

## Elaboration of orthogonal tetra-substituted aromatic scaffolds towards novel EGFR-kinase inhibitors.

Adam J. Close<sup>a</sup>, Rhiannon N. Jones<sup>a</sup>, Cory A. Ocasio, Paul Kemmitt<sup>b</sup>, S. Mark Roe<sup>c</sup>, John Spencer<sup>a,\*</sup>

<sup>a</sup>*Dept of Chemistry, School of Life Sciences, University of Sussex, Falmer, BN1 9QJ, UK.*

<sup>b</sup>*AstraZeneca, Mereside Alderley Park, Macclesfield, SK10 4TG, UK.*

<sup>c</sup>*Dept of Biochemistry, School of Life Sciences, University of Sussex, Falmer, BN1 9QJ, UK.*

<b>General experimental.....</b>	<b>1</b>
<b>Experimental .....</b>	<b>1</b>
Nitration .....	1
General procedure for reductive aminations.....	6
Method for docking of 8a-c.....	13
References .....	13

### General experimental.

Solvents and reagents were purchased from commercial suppliers and used without further purification. Microwave reactions were heated using a CEM Discovery microwave fitted with an Explorer unit; ensure a ventilated fume hood with the sash lowered is used as these reactions are under high pressure and temperature. All thermally heated reactions were heated in a fume hood. Dry degassed solvents were only used where stated. NMR spectra were recorded on a Varian 500 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm and are referenced to the residual solvent peak or to TMS used as an internal standard; note that in some cases the C-B bond is not detectable in the <sup>13</sup>C NMR.<sup>1</sup> LCMS were run with a 5 µm C18 110 Å column. Percentage purities were performed using a 30 minutes method in water/acetonitrile with 0.1% formic acid (5 min at 5%, 5%-95% over 20 min, 5 min at 95%) with the UV set to 254 nm. High resolution mass spectrometry (HRMS) was done either internally or by the National Mass Spectrometry Facility, University of Swansea on a LTQ Orbitrap XL.

### Experimental

#### Nitration

##### General procedure for nitration of benzaldehyde derivatives.

A benzaldehyde derivative (12 mmol) was dissolved in sulphuric acid (98%, 25 mL) then cooled to 0 °C. Nitric acid (70%, 3 mL, 47 mmol) in sulphuric acid (98%, 30 mL) then was added drop-wise over 20 minutes maintaining the internal temperature at 0 °C. The mixture was allowed to warm to RT and left overnight. The mixture was poured onto ice (300 g). This was allowed to warm to RT and then extracted with diethyl ether (3 x 100 mL). The combined organic layers were

washed with brine. The pH of the brine washings was monitored until they were no longer acidic and reached pH 7. The organic layer was then dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure.

#### 4-Bromo-2-fluoro-5-nitrobenzaldehyde, 2a. <sup>2</sup>

The general nitration procedure was used on a 25 mmol scale and the crude material was recrystallised from diethyl ether/hexane to give the title compound as a yellow crystalline solid.

**Yield:** 5.13 g (84 %) Analytical data are presented below.

Nitronium tetrafluoroborate (2.62 g, 20 mmol) was stirred at -20 °C under anhydrous conditions dry DCM (15 mL). A solution of 4-bromo-2-fluoro-benzaldehyde (2.50 g, 12.3 mmol) in dry DCM (15 mL) was added drop wise over 20 minutes whilst maintaining the internal temperature at -20 °C. The mixture was allowed to warm to room temperature and left to stir over night. Water (30 mL) was added slowly to the reaction. Ethyl acetate (3 x 30 mL) was used to extract from the aqueous layer, then the combined organic layers were then washed with brine (3 x 30 mL). The organic layer was then dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure. It was then purified via flash chromatography (diethyl ether: hexane 2:8) to give the title compound as a yellow crystalline solid.

**Yield:** 2.58 g (88%).

**Mpt:** 36-39 °C. TLC (hexane:diethyl ether 8:2)  $R_f$  = 0.37. FTMS (m/z) found 247.9357, calcd for  $[\text{C}_7\text{H}_3\text{BrFNO}_3\text{H}]^+$  247.9353.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.30 (s, 1H), 8.39 (d,  $^4J_{\text{FH}}$  = 6.5 Hz, 1H), 7.66 (d,  $^3J_{\text{FH}}$  = 8.8 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  184.0 (d,  $^3J_{\text{FH}}$  = 5.3 Hz), 164.2 (d,  $^1J_{\text{FC}}$  = 269.6 Hz), 146.9 (s), 126.2 (d,  $^3J_{\text{FC}}$  = 4.1 Hz), 124.1 (d,  $^2J_{\text{FC}}$  = 25.2 Hz), 123.7 (d,  $^4J_{\text{FC}}$  = 10.6 Hz), 122.7 (d,  $^2J_{\text{FC}}$  = 10.9 Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -113.1 (dd,  $J$  = 8.8, 6.5 Hz). Elemental analysis CHN (%) found C: 34.00, H: 1.18, N: 5.73, calcd for  $\text{C}_7\text{H}_3\text{BrFNO}_3$  C: 33.90, H: 1.22, N: 5.65.

#### 5-Bromo-4-fluoro-2-nitrobenzaldehyde, 2b. <sup>3</sup>

The general nitration procedure was used on a 30 mmol scale and the crude material was recrystallised from diethyl ether/hexane to give the title compound as an orange crystalline solid.

**Yield:** 4.52 g (61%).

**Mpt:** 52-55 °C. FTMS (m/z) found 247.9354, calcd for  $[\text{C}_7\text{H}_3\text{BrFNO}_3\text{H}]^+$  247.9353.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.38 (s, 1H), 8.22 (d,  $^3J_{\text{FH}}$  = 6.7 Hz, 1H), 7.90 (d,  $^4J_{\text{FH}}$  = 7.5 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  185.6, 161.4 (d,  $^1J_{\text{FC}}$  = 260.2 Hz), 149.4, 135.4, 128.3 (d,  $^4J_{\text{FC}}$  = 4.1 Hz), 117.1 (d,  $^2J_{\text{FC}}$  = 21.6 Hz), 113.4 (d,  $^2J_{\text{FC}}$  = 27.9 Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -94.1 (pt,  $J$  = 7.1 Hz). Elemental analysis CHN (%) found C: 34.01, H: 1.23, N: 5.73, calcd for  $\text{C}_7\text{H}_3\text{BrFNO}_3$  C: 33.90, H: 1.22, N: 5.65.

#### 3-Bromo-6-fluoro-2-nitrobenzaldehyde, 2c.

The general nitration procedure was used on a 30 mmol scale and the crude material was twice recrystallised from diethyl ether/hexane to give the title compound as a light yellow crystalline solid.

**Yield:** 2.18 g (30%).

**Mpt:** 71-75 °C. FTMS (m/z) found 247.9357, calcd for  $[\text{C}_7\text{H}_3\text{BrFNO}_3\text{H}]^+$  247.9353.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.20 (s, 1H), 7.92 (dd,  $^3J_{\text{HH}}$  = 8.8,  $^4J_{\text{HF}}$  = 4.9 Hz, 1H), 7.32 (pt,  $^3J_{\text{HH}}$ ,  $^3J_{\text{FH}}$   $J$  = 9.1 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  182.0 (d,  $^3J_{\text{FC}}$  = 8.1 Hz), 163.2 (d,  $^1J_{\text{FC}}$  = 263.4 Hz), 148.6 (s), 140.4 (d,  $^3J_{\text{FC}}$  = 9.7 Hz), 120.1 (d,  $^2J_{\text{FC}}$  = 22.6 Hz), 117.5 (d,  $^2J_{\text{FC}}$  = 12.6 Hz), 110.1 (d,  $^3J_{\text{FC}}$  = 3.8 Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -118.3 (dd,  $^3J_{\text{FH}}$  = 9.1,  $^4J_{\text{FH}}$  = 4.9 Hz). Elemental analysis CHN (%) found C: 33.86, H: 1.17, N: 5.57, calcd for  $\text{C}_7\text{H}_3\text{BrFNO}_3$  C: 33.90, H: 1.22, N: 5.65.

**2-Amino-5-bromo-4-fluorobenzaldehyde, 3a.**

5-Bromo-4-fluoro-2-nitrobenzaldehyde (2.678 g, 10.8 mmol) and iron powder (1.819 g, 32.4 mmol) were added to a round-bottomed flask, this was purged with argon for 5 min. Ethanol (16 mL) followed by acetic acid (16 mL) were added and this mixture was heated to 80 °C and monitored via TLC (15 % EtOAc in hexane). After 1 hr the reaction had gone to completion, and the mixture was filtered through a Celite pad, this was then washed through with ethyl acetate (3 x 10 mL). Water (50 mL) was added followed by sodium hydrogen carbonate (saturated) to adjust to pH 4, this was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were washed with brine (3 x 100 mL), dried with sodium sulphate. The organic layer was then evaporated under reduced pressure on to silica. The silica pad was then loaded on to a silica gel column and purified using a gradient of 0 % to 15 % ethyl acetate in hexane to give the title compound as a yellow solid.

**Yield:** 1.571 g (67%).

TLC (EtOAc: hexane 15 %)  $R_f$  = 0.33. FTMS APCI (m/z) found 217.9616, calcd for  $[C_7H_5BrF_1N_1O_1H]^+$  217.9611.  $^1H$  NMR (500 MHz, chloroform-d)  $\delta$  9.75 (s, 1H), 7.64 (d,  $^4J_{FH}$  = 7.4 Hz, 1H), 6.42 (d,  $^3J_{FH}$  = 10.3 Hz, 1H), 6.30 (s, 2H).  $^{13}C$  NMR (126 MHz, chloroform-d)  $\delta$  191.7, 163.4 (d,  $^1J_{FC}$  = 255.2 Hz), 151.2 (d,  $^3J_{FC}$  = 12.6 Hz), 140.7 (d,  $^3J_{FC}$  = 4.4 Hz), 117.4, 103.3 (d,  $^2J_{FC}$  = 25.8 Hz), 95.3 (d,  $^2J_{FC}$  = 23.1 Hz).  $^{19}F$  NMR (376 MHz, chloroform-d)  $\delta$  -97.63 (dd, J = 10.3, 7.4 Hz). LCMS purity >99% (UV), Ret. time = 18.83 min.

**2-Amino-3-bromo-6-fluorobenzaldehyde, 3b.**

3-Bromo-6-fluoro-2-nitrobenzaldehyde (7.44 g, 30 mmol) and iron powder (5.02 g, 90 mmol) were added to a round-bottomed flask, this was purged with argon for 5 min. Ethanol (30 mL) followed by acetic acid (30 mL) were added and this mixture was heated to 80 °C and monitored via TLC (15 % EtOAc in hexane). After 1 hr the reaction had gone to completion, and the mixture was filtered through a Celite pad, this was then washed through with ethyl acetate (3 x 30 mL). Water (150 mL) was added followed by sodium hydrogen carbonate (saturated) to adjust to pH 4, this was extracted with ethyl acetate (3 x 100 mL), the combined organic layers were washed with brine (3 x 300 mL), dried with sodium sulphate. The organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of 0 % to 15 % ethyl acetate in hexane to give the title compound as a yellow solid.

**Yield:** 5.40 g (83%).

TLC (EtOAc: hexane 15 %)  $R_f$  = 0.61. FTMS APCI (m/z) found 219.9593, calcd for  $[C_7H_5Br_1F_1N_1O_1H]^+$  219.9591.

$^1H$  NMR (500 MHz, acetone-d<sub>6</sub>)  $\delta$  10.23 (s, 1H), 7.71 (dd,  $^3J_{HH}$  = 8.7,  $^4J_{FH}$  = 5.8 Hz, 1H), 7.32 (s, 2H), 6.43 (dd,  $^3J_{FH}$  = 11.0,  $^3J_{HH}$  = 8.7 Hz, 1H).  $^{13}C$  NMR (126 MHz, acetone-d<sub>6</sub>)  $\delta$  188.9 (d,  $^3J_{FC}$  = 12.5 Hz), 166.7 (d,  $^1J_{FC}$  = 254.7 Hz), 149.4 (d,  $^3J_{FC}$  = 4.8 Hz), 140.1 (d,  $^3J_{FC}$  = 11.9 Hz), 109.1 (d,  $^3J_{FC}$  = 10.7 Hz), 104.9 (d,  $^4J_{FC}$  = 3.4 Hz), 103.4 (d,  $^2J_{FC}$  = 22.9 Hz).  $^{19}F$  NMR (376 MHz, chloroform-d)  $\delta$  -123.05 (dd, J = 11.0, 5.8 Hz). LCMS purity >99% (UV), Ret. time = 19.68 min.

**2-Fluoro-5-nitro-4-((trimethylsilyl)ethynyl)benzaldehyde, 4a.**

4-Bromo-2-fluoro-5-nitrobenzaldehyde (2.480 g, 8.0 mmol), copper iodide (181 mg, 1.0 mmol) and bis(triphenylphosphine)palladium(II) dichloride (351 mg, 0.5 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry, 24 mL), triethylamine (dry, 4.28 mL, 30.0 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (1.34 mL, 12.0 mmol). This mixture was stirred at rt for 1h. The bulk of the DMF was evaporated under reduced pressure, then diethyl ether (100 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 20 mL). Water (150 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL).

The combined organic layers were washed with brine (5 x 150 mL), dried with magnesium sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 0 % - 15 % diethyl ether in hexane, to give the title compound as a yellow solid.

**Yield:** 1.736 g (66%).

TLC (Diethyl ether: hexane 10 %)  $R_f$  = 0.40. FTMS (m/z) found 266.0638, calcd for  $[C_{12}H_{12}FNO_3SiH]^+$  266.0643.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  10.31 (s, 1H), 8.56 (d,  $^4J_{FH}$  = 6.3 Hz, 1H), 7.46 (d,  $^3J_{FH}$  = 9.9 Hz, 1H), 0.30 (d,  $J$  = 0.8 Hz, 10H).  $^{13}C$  NMR (100 MHz, chloroform-*d*)  $\delta$  184.3 (d,  $^3J_{FC}$  = 5.3 Hz), 165.1 (d,  $^1J_{FC}$  = 266.8 Hz), 146.9, 126.1, 126.0 (d,  $^3J_{FC}$  = 4.4 Hz), 123.6 (d,  $^2J_{FC}$  = 10.8 Hz), 123.2 (d,  $^4J_{FC}$  = 24.2 Hz), 111.2, 97.8, -0.5.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -114.40 (dd,  $J$  = 9.9, 6.3 Hz). LCMS purity >99 % (UV), Ret. time = 23.46 min.

#### **2-Amino-4-fluoro-5-((trimethylsilyl)ethynyl)benzaldehyde, 4b.**

2-Amino-5-bromo-4-fluorobenzaldehyde (218 mg, 1.00 mmol), copper iodide (18 mg, 0.10 mmol) and bis(triphenylphosphine)palladium(II) dichloride (35 mg, 0.05 mmol) were added to a MPS tube, this was placed under vacuum and purged with argon and cycled 3 times. DMF (dry 3 mL), triethylamine (dry, 417  $\mu$ L, 3.00 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (170  $\mu$ L, 1.20 mmol). This mixture was heated to 80 °C for 4 hr. The reaction mixture was cooled to rt and diethyl ether (20 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 5 mL). Water (50 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (5 x 50 mL), dried with sodium sulphate and evaporated under reduced pressure. The crude material was dissolved in the minimum amount of DMSO and loaded on to a reverse phase flash chromatography column, the column was ran at 100% water (0.1% formic acid modifier) for 1-3 column volumes i.e. until the UV trace has normalised from the DMSO. The column was then run at a gradient of 45% to 95% acetonitrile (0.1% formic acid) in water (0.1% formic acid). The fractions containing product were then lyophilized to the title compound as a yellow solid.

**Yield:** 105 mg (45 %).

FTMS (m/z) found 236.0903, calcd for  $[C_{12}H_{14}ONFSiH]^+$  236.0901.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  9.75 (s, 1H), 7.64 (d,  $^4J_{FH}$  = 7.6 Hz, 1H), 6.40 (bs, 2H), 6.31 (d,  $^3J_{FH}$  = 11.0 Hz, 1H), 0.25 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  192.2, 167.0 (d,  $^1J_{FC}$  = 259.7 Hz), 151.9 (d,  $^3J_{FC}$  = 13.4 Hz), 142.8 (d,  $^3J_{FC}$  = 5.7 Hz), 116.1, 102.0 (d,  $^2J_{FC}$  = 24.8 Hz), 101.4 (d,  $^2J_{FC}$  = 18.3 Hz), 97.9 (d,  $^2J_{FC}$  = 2.3 Hz), 97.4, 0.1.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -100.02 (appt,  $J$  = 9.3 Hz). LCMS purity >99 % (UV), Ret. time = 23.09 min.

#### **2-Amino-6-fluoro-3-((trimethylsilyl)ethynyl)benzaldehyde, 4c.**

2-Amino-3-bromo-6-fluorobenzaldehyde (1.144 g, 8.00 mmol), copper iodide (145 mg, 0.80 mmol) and bis(triphenylphosphine)palladium(II) dichloride (281 mg, 0.4 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry 24 mL), triethylamine (dry, 3.34 mL, 24.00 mmol) were added followed by the drop wise addition of trimethylsilylacetylene (1.34 mL, 9.6 mmol). This mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to rt and the diethyl ether (150 mL) was added to the mixture, this was then filtered through a pad of Celite, which was then washed with more diethyl ether (3 x 15 mL). Water (150 mL) was added and the organic layer separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine (5 x 150 mL), dried with sodium sulphate and evaporated under reduced pressure on to

silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 0 % - 10 % diethyl ether in hexane, to give the title compound as a green solid.

**Yield:** 1.398 g (74 %).

TLC (Diethyl ether: hexane 10 %)  $R_f$  = 0.70. FTMS (m/z) found 236.0904, calcd for  $[C_{12}H_{14}ONFSiH]^+$  236.0901.

$^1H$  NMR (500 MHz, chloroform- $d$ )  $\delta$  10.28 (s, 1H), 7.43 (dd,  $^3J_{HH}$  = 8.5,  $^4J_{FH}$  = 6.1 Hz, 1H), 6.28 (dd,  $^3J_{FH}$  = 10.3,  $^3J_{HH}$  = 8.5 Hz, 1H), 0.27 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform- $d$ )  $\delta$  188.8 (d,  $^3J_{FC}$  = 11.8 Hz), 166.6 (d,  $^1J_{FC}$  = 259.5 Hz), 152.3 (d,  $^3J_{FC}$  = 5.1 Hz), 139.7 (d,  $^2J_{FC}$  = 12.5 Hz), 107.6 (d,  $^3J_{FC}$  = 10.4 Hz), 105.7 (d,  $^4J_{FC}$  = 3.6 Hz), 102.0 (d,  $^2J_{FC}$  = 22.0 Hz), 101.6 (d,  $^5J_{FC}$  = 1.7 Hz), 99.2, 0.2.  $^{19}F$  NMR (376 MHz, chloroform- $d$ )  $\delta$  -119.33 (dd,  $J$  = 11.0, 6.1 Hz). LCMS purity >99 % (UV), Ret. time = 24.74 min.

#### **2-Fluoro-4-((6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)ethynyl)-5-n, 4d.**

4-Bromo-2-fluoro-5-nitrobenzaldehyde (143 mg, 0.575 mmol), copper iodide (9 mg, 0.05 mmol), bis(triphenylphosphine)palladium(II) dichloride (18 mg, 0.025 mmol) and ethynylboronic acid MIDA ester (90 mg, 0.5 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry, 1.5 mL), triethylamine (dry, 209  $\mu$ L, 1.5 mmol) were added this mixture was stirred at rt over night. The DMF was evaporated under reduced pressure heptane was added and evaporated under reduced pressure (3 x 5 mL) to azeotropically remove any residual DMF. The residues were dissolved in acetone (15 mL) and evaporated under reduced pressure on to silica. This crude powder was then loaded on to a silica gel column which was ran at a gradient of 30 % - 40 % acetonitrile in DCM, to give title compound as a yellow solid.

**Yield:** mg 67 (38 %).

TLC (MeCN:DCM 30 %)  $R_f$  = 0.78. FTMS (m/z) found 349.0638, calcd for  $[C_{14}H_{10}BFN_2O_7H]^+$  349.0638.  $^1H$  NMR (500 MHz, acetonitrile- $d_3$ )  $\delta$  10.25 (s, 1H), 8.51 (d,  $^4J_{FH}$  = 6.3 Hz, 1H), 7.70 (d,  $^3J_{FH}$  = 10.2 Hz, 1H), 4.11 (d,  $J$  = 17.1 Hz, 2H), 3.98 (d,  $J$  = 17.0 Hz, 2H), 3.18 (s, 3H).  $^{13}C$  NMR (126 MHz, acetonitrile- $d_3$ )  $\delta$  185.4 (d,  $^3J_{FC}$  = 4.5 Hz), 167.5, 164.7 (d,  $^1J_{FC}$  = 266.2 Hz), 146.5, 126.2 (d,  $^3J_{FC}$  = 4.6 Hz), 124.8 (d,  $^2J_{FC}$  = 12.2 Hz), 124.2 (d,  $^3J_{FC}$  = 11.2 Hz), 123.5 (d,  $^2J_{FC}$  = 24.9 Hz), 61.7, 48.1.  $^{19}F$  NMR (376 MHz, acetonitrile- $d_3$ )  $\delta$  -114.33 (dd,  $J$  = 10.2, 6.3 Hz).  $^{11}B$  NMR (128 MHz, Acetonitrile- $d_3$ )  $\delta$  6.18. LCMS purity >99 % (UV), Ret. time = 23.46 min.

#### **2-Amino-6-fluoro-3-((6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)ethynyl)benzaldehyde, 4e.**

2-Amino-3-bromo-6-fluorobenzaldehyde (429 mg, 1.97 mmol), copper iodide (31 mg, 0.17 mmol), bis(triphenylphosphine)palladium(II) dichloride (60 mg, 0.09 mmol) and ethynylboronic acid MIDA ester (310 mg, 1.71 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon and cycled 3 times. DMF (dry 6 mL), triethylamine (dry, 751  $\mu$ L, 5.13 mmol) were added this mixture was stirred at rt overnight. The DMF was evaporated under reduced pressure, heptane was added and evaporated under reduced pressure (3 x 5 mL) to azeotropically remove any residual DMF. The residue was dissolved in acetone (15 mL) and evaporated under reduced pressure on to silica. This crude powder was then loaded on to a silica gel column which was ran at a gradient of 30 % - 40 % acetonitrile in DCM, to give the title compound as a white solid.

**Yield:** 470 mg (86 %).

TLC (MeCN:DCM 30 %)  $R_f$  = 0.69. FTMS (m/z) found 319.0900, calcd for  $[C_{14}H_{12}BFN_2O_5H]^+$  319.0896.  $^1H$  NMR (500 MHz, acetonitrile- $d_3$ )  $\delta$  10.24 (s, 1H), 7.53 (dd,  $^3J_{HH}$  = 8.4,  $^4J_{FH}$  = 6.2 Hz, 1H), 7.04 (bs, 2H), 6.38 (dd,  $^3J_{FH}$  = 11.3,  $^4J_{FH}$  = 8.4 Hz, 1H),

4.04 (d,  $J = 17.1$  Hz, 2H), 3.93 (d,  $J = 17.1$  Hz, 2H), 3.09 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz, acetonitrile- $d_3$ )  $\delta$  188.7 (d,  $^3J_{\text{FC}} = 12.1$  Hz), 167.7, 166.6 (d,  $^1J_{\text{FC}} = 257.6$  Hz), 152.2 (d,  $^3J_{\text{FC}} = 5.4$  Hz), 140.2 (d,  $^2J_{\text{FC}} = 12.7$  Hz), 107.2 (d,  $^3J_{\text{FC}} = 10.5$  Hz), 105.1 (d,  $^4J_{\text{FC}} = 3.4$  Hz), 101.6 (d,  $^2J_{\text{FC}} = 22.4$  Hz), 94.0, 61.6, 48.0.  $^{19}\text{F}$  NMR (376 MHz, acetonitrile- $d_3$ )  $\delta$  -120.70 (dd,  $J = 11.3, 6.2$  Hz).  $^{11}\text{B}$  NMR (128 MHz, acetonitrile- $d_3$ )  $\delta$  6.50. LCMS purity >99 % (UV), Ret. time = 16.41 min.

#### General procedure for reductive aminations.

A benzaldehyde derivative (1 eq), sodium triacetoxyborohydride (2-2.5 eq) and a secondary amine (1.1 eq) were added to a round-bottomed flask and purged with argon. This was dissolved in THF (5 mLmmol $^{-1}$ ), acetic acid (1 eq) was added to the resulting stirred mixture and then left at rt overnight. Once there was no starting material observed via TLC water was added to quench. This was then extracted with ethyl acetate (3 times) then combined organic layers were washed with brine (3 times), the organic layer was dried ( $\text{Na}_2\text{SO}_4$ ). Alternatively on scales less than 1 mmol, hydrophobic phase separators were used with DCM extractions (3 times). The organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of ethyl acetate in hexane.

#### ***tert*-Butyl 4-(4-bromo-2-fluoro-5-nitrobenzyl)piperazine-1-carboxylate, 5a.**

The general reductive amination procedure was used on a 0.5 mmol and 8 mmol scale, with 1-Boc-piperazine and 2 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a orange solid.

**Yield:** 98 mg (0.5 mmol scale, 47 %) 2.579 g (8.0 mmol scale, 77 %).

TLC (EtOAc: hexane 20%)  $R_f = 0.20$ . HRMS-ESI ( $m/z$ ) found 418.0766, calcd for  $[\text{C}_{16}\text{H}_{21}\text{BrFN}_3\text{O}_4\text{H}]^+$  418.0772.

$^1\text{H}$  NMR (500 MHz, chloroform- $d$ )  $\delta$  8.06 (d,  $^4J_{\text{FH}} = 6.6$  Hz, 1H), 7.43 (d,  $^3J_{\text{FH}} = 8.6$  Hz, 1H), 3.56 (s, 2H), 3.46 -3.41 (m, 4H), 2.46 -2.40 (m, 4H), 1.45 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, chloroform- $d$ )  $\delta$  162.2 (d,  $^1J_{\text{FC}} = 259.2$  Hz), 154.8, 146.3, 128.5 (d,  $^3J_{\text{FC}} = 6.5$  Hz), 126.6 (d,  $^2J_{\text{FC}} = 16.4$  Hz), 122.3 (d,  $^2J_{\text{FC}} = 27.1$  Hz), 114.5 (d,  $^3J_{\text{FC}} = 10.6$  Hz), 80.0, 54.4, 53.0, 43.7, 28.6.  $^{19}\text{F}$  NMR (376 MHz, chloroform- $d$ )  $\delta$  -108.27 (appt,  $J = 7.7$  Hz). LCMS purity >99% (UV), Ret. time = 15.09 min.

#### ***tert*-Butyl 4-(2-amino-5-bromo-4-fluorobenzyl)piperazine-1-carboxylate, 5b.**

The general reductive amination procedure was used on a 0.5 mmol scale, with 1-Boc-piperazine 2.5 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

**Yield:** mg 161 mg (0.5 mmol scale, 83 %) 1.048 g (2.95 mmol scale, 91 %).

TLC (EtOAc: hexane 20%)  $R_f = 0.26$ . HRMS-ESI ( $m/z$ ) found 388.1017, calcd for  $[\text{C}_{16}\text{H}_{23}\text{BrFN}_3\text{O}_2\text{H}]^+$  388.1030.

$^1\text{H}$  NMR (500 MHz, chloroform- $d$ )  $\delta$  7.08 (d,  $^4J_{\text{FH}} = 7.5$  Hz, 1H), 6.40 (d,  $^3J_{\text{FH}} = 10.2$  Hz, 1H), 4.87 (s, 2H), 3.43 (s, 2H), 3.42-3.37 (m, 4H), 2.39- 2.31 (m, 4H), 1.45 (s, 9H).  $^{13}\text{C}$  NMR (126 MHz, chloroform- $d$ )  $\delta$  159.2 (d,  $^1J_{\text{FC}} = 244.2$  Hz), 154.7, 148.0 (d,  $^3J_{\text{FC}} = 10.0$  Hz), 134.3 (d,  $^3J_{\text{FC}} = 2.1$  Hz), 119.2 (d,  $^4J_{\text{FC}} = 2.9$  Hz), 103.3 (d,  $^2J_{\text{FC}} = 25.2$  Hz), 94.6 (d,  $^2J_{\text{FC}} = 21.3$  Hz), 79.8, 61.0, 52.5, 43.7, 28.5.  $^{19}\text{F}$  NMR (376 MHz, chloroform- $d$ )  $\delta$  -109.56 (dd,  $J = 10.2, 7.7$  Hz). LCMS purity >99% (UV), Ret. time = 12.81 min.

#### **4-Bromo-5-fluoro-2-(morpholinomethyl)aniline, 5c.**

The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2.5 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

**Yield:** mg 140 mg (97%).

TLC (EtOAc: hexane 20%)  $R_f$  = 0.30. HRMS-ESI (m/z) found 289.0355, calcd for  $[C_{11}H_{14}BrFN_2OH]^+$  289.0346.  $^1H$  NMR (500 MHz, chloroform- $d$ )  $\delta$  7.08 (d,  $^4J_{FH}$  = 7.6 Hz, 1H), 6.38 (d,  $^3J_{FH}$  = 10.3 Hz, 1H), 4.90 (s, 2H), 3.69–3.62 (m, 4H), 3.41 (s, 2H), 2.44–2.32 (m, 4H).  $^{13}C$  NMR (126 MHz, chloroform- $d$ )  $\delta$  159.2 (d,  $^1J_{FC}$  = 243.9 Hz), 148.0 (d,  $^3J_{FC}$  = 9.9 Hz), 134.3 (d,  $^3J_{FC}$  = 2.1 Hz), 119.1 (d,  $^4J_{FC}$  = 2.9 Hz), 103.2 (d,  $^2J_{FC}$  = 25.1 Hz), 94.6 (d,  $^2J_{FC}$  = 21.2 Hz), 67.0, 61.3, 53.2.  $^{19}F$  NMR (376 MHz, chloroform- $d$ )  $\delta$  -109.58 – -109.67 (m). LCMS purity >99% (UV), Ret. time = 9.38 min.

**tert-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate, 5d.**

The general reductive amination procedure was used on either a 0.5 mmol or a 6.3 mmol scale, with 1-Boc-piperazine and 2 eq of sodium triacetoxyborohydride. The crude material was columned using a 0% 10% gradient of EtOAc in hexane to give the title compound as a white crystalline solid.

**Yield:** 160 mg (0.5 mmol scale, 82 %) 2.336 g (6.3 mmol scale, 95%).

TLC (EtOAc: hexane 20%)  $R_f$  = 0.52. HRMS-ESI (m/z) found 388.1017, calcd for  $[C_{16}H_{23}BrFN_3O_2H]^+$  388.1030.  $^1H$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  7.35 (dd,  $^3J_{HH}$  = 8.8,  $^4J_{FH}$  = 5.8 Hz, 1H), 6.38 (pt,  $^3J_{HH}$ ,  $^3J_{FH}$  = 9.2 Hz, 1H), 5.62 (s, 2H), 3.59 (m, 2H), 3.37 (m, 4H), 2.40 (t,  $J$  = 5.1 Hz, 4H), 1.43 (s, 9H).  $^{13}C$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  162.1 (d,  $^1J_{FC}$  = 241.5 Hz), 155.0, 147.7 (d,  $^3J_{FC}$  = 6.6 Hz), 132.8 (d,  $^3J_{FC}$  = 10.8 Hz), 110.4 (d,  $^2J_{FC}$  = 17.4 Hz), 105.2 (d,  $^2J_{FC}$  = 25.6 Hz), 104.3 (d,  $^4J_{FC}$  = 2.8 Hz), 79.7, 53.2, 52.9, 44.5 (d,  $^3J_{FC}$  = 4.4 Hz), 28.6.  $^{19}F$  NMR (376 MHz, acetone- $d_6$ )  $\delta$  -121.00–-121.09 (m). LCMS purity > 92 % (UV), Ret. time = 13.93 min.

**6-Bromo-3-fluoro-2-(morpholinomethyl)aniline, 5e.**

The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2 eq of sodium triacetoxyborohydride. The crude material purified by column chromatography using a 0%-20% gradient of EtOAc in hexane, giving the title compound as a yellow solid.

**Yield:** 137 mg (95 %).

TLC (EtOAc: hexane 20%)  $R_f$  = 0.50. HRMS-ESI (m/z) found 289.0351, calcd for  $[C_{11}H_{14}BrFN_2OH]^+$  289.0346.  $^1H$  NMR (500 MHz, acetone- $d_6$ )  $\delta$  7.25 (dd,  $^3J_{HH}$  8.9,  $^4J_{FH}$  = 5.7 Hz, 1H), 6.29 (pt,  $^3J_{HH}$ ,  $^3J_{FH}$  = 9.1 Hz, 1H), 5.55 (s, 2H), 3.57 – 3.51 (m, 4H), 3.49 (d,  $^4J_{FH}$  = 1.9 Hz, 2H), 2.36 – 2.30 (m, 4H).  $^{13}C$  NMR (126 MHz, acetone- $d_6$ )  $\delta$  162.4 (d,  $^1J_{FC}$  = 241.4 Hz), 147.9 (d,  $^3J_{FC}$  = 6.7 Hz), 132.9 (d,  $^3J_{FC}$  = 10.7 Hz), 110.5 (d,  $^2J_{FC}$  = 17.3 Hz), 105.5 (d,  $^2J_{FC}$  = 25.8 Hz), 104.5 (d,  $^4J_{FC}$  = 2.6 Hz), 67.7, 54.1, 53.5 (d,  $^3J_{FC}$  = 4.2 Hz).  $^{19}F$  NMR (376 MHz, acetone- $d_6$ )  $\delta$  -121.22 – -121.32 (m). LCMS purity >99% (UV), Ret. time = 14.11 min.

**tert-Butyl 4-(2-amino-6-fluoro-3-((trimethylsilyl)ethynyl)benzyl)piperazine-1-carboxylate, 5f.**

The general reductive amination procedure was used on a 0.5 mmol scale, with 1-Boc-piperazine 2 eq of sodium triacetoxyborohydride. The crude material was subjected to column chromatography using a gradient of 0% to 10% EtOAc in hexane, giving the title compound as an orange solid.

**Yield:** 56 mg (28 %).

TLC (EtOAc: hexane 20%)  $R_f$  = 0.63. HRMS-ESI (m/z) found 406.2307, calcd for  $[C_{21}H_{32}BrFN_3O_2SiH]^+$  406.2321.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  7.18 (dd,  $^3J_{HH}$  = 8.6,  $^4J_{FH}$  = 6.1 Hz, 1H), 6.32 (pt,  $^3J_{HH}$ ,  $^3J_{FH}$  = 9.1 Hz, 1H), 5.50 (s, 2H), 3.56 (d,  $^4J_{FH}$  = 1.7 Hz, 2H), 3.46-3.35 (m, 4H), 2.44-2.34 (m, 4H), 1.44 (s, 9H), 0.25 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  162.2 (d,  $^1J_{FC}$  = 246.4 Hz), 154.8, 151.1 (d,  $^3J_{FC}$  = 7.2 Hz), 132.5 (d,  $^3J_{FC}$  = 10.9 Hz), 108.0 (d,  $^2J_{FC}$  = 16.8 Hz), 104.3 (d,  $^4J_{FC}$  = 2.7 Hz), 104.2 (d,  $^2J_{FC}$  = 24.8 Hz), 101.4, 99.5 (d,  $^5J_{FC}$  = 24.8 Hz), 79.9, 52.5, 52.2 (d,  $^3J_{FC}$  = 4.2 Hz), 43.8, 28.5, 0.3.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -115.18 – -115.76 (m). LCMS purity >99% (UV), Ret. time = 18.45 min.

### **3-Fluoro-2-(morpholinomethyl)-6-((trimethylsilyl)ethynyl)aniline, 5g.**

The general reductive amination procedure was used on a 0.5 mmol scale, with morpholine and 2 eq of sodium triacetoxyborohydride. The crude material was purified by column chromatography using a 0% to 10% gradient of EtOAc in hexane, giving the title compound as an orange solid.

**Yield:** 96 mg (63 %).

TLC (EtOAc: hexane 20%)  $R_f$  = 0.59. HRMS-ESI (m/z) found 307.1625, calcd for  $[C_{16}H_{22}BrFN_2OSiH]^+$  307.1636.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  7.18 (dd,  $^3J_{HH}$  = 8.6,  $^4J_{FH}$  = 6.1 Hz, 1H), 6.33 (t,  $^3J_{HH}$ ,  $^3J_{FH}$  = 9.1 Hz, 1H), 5.54 (s, 2H), 3.67 (appt,  $J$  = 4.7 Hz, 4H), 3.56 (d,  $J$  = 1.6 Hz, 2H), 2.48 - 2.39 (m, 4H), 0.26 (d,  $J$  = 0.8 Hz, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  162.3 (d,  $^1J_{FC}$  = 246.5 Hz), 151.1 (d,  $^3J_{FC}$  = 7.3 Hz), 132.4 (d,  $^3J_{FC}$  = 11.0 Hz), 107.8 (d,  $^2J_{FC}$  = 16.9 Hz), 104.2 (d,  $^2J_{FC}$  = 24.9 Hz), 104.2 (d,  $^4J_{FC}$  = 3.0 Hz), 101.5, 99.4 (d,  $^5J_{FC}$  = 1.5 Hz), 67.2, 53.1, 52.5 (d,  $^3J_{FC}$  = 4.2 Hz), 0.3.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -115.25 – -115.60 (m). LCMS purity >99% (UV), Ret. time = 13.75 min.

### **tert-Butyl 4-(5-amino-4-bromo-2-fluorobenzyl)piperazine-1-carboxylate, 3c.**

*tert*-Butyl 4-(4-bromo-2-fluoro-5-nitrobenzyl)piperazine-1-carboxylate (1.254 mg, 3 mmol) was dissolved in methanol (11 mL). To this mixture zinc powder (1.950 mg, 30 mmol) was added followed by saturated ammonium chloride (11 mL). This mixture was allowed to stir at rt for 14 h before it was filtered through a bed of celite, this was then washed with ethyl acetate (3 x 10 mL). This mixture was then extracted with ethyl acetate (3 x 30 mL), the combined organic layers were then washed with brine (2 x 20 mL) dried with sodium sulphate and evaporated onto silica. This silica pad was then loaded onto a silica gel column and was purified using ethyl acetate: hexane 50%. This gave title compound as a light yellow solid.

**Yield:** 546 mg (47 %).

TLC (EtOAc: hexane 50%)  $R_f$  = 0.30. HRMS-ESI (m/z) found 388.1017, calcd for  $[C_{16}H_{23}BrFN_3O_2H]^+$  388.1030.

$^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  7.13 (d,  $^3J_{FH}$  = 8.9 Hz, 1H), 6.80 (d,  $^4J_{FH}$  = 6.6 Hz, 1H), 3.91 (s, 2H), 3.46 (s, 2H), 3.45 – 3.39 (m, 4H), 2.45 – 2.36 (m, 5H), 1.45 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  154.9, 154.1 (d,  $^1J_{FC}$  = 240.5 Hz), 140.6 (d,  $^4J_{FC}$  = 2.6 Hz), 125.0 (d,  $^2J_{FC}$  = 16.0 Hz), 119.2 (d,  $^2J_{FC}$  = 26.6 Hz), 117.3 (d,  $^3J_{FC}$  = 4.1 Hz), 107.5 (d,  $^3J_{FC}$  = 9.8 Hz), 79.8, 55.2, 52.9, 43.8, 28.6.  $^{19}F$  NMR (376 MHz, Chloroform-*d*)  $\delta$  -129.75 – -129.83 (m). LCMS purity >99% (UV), Ret. time = 11.19 min.



**tert-Butyl 4-(3-bromo-6-fluoro-2-(1H-pyrrol-1-yl)benzyl)piperazine-1-carboxylate, 6a.**

tert-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate (58 mg, 0.15 mmol), 2,5-Dimethoxytetrahydrofuran (22 mg, 0.17 mmol) and acetic acid (1.5 mL) were added to a 10 mL microwave vial. This was loaded in to the microwave and heated at 115 °C for 15 min. The cooled reaction mixture was transferred to round-bottomed; ethyl acetate was used to transfer washing from the microwave vial and evaporated under reduced pressure. The residues were dissolved in DCM (3 mL) then saturated sodium hydrogen carbonate was added (5 mL), a hydrophobic phase separator was used with DCM extractions (3 x 3 mL). The combined organic layer was then evaporated under reduced pressure on to silica. This silica pad was then loaded on to a silica gel column and purified using a gradient of 10 % - 20% ethyl acetate in hexane, to give the title compound as a white solid.

**Yield:** 42 mg (64 %). TLC (EtOAc:Hexane 20%)  $R_f$  = 0.54. HRMS-ESI (m/z) found 338.0663, calcd for product without BOC  $[C_{15}H_{18}N_3FBrH]^+$  338.0663.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  7.58 (dd,  $^3J_{HH}$  = 8.9,  $^4J_{FH}$  = 5.5 Hz, 1H), 7.04 (appt,  $^3J_{HH}$ ,  $^3J_{FH}$  = 8.8 Hz, 1H), 6.72 (t,  $J$  = 2.1 Hz, 2H), 6.30 (t,  $J$  = 2.1 Hz, 2H), 3.33-3.29 (m, 4H), 3.22 (d,  $^4J_{FH}$  = 2.1 Hz, 2H), 2.29-2.21 (m, 4H), 1.43 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  160.8 (d,  $^1J_{FC}$  = 248.8 Hz), 154.8, 142.3 (d,  $^3J_{FC}$  = 6.0 Hz), 132.7 (d,  $^3J_{FC}$  = 9.4 Hz), 126.7 (d,  $^2J_{FC}$  = 16.6 Hz), 122.7, 118.3 (d,  $^4J_{FC}$  = 3.7 Hz), 116.8 (d,  $^2J_{FC}$  = 24.4 Hz), 108.9, 79.7, 52.7, 51.7, 43.9, 28.6.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -114.53 – -114.85 (m). LCMS purity >99% (UV), Ret. time = 16.86 min.

**tert-Butyl 4-(4-bromo-5-((6,7-dimethoxyquinazolin-4-yl)amino)-2-fluorobenzyl)-piperazine-1-carboxylate, 7a.**

tert-Butyl 4-(5-amino-4-bromo-2-fluorobenzyl)piperazine-1-carboxylate (533 mg, 1.37 mmol) and 4-chloro-6,7-dimethoxyquinazoline (341 mg, 1.51 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 15 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 6.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (30 mL) was added to the mixture. This organic layer was washed with water (50 mL) this water layer was extracted with ethyl acetate (2 x 30 mL), the combined organic layer was washed with brine (5 x 30 mL) dried with magnesium sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 5 % - 20 % methanol in dichloromethane, this also needed recrystallization from the minimum amount of hot ethyl acetate, to give the title compound as a white solid.

**Yield:** 378 mg (48 %).

TLC (MeOH:DCM 10 %)  $R_f$  = 0.68. HRMS-ESI (m/z) found 576.1616, calcd for  $[C_{26}H_{31}BrFN_5O_4H]^+$  576.1616.  $^1H$  NMR (500 MHz, chloroform-*d*)  $\delta$  8.68 (s, 1H), 8.63 (d,  $^4J_{FH}$  = 7.2 Hz, 1H), 7.51 (s, 1H), 7.35 (d,  $^3J_{FH}$  = 8.6 Hz, 1H), 7.29 (s, 1H), 7.08 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 3.63 (d,  $^4J_{FH}$  = 1.5 Hz, 2H), 3.49 – 3.42 (m, 4H), 2.53 – 2.45 (m, 4H), 1.45 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  157.0 (d,  $^1J_{FC}$  = 248.0 Hz), 155.9, 155.2, 154.9, 153.6, 150.1, 147.9, 133.0, 125.48 (d,  $^3J_{FC}$  = 3.2 Hz), 125.2 (d,  $^2J_{FC}$  = 15.7 Hz), 119.3 (d,  $^2J_{FC}$  = 26.8 Hz), 113.5 (d,  $^3J_{FC}$  = 10.1 Hz), 109.5, 108.4, 99.0, 79.8, 56.5, 56.4, 55.3, 52.8, 28.6. One carbon missing from piperazine carbamate.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -120.70 – -121.00 (m). LCMS purity >99 % (UV), Ret. time = 9.94 min.

**tert-Butyl 4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)-piperazine-1-carboxylate, 7b.**

*tert*-Butyl 4-(2-amino-5-bromo-4-fluorobenzyl)piperazine-1-carboxylate (388 mg, 1.00 mmol) and 4-chloro-6,7-dimethoxyquinazoline (225 mg, 1.10 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 16 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 2.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (25 mL) was added to the mixture. This organic layer was washed with water (50 mL) this water layer was extracted with ethyl acetate (2 x 25 mL), the combined organic layer was washed with brine (5 x 50 mL) dried with sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 90 % - 100 % ethyl acetate in hexane, to give the title compound as a light orange solid.

**Yield:** 245 mg (42%).

TLC (EtOAc 100%)  $R_f$  = 0.45. HRMS-ESI (m/z) found 576.1626, calcd for  $[C_{26}H_{31}BrFN_5O_4H]^+$  576.1616.

$^1H$  NMR (399 MHz, chloroform-*d*)  $\delta$  10.04 (s, 1H), 8.70 (s, 1H), 8.43 (d,  $^3J_{FH}$  = 11.2 Hz, 1H), 7.33 (d,  $^4J_{FH}$  = 7.4 Hz, 1H), 7.29 (s, 1H), 7.12 (s, 1H), 3.68 (s, 2H), 3.61-3.50 (m, 4H), 2.58-2.48 (m, 4H), 1.47 (s, 9H).  $^{13}C$  NMR (100 MHz, chloroform-*d*)  $\delta$  158.9 (d,  $^1J_{FC}$  = 245.1 Hz), 156.1, 155.7, 154.7, 153.7, 150.0, 148.5, 140.2 (d,  $^3J_{FC}$  = 10.6 Hz), 134.3 (d,  $^4J_{FC}$  = 2.0 Hz), 122.9 (d,  $^3J_{FC}$  = 3.4 Hz), 110.6 (d,  $^2J_{FC}$  = 28.0 Hz), 110.1, 108.5, 101.9, 101.4 (d,  $^2J_{FC}$  = 21.7 Hz), 80.5, 61.6, 57.5, 56.4, 52.8, 43.6, 28.5.  $^{19}F$  NMR (376 MHz, chloroform-*d*)  $\delta$  -106.28 --106.41 (m). LCMS purity >99 % (UV), Ret. time = 10.59 min.

***tert*-Butyl 4-(3-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-6-fluorobenzyl)-piperazine-1-carboxylate, 7c.**

*tert*-Butyl 4-(2-amino-3-bromo-6-fluorobenzyl)piperazine-1-carboxylate (1.164 g, 3.00 mmol) and 4-chloro-6,7-dimethoxyquinazoline (0.743 g, 3.3 mmol) were added to a round bottomed flask, this was placed under vacuum and then purged with argon 3 times. DMF (dry 48 mL) was added, this mixture was cooled to 0 °C, then sodium bis(trimethylsilyl)amide (1M, 6.00 mL) was added drop wise over 5 min. The mixture was allowed to stir at 0 °C for 30 min, then the mixture was stirred for further 30 min at rt. The bulk of the DMF was evaporated under reduced pressure, and then ethyl acetate (75 mL) was added to the mixture. This organic layer was washed with water (100 mL) this water layer was extracted with ethyl acetate (2 x 75 mL) the combined organic layer was washed with brine (5 x 100 mL) dried with sulphate and evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran at a gradient of 90 % - 100 % ethyl acetate in hexane, to give the title compound as a light yellow solid.

**Yield:** 1.235 mg (72 %).

TLC (EtOAc 100 %)  $R_f$  = 0.32. HRMS-ESI (m/z) found 576.1613, calcd for  $[C_{25}H_{31}BrFN_5O_4H]^+$  576.1616.  $^1H$  NMR (399 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.20 (s, 1H), 7.78 (s, 1H), 7.68 (dd,  $^3J_{HH}$  = 8.9,  $^4J_{FH}$  = 5.7 Hz, 1H), 7.19 (s, 1H), 7.10 (appt,  $^3J_{FH}$ ,  $^3J_{HH}$  = 9.0 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.52 (s, 2H), 3.09-3.02 (m, 4H), 2.26-2.20 (m, 4H), 1.37 (s, 9H).  $^{13}C$  NMR (126 MHz, chloroform-*d*)  $\delta$  160.6 (d,  $^1J_{FC}$  = 247.7 Hz), 156.5, 155.2, 154.4, 153.7, 149.8, 147.7, 140.5, 133.64 (d,  $^3J_{FC}$  = 9.5 Hz), 120.8 (d,  $^2J_{FC}$  = 15.3 Hz), 116.8, 113.9 (d,  $^2J_{FC}$  = 24.4 Hz), 110.0, 107.9, 100.1, 80.2, 56.4, 56.3, 52.8, 52.5, 43.7, 28.3.  $^{19}F$  NMR (376 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  -116.09 – -116.24 (m). LCMS purity 94 % (UV), Ret. time = 10.6 min.

***N*-(2-Bromo-4-fluoro-5-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 8a.**

*tert*-Butyl 4-(4-bromo-5-((6,7-dimethoxyquinazolin-4-yl)amino)-2-fluorobenzyl)-piperazine-1-carboxylate (99 mg, 0.17 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 1.4 mL) was added. This

mixture was stirred for 15 min and the sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then dissolved in methanol (4 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). This was then eluted with ammonia in methanol (2 M) then was then evaporated under reduced pressure to give the title compound as a white solid.

**Yield:** 130mg (55%).

HRMS-ESI (m/z) found 476.1082, calcd for  $[C_{21}H_{23}BrFN_5O_2H]^+$  476.1092.  $^1H$  NMR (500 MHz, methanol- $d_4$ )  $\delta$  8.27 (s, 1H), 7.69 (s, 1H), 7.62 (d,  $^4J_{FH} = 7.1$  Hz, 1H), 7.52 (d,  $^3J_{FH} = 9.1$  Hz, 1H), 7.17 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.59 (s, 2H), 2.87 (t,  $J = 4.9$  Hz, 4H), 2.54 (s, 4H).  $^{13}C$  NMR (126 MHz, methanol- $d_4$ )  $\delta$  159.3 (d,  $^1J_{FC} = 249.6$  Hz), 158.2, 155.5, 152.4, 149.9, 146.2, 133.6 (d,  $^3J_{FC} = 3.9$  Hz), 131.9, 124.6 (d,  $^2J_{FC} = 16.1$  Hz), 121.1 (d,  $^3J_{FC} = 7.1$  Hz), 119.6 (d,  $^2J_{FC} = 27.1$  Hz), 108.8, 105.8, 101.2, 55.5, 55.2, 54.6, 52.7, 44.7.  $^{19}F$  NMR (376 MHz, methanol- $d_4$ )  $\delta$  -109.74 – -109.81 (m). Elemental analysis CHN (%) found C: 45.97, H: 4.30, N: 12.02, calcd for  $C_{21}H_{23}BrFN_5O_2 \cdot HCl \cdot 0.6CCl_2H_2$ : 46.02, H: 4.51, N: 12.42.

***N*-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 8b.**

tert-Butyl 4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)-piperazine-1-carboxylate (288 mg, 0.5 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 4 mL) was added. This mixture was stirred for 15 min and the sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then dissolved in methanol (5 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). This was then eluted with ammonia in methanol (2 M) which was then evaporated under reduced pressure to give the title compound as a white solid.

**Yield:** 199 mg (84 %).

HRMS-ESI (m/z) found 476.1091, calcd for  $[C_{21}H_{23}BrFN_5O_2H]^+$  476.1092.  $^1H$  NMR (500 MHz, methanol- $d_4$ )  $\delta$  8.49 (s, 1H), 8.29 (d,  $^3J_{FH} = 11.2$  Hz, 1H), 7.53 (d,  $^4J_{FH} = 7.7$  Hz, 1H), 7.33 (s, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 4.00 (s, 3H), 3.68 (s, 2H), 2.93 – 2.86 (m, 4H), 2.58 – 2.48 (m, 4H).  $^{13}C$  NMR (126 MHz, methanol- $d_4$ )  $\delta$  159.7 (d,  $^1J_{FC} = 243.6$  Hz), 157.9, 157.6, 154.0, 151.6, 148.4, 141.0 (d,  $^3J_{FC} = 10.5$  Hz), 135.5 (d,  $^4J_{FC} = 1.6$  Hz), 126.8 (d,  $^3J_{FC} = 3.1$  Hz), 112.3 (d,  $^2J_{FC} = 27.6$  Hz), 110.9, 107.9, 104.0, 102.9 (d,  $^2J_{FC} = 21.5$  Hz), 61.7, 58.2, 56.7, 54.2, 46.3.  $^{19}F$  NMR (376 MHz, methanol- $d_4$ )  $\delta$  -119.49 – -119.64 (m). LCMS purity >99 % (UV), Ret. time = 9.06 min.

***N*-(6-Bromo-3-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 8c.**

tert-Butyl 4-(3-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-6-fluorobenzyl)-piperazine-1-carboxylate (99 mg, 0.17 mmol) was added to a round bottomed flask then hydrogen chloride solution in dioxane (4M, 1.4 mL) was added. This mixture was stirred for 15 min and then sonicated for a 15 min. This mixture was then evaporated under reduced pressure, the residues were then dissolved in methanol (4 mL) and the minimum amount of water was added to aid to dissolve the residues. This solution was then loaded onto a SCX column, the column was then washed with methanol (20 mL) and then acetonitrile (20 mL). The product was then eluted with ammonia in methanol (2 M) and this was then evaporated under reduced pressure to give the title compound as a white solid.

**Yield:** 80 mg (99%).

HRMS-ESI (m/z) found 476.1087, calcd for  $[C_{25}H_{31}BrFN_5O_4H]^+$  476.1092.  $^1H$  NMR (399 MHz, methanol-d<sub>4</sub>)  $\delta$  8.24 (s, 1H), 7.72 – 7.64 (m, 2H), 7.19 (s, 1H), 7.09 (t, J = 9.0 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.71 – 3.40 (m, 1H), 2.77 – 2.66 (m, 4H), 2.46 – 2.37 (m, 4H).  $^{13}C$  NMR (100 MHz, methanol-d<sub>4</sub>)  $\delta$  161.1 (d, J = 246.7 Hz), 157.5, 155.6, 152.0, 150.1, 146.1, 139.8, 132.9 (d, J = 9.5 Hz), 124.6 (d, J = 15.9 Hz), 118.6, 115.0 (d, J = 25.0 Hz), 109.3, 106.2, 101.6, 55.7, 55.3, 52.0, 51.8, 44.4.  $^{19}F$  NMR (376 MHz, chloroform-d)  $\delta$  -105.68. LCMS purity >99% (UV), Ret. time = 12.26 min.

***N*-(2-bromo-4-fluoro-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 9a.**

*N*-(2-Bromo-4-fluoro-5-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (29 mg, 0.06 mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine was added (21  $\mu$ L, 0.122 mmol). To this stirred mixture methanesulfonyl chloride (5  $\mu$ L, 0.066 mmol) was added. After 1 h of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was washed with dichloromethane (2 x 5 mL). The combined organic washes were evaporated under reduced pressure. No further purification was required giving the title compound as a white solid.

**Yield:** 21 mg (63 %).

HRMS-ESI (m/z) found 554.0864, calcd for  $[C_{22}H_{26}BrFN_5O_4SH]^+$  554.0867.  $^1H$  NMR (500 MHz, chloroform-d)  $\delta$  9.92 (s, 1H), 8.71 (s, 1H), 8.54 (d,  $^3J_{FH}$  = 11.1 Hz, 1H), 7.36 (d,  $^4J_{FH}$  = 7.4 Hz, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.74 (s, 2H), 3.45 – 3.34 (m, 4H), 2.82 (s, 3H), 2.77 – 2.66 (m, 4H).  $^{13}C$  NMR (126 MHz, chloroform-d)  $\delta$  159.0 (d,  $^1J_{FC}$  = 246.1 Hz), 156.0, 153.7, 149.8, 148.4, 140.0, 134.2, 122.1, 109.8, 108.6, 104.0, 60.9, 58.4, 56.3, 52.3, 45.3, 35.4. Three carbons missing as the compound had low solubility in low boiling point NMR solvents.  $^{19}F$  NMR (376 MHz, methanol-d<sub>4</sub>)  $\delta$  -118.78 – -118.83 (m). LCMS purity 90 % (UV), Ret. time = 9.19 min.

***N*-(4-bromo-5-fluoro-2-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)-6,7-dimethoxyquinazolin-4-amine, 9b.**

*N*-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (29 mg, 0.06 mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine was added (21  $\mu$ L, 0.122 mmol). To this stirred mixture methanesulfonyl chloride (5  $\mu$ L, 0.066 mmol) was added. After 1 hr of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic were evaporated under reduced pressure. No further purification was required giving the title compound as a white solid.

**Yield:** 33 mg (99%).

HRMS-ESI (m/z) found 554.0868, calcd for  $[C_{22}H_{26}BrFN_5O_4SH]^+$  554.0867.  $^1H$  NMR (500 MHz, chloroform-d)  $\delta$  8.64 (s, 1H), 8.54 (d,  $^4J_{FH}$  = 7.1 Hz, 1H), 7.84 (s, 1H), 7.38 (d,  $^4J_{FH}$  = 8.7 Hz, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 3.68 (d, J = 1.4 Hz, 2H), 3.31 – 3.25 (m, 4H), 2.78 (s, 3H), 2.71 – 2.64 (m, 4H).  $^{13}C$  NMR (126 MHz, chloroform-d)  $\delta$  156.9''8 (d, J = 256.5 Hz), 155.3, 152.6, 150.1, 132.8, 125.7, 124.4, 119.5, 119.2, 114.2, 109.1, 107.3, 99.2, 88.3, 56.4, 56.3, 54.8, 52.1, 45.8, 34.4.  $^{19}F$  NMR (376 MHz, chloroform-d)  $\delta$  -105.60 – -105.77 (m). LCMS purity 90 % (UV), Ret. time = 10.93 min.

### 1-(4-(5-bromo-2-((6,7-dimethoxyquinazolin-4-yl)amino)-4-fluorobenzyl)piperazin-1-yl)ethanone, 9c.

*N*-(4-Bromo-5-fluoro-2-(piperazin-1-ylmethyl)phenyl)-6,7-dimethoxyquinazolin-4-amine (29 mg, 0.061mmol) was added to a round bottomed flask, then dichloromethane (dry, 0.5 mL) followed by *N,N*-diisopropylethylamine (21  $\mu$ L, 0.122 mmol) were added. To this stirred mixture acetyl chloride (5  $\mu$ L, 0.067 mmol) was added, this reaction was monitored via TLC (10 % methanol in dichloromethane). After 1 hr of stirring at room temperature the reaction had gone to completion, dichloromethane (5 mL) was added followed by water (5 mL). This mixture was then added to a phase separator, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were evaporated under reduced pressure on to silica. This crude was then loaded on to a silica gel column which was ran with 100 % dichloromethane to give the title compound as a white solid.

**Yield:** 31 mg (98%).

TLC (MeOH: DCM 10%)  $R_f$  = 0.62. HRMS-ESI ( $m/z$ ) found 518.1190, calcd for  $[C_{23}H_{25}BrFN_5O_3H]^+$  518.1198.  $^1H$  NMR (500 MHz, chloroform- $d$ )  $\delta$  9.88 (s, 1H), 8.68 (s, 1H), 8.47 (d,  $^3J_{FH}$  = 11.4 Hz, 1H), 7.32 (d,  $^3J_{FH}$  = 7.4 Hz, 1H), 7.28 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H), 3.78 – 3.70 (m, 2H), 3.68 (s, 2H), 3.58 – 3.52 (m, 2H), 2.62 – 2.51 (m, 4H), 2.09 (s, 3H).  $^{13}C$  NMR (126 MHz, chloroform- $d$ )  $\delta$  169.0, 159.0 (d,  $^1J_{FC}$  = 245.4 Hz), 156.1, 155.9, 153.7, 150.0, 148.5, 140.2 (d,  $^3J_{FC}$  = 10.6 Hz), 134.3, 122.6 (d,  $^3J_{FC}$  = 3.3 Hz), 110.6 (d,  $^2J_{FC}$  = 28.1 Hz), 110.0, 108.6, 102.3, 101.4 (d,  $^2J_{FC}$  = 21.8 Hz), 61.4, 57.7, 56.4, 53.0, 52.9, 46.10, 41.3, 21.3.  $^{19}F$  NMR (376 MHz, methanol- $d_4$ )  $\delta$  -117.81 – -118.02 (m). LCMS purity 96 % (UV), Ret. time = 9.57 min.

#### Method for docking of 8a-c

Molecular Docking – Docking was performed using GLIDE 6.5 in Schrodinger Suite 2014-4. The structure of EGFR complexed with Gefitinib (pdb: 2ITY<sup>4</sup>) was prepared using the software's default minimization protocol in protein preparation wizard. Docking grids were generated using a box around Gefitinib.

8a-c were prepared for docking using LigPrep 3.2 in order to generate different protonation states of the piperazine moiety common to all 8a-c (EPIK 3.0).

8a-c were docked using GLIDE 6.5 using standard precision. The quinazoline and the halogenated phenyl coordinates in Gefitinib were used as constraints to guide docking of 8a-c.

#### References

- 1 J. Spencer, C. B. Baltus, H. Patel, N. J. Press, S. K. Callear, L. Male and S. J. Coles, *ACS Comb. Sci.*, 2011, **13**, 24–31.
- 2 WO 2004/031195 A1, 2004, 1–123.
- 3 WO 2009/097401 A1, 2009, 1–70.
- 4 C. H. Yun, T. J. Boggan, Y. Li, M. S. Woo, H. Greulich, M. Meyerson and M. J. Eck, *Cancer Cell*, 2007, **11**, 217–227.