Supplementary Information

1.0 Current Inhibitors

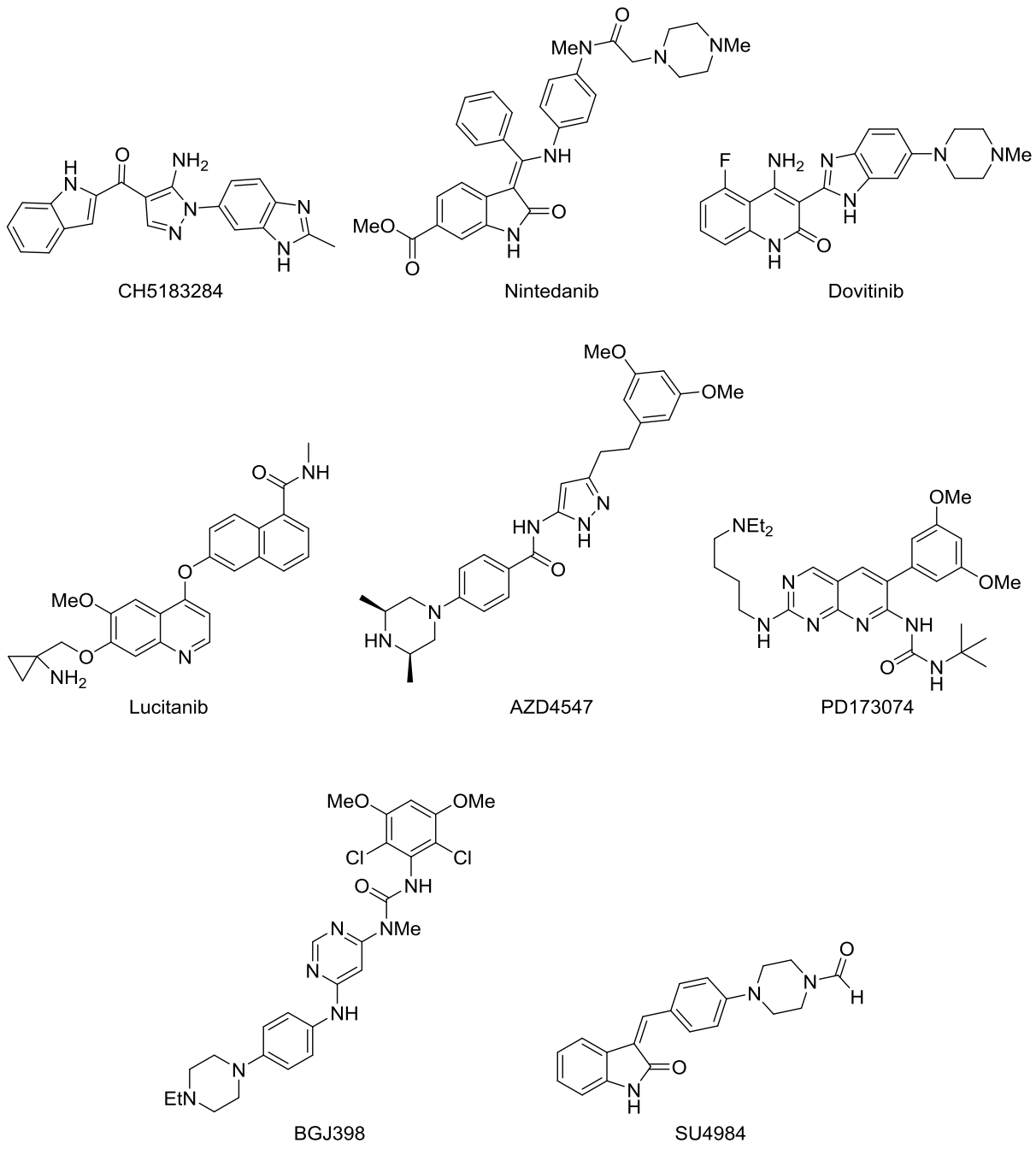
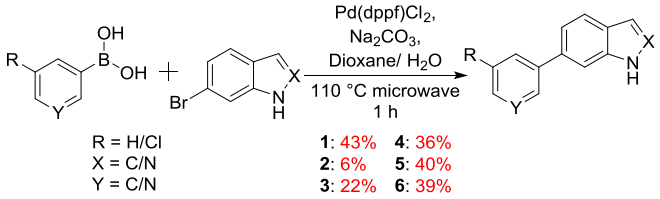


Figure 1: Examples of FGFR inhibitors in either clinical use or development.[1-13]

1.1 Synthetic Procedures

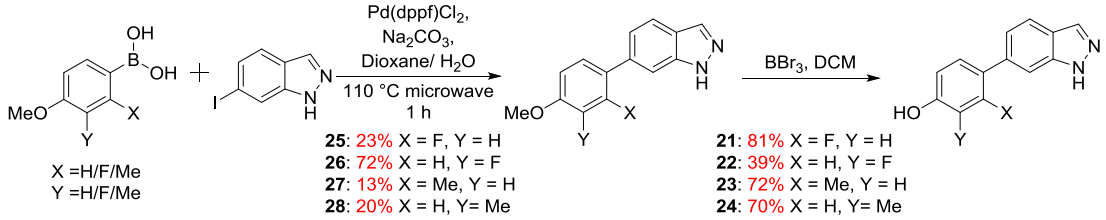


Scheme 1: Pd-catalysed microwave Suzuki couplings. Reaction yields outlined in red.

Low yield for synthesis of compound **2** was due to troublesome purification.

1.1.1 Alternative Synthesis

Due to the poor yielding Suzuki chemistry of 4-hydroxyphenylboronic acids, compounds **21-24** were synthesised according to the conditions outlined in Scheme **2**:



Scheme 2: Alternative route to phenol containing compounds.

Low yielding step for compound **22** was due to purification issues based on the high polarity of the compound.

2.0 Experimental

2.1 General Procedures and Instrumentation

All reagents were obtained from commercial sources and were used without further purification. All microwave reactions were carried out in a CEM Explorer 48 Autosampler using a power of 200 Watts and a pressure of 17 Bar unless otherwise stated.

Thin layer chromatography (TLC) analysis was performed using aluminium pre-coated silica gel plates (254 µm) supplied by Merck chemicals and visualised using either: ultraviolet light (254 nm), dipped in $KMnO_4$ solution and heated or dipped in an iodine tank and heated. R_f values are recorded to two decimal places. Normal phase flash column chromatography was carried out using Geduran® silica gel 60 4063 µm. Automated column chromatography (ACC) was carried out using either; Thomson Single Step pre-packed silica cartridges (12-40 g) at a flow rate of 12-30 mL min^{-1} for normal phase or a KP-C_{18}-HS SNAP 12g cartridge at a flow rate of 17 mL min^{-1} for reverse phase on a Biotage Isolera Spektra Four. Liquid chromatography-mass spectrometry (LC-MS) analysis was performed on a Bruker Daltronics instrument running on a gradient of increasing MeCN (5-95%) in H_2O containing 0.1% formic acid at 1 mL min^{-1} on a 50 × 20 mm C_{18} reverse phase column. High performance liquid chromatography (HPLC) was performed on an Agilent 1290 Infinity Series equipped with a UV detector using either: An Ascentis Express C_{18} reverse phase column using MeCN/H_2O (5-95%) containing 0.1% trifluoroacetic acid (TFA), at a flow rate of 0.5 mL min^{-1} over a period of five minutes; A Hyperclone C_{18} reverse phase column using MeCN/H_2O (5-95%) containing 0.1% TFA, at a flow rate of 1.0 mL min^{-1} over a period of 30 minutes. Compounds are 100% pure unless otherwise stated. High resolution-mass spectrometry (HR-MS) was carried out using a Bruker MaXis Impact Time of Flight spectrometer using electron spray ionisation (ES+/-), giving masses correct to four decimal places.

^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz respectively on a Bruker Advance 500 Fourier transform spectrometer. Chemical shifts are reported in ppm and are reported with reference to the residual solvent peak. Multiplicities are reported with coupling constants and are given to the nearest 0.1 Hz. Apparent multiplicities are denoted by app. Where needed, two-dimensional correlation spectroscopy (2D-COSY), heteronuclear single quantum coherence spectroscopy (HSQC) and heteronuclear multiple bond correlation spectroscopy (HMBC) were used Ar-q = aromatic quaternary carbon. Infrared spectra (IR) were recorded in solid phase on a Bruker Alpha Platinum ATR FTIR spectrometer with vibrational frequencies given in cm^{-1}. Melting points were measured on a Stuart SMP30. Elemental analysis was carried out using a Carlo Erba 1108 Elemental Analyzer.

2.2 General Experimental Methods

2.2.1 Method A: Suzuki Reactions

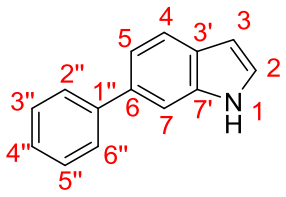
A mixture of the chosen halogenated heterocycle (1.0 eq), the chosen boronic acid (1.0-2.0 eq), $Pd(dppf)Cl_2$•DCM (0.1 eq) and Na_2CO_3 (3.0-5.0 eq) were charged with nitrogen in a microwave vial (10 mL or 35 mL). A mixture of dioxane and water ((1:1) 5-20 mL) was degassed for ten minutes and added to the reactants under nitrogen. The reaction mixture was heated to 110 °C for 1-6 h and monitored using LC-MS. The reaction mixture was allowed to cool to 20 °C and EtOAc (5 mL or 15 mL) added and the reaction vessel sonicated then filtered through a celite pad washing thoroughly with EtOAc. Where needed a 1:1 ration of DCM:MeOH was used to wash the celite pad. The filtrate was added to water (20 mL or 60 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 15 mL or 30 mL) and the combined organic layers washed with brine (10 mL or 30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to reveal the crude product. The crude product was purified using either ACC or flash column chromatography. The appropriate fractions were combined and reduced *in vacuo* to yield a solid. See individual compounds for further purification methods.

2.2.2 Method B: Methoxy Deprotections

The chosen methoxy containing compound (1.0 eq) was dissolved/suspended in DCM (5-15 mL) at 0 °C. 1 M BBr_3 in DCM (8.0 eq) was added slowly and the reaction stirred at room temperature for 2.5 h until complete. See individual compounds for work up and purification methods.

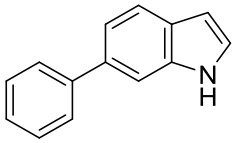
2.2.3 Compound Numbering

The compounds synthesised in this series are numbered in the following way:



2.2.4 Compounds

Preparation of 6-phenylindole

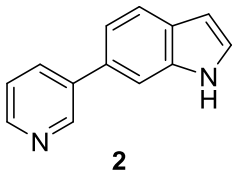


1

Synthesised using method A using 6-bromoindole (50 mg, 0.26 mmol, 1.0 eq), phenylboronic acid (34 mg, 0.28 mmol, 1.1 eq), $Pd(dppf)Cl_2$•DCM (21 mg, 0.026 mmol, 0.1 eq), Na_2CO_3 (82 mg, 0.77 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 1 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using ACC (gradient 0-40% EtOAc−hexane) and a cream solid obtained (24 mg, 0.12 mmol, 48%). The solid was recrystallised from EtOH:H_2O (1:1). The title compound **1** (20 mg, 0.10 mmol, 40%) was collected as colourless flakes.

^{1}H NMR (500 MHz, $CDCl_3$): 8.18 (1H, br.s, NH), 7.70 (1H, d, *J* 8.5, 4-H), 7.65 (2H, m, 2''-H and 6''-H), 7.60 (1H, s, 7-H), 7.44 (2H, app.t, *J* 7.5, 3''-H and 5''-H), 7.39 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.32 (1H, app.tt, *J* 7.5 and 1.0, 4''-H), 7.23 (1H, app.t, *J* 2.5, 2-H), 6.59-6.57 (1H, m, 3-H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 142.3 (6-C), 136.4 (3'-C), 135.6 (1''-C), 128.7 (3''-C and 5''-C), 127.4 (2''-C and 6''-C), 127.2 (7'-C), 126.6 (4''-C), 124.8 (2-C), 120.9 (4-C), 119.8 (5-C), 109.6 (7-C), 102.5 (3-C); **LC-MS (ES+)**: RT = 2.05-2.15 min, m/z = 194.2 ($M+H^+$); ***R*$_f$**: 0.77 (EtOAc); **HPLC**: RT = 3.17 min; **m/z (ES+)**: Found: 194.0965 ($M+H^+$), $C_{14}H_{11}N$ requires *MH* 194.0964; **IR:ν_{max}/cm^{-1} (solid)**: 3379 (N-H), 3053, 2983, 2920, 1442; **M.pt**: 158.4-160.7 °C (Lit 158-161 °C)[14].

Preparation of 6-pyridin-3-yl-indole

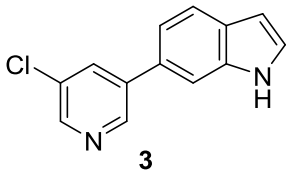


2

Synthesised using method A using 6-bromoindole (200 mg, 1.03 mmol, 1.0 eq), 3-pyridineboronic acid (139 mg, 1.13 mmol, 1.1 eq), Pd(dppf)Cl_2•DCM (84 mg, 0.103 mmol, 0.1 eq) and Na_2CO_3 (326 mg, 3.08 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a purple oil. The crude product was purified using column chromatography (gradient 30-70% EtOAc−hexane) and a green semi-solid obtained. The solid was further purified using column chromatography (1:1 EtOAc−hexane). The title compound **2** (71 mg, 0.37 mmol, 36%) was collected as a cream solid.

^{1}H NMR (500 MHz, $CDCl_3$): 8.95 (1H, d, *J* 1.5, 2''-H), 8.88 (1H, br.s, NH), 8.57 (1H, dd, *J* 5.0 and 1.5, 4''-H), 7.93 (1H, ddd, *J* 8.0, 2.5 and 1.5, 6''-H), 7.74 (1H, d, *J* 8.0, 4-H), 7.62 (1H, s, 7-H), 7.37-7.34 (2H, m, 5-H and 5''-H), 7.29 (1H, app.t, *J* 3.0, 2-H), 6.61-6.58 (1H, m, 3-H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 148.5 (2''-C), 147.7 (4''-C), 137.9 (6-C), 136.5 (3'-C), 134.6 (6''-C), 131.8 (1''-C), 127.9 (7'-C), 125.5 (2-C), 123.6 (5''-C), 121.4 (4-C), 119.4 (5-C), 109.7 (7-C), 102.6 (3-C); **LC-MS (ES+)**: RT = 1.31-1.52 min, m/z = 195.0 ($M+H^+$); ***R*$_f$**: 0.34 (EtOAc); **HPLC**: RT = 1.40 min; **m/z (ES+)**: Found: 195.0915 ($M+H^+$), $C_{13}H_{10}N_2$ requires *MH* 195.0917; **IR:ν_{max}/cm^{-1} (solid)**: 3162 (N-H), 3125, 3087, 2918, 1575; **M.pt**: 145.4-146.4 °C (Lit 146-148 °C)[15] .

Preparation of 6-(5-chloropyridin-3-yl)-indole

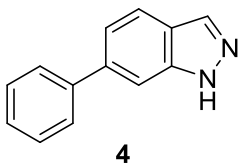


3

Synthesised using method A using 6-bromoindole (200 mg, 1.03 mmol, 1.0 eq), 5-chloro-3-pyridineboronic acid (178 mg, 1.13 mmol, 1.1 eq), Pd(dppf)Cl_2•DCM (84 mg, 0.103 mmol, 0.1 eq), Na_2CO_3 (326 mg, 3.08 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using ACC (gradient 20-50% EtOAc−hexane). The title compound **3** (51 mg, 0.22 mmol, 22%) was collected as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): 8.79 (1H, d, *J* 1.5, 2''-H), 8.57 (1H, br.s, NH), 8.52 (1H, d, *J* 2.0, 4''-H), 7.91 (1H, app.t, *J* 2.0, 6''-H), 7.74 (1H, d, *J* 8.0, 4-H), 7.58 (1H, d, *J* 1.5, 7-H), 7.32 (1H, dd, *J* 8.0 and 1.5, 5-H), 7.29 (1H, app.t, *J* 2.5, 2-H), 6.61-6.59 (1H, m, 3-H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 146.4 (4''-C), 146.2 (2''-C), 139.1 (6-C), 136.3 (3'-C), 134.2 (6''-C), 132.2 (5''-C), 130.2 (1''-C), 128.3 (7'-C), 125.8 (2-C), 121.6 (4-C), 119.3 (5-C), 109.8 (7-C), 102.8 (3-C); **LC-MS (ES+)**: RT = 1.89-2.14 min, m/z = 228.9 ($M+H^+$); ***R*$_f$**: 0.62 (EtOAc); **HPLC**: RT = 2.35 min (96%); **m/z (ES+)**: Found: 229.0529 ($M+H^+$), $C_{13}H_9ClN_2$ requires *MH* 229.0527; **IR:ν_{max}/cm^{-1} (solid)**: 3381 (N-H), 3174, 3093, 2957, 2851, 1569; **M.pt**: 137.2-138.3 °C. (Note to editor- a typo, matches now)

Preparation of 6-phenyl-1*H*-indazole

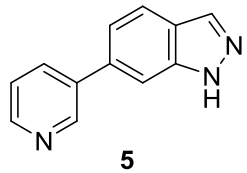


4

Synthesised using method A using 6-bromo-1*H*-indazole (50 mg, 0.26 mmol, 1.0 eq), phenylboronic acid (34 mg, 0.28 mmol, 1.1 eq), Pd(dppf)Cl_2•DCM (21 mg, 0.026 mmol, 0.1 eq) Na_2CO_3 (81 mg, 0.77 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 1 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown oil. The crude product was purified using ACC (gradient 0-50% EtOAc−hexane). The title compound **4** (26 mg, 0.13 mmol, 52%) was collected as off-white needles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.49 (1H, br.s, NH), 8.12 (1H, s, 3-H), 7.81 (1H, d, *J* 8.5, 4-H), 7.66-7.64 (3H, m, 7-H, 2''-H and 6''-H), 7.48-7.45 (2H, m, 3''-H and 5''-H), 7.43 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.40-7.36 (1H, m, 4''H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 141.3 (1''-C), 140.8 (3'-C), 140.5 (6-C), 134.9 (3-C), 128.9 (3''-C and 5''-C), 127.6 (4''-C), 127.6 (2''-C and 6''-C), 122.5 (7'-C), 121.5 (5-C), 121.1 (4-C), 107.8 (7-C); **LC-MS (ES+)**: RT = 1.82-1.99 min, m/z = 195.0 ($M+H^+$); $\boldsymbol{R_f}$: 0.32 (1:1 EtOAc−Petrol); **HPLC**: RT = 2.63 min; **m/z (ES+)**: Found: 195.0918 ($M+H^+$), $C_{13}H_{10}N_2$ requires *MH* 195.0917; **IR:ν_{max}/cm^{-1} (solid)**: 3295 (N-H), 2956, 2920, 2850, 1623; **M.pt**: 152.4-154.1 °C.

Preparation of 6-pyridin-3-yl-1*H*-indazole



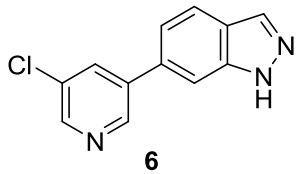
5

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3-pyridineboronic acid (138 mg, 1.12 mmol, 1.1 eq), Pd(dppf)Cl_2•DCM (82 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (gradient 20-100% EtOAc−hexane) and a yellow solid obtained. The solid was recrystallised from EtOAc. The title compound **5** (77 mg, 0.39 mmol, 39%) was collected as pale brown plates.

^{1}H NMR (500 MHz, $CDCl_3$): 11.54 (1H, br.s, NH), 8.96 (1H, d, *J* 2.0, 2''-H), 8.65 (1H, dd, *J* 4.5 and 1.5, 4''-H), 8.16 (1H, s, 3-H), 7.95 (1H, app.dt, *J* 7.5 and 2.0, 6''-H), 7.87 (1H, d, *J* 8.0, 4-H), 7.70 (1H, s, 7-H), 7.42-7.38 (2H, m, 5-H and 5''-H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 148.5 (4''-C), 148.5 (2''-C), 140.8 (3'-C), 137.1 (1''-C), 136.6 (6-C), 135.0 (6''-C), 134.8 (3-C), 123.7 (5''-C), 123.0 (7'-C), 121.7 (4-C), 120.8 (5-C), 108.3 (7-C); **LC-MS (ES+)**: RT = 1.12-1.25 min, m/z = 196.0 ($M+H^+$); $\boldsymbol{R_f}$: 0.20 (EtOAc); **HPLC**: RT = 1.01 min; **m/z (ES+)**: Found: 196.0874 ($M+H^+$), $C_{12}H_9N_3$ requires *MH* 196.0869; **IR:ν_{max}/cm^{-1} (solid)**: 3149 (N-H), 3037, 2909; **M.pt**: 163.5-164.3 °C.

Preparation of 6-(5-chloropyridin-3-yl)-1*H*-indazole

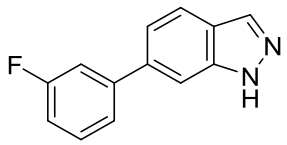
Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 5-chloro-3-pyridineboronic acid (177 mg, 1.12 mmol, 1.1 eq), Pd(dppf)Cl_2•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.08 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (1:1 EtOAc−hexane). The title compound **6** (14 mg, 0.06 mmol, 6%) was collected as off-white needles.



6

^{1}H NMR (500 MHz, $CDCl_3$): 10.47 (1H, br.s, NH), 8.79 (1H, d, *J* 2.0, 2''-H), 8.60 (1H, d, *J* 2.0, 4''-H), 8.16 (1H, s, 3-H), 7.94 (1H, app.t, *J* 2.0, 6''-H), 7.89 (1H, d, *J* 8.0, 4-H), 7.69 (1H, d, *J* 1.5, 7-H), 7.38 (1H, dd, *J* 8.0 and 1.5, 5-H); **^{13}C NMR (125 MHz, $CDCl_3$)**: 147.5 (4''-C), 146.4 (2''-C), 140.5 (3'-C), 138.1 (6-C), 135.3 (1''-C), 135.1 (3-C), 134.6 (6''-C), 132.3 (5''-C), 123.3 (7'-C), 121.9 (4-C), 120.8 (5-C), 108.3 (7-C); **LC-MS (ES+)**: RT = 1.70-1.83 min, m/z = 229.9 ($M+H^+$); $\boldsymbol{R_f}$: 0.39 (EtOAc); **HPLC**: RT = 2.02 min; **m/z (ES+)**: Found: 230.0473 ($M+H^+$), $C_{12}H_8ClN_3$ requires *MH* 230.0480; **IR:ν_{max}/cm^{-1} (solid)**: 3266 (N-H), 3053, 2958, 2851, 1628; **M.pt**: 183.8-185.0 °C.

Preparation of 6-(3-fluorophenyl)-1*H*-indazole

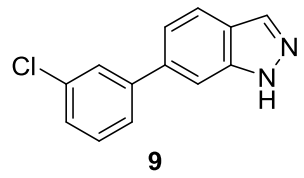


8

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3-fluorophenylboronic acid (214 mg, 1.53 mmol, 1.5 eq), $Pd(dppf)Cl_2$•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown oil. The crude product was purified using column chromatography (gradient 5-10% EtOAc−hexane). The title compound **8** (76 mg, 0.36 mmol, 35%) was collected as a colourless powder.

^{1}H NMR (500 MHz, CD_3OD): 7.95 (1H, d, *J* 1.0, 3-H), 7.72 (1H, dd, *J* 8.5 and 1.0, 4-H), 7.63-7.62 (1H, m, 7-H), 7.40-7.28 (4H, m, 5''-H, 6''-H, 2''-H and 5-H), 7.14-7.10 (1H, m, 4''-H), NH not observed; **^{13}C NMR (125 MHz, CD_3OD)**: 164.6 (d, *J* 244.3, 3''-C), 145.1 (d, *J* 7.6, 1''-C), 142.1 (3'-C), 140.0 (d, *J* 2.3, 6-C), 134.9 (3-C), 131.5 (d, *J* 8.4, 5''-C), 124.2 (d, *J* 2.8, 6''-C), 123.8 (7'-C), 122.2 (4-C), 121.7 (5-C), 115.0 (d, *J* 22.4, 4''-C), 115.0 (d, *J* 21.4, 2''-C), 109.2 (7-C); **LC-MS (ES+)**: RT = 1.86-1.98 min, m/z = 213.0 ($M+H^+$); ***R*$_f$**: 0.48 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.72 min; **m/z (ES+)**: Found: 213.0826 ($M+H^+$), $C_{13}H_9FN_2$ requires *MH* 213.0823; **IR:ν_{max}/cm^{-1} (solid)**: 3190 (N-H), 3071, 2963, 2925, 1616; **M.pt**: 114.4-116.3 °C.

Preparation of 6-(3-chlorophenyl)-1*H*-indazole

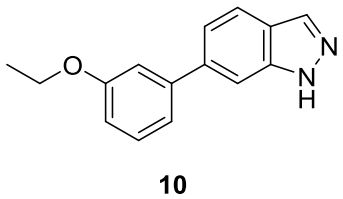


9

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3-chlorophenylboronic acid (175 mg, 1.12 mmol, 1.1 eq), $Pd(dppf)Cl_2$•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown semi-solid. The crude product was purified using column chromatography (5:95 EtOAc−hexane). The title compound **9** (42 mg, 0.18 mmol, 18%) was collected as colourless platelets.

^{1}H NMR (500 MHz, CD_3OD): 7.96 (1H, d, *J* 1.0, 3-H), 7.73 (1H, dd, *J* 8.5 and 1.0, 4-H), 7.62-7.61 (1H, m, 7-H), 7.57 (1H, app.t, *J* 2.0, 2''-H), 7.50 (1H, ddd, *J* 8.0, 2.0 and 1.0, 6''-H), 7.33 (1H, app.t, *J* 8.0, 5''-H), 7.29 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.26 (1H, ddd, *J* 8.0, 2.0 and 1.0, 4''-H), NH not observed; **^{13}C NMR (125 MHz, CD_3OD)**: 144.7 (6-C), 142.1 (3'-C), 139.8 (1''-C), 135.7 (3''-C), 134.7 (3-C), 131.3 (5''-C), 128.3 (2''-C), 126.8 (4''-C), 126.8 (6''-C), 123.9 (7'-C), 122.3 (4-C), 121.7 (5-C), 109.2 (7-C); **LC-MS (ES+)**: RT = 1.85-1.96 min, m/z = 228.9 ($M+H^+$); ***R*$_f$**: 0.51 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.98 min; **m/z (ES+)**: Found: 229.0528 ($M+H^+$), $C_{13}H_9ClN_2$ requires *MH* 229.0527; **IR:ν_{max}/cm^{-1} (solid)**: 3438 (N-H), 3138, 3056, 2920, 1625, 1594; **M.pt**: 99.8-101.9 °C.

Preparation of 6-(3-ethoxyphenyl)-1*H*-indazole



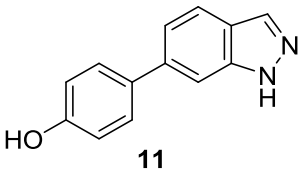
10

Synthesised using method A using 6-bromo-1*H*-indazole (112 mg, 0.57 mmol, 1.0 eq), 3-ethoxyphenylboronic acid (190 mg, 1.14 mmol, 2.0 eq), $Pd(dppf)Cl_2$•DCM (46 mg, 0.057 mmol, 0.1 eq), Na_2CO_3 (182 mg, 1.72 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. LCMS indicated the presence of starting material however the desired boronic acid reagent was unavailable so 3-carboxyphenylboronic acid (94 mg, 1.02 mmol, 1.0 eq) was added and the reaction put on for 30 minutes to consume the starting material. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (2:3 EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene. The title compound **10** (52 mg, 0.22 mmol, 39%) was collected as colourless needles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.54 (1H, br.s, NH), 8.16 (1H, d, *J* 1.0, 3-H), 7.84 (1H, dd, *J* 8.5 and 1.0, 4-H), 7.70-7.69 (1H, m, 7-H), 7.47 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.42 (1H, app.t, *J* 8.0, 5''-H), 7.26 (1H, ddd, *J* 8.0, 1.5 and 1.0, 6''-H), 7.22 (1H, app.t, *J* 2.5, 2''-H), 6.96 (1H, ddd, *J* 8.0, 1.5 and 1.0, 4''-H), 4.15 (2H, q, *J* 7.0, CH_2), 1.50 (3H, t, *J* 7.0, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 159.4 (3''-C), 142.8 (1''-C), 140.7 (3'-C), 140.4 (6-C), 134.9, (3-C), 129.8 (5''-C), 122.6 (7'-C), 121.4 (5-C), 121.0 (4-C), 120.0 (6''-C), 114.1 (2''-C), 113.5 (4''-C), 107.8 (7-C), 63.6 (CH_2), 14.91 (CH_3); **LC-MS (ES+)**: RT = 1.90-2.11 min, m/z = 239.2 ($M+H^+$); ***R*$_f$**: 0.47 (7:3 EtOAc−Petrol); **HPLC**:

RT = 2.34 min; **m/z (ES+)**: Found: 239.1191 ($M+H^+$), $C_{15}H_{14}N_2O$ requires *MH* 239.1179; **IR:ν_{max}/cm^{-1} (solid)**: 3162 (N-H), 3089, 2977, 2919, 1626, 1570; **M.pt**: 104.3-105.5 °C; **Found**: C,75.2; H, 5.90; N, 11.6; $C_{15}H_{14}N_2O$ requires C, 75.6; H, 5.92; N, 11.8%.

Preparation of 4-(1*H*-indazol-6-yl)phenol

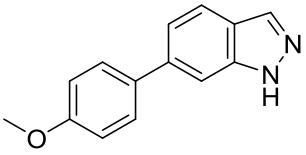


11

Synthesised using method A using 6-iodo-1*H*-indazole (300 mg, 1.23 mmol, 1.0 eq), 4-hydroxyphenylboronic acid (339 mg, 2.46 mmol, 2.0 eq), Pd(dppf)Cl_2•DCM (100 mg, 0.123 mmol, 0.1 eq), Na_2CO_3 (391 mg, 3.69 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (3:7 EtOAc−hexane). The title compound **11** (13 mg, 0.062 mmol, 5%) was collected as a yellow powder.

^{1}H NMR (500 MHz, d6-DMSO): 13.00 (1H, s, NH), 9.53 (1H, s, OH), 8.03 (1H, s, 3-H), 7.76 (1H, d, *J* 8.5, 4-H), 7.60 (1H, s, 7-H), 7.53 (2H, d, *J* 8.5, 2''-H and 6''-H), 7.33 (1H, dd, *J* 8.5 and 1.5, 5-H), 6.86 (2H, d, *J* 8.5, 3''-H and 5''-H); **^{13}C NMR (125 MHz, d6-DMSO)**: 157.1 (4''-C), 140.7 (3'-C), 138.4 (6-C), 133.3 (3-C), 131.4 (1''-C), 128.2 (2''-C and 6''-C), 121.6 (7'-C), 120.7 (4-C), 119.8 (5-C), 115.7 (3''-C and 5''-C), 106.5 (7-C); **LC-MS (ES+)**: RT = 1.59-1.81 min, m/z = 211.0 ($M+H^+$); ***R*$_f$**: 0.34 (7:3 EtOAc−Petrol); **HPLC**: RT = 1.88 min; **m/z (ES+)**: Found: 211.0866 ($M+H^+$), $C_{13}H_{10}N_2O$ requires *MH* 211.0866; **IR:ν_{max}/cm^{-1} (solid)**: 3264 (N-H), 2954, 2921, 2654, 1729, 1606; **M.pt**: >250 °C.

Preparation of 6-(4-methoxyphenyl)-1*H*-indazole

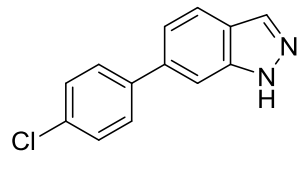


12

Synthesised using method A using 6-iodo-1*H*-indazole (300 mg, 1.23 mmol, 1.0 eq), 4-methoxyphenylboronic acid (280 mg, 1.84 mmol, 1.5 eq), Pd(dppf)Cl_2•DCM (100 mg, 0.123 mmol, 0.1 eq), Na_2CO_3 (391 mg, 3.69 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 3 h. It was observed that the product and boronic acid had similar R_f values and therefore 6-iodo-1*H*-indazole (300 mg, 1.23 mmol, 1.0 eq) was added and the reaction heated for 1 h to consume all the boronic acid. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (3:7 EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene. The title compound **12** (179 mg, 0.80 mmol, 43%) was collected as colourless fluffy microneedles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.32 (1H, br.s, NH), 8.11 (1H, d, *J* 1.0, 3-H), 7.80 (1H, dd, *J* 8.0 and 1.0, 4-H), 7.62-7.57 (3H, m, 7-H, 2''-H and 6''-H), 7.41 (1H, dd, *J* 8.0 and 1.5, 5-H), 7.02 (2H, m, 3''-H and 5''-H), 3.88 (3H, s, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 159.4 (4''-C), 140.9 (3'-C), 140.1 (6-C), 134.9 (3-C), 133.8 (1''-C), 128.6 (2''-C and 6''-C), 122.2 (7'-C), 121.2 (5-C), 121.0 (4-C), 114.3 (3''-C and 5''-C), 107.1 (7-C), 55.4 (CH_3); **LC-MS (ES)**: RT = 1.81-2.12 min, m/z = 225.4 ($M+H^+$); ***R*$_f$**: 0.61 (EtOAc); **HPLC**: RT = 2.74 min; **m/z (ES+)**: Found: 225.1022 ($M+H^+$), $C_{14}H_{12}N_2O$ requires *MH* 225.1022; **IR:ν_{max}/cm^{-1} (solid)**: 3264 (N-H), 2991, 2962, 2835, 1624, 1522; **M.pt**: 183.2-183.5 °C; **Found**: C,75.1; H, 5.40; N, 12.6; $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.39; N, 12.5%.

Preparation of 6-(4-chlorophenyl)-1*H*-indazole



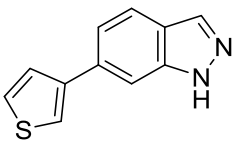
13

Synthesised using method A using 6-iodo-1*H*-indazole (162 mg, 0.67 mmol, 1.0 eq), 4-chlorophenylboronic acid (208 mg, 1.33 mmol, 2.0 eq), Pd(dppf)Cl_2•DCM (54 mg, 0.067 mmol, 0.1 eq), Na_2CO_3 (211 mg, 2.00 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown oil. The crude product was purified using column chromatography (3:7 EtOAc−hexane) and a colourless solid obtained. The solid was recrystallised from toluene. The title compound **13** (77 mg, 0.34 mmol, 51%) was collected as shiny colourless plates.

^{1}H NMR (500 MHz, $CDCl_3$): 10.42 (1H, br.s, NH), 8.13 (1H, d, *J* 0.5, 3-H), 7.83 (1H, dd, *J* 8.5 and 0.5, 4-H), 7.65-7.63 (1H, m, 7-H), 7.58 (2H, app.d, *J* 8.5, 3''-H and 5''-H), 7.45 (2H, app.d, *J* 8.5, 2'-H and 6''-H), 7.39 (1H, dd, *J* 8.5 and 1.5, 5-H); **^{13}C NMR (125 MHz, $CDCl_3$)**:

140.8 (3'-C), 139.8 (6-C), 139.2 (1'-C), 135.0 (3-C), 133.8 (4'-C), 129.0 (3''-C and 5''-C), 128.8 (2''-C and 6''-C), 122.8 (7'-C), 121.2 (4-C), 121.1 (5-C), 107.6 (7-C); **LC-MS (ES+)**: RT = 1.84-2.01 min, m/z = 229.3 ($M+H^+$); R_f: 0.69 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.32 min; **m/z (ES+)**: Found: 229.0524 ($M+H^+$), $C_{13}H_9ClN_2$ requires *MH* 229.0527; **IR:ν_{max}/cm^{-1} (solid)**: 3169 (N-H), 3049, 2953, 2859, 1622, 1487; **M.pt**: 179.6-180.7 °C.

Preparation of 6-(thiophen-3-yl)-1*H*-indazole

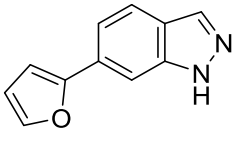


14

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3-thienylboronic acid (224 mg, 1.75 mmol, 1.7 eq), Pd(dppf)Cl_2•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (1:1 EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene *via* hot filtration. The title compound **14** (100 mg, 0.50 mmol, 49%) was collected as off-white fluffy crystals.

^{1}H NMR (500 MHz, d6-DMSO): 13.07 (1H, s, NH), 8.04 (1H, s, 3-H), 7.92 (1H, dd, *J* 3.0 and 1.5, 2''-H), 7.78-7.76 (2H, m, 7H and 4-H), 7.65 (1H, dd, *J* 5.0 and 3.0, 4''-H), 7.62 (1H, dd, *J* 5.0 and 1.5, 5''-H), 7.48 (1H, dd, *J* 8.5 and 1.5, 5-H); **^{13}C NMR (125 MHz, d6-DMSO)**: 141.8 (1''-C), 140.5 (3'-C), 133.4 (3-C), 133.1 (6-C), 127.1 (4''-C), 126.5 (5''-C), 122.0 (7'-C), 121.3 (2''-C), 120.9 (4-C), 119.7 (5-C), 106.7 (7-C); **LC-MS (ES+)**: RT = 1.78-2.00 min, m/z = 200.9 ($M+H^+$); R_f: 0.44 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.46 min; **m/z (ES+)**: Found: 201.0482 ($M+H^+$), $C_{11}H_8N_2S$ requires *MH* 201.0481; **IR:ν_{max}/cm^{-1} (solid)**: 3270 (N-H), 3187, 3052, 2930, 1621; **M.pt**: 207.9-209.5 °C; **Found**: C,65.7; H, 3.90; N, 13.7; $C_{11}H_8N_2S$ requires C, 66.0; H, 4.03; N, 14.0%.

Preparation of 6-(furan-2-yl)-1*H*-indazole

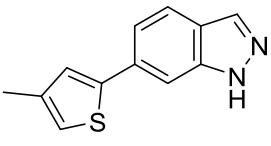


15

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3-furylboronic acid (229 mg, 2.04 mmol, 2.0 eq), Pd(dppf)Cl_2•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (2:3 EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene *via* hot filtration. The title compound **15** (107 mg, 0.58 mmol, 57%) was collected as a pale yellow powder.

^{1}H NMR (500 MHz, d6-DMSO): 13.09 (1H, s, NH), 8.05 (1H, s, 3-H), 7.79-7.76 (3H, m, 3''-H, 4-H and 7-H), 7.48 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.01 (1H, d, *J* 3.5, 5''-H), 6.61 (1H, dd, *J* 3.5 and 1.5, 4''-H); **^{13}C NMR (125 MHz, d6-DMSO)**: 153.3 (1''-C), 143.0 (3''-C), 140.2 (3'-C), 133.6 (3-C), 128.1 (6-C), 122.1 (7'-C), 121.1 (4-C), 117.0 (5-C), 112.1 (4''-C), 106.3 (5''-C), 104.0 (7-C); **LC-MS (ES+)**: RT = 1.74-1.98 min, m/z = 185.0 ($M+H^+$); R_f: 0.47 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.31 min; **m/z (ES+)**: Found: 185.0708 ($M+H^+$), $C_{11}H_8N_2O$ requires *MH* 185.0709; **IR:ν_{max}/cm^{-1} (solid)**: 3173 (N-H), 3142, 3098, 2997, 2920, 1681, 1592, 1437; **M.pt**: 143.4-145.1 °C.

Preparation of 6-(4-methylthiophen-2-yl)-1*H*-indazole



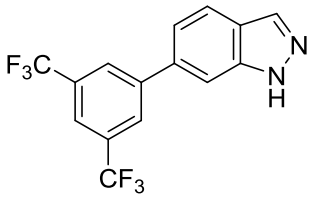
16

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 4-methylthiophene-2-boronic acid (288 mg, 2.04 mmol, 2.0 eq), Pd(dppf)Cl_2•DCM (83 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown oil. The crude product was purified using column chromatography (1:1 EtOAc−hexane) and a yellow solid obtained. The solid was recrystallised from toluene. The title compound **16** (136 mg, 0.63 mmol, 63%) was collected as off-white granules.

^{1}H NMR (500 MHz, $CDCl_3$): 8.02 (1H, d, *J* 1.0, 3-H), 7.69 (1H, dd, *J* 8.5 and 1.0, 4-H), 7.64-7.63 (1H, m, 7-H), 7.39 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.15 (1H, d, *J* 1.5, 5''-H), 6.85 (1H, app.p, *J* 1.5, 3''-H), 2.26 (3H, app.d, *J* 1.0, CH_3), NH not observed; **^{13}C NMR (125 MHz, $CDCl_3$)**: 144.1 (1''-C), 140.7 (3'-C), 138.8 (4''-C), 134.9 (3-C), 133.5 (6-C), 126.2 (5''-C), 122.6 (7'-C), 121.2 (4-C), 120.6 (3''-C),

120.1 (5-C), 106.1 (7-C), 15.9 (CH$_3$); **LC-MS (ES)**: RT = 1.88-2.08 min, m/z = 215.1 (M+H$^+$); ***R*$_f$**: 0.51 (7:3 EtOAc−Petrol); **HPLC**: RT = 2.27 min (95%); **m/z (ES+)**: Found: 215.0633 (M+H$^+$), $C_{12}H_{10}N_2S$ requires *MH* 215.0637; **IR:ν_{max}/cm^{-1} (solid)**: 3289 (N-H), 3162, 2919, 1626, 1570; **M.pt**: 151.8-153.1 °C; **Found**: C,67.1; H, 4.70; N, 12.9; $C_{12}H_{10}N_2S$ requires C, 67.3; H, 4.70; N, 13.1%.

Preparation of 6-(3,5-bis(trifluoromethyl)phenyl)-1*H*-indazole

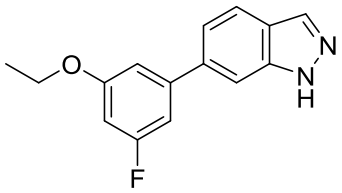


17

Synthesised using method A using 6-bromo-1*H*-indazole (200 mg, 1.02 mmol, 1.0 eq), 3,5-bis(trifluoromethyl)phenylboronic acid (527 mg, 2.04 mmol, 2.0 eq), Pd(dppf)Cl$_2$•DCM (83 mg, 0.102 mmol, 0.1 eq), Na$_2$CO$_3$ (325 mg, 3.06 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown oil. The crude product was purified using column chromatography (2:3 EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene. The title compound **17** (144 mg, 0.436 mmol, 43%) was collected as shiny colourless plates.

^{1}H NMR (500 MHz, CDCl$_3$): 10.54 (1H, br.s, NH), 8.18 (1H, s, 3-H), 8.09 (2H, s, 2''-H and 6''-H), 7.91 (1H, dd, *J* 8.5 and 1.0, 4-H), 7.90 (1H, s, 4''-H), 7.74 (1H, s, 7-H), 7.43 (1H, dd , *J* 8.5 and 1.5, 5-H); **^{13}C NMR (125 MHz, CDCl$_3$)**: 143.5 (1''-C), 140.5 (3'-C), 137.3 (6-C), 135.1 (3-C), 132.2 (q, *J* 33.3, 3''-C and 5''-C), 127.7 (q, *J* 7.0, 2''-C and 6''-C), 123.4 (7'-C), 123.3 (d, *J* 270.9, CF$_3$), 122.0 (4-C), 121.2 (sept, *J* 3.8, 4''-C), 120.9 (5-C), 108.4 (7-C); **LC-MS (ES+)**: RT = 2.08-2.31 min, m/z = 331.0 (M+H$^+$); ***R*$_f$**: 0.50 (1:1 EtOAc−Petrol); **HPLC**: RT = 3.48 min; **m/z (ES-)**: Found: 329.0529 (M-H), $C_{15}H_8F_6N_2$ requires *M-H* 329.0519; **IR:ν_{max}/cm^{-1} (solid)**: 3171 (N-H), 3135, 3023, 2930, 2871, 1623; **M.pt**: 169.3-170.1 °C.

Preparation of 6-(3-ethoxy-5-fluorophenyl)-1*H*-indazole

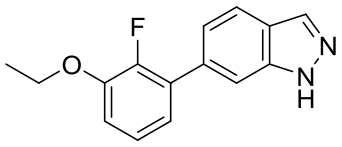


18

Synthesised using method A using 6-iodo-1*H*-indazole (200 mg, 0.82 mmol, 1.0 eq), 3-ethoxy-5-fluorophenylboronic acid (226 mg, 1.23 mmol, 1.5 eq), Pd(dppf)Cl$_2$•DCM (67 mg, 0.082 mmol, 0.1 eq), Na$_2$CO$_3$ (261 mg, 2.46 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1.5 h. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (1:4 EtOAc−hexane) and a glassy solid obtained. The solid was dissolved in Et$_2$O and petrol added until precipitation was observed and then reduced *in vacuo*. The title compound **18** (89 mg, 0.35 mmol, 42%) was collected as a cream solid.

^{1}H NMR (500 MHz, d6-DMSO): 13.15 (1H, br.s, NH), 8.09 (1H, s, 3-H), 7.82 (1H, d, *J* 8.0, 4-H), 7.76 (1H, s, 7-H), 7.41 (1H, dd, *J* 8.5 and 1.5, 5-H), 7.11 (1H, app.dt, *J* 10.0 and 1.5, 2''-H), 7.08 (1H, app.t, *J* 1.5, 6''-H), 6.81 (1H, app.dt, *J* 11.0 and 2.0, 4''-H), 4.13 (2H, q, *J* 7.0, CH$_2$), 1.35 (3H, t, *J* 7.0, CH$_3$); **^{13}C NMR (125 MHz, d6-DMSO)**: 163.3 (d, *J* 242.3, 3''-C), 160.2 (d, *J* 12.0, 5''-C), 143.6 (d, *J* 10.1, 1''-C), 140.3 (3'-C), 137.0 (d, *J* 2.7, 6-C), 133.4 (3-C), 122.6 (7'-C), 120.9 (4-C), 120.0 (5-C), 109.5 (d, *J* 2.4, 6''-C), 108.1 (7-C), 106.0 (d, *J* 22.7, 2''-C), 100.9 (d, *J* 25.2, 4''-C), 63.7 (CH$_2$), 14.5 (CH$_3$); **LC-MS (ES)**: RT = 1.97-2.16 min, m/z = 257.4 (M+H$^+$); ***R*$_f$**: 0.33 (1:1 EtOAc−Petrol); **HPLC**: RT = 15.82 min; **m/z (ES+)**: Found: 257.1092 (M+H$^+$), $C_{15}H_{13}FN_2O$ requires *MH* 257.1085; **IR:ν_{max}/cm^{-1} (solid)**: 3161 (N-H), 3124, 2978, 2919, 1602, 1450; **M.pt**: 90.4-91.1 °C; **Found**: C,69.9; H, 5.30; N, 10.6; $C_{15}H_{13}FN_2O$ requires C, 70.3; H, 5.11; N, 10.9%.

Preparation of 6-(3-ethoxy-2-fluorophenyl)-1*H*-indazole



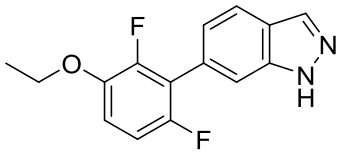
19

Synthesised using method A using 6-iodo-1*H*-indazole (200 mg, 0.82 mmol, 1.0 eq), 3-ethoxy-2-fluorophenylboronic acid (226 mg, 1.23 mmol, 1.5 eq), Pd(dppf)Cl$_2$•DCM (67 mg, 0.082 mmol, 0.1 eq) and Na$_2$CO$_3$ (260 mg, 2.46 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. LCMS indicated the reaction to be incomplete and therefore 6-iodo-1*H*-indazole (120 mg, 0.49 mmol, 0.6 eq) and Pd(dppf)Cl$_2$•DCM (34 mg, 0.04 mmol, 0.05 eq) were added and the reaction heated for a further 30 minutes. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to

reveal a brown oil. The crude product was purified using column chromatography (3:7 EtOAc−hexane) and an off-white solid obtained. The resulting solid was recrystallised from EtOH. The title compound **19** (57 mg, 0.22 mmol, 18%) was collected as off-white crystals.

^{1}H NMR (500 MHz, $CDCl_3$): 10.42 (1H, br.s, NH), 8.13 (1H, d, *J* 0.5, 3-H), 7.82 (1H, dd, *J* 8.5 and 0.5, 4-H), 7.69 (1H, s, 7-H), 7.37 (1H, app.dt, *J* 8.5 and 1.5, 5-H), 7.13 (1H, app.td, *J* 8.0 and 1.5, 5''-H), 7.07-7.04 (1H, m, 6''-H), 6.99 (1H, app.td, *J* 8.0 and 1.5, 4''-H), 4.18 (2H, q, *J* 7.0, CH_2), 1.50 (3H, t, *J* 7.0, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 150.0 (d, *J* 247.4, 2''-C), 147.6 (d, *J* 11.3, 3''-C), 140.3 (3'-C), 134.9 (3-C), 134.6 (6-C), 130.0 (d, *J* 11.3, 1'' C), 123.9 (d, *J* 4.9, 5''-C), 122.8 (d, *J* 2.4, 5-C), 122.7 (7'-C), 122.4 (d, *J* 2.3, 6''-C), 120.7 (4-C), 113.9 (d, *J* 2.0, 4''-C), 110.1 (d, *J* 3.6, 7-C), 65.2 (CH_2), 14.9 (CH_3); **LC-MS (ES+)**: RT = 1.90-2.05 min, m/z = 257.8 ($M+H^+$); ***R*$_f$**: 0.43 (1:1 EtOAc–Petrol); **HPLC**: RT = 3.44 min; **m/z (ES+)**: Found: 257.1093 ($M+H^+$), $C_{15}H_{13}FN_2O$ requires *MH* 257.1090; **IR:ν_{max}/cm^{-1} (solid)**: 3163 (N-H), 3129, 2914, 2866, 1625; **M.pt**: 132.2-132.7 °C; **Found:** C, 70.0; H, 5.10; N, 10.7; $C_{15}H_{13}FN_2O$ requires C, 70.3; H, 5.11; N, 10.9.

Preparation of 6-(3-ethoxy-2,6-difluorophenyl)-1*H*-indazole

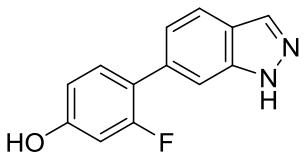


20

Synthesised using method A using 6-iodo-1*H*-indazole (200 mg, 0.82 mmol, 1.0 eq), 2,6-difluoro-3-ethoxyphenylboronic acid (231 mg, 1.23 mmol, 1.5 eq), Pd(dppf)Cl_2•DCM (67 mg, 0.082 mmol, 0.1 eq), Na_2CO_3 (261 mg, 2.46 mmol, 3.0 eq), dioxane (10 mL) and water (10 mL) and the reaction heated for 1 h. LCMS analysis showed the reaction to be incomplete and therefore 2,6-difluoro-3-ethoxyphenylboronic acid (231 mg, 1.23 mmol, 1.5 eq) was added and the reaction heated for 1 h. LCMS showed small conversion to the product but still starting material and therefore 2,6-difluoro-3-ethoxyphenylboronic acid (231 mg, 1.23 mmol, 1.5 eq) was added and the reaction heated for 1 h. LCMS showed no change and therefore the reaction was stopped*. The work up proceeded using the larger volumes of solvents and the organics reduced *in vacuo* to reveal a black semi-solid. The crude product was purified using column chromatography (1:4 EtOAc−hexane). The title compound **20** (4 mg, 0.014 mmol, 2%) was collected as an off-white solid. *Poor reactivity due to slow rate of transmetallation-sterically and electronically hindered boronic acid.

^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (1H, s, 3-H), 7.84 (1H, d, *J* 8.5, 4-H), 7.61 (1H, s, 7-H), 7.29-7.26 (1H, m, 5-H), 6.98-6.90 (2H, m, 4''-H and 5''-H), 4.14 (2H, q, *J* 7.0, CH_2), 1.47 (3H, t, *J* 7.0, CH_3), NH not observed; **^{13}C NMR (125 MHz, $CDCl_3$)**: 153.8 (dd, *J* 241.5 and 5.2, 6''-C), 150.0 (dd, *J* 248.6 and 6.7, 2''-C), 143.9 (dd, *J* 11.8 and 3.1, 3''-C), 140.0 (3'-C), 135.0 (3-C), 128.0 (7'-C), 123.6 (5-C), 123.0 (app.t, *J* 7.9, 6-C), 120.6 (4-C), 119.4 (app.t, *J* 16.0, 1''-C), 114.3 (dd, *J* 9.7 and 3.1, 4''-C), 111.6 (7-C), 110.3 (dd, *J* 24.1 and 4.2, 5''-C), 65.9 (CH_2), 14.9 (CH_3); **LC-MS (ES+)**: RT = 1.85-2.07 min, m/z = 275.6 ($M+H^+$); ***R*$_f$**: 0.49 (1:1 EtOAc−Petrol); **HPLC**: RT = 3.08 min; **m/z (ES+)**: Found: 275.0990 ($M+H^+$), $C_{15}H_{12}F_2N_2O$ requires *MH* 275.0990; **IR:ν_{max}/cm^{-1} (solid)**: 3172 (N-H), 3132, 2921, 2878, 1630; **M.pt**: 131.0-132.7 °C.

Preparation of 6-(2-fluoro-4-hydroxyphenyl)-1*H*-indazole



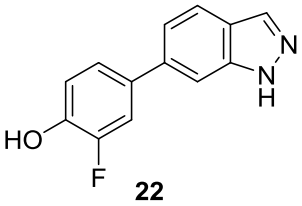
21

Synthesised using method B using 6-(2-fluoro-4-methoxyphenyl)-1*H*-indazole (50 mg, 0.21 mmol, 1.0 eq), 1M BBr_3 in DCM (1.65 mL, 1.65 mmol, 8.0 eq) and DCM (5 mL). Water (10 mL) was added and the resulting precipitate filtered and washed with water. The title compound **21** (37 mg, 0.16 mmol, 81%) was collected as colourless microcrystals.

^{1}H NMR (500 MHz, d6-DMSO): 8.07 (1H, d, *J* 0.8, 3-H), 7.78 (1H, dd, *J* 8.4 and 0.8, 4-H), 7.56 (1H, s, 7-H), 7.39 (1H, app.t, *J* 9.0, 6''-H), 7.21 (1H, app.dt, *J* 8.4 and 1.5, 5-H), 6.73 (1H, dd, *J* 8.4 and 2.4, 5''-H), 6.68 (1H, dd, *J* 12.8 and 2.4, 3''-H), NH and OH not observed; **^{13}C NMR (125 MHz, d6-DMSO)**: 159.7 (d, *J* 245.1, 2''-C), 158.4 (d, *J* 11.8, 4''-C), 140.2 (7'-C), 133.2 (d, *J* 5.0, 6-C), 133.2 (3-C), 131.5 (d, *J* 5.4, 6''-C), 121.7 (7'-C), 121.6 (d, *J* 2.3, 5-C), 120.4 (4-C), 119.1 (d, *J* 13.2, 1''-C), 112.2 (d, *J* 2.7, 5''-C), 109.5 (d, *J* 3.1, 7-C), 103.1 (d, *J* 25.2, 3''-C); **LC-MS (ES+)**: RT = 0.5-0.6 min, m/z = 229.33 ($M+H^+$); ***R*$_f$**: 0.32 (1:1 Petrol−EtOAc); **HPLC**: RT = 2.31 min; **m/z (ES+)**:

Found: 229.0770 ($M+H^+$), $C_{13}H_9FN_2O$ requires *MH* 229.0772; **IR: ν_{max}/cm^{-1} (solid)**: 3270 (br.O-H), 3002, 2804, 1624, 1596; **M.pt**: >250 °C.

Preparation of 6-(3-fluoro-4-hydroxyphenyl)-1*H*-indazole

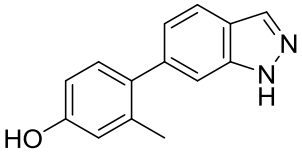


22

Synthesised using method B using 6-(3-fluoro-4-methoxyphenyl)-1*H*-indazole (50 mg, 0.21 mmol, 1.0 eq), 1M BBr_3 in DCM (1.65 mL, 1.65 mmol, 8.0 eq) and DCM (5 mL). Water (10 mL) was added but minimal precipitate was observed, therefore MeOH (10 mL) was added to aid dissolution and the organic layer separated. The aqueous layer was extracted with DCM (3 × 15 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to reveal the crude product as a yellow solid. The crude product was purified using reverse-phase ACC (0-40% MeCN−H_2O−0.1% Formic acid). The title compound **22** (18 mg, 0.08 mmol, 39%) was collected as a pale brown powder.

^{1}H NMR (500 MHz, d6-DMSO): 13.06 (1H, br.s, NH), 9.99 (1H, br.s OH), 8.05 (1H, s, 3-H), 7.78 (1H, d, *J* 8.4, 4-H), 7.65 (1H, s, 7-H), 7.51 (1H, dd, *J* 12.8 and 2.2, 2”-H), 7.38-7.33 (2H, m, 5-H and 5”-H), 7.04 (1H, app.t, *J* 8.9, 6’’-H); **^{13}C NMR (125 MHz, d6-DMSO)**: 151.3 (d, *J* 240.6, 3’’-C), 144.5 (d, *J* 12.2, 4”-C), 140.5 (7’-C), 137.1 (d, *J* 1.2, 6-C), 133.3 (3-C), 132.2 (d, *J* 6.1, 1”-C), 123.1 (d, *J* 2.8, 5”-C), 121.9 (3’-C), 120.8 (4-C), 119.7 (5-C), 118.1 (d, *J* 3.3, 6”-C), 114.6 (d, *J* 19.0, 2”-C), 106.9 (7-C); **LC-MS (ES+)**: RT = 0.5-0.6 min, m/z = 229.33 ($M+H^+$); R_f: 0.30 (1:1 Petrol−EtOAc); **HPLC**: RT = 2.26 min; **m/z (ES+)**: Found: 229.0769 ($M+H^+$), $C_{13}H_9FN_2O$ requires *MH* 229.0772; **IR: ν_{max}/cm^{-1} (solid)**: 3277 (br.O-H), 2444, 1614, 1591; **M.pt**: >250 °C.

Preparation of 6-(2-methyl-4-hydroxyphenyl)-1*H*-indazole

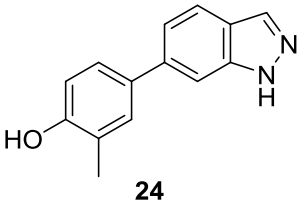


23

Synthesised using method B using 6-(2-methyl-4-methoxyphenyl)-1*H*-indazole (75 mg, 0.31 mmol, 1.0 eq), 1M BBr_3 in DCM (2.52 mL, 2.52 mmol, 8.0 eq) and DCM (5 mL). Water (10 mL) was added and the resulting precipitate filtered and washed with water. The title compound **23** (50 mg, 0.22 mmol, 72%) was collected as a colourless powder.

^{1}H NMR (500 MHz, d6-DMSO): 8.05 (1H, d, *J* 0.9, 3-H), 7.73 (1H, dd, *J* 8.3 and 0.9, 4-H), 7.33 (1H, s, 7-H), 7.05 (1H, d, *J* 8.2, 6”-H), 7.02 (1H, dd, *J* 8.3 and 1.3, 5-H), 6.70 (1H, d, *J* 2.4, 3”-H), 6.66 (1H, dd, *J* 8.2 and 2.4, 5”-H), 2.16 (3H, s, CH_3), NH and OH not observed; **^{13}C NMR (125 MHz, d6-DMSO)**: 156.5 (4’’-C), 140.0 (7’-C), 139.4 (Ar-q), 136.0 (Ar-q), 133.2 (3-C), 132.5 (Ar-q), 130.8 (6”-C), 122.6 (5-C), 121.4 (3’-C), 119.8 (4-C), 116.8 (3”-C), 112.8 (5”-C), 109.8 (7-C), 20.4 (CH_3); **LC-MS (ES+)**: RT = 0.5-0.6 min, m/z = 225.38 ($M+H^+$); R_f: 0.35 (1:1 Petrol−EtOAc); **HPLC**: RT = 2.30 min; **m/z (ES+)**: Found: 225.1020 ($M+H^+$), $C_{14}H_{12}N_2O$ requires *MH* 225.1022; **IR: ν_{max}/cm^{-1} (solid)**: 3184 (br.O-H), 2255, 1438; **M.pt**: 222.8-223.2 °C.

Preparation of 6-(3-methyl-4-hydroxyphenyl)-1*H*-indazole



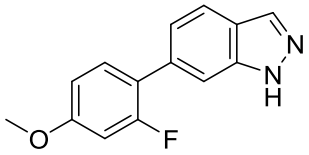
24

Synthesised using method B using 6-(3-methyl-4-methoxyphenyl)-1*H*-indazole (50 mg, 0.21 mmol, 1.0 eq), 1M BBr_3 in DCM (1.68 mL, 1.68 mmol, 8.0 eq) and DCM (5 mL). Water (10 mL) was added and the resulting precipitate filtered and washed with water. The title compound **24** (32 mg, 0.14 mmol, 70%) was collected as a colourless powder.

^{1}H NMR (500 MHz, d6-DMSO): 8.03 (1H, d, *J* 0.7, 3-H), 7.75 (1H, d, *J* 8.4, 4-H), 7.59 (1H, br.s, 7-H), 7.43 (1H, d, *J* 1.8, 2”-H), 7.36-7.31 (2H, m, 5-H and 5”-H), 6.86 (1H, d, *J* 8.3, 6’’-H), 2.19 (3H, s, CH_3), NH and OH not observed; **^{13}C NMR (125 MHz, d6-DMSO)**: 155.2 (4’’-C), 140.7 (7’-C), 138.6 (Ar-q), 133.2 (3-C), 131.2 (Ar-q), 129.4 (2’’-C), 125.4 (5’’-C), 124.3 (3’’-C), 121.5 (3’-C), 120.6 (4-C), 119.8 (5-C), 115.0 (6’’-C), 106.5 (7-C), 16.1 (CH_3); **LC-MS (ES+)**: RT = 0.5-0.6 min, m/z = 225.37 ($M+H^+$); R_f: 0.32 (1:1 Petrol−EtOAc); **HPLC**:

RT = 2.43 min; **m/z (ES+)**: Found: 225.1018 ($M+H^+$), $C_{14}H_{12}N_2O$ requires *MH* 225.1022; **IR: ν_{max}/cm^{-1} (solid)**: 3246 (br.O-H), 3203 (N-H), 2694, 2260, 1629, 1605; **M.pt**: >250 °C.

Preparation of 6-(2-fluoro-4-methoxyphenyl)-1*H*-indazole

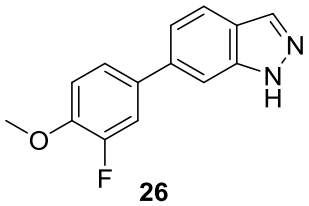


25

Synthesised using method A using 6-iodo-1*H*-indazole (250 mg, 1.02 mmol, 1.0 eq), 2-fluoro-4-methoxyphenylboronic acid (261 mg, 1.54 mmol, 1.5 eq), Pd(dppf)Cl_2•DCM (84 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.07 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 3 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (1:4 EtOAc−petrol) and an off-white solid obtained. The solid was recrystallised from EtOH. The title compound **25** (55 mg, 0.23 mmol, 23%) was collected as colourless needles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.20 (1H, br.s, NH), 8.10 (1H, s, 3-H), 7.79 (1H, d, *J* 8.4, 4-H), 7.63 (1H, s, 7-H), 7.41 (1H, app.t, *J* .8, 6”-H), 7.33 (1H, app.dt, *J* 8.4 and 1.4, 5-H), 6.82-6.79 (1H, m, 5”-H), 6.75 (1H, app. dd, *J* 12.5 and 2.5, 3”-H), 3.86 (3H, s, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 160.7 (d, *J* 11.0, 4”-C), 160.6 (d, *J* 246.2, 2”-C), 140.6 (7’-C), 135.2 (6-C), 134.8 (3-C), 131.6 (d, *J* 5.2, 6”-C), 122.9 (d, *J* 2.3, 5-C) 122.5 (3’-C), 121.6 (d, *J* 13.7, 1”-C), 120.9 (4-C), 110.6 (d, *J* 3.1, 5”-C), 109.8 (d, *J* 3.3, 7-C), 102.4 (d, *J* 26.6, 3”-C) 55.9 (CH_3); **LC-MS (ES+)**: RT = 0.6-0.6 min, m/z = 243.33 ($M+H^+$); ***R*$_f$**: 0.05 (4:1 Petrol−EtOAc); **HPLC**: RT = 3.10 min; **m/z (ES+)**: Found: 243.0925 ($M+H^+$), $C_{14}H_{11}FN_2O$ requires *MH* 243.0928; **IR: ν_{max}/cm^{-1} (solid)**: 3220 (N-H), 3052, 2987, 1620, 1580; **M.pt**: 148.8-149.9 °C.

Preparation of 6-(3-fluoro-4-methoxyphenyl)-1*H*-indazole

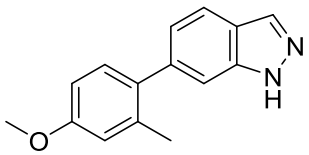


26

Synthesised using method A using 6-iodo-1*H*-indazole (250 mg, 1.02 mmol, 1.0 eq), 3-fluoro-4-methoxyphenyl boronic acid (261 mg, 1.54 mmol, 1.5 eq), Pd(dppf)Cl_2•DCM (84 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.07 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 3 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (gradient 20-30% EtOAc−hexane) and an off-white solid obtained. The solid was recrystallised from toluene. The title compound **26** (174 mg, 0.72 mmol, 72%) was collected as off-white needles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.15 (1H, br.s, NH), 8.10 (1H, br.s, *J* 1.1, 3-H), 7.80 (1H, d, *J* 8.4, 4-H), 7.60 (1H, s, 7-H), 7.41 (1H, d, *J* 2.2, 2”-H), 7.39-7.35 (2H, m, 5-H and 5”-H), 7.06 (1H, app.t, *J* 8.8, 6”-H), 3.95 (3H, s, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 152.6 (d, *J* 245.8, 3”-C), 147.3 (d, *J* 10.7, 4”-C), 140.8 (7’-C), 138.9 (d, *J* 1.2, 6-C), 135.1 (3-C), 134.5 (d, *J* 6.5, 1”-C), 123.1 (d, *J* 3.3, 5”-C), 122.5 (3’-C), 121.2 (5-C), 121.0 (4-C), 115.3 (d, *J* 19.0, 2”-C), 113.8 (d, *J* 2.3, 6”-C), 107.3 (7-C), 56.4 (CH_3); **LC-MS (ES+)**: RT = 0.6-0.6 min, m/z = 243.34 ($M+H^+$); ***R*$_f$**: 0.17 (3:7 EtOAc−petrol); **HPLC**: RT = 3.00 min; **m/z (ES+)**: Found: 243.0926 ($M+H^+$), $C_{14}H_{11}FN_2O$ requires *MH* 243.0928; **IR: ν_{max}/cm^{-1} (solid)**: 3257 (N-H), 2965, 2937, 2840, 1618, 1517; **M.pt**: 141.1-141.8 °C.

Preparation of 6-(2-methyl-4-methoxyphenyl)-1*H*-indazole

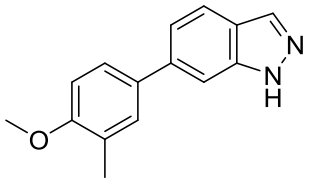


27

Synthesised using method A using 6-iodo-1*H*-indazole (250 mg, 1.02 mmol, 1.0 eq), 4-methoxy-2-methylphenylboronic acid (255 mg, 1.54 mmol, 1.5 eq), Pd(dppf)Cl_2•DCM (84 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.07 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 3 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (7:3 hexane−EtOAc) and an off-white solid obtained. The solid was recrystallised from cyclohexane. The title compound **27** (99 mg, 0.42 mmol, 41%) was collected as colourless fluffy microcrystals.

^{1}H NMR (500 MHz, $CDCl_3$): 10.26 (1H, br.s, NH), 8.11 (1H, s, 3-H), 7.75 (1H, d, *J* 8.3, 4-H), 7.38 (1H, s, 7-H), 7.20 (1H, d, *J* 8.3, 6''-H), 7.12 (1H, dd, *J* 8.3 and 1.2, 5-H), 6.84 (1H, d, *J* 2.6, 3''-H), 6.81 (1H, dd, *J* 8.3 and 2.6, 5''-H), 3.85 (3H, s, OCH_3), 2.27 (3H, s, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 159.0 (4''-C), 140.8 (7'-C), 137.5 (Ar-q), 136.9 (Ar-q), 135.0, (Ar-q), 134.6 (3-C), 131.0 (6''-C), 123.6 (5-C), 120.2 (4-C), 115.8 (3''-C), 111.2 (5''-C), 109.9 (7-C), 55.3 (OCH_3), 20.8 (CH_3), one quaternary carbon not observed; **LC-MS (ES+)**: RT = 0.6-0.7 min, m/z = 239.38 ($M+H^+$); ***R*$_f$**: 0.20 (7:3 Petrol−EtOAc); **HPLC**: RT = 3.18 min; **m/z (ES+)**: Found: 239.1178 ($M+H^+$), $C_{15}H_{14}N_2O$ requires *MH* 239.1179; **IR: ν_{max}/cm^{-1} (solid)**: 3250 (N-H), 2997, 2830, 1624, 1606, 1566; **M.pt**: 115.1-115.9 °C.

Preparation of 6-(3-methyl-4-methoxyphenyl)-1*H*-indazole



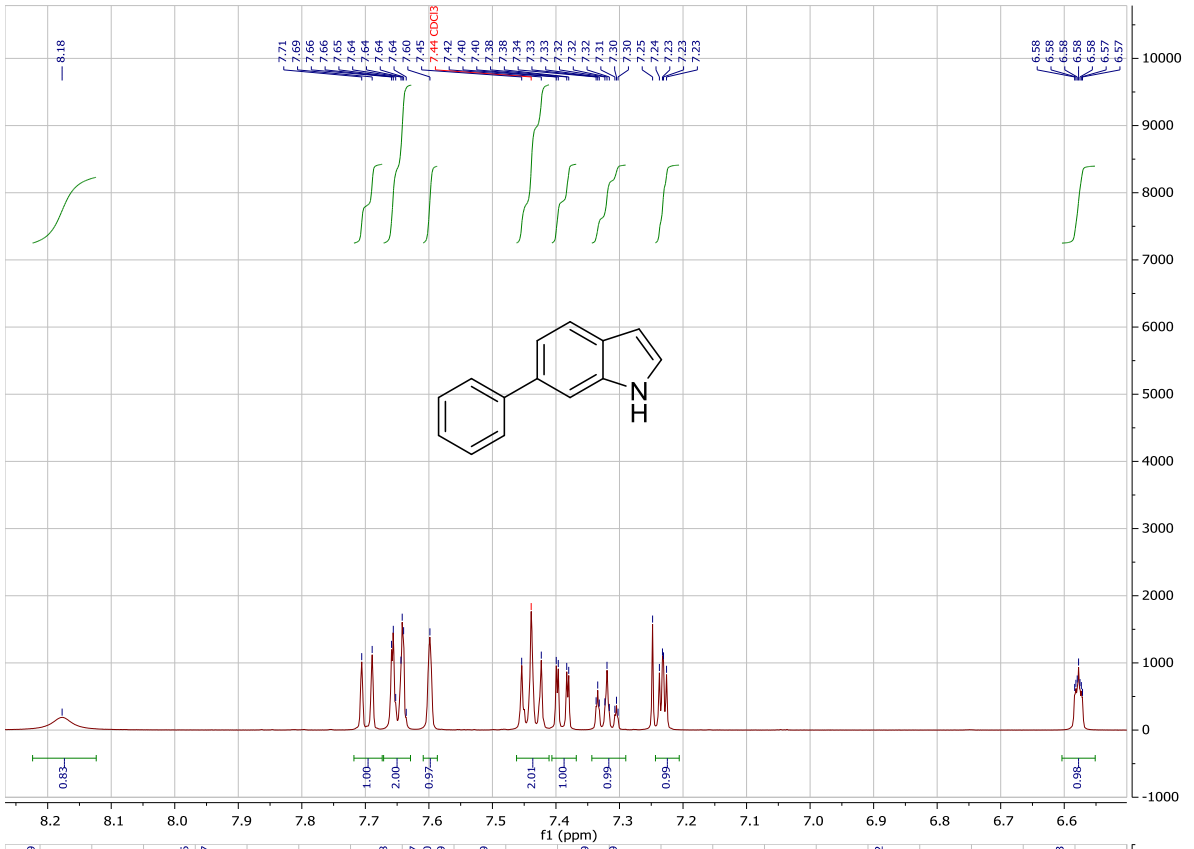
28

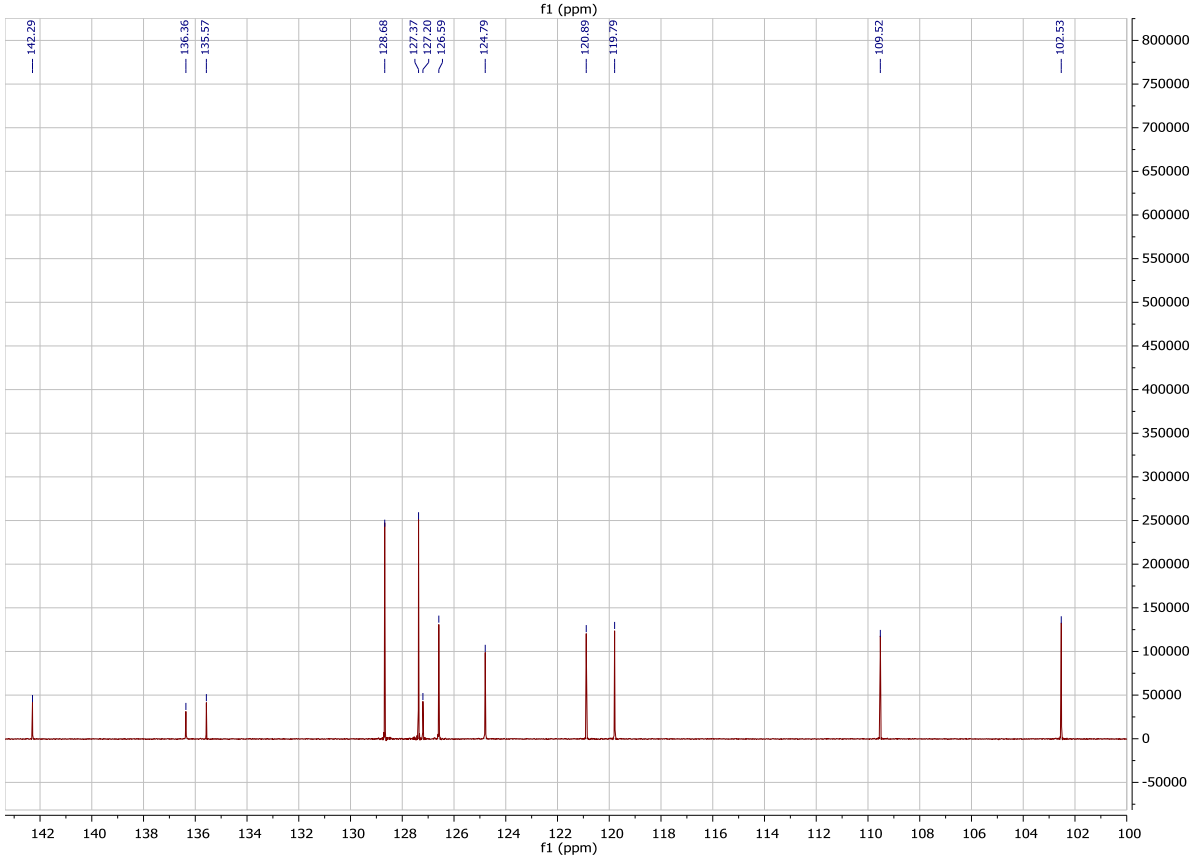
Synthesised using method A using 6-iodo-1*H*-indazole (250 mg, 1.02 mmol, 1.0 eq), 4-methoxy-3-methylphenyl boronic acid (255 mg, 1.54 mmol, 1.5 eq), $Pd(dppf)Cl_2$•DCM (84 mg, 0.102 mmol, 0.1 eq), Na_2CO_3 (325 mg, 3.07 mmol, 3.0 eq), dioxane (2.5 mL) and water (2.5 mL) and the reaction heated for 3 h. LCMS analysis indicated the reaction to be incomplete and therefore 6-iodo-1*H*-indazole (125 mg, 0.51 mmol, 0.5 eq), $Pd(dppf)Cl_2$•DCM (42 mg, 0.051 mmol, 0.05 eq) and Na_2CO_3 (163 mg, 1.53 mmol, 1.5 eq) were added and the reaction heated for a further 1 h. The work up proceeded using the smaller volumes of solvents and the organics reduced *in vacuo* to reveal a brown solid. The crude product was purified using column chromatography (7:3 Petrol−EtOAc) and an off-white solid obtained. The solid was recrystallised using a mixed solvent recrystallisation using EtOH and cyclohexane as the antisolvent. The title compound **28** (66 mg, 0.28 mmol, 21%) was collected as colourless needles.

^{1}H NMR (500 MHz, $CDCl_3$): 10.17 (1H, br.s, NH), 8.09 (1H, d, *J* 1.1, 3-H), 7.78 (1H, dd, *J* 8.4 and 1.1, 4-H), 7.61 (1H, s, 7-H), 7.47-7.44 (2H, m, 2''-H and 5''-H), 7.41 (1H, dd, *J* 8.4 and 1.4, 5-H), 6.94-6.90 (1H, m, 6''-H), 3.89 (3H, s, OCH_3), 2.31 (3H, s, CH_3); **^{13}C NMR (125 MHz, $CDCl_3$)**: 157.6 (4''-C), 140.9 (7'-C), 140.3 (6-C), 135.0 (3-C), 133.3 (1''-C), 129.9 (2''-C), 127.1 (3''-C), 125.9 (5''-C), 122.1 (3'-C), 121.3 (5-C), 120.9 (4-C), 110.3 (6''-C), 107.0 (7-C), 55.5 (OCH_3), 16.4 (CH_3); **LC-MS (ES+)**: RT = 0.6-0.7 min, m/z = 239.36 ($M+H^+$); ***R*$_f$**: 0.16 (7:3 Petrol−EtOAc); **HPLC**: RT = 3.31 min; **m/z (ES+)**: Found: 239.1177 ($M+H^+$), $C_{15}H_{14}N_2O$ requires *MH* 239.1179; **IR: ν_{max}/cm^{-1} (solid)**: 3229 (N-H), 2921, 2837, 1625, 1518; **M.pt**: 152.8-153.7 °C.

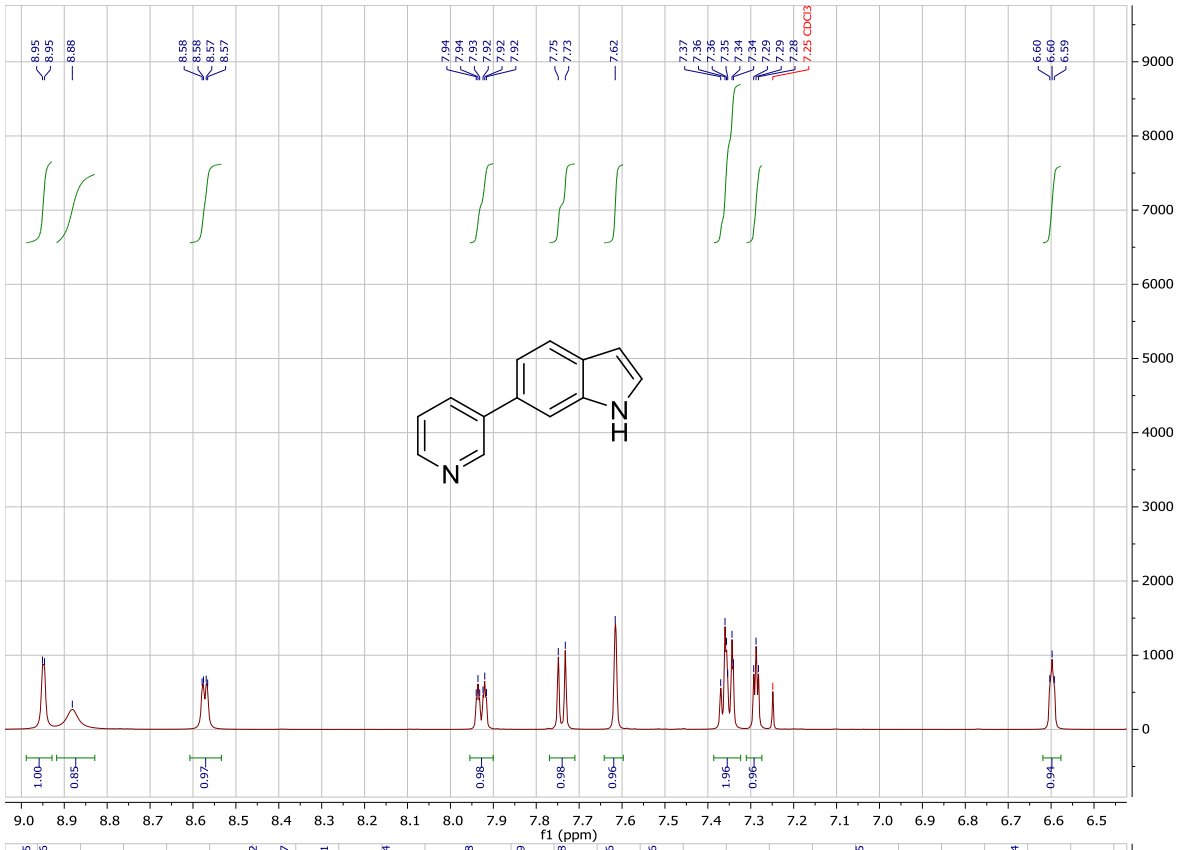
2.3 NMR Spectra- (Note to editor-all ^{1}H NMR spectra now have visible the solvent peak outlined in red)

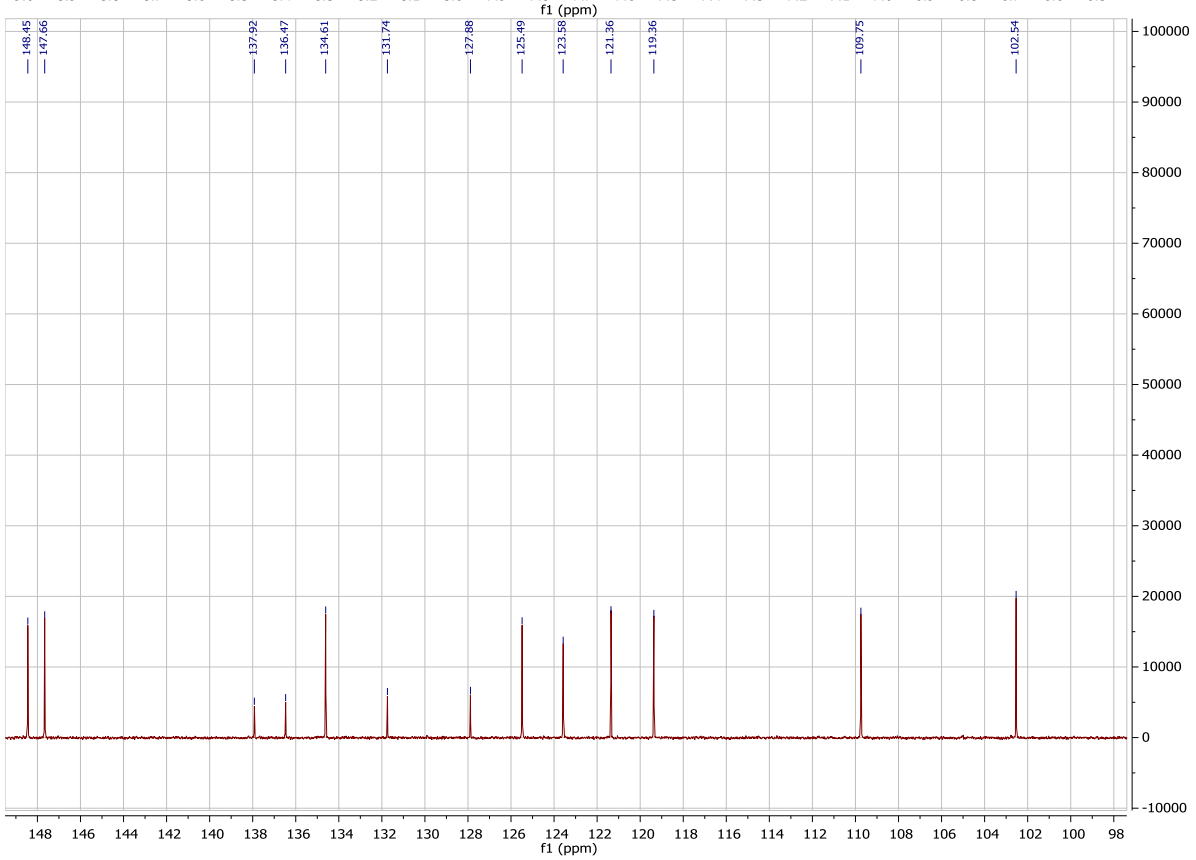
Compound 1



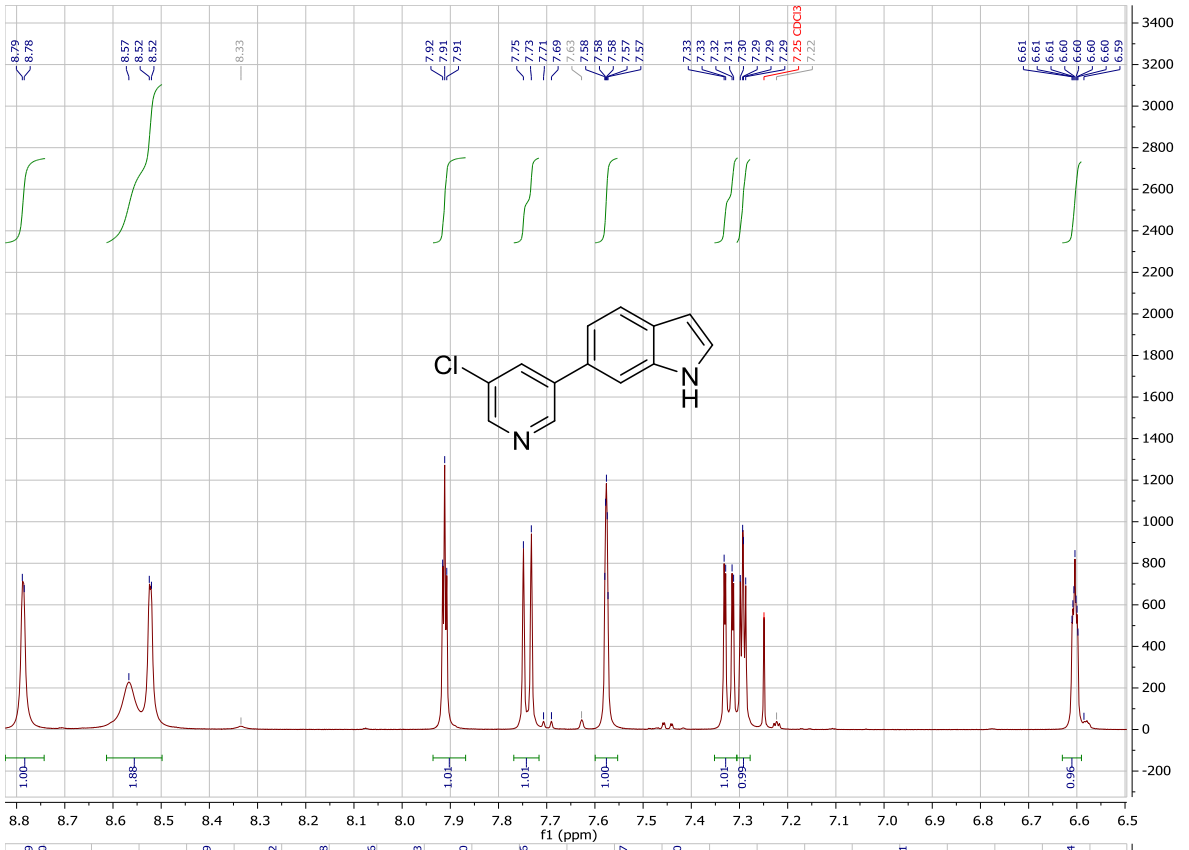


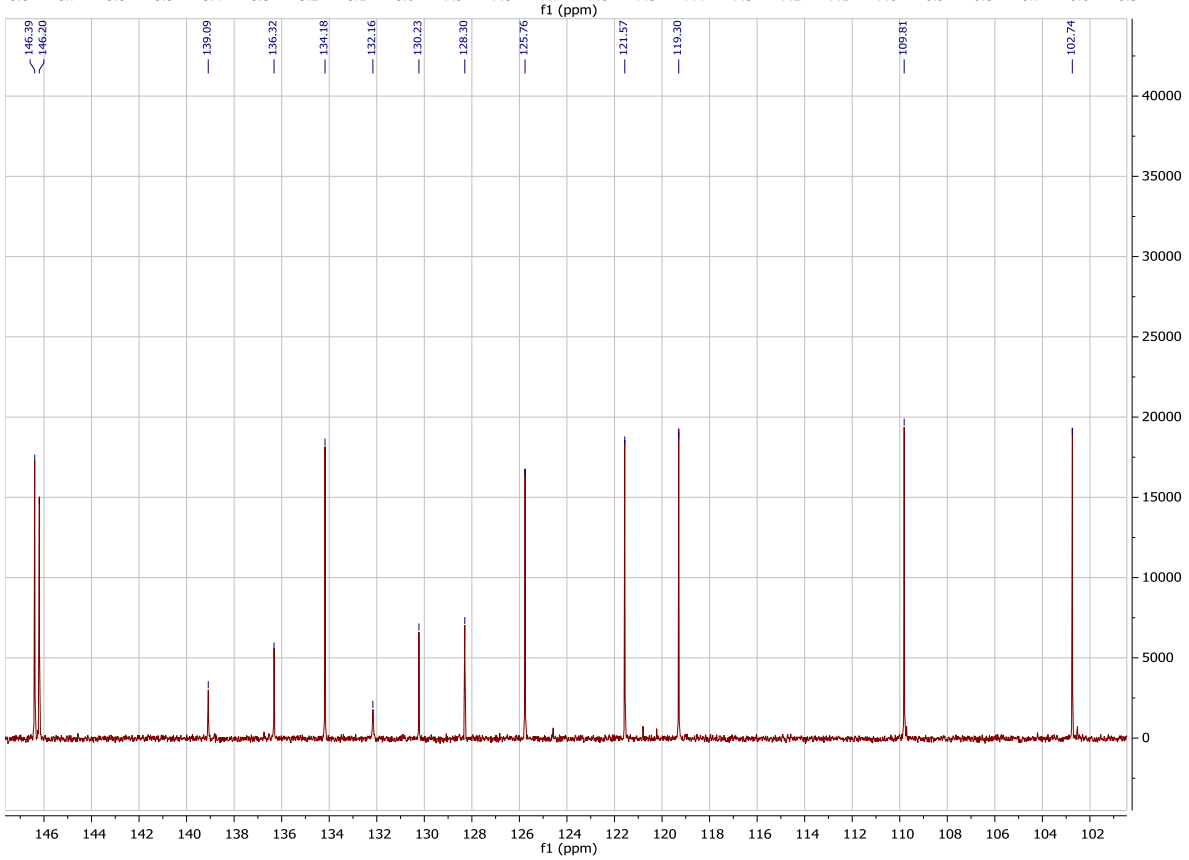
Compound 2


8.95
8.95
8.88
8.58
8.58
8.57
8.57
7.94
7.94
7.93
7.92
7.92
7.92
7.75
7.73
7.62
7.37
7.36
7.36
7.35
7.34
7.34
7.29
7.29
7.28
7.25 CDCl3
6.60
6.60
6.59
N
H
N
1.00
0.85
0.97
0.98
0.98
0.96
1.96
0.96
0.94
f1 (ppm)

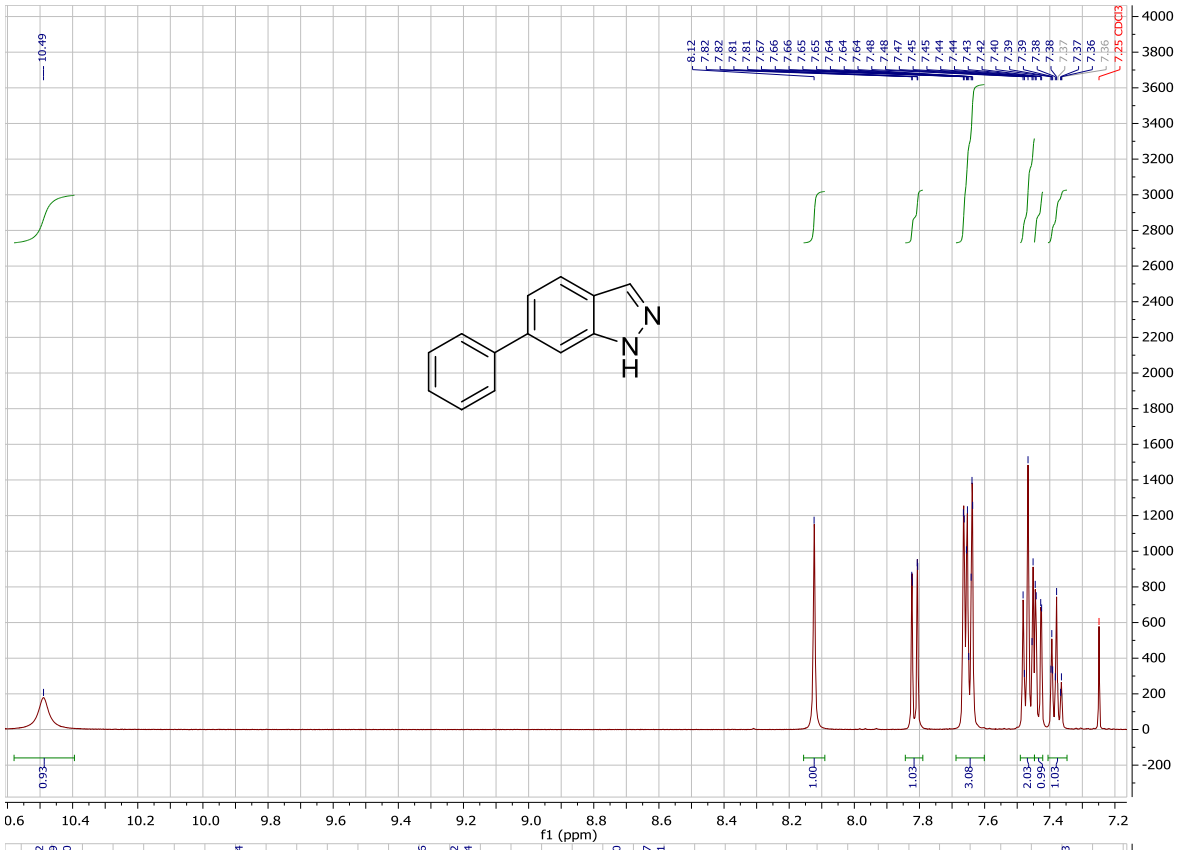

148.45
147.66
137.92
136.47
134.61
131.74
127.88
125.49
123.58
121.36
119.36
109.75
102.54
f1 (ppm)

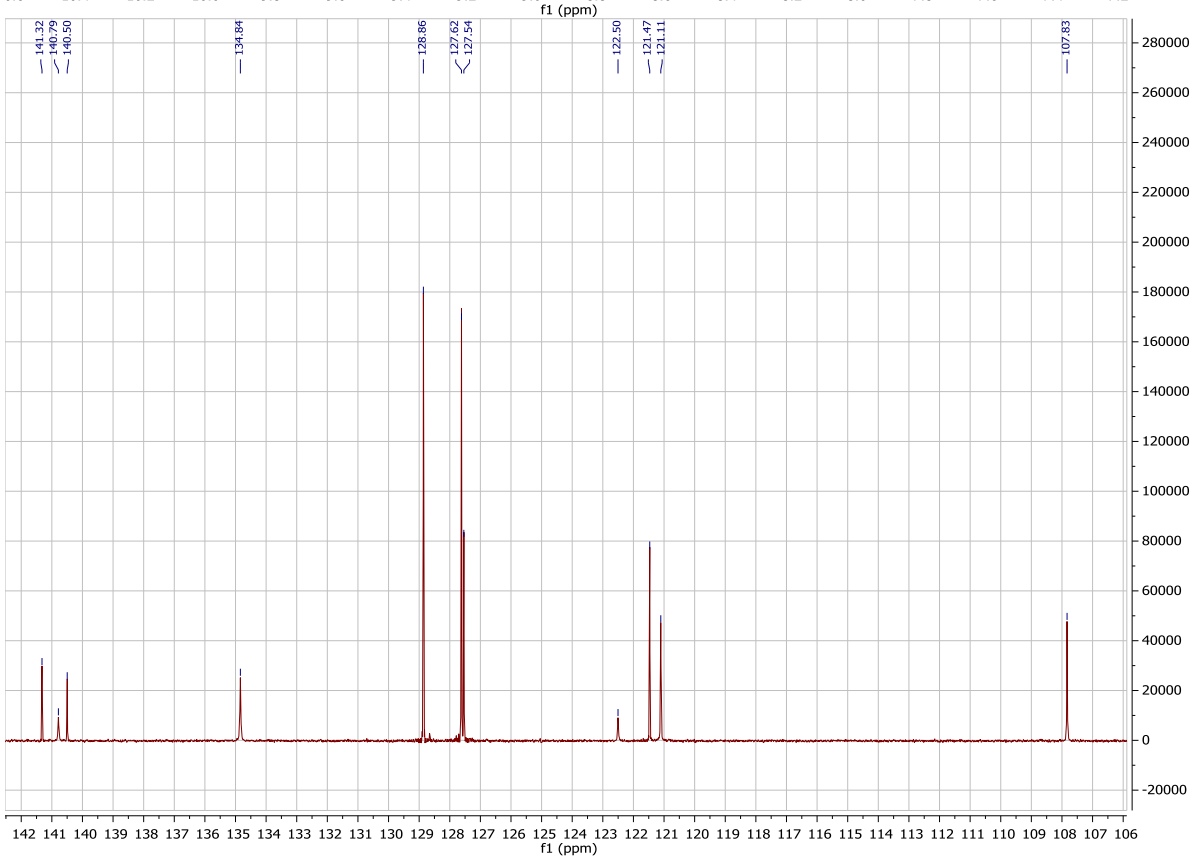
Compound 3


8.79
8.78
8.57
8.52
8.52
8.33
7.92
7.91
7.91
7.75
7.73
7.71
7.69
7.63
7.58
7.58
7.58
7.57
7.57
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.29
7.25 CDCl3
7.22
6.61
6.61
6.61
6.60
6.60
6.60
6.60
6.60
6.59
Cl
N
H
N
1.00
1.88
1.01
1.01
1.00
1.01
0.99
0.96
f1 (ppm)

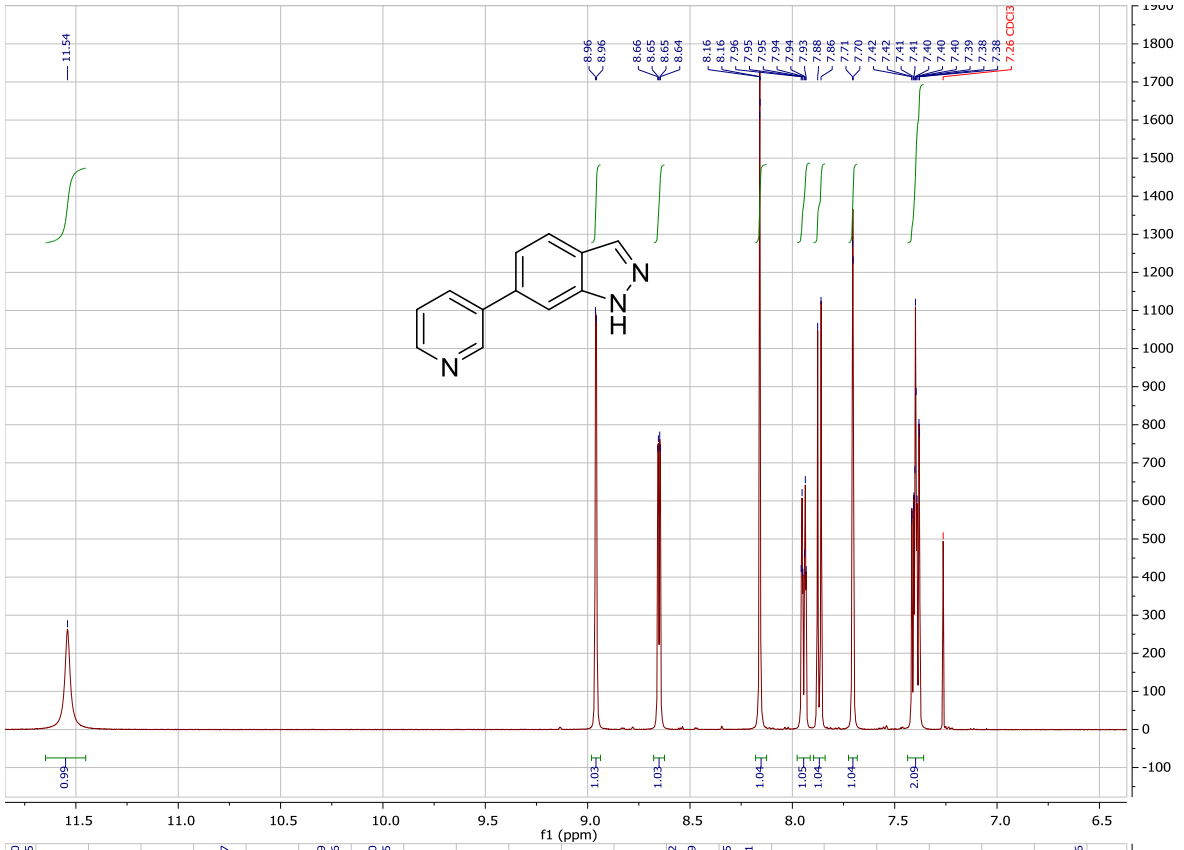

146.39
146.20
139.09
136.32
134.18
132.16
130.23
128.30
125.76
121.57
119.30
109.81
102.74
f1 (ppm)

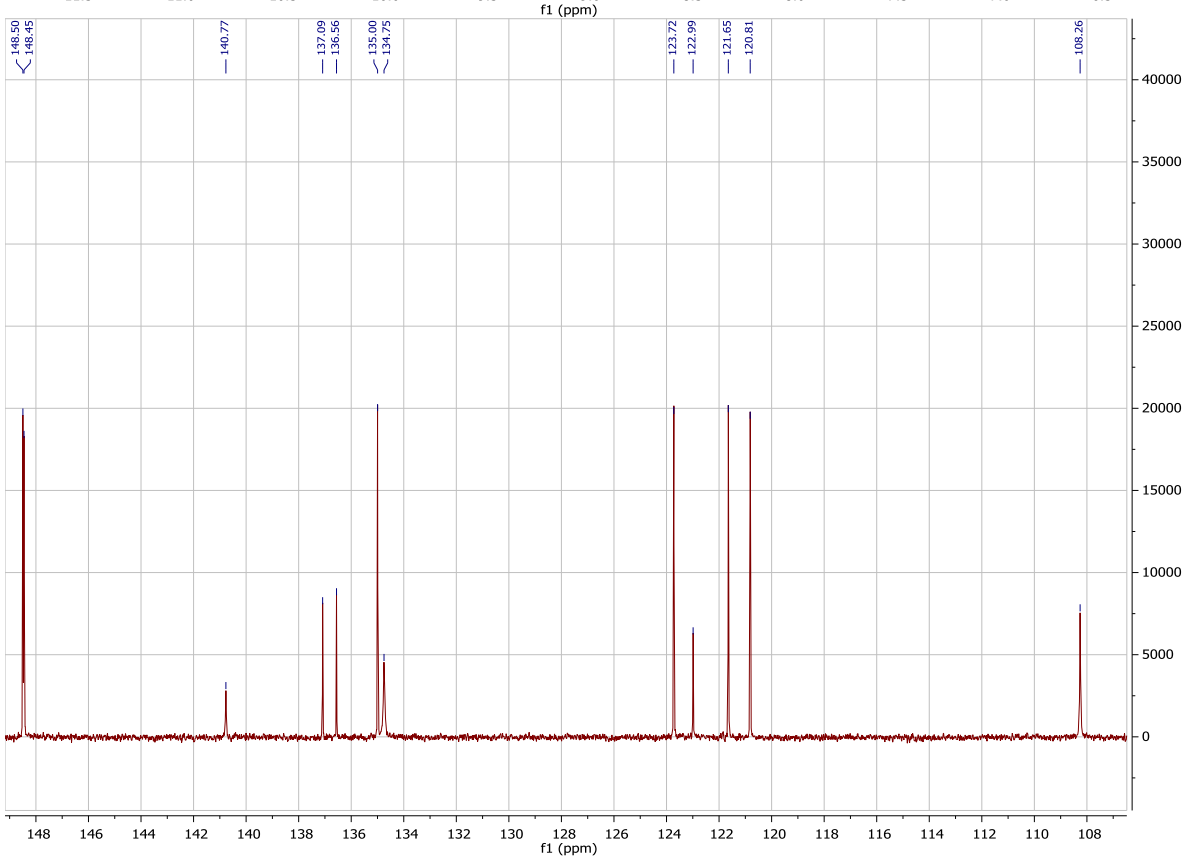
Compound 4


10.49
8.12
7.82
7.82
7.81
7.81
7.67
7.66
7.66
7.65
7.65
7.64
7.64
7.64
7.48
7.47
7.45
7.44
7.44
7.43
7.42
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.25 CDCl3
N
N
H
0.93
1.00
1.03
3.08
2.03
0.99
1.03
f1 (ppm)

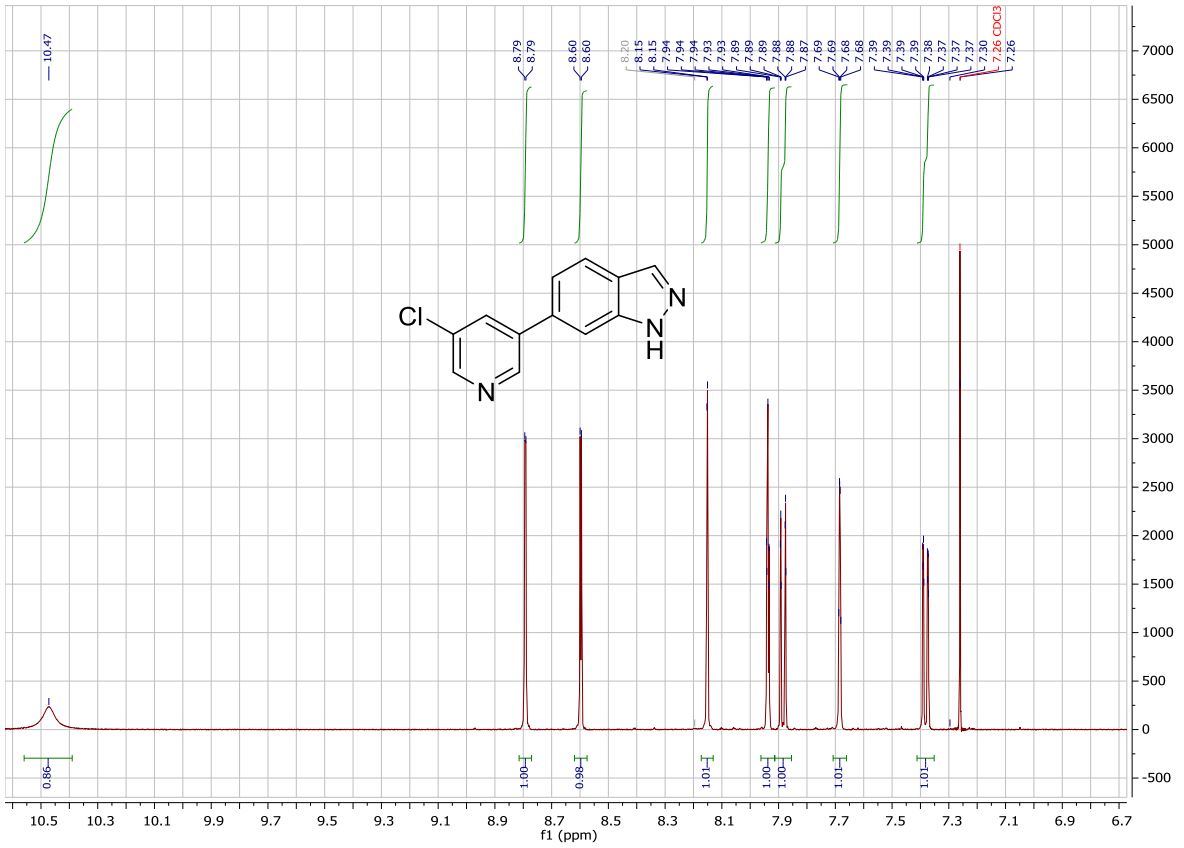

141.32
140.79
140.50
134.84
128.86
127.62
127.54
122.50
121.47
121.11
107.83
f1 (ppm)

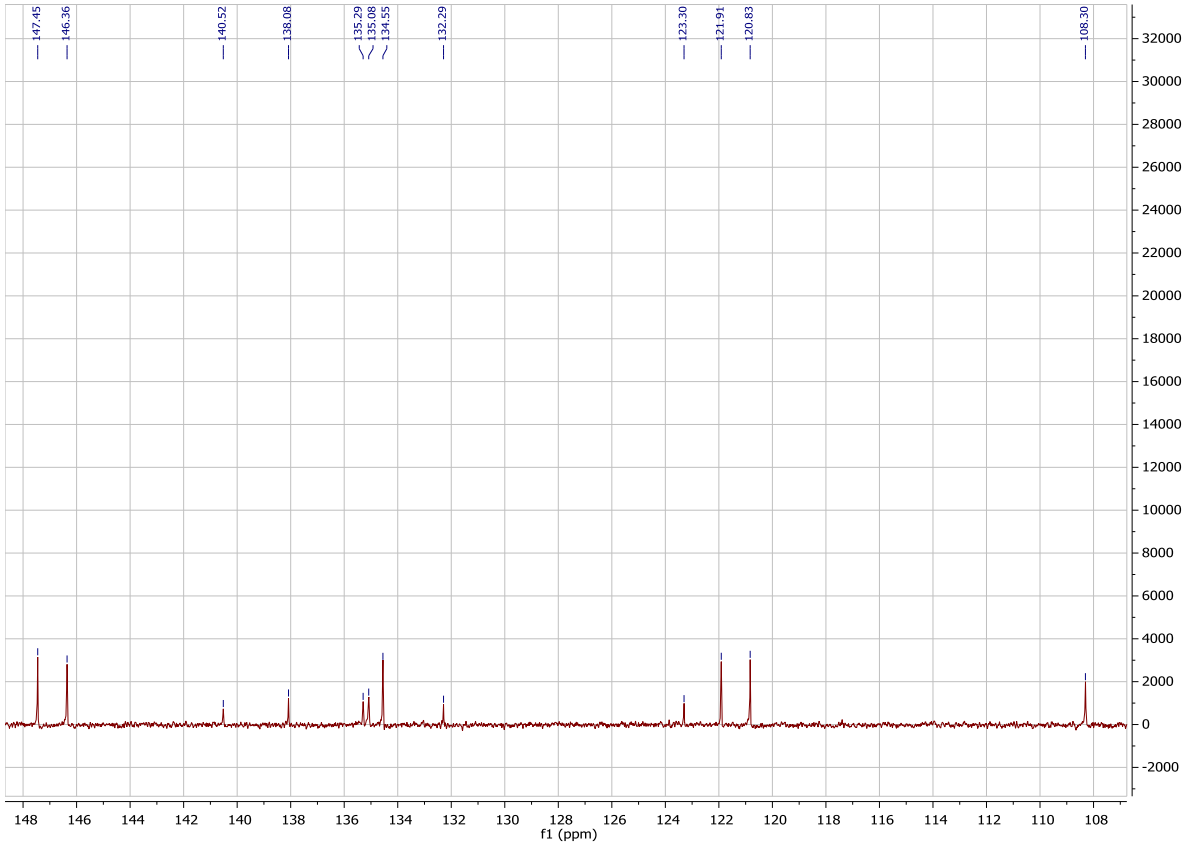
Compound 5


11.54
8.96
8.96
8.66
8.65
8.65
8.64
8.16
8.16
7.96
7.95
7.95
7.94
7.94
7.93
7.88
7.86
7.71
7.70
7.42
7.42
7.41
7.41
7.40
7.40
7.40
7.39
7.38
7.38
7.26 CDCl3
N
N
H
N
0.99
1.03
1.03
1.04
1.05
1.04
1.04
2.09
f1 (ppm)

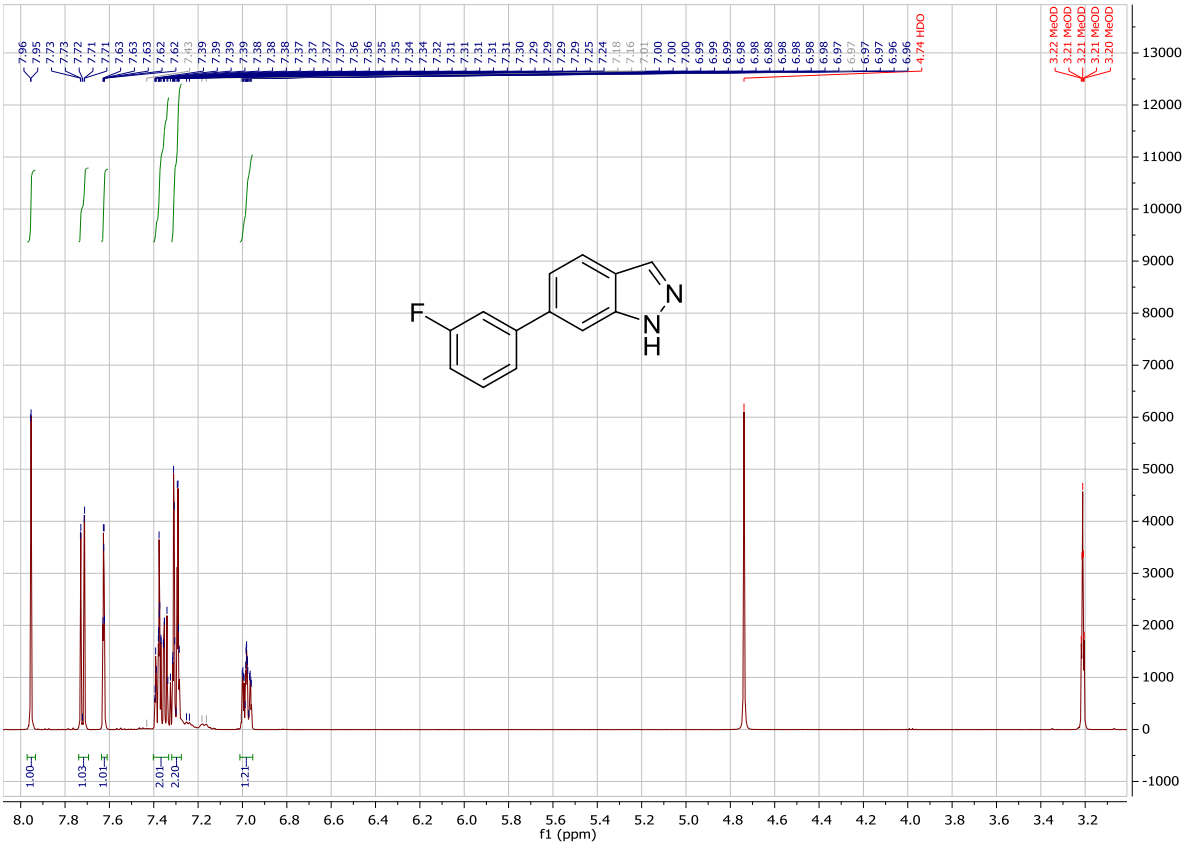

148.50
148.45
140.77
137.09
136.56
135.00
134.75
123.72
122.99
121.65
120.81
108.26
f1 (ppm)

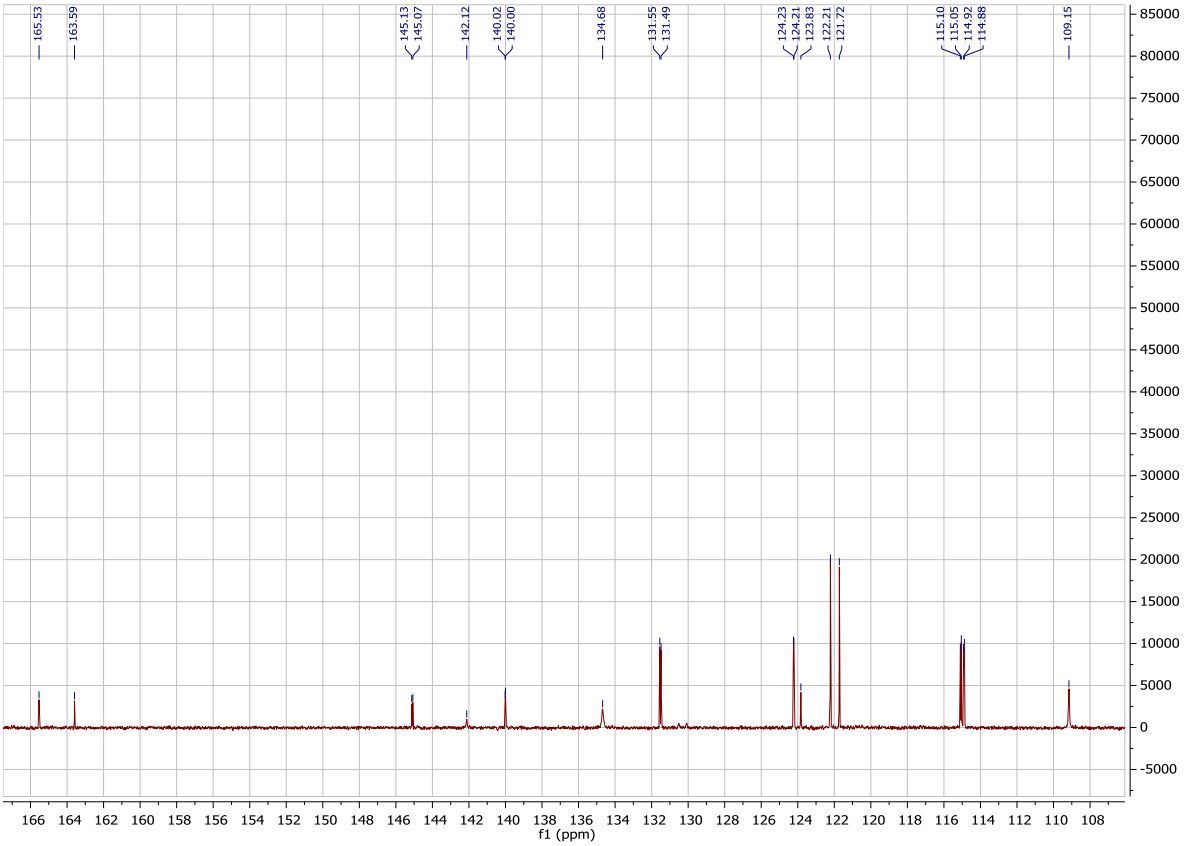
Compound 6


10.47
8.79
8.79
8.60
8.60
8.20
8.15
8.15
7.94
7.94
7.94
7.93
7.93
7.89
7.89
7.89
7.88
7.88
7.87
7.69
7.69
7.68
7.68
7.39
7.39
7.39
7.39
7.38
7.37
7.37
7.37
7.30
7.26 CDCl3
7.26
Cl
N
N
H
N
0.86
1.00
0.98
1.01
1.00
1.00
1.01
1.01
f1 (ppm)

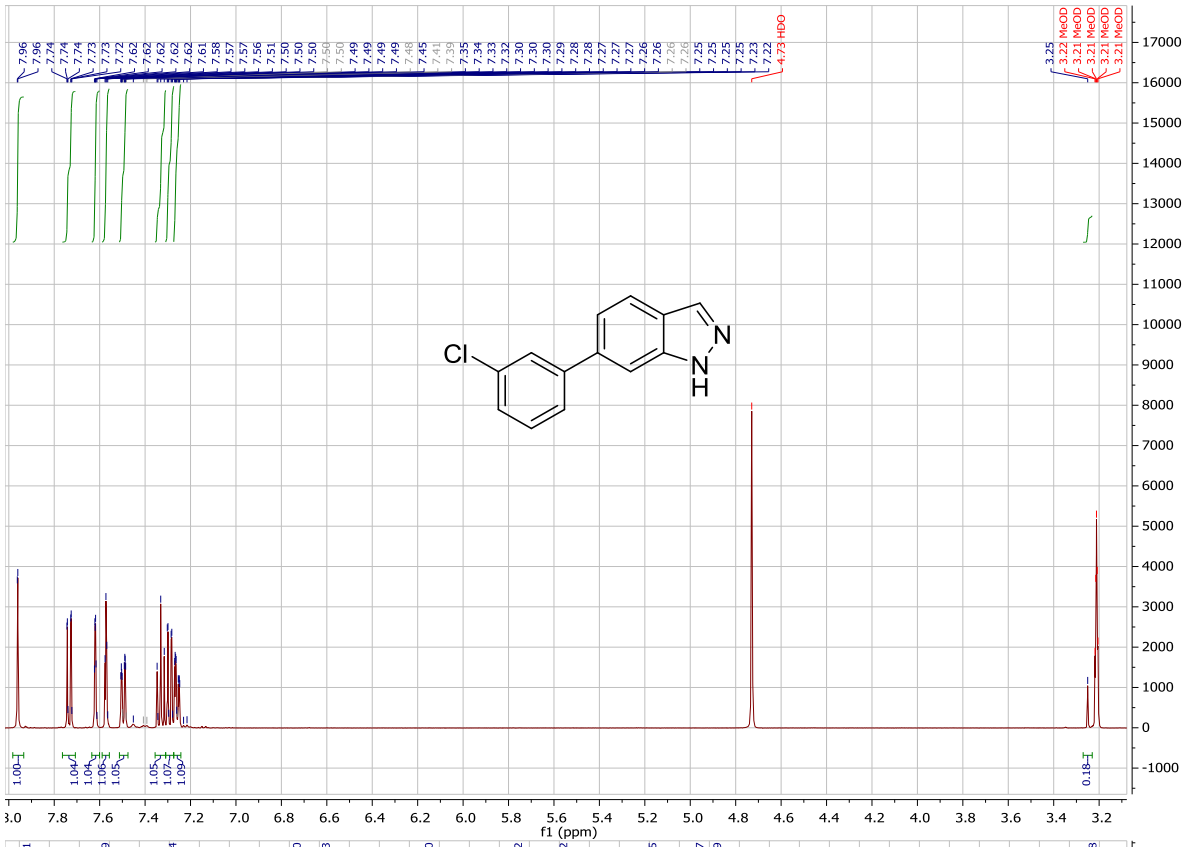

147.45
146.36
140.52
138.08
135.29
135.08
134.55
132.29
123.30
121.91
120.83
108.30
f1 (ppm)

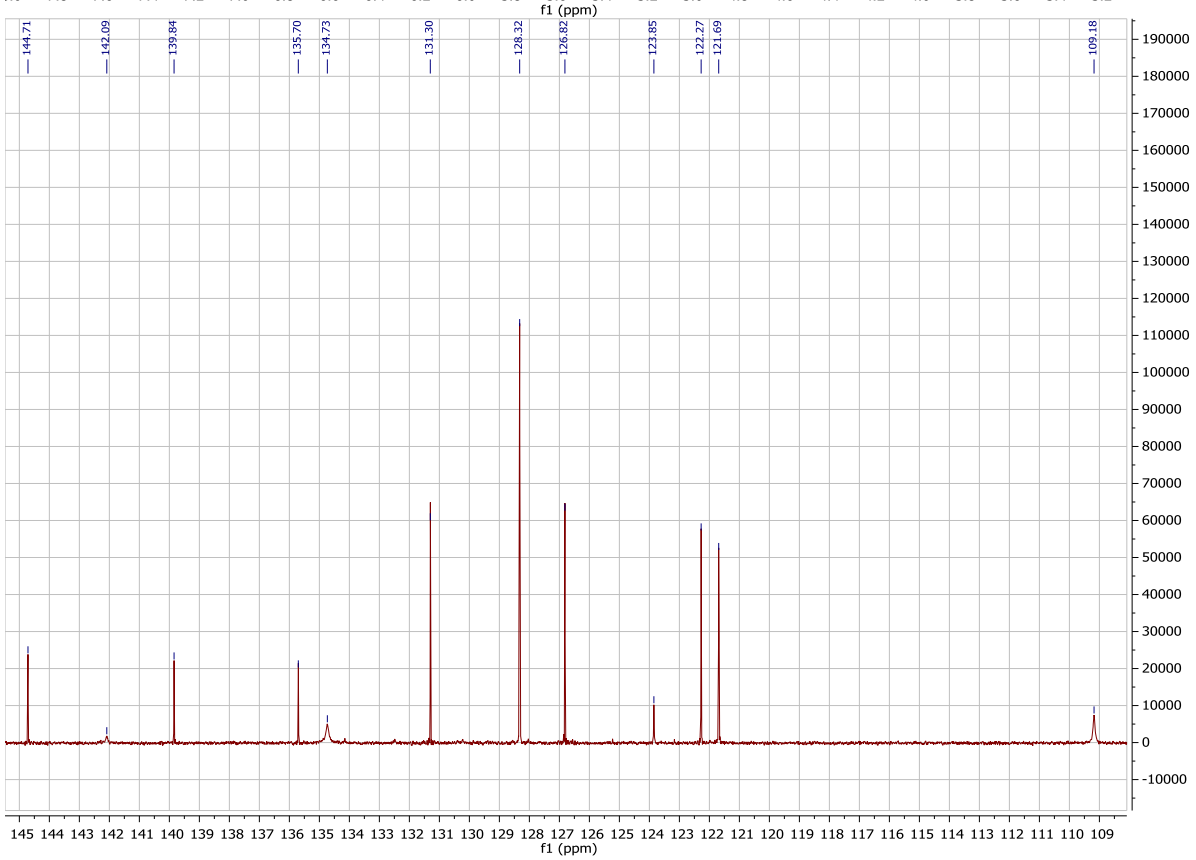
Compound 8



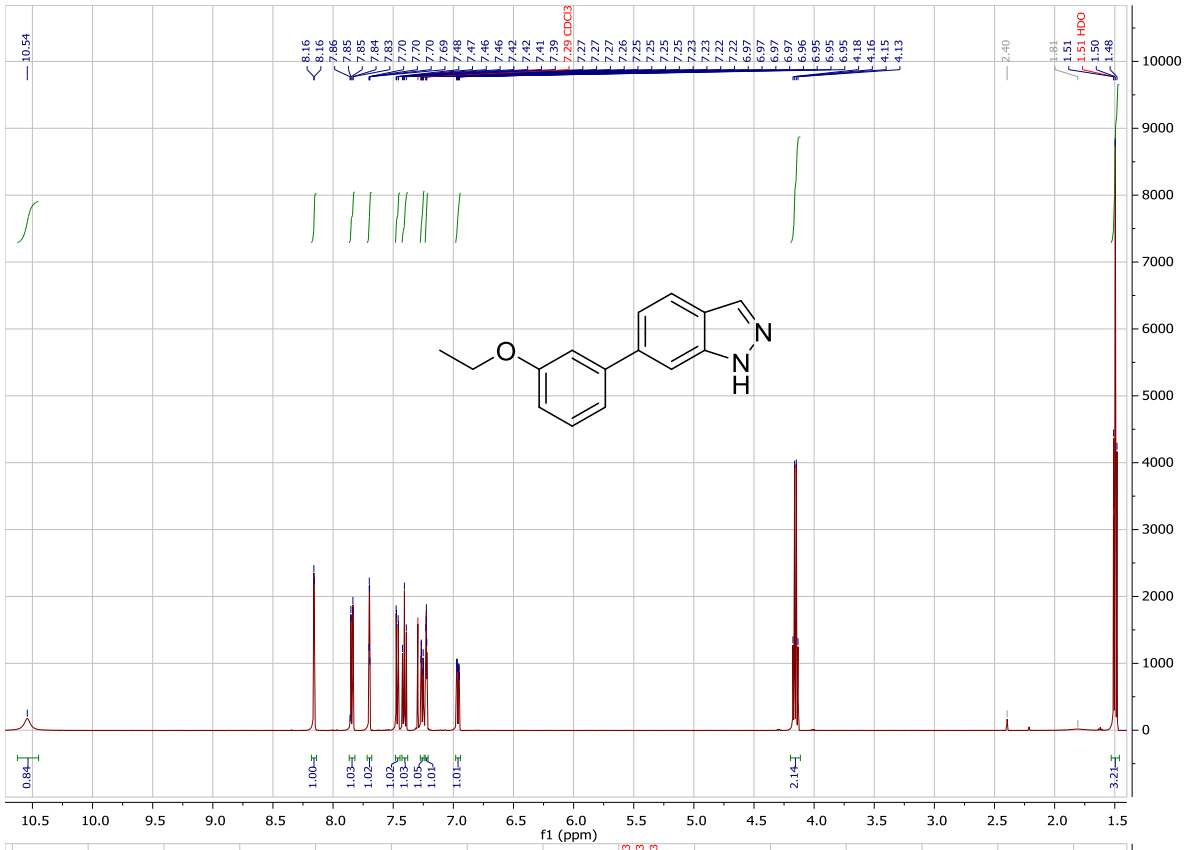


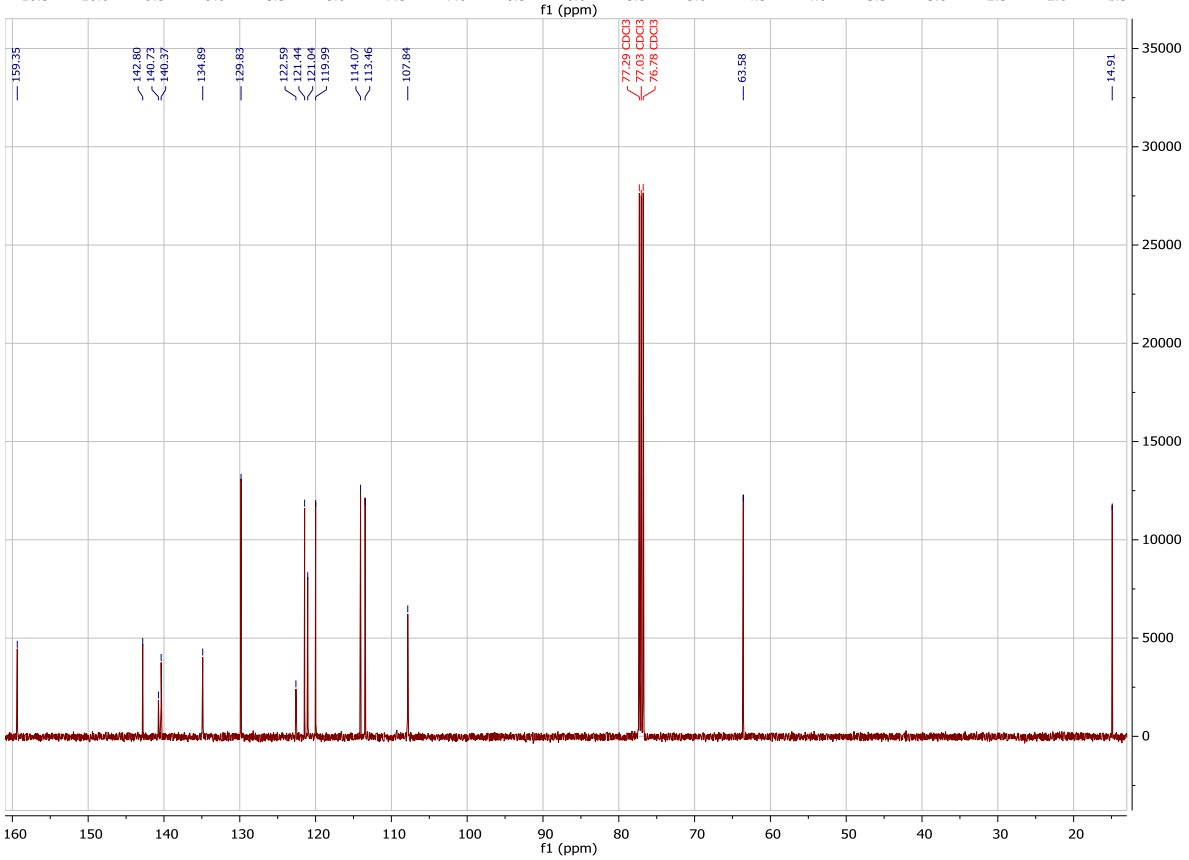
Compound 9



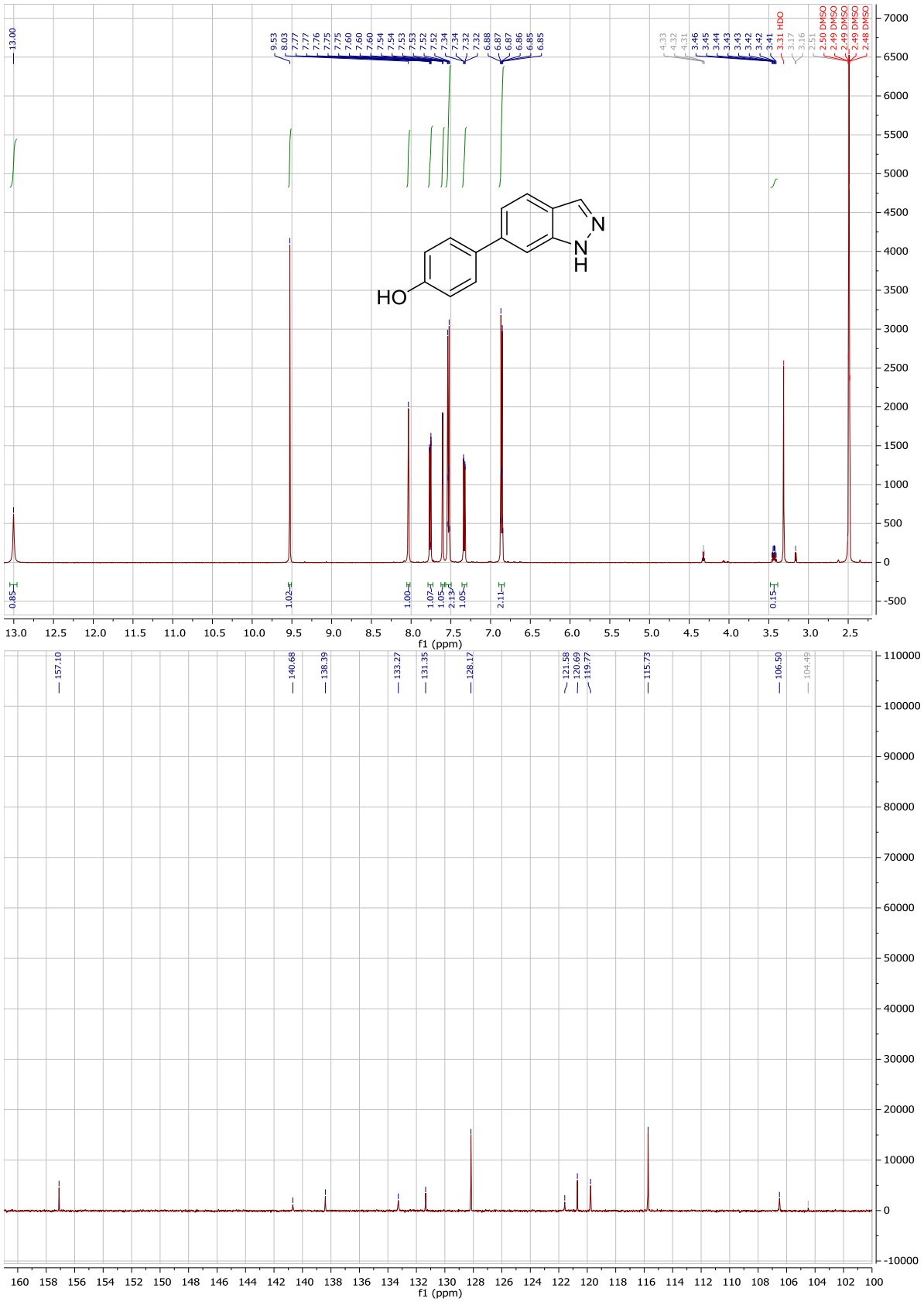


Compound 10

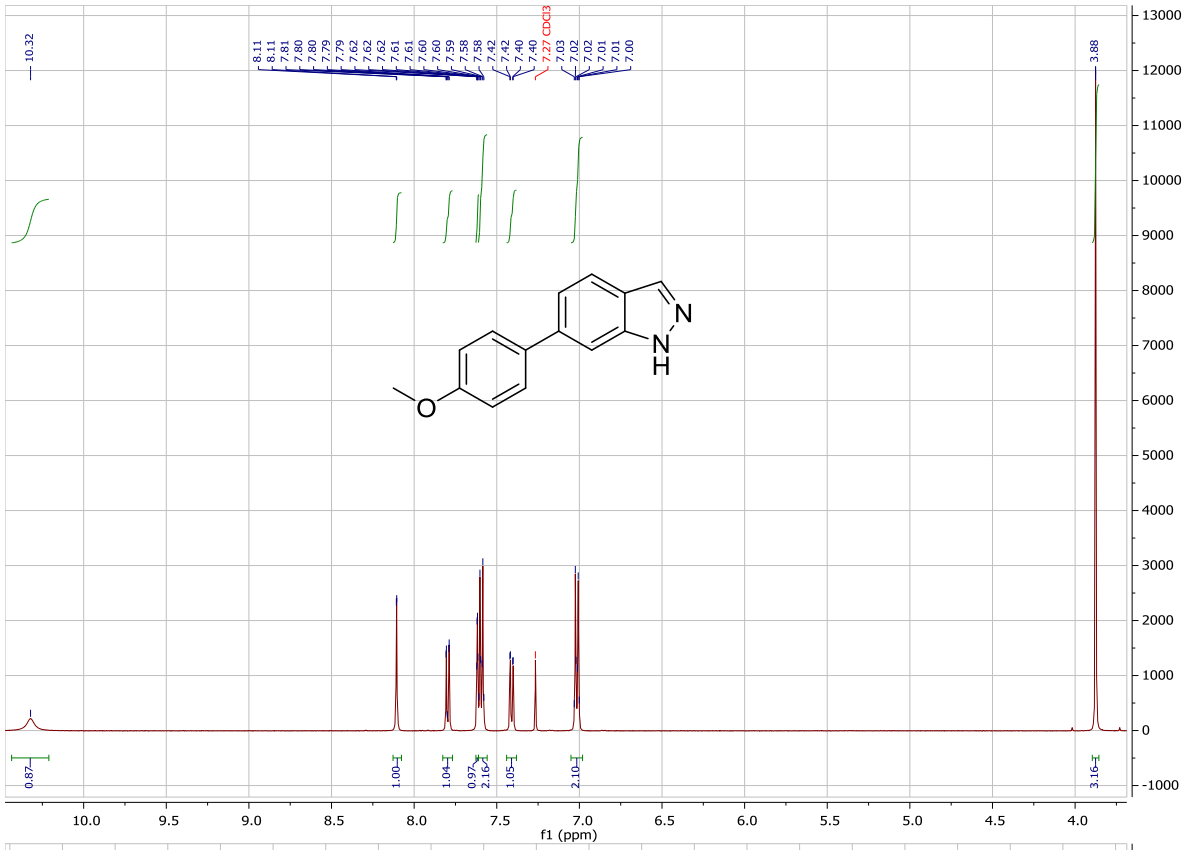

10.54
8.16
8.16
7.86
7.85
7.85
7.84
7.83
7.70
7.70
7.70
7.69
7.48
7.47
7.46
7.46
7.42
7.42
7.41
7.39
7.29 CDCl3
7.27
7.27
7.27
7.26
7.25
7.25
7.25
7.25
7.23
7.23
7.22
7.22
6.97
6.97
6.97
6.97
6.96
6.95
6.95
6.95
4.18
4.16
4.15
4.13
2.40
1.81
1.51
1.51 HDO
1.50
1.48
N
N
H
O
0.84
1.00
1.03
1.02
1.02
1.03
1.05
1.01
1.01
2.14
3.21
f1 (ppm)

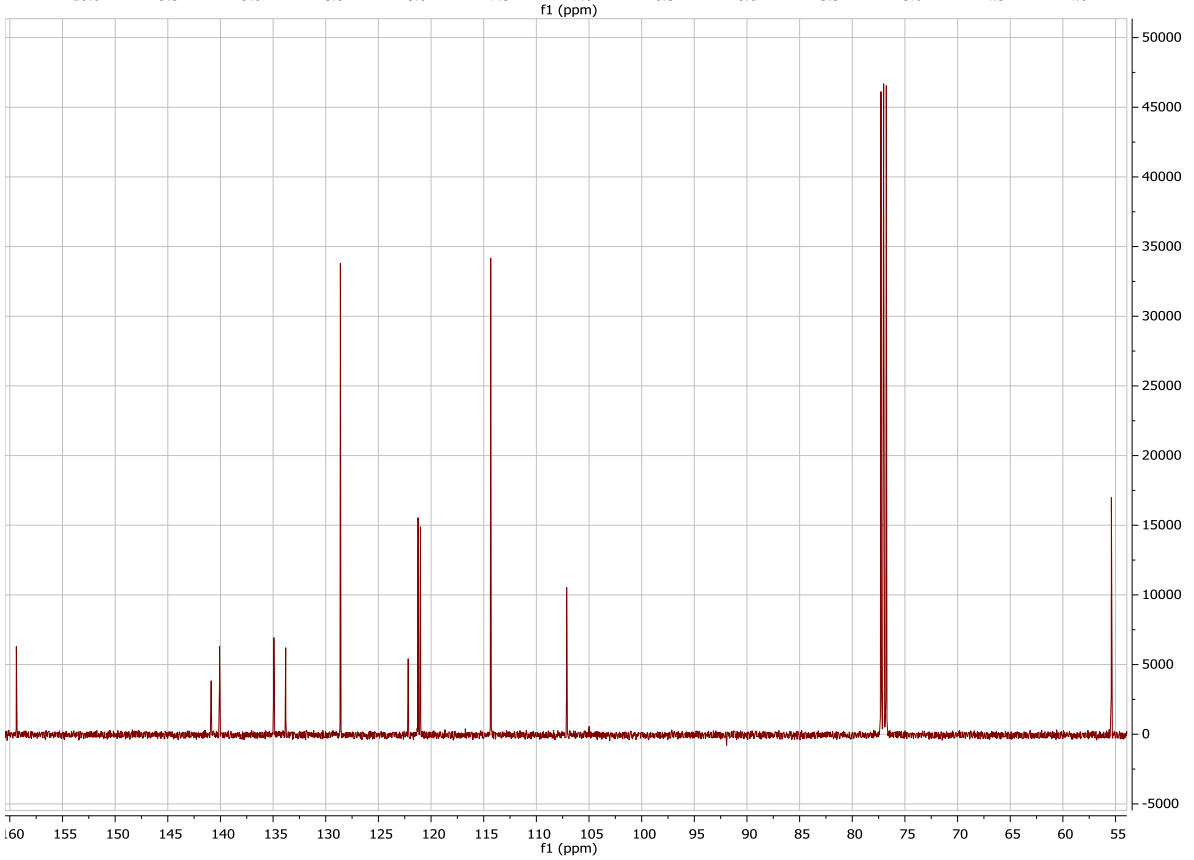

159.35
142.80
140.73
140.37
134.89
129.83
122.59
121.44
121.04
119.99
114.07
113.46
107.84
77.29 CDCl3
77.03 CDCl3
76.78 CDCl3
63.58
14.91
f1 (ppm)

Compound 11

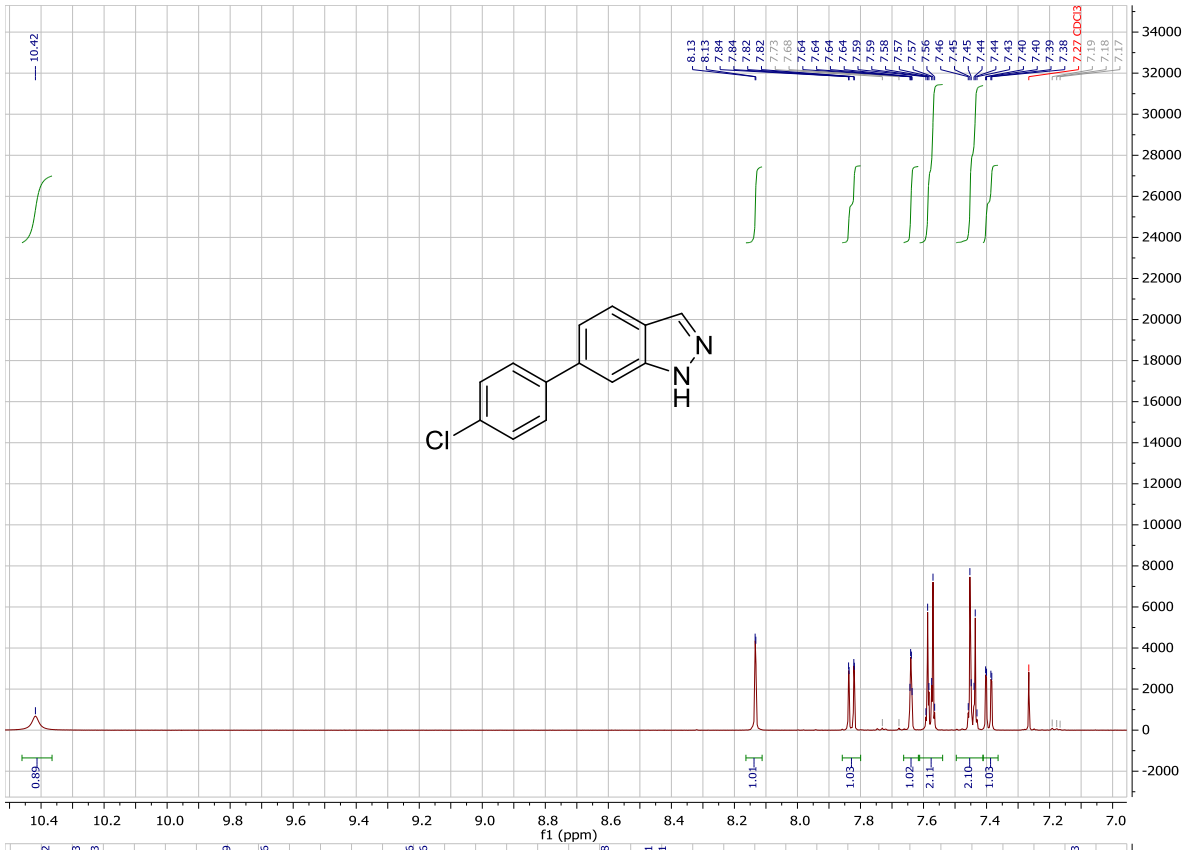

13.00
9.53
8.03
7.77
7.77
7.76
7.75
7.75
7.60
7.60
7.54
7.54
7.53
7.52
7.52
7.34
7.34
7.32
7.32
6.88
6.87
6.87
6.86
6.85
6.85
4.33
4.32
4.31
3.46
3.45
3.44
3.43
3.43
3.42
3.42
3.41
3.31 HDO
3.17
3.16
2.51
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
HO
N
N
H
0.85
1.02
1.00
1.07
1.05
2.13
1.05
2.11
0.15
f1 (ppm)
157.10
140.68
138.39
133.27
131.35
128.17
121.58
120.69
119.77
115.73
106.50
104.49
f1 (ppm)

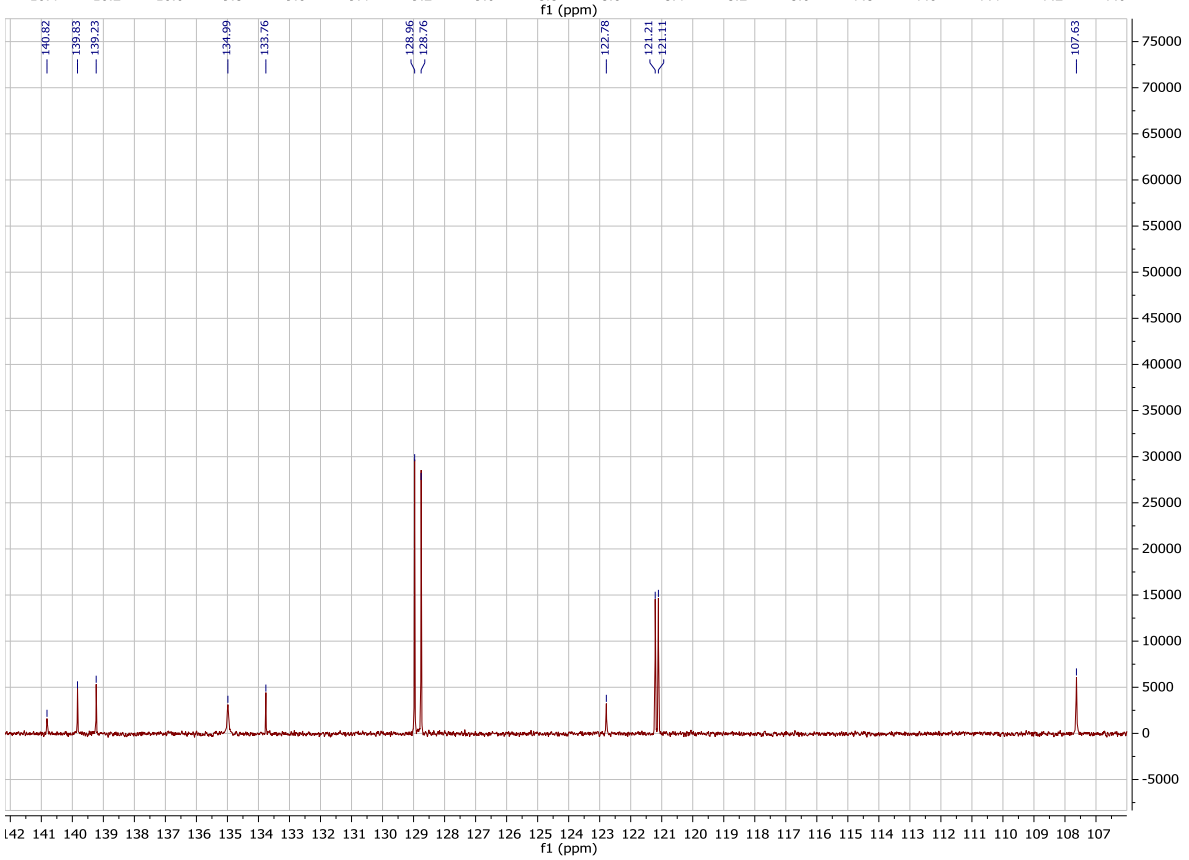
Compound 12


10.32
8.11
8.11
7.81
7.80
7.80
7.79
7.79
7.62
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.58
7.58
7.42
7.42
7.40
7.40
7.27 CDCl3
7.03
7.02
7.02
7.01
7.01
7.00
3.88
N
N
H
O
0.87
1.00
1.04
0.97
2.16
1.05
2.10
3.16
f1 (ppm)

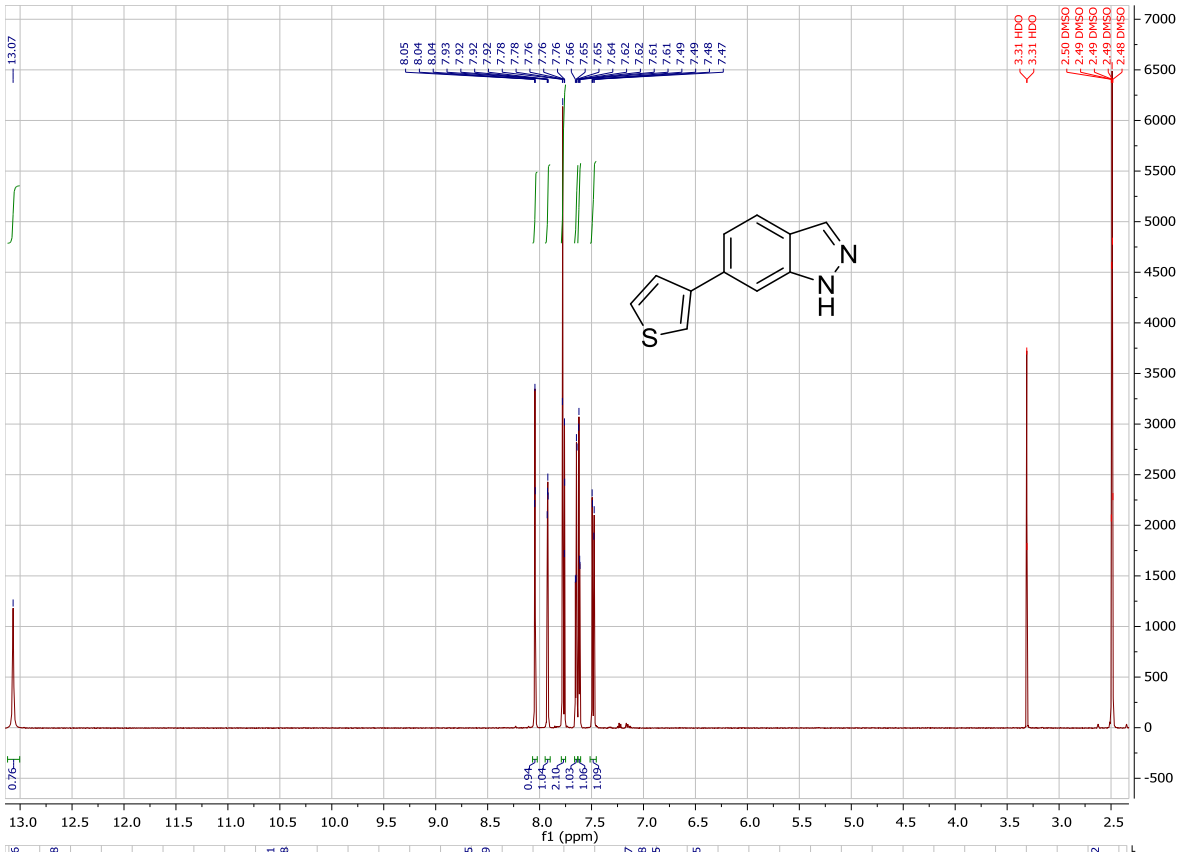

f1 (ppm)

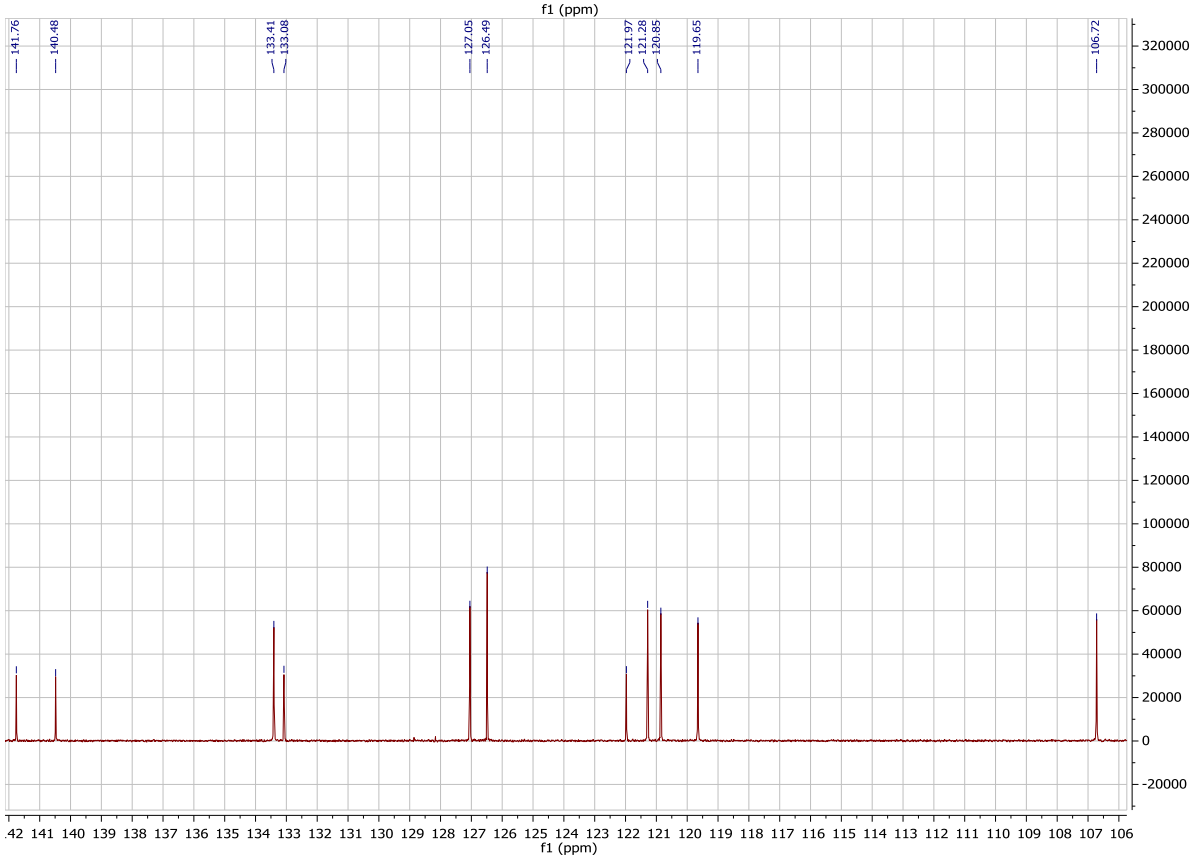
Compound 13


10.42
8.13
8.13
7.84
7.84
7.82
7.82
7.73
7.68
7.64
7.64
7.64
7.64
7.59
7.59
7.58
7.57
7.57
7.56
7.46
7.45
7.45
7.44
7.44
7.43
7.40
7.40
7.39
7.38
7.27 CDCl3
7.19
7.18
7.17
N
N
H
Cl
0.89
1.01
1.03
1.02
2.11
2.10
1.03
f1 (ppm)

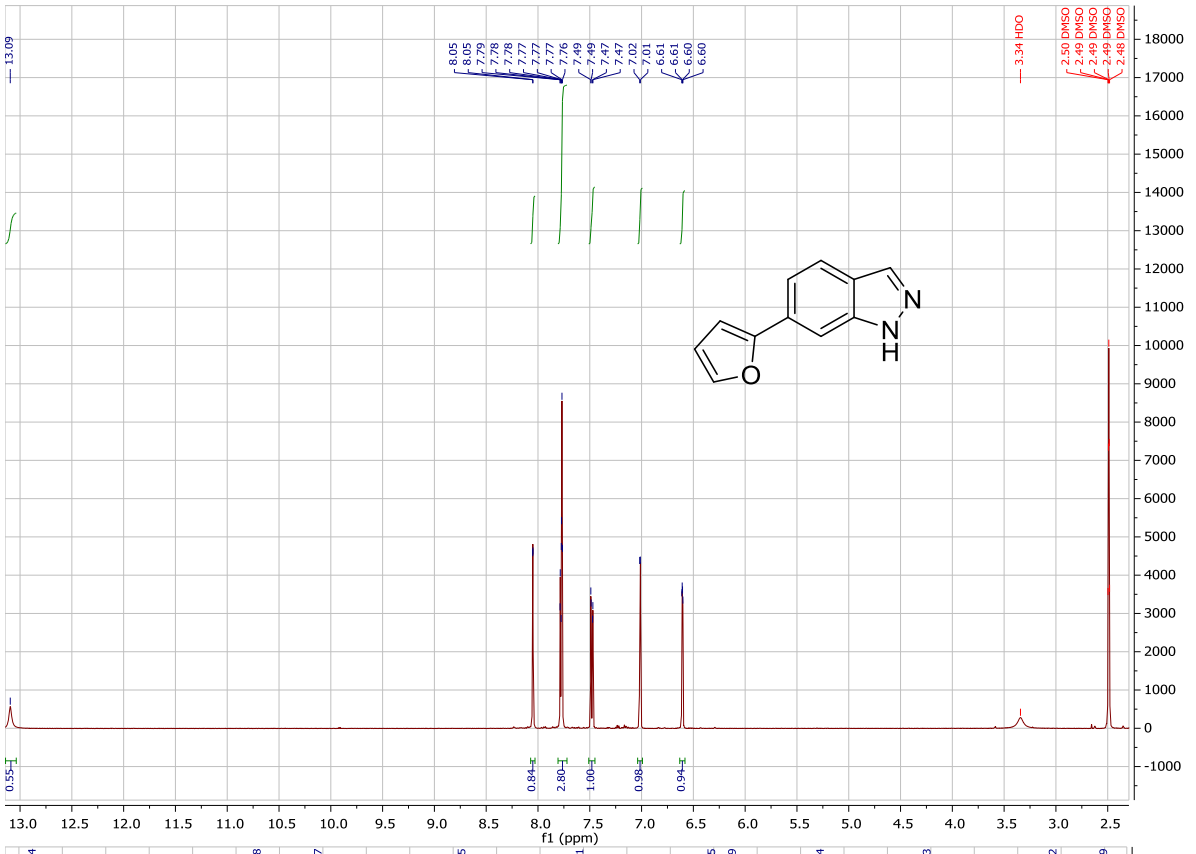

140.82
139.83
139.23
134.99
133.76
128.96
128.76
122.78
121.21
121.11
107.63
f1 (ppm)

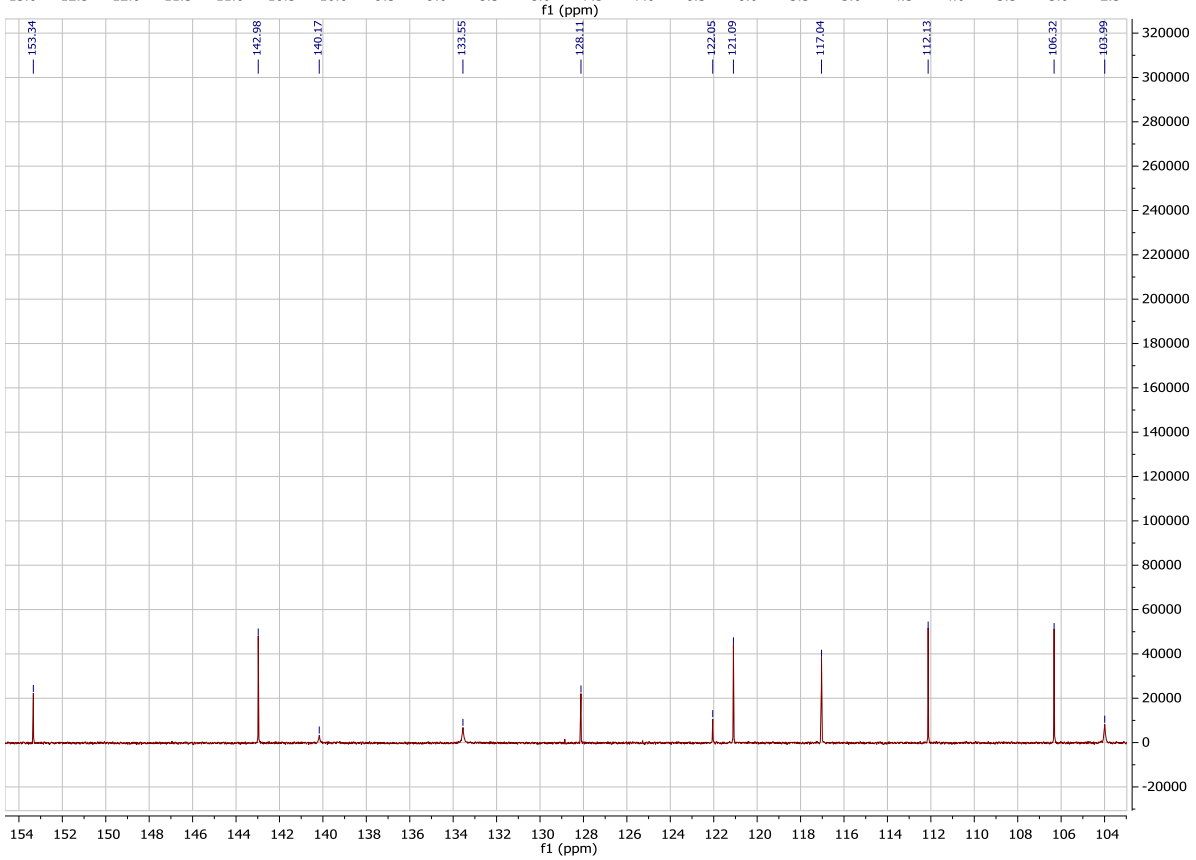
Compound 14


13.07
8.05
8.04
8.04
7.93
7.92
7.92
7.78
7.78
7.76
7.76
7.76
7.66
7.65
7.65
7.64
7.62
7.62
7.61
7.61
7.49
7.49
7.48
7.47
3.31 HDO
3.31 HDO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
0.76
0.94
1.04
2.10
1.03
1.06
1.09
N
N
H
S
f1 (ppm)

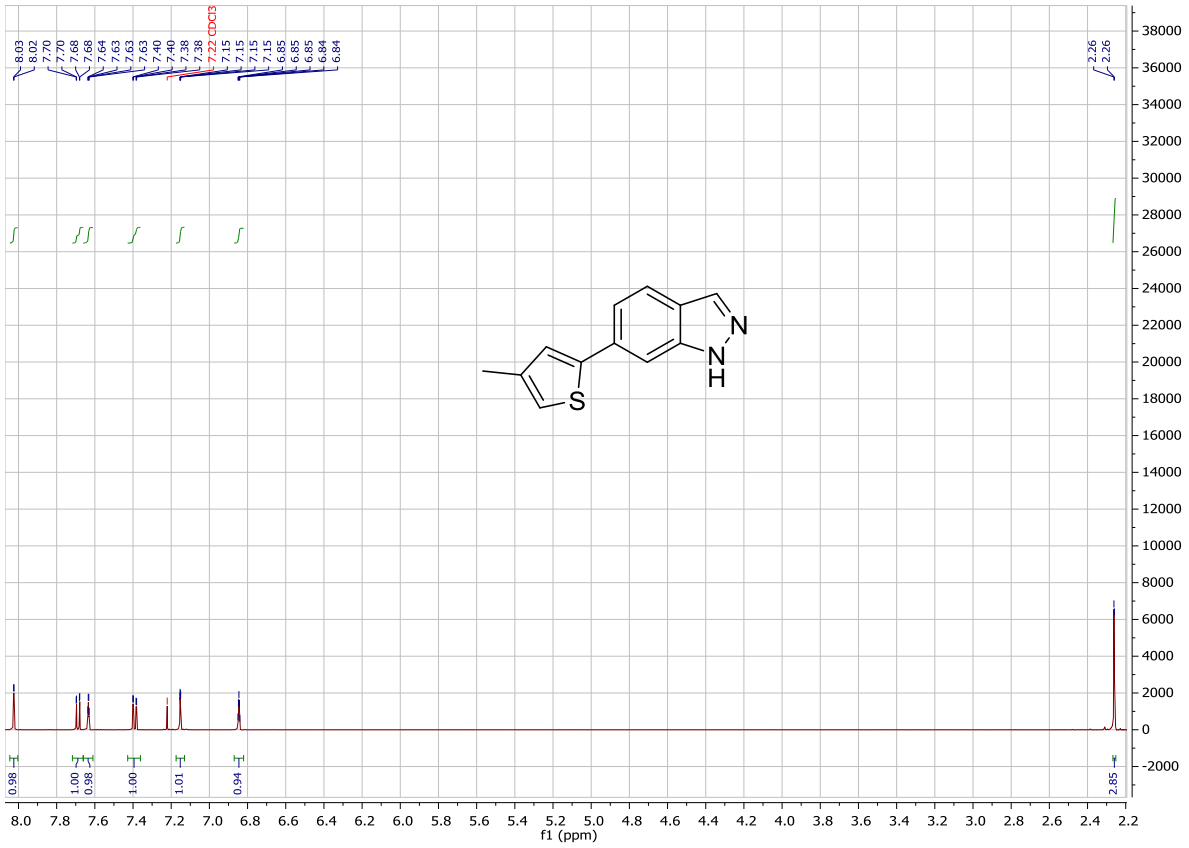

141.76
140.48
133.41
133.08
127.05
126.49
121.97
121.28
120.85
119.65
106.72
f1 (ppm)

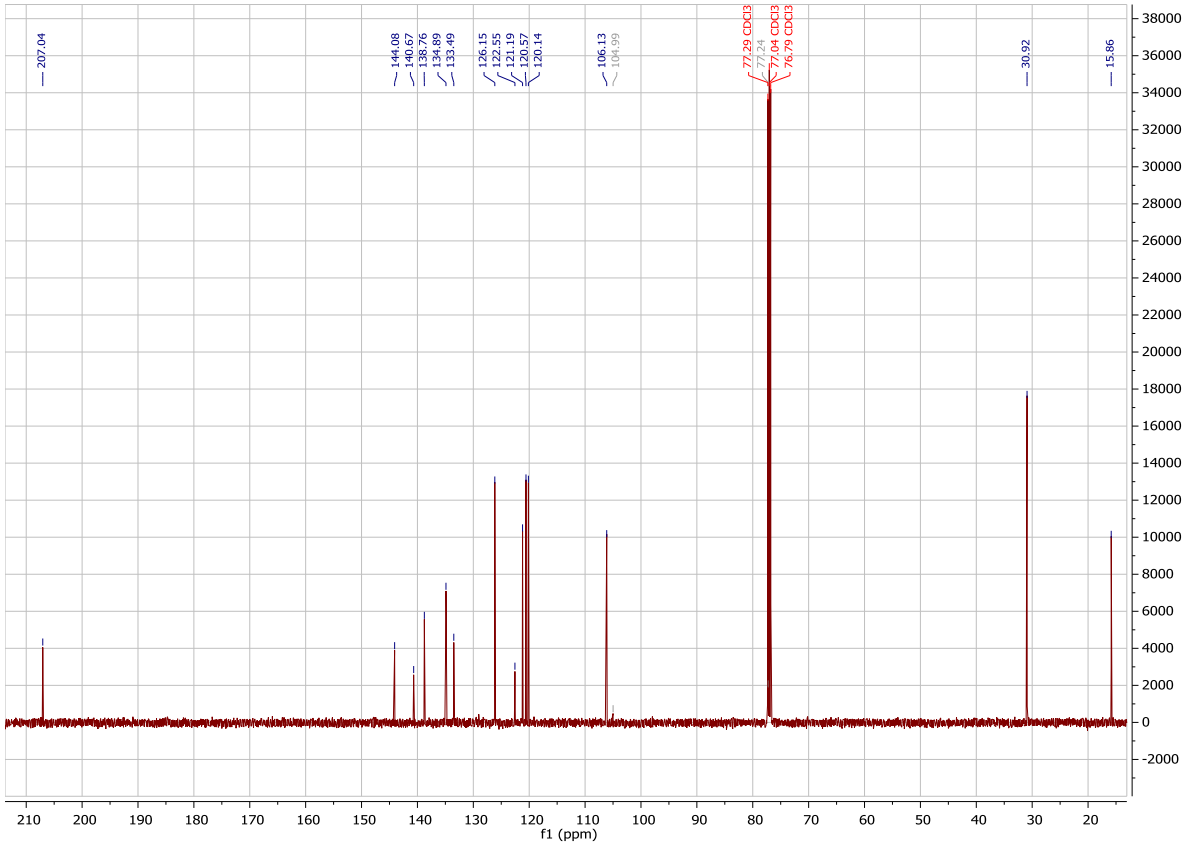
Compound 15


13.09
8.05
8.05
7.79
7.78
7.78
7.77
7.77
7.77
7.76
7.49
7.49
7.47
7.47
7.02
7.01
6.61
6.61
6.60
6.60
3.34 HDO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
0.55
0.84
2.80
1.00
0.98
0.94
N
N
H
O
f1 (ppm)

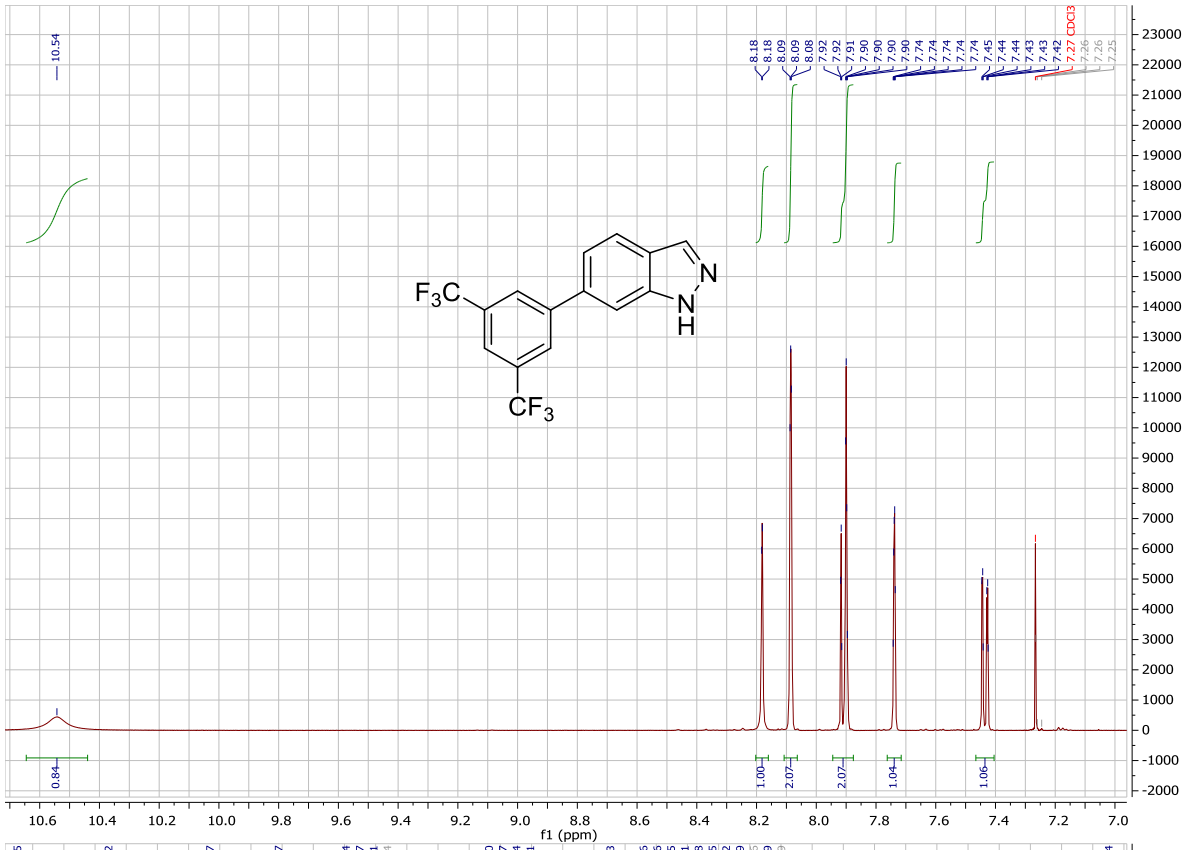

153.34
142.98
140.17
133.55
128.11
122.05
121.09
117.04
112.13
106.32
103.99
f1 (ppm)

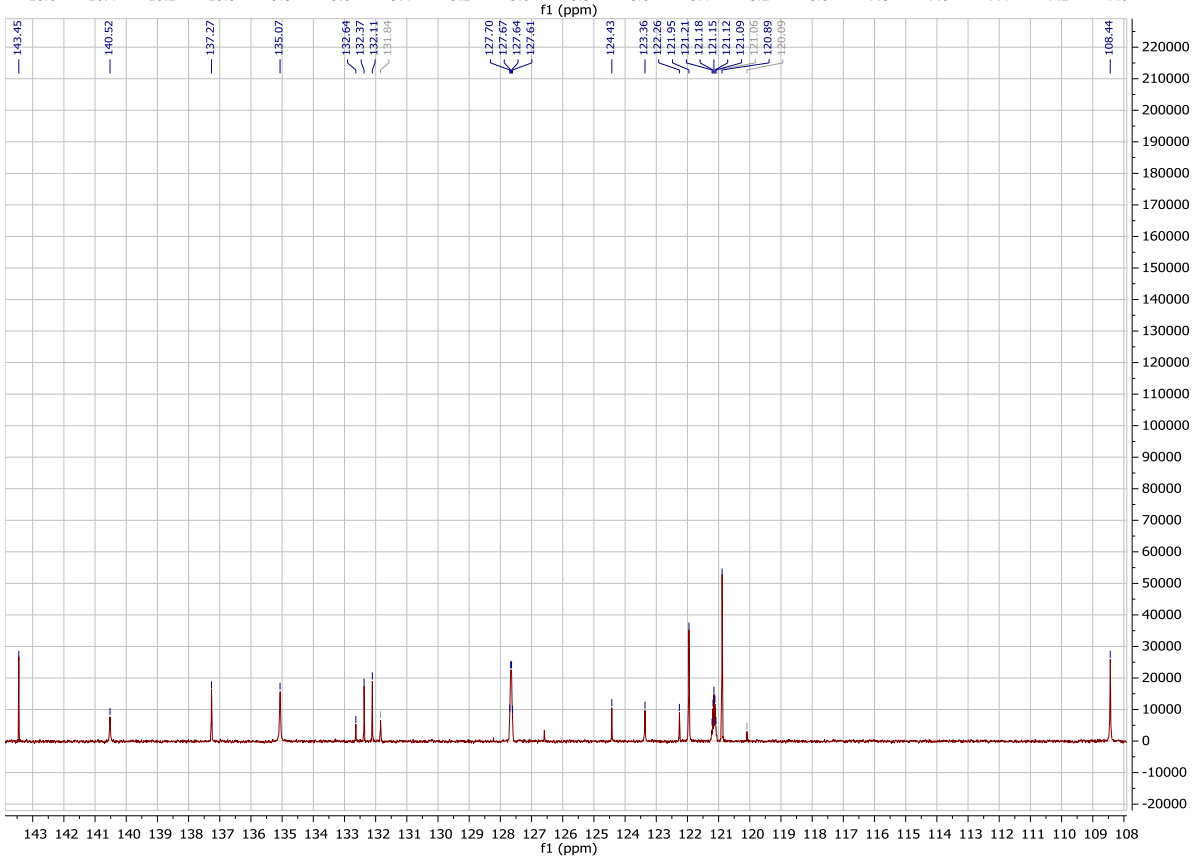
Compound 16


8.03
8.02
7.70
7.70
7.68
7.68
7.64
7.63
7.63
7.63
7.40
7.40
7.38
7.38
7.22 CDCl3
7.15
7.15
7.15
6.85
6.85
6.85
6.84
6.84
2.26
2.26
N
N
H
S
0.98
1.00
0.98
1.00
1.01
0.94
2.85
f1 (ppm)

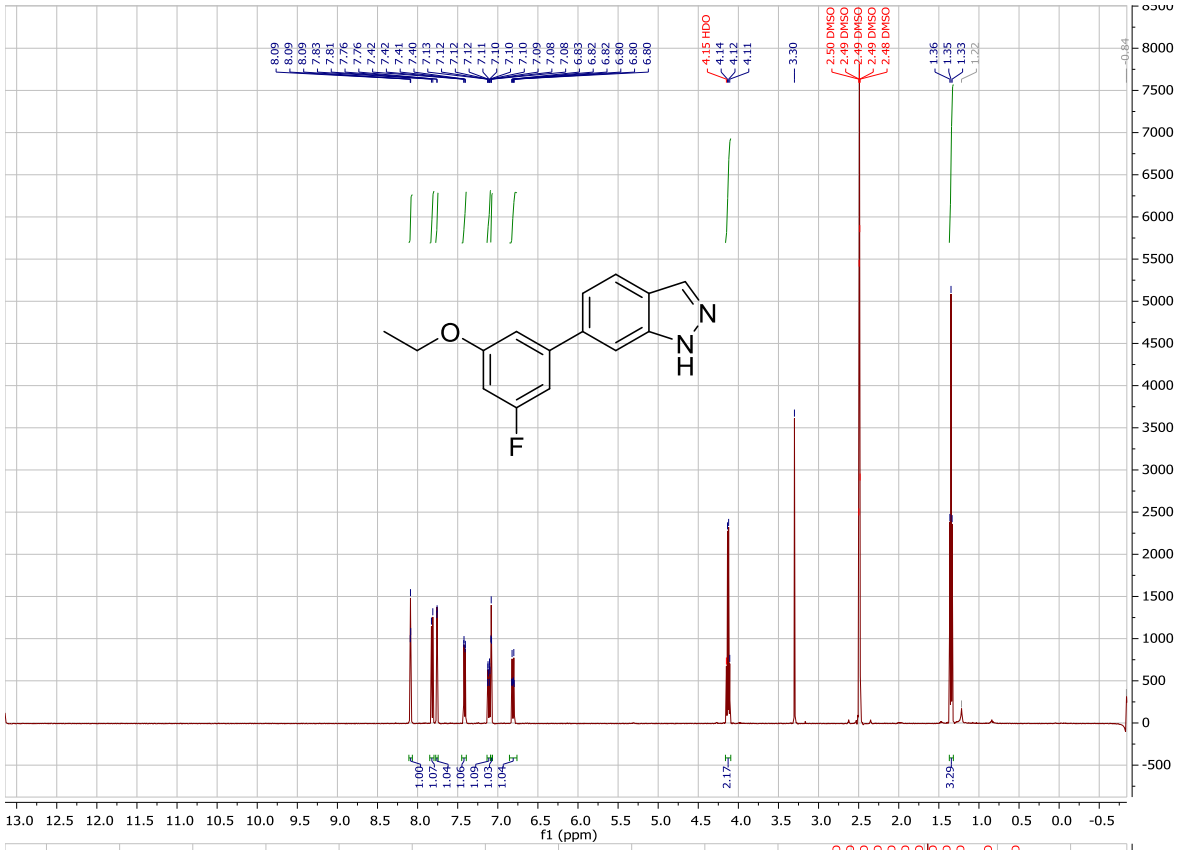

207.04
144.08
140.67
138.76
134.89
133.49
126.15
122.55
121.19
120.57
120.14
106.13
104.99
77.29 CDCl3
77.24
77.04 CDCl3
76.79 CDCl3
30.92
15.86
f1 (ppm)

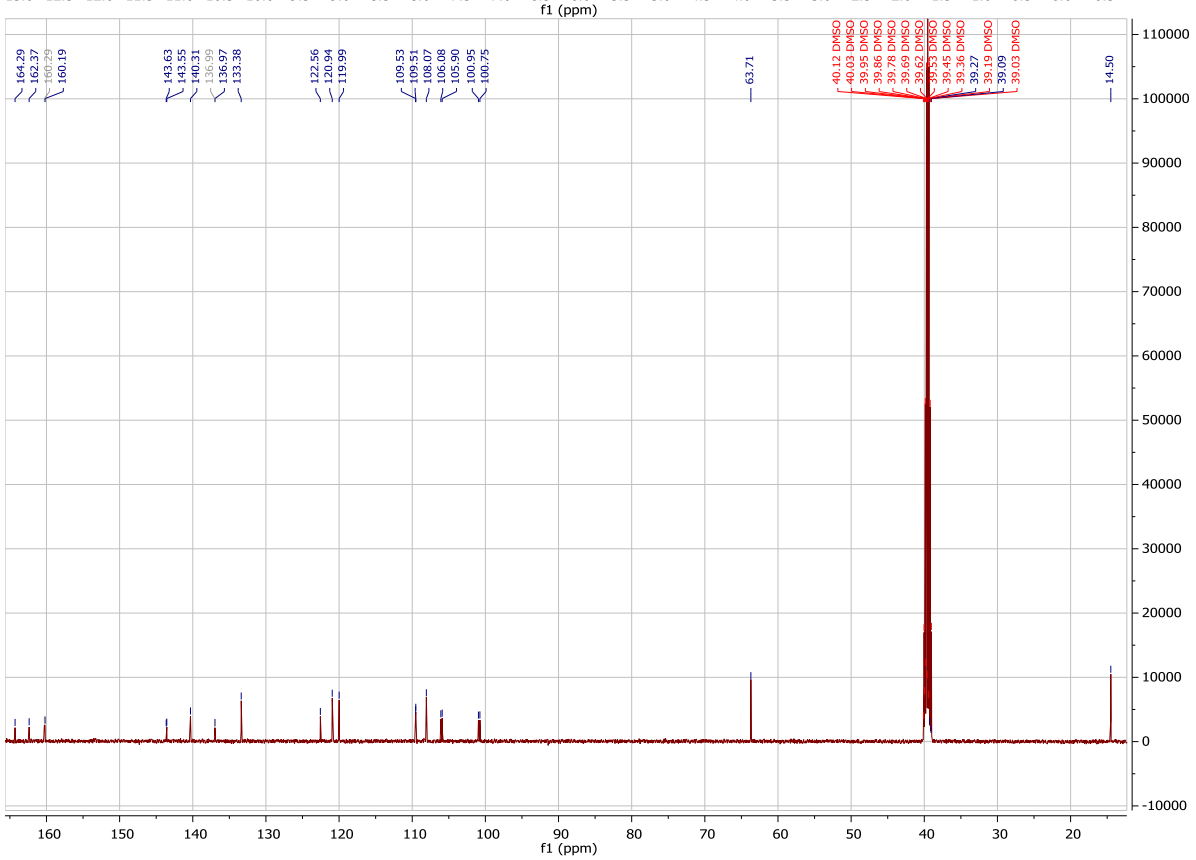
Compound 17


10.54
8.18
8.18
8.09
8.09
8.08
7.92
7.92
7.91
7.90
7.90
7.90
7.90
7.74
7.74
7.74
7.74
7.74
7.45
7.44
7.44
7.43
7.43
7.42
7.27 CDCl3
7.26
7.26
7.25
F3C
CF3
N
N
H
0.84
1.00
2.07
2.07
1.04
1.06
f1 (ppm)

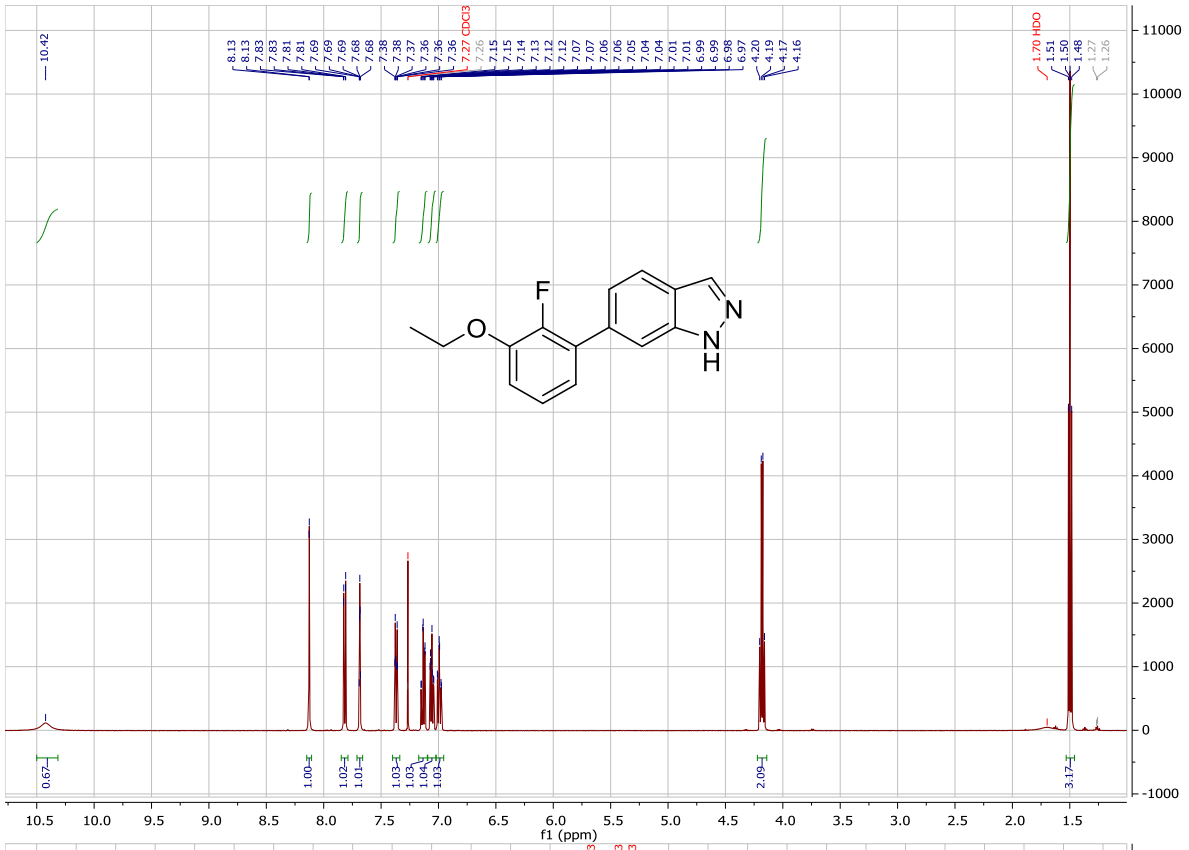

143.45
140.52
137.27
135.07
132.64
132.37
132.11
131.84
127.70
127.67
127.64
127.61
124.43
123.36
122.26
121.95
121.71
121.18
121.15
121.12
121.09
121.05
120.89
120.69
108.44
f1 (ppm)

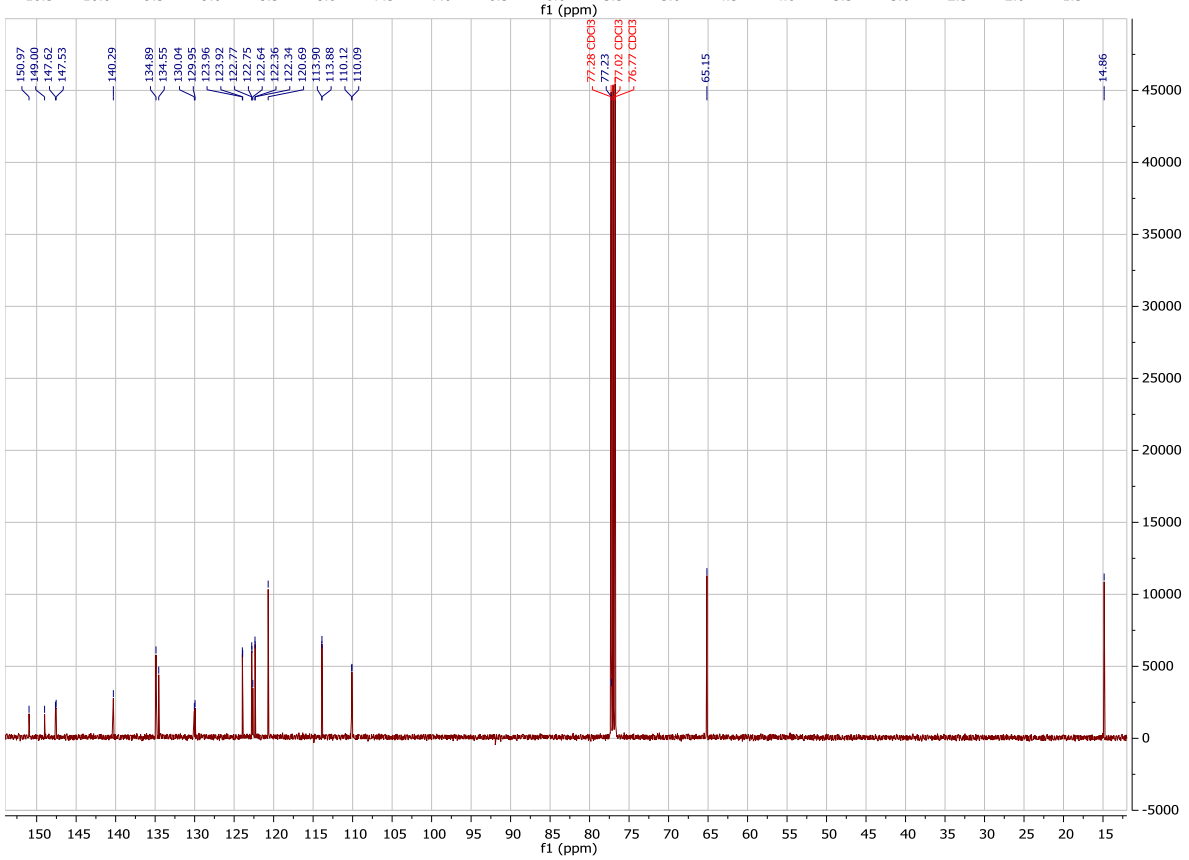
Compound 18


8.09
8.09
8.09
7.83
7.81
7.76
7.76
7.42
7.42
7.41
7.40
7.13
7.12
7.12
7.12
7.11
7.10
7.10
7.10
7.09
7.08
7.08
6.83
6.82
6.82
6.80
6.80
6.80
4.15 HDO
4.14
4.12
4.11
3.30
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
1.36
1.35
1.33
1.22
0.84
O
N
N
H
F
1.00
1.07
1.04
1.06
1.09
1.03
1.04
2.17
3.29
f1 (ppm)

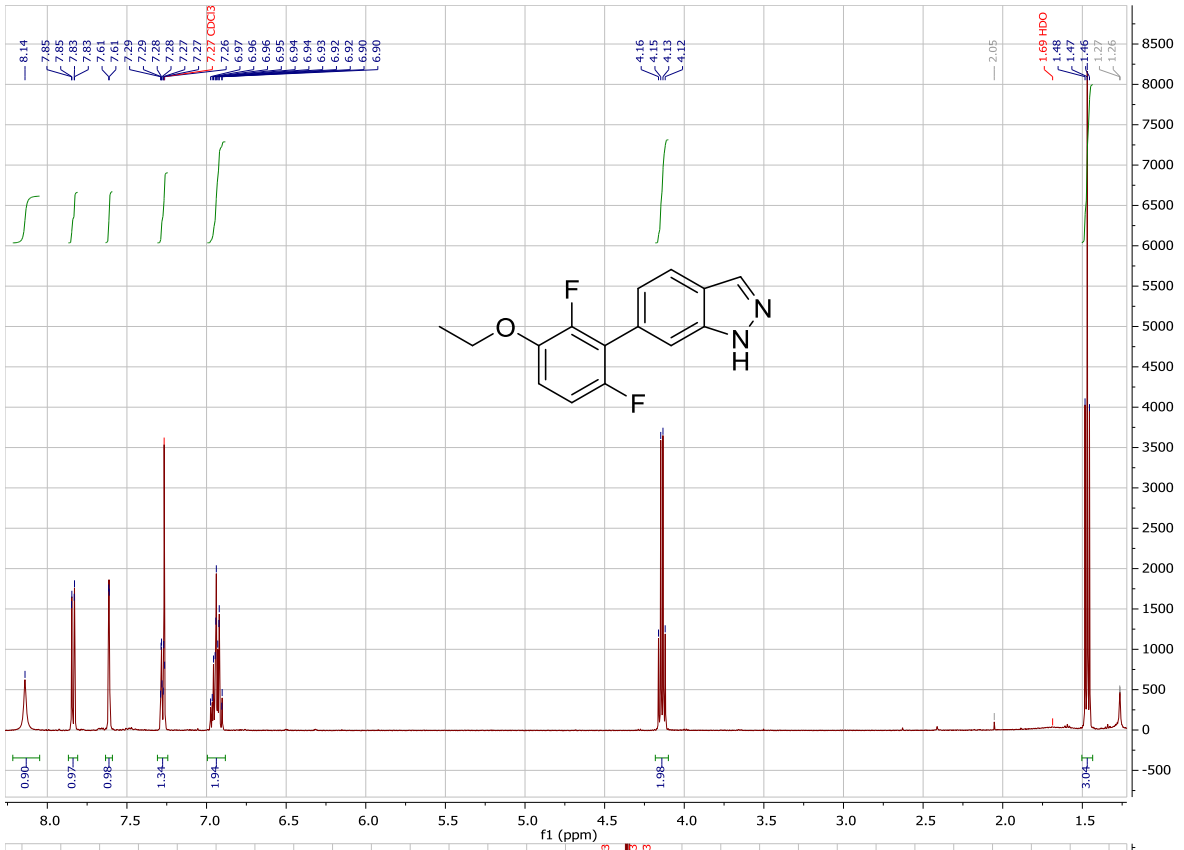

164.29
162.37
160.29
160.19
143.63
143.55
140.31
136.99
136.97
133.38
122.56
120.94
119.99
109.53
109.51
108.07
106.08
105.90
100.95
100.75
63.71
40.12 DMSO
40.03 DMSO
39.95 DMSO
39.86 DMSO
39.78 DMSO
39.69 DMSO
39.62 DMSO
39.53 DMSO
39.45 DMSO
39.36 DMSO
39.27
39.19 DMSO
39.09
39.03 DMSO
14.50
f1 (ppm)

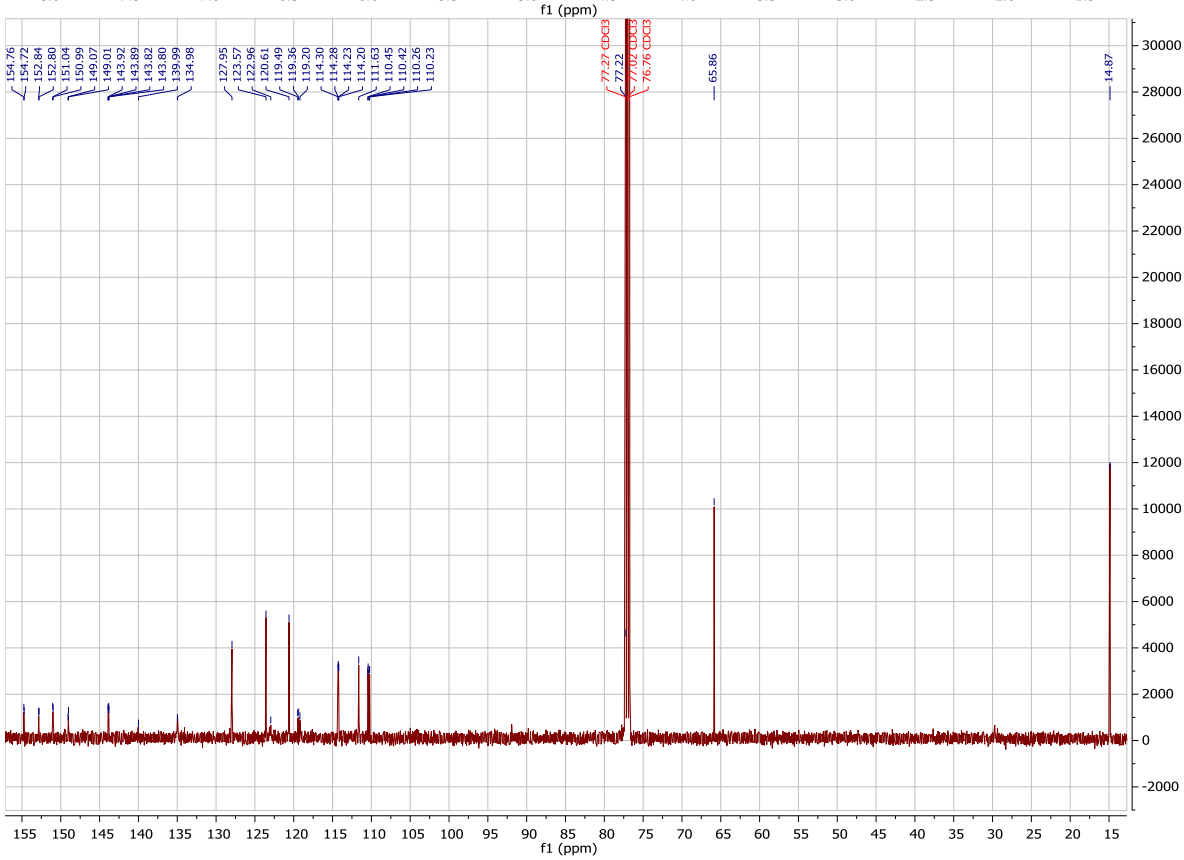
Compound 19



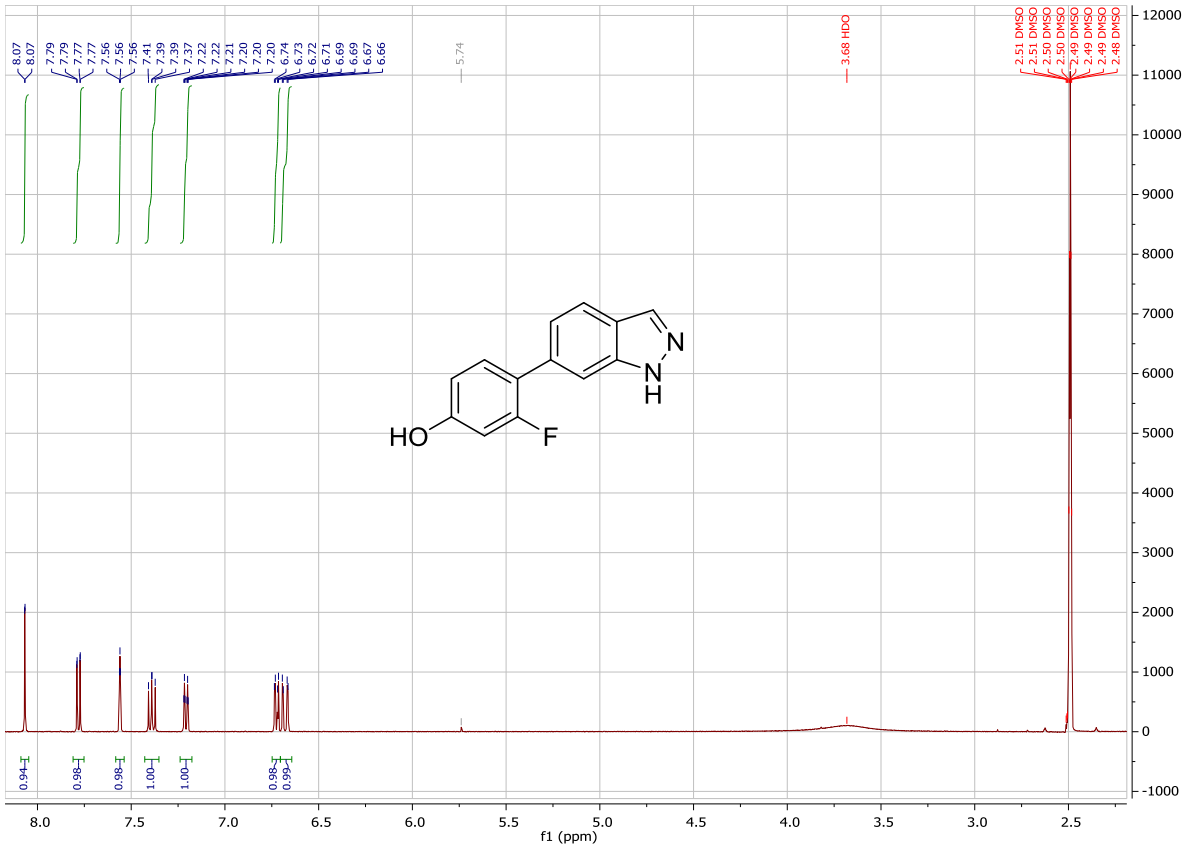


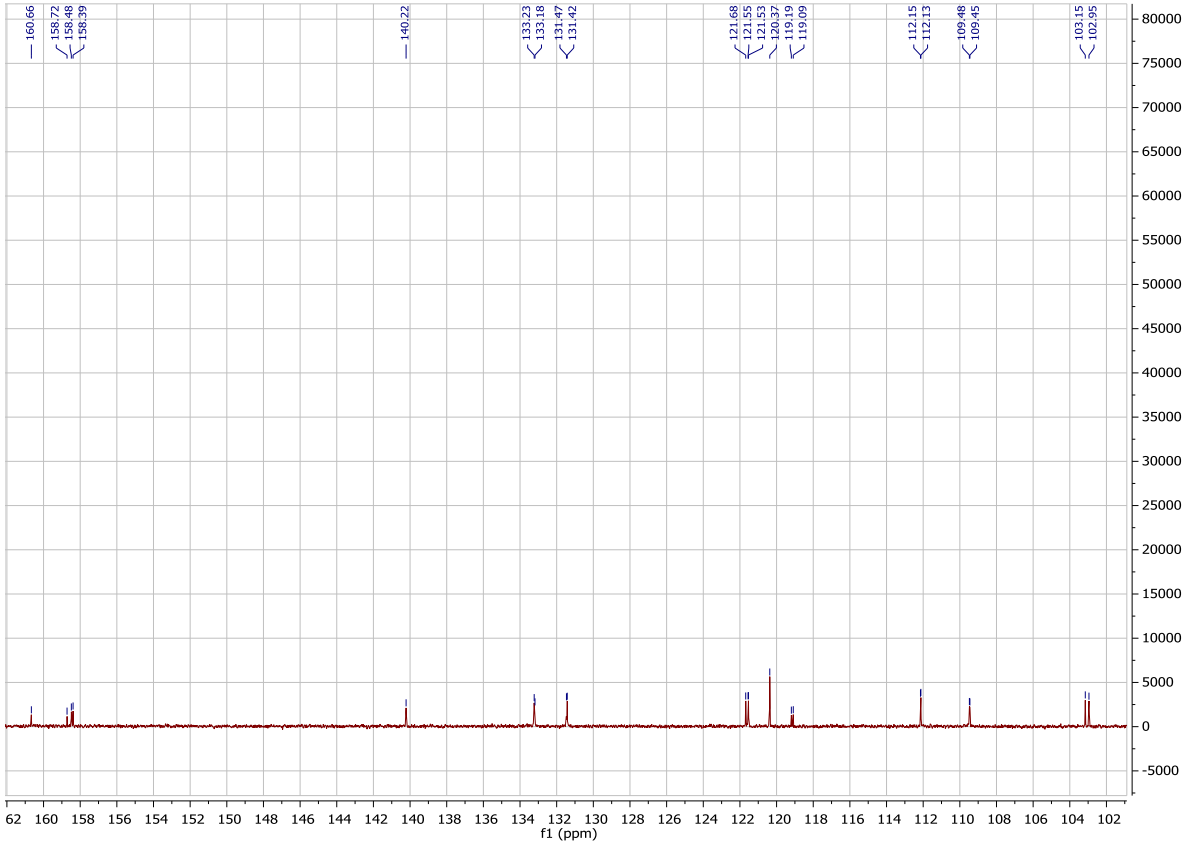
Compound 20



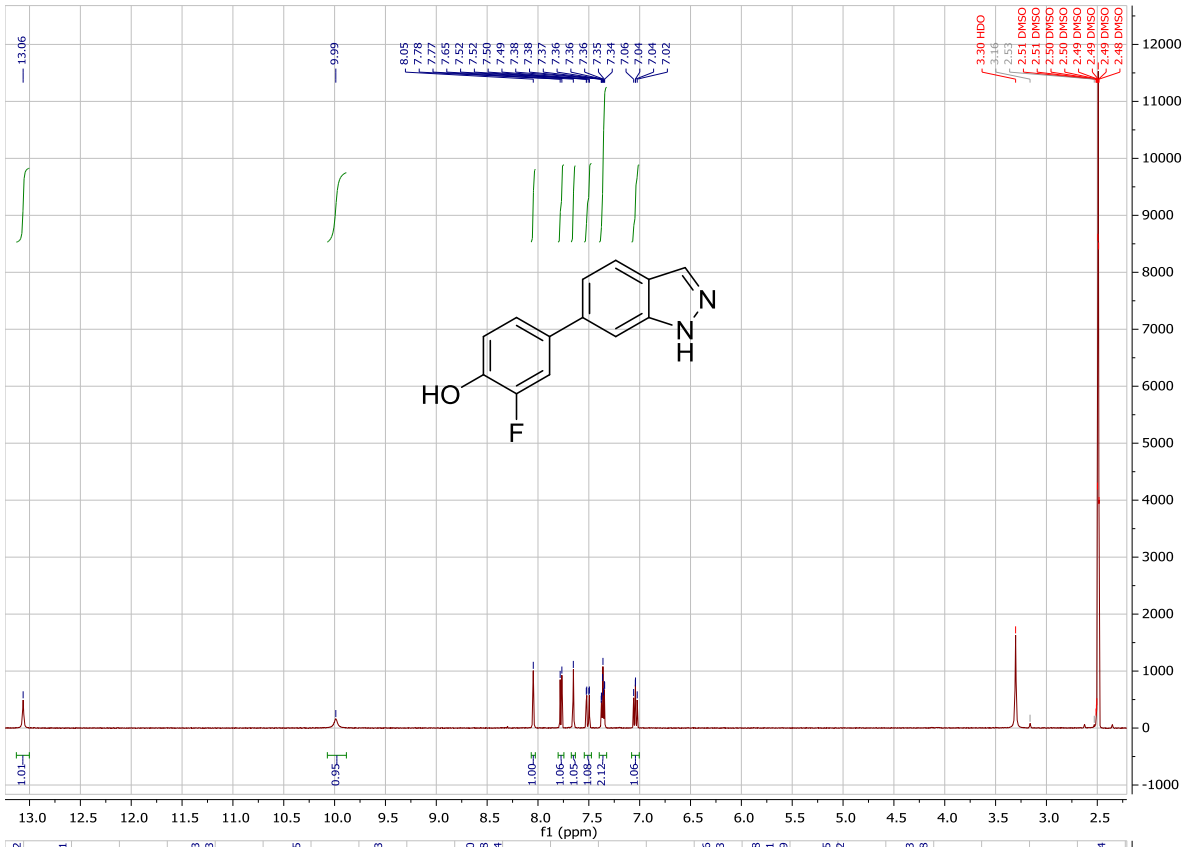


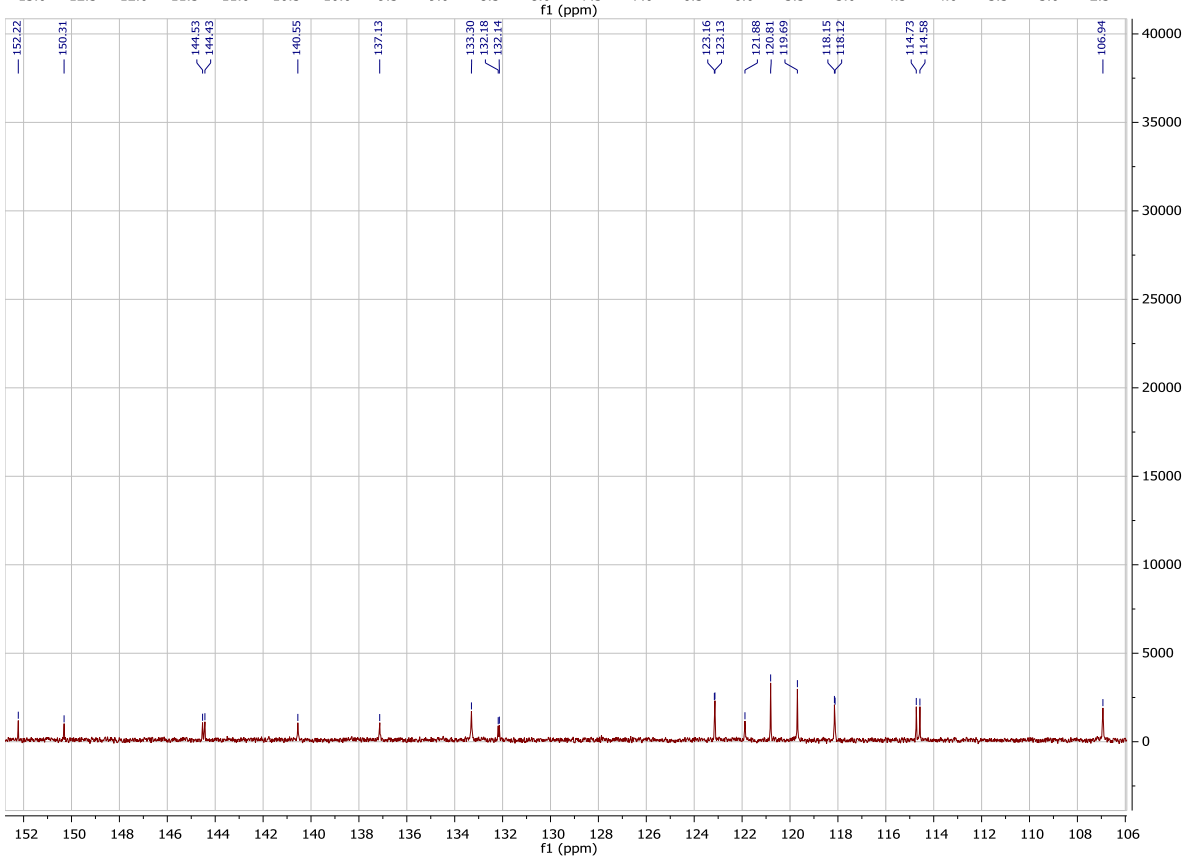
Compound 21


8.07
8.07
7.79
7.79
7.77
7.77
7.56
7.56
7.56
7.41
7.39
7.39
7.37
7.22
7.22
7.21
7.20
7.20
7.20
6.74
6.73
6.72
6.71
6.69
6.69
6.67
6.66
5.74
3.68 HDO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
HO
F
N
N
H
0.94
0.98
0.98
1.00
1.00
0.98
0.99
f1 (ppm)

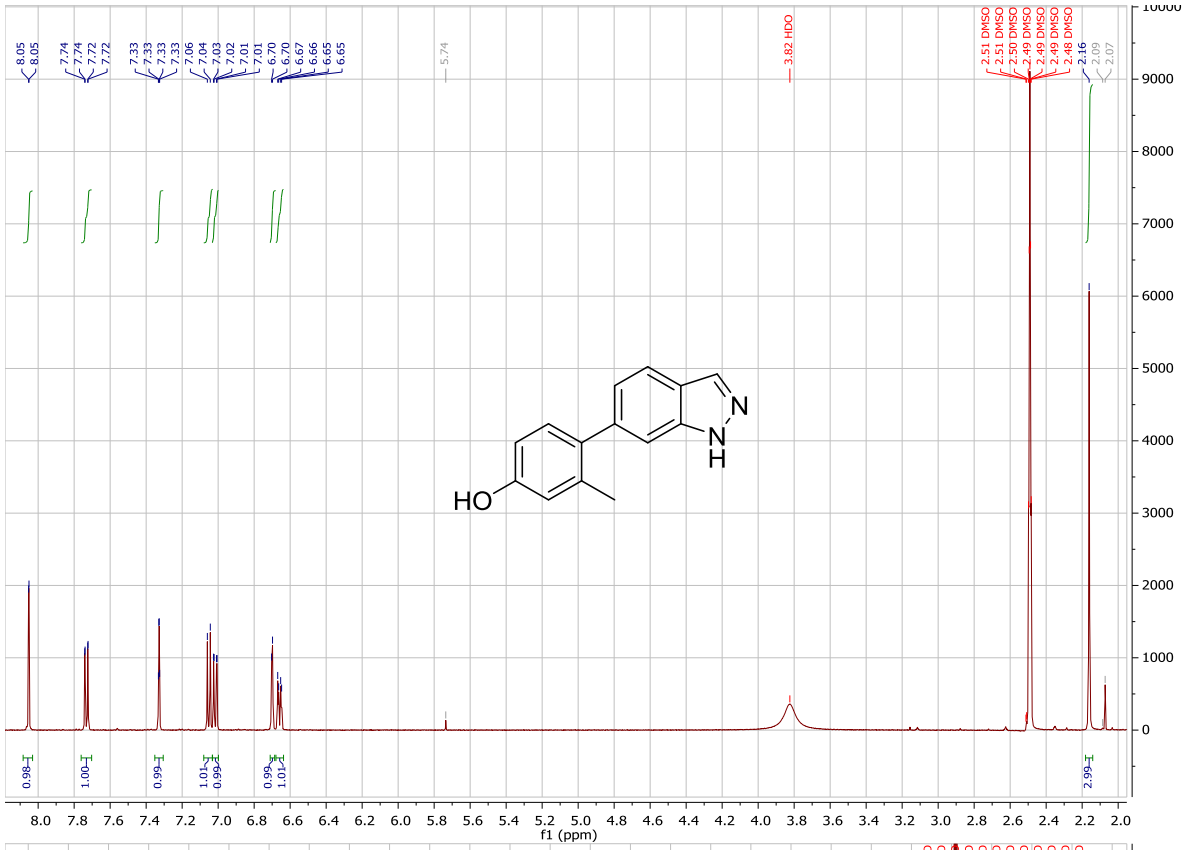

160.66
158.72
158.48
158.39
140.22
133.23
133.18
131.47
131.42
121.68
121.55
121.53
120.37
119.19
119.09
112.15
112.13
109.48
109.45
103.15
102.95
f1 (ppm)

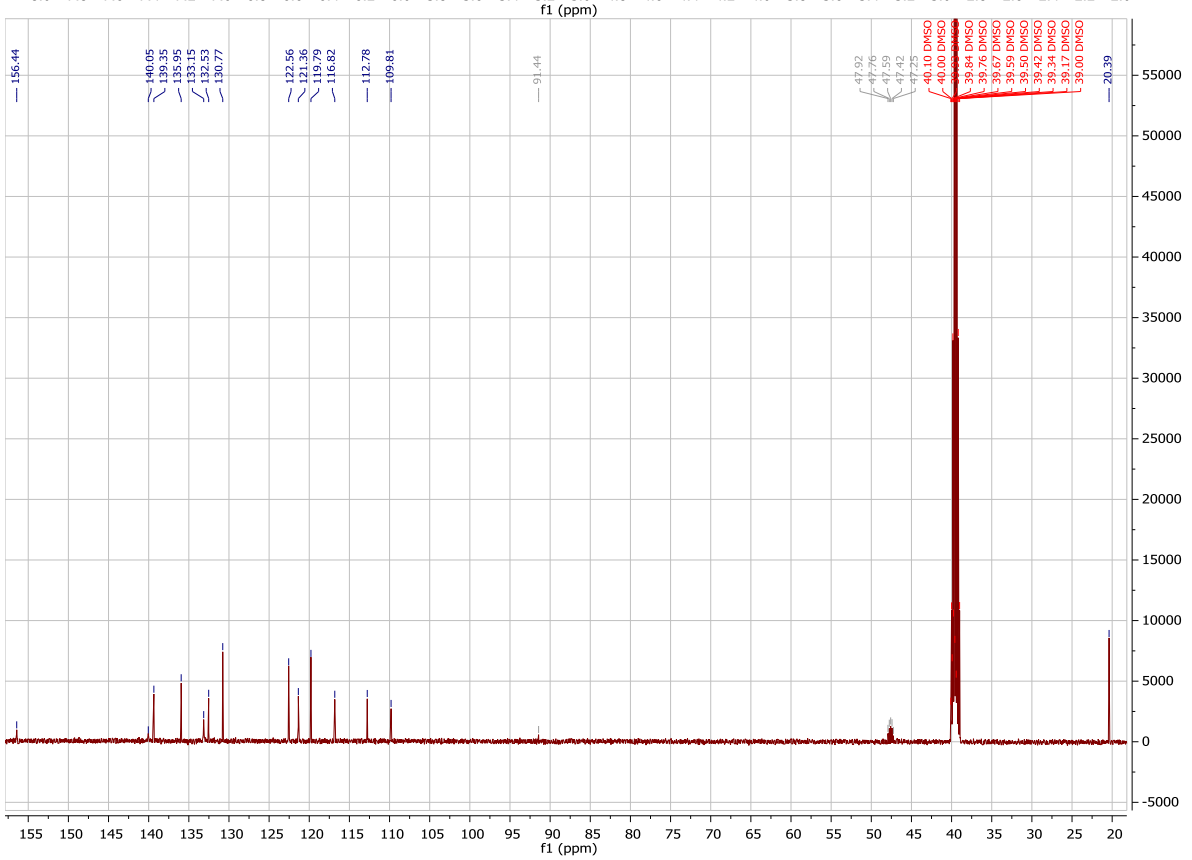
Compound 22


13.06
9.99
8.05
7.78
7.77
7.65
7.52
7.52
7.50
7.49
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.06
7.04
7.04
7.02
3.30 HDO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
1.01
0.95
1.00
1.06
1.05
1.08
2.12
1.06
HO
F
N
N
H
f1 (ppm)

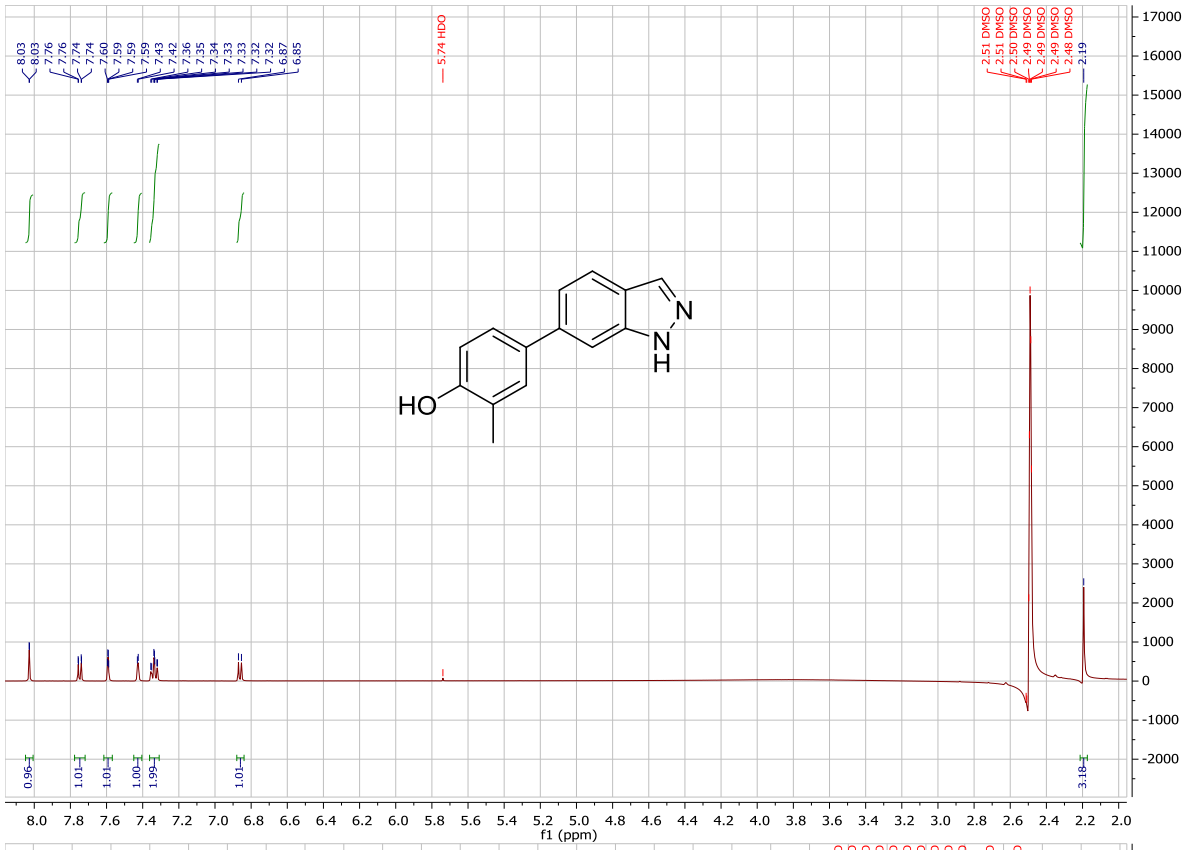

152.22
150.31
144.53
144.43
140.55
137.13
133.30
132.18
132.14
123.16
123.13
121.88
120.81
119.69
118.15
118.12
114.73
114.58
106.94
f1 (ppm)

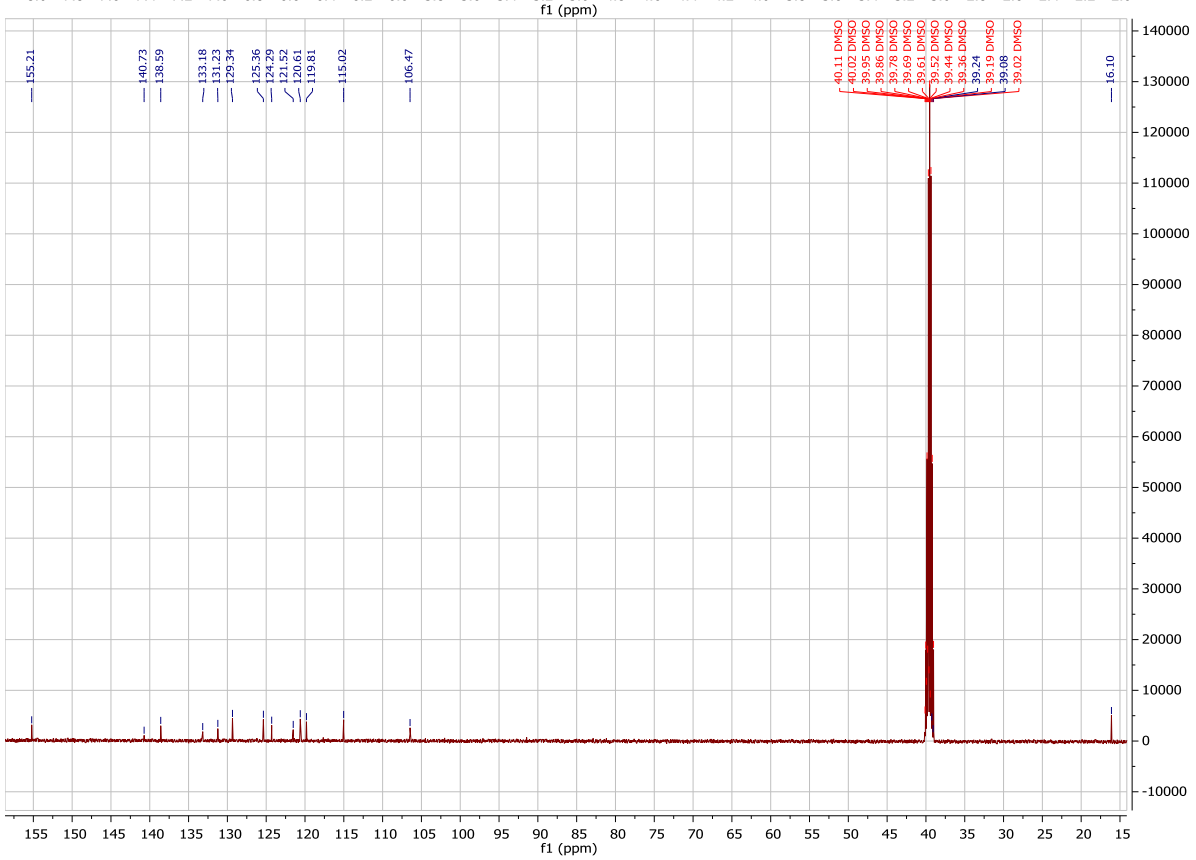
Compound 23


8.05
8.05
7.74
7.74
7.72
7.72
7.33
7.33
7.33
7.33
7.06
7.04
7.03
7.02
7.01
7.01
6.70
6.70
6.67
6.66
6.65
6.65
5.74
3.82 HDO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
2.16
2.09
2.07
HO
N
N
H
0.98
1.00
0.99
1.01
0.99
0.99
1.01
2.99
f1 (ppm)

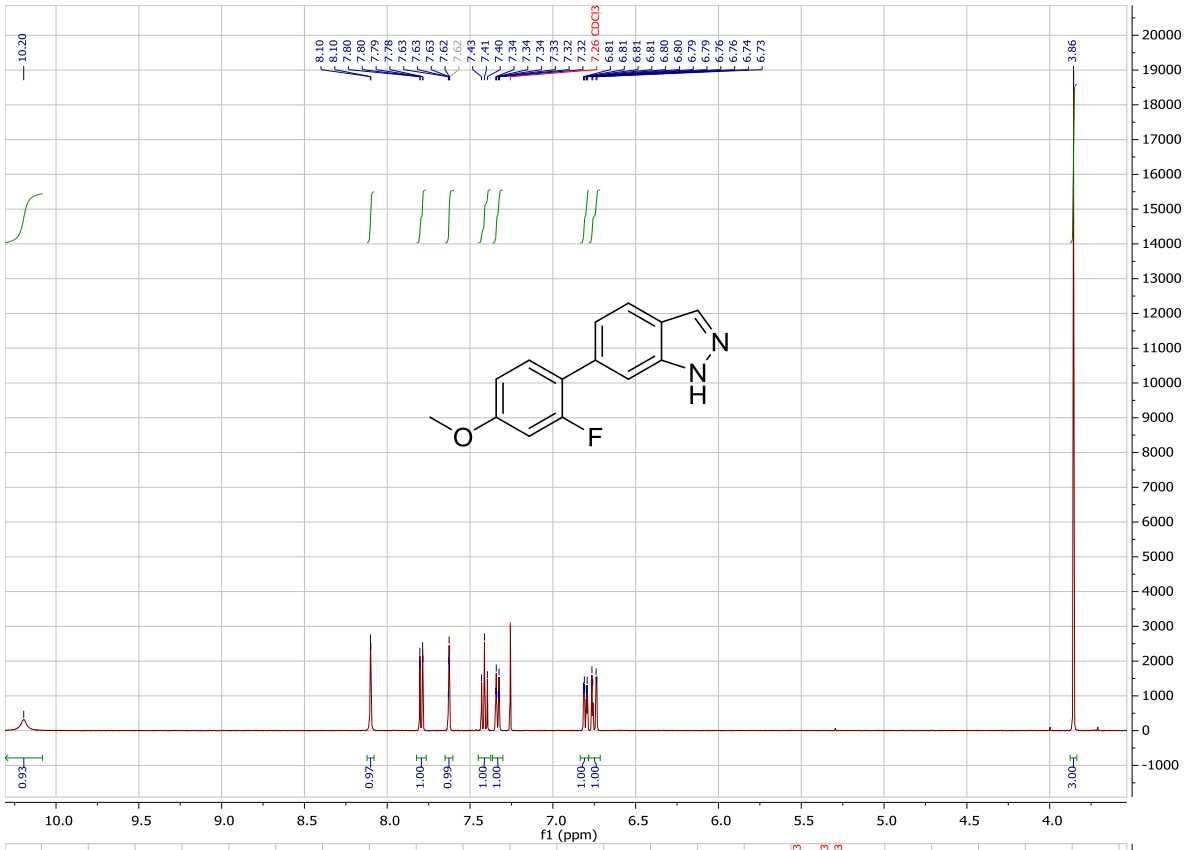

156.44
140.05
139.35
135.95
133.15
132.53
130.77
122.56
121.36
119.79
116.82
112.78
109.81
91.44
47.92
47.76
47.59
47.42
47.25
40.10 DMSO
40.00 DMSO
39.84 DMSO
39.76 DMSO
39.67 DMSO
39.59 DMSO
39.50 DMSO
39.42 DMSO
39.34 DMSO
39.17 DMSO
39.00 DMSO
20.39
f1 (ppm)

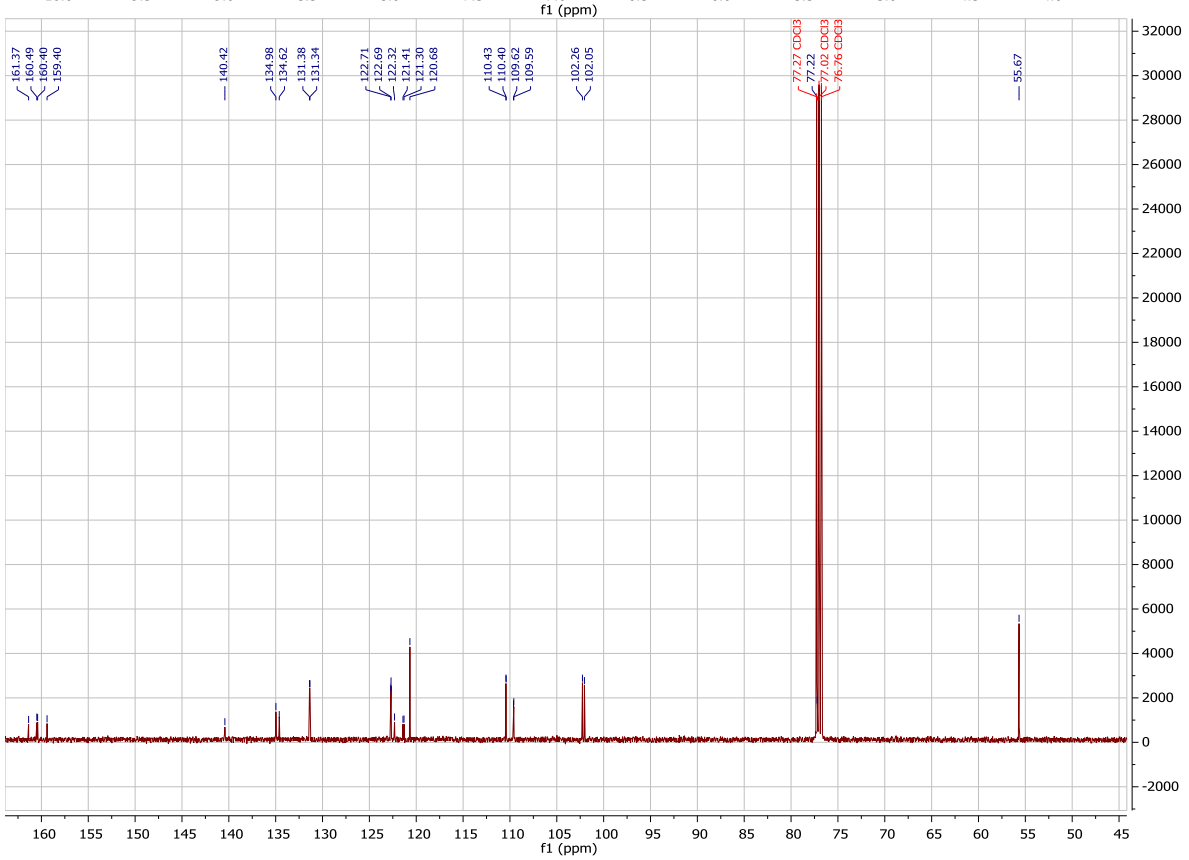
Compound 24


8.03
8.03
7.76
7.76
7.74
7.74
7.60
7.59
7.59
7.59
7.43
7.42
7.36
7.35
7.34
7.33
7.33
7.32
7.32
6.87
6.85
5.74 HDO
2.51 DMSO
2.51 DMSO
2.50 DMSO
2.49 DMSO
2.49 DMSO
2.49 DMSO
2.48 DMSO
2.19
HO
N
N
H
0.96
1.01
1.01
1.00
1.99
1.01
3.18
f1 (ppm)

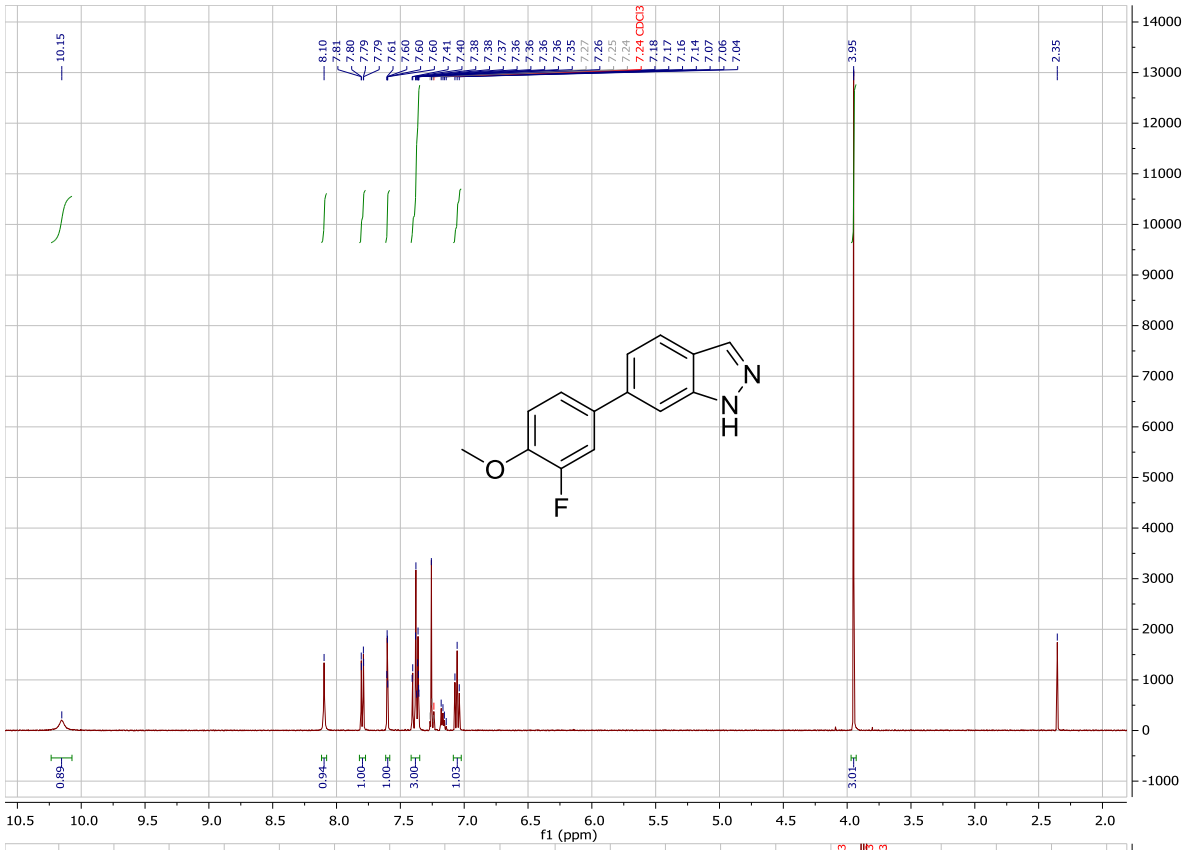

155.21
140.73
138.59
133.18
131.23
129.34
125.36
124.29
121.52
120.61
119.81
115.02
106.47
40.11 DMSO
40.02 DMSO
39.95 DMSO
39.86 DMSO
39.78 DMSO
39.69 DMSO
39.61 DMSO
39.52 DMSO
39.44 DMSO
39.36 DMSO
39.24
39.19 DMSO
39.08
39.02 DMSO
16.10
f1 (ppm)

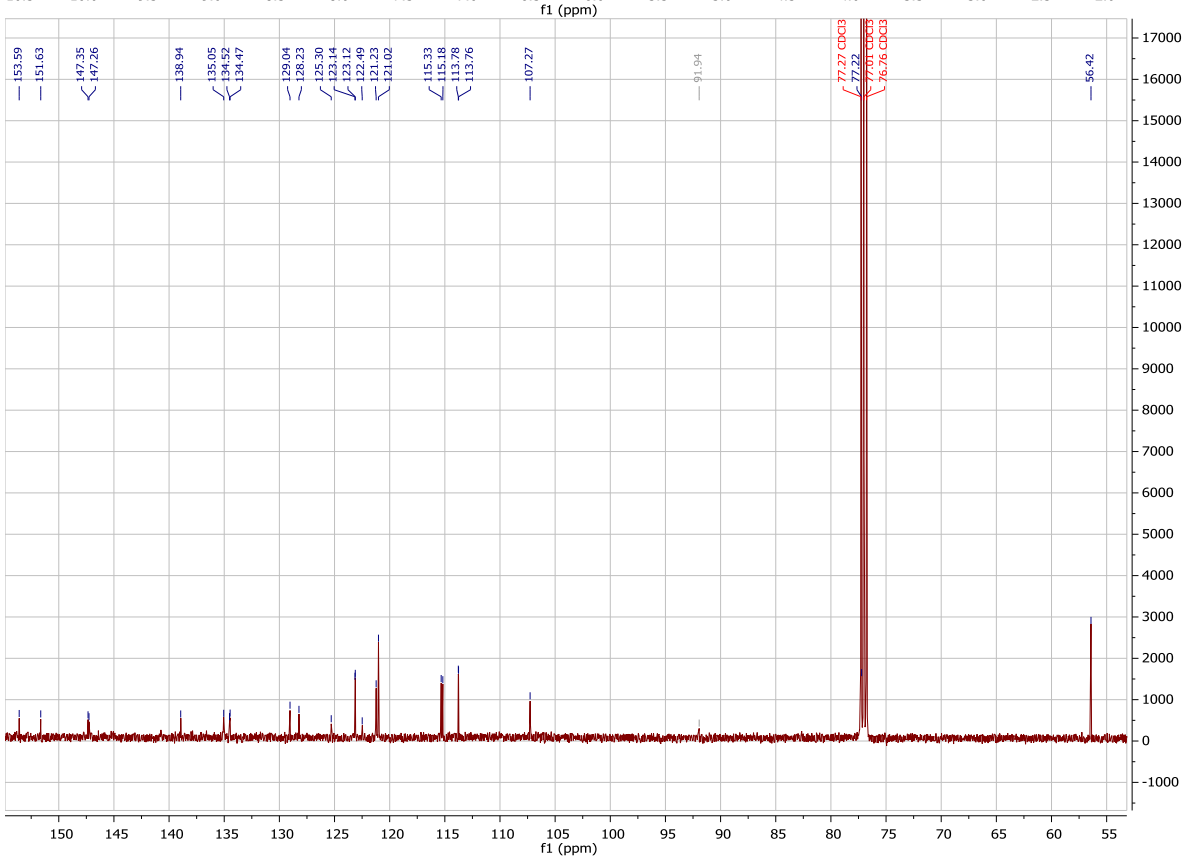
Compound 25


10.20
8.10
8.10
7.80
7.80
7.79
7.78
7.63
7.63
7.63
7.62
7.62
7.43
7.41
7.40
7.34
7.34
7.34
7.33
7.32
7.26 CDCl3
6.81
6.81
6.81
6.81
6.80
6.80
6.79
6.79
6.76
6.76
6.74
6.73
3.86
N
N
H
O
F
0.93
0.97
1.00
0.99
1.00
1.00
1.00
1.00
3.00
f1 (ppm)


161.37
160.49
160.40
159.40
140.42
134.98
134.62
131.38
131.34
122.71
122.69
122.32
121.41
121.30
120.68
110.43
110.40
109.62
109.59
102.26
102.05
77.27 CDCl3
77.22
77.02 CDCl3
76.76 CDCl3
55.67
f1 (ppm)

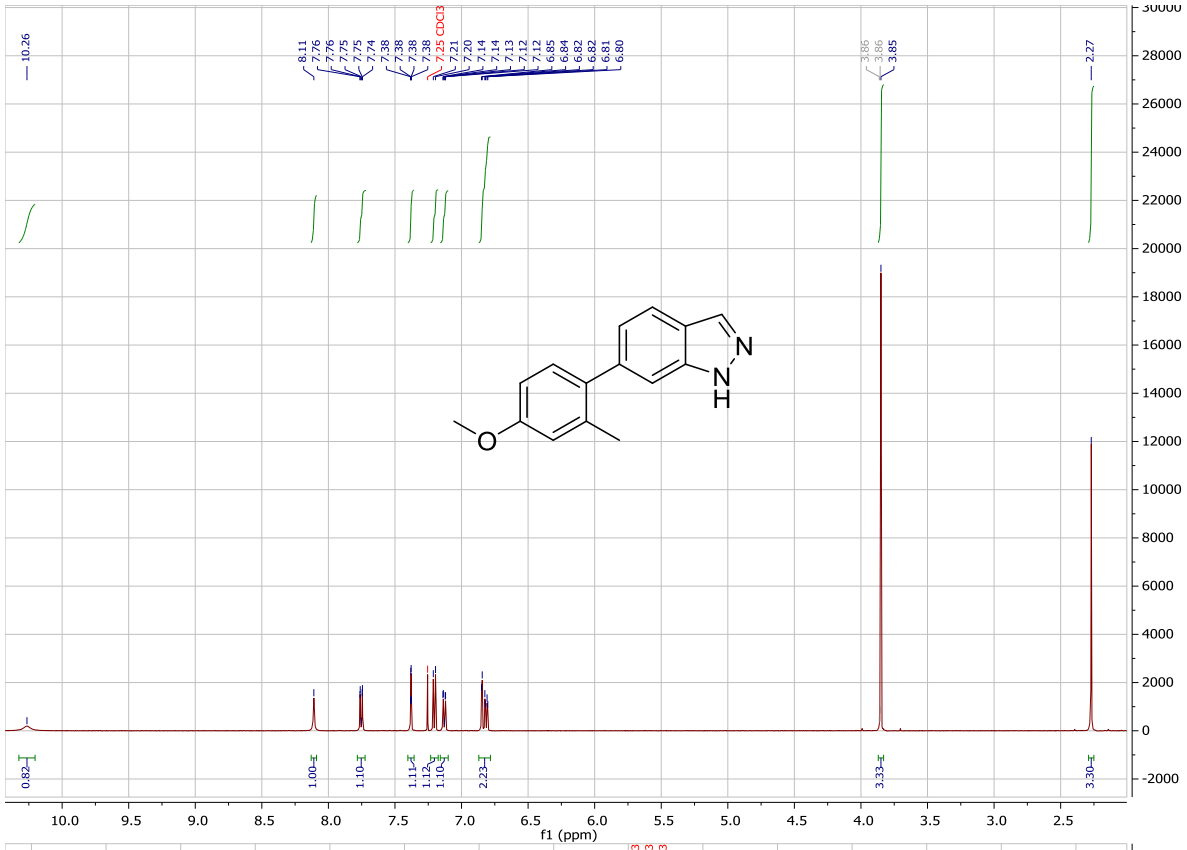
Compound 26

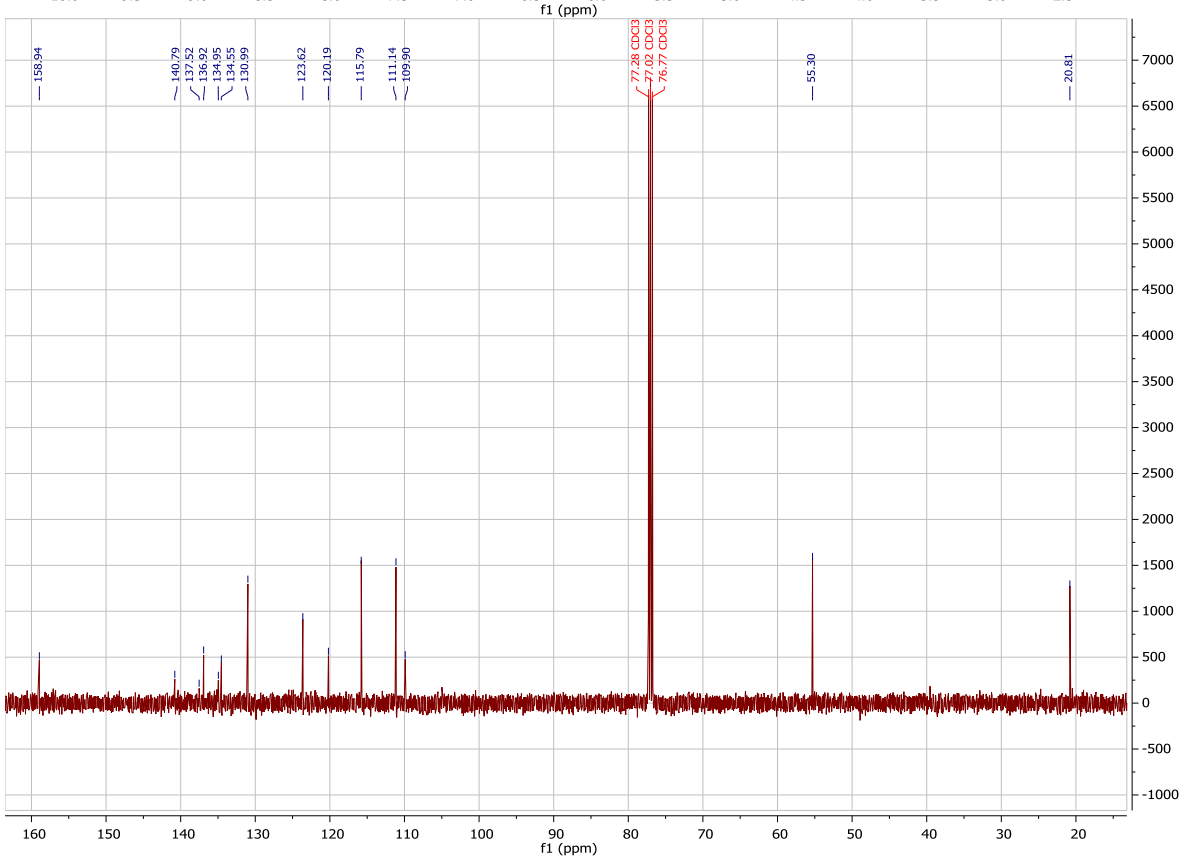




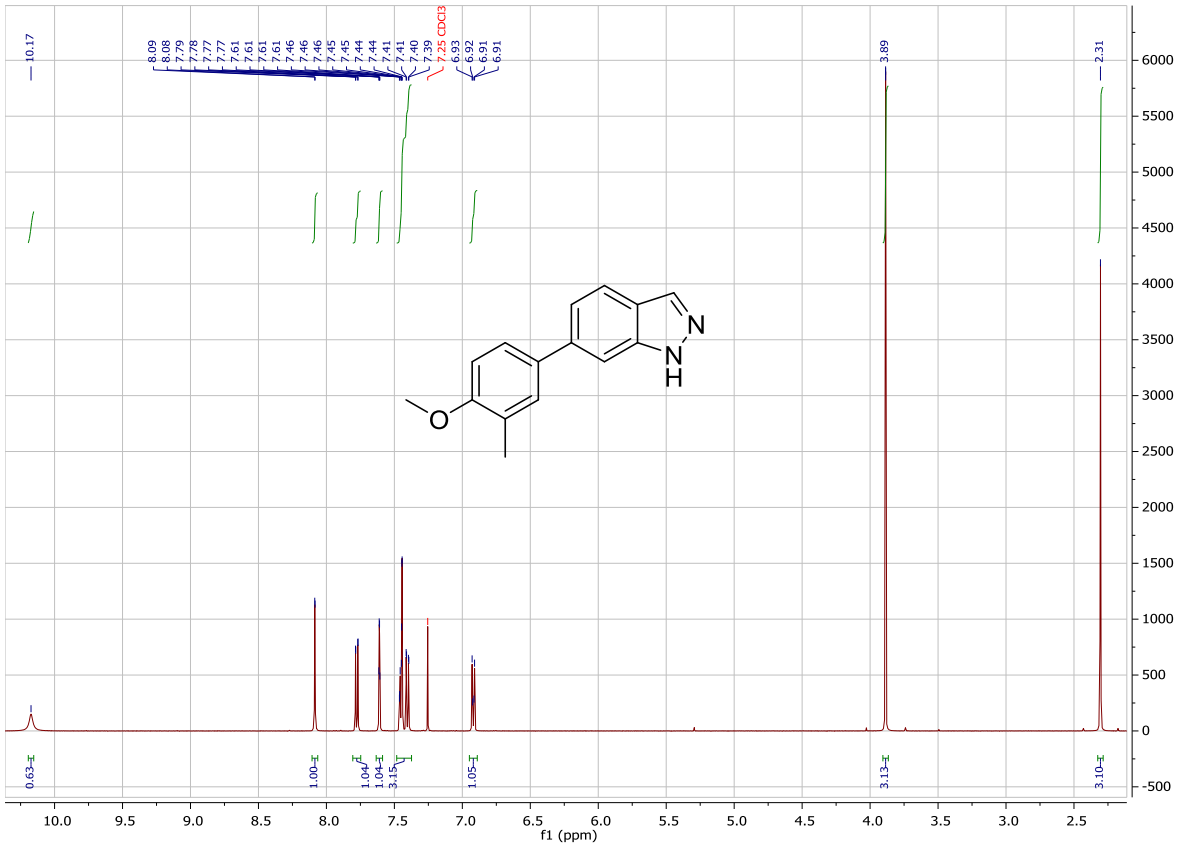
20% impurity of toluene present from recrystallisation.

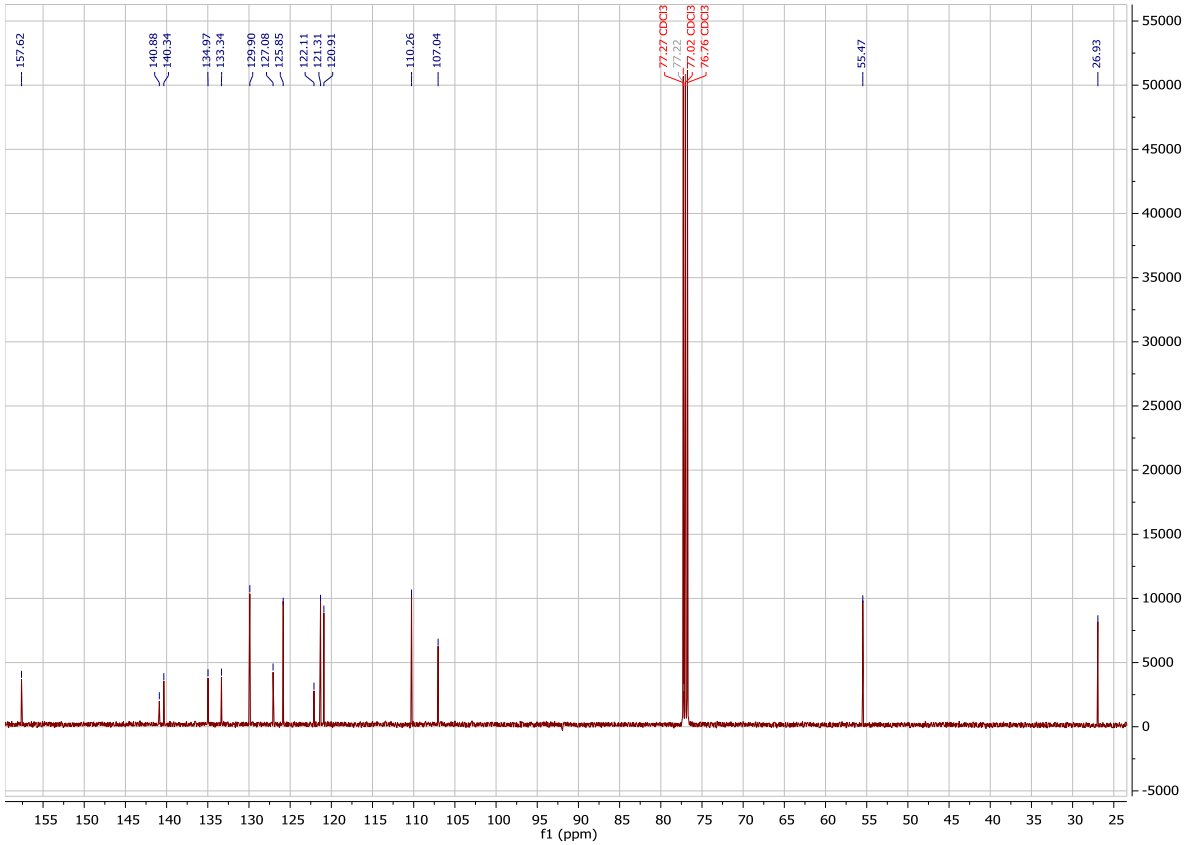
Compound 27


10.26
8.11
7.76
7.76
7.75
7.75
7.74
7.38
7.38
7.38
7.38
7.25 CDCl3
7.21
7.20
7.14
7.14
7.13
7.12
7.12
6.85
6.84
6.82
6.82
6.81
6.80
3.86
3.86
3.85
2.27
0.82
1.00
1.10
1.11
1.12
1.10
2.23
3.33
3.30
N
N
H
O
f1 (ppm)


158.94
140.79
137.52
136.92
134.95
134.55
130.99
123.62
120.19
115.79
111.14
109.90
77.28 CDCl3
77.02 CDCl3
76.77 CDCl3
55.30
20.81
f1 (ppm)

Compound 28


10.17
8.09
8.08
7.79
7.78
7.77
7.77
7.61
7.61
7.61
7.61
7.46
7.46
7.45
7.45
7.44
7.44
7.41
7.41
7.40
7.39
7.25 CDCl3
6.93
6.92
6.91
6.91
3.89
2.31
N
N
H
O
0.63
1.00
1.04
1.04
3.15
1.05
3.13
3.10
f1 (ppm)


157.62
140.88
140.34
134.97
133.34
129.90
127.08
125.85
122.11
121.31
120.91
110.26
107.04
77.27 CDCl3
77.22
77.02 CDCl3
76.76 CDCl3
55.47
26.93
f1 (ppm)

3.0 Biological Assay

3.1 FRET-Based Z'-Lyte Assay®

All biological measurements were carried out by Life Technologies Ltd and use the following method:

The Z'-Lyte assay is a competitive inhibition FRET-based assay that uses a fluorescence-based, coupled-enzyme format and is based on the differential sensitivity of non-phosphorylated and phosphorylated peptides to proteolytic cleavage. The assay involves two reactions. The first reaction involves the phosphorylation of a specific tyrosine residue on a specific protein. This protein is labelled with two fluorophores; Coumarin (donor) and Fluorescein (acceptor) and these make up a FRET pair (Figure **2**).[16]

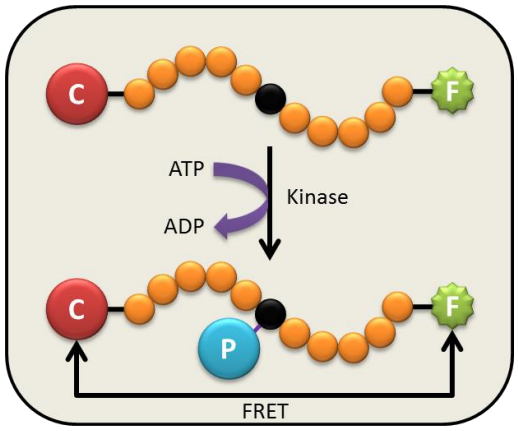


Figure 2. Kinase reaction for FRET-based Z'-lyte assay. Adapted from reference 16.

The second reaction is a development reaction in which a site-specific protease cleaves non-phosphorylated protein, leaving phosphorylated protein unaffected. The cleavage disrupts the FRET between the donor and the acceptor which is measurable (Figure **3**).[16] The ratio of donor emission to acceptor emission quantifies reaction progress and is calculated (Equation **1**).[16]

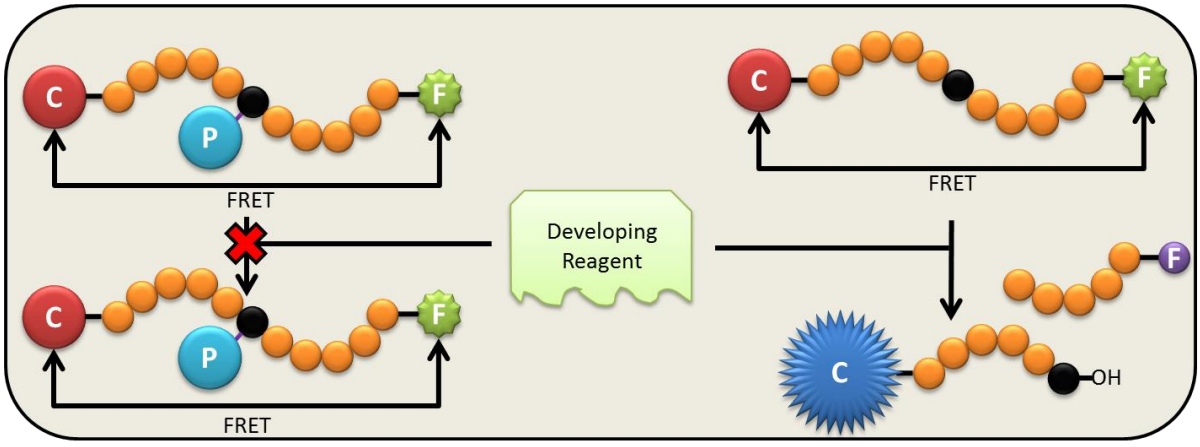


Figure 3. Development reaction for FRET-based Z'-lyte assay. Adapted from reference 16.

$$\textbf{Emission Ratio} = \frac{\textbf{Courmarin Emission (445 nm)}}{\textbf{Fluorescein (520 nm)}}$$

Equation 1: Adapted from reference 16.

For each assay a Z-prime value is calculated and is a measure of assay robustness. This calculation incorporates the standard deviation observed in each control experiment and is a common measure of assay performance.

3.1.1 FGFR1 Assay Conditions

The 2X FGFR1/Tyr 04 mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 4 mM $MnCl_2$, 1 mM EGTA, 2 mM DTT. The final 10 µL Kinase Reaction consists of 0.44-2.45 ng FGFR1 and 2 µM Tyr 04 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 2 mM $MnCl_2$, 1 mM EGTA, 1 mM DTT. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:64 dilution of Development Reagent B is added. K_m app = 25 µM.

3.1.2 FGFR2 Assay Conditions

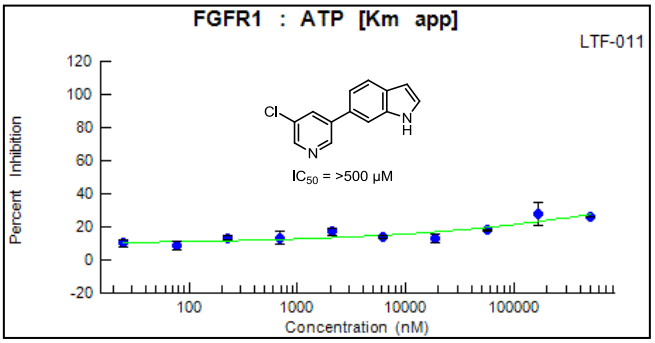
The 2X FGFR2/Tyr 04 mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 4 mM MnCl2, 1 mM EGTA, 2 mM DTT. The final 10 µL Kinase Reaction consists of 0.19 - 1.99 ng FGFR2 and 2 µM Tyr 04 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 2 mM MnCl2, 1 mM EGTA, 1 mM DTT. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:64 dilution of Development Reagent B is added. K_m app = 5 µM.

3.1.3 FGFR3 Assay Conditions

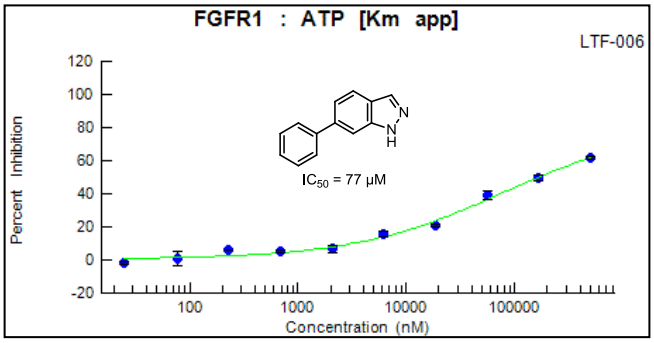
The 2X FGFR3 / Tyr 04 mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 4 mM MnCl2, 1 mM EGTA, 2 mM DTT. The final 10 µL Kinase Reaction consists of 0.56 - 3.5 ng FGFR3 and 2 µM Tyr 04 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM MgCl2, 2 mM MnCl2, 1 mM EGTA, 1 mM DTT. After the 1 hour Kinase Reaction incubation, 5 µL of a 1:64 dilution of Development Reagent B is added. K_m app = 75 µM.

3.2 IC_{50} Curves

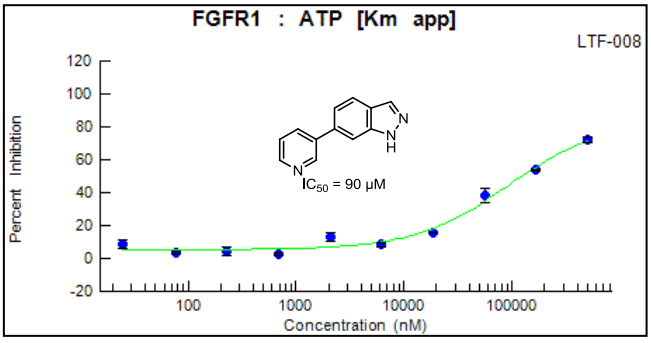
Compound 3



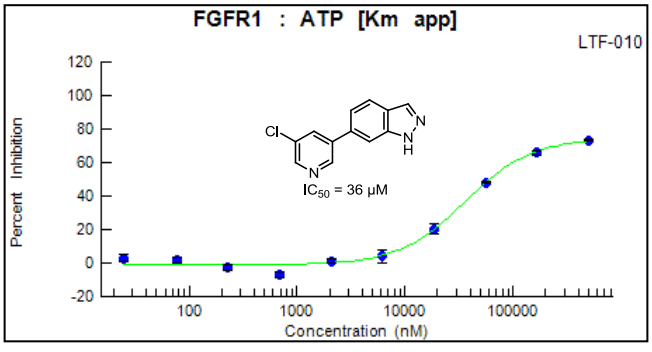
Compound 4



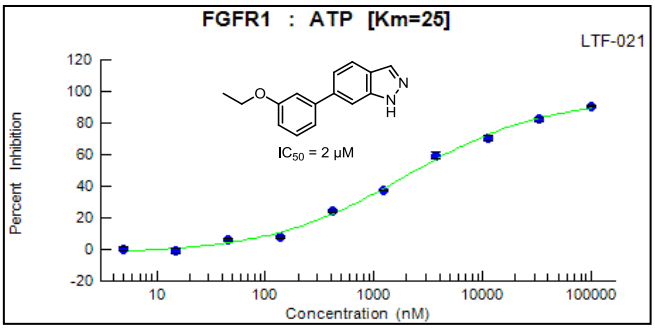
Compound 5

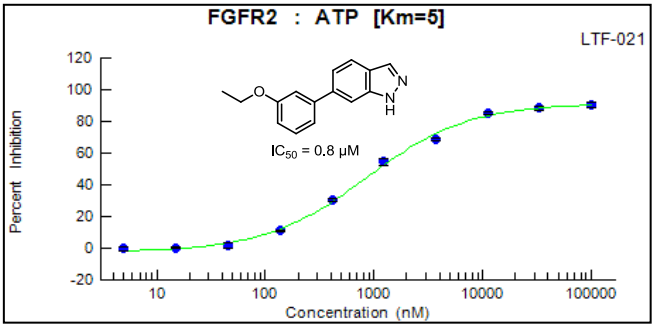


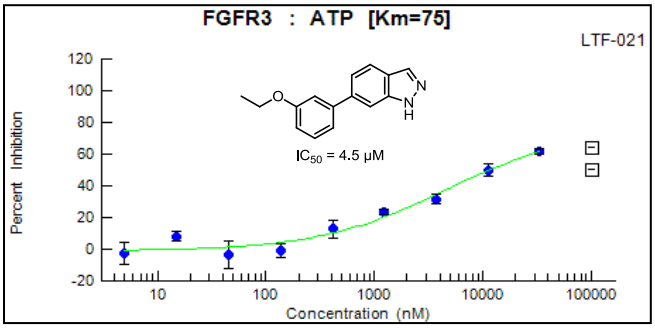
Compound 6



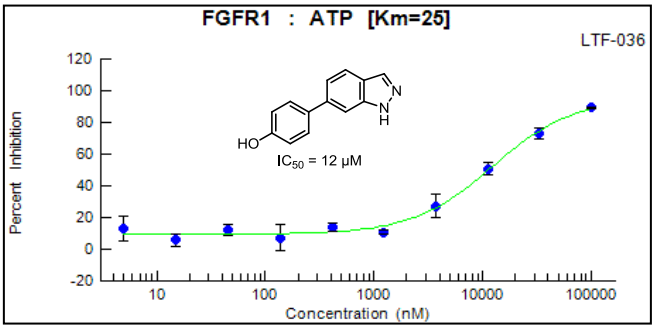
Compound 10

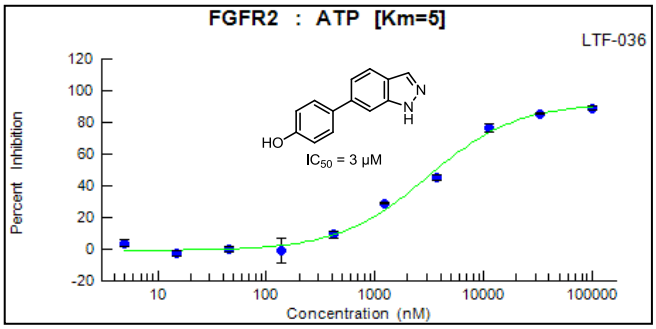


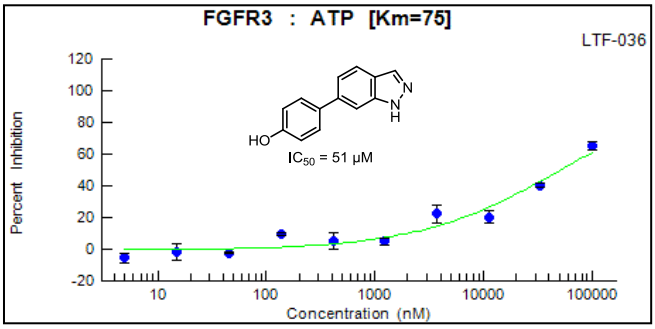




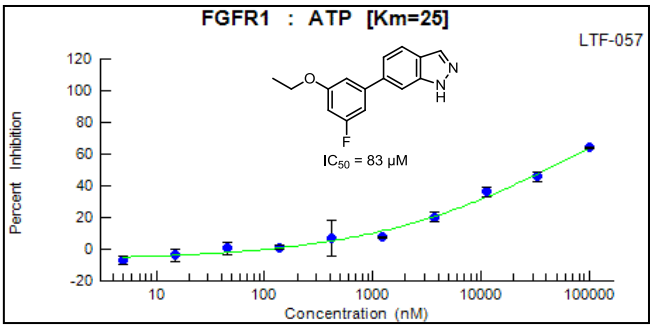
Compound 11

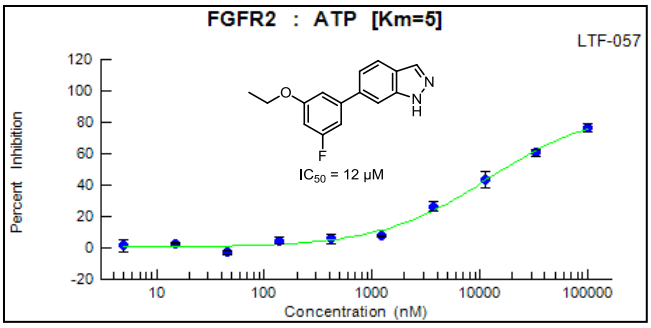


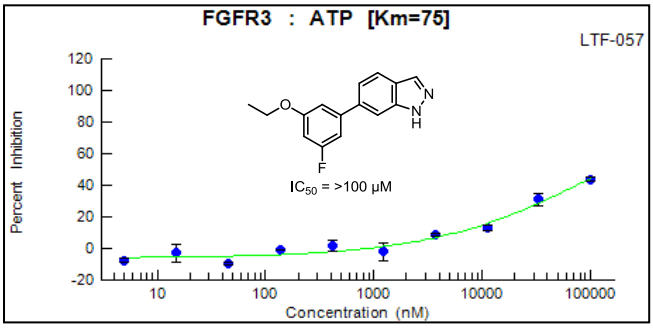




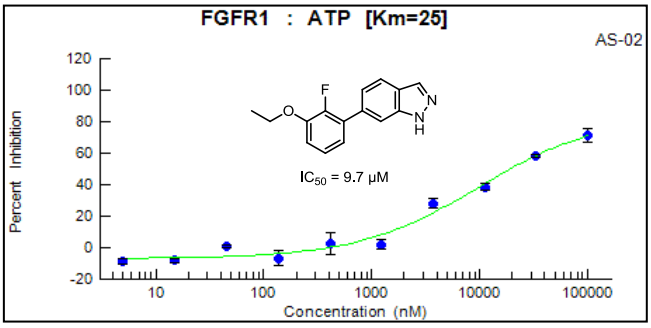
Compound 18

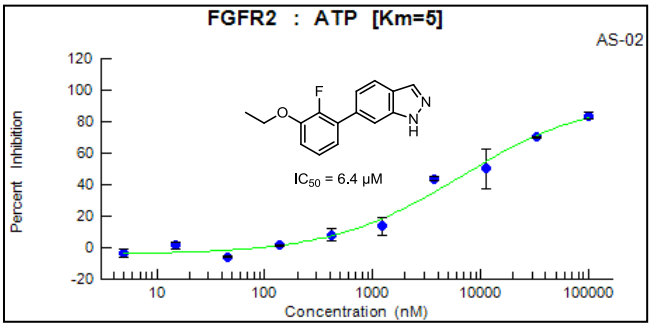


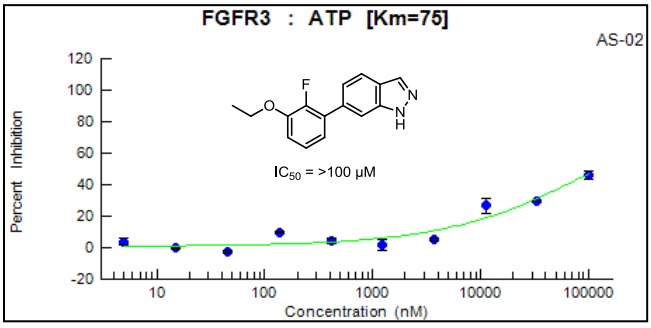




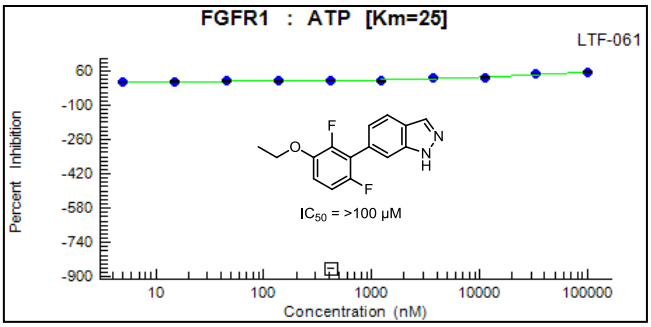
Compound 19

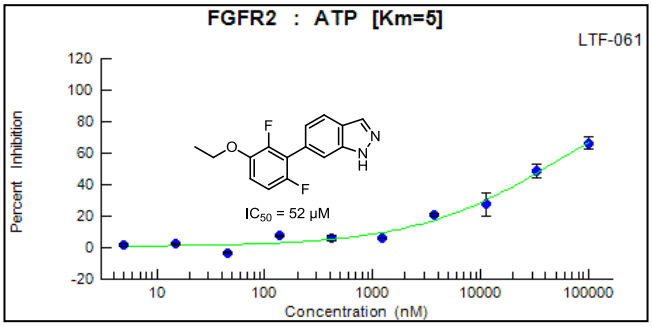


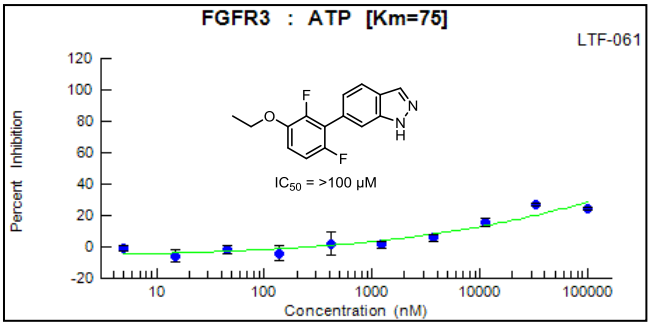




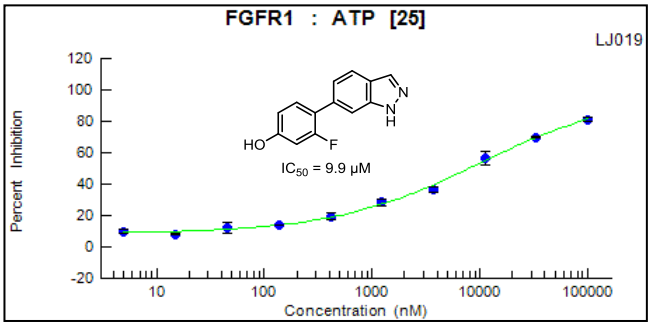
Compound 20

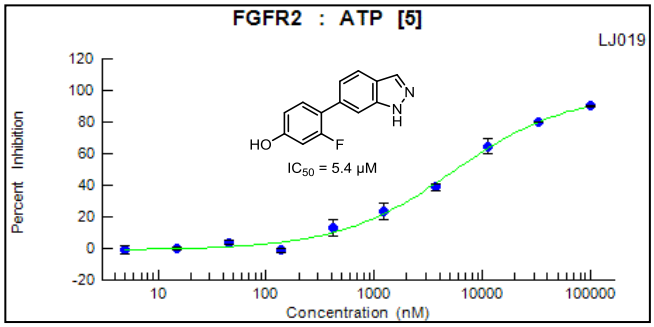


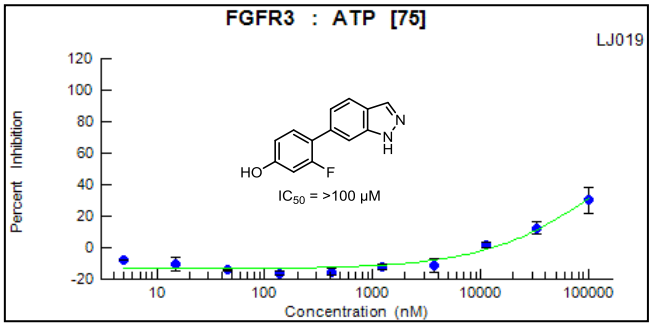




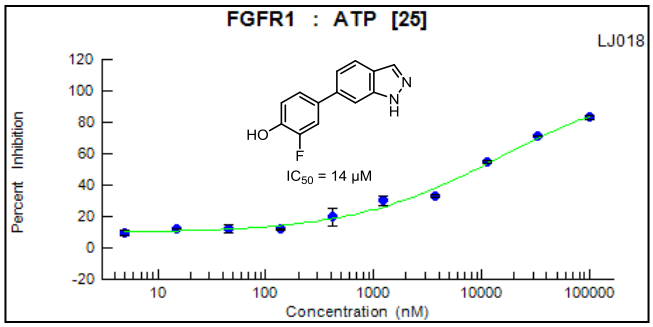
Compound 21

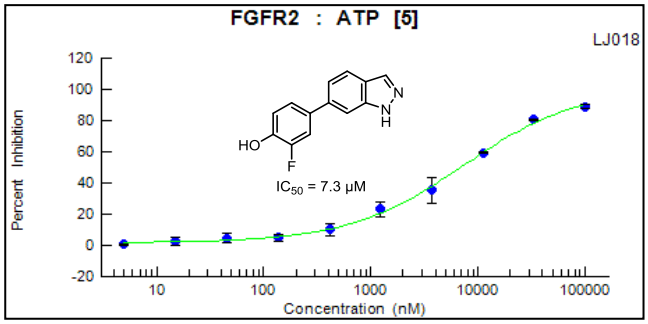




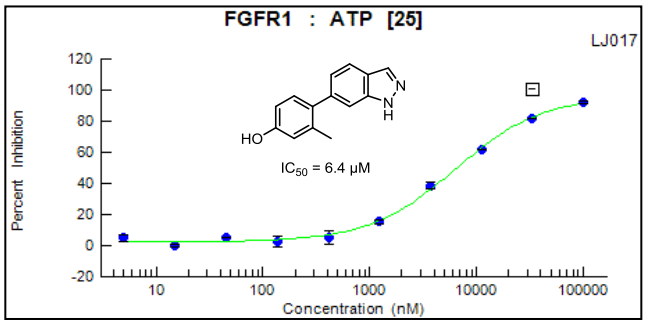


Compound 22

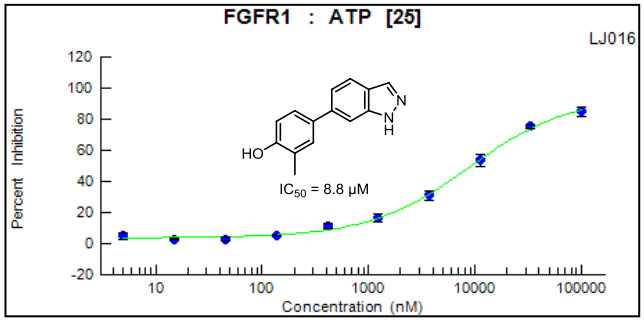




Compound 23



Compound 24



4.0 Computational

4.1 SPROUT

The design of novel drug-like molecules can be carried out using *de novo* design software such as SPROUT. SPROUT carries out this process using several modules:[17]

1. **CANGAROO**- This module stands for **C**left **AN**alysis by **G**eometry based **A**lgorithm **R**egardless **O**f the **O**rientation. In this module the receptor site and cavity (ligand) are defined.
2. **HIPPO**- This module stands for **H**ydrogen-bonding **I**nteraction site **P**rediction as **P**ositions with **O**rientations. In this module potential binding sites are outlined. Such sites are amino acids that can provide hydrogen bonding capability whether it be donating or accepting. Hydrophobic binding regions and metal interactions can also be defined.
3. **ELEFANT**- This module stands for **ELE**ction of **F**unctional groups and **A**nchoring them to **T**arget sites. In this module small fragments that contain H-bonding functionality are chosen and assigned to complementary target sites.
4. **SPIDER**- This module stands for **S**tructure **P**roduction with **I**nteractive **D**esign of **R**esults. In this module spacer templates are chosen to link the fragments selected in **ELEFANT**. Structures are then generated following the constraints of the target site and boundary surface.
5. **ALLIGATOR**- This module stands for **A**nalyse **L**ots of **LIGA**nds, **T**est and **O**rder **R**esults. This module clusters groups of molecules based on parameters set by the user. Such parameters include; hydrogen bonding interactions, rotatable bonds and hydrophobic interactions.

4.2 Docking Models

All docking models were visualised using PyMol.[18] Compounds were subject to consensus docking using both eHiTS and Glide.[19,20] Glide gave the best result and therefore was the preferred docking method.

Compound 5

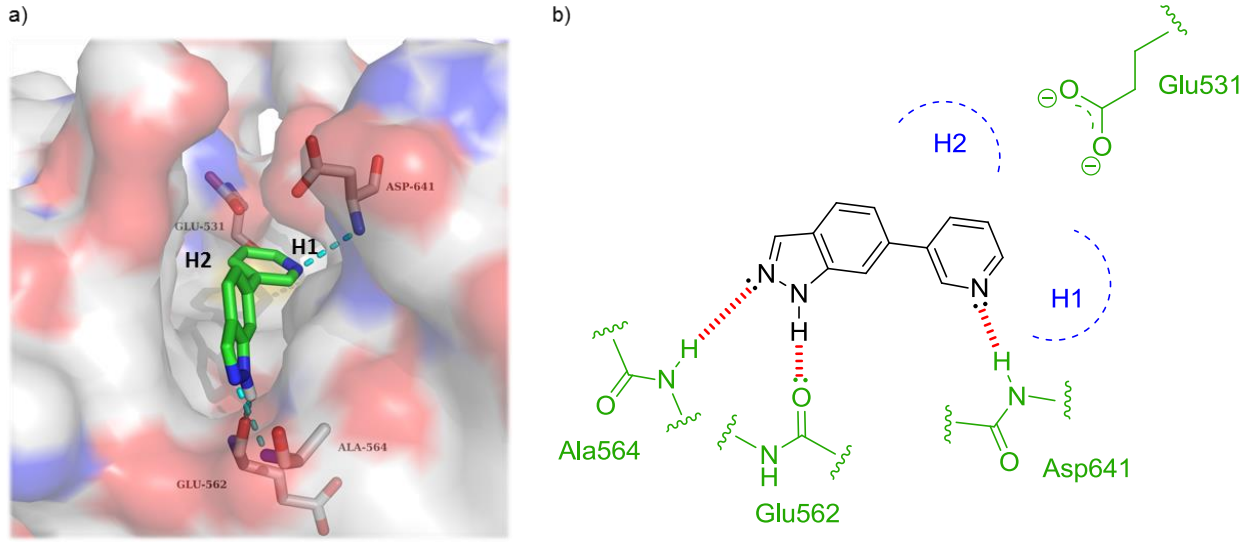


Figure 4. a) Glide docking model of compound **5** bound within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **5**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the pyridyl nitrogen with the backbone NH of Asp 641.

It is unlikely that pyridyl nitrogen is H-bonding with the backbone NH of Asp641 as the results show that compound **4** is more active. The difference in the activity between compound **4** and **5** is unclear but could be due to electrostatic repulsion between the pyridyl nitrogen and the hydrophobic floor of the ATP binding pocket as this would have a detrimental effect upon binding.

Compound 6

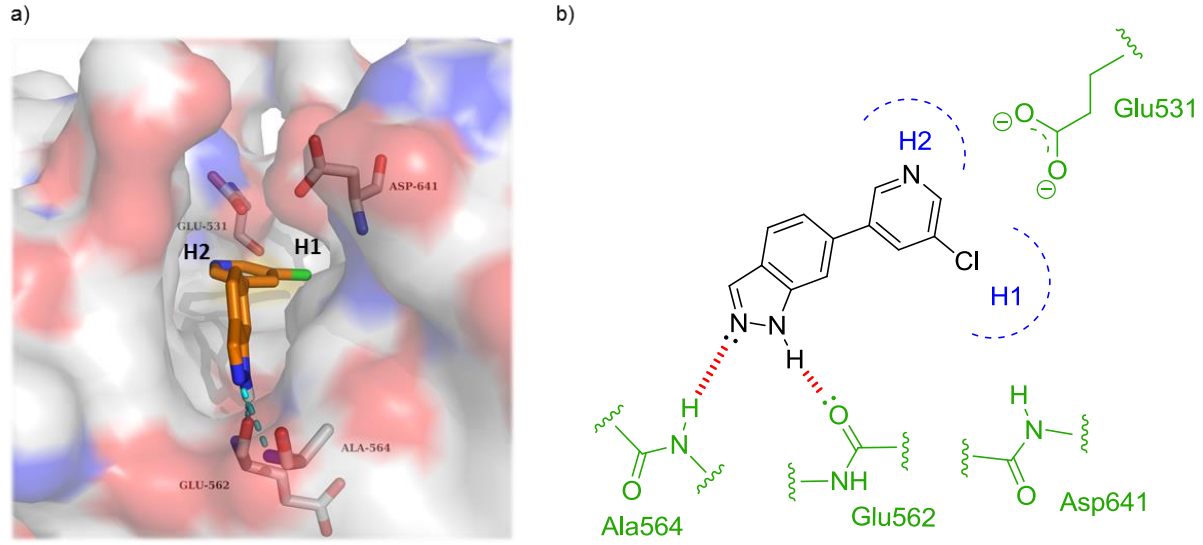


Figure 5. a) Glide docking model of compound **6** bound within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **6**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562. The Cl atom is predicted to occupy the H1 sub-pocket and the pyridyl ring is predicted to face towards the H2 sub-pocket.

The Cl atom in compound **6** was hypothesised to occupy the H2 sub-pocket while the pyridyl N participates in an H-bond with the backbone NH of Asp 641. Unexpectedly, the conformation of the 6-position phenyl ring has flipped 180° after being docked. This is due to the Cl atom

sitting more favorably into the larger H1 sub-pocket; this places the pyridyl N out of position and therefore is unlikely to be having a positive effect upon binding.

Compound 10

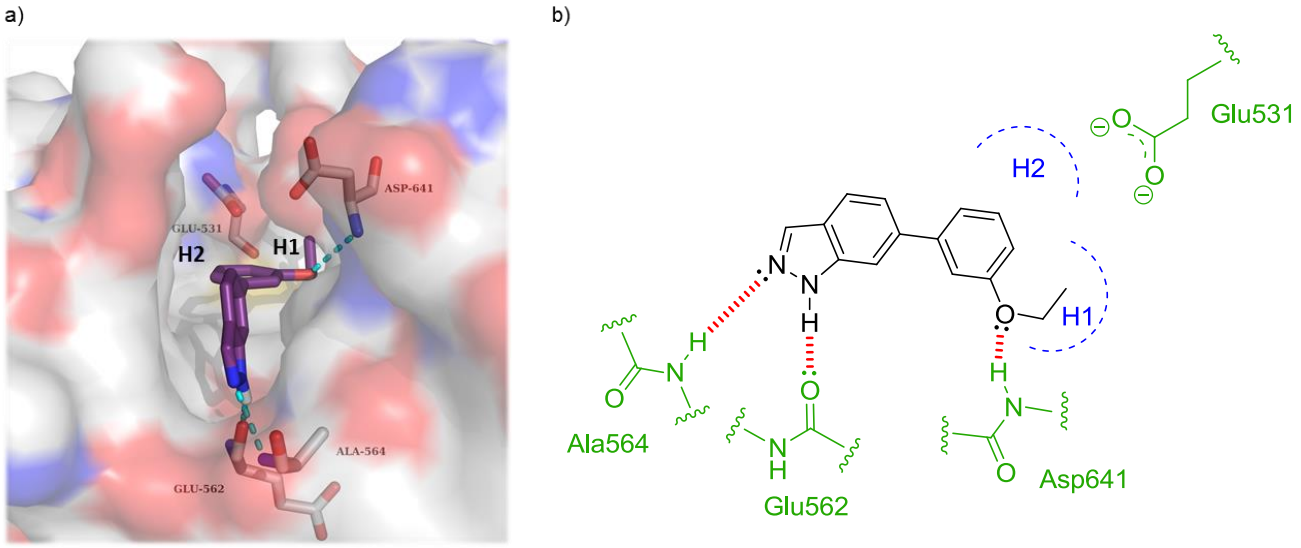


Figure 6. a) Glide docking model of compound **10** bound within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **10**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the ethoxy oxygen with the backbone NH of Asp641. The ethyl group is predicted to lie deep within the H1 sub-pocket.

The increase in potency between compound **6** and compound **10** can be explained by the addition of the larger ethoxy group in the 3-position of the phenyl ring. The ethoxy oxygen is predicted to H-bond and also the larger ethyl group sits tighter in the H1 sub-pocket than the Cl atom.

Compound 11

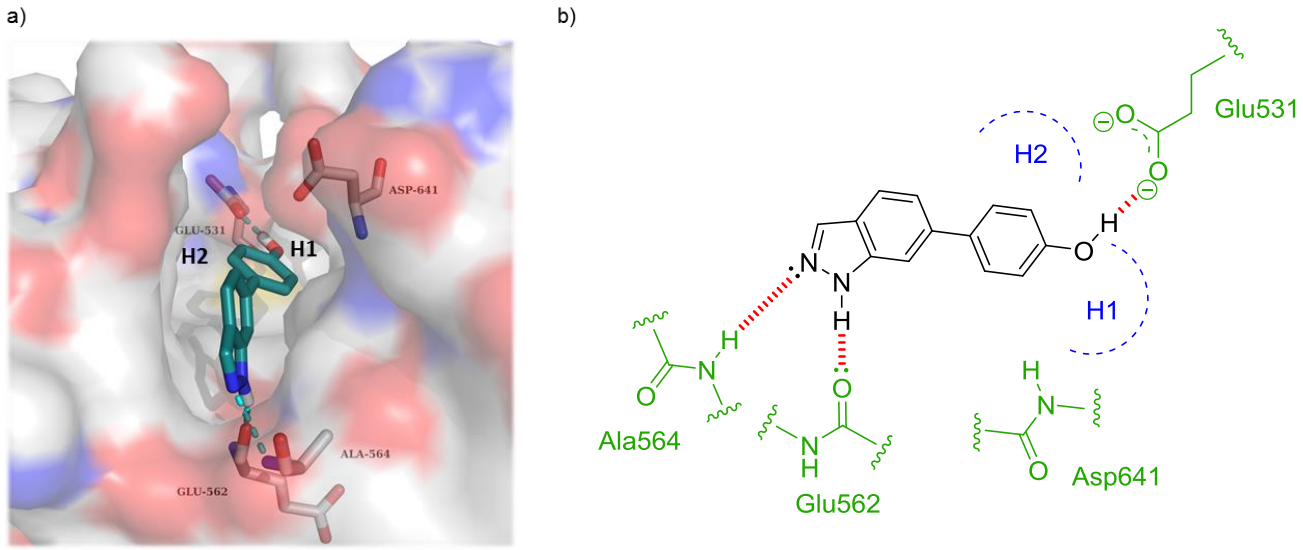


Figure 6. a) Glide docking model of compound **11** bound within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **11**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the hydroxy H with a side chain carboxy oxygen of Glu531.

Compound 12

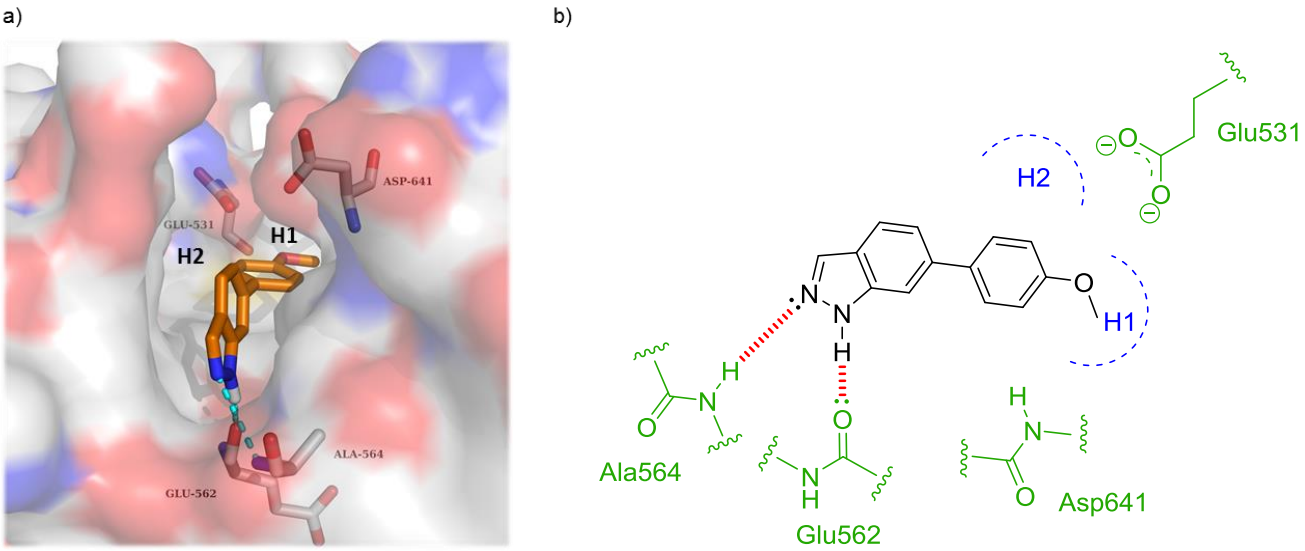


Figure 7. a) Glide docking model of compound **12** bound within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **12**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562. The methoxy group is predicted to occupy the H1 sub-pocket.

The methoxy group is predicted to occupy the H1. The replacement of OH to OMe on the phenyl ring has resulted in the loss of an H-bond, this is reflected by the biological results.

Compound 18

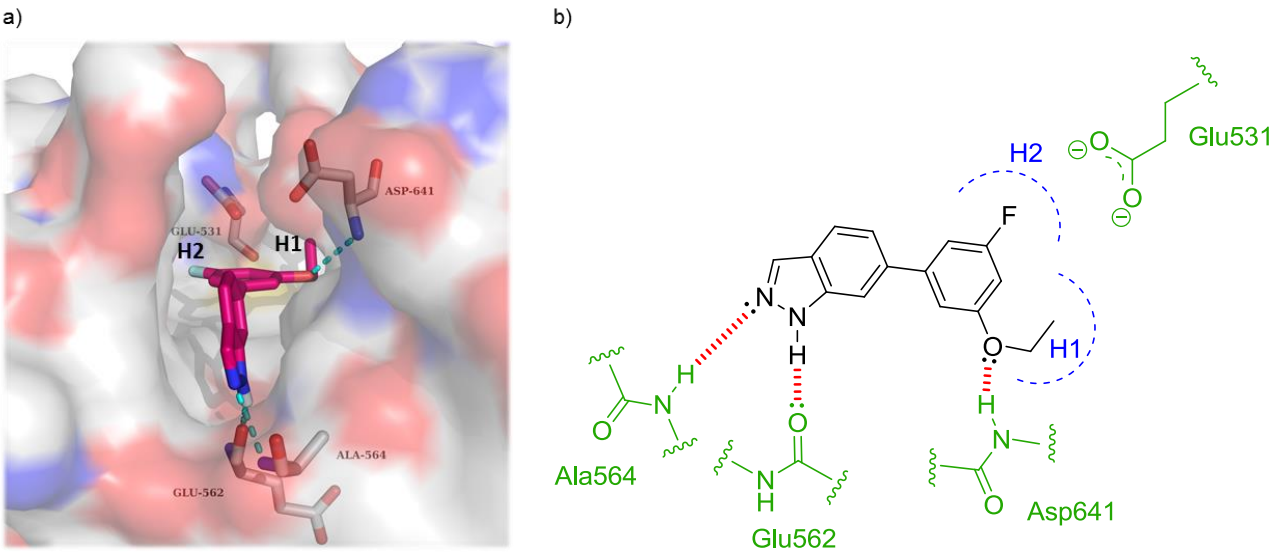


Figure 8. a) Glide docking model of compound **18** within FGFR1. H-bonds are indicated using cyan dashes. **b)** Schematic of binding pose of compound **18**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the ethoxy oxygen with the backbone NH of Asp641. The ethyl group is predicted to lie deep in the H1 sub-pocket and the F atom is predicted to occupy the H2 sub-pocket.

Compound **18** docks in a similar fashion to that of compound **10** (Figure **5**). In addition the F atom is predicted to occupy the H2 sub-pocket and appears to bind in a better fashion. Compound **18** is less active than compound **10** and therefore does not reflect the docking model.

Compound 21

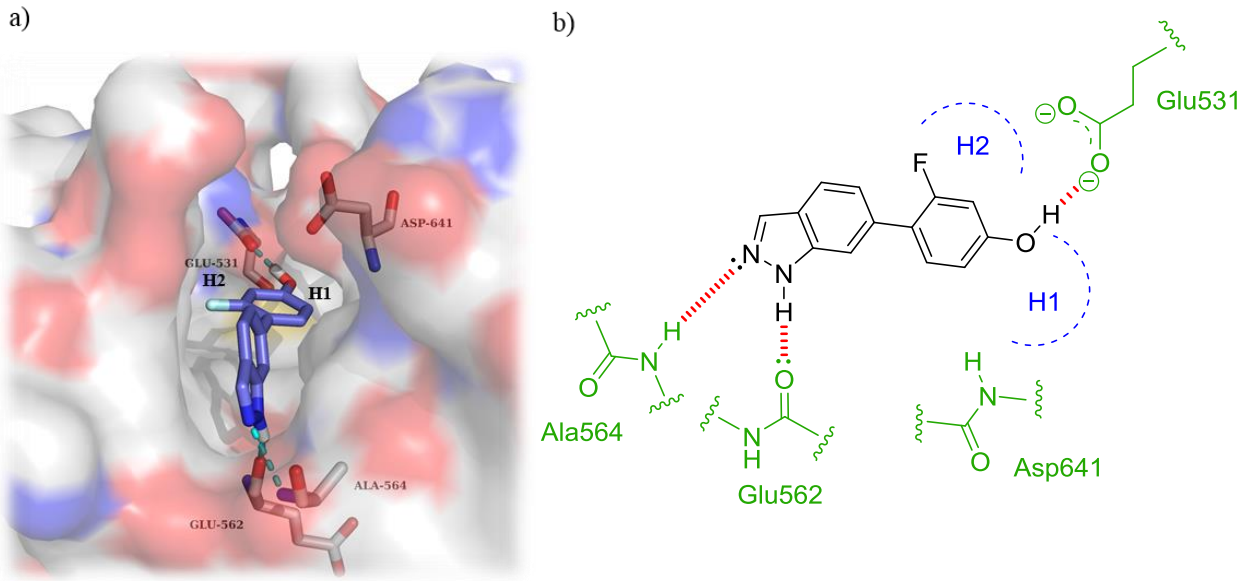


Figure 9. a) Glide docking model of compound **21** bound within FGFR1. H-bonds are indicated using cyan dashes. b) Schematic of binding pose of compound **21**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the hydroxy H with a side chain carboxy oxygen of Glu531. The F atom is predicted to occupy a small hydrophobic space located adjacent to the H2 sub-pocket.

Compound 22

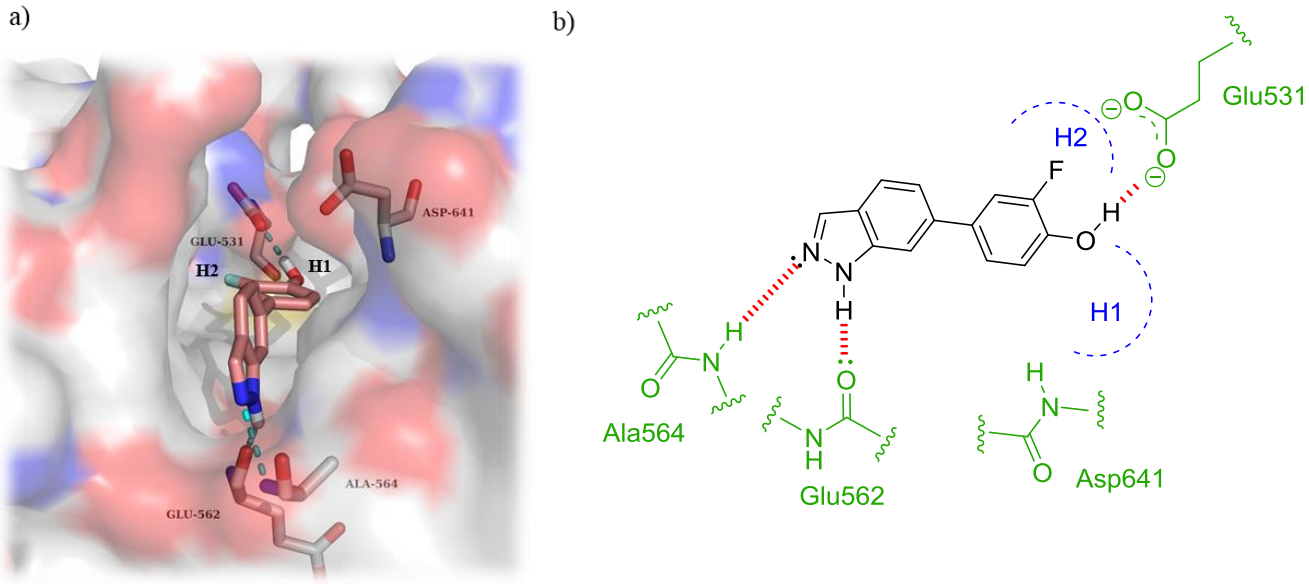


Figure 10. a) Glide docking model of compound **22** bound within FGFR1. H-bonds are indicated using cyan dashes. b) Schematic of binding pose of compound **22**. Intermolecular interactions that are predicted are: the 2-position N with the backbone NH of Ala564; the indazole NH with the backbone carbonyl of Glu562 and the hydroxy H with a side chain carboxy oxygen of Glu531. The F atom is predicted to occupy the H2 sub-pocket.

The F atom within compound **22** is predicted to occupy the H2 sub-pocket whereas the F atom in compound **21** does not occupy the H2 sub-pocket. Compound **21** is more active than compound **22** and therefore the occupation of the H2 pocket seems to be less important than having an ortho hydrophobic substituent on the phenyl ring, according to the docking model.

5.0 References

1. Nakanishi, Y.; Akiyama, N.; Tsukaguchi, T.; Fujii, T.; Sakata, K.; Sase, H.; Isobe, T.; Morikami, K.; Shindoh, H.; Mio, T.; Ebiike, H.; Taka, N.; Aoki, Y.; Ishii, N., The Fibroblast Growth Factor Receptor Genetic Status as a Potential Predictor of the Sensitivity to CH5183284/Debio 1347, a Novel Selective FGFR Inhibitor. *Mol Cancer Ther* **2014,** *13* (11), 2547-2558.
2. Roth, G. J.; Binder, R.; Colbatzky, F.; Dallinger, C.; Schlenker-Herceg, R.; Hilberg, F.; Wollin, S. L.; Kaiser, R., Nintedanib: From Discovery to the Clinic. *J Med Chem* **2015,** *58* (3), 1053-1063.
3. Shaw, A. T.; Hsu, P. P.; Awad, M. M.; Engelman, J. A., Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat Rev Cancer* **2013,** *13* (11), 772-787.
4. Chase, A.; Grand, F. H.; Cross, N. C. P., Activity of TK1258 against primary cells and cell lines with FGFR1 fusion genes associated with the 8p11 myeloproliferative syndrome. *Blood* **2007,** *110* (10), 3729-3734.
5. André, F.; Bachelot, T.; Campone, M.; Dalenc, F.; Perez-Garcia, J. M.; Hurvitz, S. A.; Turner, N.; Rugo, H.; Smith, J. W.; Deudon, S., Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. *Clin Cancer Res* **2013,** *19* (13), 3693-3702.
6. Bello, E.; Colella, G.; Scarlato, V.; Oliva, P.; Berndt, A.; Valbusa, G.; Serra, S. C.; D'Incalci, M.; Cavalletti, E.; Giavazzi, R.; Damia, G.; Camboni, G., E-3810 Is a Potent Dual Inhibitor of VEGFR and FGFR that Exerts Antitumor Activity in Multiple Preclinical Models. *Cancer Res* **2011,** *71* (4), 1396-1405.
7. Gavine, P. R.; Mooney, L.; Kilgour, E.; Thomas, A. P.; Al-Kadhimi, K.; Beck, S.; Rooney, C.; Coleman, T.; Baker, D.; Mellor, M. J.; Brooks, A. N.; Klinowska, T., AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family. *Cancer Res* **2012,** *72* (8), 2045-2056.
8. Smyth, E. C.; Turner, N. C.; Pearson, A.; Peckitt, C.; Chau, I.; Watkins, D. J.; Starling, N.; Rao, S.; Gillbanks, A.; Kilgour, E.; Sumpter, K. A.; Smith, N. R.; Cutts, R.; Rooney, C.; Thomas, A. L.; Ajaz, M. A.; Chua, S.; Brown, G.; Popat, S.; Cunningham, D., Phase II study of AZD4547 in FGFR amplified tumours: Gastroesophageal cancer (GC) cohort pharmacodynamic and biomarker results. *J Clin Oncol* **2016,** *34* (4), 1.
9. Mohammadi, M.; Froum, S.; Hamby, J. M.; Schroeder, M. C.; Panek, R. L.; Lu, G. H.; Eliseenkova, A. V.; Green, D.; Schlessinger, J.; Hubbard, S. R., Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain. *Embo J* **1998,** *17* (20), 5896-5904.
10. Miyake, M.; Ishii, M.; Koyama, N.; Kawashima, K.; Kodama, T.; Anai, S.; Fujimoto, K.; Hirao, Y.; Sugano, K., 1-tert-Butyl-3- 6-(3,5-dimethoxy-phenyl)-2-(4-diethylamino-butylamino)- pyrido 2,3-d pyrimidin-7-yl -urea (PD173074), a Selective Tyrosine Kinase Inhibitor of Fibroblast Growth Factor Receptor-3 (FGFR3), Inhibits Cell Proliferation of Bladder Cancer Carrying the FGFR3 Gene Mutation along with Up-Regulation of p27/Kip1 and G(1)/G(0) Arrest. *J Pharmacol Exp Ther* **2010,** *332* (3), 795-802.
11. Guagnano, V.; Kauffmann, A.; Wohrle, S.; Stamm, C.; Ito, M.; Barys, L.; Pornon, A.; Yao, Y.; Li, F.; Zhang, Y.; Chen, Z.; Wilson, C. J.; Bordas, V.; Le Douget, M.; Gaither, L. A.; Borawski, J.; Monahan, J. E.; Venkatesan, K.; Brummendorf, T.; Thomas, D. M.; Garcia-Echeverria, C.; Hofmann, F.; Sellers, W. R.; Graus-Porta, D., FGFR Genetic Alterations Predict for Sensitivity to NVP-BGJ398, a Selective Pan-FGFR Inhibitor. *Cancer Discov* **2012,** *2* (12), 1118-1133.
12. Mohammadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B. K.; Hubbard, S. R.; Schlessinger, J., Structures of the tyrosine kinase domain of fibroblast growth factor receptor in complex with inhibitors. *Science* **1997,** *276* (5314), 955-960.
13. Liu, J.; Peng, X.; Dai, Y.; Zhang, W.; Ren, S. M.; Ai, J.; Geng, M. Y.; Li, Y. X., Design, synthesis and biological evaluation of novel FGFR inhibitors bearing an indazole scaffold. *Org Biomol Chem* **2015,** *13* (28), 7643-7654.
14. Tischler, A. N.; Lanza, T. J., 6-substituted indoles from o-halonitrobenzenes. *Tetrahedron Letters* **1986,** *27* (15), 1653-1656.
15. Molander, G. A.; Canturk, B.; Kennedy, L. E., Scope of the Suzuki-Miyaura Cross-Coupling Reactions of Potassium Heteroaryltrifluoroborates. *Journal of Organic Chemistry* **2009,** *74* (3), 973-980.
16. Z'-Lyte ® Screening Protocol and Assay Conditions. Life Technologies, Paisley, Scotland, 2015.
17. Simmons, K. J.; Chopra, I.; Fishwick, C. W. G., Structure-based discovery of antibacterial drugs. *Nat Rev Microbiol* **2010,** *8* (7), 501-510.
18. DeLano, W. L., The PyMOL molecular graphics system. **2002**.
19. Zsoldos, Z.; Johnson, A. P.; Simon, A.; Szabo, I.; Szabo, Z., eHiTS: novel algorithm for fast, exhaustive flexible ligand docking and scoring. SimBioSys Inc. [online], (2002)
20. Babine, R. E.; Bleckman, T. M.; Kissinger, C. R.; Showalter, R.; Pelletier, L. A.; Lewis, C.; Tucker, K.; Moomaw, E.; Parge, H. E.; Villafranca, J. E., Design, Synthesis and X-Ray Crystallographic Studies of Novel FKBP-12 Ligands. *Bioorg. Med. Chem. Lett.* **1995,** *5* (15), 1719-1724.