Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Electronic Supplementary Information

Dual aromatase-sulfatase inhibitors based on the Anastrozole template: synthesis, *in vitro* SAR, molecular modelling and *in vivo* activity

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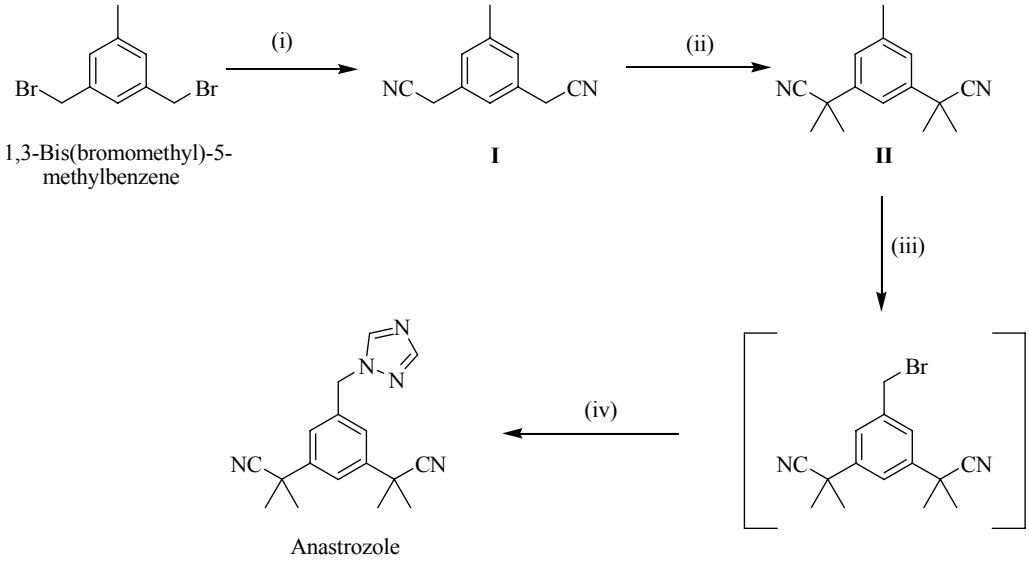
I) Synthesis of Anastrozole: Route (A)[†]



Scheme A. *Reagents and conditions.* (i) KCN, TBAB, H_2O/CH_2Cl_2, Δ, 92%; (ii) 4NaH, 4MeI, DMF, 88%; (iii) $NaBrO_3$, $NaHSO_3$, H_2O/EtOH; (iv) 1,2,4-triazole, sodium salt, K_2CO_3, DMF, 69%

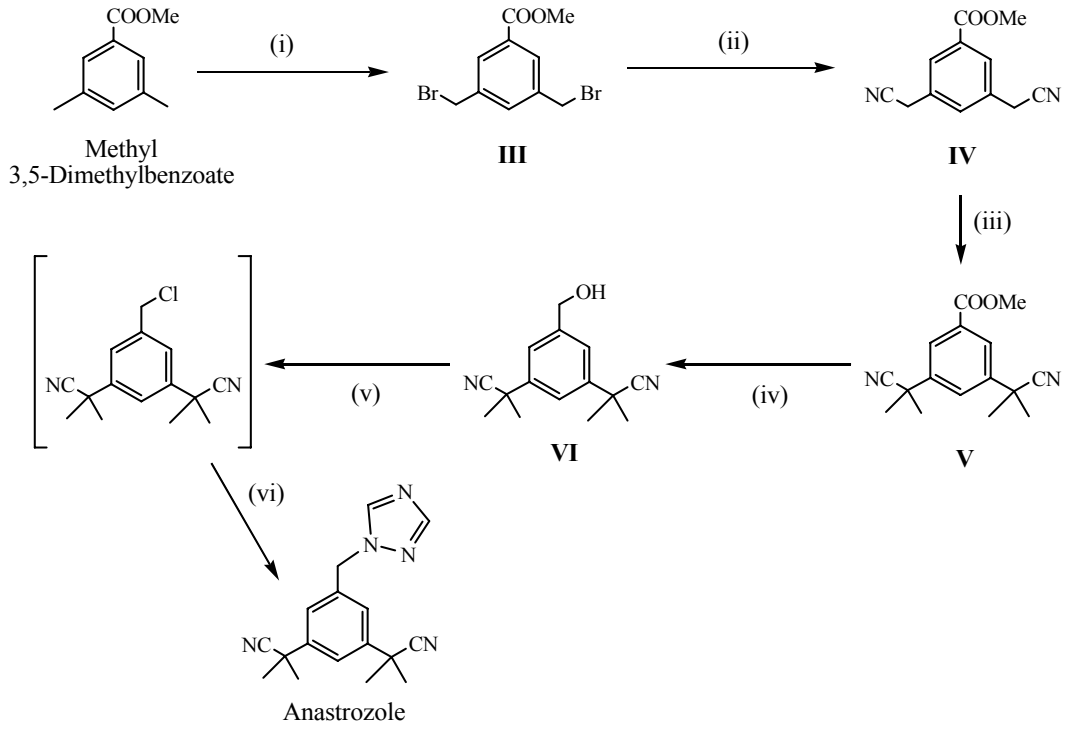
(3-Cyanomethyl-5-methyl-phenyl)-acetonitrile I. 1,3-Bis(bromomethyl)-5-methylbenzene (5.00 g, 18.0 mmol), KCN (3.00 g, 42.0 mmol) and tetrabutylammonium bromide (0.200 g, 0.602 mmol) in CH_2Cl_2 (15 mL) and H_2O (5 mL) were refluxed with vigorous stirring for 16 h. Upon cooling, dichloromethane was removed *in vacuo* and the resulting mixture diluted with EtOAc (50 mL). The organic layer was separated and washed with brine (100 mL), dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give yellow residues. Recrystallisation (EtOAc/hexane) gave the *title compound* as a white solid (2.83 g, 92%), mp 73–75 °C (lit.[1] 73-74 °C). δ_H (270 MHz, $CDCl_3$) 2.37 (3H, s, CH_3), 3.71 (4H, s, CH_2), 7.06 (1H, s, ArH) and 7.12 (2H, s, ArH); δ_C (67.9 MHz, $CDCl_3$) 21.3 (CH_3), 23.6 (CH_2), 117.8 (C), 124.6 (CH), 128.6 (CH), 130.8 (C) and 140.5 (C); *m/z* (ES^-) 168 ($(M - H)^-$, 100%); HRMS (ES^+) 171.0915. $C_{11}H_{11}N_2$ requires 171.0917.

2-[3-(Cyano-dimethyl-methyl)-5-methyl-phenyl]-2-methyl-propionitrile II. To a solution of **I** (2.70 g, 16.0 mmol) in anhydrous DMF (100 mL) at 0 °C was added cautiously NaH (2.30 g, 96.0 mmol) with stirring under an inert atmosphere. After 15 min, iodomethane (6.60 mL, 96.0 mmol) was added and the resulting suspension was set to stir at room temperature for 12h. The resulting light orange suspension was diluted with EtOAc (50 mL) and washed with distilled H_2O (50 mL x 4) and brine (50 mL) and dried ($MgSO_4$). Solvent was removed *in vacuo* to give dark yellow residues. Recrystallisation (EtOAc/hexane) gave the *title compound* as a cream solid (2.43 g, 88%), mp 124–129 °C (lit.[1] 126-127 °C). δ_H (270 MHz, $CDCl_3$) 1.72 (12H, s, CH_3), 2.39 (3H, s, CH_3), 7.22 (2H, s, ArH) and 7.30 (1H, s, ArH); δ_C (67.9 MHz, $CDCl_3$) 29.3 (CH_3), 37.3 (C), 118.7 (CH), 124.5 (C), 125.6 (CH), 139.7 (C) and 142.3 (C) (one overlapping resonance); *m/z* (ES^+) 249 ($(M + Na)^+$, 100%); HRMS (ES^+) 227.1541. $C_{15}H_{19}N_2$ requires 227.1543.

2-[3-(Cyano-dimethyl-methyl)-5-[1,2,4]triazol-1-ylmethyl-phenyl]-2-methyl-propionitrile (Anastrozole). To a biphasic mixture of **II** (2.40 g, 10.7 mmol) in EtOAc (100 mL) and $NaBrO_3$ (5.00 g, 32.0 mmol) in H_2O (150 mL),

at 0 °C, was added a solution of $NaHSO_3$ (3.50 g, 32.0 mmol) drop wise over 15 minutes. The resulting brown mixture was stirred at room temperature overnight. The phases were separated and the aqueous layer extracted with ethyl acetate (50 mL x 2). The combined organic phases were washed with $NaS_2O_{3\ (aq)}$ (100 mL), distilled H_2O (100 mL x 2) and brine (100 mL), then dried ($MgSO_4$) and solvent removed *in vacuo* to give dark yellow residues. To a solution of these residues in anhydrous DMF (10 mL) at 0 °C and under inert conditions was added 1,2,4-triazole, sodium salt (1.72 g, 19.0 mmol). The resulting light brown suspension was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with distilled H_2O (50 mL x 3) and brine (50 mL), dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give a yellow oil. Column chromatography (EtOAc) eluted the *title compound* as a white solid (2.12 g, 69%), mp 77-81 °C (lit.[1] 81-82 °C) (Found: C, 69.6; H, 6.4; N, 23.9. $C_{17}H_{19}N_5$ requires C, 69.6; H, 6.5; N, 23.9%). δ_H (270 MHz, $CDCl_3$) 1.71 (12H, s, CH_3), 5.39 (2H, s, CH_2), 7.32 (2H, m, ArH), 7.53 (1H, t, J = 1.7 Hz, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.14 (1H, s, $C_2H_2N_3$); δ_H (270 MHz, $CDCl_3$) 29.2 (CH_3), 37.4 (C), 53.1 (CH_2), 122.2 (CH), 123.9 (C), 124.4 (CH), 136.7 (C), 143.3 (C), 143.5 (CH) and 152.6 (CH); *m/z* (FAB$^+$) 316 ((M + Na)$^+$, 100%); HRMS (ES$^+$) 294.1700. $C_{17}H_{20}N_5$ requires 294.1713.

II) Synthesis of Anastrozole: Route (B)[†]



Scheme B. *Reagents and conditions.* (i) NBS, Bz_2O_2, CCl_4, Δ; (ii) KCN, TBAB, H_2O/CH_2Cl_2, Δ, 58%; (iii) 4NaH, 4MeI, DMF, 97%; (iv) $LiBH_4$, THF, Δ, 93%; (v) Pyr, CH_2Cl_2, $SOCl_2$; (vi) 1,2,4-triazole, sodium salt, K_2CO_3, DMF, 43%

3,5-Bis-bromomethyl-benzoic acid methyl ester III. To a solution of methyl 3,5-dimethylbenzoate (15.0 g, 89.5 mmol) in CCl_4 (150 mL) was added *N*-bromosuccinimide (16.1 g, 89.5 mmol) and benzoyl peroxide (0.200 g, 0.826 mmol). The resulting light yellow suspension was set to reflux and a deep orange colouration developed. When the colour of the suspension returned to light yellow again about 45 min later, the reflux was terminated. After cooling to room temperature, the suspension was filtered and the filtrates were evaporated to give a yellow liquid. Column chromatography (EtOAc/hexane 10:90 increasing to 50:50) eluted the *title compound* as a white crystalline solid (1.99 g, 7%), mp 100-103 °C (lit.[1] 99-101 °C). δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, $COOCH_3$), 4.49 (4H, s, CH_2), 7.60 (1H, t, J = 2.0 Hz, ArH) and 7.97 (2H, d, J = 2.0 Hz, ArH).

3,5-Bis-cyanomethyl-benzoic acid methyl ester IV. Compound **III** (2.87 g, 8.91 mmol), KCN (1.45 g, 21.4 mmol) and tetrabutylammonium bromide (0.100 g, 0.301 mmol) in CH_2Cl_2 (15 mL) and H_2O (5 mL) were refluxed with vigorous stirring for 4 h. Upon cooling, dichloromethane was removed *in vacuo* and the resulting mixture diluted with EtOAc (50 mL). The organic layer was separated and washed with brine (100 mL), dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give yellow residues. Column chromatography (EtOAc

/hexane, 50:50) eluted the *title compound* as a white solid (1.11 g, 58%), mp 91–93 °C (lit.[1] 90-92 °C) (Found: C, 67.1; H, 4.7; N 13.0. $C_{12}H_{10}N_2O_2$ requires C, 67.3; H, 4.7; N, 13.1%); δ_H (270 MHz, $CDCl_3$) 3.82 (4H, s, CH_2), 3.95 (3H, s, $COOCH_3$), 7.53 (1H, s, ArH) and 7.99 (2H, s, ArH).

3,5-Bis-(cyano-dimethyl-methyl)-benzoic acid methyl ester V. To a solution of **IV** (1.09 g, 5.09 mmol) in anhydrous DMF (20 mL) at 0 °C was added cautiously NaH (0.537 g, 22.4 mmol) with stirring under an inert atmosphere. After 15 min, iodomethane (1.39 mL, 22.4 mmol) was added and the resulting suspension was set to stir at room temperature for 12h. The resulting light orange suspension was diluted with EtOAc (50 mL) and washed with distilled H_2O (50 mL x 4) and brine (50 mL) and dried ($MgSO_4$). Solvent was removed *in vacuo* to give dark yellow residues. Column chromatography (EtOAc/hexane 50:50) eluted the *title compound* as a cream solid (1.33 g, 97%), mp 85–87 °C (lit.[1] 83-85 °C) (Found: C, 71.1; H, 6.8; N, 10.3. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%); δ_H (270 MHz, $CDCl_3$) 1.77 (12H, s, CH_3), 3.95 (3H, s, $COOCH_3$), 7.80 (1H, t, J = 2.0 Hz, ArH) and 8.08 (2H, d, J = 2.0 Hz, ArH).

2-[3-(Cyano-dimethyl-methyl)-5-hydroxymethyl-phenyl]-2-methyl-propionitrile VI. To a mixture of **V** (0.540 g, 0.200 mmol) and $LiBH_4$ (0.087 g, 0.400 mmol) at room temperature and under inert conditions was added anhydrous THF (10 mL). The resulting yellow solution was set to reflux for 3 h, then cooled to 0 °C and treated drop wise with 1M $HCl_{(aq)}$ until the mixture remained acidic. EtOAc (100 mL) was added and the organic layer was washed with distilled H_2O (50 mL x 3) and brine (50 mL) and dried ($MgSO_4$). Solvent was removed *in vacuo* to give the *title compound* as a white solid (0.460 g, 99%), mp 150–160 °C (lit.[1] 151-153 °C); δ_H (270 MHz, CDCl3) 1.75 (12H, s, CH3), 4.76 (2H, s, C*H*$_2$OH), 7.44 (2H, br s, ArH) and 7.46 (1H, d, J = 1.7 Hz, ArH) [$ArCH_2OH$ signal not found]; *m/z* (FAB^+) 396 ((M + H + NBA)$^+$, 25%), 225 ((M – OH)$^+$, 100).

2-[3-(Cyano-dimethyl-methyl)-5-[1,2,4]triazol-1-ylmethyl-phenyl]-2-methyl-propionitrile (Anastrozole). To a solution of **VI** (0.443 g, 1.83 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C under inert conditions was added anhydrous pyridine (0.15 mL, 1.90 mmol) followed by $SOCl_2$ (0.19 mL, 2.59 mmol). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 2 h before subjecting to reflux for 1 h. Upon cooling, the solvent was removed *in vacuo* to leave white residues which were dissolved in EtOAc (50 mL). The solution was washed with distilled H_2O (50 mL x 3) and brine (50 mL) and dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give pale yellow residues. To a solution of these residues in anhydrous DMF (4 mL) at 0 °C and in inert conditions was added 1,2,4-triazole, sodium salt (0.367 g, 3.63 mmol). The resulting light brown suspension was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with distilled H_2O (50 mL x 3) and brine (50 mL), dried ($MgSO_4$), filtered and solvent removed *in vacuo* to give a yellow oil. Column chromatography (EtOAc) eluted the *title compound* as a white solid (0.279 g, 52%). Analytical data corresponds to that obtained by method (A).

Notes and References

1. U. S. Patent 4,935,437

† Routes are adapted from U.S. Patent 4,935,437 and U.S. Patent RE 36617. Spectroscopic and additional analytical data are provided.

III) Experimental data for 1, 2, 3(a)–(c), 4(a)–(c), 5(a)-(c), 20–23

3-Bromomethyl-5-methyl-benzoic acid methyl ester 1. To a solution of $NaBrO_3$ (13.8 g, 91.5 mmol) in distilled H_2O (45.8 mL) was added methyl 3,5-dimethylbenzoate (5.00 g, 30.5 mmol) in EtOAc (15.3 mL). To this mixture $NaHSO_3$ (11.0 g, 91.5 mmol) in distilled H_2O (91.5 mL) was added drop wise with vigorous stirring over 1 h. The reaction mixture was stirred for a further 4 h at room temperature. The organic portion was separated and diluted with Et_2O (100 mL). This was then washed with saturated $Na_2SO_{3(aq)}$ (50 mL), distilled H_2O (50 mL x 2), and brine (50 mL). Dried ($MgSO_4$), filtered and solvent removed *in vacuo* to leave yellow residues. The residues were dissolved in hexane (50 mL) and the resulting solution cooled to 0 °C for 30 min. A white ppt (3,5-bis-bromomethylbenzoic acid methyl ester) was removed via filtration. The filtrate was reduced *in vacuo* to a yellow viscous oil. Column chromatography (EtOAc/hexane 10:90) eluted **1** (6.30 g, 85%) as a clear colourless oil. δ_H (270 MHz, $CDCl_3$) 2.37 (3H, s, $ArCH_3$), 3.89 (3H, s, $ArCO_2CH_3$), 4.47 (2H, s, $ArCH_2Br$), 7.38 (1H, s, ArH), 7.77 (1H, s, ArH) and 7.84 (1H, s, ArH); *m/z* ($APCI^+$) 245 ((^{81}BrM + H)$^+$, 100%), 243 ((^{79}BrM + H)$^+$, 90).

3-Cyanomethyl-5-methyl-benzoic acid methyl ester 2. With vigorous stirring a mixture of **1** (19.5 g, 80.1 mmol), KCN (6.26 g, 96.1 mmol) and tetrabutylammonium bromide (1.33 g, 4.00 mmol) with CH_2Cl_2 (100 mL) and distilled H_2O (40 mL) was set to reflux for 24 h. On cooling the organic fraction was separated and washed

with distilled H_2O (100 mL x 2) and brine (100 mL) then dried ($MgSO_4$) and solvent removed *in vacuo* to leave a red/orange oil. Column chromatography (hexane/EtOAc 50:50) gave **2** (11.39 g, 75%) as a pale yellow solid, mp 56-57 °C. δ_H (270 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 3.79 (2H, s, $ArCH_2CN$), 3.89 (3H, s, $ArCO_2CH_3$), 7.34 (1H, s, ArH), 7.76 (1H, s, ArH) and 7.79 (1H, s, ArH); *m/z* ($APCI^-$) 188 ($(M - H)^-$, 100%); HRMS (ES^+) 190.0867. $C_{11}H_{12}NO_2$ requires 190.0863.

3-(Cyano-dimethyl-methyl)-5-methyl-benzoic acid methyl ester 3(a). Under inert conditions **2** (7.00 g, 37.0 mmol) was dissolved in anhydrous THF (20 mL) to give a yellow solution. With stirring this solution was cooled to 0 °C under inert conditions and NaH (2.22 g, 92.5 mmol) was added gradually and then left to stir at 0 °C for 15 min. Iodomethane (11.6 mL, 81.4 mmol) was then added drop wise. The resulting suspension was left to stir at room temperature for 16 h. Propan-2-ol (5 mL) was carefully added to the reaction mixture followed by CH_2Cl_2 (50 mL) which was then washed with distilled H_2O (50 mL x 2) and brine (50 mL). Dried ($MgSO_4$) and solvent removed *in vacuo* to leave a red/orange oil. Column chromatography (EtOAc/hexane 10:90) eluted **3(a)** as a light yellow solid (6.29 g, 78%), mp 53-55 °C. δ_H (270 MHz, $CDCl_3$) 1.73 (6H, s, $ArC(CH_3)_2CN$), 2.41 (3H, s, $ArCH_3$), 3.91 (3H, s, $ArCO_2CH_3$), 7.51 (1H, s, ArH), 7.79 (1H, s, ArH) and 7.87 (1H, s, ArH); *m/z* ($APCI^+$) 218 ($(M + H)^+$, 83 %), 192 ($(M – CN)^+$, 100); HRMS (ES^+) 218.1181. $C_{13}H_{16}NO_2$ requires 218.1176.

3-(1-Cyano-cyclobutyl)-5-methyl-benzoic acid methyl ester 3(b). Under inert conditions compound **2** (1.50 g, 7.93 mmol) was dissolved in anhydrous DMF (10 mL) and the solution cooled with stirring to 0 °C. NaH (0.476 g, 19.8 mmol) was carefully added resulting in a deep red colouration and evolution of gas. After 15 min at 0 °C 1,3-dibromopropane (0.960 mL, 9.48 mmol) was added drop wise over 5 min. The reaction was allowed to warm to room temperature and left to stir for 1 h. EtOAc (50 mL) was added to the reaction mixture and this was washed with distilled H_2O (50 mL x 4) and brine (50 mL). The organic layer was separated and dried ($MgSO_4$), filtered and solvent removed *in vacuo*. Column chromatography (EtOAc/hexane 30:70) eluted **3(b)** as a colourless oil (0.783 g, 43%). δ_H (270 MHz, $CDCl_3$) 2.00-2.23 (1H, m, CH_2), 2.35-2.52 (4H, m, $ArCH_3$ & CH_2), 2.55-2.69 (2H, m, CH_2), 2.77-2.89 (2H, m, CH_2), 3.91 (3H, s, $ArCO_2CH_3$), 7.39 (1H, s, ArH), 7.79 (1H, s, ArH) and 7.85 (1H, s, ArH); *m/z* ($APCI^-$) 230 ($(M - H)^-$, 22 %), 203 ($(M – CN)^-$, 100)); HRMS (ES^+) 230.1176. $C_{14}H_{16}NO_2$ requires 230.1176.

3-(1-Cyano-cyclopropyl)-5-methyl-benzoic acid methyl ester 3(c). Compound **3(c)** was prepared from **2** using similar conditions to those described for the synthesis of compound **3(b)**. Column chromatography (EtOAc/hexane 30:70) eluted **3(c)** as a colourless oil (0.600 g, 35%), (Found: C, 72.3; H, 6.0; N, 6.4. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5 %). δ_H (270 MHz, $CDCl_3$) 1.40-1.45 (2H, dd, J = 3.0 & 5.0 Hz, CH_2), 1.71-1.76 (2H, dd, J = 3.7 & 5.0 Hz, CH_2), 2.39 (3H, s, $ArCH_3$), 3.89 (3H, s, $ArCO_2CH_3$), 7.39 (1H, s, ArH), 7.62 (1H, s, ArH) and 7.75 (1H, s, ArH); *m/z* ($APCI^+$) 216 ($(M + H)^+$, 100 %), 158 (92).

3-Bromomethyl-5-(cyano-dimethyl-methyl)-benzoic acid methyl ester 4(a). Compound **4(a)** was prepared from **3(a)** using similar conditions to those described for the synthesis of compound **1**. Compound **4(a)** was isolated as a light brown viscous oil (9.30 g, 75%) and used without further purification. *m/z* ($APCI^+$) 298 ($(^{81}BrM+ H)^+$, 15%), 296 ($(^{79}BrM + H)^+$, 15), 272 ($(^{81}BrM - CN)^+$, 100), 270 ($(^{79}BrM - CN)^+$, 100).

3-Bromomethyl-5-(1-cyano-cyclobutyl)-benzoic acid methyl ester 4(b). Compound **4(b)** was prepared from **3(b)** using similar conditions to those described for the synthesis of compound **1**. Column chromatography (EtOAc/hexane 25:75) eluted **4(b)** as a white crystalline solid (1.00 g, 96%), mp 94-95 °C. δ_H (270 MHz, $CDCl_3$) 2.04-2.21 (1H, m, CH_2), 2.31-2.54 (1H, m, CH_2), 2.57-2.70 (2H, dd, J = 2.0 & 9.7 Hz, CH_2), 2.81-2.90 (2H, m, CH_2), 3.93 (3H, s, $ArCO_2CH_3$), 4.50 (2H, s, $ArCH_2Br$), 7.61 (1H, s, ArH) and 8.00 (2H, s, ArH); *m/z* (EI^+) 309 ($(^{81}BrM + H)^+$, 19%), 307 ($(^{79}BrM + H)^+$, 21), 280 ($(^{81}BrM - CN)^+$, 53), 278 ($(^{79}BrM - CN)^+$, 54), 200 (((M - CN) – $Br)^+$, 100).

3-Bromomethyl-5-(1-cyano-cyclopropyl)-benzoic acid methyl ester 4(c). Compound **4(c)** was prepared from **3(c)** using similar conditions to those described for the synthesis of compound **1**. Column chromatography (EtOAc/hexane 25:75) eluted **4(c)** as a white crystalline solid (0.760 g, 96%), mp 78-80 °C. δ_H (270 MHz, $CDCl_3$) 1.44-1.49 (2H, dd, J = 2.7 & 5.0 Hz, CH_2), 1.76-1.79 (2H, dd, J = 2.7 & 5.0 Hz, CH_2), 3.91 (3H, s, $ArCO_2CH_3$), 4.48 (2H, s, $ArCH_2Br$), 7.59 (1H, s, ArH), 7.76 (1H, s, ArH) and 7.97 (1H, s, ArH); *m/z* ($APCI^+$) 296 ($(^{81}BrM + H)^+$, 65%), 294 ($(^{79}BrM + H)^+$, 70), 214 ($(M – Br)^+$, 100).

3-(Cyano-dimethyl-methyl)-5-[1,2,4]triazol-1-ylmethyl-benzoic acid methyl ester 5(a). Compound **4(a)** (9.30 g, 31.4 mmol), 1,2,4-triazole (3.25 g, 47.1 mmol), K_2CO_3 (4.34 g, 31.4 mmol), KI (0.31 g, 1.85 mmol) and acetone (200 mL) were loaded to a reaction vessel. With vigorous stirring this mixture was set to reflux for 22 h. The reaction mixture was allowed to cool and acetone was removed *in vacuo*. The residues were taken up in EtOAc (50

mL) and washed with distilled H_2O (50 mL x 3) and brine (50 mL). Dried ($MgSO_4$) and solvent removed *in vacuo* to leave dark brown residues. Column chromatography (EtOAc/hexane 15:85 then EtOAc) eluted **5(a)** as a brown solid (3.70 g, 60%), mp 78-79 °C. δ_H (270 MHz, $CDCl_3$) 1.72 (6H, s, $ArC(CH_3)_2CN$), 3.90 (3H, s, $ArCO_2CH_3$), 5.40 (2H, s, $ArCH_2Br$), 7.60 (1H, s, ArH), 7.85 (1H, s, ArH), 7.98 (1H, s, $C_2H_2N_3$), 8.07 (1H, s, ArH) and 8.14 (1H, s, $C_2H_2N_3$); *m/z* ($APCI^+$) 285 ($(M + H)^+$, 100%), 216 (45); HRMS (ES^+) 285.1342. $C_{15}H_{17}N_4O_2$ requires 285.1346.

3-(1-Cyano-cyclobutyl)-5-[1,2,4]triazol-1-ylmethyl-benzoic acid methyl ester 5(b). Compound **5(b)** was prepared from **4(b)** using similar conditions to those described for the synthesis of compound **5(a)**. Column chromatography (EtOAc/hexane 50:50 then EtOAc) eluted **5(b)** as a colourless viscous oil (0.410 g, 43%). δ_H (270 MHz, $CDCl_3$) 1.99-2.13 (1H, m, CH_2), 2.36-2.50 (1H, m, CH_2), 2.52-2.66 (2H, m, CH_2), 2.77-2.88 (2H, m, CH_2), 3.91 (3H, s, $ArCO_2CH_3$), 5.39 (2H, s, $ArCH_2N$), 7.49 (1H, s, ArH), 7.85 (1H, s, ArH), 7.97 (1H, s, $C_2H_2N_3$), 8.04 (1H, s, ArH) and 8.14 (2H, s, $C_2H_2N_3$); *m/z* ($APCI^+$) 297 ($(M + H)^+$, 100%), 214 (50); HRMS (ES^+) 297.1335. $C_{16}H_{17}N_4O_2$ requires 297.1346.

3-(1-Cyano-cyclopropyl)-5-[1,2,4]triazol-1-ylmethyl-benzoic acid methyl ester 5(c). Compound **5(c)** was prepared from **4(c)** using similar conditions to those described for the synthesis of compound **5(a)**. Column chromatography (EtOAc/hexane 25:75 then EtOAc) eluted **5(c)** as a colourless viscous oil (0.444 g, 59%) (Found: C, 63.5; H, 5.0; N, 19.8. $C_{15}H_{14}N_4O_2$ requires C, 63.8; H, 5.0; N, 19.9%). δ_H (270 MHz, $CDCl_3$) 1.39-1.45 (2H, dd, J = 3.0 & 5.8 Hz, CH_2), 1.76-1.80 (2H, dd, J = 3.0 & 5.8 Hz, CH_2), 3.89 (3H, s, $ArCO_2CH_3$), 5.38 (2H, s, $ArCH_2N$), 7.49 (1H, s, ArH), 7.80 (1H, s, ArH), 7.82 (1H, s, ArH), 7.98 (1H, s, $C_2H_2N_3$), and 8.12 (1H, s, $C_2H_2N_3$); *m/z* ($APCI^+$) 283 ($(M + H)^+$, 100%), 214 (75).

1-Bromo-3-bromomethyl-5-methylbenzene 20. Compound **20** was prepared from 5-bromo-*m*-xylene (16.76 g, 91.55 mmol) using similar conditions to those described for the synthesis of compound **1**. Column chromatography (hexane) eluted **20** as a clear, colourless oil that crystallised on standing to give a white crystalline solid (14.5 g, 54.93 mmol, 60%), mp 57-60 °C. δ_H (270 MHz, $CDCl_3$) 2.31 (3H, s, $ArCH_3$), 4.38 (2H, s, $ArCH_2Br$), 7.11 (1H, s, ArH), 7.25 (1H, s, ArH) and 7.32 (1H, s, ArH).

(3-Bromo-5-methyl-phenyl)acetonitrile 21. Compound **21** was prepared from **20** (11.25 g, 42.65 mmol) using similar conditions to those described for the synthesis of compound **2**. Column chromatography (hexane/CH_2Cl_2 50:50) eluted **21** as a clear yellow oil (6.63 g, 31.56 mmol, 74%). δ_H (270 MHz, $CDCl_3$) 2.31 (3H, s, $ArCH_3$), 3.66 (2H, s, $ArCH_2CN$), 7.06 (1H, s, ArH), 7.25 (1H, s, ArH) and 7.27 (1H, s, ArH); *m/z* ($APCI^+$) 212 ($(^{81}BrM + H)^+$, 53%), 210 ($(^{79}BrM + H)^+$, 55), 185 (80), 183 (76).

2-(3-Bromo-5-methylphenyl)-2-methyl-propionitrile 22. Compound **22** was prepared from **21** (6.0 g, 28.59 mmol) using similar conditions to those described for the synthesis of compound **3(a)**. Column chromatography (hexane/CH_2Cl_2 50:50) eluted **22** as a light yellow oil (5.65 g, 23.73 mmol, 83%). δ_H (270 MHz, $CDCl_3$) 1.68 (6H, s, $ArC(CH_3)_2CN$), 2.33 (3H, s, $ArCH_3$), 7.20 (1H, s, ArH), 7.26 (1H, s, ArH) and 7.34 (1H, s, ArH); *m/z* ($APCI^+$) 240 ($(^{81}BrM + H)^+$, 3%), 238 ($(^{79}BrM + H)^+$, 4), 213 ($(^{81}BrM - CN)^+$, 100), 211 ($(^{79}BrM - CN)^+$, 96), 158 (18).

2-(3-Bromo-5-bromomethyl-phenyl)-2-methylpropionitrile 23. Compound **23** was prepared from **22** (5.06 g, 21.25 mmol) using similar conditions to those described for the synthesis of compound **1**. Column chromatography (hexane/CH_2Cl_2 50:50) eluted **23** as a colourless viscous oil (3.64 g, 11.48 mmol, 54%). δ_H (270 MHz, $CDCl_3$) 1.71 (6H, s, $ArC(CH_3)_2CN$), 4.41 (2H, s, $ArCH_2Br$), 7.40-7.41 (1H, t, J = 1.7 Hz, ArH) and 7.48-7.51 (2H, m, ArH); *m/z* (FAB^+) 319 ($(^{81}BrM + H)^+$, 100%), 317 ($(^{79}BrM + H)^+$, 100).