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 SOCl₂ (100 mL) set to reflux for 20 h. The reaction was then allowed to cool and excess SOCl₂ 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 H₂O. After drying under vacuum at 70 °C 3 was obtained as an off white solid (18.8 g, 94%), mp 176-177 °C (lit.11 175 °C). ¹H NMR (270 MHz, DMSO-d₆) δ 2.31 (3H, s, ArCH₃), 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, ArCONH₂) and 7.79 (1H, bs, ArCONH₂); ¹³C NMR (67.9 MHz, DMSO-d₆) δ 20.9 (CH₃), 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 ([M+H]+, 90%), 214 ([M+Br+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; ¹H NMR (270 MHz, DMSO-d₆) δ 2.31 (3H, s, ArCH₃), 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, ArCONH₂) and 7.83 (1H, bs, ArCONH₂); ¹³C NMR (67.9 MHz, DMSO-d₆) δ 20.8 (CH₃), 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 ([M+Br+H]+, 87%), 214 ([M+Br+H]+, 100).

2-Bromo-4-(bromomethyl)-1-chlorobenzene 14. POCl₃ (52.4 mL, 561 mmol), 3 (18.5 g, 86.4 mmol) and NaCl (5.56 g, 95.0 mmol) were refluxed with stirring for 4 h. The mixture was allowed to cool and excess POCl₃ 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 H₂O 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.12 50-51 °C). ¹H NMR (270 MHz, CDCl₃) δ 2.39 (3H, s, ArCH₃), 7.18-7.22 (1H, m, ArH) and 7.49-7.53 (2H, m, ArH); ¹³C NMR (67.9 MHz, CDCl₃) δ 21.7 (CH₃), 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 ([M+Br+H]+, 95%), 196 ([M+Br+H]+, 100).

2-Bromo-4-(bromomethyl)benzonitrile 5. POCl₃ (52.4 mL, 561 mmol), 3 (18.5 g, 86.4 mmol) and NaCl (5.56 g, 95.0 mmol) were refluxed with stirring for 4 h. The mixture was allowed to cool and excess POCl₃ 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 H₂O and dried under vacuum at 70 °C. Recrystallisation (hexane) gave 5 as an off white crystalline solid (17.8 g, 80%) which was used without further purification. LCMS (APCI) m/z 198 ([M+Br+H]+, 95%), 196 ([M+Br+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 CCl₄ (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 CH₂Cl₂ (100 mL) and washed with Na₂S₂O₃(aq.) distilled H₂O (50 mL x 3) and brine (50 mL x 2). Dried (MgSO₄) and solvent removed in vacuo to leave yellow residues. Column chromatography (CH₂Cl₂/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-78Br]+, 100), 195 ([M-81Br]+, 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 (CH₂Cl₂/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 (CH₂Cl₂/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 (CH₂Cl₂/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%). ¹H NMR (270 MHz, CDCl₃) δ 2.43 (3H, s, ArCH₃), 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); ¹³C NMR (67.9 MHz, CDCl₃) δ 21.5 (CH₃), 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 (CH₂Cl₂/hexane 40:60) eluted 71 as a colourless viscous oil (0.523 g, 93%). ¹H NMR (270 MHz, CDCl₃) δ 4.56 (2H, s, ArCH₂Br) and 7.43-7.81 (8H, m, ArH).

References


