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ARTICLE

Supplementary Information for 'PK 11195 derivatives: Exploring the influence of amide and heterocyclic substitution on A147T TSPO discrimination'

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Supplementary Experimental Section

General Procedure 1: Synthesis of 1-(3-Methoxyphenyl)-*N*-methylmethanamine and *N*-(3-Methoxybenzyl)ethanamine

To a solution of methylamine or ethylamine in methanol (2.0 M, 8.81 mmol, 1.20 equiv.) was added 3-methoxybenzaldehyde (900 µL, 7.34 mmol, 1.00 equiv.). The resulting mixture was stirred for 1 hour at ambient temperature. The reaction mixture was then cooled to 0 °C and sodium borohydride (556 mg, 14.7 mmol, 2.00 equiv.) was added portionwise. The resulting suspension was warmed to ambient temperature and stirred for 4 hours. The suspension was then quenched with methanol (20 mL), evaporated under reduced pressure and partitioned between ethyl acetate (30 mL) and water (15 mL). The aqueous layer was separated and the organic layer was extracted with a solution of hydrochloric acid (3 M, 2×10 mL). A solution of sodium hydroxide (10 M) was then used to basify the combined acidic aqueous extracts. The aqueous layer was extracted with ethyl acetate (3×15 mL). The organic extracts were combined, washed with water (10 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the secondary amine. No further purification was required.

1-(3-Methoxyphenyl)-*N*-methylmethanamine

General procedure 1 was followed and gave the desired product as a colourless oil (1.03 g, 6.81 mmol, 93%).

R_f 0.26 (methanol/dichloromethane, 1:9 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16–7.04 (m, 1H), 6.79–6.66 (m, 3H), 3.67 (s, 3H), 3.60 (s, 2H), 2.33 (s, 3H); LRMS (+ESI) 152 [(M+ H)$^+$ 100%]. The spectra for this compound is consistent with those previously reported.[1]

N-(3-Methoxybenzyl)ethanamine

General procedure 1 was followed and gave the desired product as a colourless oil (1.12 g, 6.78 mmol, 92%).

R_f 0.30 (methanol/dichloromethane, 1:9 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.13–7.06 (m, 1H), 6.78–6.63 (m, 3H), 3.65 (s, 3H), 3.63 (s, 2H), 2.55 (q, J = 7.1 Hz, 2H), 1.01 (t, J = 7.1 Hz, 3H); LRMS (+ESI) 166 [(M + H)$^+$ 100%]. The spectra for this compound is consistent with those previously reported.[2]

Isoquinoline Carboxamide Ligands

The spectroscopic data for all intermediates synthesized (**7–10**) was consistent with previously reported data from the literature.[3]

Methyl 1-oxo-1,2-dihydroisoquinoline-3-carboxylate (7)

A suspension of methyl 2-iodobenzoate (5, 560 µL, 3.82 mmol, 1.00 equiv.), methyl 2-acetamidoacrylate (6, 546 mg, 3.82 mmol, 1.00 equiv.) and tetrabutylammonium chloride (2.12 g, 7.63 mmol, 2.00 equiv.) in *N,N*-dimethylformamide (0.1 M) was degassed under argon for 10 minutes. Palladium acetate (43 mg, 0.191 mmol, 5 mol%) was added under argon and the mixture was then heated to 90 °C for 18 hours. The reaction mixture was cooled to ambient temperature and evaporated under reduced pressure. The crude residue was diluted with ethyl acetate and filtered through a pad of Celite®. The pad of Celite® was washed with ethyl acetate (15 mL) and the organic solvent was then concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/hexane (3:7 v/v) gave the desired product as a colourless powder (600 mg, 2.95 mmol, 77%).

R_f 0.23 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 9.22 (s, 1H), 8.55–8.44 (m, 1H), 7.79–7.62 (m, 3H), 7.40 (s, 1H), 4.02 (s, 3H); LRMS (+ESI) 226 ([M + Na]$^+$ 100%).

Methyl 1-bromoisoquinoline-3-carboxylate (8)

To a suspension of **7** (550 mg, 2.71 mmol, 1.00 equiv.) and potassium carbonate (748 mg, 5.41 mmol, 2.00 equiv.) in acetonitrile (0.1 M) was added phosphorus(V) oxybromide (550

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µL, 5.41 mmol, 2.00 equiv.). The reaction mixture was stirred at reflux for 24 hours. The reaction mixture was then poured into ice-cold water (10 mL) and diluted with ethyl acetate (20 mL). The organic layer was extracted, and the aqueous layer was further extracted with ethyl acetate (3×10 mL). The organic extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel using ethyl acetate/hexane (1:4 v/v) gave the desired product as a colourless powder (590 mg, 2.22 mmol, 82%).

R_f 0.54 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.57 (s, 1H), 8.45–8.37 (m, 1H), 8.04–7.96 (m, 1H), 7.91–7.82 (m, 2H), 4.07 (s, 3H); LRMS (+ESI) 290/288 ([M + Na]$^+$ 100%).

Methyl 1-(2-chlorophenyl)isoquinoline-3-carboxylate (9)

A suspension of **8** (550 mg, 2.07 mmol, 1.00 equiv.), 2-chlorophenylboronic acid (485 mg, 3.10 mmol, 1.50 equiv.) and caesium carbonate (1.68 g, 5.17 mmol, 2.50 equiv.) in toluene/water (20 mL, 3:1 v/v) was degassed under argon for 10 minutes. Pd(dppf)Cl_2 (15 mg, 0.021 mmol, 0.10 equiv.) was added under argon and the reaction mixture was then stirred at 80 °C for 16 hours. The reaction mixture was cooled to ambient temperature and evaporated under reduced pressure. Purification by flash chromatography on silica gel using ethyl acetate/hexane (1:4 v/v) furnished the desired product as a colourless powder (470 mg, 1.58 mmol, 76%).

R_f 0.31 (ethyl acetate/hexane, 1:4 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.69 (s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.80 (ddd, *J* = 8.2, 6.3, 1.8 Hz, 1H), 7.74–7.62 (m, 2H), 7.60–7.40 (m, 4H), 4.07 (s, 3H); LRMS (+ESI) 322/320 ([M + Na]$^+$ 30/100%).

1-(2-Chlorophenyl)isoquinoline-3-carboxylic acid (10)

A suspension of **9** (450 mg, 1.51 mmol, 1.00 equiv.) and lithium hydroxide (145 mg, 6.05 mmol, 4.00 equiv.) in methanol/water (0.1 M, 1:1 v/v) was stirred at reflux for 6 hours. The reaction mixture was cooled to ambient temperature and the solvents were evaporated under reduced pressure. The mixture was acidified using aqueous hydrochloric acid (1 M, 20 mL) and diluted with ethyl acetate (30 mL). The organic layer was extracted, and the aqueous layer was further extracted with ethyl acetate (3×10 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification was achieved by recrystallisation from toluene and gave the desired product as colourless crystals (400 mg, 1.41 mmol, 93%).

R_f 0.34 (methanol/dichloromethane, 1:9 v/v); ^{1}H NMR (400 MHz; DMSO-d_6) δ = 8.73 (s, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 7.92–7.87 (m, 1H), 7.80–7.68 (m, 3H), 7.61–7.54 (m, 3H); LRMS (-ESI) 284/282 ([M - Na]$^-$ 35/100%).

General Procedure 2: Amide Coupling

To a solution of the appropriate carboxylic acid (1.00 equiv.), HBTU (1.50 equiv.) and the appropriate secondary amine (1.10 equiv.) in anhydrous *N,N*-dimethylformamide (0.1 M) was added *N,N*-diisopropylethylamine (2.00 equiv.). The mixture was stirred at ambient temperature for 16 hours. Following completion, water was added and the aqueous mixture was extracted with ethyl acetate (3×10 mL). The organic extracts were combined and sequentially washed with an aqueous solution of saturated sodium bicarbonate (10 mL), aqueous hydrochloric acid (2 M, 10 mL), water (2×5 mL) and brine (5 mL). The organic extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo.*

***N*-Benzyl-1-(2-chlorophenyl)-*N*-methylisoquinoline-3-carboxamide (1a)**

General procedure 2 was followed using **10** (50 mg, 0.176 mmol) and *N*-benzylmethylamine (25 µL, 0.194 mmol) and gave the desired product as a colourless oil (52 mg, 0.134 mmol, 76%).

R_f 0.47 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.21 (s, 1H), 8.01–7.97 (m, 1H), 7.78–7.74–7.65 (m, 1H), 7.61–7.16 (m, 11H), 4.86 (s, 2H), 3.09 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 169.5, 158.4, 147.3, 136.6, 136.6, 134.0, 130.4, 130.3, 129.2, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 128.0, 127.5, 127.2, 126.9, 122.3, 52.0, 33.0; LRMS (+ESI) 411/409 ([M + Na]$^+$ 30/100%); IR (ν_{max}/cm^{-1}) 2983, 2966, 1687, 1614, 1423, 1294, 1052, 965, 655; Found: C, 74.52; H, 4.96; N, 7.26. Calc for $C_{24}H_{19}ClN_2O$: C, 74.51; H, 4.95; N, 7.24%

***N*-Benzyl-1-(2-chlorophenyl)-*N*-ethylisoquinoline-3-carboxamide (1b)**

General procedure 2 was followed using **10** (50 mg, 0.176 mmol) and *N*-ethylbenzylamine (30 µL, 0.194 mmol) and gave the desired product as a colourless oil (59 mg, 0.147 mmol, 84%).

R_f 0.56 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.23 (s, 1H), 7.89–7.81 (m, 1H), 7.77–7.70 (m, 1H), 7.64–7.16 (m, 11H), 4.82 (s, 2H), 3.36 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 169.7, 158.4, 147.2, 136.7, 136.6, 134.1, 130.5, 130.2, 129.2, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.0, 127.7, 127.4, 127.1, 122.4, 52.0, 42.3, 13.4; LRMS (+ESI) 425/423 ([M + Na]$^+$ 33/100%); IR (ν_{max}/cm^{-1}) 2980, 2835, 1686, 1613, 1423, 1292, 1237, 1053, 964, 658; Found: C, 74.89; H, 5.25; N, 7.01. Calc for $C_{25}H_{21}ClN_2O$: C, 74.90; H, 5.28; N, 6.99%

1-(2-Chlorophenyl)-*N,N*-diethylisoquinoline-3-carboxamide (1c)

General procedure 2 was followed using **10** (50 mg, 0.176 mmol) and diethylamine (20 µL, 0.194 mmol) and gave the desired product as a colourless powder (47 mg, 0.139 mmol, 79%).

R_f 0.42 (ethyl acetate/hexane, 3:7 v/v); mp 146–148 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.19 (s, 1H), 7.86–7.79 (m, 1H), 7.77–7.70 (m, 1H), 7.66–7.38 (m, 6H), 3.38 (q, *J* = 7.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 169.7, 158.4, 147.2, 136.7, 134.8, 131.3, 130.7, 129.9, 129.7, 128.6, 128.5, 127.8, 127.4, 127.1, 127.0, 126.0, 42.7, 12.7; LRMS (+ESI) 363/361 ([M

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+ Na]$^+$ 32/100%); IR (ν_{max}/cm^{-1}) 2980, 2939, 2831, 1626, 1646, 1429, 1392, 1051, 958, 658; Found: C, 70.88; H, 5.68; N, 8.26. Calc for $C_{20}H_{19}ClN_2O$: C, 70.90; H, 5.65; N, 8.27%

1-(2-Chlorophenyl)-*N*-(3-methoxybenzyl)-*N*-methylisoquinoline-3-carboxamide (1d)

General procedure 2 was followed using **10** (50 mg, 0.176 mmol) and 1-(3-methoxyphenyl)-*N*-methylmethanamine (29 mg, 0.194 mmol) and gave the desired product as a colourless oil (54 mg, 0.130 mmol, 74%).

R_f 0.40 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.21 (s, 1H), 8.05–7.92 (m, 1H), 7.84–7.71 (m, 1H), 7.71–7.34 (m, 5H), 7.31–7.13 (m, 1H), 7.00 (d, *J* = 4.5 Hz, 1H), 6.95–6.69 (m, 3H), 4.68 (s, 2H), 3.62 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 169.7, 159.8, 157.6, 147.2, 138.6, 136.7, 131.3, 130.8, 130.0, 129.7, 129.6, 129.4, 128.5, 127.8, 127.4, 127.2, 126.8, 121.5, 120.6, 120.0, 113.5, 112.8, 55.0, 51.5, 33.6; LRMS (+ESI) 441/439 ([M + Na]$^+$ 30/100%); IR (νmax/cm^{-1}) 2981, 2834, 1686, 1421, 1296, 1240, 1052, 963, 659; Found: C, 72.00; H, 5.08; N, 6.73. Calc for $C_{25}H_{21}ClN_2O_2$: C, 72.02; H, 5.08; N, 6.72%

1-(2-Chlorophenyl)-*N*-ethyl-*N*-(3-methoxybenzyl)isoquinoline-3-carboxamide (1e)

General procedure 2 was followed using **10** (50 mg, 0.176 mmol) and *N*-(3-methoxybenzyl)ethanamine (32 mg, 0.194 mmol) and gave the desired product as a colourless oil (48 mg, 0.111 mmol, 63%).

R_f 0.49 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.19 (s, 1H), 8.01–7.96 (m, 1H), 7.83–7.71 (m, 1H), 7.69–7.32 (m, 5H), 7.30–7.14 (m, 1H), 7.02 (d, *J* = 4.4 Hz, 1H), 6.87–6.74 (m, 3H), 4.81 (s, 2H), 3.84 (s, 3H), 3.50 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 169.5, 159.7, 157.4, 147.6, 139.1, 136.6, 131.4, 131.3, 130.7, 129.7, 129.5, 129.2, 128.4, 127.8, 127.1, 126.7, 121.3, 120.5, 120.1, 113.6, 113.5, 112.9, 55.2, 52.1, 43.3, 13.9; LRMS (+ESI) 455/453 ([M + Na]$^+$ 33/100%); IR (νmax/cm^{-1}) 2979, 2836, 1685, 1421, 1296, 1236, 1051, 962, 659; Found: C, 72.50; H, 5.41; N, 6.50. Calc for $C_{26}H_{23}ClN_2O_2$: C, 72.47; H, 5.38; N, 6.50%

Quinazoline Carboxamide Ligands

(2-Aminophenyl)(2-chlorophenyl)methanone (13)

The Grignard reagent was first prepared by the addition of 1-bromo-2-chlorobenzene (11, 13.0 mL, 114.3 mmol, 3.00 equiv.) to a mixture of magnesium turnings (3.80 g, 114.3 mmol, 3.00 equiv.) in anhydrous diethyl ether (40 mL). Upon formation of the Grignard reagent, the reaction mixture was cooled to 0 °C and 2-aminobenzonitrile (12, 4.50 g, 38.1 mmol, 1.00 equiv.) in anhydrous diethyl ether (20 mL) was added dropwise. The reaction mixture was warmed to ambient temperature and stirred at reflux for 24 hours. The mixture was then cooled to 0 °C and aqueous hydrochloric acid (1 M, 40 mL) was added. The resulting mixture was stirred vigorously for 2 hours. The mixture was then partitioned between a saturated solution of sodium hydrogen carbonate (50 mL) and ethyl acetate (50 mL). The organic layer was extracted and the aqueous layer was further extracted with ethyl acetate (2×30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on a silica gel column using ethyl acetate/hexane (1:4 v/v) furnished the desired product as a yellow solid (1.20 g, 5.18 mmol, 26%).

R_f 0.32 (ethyl acetate/hexane, 1:4 v/v); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.42–7.19 (m, 5H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.49–6.39 (m, 1H), 6.05 (br s, 2H); LRMS (+ESI) 234/232 [(M + H)$^+$ 35/100%]. The spectra for this compound is consistent with those previously reported.[4]

4-(2-Chlorophenyl)-2,3-dihydroquinazoline-2-carboxylic acid (14)

Compound **13** (1.00 g, 4.32 mmol, 1.00 equiv.) was added dropwise to a solution of glyoxylic acid (50% w/w in water, 639 mg, 4.32 mmol, 1.00 equiv.) and ammonium acetate (693 mg, 12.95 mmol, 3.00 equiv.) in ethanol (95%, 0.1 M). The reaction mixture was stirred at ambient temperature for 30 minutes. The orange coloured reaction mixture gave a precipitate within this time. After the addition of water (15 mL), the orange solid was collected by filtration. The orange product was washed with ethanol (95%, 10 mL), followed by diethyl ether (10 mL) to give the desired product as an orange powder (940 mg, 3.28 mmol, 76%).

R_f 0.18 (methanol/dichloromethane, 1:9 v/v); mp 125–127 °C; ^{1}H NMR (400 MHz; DMSO-d_6) δ = 7.51–7.43 (m, 4H), 7.28–7.16 (m, 1H), 6.94 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.60–6.57 (m, 1H), 5.34 (s, 1H); ^{13}C NMR (101 MHz; DMSO-d_6) δ = 172.3, 147.6, 138.2, 133.2, 129.8, 129.3, 128.5, 128.2, 117.01, 116.4, 114.8, 122.5, 100.4, 88.3, 70.0; LRMS (-ESI) 287/285 [(M - H)$^-$ 35/100%]; IR (ν_{max}/cm^{-1}) 3168, 3068, 1762, 1594, 1469, 1259, 1393, 741, 455.

4-(2-Chlorophenyl)quinazoline-2-carboxylic acid (15)

A solution of 14 (900 mg, 3.14 mmol, 1.00 equiv.) in *N,N*-dimethylformamide (0.1 M) was allowed to stand for 12 hours under external light irradiation using a 20W halogen tungsten lamp. The mixture was cooled to 0 °C and water was added (10 mL). The resulting precipitate was collected by filtration, washed with water (10 mL) and diethyl ether (10 mL) to give the desired product as a colourless powder (630 mg, 2.21 mmol, 71%).

R_f 0.25 (methanol/dichloromethane, 1:9 v/v); mp 170–172 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ = 8.23–8.20 (m, 1H), 8.15–8.09 (m, 1H), 7.90–7.85 (m, 1H), 7.72–7.59 (m, 5H); LRMS (-ESI) 285/283 [(M - H)$^-$ 33/100%]; The spectra for this compound is consistent with those previously reported.[5]

***N*-Benzyl-4-(2-chlorophenyl)-*N*-methylquinazoline-2-carboxamide (2a)**

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and *N*-benzylmethylamine (50 µL, 0.386 mmol) and gave

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the desired product as a colourless powder (104 mg, 0.268 mmol, 76%).

R_f 0.32 (ethyl acetate/hexane, 3:7 v/v); mp 126–128 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.18–8.06 (m, 1H), 8.03–7.91 (m, 1H), 7.77–7.17 (m, 11H), 4.71 (s, 2H), 2.89 (s, 3H); LRMS (+ESI) 412/410 [(M + Na)$^+$ 32/100%]; Found: C, 71.14; H, 4.66; N, 10.81. Calcd for $C_{23}H_{18}ClN_3O$: C, 71.22; H, 4.68; N, 10.83%. The spectra for this compound is consistent with those previously reported.[6]

_N_-Benzyl-4-(2-chlorophenyl)-_N_-ethylquinazoline-2-carboxamide (2b)

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and *N*-benzylethylamine (60 µL, 0.386 mmol) and gave the desired product as a colourless powder (114 mg, 0.284 mmol, 81%).

R_f 0.36 (ethyl acetate/hexane, 3:7 v/v); mp 169–170 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ = 8.23–8.08 (m, 1H), 7.98–7.89 (m, 1H), 7.87–7.77 (m, 1H), 7.75–7.23 (m, 10H), 4.87 (s, 2H), 3.59 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); LRMS (+ESI) 426/424 [(M + Na)$^+$ 33/100%]; Found: C, 71.74; H, 5.04; N, 10.43. Calcd for $C_{24}H_{20}ClN_3O$: C, 71.73; H, 5.02; N, 10.46%. The spectra for this compound is consistent with those previously reported.[6]

4-(2-Chlorophenyl)-_N,N_-diethylquinazoline-2-carboxamide (2c)

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and diethylamine (40 µL, 0.386 mmol) and gave the desired product as a colourless powder (98 mg, 0.288 mmol, 82%).

R_f 0.22 (ethyl acetate/hexane, 3:7 v/v); mp 133–135 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.37 (d, *J* = 4.6 Hz, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 7.59–7.20 (m, 6H), 3.63 (q, *J* = 7.0 Hz, 4H), 1.28 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 179.3, 165.3, 147.8, 144.8, 134.8, 131.5, 130.8, 130.0, 129.9, 129.8, 128.7, 127.8, 119.8, 117.8, 110.8, 41.7, 13.9; LRMS (+ESI) 364/362 [(M + Na)$^+$ 30/100%]; IR (ν_{max}/cm^{-1}) 2976, 2940, 1635, 1616, 1560, 1543, 1473, 1392, 744, 544, 423; Found: C, 67.14; H, 5.34; N, 12.41. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37%

4-(2-chlorophenyl)-_N_-(3-methoxybenzyl)-_N_-methylquinazoline-2-carboxamide (2d)

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and 1-(3-methoxyphenyl)-*N*-methylmethanamine (58 mg, 0.386 mmol) and gave the desired product as a colourless oil (122 mg, 0.292 mmol, 83%).

R_f 0.34 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.21–8.10 (m, 1H), 8.04–7.93 (m, 1H), 7.89–7.67 (m, 10H), 4.73 (s, 2H), 3.67 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 169.8, 166.6, 160.0, 157.7, 151.2, 139.7, 137.9, 135.4, 131.0, 130.3, 129.6, 129.2, 128.7, 127.8, 123.1, 122.4, 121.2, 121.0, 119.1, 114.6, 114.3, 56.0, 48.2, 34.2; LRMS (+ESI) 442/440 [(M + Na)$^+$ 32/100%]; IR (ν_{max}/cm^{-1}) 2932, 1642, 1481, 1256, 1393, 747, 544, 421; Found: C, 69.99; H, 4.83; N, 9.48. Calcd for $C_{24}H_{20}ClN_3O_2$: C, 69.98; H, 4.82; N, 8.48%.

4-(2-Chlorophenyl)-_N_-ethyl-_N_-(3-methoxybenzyl)quinazoline-2-carboxamide (2e)

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and *N*-(3-methoxybenzyl)ethanamine (64 mg, 0.386 mmol) and gave the desired product as a colourless oil (100 mg, 0.232 mmol, 66%).

R_f 0.41 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.20–8.08 (m, 1H), 7.98–7.90 (m, 1H), 7.86–7.63 (m, 10H), 4.81 (s, 2H), 3.80 (s, 3H), 3.57 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 170.0, 166.9, 160.2, 157.7, 151.2, 139.9, 137.8, 135.3, 131.1, 130.2, 129.6, 129.4, 129.0, 128.0, 123.1, 122.4, 121.1, 121.0, 118.8, 114.4, 114.1, 55.5, 47.3, 39.9, 12.7; LRMS (+ESI) 456/454 [(M + Na)$^+$ 30/100%]; IR (ν_{max}/cm^{-1}) 2936, 1644, 1482, 1252, 1390, 746, 544, 420; Found: C, 69.55; H, 5.08; N, 9.77. Calcd for $C_{25}H_{22}ClN_3O_2$: C, 69.52; H, 5.13; N, 9.73%

***(R)*-_N_-*sec*-Butyl-4-(2-chlorophenyl)quinazoline-2-carboxamide (16)**

General procedure 2 was followed using **15** (100 mg, 0.351 mmol) and *(R)-sec*-butylamine (40 µL, 0.386 mmol) and gave the desired product as a colourless powder (86 mg, 0.253 mmol, 72%).

R_f 0.30 (ethyl acetate/hexane, 3:7 v/v); mp 134–136 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.36 (d, *J* = 4.6 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.62–7.22 (m, 6H), 4.19 (sext, *J* = 7.0 Hz, 1H), 1.56 (p, *J* = 6.9 Hz, 2H), 1.22 (d, *J* = 6.6 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 178.7, 165.4, 147.7, 144.8, 134.7, 131.5, 132.8, 130.0, 129.8, 129.7, 128.8, 127.7, 119.8, 117.9, 110.8, 50.9, 24.7, 14.2, 12.2; LRMS (+ESI) 365/363 [(M + Na)$^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 3363, 2964, 2932, 1665, 1560, 1544, 1476, 1393, 743, 539, 426; Found: C, 67.15; H, 5.36; N, 12.38. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37%; $[\alpha]^{26}_D$ = -8.7 (*c* = 0.1 in EtOH).

General Procedure 3: Amide Alkylation

Potassium *tert*-butoxide (2.00 equiv.) was added portion-wise to a solution of the appropriate secondary amide (1.00 equiv.) in tetrahydrofuran (0.3 M). The reaction mixture was stirred for 30 minutes at ambient temperature. The appropriate iodoalkane (1.50 equiv.) was added dropwise at 0 °C and the mixture was then warmed to ambient temperature and stirred for 17 hours. The reaction mixture was neutralised with aqueous hydrochloric acid (1 M, 10 mL). The organic layer was collected, and the aqueous layer was further extracted with ethyl acetate (3×10 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo*.

***(R)*-_N_-*sec*-Butyl-4-(2-chlorophenyl)-_N_-methylquinazoline-2-carboxamide (2f)**

General procedure 3 was followed using **16** (50 mg, 0.147 mmol) and methyl iodide (15 µL, 0.221 mmol). Purification by flash chromatography on a silica gel column using ethyl

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acetate/hexane (3:7 v/v) gave the desired product as a colourless powder (41 mg, 0.116 mmol, 79%).

R_f 0.40 (ethyl acetate/hexane, 3:7 v/v); mp 101–103 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.26 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.63–7.21 (m, 6H), 3.96 (sext, *J* = 7.0 Hz, 1H), 3.01 (s, 3H), 1.62 (p, *J* = 6.9 Hz, 2H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); LRMS (+ESI) 378/376 [$(M + Na)^+$ 35/100%]; Found: C, 67.90; H, 5.68; N, 11.88. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.89; H, 5.70; N, 11.88%; $[\alpha]^{26}_D$ = -23.6 (*c* = 0.56 in EtOH). The spectra for this compound is consistent with those previously reported.[5]

Indole Carboxamide Series

Methyl 1-(2-nitrophenyl)-1*H*-indole-3-carboxylate (19)

Sodium hydroxide (204 mg, 5.13 mmol, 1.00 equiv.) was added portionwise to a cooled (0 °C) solution of methyl 1*H*-indole-3-carboxylate (17, 900 mg, 5.13 mmol, 1.00 equiv.) and 1-fluoro-2-nitrobenzene (18, 600 µL, 5.64 mmol, 1.10 equiv.) in dimethyl sulfoxide (0.1 M). The resulting mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was quenched with an aqueous solution of saturated ammonium chloride (20 mL) and diluted with ethyl acetate (30 mL). The organic layer was collected, and the aqueous layer was further extracted with ethyl acetate (2×20 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the desired product as a yellow powder (1.29 g, 4.35 mmol, 85%).

R_f 0.38 (ethyl acetate/hexane, 3:7 v/v); mp 149–151 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.24 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.89 (s, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.41–7.19 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 165.0, 146.2, 137.5, 134.2, 134.1, 131.6, 130.1, 129.8, 126.4, 125.8, 124.0, 122.9, 122.1, 110.5, 109.9, 51.2; LRMS (+ESI) 319 [$(M + Na)^+$ 100%]; IR (ν_{max}/cm^{-1}) 3240, 3118, 2951, 1700, 1522, 1494, 1346, 1283, 1193, 849, 745, 425; Found: C, 64.87; H, 4.06; N, 9.42. Calc for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46%

Methyl 1-(2-aminophenyl)-1*H*-indole-3-carboxylate (20)

A mixture of **19** (1.20 g, 4.05 mmol, 1.00 equiv.) and palladium on carbon (120 mg, 10% w/w) in ethyl acetate (0.1 M) was stirred at ambient temperature for 5 hours under a hydrogen atmosphere (1 atm). The mixture was filtered through a pad of Celite® and the pad was then washed with ethyl acetate (40 mL). The organic filtrate was concentrated *in vacuo*. Purification was achieved by trituration with diethyl ether to afford the desired product as a colourless powder (930 mg, 3.48 mmol, 86%).

R_f 0.43 (ethyl acetate/hexane, 1:4 v/v); mp 156–158 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.16 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.28–7.12 (m, 3H), 7.11–6.96 (m, 2H), 6.83–6.70 (m, 2H), 3.82 (s, 3H), 3.38 (br s, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 165.4, 142.9, 136.9, 135.0, 131.2, 130.0, 128.4, 126.4, 123.4, 122.5, 121.7, 118.7, 116.5, 111.3, 109.0, 51.1; LRMS (+ESI) 289 [$(M + Na)^+$ 100%], 267 [$(M + H)^+$ 15%]; IR (ν_{max}/cm^{-1}) 3461, 3367, 3112, 2943, 1692, 1625, 1523, 1483, 1201, 1052, 747, 425; Found: C, 72.08; H, 5.20; N, 10.47. Calc for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52%

Methyl 1-(2-chlorophenyl)-1*H*-indole-3-carboxylate (21)

To a stirred suspension of copper(II) chloride (546 mg, 4.05 mmol, 1.20 equiv.) in anhydrous acetonitrile (0.1 M) was added *tert*-butyl nitrite (600 µL, 5.07 mmol, 1.50 equiv.). The dark green suspension was stirred at ambient temperature for 30 minutes. A solution of **20** (900 mg, 3.39 mmol, 1.00 equiv.) in anhydrous acetonitrile (25 mL) was added to the suspension dropwise over 10 minutes. The resulting dark red solution was stirred for 1.5 hours at ambient temperature and then poured into an aqueous hydrochloric acid solution (1 M, 30 mL). The aqueous solution was extracted with ethyl acetate (3×20 mL). The organic extracts were combined and sequentially washed with an aqueous solution of saturated sodium bicarbonate (20 mL), followed by brine (20 mL). The organic extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude red solid was purified by flash chromatography on silica gel using ethyl acetate/hexane (1:9 v/v) and gave the desired product as a colourless powder (642 mg, 2.25 mmol, 66%).

R_f 0.67 (ethyl acetate/hexane, 1:4 v/v); mp 90–92 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.30 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 1.9 Hz, 1H), 7.70–7.60 (m, 1H), 7.55–7.43 (m, 3H), 7.42–7.23 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 165.3, 137.4, 135.7, 135.0, 131.9, 130.9, 130.1, 129.3, 127.88, 126.2, 123.5, 122.5, 121.7, 111.0, 109.2, 51.2; LRMS (+ESI) 310/308 [$(M + Na)^+$ 35/100%], 288/286 [$(M + H)^+$ 3/10%]; IR (νmax/cm^{-1}) 3126, 2940, 1701, 1527, 1482, 1385, 1201, 1107, 1046, 741, 423; Found: C, 67.31; H, 4.33; N, 4.92. Calc for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90%

1-(2-Chlorophenyl)-1*H*-indole-3-carboxylic acid (22)

To a stirred solution of **21** (600 mg, 2.10 mmol, 1.00 equiv.) in a tetrahydrofuran/water mixture (20 mL, 1:1 v/v) was added lithium hydroxide (152 mg, 6.28 mmol, 3.00 equiv.). The reaction mixture was stirred at reflux for 6 hours. Following completion, the reaction mixture was acidified with aqueous hydrochloric acid (2 M) and extracted with ethyl acetate (3×20 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification was achieved by trituration with diethyl ether and gave the desired product as a colourless powder (536 mg, 1.97 mmol, 94%).

R_f 0.50 (methanol/dichloromethane, 1:9 v/v); mp 203–205 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.25 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 1.6 Hz, 1H), 7.61–7.50 (m, 1H), 7.39 (d, *J* = 2.0 Hz, 3H), 7.34–7.14 (m, 2H), 7.05 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 170.5, 137.6, 136.2, 135.5, 131.9, 131.0, 130.2, 129.3, 127.9, 126.4, 123.7, 122.8, 121.9, 111.1, 108.6; LRMS (+ESI) 296/294 [$(M + Na)^+$ 35/100%]; IR (νmax/cm^{-1}) 2891, 1661, 1536, 1481, 1452, 1433, 1213, 1031, 757, 626, 423; Found: C, 66.42; H, 3.64; N, 5.19. Calc for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.71; N, 5.16%

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_N_-Benzyl-1-(2-chlorophenyl)-_N_-methyl-1_H_-indole-3-carboxamide (3a)

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and *N*-methylbenzylamine (25 μL, 202 mmol) and gave the desired product as a colourless powder (56 mg, 0.149 mmol, 81%).

R_f 0.51 (ethyl acetate/hexane, 3:7 v/v); mp 75–77 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.89 (d, *J* = 7.5 Hz, 1H), 7.50–7.01 (m, 13H), 4.76 (s, 2H), 3.04 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 167.2, 137.4, 136.7, 135.9, 131.7, 130.9, 129.8, 129.7, 129.3, 128.8, 127.9, 127.5, 127.4, 126.9, 123.3, 121.8, 121.4, 112.2, 110.8, 55.3, 36.2; LRMS (+ESI) 399/397 [(M + Na)$^+$ 33/100%]; IR (ν_{max}/cm^{-1}) 3061, 1614, 1539, 1492, 1454, 1400, 1312, 1223, 1101, 1026, 745; Found: C, 73.71; H, 5.10; N, 7.46. Calc for $C_{23}H_{19}ClN_2O$: C, 73.69; H, 5.11; N, 7.47%

_N_-Benzyl-1-(2-chlorophenyl)-_N_-ethyl-1_H_-indole-3-carboxamide (3b)

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and *N*-ethylbenzylamine (30 μL, 0.202 mmol) and gave the desired product as a colourless powder (61 mg, 0.157 mmol, 85%).

R_f 0.56 (ethyl acetate/hexane, 3:7 v/v); mp 84–86 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.88 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.39–7.30 (m, 4H), 7.28–7.24 (m, 4H), 7.22–7.14 (m, 3H), 7.06–7.03 (m, 1H), 4.78 (s, 2H), 3.51 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 167.0, 137.8, 136.66, 135.9, 131.6, 130.9, 129.6, 129.3, 128.8, 128.8, 128.7, 127.8, 127.3, 127.0, 123.3, 121.7, 121.2, 112.5, 110.7, 57.7, 41.6, 13.3; LRMS (+ESI) 413/411 [(M + Na)$^+$ 35/100%], 391/389 [(M + H)$^+$ 10/25%]; IR (ν_{max}/cm^{-1}) 3373, 2978, 1679, 1598, 1528, 1421, 1356, 1257, 1203, 1112, 1049, 975, 801, 777, 748, 695, 626, 583, 469; HPLC τ_R = 25.91 min (99.5% purity).

1-(2-Chlorophenyl)-_N,N_-diethyl-1_H_-indole-3-carboxamide (3c)

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and diethylamine (20 μL, 0.202 mmol) and gave the desired product as a colourless powder (44 mg, 0.135 mmol, 73%).

R_f 0.51 (ethyl acetate/hexane, 3:7 v/v); mp 105–107 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.80 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.44–7.33 (m, 1H), 7.16 (d, *J* = 2.0 Hz, 3H), 7.09–7.03 (m, 3H), 3.53 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 166.3, 136.6, 136.1, 131.7, 130.9, 129.6, 129.4, 128.4, 127.8, 126.8, 123.2, 121.5, 121.0, 113.1, 110.7, 41.9, 13.9; LRMS (+ESI) 351/349 [(M + Na)$^+$ 35/100%], 329/327 [(M + H)$^+$ 7/20%]; IR (ν_{max}/cm^{-1}) 3373, 2974, 1705, 1680, 1542, 1479, 1451, 1378, 1310, 1269, 1107, 1040, 852, 779, 735, 617, 462, 426; Found: C, 69.76; H, 5.79; N, 8.53. Calc for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57%

1-(2-Chlorophenyl)-_N_-(3-methoxybenzyl)-_N_-methyl-1_H_-indole-3-carboxamide (3d)

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and 1-(3-methoxyphenyl)-*N*-methylmethanamine (31 mg, 202 mmol) and gave the desired product as a colourless sticky mass (62 mg, 0.153 mmol, 83%).

R_f 0.38 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 8.01 (d, *J* = 8.0 Hz, 1H), 7.63–7.58 (m, 1H), 7.52–7.41 (m, 4H), 7.33–7.25 (m, 3H), 7.16–7.14 (m, 1H), 6.96–6.84 (m, 3H), 5.03 (s, 2H), 3.82 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 167.2, 160.1, 139.1, 136.7, 135.9, 131.7, 131.0, 130.9, 129.8, 129.8, 129.7, 129.3, 127.9, 127.0, 123.4, 121.8, 121.4, 114.0, 112.9, 112.2, 110.8; 55.3, 55.2, 53.5; LRMS (+ESI) 429/427 [(M + Na)$^+$ 33/100%]; IR (ν_{max}/cm^{-1}) 2980, 1612, 1540, 1490, 1455, 1399, 1261, 1067, 747, 473; Found: C, 71.17; H, 5.19; N, 6.93. Calc for $C_{24}H_{21}ClN_2O_2$: C, 71.19; H, 5.23; N, 6.92%

1-(2-Chlorophenyl)-_N_-ethyl-_N_-(3-methoxybenzyl)-1_H_-indole-3-carboxamide (3e)

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and *N*-(3-methoxybenzyl)ethanamine (33 mg, 202 mmol) and gave the desired product as a colourless sticky mass (58 mg, 0.138 mmol, 75%).

R_f 0.48 (ethyl acetate/hexane, 3:7 v/v); ^{1}H NMR (300 MHz; $CDCl_3$) δ = 7.89 (d, *J* = 7.4 Hz, 1H), 7.53–7.44 (m, 1H), 7.34–7.29 (m, 4H), 7.21–7.13 (m, 3H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.85–6.72 (m, 3H), 4.74 (s, 2H), 3.70 (s, 3H), 3.50 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 167.0, 160.0, 139.5, 136.7, 135.9, 131.6, 131.0, 129.8, 129.6, 129.3, 128.9, 127.8, 127.1, 123.3, 121.7, 121.2, 119.6, 113.4, 112.9, 112.3, 110.7, 55.2, 45.3, 41.6, 13.3; LRMS (+ESI) 443/441 [(M + Na)$^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 2917, 1601, 1535, 1490, 1455, 1262, 1225, 1039, 841, 746, 557; Found: C, 71.68; H, 5.53; N, 6.68. Calc for $C_{25}H_{23}ClN_2O_2$: C, 71.68; H, 5.53; N, 6.69%

***(R)*-_N_-(*sec*-Butyl)-1-(2-chlorophenyl)-1_H_-indole-3-carboxamide (23)**

General procedure 2 was followed using **22** (50 mg, 0.184 mmol) and *(R)-sec*-butylamine (20 μL, 202 mmol) and gave the desired product as a colourless powder (50 mg, 0.153 mmol, 83%).

R_f 0.51 (ethyl acetate/hexane, 3:7 v/v); mp 175–177 °C; ^{1}H NMR (400 MHz; DMSO-d_6) δ = 8.31–8.23 (m, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.74–7.52 (m, 4H), 7.29–7.13 (m, 2H), 7.09–6.96 (m, 1H), 3.97 (sext, *J* = 7.0 Hz, 1H), 1.51 (p, *J* = 6.9 Hz, 2H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz; DMSO-d_6) δ = 163.7, 137.1, 135.8, 131.3, 131.1, 131.1, 130.4, 129.1, 127.0, 123.4, 122.1, 121.8, 112.8, 111.0, 100.0, 46.1, 29.6, 21.0, 11.2; LRMS (+ESI) 351/349 [(M + Na)$^+$ 33/100%]; IR (νmax/cm^{-1}) 3278, 2960, 1619, 1542, 1488, 1452, 1290, 1229, 1050, 777, 430; HRMS (+ESI) Calcd for $C_{19}H_{19}ClN_2O$ ([M + Na]+ 351.1096/349.1098. Found: 351.1095/349.1100; $[\alpha]^{26}_D$ = -5.6 (*c* = 0.64 in EtOH).

***(R)*-_N_-(*sec*-Butyl)-1-(2-chlorophenyl)-_N_-methyl-1_H_-indole-3-carboxamide (3f)**

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General procedure 3 was followed using **23** (40 mg, 0.122 mmol) and methyl iodide (12 µL, 0.183 mmol). Purification by flash chromatography on a silica gel column using ethyl acetate/hexane (3:7 v/v) gave the desired product as a colourless powder (33 mg, 0.097 mmol, 81%).

R_f 0.43 (ethyl acetate/hexane, 3:7 v/v); mp 126–128 °C; ^{1}H NMR (400 MHz; $CDCl_3$) δ = 7.89–7.85 (m, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.54–7.42 (m, 4H), 7.31–7.10 (m, 2H), 7.18–7.10 (m, 1H), 4.47 (sext, *J* = 7.0 Hz, 1H), 3.02 (s, 3H), 1.62 (p, *J* = 6.9 Hz, 2H), 1.26 (d, *J* = 6.7 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz; $CDCl_3$) δ = 163.6, 136.6, 136.1, 131.7, 130.9, 129.6, 129.4, 127.8, 126.7, 123.1, 122.9, 121.4, 121.0, 113.6, 110.7, 60.4, 33.1; 24.7; 14.2, 11.1; LRMS (+ESI) 365/363 [(M + Na)$^+$ 30/100%]; IR (ν_{max}/cm^{-1}) 2965, 1613, 1540, 1491, 1455, 1401, 1309, 1227, 1069, 745; HPLC τ_R = 28.52 min (98.8% purity); $[\alpha]^{26}_D$ = -19.2 (*c* = 0.52 in EtOH).

Azaindole Carboxamide Ligands

2,2,2-Trichloro-1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-one (25)

To a cooled (0 °C) solution of 7-azaindole (24, 1.00 g, 8.46 mmol, 1.00 equiv.) in anhydrous dichloromethane (0.1 M), was added aluminium chloride (2.82 g, 21.2 mmol, 2.50 equiv.) portionwise, followed by the dropwise addition of trichloroacetyl chloride (1.05 mL, 9.31 mmol, 1.10 equiv.). The reaction mixture was warmed to ambient temperature and stirred for 3 hours. Following completion, the mixture was quenched at 0 °C with ice-cold water (20 mL). The resulting precipitate was filtered off and washed with diethyl ether (20 mL) to give the desired product as a colourless powder (2.05 g, 7.78 mmol, 92%).

R_f 0.34 (methanol/dichloromethane, 5:95 v/v); mp 252–253 °C; ^{1}H NMR (400 MHz; DMSO-d_6) δ = 13.15 (s, 1H), 8.69 (s, 1H), 8.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H); LRMS (-ESI) 263/261 [(M - H)$^-$ 100%]. The spectra for this compound is consistent with those previously reported.[7]

Methyl *1H*-pyrrolo[2,3-b]pyridine-3-carboxylate (26)

To a suspension of **25** (2.00 g, 7.59 mmol, 1.00 equiv.) in methanol (0.1 M), was added sodium hydrogen carbonate (1.28 g, 15.18 mmol, 2.00 equiv.). The reaction mixture was stirred at reflux for 4 hours. Following completion, the reaction mixture was cooled to ambient temperature and evaporated under reduced pressure. The crude residue was then dissolved in ethyl acetate (20 mL) and extracted in aqueous hydrochloric acid (1 M, 15 mL). The aqueous layer was further extracted (3×10 mL) and the organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give the desired product as a colourless powder (1.19 g, 6.75 mmol, 89%).

R_f 0.54 (methanol/dichloromethane, 5:95 v/v); mp 210–212 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 11.78 (s, 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.97 (s, 1H), 7.14–7.09 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 159.7, 143.6, 138.2, 126.4, 125.3, 113.8, 112.7, 102.0, 51.3; LRMS (+ESI) 199 [(M + Na)$^+$ 100%]; IR (ν_{max}/cm^{-1}) 3103, 2731, 1686, 1586, 1308, 1160, 1047, 757, 595; Found: C, 61.31; H, 4.52; N, 15.85. Calc for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90%

Methyl 1-(2-nitrophenyl)-*1H*-pyrrolo[2,3-b]pyridine-3-carboxylate (27)

Sodium hydride (60% w/w dispersion in mineral oil, 454 mg, 11.4 mmol, 2.00 equiv.) was added portion-wise to a cooled (0 °C) solution of **26** (1.00 g, 5.68 mmol, 1.00 equiv.) in *N,N*-dimethylformamide (0.1 M). The reaction mixture was stirred for 30 minutes at ambient temperature before being cooled back down to 0 °C. 1-Fluoro-2-nitrobenzene (18, 660 µL, 6.24 mmol, 1.10 equiv.) was added at 0 °C and the mixture was warmed to ambient temperature and stirred for 8 hours. Following completion, the reaction mixture was poured into ice-cold water (40 mL) and the precipitate collected. The filtered product was washed with hexane (10 mL) to give the desired product as a colourless powder (1.56 g, 5.25 mmol, 92%).

R_f 0.25 (ethyl acetate/hexane, 3:7 v/v); mp 248–250 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ = 8.65 (s, 1H), 8.48–8.38 (m, 1H), 8.31–8.21 (m, 2H), 7.97 (t, *J* = 7.7 Hz, 1H), 7.91–7.75 (m, 2H), 7.37 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz; DMSO-d_6) δ = 163.7, 147.4, 145.1, 144.5, 134.9, 134.8, 130.1, 129.9, 129.8, 129.5, 125.5, 119.0, 118.3, 107.3, 51.3; LRMS (+ESI) 320 [(M + Na)$^+$ 100%], 298 [(M + H)$^+$ 50%]; IR (ν_{max}/cm^{-1}) 3118, 3062, 2949, 1704, 1593, 1527, 1423, 1355, 1264, 1221, 1195, 1048, 853, 801, 777, 754, 667, 600, 419; Found: C, 60.55; H, 3.73; N, 14.05. Calc for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.73; N, 14.14%

Methyl 1-(2-aminophenyl)-*1H*-pyrrolo[2,3-b]pyridine-3-carboxylate (28)

A mixture of **27** (1.50 g, 5.05 mmol, 1.00 equiv.) and palladium on carbon (150 mg, 10% w/w) in ethyl acetate (0.1 M) was stirred at ambient temperature for 8 hours under a hydrogen atmosphere (1 atm). The mixture was filtered through a pad of Celite® and the pad was washed with ethyl acetate (50 mL). The organic filtrate was concentrated *in vacuo* to afford a crude off-white solid. Purification was achieved by trituration with diethyl ether to afford the desired product as a colourless powder (1.24 g, 4.64 mmol, 92%).

R_f 0.34 (ethyl acetate/hexane, 3:7 v/v); mp 177–179 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ = 8.42 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.30 (d, *J* = 4.7 Hz, 1H), 8.25–8.06 (m, 1H), 7.30 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.24–7.06 (m, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 4.81 (br s, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz; DMSO-d_6) δ = 163.8, 147.9, 144.4, 144.1, 135.7, 129.3, 129.3, 128.3, 123.7, 122.0, 118.5, 118.1, 116.3, 106.2, 50.9; LRMS (+ESI) 290 [(M + Na)$^+$ 100%], 268 [(M + H)$^+$ 60%]; IR (νmax/cm^{-1}) 3470, 3373, 3116, 2948, 1678, 1525, 1437, 1421, 1356, 1256, 1205, 1152, 1050, 801, 780, 757, 626, 587; Found: C, 67.38; H, 4.91; N, 15.74. Calc for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72%

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Methyl 1-(2-chlorophenyl)-*1H*-pyrrolo[2,3-b]pyridine-3-carboxylate (29)

To a stirred suspension of copper(II) chloride (724 mg, 5.39 mmol, 1.20 equiv.) in anhydrous acetonitrile (15 mL) was added *tert*-butyl nitrite (800 µL, 6.73 mmol, 1.50 equiv.). The dark green suspension was stirred at ambient temperature for 30 minutes. A solution of **28** (1.20 g, 4.49 mmol, 1.00 equiv.) in anhydrous acetonitrile (20 mL) was added to the suspension dropwise over 10 minutes. The resulting dark red solution was stirred for 2 hours at ambient temperature and then poured into aqueous hydrochloric acid (1 M, 20 mL). The aqueous solution was extracted with ethyl acetate (3×20 mL). The organic extracts were combined and sequentially washed with an aqueous solution of saturated sodium bicarbonate (20 mL), followed by brine (20 mL). The organic extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude red solid was purified by flash chromatography on silica gel using ethyl acetate/hexane (1:9 v/v) and gave the desired product as a colourless powder (720 mg, 2.51 mmol, 56%).

R_f 0.56 (ethyl acetate/hexane, 3:7 v/v); mp 175–177 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.50–8.38 (m, 1H), 8.35–8.26 (m, 1H), 7.99 (s, 1H), 7.54 (dd, *J* = 5.9, 3.7 Hz, 1H), 7.46 (dd, *J* = 6.1, 3.6 Hz, 1H), 7.38 (dt, *J* = 6.1, 3.9 Hz, 2H), 7.20 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 164.7, 148.4, 144.9, 135.0, 134.6, 131.8, 130.8, 130.3, 130.2, 129.8, 127.8, 118.8, 118.6, 107.4, 51.3; LRMS (+ESI) 311/309 [$(M + Na)^+$ 20/50%], 289/287 [$(M + H)^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 3059, 1705, 1537, 1264, 1199, 1071, 1040, 763, 752; Found: C, 62.81; H, 3.83; N, 9.72. Calc for $C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87; N, 9.77%

1-(2-Chlorophenyl)-*1H*-pyrrolo[2,3-b]pyridine-3-carboxylic acid (30)

To a stirred suspension of 29 (700 mg, 2.44 mmol, 1.00 equiv.) in a tetrahydrofuran/water mixture (20 mL, 1:1 v/v) was added lithium hydroxide (175 mg, 7.32 mmol, 3.00 equiv.). The reaction mixture was stirred at reflux for 6 hours. Following completion, the reaction mixture was acidified with aqueous hydrochloric acid (2 M), then extracted with ethyl acetate (3×20 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification was achieved by trituration with diethyl ether and gave the desired product as a colourless powder (590 mg, 2.16 mmol, 89%).

R_f 0.30 (methanol/dichloromethane, 5:95 v/v); mp 278–280 °C; ^{1}H NMR (300 MHz; DMSO-d_6) δ = 8.44 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.38–8.24 (m, 2H), 7.80–7.72 (m, 1H), 7.72–7.64 (m, 1H), 7.63–7.54 (m, 2H), 7.35 (dd, *J* = 7.9, 1.7 Hz, 1H); ^{13}C NMR (75 MHz; DMSO-d_6) δ = 173.0, 148.2, 144.3, 135.5, 134.3, 131.1, 130.6, 130.5, 130.1, 129.5, 128.1, 118.4, 118.4, 107.6; LRMS (-ESI) 273/271 [$(M - H)^-$ 35/100%]; IR (ν_{max}/cm^{-1}) 3345, 2969, 1702, 1467, 1159, 1127, 1069, 1043, 950, 816, 597; Found: C, 61.66; H, 3.33; N, 10.31. Calc for $C_{14}H_9ClN_2O_2$: C, 61.67; H, 3.33; N, 10.27%

***N*-Benzyl-1-(2-chlorophenyl)-*N*-methyl-*1H*-pyrrolo[2,3-b]pyridine-3-carboxamide (4a)**

General procedure 2 was followed using **30** (50 mg, 0.183 mmol) and *N*-benzylmethylamine (30 µL, 0.202 mmol) and gave the desired product as a colourless powder (44 mg, 0.117 mmol, 64%).

R_f 0.22 (ethyl acetate/hexane, 3:7 v/v); mp 101–103 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.40 (d, *J* = 5.1 Hz, 2H), 7.62–7.26 (m, 11H), 4.88 (s, 2H), 3.20 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 166.3, 147.8, 144.9, 137.1, 134.7, 130.7, 130.3, 129.84, 129.8, 128.9, 128.6, 128.0, 127.9, 127.8, 127.5, 119.9, 118.1, 110.0, 50.6, 30.3; LRMS (+ESI) 400/398 [$(M + Na)^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 3109, 2919, 1604, 1530, 1480, 1405, 1191, 1069, 737, 699, 573; Found: C, 70.34; H, 4.83; N, 11.19. Calc for $C_{22}H_{18}ClN_3O$: C, 70.30; H, 4.83; N, 11.18%

***N*-Benzyl-1-(2-chlorophenyl)-*N*-ethyl-*1H*-pyrrolo[2,3-b]pyridine-3-carboxamide (4b)**

General procedure 2 was followed using **30** (50 mg, 0.183 mmol) and *N*-ethylbenzylamine (30 µL, 0.202 mmol) and gave the desired product as a colourless powder (39 mg, 0.100 mmol, 55%).

R_f 0.84 (methanol/dichloromethane, 1:9 v/v); mp 84–86 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.38 (d, *J* = 5.2 Hz, 2H), 7.71–7.08 (m, 11H), 4.87 (s, 2H), 3.61 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 162.3, 147.6, 144.7, 137.5, 134.1, 130.7, 129.8, 129.8, 128.8, 128.4, 128.3, 127.8, 127.5, 127.1, 126.9, 120.1, 118.0, 110.0, 51.9, 42.6, 12.3; LRMS (+ESI) 414/412 [$(M + Na)^+$ 35/100%], 392/390 [$(M+ H)^+$ 3/10%]; IR (ν_{max}/cm^{-1}) 3110, 2914, 1636, 1526, 1481, 1406, 1190, 1069, 739, 699, 572; Found: C, 70.34; H, 4.83; N, 11.19; Found: C, 70.84; H, 5.16; N, 10.77. Calc for $C_{23}H_{20}ClN_3O$: C, 70.86; H, 5.17; N, 10.78%

1-(2-Chlorophenyl)-*N,N*-diethyl-*1H*-pyrrolo[2,3-b]pyridine-3-carboxamide (4c)

General procedure 2 was followed using **30** (50 mg, 0.183 mmol) and diethylamine (20 µL, 0.202 mmol) and gave the desired product as a colourless powder (39 mg, 0.119 mmol, 65%).

R_f 0.77 (methanol/dichloromethane, 1:9 v/v); mp 105–107 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.46–8.15 (m, 2H), 7.62–7.57 (m, 2H), 7.51–7.31 (m, 2H), 7.24–7.20 (m, 2H), 3.63 (q, *J* = 7.1 Hz, 4H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 165.3, 147.8, 144.8, 134.8, 131.5, 130.7, 130.0, 129.9, 129.7, 128.7, 127.8, 119.8, 117.8, 110.9, 41.6, 13.9; LRMS (+ESI) 352/350 [$(M + Na)^+$ 35/100%], 330/328 [$(M + H)^+$ 20/60%]; IR (ν_{max}/cm^{-1}) 3117, 2982, 1687, 1530, 1418, 1347, 1274, 1148, 1053, 743; Found: C, 65.94; H, 5.53; N, 12.85. Calc for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82%

1-(2-Chlorophenyl)-*N*-(3-methoxybenzyl)-*N*-methyl-*1H*-pyrrolo[2,3-b]pyridine-3-carboxamide (4d)

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General procedure 1.2 was followed using **30** (50 mg, 0.183 mmol) and 1-(3-methoxyphenyl)-*N*-methylmethanamine (31 mg, 0.202 mmol) and gave the desired product as a colourless powder (45 mg, 0.111 mmol, 61%).

R_f 0.18 (ethyl acetate/hexane, 3:7 v/v); mp 117–119 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.41–8.38 (m, 2H), 7.66–7.54 (m, 3H), 7.51–7.39 (m, 2H), 7.37–7.21 (m, 2H), 6.98–6.80 (m, 3H), 4.85 (s, 2H), 3.82 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 165.8, 160.1, 147.8, 144.9, 138.8, 134.7, 131.5, 130.8, 130.3, 129.9, 129.9, 129.8, 129.7, 129.6, 127.8, 124.2, 119.9, 118.1, 112.9, 110.0, 55.3, 48.9, 31.6; LRMS (+ESI) 430/428 [$(M + Na)^+$ 33/100%]; IR (ν_{max}/cm^{-1}) 3112, 2911, 1606, 1528, 1483, 1400, 1249, 1101, 1025, 806, 743, 694, 574; Found: C, 68.04; H, 4.98; N, 10.35. Calc for $C_{23}H_{20}ClN_3O_2$: C, 68.06; H, 4.97; N, 10.35%

1-(2-Chlorophenyl)-*N*-ethyl-*N*-(3-methoxybenzyl)-*1H*-pyrrolo[2,3-b]pyridine-3-carboxamide (4e)

General procedure 2 was followed using **30** (50 mg, 0.183 mmol) and *N*-(3-methoxybenzyl)ethanamine (33 mg, 0.202 mmol) and gave the desired product as a colourless powder (46 mg, 0.110 mmol, 59%).

R_f 0.22 (ethyl acetate/hexane, 3:7 v/v); mp 131–133 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.40–8.38 (m, 2H), 7.60–7.56 (m, 3H), 7.49–7.41 (m, 2H), 7.33–7.25 (m, 2H), 6.94–6.81 (m, 3H), 4.92 (s, 2H), 3.80 (s, 3H), 3.36 (q, *J* = 7.1 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 166.3, 159.8, 149.0, 144.9, 139.7, 134.3, 131.7, 130.7, 130.2, 129.9, 129.8, 129.7, 129.7, 129.5, 127.7, 124.2, 120.0, 118.2, 113.2, 110.1, 55.6, 48.2, 44.1, 14.1; LRMS (+ESI) 444/442 [$(M + Na)^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 3098, 2852, 1605, 1526, 1449, 1399, 1250, 1102, 1025, 808, 744, 694, 576; Found: C, 68.64; H, 5.26; N, 10.01. Calc for $C_{24}H_{22}ClN_3O_2$: C, 68.65; H, 5.28; N, 10.01%

***(R)*-*N*-(*sec*-Butyl)-1-(2-chlorophenyl)-N-methyl-1*H*-pyrrolo[2,3-b]pyridine-3- carboxamide (31)**

General procedure 2 was followed using **30** (50 mg, 0.183 mmol) and *(R)-sec*-butylamine (20 µL, 0.202 mmol) and gave the desired product as a colourless powder (52 mg, 0.159 mmol, 87%).

R_f 0.10 (ethyl acetate/hexane, 3:7 v/v); mp 145–147 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.37 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.28 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.63–7.54 (m, 3H), 7.44–7.21 (m, 4H), 3.96 (sext, *J* = 7.0 Hz, 1H), 1.49 (p, *J* = 6.9 Hz, 2H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 166.3, 147.7, 144.7, 134.9, 131.5, 130.9, 129.98, 129.96, 129.6, 128.2, 127.8, 120.1, 118.1, 111.2, 46.1, 29.6, 21.0, 11.2; LRMS (+ESI) 352/350 [$(M + Na)^+$ 35/100%]; IR (ν_{max}/cm^{-1}) 3379, 2964, 1616, 1557, 1448, 1406, 1284, 1155, 1071, 1053, 827, 555; Found: C, 65.94; H, 5.55; N, 10.79. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 10.81; $[\alpha]^{26}_D$ = -11.6 (*c* = 0.92 in EtOH).

***(R)*-*N*-(*sec*-Butyl)-1-(2-chlorophenyl)-*N*-methyl-*1H*-pyrrolo[2,3-b]pyridine-3- carboxamide (4f)**

General procedure 3 was followed using **31** (40 mg, 0.122 mmol) and methyl iodide (10 µL, 0.183 mmol). Purification by flash chromatography on a silica gel column using ethyl acetate/hexane (3:7 v/v) gave the desired product as a colourless powder (36 mg, 0.105 mmol, 86%).

R_f 0.16 (ethyl acetate/hexane, 3:7 v/v); mp 120–122 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ = 8.27 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.63–7.51 (m, 3H), 7.49–7.17 (m, 3H), 4.01 (sext, *J* = 7.0 Hz, 1H), 3.02 (s, 3H), 1.58 (p, *J* = 6.9 Hz, 2H), 1.11 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ = 166.2, 147.6, 144.7, 134.0, 131.5, 130.8, 129.94, 129.89, 129.6, 128.2, 127.8, 120.1, 118.1, 110.6, 60.0, 33.2, 24.6, 14.2, 11.2; LRMS (+ESI) 366/364 [$(M + Na)^+$ 33/100%]; IR (ν_{max}/cm^{-1}) 2966, 2929, 1612, 1527, 1423, 1346, 1281, 852, 782, 698; Found: C, 66.74; H, 5.90; N, 12.27. Calcd for $C_{19}H_{20}ClN_3O$: C, 66.76; H, 5.90; N, 12.29; $[\alpha]^{26}_D$ = -26.8 (*c* = 0.84 in EtOH).

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Supplementary Results

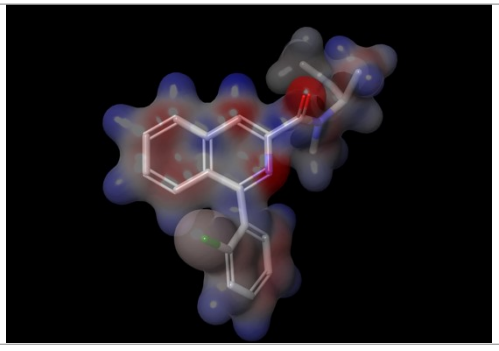
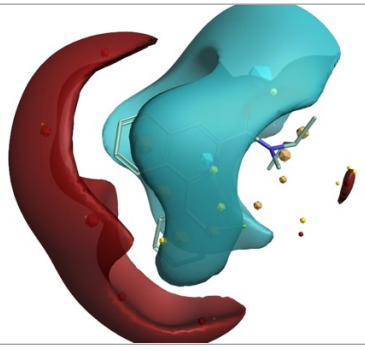
Table S1. Induced-fit docking and MM-GBSA ΔG binding scores and key interacting residues for compounds docked into WT and A147T homology models.

Ligand	Protein	Docking Score[a] (kcal/mol)	MM-GBSA ΔG Bind[b] (kcal/mol)	Interacting Residues[c]
PK 11195	WT	-11.595	-91.95	Arg24, His43, Trp95
	A147T	-10.780	-85.16	Trp53, Trp95
1a	WT	-9.944	-95.31	His43, Trp53, Trp95
	A147T	-13.387	-61.64	Tyr34, Trp53, Tyr57, Trp95, Phe100, Trp143
2a	WT	-10.782	-97.5	Trp53, Phe100, Trp143
	A147T	-11.078	-93.64	Arg24, His43, Trp53, Asn92, Trp95, Phe99
2f	WT	-10.280	-90.68	Arg24
	A147T	-10.070	-69.93	Trp53
3a	WT	-10.013	-76.64	Tyr34, Trp43, Trp95, Trp143
	A147T	-8.721	-78.89	Arg24, Trp53, Tyr57, Phe100, Trp143
3f	WT	-9.529	-70.34	Arg24, Tyr34, Trp53
	A147T	-11.952	-70.57	Trp53, Tyr57, Trp95
4a	WT	-11.959	-84.38	Trp95, Phe99, Phe100, Asn151
	A147T	-12.570	-66.92	Arg24, His43, Trp53, Trp95, Phe100
4f	WT	-10.108	-54.14	Arg24, Trp95
	A147T	-13.343	-55.74	Arg24, Tyr34, Trp53, Trp143, Thr147

[a]Docking scores obtained from Induced Fit Docking Studies are an estimate of protein-ligand binding energies. More negative scores indicate more favourable binding interactions.

[b]MM-GBSA binding energies are approximate free energies of binding. More negative scores indicate more favourable binding interactions.

[c]Key interactions residues are taken from the 2D ligand interaction function of Maestro v12.8.

Ligand	Schrodinger	Cresset
PK 11195		

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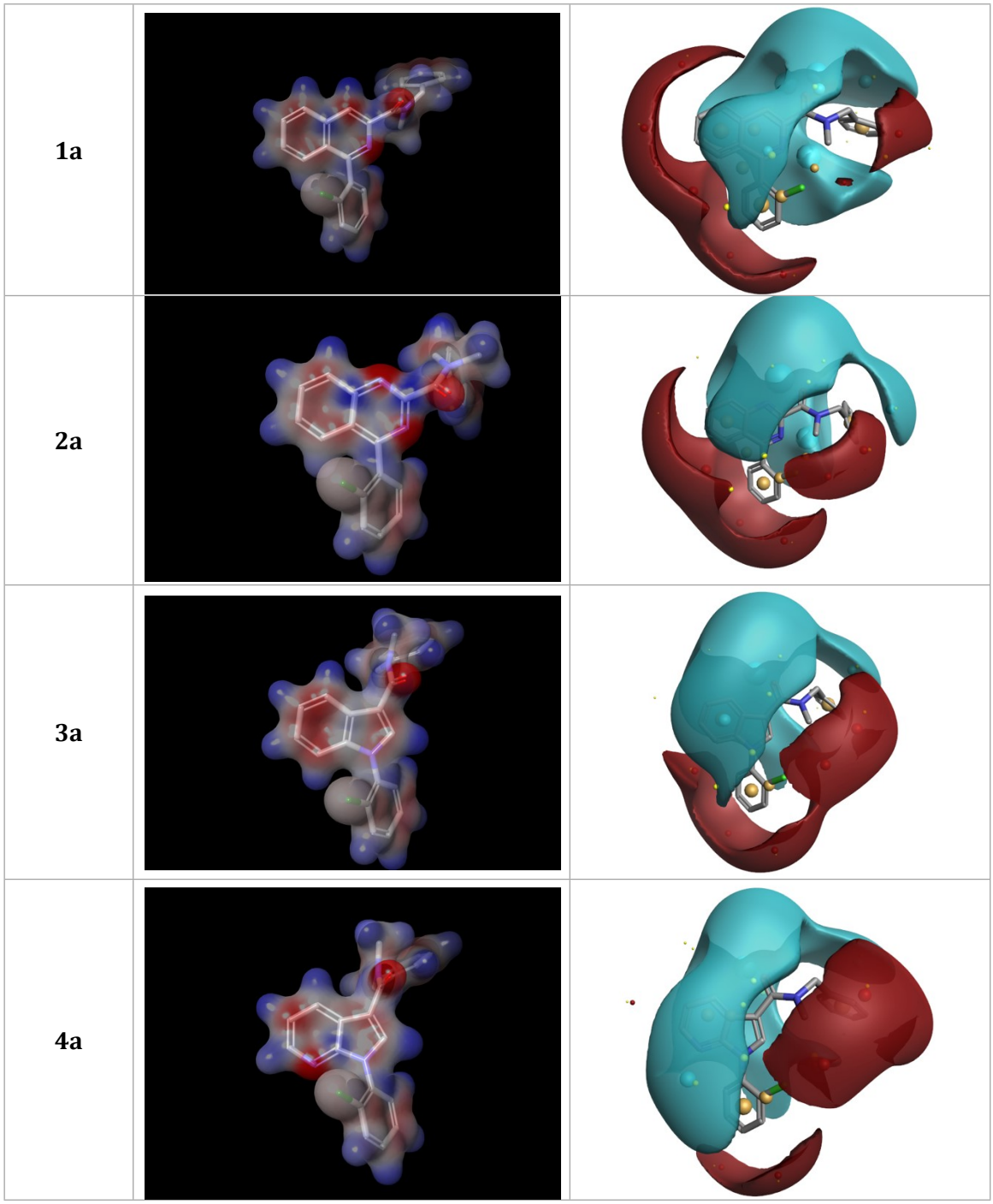


Figure S1. Electrostatic potential surfaces were generated for PK 11195, **1a**, **2a**, **3a** and **4a** in Maestro v12.8 (Schrödinger, LLC, New York, USA) and Spark™ v10.5.6 (Cresset®, Litlington, Cambridgeshire, UK). Blue represents areas of positive character and red represents areas of negative character.

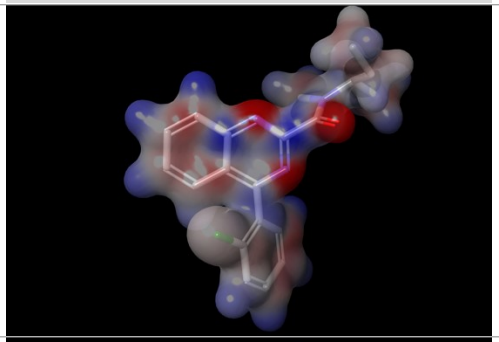
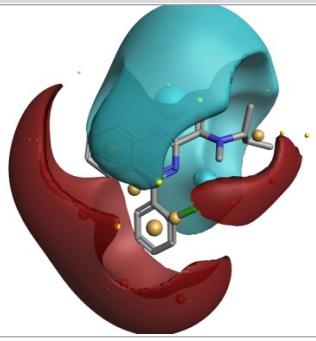
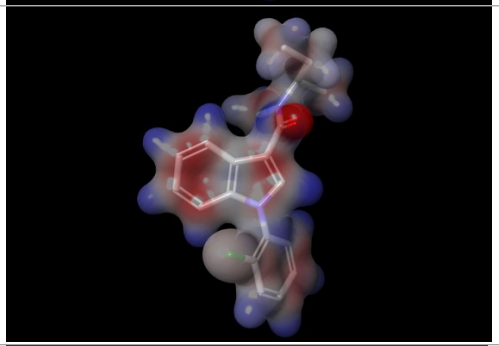
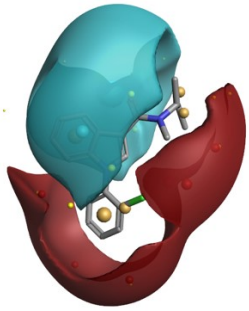
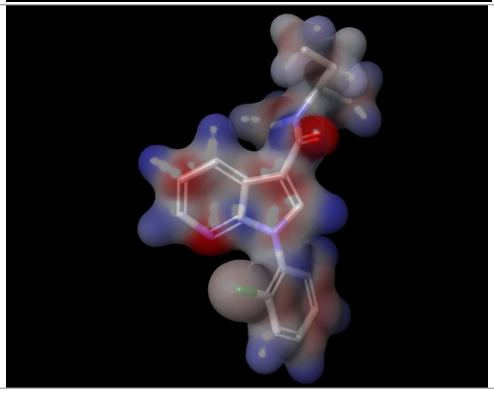
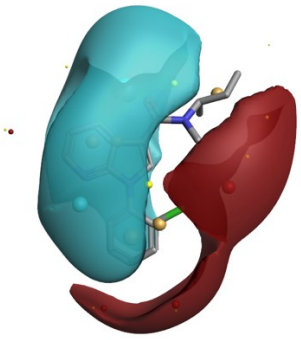
Ligand	Schrodinger	Cresset
PK 11195		
2f		
3f		
4f		

Figure S2. Electrostatic potential surfaces were generated for PK 11195, **2f**, **3f** and **4f** in Maestro v12.8 (Schrödinger, LLC, New York, USA) and Spark™ v10.5.6 (Cresset®, Litlington, Cambridgeshire, UK). Blue represents areas of positive character and red represents areas of negative character.

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