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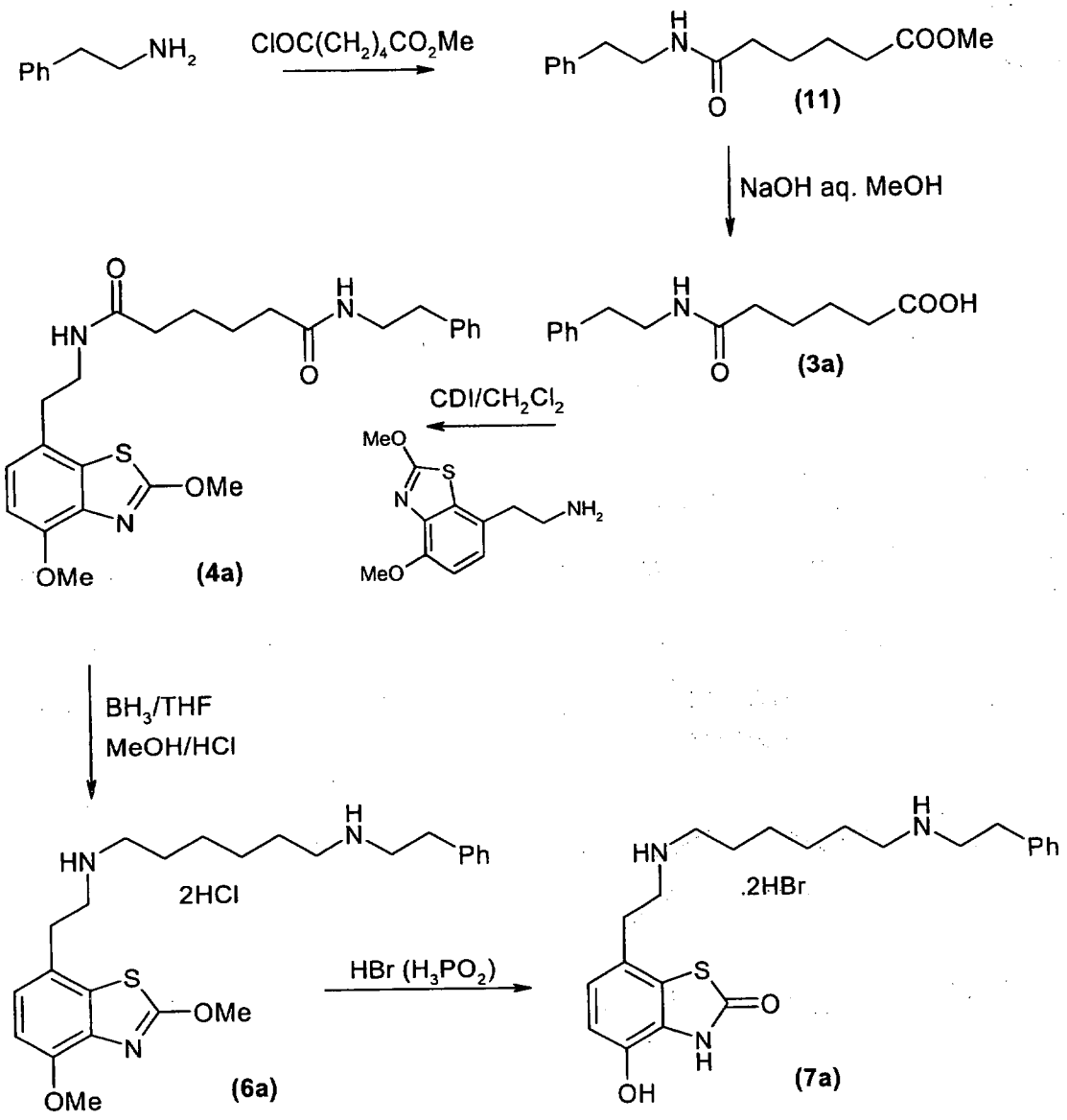
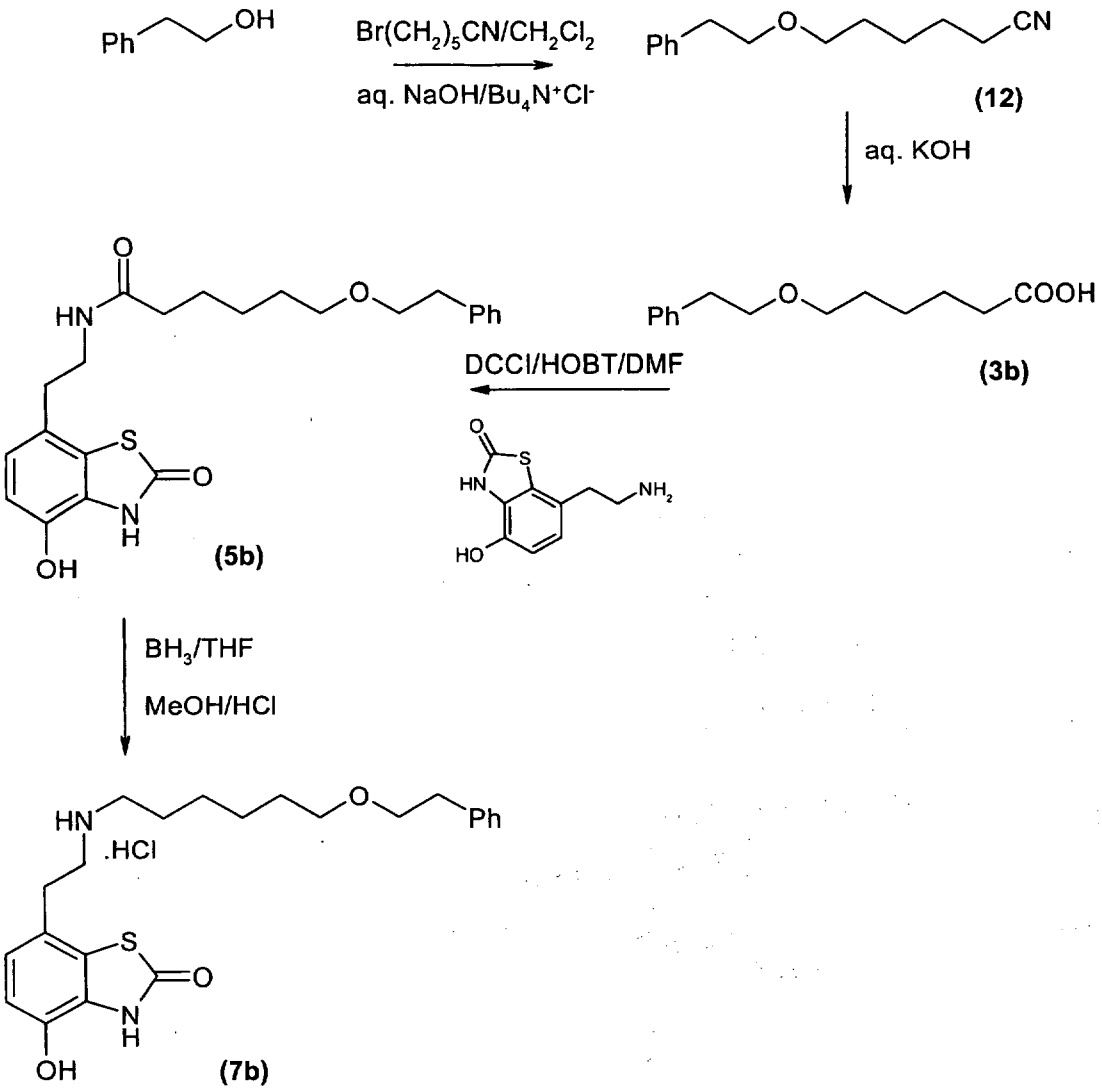
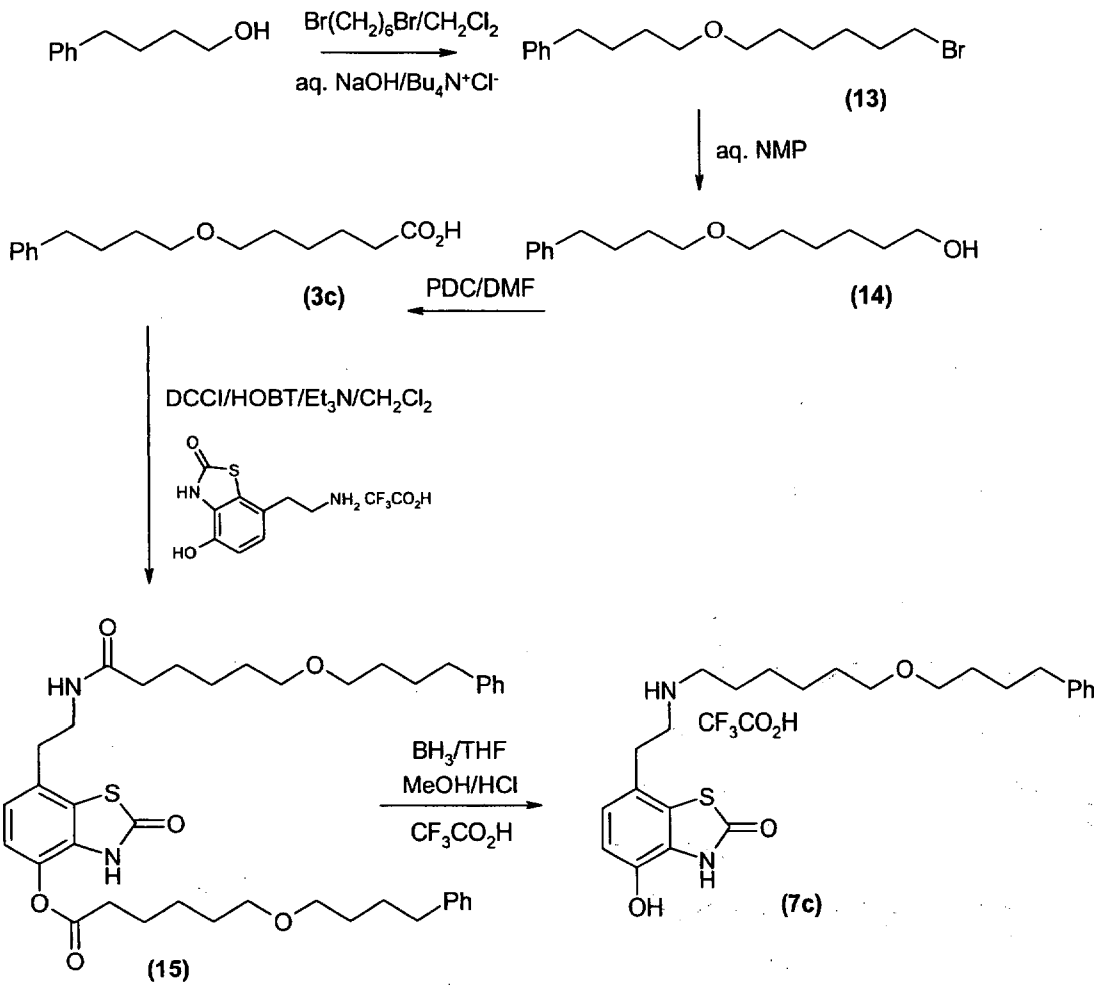
Reaction scheme for the synthesis of 7a



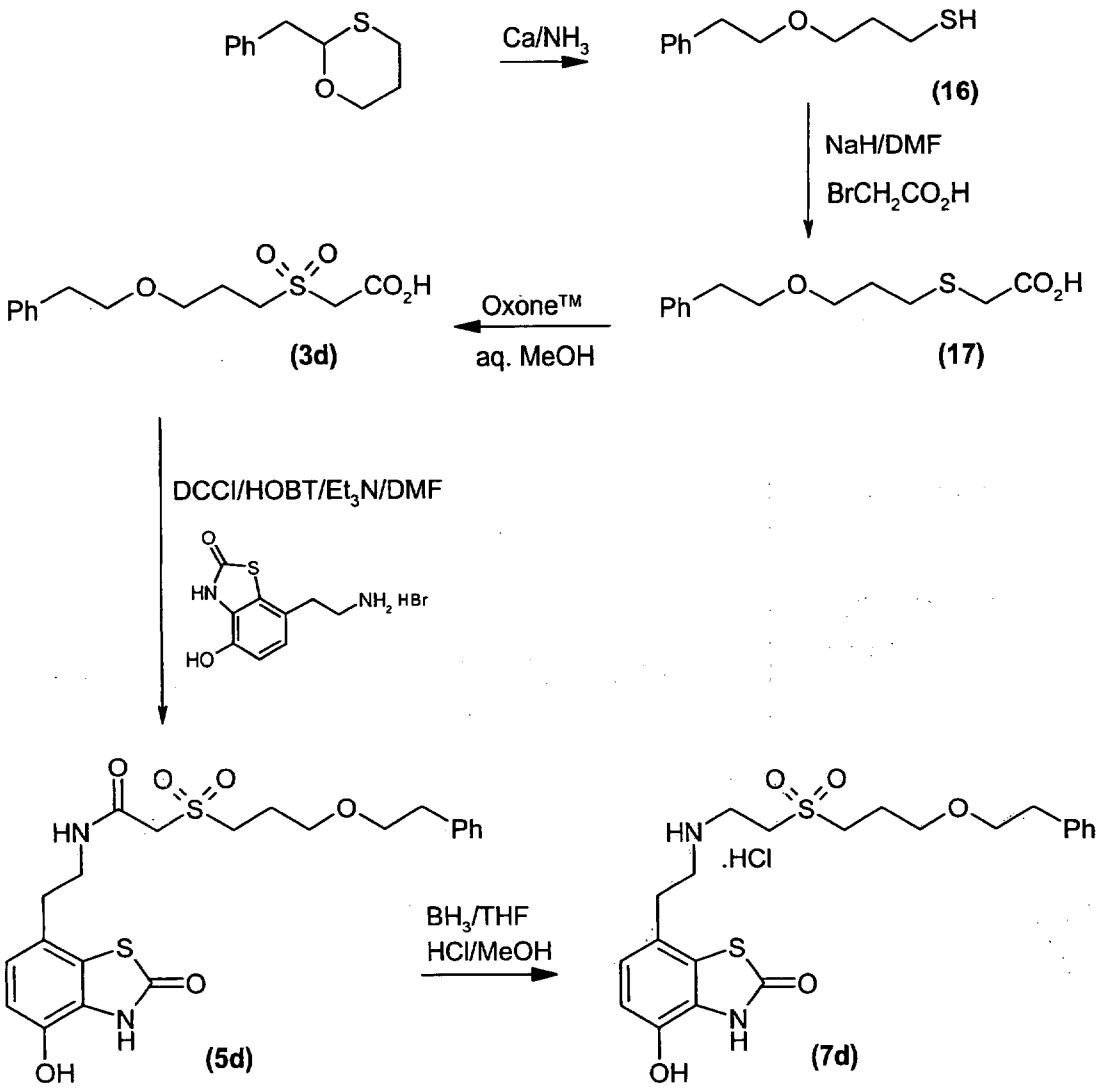
Reaction scheme for the synthesis of 7b



Reaction scheme for the synthesis of 7c



Reaction scheme for the synthesis of 7d



Experimental

General Experimental

Anhydrous tetrahydrofuran (THF) and dimethylformamide (DMF) were purchased from Aldrich. AR grade solvents were used for chromatography; in other cases SLR grade solvents were generally used. Unless otherwise stated, evaporation refers to the process of removing solvents under reduced pressure using a rotary evaporator with variable temperature water bath. Analytical thin layer chromatography was carried out on commercially available aluminium sheets coated with silica gel (Whatman silica gel F254), spots were visualised with UV light. Flash chromatography refers to the method of Still *et al.*[1] using silica gel (Matrix Silica 60). HPLC purifications were carried out using a Dynamax C18 reverse phase column eluting with water containing 0.1% trifluoroacetic acid and the appropriate amount of methanol co-solvent or using water containing with 0.1% trifluoroacetic acid and a gradient of methanol as co-solvent. Proton magnetic resonance spectra were obtained using a Bruker AM 360 MHz spectrometer and the signals are quoted on the δ scale from tetramethylsilane as the internal standard. Infrared spectra were recorded using a Perkin Elmer 1720X FT IR spectrometer with absorptions being quoted in cm^{-1}; solids were mixed with potassium bromide and spectra measured by diffuse reflectance whereas liquids were measured as thin films. Mass spectra were obtained with a VG analytical 70-250SEQ or a VG analytical 70-250S instrument; spectra were recorded using electron impact (EI), or fast atom bombardment (FAB) ionisation techniques (some samples were derivatised with N,O-bis(trimethylsilyl)trifluoroacetamide prior to the measurement of the mass spectrum by EI). Microanalyses were performed using a Carlo Erba EA

1108 elemental analyser; unless otherwise stated analyses agree with the calculated data within ±0.4 %.

4-Hydroxy-7-[2-[6-(2-phenylethylamino)hexyl]aminoethyl]benzothiazol-2(3H)-one dihydrobromide (7a).

6-Oxo-6-(2-phenylethyl)aminohexanoic acid, methyl ester (11). 5-Chloroformylpentanoic acid, methyl ester (17.9 g, 0.1 mol) in dichloromethane (50 mL) was added dropwise to solution of 2-phenylethylamine (12.5 mL, 0.1 mol) and triethylamine (14 mL, 0.1 mol) in dichloromethane (100 mL). The mixture was stirred at room temperature for 1 h and then heated at reflux temperature for 1 h. The solvent was evaporated and ethyl acetate added. The organic phase was separated and washed with dilute HCl, water and $NaHCO_3$ solution, dried ($MgSO_4$) and filtered. The filtrate was evaporated affording **11** as a cream solid (24.6 g, 93 %): ^{1}H NMR ($CDCl_3$) 1.6 (m, 4H), 2.1 (t, 2H), 2.3 (t, 2H), 2.8 (t, 2H), 3.5 (q, 2H), 3.7 (s, 3H), 5.6 (s, 1H), 7.2 (m, 5H); MS (EI) m/z: 263 [M^+], 104 (100 %).

6-Oxo-6-(2-phenylethyl)aminohexanoic acid (3a). To a solution of **11** (24.6g, 93.5 mmol) in methanol (150 mL) was added a solution of sodium hydroxide (4 g, 10.3 mmol) in water (50 mL) and the mixture heated at reflux temperature for 2 h. The methanol was evaporated, the residue acidified with dilute HCl and extracted with ethyl acetate. The organic phase was separated, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated and the crude product crystallised from ethyl acetate affording **3a** as a white solid (15.6 g, 67 %): mp 114 ^{0}C; ^{1}H NMR ($CDCl_3$) 1.6 (m, 4H), 2.1 (t, 2H), 2.4 (t, 2H), 2.8 (t, 2H), 3.5 (q, 2H), 3.6 (q, 2H), 5.6 (s, 1H), 7.2 (m, 5H), 8.1 (s, 1H); IR 1642, 1695, 2950, 3300; MS (EI) m/z: 249 [M^+], 104 (100%). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

***N*-[2-(2,4-dimethoxybenzothiazol-7-yl)ethyl]-*N'*-(2-phenylethyl)hexanediamide (4a).** A solution of **3a** (1.92 g, 7.7 mmol) in dichloromethane (80 mL) was stirred under an atmosphere of nitrogen during the addition of *N,N'*-carbonyldiimidazole (1.26 g, 7.8 mmol). After 1.75 h, 2-(2,4-dimethoxybenzothiazol-7-yl)ethanamine[2] (1.7 g, 7.1 mmol) in dichloromethane (50 mL) was added and the mixture stirred for 72 h. Water was added and the product extracted with dichloromethane. The organic phase was washed with dilute HCl, water, $NaHCO_3$ solution and water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to yield **4a** which was used without further purification (1.81 g, 54 %): MS (FAB) m/z: 470 (100 %) $[(M+H)^+]$.

***N*-[2-(2,4-Dimethoxybenzothiazol-7-yl)ethyl]-*N'*-(2-phenylethyl)hexane-1,6-diamine dihydrochloride (6a).** A suspension of **4a** (1.81 g, 3.9 mmol) in dry THF (150 mL) was stirred under an atmosphere of nitrogen. A solution of borane in THF (35 mL of a 1M solution, 35 mmol) was added and the mixture heated at reflux temperature for 5 h and then cooled to room temperature. After the gradual addition of methanol (100 mL) the mixture was stirred for 72 h. The solvents were evaporated, methanol (100 mL) and concentrated HCl (5 mL) were added and the mixture was heated at reflux temperature for 1.5 h. The methanol was evaporated affording **6a** as an oil that was used without further purification (2 g, 64 %): MS (FAB) m/z: 442 $[(M+H)^+]$.

4-Hydroxy-7-[2-[6-(2-phenylethyl)aminohexyl]aminoethyl]benzothiazol-2(3H)-one dihydrobromide (7a). A solution of **6a** (2 g, 4.5 mmol) in a mixture of 48% aqueous hydrobromic acid (50 mL) and hypophosphorous acid (0.2 mL) was heated at reflux temperature for 5 h. The mixture was evaporated and the residue treated with methanol/diethyl ether to give the crude product. This was purified by reverse phase HPLC and, after conversion to the dihydrobromide salt, afforded **7a** as a white solid

(0.06 g, 2 %): mp 302-303 °C (dec); ^{1}H NMR (d_6-DMSO) 1.3-1.4 (br, 4H), 1.57-1.68 (br, 4H), 2.82-3.02 (m, 8H), 3.05-3.22 (m, 4H), 6.75-7.39 (m, 7H), 8.58 (brs, 4H), 10.10 (s, 1H), 11.76.(s, 1H); MS(FAB) m/z: 414 [$(M+H)^+$]; IR 1444, 1519, 1594, 1657, 2431, 2804, 2949, 3310. Anal. ($C_{23}H_{31}N_3O_2S.2HBr$) C, H, N, S.

4-Hydroxy-7-[2-[6-(2-phenylethoxy)hexyl]aminoethyl]benzothiazol-2(3H)-one hydrochloride (7b).

6-(2-Phenylethoxy)hexanonitrile (12). Sodium hydroxide (97.7 g, 2.44 mol) was dissolved in water (200 mL) and the solution cooled to room temperature, 2-phenylethanol (36.6 g, 0.3 mol) was added, followed by 6-bromocapronitrile (43.0 g, 0.244 mol), tetrabutylammonium chloride (10 g) and dichloromethane (10 mL). The mixture was stirred vigorously at room temperature for 2 days. A further portion of 2-phenylethanol (10 mL) was added and stirring continued for 3 days. The aqueous layer was separated and extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) eluting with petroleum ether : diethyl ether (1:1) affording **12** as an oil which was used without further purification (34.2 g, 65 %): ^{1}H NMR ($CDCl_3$) 1.49 (m, 2H), 1.62 (m, 4H), 2.31 (t, 2H), 2.88 (t, 2H), 3.44 (t, 2H), 3.61 (t, 2H), 7.2 (m, 5H); GC/MS m/z: 217 [M^+ (weak)], 96 (100%). Anal. ($C_{14}H_{19}NO$) C, H, N.

6-(2-Phenylethoxy)hexanoic acid (3b). **12** (4.4 g, 0.02 mol) was mixed with water (5 mL), ethanol (50 mL) and potassium hydroxide (10 g, 0.18 mol) and heated on a steam bath for 18 h. The mixture was diluted with water and washed with diethyl ether. The aqueous layer was acidified with concentrated HCl and extracted with diethyl ether. The ethereal extracts were dried ($MgSO_4$), filtered and the filtrate

evaporated under reduced pressure to afford an orange oil that was distilled (Kugelrohr) to give **3b** as a pale yellow oil (4.29 g, 89 %): bp 162 °C @ 5 mm Hg; ^{1}H NMR ($CDCl_3$) 1.38 (m, 2H), 1.61 (m, 4H), 2.34.(t, 2H), 2.88 (t, 2H), 3.43 (t, 2H), 3.62 (t, 2H), 7.26 (m, 5H); MS (EI) m/z: 308 [$(M+TMS)^+$], 105 (100 %).

***N*-[2-(4-Hydroxy-2-oxo-3H-benzothiazol-7-yl)ethyl]-6-(2-phenylethoxy)hexanamide (5b).** 7-(2-Aminoethyl)-4-hydroxybenzothiazol-2(3H)-one[2] (3.3 g, 15.7 mmol) was stirred under an atmosphere of nitrogen in dry DMF (100 mL) with *N*-hydroxybenzotriazole (2.33 g, 17.3 mmol), **3b** (3.71 g, 15.7 mmol) and dicyclohexylcarbodiimide (3.56 g, 17.3 mmol) for 18 h at room temperature. Acetic acid (2 mL) was added and the solvent was evaporated. The residue was extracted with ethyl acetate and the combined extracts filtered. The filtrate was washed with dilute HCl and brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated and the crude product purified by flash chromatography (SiO_2) using dichloromethane : methanol (9 : 1) as eluant, and then by reverse phase HPLC affording **5b** (2 g, 30%): mp 139 ^{0}C; ^{1}H NMR (d_6-DMSO) 1.20 (m, 2H), 1.45 (m, 4H), 2.00 (t, 2H), 2,77 (t, 2H), 3.23 (q, 2H), 3,34 (m, 4H+H20), 3,55 (t, 2H), 6.69 (d, 1H), 6.78 (d, 1H), 7.16-7.28 (m, 5H), 7.84 (t, 1H); MS (FAB) m/z: 429 [$(M+H)^+$]. Anal. ($C_{23}H_{28}N_2O_4S$) C, H, N; S: calc, 7.48; found, 6.84.

4-Hydroxy-7-[2-[6-(2-phenylethoxy)hexyl]aminoethyl]benzothiazol-2(3H)-one hydrochloride (7b). **7b** was prepared by the general method outlined for the preparation of **6a** using **5b** (2g, 4.6 mmol), dry THF (175 mL), borane in THF (43 mL of a 1M solution, 43 mmol). The crude material was purified by reverse phase HPLC and, after conversion to the hydrochloride salt, afforded **7b** as a white solid (0.233 g, 10 %): mp 219-222 ^{0}C (dec).; ^{1}H NMR (d_6-DMSO) 1.22-1,37 (m, 4H), 1.47 (t, 2H), 1.54-1.64 (m, 2H), 2.8-2.9 (m, 6H),. 3.01-3.12 (brm, 2H), 3.34-3.47 (m, 2H),

3.55 (t, 2H), 6.76 (d, 1H), 6.88 (d, 1H), 7.06-7.32 (m, 5H), 8.87 (brs, 2H), 10.15 (s, IH), 11.78 (s, 1H); MS (FAB) m/z: 415 [$(M+H)^+$]. Anal. ($C_{23}H_{30}N_2O_3S.1.075HCl$) C, H, N, S.

4-Hydroxy-7-[2-[6-(4-phenylbutoxy)hexyl]aminoethyl]benzothiazol-2(3H)-one trifluoroacetate (7c).

6-(4-Phenylbutoxy)hexylbromide (13). Sodium hydroxide (36 g, 0.9 mol) was dissolved in water (300 mL) and the solution cooled to room temperature. 4-phenylbutanol (50 g, 0.33 mol) was added, followed by 1,6-dibromohexane (140 mL, 0.9 mol) and tetrabutylammonium chloride (10 g). The mixture was stirred vigorously at room temperature for 2 days. The aqueous layer was separated and extracted with ether. The ethereal extracts were dried ($NaSO_4$) and filtered. The filtrate was evaporated and the crude product purified by flash chromatography (SiO_2) eluting with petroleum ether : diethyl ether (1:1) affording **13** as an oil that was used without further purification (34.2 g, 32 %).

6-(4-Phenylbutoxy)hexan-1-ol (14). A solution of **13** (47.6 g, 0.152 mol) in a mixture of *N*-methylpyrrolidin-2-one (250 mL) and water (60 mL) and heated on a steam bath for 18 h. The reaction mixture was diluted with water (250 mL) and extracted with ether. The combined extracts were dried ($NaSO_4$), filtered and the filtrate evaporated. The crude product was purified by flash chromatography (SiO_2) eluting with petroleum ether : diethyl ether (1:1) to give **14** that was used without further purification (28.21 g, 81 %): ^{1}H NMR ($CDCl_3$) 1.35 (m, 4H), 1.42 (brs, 1H), 1.61 (m, 8H), 2.63(t, 2H), 3.39 (m, 4H), 3.64 (t, 2H), 7.22 (m, 5H); MS (EI) m/z: 308 [$(M+TMS)^+$], 105 (100 %).

6-(4-Phenylbutoxy)hexanoic acid (3c). Pyridinium dichromate (131 g, 0.35 mol) was added to a solution of **14** (25 g, 0.1 mol) in DMF (250 ml). The mixture was stirred at room temperature for 18 h, treated with water, extracted into diethyl ether. The ethereal extracts were washed with dilute HCl and brine, dried (Na_2SO_4) and filtered. The filtrate was evaporated and the crude product purified by flash chromatography eluting with petroleum ether : diethyl ether (1:1) to afford **3c** (16.8g 63 %): ^{1}H NMR ($CDCl_3$) 1.40 (m, 2H), 1.62 (m, 8H), 2.35(t, 2H), 2.62 (t, 2H), 3.40 (t, 4H), 7.22 (m, 5H).

6-(4-Phenylbutoxy)hexanoic acid, 2-oxo-3H-7-[2-[1-oxo-6-(4-phenylbutoxy)hexylamino]ethyl]benzothiazol-4-yl ester (15). A solution of **3c** (2.5g, 9.6 mmol) in dry dichloromethane (100 mL) was stirred under an atmosphere of nitrogen and *N*-hydroxybenzotriazole (0.91 g, 6,7 mmol), triethylamine (0.47 mL, 3.4 mmol) and 7-(2-aminoethyl)-4-hydroxybenzothiazol-2(3H)-one trifluoroacetate (1.56g, 4.8 mmol) added. The mixture was cooled in ice and dicyclohexylcarbodiimide (1.39g, 6.7 mmol) in dry dichloromethane (40 mL) was added gradually and then stirred for 18 h at room temperature. Acetic acid (0.5 mL) was added and the mixture was filtered. The filtrate was evaporated affording **15** as a pale yellow solid that was used without further purification (2.1 g, 62 %): MS (FAB) m/z: 703 [$(M+H)^+$], 91(100%).

4-Hydroxy-7-[2-[6-(4-phenylbutoxy)hexyl]aminoethy]benzothiazol-2(3H)-one trifluoroacetate (7c). A solution of **15** (2.1g, 3 mmol) in dry THF (150 mL) was stirred under nitrogen during the addition of a solution of borane in THF (34 mL of 1M solution, 34 mol). The mixture was heated at reflux temperature for 5 h, allowed to cool to room temperature, methanol (50 mL) was added cautiously and the solvents were evaporated. Methanol (100 mL) and concentrated HCl (8 mL) were added and

the mixture was stirred at room temperature for 18 h. The methanol was evaporated and the residue was purified by flash chromatography (SiO_2) using dichloromethane : methanol (95 : 5) as eluant and then by reverse phase HPLC affording **7c** as a solid (0.14 g, 9 %): mp 222-225 ^{0}C (dec); ^{1}H NMR (d_6-DMSO) 1.27-1.37 (m, 4H), 1.44-1.64 (m, 8H), 2.58 (t, 2H), 2.77-2.85 (m, 2H), 2.87-2.97 (br, 2H), 3.04-3.13 (br, 2H) 3.30-3.38 (m, 4H+H_2O),6.74-7.3 (m, 7H), 8.54 (brs, 2H), 10.17(s, 1H), 11.75(s, 1H); IR 1424, 1514, 1640, 2857, 2935; MS (FAB) m/z: 443 [$(M+H)^+$]. Anal. ($C_{25}H_{34}N_2O_3S.0.92C_2HO_2F_3$) C, H, N, S.

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulphonyl]ethylamino]ethyl] benzothiazol-2(3H)-one hydrochloride (7d).

3-[2-Phenylethoxy]propanethiol (16). Calcium turnings (3.5 g, 87.5 mmol) were added portion wise to liquid ammonia (500 mL) and stirred vigorously for 10 minutes. 2-Phenylmethyl-1,3-oxathiane (10 g, 52 mmol) was added dropwise to the dark blue solution over a period of 7 minutes. The mixture was stirred for 2 hours and then quenched with ammonium chloride until the effervescence had ceased. The excess ammonia was allowed to evaporate by purging with nitrogen overnight. The remaining solid was acidified using dilute HCl (pH 1-2) and the product extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to give **16** (8.29 g, 82 %): ^{1}H NMR ($CDCl_3$) 1.29 (d, 1H), 1.86 (m, 2H), 2.56 (q, 2H), 2.87 (t, 2H), 3.49 (t, 2H), 3.64 (t, 2H), 6.87-7.31 (m, 5H); MS (EI) m/z: 196 [M^+].

2-[3-(2-Phenylethoxy)propylthio]acetic acid (17). Sodium hydride (60% dispersion in oil, 3.38 g, 84.6 mmol) was washed with petroleum ether and suspended in DMF (5 mL) at 0°C. A solution of **16** (8.29 g, 42.3 mmol) in DMF (10 mL) was added

dropwise. Stirring was continued for 2 h at 0-8 °C at which point a solution of bromoacetic acid (5.88 g, 42.3 mmol) in DMF (15 mL) was added dropwise. A further quantity of DMF (20 mL) was added to aid stirring. After 17 h at room temperature the DMF was removed under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ solution and diethyl ether (the ethereal layer was discarded). The aqueous layer was acidified with concentrated HCl (pH 1-2) and extracted with diethyl ether. The combined ethereal extracts were washed with water and brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure and the crude product purified by flash chromatography (SiO_2) using petroleum ether (bp 60-80°) : ether (1:1) as eluant gave **17** (7.10 g, 66 %): ^{1}H NMR ($CDCl_3$) 1.86 (m, 2H), 2.70 (t, 2H), 2.87 (t, 2H), 3.21 (s, 2H), 3.51 (t, 2H), 3.63 (t, 2H), 7.17-7.30 (m, 5H), 9.74 (s, IH).

2-[3-(2-Phenylethoxy)propylsulphonyl]acetic acid (3d). Oxone® (21.8 g, 35.4 mmol) was dissolved in water (70 mL) and added to a solution of **17** (3 g, 11.8 mmol) in methanol (30 mL) during 10 min at 0 °C. A white precipitate was formed and the mixture was allowed to warm to room temperature for 5 h. The reaction mixture was diluted with water and extracted with chloroform. The combined chloroform extracts were washed with water and saturated brine, dried ($MgSO_4$) and filtered. The filtrate was evaporated under reduced pressure to afford **3d** which was used without further purification (3 g, 89 %): ^{1}H NMR ($CDCl_3$) 2.12 (m, 2H), 2.87 (t, 2H), 3.41 (t, 2H), 3.58 (t, 2H), 3.67 (t,2H), 3.97 (s, 2H), 7.00-7.43 (m, 5H), 8.79 (s, 1H); MS (FAB) m/z: 287 [$(M+H)^+$].

***N*-[2-(4-Hydroxy-2-oxo-3H-benzothiazol-7-yl)ethyl]-2-[3-(2-phenylethoxy)propylsulphonyl]acetamide (5d).** **5d** was prepared by the general method described for the preparation of **5b** using **3d** (2 g, 6.98 mmol), 7-(2-

aminoethyl)-4-hydroxybenzothiazol-2(3H)-one hydrobromide (2.03g, 6.98 mmol), *N*-hydroxybenzotriazole (0.94 g, 6.98 mmol), dicyclohexylcarbodiimide (1.44 g, 6.98 mmol) and triethylamine (1 mL, 7.2 mmol). The crude product was purified by flash chromatography (SiO_2) using dichloromethane : methanol (9 :1) as eluant affording **5d** as an off-white solid (2.19 g, 66 %): ^{1}H NMR (d_6-DMSO) 1.92 (q, 2H), 2.62 (t, 2H), 2.81 (t, 2H), 3.27 (m, 4H), (t, 2H), 3.58 (t, 2H), 4.04 (s, 2H), 6.70 (d, 1H), 6.83 (d, 1H), 7.17-7.29 (m, 5H), 8.47 (t, 1H), 9.96 (s, 1H), 11.66 (d 1H); MS (FAB) m/z: 479 [$(M+H)^+$].

4-Hydroxy-7-[2-[2-[3-(2-phenylethoxy)propylsulphonyl]ethylamino]ethyl] benzothiazol-2(3H)-one hydrochloride (7d). **7d** was prepared by the general method described for the preparation of **6a** using **5d** (1 g, 2.1 mmol) and a solution of borane in THF (7.3 mL of 1M solution, 7.3 mmole). The crude product was purified by reverse phase HPLC followed by formation of the hydrochloride salt affording **7d** as a white solid (0.326 g, 31 %): mp 217-220 ^{0}C; ^{1}H NMR (d_6-DMSO) 1.91 (quin, 2H), 2.81 (t, 2H), 2.87 (t, 2H), 3.20 (m, 4H), 3.34 (t, 2H), 3.51 (t, 2H), 3.57 (q, 4H), 6.77 (d, 1H), 6.86 (d, 1H), 7.17-7.31 (m, 5H), 9.27 (s, 2H), 10.15 (s, 1H), 11.77 (s, 1H); MS (FAB) m/z: 465 [$(M+H)^+$]. Anal. ($C_{22}H_{28}N_2O_5S_2$.HCl) C, H, N, S.

References

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