10h** $R^1$= $CH(CH_3)_2$, $R^2$=Cl). Prepared from (1-(4-chlorophenyl)-3-(4-isopropoxyphenyl)-1*H*-pyrazol-4-yl)methanol (**9h**) (0.7 g, 2.0 mmol). Yield 0.68 g (94%) as a brown oil. $R_f$: 0.68 (petroleum ether - EtOAc 4:1 v/v). $^1$H NMR (DMSO-$d_6$): δ 8.75 (s, 1H, pyrazole), 7.92 (d, *J* = 9.0 Hz, 2H, Ar), 7.76 (d, *J* = 9.0 Hz, 2H, Ar), 7.60 (d, *J* = 9.0 Hz, 2H, Ar), 7.06 (d, *J* = 8.50 Hz, 2H, Ar), 4.89 (s, 2H, $CH_2Cl$), 4.69 (m, 1H, CH), 1.31 (d, *J* = 6.0 Hz, 6H, 2 x $CH_3$). $^{13}$C NMR (DMSO-$d_6$): δ 158.20 (C, Ar), 151.13 (C, pyrazole), 138.48 (C, Ar), 131.01 (C, Ar), 130.76 (CH, pyrazole), 130.0 (2 x CH, Ar), 129.23 (2 x CH, Ar), 124.57 (C, Ar), 120.32 (2 x CH, Ar), 117.97 (C, pyrazole), 116.19 (2 x CH, Ar), 69.69 (CH), 38.33 ($CH_2Cl$), 22.30 (2 x $CH_3$).

**Reference**

1. F.A. Ragab, N.M. Abdel Gawad, H.H. Georgey, and M.F. Said. *Eur. J. Med. Chem.* 2013, **63**, 645–654.

**HPLC analysis**

The purity of the final compound **12h** was determined by HPLC UV with correlating MS in Positive ionization mode on a Zorbax Eclipse Plus C18 Rapid Resolution 2.1 x 50 mm, 1.8 µm particle size using a 7.5-minute gradient method 5:95 v/v water: methanol with 0.1% formic acid as additive.

The HPLC data of compound **12h (**HPLC purity 97.0 %. Peak at 4.88 min**):**

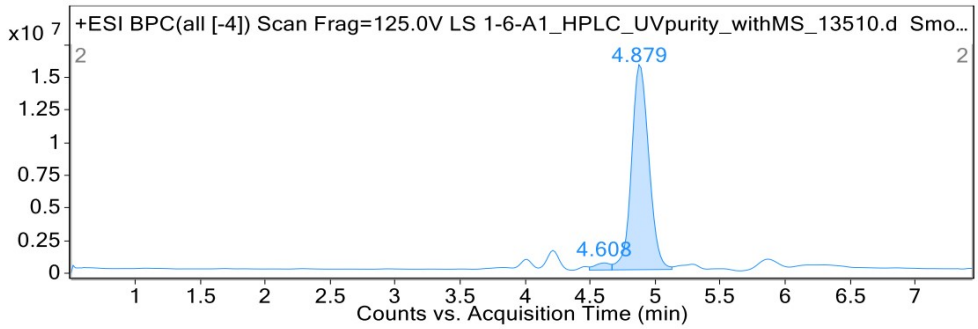



Figure 1: Base peak chromatogram

**User Chromatogram Peak List**

| RT (min) | Area | Area % | Area Sum (%) | Base Peak (m/z) | Width (min) |
|---|---|---|---|---|---|
| 4.61 | 4476097 | 3.06 | 2.97 | 388.0761 | 0.126 |
| 4.88 | 146185884 | 100.00 | 97.03 | 394.1378 | 0.148 |

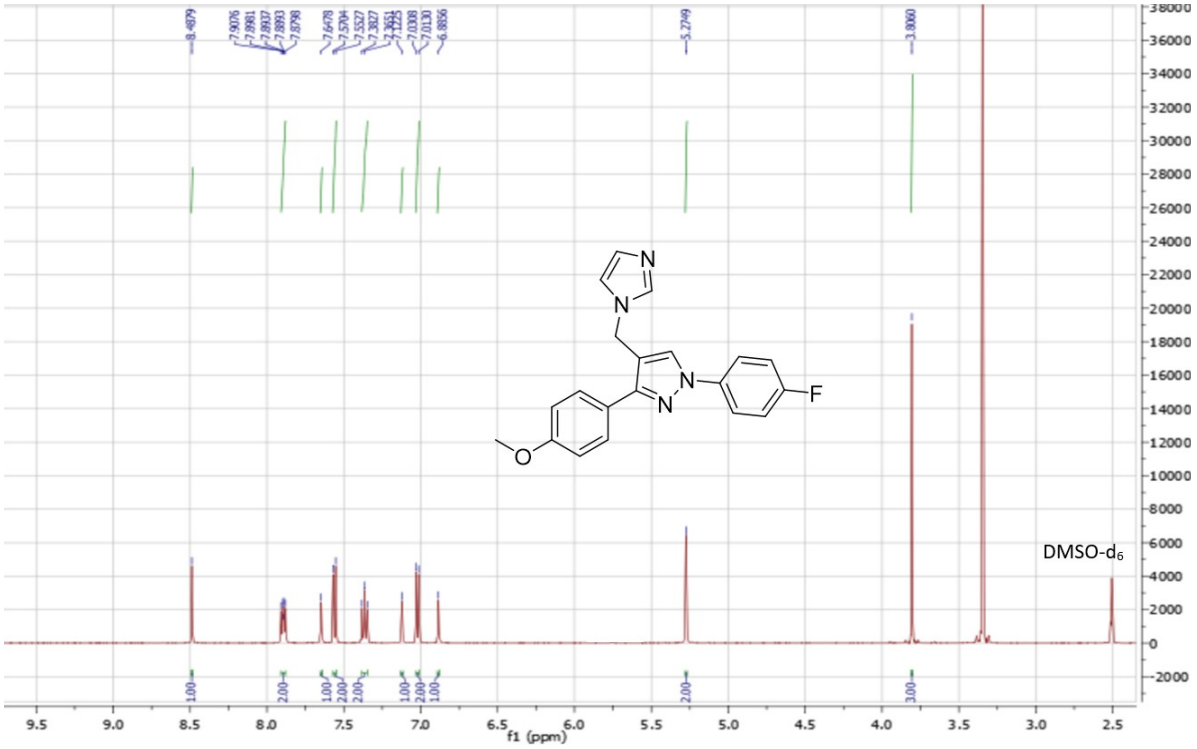
**Compound Table**

| Compound Label | RT (min) | Observed mass (m/z) | Neutral observed mass (Da) | Theoretical mass (Da) | Mass error (ppm) | Isotope match score (%) |
|---|---|---|---|---|---|---|
| Cpd 1: C21 H20 Cl N5 O | 4.88 | 394.1443 | 393.1371 | 393.1356 | 3.74 | 92.41 |

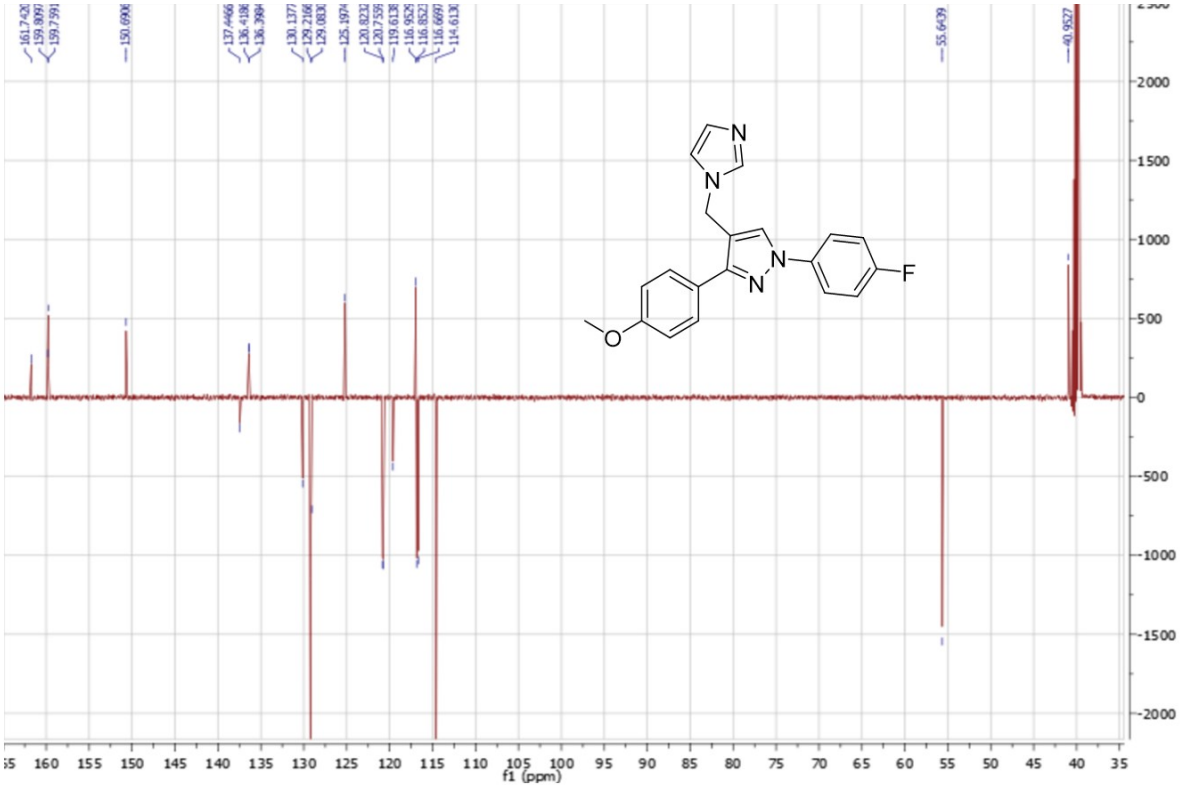
Mass errors of between -5.00 and 5.00 ppm with isotope match scores above 60% are considered confirmation of molecular formulae

**The $^{1}$H- and $^{13}$C-NMR spectra of all final compounds are shown here:**

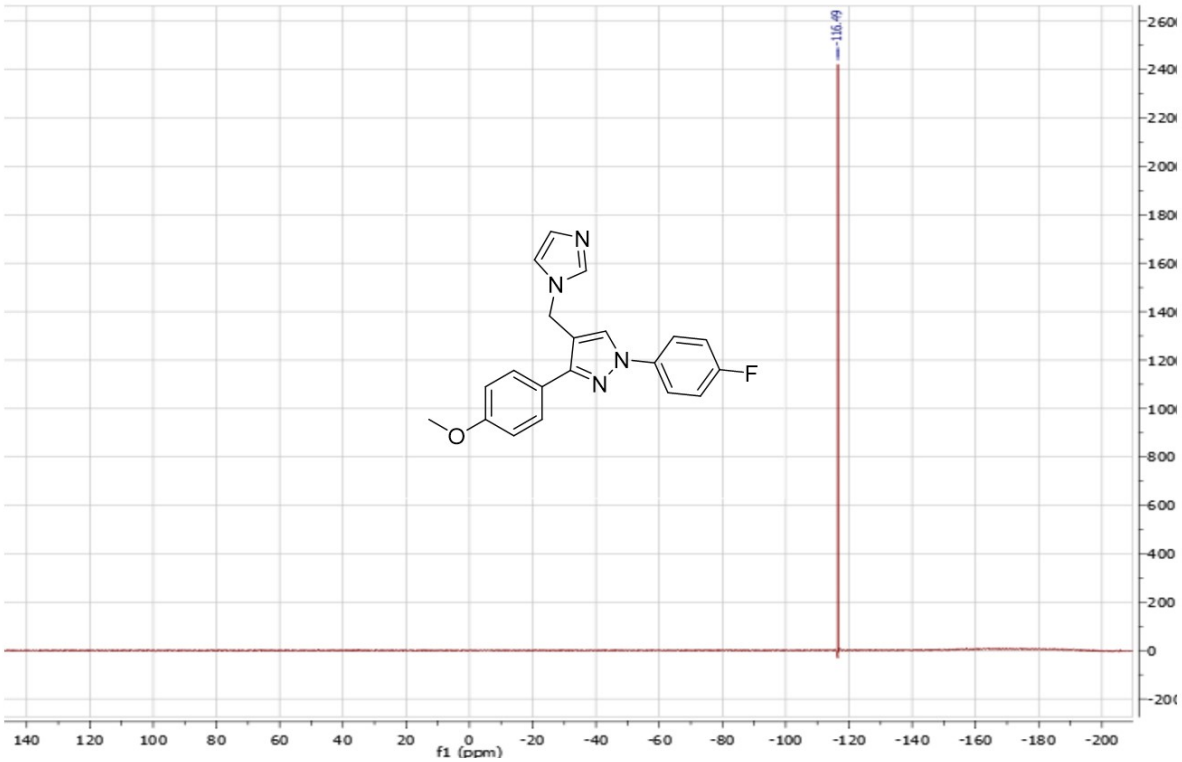
$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11a**:



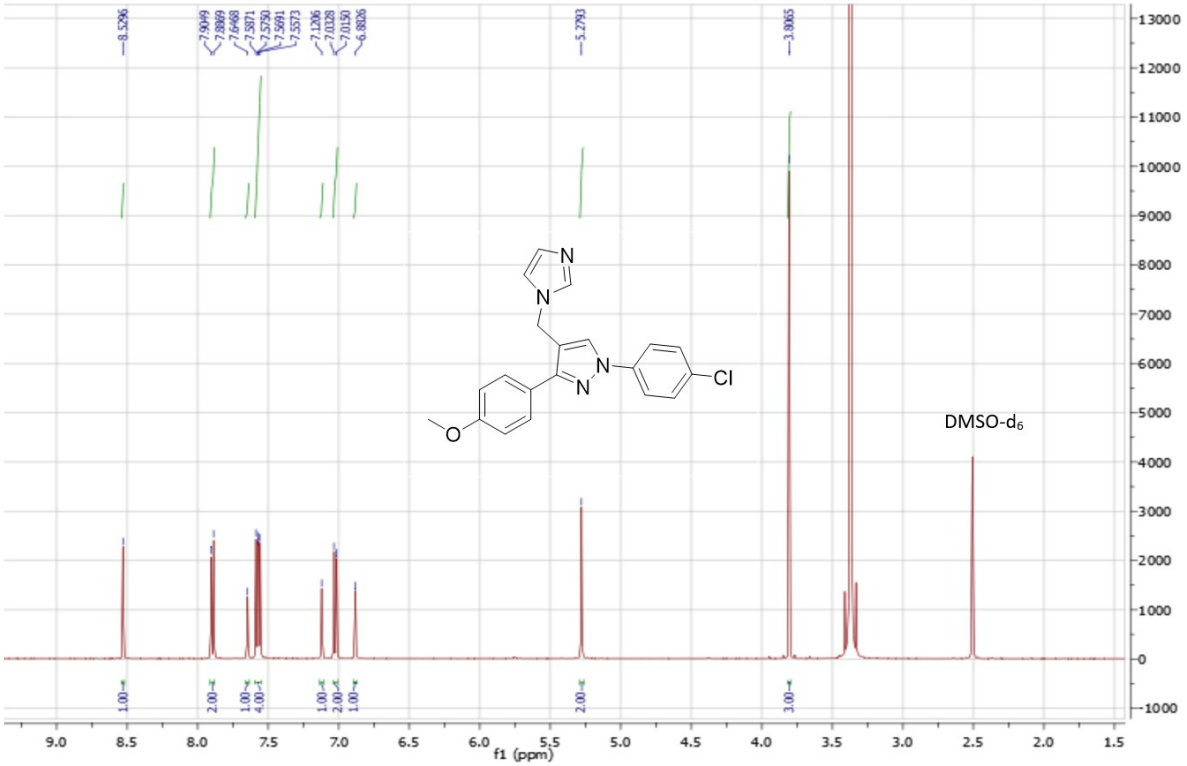

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11a**:



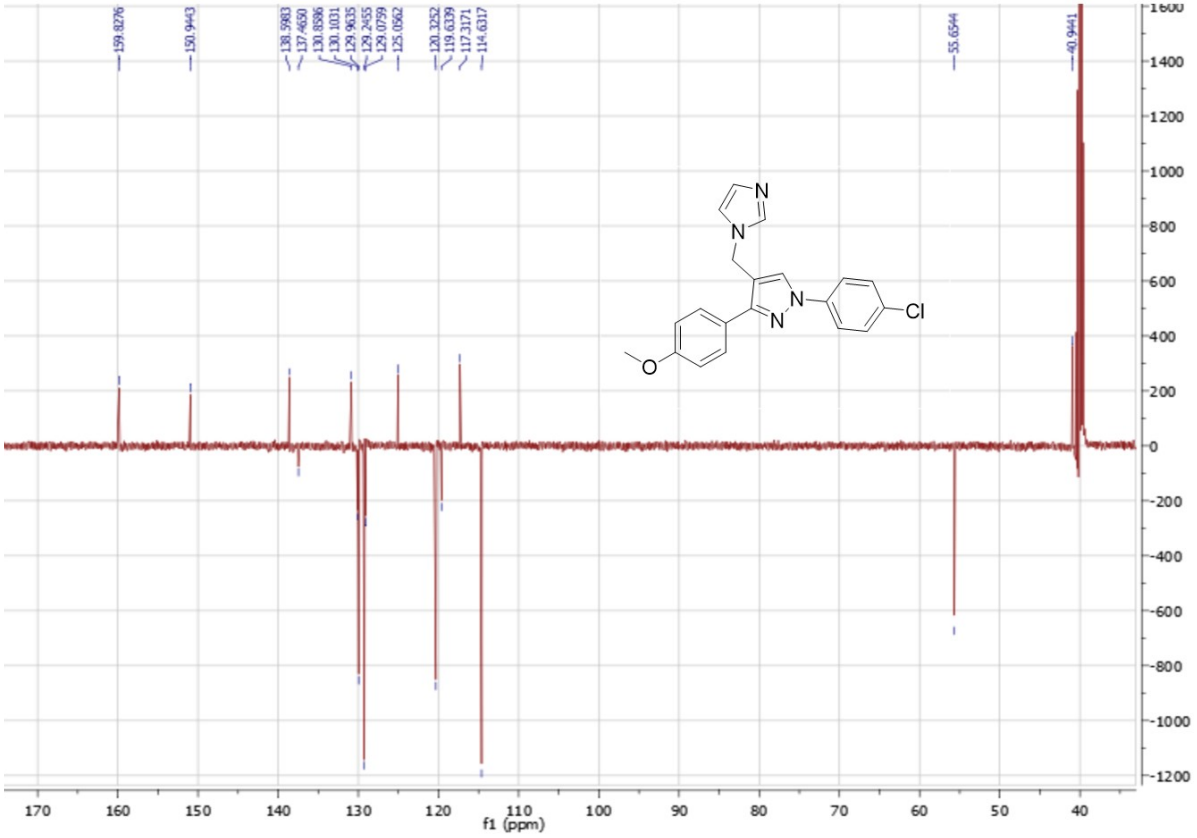
$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **11a**:



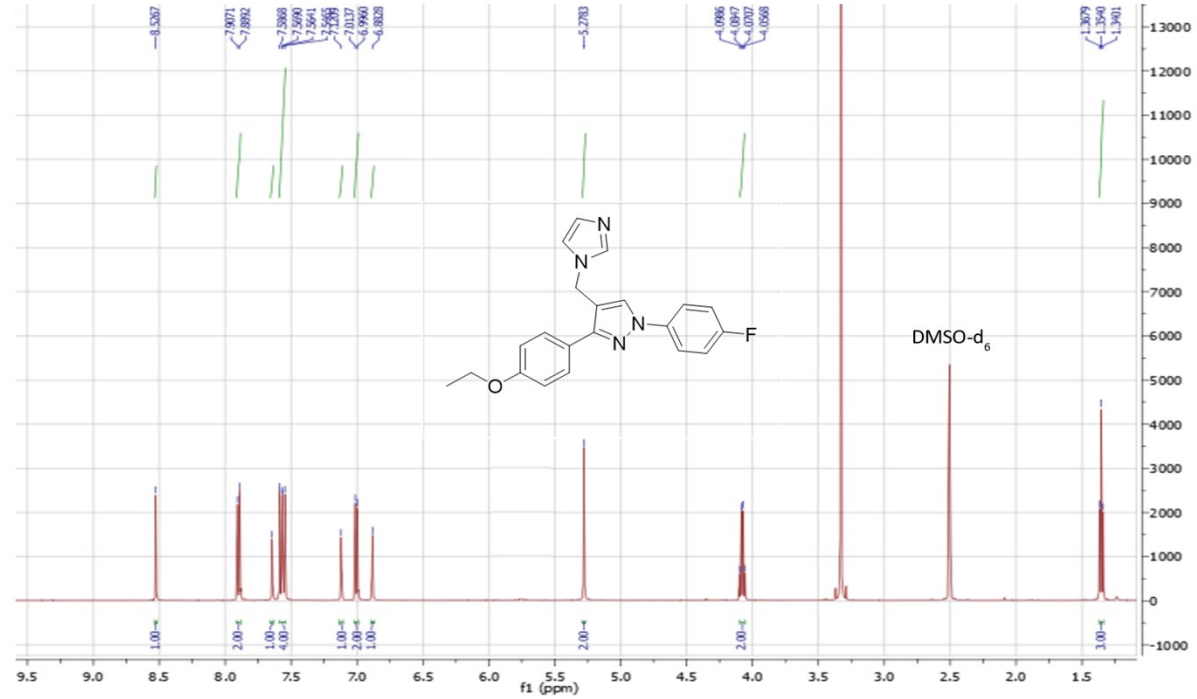

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11b**:



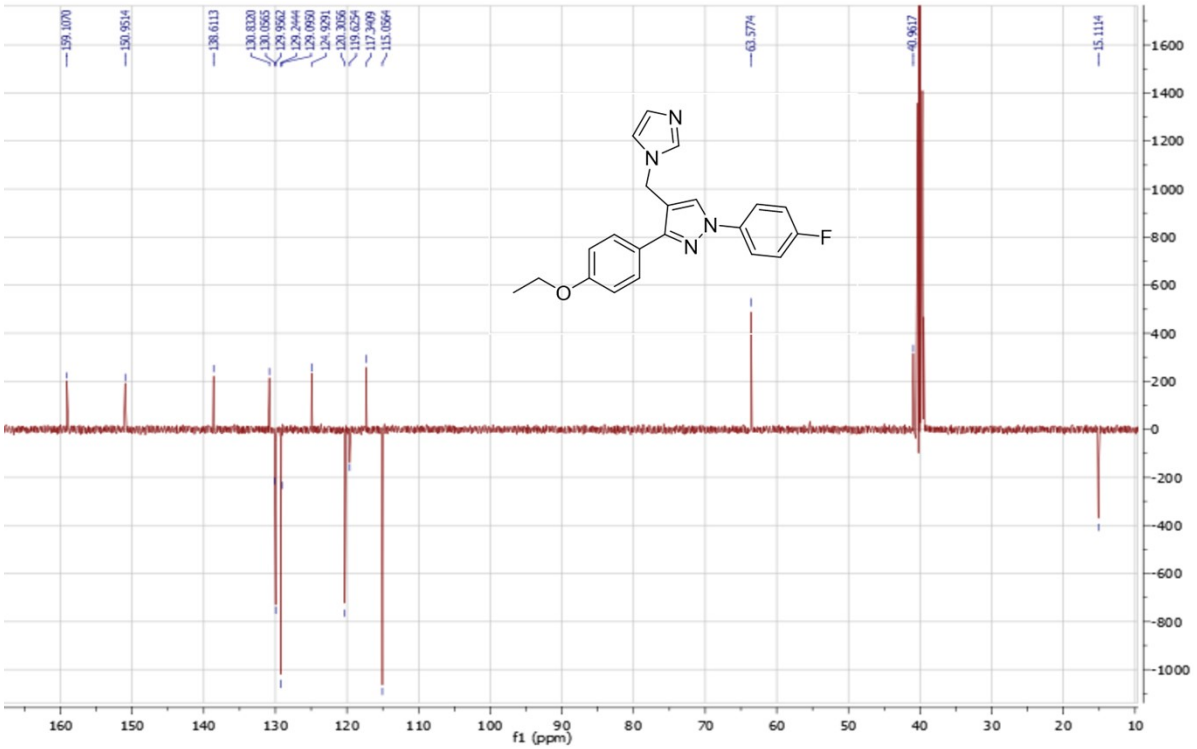
$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11b**:



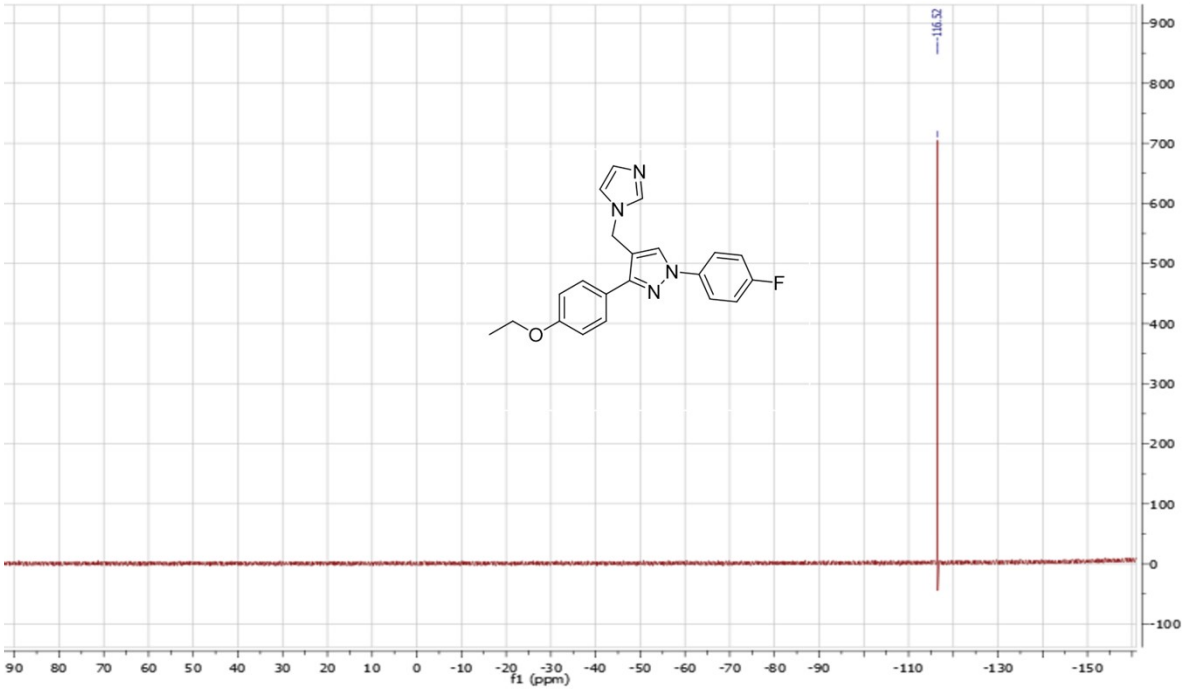

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11c**:



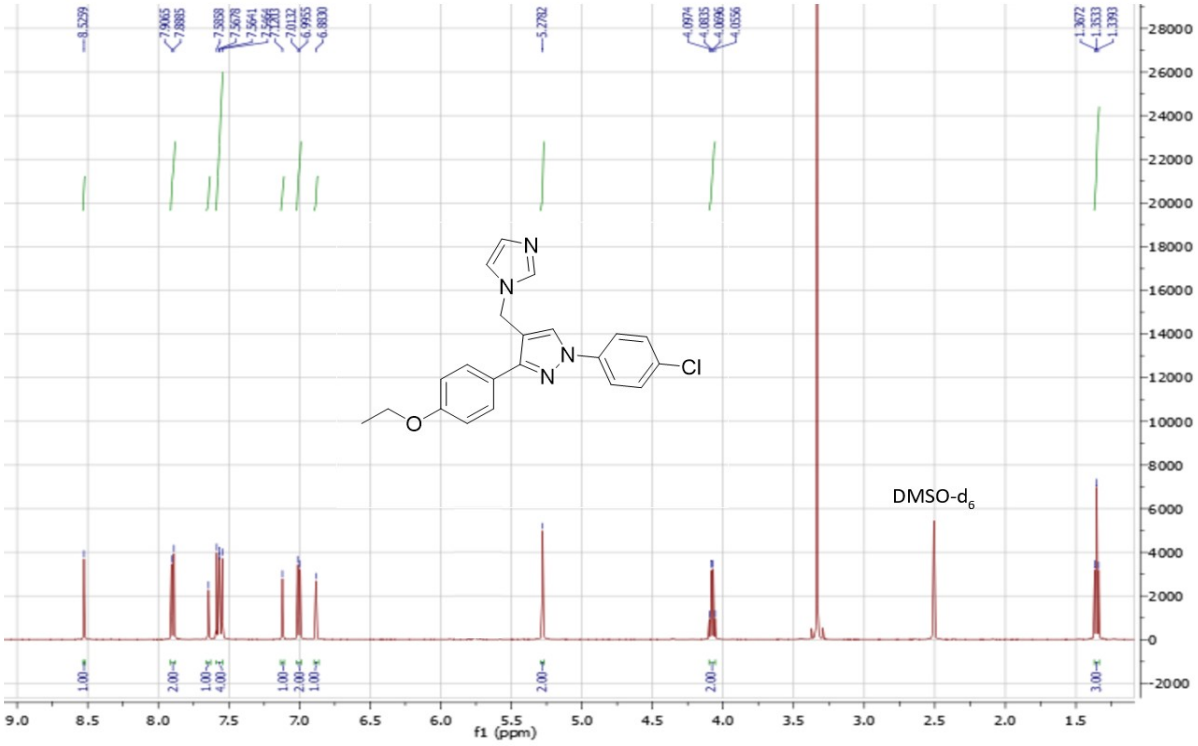
$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11c:**



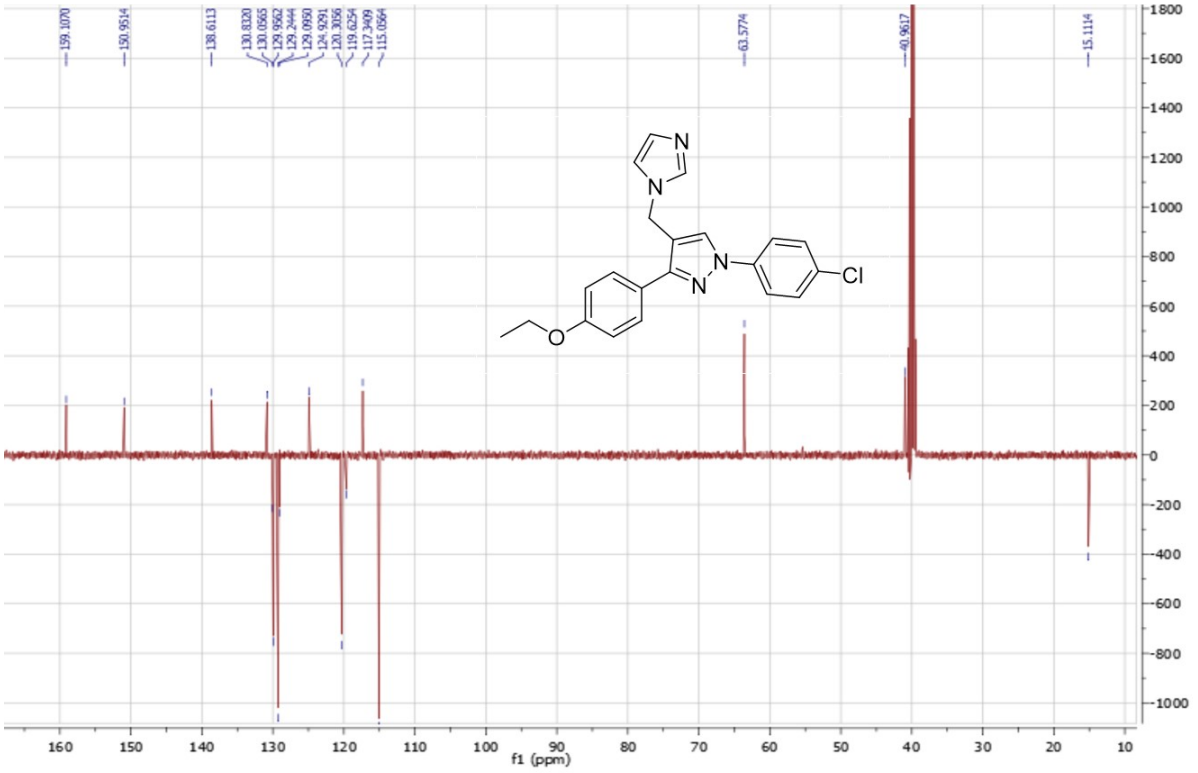

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **11c**:



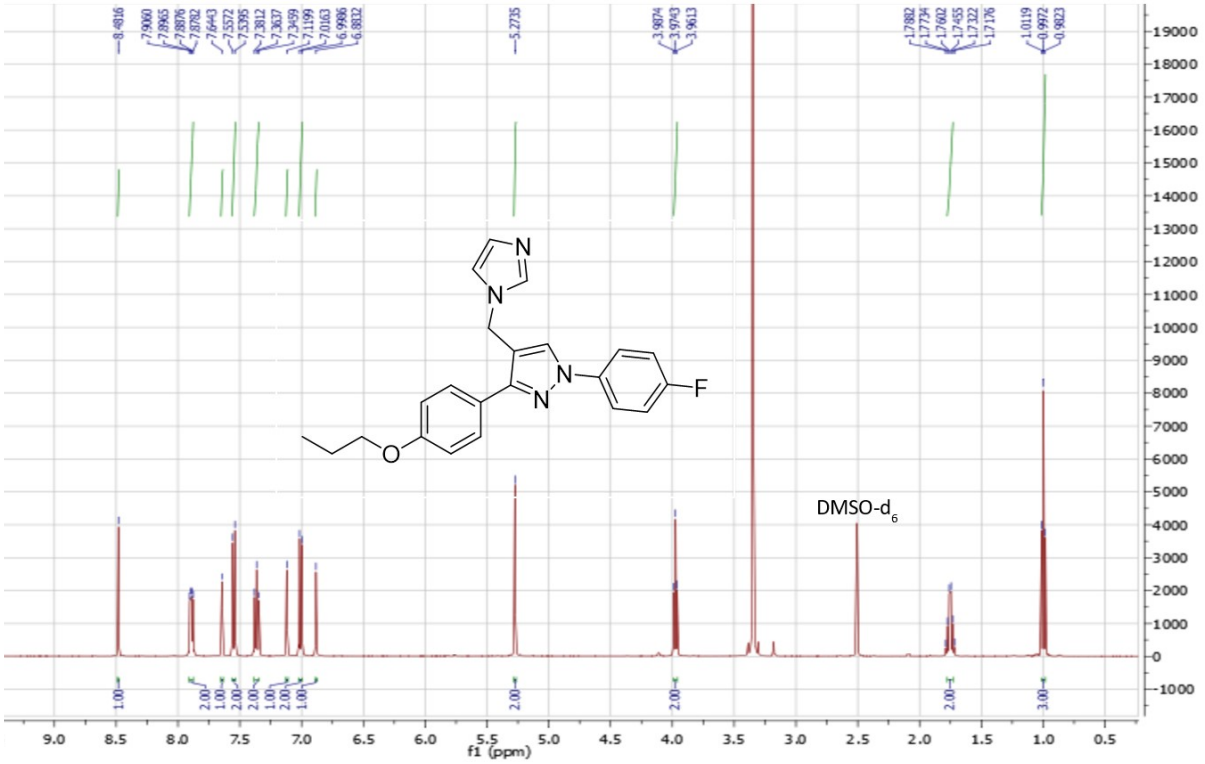
$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11d**:



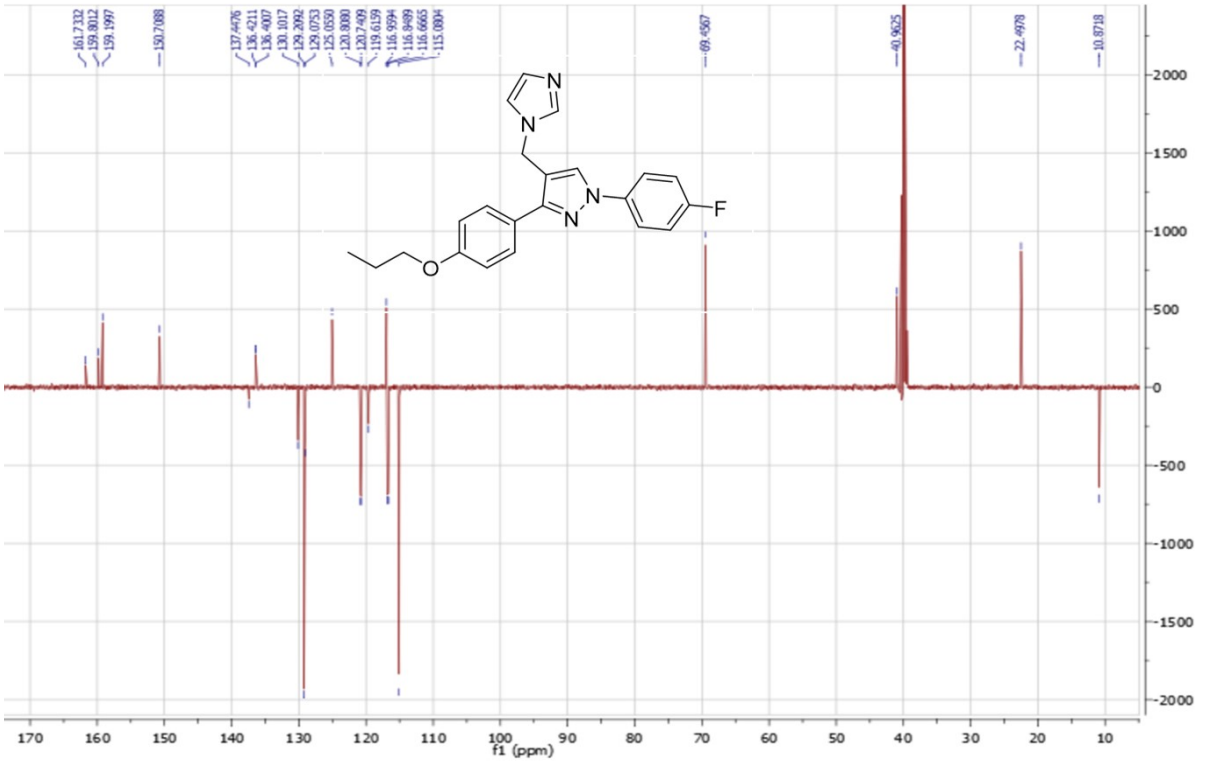

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11d:**



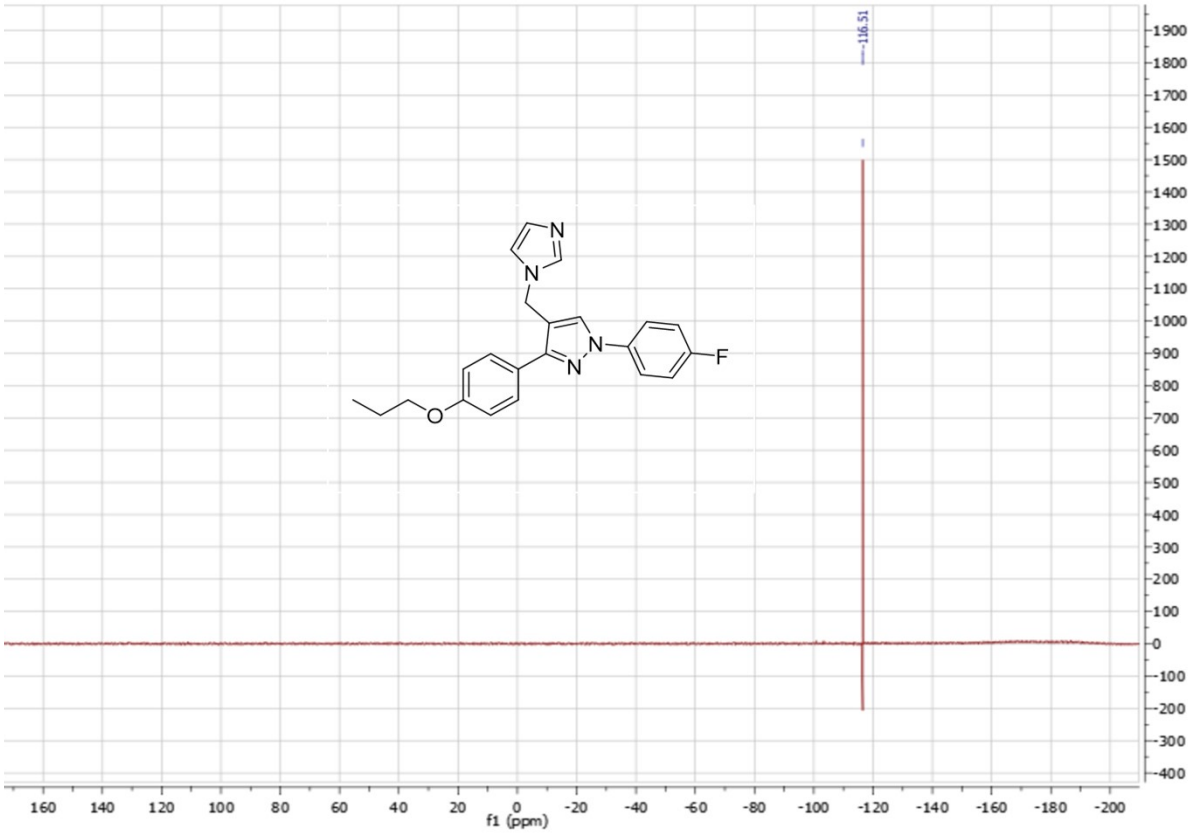
$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11e**:



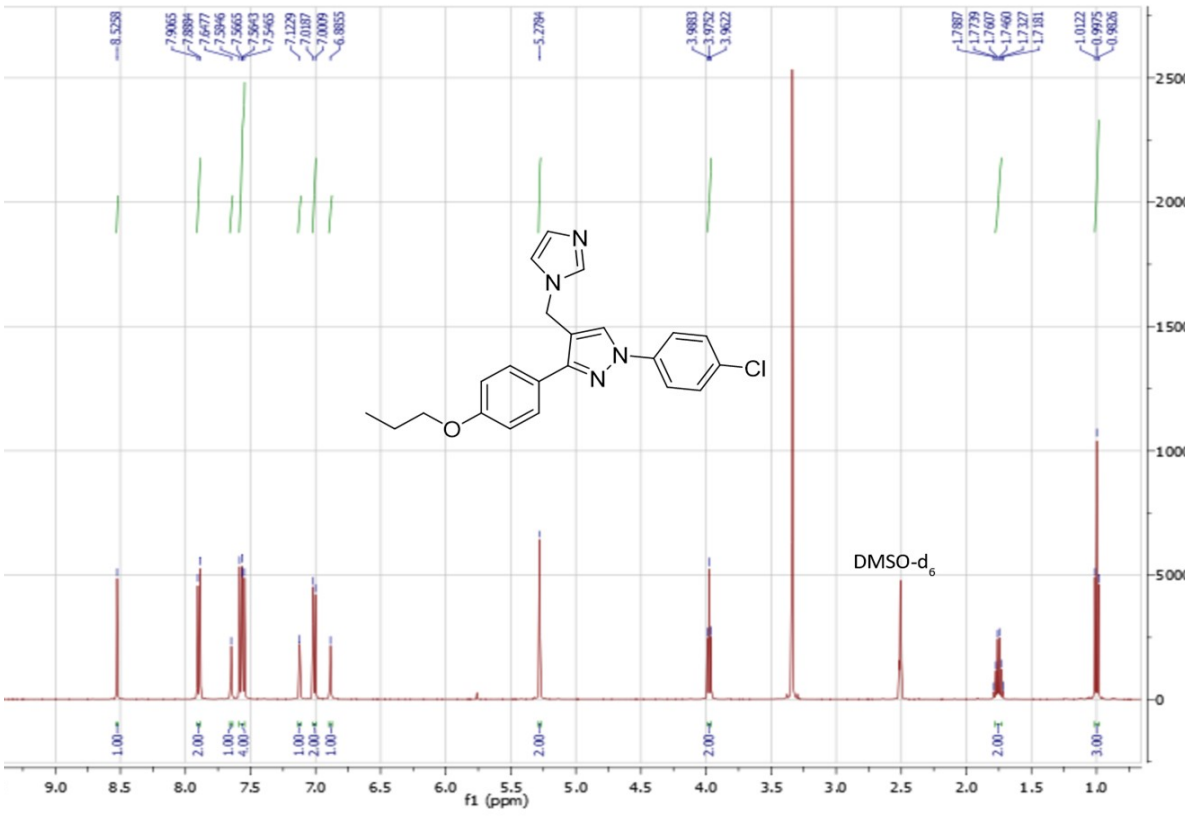

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11e:**



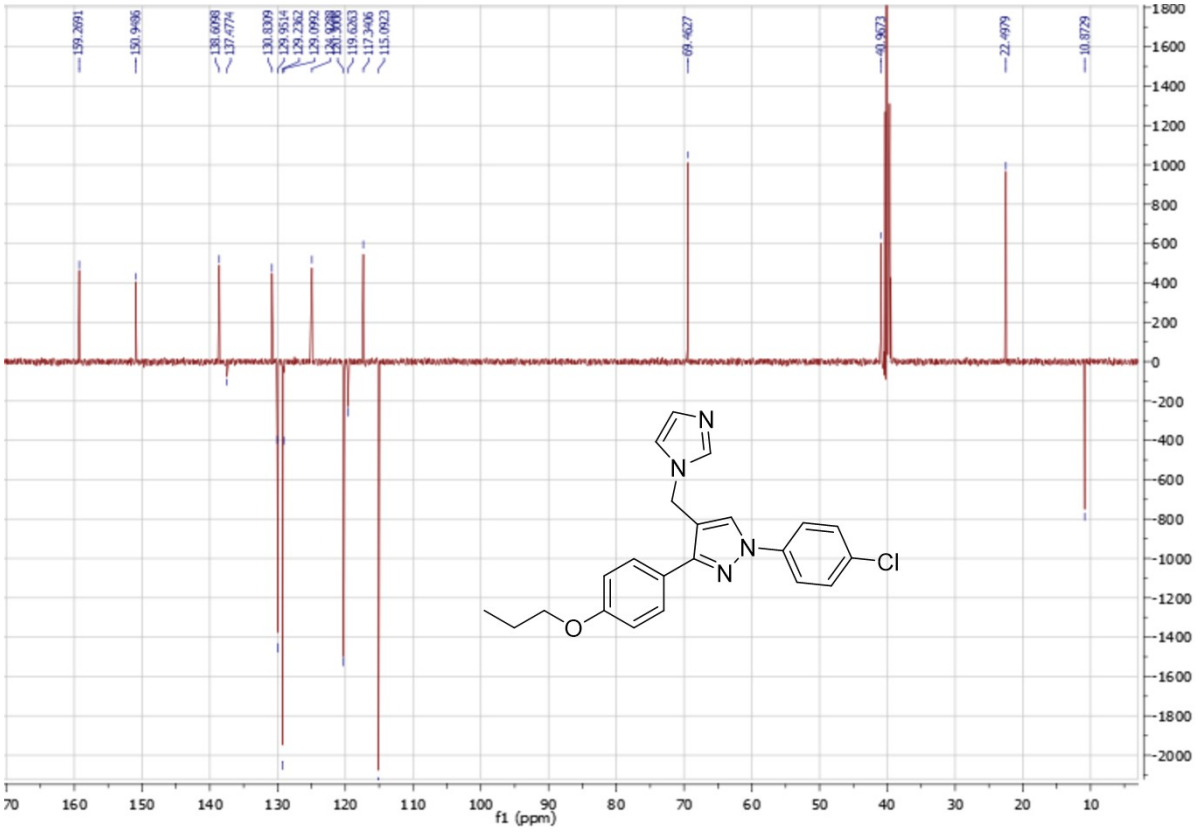
$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **11e**:



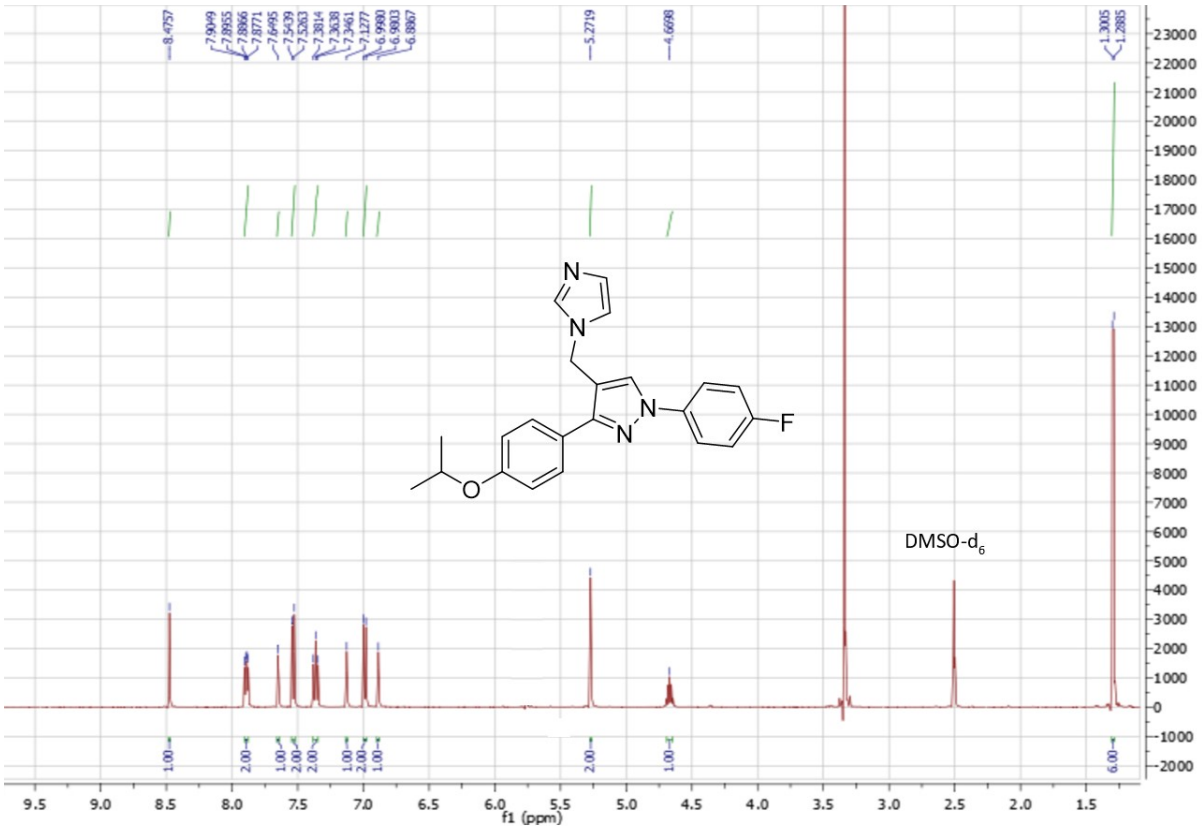

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11f**:



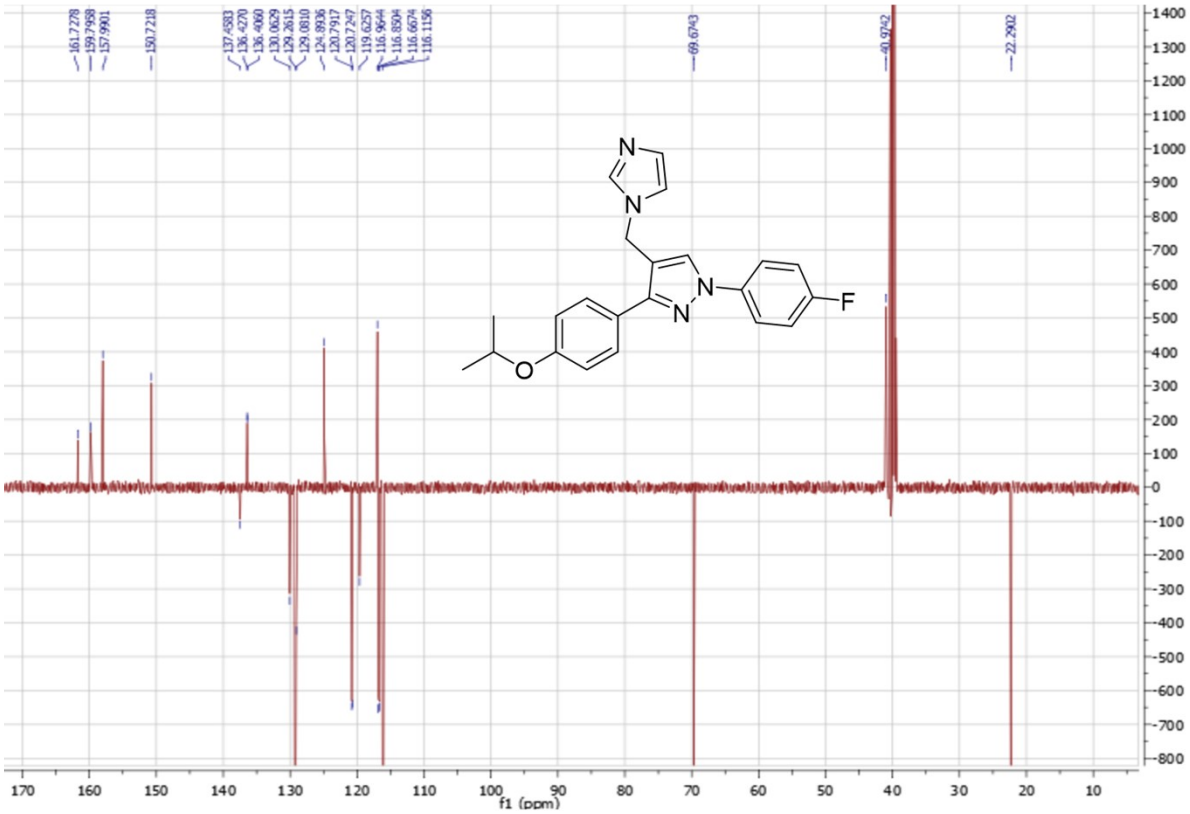

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11f:**



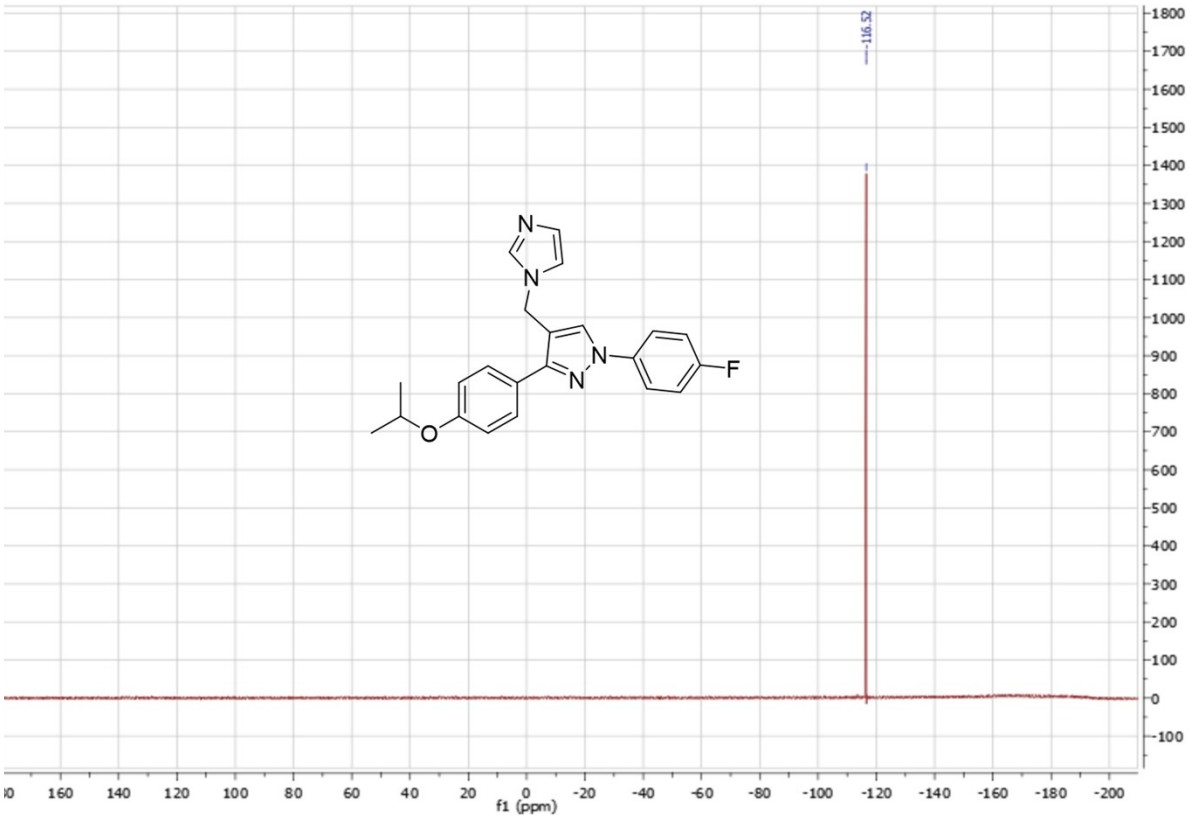

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11g**:



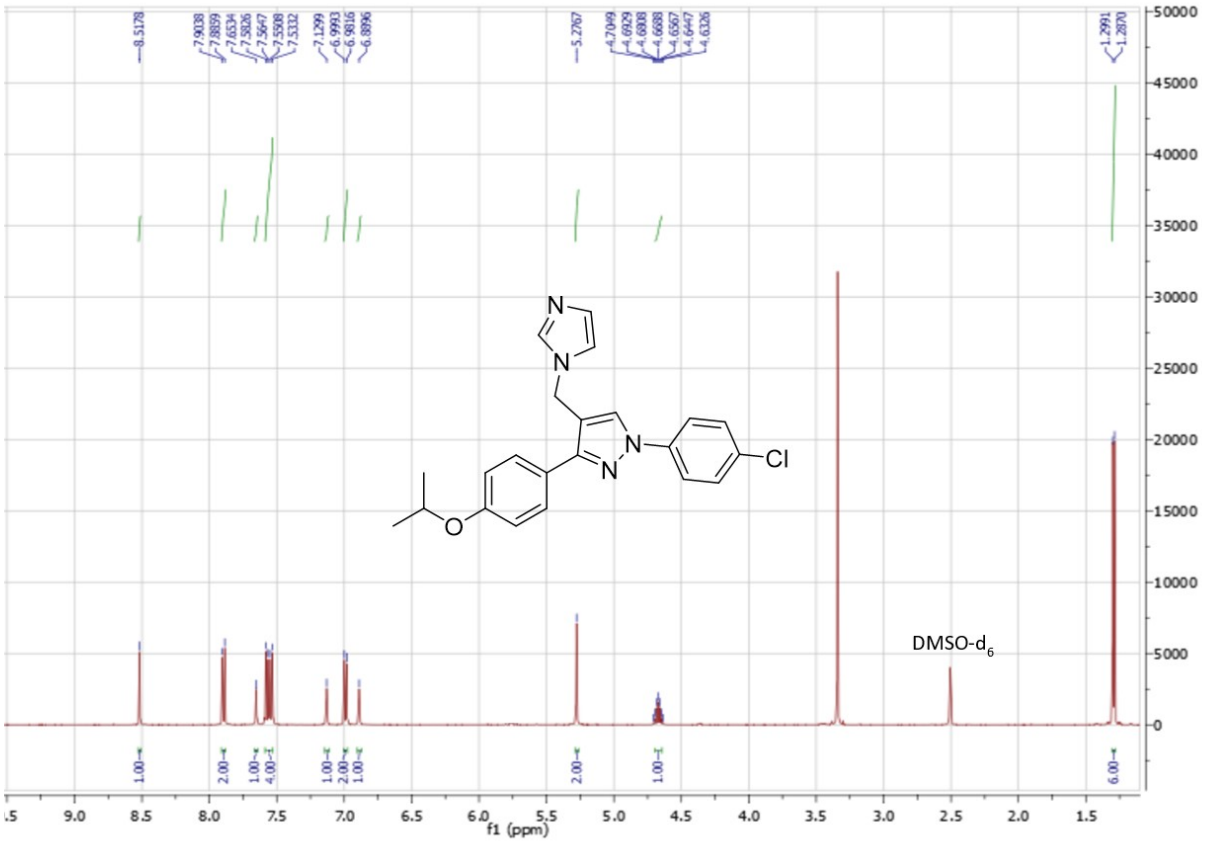

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11g:**



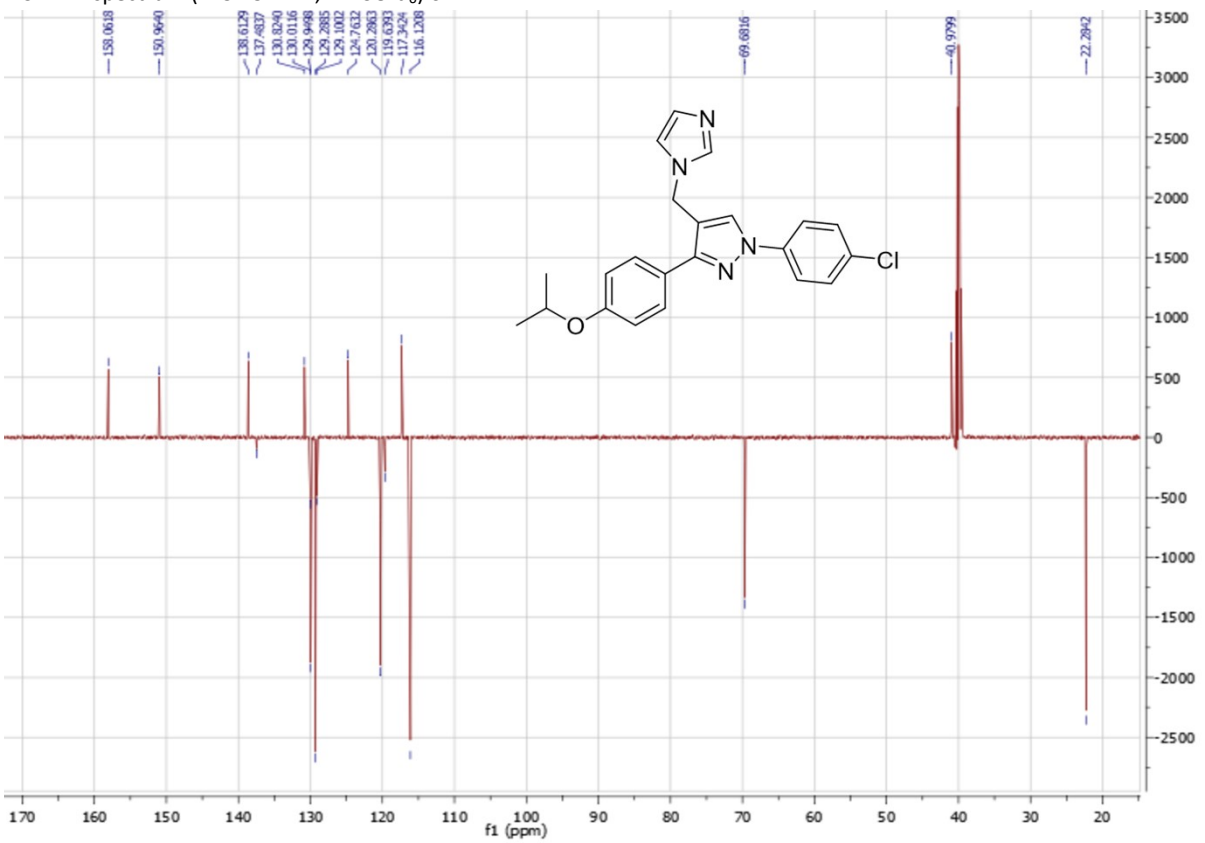

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **11g**:



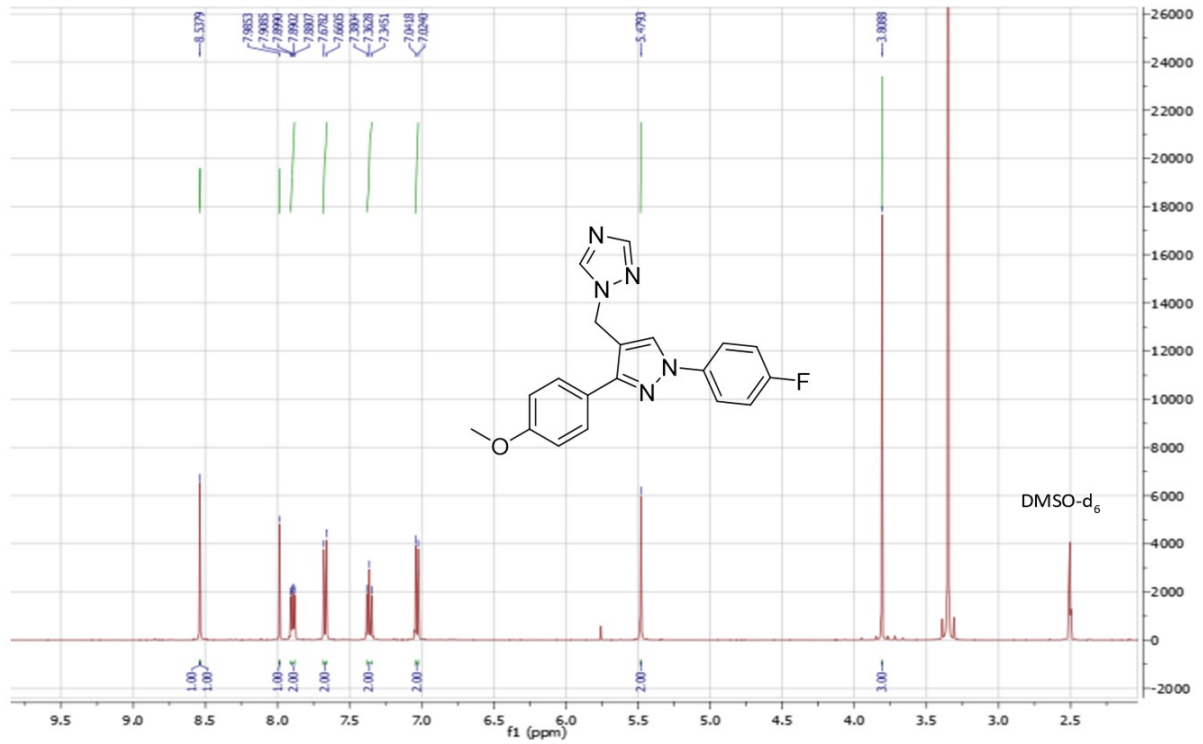

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **11h**:



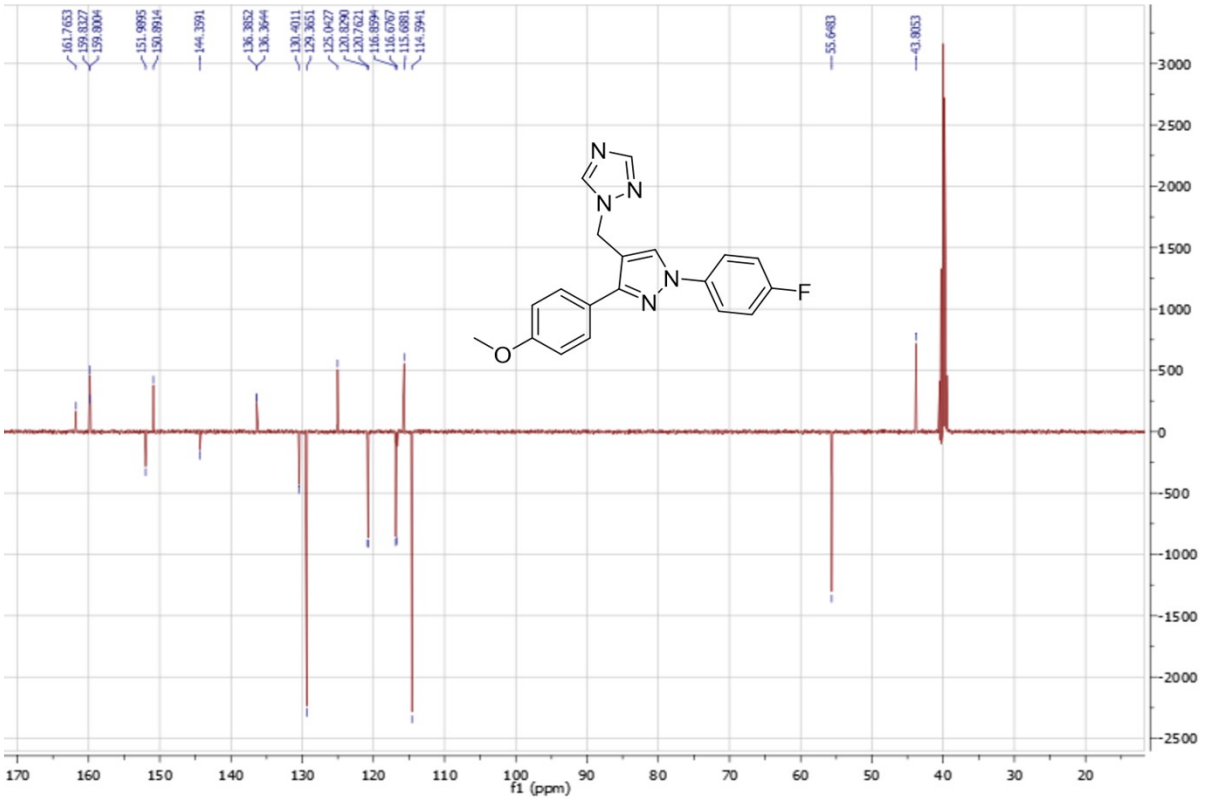

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **11h:**



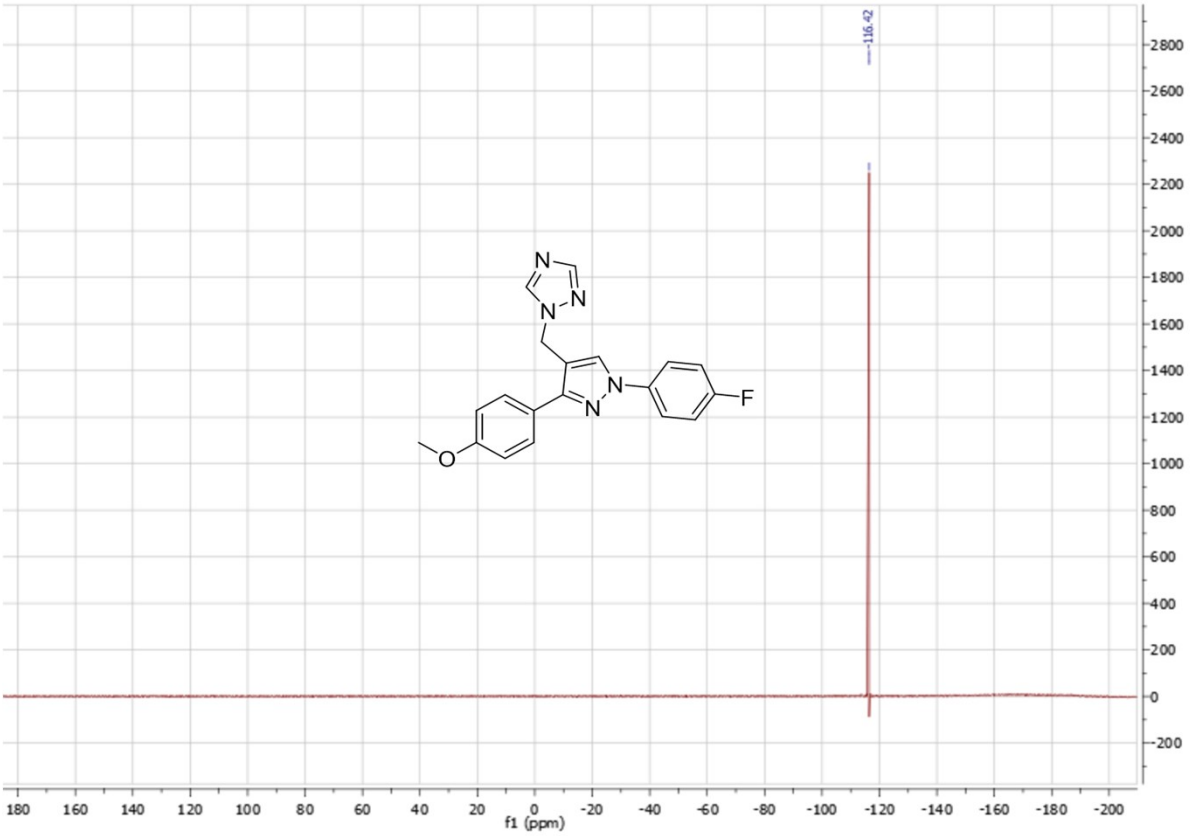

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12a**:



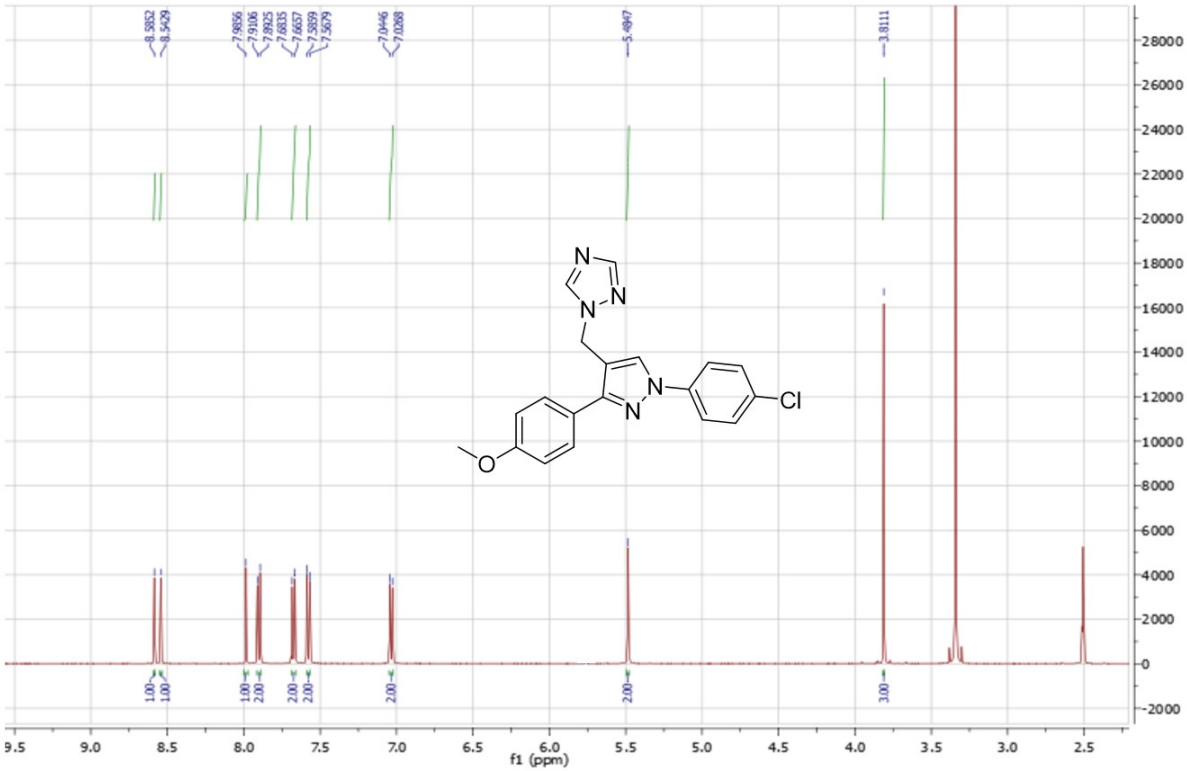

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12a:**



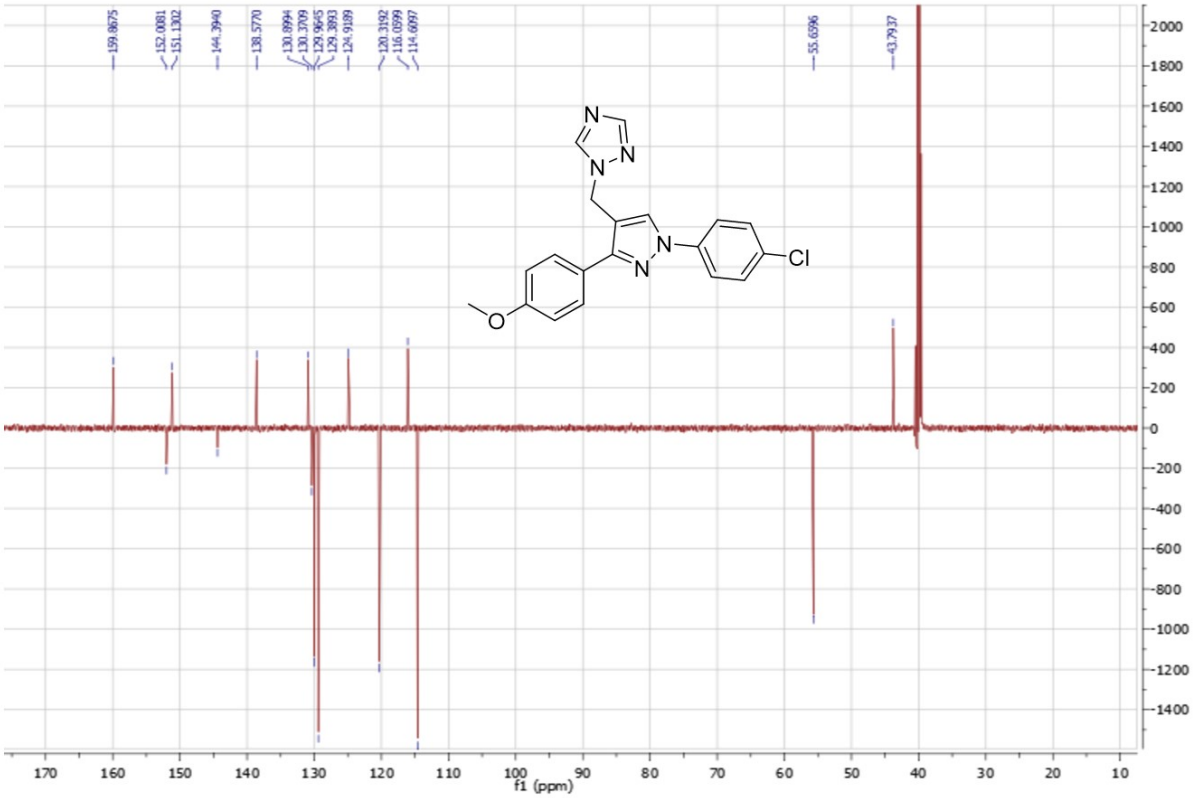

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **12a**:



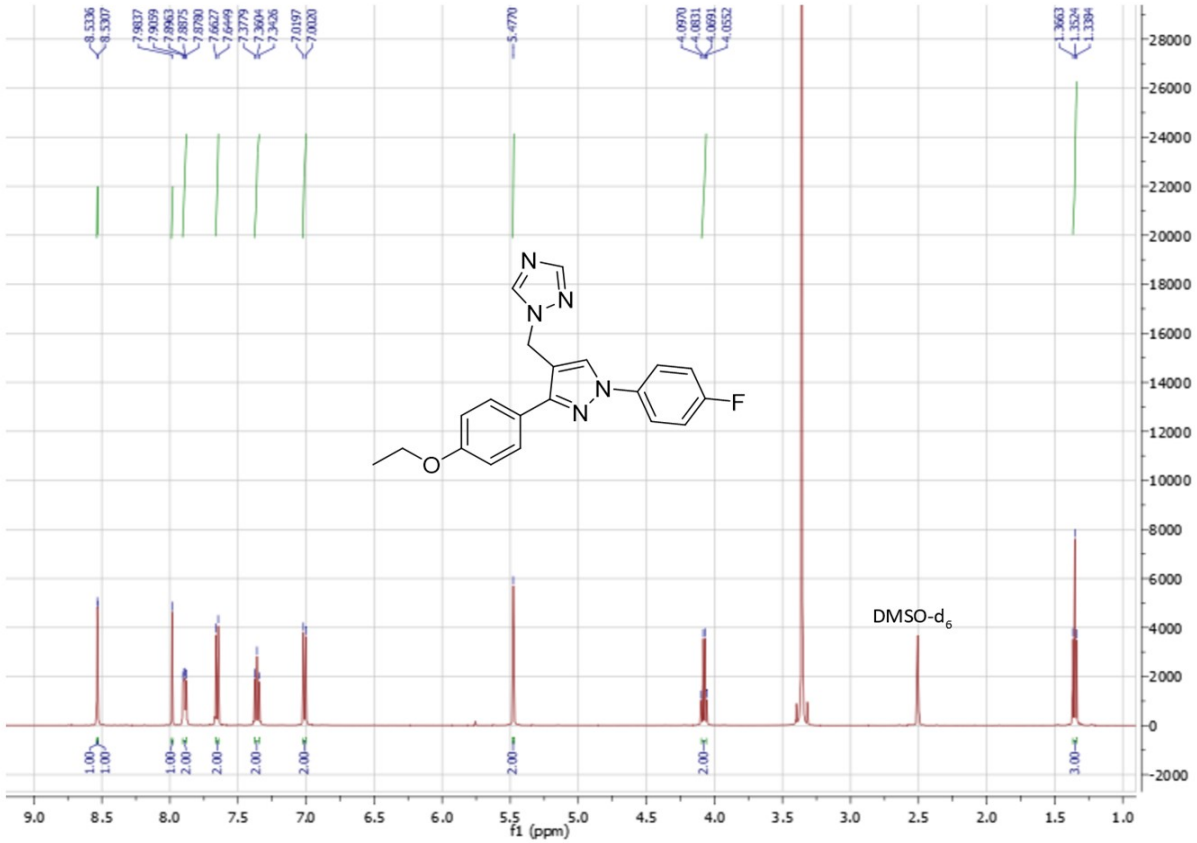

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12b**:



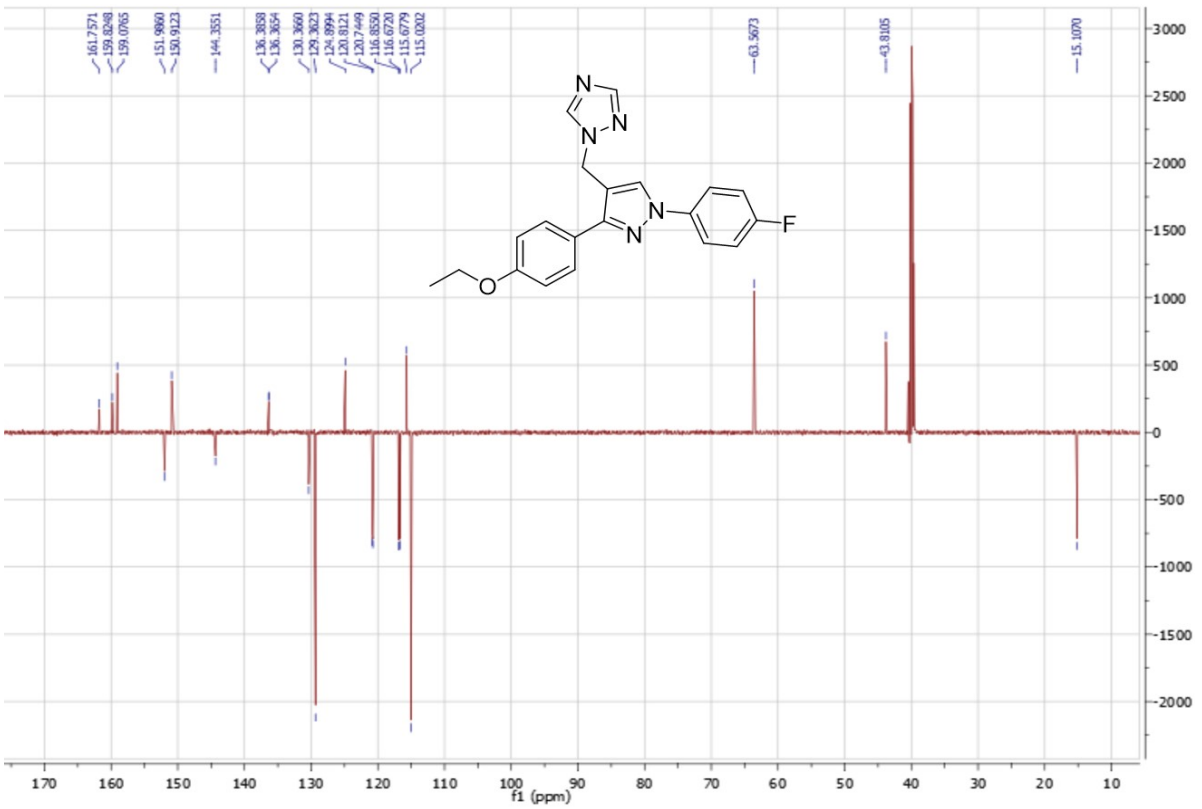

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12b:**



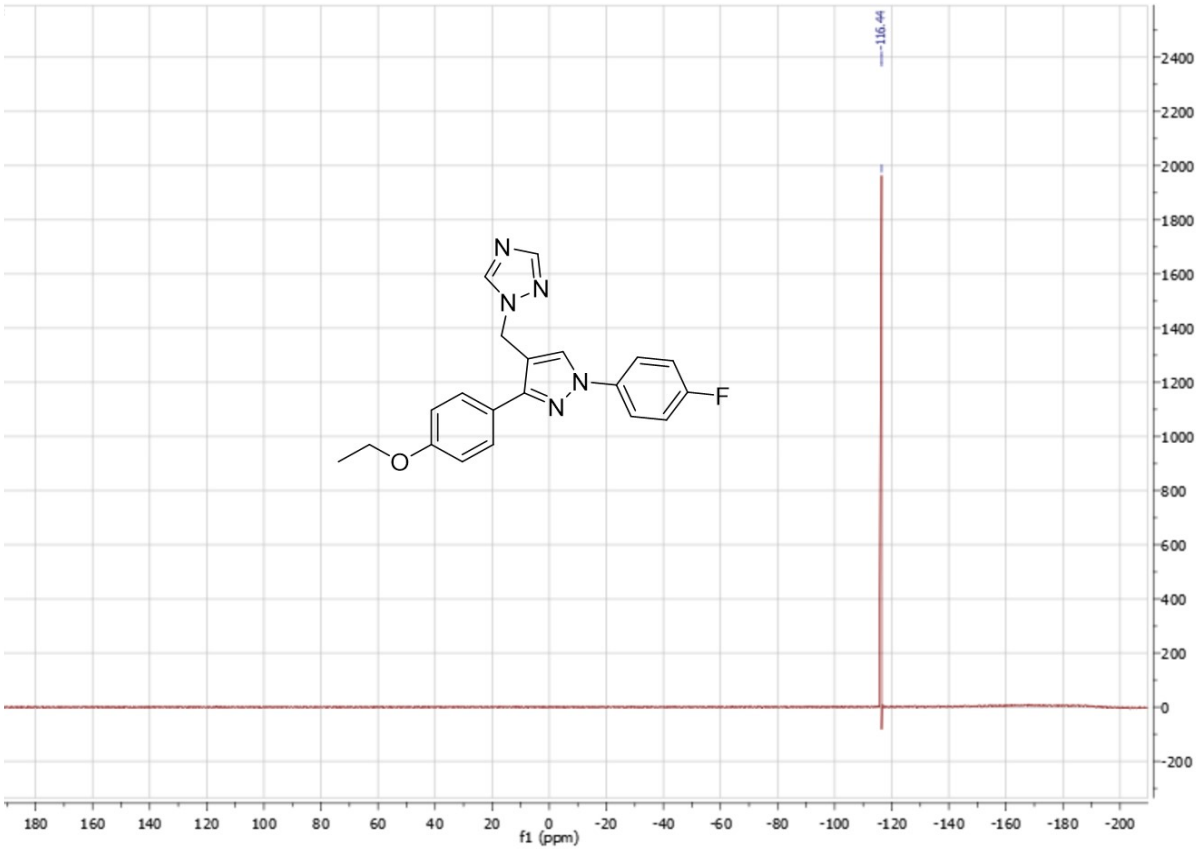

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12c**:



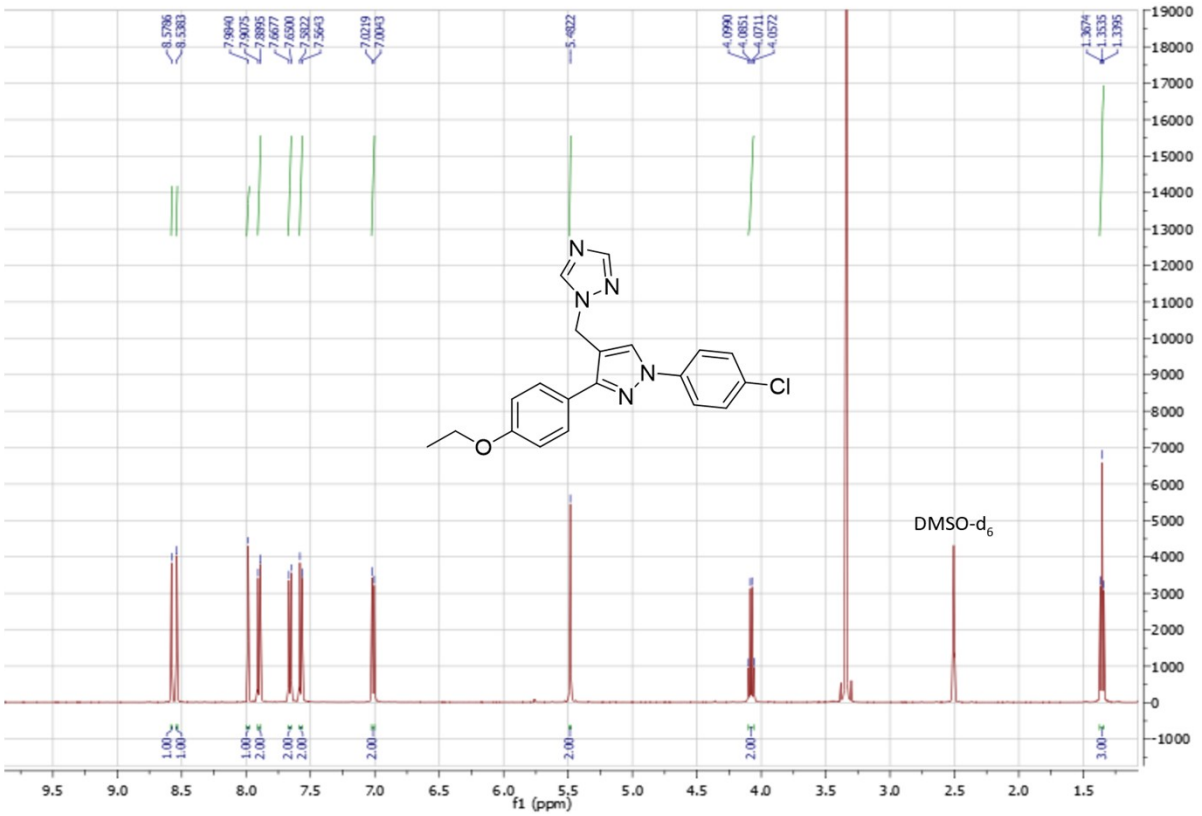

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12c:**



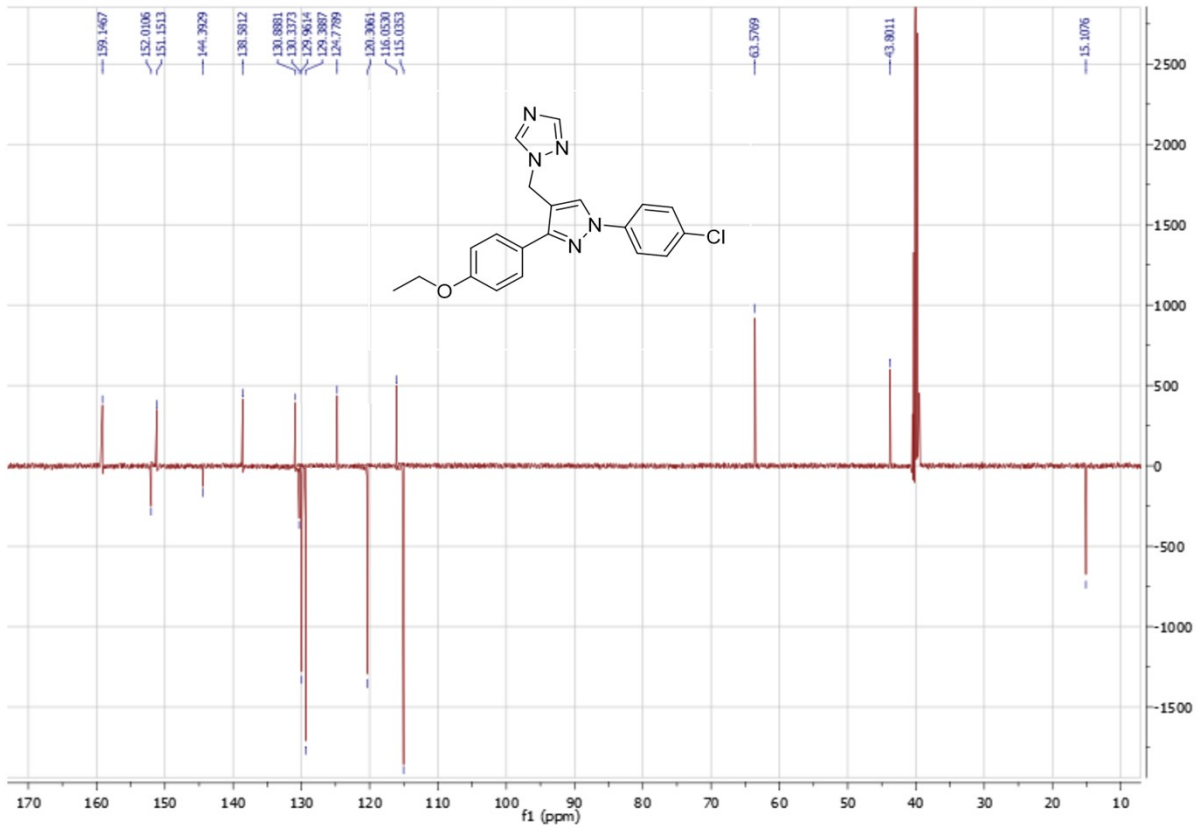

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **12c**:



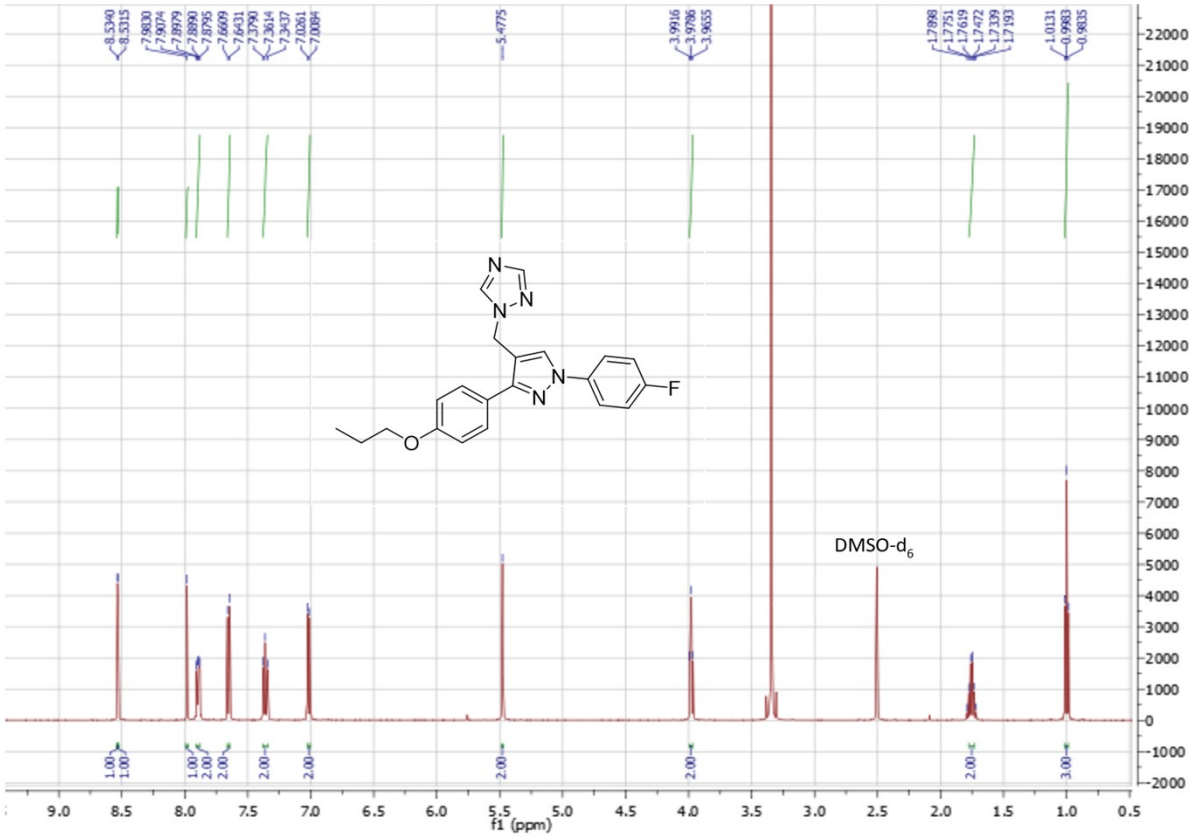

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12d**:



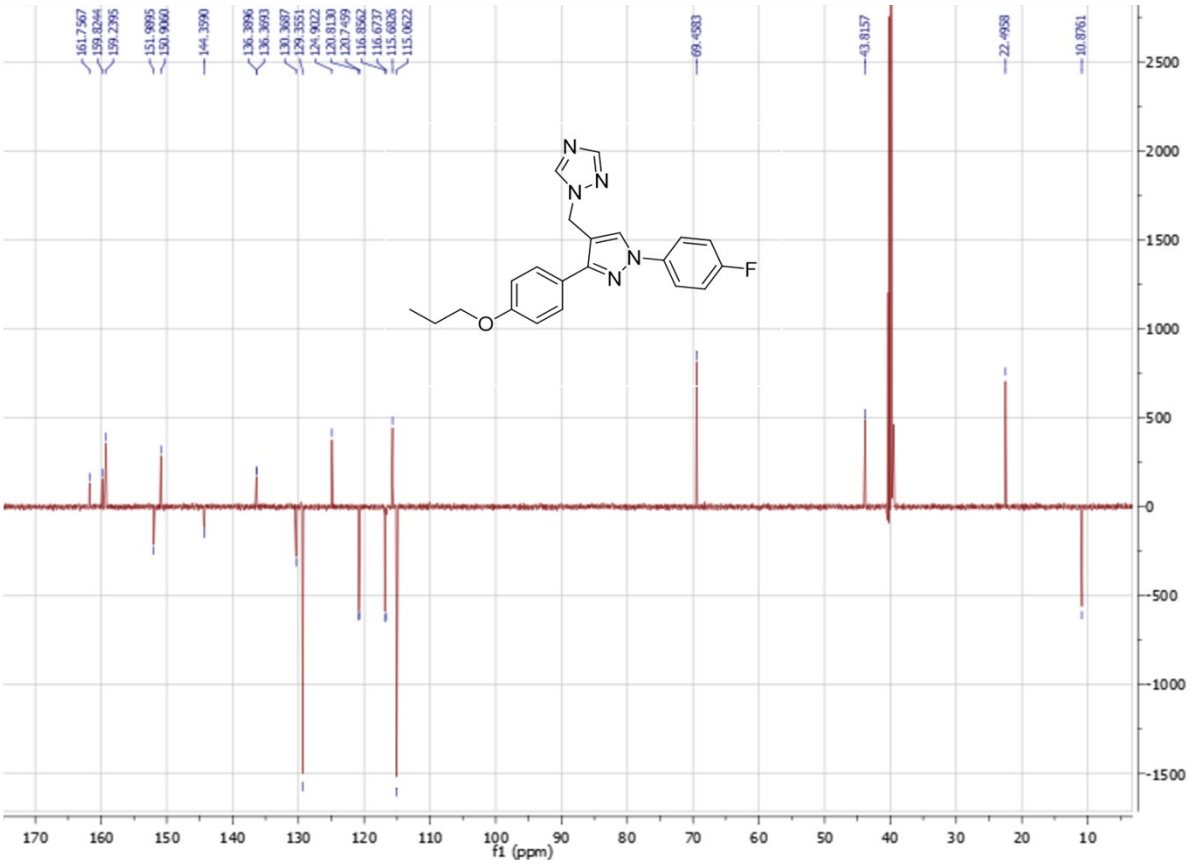

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12d:**



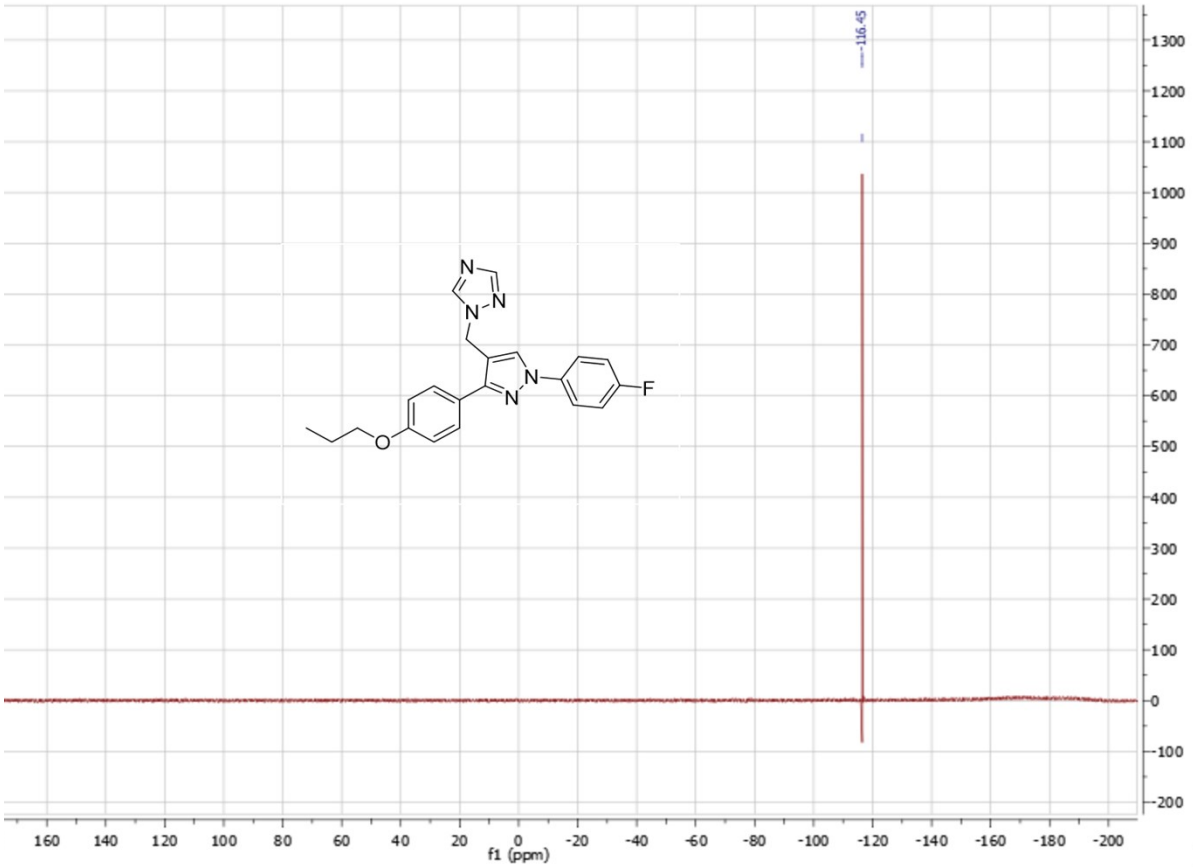

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12e**:



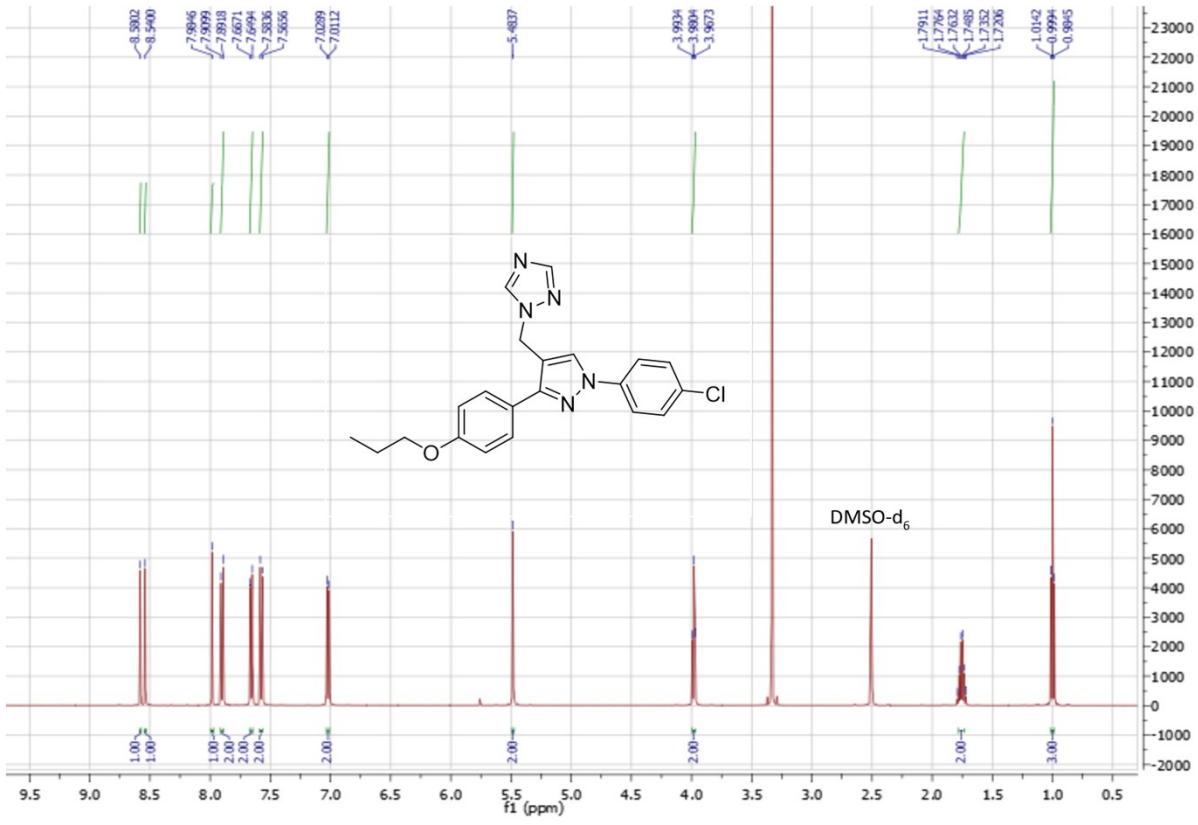

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12e:**



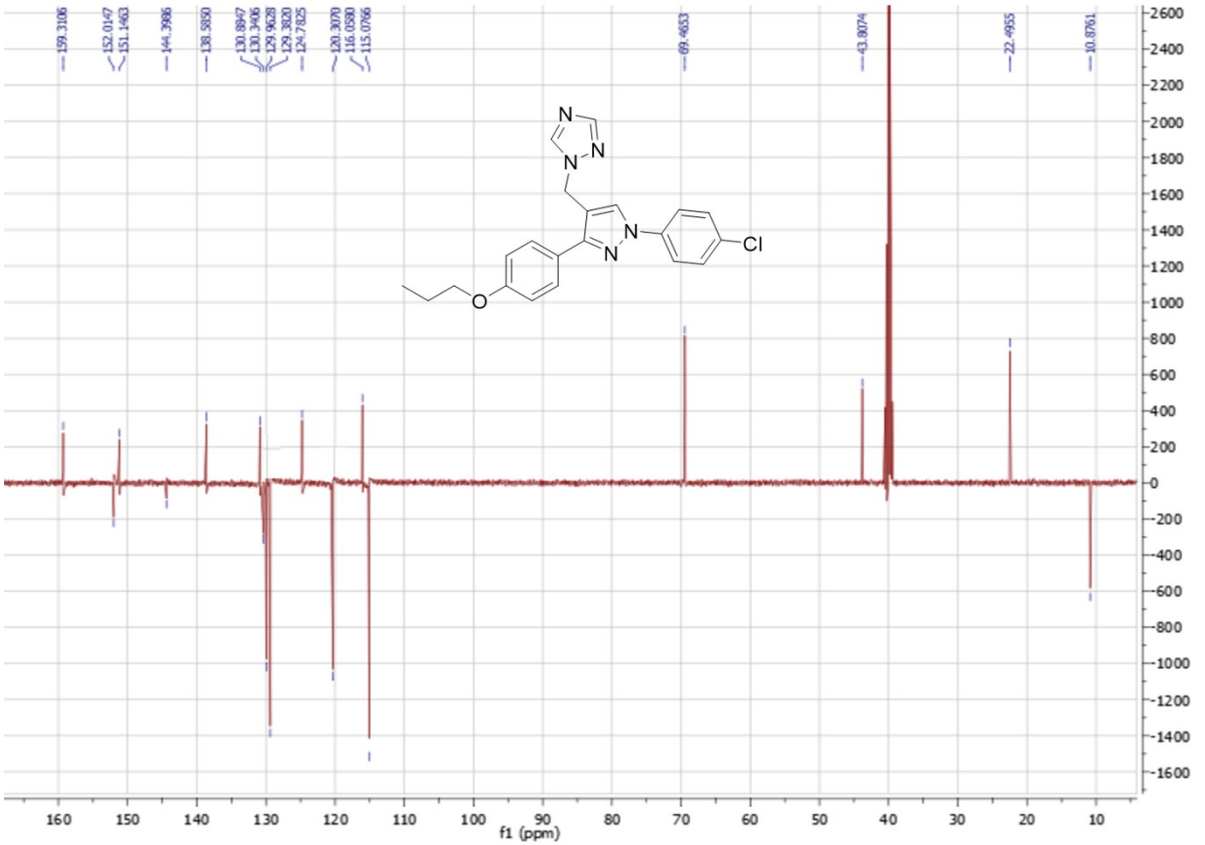

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **12e**:



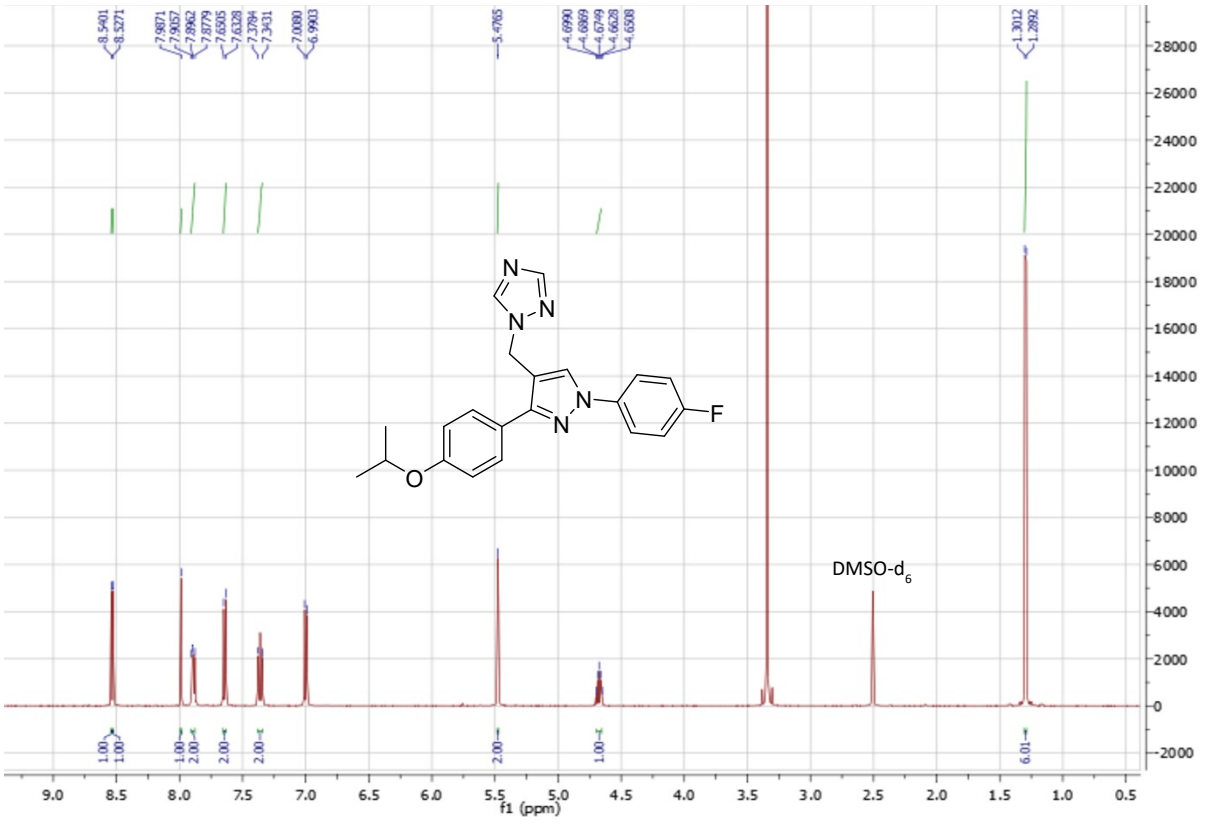

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12f**:



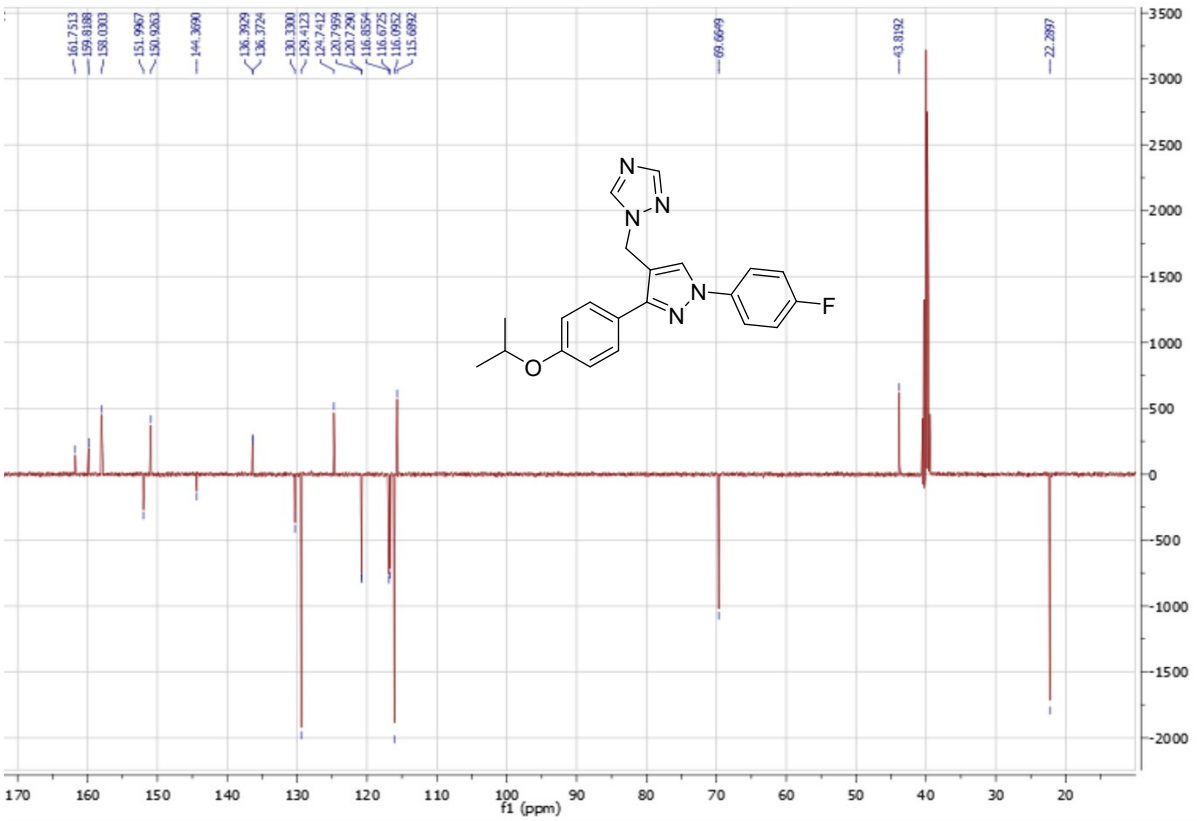

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12f:**



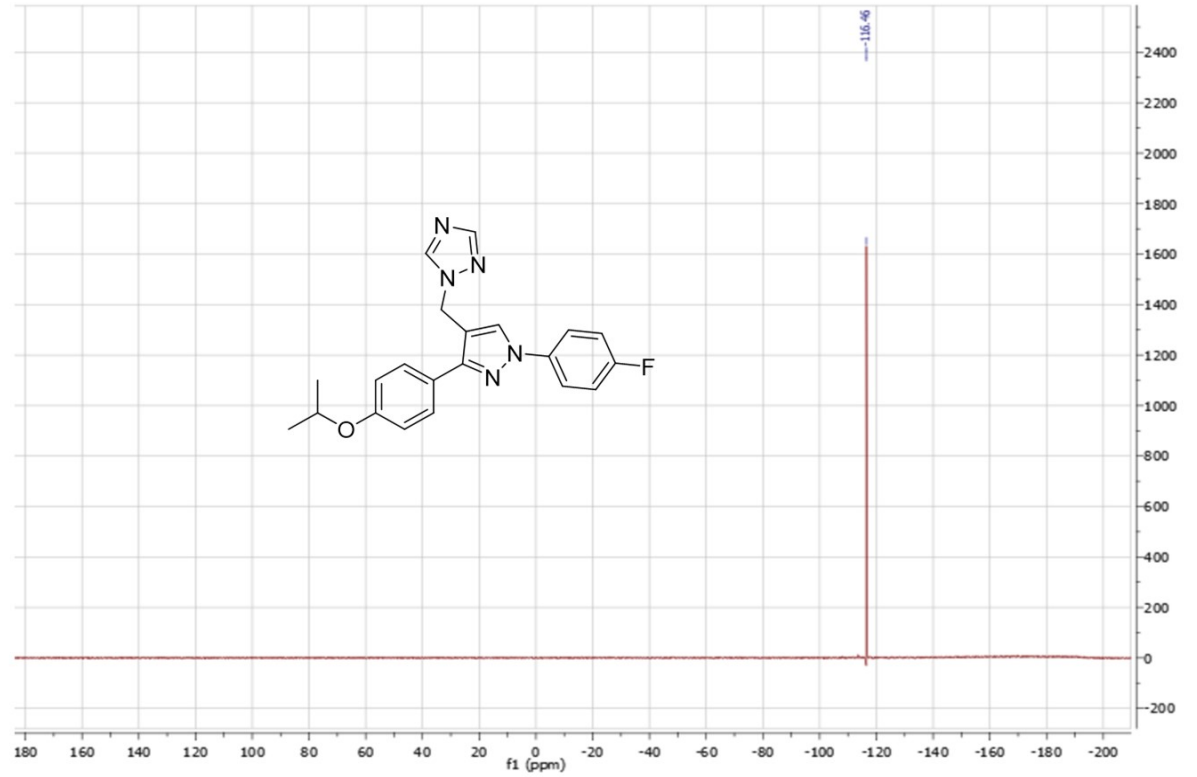

$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12g**:



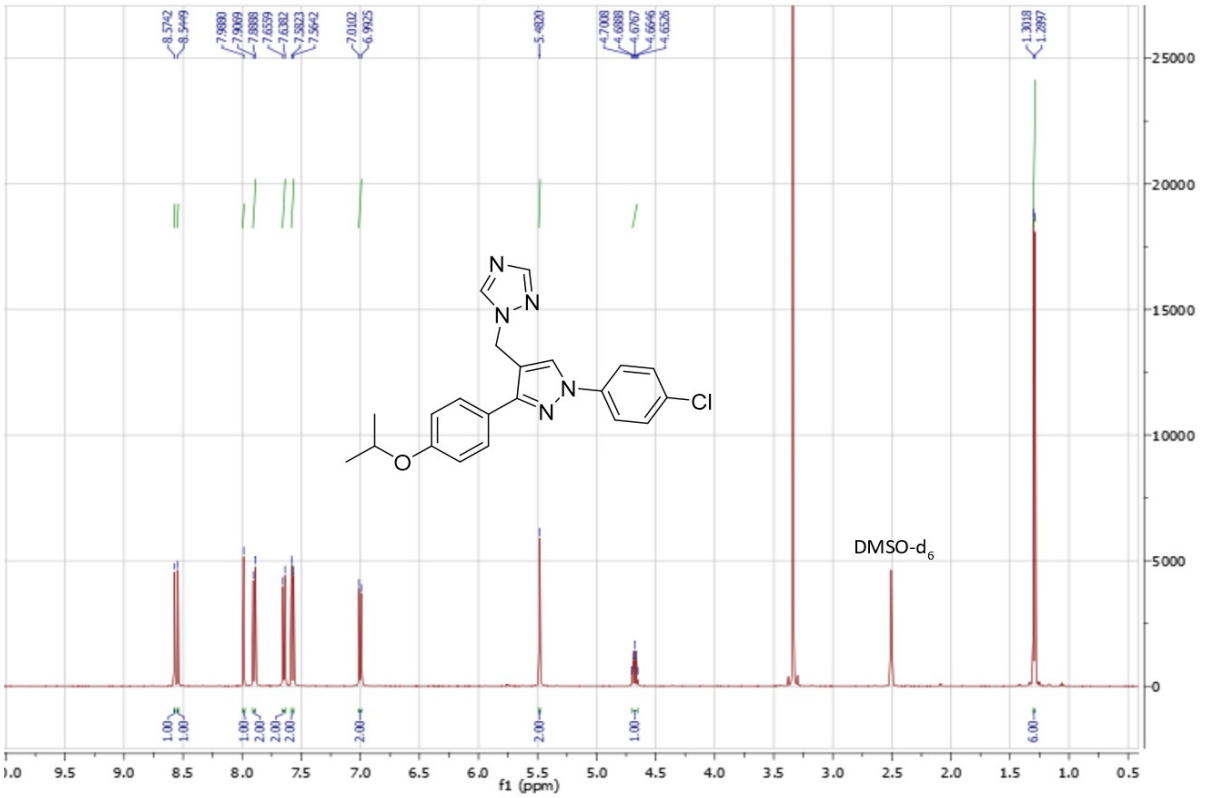

$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12g:**



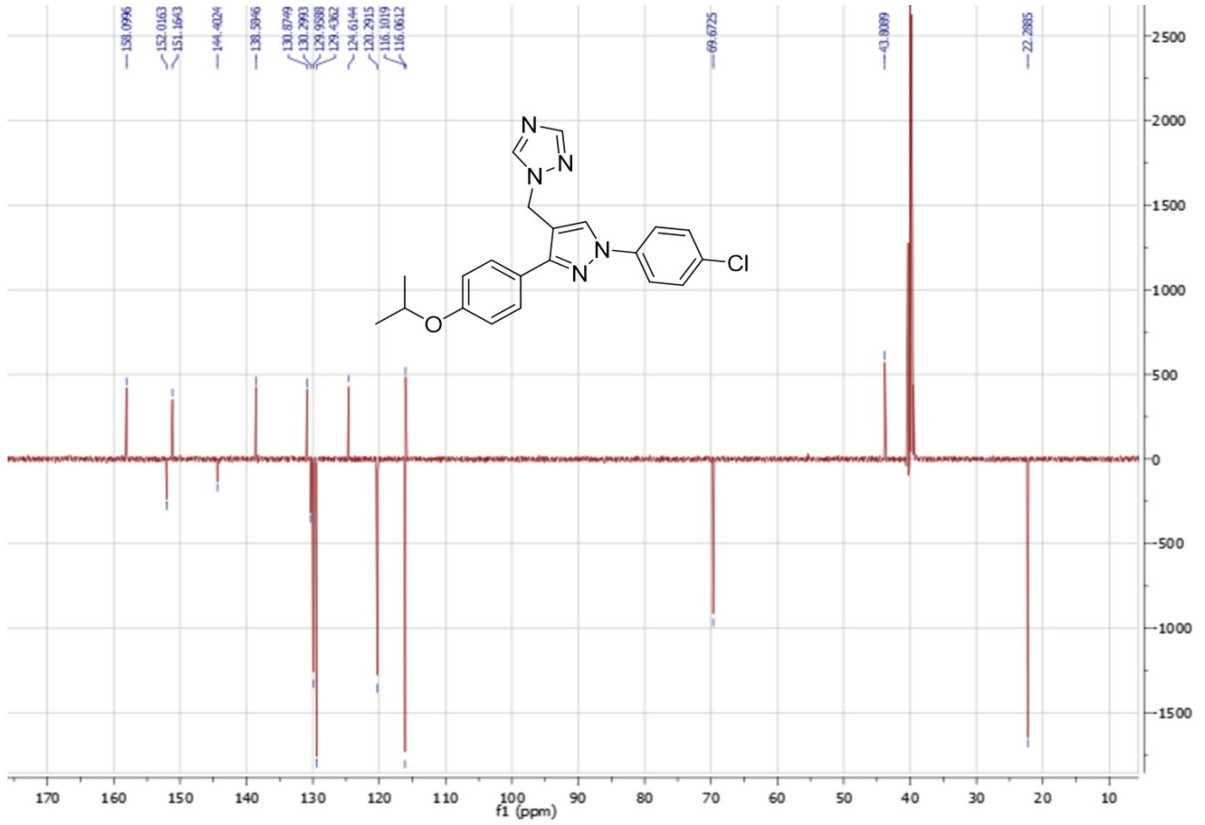

$^{19}$F NMR (470 MHz, DMSO-$d_6$) of **12g**:




$^{1}$H NMR spectrum (500 MHz, DMSO-$d_6$) of **12h**:




$^{13}$C NMR spectrum (125.75 MHz, DMSO-$d_6$) of **12h:**




| 11a | 11c | 11d | 11e |
|---|---|---|---|

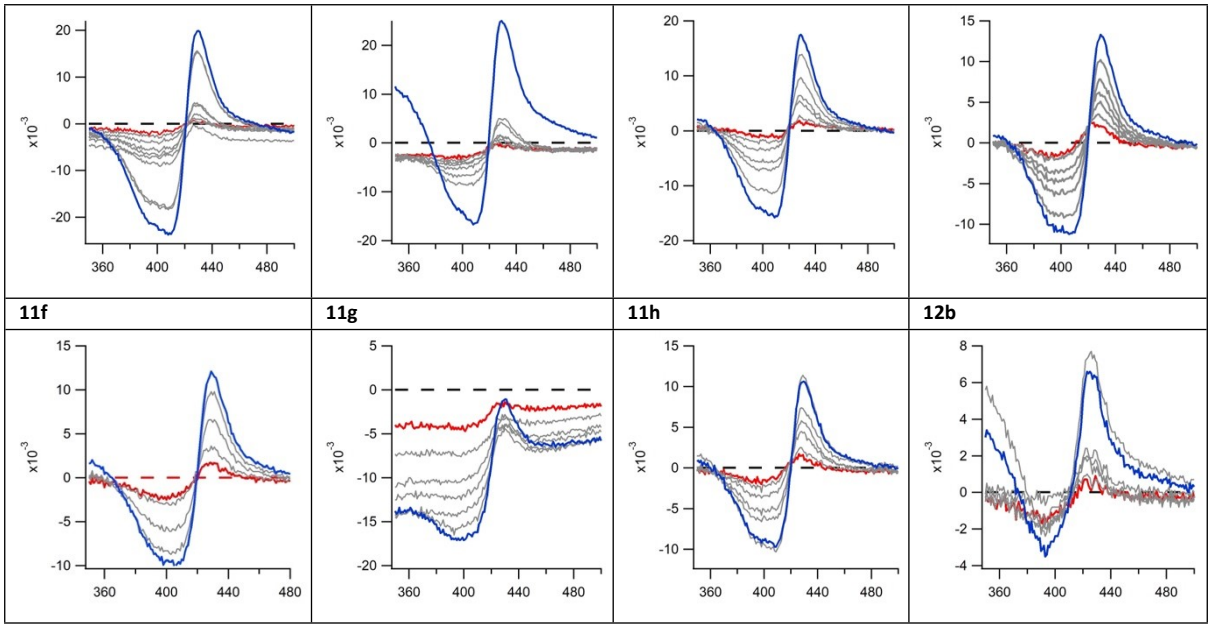



**Figure S1**. Binding difference spectra of pyrazole derivatives **11a, 11c-11h** and **12b**

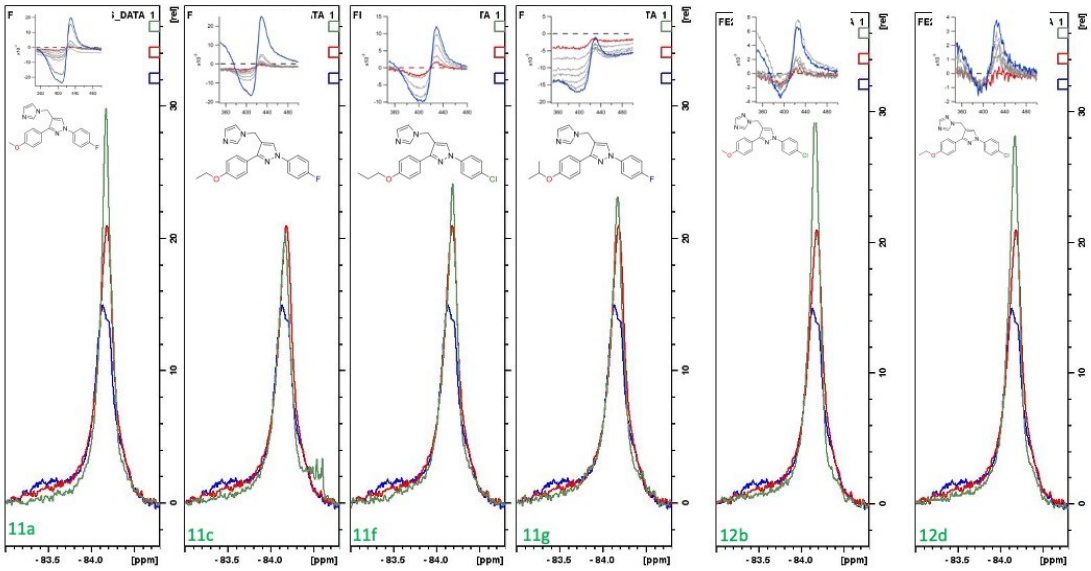



**Figure S2**. $^{19}F$ NMR spectra of BTFA-labelled CYP121_S171C (blue) alone, with cYY bound (red) and with exemplar pyrazole ligands (green)

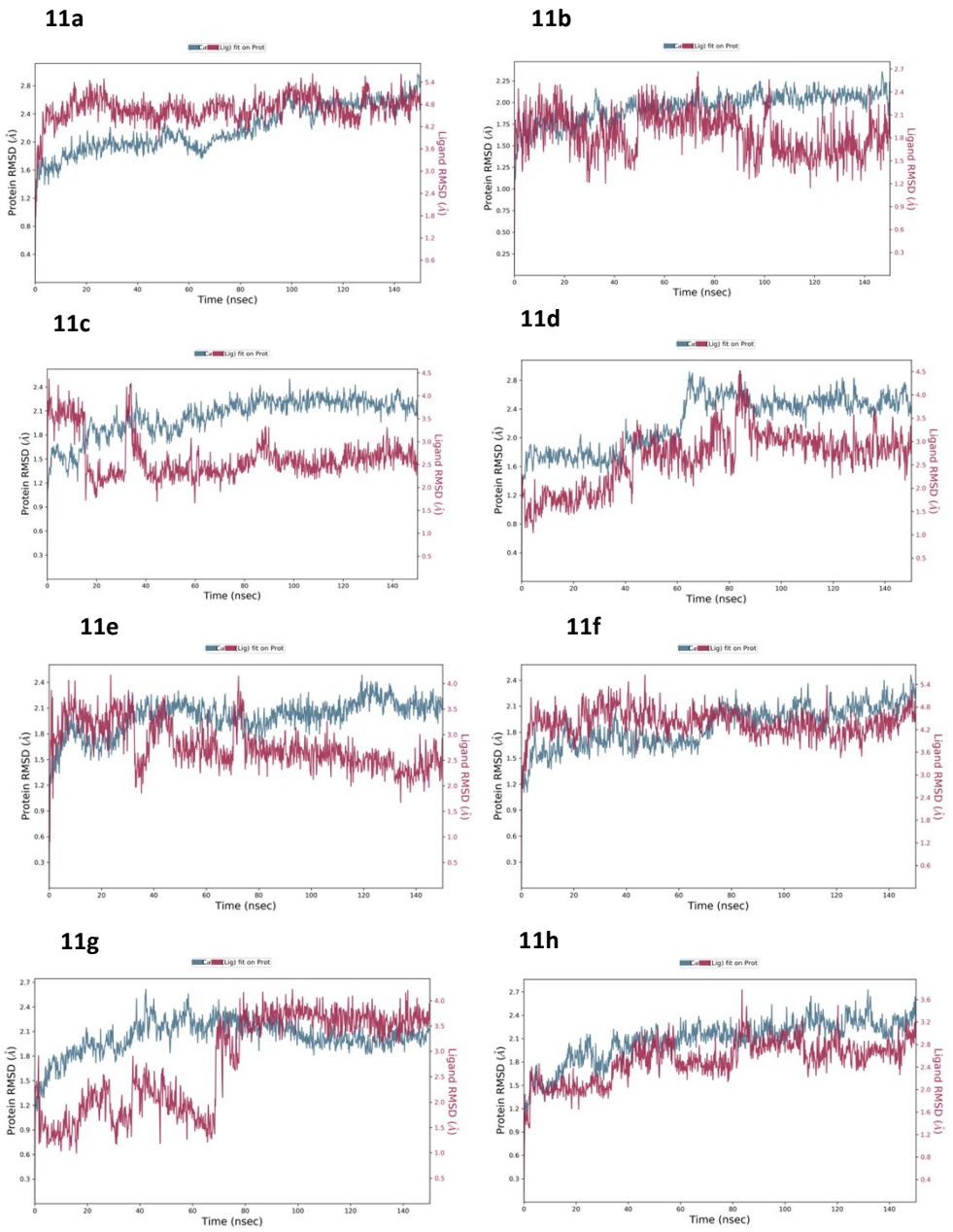



**Figure S3**. Ligand-protein complex stability through protein-ligand RMSD over 150 ns MD simulation for compounds **11**. Ligand RMSD in red and protein RMSD in blue.

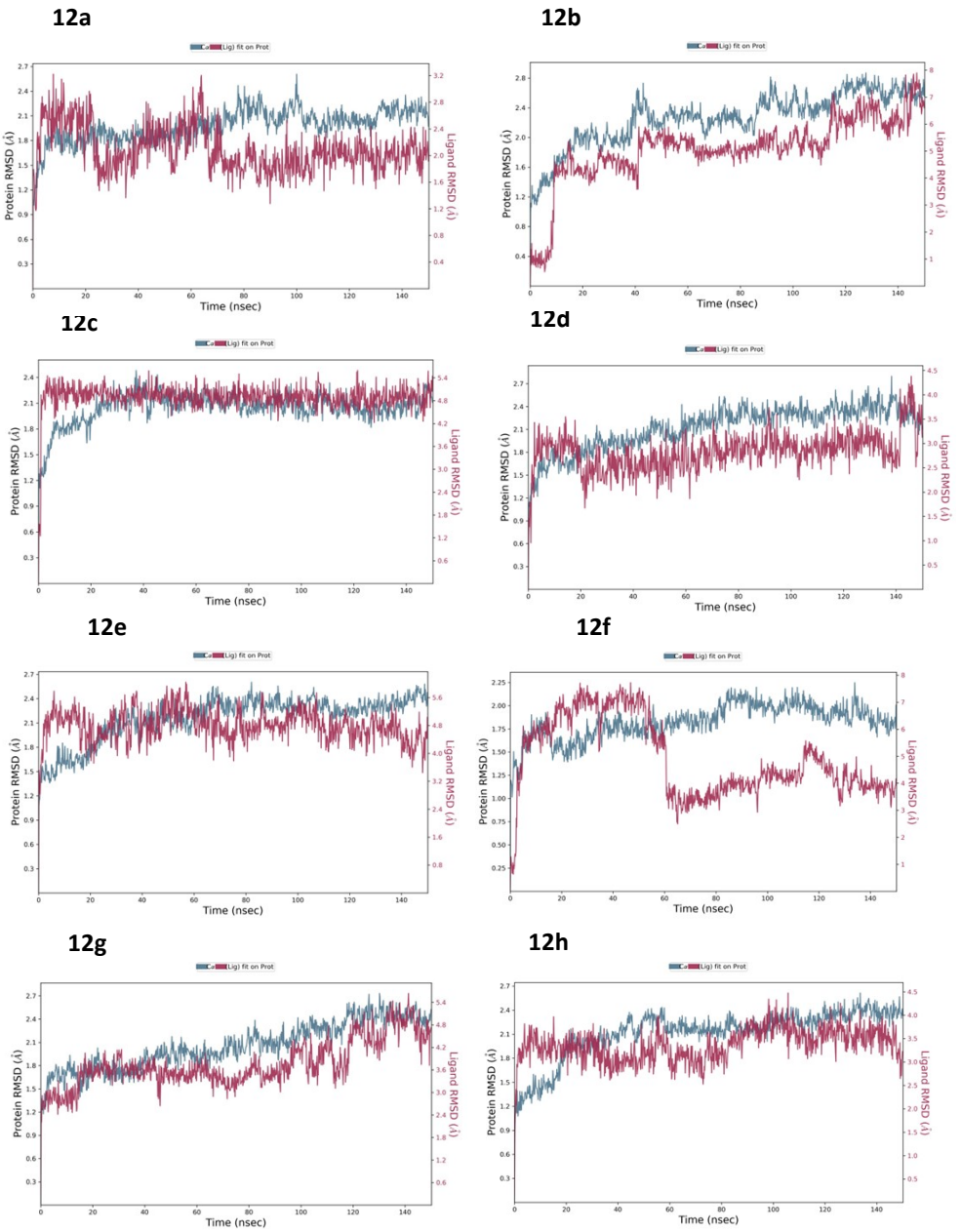



**Figure S4**. Ligand-protein complex stability through protein-ligand RMSD over 150 ns MD simulation for compounds **12**. Ligand RMSD in red and protein RMSD in blue.