Supporting Information

Benzoxepin derived estrogen receptor modulators – a novel molecular scaffold for the estrogen receptor

David G. Lloyd, Rosario B. Hughes, Daniela M. Zisterer, D. Clive Williams, Caterina Fattorusso, Bruno Catalanotti, Giuseppe Campiani, Mary J. Meegan.

Supporting Information Available: Experimental chemistry procedures, NMR spectra (^{1}H ^{13}C ^{11}B where appropriate), mass spectra, biochemical procedures, computational procedures, appendix of elemental analysis

All reagents used were commercial grade chemicals from freshly opened containers. IR spectra were collected as thin films on NaCl plates on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance DPX 400 instrument at room temperature. All J values are quoted in Hz. Low resolution mass spectra were run on a Hewlett-Packard 5973 MSD GC–MS system, while high resolution accurate mass determinations were made on a Kratos Prohile HV-4 mass spectrometer using the direct insertion probe and electron impact ionisation techniques by the High Resolution Mass Spectrometry Service in the Department of Chemistry, University College Cork. Flash chromatography was carried out using standard silica gel 60 (230-400 mesh) obtained from Merck. All products isolated were homogenous on TLC. Analytical HPLC work was performed on a chromatographic system comprising a Waters 501 pump (flow-rate 2 ml/min / sample loop 20 μl) and a Waters Spherisorb® S5 ODS2 (4.6x250mm) reversed phase C18 analytical column. Detection was on a Waters 486 Tunable Absorbance Detector with λ=241, chart recorder speed at 1/6 cm per min. The mobile phase used was prepared from HPLC grade solvents and comprised ACN:H_2O:THF:18M NH_3 Buffer 30:12.5:7.5:2 respectively. Retention times are given in minutes. Unless otherwise stated all reactions were carried out under a nitrogen atmosphere.

General Method for Boronic acid preparation (utilized in formation of **12-19** via Suzuki reaction)

n-Butyllithium (16.8mL, 2.5M in hexane) was added over 5min to a stirred suspension of an appropriately substituted bromoarylcompound (42 mmol) in dry THF (120mL) at -78°C under nitrogen (vacuum dried apparatus). The suspension was allowed to warm up (*ca*. -10°C) until all solid material is dissolved, then recooled to -78°C, and stirred for 1 h. Triisopropyl borate (42 mmol) was then added dropwise over 5-10min and the mixture was stirred for a further hour at -78°C under N_2. This solution was warmed up to room temperature and water (40mL) was added slowly with stirring until precipitation occurred. The product reaction mixture was stirred vigorously at room temperature for 10-15min and then vacuum filtered, washed with water (20mL), and then with hexane (50mL). If precipitation did not occur on addition of water, the mixture was partitioned between diethyl ether (3x25mL), saturated NH_4Cl (10mL) and water (40mL). The diethyl ether layer was washed with saturated sodium sulphate, dried over Na_2SO_4 and the solvent is extracted <35°C. The resulting boronic acids were vacuum dried for 1-2 days at ambient temperatures

4-Methoxyphenylboronic acid

The general method was employed using 4-bromoanisole (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product precipitated out through addition of water. The compound was vacuum dried (<30°C) affording a colourless powder in 91% yield; m.p. 159-164°C [lit. m.p. 160-163°C](Thompson *et al*., 1988) .IR ν_{max}(KBr) 3733-3016 (OH), 2955-2833, 2567 (CHs), 1604 (C=C), 1512 (OCH_3), 1169, 1112 (B-OH) cm^{-1}. ^1H NMR (CD_3OD) δ 3.76 (3H, s, OCH_3), 6.85-6.87 (2H, d, J = 8.04Hz, H-3, H-5), 7.68-7.70 (2H, d, J = 7.52Hz, H-2, H-6). ^{13}C NMR (CD_3OD) δ55.13 (OCH_3), 113.20 (C-3, C-5), 132.22 (C-2, C-6), 159.10 (C-4), 172.71 (C-1). ^{11}B NMR (CD_3OD) δ 375 ($RB(OH)_2$).

3-Methoxyphenylboronic acid

The general method was employed using 3-bromoanisole (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted with diethyl ether. The compound was purified with column chromatography (eluant CH_2Cl_2:EtOAc; 90:10) and vacuum dried (<30°C) affording a colourless powder in 29% yield; m.p. 158-162°C [lit. m.p. 160-163°C](Huth *et al*., 1989). IR ν_{max}(KBr) 3278 (OH), 3014-2937 (CHs), 1593, 1583 (C=C), 14196 (OCH_3)

cm^{-1} ^{1}H NMR (CD_3OD) δ 3.80 (3H, s, OCH_3), 6.94-6.97 (1H, dd, J = 2.00, 8.04Hz, H-2), 7.15 (1H, m, H-4), 7.24-7.33 (2H, m, H-5, H-6). ^{13}C NMR (CD_3OD) δ 54.07 (OCH_3), 114.77 (C-2), 118.24 (C-4), 125.10 (C-5), 128.15 (C-6), 158.65 (C-3). ^{11}B NMR (CD_3OD) δ 379 ($RB(OH)_2$).

2-Methoxyphenylboronic acid

The general method was employed using 2-bromoanisole (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted with diethyl ether. The compound was isolated with column chromatography (eluant CH_2Cl_2:EtOAc; 95:5) and vacuum dried (<30°C) affording a colourless crystalline solid in 69% yield; m.p. 106-108°C [lit. m.p. 105-107°C](Baret *et al*., 1998). IR ν_{max}(KBr) 3354 (OH), 2971-2820 (CHs), 1604, 1575 (C=C), 1486 (OCH_3), 1164, 1105 (B-OH) $cm^{-1}$$^{1}H$ NMR (CD_3OD) δ 3.81 (3H, s, OCH_3), 6.89-6.95 (2H, m, H-4, H-5), 7.36 (1H, t, J = 7.78Hz, H-3), 7.67-7.68 (1H, d, J = 7.00Hz, H-6). ^{13}C NMR (CD_3OD) δ 54.85 (OCH_3), 110.05 (C-4), 120.74 (C-5), 132.20 (C-3), 135.92 (C-6), 164.54 (C-2). ^{11}B NMR (CD_3OD) δ 377 ($RB(OH)_2$).

4-Methylphenylboronic acid

The general method was employed using 4-bromotoluene (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted using diethyl ether and concentrated down. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc; 98:2) and vacuum dried (<30°C) affording a solid in 52% yield; m.p. 259-260°C [lit. m.p. 256-263°C](Juneja *et al*., 1993). IR ν_{max}(KBr) 3250 (OH), 3098-2987 (CHs), 1615 (C=C), 1363 (CH_3), 1164, 1105 (B-OH) cm^{-1}. ^{1}H NMR (CD_3OD) δ 2.21 (3H, s, CH_3), 7.12-7.14 (2H, d, J = 7.04Hz, H-3, H-5), 7.48-7.50 (1H, d, J = 6.52Hz, H-2), 7.65-7.67 (1H, d, J = 7.04Hz, H-6). ^{13}C NMR (CD_3OD) δ 19.81 (CH_3), 127.41, 127.51 (C-3, C-5), 132.84, 133.15 (C-2, C-6), 139.42 (C-4). ^{11}B NMR (CD_3OD) δ 415 ($RB(OH)_2$).

3-Methylphenylboronic acid

The general method was applied using 3-bromotoluene (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted using diethyl ether and concentrated under reduced pressure. The product was purified using column chromatography (eluant CH_2Cl_2:EtOAc; 98:2) and vacuum dried (<30°C) affording a colourless solid in

57% yield; m.p. 74-76°C [lit. m.p. 69-71°C](Qian *et al.*, 1996) IR ν_{max}(KBr) 3272 (OH), 3033-2917 (CHs), 1605, 1582 (C=C), 1348 (CH_3) cm^{-1}.^{1}H NMR (CD_3OD) δ 2.33 (3H, s, CH_3), 7.20-7.24 (2H, m, H-2, H-4), 7.37-7.38 (1H, m, H-5), 7.54-7.58 (1H, m, H-6). ^{13}C NMR (CD_3OD) δ 19.66 (CH_3), 126.72 (C-2), 129.52 (C-4), 133.62 (C-5), 136.21 (C-6). ^{11}B NMR (CD_3OD) δ 377 ($RB(OH)_2$).

4-Chlorophenylboronic acid

The general method 3.7 was employed using 4-chlorobromobenzene (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted using diethyl ether and concentrated down. The product was purified using column chromatography (eluant CH_2Cl_2:EtOAc; 95:5) and vacuum dried (<30°C) affording a colourless crystalline solid in 34% yield; m.p. 278-280°C [lit. m.p. 284-289°C](Mueller *et al.*, 1992). IR ν_{max}(KBr) 3262 (OH), 2980-2954 (CHs), 1595, 1563 (C=C), ~1257 (C-Cl) cm^{-1}. ^{1}H NMR (CD_3OD) δ 7.34 (2H, m, H-3, H-5), 7.60-7.71 (2H, m, H-2, H-6). ^{13}C NMR (CD_3OD) δ 126.86 (C-3, C-5), 134.32 (C-2, C-6). ^{11}B NMR (CD_3OD) δ 373 ($RB(OH)_2$).

3-Nitrophenylboronic acid

In an ice-salt freezing mixture colourless fuming nitric acid (50 mL, 1.20M), to which a little urea had a little had been added, was cooled to –15°C. Phenyl boronic acid (9.02 g, 74 mmol) was added slowly over a period of 1-2h, so that the temperature did not rise above –9°C. The mixture was then stirred for a further 15-30min, after which it was poured onto ice and the product precipitated. The precipitated nitrophenylboronic acid was vacuum filtered, recrystallised from a small volume of water, with the addition of decolorising charcoal. Hot vacuum filtration was then carried out to discard charcoal, washed initially with water and then methanol. The original filtrate was cooled in an ice-bath, neutralised to an orange / red solution with 12N NaOH solution and then acidulated with nitric acid. The solution was extracted with diethyl ether, washed with water and concentrated down at room temperature. Both fractions from the work up were combined and column chromatography (eluant C_6H_{12}:CH_2Cl_2;80:20), removed all traces of impurities to afford lemon prismatic crystals in 28% yield; m.p. 282-286°C (char), [lit. m.p. 284-285°C (char.)](Cundy and Forsyth, 1998) IR ν_{max}(KBr) 3440 (OH), 2927-2855 (CHs), 1616, 1583 (C=C), 1529, 1349 (C-NO_2) cm^{-1}. ^{1}H NMR (CD_3COCD_3) δ 7.68 (1H, t, J = 7.78Hz, H-6),

8.27-8.32 (2H, m, H-4, H-5), 8.70 (1H, s, H-2). ^{13}C NMR (CD_3COCD_3) δ 125.43 (C-2), 128.89 (C-4), 129.50 (C-5), 140.88 (C-6). ^{11}B NMR (CD_3OD) δ 378 ($RB(OH)_2$).

4-Cyanophenylboronic acid

The general method was employed using 4-bromobenzonitrile (42 mmol), dry THF (120mL), *n*-BuLi (42 mmol) and triisopropyl borate (42 mmol) under nitrogen. The product was extracted using diethyl ether and concentrated. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc; 75:25) was vacuum dried (<30°C) affording a colourless solid in 6% yield; m.p. >270°C. IR ν_{max}(KBr) 3511-3342 (OH), 3068-3025 (CHs), 2229 (C≡N), 1610, 1506 (C=C) cm^{-1}. ^{1}H NMR (CD_3OD) δ 7.43-7.51 (4H, m, H-2, H-3, H-7, H-8), 7.78-7.85 (3H, m, H-4, H-5, H-6). ^{13}C NMR (CD_3OD) δ 112.43 (C≡N), 118.10 (C-B), 130.22 (C-3, C-5), 133.54 (C-2, C-6). ^{11}B NMR (CD_3OD) δ 376 ($RB(OH)_2$). The product was used in subsequent reactions without further purification.

2,3,4,5-Tetrahydro-1-benzoxepin-5-one (2)

A mixture of polyphosphoric acid (0.84M) and 4-phenoxybutyric acid (0.11M) were heated on a steam bath for 2-3hr with occasional shaking. The resulting syrup was poured onto crushed ice, and the organic layer was extracted with ethyl acetate, washed with water, 3N NaOH (2x20mL), dried over Na_2SO_4 and concentrated down. The product was isolated from column chromatography (eluant C_6H_{12}:CH_2Cl_2; 50:50) as a viscous oil in 76% yield (product homogenous on TLC with R_f=0.36; 95:5 C_6H_{12}/ EtOAc),(Tandon *et al*., 1990) ; IR ν_{max} (KBr) 3080-2943, 2939-2834 (CHs), 1689 (C=O), 1604 (C=C), 1480, 1449 (CH_2), 1289 (C-O-C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.56 (2H, m, H-3), 2.93 (2H, t, J = 6.99Hz, H-2), 4.27 (2H, t, J = 6.55Hz, H-4), 6.95-7.14 (2H, m, H-7, H-9), 7.45 (1H, m, H-8), 7.79-8.81 (2H, dd, J = 7.76, 1.78Hz, H-6). ^{13}C NMR ($CDCl_3$) δ 26.33 (C-3), 40.61(C-4), 72.80 (C-2), 121.75, 122.74 (C-7, C-8), 129.33 (C-9a), 129.42 (C-6), 133.69 (C-9), 161.62 (C-5a), 200.21 (C-5).

5-(4-Methoxyphenyl)-2,3-dihydro-1-benzoxepin (3)

Compound **2** was reacted with *n*-BuLi (12.0mL, 2.5M in hexane), and 4-bromoanisole (30 mmol), in dry THF (40mL) at -78°C. Dehydration was facilitated through the addition of H_2SO_4 (4mL) in ethanol (20mL). The product was then purified using column chromatography (eluant C_6H_{12}/ EtOAc; 85:15) and recrystallised from ethanol to afford colourless crystals in 55% yield (product homogenous on TLC with R_f

=0.54; 80:15 C_6H_{12}: EtOAc) m.p. 79-81°C. IR ν_{max} (film) 3068-2963, 2878 (CHs), 1599, 1571 (C=C), 1464 (CH_2), 1448 (OCH_3), 1287, 1219 (C-O-C) cm^{-1}.^{1}H NMR ($CDCl_3$) δ 2.50 (2H, q, J = 6.01Hz, H-3), 3.85 (3H, s, OCH_3), 4.52 (2H, t, J = 6.02Hz, H-2), 6.28 (1H, t, J = 6.28Hz, H-4), 6.88-6.90 (2H,m, H-3', H-5'), 7.01-7.03 (2H, m, H-6, H-7), 7.11-7.14 (1H, m, H-9), 7.19-7.28 (3H, m, H-2', H-6', H-8). ^{13}C NMR ($CDCl_3$) δ 29.45 (C-3), 54.82 (OCH_3), 77.28 (C-2), 113.10 (C-3', C-5'), 121.37 (C-9), 122.66 (C-7), 126.58 (C-4), 127.90 (C-8), 129.20 (C-2', C-6'), 130.66 (C-6), 132.49 (C-5), 134.87 (C-1'), 157.46 (C-9a). Calculated.for $C_{17}H_{16}O_2$: C, 80.92; H, 6.40; found: C, 80.90; H, 6.46.

4-Bromo-5-(4-methoxyphenyl)-2,3-dihydro-1-benzoxepin (**4**)

Compound **3** (4 mmol) was dissolved in dry dichloromethane (30mL) and allowed to stir at 0°C for 30 min. Pyridinium bromide perbromide (5.7 mmol) was added in portions over 15min. The solution was allowed to stir for 12h after which TLC monitoring indicated the complete consumption of the starting material. The solution was washed with $NaHCO_3$ (10% w/v, 2x20mL), water (30mL), extracted with dichloromethane (2x25mL), dried over Na_2SO_4 and concentrated down. Column chromatography (eluant C_6H_{12}:EtOAc; 97:3) was carried out to purify the product followed by recrystallisation with ethanol to produce needle-like colourless crystals in 92% yield (product homogenous on TLC with rf=0.44 70/30 CH_2Cl_2:Et_2O). IR ν_{max} (KBr) 3067-2970, 2878 (CHs), 1599, 1568 (C=C), 1476 (CH_2), 1448 (OCH_3), 1286, 1202 (C-O-C) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.04 (2H, t, J = 5.86Hz, H-3), 3.86 (3H, s, OCH_3), 4.61 (2H, t, J = 5.88Hz, H-2), 6.80-6.82 (1H,dd, J = 7.80, 1.70Hz, H-6), 6.91-6.98 (3H, m, H-7, H-3', H-5'), 7.08-7.10 (2H, d, J = 8.32Hz, H-9,), 7.18-7.22 (3H, m, H-2', H-6', H-8). ^{13}C NMR ($CDCl_3$) δ 40.74 (C-3), 54.73 (OCH_3), 77.24 (C-2), 113.01 (C-3', C-5'), 121.51 (C-4), 122.92 (C-7, C-9), 126.36 (C-6), 130.69 (C-2', C-6'), 130.96 (C-8), 133.06 (C-5), 134.35 (C-1'), 139.01 (C-5a). Calculated for $C_{17}H_{15}BrO_2$: C, 61.65; H, 4.56; found: C, 61.20; H, 4.56.

5-(4-Methoxyphenyl)-4-phenyl-2,3-dihydro-1-benzoxepin (5)

A solution of phenyl zinc chloride was prepared by addition of phenyl lithium (1.1mL of a 1.8M solution in hexane / ether, 2 mmol) to a stirred solution of zinc chloride (2 mmol), dry THF (4mL) under nitrogen at 0°C. This was allowed to stir for 1 h at room temperature. To this was added a solution of **4** (0.7 mmol) in dry THF (6mL) containing tetrakis(triphenylphosphine)palladium (40mg, 36.64 μM). The mixture

was then heated to reflux and maintained at same for 4-5h. After this period it was cooled to room temperature and let stir overnight. The reaction mixture was washed with 1M HCl (30mL), water, extracted with diethyl ether (3x20mL), dried over sodium sulphate and concentrated. Column chromatography (eluant C_6H_{12}:CH_2Cl_2; 80:20) was necessary to purify the product followed by recrystallisation from ethanol to afford colourless crystals in 89% yield (product homogenous on TLC with R_f =0.33; 70:30 CH_2Cl_2:C_6H_{12}). IR ν_{max} (KBr) 3115-2930, 2810-2723 (CHs), 1608, 1580 (C=C), 1482, 1458 (CH_2), 1442 (OCH_3), 1246, 1217 (C-O-C) cm^{-1}.^{1}H NMR (CD_3OD) δ 2.74 (2H, t, J = 6.28Hz, H-3), 3.76 (3H, s, OCH_3), 4.55 (2H, t, J = 6.04Hz, H-2), 6.66-6.68 (2H, dd, J = 6.52, 2.04Hz, H-3', H-5'), 6.90-6.92 (2H, dd, J = 6.50, 2.02Hz, H-2', H-6'), 6.98-7.02 (1H, dt, J = 8.28, 1.50Hz, H-9), 7.08-7.24 (8H, m, ArH). ^{13}C NMR (CD_3OD) δ 35.72 (C-3), 55.07 (OCH_3), 80.44 (C-2), 113.07 (C-3', C-5'), 122.06 (C-4, C-9), 123.49 (C-7), 126.28 (C-6), 127.97 (C-4''), 128.39 (C-2'', C-6''), 129.50 (C-3'', C-5''), 131.02 (C-2', C-6'), 132.52 (C-8), 133.81 (C-5), 156.17 (C-9a), 158.16 (C-4') Low Res. EIMS M^+ = 328; Calculated for $C_{23}H_{20}O_2$: C, 84.11; H, 6.14; found: C, 83.89; H, 6.27.

5-(4-Hydroxyphenyl)-4-phenyl-2,3-dihydro-1-benzoxepin (6)

A mixture of **5** (1.7 mmol) and pyridine hydrochloride (9.6 mmol) were stirred and heated by means of an oil bath maintained at 200°C. After 4h, the mixture was cooled to ambient temperature and dissolved in dichloromethane (10mL). This solution was diluted with diethyl ether (2x20mL), washed with dilute HCl (1M, 15mL), water (2x25mL), dried with magnesium sulphate and concentrated. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc; 98:2) to afford an oil in 61% yield (product homogenous on TLC with R_f =0.74; 90:10 CH_2Cl_2:EtOAc). IR ν_{max} (film) 3339 (OH), 3056-2961, 2921-2855 (CHs), 1609 (C=C), 1484, 1443 (CH_2), 1255, 1217 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.74 (2H, t, J = 6.02Hz, H-3), 4.64 (2H, t, J = 6.26Hz, H-2), 6.68-6.70 (2H, dd, J =8.52, 2.00Hz, H-3', H-5'), 6.93-6.95 (2H, dd, J = 8.52, 2.00Hz, H-2', H-6'), 6.98-7.02 (1H, d, J = 7.54, 1.25Hz, H-9), 7.14-7.28 (8H, m, ArH) ^{13}C NMR δ($CDCl_3$) 35.23 (C-3), 79.97 (C-2), 114.13 (C-3', C-5'), 121.60 (C-4, C-9), 123.07 (C-7), 125.84 (C-6), 126.50 (C-4''), 127.96 (C-2'', C-6''), 129.03 (C-3'', C-5''), 130.53 (C-2', C-6'), 132.25 (C-8). EIMS (LR) M^+ =314, ($C_{22}H_{18}O_2$) : – This product was used in subsequent reactions without further purification.

5-[(4-Dimethylaminoethoxy)phenyl]-4-phenyl-2,3-dihydro-1-benzoxepin (7)

Compound **6** (0.48 mmol) was dissolved in dry acetone (20mL), to which anhydrous K_2CO_3 (4.8 mmol) and 2-dimethylaminoethylchloride hydrochloride (1.3 mmol) were added under nitrogen. The reaction mixture was refluxed for 6h. The product was purified using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 70:30:2), to afford an oil in 44% yield (product homogenous on TLC with R_f=0.15; 75:20:5 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 10.20 mins. IR ν_{max} (film) 3003-2926, 2863-2774 (CHs), 1608, 1591 (C=C), 1483, 1462 (CH_2), 1441 (CH_3), 1172 (C-O-C) cm^{-1}. ^{1}H NMR $\delta(CDCl_3)$ 2.35 (6H, s, $N(CH_3)_2$), 2.72 (4H, m, CH_2N, H-3), 4.02 (2H, t, J = 5.78Hz, CH_2O), 4.64 (2H, t, J = 6.02Hz, H-2), 6.67-6.69 (2H, dd, J = 9.04Hz, H-3', H-5'), 6.88-7.02 (3H, m, H-2', H-6', H-9), 7.04-7.28 (8H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 35.25 (C-3), 45.42 ($N(CH_3)_2$), 57.85 (NCH_2), 65.37 (CH_2O), 79.97 (C-2), 113.24, 113.32 (C-3', C-5'), 121.59 (C-4, C-9), 123.02 (C-7), 125.81 (C-6), 127.49 (C-4"), 127.92, 128.14 (C-2'', C-6''), 129.04 (C-3'', C-5''), 130.57 (C-2', C-6'), 132.01 (C-8). EIMS (HR) calculated for $C_{26}H_{27}NO_2$, 385.2042; found, 385.2050.

5-[(4-Diethylaminoethoxy)phenyl]-4-phenyl-2,3-dihydro-1-benzoxepin (8)

The target compound was prepared using the general method described for **7** above reacting **6** (0.49 mmol), dry acetone (25mL), anhydrous K_2CO_3 (4.9 mmol) and 2-diethylaminoethyl chloride hydrochloride (1.3 mmol) under nitrogen. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 60:40:10), to afford an oil in 66% yield (product homogenous on TLC with rf=0.25; 79:20:1 CH_2Cl_2:EtOAc:MeOH), with the following physical properties. HPLC T_R = 10.20 mins. IR ν_{max} (film) 3058-3026, 2967-2813 (CHs), 1606, 1572 (C=C), 1508, 1481 (CH_2), 1442 (CH_3), 1175 (C-O-C) cm^{-1}. ^{1}H NMR $\delta(CDCl_3)$ 1.10 (3H, t, J = 7.28Hz, $(CH_3)_2$), 2.66-2.75 (6H, m, $(CH_2)_2$, CH_2N), 2.90 (2H, t, J = 6.26Hz, H-3), 4.02 (2H, t, J = 6.02Hz, CH_2O), 4.64 (2H, t, J = 6.02Hz, H-2), 6.66-6.68 (2H,d, J = 9.04Hz, H-3', H-5'), 6.89-7.05 (3H, m, H-2', H-6', H-9), 7.13-7.29 (8H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 11.20 ($(CH_3)_2$), 35.26 (C-3), 47.36 ($(CH_2)_2$), 51.19 (NCH_2), 65.69 (CH_2O), 79.96 (C-2), 113.23 (C-3', C-5'), 121.60 (C-4, C-9), 123.03 (C-7), 125.82 (C-6), 127.51 (C-4''), 127.94 (C-2'', C-6''), 129.04 (C-3'', C-5''), 130.57 (C-2', C-6'), 132.05 (C-8). EIMS (HR) calculated for $C_{28}H_{31}NO_2$, 413.2355; found, 413.2355.

5-[(4-Morpholin-4-ylethoxy)phenyl]-4-phenyl-2,3-dihydro-1-benzoxepin (9)

The target compound was prepared using the general method described for **7** above reacting **6** (0.16 mmol), dry acetone (20mL), anhydrous K_2CO_3 (1.6 mmol) and 4-(2-

chloroethyl)morpholine hydrochloride (0.41 mmol) under nitrogen. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc; 80:20), to afford an oil in 78% yield, (product homogenous on TLC with R_f =0.51; 90/8/2 CH_2Cl_2:EtOAc:MeOH) with the following physical properties. HPLC T_R = 10.20 mins. IR ν_{max} (film) 3059-2926, 2856 (CHs), 1607, 1592 (C=C), 1509, 1483, 1453 (CH_2), 1442 (CH_3), 1144 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.55 (2H, t, J = 5.50Hz, CH_2N), 2.74 (6H, m, H-1'''', H-4'''', H-3), 3.60 (4H, m, H-2'''', H-3''''), 4.05 (2H, t, J = 5.52Hz, CH_2O), 4.63 (2H, t, J = 6.02Hz, H-2), 6.64-6.67 (2H, d, J = 8.52Hz, H-3', H-5'), 6.87-7.03 (3H, m, H-2', H-6', H-9), 7.12-7.27 (8H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 35.26 (C-3), 53.11, 53.65 (C-1'''', C-4''''), 57.25 (NCH_2), 65.22 (CH_2O), 66.38, 66.46 (C-2'''', C-3''''), 79.95 (C-2), 113.26 (C-3', C-5'), 121.60 (C-4, C-9), 123.00 (C-7), 125.81 (C-6), 127.49 (C-4''), 127.94 (C-2'', C-6''), 129.02 (C-3'', C-5''), 130.53 (C-2', C-6'), 132.04 (C-8). EIMS (HR) calculated for $C_{28}H_{29}NO_3$, 427.2147; found, 427.2158.

4-Phenyl-5-[(4-piperidin-1-ylethoxy)phenyl]-2,3-dihydro-1-benzoxepin (10)

The target compound was prepared using the general method described for **7** above reacting **6** (0.19 mmol), dry acetone (25mL), anhydrous K_2CO_3 (1.9 mmol) and 1-(2-chloroethyl)piperidine monohydrochloride (0.5 mmol) under nitrogen. The product was purified using flash column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 60:40:2), to afford the pure product as an oil in 52% yield (product homogenous on TLC with R_f =0.44; 80:15:5, CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 10.20 mins. IR ν_{max} (film) 3063-2923, 2848-2782 (CHs), 1607, 1569 (C=C), 1484, 1462, 1440 (CH_2), 1172 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 1.47 (2H, m, H-3''''), 1.63 (4H, m, H-2'''', H-4''''), 2.53 (4H, m, H-1'''', H-5''''), 2.73 (2H, t, J = 6.02Hz, CH_2N), 2.77 (2H, t, J = 6.02Hz, H-3), 4.06 (2H, t, J = 6.02Hz, CH_2O), 4.63 (2H, t, J = 6.28Hz, H-2), 6.64-6.67 (2H, d, J = 9.04Hz, H-3', H-5'), 6.87-7.04 (3H, m, H-2', H-6', H-9), 7.13-7.28 (8H, m, ArH) ^{13}C NMR $\delta(CDCl_3)$ 23.48 (C-3''''), 25.09 (C-2'''', C-4''''), 35.25 (C-3), 54.44 (C-1'''', C-5''''), 57.31 (NCH_2), 65.00 (CH_2O), 79.96 (C-2), 113.26 (C-3', C-5'), 121.59 (C-4, C-9), 123.01 (C-7), 125.82 (C-6), 127.50 (C-4''), 127.92 (C-2'', C-6''), 129.02 (C-3'', C-5''), 130.55, 130.69 (C-2', C-6'), 132.04 (C-8). EIMS (HR) calculated for $C_{29}H_{31}NO_2$, 425.2355; found, 425.2341.

4-Phenyl-5-[(4-pyrrolidin-1-ylethoxy)phenyl]-2,3-dihydro-1-benzoxepin (11)

The target compound was prepared using the general method described for **7** above by reacting **6** (0.23 mmol), dry acetone (25mL), anhydrous K_2CO_3 (2.3 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (0.59 mmol) under nitrogen. Column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 90:10:2), was used to isolate the product as an oil in 38% yield (product homogenous on TLC with R_f=0.33; 60:34:6 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 10.80 mins IR ν_{max} (film) 3062-2927, 2868-2846 (CHs), 1599, 1577 (C=C), 1484, 1458, 1443 (CH_2), 1175 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 1.84-1.87 (4H, m, H-2'''', H-3''''), 2.71-2.75 (4H, m, H-1'''', H-4''''), 2.84 (2H, t, J = 5.52Hz, CH_2N), 2.97 (2H, t, J = 5.78Hz, H-3), 4.10 (2H, t, J = 5.52Hz, CH_2O), 4.63 (2H, t, J = 6.26Hz, H-2), 6.52-6.54 (2H, dd, J = 9.04Hz, H-3', H-5'), 6.66-7.28 (11H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 23.30, 23.39 (C-2'''', C-3''''), 35.65 (C-3), 54.39, 54.45 (C-1'''', C-4''''), 54.83 (NCH_2), 66.22, 66.36 (CH_2O), 80.36 (C-2), 112.92, 113.65 (C-3', C-5'), 120.88, 121.99 (C-4, C-9), 123.43 (C-7), 126.24 (C-6), 127.25 (C-4''), 127.91, 127.87 (C-2'', C-6''), 128.03, 128.34 (C-3'', C-5''), 129.43, 130.53 (C-2', C-6'), 131.24 (C-8) EIMS (HR) : calculated for $C_{28}H_{29}NO_2$, 411.2198; found, 411.2184.

4-Bromo-5-(4-hydroxyphenyl)-2,3-dihydro-1-benzoxepin (20)

Compound **4** (6.1 mmol) was dissolved in dry dichloromethane (25mL) to which boron tribromide (35 mmol) was slowly added. This solution was stirred at –78°C for 1 h under nitrogen. The target product was isolated using column chromatography (eluant C_6H_{12}:EtOAc; 80:20) affording an oil in 48% yield (product homogenous on TLC with R_f =0.39; 85:15 C_6H_{12}:EtOAc). IR ν_{max} (film) 3402 (OH), 2945-2929, 2871 (CHs), 1610, 1574 (C=C), 1481 (CH_2), 1234, 1171 (C-O-C) cm^{-1}. ^{1}H NMR $\delta(CDCl_3)$ 3.03 (2H, t, J = 5.78Hz, H-3), 4.60 (2H, t, J = 6.02Hz, H-2), 6.81-6.88 (4H, m, H-3', H-5', H-6, H-7), 6.96-6.98 (1H, m, H-9), 7.07-7.24 (3H, m, H-2', H-6', H-8). ^{13}C NMR $\delta(CDCl_3)$ 41.07 (C-3), 77.35 (C-2), 114.97, 115.21 (C-3', C-5'), 121.92 (C-4, C-9), 123.42 (C-7), 128.80 (C-6), 129.01 (C-2', C-6'), 131.21 (C-8), 133.73 (C-5), 134.08 (C-1'), 138.99 (C-5a) EIMS (LR) M^+=314 ($C_{22}H_{18}O_2$). This compound was used in subsequent reactions without further purification.

General Method for compounds 21-28; Suzuki coupling reactions

To a stirred solution of **20** (0.2 mmol) in dry THF (20mL) was added $Pd(PPh_3)_4$ (10mg, 8.65 μM) and stirred for 10-15 min prior to addition of the appropriately substituted arylboronic acid, followed by 2M sodium carbonate (1.4 mmol). The

mixture was heated on an oil bath to 80°C for 6-8h and then cooled to room temp and left stirring for 10-12h. The mixture was then poured onto water (35mL), washed with brine, extracted with dichloromethane and dried over Na_2SO_4, filtered and the solvent removed *in vacuo*.

5-(4-Hydroxyphenyl)-4-methoxyphenyl-2,3-dihydro-1-benzoxepin (21)

The general Suzuki method was employed using **20** (0.18 mmol), dry THF (20mL) and $Pd(PPh_3)_4$ (10mg, 8.65 μM). To this 4-methoxyphenylboronic acid (0.72 mmol) and 2M sodium carbonate (1.4 mmol) were added and refluxed at 80°C. The product was isolated using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 80:10:10) to afford an oil in 80% yield (product homogenous on TLC with R_f =0.89; 70:30 CH_2Cl_2:EtOAc). IR ν_{max} (film) 3402 (OH), 3061-2960, 2896-2732 (CHs), 1608 (C=C), 1462 (CH_2), 1432 (OCH_3), 1283 (C-OH), 1247, 1195 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.71 (2H, t, J = 5.78Hz, H-3), 3.79 (3H, s, OCH_3), 4.64 (2H, t, J = 6.02Hz, H-2), 6.59-6.61 (2H, d, J = 8.04Hz, H-3'', H-5''), 6.73-7.15 (10H, m, ArH). ^{13}C NMR δ($CDCl_3$) 35.18 (C-3), 54.72 (OCH_3), 80.17 (C-2), 113.00, 114.22 (C-3'', C-5''), 114.55, 115.61 (C-3', C-5'), 121.60 (C-4, C-9), 123.15 (C-7), 127.45 (C-6), 127.80 (C-4''), 130.16, 130.21 (C-2'', C-6''), 130.48, 130.90 (C-2', C-6'), 132.17 (C-3), 132.23 (C-8). EIMS (LR) $C_{23}H_{20}O_3$: M^+=344. This product was used in subsequent reactions without further purification.

5-(4-Hydroxyphenyl)-4-(2-methoxyphenyl)-2,3-dihydro-1-benzoxepin (22)

The general Suzuki method was employed using **20** (0.22 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), *o*-methoxyphenylboronic acid (0.72 mmol) and 2M sodium carbonate (1.4 mmol) and the reaction was refluxed at 80°C. The product was purified using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 50:5:50) to afford a viscous oil in 85% yield. (product homogenous on TLC with R_f=0.87; 80/20 CH_2Cl_2:EtOAc) IR ν_{max} (film) 3421-3114 (OH), 2951-2914, 2872 (CHs), 1597, 1574 (C=C), 1484, 1460 (CH_2), 1434 (OCH_3), 1281 (C-OH), 1235, 1198 (C-O-C) cm^{-1}. ^{1}H NMR δ($CDCl_3$) 2.66 (2H, t, J = 6.78Hz, H-3), 3.83 (3H, s, OCH_3), 4.61 (2H, t, J = 6.02Hz, H-2), 6.56-6.59 (2H,dd, J = 2.04, 6.52Hz, H-4'', H-5''), 6.73-7.24 (8H, m, ArH), 7.46-7.48 (1H, dt, J = 2.00, 7.04Hz, H-3''), 7.86-7.88 (1H, dd, J = 1.52, 7.35Hz, H-6''). ^{13}C NMR δ($CDCl_3$) 34.64 (C-3), 55.41 (OCH_3), 79.95 (C-2), 110.45 (C-4''), 114.31 (C-3', C-5'), 120.35 (C-5''), 121.19 (C-4, C-9), 123.18 (C-7), 127.83 (C-6), 131.49 (C-5), 131.94 (C-8), 132.79 (C-3''), 136.77 (C-6''). EIMS (LR) $C_{23}H_{20}O_3$: M^+=344. This product was used in subsequent reactions without further purification.

5-(4-Hydroxyphenyl)-4-(3-methoxyphenyl)-2,3-dihydro-1-benzoxepin (23)

The general Suzuki method was applied using **20** (0.25 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), *m*-methoxyphenylboronic acid (1 mmol) and 2M sodium carbonate (1.6 mmol) and the reaction was refluxed at 80°C. The product was purified using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 40:1:40) to afford an oil in 48% yield, (product homogenous on TLC with R_f =0.54; 80:20 CH_2Cl_2:EtOAc) with the following physical properties; IR ν_{max} (film) 3421 (OH), 2955-2924, 2850-2732 (CHs), 1614 (C=C), 1484, 1464 (CH_2), 1377 (OCH_3), 1284 (C-OH), 1248, 1168 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.73 (2H, t, J = 6.02Hz, H-3), 3.80 (3H, s, OCH_3), 4.63 (2H, m, H-2), 6.56-6.59 (2H, dd, J = 2.04, 6.52Hz, H-4'', H-5''), 6.44-7.17 (10H, m, ArH). ^{13}C NMR δ($CDCl_3$) 35.12 (C-3), 54.79 (OCH_3), 80.04 (C-2), 114.17-115.71 (C-3', C-5'), 115.85, 115.95 (C-2''), 118.63 (C-4''), 121.29, 121.59 (C-4, C-9), 123.12, 123.36 (C-7), 124.04 (C-5''), 128.39 (C-6''), 128.47 (C-6), 129.16, 129.63 (C-2', C-5'), 132.04 (C-5), 132.12 (C-8), 158.67 (C-3'') EIMS (LR) $C_{23}H_{20}O_3$: M^+=344. This product was used in subsequent reactions without further purification.

5-(4-Hydroxyphenyl)-4-(4-methylphenyl)-2,3-dihydro-1-benzoxepin (24)

The general Suzuki method was applied using **20** (0.22 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), 4-methylphenylboronic acid (0.7 mmol) and 2M sodium carbonate (1.4 mmol) and the reaction was refluxed at 80°C. The product was isolated using flash column chromatography (eluant C_6H_{12}:CH_2Cl_2; 70:30) to afford an oil in 93% yield, (product homogenous on TLC with R_f =0.87; 90:10 CH_2Cl_2:EtOAc)with the following physical properties: IR ν_{max} (film) 3612-3007 (OH), 2924, 2876 (CHs), 1610 (C=C), 1478 (CH_2), 1458 (CH_3), 1262 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.31 (3H, s, CH_3), 2.72 (2H, m, H-3), 4.63 (2H, m, H-2), 6.59-6.61 (2H, d, J = 8.04Hz, H-3'', H-5''), 6.83-7.28 (10H, m, ArH).^{13}C NMR δ($CDCl_3$) 20.65 (CH_3), 35.24 (C-3), 80.04 (C-2), 114.37, 114.53 (C-3', C-5'), 120.14, 121.52 (C-4, C-9), 122.96, 123.05 (C-7), 127.83 (C-6), 128.23 (C-4''), 128.29, 128.40 (C-2'', C-6''), 128.83, 128.91 (C-3'', C-5''), 130.50 (C-2', C-6'), 131.30 (C-5), 132.55 (C-8). EIMS (LR) $C_{23}H_{20}O_2$: M^+=328. This product was used in subsequent reactions without further purification.

5-(4-Hydroxyphenyl)-4-(3-methylphenyl)-2,3-dihydro-1-benzoxepin (25)

The general Suzuki method was applied using **20** (0.16 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), *m*-methylphenylboronic acid (0.5 mmol) and 2M sodium

carbonate (1 mmol) and the reaction was refluxed at 80°C. The product was purified using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 40:2:60) to afford an oil in 54% yield, (product homogenous on TLC with R_f =0.74; 80:20 CH_2Cl_2:EtOAc) with the following physical properties: IR ν_{max} (film) 3389 (OH), 2917, 2848 (CHs), 1462 (CH_2), 1432 (CH_3), 1282 (C-OH), 1196 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.25 (3H, s, CH_3), 2.72 (2H, t, J = 6.26, H-3), 4.63 (2H, m, H-2), 6.58-6.60 (2H, d, J = 8.52Hz, H-2'', H-4''), 6.84-7.15 (10H, m, ArH).^{13}C NMR $\delta(CDCl_3)$ 20.88 (CH_3), 35.23 (C-3), 79.97 (C-2), 114.06, 114.53 (C-3', C-5'), 121.52, 121.59 (C-4, C-9), 122.94 (C-7), 126.61 (C-2''), 127.33 (C-6), 127.89 (C-4'), 129.61 (C-4''), 130.52, 130.92 (C-2', C-6'), 132.22 (C-5, C-8), 133.68 (C-5''), 136.47 (C-6''). EIMS (LR) $C_{23}H_{20}O_2$: M^+=328. This product was used in subsequent reactions without further purification.

4-(4-Chlorophenyl)-5-(4-hydroxyphenyl)-2,3-dihydro-1-benzoxepin (26)

The general Suzuki method was applied using **20** (0.16 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), 4-chlorophenylboronic acid (0.5 mmol) and 2M sodium carbonate (1.4 mmol) and the reaction was refluxed at 80°C. The product was isolated using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 60:1:40) to afford an oil in 70% yield, (product homogenous on TLC with R_f =0.81; 80:20 CH_2Cl_2/EtOAc) with the following physical properties. IR ν_{max} (film) 3401 (OH), 2955-2919, 2880-2849 (CHs), 1603 (C=C), 1481, 1463 (CH_2), ~1259 (C-Cl)), 1161 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.70 (2H, t, J = 6.02Hz, H-3), 4.62 (2H, m, H-2), 6.61-6.63 (2H,d, J = 8.56Hz, H-3'', H-5''), 6.78-7.23 (10H, m, ArH) ^{13}C NMR $\delta(CDCl_3)$ 35.04 (C-3), 79.10 (C-2), 114.34, 116.22 (C-3', C-5'), 121.53, 121.63 (C-4, C-9), 123.07 (C-7), 125.76 (C-3'', C-5''), 128.24 (C-6), 128.99, 129.09 (C-2', C-6'), 130.36, 130.93 (C-2'', C-6''), 132.22 (C-4'', C-5, C-8). EIMS (LR) $C_{22}H_{17}ClO_2$: M^+=348. This product was used in subsequent reactions without further purification.

5-(4-Hydroxyphenyl)-4-(3-nitrophenyl)-2,3-dihydro-1-benzoxepin (27)

The general Suzuki method was employed using **20** (0.22 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), *m*-nitrophenylboronic acid (0.87 mmol) and 2M sodium carbonate (1.4 mmol) and the reaction was refluxed at 80°C. The product was purified using column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 40:5:55) to present an oil in 47% yield (product homogenous on TLC with R_f =0.92; 80/20 CH_2Cl_2:EtOAc). IR ν_{max} (film) 3488 (OH), 3108-2929, 2872-2776 (CHs), 1604, 1574 (C=C), 1486, 1443 (CH_2), 1538, 1349 (C-NO_2), 1250, 1184 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.69

(2H, m, H-3), 4.62 (2H, m, H-2), 6.60-6.62 (2H, d, J = 8.52Hz, H-3', H-5'), 6.77-7.19 (10H, m, ArH).^{13}C NMR δ($CDCl_3$) 35.21 (C-3), 79.96 (C-2), 114.26, 115.80 (C-3', C-5'), 121.44, 121.61 (C-4, C-9), 123.21 (C-7), 124.93 (C-2''), 128.08 (C-6), 128.37 (C-2', C-6'), 128.41 (C-4''), 129.71 (C-5''), 130.91 (C-8), 132.21 (C-5), 140.57 (C-6''). This product was found to decompose under those conditions used for mass spectral analysis and was used in subsequent reactions without further purification.

4-(4-Cyanophenyl)-5-(4-hydroxyphenyl)-2,3-dihydro-1-benzoxepin (28)

The general Suzuki method was applied using **20** (0.22 mmol), dry THF (20mL), $Pd(PPh_3)_4$ (10mg, 8.65 μM), 4-cyanophenylboronic acid (0.87 mmol) and 2M sodium carbonate (1.4 mmol) and the reaction was refluxed at 80°C. The product was isolated using flash column chromatography (eluant C_6H_{12}:EtOAc:CH_2Cl_2; 50:8:50) to afford an oil in 34% yield, (product homogenous on TLC with R_f =0.81; 85:15 CH_2Cl_2:EtOAc) with the following physical properties: IR ν_{max} (film) 3401 (OH), 2923, 2849 (CHs), 2251 (C≡N), 1607 (C=C), 1481, 1448 (CH_2), 1248, 1166 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.73 (2H, t, J = 6.04Hz, H-3), 4.62 (2H, t, J = 6.02Hz, H-2), 6.16-7.55 (12H, m, ArH). ^{13}C NMR δ($CDCl_3$) 34.76 (C-3), 79.80 (C-2), 104.19 (C≡N), 114.49-115.90 (C-3', C-5'), 121.71 (C-4, C-9), 123.42 (C-7), 128.72 (C-6), 129.79 (C-2', C-6'), 130.67 (C-3'', C-5''), 131.40 (C-8), 132.23 (C-5), 133.02 (C-2'', C-6''), 133.81 (C-1'). EIMS (LR) $C_{23}H_{17}NO_2$: M^+=339. This product was used in subsequent reactions without further purification.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(4-methoxyphenyl)-2,3-dihydro-1-benzoxepin (12)

The general alkylation method employed for the formation of **7** was applied in the preparation of this compound: – **21** (0.13 mmol), dry acetone (20mL), anhydrous K_2CO_3 (1.3 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.32 mmol) were combined under nitrogen. The reaction mixture was refluxed for 6h. The product was isolated directly to afford a viscous oil in 60% yield (product homogenous on TLC with R_f =0.19; 70:25:5 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 11.4 mins. IR ν_{max} (film) 3032-2928, 2868-2772 (CHs), 1607 (C=C), 1483, 1464 (CH_2), 1442 (OCH_3), 1234, 1175 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.38 (6H, s, $N(CH_3)_2$), 2.70 (4H, m, NCH_2, H-3), 3.77 (3H, s, OCH_3), 4.03 (2H, m, CH_2O), 4.61 (2H, t, J = 6.02Hz, H-2), 6.66-7.21 (12H, m, ArH). ^{13}C NMR δ($CDCl_3$) 31.23 (C-3), 45.41, 45.45 ($N(CH_3)_2$), 54.66 (OCH_3), 57.89, 57.95 (NCH_2), 65.42 (CH_2O), 80.09 (C-2), 113.20, 113.29 (C-3'', C-5''), 114.17, 115.12 (C-3', C-5'), 121.55 (C-4), 122.99 (C-7),

127.71 (C-4''), 128.75 (C-6), 130.18 (C-2'', C-6'), 130.47 (C-2', C-6'), 131.98 (C-3) EIMS (HR) calculated for $C_{27}H_{29}NO_3$, 415.2147; found, 415.2137.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(2-methoxyphenyl)-2,3-dihydro-1-benzoxepin (13)

The general method for **7** was employed using **22** (0.12 mmol), dry acetone (20mL), anhydrous K_2CO_3 (1.2 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.32 mmol) under nitrogen. The product was purified using flash column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 90:5:5) to afford a viscous oil in 50% yield (product homogenous on TLC with R_f =0.40; 60/35/5 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 10.8 mins. IR ν_{max} (film) 3057-2932, 2867-2770 (CHs), 1606, 1576 (C=C), 1484, 1462 (CH_2), 1440 (OCH_3), 1372 (CH_3), 1240, 1174 (C-O-C) cm^{-1}. ^1H NMR $\delta(CDCl_3)$ 2.33 (6H, s, $N(CH_3)_2$), 2.65-2.72 (4H, m, NCH_2, H-3), 3.83 (3H, s, OCH_3), 3.99 (2H, t, J = 5.76Hz, CH_2O), 4.61 (2H, t, J = 6.02Hz, H-2), 6.63-7.16 (12H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 34.64 (C-3), 45.78 ($N(CH_3)_2$), 55.23 (OCH_3), 58.23 (NCH_2), 65.72 (CH_2O), 79.96 (C-2), 110.45 (C-4''), 113.42, 113.63 (C-3', C-5'), 120.37 (C-5''), 121.87 (C-4, C-9), 123.13 (C-7), 127.80 (C-6), 128.12 (C-4'), 131.15, 131.52 (C-2', C-6'), 131.63 (C-5), 131.71 (C-8), 131.80 (C-3''), 136.15 (C-6''). EIMS (HR) calculated for $C_{27}H_{29}NO_3$, 415.2147; found, 415.2131.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(3-methoxyphenyl)-2,3-dihydro-1-benzoxepin (14)

The general method for **7** was applied using **23** (0.06 mmol), dry acetone (20mL), anhydrous K_2CO_3 (0.6 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.2 mmol) under nitrogen. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 80:20:2) to afford an oil in 54% yield (product homogenous on TLC with R_f =0.10; 70:25:5 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 10.95 mins IR ν_{max} (film) 3050-2927, 2854-2777 (CHs), 1605 (C=C), 1508, 1485 (CH_2), 1465 (OCH_3), 1241, 1174 (C-O-C) cm^{-1}.^1H NMR $\delta(CDCl_3)$ 2.56 (6H, s, $N(CH_3)_2$), 2.87 (2H, m, NCH_2), 3.03 (2H, m, H-3), 3.80 (3H, s, OCH_3), 4.23 (2H, m, CH_2O), 4.60 (2H, m, H-2), 6.50-7.21 (12H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 34.18 (C-3), 45.20 ($N(CH_3)_2$), 55.25 (OCH_3), 57.54 (NCH_2), 64.67 (CH_2O), 80.43 (C-2), 113.74, 113.95 (C-3', C-5'), 115.76 (C-2''), 120.74 (C-4''), 121.92, 122.73 (C-4, C-9), 123.36 (C-7), 123.74 (C-5''), 128.13 (C-6''), 128.13 (C-6), 129.20, 129.47 (C-2', C-6'), 131.97 (C-8), 132.38 (C-5) EIMS (HR): calculated for $C_{27}H_{29}NO_3$, 415.2147; found, 415.2116.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(4-methylphenyl)-2,3-dihydro-1-

benzoxepin (15)

The general method for **7** was applied using **24** (0.12 mmol), dry acetone (20mL), anhydrous K_2CO_3 (1.2 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.31 mmol) under argon. The reaction mixture was refluxed for 5h. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 90:5:5) to afford a viscous oil in 64% yield, (product homogenous on TLC with R_f =0.45; 60:38:2 CH_2Cl_2:EtOAc:MeOH) with the following physical properties. HPLC T_R = 13.90 mins. IR ν_{max} (film) 2924, 2856-2772 (CHs), 1606, 1575 (C=C), 1477, 1461 (CH_2), 1376 (CH_3), 1239, 1174 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.30 (3H, s, CH_3), 2.36 (6H, s, $N(CH_3)_2$), 2.69-2.80 (4H, m, NCH_2, H-3), 4.13 (2H, m, CH_2O), 4.62 (2H, m, H-2), 6.67-6.69 (2H, m, H-3'', H-5''), 6.86-7.19 (10H, m, ArH) ^{13}C NMR $\delta(CDCl_3)$ 20.64 (CH_3), 35.24 (C-3), 45.34 ($N(CH_3)_2$), 57.79 (NCH_2), 65.28 (CH_2O), 80.03 (C-2), 113.24, 113.61 (C-3'', C-5''), 121.50, 121.57 (C-4, C-9), 122.92 (C-7), 127.79 (C-6), 128.23 (C-4''), 128.28, 128.36 (C-2'', C-6''), 128.83, 128.92 (C-3', C-5'), 130.52, 130.67 (C-2', C-6'), 131.35 (C-5), 131.99 (C-8) EIMS (HR) calculated for $C_{27}H_{29}NO_2$, 399.2198; found, 399.2195.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(3-methylphenyl)-2,3-dihydro-1-benzoxepin (16)

The general method for **7** was employed using **25** (0.06 mmol), dry acetone (15mL), anhydrous K_2CO_3 (0.6 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.17 mmol) under nitrogen. The product was isolated directly to present an oil in 41% yield (product homogenous on TLC with R_f =0.11; 60:38:2 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 13.50 mins IR ν_{max} (film) 3051-2925, 2854-2775 (CHs), 1606 (C=C), 1482, 1462 (CH_2), 1376 (CH_3), 1242, 1174 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.37 (3H, s, CH_3), 2.65 (6H, s, $N(CH_3)_2$), 2.69-2.73 (4H, m, NCH_2, H-3), 4.01 (2H, t, J = 5.78Hz, CH_2O), 4.61 (2H, m, H-2), 6.63-6.68 (2H, d, J = 8.52Hz, H-2'', H-4''), 6.88-7.26 (10H, m, ArH) ^{13}C NMR $\delta(CDCl_3)$ 22.64 (CH_3), 35.57 (C-3), 45.20, 45.79 ($N(CH_3)_2$), 58.19 (NCH_2), 65.61 (CH_2O), 80.48 (C-2), 113.54, 117.04 (C-3', C-5'), 121.98 (C-4, C-9), 123.45 (C-7), 126.68 (C-2''), 126.82 (C-6), 126.99 (C-4'), 127.73 (C-4''), 129.99, 130.94 (C-2', C-6'), 132.38 (C-5, C-8). EIMS (HR) : Calculated for $C_{27}H_{29}NO_2$, 399.2198; found, 399.2195.

4-(4-Chlorophenyl)-5-[(4-dimethylaminoethoxy)phenyl]-2,3-dihydro-1-benzoxepin (17)

The general method for **7** was employed using **26** (0.06 mmol), dry acetone (20mL), anhydrous K_2CO_3 (0.6 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.16

mmol) under argon. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 70:28:2) to afford an oil in 95% yield, (product homogenous on TLC with R_f =0.10; 60:35:5 CH_2Cl_2:EtOAc:MeOH) with the following physical properties. HPLC T_R = 15.75 mins. IR ν_{max} (film) 3058-2926, 2870-2774 (CHs), 1602 (C=C), 1491, 1465 (CH_2), ~1284 (C-Cl), 1243, 1173 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 2.36 (6H, s, $N(CH_3)_2$), 2.74 (2H, m, NCH_2), 2.92 (2H, t, J = 6.78Hz, H-3), 4.05 (2H, m, CH_2O), 4.62 (2H, m, H-2), 6.69-7.45 (12H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 35.45 (C-3), 45.79 ($N(CH_3)_2$), 58.20 (NCH_2), 65.65 (CH_2O), 80.38 (C-2), 113.74, 115.77 (C-3', C-5'), 120.74, 121.92 (C-4, C-9), 123.36 (C-7), 128.13, 128.53 (C-3'', C-5''), 128.77 (C-6), 129.20, 129.47 (C-2', C-6'), 130.79, 130.95 (C-2'', C-6''), 131.36, 134.97 (C-5, C-8) 132.38 (C-4''). EIMS (HR): Calculated for $C_{26}H_{26}ClNO_2$, 419.1652; found, 419.1645.

5-[(4-Dimethylaminoethoxy)phenyl]-4-(3-nitrophenyl)-2,3-dihydro-1-benzoxepin (18)

The general method for **7** was applied using **27** (0.08 mmol), dry acetone (15mL), anhydrous K_2CO_3 (0.8 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.3 mmol) under nitrogen. The product was isolated using column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 60:25:15) to afford an oil in 78% yield, (product homogenous on TLC with R_f =0.18; 50:45:5 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 8.40 mins IR ν_{max} (film) 3035-2926, 2855-2707 (CHs), 1605 (C=C), 1530 (C-NO_2), 1482, 1442 (CH_2), 1351 (CH_3, Ar-NO_2), 1243, 1176 (C-O-C) cm^{-1}.^{1}H NMR $\delta(CDCl_3)$ 3.04 (6H, s, $N(CH_3)_2$), 3.48-3.63 (4H, m, NCH_2, H-3), 4.55-4.64 (4H, m, CH_2O, H-2), 6.66-7.92 (12H, m, ArH). ^{13}C NMR $\delta(CDCl_3)$ 35.68 (C-3), 44.11 ($N(CH_3)_2$), 58.64 (NCH_2), 62.54 (CNO_2), 63.32 (CH_2O), 80.38 (C-2), 113.64, 115.13 (C-3', C-5'), 121.19, 121.99 (C-4, C-9), 123.46 (C-7), 123.62 (C-2''), 128.60 (C-6), 128.94 (C-2', C-6', C-4''), 130.79 (C-5''), 130.95 (C-8), 132.72 (C-5), 137.29 (C-6''). EIMS (HR): calculated for $C_{26}H_{26}N_2O_4$, 430.1893; found 430.1897.

4-(4-Cyanophenyl)-5-[(4-dimethylaminoethoxy)phenyl]-2,3-dihydro-1-benzoxepin (19)

The general method for **7** was employed using **28** (0.06 mmol), dry acetone (20mL), anhydrous K_2CO_3 (0.6 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.16 mmol) under nitrogen. The product was purified using flash column chromatography (eluant CH_2Cl_2:EtOAc:MeOH; 40:60:10) to afford an oil in 83% yield (product homogenous on TLC with R_f =0.08; 60:40:2 CH_2Cl_2:EtOAc:MeOH). HPLC T_R = 7.70 mins IR ν_{max} (film) 2923, 2880-2850 (CHs), 2225 (C≡N), 1608 (C=C), 1467, 1434

(CH_2), 1372 (CH_3), 1259, 1156 (C-O-C) cm^{-1}.^{1}H NMR δ($CDCl_3$) 2.19 (6H, s, $N(CH_3)_2$), 2.37 (2H, m, NCH_2), 2.83 (2H, m, H-3), 3.37 (2H, m, CH_2O), 4.35 (2H, m, H-2), 6.68-7.88 (12H, m, ArH). ^{13}C NMR δ($CDCl_3$) 33.99 (C-3), 44.50 ($N(CH_3)_2$), 56.94 (NCH_2), 65.41 (CH_2O), 113.87 (C-3', C-5'), 122.20 (C-4, C-9), 124.94 (C-7), 128.98 (C-6), 129.92 (C-2', C-6'), 130.17 (C-3'', C-5''), 131.85 (C-8), 132.66 (C-5), 135.14 (C-2'', C-6''). EIMS (HR) Calculated for $C_{27}H_{26}N_2O_2$, 410.1994; found, 410.2003.

Biochemical evaluation of activity

All assays were performed in triplicate for the determination of mean values reported. Compounds were assayed as the free bases isolated from reaction.

Antiproliferation studies

The human breast tumor cell line MCF-7 was cultured in Eagles minimum essential medium in a 5% CO_2 atmosphere with 10% fetal calf serum. The medium was supplemented with 1% non-essential amino acids. Cells were trypsinized and seeded at a density of 1.5 x 10^4 into a 96-well plate and incubated at 37^{o}C, 5% CO_2 atmosphere for 24 h. After this time they were treated with 2 μl volumes of test compound which had been pre-prepared as stock solutions in ethanol to furnish the concentration range of study, 1 nM–100 μM, and re-incubated for a further 72 h. Control wells contained the equivalent volume of the vehicle ethanol (1% v/v). The culture medium was then removed and the cells washed with 100 μl phosphate buffered saline (PBS) and 50 μl MTT added, to reach a final concentration of 1 mg/ml MTT added. Cells were incubated for 2 h in darkness at 37^{o}C. At this point solubilization was begun through the addition of 200 μl DMSO and the cells maintained at room temperature in darkness for 20 min to ensure thorough colour diffusion before reading the absorbance. The absorbance value of control cells (no added compound) was set to 100 % cell viability and from this graphs of absorbance versus cell density per well were prepared to assess cell viability and from these, graphs of percentage cell viability versus concentration of subject compound added were drawn.

Cytotoxicity studies

Human MCF-7 breast cancer cells were plated at a density of 1.5 x 10^4 per well in a 96-well plate, then incubated at 37^{o}C, 5% CO_2 atmosphere for 24 h. Cells were treated with the compound of choice at varying concentrations (1nM–100 μM),

then incubated for a further 72 h. Following incubation 50 µl aliquots of medium were removed to a fresh 96-well plate. Cytotoxicity was determined using and LDH assay kit obtained from Promega, following the manufacturer's instructions for use. A 50 µl per well LDH substrate mixture was added and the plate left in darkness at room temperature for equilibration. Stop solution (50 µl) was added to all wells before reading the absorbance at 490 nm. A control of 100% lysis was determined for a set of untreated cells which were lysed through the addition of 20 µl lysis solution to the media 45 min prior to harvesting. Data was presented following calculation, as percentage cell lysis versus concentration of subject compound.

Receptor Binding Assay

Estrogen receptor-rich cytosol was obtained from the uteri of externally sourced humanely sacrificed Sprague-Dawley immature rats (100–150 g mass). Briefly, the uteri were homogenized in 0.01M sodium phosphate buffer, pH 7.3, containing 0.15M NaCl, 0.1% gelatin and 0.01% sodium azide. The homogenate was then centrifuged at 100,000 x *g*, 4^{o}C . The cytosol (predominantly ER-alpha) thus isolated was pretreated with dextran coated charcoal (DCC on ice) (Fishman, 1983), and re-isolated using centrifugation, before freezing at –20^{o}C for later use. The protein concentration of cytosol samples was determined using a standard Bradford protein assay and an appropriate protein concentration range (150 µg protein in a total volume of 0.14 ml) for assay prepared. The required amounts of tritium-labeled (hot) (Amersham) and non-labeled (cold) estradiol were calculated using standard saturation curve techniques.

A fresh buffer solution was prepared (Tris[tris (hydroxymethyl) amino methane] buffer – 10 mM, pH 7.4, containing 1.5 mM EDTA and 3 mM sodium azide). Displacement testing of the compounds of choice was facilitated through the incubation of a buffered solution of a known concentration of the test compound with hot estradiol solution (specific activity 157 Ci/mmol – final conc. 5 nM / tube), followed by the addition of estrogen receptor-rich cytosol (150 µg protein). Total and non-specific binding control assays were determined in the absence and presence of 14 µl of a 0.2 mM cold estradiol solution respectively, properly corrected for the presence of ethanol in the test (displacement) samples. Samples were vortexed to ensure homogeneity and refrigerated at 4^{o}C for 16-20 h. After this time the samples were retreated with DCC on ice and centrifuged for ten min at 3500 x g. A 170 µl sample was pipetted from each vial and diluted with 10 ml scintillation fluid

(Ecoscint). A scintillation control containing 28 µl of 5 nM hot estradiol in 10 ml scintillation fluid was also prepared to facilitate theoretical activity calculations. The samples thus prepared were counted for radioactivity by liquid scintillation counting. Binding values were obtained as counts per minute (cpm) and were converted to disintegrations per minute (dpm) and computationally analyzed using sigmoidal curve fitting programs EBDA and LIGAND (Munson and Rodbard, 1980), to fit the displacement curves and to calculate binding affinity values (Ki) for the test compounds.

Computational procedures

Compounds **7-19** were built using PC Spartan Pro 1.0.5 (Wavefunction Inc.). Initial low energy conformers were generated using a Monte Carlo conformer search under the Spartan implementation of the MMFF94 force field. (Halgren T. A.; Nachbar, R.B. Merck molecular force field .4. Conformational energies and geometries for MMFF94

J. Comp. Chem. **1996** 17 (5-6): 587-615.) **Flexible Docking –** The crystal structure of estrogen receptor alpha complexed with 4-hydroxytamoxifen was downloaded from the RCSB database.(code: 3ERT; Shiau, A.K.; Barstad, D.; Loria, P.M.; Cheng, L.; Kushner, P.J.; Agard, D.A.; Greene, G.L. The structural basis of estrogen receptor / coactivator recognition and the antagonism of this interaction by tamoxifen. *Cell* , **1998,** *95,* 927.). A visual inspection of the previously obtained low energy conformers, placed in the 3ERT active site, led to the selection of each starting ligand-protein complex. In particular, ligands were superimposed along the common vinyl backbone on the receptor bound hydroxytamoxifen structure, so as to replace the crystal ligand with the compound of interest and define a starting location for subsequent flexible docking study. Waters of crystalisation were maintained during all calculations. Flexible ligand docking was achieved through the *Affinity* module of the InsightII suite from Accelyrs (Accelrys, San Diego), using the Grid-Docking method. A binding domain area subset, including all residues and water molecules within 6 Å radius from any given ligand atom, was defined. All atoms included in the binding domain area, were left free to move during the entire docking calculations. Docking calculations were performed under the CVFF forcefield (Dauber-Osguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. T. Structure and energetics of ligand binding to proteins: E. coli dihydrofolate

reductase-trimethoprim, a drug-receptor system. *Proteins* **1988**, 4, 31-47.) using a distance dependent dielectric constant set to 1. A Monte Carlo/minimization approach for random generation of a maximum of three structures was used, with an energy tolerance of 10^3 Kcal/Mol to ensure a wide variance of the input structures to be minimized (2500 iterations; ε=1*r). During this step the ligand is moved by a random combination of translation, rotation, and torsional changes (Flexible_Ligand option, considering all rotatable bonds), to sample both the conformational space of the ligand and its orientation with respect to the enzyme. The Metropolis test, at a temperature of 310 K, and a structure similarity check (RMS tolerance = 0.3 kcal/Å), were applied to select acceptable structures. After the docking procedure, the resulting complexes were further minimized by a combination of Steepest Descent (maximum RMS derivative less than 0.1 Kcal/Å) and Conjugate Gradient algorithms (maximum RMS derivative less than 0.01 Kcal/Å). This final geometry optimization was extended to a subset including all residues within 8 Å radius from any given ligand atom.

Appendix – elemental analysis / high resolution mass analysis for target compounds

Compound	Calculated	Found
7 $C_{26}H_{27}NO_2$	385.2042	385.2050
8: $C_{28}H_{31}NO_2$	413.2355	413.2355
9: $C_{28}H_{29}NO_3$	427.2147	427.2158
10 : $C_{29}H_{31}NO_2$	425.2355	425.2341.
11 : $C_{28}H_{29}NO_2$	411.2198	411.2184
12 : $C_{27}H_{29}NO_3$	415.2147	415.2137
13: $C_{27}H_{29}NO_3$	415.2147	415.2131
14: $C_{27}H_{29}NO_3$	415.2147	415.2116
15: $C_{27}H_{29}NO_2$	399.2198	399.2195
16: $C_{27}H_{29}NO_2$,	399.2198	399.2195
17: $C_{26}H_{26}ClNO_2$	419.1652.	419.1645
18: $C_{26}H_{26}N_2O_4$	430.1893	430.1897
19:$C_{27}H_{26}N_2O_2$	410.1994	410.2003