Supporting Information

Development of Subnanomolar Fluorinated (2-Pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine pan-Trk Radiolabeled Inhibitors as Candidate PET Imaging Probes

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CONTENT OF SUPPORTING INFORMATION

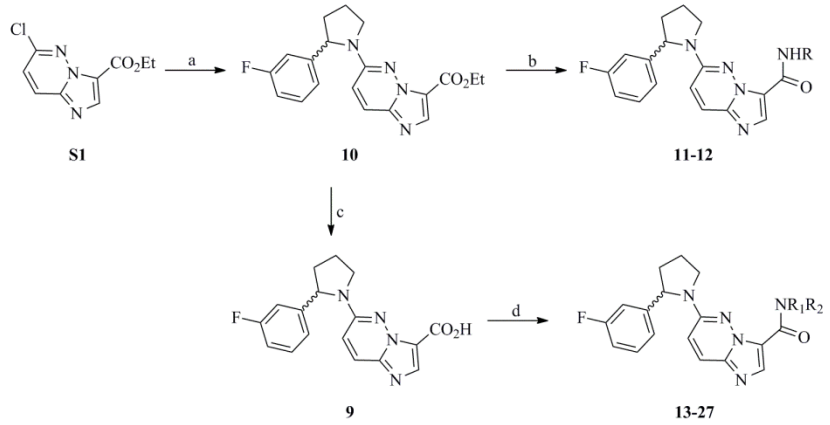
2. ORGANIC SYNTHESES

2.1 Material and Methods

General Procedures. All moisture sensitive reactions were carried out in oven-dried flasks under nitrogen atmosphere with dry solvents. Reagents and solvents were purchased at the highest commercial quality from Fisher, Sigma-Aldrich, Alfa-Aesar, Synthonix or Oakwood Products and were used without further purification unless specified otherwise. GNF-5837 (≥ 98%) was purchased from EMD Millipore. 2-Fluoroethyl 4-methylbenzenesulfonate (**32**) was synthesized as previously described. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator. In general, reactions were magnetically stirred and monitored by TLC performed on pre-coated glass-backed TLC plates (Analtech, 250 microns) and chromatographic purification of products was accomplished using flash chromatography on Alfa-Aesar silica gel (230-450 mesh). TLC visualization was performed by fluorescence quenching, $KMnO_4$ or ninhydrin. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Agilent/Varian DD2 MR two channel 400 MHz spectrometer, a Agilent/Varian VNMRS two-channel 500 MHz spectrometer or a Agilent/Varian Inova four-channel 500 MHz spectrometer in $CDCl_3$ or d_6-DMSO and peak positions are given in parts per million using TMS as internal standard. Peaks are reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. High Resolution Mass Spectra (HRMS) analysis was obtained from the Mass Spectrometry Facility of the Chemistry Department of the University of Alberta (Agilent Technologies 6220 oaTOF). Compounds tested in vitro were >95% pure (HPLC). Crystallographic analyses were performed by the X-Ray crystallography laboratory at the Chemistry Department of the University of Alberta. .

2.2 Chemical Synthesis.

Scheme S1. Syntheses of amides 11-27[a]



[a] Reagents and conditions: (a) 2-(3-Fluorophenyl)pyrrolidine, KF, DMSO, 100°C, 22 h (77%). (b) ammonia solution (7.0 M in methanol) or methylamine solution (33 wt. % in absolute ethanol), rt, 15 h (96-100%). (c) EtOH, H_2O, KOH, rt, 3 h (72%). (d) amine, HATU, DIPEA, DMF, rt, 12-14 h (43-100%).

Ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (10). To a solution of ethyl 6-chloroimidazo[1,2-b]pyridazine-3-carboxylate (1.13 g, 5.0 mmol) in DMSO (6.0 mL) was added KF (872 mg, 15 mmol). This reaction mixture was heated at 100°C and 2-(3-fluorophenyl)pyrrolidine (991 mg, 6.0 mmol) was added. After stirring the reaction mixture at this temperature for 12 h, additional portions of 2-(3-fluorophenyl)pyrrolidine (165 mg, 1.0 mmol) and KF (58 mg, 1.0 mmol) were successively added. Third portions of 2-(3-fluorophenyl)pyrrolidine (165 mg, 1.0 mmol) and KF (58 mg, 1.0 mmol) were added 5 h after the second addition step and the reaction mixture was stirred at 100°C for an additional 5 h. The heterogeneous mixture was cooled at room temperature, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by flash chromatography (gradient 1/19/80 Et_3N/hexane/EtOAc – 1/99; Et_3N /EtOAc) and afforded the title compound (1.37 g, 77%) as a pale yellow solid. R_f 0.15 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^1H NMR (498 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.60 - 7.55 (m, J = 9.9 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.95 - 6.88 (m, 2H), 6.49 - 6.43 (m, J = 9.9 Hz, 1H), 5.01 - 4.94 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H),

3.96 (s, 1H), 3.80 (s, 1H), 2.51 - 2.42 (m, 1H), 2.08 - 1.96 (m, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.11 (d, J = 247.0 Hz, 1C), 159.24, 152.87, 146.01 (d, J = 6.5 Hz, 1C), 139.35, 138.86, 130.37 (br d, J = 8.0 Hz, 1C), 125.75, 121.32 (d, J = 2.6 Hz, 1C), 119.54, 114.19 (br d, J = 21.2 Hz, 1C), 112.76 (br d, J = 22.2 Hz, 1C), 111.82, 61.91, 60.25, 48.58, 35.97, 22.84, 14.43; HRMS: Calcd *m/z* for $C_{19}H_{20}FN_4O_2$ $[M+H]^+$: 355.1565, Found: 355.1566.

6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (9). To a solution of ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (1.06 g, 3 mmol) in ethanol (20 mL) and water (1 mL) was added KOH (842 mg, 15 mmol). The reaction mixture was stirred at room temperature for 3 h and evaporated to dryness. The residue was diluted with water (10 mL) and the pH was adjusted to 5-6 using concentrated hydrochloric acid. The aqueous phase was extracted with CH_2Cl_2 (2 X 25 mL) and EtOAc (2 X 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in *vacuo* to afford the title compound (701 mg, 72%) as a white yellow solid. R_f 0.10 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.86 (d, J = 9.9 Hz, 1H), 7.37 - 7.27 (m, 1H), 7.16 - 7.06 (m, 2H), 7.06 - 6.97 (m, 1H), 7.02 (br t, J = 8.4 Hz, 1H), 5.14 (dd, J=2.8, 8.1 Hz, 1H), 3.93 - 3.85 (m, 1H), 3.63 (br d, J = 10.4 Hz, 1H), 2.47 - 2.35 (m, 1H), 2.03 - 1.93 (m, 2H), 1.93 - 1.83 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.75 (d, J = 243.6 Hz, 1C), 159.70, 152.73, 147.11 (d, J = 6.5 Hz, 1C), 138.98, 138.43, 130.89 (br d, J = 8.5 Hz, 1C), 126.50, 122.35 (br d, J = 2.1 Hz, 1C), 119.67, 114.15 (d, J = 20.9 Hz, 1C), 113.36 (br d, J = 21.9 Hz, 1C), 113.06, 61.46, 48.74, 35.63, 23.05; HRMS: Calcd *m/z* for $C_{17}H_{15}FN_4NaO_2$ $[M+Na]^+$: 349.1074, Found: 349.1071.

General procedure A: Coupling of carboxylic acid 10 with amines. DIPEA (44 μL, 0.25 mmol, 2.5 equiv) was added to a solution of 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (33 mg, 0.10 mmol, 1 equiv) in DMF (1 mL). Solutions of HATU (38 mg, 0.10 mmol, 1

equiv) and the appropriate amine (0.12 mmol, 1.2 equiv; free amine or hydrochloric salt) in DMF (0.5 mL) were successively added dropwise. The reaction mixture was stirred at room temperature for 12 – 14 h. After completion, the reaction mixture was diluted with EtOAc (100 mL), washed with water (25 mL) and brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by flash chromatography (gradient 1/99; MeOH/ CH_2Cl_2 – 3/97; MeOH/ CH_2Cl_2).

_N_-(2-Fluoroethyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (13). The general procedure A was used with 2-fluoroethylamine hydrochloride. The title compound was obtained as a pale yellow solid (37 mg, quantitative). R_f 0.27 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 8.21 (br s, 1H), 7.72 (br d, *J* = 9.8 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.97 (dt, *J* = 1.9, 8.4 Hz, 1H), 6.92 (d, *J* = 9.7 Hz, 1H), 6.59 (br d, *J* = 7.6 Hz, 1H), 5.07 (br d, *J* = 8.0 Hz, 1H), 4.58 (td, *J* = 4.1, 47.3 Hz, 2H), 3.95 - 3.80 (m, 2H), 3.73 - 3.66 (m, 1H), 3.57 (br s, 1H), 2.57 - 2.47 (m, 1H), 2.17 - 2.01 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ163.16 (d, *J* = 247.2 Hz, 1C), 159.38, 151.87, 145.27 (d, *J* = 6.2 Hz, 1C), 136.32 (br s, 1C), 135.42, 130.55 (d, *J* = 8.3 Hz, 1C), 126.96, 121.10, 121.02 (br d, *J* = 2.8 Hz, 1C), 114.41 (br d, *J* = 21.2 Hz, 1C), 112.49 (br d, *J* = 21.9 Hz, 1C), 110.70, 83.17 (d, *J* = 166.2 Hz, 1C), 62.02, 48.61, 39.14 (d, *J* = 19.4 Hz, 1C), 35.80, 22.84; HRMS: Calcd *m/z* for $C_{19}H_{19}F_2N_5NaO$ $[M+Na]^+$: 394.1450, Found: 394.1453.

6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)-_N_-(3-fluoropropyl)imidazo[1,2-*b*]pyridazine-3-carboxamide (14). The general procedure A was used with 2-fluoropropylamine hydrochloride. The title compound was obtained as a beige solid (36 mg, 92 %). R_f 0.27 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.17 (s, 1H), 7.72 (br d, *J* = 9.8 Hz, 1H), 7.33 (dt, *J* = 5.8, 7.9 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.96 (dt, *J* = 2.1, 8.4 Hz, 1H), 6.93 - 6.84 (m, 3H), 6.70 - 6.55 (m, 1H), 5.14 - 5.01 (m, 1H), 4.64 - 4.42 (m, 2H), 3.94 - 3.85 (m, 1H), 3.72 - 3.63 (m, 1H), 3.59 - 3.49 (m, 1H), 3.39 (br s, 1H),

2.57 - 2.48 (m, 1H), 2.16 - 2.08 (m, 2H), 2.07 - 2.01 (m, 1H), 2.01 - 1.81 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 163.17 (d, *J* = 247.2 Hz, 1C), 159.44, 151.90, 145.23 (d, *J* = 6.2 Hz, 1C), 137.10, 130.68 (br d, *J* = 8.0 Hz, 1C), 126.97, 122.43, 120.94, 120.92, 114.37 (d, *J* = 21.2 Hz, 1C), 112.30 (d, *J* = 22.2 Hz, 1C), 110.50, 81.97 (d, *J* = 164.4 Hz, 1C), 62.07, 48.69, 35.73, 35.28 (d, *J* = 5.2 Hz, 1C), 30.59 (d, *J* = 19.4 Hz, 1C), 22.91; HRMS: Calcd *m/z* for $C_{20}H_{21}F_2N_5NaO$ $[M+Na]^+$: 408.1606, Found: 408.1608.

***N*-((3-Fluorocyclobutyl)methyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (15)**. The general procedure A was used with (3-fluorocyclobutyl)methanamine hydrochloride. The title compound was obtained as a white solid (37 mg, 90 %). R_f 0.25 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 8.18 (s, 1H), 7.72 (br d, *J* = 9.7 Hz, 1H), 7.33 (dt, *J* = 5.9, 8.0 Hz, 1H), 7.06 - 6.96 (m, 2H), 6.90 (td, *J* = 1.9, 9.7 Hz, 1H), 6.60 (br d, *J* = 8.6 Hz, 1H), 5.25 - 5.08 (m, 1H), 5.05 (br d, *J* = 7.3 Hz, 1H), 3.92 - 3.82 (m, 1H), 3.73 - 3.61 (m, *J* = 8.1 Hz, 1H), 3.53 - 3.42 (m, 1H), 3.34 (br s, 1H), 2.44 - 2.44 (m, 1H), 2.59 - 2.42 (m, 2H), 2.41 - 2.28 (m, 2H), 2.20 - 2.20 (m, 1H), 2.28 - 2.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.19 (d, *J* = 247.5 Hz, 1C), 159.47, 152.00, 145.08 (d, *J* = 6.2 Hz, 1C), 137.78, 137.22, 130.65 (br d, *J* = 8.3 Hz, 1C), 127.02, 122.38, 120.92 (d, *J* = 2.6 Hz, 1C), 114.48 (br d, *J* = 21.2 Hz, 1C), 112.42 (d, *J* = 21.9 Hz, 1C), 110.53, 87.30 (br d, *J* = 206.5 Hz, 1C), 62.10, 48.62, 43.31, 35.79, 33.88 (d, *J* = 4.4 Hz, 1C), 33.71 (d, *J* = 4.6 Hz, 1C), 27.62 (br d, *J* = 11.9 Hz, 1C), 22.81; HRMS: Calcd *m/z* for $C_{22}H_{23}F_2N_5NaO$ $[M+Na]^+$: 434.1763, Found: 434.1767.

***N*-(3-Fluorocyclobutyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (16)**. The general procedure A was used with 3-fluorocyclobutanamine hydrochloride (cis-trans). The title compound was obtained as a white solid (35 mg, 88 %). R_f 0.25 (1/1/98; Et_3N/MeOH/ CH_2Cl_2). The NMR characterization was achieved on the inseparable diastereoisomeric mixture.

Whenever distinguishable, chemical shifts given are for one isomer with those of the second one listed in square brackets. ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.77 (d, *J* = 34.6 Hz, 1H), 8.18 (s, 1H), 7.69 (br d, *J* = 9.9 Hz, 1H), 7.41 - 7.29 (m, 1H), 7.08 - 6.94 (m, 2H), 6.93 - 6.85 (m, 1H), 6.55 (br d, *J* = 8.6 Hz, 1H), 5.19 (d, *J* = 56.8 Hz, 0.5H), 5.09 (br t, *J* = 7.0 Hz, 1H), [4.86 (q, *J* =6.6, 55.7 Hz, 0.5H)], 4.74 - 4.62 (m, 0.5H), [4.21 (br sxt, *J* = 7.8 Hz, 0.5H)], 3.95 - 3.84 (m, 1H), 3.76 - 3.65 (m, 1H), 3.01 - 2.90 (m, 1H), 2.76 - 2.60 (m, 1H), 2.59 - 2.50 (m, 1H), 2.42 - 1.94 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.19 (d, *J* = 247.8 Hz, 1C), 158.89, [158.57], 152.09, [152.06], 144.73, 137.84, 137.31, 130.81 (d, *J* = 8.3 Hz, 1C), [130.67 (br d, *J* = 8.0 Hz, 1C)], 127.03, [127.00], 122.31, [122.14], 121.23 (br d, *J* = 2.6 Hz, 1C), [121.10 (br d, *J* = 2.6 Hz, 1C)], 114.54 (br d, *J* = 21.2 Hz, 1C), 112.62 (d, *J* = 4.9 Hz, 1C), [112.47 (br d, *J* = 4.9 Hz, 1C)], 110.71, [110.62], 86.84 (br d, *J* = 200.3 Hz, 1C), [81.67 (br d, *J* = 210.6 Hz, 1C)], 61.84, 48.53, [48.46], 40.57 (d, *J* = 8.3 Hz, 1C), 39.97 (d, *J* = 20.1 Hz, 1C), [39.83 (d, *J* = 21.2 Hz, 1C)], 38.55 (d, *J* = 3.4 Hz, 1C), [38.37 (br d, *J* = 3.6 Hz, 1C)], 35.84, [35.80], [34.35 (br d, *J* = 23.0 Hz, 1C)], 22.74, [22.70]; HRMS: Calcd for $C_{21}H_{21}F_2N_5NaO$ $[M+Na]^+$: 420.1606, Found: 420.1610.

(3-Fluoroazetidin-1-yl)(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanone (17). The general procedure A was used with 3-fluoroazetidine hydrochloride. The title compound was obtained as a white solid (36 mg, 95 %). R_f 0.27 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.60 (d, *J* = 9.9 Hz, 1H), 7.27 (br s, 1H), 7.01 (br d, *J* = 7.7 Hz, 1H), 6.92 (br d, *J* = 9.0 Hz, 2H), 6.51 (br d, *J* = 9.9 Hz, 1H), 5.23 (br d, *J* = 59.7 Hz, 1H), 5.02 (d, *J* = 7.0 Hz, 1H), 4.50 - 4.17 (m, 4H), 4.00 - 3.89 (m, 1H), 3.78 - 3.69 (m, 1H), 2.53 - 2.38 (m, 1H), 2.11 - 1.94 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.12 (d, *J* = 247.0 Hz, 1C), 161.37, 152.73, 138.07, 135.43, 130.44, 130.38, 125.96, 121.56, 121.22 (d, *J* = 2.6 Hz, 1C), 114.19 (d, *J* = 21.2 Hz, 1C), 112.68 (br d, *J* = 22.2 Hz, 1C), 111.30, 82.43 (br d, *J* = 204.7 Hz, 1C), 61.92, 48.71, 38.58, 36.43, 35.78, 22.84; HRMS: Calcd *m/z* for $C_{20}H_{20}F_2N_5O$ $[M+H]^+$: 384.1630, Found: 384.1632.

174

175 ***N*-(4,4-Difluorocyclohexyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-**
176 **carboxamide (18)**. The general procedure A was used with 4,4-difluorocyclohexanamine hydrochloride.
177 The title compound was obtained as a white solid (30 mg, 68 %). R_f 0.22 (1:1:98 Et_3N/MeOH/ CH_2Cl_2).
178 ^1H NMR (498 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 8.19 (s, 1H), 7.70 (br d, *J* = 9.9 Hz, 1H), 7.34 (dt, *J* = 5.9,
179 7.9 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.97 (dt, *J* = 2.0, 8.2 Hz, 1H), 6.87 (br d, *J* = 9.5 Hz, 1H), 6.55 (br
180 d, *J* = 8.6 Hz, 1H), 5.06 (br d, *J* = 7.7 Hz, 1H), 4.18 - 4.07 (m, 1H), 3.90 - 3.81 (m, 1H), 3.67 (dt, *J* = 7.1,
181 9.6 Hz, 1H), 2.52 (s, 1H), 2.23 - 1.81 (m, 9H), 1.68 - 1.51 (m, 2H), 1.45 - 1.29 (m, 1H); ^{13}C NMR (125
182 MHz, $CDCl_3$) δ 163.19 (d, *J* = 247.5 Hz, 1C), 158.69, 152.10, 144.69, 137.86, 137.28, 130.73 (br d, *J* =
183 8.3 Hz, 1C), 127.03, 122.34, 121.23 (d, *J* = 2.8 Hz, 1C), 114.49 (br d, *J* = 21.2 Hz, 1C), 112.53 (br d, *J* =
184 22.2 Hz, 1C), 110.63, 61.82, 48.51, 45.54, 38.59, 35.80, 32.43 (br t, *J* = 24.8 Hz, 1C), 32.36 (br t, *J* = 24.6
185 Hz, 1C), 28.92 (br dd, *J* = 9.3, 30.7 Hz, 1C), 22.69; HRMS: Calcd *m/z* for $C_{23}H_{25}F_3N_5O$ $[M+H]^+$:
186 444.2006, Found: 444.2009.

187

188 ***N*-(2-(2-Fluoroethoxy)ethyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine-3-**
189 **carboxamide (19)**. The general procedure A was used with 2-(2-fluoroethoxy)ethanamine hydrochloride.
190 The title compound was obtained as a white solid (41 mg, 98 %). R_f 0.23 (1:1:98 Et_3N/MeOH/ CH_2Cl_2).
191 ^1H NMR (498 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 8.16 (s, 1H), 7.68 (br d, *J* = 9.9 Hz, 1H), 7.28 - 7.28 (m,
192 1H), 7.29 (dt, *J* = 5.9, 8.1 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.99 - 6.89 (m, 2H), 6.56 (br d, *J* = 8.4 Hz,
193 1H), 5.07 (br d, *J* = 7.3 Hz, 1H), 4.74 - 4.72 (m, 1H), 4.66 - 4.51 (m, 2H), 3.95 - 3.89 (m, 1H), 3.88 - 3.81
194 (m, 1H), 3.80 - 3.71 (m, 2H), 3.71 - 3.57 (m, 3H), 3.46 (br s, 1H), 2.56 - 2.45 (m, 1H), 2.15 - 1.96 (m,
195 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.12 (d, *J* = 247.0 Hz, 1C), 159.31, 151.78, 145.54 (d, *J* = 6.5 Hz,
196 1C), 137.74, 137.11, 130.48 (br d, *J* = 8.0 Hz, 1C), 126.81, 122.39, 121.09 (d, *J* = 3.1 Hz, 1C), 114.30 (br
197 d, *J* = 21.2 Hz, 1C), 112.56 (br d, *J* = 22.2 Hz, 1C), 110.60, 82.89 (d, *J* = 169.8 Hz, 1C), 70.70, 70.26 (d,

198 *J* = 19.6 Hz, 1C), 61.90, 48.62, 38.46, 35.71, 22.83; HRMS: Calcd *m/z* for $C_{21}H_{23}F_2N_5NaO_2$ $[M+Na]^+$:
199 438.1712, Found: 438.1714.

200

201 ***N*-(4-Fluorobenzyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide**
202 **(20)**. The general procedure A was used with (4-fluorophenyl)methanamine. The title compound was
203 obtained as a white solid (41 mg, 95 %). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^1H NMR (400 MHz,
204 $CDCl_3$) δ 8.74 (br s, 1H), 8.17 (s, 1H), 7.68 (br d, *J* = 9.8 Hz, 1H), 7.34 - 7.24 (m, 2H), 7.20 (dt, *J* = 5.9,
205 7.8 Hz, 1H), 7.06 - 6.97 (m, 2H), 6.87 (dd, *J* = 2.3, 8.4 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.73 (br d, *J* =
206 9.7 Hz, 1H), 6.55 (d, *J* = 8.5 Hz, 1H), 4.94 - 4.86 (m, 1H), 4.62 (dd, *J* = 6.2, 14.8 Hz, 1H), 4.33 (br dd, *J* =
207 5.9, 19.8 Hz, 1H), 3.58 (br s, 1H), 3.46 - 3.30 (m, 1H), 2.48 - 2.35 (m, 1H), 2.05 - 1.89 (m, 3H); ^{13}C NMR
208 (101 MHz, $CDCl_3$) δ 163.31 - 163.28 (m, 1C), 163.31 - 163.28 (m, 1C), 163.80 (d, *J* = 97.0 Hz, 1C),
209 161.35 (d, *J* = 95.0 Hz, 1C), 159.17, 151.78, 145.01 (d, *J* = 6.2 Hz, 1C), 137.22, 134.43 (d, *J* = 3.3 Hz,
210 1C), 130.55 (br d, *J* = 8.3 Hz, 1C), 129.31 (br d, *J* = 8.3 Hz, 1C), 126.97, 122.17, 120.78 (br d, *J* = 2.5 Hz,
211 1C), 115.37 (br d, *J* = 21.6 Hz, 1C), 114.36 (d, *J* = 21.1 Hz, 1C), 112.24 (br d, *J* = 22.0 Hz, 1C), 110.59,
212 61.96, 48.48, 42.21, 35.67, 22.67; HRMS: Calcd *m/z* for $C_{24}H_{21}F_2N_5NaO$ $[M+Na]^+$: 456.1606, Found:
213 456.1615.

214

215 ***N*-(3-Fluorobenzyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide**
216 **(21)**. The general procedure A was used with (3-fluorophenyl)methanamine. The title compound was
217 obtained as a white solid (41 mg, 95 %). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^1H NMR (498 MHz,
218 $CDCl_3$) δ 8.77 (br s, 1H), 8.22 (s, 1H), 7.73 (br d, *J* = 9.7 Hz, 1H), 7.32 (dt, *J* = 6.1, 7.8 Hz, 1H), 7.22 (br
219 q, *J* = 7.7 Hz, 1H), 7.12 (br d, *J* = 7.5 Hz, 1H), 7.03 (br d, *J* = 9.5 Hz, 1H), 6.99 (dt, *J* = 2.2, 8.4 Hz, 1H),
220 6.93 - 6.81 (m, 2H), 6.75 (br d, *J* = 9.5 Hz, 1H), 6.60 (br d, *J* = 6.6 Hz, 1H), 4.99 - 4.92 (m, 1H), 4.69 (dd,
221 *J* = 6.2, 15.2 Hz, 1H), 4.42 (br s, 1H), 3.66 (br s, 1H), 3.54 - 3.40 (m, 1H), 2.45 (br qd, *J* = 8.5, 11.8 Hz,

1H), 2.02 (dt, *J* = 4.8, 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.09 (br d, *J* = 247.2 Hz, 1C), 163.03 (d, *J* = 246.2 Hz, 1C), 159.26, 151.83, 145.02 (d, *J* = 6.2 Hz, 1C), 141.34 (d, *J* = 6.7 Hz, 1C), 137.82, 137.41, 130.57 (br d, *J* = 8.3 Hz, 1C), 130.13 (d, *J* = 8.3 Hz, 1C), 127.06, 122.18, 120.77, 114.30 (d, *J* = 21.2 Hz, 1C), 114.13 (br d, *J* = 20.9 Hz, 1C), 112.32, 112.14, 110.56, 62.04, 48.61, 42.36, 35.67, 22.75; HRMS: Calcd *m/z* for $C_{24}H_{22}F_2N_5O$ $[M+H]^+$: 434.1787, Found: 434.1794.

N-(2,4-Difluoro-3-methoxybenzyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (22). The general procedure A was used with (2,4-difluoro-3-methoxyphenyl)methanamine. The title compound was obtained as a white solid (22 mg, 46 %). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.85 (br s, 1H), 8.22 (s, 1H), 7.75 (br d, *J*=9.6 Hz, 1H), 7.33 - 7.25 (m, 1H), 7.06 - 7.00 (m, 1H), 6.96 - 6.84 (m, 4H), 6.61 (br d, *J*=9.2 Hz, 1H), 5.02 (dd, *J*=1.2, 8.7 Hz, 1H), 4.69 - 4.62 (m, 1H), 4.54 - 4.43 (m, 1H), 4.06 - 4.03 (m, 3H), 3.84 - 3.76 (m, 1H), 3.64 - 3.56 (m, 1H), 2.56 - 2.47 (m, 1H), 2.13 - 2.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.17 (d, *J*=247.4 Hz, 1C), 159.37, 155.15 (br d, *J* = 252.1 Hz, 1C), 151.86, 148.25 (d, *J* = 181.2 Hz, 1C), 145.13, 145.08, 137.84, 137.51, 130.61 (br d, *J*=8.2 Hz, 1C), 127.15, 122.80 (d, *J* = 10.1 Hz, 1C), 122.20, 120.86 (br d, *J* = 2.3 Hz, 1C), 114.45 (d, *J* = 21.1 Hz, 1C), 112.30 (d, *J* = 21.9 Hz, 1C), 111.82 (br d, *J* = 19.3 Hz, 1C), 111.79 (br d, *J* = 19.3 Hz, 1C), 110.57, 62.10, 62.02 - 61.92 (m, 1C), 48.57, 36.60, 35.82, 22.84; HRMS: Calcd *m/z* for $C_{25}H_{23}F_3N_5NaO_2$ $[M+Na]^+$: 504.1618, Found: 504.1623.

N-(4-Fluorophenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (23). The general procedure A was used with 4-fluoroaniline. The title compound was obtained as a white solid (18 mg, 43 %). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 10.50 (br s, 1H), 8.31 (br s, 1H), 7.73 (d, *J* = 9.9 Hz, 1H), 7.49 (br s, 2H), 7.33 - 7.28 (m, 1H), 7.05 (t, *J* = 8.7 Hz, 2H), 7.02 - 6.96 (m, 2H), 6.92 (td, *J* = 2.0, 9.5 Hz, 1H), 6.58 (br d, *J* = 8.1 Hz, 1H), 5.12 (br d, *J* = 8.1 Hz,

1H), 4.02 - 3.96 (m, 1H), 3.83 - 3.76 (m, 1H), 2.62 - 2.53 (m, 1H), 2.25 - 2.10 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.24 (d, *J* = 247.8 Hz, 1C), 159.37 (d, *J* = 243.4 Hz, 1C), 157.15, 152.12, 144.68, 130.70 (br d, *J* = 8.3 Hz, 1C), 127.17, 122.14, 122.10 (br s, 1C), 121.13, 121.11, 115.65 (br d, *J* = 22.7 Hz, 1C), 114.64 (d, *J*=21.4 Hz, 1C), 112.59 (d, *J* = 22.2 Hz, 1C), 110.91, 62.08, 48.66, 35.86, 22.79; HRMS: Calcd *m/z* for $C_{23}H_{20}F_2N_5O$ $[M+H]^+$: 420.1630, Found: 420.1635.

***N*-(3-Fluorophenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (24)**. The general procedure A was used with 3-fluoroaniline. The title compound was obtained as a white solid (21 mg, 50 %). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 10.64 (br s, 1H), 8.29 (s, 1H), 7.69 (br d, *J* = 9.7 Hz, 1H), 7.57 (br d, *J* = 6.8 Hz, 1H), 7.33 (br dt, *J* = 6.0, 7.9 Hz, 1H), 7.26 (dt, *J* = 6.6, 8.1 Hz, 1H), 7.18 - 7.06 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.01 - 6.99 (m, 1H), 6.99 (dt, *J* = 2.0, 8.4 Hz, 1H), 6.93 (br td, *J* = 2.1, 9.6 Hz, 1H), 6.81 (ddt, *J* = 0.7, 2.6, 8.3 Hz, 1H), 6.55 (br d, *J* = 9.3 Hz, 1H), 5.12 (br d, *J* = 7.9 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.85 - 3.75 (m, 1H), 2.66 - 2.55 (m, 1H), 2.16 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.25 (d, *J* = 247.8 Hz, 1C), 163.00 (d, *J* = 244.7 Hz, 1C), 157.16, 152.14, 144.67 (br d, *J* = 7.7 Hz, 1C), 139.50 (br d, *J* = 11.1 Hz, 1C), 138.17, 130.76 (br d, *J* = 8.3 Hz, 1C), 130.01 (br d, *J* = 9.3 Hz, 1C), 127.10, 122.22, 121.15 (d, *J* = 2.8 Hz, 1C), 115.41, 114.69 (br d, *J* = 21.2 Hz, 1C), 112.60 (br d, *J* = 22.2 Hz, 1C), 111.13, 110.82 (br d, *J* = 21.4 Hz, 1C), 107.74 (br d, *J*=26.6 Hz, 1C), 62.12, 48.66, 35.88, 22.75; HRMS: Calcd *m/z* for $C_{23}H_{20}F_2N_5O$ $[M+H]^+$: 420.1630, Found: 420.1638.

***N*-(2-Fluorophenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (25)**. The general procedure A was used with 2-fluoroaniline. The title compound was obtained as a white solid (41 mg, quantitative). R_f 0.19 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 10.73 (br s, 1H), 8.58 (t, *J* = 7.9 Hz, 1H), 8.35 (s, 1H), 8.79 - 8.09 (m, 1H), 7.69 (d, *J* = 9.9 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.24 - 7.19 (m, 1H), 7.19 - 7.09 (m, 3H), 7.04 - 6.99 (m, 1H), 6.96 (dt, *J* = 2.3, 8.4 Hz, 1H), 6.91

(td, *J* = 1.8, 9.5 Hz, 1H), 6.51 (d, *J* = 9.9 Hz, 1H), 5.07 (dd, *J* = 1.7, 8.0 Hz, 1H), 4.09 - 4.01 (m, 1H), 3.89 - 3.81 (m, 1H), 2.62 - 2.52 (m, 1H), 2.19 - 2.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.22 (d, *J* = 247.8 Hz, 1C), 157.32, 152.31, 152.87 (d, *J* = 242.8 Hz, 1C), 145.19 (d, *J* = 5.9 Hz, 1C), 138.41, 138.19, 130.65 (br d, *J* = 8.5 Hz, 1C), 126.89, 126.66, 124.67 (d, *J* = 3.1 Hz, 1C), 124.24 (br d, *J* = 8.0 Hz, 1C), 122.88, 122.51, 121.08 (d, *J* = 3.1 Hz, 1C), 114.74 (d, *J* = 19.1 Hz, 1C), 114.55 (d, *J* = 21.2 Hz, 1C), 112.54 (br d, *J* = 22.2 Hz, 1C), 111.39, 62.30, 48.58 (d, *J* = 9.8 Hz, 1C), 36.04, 22.78; HRMS: Calcd *m/z* for $C_{23}H_{20}F_2N_5O$ $[M+H]^+$: 420.1630, Found: 420.1636.

***N*-(3-Fluoro-4-methoxyphenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (26)**. The general procedure A was used with 3-fluoro-4-methoxyaniline. The title compound was obtained as a white solid (45 mg, quantitative). R_f 0.20 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 8.27 (s, 1H), 7.69 (br d, *J* = 9.9 Hz, 1H), 7.48 (br s, 1H), 7.31 (dt, *J* = 6.0, 7.9 Hz, 1H), 7.10 (br d, *J* = 4.4 Hz, 1H), 7.01 (td, *J* = 0.7, 7.7 Hz, 1H), 6.98 (dt, *J* = 2.6, 8.5 Hz, 2H), 6.95 - 6.84 (m, 2H), 6.55 (br d, *J* = 8.2 Hz, 1H), 5.11 (br d, *J* = 7.9 Hz, 1H), 3.97 (br s, 1H), 3.89 (s, 3H), 3.78 (br d, *J* = 19.4 Hz, 1H), 2.65 - 2.54 (m, 1H), 2.24 - 2.11 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.22, 163.23 (d, *J* = 247.8 Hz, 1C), 157.01, 152.08, 151.09, 149.10 - 149.10 (m, 1C), 150.10 (br d, *J* = 247.8 Hz, 1C), 144.47 (br d, *J* = 63.7 Hz, 1C), 131.41 (br d, *J* = 7.5 Hz, 1C), 131.37 - 131.29 (m, 1C), 131.37 - 131.29 (m, 1C), 130.73 (br d, *J* = 8.5 Hz, 1C), 127.04, 122.29, 121.13 (br d, *J*=2.6 Hz, 1C), 114.64 (br d, *J*=21.4 Hz, 1C), 113.73, 112.58 (br d, *J* = 21.9 Hz, 1C), 110.97, 62.09, 56.60, 48.64, 35.87, 22.77; HRMS: Calcd *m/z* for $C_{24}H_{22}F_2N_5O_2$ $[M+H]^+$: 450.1736, Found: 450.1746.

***N*-(4-(2-Fluoroethyl)phenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (27)**. The general procedure A was used with 4-(2-fluoroethyl)aniline. The title compound was obtained as a white solid (28 mg, 62 %). R_f 0.22 (1:1:98 Et_3N/MeOH/ CH_2Cl_2). ^{1}H NMR (498 MHz,

$CDCl_3$) δ 10.54 (br s, 1H), 8.28 (s, 1H), 7.65 (d, *J* = 9.9 Hz, 1H), 7.57 - 7.42 (m, 2H), 7.33 - 7.28 (m, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.02 - 6.95 (m, 2H), 6.91 (td, *J* = 1.9, 9.6 Hz, 1H), 6.51 (br d, *J* = 9.2 Hz, 1H), 5.09 (br d, *J* = 8.1 Hz, 1H), 4.65 (td, *J* = 6.4, 47.1 Hz, 2H), 4.01 - 3.94 (m, 1H), 3.80 - 3.71 (m, 1H), 3.01 (td, *J* = 6.4, 23.4 Hz, 2H), 2.60 (s, 1H), 2.22 - 2.09 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.22 (d, *J* = 247.5 Hz, 1C), 157.08, 152.05, 144.85, 144.80, 137.89, 136.57, 133.03, 132.98, 130.67 (br d, *J* = 8.3 Hz, 1C), 129.54, 126.96, 121.15 (br d, *J* = 2.6 Hz, 1C), 120.53, 114.60 (br d, *J* = 21.2 Hz, 1C), 112.60 (br d, *J* = 21.9 Hz, 1C), 110.96, 84.10 (d, *J* = 168.8 Hz, 1C), 62.08, 48.63, 36.39 (d, *J* = 20.4 Hz, 1C), 35.87, 22.73; HRMS: Calcd *m/z* for $C_{25}H_{24}F_2N_5O$ $[M+H]^+$: 448.1943, Found: 448.1948.

6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (11). Ethyl 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (89 mg, 0.25 mmol) was dissolved in an ammonia solution (7.0 M in methanol, 5 mL). The reaction mixture was stirred at room temperature for 15 h then concentrated and dried in *vacuo* to afford the title compound (78 mg, 96 %) as a white solid. R_f 0.10 (1:99 MeOH/ CH_2Cl_2).^{1}H NMR (498 MHz, DMSO-d_6) δ 8.04 - 7.87 (m, 2H), 7.87 - 7.72 (m, 1H), 7.71 - 7.58 (m, 1H), 7.39 - 7.29 (m, 1H), 7.14 - 6.96 (m, 3H), 6.84 (br s, 1H), 5.17 - 5.05 (m, 1H), 3.93 (br s, 1H), 3.61 (br d, *J* = 9.6 Hz, 1H), 2.47 - 2.40 (m, 1H), 2.04 - 1.90 (m, 2H), 1.81 (br s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.41 (d, *J* = 244.1 Hz, 1C), 159.44, 151.75, 146.33 (d, *J* = 6.4 Hz, 1C), 137.43, 135.99, 130.64 (br d, *J* = 8.2 Hz, 1C), 126.65, 122.07, 121.58 (br d, *J* = 2.1 Hz, 1C), 113.74 (br d, *J* = 20.9 Hz, 1C), 112.18 (br d, *J* = 21.4 Hz, 1C), 111.84, 61.23, 48.28, 35.24, 22.50; HRMS: Calcd *m/z* for $C_{17}H_{16}FN_5O$ $[M+H]^+$: 326.1412, Found: 326.1418.

316 **6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)-*N*-methylimidazo[1,2-*b*]pyridazine-3-carboxamide (12)**. Ethyl
317 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate (89 mg, 0.25 mmol) was
318 dissolved in a methylamine solution (33 wt. % in absolute ethanol, 5 mL). The reaction mixture was
319 stirred at room temperature for 15 h then concentrated and dried in *vacuo* to afford the title compound (85
320 mg, quantitative) as a tan solid. R_f 0.10 (1:99 MeOH/ CH_2Cl_2).^{1}H NMR (498 MHz, DMSO-d_6) δ 8.18 -
321 7.98 (m, 1H), 7.95 (br d, *J* = 9.9 Hz, 1H), 7.87 (s, 1H), 7.37 (dt, *J* = 6.1, 8.0 Hz, 1H), 7.17 - 7.09 (m, 2H),
322 7.07 - 7.01 (m, 1H), 7.01 - 6.86 (m, 1H), 5.16 (dd, *J* = 2.7, 8.3 Hz, 1H), 4.00 - 3.93 (m, 1H), 3.68 - 3.60
323 (m, 1H), 2.82 - 2.61 (m, 3H), 2.47 - 2.39 (m, 1H), 2.06 - 1.94 (m, 2H), 1.89 - 1.79 (m, 1H); ^{13}C NMR
324 (125 MHz, DMSO-d_6) δ 162.88 (br d, *J* = 243.9 Hz, 1C), 159.05, 152.10, 146.94 (br d, *J* = 6.2 Hz, 1C),
325 137.70, 135.99, 131.12 (d, *J*=8.0 Hz, 1C), 127.17, 122.18, 121.86, 114.11 (br d, *J* = 20.6 Hz, 1C), 112.72
326 (br d, *J* = 20.1 Hz, 1C), 112.36, 61.68, 48.88, 35.66, 25.63, 23.09; HRMS: Calcd *m/z* for $C_{18}H_{18}FN_5NaO$
327 $[M+Na]^+$: 362.1388, Found: 362.1391.
328
329 ***tert*-Butyl (2-(2-fluoroethoxy)ethyl)carbamate (29)**. To a solution of *N*-Boc-ethanolamine (0.75 g, 4.71
330 mmol, 1.03) and 2-fluoroethyl tosylate (1.00 g, 4.58 mmol) in DMF (10 mL) was added NaH (60% disp.
331 in oil, 0.19 g, 4.75 mmol) in portions. After 12 hours, the reaction mixture was diluted with EtOAc and
332 water was slowly added. The aqueous layer was extracted with EtOAc and the combined organic phases
333 were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a crude yellow
334 oil. Purification by flash chromatography (gradient 9/1; hexane/EtOAc – 6/4; hexane/EtOAc) yielded
335 0.47 g of the title compound as clear oil (50%). R_f 0.27 (6:4 hexanes/EtOAc). ^{1}H NMR (498 MHz,
336 $CDCl_3$) δ 4.94 (br s, 1H), 4.62 - 4.47 (m, 2H), 3.75 - 3.65 (m, 2H), 3.57 (t, *J* = 5.2 Hz, 2H), 3.33 (br q, *J* =
337 5.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.95, 82.95 (d, *J* = 169.0 Hz, 1C), 79.21,
338 70.43, 70.08 (d, *J* = 19.6 Hz, 1C), 28.38; HRMS: Calcd *m/z* for $C_9H_{18}FNNaO_3$ $[M+Na]^+$: 230.1163,
339 Found: 230.1164.
340

2-(2-Fluoroethoxy)ethanamine hydrochloride (30). To a solution of *tert*-butyl (2-(2-fluoroethoxy)ethyl)carbamate (0.42 g, 2.03 mmol) in dichloromethane (2 mL) was added TFA (2 mL). After 1 hour, the reaction mixture was concentrated under reduced pressure to a crude brown oil. The crude product precipitated as the amine hydrochloride salt upon addition of a 1 M solution of HCl in diethyl ether (4 mL), filtered and obtained as a white powder (0.28 g, 98% yield). ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.40 - 8.13 (m, 3H), 4.72 - 4.56 (m, 2H), 3.87 (t, *J* = 4.8 Hz, 2H), 3.81 (td, *J* = 3.8, 30.0 Hz, 2H), 3.34 - 3.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.14 (d, *J* = 168.0 Hz, 1C), 70.29 (d, *J* = 19.4 Hz, 1C), 66.77, 39.59; HRMS: Calcd *m/z* for $C_4H_{11}FNO$ $[M^*]^+$: 108.0819, Found: 108.0822.

***tert*-Butyl (4-(2-hydroxyethyl)phenyl)carbamate (32)**. To a solution of 2-(4-aminophenyl)ethanol (1.0 g, 7.3 mmol) in THF (20 mL) at 0°C was added Et_3N (1.01 mL, 7.3 mmol) followed by Boc_2O in 3 portions (1.59 g, 7.3 mmol). The reaction mixture was left to warm to room temperature and stirred overnight. The mixture was diluted with EtOAc and washed with water. The aqueous phase was further extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (20% EtOAc/CH_2Cl_2) to afford 1.47 g of the title compound as a white solid (85%). R_f 0.35 (1:4 EtOAc/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 7.4 Hz, 2H), 6.47 (br s, 1H), 3.82 (t, *J* = 6.6 Hz, 2H), 2.81 (t, *J* = 6.6 Hz, 2H), 1.51 (s, 9H), 1.49 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.83, 136.78, 133.07, 129.50, 118.93, 80.47, 63.70, 38.49, 28.34; HRMS: Calcd *m/z* for $C_{13}H_{23}N_2O_3$ $[M+NH_4]^+$: 255.1703, Found: 255.1700.

***tert*-Butyl (4-(2-fluoroethyl)phenyl)carbamate (33)**. To a solution of *tert*-butyl (4-(2-hydroxyethyl)phenyl)carbamate (949 mg, 4 mmol) in CH_2Cl_2 (25 mL, plastic vessel) at -78°C under nitrogen was added DAST (1.06 mL, 8 mmol) dropwise. After 30 min, the reaction mixture was left to

warm to 0°C and stirred at this temperature for 6 h. Unreacted DAST was carefully quenched by water under vigorous stirring followed by addition of saturated K_2CO_3 aqueous solution. The phases were separated and the aqueous layer extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (10% EtOAc/CH_2Cl_2) to afford 824 mg of the title compound as a pale yellow crystalline solid (86%). R_f 0.90 (1:9 EtOAc/CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ 7.32 (br d, J = 8.2 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 6.46 (br s, 1H), 4.60 (td, J = 6.6, 47.1 Hz, 2H), 2.98 (td, J = 6.6, 22.9 Hz, 2H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.77, 136.98, 131.67 (br d, J = 6.7 Hz, 1C), 129.48, 129.35, 118.79, 84.15 (br d, J = 169.0 Hz, 1C), 80.49, 38.54, 36.25 (br d, J = 20.4 Hz, 1C), 28.35; HRMS: Calcd *m/z* for $C_{13}H_{18}FNNa_2O_2$ $[M+Na]^+$: 262.1214, Found: 262.1213.

4-(2-Fluoroethyl)aniline (34). To an ice cold solution of *tert*-Butyl (4-(2-fluoroethyl)phenyl)carbamate (600 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added TFA (1.15 mL, 15 mmol). The reaction mixture was left to warm to room temperature and stirred for 5 h. The volatiles were removed in *vacuo* and the residue was dissolved in EtOAc and washed with aqueous saturated $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to afford 325 mg of the title compound as a pale yellow oil (93%). R_f 0.31 (3:7 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 - 7.00 (m, 2H), 6.67 - 6.63 (m, 2H), 4.57 (td, J = 6.8, 47.2 Hz, 2H), 3.75 - 3.28 (m, 2H), 2.91 (td, J = 6.8, 22.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.03, 129.80, 126.80 (d, J = 7.3 Hz, 1C), 115.30, 84.50 (br d, J = 169.0 Hz, 1C), 36.08 (d, J = 20.1 Hz, 1C); HRMS: Calcd *m/z* for $C_8H_{11}FN$ $[M+H]^+$: 140.0870, Found: 140.0871.

6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)-*N*-(3-hydroxycyclobutyl)imidazo[1,2-*b*]pyridazine-3-carboxamide (35). To a solution of 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-

carboxylic acid (90 mg, 0.28 mmol) in DMF (4 mL) was added DIPEA (0.12 mL, 0.7 mmol) and HATU (107 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 5 min and 3-aminocyclobutanol hydrochloride (42 mg, 0.34 mmol) was added in one portion. The reaction mixture was stirred overnight and then diluted with EtOAc and poured into water. The aqueous phase was extracted three times with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford 110 mg of the title compound as a beige solid (99%). R_f 0.15 (5:95 MeOH/CH_2Cl_2). The NMR characterization was achieved on the inseparable diastereoisomeric mixture. Whenever distinguishable, chemical shifts given are for one isomer with those of the second one listed in square brackets. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (br s, 1H), 8.22 (d, *J* = 3.7 Hz, 1H), 7.74 (br d, *J* = 9.9 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.09 - 6.97 (m, 2H), 6.97 - 6.91 (m, 1H), 6.63 - 6.49 (m, 1H), 5.10 (br d, *J* = 7.3 Hz, 1H), 4.71 - 4.52 (m, 1H), 4.21 - 4.12 (m, 1H), 3.98 - 3.90 (m, 1H), 3.79 - 3.72 (m, 1H), 3.20 (dq, *J* = 4.2, 7.5 Hz, 1H), [2.97 - 2.91 (m, 1H)], 2.61 - 2.53 (m, 1H), 2.52 - 2.42 (m, 1H), 2.42 - 2.28 (m, 1H), 2.28 - 2.04 (m, 3H), 2.00 - 1.91 (m, 1H), 1.85 (br d, *J* = 9.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.24 (br d, *J* = 247.5 Hz, 1C), [163.21 (br d, *J* = 247.5 Hz, 1C)], 158.93, [158.70], 152.14, [152.07], 144.84, 137.79, 137.20 (br d, *J* = 7.3 Hz, 1C), 130.76 (d, *J* = 8.5 Hz, 1C), [130.71 (d, *J* = 8.5 Hz, 1C)], 127.05, [127.01], 122.47 (br s, 1C), [122.36 (br s, 1C)], 121.21 (d, *J* = 2.8 Hz, 1C), [121.14 (d, *J* = 2.8 Hz, 1C)], 114.57 (br d, *J*=21.3 Hz, 1C), [114.59 (br dd, *J* = 3.4, 21.2 Hz, 1C)], 112.63 (br d, *J* = 22.3 Hz, 1C), [112.65 (br d, *J* = 21.8 Hz, 1C)], 110.69, [110.65], 65.28, 61.92, [61.42], 55.75, 48.59, [48.47], 41.78, [41.63], 40.50, [40.38], 35.88, [35.75], 22.77, [22.76]; HRMS: Calcd *m/z* for $C_{21}H_{22}FN_5NaO_2$ $[M+Na]^+$: 418.1650, Found: 418.1650.

3-(6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamido)cyclobutyl 4-methylbenzenesulfonate (36). To an ice cold solution of 6-(2-(3-Fluorophenyl)pyrrolidin-1-yl)-*N*-(3-hydroxycyclobutyl)imidazo[1,2-b]pyridazine-3-carboxamide (156 mg, 0.40 mmol) in CH_2Cl_2 (15 mL)

was successively added Et_3N (84 μL, 0.60 mmol) and 4-toluenesulfonyl chloride (81 mg, 0.42 mmol). The reaction was left to warm to room temperature and allowed to stir for 2 days. The reaction mixture was then diluted with CH_2Cl_2 and poured into water. The layers were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford 149 mg of the title compound as a tan solid (70 %). R_f 0.46 (5:95 MeOH/CH_2Cl_2). The NMR characterization was achieved on the inseparable diastereoisomeric mixture. Whenever distinguishable, chemical shifts given are for one isomer with those of the second one listed in square brackets. ^{1}H NMR (498 MHz, $CDCl_3$) δ 8.76 (br s, 1H), 8.14 (br s, 1H), 7.81 - 7.74 (m, 2H), 7.70 - 7.64 (m, 1H), 7.39 - 7.29 (m, 3H), 7.07 - 7.00 (m, 1H), 6.99 - 6.94 (m, 1H), 6.90 - 6.84 (m, 1H), 6.54 (br s, 1H), 5.09 - 5.04 (m, 1H), 4.56 - 4.49 (m, 1H), 4.23 - 4.15 (m, 1H), 3.87 (br d, *J* = 8.6 Hz, 1H), 3.73 - 3.64 (m, 1H), [3.39 - 3.24 (m, 1H)], 2.87 - 2.79 (m, 1H), 2.74 (br s, 1H), [2.62 - 2.50 (m, 2H)], 2.44 (d, *J* = 4.7 Hz, 3H), 2.39 - 2.07 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.20 (br d, *J* = 247.5 Hz, 1C), [163.23 (br d, *J* = 247.5 Hz, 1C), 144.78 (br d, *J* = 6.0 Hz, 1C), 144.66 (br d, *J* = 6.0 Hz, 1C), 131.01 (d, *J* = 8.0 Hz, 1C), 130.76 (d, *J* = 8.0 Hz, 1C), 129.98, 129.93, 127.92, 127.77, 121.27 (br d, *J* = 2.5 Hz, 1C), 121.11 (d, *J* = 2.5 Hz, 1C), 114.64 (br d, *J* = 21.3 Hz, 1C), 114.60 (br d, *J* = 21.1 Hz, 1C), 112.57 (br d, *J* = 22.1 Hz, 1C), 112.51 (br d, *J* = 22.1 Hz, 1C), 37.75, 35.89, 22.77, 21.69; HRMS: Calcd *m/z* for $C_{28}H_{29}FN_5O_4S$ $[M+H]^+$: 550.1919, Found: 550.1926.

4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)aniline (38). A solution of TBDPSCl (1.32 g, 4.8 mmol) in DMF (5 mL) was added to a mixture of 2-(4-aminophenyl)ethanol (660 mg, 4.8 mmol) and imidazole (654 mg, 9.6 mmol) in DMF (20 mL) at room temperature. The reaction mixture was stirred overnight and water was added. The mixture was extracted with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (30% EtOAc/hexane) to afford 1.44 g of the title

compound as a yellow oil (80 %). R_f 0.48 (30% EtOAc/hexane). ^{1}H NMR (498 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 7.0 Hz, 4H), 7.49 - 7.38 (m, 6H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 7.8 Hz, 2H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.57 (br s, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 144.56, 135.64, 134.00, 130.03, 129.54, 129.09, 127.62, 115.13, 65.62, 38.52, 26.92, 19.22; HRMS: Calcd *m/z* for $C_{24}H_{30}NOSi$ $[M+H]^+$: 376.2091, Found: 376.2091.

***N*-(4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)phenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide (39).** To a solution of 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid (**38**) (90 mg, 0.28 mmol) in DMF (3 mL) was added DIPEA (0.12 mL, 0.7 mmol) and HATU (107 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 5 min and a solution of **38** (128 mg, 0.34 mmol) in DMF (1 mL) was added in one portion. The reaction mixture was stirred overnight and then diluted with EtOAc and poured into water. The aqueous phase was extracted three times with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (1% MeOH/CH_2Cl_2) to afford 191 mg of the title compound as a beige solid (99%). R_f 0.24 (1:99 MeOH/CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ = 10.64 - 10.46 (m, 1H), 8.31 (s, 1H), 7.71 (br d, *J* = 10.0 Hz, 1H), 7.66 - 7.57 (m, 4H), 7.25 - 7.23 (m, 1H), 7.53 - 7.13 (m, 11H), 7.04 - 6.87 (m, 3H), 6.60 - 6.49 (m, 1H), 5.11 (br d, *J* = 7.6 Hz, 1H), 4.00 (br t, *J* = 7.0 Hz, 1H), 3.90 - 3.76 (m, 3H), 2.87 (t, *J* = 6.8 Hz, 2H), 2.63 - 2.51 (m, 1H), 2.25 - 2.05 (m, 3H), 1.07 (s, 9H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.24 (d, *J* = 247.5 Hz, 1C), 157.06, 152.10, 144.84 (br s, 1C), 144.80 (br s, 1C), 136.09, 135.58, 135.51, 135.18, 133.81, 130.73, 129.80, 129.57, 127.63, 127.09, 122.62, 121.16, 120.29, 114.62 (br d, *J* = 21.2 Hz, 1C), 112.60 (br d, *J* = 22.2 Hz, 1C), 110.90, 65.17, 62.05, 48.65, 38.78, 35.88, 26.87, 22.75, 19.20; HRMS: Calcd *m/z* for $C_{41}H_{42}FN_5NaO_2Si$ $[M+Na]^+$: 706.2984, Found: 706.2999.

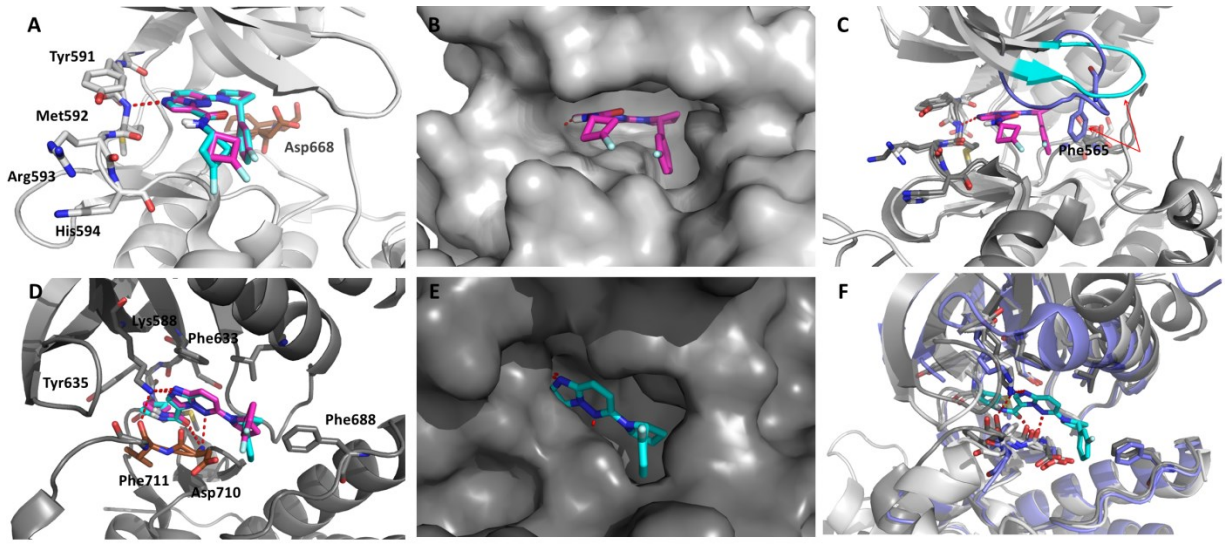
6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-N-(4-(2-hydroxyethyl)phenyl)imidazo[1,2-b]pyridazine-3-carboxamide (40). To a solution of *N*-(4-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)phenyl)-6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazine-3-carboxamide (180 mg, 0.26 mmol) in THF (8 mL) was added TBAF (1.0 M in THF, 0.39 mL, 0.39 mmol) and the reaction mixture was stirred at room temperature for 2 h then diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford 103 mg of the title compound as a beige solid (89%). R_f 0.42 (10:90 MeOH/CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ = 10.56 (br s, 1H), 8.28 (s, 1H), 7.68 (br d, *J* = 9.7 Hz, 1H), 7.57 - 7.39 (m, 2H), 7.32 (dt, *J* = 6.0, 7.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.99 (dt, *J* = 2.2, 8.4 Hz, 1H), 6.96 - 6.91 (m, 1H), 6.54 (br d, *J* = 9.4 Hz, 1H), 5.11 (br d, *J* = 7.8 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.89 (t, *J* = 6.5 Hz, 2H), 3.84 - 3.75 (m, 1H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.65 - 2.52 (m, 1H), 2.27 - 2.07 (m, 3H), 1.98 - 1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.25 (d, *J* = 247.5 Hz, 1C), 157.09, 152.10, 144.79, 137.97, 136.31, 134.55, 130.70 (d, *J* = 8.0 Hz, 1C), 129.59, 127.01, 122.49, 121.16, 121.14, 120.53, 114.63 (d, *J* = 20.6 Hz, 1C), 112.65 (br d, *J* = 21.9 Hz, 1C), 110.96, 63.62, 62.11, 48.66, 38.72, 35.90, 22.76; HRMS: Calcd *m/z* for $C_{25}H_{25}FN_5O_2$ $[M+H]^+$: 446.1987, Found: 446.1994.

4-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-*b*]pyridazine-3-carboxamido)phenethyl 4-methylbenzenesulfonate (41). To an ice cold solution of 6-(2-(3-fluorophenyl)pyrrolidin-1-yl)-N-(4-(2-hydroxyethyl)phenyl)imidazo[1,2-*b*]pyridazine-3-carboxamide (100 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was successively added Et_3N (46 μL, 0.33 mmol) and 4-toluenesulfonyl chloride (50 mg, 0.26 mmol). The reaction was left to warm at room temperature and allowed to stir for 4 days. The reaction mixture was then diluted with CH_2Cl_2 and poured into water. The layers were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography (5% MeOH/CH_2Cl_2) to afford 84 mg of the title compound as a tan solid (64 %). R_f 0.52 (10:90 MeOH/CH_2Cl_2). ^{1}H NMR (498 MHz, $CDCl_3$) δ = 10.59 (br s, 1H), 8.32 (s, 1H), 7.77 - 7.70 (m, 3H), 7.53 - 7.41 (m, 2H), 7.36 - 7.29 (m, 3H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.05 - 6.96 (m, 2H), 6.95 - 6.90 (m, 1H), 6.61 - 6.54 (m, 1H), 5.16 - 5.09 (m, 1H), 4.23 (t, *J* = 7.0 Hz, 2H), 4.06 - 3.99 (m, 1H), 3.87 - 3.79 (m, 1H), 2.97 (t, *J* = 6.9 Hz, 2H), 2.63 - 2.53 (m, 1H), 2.45 (s, 3H), 2.25 - 2.13 (m, 3H)**;** ^{13}C NMR (125 MHz, $CDCl_3$) δ = 163.23 (d, *J* = 247.8 Hz, 1C), 157.11, 156.02, 152.14, 144.78, 136.81, 132.91, 132.09, 130.73 (br d, *J* = 8.3 Hz, 1C), 129.83, 129.52, 127.82, 127.14, 122.48, 121.16 (br d, *J* = 2.8 Hz, 1C), 120.57 (br s, 1C), 120.54, 114.64 (br d, *J* = 20.9 Hz, 1C), 112.60 (d, *J* = 22.2 Hz, 1C), 110.98, 70.64, 62.11, 48.69, 35.89, 34.84, 22.78, 21.64; HRMS: Calcd *m/z* for $C_{32}H_{30}FN_5NaO_4S$ $[M+Na]^+$: 622.1895, Found: 622.1903.

3. DOCKING STUDIES[1]

Molecular docking simulations of compounds **9**-**27** were performed using the X-ray co-crystal structure of TrkA-N^4-(4-morpholinophenyl)-N^6-(pyridin-3-ylmethyl)pyrido[3,2-*d*]pyrimidine-4,6-diamine complex (PDB 4PMT), TrkA-*N*-(3-cyclopropyl-1-phenyl-1*H*-pyrazol-5-yl)-2-{4-[3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]-1*H*-1,2,3-triazol-1-yl}acetamide complex (PDB 4PMM), TrkB-cpd5n complex (PDB 4AT3), TrkB-EX429 complex (PDB 4AT4) and TrkC-GNF-5837 (PDB 3V5Q) using FITTED 3.5 program (FORECASTER platform).[1] Docking structures and figures were prepared using PyMOL.



Figures S1. Comparison of the predicted binding poses for (*R*)-**16** bound to TrkA/B/C in DFG-in (A-C) and DFG-out (D-F) conformations. (A) Docking of (*R*)-**16** (*trans*-substituted cyclobutyl: cyan; *cis*-substituted cyclobutyl: purple) to the ATP binding site of TrkA (PDB 4PMT). The DFG motif highlighted in brown. (B) Surface model of *cis*-(*R*)-**16** docked to TrkA (*trans*-(*R*)-**16** omitted for simplicity). (C) Superposition of TrkB (dark gray, DFG-in, PDB 4AT3) and the docking of *trans*-(*R*)-**16** with TrkA. The TrkA (cyan) and TrkB (blue) glycine-rich loops are highlighted. (D) Docking of *cis*-(*R*)-**16** (purple) and *trans*-(*R*)-**16** (cyan) to the ATP binding site of TrkB (PDB 4AT4). (E) Surface model of *trans*-(*R*)-**16** docked to TrkB (*cis*-(*R*)-**16** omitted for simplicity). (C) Superposition of TrkA (pale gray, PDB 4PMM), TrkC (blue, PDB 3V5Q) and the docking of *trans*-(*R*)-**16** with TrkB.

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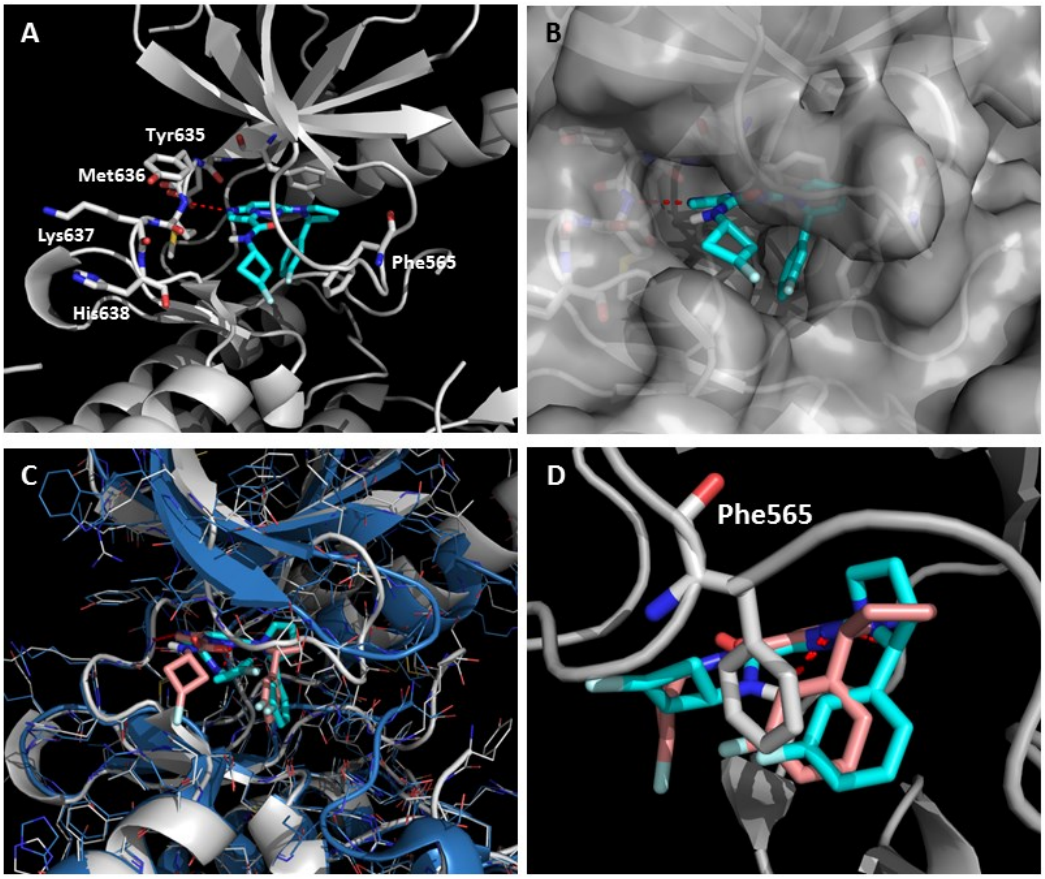

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521 **Figures S2**. (A) Docking of *trans*-(*S*)-**16** to the ATP binding site of TrkB (PDB 4AT3). (B) Surface
522 model of *trans*-(*S*)-**16** docked to TrkB. (C) Superposition of TrkA (blue, PDB 4PMT) and TrkB (pale
523 gray, PDB 4AT3) and the docking of *trans*-(*S*)-**16** (cyan) and *trans*-(*R*)-**16** (light pink) to TrkB. (D) The
524 key Pi-interaction between the 3-fluorophenyl moiety positioned in the ribose binding pocket and the
525 Phe565 form the glycine-rich loop is conserved due to the rotation of the C_6 – *N*-pyrrolidine bond and
526 concomitant rearrangement of the pyrrolidine ring.

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4. RADIOCHEMISTRY

Radiochemistry. The manual radiosyntheses of [^{18}F]-(±)-**IPMICF6** ([^{18}F]**16**) and [^{18}F]-(±)-**IPMICF10** ([^{18}F]**27**) were performed and optimized in the radiochemistry laboratory of the Edmonton PET Center Site (ACSI 19/9 MeV cyclotron). For in vitro autoradiography experiments, the radiotracers [^{18}F]-(±)-**IPMICF6** and [^{18}F]-(±)-**IPMICF10** were produced at the cyclotron laboratory (IBA Cyclon 18/9 MeV cyclotron) of the McConnell Brain Imaging Center Site (Montreal Neurological Institute, McGill University) using radiosynthesis module Scintomics GRP (Germany). No-carrier-added (n.c.a) aqueous [^{18}F]Fluoride was produced by a ^{18}O(p,n)^{18}F nuclear reaction on an enriched [^{18}O]water target.

4.1 Edmonton PET Center Site.

HPLC Methods. Semi preparative, radio-preparative high performance liquid chromatography (HPLC) purifications and quality control analyses were performed using a Phenomenex LUNA® C18 column (100 Å, 250 × 10 mm, 10 μm) using a Gilson 322 Pump module fitted with a 171 Diode Array and a radio detector. Method A: elution at 3.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 40% A and 60% B (t_r [18F]-(±)-IPMICF6(**16**) = 10.81 min). Method B: elution at 3.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 43% A and 57% B (t_r [18F]-(±)-IPMICF6(**16**) = 12.40 min). Method C: elution at 3.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 32% A and 68% B (t_r [18F]-(±)-IPMICF10(**27**) = 13.20 min).

*Radiosynthesis of [^{18}F]-(±)-**IPMICF6***. No-carrier-added (n.c.a) aqueous [^{18}F]fluoride was passed through a Sep-Pak Light QMA cartridge (Waters) (typically 1-2 GBq in 2.0 mL water). The cartridge was dried by airflow, and the ^{18}F activity was eluted with 1.0 mL of a Kryptofix 2.2.2/K_2CO_3 solution (from a 10.0 mL stock solution of 22.6 mg of Kryptofix 222 and 4.2 mg of

K_2CO_3 in acetonitrile/water (95/5)) to a 10.0 mL conical vial. The solvent was removed at 100°C under atmospheric pressure and a stream of nitrogen gas. The residue was azeotropically dried with a total of 6.0 mL of anhydrous acetonitrile at 100°C to afford the dried K2.2.2/K[^{18}F]F complex residue which was dissolved in a solution of the tosylate precursor **36** (2.5 mg) in DMF (300 μL) and heated at 120°C for 10 min. The reaction mixture was cooled to room temperature and diluted with 600 μL of a mixture of MeCN/H_2O (1:1) and purified by semi-preparative HPLC (HPLC Method A or B). The eluates were monitored for radioactivity and for UV absorbance (254 nm) and the peak corresponding to [^{18}F]-(±)-**IPMICF6** was collected and diluted with 15 mL of water followed by trapping on a preconditioned (10 mL EtOH followed by 10 mL water) Sep-Pak C18 Ligth. The cartridge was eluted with 0.6 mL EtOH. The identity of [^{18}F]-(±)-**IPMICF6** was further confirmed by co-injection with nonradioactive **16**. The tracer was obtained in 24.8 ± 2.6 % RCY (n = 3, non-decay corrected isolated yield from injected activity) and >99% radiochemical purities. (< 50 min procedure from end of bombardment).

*Radiosynthesis of [^{18}F]-(±)-**IPMICF10***. The K2.2.2/K[^{18}F]F complex residue from the drying step (1-2 GBq) was dissolve in a solution of the tosylate precursor **41** (2.5 mg) in MeCN (250 μL) and heated at 100°C for 20 min. The reaction mixture was cooled to room temperature and diluted with a 600 μL of a mixture of MeCN/H_2O (1:1) and purified by semi-preparative HPLC (HPLC Method C). The eluates were monitored for radioactivity and for UV absorbance (254 nm) and the peak corresponding to [^{18}F]-(±)-**IPMICF10** was collected and diluted with 15 mL of water followed by trapping on a preconditioned (10 mL EtOH followed by 10 mL water) Sep-Pak C18 Ligth. The cartridge was eluted with 0.6 mL EtOH. The identity of [^{18}F]-(±)-**IPMICF10** was further confirmed by co-injection with nonradioactive **27**. The tracer was

obtained in 18.4 ± 3.7 % RCY (n = 3, non-decay corrected isolated yield from injected activity) and >99% radiochemical purities. (< 60 min procedure from end of bombardment).

4.2 McConnell Brain Imaging Center Site.

HPLC Methods. Semi preparative, radio-preparative high performance liquid chromatography (HPLC) purifications were performed using a Phenomenex LUNA® C18 column (100 Å, 250 × 10 mm, 10 μm). Method D: elution at 3.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 43% A and 57% B ($t_{r\ [18F]\text{-}(\pm)\text{-}IPMICF6(\mathbf{16})}$ = 12.60 min). Method E: elution at 3.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 32% A and 68% B ($t_{r\ [18F]\text{-}(\pm)\text{-}IPMICF10(\mathbf{27})}$ = 14.30 min). Quality control analysis was performed on an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA; running on Agilent ChemStation software) equipped with a Raytest Gabi Star radioactivity detector (Raytest Isotopenmessgeräte GmbH, Straubenhardt, Germany) using a Phenomenex Partisil ODS-3 (250 × 4.6 mm, 5 μm) column. Method F: elution at 1.0 ml min^{-1} with a mixture of H_2O (A) and MeCN (B) isocratic at 30% A and 70% B ($t_{r\ [18F]\text{-}(\pm)\text{-}IPMICF6(\mathbf{16})}$ = 7.39 min; $t_{r\ [18F]\text{-}(\pm)\text{-}IPMICF10(\mathbf{27})}$ = 9.73 min).

*Radiosynthesis of [^{18}F]-(±)-**IPMICF6***. The azeotropic drying of $^{18}F^-$ and the radiosyntheses were carried out using a radiosynthesis module Scintomics GRP (Germany) with a home-made manifold setup operated with Scintomics software. The module was equipped with a radioactivity detector and a Knauer UV detector. The [^{18}F]F^-/H_2O (32.2 GBq – 870 mCi) was passed through a Sep-Pak Light QMA cartridge (Waters) as an aqueous solution in ^{18}O-enriched water and the ^{18}F activity was eluted with 1.5 mL of a Kryptofix2.2.2./K_2CO_3 solution (Kryptofix2.2.2. - 10-12 mg, dissolved in 150 μL of 0.125M K_2CO_3 + 1.3 mL MeCN) to a disposable plastic reactor. The solvent was removed at 100°C under reduced pressure and a

599 stream of argon gas. The residue was azeotropically dried with 0.5 mL of anhydrous acetonitrile
600 twice at 100°C. Following azeotropic drying, the reaction vial was charged with tosylate
601 precursor **36** (2.5 mg, in 0.5 mL DMF) and the mixture was allowed to react for 10 min at
602 120°C. The crude mixture was then diluted with HPLC eluent (1.5 mL, 57% MeCN, 43% H_2O)
603 and injected on HPLC. The pure [^{18}F]-(±)-**IPMICF6** was obtained in 7.9 % RCY (EOS, non-
604 decay corrected isolated yield from $^{18}F^-/H_2O$; HPLC method D), > 99% radiochemical purity and
605 specific activity of 163 GBq/μmol (4414 Ci/mmol). An aliquot of the product fraction
606 corresponding to [^{18}F]-(±)-**IPMICF6** was collected and diluted with 15 mL H_2O and passed
607 through a preconditioned (10 mL EtOH followed by 10 mL water) Sep-Pak C18 Plus Cartridge
608 and then eluted with 0.5 mL EtOH and used directly in the autoradiography experiments. Quality
609 control, of the isolated [^{18}F]-(±)-**IPMICF6** was performed using HPLC method F.

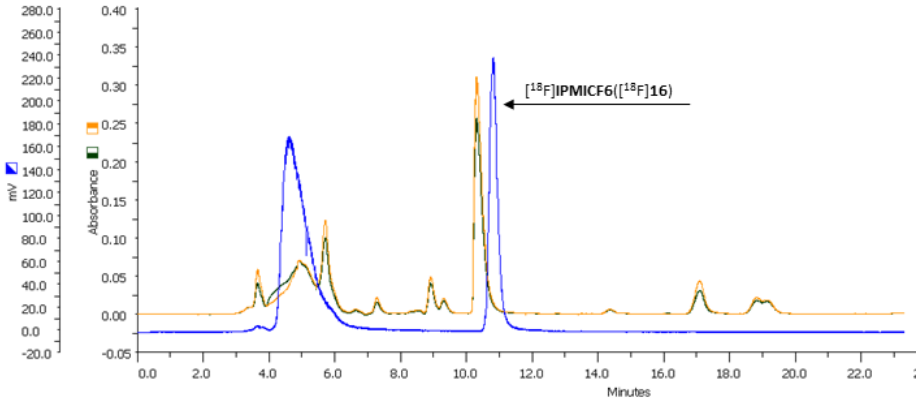
610 *Radiosynthesis of [^{18}F]-(±)-**IPMICF10***. The radiotracer was synthesized in a similar procedure
611 using the precursor **41** (2.5 mg, in 0.5 mL MeCN). The reaction was carried out for 20 min at
612 95°C and led to the isolation of [^{18}F]-(±)-**IPMICF10** in 3.4 % RCY (EOS, non-decay corrected
613 isolated yield from $^{18}F^-/H_2O$; HPLC method D), > 98.5% radiochemical purity and specific
614 activity of 242 GBq/μmol (6549 Ci/mmol). Quality control, of the isolated [^{18}F]-(±)-**IPMICF10**
615 was performed using HPLC method F.

616

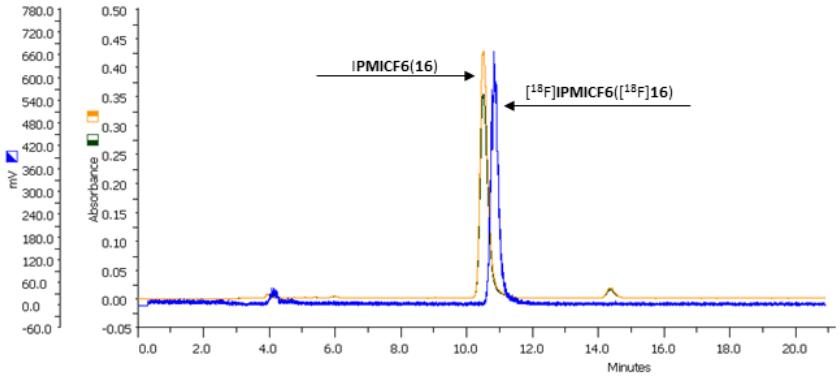
617 **4.3 Plasma Stability.**

618 Compound [^{18}F]-(±)-**IPMICF6** and [^{18}F]-(±)-**IPMICF10** (radiochemical purity > 99%) were
619 incubated in human plasma (500 μL) at 37°C and ice-cold acetonitrile (250 μL, after 60 min) was
620 added for protein precipitation at different time points followed by centrifugation. The amount of

intact [^{18}F]-(±)-**IPMICF6** and [^{18}F]-(±)-**IPMICF10** was determined by HPLC analysis of the supernatant.

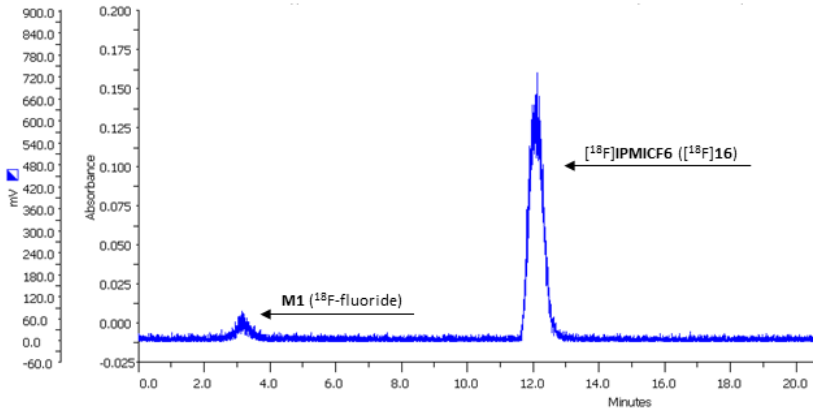


Figures S3. Typical semi-preparative HPLC chromatogram of the radiofluorination of the tolylate precursor **36** leading to the formation of [^{18}F]-(±)-**IPMICF6** (HPLC Method A). (In this instance, the UV peak at t =10.5 min in this chromatogram is expected to be an elimination products from the tosylate precursor which was observed when the reaction mixture was injected on HPLC >15 min after quenching. It illustrates the fact that the precursor readily degrades after quenching and that isolation as to be performed immediately after the reaction mixture is diluted with HPLC eluent.)



Figures S4. Representative HPLC-QC chromatogram of the collected [^{18}F]-(±)-**IPMICF6** co-injected with the non-radioactive standard **16** (HPLC Method A).

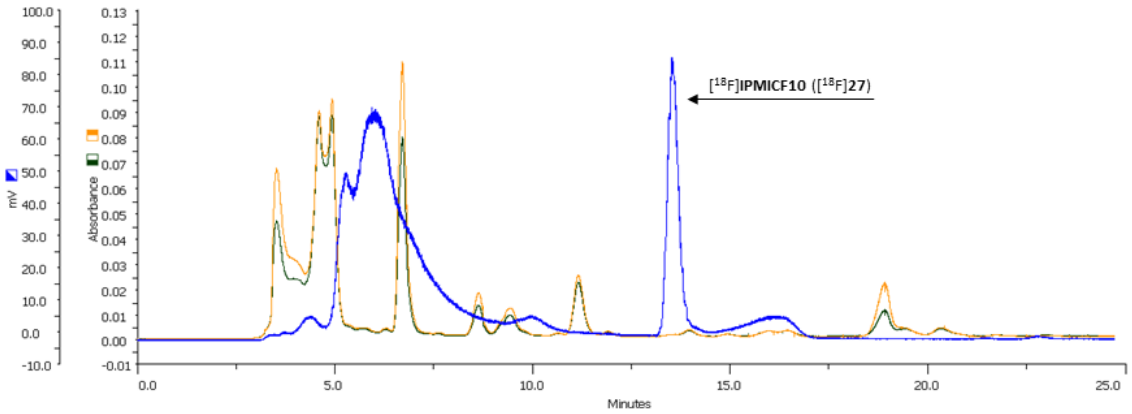
637



638

639 **Figures S5.** HPLC analysis of human plasma at 60 min after [^{18}F]-(±)-**IPMICF6** incubation at 37°C
640 (HPLC Method B).

641

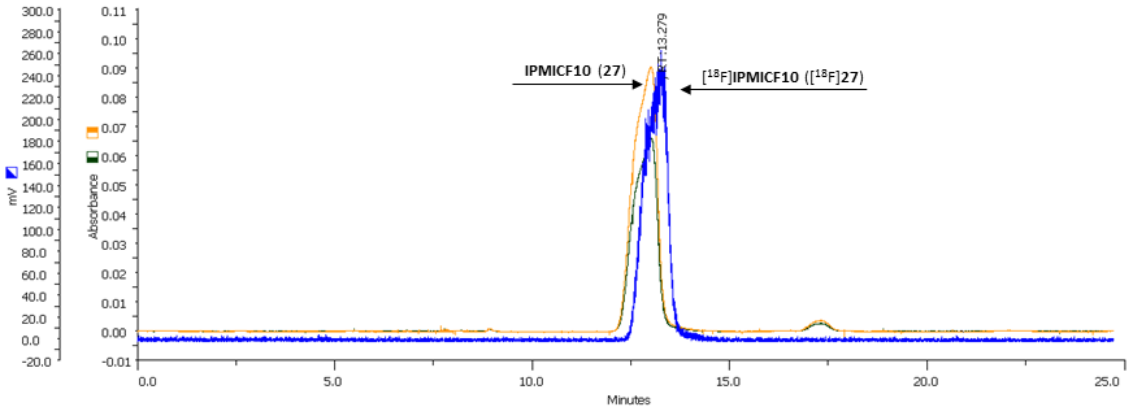


642

643 **Figures S6.** Typical semi-preparative HPLC chromatogram of the radiofluorination of the tolylate
644 precursor **41** leading to the formation of [^{18}F]-(±)-**IPMICF10** (HPLC Method C).

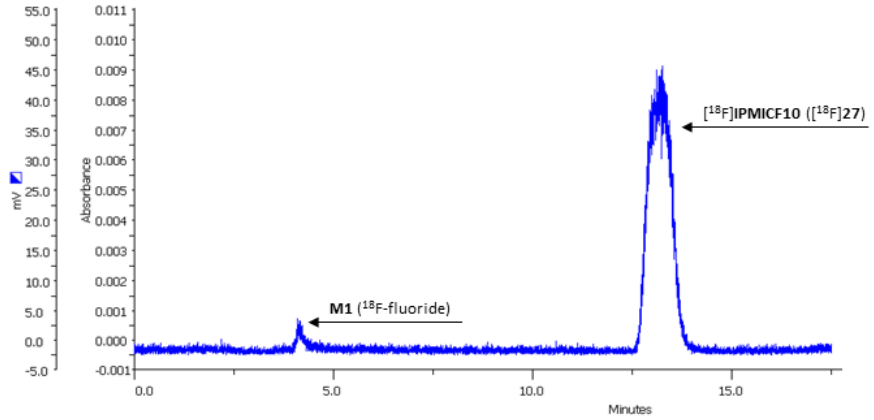
645

646



647

648 **Figures S7.** Representative HPLC-QC chromatogram of the collected [^{18}F]-(±)-**IPMICF10** co-injected
649 with the non-radioactive standard **27** (HPLC Method C).



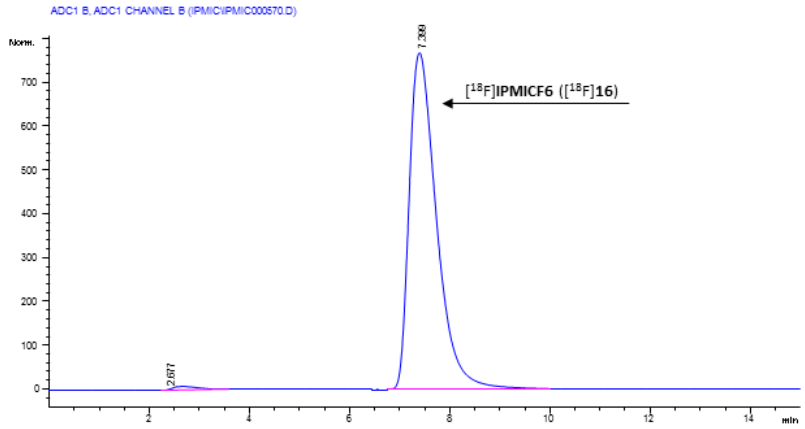
650

651 **Figures S8.** HPLC analysis of human plasma at 60 min after [^{18}F]-(±)-**IPMICF10** incubation at 37°C
652 (HPLC Method C).

653

654

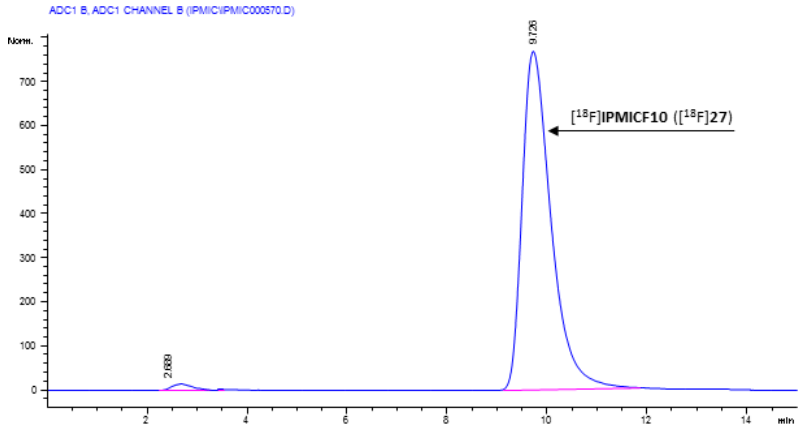
655 4.2 McConnell Brain Imaging Center Site



656

657 **Figures S9.** HPLC-QC chromatogram of the collected/formulated [^{18}F]-(±)-**IPMICF6** (HPLC Method F).

658



659

660 **Figures S10.** HPLC-QC chromatogram of the collected/formulated [^{18}F]-(±)-**IPMICF10** (HPLC Method
661 F).

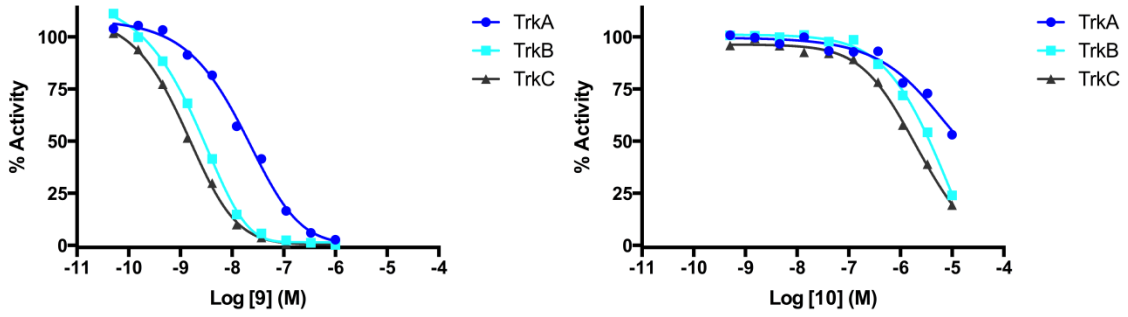
662

5. BIOLOGICAL EVALUATION

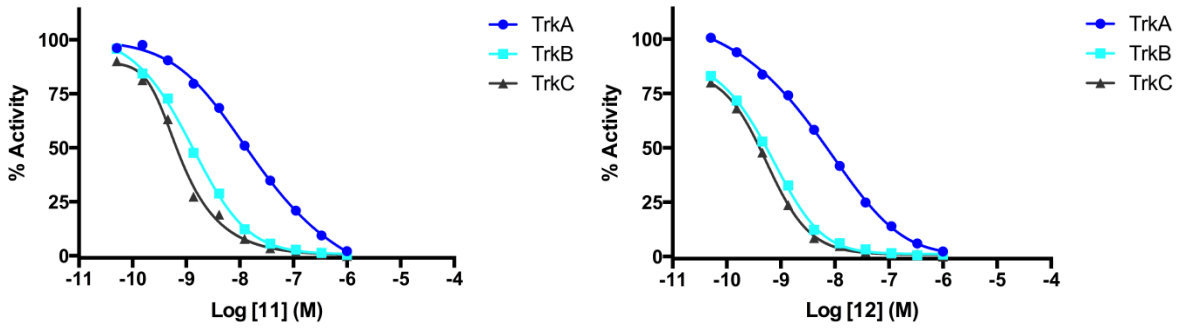
5.1 [γ-33P]ATP-Based Enzymatic Assay.

Compounds **9-27** were tested in a [γ-^{33}P]ATP based enzymatic assay by Reaction Biology Corporation (Malvern, PA). Briefly, the compound was tested in a 10-concentration IC_{50} curve with 3-fold serial dilution starting at 1 or 10 μM (when required, additional dilutions were made). The reactions were initially performed with 1 μM ATP and profiled against 3 tyrosine kinases (tropomyosin receptor kinase A (TrkA), tropomyosin receptor kinase B (TrkB), tropomyosin receptor kinase C (TrkC)) in singlicate with staurosporine as a control. Additional measurements were carried out for selected compounds (triplicates for inhibitors **13-16** and **25-27**). Compounds **16** and **27** were subsequently investigated for off-Trk kinase activity (Reaction Biology Corporation). Compounds **16** and **27** were tested for inhibitory activity at (0.1 μM) on a panel of 20 selected kinases (SYK, RET, PDK1/PDHK1, PDGFRa, P38a/MAPK14, KDR/VEGFR2, JNK1, JAK1, ITK, FMS, FLT3, ERK1, ERBB2/HER2, EGFR, c-SRC, c-MET, c-KIT, BRAF, ALK, ABL1) under similar conditions as previously described (n = 2) (Table S1, S2).

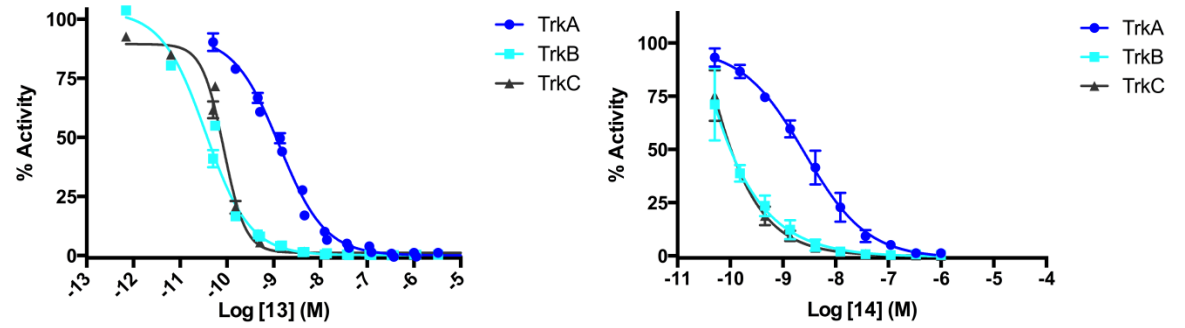
5.2 Dose Response Curves for Compounds 9-27



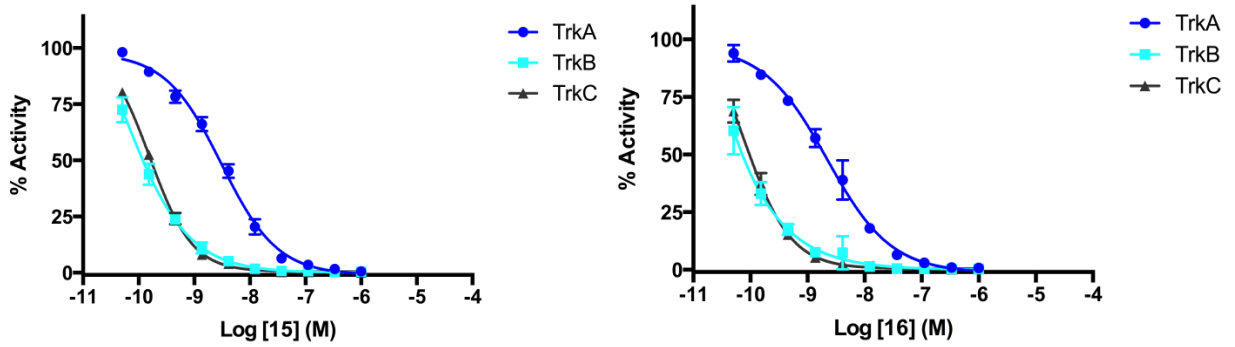
Figures S11. Dose-response curve for inhibitor **9** (left; $n = 1$) and **10** (right; $n = 1$) versus TrkA, TrkB and TrkC.



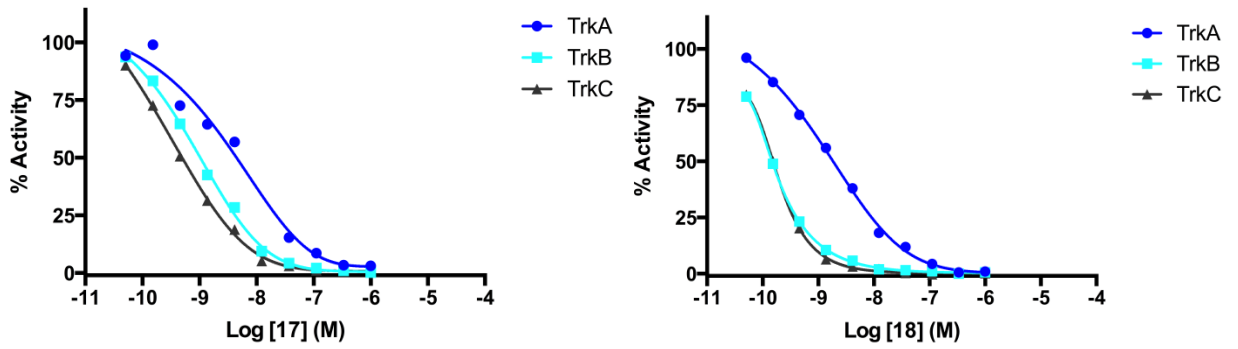
Figures S12. Dose-response curve for inhibitor **11** (left; $n = 1$) and **12** (right; $n = 1$) versus TrkA, TrkB and TrkC.



Figures S13. Dose-response curve for inhibitor **13** (left; $n = 3$) and **14** (right; $n = 3$) versus TrkA, TrkB and TrkC (error bars represent standard deviation from the mean).



Figures S14. Dose-response curve for inhibitor **15** (left; $n = 3$) and **16** (right; $n = 3$) versus TrkA, TrkB and TrkC (error bars represent standard deviation from the mean).

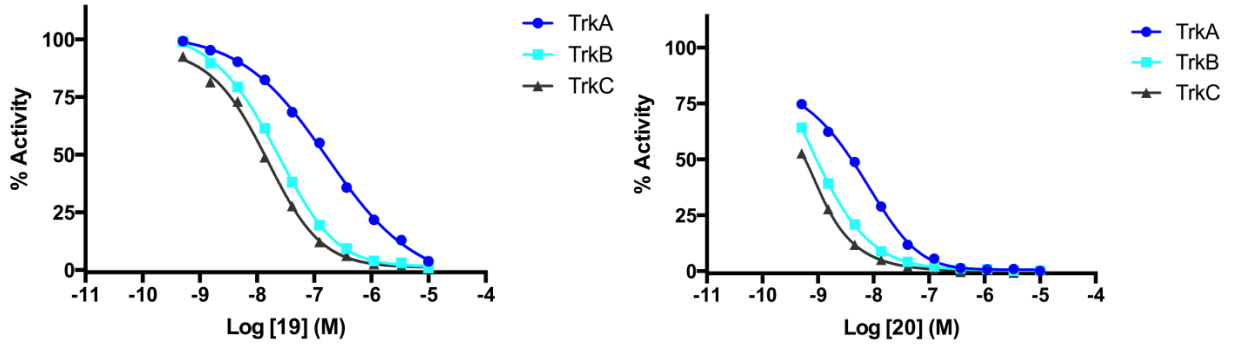


694

695 **Figures S15.** Dose-response curve for inhibitor **17** (left; n = 1) and **18** (right; n = 1) versus TrkA, TrkB
696 and TrkC.

697

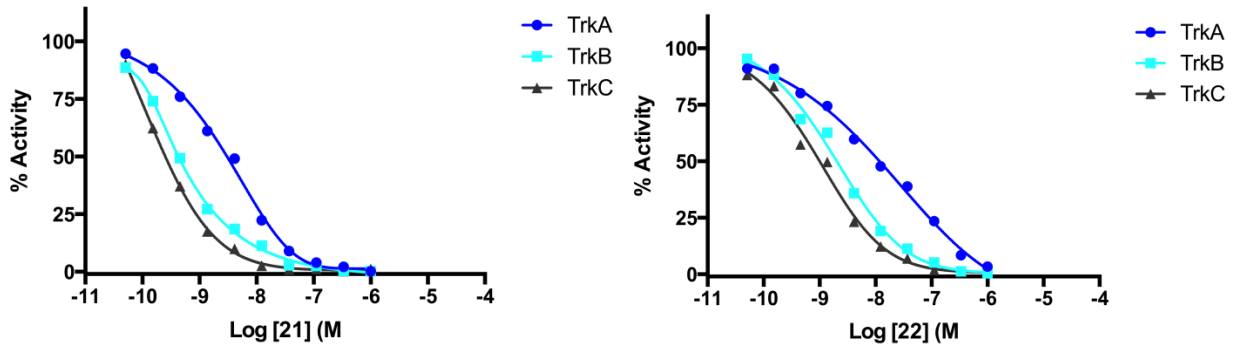
698



699

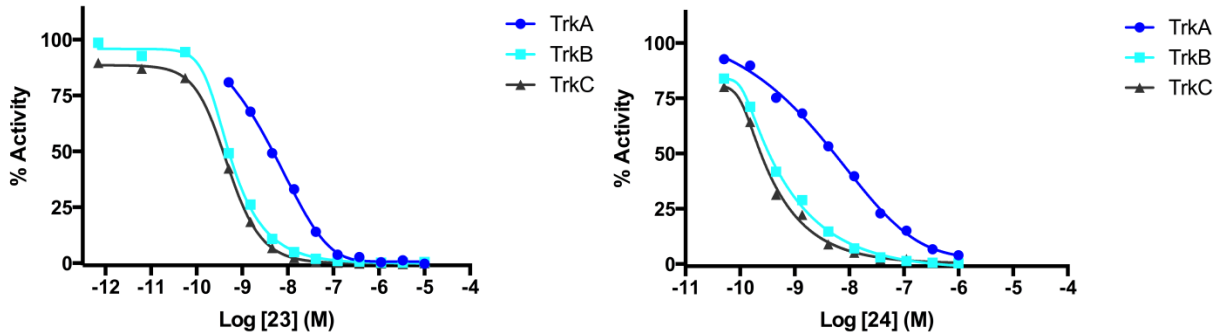
700 **Figures S16.** Dose-response curve for inhibitor **19** (left; n = 1) and **20** (right; n = 1) versus TrkA, TrkB
701 and TrkC.

702

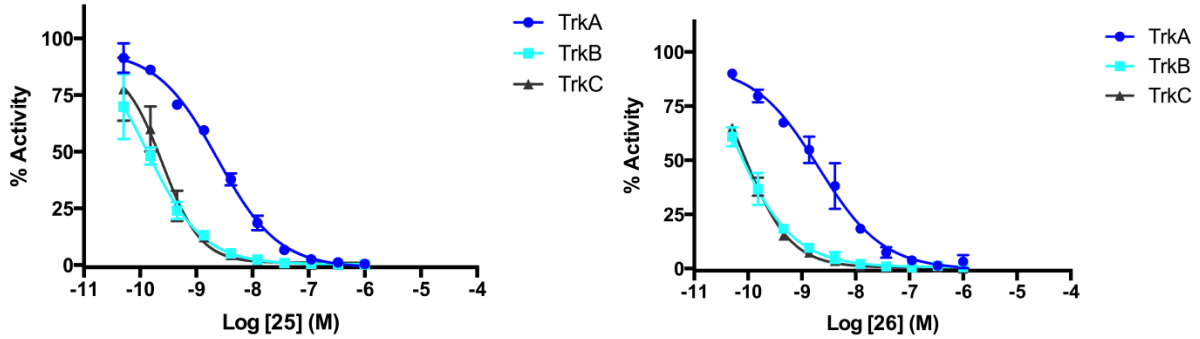


703

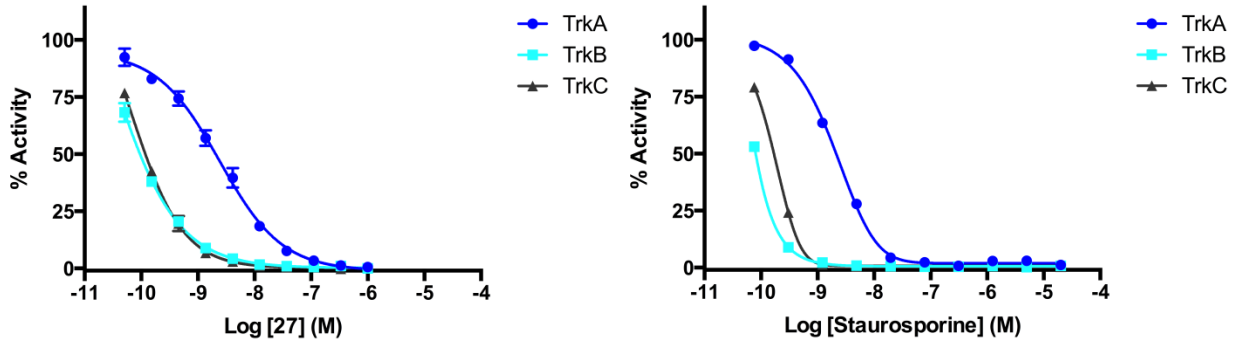
704 **Figures S17.** Dose-response curve for inhibitor **21** (left; n = 1) and **22** (right; n = 1) versus TrkA, TrkB
705 and TrkC.



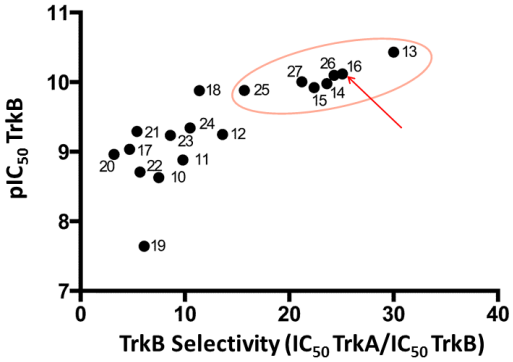
Figures S18. Dose-response curve for inhibitor **23** (left; $n = 1$) and **24** (right; $n = 1$) versus TrkA, TrkB and TrkC.



Figures S19. Dose-response curve for inhibitor **25** (left; $n = 3$) and **26** (right; $n = 3$) versus TrkA, TrkB and TrkC (error bars represent standard deviation from the mean).



Figures S20. Dose-response curve for inhibitor **27** (left; $n = 3$) and staurosporine (control, right; $n = 1$) versus TrkA, TrkB and TrkC (error bars represent standard deviation from the mean).



719

720 **Figures S21.** Inhibition of TrkB kinase versus TrkB selectivity with regard to TrkA. The potencies are
721 expressed as $-\log_{10}(IC_{50})$. Inbibitor **16** and **27** were selected based on TrkB potency, selectivity and
722 radiolabeling amenability.

723

724

725 **5.3 Selectivity Profiling.**

726 **Table S1.** Data for off-Trk inhibitory activity of compound **16** (0.1 μM)

727

Kinases	% Enzyme Activity (relative to DMSO controls) IPMICF6 Data 1	Data 2	IC50 (M) Staurosporine*	IC50 (M) Alternate Control cpd*.	Alternate compound ID
ABL1	95.96	95.31	**1.85E-08**		
ALK	94.54	92.85	**8.60E-10**		
BRAF	101.34	99.25	**ND**	**2.37E-08**	**GW5074**
c-Kit	105.16	104.36	**4.46E-08**		
c-MET	95.81	93.81	**4.36E-08**		
c-Src	97.38	96.64	**2.34E-09**		
EGFR	68.08	65.22	**3.12E-08**		
ERBB2/HER2	49.99	49.22	**1.97E-08**		
ERK1	103.46	103.35	**3.93E-06**		
FLT3	85.14	84.99	**1.08E-09**		
FMS	103.17	101.89	**6.24E-10**		
ITK	93.59	93.22	**7.75E-09**		
JAK1	90.97	90.37	**2.96E-10**		
JNK1	99.49	99.38	**1.67E-07**		
KDR/VEGFR2	110.38	109.61	**4.00E-09**		
P38a/MAPK14	99.59	97.36	**ND**	**2.09E-08**	**SB202190**
PDGFRa	100.61	99.00	**2.07E-10**		
PDK1/PDHK1	85.56	85.37	**ND**	**1.88E-05**	**GW5074**
RET	90.98	89.43	**9.79E-10**		
SYK	105.23	104.84	**7.74E-10**		

730

731 **Table S2.** Data for off-Trk inhibitory activity of compound **27** (0.1 μM)

732

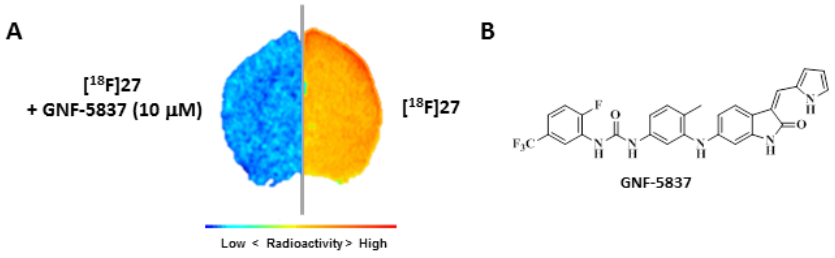
Kinase:	% Enzyme Activity (relative to DMSO controls)		Compound IC50* (M):		
	IPMICF10		Staurosporine	Alternate Control cpd.	Alternate compound ID
	Data 1	Data 2			
ABL1	91.79	90.89	**3.51E-08**		
ALK	89.40	88.60	**8.92E-10**		
BRAF	95.46	92.68		**2.98E-08**	**GW5074**
c-Kit	101.20	100.52	**5.74E-08**		
c-MET	98.31	95.79	**2.60E-08**		
c-Src	103.39	102.83	**1.61E-09**		
EGFR	96.51	89.72	**2.08E-08**		
ERBB2/HER2	79.72	79.54	**1.64E-08**		
ERK1	101.56	100.99	**1.21E-06**		
FLT3	96.07	94.11	**9.65E-10**		
FMS	107.46	102.33	**9.87E-11**		
ITK	98.19	97.06	**4.16E-09**		
JAK1	100.70	98.68	**1.32E-10**		
JNK1	100.68	99.80	**1.41E-07**		
KDR/VEGFR2	95.60	94.49	**1.26E-09**		
P38a/MAPK14	99.59	99.49		**2.09E-08**	**SB202190**
PDGFRa	99.55	99.48	**7.30E-12**		
PDK1/PDHK1	79.08	78.71		**1.37E-04**	**GW5074**
RET	105.91	105.83	**1.44E-09**		
SYK	104.34	103.51	**7.96E-10**		

733

734

735 **5.4 Autoradiography.**

736 A rat was decapitated, the brains rapidly removed, frozen in 2-methylbutane (−40°C), and stored
737 at −80°C. Brain sections (20 μm thick) were thawed and mounted onto Superfrost Plus slides
738 (Thermo Scientific) and stored at −80°C. After pre-incubation in PBS buffer (30 mmol/L; pH 7.4
739 containing 137 mmol/L NaCl, 27 mmol/L) for 10 minutes at room temperature, rat and tumor
740 sections were incubated 2 h 30 (room temperature) in buffer containing [^{18}F]-(±)-**IPMICF6** (67
741 µCi in 200 mL buffer total) and 2 h 30 (room temperature) for [^{18}F]-(±)-**IPMICF10** (279 µCi in
742 200 mL buffer total). Compound **16** (**IPMICF6**; 1.0 µM) and GNF-5839 (10 µM) were used to
743 determine the specific binding of [^{18}F]-(±)-**IPMICF6** and [^{18}F]-(±)-**IPMICF10** respectively.
744 After three washes in incubation buffer (5 minutes, 4°C) and a rapid rinse with ice-cold water
745 (15 seconds), the sections were dried in a stream of air (room temperature). Sections were then
746 dried further in a vacuum container with formaldehyde powder for mild fixation. Labeled
747 sections were placed on phosphor-imaging plates (BAS 2025; Fuji, Japan), with industrial tritium
748 activity standards (Amersham Biosciences, Piscataway, NJ, USA). On exposure, the plates were
749 scanned with a plate reader (spatial resolution of 50 μm; BAS 5000; Fuji or Typhoon Trio +
750 Variable Mode Imager).



751

752 **Figures S22.** (A) Representative in vitro autoradiograms from coronal sections of rat brain showing the
753 binding of [^{18}F]**27** (A, right) and competition experiments with **GNF-5837** (10 µM) (A, left). (B)
754 Structure of GNF-5837

Table S3. PSL Data ^{18}F-IPMIC6 Autoradiography

^{18}F-IPMICF6 MEAN

The area of brain Rat	NORMAL	CRTL NS-SPECIFIC IPMICF6 1.0 µM	%CHANGE IN RAT IPMICF6
Prefrontal cortex	2611,793	1913,229	26,75
Posterior cortex	2702,114	1950,547	27,81
Hippocampus	2586,560	1904,214	26,38
Cerebellum	2457,055	1860,967	24,26

Table S4. PSL Data for ^{18}F-IPMIC10 Autoradiography

^{18}F-IPMICF10 MEAN

The area of brain Rat	NORMAL RAT	CRTL NS-SPECIFIC GNF-5837 10 µM	%CHANGE IN RAT GNF-5837
Anterior cortex	54801,107	39985,001	27,04
Posterior cortex	55746,791	40286,937	27,73
Hippocampus	54356,573	39561,146	27,22
Cerebellum	57319,550	41240,174	28,05

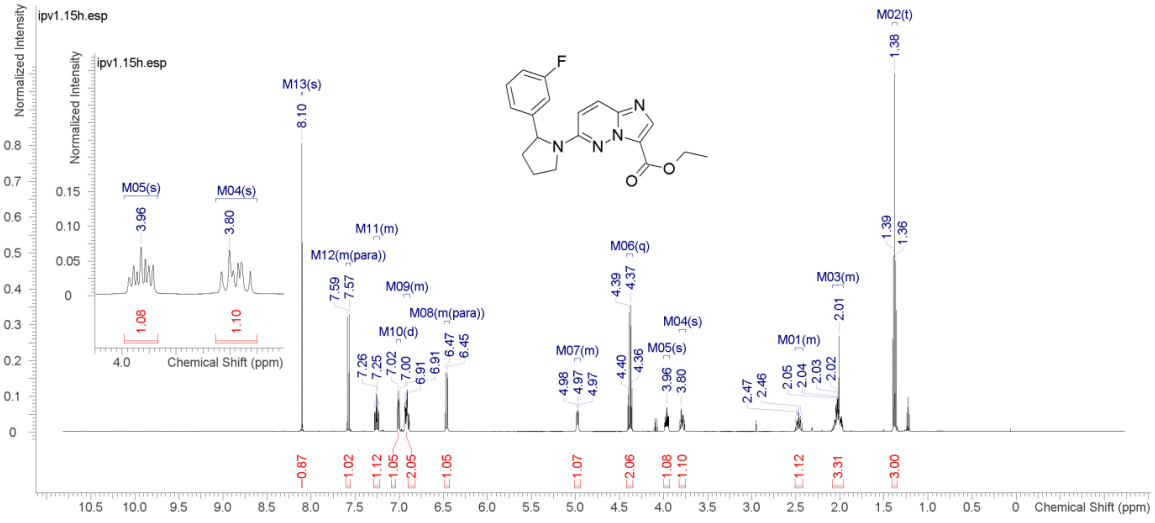
6. NMR SPECTRUM

6.1 ^{1}H NMR and ^{13}C NMR for compound **10**

IPV 1.15X 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 19.91	***Number of Nuclei*** 19 H's		
Acquisition Time (sec) 4.9997	***Comment*** IPV 1.15X 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Jan 7 2015	***Date Stamp*** Jan 7 2015	***File Name*** G:\2015.01\2015.01.07.i5_IPV_1.15X_H1_1D.fid\fid	
Frequency (MHz) 498.1178	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 30001
Points Count 32768	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60
Solvent CHLOROFORM-d	***Spectrum Offset (Hz)*** 2388.2478	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.42
Temperature (degree C) 26.400			

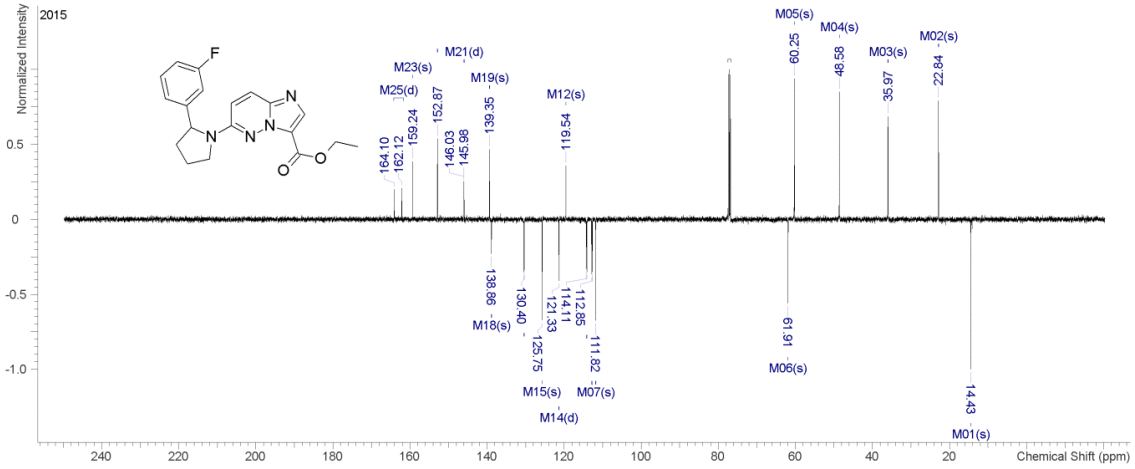
^{1}H NMR (498MHz, CHLOROFORM-d) δ = 8.10 (s, 1H), 7.60 - 7.55 (m, *J*=9.9 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.01 (d, *J*=7.5 Hz, 1H), 6.95 - 6.88 (m, 2H), 6.49 - 6.43 (m, *J*=9.9 Hz, 1H), 5.01 - 4.94 (m, 1H), 4.38 (q, *J*=7.1 Hz, 2H), 3.96 (s, 1H), 3.80 (s, 1H), 2.51 - 2.42 (m, 1H), 2.08 - 1.96 (m, 3H), 1.38 (t, *J*=7.1 Hz, 3H)



IPV 1.15X 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 19 C's				
Acquisition Time (sec) 1.9958					
Comment IPV 1.15X 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Jan 7 2015	***Date Stamp*** Jan 7 2015				
File Name C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.07.i5_IPV_1.15X_C13_APT_ad.fid\fid					
Frequency (MHz) 125.2656	***Nucleus*** 13C		***Number of Transients*** 104		
Original Points Count 67510	***Points Count*** 131072		***Pulse Sequence*** APT_ad		
Receiver Gain 30.00	***SW(cyclical) (Hz)*** 33826.64		***Solvent*** cdcl3		
Spectrum Offset (Hz) 14370.3086	***Spectrum Type*** APT		***Sweep Width (Hz)*** 33826.38		
Temperature (degree C) 26.400					

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.11 (d, *J*=247.0 Hz, 1C), 159.24, 152.87, 146.01 (d, *J*=6.5 Hz, 1C), 139.35, 138.86, 130.37 (br d, *J*=8.0 Hz, 1C), 125.75, 121.32 (d, *J*=2.6 Hz, 1C), 119.54, 114.19 (br d, *J*=21.2 Hz, 1C), 112.76 (br d, *J*=22.2 Hz, 1C), 111.82, 61.91, 60.25, 48.58, 35.97, 22.84, 14.43

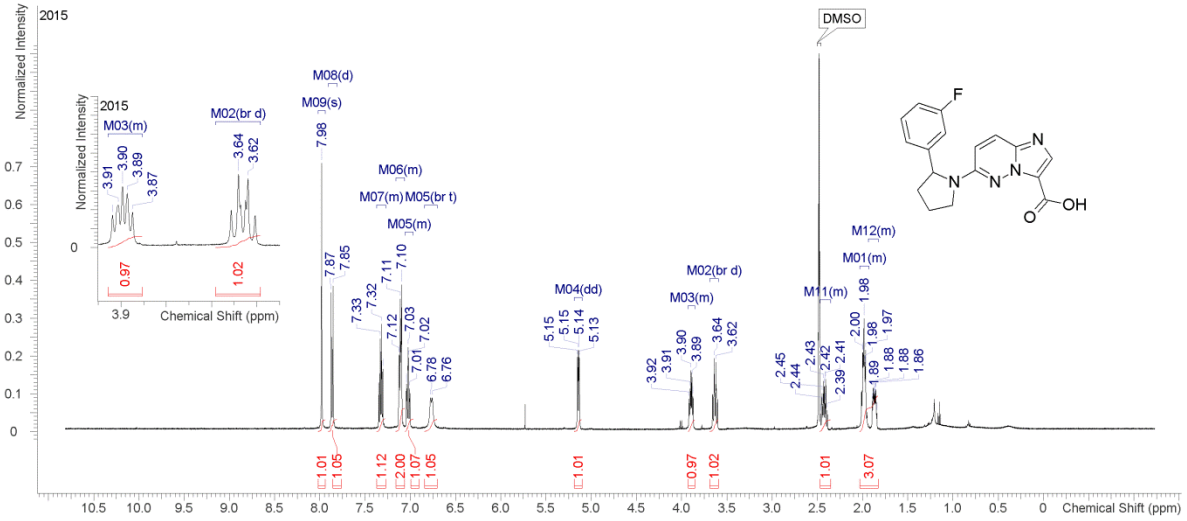


6.2 ^{1}H NMR and ^{13}C NMR for compound **9**

IPV 1.16 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	14.38	***Number of Nuclei***	14 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.16 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 16 2015	***Date Stamp***	Jan 16 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.16_H1_1D.fid\fid					***Frequency (MHz)***	498.1202
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	dmso
Spectrum Offset (Hz)	2388.2527	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

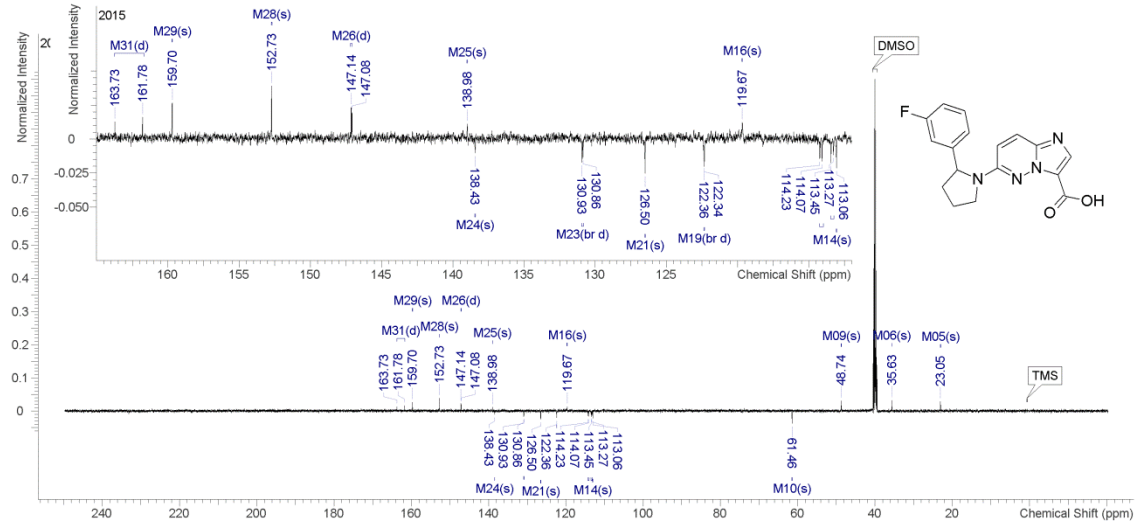
^{1}H NMR (498MHz, dmso) δ = 7.98 (s, 1H), 7.86 (d, *J*=9.9 Hz, 1H), 7.37 - 7.27 (m, 1H), 7.16 - 7.06 (m, 2H), 7.06 - 6.97 (m, 1H), 7.02 (br t, *J*=8.4 Hz, 1H), 5.14 (dd, *J*=2.8, 8.1 Hz, 1H), 3.93 - 3.85 (m, 1H), 3.63 (br d, *J*=10.4 Hz, 1H), 2.47 - 2.35 (m, 1H), 2.03 - 1.93 (m, 2H), 1.93 - 1.83 (m, 1H)



IPV 1.16 125.266 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	17 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.16 125.266 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 16 2015	***Date Stamp***	Jan 16 2015	***File Name***	F:\Schirrma\2015.01\2015.01.16.i5_IPV_1.16_C13_APT_ad.fid\fid
Frequency (MHz)	125.2662	***Nucleus***	13C	***Number of Transients***	512
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	14370.3350	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, DMSO-d$_6$) δ = 162.75 (d, *J*=243.6 Hz, 1C), 159.70, 152.73, 147.11 (d, *J*=6.5 Hz, 1C), 138.98, 138.43, 130.89 (br d, *J*=8.5 Hz, 1C), 126.50, 122.35 (br d, *J*=2.1 Hz, 1C), 119.67, 114.15 (d, *J*=20.9 Hz, 1C), 113.36 (br d, *J*=21.9 Hz, 1C), 113.06, 61.46, 48.74, 35.63, 23.05

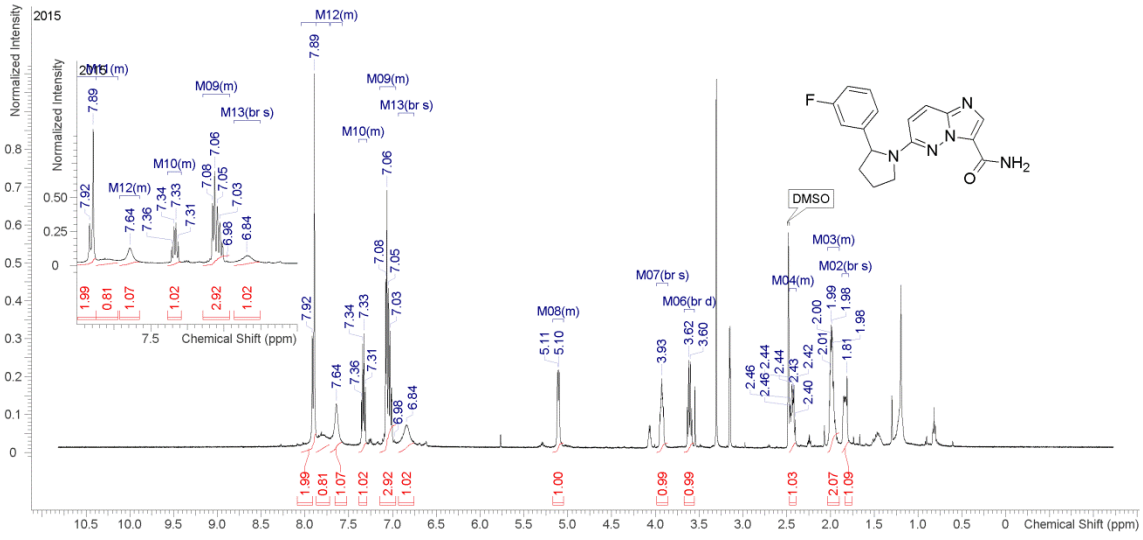


6.3 ^{1}H NMR and ^{13}C NMR for compound **11**

IPV 1.45 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 16.00	***Number of Nuclei*** 16 H's		
Acquisition Time (sec) 4.9997	***Comment*** IPV 1.45 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Feb 17 2015	***Date Stamp*** Feb 17 2015	***File Name*** F:\Schirrma\2015.02\2015.02.17.i5_IPV_1.45_H1_1D.fid\fid	
Frequency (MHz) 498.1202	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 30001
Points Count 65536	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60
Solvent DMSO-d6	***Spectrum Offset (Hz)*** 2388.2983	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.51
Temperature (degree C) 26.400			

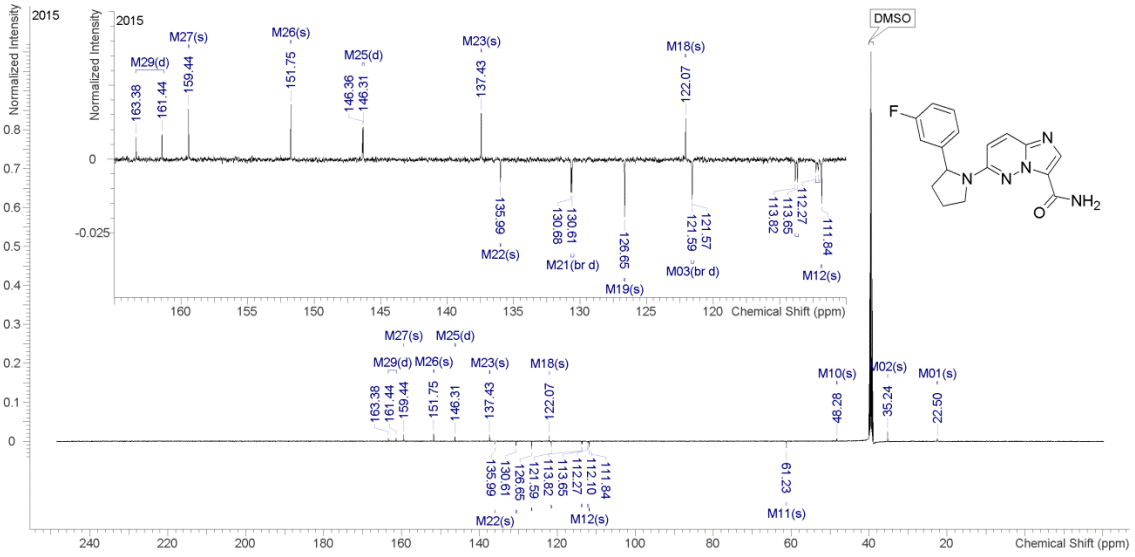
^{1}H NMR (498MHz, DMSO-d_6) δ = 8.04 - 7.87 (m, 2H), 7.87 - 7.72 (m, 1H), 7.71 - 7.58 (m, 1H), 7.39 - 7.29 (m, 1H), 7.14 - 6.96 (m, 3H), 6.84 (br s, 1H), 5.17 - 5.05 (m, 1H), 3.93 (br s, 1H), 3.61 (br d, *J*=9.6 Hz, 1H), 2.47 - 2.40 (m, 1H), 2.04 - 1.90 (m, 2H), 1.81 (br s, 1H)



Jamie_Bailey, IPV1_45x 125.691 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 17 C's				
Acquisition Time (sec) 2.0000					
Comment Jamie_Bailey, IPV1_45x 125.691 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Apr 28 2015		***Date Stamp*** Apr 28 2015			
File Name F:\Schirrma\2015.04\2015.04.28.u5_IPV1_45x_loc8_13.47_C13_APT_ad.fid\fid				***Frequency (MHz)***	125.6908
Nucleus 13C		***Number of Transients***	308	***Original Points Count***	67568
Points Count 131072		***Pulse Sequence***	APT_ad	***Receiver Gain***	30.00
SW(cyclical) (Hz) 33783.79		***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	14348.9590
Spectrum Type APT		***Sweep Width (Hz)***	33783.53	***Temperature (degree C)***	27.600

^{13}C NMR (126MHz, DMSO-d_6) δ = 162.41 (d, *J*=244.1 Hz, 1C), 159.44, 151.75, 146.33 (d, *J*=6.4 Hz, 1C), 137.43, 135.99, 130.64 (br d, *J*=8.2 Hz, 1C), 126.65, 122.07, 121.58 (br d, *J*=2.1 Hz, 1C), 113.74 (br d, *J*=20.9 Hz, 1C), 112.18 (br d, *J*=21.4 Hz, 1C), 111.84, 61.23, 48.28, 35.24, 22.50

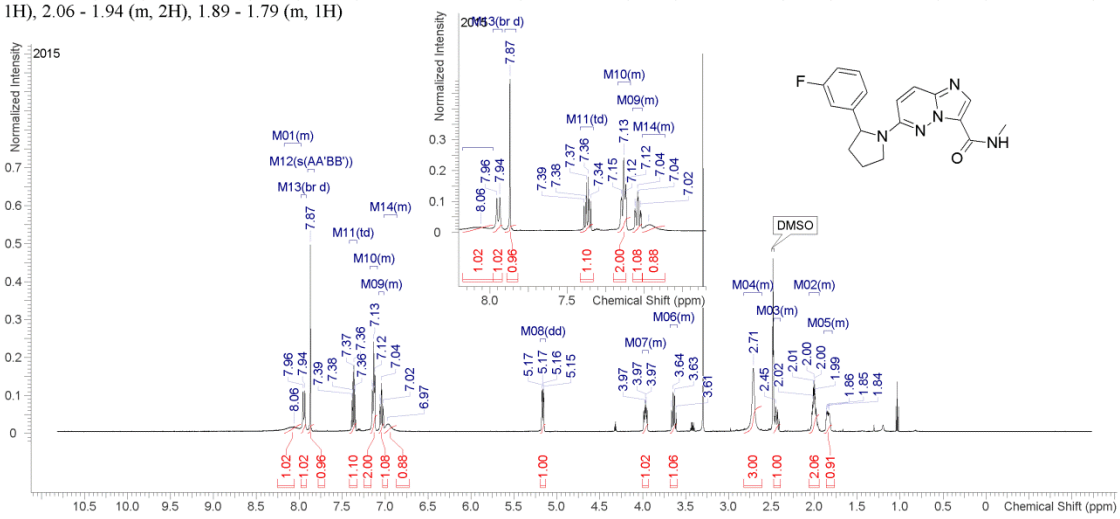


6.4 ^{1}H NMR and ^{13}C NMR for compound **12**

IPV 1.44 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 18.13	***Number of Nuclei*** 18 H's		
Acquisition Time (sec) 4.9997	***Comment*** IPV 1.44 498.120 MHz H1 1D in dmso (ref. to DMSO @ 2.49 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Feb 17 2015	***Date Stamp*** Feb 17 2015	***File Name*** F:\Schirrma\2015.02\2015.02.17.i5_IPV_1.44_H1_1D.fid\fid	
Frequency (MHz) 498.1202	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 30001
Points Count 65536	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60
Solvent DMSO-d6	***Spectrum Offset (Hz)*** 2388.2983	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.51
Temperature (degree C) 26.400			

^{1}H NMR (498MHz, DMSO-d_6) δ = 8.18 - 7.98 (m, 1H), 7.95 (br d, *J*=9.9 Hz, 1H), 7.87 (s, 1H), 7.37 (dt, *J*=6.1, 8.0 Hz, 1H), 7.17 - 7.09 (m, 2H), 7.07 - 7.01 (m, 1H), 7.01 - 6.86 (m, 1H), 5.16 (dd, *J*=2.7, 8.3 Hz, 1H), 4.00 - 3.93 (m, 1H), 3.68 - 3.60 (m, 1H), 2.82 - 2.61 (m, 3H), 2.47 - 2.39 (m, 1H), 2.06 - 1.94 (m, 2H), 1.89 - 1.79 (m, 1H)

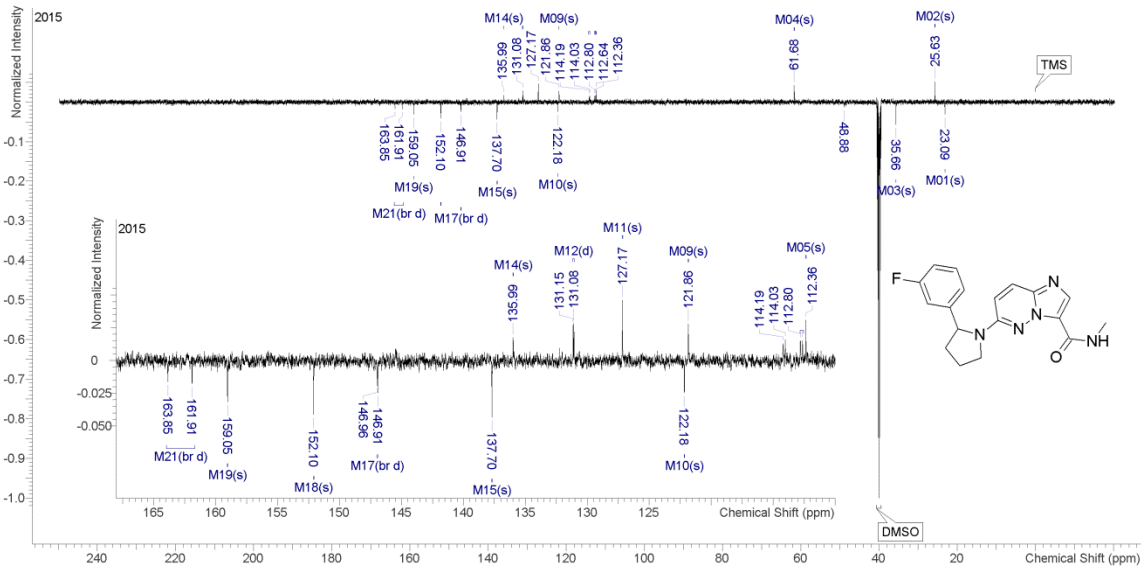


771

IPV 1.44 125.266 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 17 C's				
Acquisition Time (sec) 1.9958					
Comment IPV 1.44 125.266 MHz C13[H1] APT_ad in dmso (ref. to DMSO @ 39.5 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Feb 17 2015	***Date Stamp*** Feb 17 2015		***File Name*** F:\Schirrma\2015.02\2015.02.17.i5_IPV_1.44_C13_APT_ad.fid\fid		
Frequency (MHz) 125.2662	***Nucleus*** 13C		***Number of Transients*** 176		
Original Points Count 67510	***Points Count*** 131072		***Pulse Sequence*** APT_ad		
Receiver Gain 30.00	***SW(cyclical) (Hz)*** 33826.64		***Solvent*** DMSO-d6		
Spectrum Offset (Hz) 14370.3350	***Spectrum Type*** APT		***Sweep Width (Hz)*** 33826.38		
Temperature (degree C) 26.400					

^{13}C NMR (125MHz, DMSO-d_6) δ = 162.88 (br d, *J*=243.9 Hz, 1C), 159.05, 152.10, 146.94 (br d, *J*=6.2 Hz, 1C), 137.70, 135.99, 131.12 (d, *J*=8.0 Hz, 1C), 127.17, 122.18, 121.86, 114.11 (br d, *J*=20.6 Hz, 1C), 112.72 (br d, *J*=20.1 Hz, 1C), 112.36, 61.68, 35.66, 25.63, 23.09



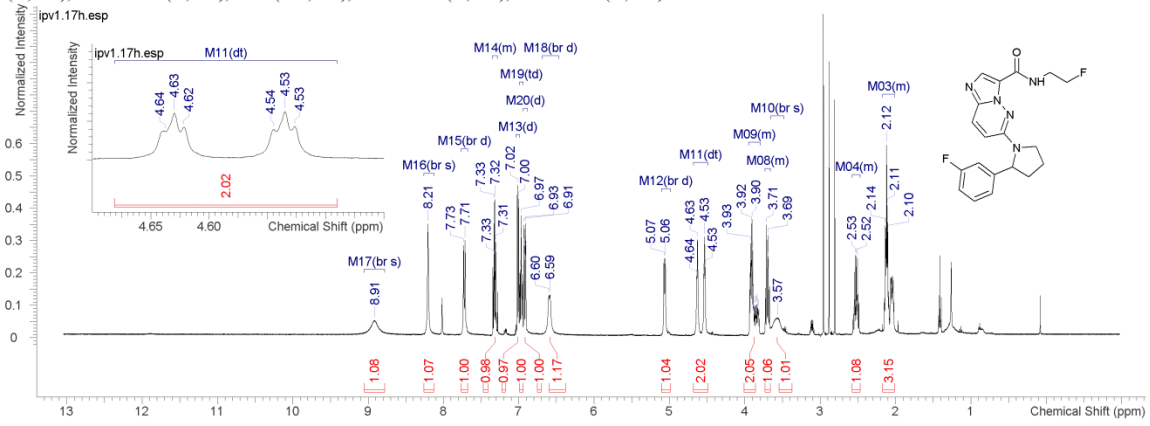
772

6.5 ^{1}H NMR and ^{13}C NMR for compound **13**

IPV 1.17 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 19.68	***Number of Nuclei*** 19 H's		
Acquisition Time (sec) 4.9935	***Comment*** IPV 1.17 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Jan 16 2015	***Date Stamp*** Jan 16 2015	***File Name*** G:\2015.01\2015.01.16.i5_IPV_1.17_H1_1D.fid\fid	
Frequency (MHz) 498.1184	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 34868
Points Count 65536	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6982.63
Solvent CHLOROFORM-d	***Spectrum Offset (Hz)*** 3005.9861	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6982.52
Temperature (degree C) 26.400			

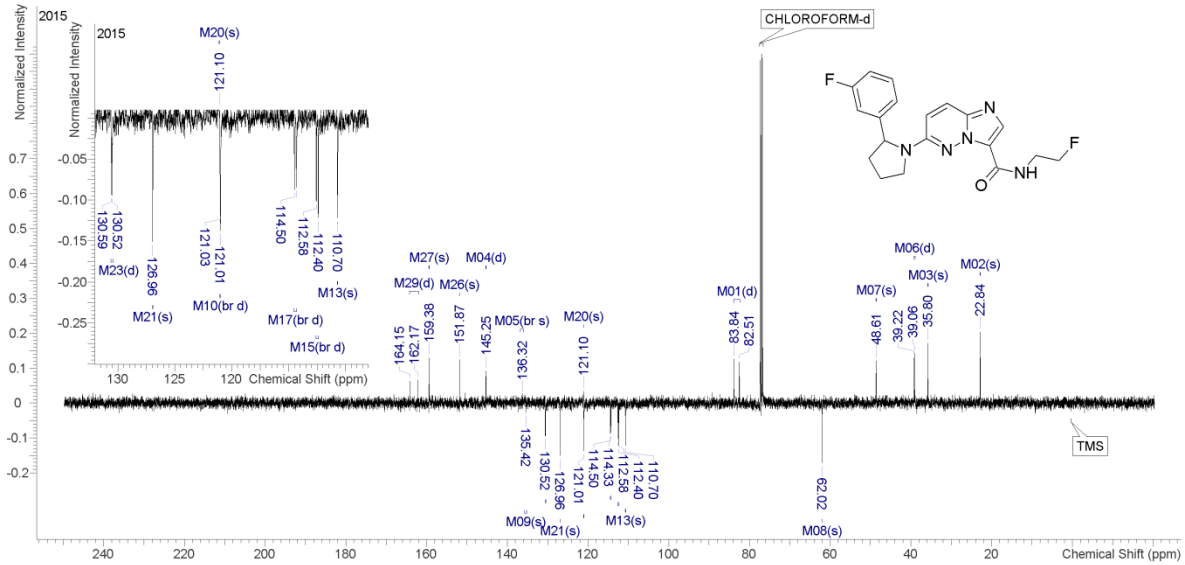
^{1}H NMR (498MHz, CHLOROFORM-d) δ = 8.91 (br s, 1H), 8.21 (br s, 1H), 7.72 (br d, *J*=9.8 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.01 (d, *J*=7.8 Hz, 1H), 6.97 (dt, *J*=1.9, 8.4 Hz, 1H), 6.92 (d, *J*=9.7 Hz, 1H), 6.59 (br d, *J*=7.6 Hz, 1H), 5.07 (br d, *J*=8.0 Hz, 1H), 4.58 (td, *J*=4.1, 47.3 Hz, 2H), 3.95 - 3.80 (m, 2H), 3.73 - 3.66 (m, 1H), 3.57 (br s, 1H), 2.57 - 2.47 (m, 1H), 2.17 - 2.01 (m, 3H)



IPV 1.17 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 19 C's		
Acquisition Time (sec) 1.9958			
Comment IPV 1.17 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal			
Date Jan 16 2015	***Date Stamp*** Jan 16 2015	***File Name*** F:\Schirrma\2015.01\2015.01.16.i5_IPV_1.17_C13_APT_ad.fid\fid	
Frequency (MHz) 125.2656	***Nucleus*** 13C	***Number of Transients*** 204	
Original Points Count 67510	***Points Count*** 131072	***Pulse Sequence*** APT_ad	
Receiver Gain 30.00	***SW(cyclical) (Hz)*** 33826.64	***Solvent*** CHLOROFORM-d	
Spectrum Offset (Hz) 14370.3086	***Spectrum Type*** APT	***Sweep Width (Hz)*** 33826.38	
Temperature (degree C) 26.400			

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.16 (d, *J*=247.2 Hz, 1C), 159.38, 151.87, 145.27 (d, *J*=6.2 Hz, 1C), 136.32 (br s, 1C), 135.42, 130.55 (d, *J*=8.3 Hz, 1C), 126.96, 121.10, 121.02 (br d, *J*=2.8 Hz, 1C), 114.41 (br d, *J*=21.2 Hz, 1C), 112.49 (br d, *J*=21.9 Hz, 1C), 110.70, 83.17 (d, *J*=166.2 Hz, 1C), 62.02, 48.61, 39.14 (d, *J*=19.4 Hz, 1C), 35.80, 22.84



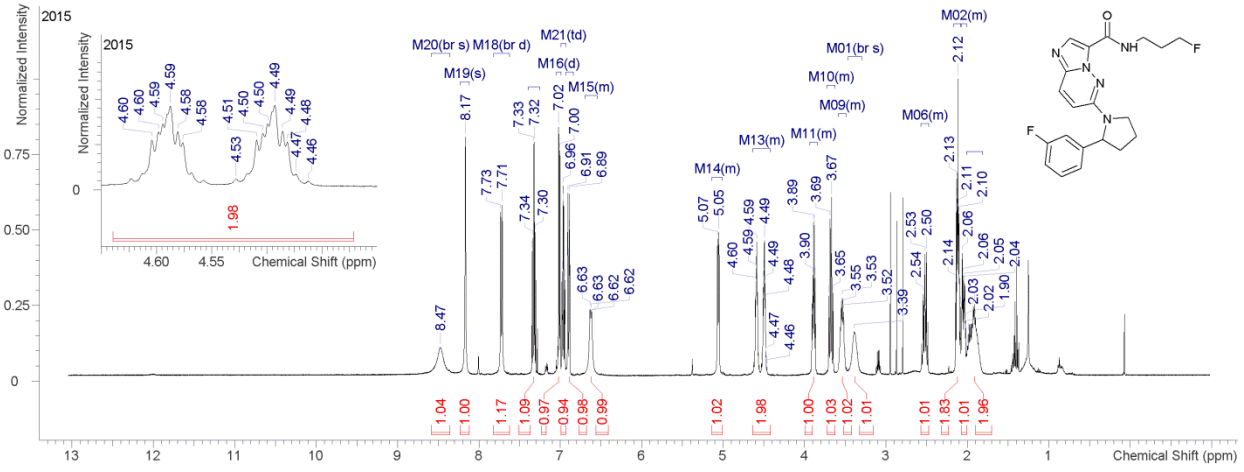
6.6 ^{1}H NMR and ^{13}C NMR for compound **14**

IPV 1.18 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	21.05	***Number of Nuclei***	23 H's

Acquisition Time (sec)	4.9935	***Comment***	IPV 1.18 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 16 2015	***Date Stamp***	Jan 16 2015	***File Name***	G:\2015.01\2015.01.16.i5_IPV_1.18_H1_1D.fid\fid		
Frequency (MHz)	498.1184	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	34868
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6982.63
Solvent	cdcl3	***Spectrum Offset (Hz)***	3005.9861	***Spectrum Type***	standard	***Sweep Width (Hz)***	6982.52
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, $cdcl_3$) δ = 8.47 (br s, 1H), 8.17 (s, 1H), 7.72 (br d, *J*=9.8 Hz, 1H), 7.33 (dt, *J*=5.8, 7.9 Hz, 1H), 7.01 (d, *J*=7.7 Hz, 1H), 6.96 (dt, *J*=2.1, 8.4 Hz, 1H), 6.93 - 6.84 (m, 3H), 6.70 - 6.55 (m, 1H), 5.14 - 5.01 (m, 1H), 4.64 - 4.42 (m, 2H), 3.94 - 3.85 (m, 1H), 3.72 - 3.63 (m, 1H), 3.59 - 3.49 (m, 1H), 3.39 (br s, 1H), 2.57 - 2.48 (m, 1H), 2.16 - 2.08 (m, 2H), 2.07 - 2.01 (m, 1H), 2.01 - 1.81 (m, 2H)



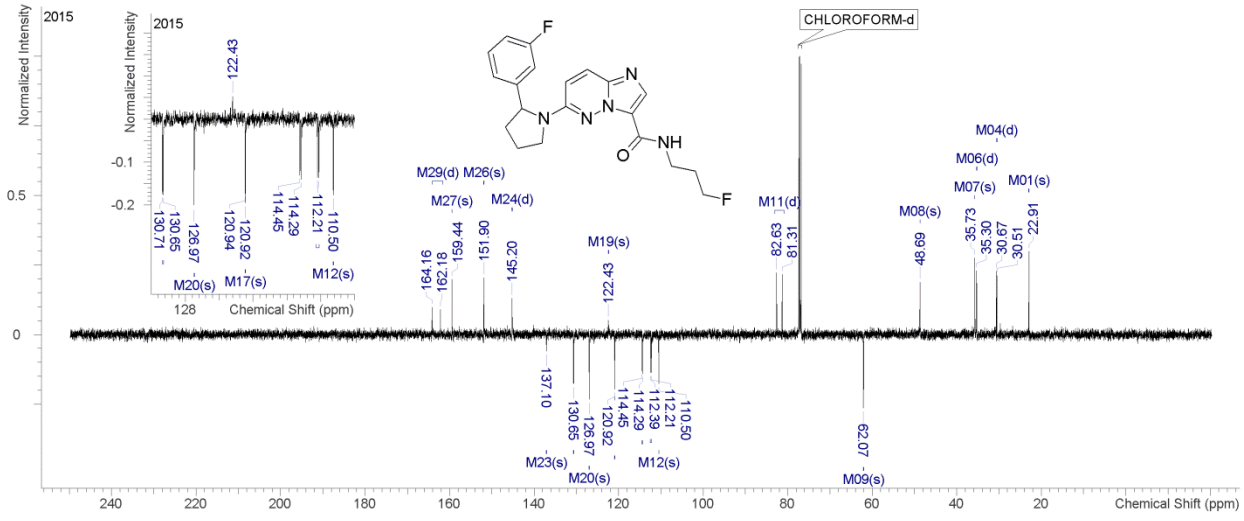
778

IPV 1.18 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	20 C's

Acquisition Time (sec)	1.9958				
Comment	IPV 1.18 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 16 2015	***Date Stamp***	Jan 16 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.18_C13_APT_ad.fid\fid				
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	104
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	cdcl3
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.17 (d, *J*=247.2 Hz, 1C), 159.44, 151.90, 145.23 (d, *J*=6.2 Hz, 1C), 137.10, 130.68 (br d, *J*=8.0 Hz, 1C), 126.97, 122.43, 120.94, 120.92, 114.37 (d, *J*=21.2 Hz, 1C), 112.30 (d, *J*=22.2 Hz, 1C), 110.50, 81.97 (d, *J*=164.4 Hz, 1C), 62.07, 48.69, 35.73, 35.28 (d, *J*=5.2 Hz, 1C), 30.59 (d, *J*=19.4 Hz, 1C), 22.91



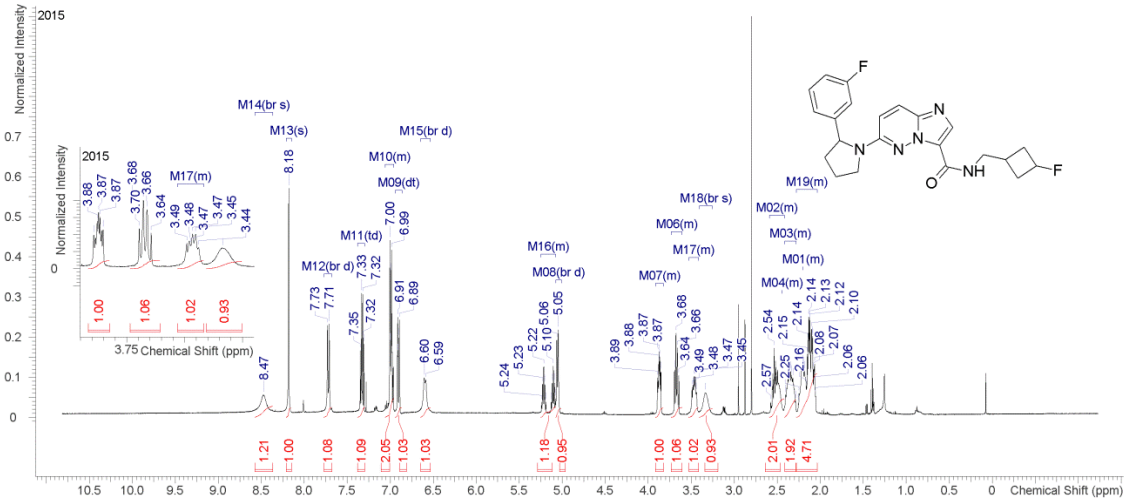
779

6.7 ^{1}H NMR and ^{13}C NMR for compound **15**

IPV 1.21 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 23.28	***Number of Nuclei*** 24 H's		
Acquisition Time (sec) 4.9997	***Comment*** IPV 1.21 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Jan 16 2015	***Date Stamp*** Jan 16 2015		
File Name C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.21_H1_1D.fid\fid			
Nucleus 1H	***Number of Transients*** 16	***Original Points Count*** 30001	***Frequency (MHz)*** 498.1178
Pulse Sequence s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60	***Points Count*** 32768
Spectrum Offset (Hz) 2388.2478	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.42	***Solvent*** cdcl3
			Temperature (degree C) 26.400

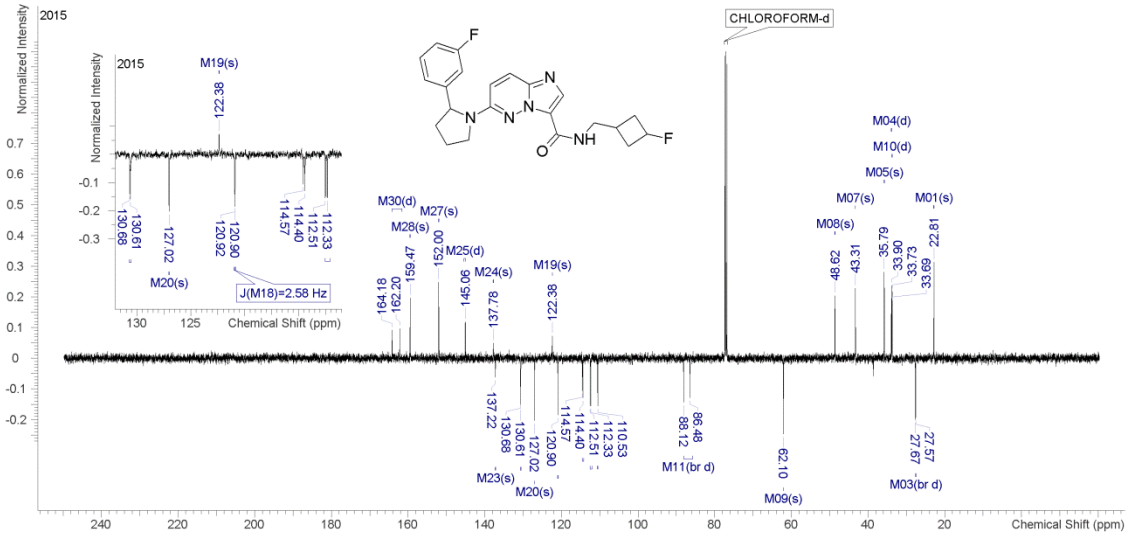
^{1}H NMR (498MHz, $cdcl_3$) δ = 8.47 (br s, 1H), 8.18 (s, 1H), 7.72 (br d, *J*=9.7 Hz, 1H), 7.33 (dt, *J*=5.9, 8.0 Hz, 1H), 7.06 - 6.96 (m, 2H), 6.90 (td, *J*=1.9, 9.7 Hz, 1H), 6.60 (br d, *J*=8.6 Hz, 1H), 5.25 - 5.08 (m, 1H), 5.05 (br d, *J*=7.3 Hz, 1H), 3.92 - 3.82 (m, 1H), 3.73 - 3.61 (m, *J*=8.1 Hz, 1H), 3.53 - 3.42 (m, 1H), 3.34 (br s, 1H), 2.44 - 2.44 (m, 1H), 2.59 - 2.42 (m, 2H), 2.41 - 2.28 (m, 2H), 2.20 - 2.20 (m, 1H), 2.28 - 2.04 (m, 4H)



IPV 1.21 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 22 C's				
Acquisition Time (sec) 1.9958					
Comment	IPV 1.21 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 16 2015	***Date Stamp***	Jan 16 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.21_C13_APT_ad.fid\fid				
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	196
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	cdcl3
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.19 (d, *J*=247.5 Hz, 1C), 159.47, 152.00, 145.08 (d, *J*=6.2 Hz, 1C), 137.78, 137.22, 130.65 (br d, *J*=8.3 Hz, 1C), 127.02, 122.38, 120.92 (d, *J*=2.6 Hz, 1C), 114.48 (br d, *J*=21.2 Hz, 1C), 112.42 (d, *J*=21.9 Hz, 1C), 110.53, 87.30 (br d, *J*=206.5 Hz, 1C), 62.10, 48.62, 43.31, 35.79, 33.88 (d, *J*=4.4 Hz, 1C), 33.71 (d, *J*=4.6 Hz, 1C), 27.62 (br d, *J*=11.9 Hz, 1C), 22.81

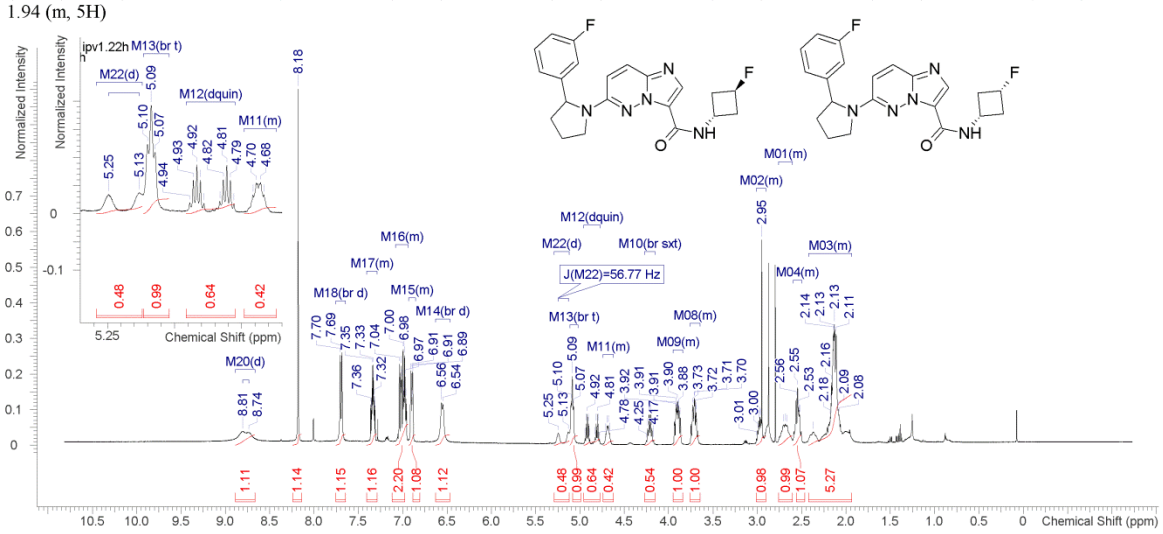


6.8 ^{1}H NMR and ^{13}C NMR for compound **16**

IPV 1.22 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 22.32	***Number of Nuclei*** 23 H's		
Acquisition Time (sec) 4.9997	***Comment***	IPV 1.22 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe	
Date Jan 16 2015	***Date Stamp*** Jan 16 2015	***File Name***	G:\2015.01\2015.01.16.i5_IPV_1.22_H1_1D.fid\fid
Frequency (MHz) 498.1178	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 30001
Points Count 32768	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60
Solvent CHLOROFORM-d	***Spectrum Offset (Hz)*** 2388.2478	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.42
Temperature (degree C) 26.400			

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 8.77 (d, *J*=34.6 Hz, 1H), 8.18 (s, 1H), 7.69 (br d, *J*=9.9 Hz, 1H), 7.41 - 7.29 (m, 1H), 7.08 - 6.94 (m, 2H), 6.93 - 6.85 (m, 1H), 6.55 (br d, *J*=8.6 Hz, 1H), 5.19 (d, *J*=56.8 Hz, 1H), 5.09 (br t, *J*=7.0 Hz, 1H), 4.86 (quind, *J*=6.6, 55.7 Hz, 1H), 4.74 - 4.62 (m, 1H), 4.21 (br sxt, *J*=7.8 Hz, 1H), 3.95 - 3.84 (m, 1H), 3.76 - 3.65 (m, 1H), 3.01 - 2.90 (m, 1H), 2.76 - 2.60 (m, 1H), 2.59 - 2.50 (m, 1H), 2.42 - 1.94 (m, 5H)

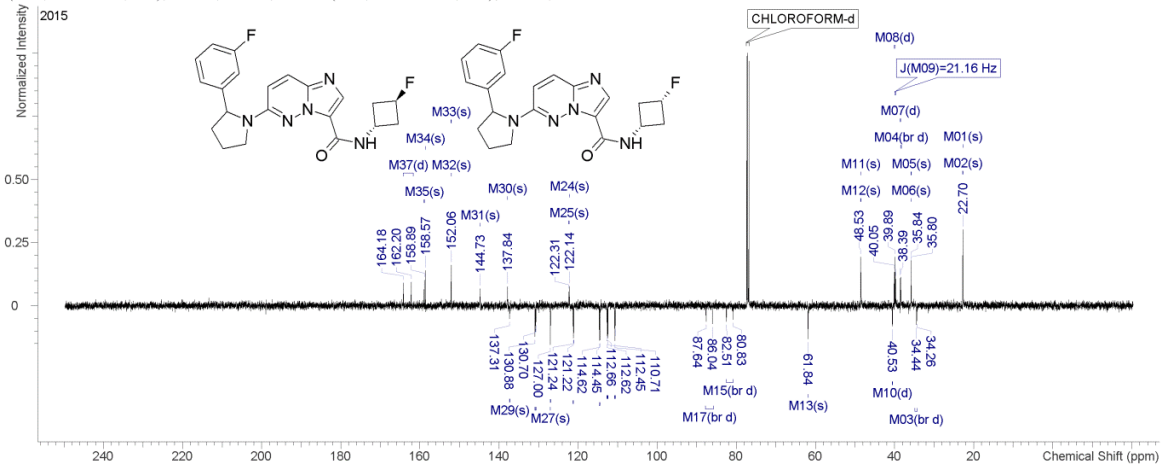


785

IPV 1.22 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 37 C's				
Acquisition Time (sec) 1.9958					
Comment	IPV 1.22 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date Jan 16 2015	***Date Stamp*** Jan 16 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.22_C13_APT_ad.fid\fid				
Frequency (MHz) 125.2656	***Nucleus*** 13C		***Number of Transients*** 220		
Original Points Count 67510	***Points Count*** 131072		***Pulse Sequence*** APT_ad		
Receiver Gain 32.00	***SW(cyclical) (Hz)*** 33826.64		***Solvent*** cdcl3		
Spectrum Offset (Hz) 14370.3086	***Spectrum Type*** APT		***Sweep Width (Hz)*** 33826.38		
Temperature (degree C) 26.400					

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.19 (d, *J*=247.8 Hz, 1C), 158.89, 158.57, 152.09, 152.06, 144.73, 137.84, 137.31, 130.81 (d, *J*=8.3 Hz, 1C), 130.71 - 130.64 (m, 1C), 130.67 (br d, *J*=8.0 Hz, 1C), 127.03, 127.00, 122.31, 122.14, 121.23 (br d, *J*=2.6 Hz, 1C), 121.10 (br d, *J*=2.6 Hz, 1C), 114.54 (br d, *J*=21.2 Hz, 1C), 112.62 (d, *J*=4.9 Hz, 1C), 112.47 (br d, *J*=4.9 Hz, 1C), 110.71, 110.62, 86.84 (br d, *J*=200.3 Hz, 1C), 81.67 (br d, *J*=210.6 Hz, 1C), 61.84, 48.53, 48.46, 40.57 (d, *J*=8.3 Hz, 1C), 39.97 (d, *J*=20.1 Hz, 1C), 39.83 (d, *J*=21.2 Hz, 1C), 38.55 (d, *J*=3.4 Hz, 1C), 38.37 (br d, *J*=3.6 Hz, 1C), 35.84, 35.80, 34.35 (br d, *J*=23.0 Hz, 1C), 22.74, 22.70



786

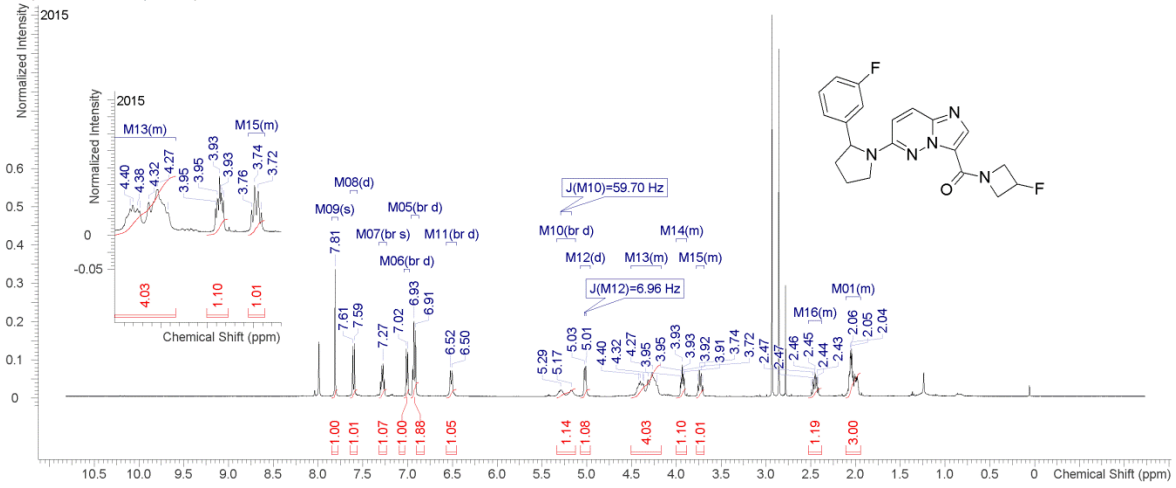
6.9 ^{1}H NMR and ^{13}C NMR for compound **17**

IPV 1.19 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	19.58	**Number of Nuclei**	19 H's

Acquisition Time (sec)	4.9997	**Comment**	IPV 1.19 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 16 2015	**Date Stamp**	Jan 16 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.19_H1_1D.fid\fid					**Frequency (MHz)**	498.1178
Nucleus	1H	**Number of Transients**	16	**Original Points Count**	30001	**Points Count**	32768
Pulse Sequence	s2pul	**Receiver Gain**	32.00	**SW(cyclical) (Hz)**	6000.60	**Solvent**	cdcl3
Spectrum Offset (Hz)	2388.2478	**Spectrum Type**	standard	**Sweep Width (Hz)**	6000.42	**Temperature (degree C)**	26.400

^{1}H NMR (498MHz, $cdcl_3$) δ = 7.81 (s, 1H), 7.60 (d, *J*=9.9 Hz, 1H), 7.27 (br s, 1H), 7.01 (br d, *J*=7.7 Hz, 1H), 6.92 (br d, *J*=9.0 Hz, 2H), 6.51 (br d, *J*=9.9 Hz, 1H), 5.23 (br d, *J*=59.7 Hz, 1H), 5.02 (d, *J*=7.0 Hz, 1H), 4.50 - 4.17 (m, 4H), 4.00 - 3.89 (m, 1H), 3.78 - 3.69 (m, 1H), 2.53 - 2.38 (m, 1H), 2.11 - 1.94 (m, 3H)



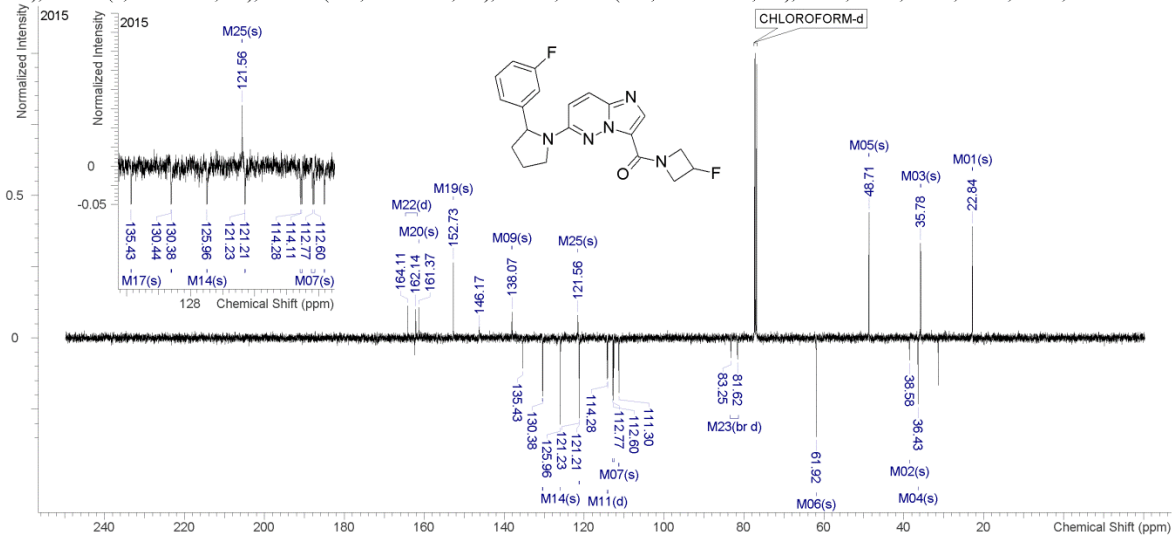
789

IPV 1.19 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	**Number of Nuclei**	20 C's

Acquisition Time (sec)	1.9958						
Comment	IPV 1.19 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal						
Date	Jan 16 2015	**Date Stamp**	Jan 16 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.16.i5_IPV_1.19_C13_APT_ad.fid\fid						
Frequency (MHz)	125.2656	**Nucleus**	13C	**Number of Transients**	188		
Original Points Count	67510	**Points Count**	131072	**Pulse Sequence**	APT_ad		
Receiver Gain	30.00	**SW(cyclical) (Hz)**	33826.64	**Solvent**	cdcl3		
Spectrum Offset (Hz)	14370.3086	**Spectrum Type**	APT	**Sweep Width (Hz)**	33826.38		
Temperature (degree C)	26.400						

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.12 (d, *J*=247.0 Hz, 1C), 161.37, 152.73, 138.07, 135.43, 130.44, 130.38, 125.96, 121.56, 121.22 (d, *J*=2.6 Hz, 1C), 114.19 (d, *J*=21.2 Hz, 1C), 112.68 (br d, *J*=22.2 Hz, 1C), 111.30, 82.43 (br d, *J*=204.7 Hz, 1C), 61.92, 48.71, 38.58, 36.43, 35.78, 22.84



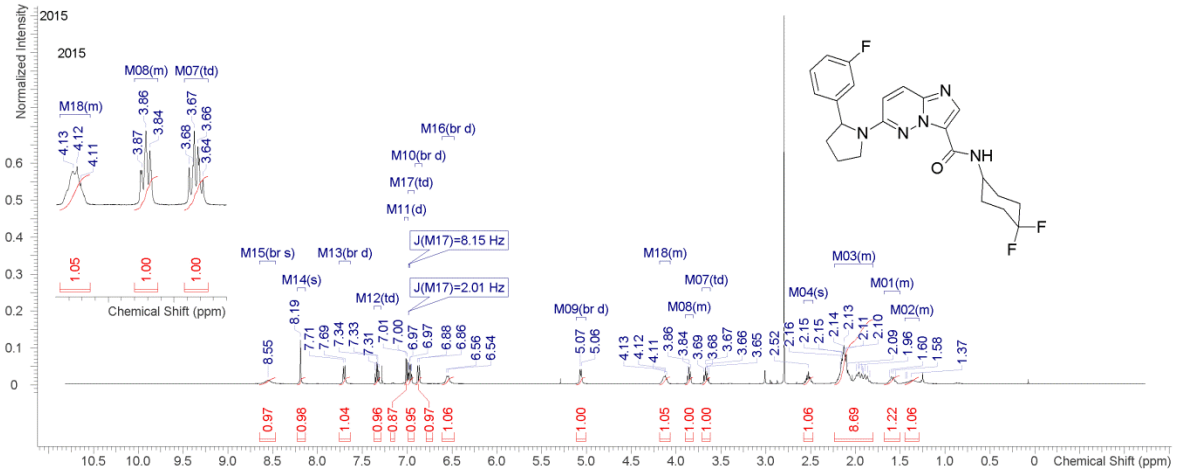
790

6.10 ^{1}H NMR and ^{13}C NMR for compound **18**

IPV 1.28XX 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	23.89	***Number of Nuclei***	25 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.28XX 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 27 2015	***Date Stamp***	Jan 27 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.27.i5_IPV_1.28XX_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

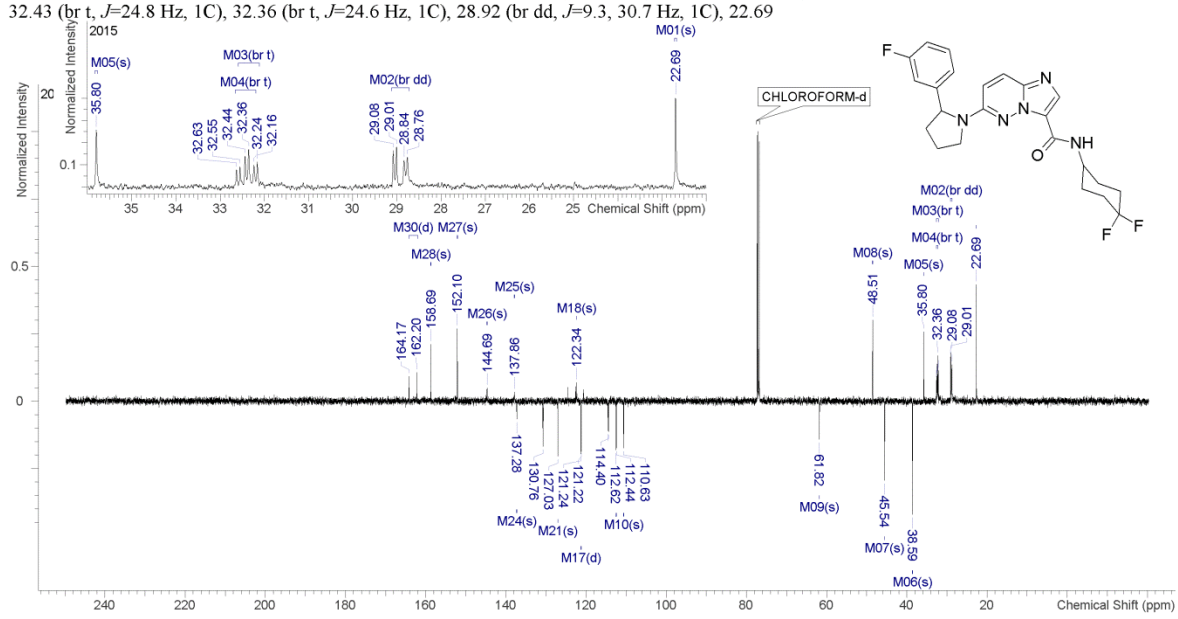
^{1}H NMR (498MHz, $cdcl_3$) δ = 8.55 (br s, 1H), 8.19 (s, 1H), 7.70 (br d, *J*=9.9 Hz, 1H), 7.34 (dt, *J*=5.9, 7.9 Hz, 1H), 7.01 (d, *J*=7.7 Hz, 1H), 6.97 (dt, *J*=2.0, 8.2 Hz, 1H), 6.87 (br d, *J*=9.5 Hz, 1H), 6.55 (br d, *J*=8.6 Hz, 1H), 5.06 (br d, *J*=7.7 Hz, 1H), 4.18 - 4.07 (m, 1H), 3.90 - 3.81 (m, 1H), 3.67 (dt, *J*=7.1, 9.6 Hz, 1H), 2.52 (s, 1H), 2.23 - 1.81 (m, 9H), 1.68 - 1.51 (m, 2H), 1.45 - 1.29 (m, 1H)



IPV 1.28XX 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	22 C's				
Acquisition Time (sec)	1.9958						
Comment	IPV 1.28XX 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal						
Date	Jan 27 2015	***Date Stamp***	Jan 27 2015				
File Name	F:\Schirrma\2015.01\2015.01.27.i5_IPV_1.28XX_C13_APT_ad.fid\fid					***Frequency (MHz)***	125.2656
Nucleus	13C	***Number of Transients***	220			***Original Points Count***	67510
Points Count	131072	***Pulse Sequence***	APT_ad			***Receiver Gain***	30.00
SW(cyclical) (Hz)	33826.64	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	14370.3086
Spectrum Type	APT	***Sweep Width (Hz)***	33826.38			***Temperature (degree C)***	26.400

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.19 (d, *J*=247.5 Hz, 1C), 158.69, 152.10, 144.69, 137.86, 137.28, 130.73 (br d, *J*=8.3 Hz, 1C), 127.03, 122.34, 121.23 (d, *J*=2.8 Hz, 1C), 114.49 (br d, *J*=21.2 Hz, 1C), 112.53 (br d, *J*=22.2 Hz, 1C), 110.63, 61.82, 48.51, 45.54, 38.59, 35.80, 32.43 (br t, *J*=24.8 Hz, 1C), 32.36 (br t, *J*=24.6 Hz, 1C), 28.92 (br dd, *J*=9.3, 30.7 Hz, 1C), 22.69

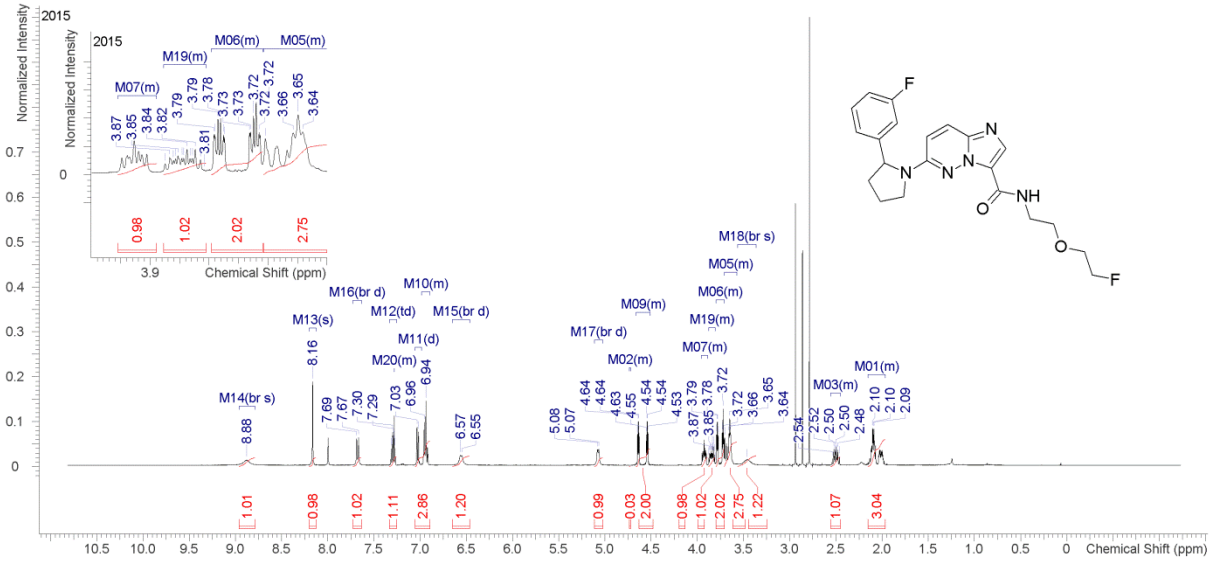


6.11 ^{1}H NMR and ^{13}C NMR for compound **19**

IPV 1.23 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	23.29	***Number of Nuclei***	25 H's		
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.23 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date	Jan 20 2015	***Date Stamp***	Jan 20 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.20.i5_IPV_1.23_H1_1D.fid\fid			***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

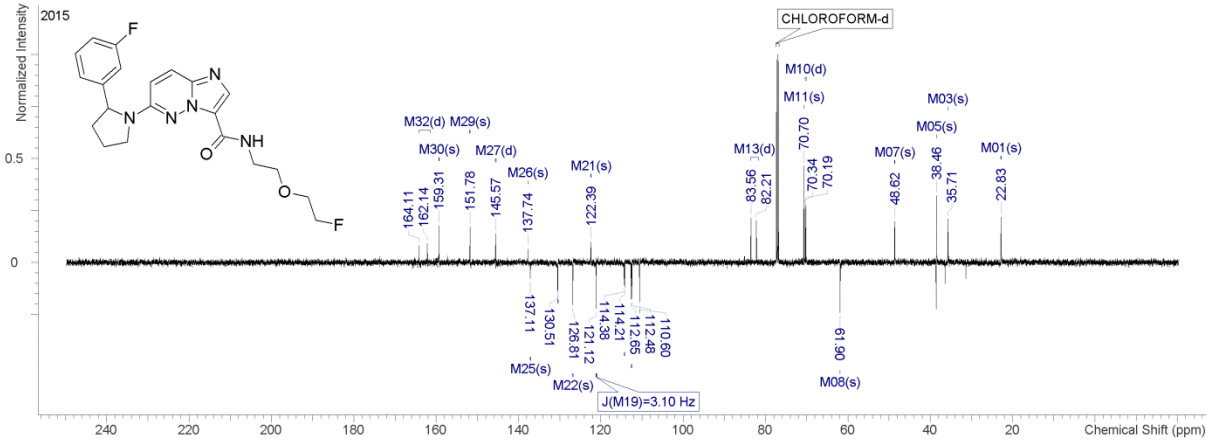
^{1}H NMR (498MHz, cdcl$_3$) δ = 8.88 (br s, 1H), 8.16 (s, 1H), 7.68 (br d, *J*=9.9 Hz, 1H), 7.28 - 7.28 (m, 1H), 7.29 (dt, *J*=5.9, 8.1 Hz, 1H), 7.03 (d, *J*=7.7 Hz, 1H), 6.99 - 6.89 (m, 2H), 6.56 (br d, *J*=8.4 Hz, 1H), 5.07 (br d, *J*=7.3 Hz, 1H), 4.74 - 4.72 (m, 1H), 4.66 - 4.51 (m, 2H), 3.95 - 3.89 (m, 1H), 3.88 - 3.81 (m, 1H), 3.80 - 3.71 (m, 2H), 3.71 - 3.57 (m, 3H), 3.46 (br s, 1H), 2.56 - 2.45 (m, 1H), 2.15 - 1.96 (m, 3H)



IPV 1.23 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	21 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.23 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 20 2015	***Date Stamp***	Jan 20 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.20.i5_IPV_1.23_C13_APT_ad.fid\fid				
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	192
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	cdcl3
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, cdcl$_3$) δ = 163.12 (d, *J*=247.0 Hz, 1C), 159.31, 151.78, 145.54 (d, *J*=6.5 Hz, 1C), 137.74, 137.11, 130.48 (br d, *J*=8.0 Hz, 1C), 126.81, 122.39, 121.09 (d, *J*=3.1 Hz, 1C), 114.30 (br d, *J*=21.2 Hz, 1C), 112.56 (br d, *J*=22.2 Hz, 1C), 110.60, 82.89 (d, *J*=169.8 Hz, 1C), 70.70, 70.26 (d, *J*=19.6 Hz, 1C), 61.90, 48.62, 38.46, 35.71, 22.83



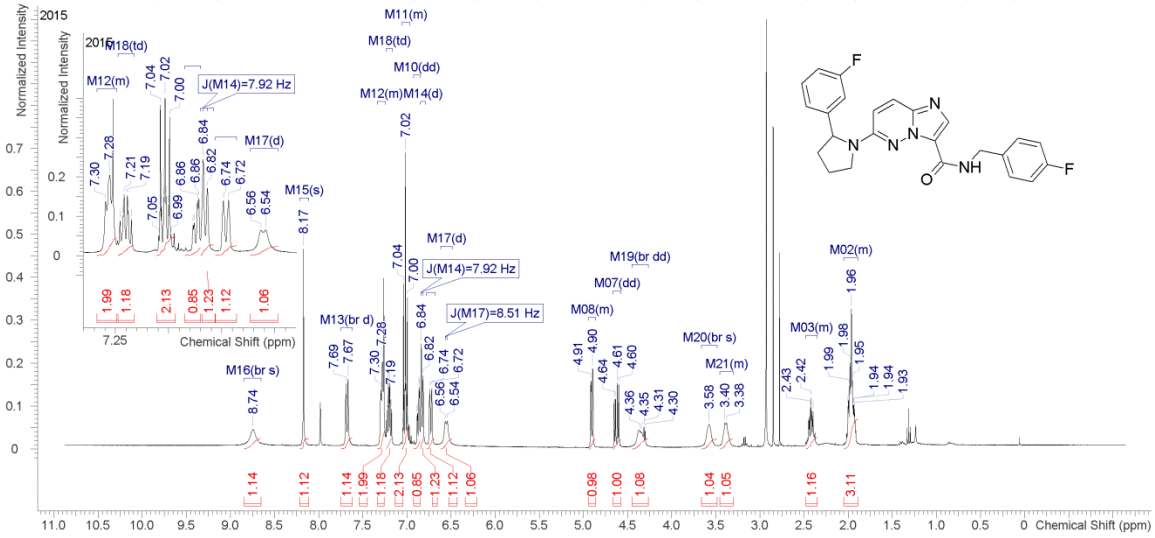
6.12 ^{1}H NMR and ^{13}C NMR for compound **20**

IPV 1.31 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

Multiplets Integrals Sum	22.38	***Number of Nuclei***	21 H's

Acquisition Time (sec)	4.9999	***Comment***	IPV 1.31 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.mr4_IPV_1.31_H1_1D.fid\fid					***Frequency (MHz)***	399.9845
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	24038	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	24.00	***SW(cyclical) (Hz)***	4807.69	***Solvent***	cdcl3
Spectrum Offset (Hz)	1947.6067	***Spectrum Type***	standard	***Sweep Width (Hz)***	4807.55	***Temperature (degree C)***	25.900

^{1}H NMR (400MHz, $cdcl_3$) δ = 8.74 (br s, 1H), 8.17 (s, 1H), 7.68 (br d, *J*=9.8 Hz, 1H), 7.34 - 7.24 (m, 2H), 7.20 (dt, *J*=5.9, 7.8 Hz, 1H), 7.06 - 6.97 (m, 2H), 6.87 (dd, *J*=2.3, 8.4 Hz, 1H), 6.83 (d, *J*=7.9 Hz, 1H), 6.73 (br d, *J*=9.7 Hz, 1H), 6.55 (d, *J*=8.5 Hz, 1H), 4.94 - 4.86 (m, 1H), 4.62 (dd, *J*=6.2, 14.8 Hz, 1H), 4.33 (br dd, *J*=5.9, 19.8 Hz, 1H), 3.58 (br s, 1H), 3.46 - 3.30 (m, 1H), 2.48 - 2.35 (m, 1H), 2.05 - 1.89 (m, 3H)

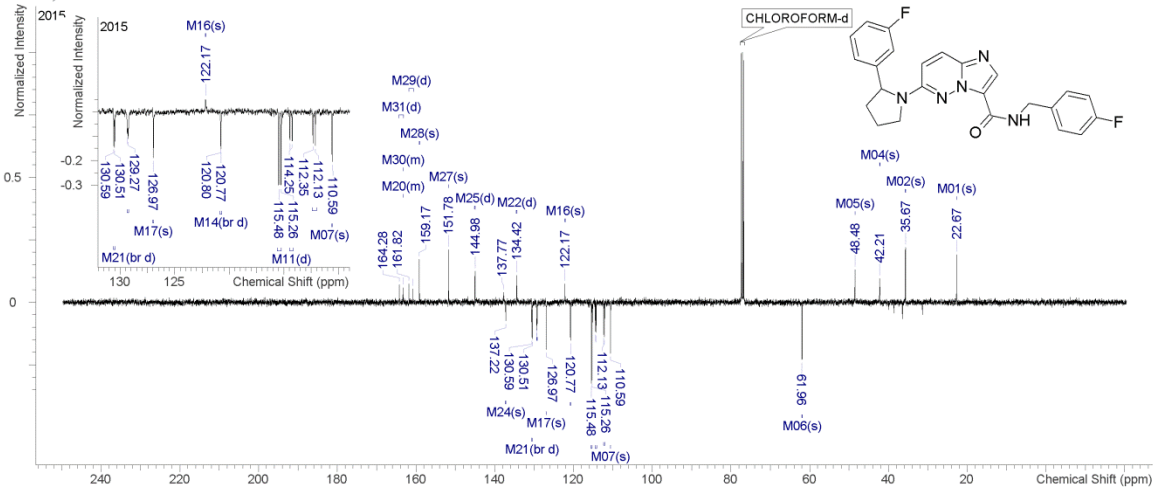


IPV 1.31 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	23 C's

Acquisition Time (sec)	2.0000				
Comment	IPV 1.31 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.mr4_IPV_1.31_C13_APT_ad.fid\fid				
Frequency (MHz)	100.5872	***Nucleus***	13C	***Number of Transients***	476
Original Points Count	54348	***Points Count***	65536	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	27173.91	***Solvent***	cdcl3
Spectrum Offset (Hz)	11531.6846	***Spectrum Type***	APT	***Sweep Width (Hz)***	27173.50
Temperature (degree C)	25.900				

^{13}C NMR (101MHz, $cdcl_3$) δ = 163.31 - 163.28 (m, 1C), 163.31 - 163.28 (m, 1C), 163.80 (d, *J*=97.0 Hz, 1C), 161.35 (d, *J*=95.0 Hz, 1C), 159.17, 151.78, 145.01 (d, *J*=6.2 Hz, 1C), 137.22, 134.43 (d, *J*=3.3 Hz, 1C), 130.55 (br d, *J*=8.3 Hz, 1C), 129.31 (br d, *J*=8.3 Hz, 1C), 126.97, 122.17, 120.78 (br d, *J*=2.5 Hz, 1C), 115.37 (br d, *J*=21.6 Hz, 1C), 114.36 (d, *J*=21.1 Hz, 1C), 112.24 (br d, *J*=22.0 Hz, 1C), 110.59, 61.96, 48.48, 42.21, 35.67, 22.67

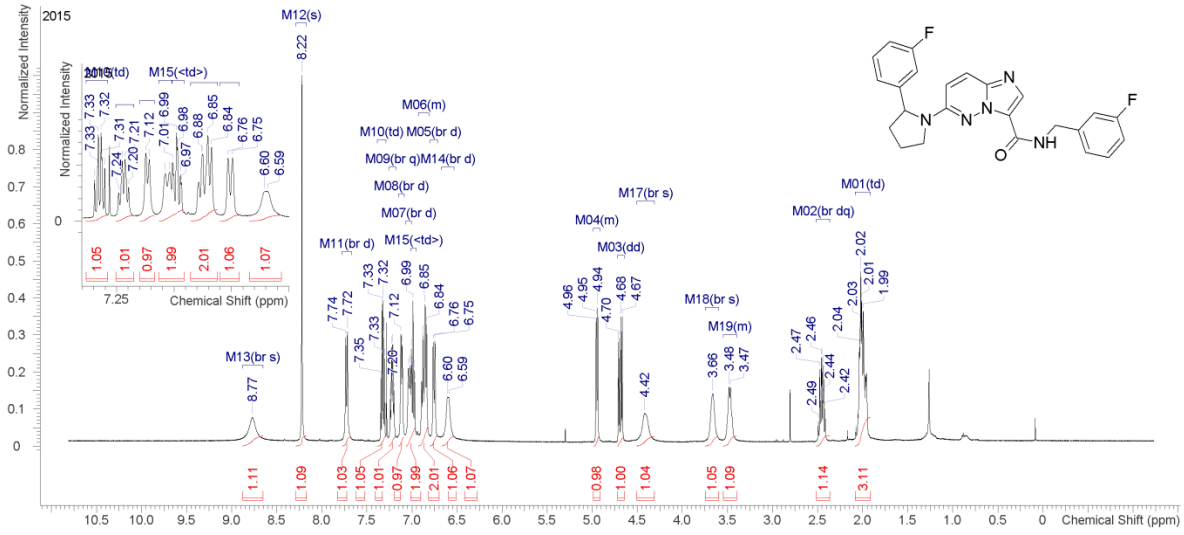


6.13 ^{1}H NMR and ^{13}C NMR for compound **21**

IPV 1.29XX 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	21.81	***Number of Nuclei***	21 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.29XX 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 27 2015	***Date Stamp***	Jan 27 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.27.i5_IPV_1.29XX_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

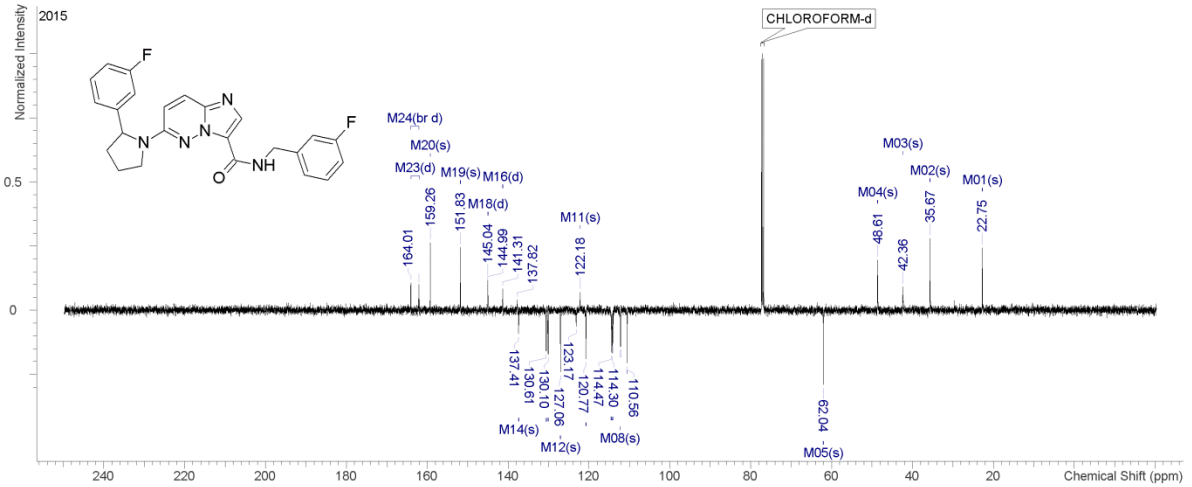
^{1}H NMR (498MHz, cdcl$_3$) δ = 8.77 (br s, 1H), 8.22 (s, 1H), 7.73 (br d, *J*=9.7 Hz, 1H), 7.32 (dt, *J*=6.1, 7.8 Hz, 1H), 7.22 (br q, *J*=7.7 Hz, 1H), 7.12 (br d, *J*=7.5 Hz, 1H), 7.03 (br d, *J*=9.5 Hz, 1H), 6.99 (dt, *J*=2.2, 8.4 Hz, 1H), 6.93 - 6.81 (m, 2H), 6.75 (br d, *J*=9.5 Hz, 1H), 6.60 (br d, *J*=6.6 Hz, 1H), 4.99 - 4.92 (m, 1H), 4.69 (dd, *J*=6.2, 15.2 Hz, 1H), 4.42 (br s, 1H), 3.66 (br s, 1H), 3.54 - 3.40 (m, 1H), 2.45 (br qd, *J*=8.5, 11.8 Hz, 1H), 2.02 (dt, *J*=4.8, 7.9 Hz, 3H)



IPV 1.29XX 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	22 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.29XX 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 27 2015	***Date Stamp***	Jan 27 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.27.i5_IPV_1.29XX_C13_APT_ad.fid\fid				
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	172
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	32.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	cdcl3
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, cdcl$_3$) δ = 163.09 (br d, *J*=247.2 Hz, 1C), 163.03 (d, *J*=246.2 Hz, 1C), 159.26, 151.83, 145.02 (d, *J*=6.2 Hz, 1C), 141.34 (d, *J*=6.7 Hz, 1C), 137.41, 130.57 (br d, *J*=8.3 Hz, 1C), 130.13 (d, *J*=8.3 Hz, 1C), 127.06, 122.18, 120.77, 114.30 (d, *J*=21.2 Hz, 1C), 114.13 (br d, *J*=20.9 Hz, 1C), 112.32, 112.14, 110.56, 62.04, 48.61, 42.36, 35.67, 22.75



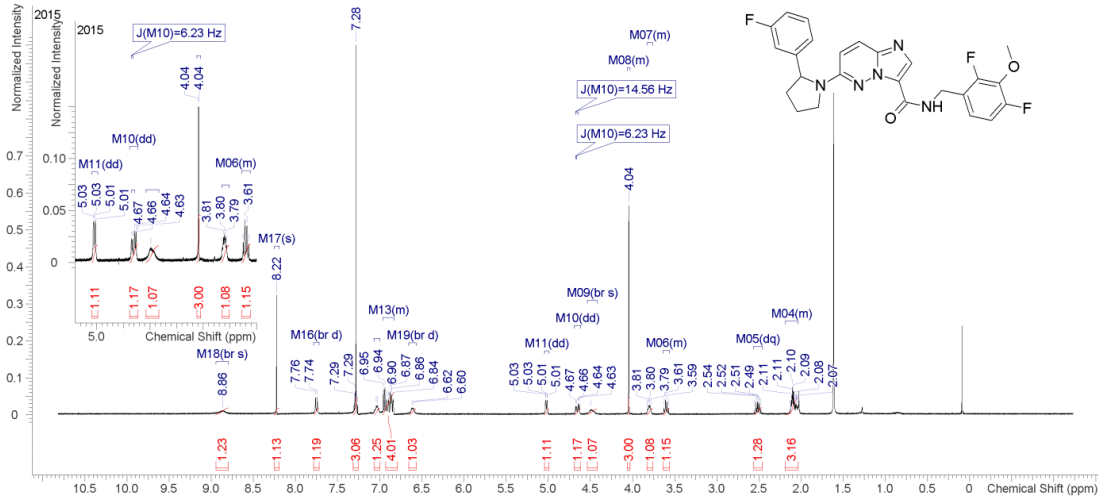
6.14 ^{1}H NMR and ^{13}C NMR for compound **22**

IPV 1.34 HPLC pure fraction 20.3 min - 22.0 min 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	25.93	***Number of Nuclei***	24 H's

Acquisition Time (sec)	4.9997				
Comment	IPV 1.34 HPLC pure fraction 20.3 min - 22.0 min 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Apr 14 2015	***Date Stamp***	Apr 14 2015	***File Name***	F:\Schirrma\2015.04\2015.04.14.i5_IPV_1.34_20.3-22.0_H1_1D.fid\fid
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	30001	***Points Count***	65536	***Pulse Sequence***	s2pul
Receiver Gain	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400				

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 8.86 (br s, 1H), 8.22 (s, 1H), 7.75 (br d, *J*=9.6 Hz, 1H), 7.32 - 7.25 (m, 3H), 7.03 (br d, *J*=6.3 Hz, 1H), 6.96 - 6.83 (m, 4H), 6.61 (br d, *J*=9.4 Hz, 1H), 5.02 (dd, *J*=1.7, 8.7 Hz, 1H), 4.66 (dd, *J*=6.2, 14.6 Hz, 1H), 4.49 (br s, 1H), 4.06 - 4.03 (m, 3H), 3.83 - 3.76 (m, 1H), 3.64 - 3.56 (m, 1H), 2.51 (qd, *J*=8.7, 11.9 Hz, 1H), 2.19 - 2.04 (m, 3H)

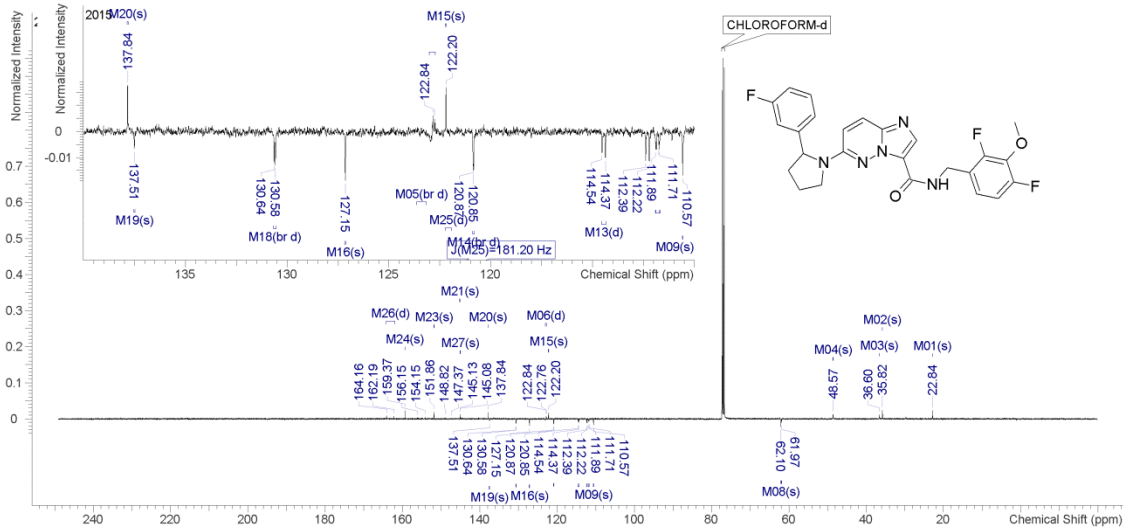


Jamie_Bailey, IPV_1_34 125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	25 C's

Acquisition Time (sec)	2.0000				
Comment	Jamie_Bailey, IPV_1_34 125.690 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	May 13 2015	***Date Stamp***	May 13 2015		
File Name	F:\Schirrma\2015.05\2015.05.13.u5_IPV_1_34_loc12_12.20_C13_APT_ad.fid\fid			***Frequency (MHz)***	125.6902
Nucleus	13C	***Number of Transients***	648	***Original Points Count***	67568
Points Count	131072	***Pulse Sequence***	APT_ad	***Receiver Gain***	30.00
SW(cyclical) (Hz)	33783.79	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	14411.0176
Spectrum Type	APT	***Sweep Width (Hz)***	33783.53	***Temperature (degree C)***	27.600

^{13}C NMR (126MHz, CHLOROFORM-d) δ = 163.17 (d, *J*=247.4 Hz, 1C), 159.37, 155.15 (br d, *J*=252.1 Hz, 1C), 151.86, 148.25 (d, *J*=181.2 Hz, 1C), 145.13, 145.08, 137.84, 137.51, 130.61 (br d, *J*=8.2 Hz, 1C), 127.15, 122.80 (d, *J*=10.1 Hz, 1C), 122.20, 120.86 (br d, *J*=2.3 Hz, 1C), 114.45 (d, *J*=21.1 Hz, 1C), 112.30 (d, *J*=21.9 Hz, 1C), 111.82 (br d, *J*=19.3 Hz, 1C), 111.79 (br d, *J*=19.3 Hz, 1C), 110.57, 62.10, 62.02 - 61.92 (m, 1C), 48.57, 36.60, 35.82, 22.84



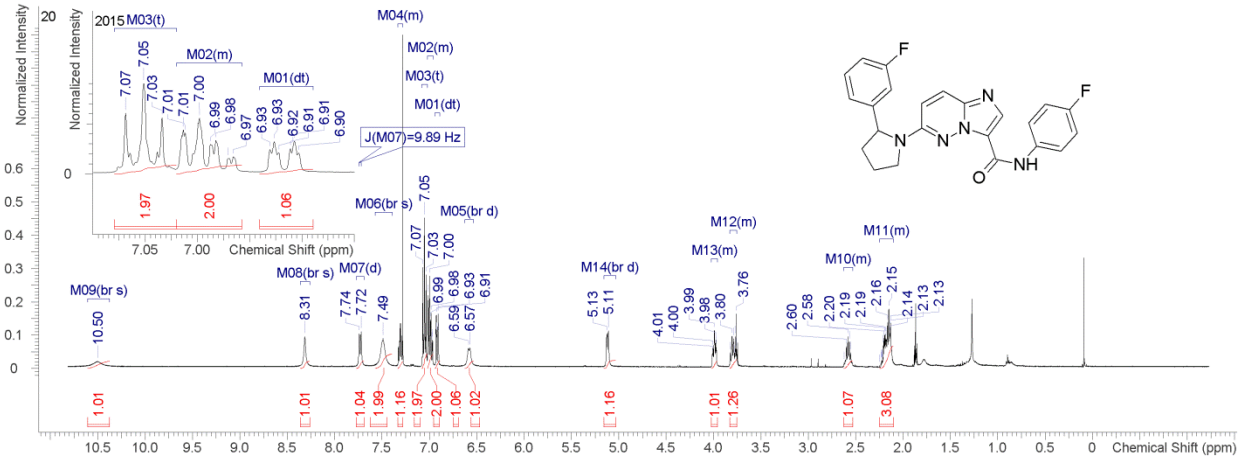
806 6.15 ^{1}H NMR and ^{13}C NMR for compound **23**

IPV 1.33 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	19.83	***Number of Nuclei***	19 H's

Acquisition Time (sec)	4.9997	***Comment***	IPV 1.33 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.i5_IPV_1.33_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

^{1}H NMR (498MHz, $cdcl_3$) δ = 10.50 (br s, 1H), 8.31 (br s, 1H), 7.73 (d, *J*=9.9 Hz, 1H), 7.49 (br s, 2H), 7.33 - 7.28 (m, 1H), 7.05 (t, *J*=8.7 Hz, 2H), 7.02 - 6.96 (m, 2H), 6.92 (td, *J*=2.0, 9.5 Hz, 1H), 6.58 (br d, *J*=8.1 Hz, 1H), 5.12 (br d, *J*=8.1 Hz, 1H), 4.02 - 3.96 (m, 1H), 3.83 - 3.76 (m, 1H), 2.62 - 2.53 (m, 1H), 2.25 - 2.10 (m, 3H)



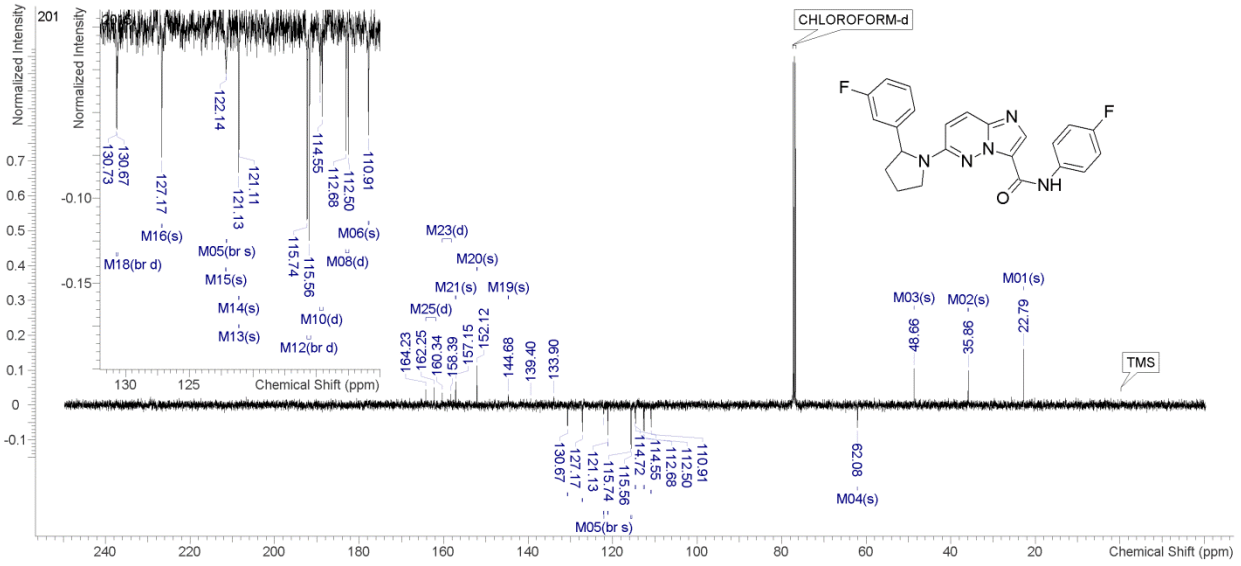
807

IPV 1.33 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	19 C's

Acquisition Time (sec)	1.9958				
Comment	IPV 1.33 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015	***File Name***	F:\Schirrma\2015.01\2015.01.23.i5_IPV_1.33_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	276
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.24 (d, *J*=247.8 Hz, 1C), 159.37 (d, *J*=243.4 Hz, 1C), 157.15, 152.12, 144.68, 130.70 (br d, *J*=8.3 Hz, 1C), 127.17, 122.14, 122.10 (br s, 1C), 121.13, 121.11, 115.65 (br d, *J*=22.7 Hz, 1C), 114.64 (d, *J*=21.4 Hz, 1C), 112.59 (d, *J*=22.2 Hz, 1C), 110.91, 62.08, 48.66, 35.86, 22.79



808

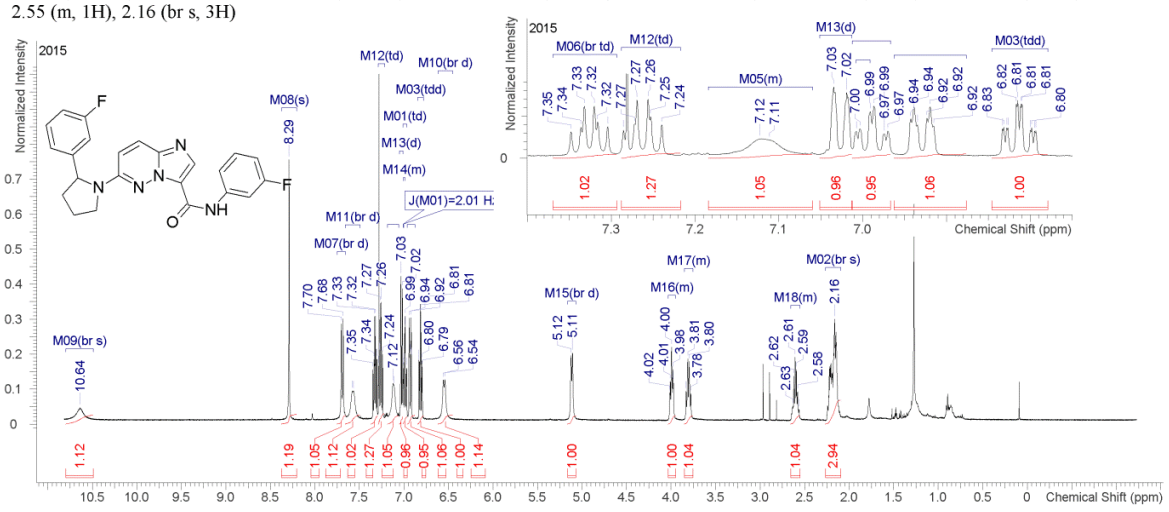
6.16 ^{1}H NMR and ^{13}C NMR for compound **24**

IPV 1.36 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 19.94	***Number of Nuclei*** 20 H's		

Acquisition Time (sec)	4.9997	***Comment***	IPV 1.36 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.i5_IPV_1.36_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

^{1}H NMR (498MHz, $cdcl_3$) δ = 10.64 (br s, 1H), 8.29 (s, 1H), 7.69 (br d, *J*=9.7 Hz, 1H), 7.57 (br d, *J*=6.8 Hz, 1H), 7.33 (br dt, *J*=6.0, 7.9 Hz, 1H), 7.26 (dt, *J*=6.6, 8.1 Hz, 1H), 7.18 - 7.06 (m, 1H), 7.03 (d, *J*=7.9 Hz, 1H), 7.01 - 6.99 (m, 1H), 6.99 (dt, *J*=2.0, 8.4 Hz, 1H), 6.93 (br td, *J*=2.1, 9.6 Hz, 1H), 6.81 (ddt, *J*=0.7, 2.6, 8.3 Hz, 1H), 6.55 (br d, *J*=9.3 Hz, 1H), 5.12 (br d, *J*=7.9 Hz, 1H), 4.03 - 3.95 (m, 1H), 3.85 - 3.75 (m, 1H), 2.66 - 2.55 (m, 1H), 2.16 (br s, 3H)

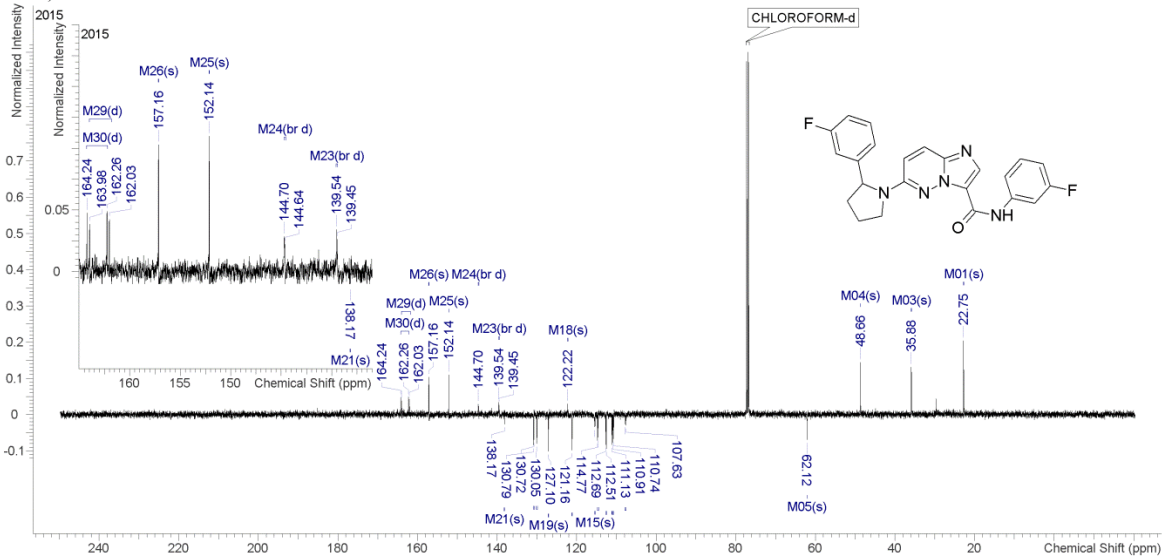


IPV 1.36 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 22 C's		

Acquisition Time (sec)	1.9958				
Comment	IPV 1.36 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015	***File Name***	F:\Schirrma\2015.01\2015.01.23.i5_IPV_1.36_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	512
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	32.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.25 (d, *J*=247.8 Hz, 1C), 163.00 (d, *J*=244.7 Hz, 1C), 157.16, 152.14, 144.67 (br d, *J*=7.7 Hz, 1C), 139.50 (br d, *J*=11.1 Hz, 1C), 138.17, 130.76 (br d, *J*=8.3 Hz, 1C), 130.01 (br d, *J*=9.3 Hz, 1C), 127.10, 122.22, 121.15 (d, *J*=2.8 Hz, 1C), 115.41, 114.69 (br d, *J*=21.2 Hz, 1C), 112.60 (br d, *J*=22.2 Hz, 1C), 111.13, 110.82 (br d, *J*=21.4 Hz, 1C), 107.74 (br d, *J*=26.6 Hz, 1C), 62.12, 48.66, 35.88, 22.75

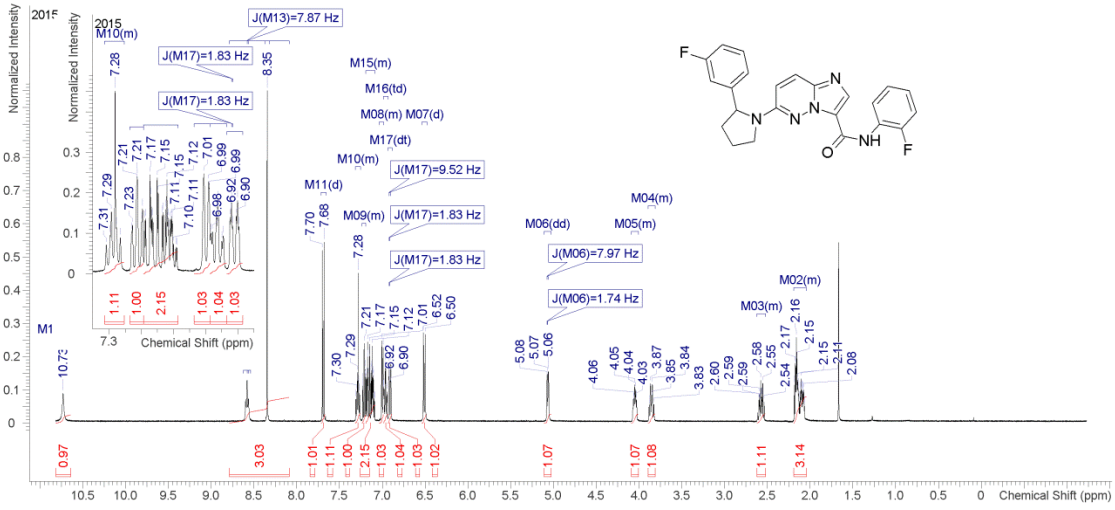


6.17 ^{1}H NMR and ^{13}C NMR for compound **25**

IPV 1.37 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	20.87	***Number of Nuclei***	21 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.37 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	May 6 2015	***Date Stamp***	May 6 2015	***File Name***	F:\Schirrma\2015.05\2015.05.06.i5_IPV_1.37_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

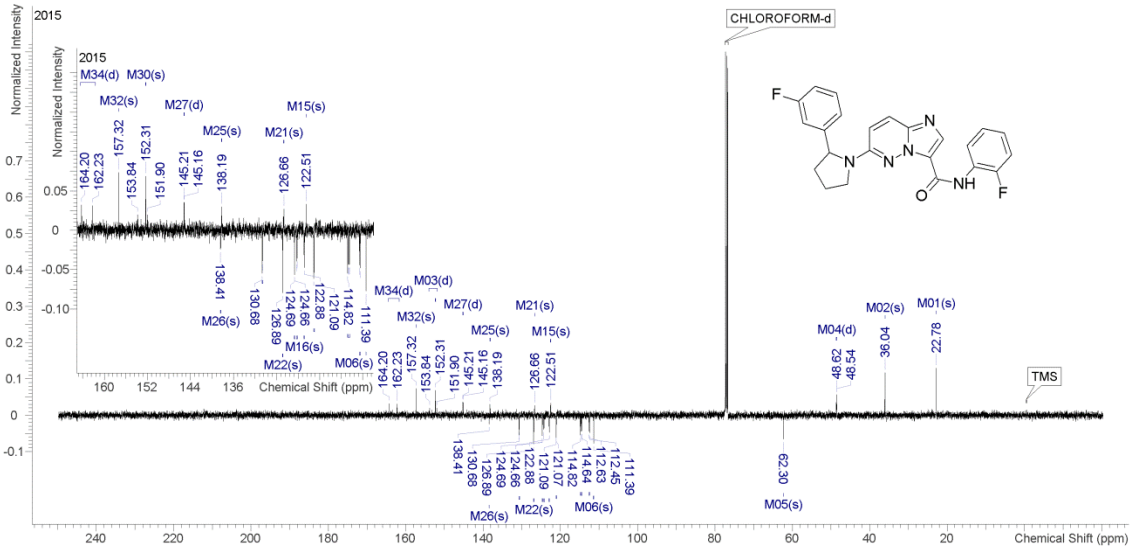
^{1}H NMR (498MHz, CHLOROFORM-d) δ = 10.73 (br s, 1H), 8.58 (t, *J*=7.9 Hz, 1H), 8.35 (s, 1H), 8.79 - 8.09 (m, 1H), 7.69 (d, *J*=9.9 Hz, 1H), 7.31 - 7.25 (m, 1H), 7.24 - 7.19 (m, 1H), 7.19 - 7.09 (m, 3H), 7.04 - 6.99 (m, 1H), 6.96 (dt, *J*=2.3, 8.4 Hz, 1H), 6.91 (td, *J*=1.8, 9.5 Hz, 1H), 6.51 (d, *J*=9.9 Hz, 1H), 5.07 (dd, *J*=1.7, 8.0 Hz, 1H), 4.09 - 4.01 (m, 1H), 3.89 - 3.81 (m, 1H), 2.62 - 2.52 (m, 1H), 2.19 - 2.04 (m, 3H)



IPV 1.37 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	23 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.37 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	May 6 2015	***Date Stamp***	May 6 2015	***File Name***	F:\Schirrma\2015.05\2015.05.06.i5_IPV_1.37_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	444
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.22 (d, *J*=247.8 Hz, 1C), 157.32, 152.31, 152.87 (d, *J*=242.8 Hz, 1C), 145.19 (d, *J*=5.9 Hz, 1C), 138.41, 138.19, 130.65 (br d, *J*=8.5 Hz, 1C), 126.89, 126.66, 124.67 (d, *J*=3.1 Hz, 1C), 124.24 (br d, *J*=8.0 Hz, 1C), 122.88, 122.51, 121.08 (d, *J*=3.1 Hz, 1C), 114.74 (d, *J*=19.1 Hz, 1C), 114.55 (d, *J*=21.2 Hz, 1C), 112.54 (br d, *J*=22.2 Hz, 1C), 111.39, 62.30, 48.58 (d, *J*=9.8 Hz, 1C), 36.04, 22.78

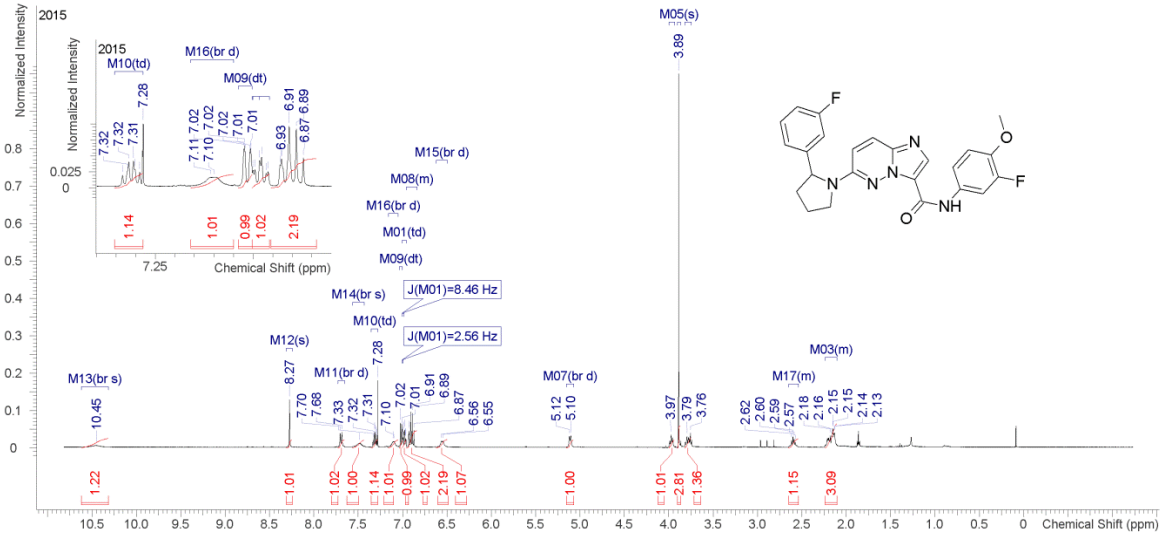


6.18 ^{1}H NMR and ^{13}C NMR for compound **26**

IPV 1.32 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	22.09	***Number of Nuclei***	22 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.32 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.i5_IPV_1.32_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

^{1}H NMR (498MHz, $cdcl_3$) δ = 10.45 (br s, 1H), 8.27 (s, 1H), 7.69 (br d, *J*=9.9 Hz, 1H), 7.48 (br s, 1H), 7.31 (dt, *J*=6.0, 7.9 Hz, 1H), 7.10 (br d, *J*=4.4 Hz, 1H), 7.01 (td, *J*=0.7, 7.7 Hz, 1H), 6.98 (dt, *J*=2.6, 8.5 Hz, 2H), 6.95 - 6.84 (m, 2H), 6.55 (br d, *J*=8.2 Hz, 1H), 5.11 (br d, *J*=7.9 Hz, 1H), 3.97 (br s, 1H), 3.89 (s, 3H), 3.78 (br d, *J*=19.4 Hz, 1H), 2.65 - 2.54 (m, 1H), 2.24 - 2.11 (m, 3H)

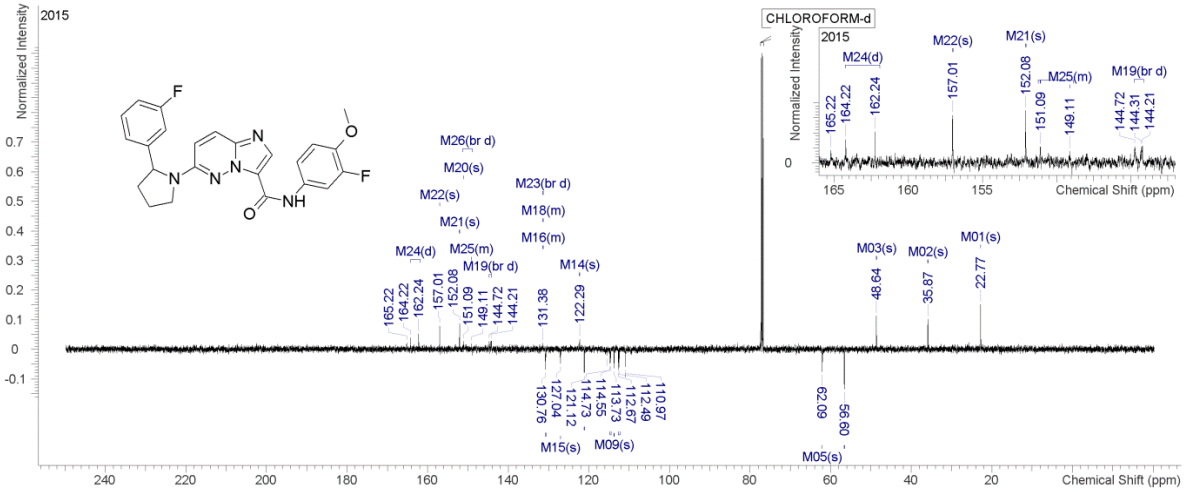


816

IPV 1.32 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	23 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.32 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015		
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.i5_IPV_1.32_C13_APT_ad.fid\fid				
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	508
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	cdcl3
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, $cdcl_3$) δ = 163.23 (d, *J*=247.8 Hz, 1C), 157.01, 152.08, 151.09, 149.10 - 149.10 (m, 1C), 150.10 (br d, *J*=247.8 Hz, 1C), 144.47 (br d, *J*=63.7 Hz, 1C), 131.41 (br d, *J*=7.5 Hz, 1C), 131.37 - 131.29 (m, 1C), 131.37 - 131.29 (m, 1C), 130.73 (br d, *J*=8.5 Hz, 1C), 127.04, 122.29, 121.13 (br d, *J*=2.6 Hz, 1C), 114.64 (br d, *J*=21.4 Hz, 1C), 113.73, 112.58 (br d, *J*=21.9 Hz, 1C), 110.97, 62.09, 56.60, 48.64, 35.87, 22.77



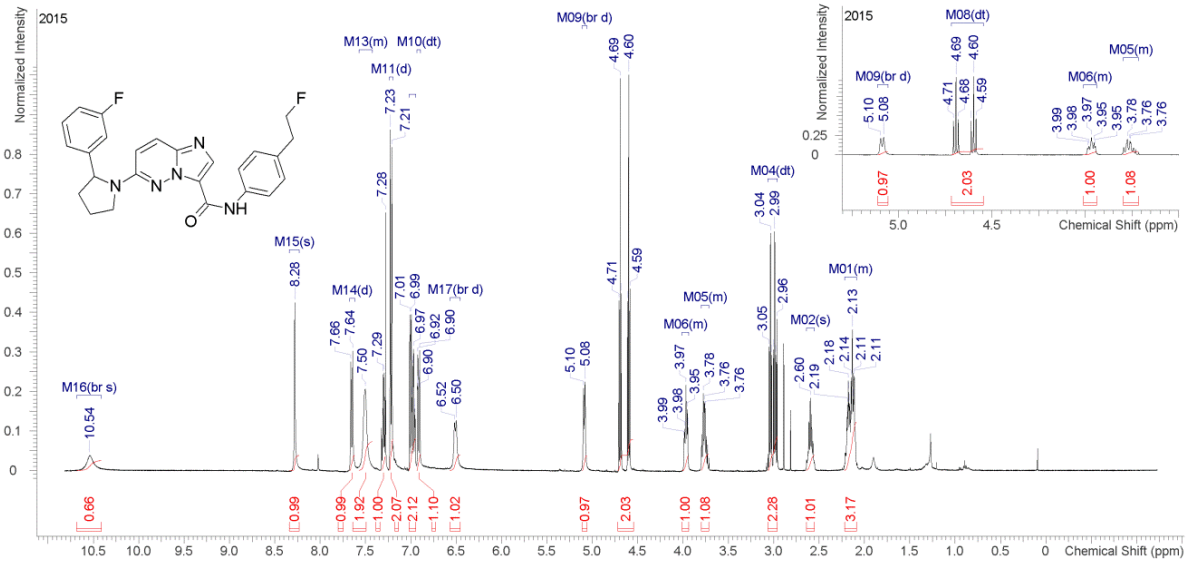
817

6.19 ^{1}H NMR and ^{13}C NMR for compound **27**

IPV 1.26 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	23.41	***Number of Nuclei***	23 H's				
Acquisition Time (sec)	4.9997	***Comment***	IPV 1.26 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015				
File Name	C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.23.i5_IPV_1.26_H1_1D.fid\fid					***Frequency (MHz)***	498.1178
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	30001	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42	***Temperature (degree C)***	26.400

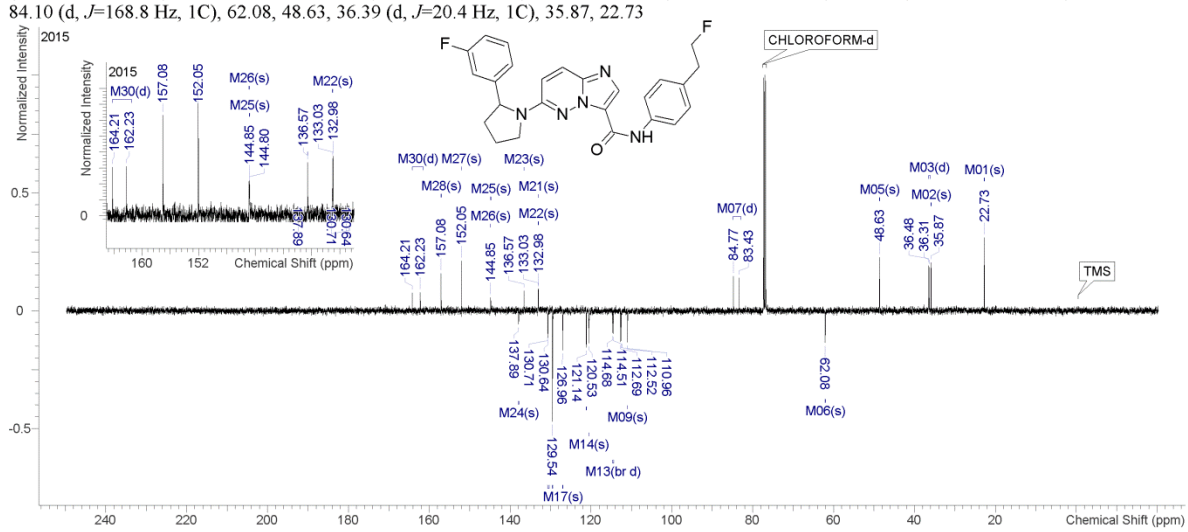
^{1}H NMR (498MHz, $cdcl_3$) δ = 10.54 (br s, 1H), 8.28 (s, 1H), 7.65 (d, *J*=9.9 Hz, 1H), 7.57 - 7.42 (m, 2H), 7.33 - 7.28 (m, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.02 - 6.95 (m, 2H), 6.91 (td, *J*=1.9, 9.6 Hz, 1H), 6.51 (br d, *J*=9.2 Hz, 1H), 5.09 (br d, *J*=8.1 Hz, 1H), 4.65 (td, *J*=6.4, 47.1 Hz, 2H), 4.01 - 3.94 (m, 1H), 3.80 - 3.71 (m, 1H), 3.01 (td, *J*=6.4, 23.4 Hz, 2H), 2.60 (s, 1H), 2.22 - 2.09 (m, 3H)



IPV 1.26 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	23 C's		
Acquisition Time (sec)	1.9958				
Comment	IPV 1.26 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Jan 23 2015	***Date Stamp***	Jan 23 2015	***File Name***	F:\Schirrma\2015.01\2015.01.23.i5_IPV_1.26_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	244
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.22 (d, *J*=247.5 Hz, 1C), 157.08, 152.05, 144.85, 144.80, 137.89, 136.57, 133.03, 132.98, 130.67 (br d, *J*=8.3 Hz, 1C), 129.54, 126.96, 121.15 (br d, *J*=2.6 Hz, 1C), 120.53, 114.60 (br d, *J*=21.2 Hz, 1C), 112.60 (br d, *J*=21.9 Hz, 1C), 110.96, 84.10 (d, *J*=168.8 Hz, 1C), 62.08, 48.63, 36.39 (d, *J*=20.4 Hz, 1C), 35.87, 22.73



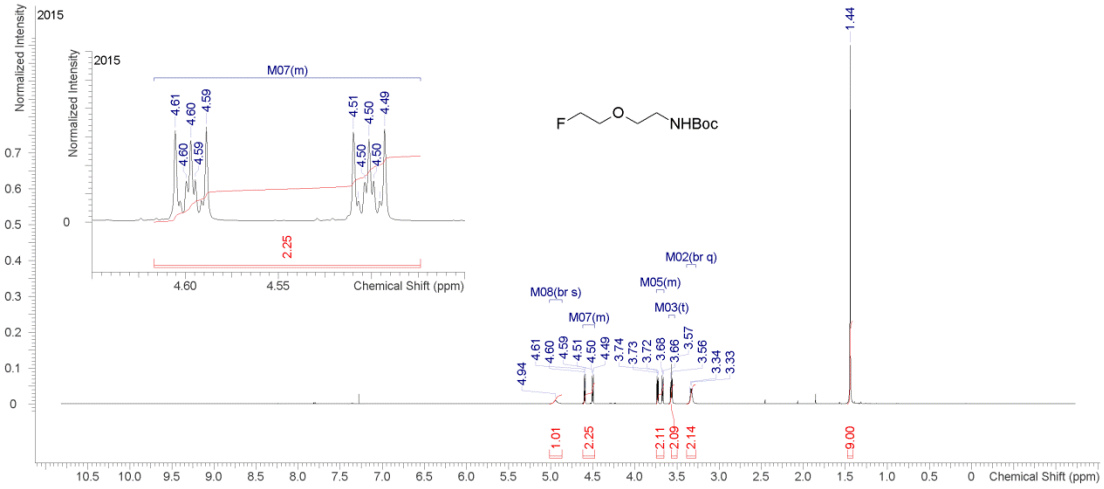
821 6.20 ^{1}H NMR and ^{13}C NMR for compound **29**

822

JB-RAN-03 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 18.60	***Number of Nuclei*** 18 H's		
Acquisition Time (sec) 4.9997	***Comment*** JB-RAN-03 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Jan 12 2015	***Date Stamp*** Jan 12 2015		
File Name C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.12.i5_JB-RAN-03_H1_1D.fid\fid			***Frequency (MHz)*** 498.1178
Nucleus 1H	***Number of Transients*** 16	***Original Points Count*** 30001	***Points Count*** 32768
Pulse Sequence s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60	***Solvent*** cdcl3
Spectrum Offset (Hz) 2388.2478	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.42	***Temperature (degree C)*** 26.400

^{1}H NMR (498MHz, cdcl$_3$) δ = 4.94 (br s, 1H), 4.62 - 4.47 (m, 2H), 3.75 - 3.65 (m, 2H), 3.57 (t, *J*=5.2 Hz, 2H), 3.33 (br q, *J*=5.1 Hz, 2H), 1.44 (s, 9H)

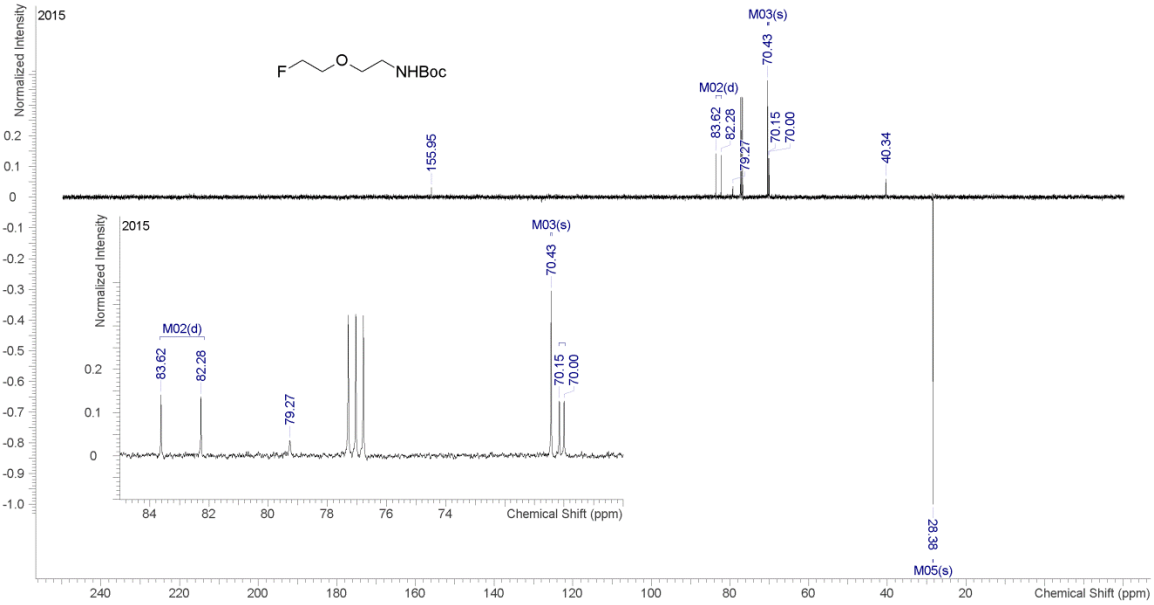


823

JB-RAN-03 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 4 C's				
Acquisition Time (sec) 1.9958					
Comment JB-RAN-03 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Jan 12 2015		***Date Stamp*** Jan 12 2015			
File Name C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.12.i5_JB-RAN-03_C13_APT_ad.fid\fid					
Frequency (MHz) 125.2656		***Nucleus*** 13C		***Number of Transients*** 92	
Original Points Count 67510		***Points Count*** 131072		***Pulse Sequence*** APT_ad	
Receiver Gain 30.00		***SW(cyclical) (Hz)*** 33826.64		***Solvent*** cdcl3	
Spectrum Offset (Hz) 14370.3086		***Spectrum Type*** APT		***Sweep Width (Hz)*** 33826.38	
Temperature (degree C) 26.400					

^{13}C NMR (125MHz, cdcl$_3$) δ = 82.95 (d, *J*=169.0 Hz, 1C), 70.43, 70.08 (d, *J*=19.6 Hz, 1C), 28.38



824

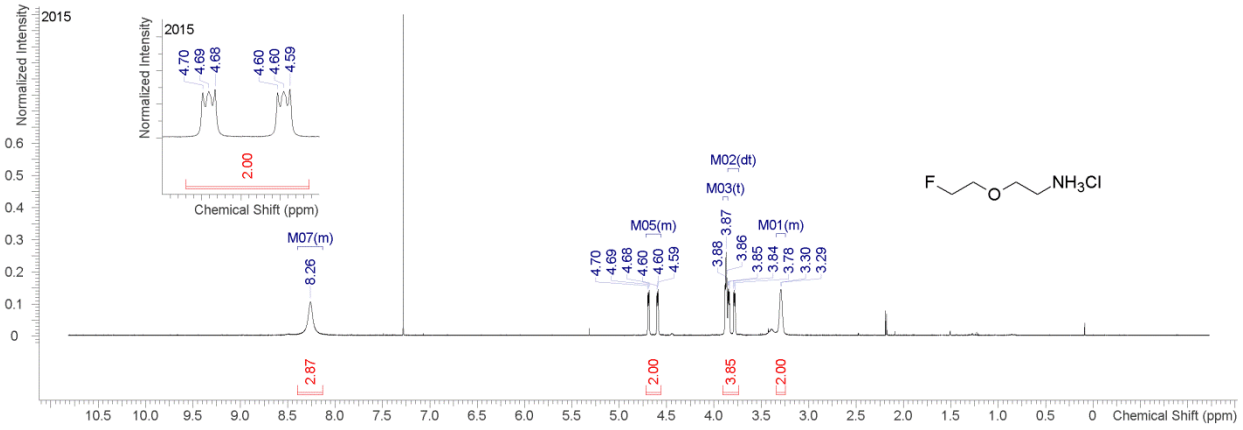
825 6.21 ^{1}H NMR and ^{13}C NMR for compound **30**

826

JB-RAN-04 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum 10.72	***Number of Nuclei*** 11 H's		
Acquisition Time (sec) 4.9997	***Comment*** JB-RAN-04 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe		
Date Jan 12 2015	***Date Stamp*** Jan 12 2015	***File Name*** G:\2015.01\2015.01.12.i5_JB-RAN-04_H1_1D.fid\fid	
Frequency (MHz) 498.1178	***Nucleus*** 1H	***Number of Transients*** 16	***Original Points Count*** 30001
Points Count 32768	***Pulse Sequence*** s2pul	***Receiver Gain*** 32.00	***SW(cyclical) (Hz)*** 6000.60
Solvent cdcl3	***Spectrum Offset (Hz)*** 2388.2478	***Spectrum Type*** standard	***Sweep Width (Hz)*** 6000.42
Temperature (degree C) 26.400			

^{1}H NMR (498MHz, $cdcl_3$) δ = 8.40 - 8.13 (m, 3H), 4.72 - 4.56 (m, 2H), 3.87 (t, *J*=4.8 Hz, 2H), 3.81 (td, *J*=3.8, 30.0 Hz, 2H), 3.34 - 3.24 (m, 2H)

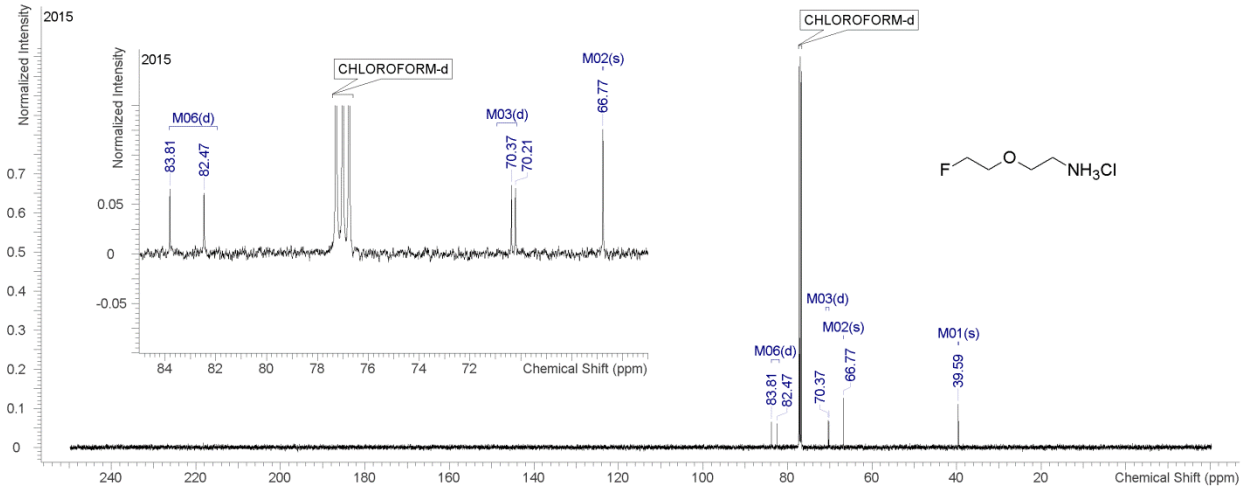


827

JB-RAN-04 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 4 C's				
Acquisition Time (sec) 1.9958					
Comment JB-RAN-04 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Jan 12 2015	***Date Stamp*** Jan 12 2015				
File Name C:\Users\admin\Documents\NMR jan2015\2015.01\2015.01.12.i5_JB-RAN-04_C13_APT_ad.fid\fid					
Frequency (MHz) 125.2656	***Nucleus*** 13C		***Number of Transients*** 1040		
Original Points Count 67510	***Points Count*** 131072		***Pulse Sequence*** APT_ad		
Receiver Gain 30.00	***SW(cyclical) (Hz)*** 33826.64		***Solvent*** cdcl3		
Spectrum Offset (Hz) 14370.3086	***Spectrum Type*** APT		***Sweep Width (Hz)*** 33826.38		
Temperature (degree C) 26.400					

^{13}C NMR (125MHz, $cdcl_3$) δ = 83.14 (d, *J*=168.0 Hz, 1C), 70.29 (d, *J*=19.4 Hz, 1C), 66.77, 39.59



828

829

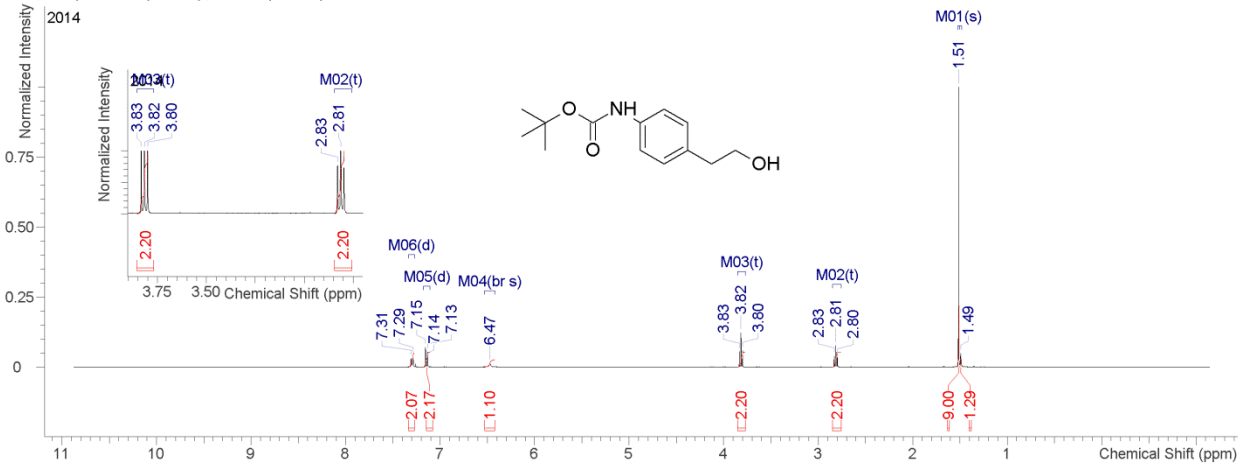
6.22 ^{1}H NMR and ^{13}C NMR for compound **32**

IPV 1.2 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

Multiplets Integrals Sum	20.04	***Number of Nuclei***	19 H's

Acquisition Time (sec)	4.9999				
Comment	IPV 1.2 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe				
Date	Oct 23 2014	***Date Stamp***	Oct 23 2014	***File Name***	F:\2014.10\2014.10.23.mr4_IPV-1_2_H1_1D.fid\fid
Frequency (MHz)	399.9845	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	24038	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	38.00	***SW(cyclical) (Hz)***	4807.69	***Solvent***	cdcl3
Spectrum Offset (Hz)	1947.6067	***Spectrum Type***	standard	***Sweep Width (Hz)***	4807.55
Temperature (degree C)	25.900				

^{1}H NMR (400MHz, cdcl$_3$) δ = 7.30 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=7.4 Hz, 2H), 6.47 (br s, 1H), 3.82 (t, *J*=6.6 Hz, 2H), 2.81 (t, *J*=6.6 Hz, 2H), 1.51 (s, 9H), 1.49 (s, 1H)

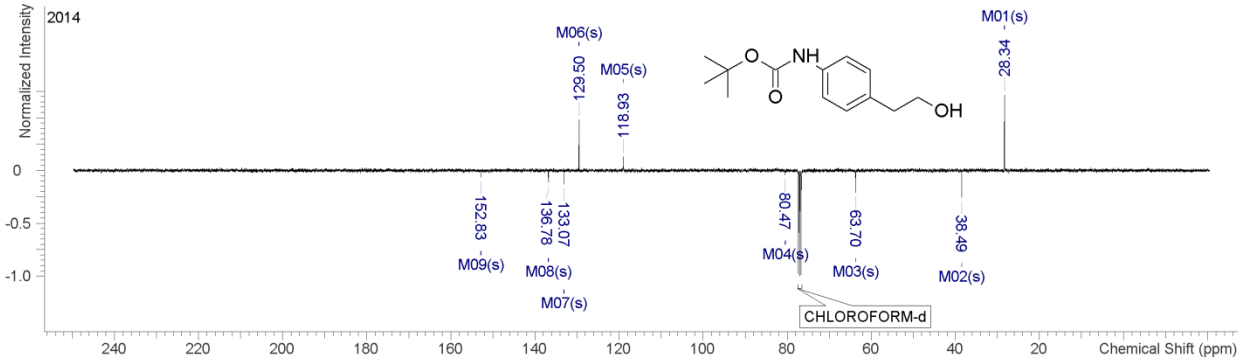


IPV 1.2 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	9 C's

Acquisition Time (sec)	2.5000				
Comment	IPV 1.2 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Oct 23 2014	***Date Stamp***	Oct 23 2014		
File Name	F:\2014.10\2014.10.23.mr4_IPV-1_2_C13_APT_ad.fid\fid			***Frequency (MHz)***	100.5872
Nucleus	13C	***Number of Transients***	264	***Original Points Count***	67935
Points Count	131072	***Pulse Sequence***	APT_ad	***Receiver Gain***	38.00
SW(cyclical) (Hz)	27173.91	***Solvent***	cdcl3	***Spectrum Offset (Hz)***	11531.7881
Spectrum Type	APT	***Sweep Width (Hz)***	27173.71	***Temperature (degree C)***	25.900

^{13}C NMR (101MHz, cdcl$_3$) δ = 152.83, 136.78, 133.07, 129.50, 118.93, 80.47, 63.70, 38.49, 28.34



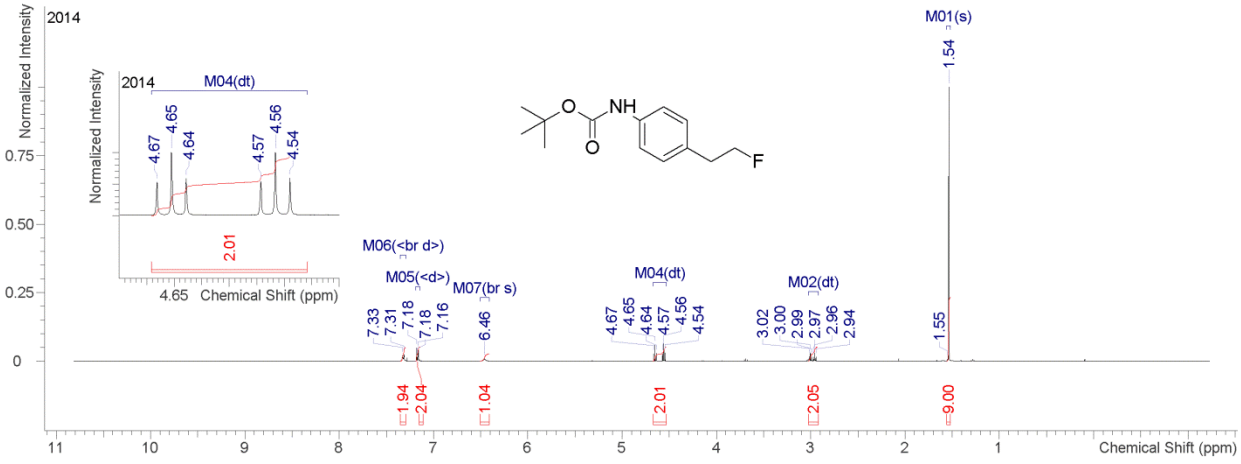
6.23 ^{1}H NMR and ^{13}C NMR for compound **33**

IPV 1.3 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	18.07	***Number of Nuclei***	18 H's

Acquisition Time (sec)	4.9997				
Comment	IPV 1.3 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Oct 28 2014	***Date Stamp***	Oct 28 2014	***File Name***	F:\2014.10\2014.10.28.i5_IPV-1_3_H1_1D.fid\fid
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	30001	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	32.00	***SW(cyclical) (Hz)***	6000.60	***Solvent***	cdcl3
Spectrum Offset (Hz)	2388.2478	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.42
Temperature (degree C)	26.400				

^{1}H NMR (498MHz, cdcl$_3$) δ = 7.32 (br d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=7.9 Hz, 2H), 6.46 (br s, 1H), 4.60 (td, *J*=6.6, 47.1 Hz, 2H), 2.98 (td, *J*=6.6, 22.9 Hz, 2H), 1.54 (s, 9H)

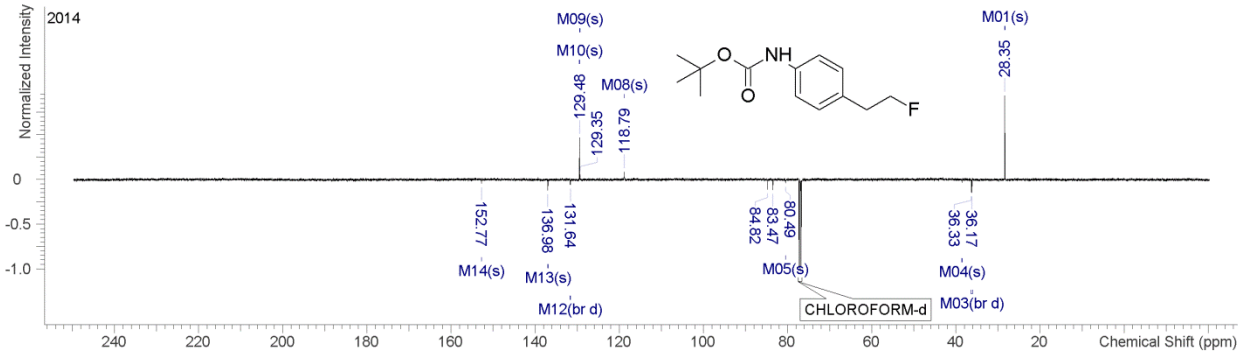


IPV 1.3 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	11 C's

Acquisition Time (sec)	2.4948				
Comment	IPV 1.3 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Oct 28 2014	***Date Stamp***	Oct 28 2014		
File Name	F:\2014.10\2014.10.28.i5_IPV-1_3_C13_APT_ad.fid\fid			***Frequency (MHz)***	125.2656
Nucleus	13C	***Number of Transients***	376	***Original Points Count***	84389
Points Count	131072	***Pulse Sequence***	APT_ad	***Receiver Gain***	38.00
SW(cyclical) (Hz)	33826.64	***Solvent***	cdcl3	***Spectrum Offset (Hz)***	14370.3086
Spectrum Type	APT	***Sweep Width (Hz)***	33826.38	***Temperature (degree C)***	26.400

^{13}C NMR (125MHz, cdcl$_3$) δ = 152.77, 136.98, 131.67 (br d, *J*=6.7 Hz, 1C), 129.48, 129.35, 118.79, 84.15 (br d, *J*=169.0 Hz, 1C), 80.49, 38.54, 36.25 (br d, *J*=20.4 Hz, 1C), 28.35

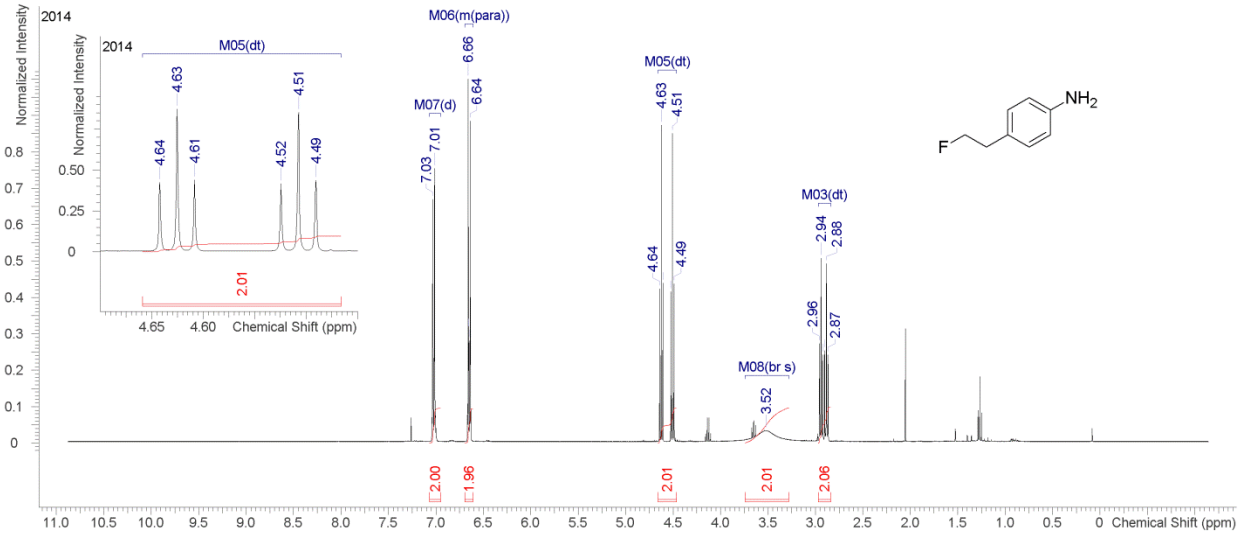


6.24 ^{1}H NMR and ^{13}C NMR for compound **34**

IPV 1.4 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe

Multiplets Integrals Sum 10.04	***Number of Nuclei*** 10 H's		
Acquisition Time (sec) 4.9999	***Comment*** IPV 1.4 399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe		
Date Oct 30 2014	***Date Stamp*** Oct 30 2014		
File Name C:\Users\admin\Documents\Master NMR\2014.10\2014.10.30.mr4_IPV-1_4_H1_1D.fid\fid			***Frequency (MHz)*** 399.9845
Nucleus 1H	***Number of Transients*** 16	***Original Points Count*** 24038	***Points Count*** 32768
Pulse Sequence s2pul	***Receiver Gain*** 24.00	***SW(cyclical) (Hz)*** 4807.69	***Solvent*** cdcl3
Spectrum Offset (Hz) 1947.6067	***Spectrum Type*** standard	***Sweep Width (Hz)*** 4807.55	***Temperature (degree C)*** 25.900

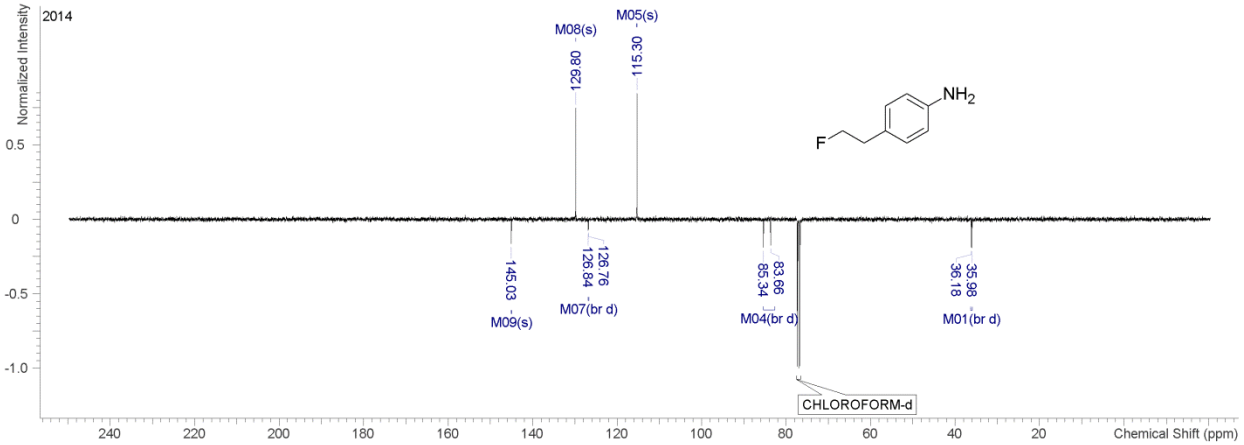
^{1}H NMR (400MHz, cdcl$_3$) δ = 7.02 (d, *J*=8.2 Hz, 2H), 6.70 - 6.61 (m, 2H), 4.57 (td, *J*=6.6, 47.2 Hz, 2H), 3.52 (br s, 2H), 2.91 (td, *J*=6.8, 22.2 Hz, 2H)



IPV 1.4 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum 0.00	***Number of Nuclei*** 6 C's				
Acquisition Time (sec) 2.5000					
Comment IPV 1.4 100.587 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe C & CH2 same, CH & CH3 opposite side of solvent signal					
Date Oct 30 2014	***Date Stamp*** Oct 30 2014				
File Name C:\Users\admin\Documents\Master NMR\2014.10\2014.10.30.mr4_IPV-1_4_C13_APT_ad.fid\fid					
Frequency (MHz) 100.5872	***Nucleus*** 13C		***Number of Transients*** 272		
Original Points Count 67935	***Points Count*** 131072		***Pulse Sequence*** APT_ad		
Receiver Gain 38.00	***SW(cyclical) (Hz)*** 27173.91		***Solvent*** cdcl3		
Spectrum Offset (Hz) 11531.7881	***Spectrum Type*** APT		***Sweep Width (Hz)*** 27173.71		
Temperature (degree C) 25.900					

^{13}C NMR (101MHz, cdcl$_3$) δ = 145.03, 129.80, 126.80 (br d, *J*=7.3 Hz, 1C), 115.30, 84.50 (br d, *J*=169.0 Hz, 1C), 36.08 (br d, *J*=20.1 Hz, 1C)



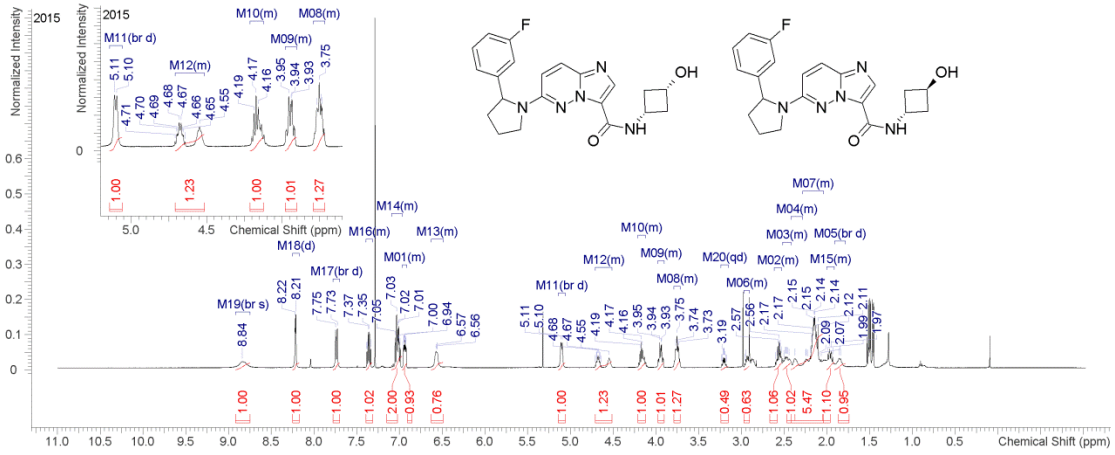
842 6.25 ^{1}H NMR and ^{13}C NMR for compound **35**

Jamie_Bailey, IPVI_58 499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

Multiplets Integrals Sum	23.96	***Number of Nuclei***	23 H's

Acquisition Time (sec)	5.0000				
Comment	Jamie_Bailey, IPVI_58 499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe				
Date	Apr 1 2015	***Date Stamp***	Apr 1 2015	***File Name***	F:\Schirrma\2015.04\2015.04.1.u5_IPVI_58_loc11_15.19_H1_1D.fid\fid
Frequency (MHz)	499.8064	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	30048	***Points Count***	32768	***Pulse Sequence***	PRESAT
Receiver Gain	50.00	***SW(cyclical) (Hz)***	6009.62	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2493.3027	***Spectrum Type***	standard	***Sweep Width (Hz)***	6009.43
Temperature (degree C)	27.700				

^{1}H NMR (500MHz, CHLOROFORM-d) δ = 8.84 (br s, 1H), 8.22 (d, *J*=3.7 Hz, 1H), 7.74 (br d, *J*=9.9 Hz, 1H), 7.39 - 7.32 (m, 1H), 7.09 - 6.97 (m, 2H), 6.97 - 6.91 (m, 1H), 6.63 - 6.49 (m, 1H), 5.10 (br d, *J*=7.3 Hz, 1H), 4.71 - 4.52 (m, 1H), 4.21 - 4.12 (m, 1H), 3.98 - 3.90 (m, 1H), 3.79 - 3.72 (m, 1H), 3.20 (dq, *J*=4.2, 7.5 Hz, 1H), 2.97 - 2.91 (m, 1H), 2.61 - 2.53 (m, 1H), 2.52 - 2.42 (m, 1H), 2.42 - 2.28 (m, 1H), 2.28 - 2.04 (m, 3H), 2.00 - 1.91 (m, 1H), 1.85 (br d, *J*=9.2 Hz, 1H)



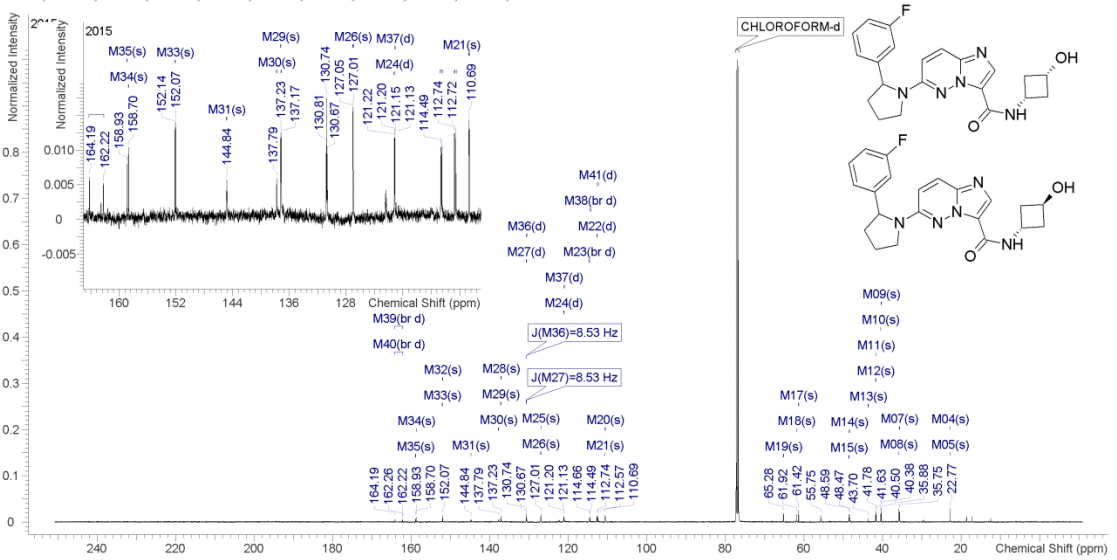
843

Jamie_Bailey, IPVI_58 125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

Multiplets Integrals Sum	0.00	***Number of Nuclei***	36 C's

Acquisition Time (sec)	2.5000				
Comment	Jamie_Bailey, IPVI_58 125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe				
Date	Apr 1 2015	***Date Stamp***	Apr 1 2015	***File Name***	F:\Schirrma\2015.04\2015.04.1.u5_IPVI_58_loc11_15.20_C13_1D.fid\fid
Frequency (MHz)	125.6909	***Nucleus***	13C	***Number of Transients***	576
Original Points Count	82237	***Points Count***	131072	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***SW(cyclical) (Hz)***	32894.74	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	15081.4736	***Spectrum Type***	standard	***Sweep Width (Hz)***	32894.49
Temperature (degree C)	27.700				

^{13}C NMR (126MHz, CHLOROFORM-d) δ = 163.24 (br d, *J*=247.5 Hz, 1C), 163.21 (br d, *J*=247.5 Hz, 1C), 158.93, 158.70, 152.14, 152.07, 144.84, 137.79, 137.23, 137.17, 130.76 (d, *J*=8.5 Hz, 1C), 130.71 (d, *J*=8.5 Hz, 1C), 127.05, 127.01, 121.21 (d, *J*=2.8 Hz, 1C), 121.14 (d, *J*=2.8 Hz, 1C), 114.67 (br d, *J*=3.3 Hz, 1C), 114.50 (br d, *J*=3.5 Hz, 1C), 112.73 (d, *J*=3.3 Hz, 1C), 112.55 (d, *J*=3.8 Hz, 1C), 110.69, 110.65, 65.28, 61.92, 61.42, 48.59, 48.47, 43.70, 41.78, 41.63, 40.50, 40.38, 35.88, 35.75, 22.77, 22.76



844

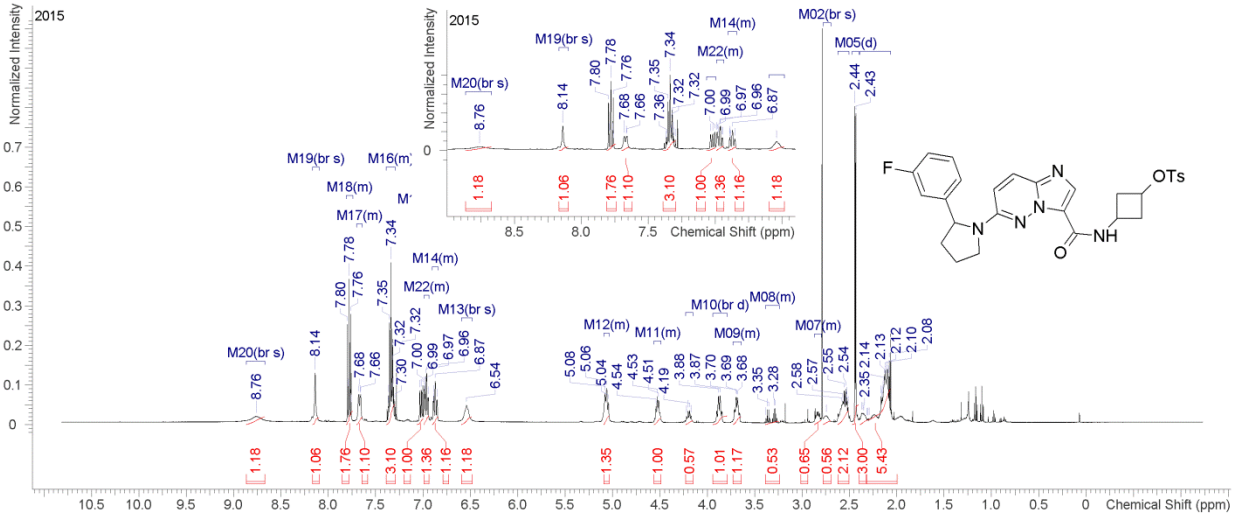
6.26 ^{1}H NMR and ^{13}C NMR for compound **36**

498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	30.30	***Number of Nuclei***	30 H's

Acquisition Time (sec)	4.9997	***Comment***	498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Apr 8 2015	***Date Stamp***	Apr 8 2015	***File Name***	F:\Schirrma\2015.04\2015.04.08.i5_IPV_1.60X_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 8.76 (br s, 1H), 8.14 (br s, 1H), 7.81 - 7.74 (m, 2H), 7.70 - 7.64 (m, 1H), 7.39 - 7.29 (m, 3H), 7.07 - 7.00 (m, 1H), 6.99 - 6.94 (m, 1H), 6.90 - 6.84 (m, 1H), 6.54 (br s, 1H), 5.09 - 5.04 (m, 1H), 4.56 - 4.49 (m, 1H), 4.23 - 4.15 (m, 1H), 3.87 (br d, *J*=8.6 Hz, 1H), 3.73 - 3.64 (m, 1H), 3.39 - 3.24 (m, 1H), 2.87 - 2.79 (m, 1H), 2.74 (br s, 1H), 2.62 - 2.50 (m, 2H), 2.44 (d, *J*=4.7 Hz, 3H), 2.39 - 2.07 (m, 5H)

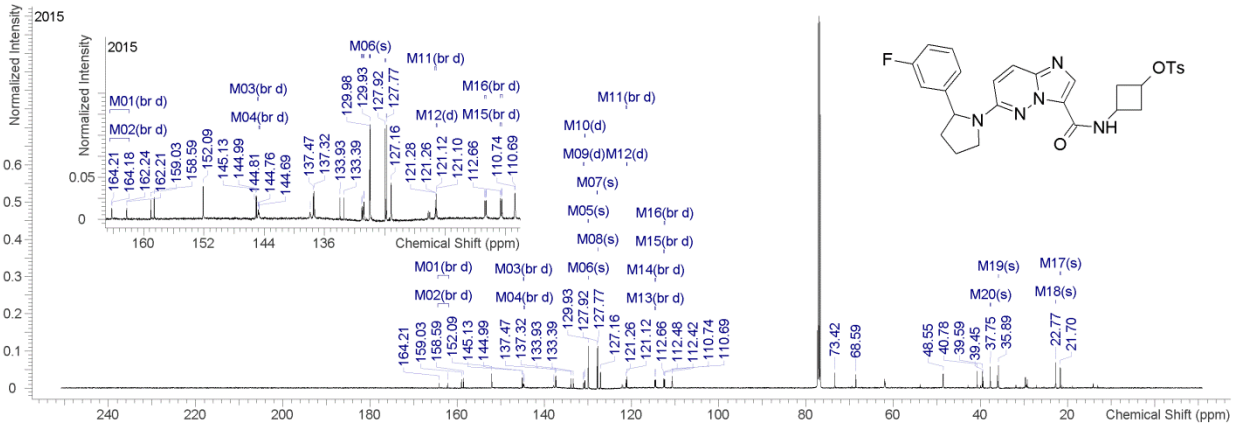


Jamie_Bailey, IPV1_60A 125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe

Multiplets Integrals Sum	0.00	***Number of Nuclei***	20 C's

Acquisition Time (sec)	2.5000				
Comment	Jamie_Bailey, IPV1_60A 125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe				
Date	Apr 1 2015	***Date Stamp***	Apr 1 2015		
File Name	F:\Schirrma\2015.04\2015.04.1.u5_IPV1_60A_loc12_15.52_C13_1D.fid\fid			***Frequency (MHz)***	125.6909
Nucleus	13C	***Number of Transients***	576	***Original Points Count***	82237
Points Count	131072	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00
SW(cyclical) (Hz)	32894.74	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	15081.4736
Spectrum Type	standard	***Sweep Width (Hz)***	32894.49	***Temperature (degree C)***	27.700

^{13}C NMR (126MHz, CHLOROFORM-d) δ = 163.20 (br d, *J*=247.5 Hz, 1C), 163.23 (br d, *J*=247.5 Hz, 1C), 144.78 (br d, *J*=6.0 Hz, 1C), 144.66 (br d, *J*=6.0 Hz, 1C), 131.01 (d, *J*=8.0 Hz, 1C), 130.76 (d, *J*=8.0 Hz, 1C), 129.98, 129.93, 127.92, 127.77, 121.27 (br d, *J*=2.5 Hz, 1C), 121.11 (d, *J*=2.5 Hz, 1C), 114.64 (br d, *J*=21.3 Hz, 1C), 114.60 (br d, *J*=21.1 Hz, 1C), 112.57 (br d, *J*=22.1 Hz, 1C), 112.51 (br d, *J*=22.1 Hz, 1C), 37.75, 35.89, 22.77, 21.69



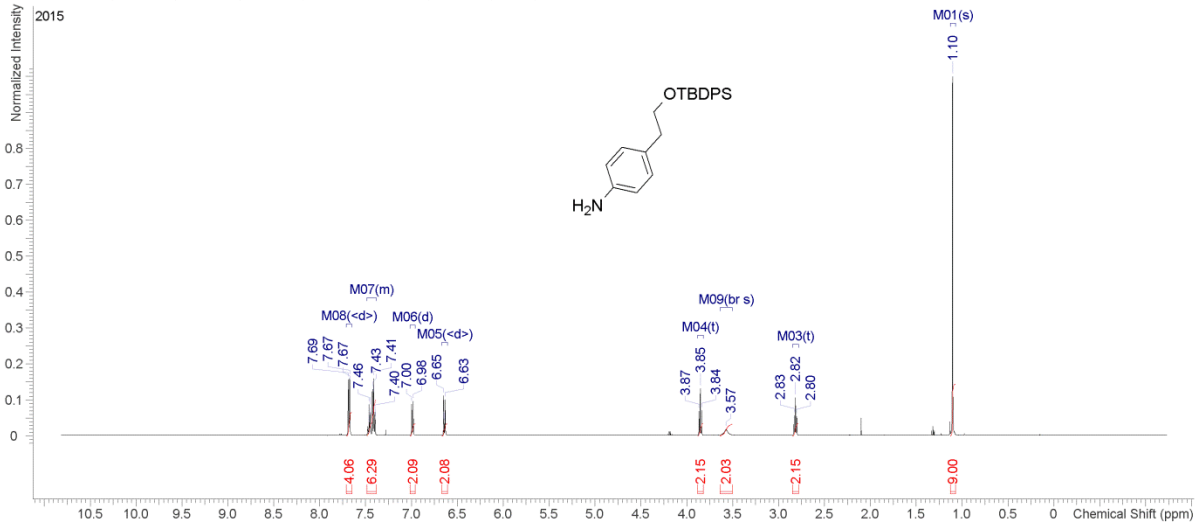
6.27 ^{1}H NMR and ^{13}C NMR for compound **38**

MV 1.10 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	29.85	***Number of Nuclei***	29 H's

Acquisition Time (sec)	4.9997	***Comment***	MV 1.10 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Mar 6 2015	***Date Stamp***	Mar 6 2015	***File Name***	F:\Schirrma\2015.03\2015.03.06.i5_MV_1.10_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 7.68 (d, *J*=7.0 Hz, 4H), 7.49 - 7.38 (m, 6H), 6.99 (d, *J*=8.3 Hz, 2H), 6.64 (d, *J*=7.8 Hz, 2H), 3.85 (t, *J*=7.1 Hz, 2H), 3.57 (br s, 2H), 2.82 (t, *J*=7.1 Hz, 2H), 1.10 (s, 9H)

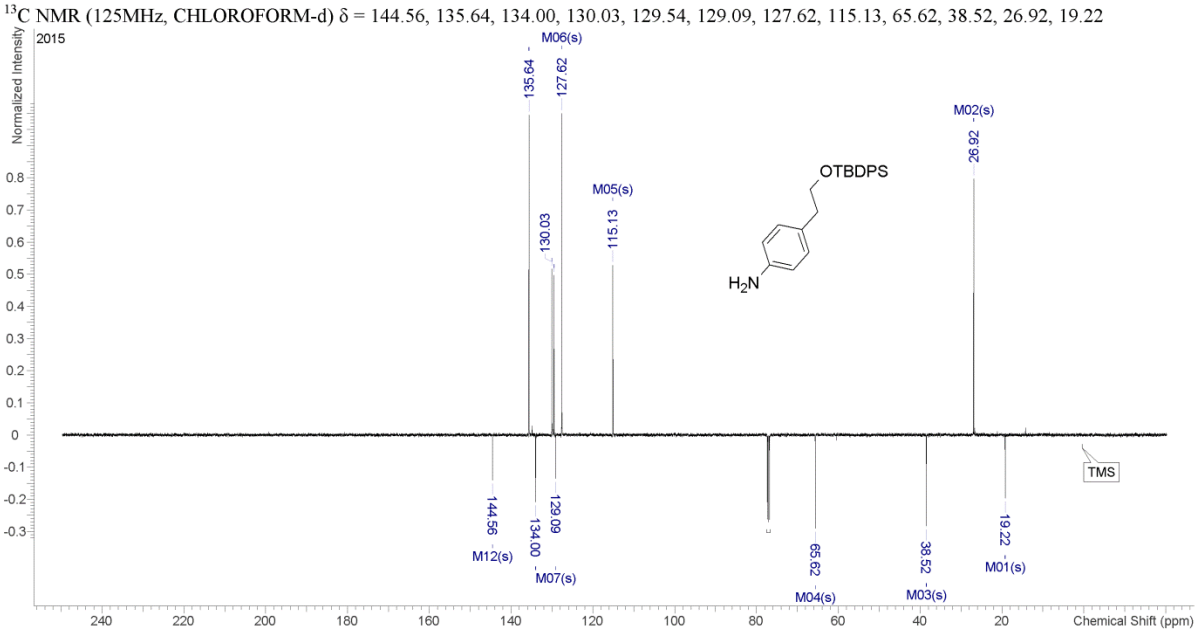


MV 1.10 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	12 C's

Acquisition Time (sec)	1.9958				
Comment	MV 1.10 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Mar 6 2015	***Date Stamp***	Mar 6 2015	***File Name***	F:\Schirrma\2015.03\2015.03.06.i5_MV_1.10_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	124
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 144.56, 135.64, 134.00, 130.03, 129.54, 129.09, 127.62, 115.13, 65.62, 38.52, 26.92, 19.22



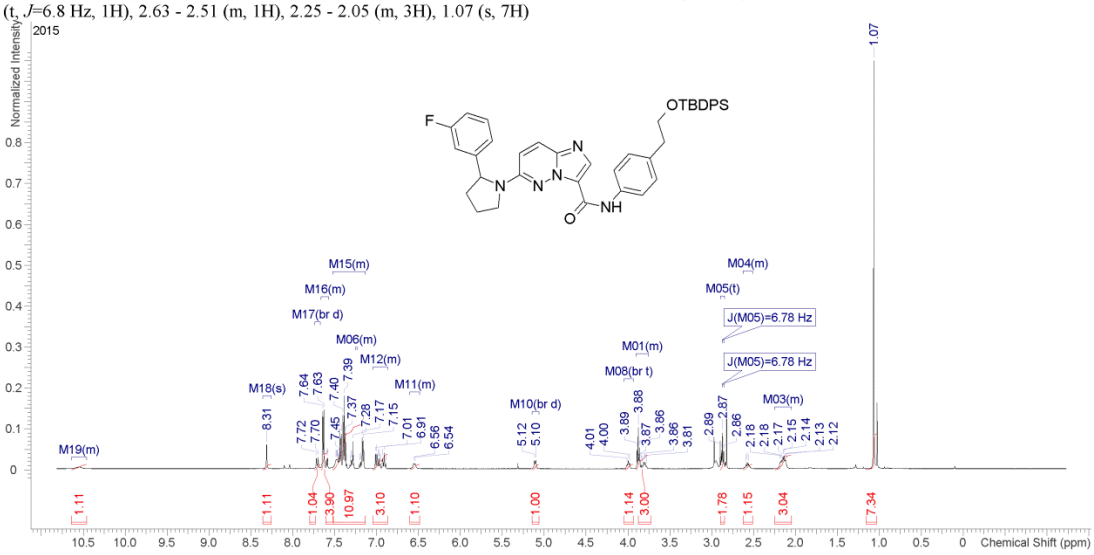
852 6.28 ^{1}H NMR and ^{13}C NMR for compound **39**

IPV 1.59 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	40.77	***Number of Nuclei***	39 H's

Acquisition Time (sec)	4.9997	***Comment***	IPV 1.59 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Apr 1 2015	***Date Stamp***	Apr 1 2015	***File Name***	F:\Schirrma\2015.04\2015.04.01.i5_IPV_1.59_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 10.64 - 10.46 (m, 1H), 8.31 (s, 1H), 7.71 (br d, *J*=10.0 Hz, 1H), 7.66 - 7.57 (m, 4H), 7.25 - 7.23 (m, 1H), 7.53 - 7.13 (m, 10H), 7.04 - 6.87 (m, 3H), 6.60 - 6.49 (m, 1H), 5.11 (br d, *J*=7.6 Hz, 1H), 4.00 (br t, *J*=7.0 Hz, 1H), 3.90 - 3.76 (m, 3H), 2.87 (t, *J*=6.8 Hz, 1H), 2.63 - 2.51 (m, 1H), 2.25 - 2.05 (m, 3H), 1.07 (s, 7H)



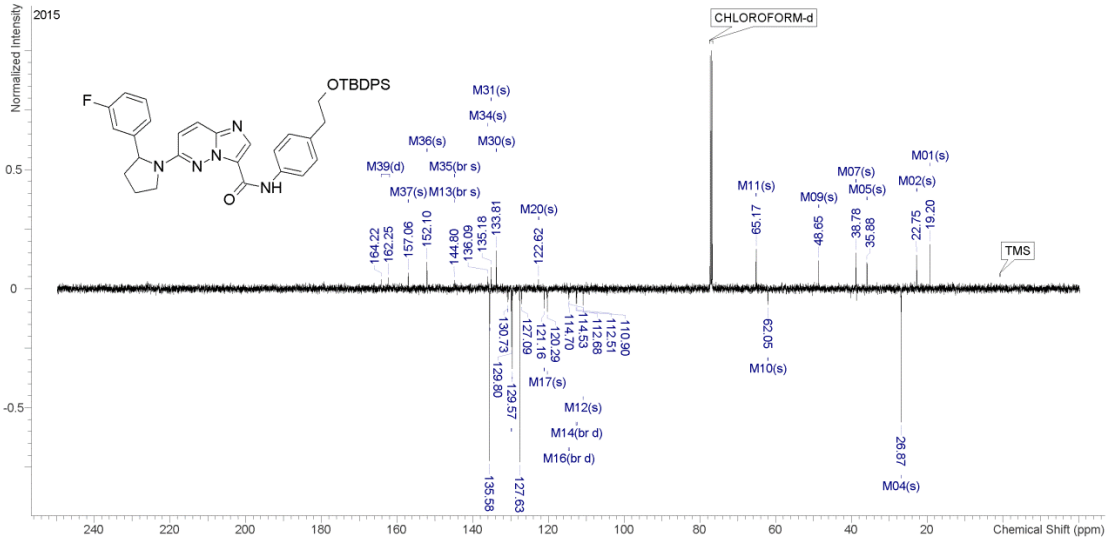
853

IPV 1.59 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	30 C's

Acquisition Time (sec)	1.9958				
Comment	IPV 1.59 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Apr 1 2015	***Date Stamp***	Apr 1 2015	***File Name***	F:\Schirrma\2015.04\2015.04.01.i5_IPV_1.59_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	200
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.24 (d, *J*=247.5 Hz, 1C), 157.06, 152.10, 144.84 (br s, 1C), 144.80 (br s, 1C), 136.09, 135.58, 135.51, 135.18, 133.81, 130.73, 129.80, 129.57, 127.63, 127.09, 122.62, 121.16, 120.29, 114.62 (br d, *J*=21.2 Hz, 1C), 112.60 (br d, *J*=22.2 Hz, 1C), 110.90, 65.17, 62.05, 48.65, 38.78, 35.88, 26.87, 26.80, 22.75, 19.20



854

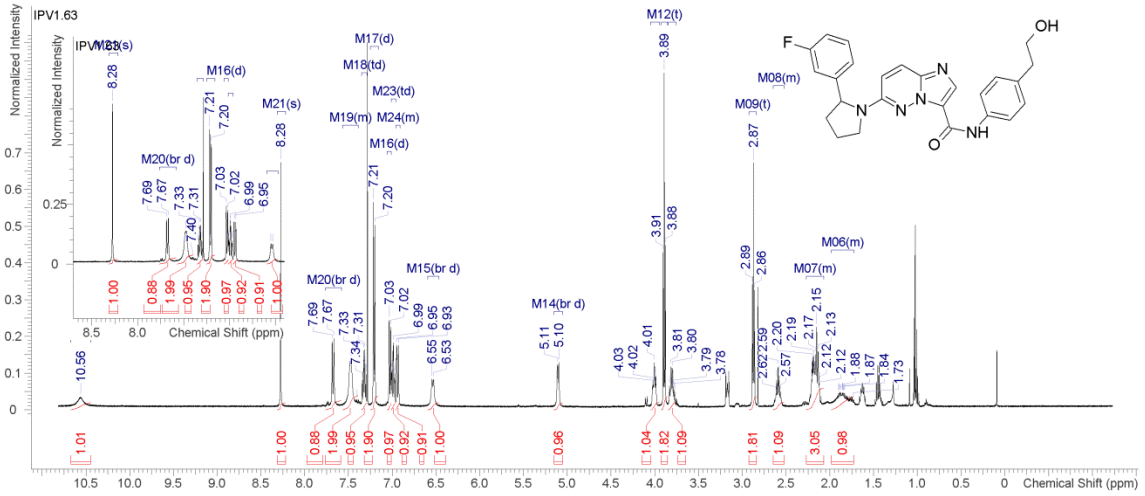
6.29 ^{1}H NMR and ^{13}C NMR for compound **40**

IPV 1.63 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	23.38	***Number of Nuclei***	26 H's

Acquisition Time (sec)	4.9997	***Comment***	IPV 1.63 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Apr 8 2015	***Date Stamp***	Apr 8 2015	***File Name***	F:\Schirrma\2015.04\2015.04.08.i5_IPV_1.63_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 10.56 (br s, 3H), 8.28 (s, 1H), 7.68 (br d, *J*=9.7 Hz, 1H), 7.57 - 7.39 (m, 2H), 7.32 (dt, *J*=6.0, 7.8 Hz, 1H), 7.21 (d, *J*=8.4 Hz, 2H), 7.03 (d, *J*=7.7 Hz, 1H), 6.99 (dt, *J*=2.2, 8.4 Hz, 1H), 6.96 - 6.91 (m, 1H), 6.54 (br d, *J*=9.4 Hz, 1H), 5.11 (br d, *J*=7.8 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.89 (t, *J*=6.5 Hz, 2H), 3.84 - 3.75 (m, 1H), 2.87 (t, *J*=6.5 Hz, 2H), 2.65 - 2.52 (m, 1H), 2.27 - 2.07 (m, 3H), 1.98 - 1.73 (m, 1H)

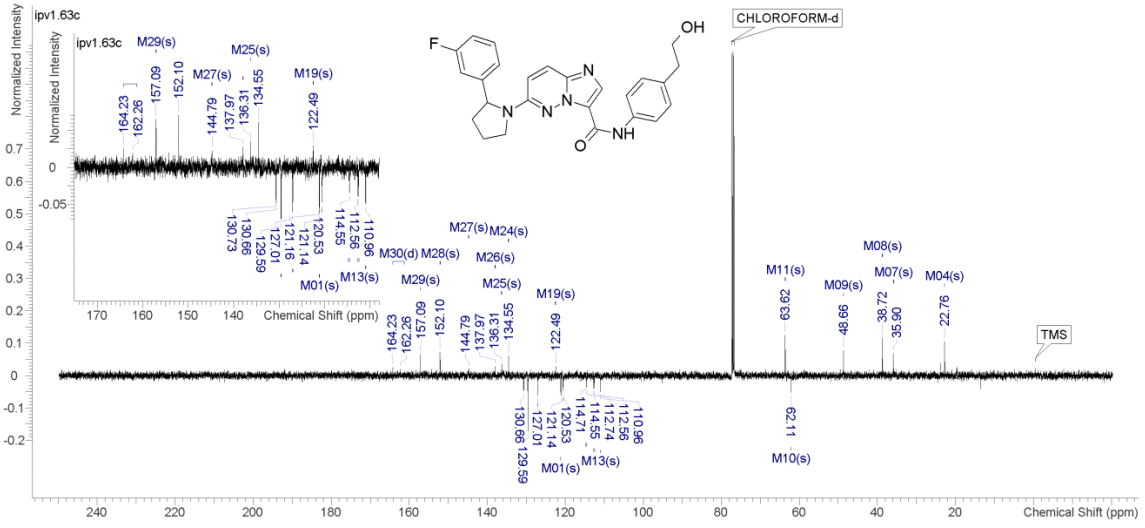


IPV 1.63 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	23 C's

Acquisition Time (sec)	1.9958				
Comment	IPV 1.63 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	Apr 8 2015	***Date Stamp***	Apr 8 2015	***File Name***	F:\Schirrma\2015.04\2015.04.08.i5_IPV_1.63_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	280
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.25 (d, *J*=247.5 Hz, 1C), 157.09, 152.10, 144.79, 137.97, 136.31, 134.55, 130.70 (d, *J*=8.0 Hz, 1C), 129.59, 127.01, 122.49, 121.16, 121.14, 120.53, 114.63 (d, *J*=20.6 Hz, 1C), 112.65 (br d, *J*=21.9 Hz, 1C), 110.96, 63.62, 62.11, 48.66, 38.72, 35.90, 22.76



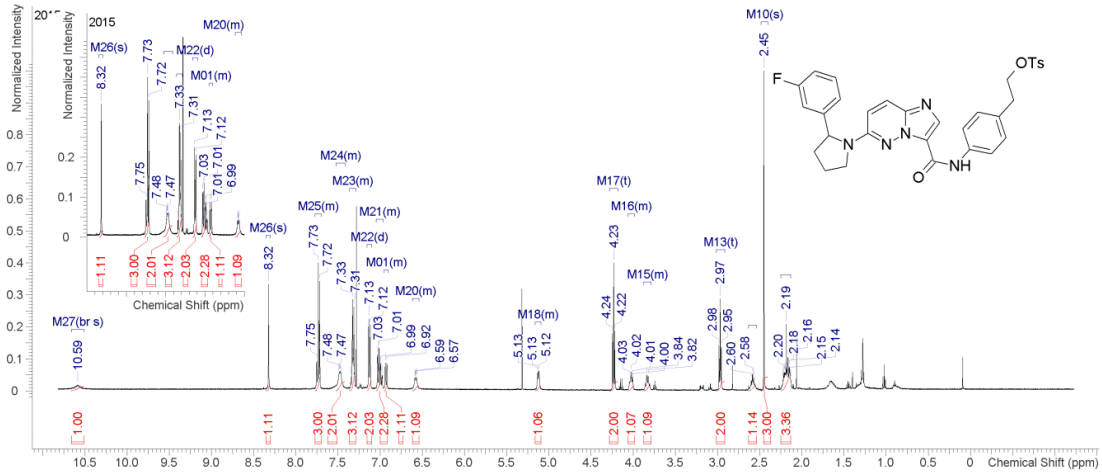
858 6.30 ^{1}H NMR and ^{13}C NMR for compound **41**

IPV 1.64 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe

Multiplets Integrals Sum	31.48	***Number of Nuclei***	30 H's

Acquisition Time (sec)	4.9997	***Comment***	IPV 1.64 498.118 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe				
Date	Apr 14 2015	***Date Stamp***	Apr 14 2015	***File Name***	F:\Schirrma\2015.04\2015.04.14.i5_IPV_1.64_H1_1D.fid\fid		
Frequency (MHz)	498.1178	***Nucleus***	1H	***Number of Transients***	16	***Original Points Count***	30001
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***SW(cyclical) (Hz)***	6000.60
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	2388.2935	***Spectrum Type***	standard	***Sweep Width (Hz)***	6000.51
Temperature (degree C)	26.400						

^{1}H NMR (498MHz, CHLOROFORM-d) δ = 10.59 (br s, 1H), 8.32 (s, 1H), 7.77 - 7.70 (m, 3H), 7.53 - 7.41 (m, 2H), 7.36 - 7.29 (m, 3H), 7.13 (d, *J*=8.3 Hz, 2H), 7.05 - 6.96 (m, 2H), 6.95 - 6.90 (m, 1H), 6.61 - 6.54 (m, 1H), 5.16 - 5.09 (m, 1H), 4.23 (t, *J*=7.0 Hz, 2H), 4.06 - 3.99 (m, 1H), 3.87 - 3.79 (m, 1H), 2.97 (t, *J*=6.9 Hz, 2H), 2.63 - 2.53 (m, 1H), 2.45 (s, 3H), 2.25 - 2.13 (m, 3H)



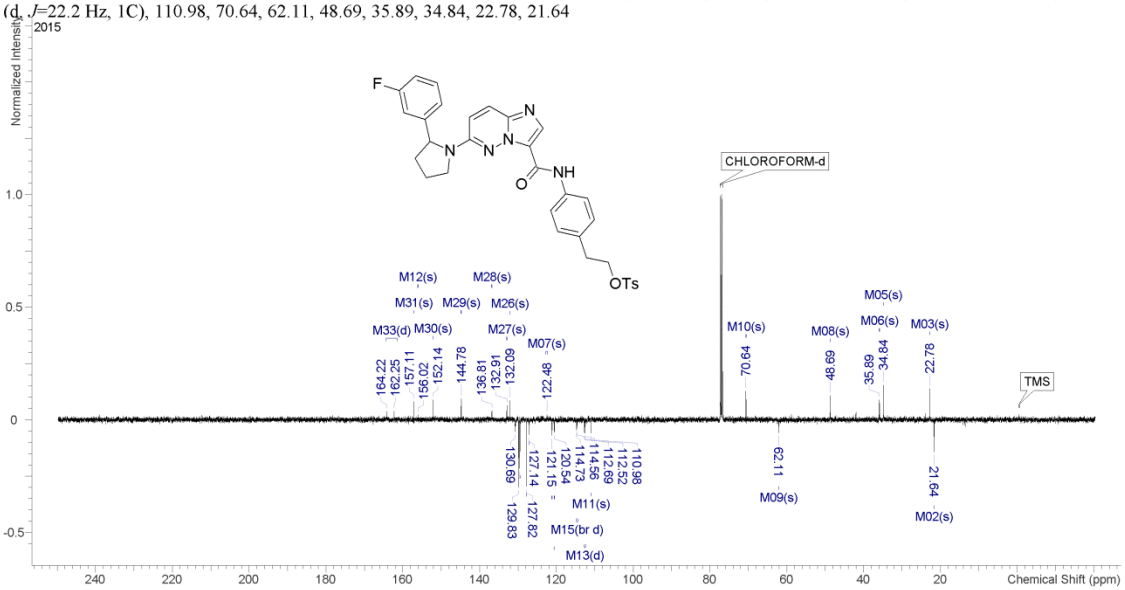
859

IPv 1.64x 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal

Multiplets Integrals Sum	0.00	***Number of Nuclei***	27 C's

Acquisition Time (sec)	1.9958				
Comment	IPv 1.64x 125.266 MHz C13[H1] APT_ad in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 26.4 C -> actual temp = 27.0 C, autoxdb probe C & CH2 same, CH & CH3 opposite side of solvent signal				
Date	May 29 2015	***Date Stamp***	May 29 2015	***File Name***	F:\Schirrma\2015.05\2015.05.29.i5_IPV_1.64x_C13_APT_ad.fid\fid
Frequency (MHz)	125.2656	***Nucleus***	13C	***Number of Transients***	256
Original Points Count	67510	***Points Count***	131072	***Pulse Sequence***	APT_ad
Receiver Gain	30.00	***SW(cyclical) (Hz)***	33826.64	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	14370.3086	***Spectrum Type***	APT	***Sweep Width (Hz)***	33826.38
Temperature (degree C)	26.400				

^{13}C NMR (125MHz, CHLOROFORM-d) δ = 163.23 (d, *J*=247.8 Hz, 1C), 157.11, 156.02, 152.14, 144.78, 136.81, 132.91, 132.09, 130.73 (br d, *J*=8.3 Hz, 1C), 129.83, 129.52, 127.82, 127.14, 122.48, 121.16 (br d, *J*=2.8 Hz, 1C), 120.57 (br s, 1C), 120.54, 114.64 (br d, *J*=20.9 Hz, 1C), 112.60 (d, *J*=22.2 Hz, 1C), 110.98, 70.64, 62.11, 48.69, 35.89, 34.84, 22.78, 21.64



860

7. CRYSTALLOGRAPHIC DATA FOR COMPOUND 22

STRUCTURE REPORT

XCL Code:	UNI1504	**Date:**	22 May 2015
Compound:	*N*-(2,4-difluoro-3-methoxybenzyl)-6-{2-(3-fluorophenyl)pyrrolidin-1-yl}imidazo[1,2-*b*]pyridazine-3-carboxamide•1.4H_2O		
Formula:	$C_{25}H_{23.8}F_3N_5O_{3.4}$ ($C_{25}H_{22}F_3N_5O_2$•1.4H_2O)		
Clients:	J. Bailey and Prof. R. Schirrmacher, Department of Oncology		
Crystallographer:	R. McDonald		

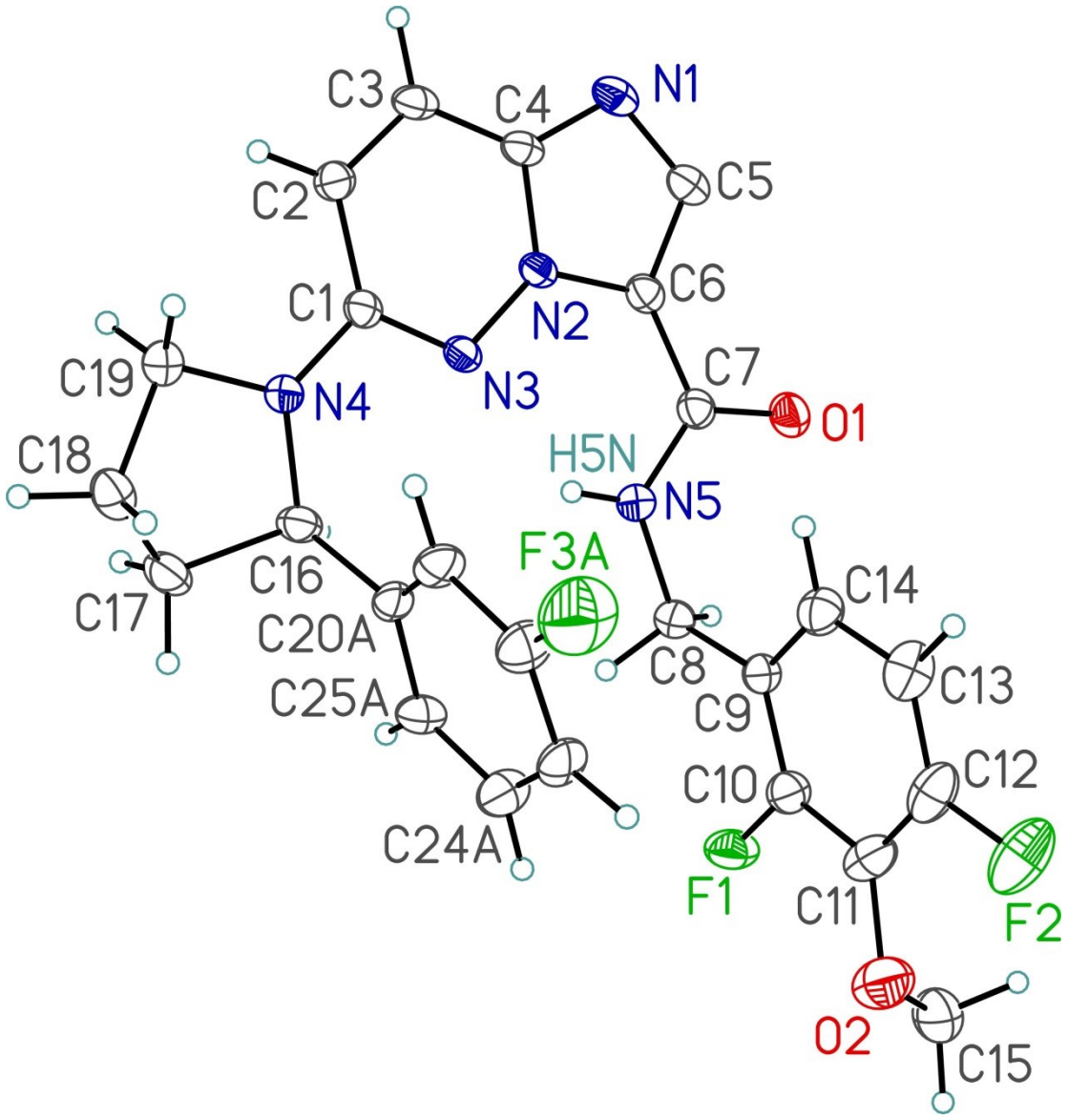
874 **Figure Legends**

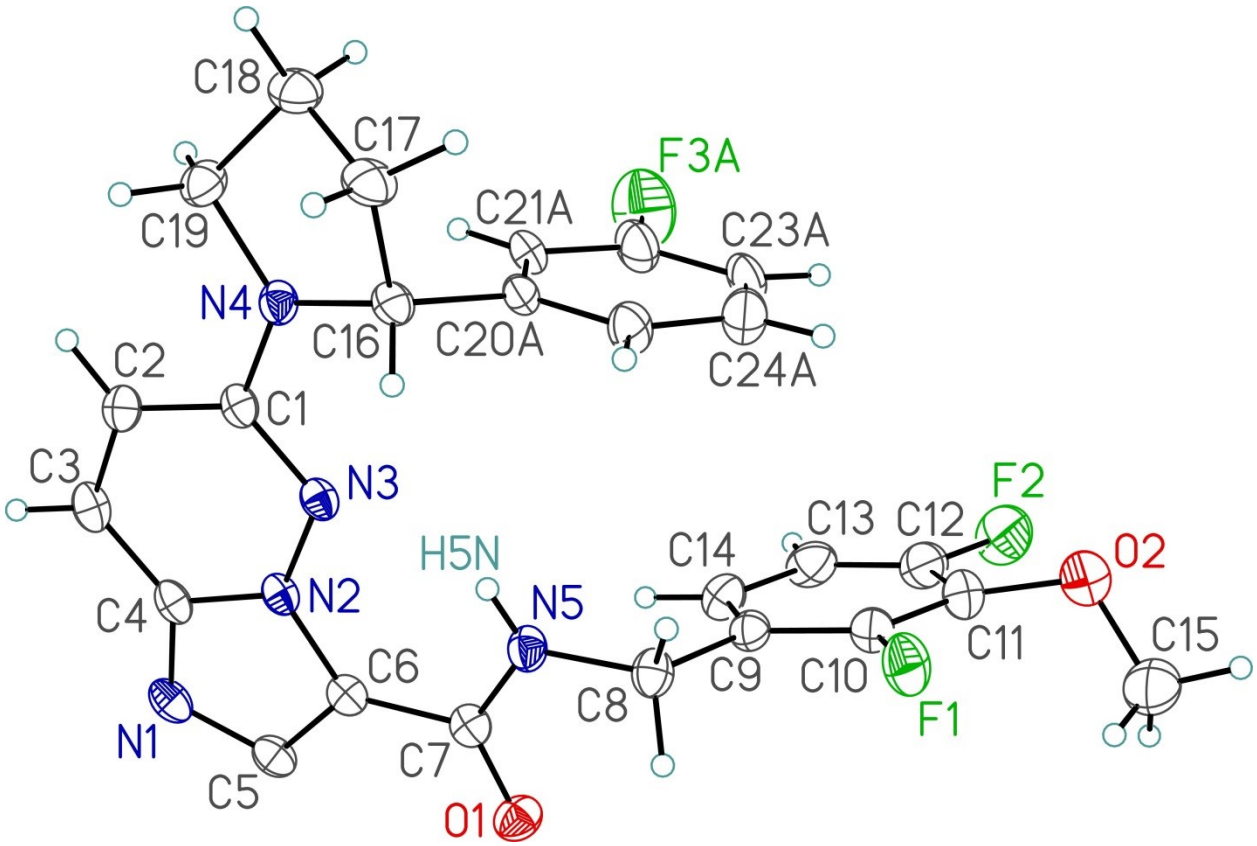
875

876 **Figure 1.** Perspective view of the *N*-(2,4-difluoro-3-methoxybenzyl)-6-{2-(3-fluorophenyl)-
877 pyrrolidin-1-yl}imidazo[1,2-*b*]pyridazine-3-carboxamide molecule showing the atom
878 labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the
879 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal
880 parameters.

881

882 **Figure 2.** Alternate view of the molecule.


C3
C4
N1
C2
C5
C1
N2
C6
C19
N4
N3
C7
O1
C18
H5N
N5
F3A
C16
C14
C17
C20A
C8
C13
C25A
C9
C10
C12
C24A
F1
C11
F2
O2
C15


C18
C17
F3A
C21A
C23A
C19
N4
C16
C20A
C24A
C2
C1
C3
N3
F2
C13
C12
H5N
C14
O2
N2
N5
C4
C11
C15
C6
C9
C10
C8
F1
N1
C7
C5
O1

List of Tables

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{25}H_{23.8}F_3N_5O_{3.4}$
formula weight	505.69
crystal dimensions (mm)	$0.29 \times 0.24 \times 0.02$
crystal system	monoclinic
space group	$P2_1/c$ (No. 14)
unit cell parameters[a]	
a (Å)	13.8619 (3)
b (Å)	10.1495 (2)
c (Å)	17.3464 (4)
β (deg)	104.9414 (13)
V (Å^3)	2357.98 (9)
Z	4
ρ_{calcd} (g cm^{-3})	1.424
μ (mm^{-1})	0.959
B. Data Collection and Refinement Conditions	
diffractometer	Bruker D8/APEX II CCD[b]
radiation (λ [Å])	Cu Kα (1.54178) (microfocus source)
temperature (°C)	–100
scan type	ω and ϕ scans (1.0°) (5 s exposures)
data collection 2θ limit (deg)	145.48
total data collected	14514 ($-14 \le h \le 16$, $-12 \le k \le 12$, $-21 \le l \le 21$)
independent reflections	4601 (R_{int} = 0.0576)
number of observed reflections (*NO*)	3236 [$F_o^2 \ge 2\sigma(F_o^2)$]

structure solution method	direct methods/dual space (*SHELXD*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–2014*[d])
absorption correction method	Gaussian integration (face-indexed)
range of transmission factors	1.0000–0.6593
data/restraints/parameters	4601 / 12[e] / 402
goodness-of-fit (*S*)[f] [all data]	1.054
final *R* indices[g]	
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0726
wR_2 [all data]	0.2321
largest difference peak and hole	0.928 and –0.357 e Å^{-3}

[a]Obtained from least-squares refinement of 5514 reflections with 6.60° < 2θ < 145.20°.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[c]Schneider, T. R.; Sheldrick, G. M. *Acta Crystallogr.* **2002**, *D58*, 1772-1779.

[d]Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3–8.

[e](a) The C16–C20A and C16–C20B distances were constrained to be equal (within 0.03 Å) during refinement. (b) The carbon atoms of the minor (40%) conformer of the disordered 3-fluorophenyl group were refined as an idealized regular hexagon, with C–C bond distances of 1.390 Å and C–C–C bond angles of 120.0º. (c) The O–H and H···H distances within the disordered solvent water molecules were constrained to be 0.840(3) Å and 1.370(3) Å during refinement. (c) The H1SB···N1(at 1–*x*, $\overline{y}$, 1–*z*) distance was constrained to be 2.22(2) Å during refinement. (e) The H1SD···N1(at 1–*x*, $\overline{y}$, 1–*z*) distance was constrained to be 1.97(2) Å during refinement.

[f]$S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.1241P)^2 + 1.7884P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

(a) atoms of N-(2,4-difluoro-3-methoxybenzyl)-6-{2-(3-fluorophenyl)pyrrolidin-1-yl}imidazo[1,2-b]pyridazine-3-carboxamide

Atom	*x*	*y*	*z*	U_{eq}, Å^2
F1	0.29978(16)	0.4603(2)	0.05861(12)	0.0561(6)*
F2	0.05424(19)	0.1307(3)	0.01556(16)	0.0846(9)*
F3A[a]	-0.0203(4)	0.3952(6)	0.2866(3)	0.1031(18)*
F3B[b]	0.0855(6)	0.5225(13)	0.1295(4)	0.153(5)*
O1	0.47929(19)	0.1999(2)	0.30617(13)	0.0460(6)*
O2	0.1364(2)	0.3422(3)	-0.04391(17)	0.0733(9)*
N1	0.50741(19)	0.2115(2)	0.55712(16)	0.0394(6)*
N2	0.41956(18)	0.3635(2)	0.47520(13)	0.0300(5)*
N3	0.35888(18)	0.4688(2)	0.44806(14)	0.0308(5)*
N4	0.26532(19)	0.6351(2)	0.47788(14)	0.0338(6)*
N5	0.3869(2)	0.3850(3)	0.30329(15)	0.0375(6)*
C1	0.3284(2)	0.5324(3)	0.50423(16)	0.0307(6)*
C2	0.3590(2)	0.4991(3)	0.58702(17)	0.0357(6)*
C3	0.4208(2)	0.3947(3)	0.61077(18)	0.0370(7)*
C4	0.4515(2)	0.3211(3)	0.55273(17)	0.0329(6)*
C5	0.5105(2)	0.1855(3)	0.48105(19)	0.0378(7)*
C6	0.4569(2)	0.2773(3)	0.42802(18)	0.0340(6)*
C7	0.4415(2)	0.2850(3)	0.34104(18)	0.0355(6)*
C8	0.3713(3)	0.4071(3)	0.21827(17)	0.0396(7)*
C9	0.2846(2)	0.3297(3)	0.16709(17)	0.0358(7)*
C10	0.2534(3)	0.3601(3)	0.08689(19)	0.0424(7)*
C11	0.1749(3)	0.2973(4)	0.0338(2)	0.0538(9)*
C12	0.1301(3)	0.1949(4)	0.0657(2)	0.0572(10)*
C13	0.1572(3)	0.1618(4)	0.1439(2)	0.0534(9)*
C14	0.2361(3)	0.2298(3)	0.1952(2)	0.0454(8)*
C15	0.1970(4)	0.3200(4)	-0.0949(3)	0.0697(12)*
C16	0.2482(2)	0.6875(3)	0.39732(17)	0.0378(7)*
C17	0.2103(3)	0.8272(3)	0.4074(2)	0.0481(8)*
C18	0.1524(3)	0.8091(3)	0.4702(2)	0.0471(8)*
C19	0.2204(3)	0.7165(3)	0.53000(19)	0.0432(8)*
C20A[a]	0.1767(7)	0.6164(11)	0.3288(5)	0.0392(19)*
C21A[a]	0.1084(6)	0.5319(8)	0.3415(4)	0.0421(17)*
C22A[a]	0.0476(5)	0.4782(7)	0.2770(5)	0.0538(16)*
C23A[a]	0.0500(6)	0.5044(8)	0.1989(5)	0.0491(17)*
C24A[a]	0.1185(6)	0.5977(7)	0.1880(4)	0.0573(18)*
C25A[a]	0.1841(6)	0.6549(7)	0.2520(4)	0.0442(15)*

C20B[b]	0.1701(7)	0.5890(9)	0.3431(5)	0.064(9)*
C21B[b]	0.1614(6)	0.5934(8)	0.2615(5)	0.051(2)*

Table 2. Atomic Coordinates and Displacement Parameters (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
C22B[b]	0.0933(6)	0.5121(10)	0.2102(4)	0.070(5)*
C23B[b]	0.0340(5)	0.4263(9)	0.2404(5)	0.071(3)*
C24B[b]	0.0427(5)	0.4219(7)	0.3220(5)	0.066(3)*
C25B[b]	0.1108(7)	0.5032(9)	0.3734(4)	0.045(3)*
H5N	0.367(3)	0.439(4)	0.331(2)	0.052(11)

(b) solvent water atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1SA[a]	0.3735(4)	-0.0600(5)	0.2970(3)	0.0588(13)
H1SA[a,c]	0.413(4)	0.003(4)	0.297(5)	0.088
H1SB[a,c]	0.403(4)	-0.119(3)	0.329(2)	0.088
O1SB[b]	0.3829(5)	-0.0348(7)	0.3282(4)	0.0464(15)
H1SC[b,c]	0.421(5)	0.025(6)	0.320(5)	0.070
H1SD[b,c]	0.414(5)	-0.081(5)	0.367(3)	0.070
O2SB[b]	0.3413(6)	0.7538(9)	0.2265(5)	0.077(2)
H2SA[b,c]	0.356(6)	0.824(5)	0.252(5)	0.115
H2SB[b,c]	0.394(3)	0.717(8)	0.222(6)	0.115

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$. [a]Refined with an occupancy factor of 0.6. [b]Refined with an occupancy factor of 0.4. [c]Refined with an isotropic displacement parameter 150% of that of the attached oxygen atom.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
F1	C10	1.361(4)	C9	C10	1.381(4)
F2	C12	1.347(4)	C9	C14	1.374(4)
F3A	C22A	1.305(9)	C10	C11	1.386(5)
F3B	C22B	1.380(10)	C11	C12	1.396(6)
O1	C7	1.245(4)	C12	C13	1.353(5)
O2	C11	1.393(4)	C13	C14	1.402(5)
O2	C15	1.388(5)	C16	C17	1.538(4)
N1	C4	1.346(4)	C16	C20A	1.520(7)[a]
N1	C5	1.357(4)	C16	C20B	1.591(6)[a]
N2	N3	1.366(3)	C17	C18	1.521(5)
N2	C4	1.372(3)	C18	C19	1.532(5)
N2	C6	1.386(4)	C20A	C21A	1.337(13)
N3	C1	1.326(4)	C20A	C25A	1.416(12)
N4	C1	1.362(4)	C21A	C22A	1.331(10)
N4	C16	1.456(4)	C22A	C23A	1.389(11)
N4	C19	1.475(4)	C23A	C24A	1.387(10)
N5	C7	1.333(4)	C24A	C25A	1.370(10)
N5	C8	1.452(4)	C20B	C21B	1.390[a]
C1	C2	1.429(4)	C20B	C25B	1.390[a]
C2	C3	1.358(4)	C21B	C22B	1.390[a]
C3	C4	1.405(4)	C22B	C23B	1.390[a]
C5	C6	1.384(4)	C23B	C24B	1.390[a]
C6	C7	1.470(4)	C24B	C25B	1.390[a]
C8	C9	1.516(4)			

[a]Distances restrained during refinement. See footnote *e* of Table 1 for details.

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C11	O2	C15	114.9(3)	C10	C11	C12	115.6(3)
C4	N1	C5	105.5(2)	F2	C12	C11	117.2(4)
N3	N2	C4	126.7(2)	F2	C12	C13	119.7(4)
N3	N2	C6	125.5(2)	C11	C12	C13	123.0(3)
C4	N2	C6	107.8(2)	C12	C13	C14	119.0(4)
N2	N3	C1	114.4(2)	C9	C14	C13	120.7(3)
C1	N4	C16	122.2(2)	N4	C16	C17	101.7(2)
C1	N4	C19	124.0(2)	N4	C16	C20A	119.3(6)[a]
C16	N4	C19	113.2(2)	N4	C16	C20B	104.8(4)[a]
C7	N5	C8	122.2(3)	C17	C16	C20A	110.7(5)[a]
N3	C1	N4	115.2(2)	C17	C16	C20B	116.5(5)[a]
N3	C1	C2	123.7(3)	C16	C17	C18	103.2(3)
N4	C1	C2	121.1(3)	C17	C18	C19	102.3(3)
C1	C2	C3	119.3(3)	N4	C19	C18	102.2(2)
C2	C3	C4	118.8(3)	C16	C20A	C21A	121.5(9)[a]
N1	C4	N2	110.5(3)	C16	C20A	C25A	114.4(9)[a]
N1	C4	C3	132.5(3)	C21A	C20A	C25A	123.9(6)
N2	C4	C3	117.0(3)	C20A	C21A	C22A	116.5(7)
N1	C5	C6	111.7(3)	F3A	C22A	C21A	118.6(7)
N2	C6	C5	104.5(3)	F3A	C22A	C23A	116.6(7)
N2	C6	C7	126.5(3)	C21A	C22A	C23A	124.9(7)
C5	C6	C7	129.0(3)	C22A	C23A	C24A	116.9(7)
O1	C7	N5	123.1(3)	C23A	C24A	C25A	120.9(6)
O1	C7	C6	119.6(3)	C20A	C25A	C24A	116.8(7)
N5	C7	C6	117.3(3)	C16	C20B	C21B	116.7(5)[a]
N5	C8	C9	113.8(3)	C16	C20B	C25B	123.3(5)[a]
C8	C9	C10	118.0(3)	C21B	C20B	C25B	120.0[a]
C8	C9	C14	124.1(3)	C20B	C21B	C22B	120.0[a]
C10	C9	C14	117.9(3)	F3B	C22B	C21B	117.9(8)[a]
F1	C10	C9	118.4(3)	F3B	C22B	C23B	122.1(8)[a]
F1	C10	C11	117.9(3)	C21B	C22B	C23B	120.0[a]
C9	C10	C11	123.7(3)	C22B	C23B	C24B	120.0[a]
O2	C11	C10	122.1(4)	C23B	C24B	C25B	120.0[a]
O2	C11	C12	121.9(4)	C20B	C25B	C24B	120.0[a]

[a]Angle includes distance(s) restrained during refinement. See footnote *e* of Table 1 for details.

Table 5. Hydrogen-Bonded Interactions

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	∠D–H···A (deg)
N5–H5N···N3	0.82(4)	2.09(4)	2.772(4)	141(4)
O1SA–H1SA···O1	0.840(3)	2.19(2)	3.002(6)	163(7)
O1SA–H1SB···N1[a]	0.841(3)	2.256(16)	3.056(6)	159(4)
O1SB–H1SC···O1	0.840(3)	1.99(3)	2.805(7)	163(8)
O1SB–H1SD···N1[a]	0.841(3)	1.985(14)	2.816(7)	169(7)
O2SB–H2SA···O1SB[b]	0.840(3)	1.92(2)	2.743(11)	168(10)
O2SB–H2SB···O1[c]	0.840(3)	1.95(4)	2.745(9)	157(10)

[a]At 1–*x*, $\overline{y}$, 1–*z*.

[b]At *x*, 1+*y*, *z*.

[c]At 1–*x*, $^1/_2$+*y*, $^1/_2$–*z*.

Table 6. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C15	O2	C11	C10	72.8(5)	N2	C6	C7	O1	-179.6(3)
C15	O2	C11	C12	-114.1(5)	N2	C6	C7	N5	0.5(5)
C5	N1	C4	N2	0.2(3)	C5	C6	C7	O1	0.5(5)
C5	N1	C4	C3	179.2(3)	C5	C6	C7	N5	-179.3(3)
C4	N1	C5	C6	-0.2(3)	N5	C8	C9	C10	169.5(3)
C4	N2	N3	C1	-1.1(4)	N5	C8	C9	C14	-11.6(4)
C6	N2	N3	C1	176.4(3)	C8	C9	C10	F1	-2.0(4)
N3	N2	C4	N1	177.7(2)	C8	C9	C10	C11	-179.7(3)
N3	N2	C4	C3	-1.5(4)	C14	C9	C10	F1	179.0(3)
C6	N2	C4	N1	-0.1(3)	C14	C9	C10	C11	1.3(5)
C6	N2	C4	C3	-179.3(3)	C8	C9	C14	C13	-179.3(3)
N3	N2	C6	C5	-177.9(2)	C10	C9	C14	C13	-0.4(5)
N3	N2	C6	C7	2.3(4)	F1	C10	C11	O2	-6.8(5)
C4	N2	C6	C5	0.0(3)	F1	C10	C11	C12	179.8(3)
C4	N2	C6	C7	-179.8(3)	C9	C10	C11	O2	170.9(3)
N2	N3	C1	N4	-178.1(2)	C9	C10	C11	C12	-2.6(5)
N2	N3	C1	C2	2.7(4)	O2	C11	C12	F2	7.3(6)
C16	N4	C1	N3	-11.5(4)	O2	C11	C12	C13	-170.4(4)
C16	N4	C1	C2	167.7(3)	C10	C11	C12	F2	-179.2(3)
C19	N4	C1	N3	178.2(3)	C10	C11	C12	C13	3.1(6)
C19	N4	C1	C2	-2.5(4)	F2	C12	C13	C14	-179.9(3)
C1	N4	C16	C17	-158.1(3)	C11	C12	C13	C14	-2.3(6)
C1	N4	C16	C20A	79.9(5)[a]	C12	C13	C14	C9	0.8(6)
C1	N4	C16	C20B	80.2(5)[a]	N4	C16	C17	C18	-33.8(3)
C19	N4	C16	C17	13.1(3)	C20A	C16	C17	C18	94.0(6)[a]
C19	N4	C16	C20A	-108.9(5)[a]	C20B	C16	C17	C18	79.5(5)[a]
C19	N4	C16	C20B	-108.6(5)[a]	N4	C16	C20A	C21A	19.5(10)[a]
C1	N4	C19	C18	-176.4(3)	N4	C16	C20A	C25A	-165.0(5)[a]
C16	N4	C19	C18	12.5(4)	C17	C16	C20A	C21A	-97.9(9)[a]
C8	N5	C7	O1	-3.4(5)	C17	C16	C20A	C25A	77.5(7)[a]
C8	N5	C7	C6	176.5(3)	N4	C16	C20B	C21B	-162.6(4)[a]
C7	N5	C8	C9	85.7(4)	N4	C16	C20B	C25B	18.7(6)[a]
N3	C1	C2	C3	-1.8(4)	C17	C16	C20B	C21B	85.9(6)[a]
N4	C1	C2	C3	179.0(3)	C17	C16	C20B	C25B	-92.8(6)[a]
C1	C2	C3	C4	-1.0(4)	C16	C17	C18	C19	42.0(3)
C2	C3	C4	N1	-176.5(3)	C17	C18	C19	N4	-33.1(3)
C2	C3	C4	N2	2.5(4)	C16	C20A	C21A	C22A	178.0(8)[a]
N1	C5	C6	N2	0.1(3)	C25A	C20A	C21A	C22A	3.0(12)
N1	C5	C6	C7	180.0(3)	C16	C20A	C25A	C24A	-177.4(7)[a]

C21A	C20A	C25A	C24A	-2.1(12)
C20A	C21A	C22A	F3A	-179.9(8)

Table 6. Torsional Angles (continued)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C20A	C21A	C22A	C23A	-0.5(12)	C21B	C20B	C25B	C24B	0.0[a]
F3A	C22A	C23A	C24A	176.7(7)	C20B	C21B	C22B	F3B	178.4(8)[a]
C21A	C22A	C23A	C24A	-2.8(12)	C20B	C21B	C22B	C23B	0.0[a]
C22A	C23A	C24A	C25A	3.7(11)	F3B	C22B	C23B	C24B	-178.3(9)[a]
C23A	C24A	C25A	C20A	-1.4(11)	C21B	C22B	C23B	C24B	0.0[a]
C16	C20B	C21B	C22B	-178.7(8)[a]	C22B	C23B	C24B	C25B	0.0[a]
C25B	C20B	C21B	C22B	0.0[a]	C23B	C24B	C25B	C20B	0.0[a]
C16	C20B	C25B	C24B	178.7(9)[a]					

[a]Angle includes distance(s) restrained during refinement. See footnote *e* of Table 1 for details.

Table 7. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.0632(14)	0.0569(12)	0.0442(11)	0.0170(9)	0.0067(9)	-0.0047(10)
F2	0.0550(16)	0.119(2)	0.0765(17)	-0.0365(16)	0.0115(12)	-0.0316(15)
F3A	0.097(4)	0.101(4)	0.101(4)	-0.005(3)	0.007(3)	-0.040(3)
F3B	0.088(5)	0.313(14)	0.035(3)	-0.064(5)	-0.026(3)	0.099(7)
O1	0.0567(15)	0.0370(11)	0.0475(13)	0.0001(10)	0.0190(11)	0.0073(10)
O2	0.070(2)	0.092(2)	0.0543(17)	-0.0022(15)	0.0086(14)	0.0196(17)
N1	0.0335(14)	0.0349(13)	0.0450(15)	0.0107(11)	0.0014(11)	0.0003(10)
N2	0.0299(13)	0.0251(11)	0.0315(12)	0.0042(9)	0.0016(9)	-0.0020(9)
N3	0.0317(13)	0.0249(11)	0.0321(12)	0.0032(9)	0.0018(9)	-0.0001(9)
N4	0.0398(15)	0.0296(12)	0.0293(12)	0.0002(9)	0.0041(10)	0.0019(10)
N5	0.0449(16)	0.0343(13)	0.0307(13)	0.0006(10)	0.0053(11)	0.0038(11)
C1	0.0310(15)	0.0259(12)	0.0319(14)	0.0008(10)	0.0021(11)	-0.0052(10)
C2	0.0412(17)	0.0332(14)	0.0316(15)	0.0002(11)	0.0072(12)	-0.0050(12)
C3	0.0397(18)	0.0348(15)	0.0321(14)	0.0098(11)	0.0011(12)	-0.0086(12)
C4	0.0299(15)	0.0313(13)	0.0329(15)	0.0074(11)	0.0000(11)	-0.0049(11)
C5	0.0333(17)	0.0326(15)	0.0449(17)	0.0075(12)	0.0055(13)	0.0009(12)
C6	0.0324(16)	0.0298(14)	0.0379(16)	0.0017(11)	0.0056(12)	-0.0010(11)
C7	0.0363(17)	0.0309(14)	0.0379(16)	0.0000(11)	0.0068(12)	-0.0021(12)
C8	0.0480(19)	0.0358(15)	0.0340(15)	0.0031(12)	0.0091(13)	-0.0011(13)
C9	0.0401(18)	0.0337(14)	0.0335(15)	-0.0008(11)	0.0096(12)	0.0048(12)
C10	0.0436(19)	0.0441(17)	0.0393(17)	0.0001(13)	0.0101(13)	0.0036(14)
C11	0.048(2)	0.071(2)	0.0382(18)	-0.0054(16)	0.0033(15)	0.0031(18)
C12	0.041(2)	0.074(3)	0.055(2)	-0.0229(19)	0.0094(16)	-0.0089(18)
C13	0.045(2)	0.060(2)	0.059(2)	-0.0116(17)	0.0220(17)	-0.0129(17)
C14	0.050(2)	0.0471(18)	0.0419(17)	-0.0018(14)	0.0169(15)	-0.0041(15)
C15	0.084(3)	0.060(2)	0.066(3)	-0.003(2)	0.021(2)	0.018(2)
C16	0.0384(17)	0.0407(16)	0.0327(15)	0.0079(12)	0.0059(12)	0.0086(13)
C17	0.051(2)	0.0408(17)	0.051(2)	0.0117(14)	0.0112(16)	0.0149(15)
C18	0.047(2)	0.0382(16)	0.056(2)	0.0007(14)	0.0123(15)	0.0087(14)
C19	0.054(2)	0.0374(16)	0.0391(17)	-0.0011(13)	0.0139(14)	0.0069(14)
C20A	0.037(5)	0.043(3)	0.030(4)	-0.005(4)	-0.004(3)	0.013(3)
C21A	0.030(3)	0.055(4)	0.035(4)	-0.002(3)	-0.004(3)	0.004(3)
C22A	0.042(4)	0.062(4)	0.048(4)	-0.006(3)	-0.004(3)	-0.006(3)
C23A	0.036(5)	0.058(4)	0.042(4)	-0.012(3)	-0.012(3)	0.000(3)
C24A	0.065(5)	0.064(4)	0.040(3)	-0.002(3)	0.007(3)	0.005(3)
C25A	0.050(4)	0.046(4)	0.036(3)	0.011(3)	0.009(2)	0.001(3)
C20B	0.055(12)	0.111(19)	0.016(5)	-0.006(7)	-0.009(6)	0.060(12)
C21B	0.042(6)	0.072(8)	0.037(6)	0.008(5)	0.008(4)	0.020(5)

C22B	0.030(8)	0.121(13)	0.044(7)	-0.044(7)	-0.019(6)	0.019(8)	
C23B	0.036(7)	0.102(11)	0.066(8)	-0.025(8)	-0.003(5)	0.005(6)	

Table 7. Anisotropic Displacement Parameters (continued)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C24B	0.039(6)	0.060(6)	0.081(8)	-0.032(6)	-0.020(5)	-0.005(5)
C25B	0.043(6)	0.043(5)	0.043(6)	-0.005(5)	-0.002(5)	0.009(4)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2	0.3364	0.5495	0.6251	0.043
H3	0.4428	0.3719	0.6656	0.044
H8A	0.4330	0.3828	0.2029	0.047
H8B	0.3593	0.5022	0.2071	0.047
H13	0.1233	0.0935	0.1637	0.064
H14	0.2564	0.2065	0.2501	0.055
H15A	0.1644	0.3545	-0.1480	0.084
H15B	0.2612	0.3647	-0.0743	0.084
H15C	0.2084	0.2251	-0.0985	0.084
H16	0.3142	0.6953	0.3844	0.045
H17A	0.2665	0.8894	0.4260	0.058
H17B	0.1663	0.8601	0.3567	0.058
H18A	0.0863	0.7686	0.4471	0.057
H18B	0.1431	0.8941	0.4954	0.057
H19A	0.2721	0.7662	0.5693	0.052
H19B	0.1816	0.6619	0.5586	0.052
H21A[a]	0.1035	0.5113	0.3938	0.051
H23A[a]	0.0068	0.4605	0.1550	0.059
H24A[a]	0.1198	0.6222	0.1355	0.069
H25A[a]	0.2323	0.7174	0.2453	0.053
H21B[b]	0.2019	0.6521	0.2408	0.061
H23B[b]	-0.0126	0.3708	0.2053	0.085
H24B[b]	0.0022	0.3632	0.3427	0.080
H25B[b]	0.1168	0.5001	0.4292	0.054

[a]Included with an occupancy factor of 0.6. [b]Included with an occupancy factor of 0.4.

8. REFERENCES

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