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Supporting Information

Supplementary Information

Novel Non-steroidal Aromatase Inhibitors Based On a Biphenyl Scaffold: Synthesis, *in vitro* SAR and Molecular Modelling

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2-Bromo-4-methylbenzamide 3. 2-Bromo-4-methylbenzoic acid **1** (20 g, 93.0 mmol) and $SOCl_2$ (100 mL) set to reflux for 20 h. The reaction was then allowed to cool and excess $SOCl_2$ was removed *in vacuo* to leave dark brown residues. These residues were dissolved in THF (50 mL) and added, with stirring, to ammonia water (35%, 100 mL) which had been cooled to 0 °C. Left to stir for 1 h. Conc. $HCl_{(aq)}$ was carefully added drop wise until the mixture had reached pH 3-5. THF was removed *in vacuo* and the solids were filtered and washed thoroughly with distilled H_2O. After drying under vacuum at 70 °C **3** was obtained as an off white solid (18.8 g, 94%), mp 176-177 °C (lit.[1] 175 °C). ^{1}H NMR (270 MHz, DMSO-d_6) d 2.31 (3H, s, $ArCH_3$), 7.19-7.23 (1H, d, J=8.2 Hz, ArH), 7.28-7.31 (1H, d, J=7.7 Hz, ArH), 7.47 (1H, s, ArH), 7.50 (1H, bs, $ArCONH_2$) and 7.79 (1H, bs, $ArCONH_2$); ^{13}C NMR (67.9 MHz, DMSO-d_6) d 20.9 (CH_3), 119.1 (C), 128.6 (CH), 129.0 (CH), 133.5 (CH), 136.9 (C), 141.3 (C) and 169.6 (C); LCMS (APCI) *m/z* 216 ((^{81}BrM + H)$^+$, 90%), 214 ((^{79}BrM + H)$^+$, 100).

2-Bromo-5-methylbenzamide 4. Compound **4** was prepared from **2** (5.02 g, 23.36 mmol) using similar conditions to those described for the synthesis of compound **3**. Compound **4** was obtained as a white solid (4.30 g, 86%), mp 196-197 °C; ^{1}H NMR (270 MHz, DMSO-d_6) d 2.31 (3H, s, $ArCH_3$), 7.12-7.16 (1H, d, J=8.2 Hz, ArH), 7.21-7.22 (1H, d, J=2.0 Hz, ArH), 7.48-7.51 (1H, d, J=8.2 Hz, ArH), 7.54 (1H, bs, $ArCONH_2$) and 7.83 (1H, bs, $ArCONH_2$); ^{13}C NMR (67.9 MHz, DMSO-d_6) d 20.8 (CH_3), 115.8 (C), 129.6 (CH), 131.8 (CH), 133.0 (CH), 137.6 (C), 139.7 (C) and 169.7 (C); LCMS (APCI) *m/z* 216 ((^{81}BrM + H)$^+$, 87%), 214 ((^{79}BrM + H)$^+$, 100).

2-Bromo-4-methylbenzonitrile 5. $POCl_3$ (52.4 mL, 561 mmol), **3** (18.5 g, 86.4 mmol) and NaCl (5.56 g, 95.0 mmol) were reflux with stirring for 4 h. The mixture was allowed to cool and excess $POCl_3$ was removed *in vacuo*. The resulting brown residues were poured into ice water with stirring and left for 10 min. A brown precipitate formed and was collected via filtration, washed thoroughly with distilled H_2O and dried under vacuum at 70 °C. Recrystallisation (hexane) gave **5** as an off white crystalline solid (15.8 g, 93%), mp 52-53 °C (lit.[2] 52 °C). ^{1}H NMR (270 MHz, $CDCl_3$) d 2.39 (3H, s, ArH), 7.18-7.22 (1H, m, ArH) and 7.49-7.53 (2H, m, ArH); ^{13}C NMR (67.9 MHz, $CDCl_3$) d 21.7 (CH_3), 112.8 (C), 117.5 (C), 125.2 (C), 128.6 (CH), 133.8 (CH), 134.1 (CH) and 145.5 (C); LCMS (APCI) *m/z* 198 ((^{81}BrM + H)$^+$, 95%), 196 ((^{79}BrM + H)$^+$, 100).

2-Bromo-5-methylbenzonitrile 6. Compound **6** was prepared from compound **4** (3.63 g, 16.94 mmol) using similar conditions to those described for the synthesis of compound **5**. Recrystallisation (hexane) gave **6** as a white crystalline solid (3.32 g, 84%), mp 62-63 °C (lit.[3] 64-65 °C). ^{1}H NMR (270 MHz, $CDCl_3$) d 2.34 (3H, s, $ArCH_3$), 7.23-7.27 (1H, m, ArH), 7.44-7.45 (1H, d, J 1.7 Hz, ArH) and 7.52-7.54 (1H, d, J 8.4 Hz, ArH); ^{13}C NMR (67.9 MHz, $CDCl_3$) d 20.8 (CH_3), 115.5 (C), 117.4 (C), 121.9 (C), 133.0 (CH), 134.8 (CH), 135.0 (CH) and 138.1 (C); LCMS (APCI) *m/z* 198 ((^{81}BrM + H)$^+$, 95%), 196 ((^{79}BrM + H)$^+$, 100).

2-Bromo-4-(bromomethyl)benzonitrile 12. Compound **5** (5.00 g, 25.5 mmol), *N*-bromosuccinimide (4.99 g, 28.1 mmol), benzyl peroxide (0.198 g, 0.816 mmol) and CCl_4 (100 mL) were set to reflux for 6 h. Once cooled the succinimide was removed by filtration and solvent removed *in vacuo* to leave a viscous orange oil. The residues were dissolved in CH_2Cl_2 (100 mL) and washed with $Na_2S_2O_{3\,(aq)}$, distilled H_2O (50 mL x 3) and brine (50 mL x 2). Dried ($MgSO_4$) and solvent removed *in vacuo* to leave yellow residues. Column chromatography (CH_2Cl_2/hexane 40:60) eluted **12** as a white solid (17.8 g, 80%) which was used without further purification. LCMS (APCI) *m/z* 276 ((M + H)$^+$, 50%), 197 ((M - ^{79}Br)$^+$, 100), 195 ((M - ^{81}Br)$^+$, 100);

2-Bromo-4-(bromomethyl)-1-fluorobenzene 13. Compound **14** was prepared from **7** (5.03 g, 26.61 mmol) using similar conditions to those described for the synthesis of compound **12**. Column chromatography (EtOAc) eluted **13** as a colourless liquid (6.06 g, 85%) which was used without further purification.

2-Bromo-4-(bromomethyl)-1-chlorobenzene 14. Compound **14** was prepared from **8** (5.02 g, 24.41 mmol) using similar conditions to those described for the synthesis of compound **12**. Column chromatography (EtOAc) eluted **14** as a colourless liquid (5.97 g, 86%) which was used without further purification.

4-Bromo-2-(bromomethyl)benzonitrile 15. Compound **15** was prepared from **9** (4.95 g, 25.26 mmol), using similar conditions to those described for the synthesis of compound **12**. Column chromatography (CH_2Cl_2/hexane 40:60) eluted **15** as a white solid (5.07 g, 73%) which was used without further purification. MS (EI) *m/z* 274 ((M + H)$^+$, 34%).

2-Bromo-5-(bromomethyl)benzonitrile 17. Compound **17** was prepared from compound **6** (3.28 g, 16.75 mmol) using similar conditions to those described for the synthesis of compound **12**. Column chromatography (CH_2Cl_2/hexane 40:60) eluted **17** a white solid (4.33 g, 94%) which was used without further purification.

3-Bromo-4-(bromomethyl)benzonitrile 18. Compound **18** was prepared from **10** (2.75 g, 14.05 mmol) using similar conditions to those described for the synthesis of compound **12**. Column chromatography (CH_2Cl_2/hexane 40:60) eluted **18** as a viscous colourless oil (3.36 g, 87%) which was used without further purification.

3'-Methylbiphenyl-2-carbonitrile 70. Compound **70** was prepared from **69** (449 mg, 2.469 mmol) and *m*-tolylboronic acid using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **70** as a colourless liquid (0.458 g, 96%). ^{1}H NMR (270 MHz, $CDCl_3$) *d* 2.43 (3H, s, $ArCH_3$), 7.23-7.27 (1H, m, ArH), 7.35-7.45 (4H, m, ArH), 7.48-7.51 (1H, m, ArH), 7.59-7.65 (1H, m, ArH) and 7.73-7.76 (1H, m, ArH); ^{13}C NMR (67.9 MHz, $CDCl_3$) *d* 21.5 (CH_3), 111.4 (C), 118.8 (C), 125.9 (CH), 127.5 (CH), 128.7 (CH), 129.5 (CH), 130.1 (CH), 132.8 (CH), 133.8 (CH), 138.2 (C), 138.5 (C) and 145.8 (C) (one overlapping resonance); LCMS (APCI) *m/z* 216 ($(M + Na)^+$, 100%).

3-Bromomethyl-2-cyanobiphenyl 71. Compound **71** was prepared from compound **70** (399 mg, 2.066 mmol) using similar conditions to those described for the synthesis of compound **12**. Column chromatography (CH_2Cl_2/hexane 40:60) eluted **71** as a colourless viscous oil (0.523 g, 93%). ^{1}H NMR (270 MHz, $CDCl_3$) *d* 4.56 (2H, s, $ArCH_2Br$) and 7.43-7.81 (8H, m, ArH).

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