Supporting information

Multi-structure 3D-QSAR studies on a series of conformationally constrained butyrophenones docked into a new homology model of the 5-HT_{2A} receptor.

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Contents of supporting information: Experimental procedures, spectroscopic data and elemental analyses for compounds **1**-**6** and **9**-**24**.

Melting points were determined with a Kofler hot stage instrument or a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 1600 FTIR spectrophotometer; the main bands are given, in cm^{-1}. ^1H NMR spectra were recorded with a Bruker WM AMX (300 MHz); chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS). Mass spectra were performed on Kratos MS-50 or Varian Mat-711 mass spectrometers in chemical ionization (CI) mode or by electron impact (EI). Flash column chromatography was performed using Kieselgel 60 (60-200 mesh, E. Merck AG, Darmstadt, Germany). Reactions were monitored by thin layer chromatography (TLC) on Merck 60 GF254 chromatogram sheets using iodine vapour and/or UV light for detection; unless otherwise stated the purified compounds each showed a single spot. Elemental combustion analyses were performed on a Perkin Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela; unless otherwise stated all reported values are within ± 0.4% of the theoretical compositions. Solvents were purified by distillation over an appropriate drying agent under an argon atmosphere and were used immediately.

General Procedure for the Synthesis of β-benzoyl-γ-aminobutyric acids. A mixture of β-benzoylpropionic acid (1.0 g, 5.6 mmol), 37% aqueous formaldehyde (0.44 mL, 5.6 mmol) and the corresponding amine (5.6 mmol) was carefully warmed to obtain a homogeneous solution,

which was left at room temperature for 3-10 d. The Mannich base formed was collected, washed with acetone and dried. The following butyric acids were prepared by this way.

β-Benzoyl-γ-[4-(6-fluorobenzisoxazol-3-yl)piperidin-1-yl]butyric acid (1). Obtained in 80% yield as a white solid, mp 112–114 ºC. IR: 1616. Anal. ($C_{23}H_{23}FN_2O_4$) C, H, N.

β-Benzoyl-γ-piperazin-1-ylbutyric acid (2). Obtained in 78% yield as a white solid, mp 141–143 ºC (EtOH). IR: 1683. Anal. ($C_{15}H_{20}N_2O_3$) C, H, N.

General Procedure for the Synthesis of 5-aminomethyl-6-phenyl-4,5-dihydro-2H-pyridazin-3-ones. Hydrazine hydrate (1.1 mL, 22.5 mmol) was added to a solution of ketoacid **1** or **2** (4.5 mmol) in ethanol (15 mL), and the mixture was refluxed for 2 h; on cooling, the solvent was evaporated under reduced pressure and the oily residue was dissolved in methylene chloride, washed with water and dried over Na_2SO_4. Evaporation of the solvent left a yellowish solid that was crystallized from alcohol.

5-[4-(6-Fluorobenzisoxazol-3-yl)piperidinylmethyl]-6-phenyl-4,5-dihydro-2H-pyridazin-3-one (3). Obtained from acid **1** in 40% yield as a white solid, mp 157–158 ºC (i-PrOH). IR: 1670, 1613. ^{1}H NMR ($CDCl_3$): δ 2.01 (m, 4H), 2.21 (m, 1H), 2.34 (m, 1H), 2.55 (m, 3H), 2.99 (m, 4H), 3.48 (m, 1H), 7.06 (dt, *J* = 1.6, 8.9 Hz, 1H), 7.23 (dt, *J* = 1.5, 8.5 Hz, 1H), 7.43 (m, 3H), 7.64 (dd, *J* = 5.1, 8.6 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 2H), 8.78 (s, 1H). MS (EI, *m/z*): 233 ([RRN-CH_2]$^+$, 100%). Anal. ($C_{23}H_{23}FN_4O_2$) C, H, N. *Hydrochloride*: mp 268-270 ºC (EtOH).

5-(Piperazin-1-ylmethyl)-6-phenyl-4,5-dihydro-2H-pyridazin-3-one (4). Prepared from acid **2** in 65% yield as a white solid, mp 167–168 ºC (i-PrOH). IR: 1680. ^{1}H NMR ($CDCl_3$): δ 1.71 (s, 1H), 2.45 (6H, m), 2.84 (5H, m), 3.03 (d, *J* = 17.0 Hz, 1H); 3.43 (m, 1H), 7.43 (m, 3H), 7.73 (m, 2H), 8.50 (s, 1H). MS (EI, *m/z*): 99 ([RRN-CH_2]$^+$, 100%). Anal. ($C_{15}H_{20}N_4O$) C, H, N. *Hydrochloride:* mp 235–240 ºC (EtOH).

5-[4-(3-(*p*-Fluorobenzoyl)propyl)piperazin-1-ylmethyl]-6-phenyl-4,5-dihydro-2H-pyridazin-3-one (5). To a mixture of **4** (0.50 g, 1.8 mmol), anhydrous Na_2CO_3 (0.50 g, 4.7 mmol) and a catalytic amount of KI in methylisobutylketone (12 mL), a solution of 4-chloro-1,1-ethylenedioxy-1-(*p*-fluorophenyl)butane (0.38 g, 1.47 mmol) in methylisobutylketone (8

mL) was added dropwise. The mixture was refluxed for 12 h and, after cooling, the solid was filtered out. The filtrate was concentrated under vacuo and the residue was dissolved in methanol (15 mL), and 2N HCl (6 mL) was added; the solution was stirred at reflux temperature for 2 h and at room temperature overnight. Then, the organic solvent was removed at reduced pressure, and the residue was diluted with water (10 mL), basified with 0.5N NaOH and extracted with CH_2Cl_2; the organic extracts were dried over Na_2SO_4. Evaporation of the solvent left a brown oil which was purified by silica gel column chromatography (EtOAc) to give compound **5** (0.47 g, 60%) as a white solid, mp 135–136 ºC (EtOH). IR: 1682. ^{1}H NMR ($CDCl_3$): δ 1.90 (q, *J* = 7.1 Hz, 2H), 2.35 (m, 9H), 2.50 (m, 4H), 2.93 (dd, *J* = 6.2, 7.3 Hz, 2H), 2.98 (d, *J* = 17.1 Hz, 1H), 3.38 (q, *J* = 5.1 Hz, 1H), 7.08 (t, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 3.7 Hz, 3H), 7.72 (d, *J* = 3.7 Hz, 2H), 7.96 (dd, *J* = 5.5, 8.5 Hz, 2H), 9.16 (s, 1H). MS (EI, *m/z*): 263 ([RRN-CH_2]$^+$, 100%). Anal. ($C_{25}H_{29}FN_4O_2$) C, H, N. *Hydrochloride*: mp 150–151 ºC (EtOH).

5-[4-(3-(*p*-Fluorobenzoyl)butyl)piperazin-1-ylmethyl]-6-phenyl-4,5-dihydro-2H-pyridazin-3-one (6). To a mixture of **4** (0.40 g, 1.47 mmol), anhydrous Na_2CO_3 (0.40 g, 3.77 mmol) and a catalytic amount of KI in methylisobutylketone (10 mL), a solution of 5-bromo-1-(*p*-fluorophenyl)-1-pentanone (0.38 g, 1.47 mmol) in methylisobutylketone (6 mL) was added dropwise. The mixture was refluxed for 9 h and, after cooling, the solid was filtered out. The filtrate was concentrated under vacuo and the residue was crystallized from methanol to give pyridazinone **6** (0.40 g, 60%) as a white solid of mp 139-140 ºC. IR: 1677. ^{1}H NMR ($CDCl_3$): δ 1.51 (q, *J* = 7.5 Hz, 2H), 1.69 (q, *J* = 7.5 Hz, 2H), 2.45 (m, 3H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.95 (d, *J* = 17.0 Hz, 1H), 3.38 (m, 1H), 7.05 (t, *J* = 8.6 Hz, 2H), 7.34 (m, 3H), 7.70 (m, 2H), 7.91 (m, 2H), 9.70 (s, 1H). MS (EI, *m/z*): 277 ([RRN-CH_2]$^+$, 100%). Anal. ($C_{26}H_{31}FN_4O_2$) C, H, N. *Hydrochloride*: mp 152–153 ºC (EtOH).

General Procedure for Synthesis of the 3-aminomethyltetralones 9 and 10. A solution of tosylate **7** or **8** (1 mmol), the spiro amine (5 mmol), Et_3N (0.14 mL, 1 mmol) and IK (catalytic) in DMF (7 mL) was stirred at 85 ºC for 48 h. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. Purification by column chromatography

(CH_2Cl_2/CH_3OH/Et_3N 94:5:1) afforded the free base as a white solid. The results of each particular amine are described bellow.

8-[2-(1-Oxo-1,2,3,4-tetrahydro-3-naphtyl)methyl]-1,3,8-triazaspiro[4.5]decan-4-one (9). Prepared from tosylate **7** and 1,3,8-triazaspiro[4.5]decane-4-one in 20% yield as a white solid, mp 171–173 ºC. IR: 1705, 1680. ^{1}H NMR (DMSO): δ 1.65–1.70 (m, 2H); 1.90–2.13 (m, 3H); 2.20–2.48 (m, 4H); 2.69–2.90 (m, 4H); 3.00–3.18 (m, 3H); 4.35 (s, 2H); 7.23–7.33 (m, 3H); 7.48 (dt, *J* = 7.4, 1.5 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H). MS (EI, *m/z*): 313 (M^+, 34%). *Hydrochloride*: mp 245–247 °C. Anal. ($C_{18}H_{23}FN_3O_2$·2HCl·¼H_2O) C, H, N.

8-[2-(6,7-Dimethoxy-1-oxo-1,2,3,4-tetrahydro-3-naphtyl)methyl]-1,3,8-triazaspiro[4.5]decan-2,4-dione (10). Prepared from tosylate **8** and 1,3,8-triazaspiro[4.5]decane-2,4-dione in 23% yield as a white solid, mp 253–254 ºC. IR: 1772, 1729. ^{1}H NMR (DMSO): δ 1.80–1.92 (m, 2H); 2.05–2.20 (m, 2H); 2.35–2.40 (m, 1H); 2.62–2.85 (m, 4H); 3.00–3.21 (m, 4H); 3.48–3.72 (m, 2H); 3.77 (s, 3H); 3.87 (s, 3H); 6.90 (s, 1H); 7.33 (s, 1H); 8.62 (s, 1H); 10.93 (s, 1H). MS (CI, *m/z*): 388 (MH^+, 51%). *Hydrobromide*: mp 275–277 ºC (MeOH). Anal. ($C_{20}H_{25}N_3O_5$·2BrH·CH_3OH) C, H, N.

***tert*-Butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (11).** To a solution of N-(2-hydroxyetyl)piperazine (5.0 g, 38.4 mmol) in $CHCl_3$ (100 mL) at 0 °C, a solution of di-*tert*-butyl dicarbonate (8.38 g, 38.4 mmol) in $CHCl_3$ (20 mL) was added dropwise. After stirring at room temperature for 24 h, the solvent was evaporated in vacuum and the residue purified by bulb-to-bulb distillation to give carbamate **11** (8.0 g, 90% yield) as a colourless oil. Bp 140 °C/1 mm Hg. IR: 1691. ^{1}H-NMR ($CDCl_3$): δ= 1.46 (s, 9H); 2.44 (t, *J* = 4.0 Hz, 4H); 2.55 (t, *J* = 5.2 Hz, 2H); 3.43 (t, *J* = 4.3 Hz, 4H); 3.63 (t, *J* = 5.3 Hz, 2H). MS (IE): *m/z* = 230 (M^+, 3%).

***tert*-Butyl 4-(formylmethyl)piperazine-1-carboxylate (12).** Dimethyl sulfoxide (0.82 g, 10.60 mmol) was added slowly to a solution of oxalyl chloride (0.61 g, 4.86 mmol) in CH_2Cl_2 (10 mL) at -60 ºC. After 15 min, a solution of alcohol **11** (1.0 g, 4.34 mmol) in CH_2Cl_2 (10 mL) was added slowly to the mixture, which was then stirred at -60 ºC for 3 h. Et_3N (2.13 g, 21.17 mmol) was added to the mixture slowly. The mixture was warmed to room temperature, treated

with H_2O (10 mL), washed with saturated $NaHCO_3$ solution (10 mL), and water (10 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave aldehyde **12** (0.5 g, 50%) as a yellow oil. IR: 1732, 1694. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H); 2.48 (t, *J* = 4.9 Hz, 4H); 3.20 (s, 1H); 3.49 (t, *J* = 5.0 Hz, 4H); 9.70 (s, 1H). MS (EI, *m/z*): 228 (M^+, 10%).

1-[β-(4-Oxo-4,5,6,7-tetrahydrobenzofuran-5-yliden)ethyl]-4-*tert*-butoxycarbonyl)piperazine (13). In a flame-dried flask, 2.5 M butyllithium (0.68 mL, 1.72 mmol) was added to a solution of diisopropylamine (0.17 g, 1.72 mmol) in dry THF (15 mL) at –20 ºC. The mixture was cooled to –78 ºC and a solution of 4-oxo-4,5,6,7-tetrahydrobenzofuran (0.23 g, 1.72 mmol) and HMPA (0.31 g, 1.72 mmol) in dry THF (15 mL) was added dropwise and the reaction stirred for 3 h. Aldehyde **12** (0.39 g, 1.72 mmol) was added and the reaction was stirred at –78 ºC for 12 h and warmed to room temperature overnight. THF was removed in vacuo and the residue dissolved in AcOEt (50 mL), washed with 1% NH_4Cl and water. The organic phase was dried (Na_2SO_4), filtered and concentrated at reduced pressure. Column chromatography (AcOEt) of the residue afforded piperazine **13** (0.29 g, 49%) as a brown oil. IR: 1697, 1683. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H); 2.39–2.45 (m, 2H); 2.48 (t, *J* = 4.9 Hz, 4H); 2.85–2.95 (m, 2H); 3.15–3.20 (m, 2H); 3.45 (t, *J* = 5.0 Hz, 4H); 6.73 (d, *J* = 2.0 Hz, 1H); 6.82–6.88 (m, 1H); 7.35 (d, *J* = 1.9 Hz, 1H). MS (EI, *m/z*): 46 (M^+, 11%).

1-[β-(4-Oxo-4,5,6,7-tetrahydrobenzofuran-5-yl)ethyl]-4-*tert*-butoxycarbonyl)piperazine (14). A mixture of amine **13** (500 mg, 1.4 mmol) and 10% Pd-C (5 mg) in anhydrous THF (50 mL) was stirred at room temperature under H_2 for 6 h. Then, the mixture was filtered through Celite and the solvent was evaporated under vacuum to give amine **14** (472 mg, 94% yield) as a colourless oil. IR: 1697, 1683. ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H); 1.50–1.65 (m, 1H); 1.92–2.05 (m, 1H); 2.08–2.32 (m, 2H); 2.38–2.46 (m, 7H); 2.88–2.93 (m, 2H); 3.39–3.43 (m, 4H); 6.66 (d, *J* = 2.0 Hz, 1H); 7.31 (d, *J* = 1.9 Hz, 1H). MS (EI, *m/z*): 348 (M^+, 17%).

1-[β-(4-Oxo-4,5,6,7-tetrahydrobenzofuran-5-yl)ethyl]piperazine (15). To a solution of amine **14** (250 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (5 mL) trifluoroacetic acid (0.53 mL, 7.1 mmol) was added. The mixture was stirred at room temperature for 5 h, concentrated at reduced

pressure, and the residue was dissolved in CH_2Cl_2, and washed with 10% $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated to afford amine **15** (160 mg, 90% yield) as a reddish oil. IR: 1672. ^{1}H NMR ($CDCl_3$): δ 1.56 (dt, *J* = 13.9, 7.1 Hz, 1H); 1.87–1.96 (m, 1H); 2.00–2.30 (m, 2H); 2.40–2.45 (m, 7H); 2.87–2.95 (m, 6H); 6.63 (d, *J* = 1.9 Hz, 1H); 7.28 (d, *J* = 2.0 Hz, 1H). MS (EI, *m/z*): 248 (M^+, 8%)

1-[β-(4-Oxo-4,5,6,7-tetrahydrobenzofuran-5-yl)ethyl]-4-(4-fluorobenzoyl)piperazine (16). A solution of piperazine **15** (160 mg, 0.64 mmol), 1-hydroxy benzotriazole (HOBt) (87 mg, 0.64 mmol) and 4-fluorobenzoic acid (94 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred under argon at room temperature for 15 min and then cooled to 0 ºC. At this temperature, dicyclohexylcarbodiimide (DCC) (130 mg, 0.64 mmol) was added and the reaction mixture was kept at 0-5 ºC for 1 h and then allowed to reach room temperature and left overnight. The precipitated dicyclohexylurea was filtered off, and the filtrate was washed several times with 5% $NaHCO_3$ and water, dried (Na_2SO_4) and condensed to dryness. The oily residue was purified by flash chromatography (CH_2Cl_2/MeOH 9.5:0.5) to give the target compound **16** (180 mg, 78%) as a white crystalline solid of mp 121–122 °C (i-PrOH). IR: 1673, 1624. ^{1}H NMR ($CDCl_3$): δ 1.55 (dt, *J* = 13.9, 7.1 Hz, 1H); 1.86–1.96 (m, 1H); 2.03–2.23 (m, 2H); 2.39–2.45 (m, 7H); 2.80–2.86 (m, 2H); 3.36–3.65 (m, 4H); 6.57 (d, *J* = 2.0 Hz, 1H); 7.00 (t, *J* = 8.6 Hz, 2H'); 7.23 (d, *J* = 1.9 Hz, 1H); 7.32 (dd, *J* = 8.6, 5.3 Hz, 2H). MS (EI, *m/z*): 370 (M+, 4%). *Hydrochloride*: mp 252–253 °C. Anal. ($C_{21}H_{23}FN_2O_3 \cdot HCl \cdot ¼H_2O$) C, H, N.

4-Oxo-4-(5-pentylthiophen-2-yl)butyric acid (17). To an ice cooled solution of succinic anhydride (5.83 g, 58.3 mmol) in anhydrous CH_2Cl_2 (150 mL) was slowly added anhydrous $AlCl_3$ (19.44 g, 145.8 mmol) and the mixture was stirred at 0 ºC for 30 min. Then a solution of 2-pentylthiophene (9.0 g, 58.3 mmol) in anhydrous CH_2Cl_2 (50 mL) was added, and the mixture stirred at 0 ºC for 30 min, and at room temperature for 2 h. After evaporating the solvent, the residue was dissolved in 10% NaOH (50 mL) and then neutralized with concentrated HCl. The solid precipitated was collected by filtration to give the butyric acid **17** (11.31 g, 76%) as a white solid of mp 91-92 °C. IR: (film): 1701, 1654. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, *J* = 7.1 Hz,

3H); 1.23-1.40 (m, 4H); 1.60-1.72 (m, 2H); 2.74-2.84 (m, 4H); 3.18 (t, *J* = 6.7 Hz, 1H); 6.80 (d, *J* = 3.8 Hz, 1H); 7.58 (d, *J* = 3.8 Hz, 1H); 10.65 (s, 1H). MS (EI, *m/z*): 254 (M^+, 70%).

4-(5-Pentylthiophen-2-yl)butyric acid (18). A mixture of Zn (16.59 g), $HgCl_2$ (1.65 g), concentrated HCl (10 mL) and H_2O (25 mL) was stirred at room temperature for 30 min. Then toluene (50 mL), 4-(5-pentylthiophen-2-yl)-4-oxo-butyric acid **17** (4.3 g, 16.92 mmol) and glacial acetic acid (1 mL) were added. The mixture was refluxed and concentrated HCl (10 mL) and glacial acetic acid (1 mL) were added every 18 h. After refluxing for 72 h, the reaction mixture was cooled and the organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by chromatography (AcOEt/hexane 1:3) to give the acid **18** (7.27 g, 70%) as a yellow oil. IR: 1707. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, *J* = 6.7 Hz, 3H); 1.43-1.44 (m, 4H); 1.69-1.79 (m, 2H); 2.01-2.11 (m, 2H); 2.45-2.50 (t, *J* =7.3 Hz, 2H); 2.80-2.91 (m, 4H); 6.64 (s, 2H); 10.45 (s, 1H). MS (EI, *m/z*): 240 (M^+, 67%).

4-Oxo-2-pentil-4,5,6,7-tetrahydrobenzothiophene (19). To a solution of 4-(5-pentylthiophen-2-yl)butyric acid **18** (3.0 g, 12.5 mmol) in CF_3COOH (80 mL), $(CF_3CO)_2O$ (4 mL) was added at 0 °C. The solution was stirred at room temperature for 12 h and then poured onto ice-water and basified with solid $NaHCO_3$. The basic solution was extracted three times with CH_2Cl_2 and the organic extracts were dried (Na_2SO_4), filtered and concentrated at reduced pressure. The residue obtained was purified by column chromatography (AcOEt/hexane 9.5:0.5) to afford ketone **19** (2.08 g, 75%) as a reddish oil. IR: 1673. ^{1}H NMR ($CDCl_3$): δ 0.82 (t, *J* = 7.2 Hz, 3H); 1.16–1.31 (m, 4H); 1.49–1.59 (m, 2H); 2.03–2.11 (m, 2H); 2.39 (t, *J* = 6.5 Hz, 2H); 2.61 (t, *J* = 7.5 Hz, 2H); 2.84 (t, *J* = 6.0 Hz, 2H); 6.93 (s, 1H,). MS (EI, *m/z*): 222 (M^+, 26%).

Ethyl 2-(4-oxo-2-pentyl-4,5,6,7-tetrahydrobenzothiophen-5yl)acetate (20). To a stirred mixture of diisopropylamine (0.22 g, 2.25 mmol) in dry THF (25 mL) at –20 ºC, a 2.5 M solution of n-BuLi in hexane (0.9 ml, 2.25 mmol) was added. The mixture was stirred for 30 min at –20 ºC and for another 30 min at –70 ºC. After this time, a solution of 4-oxo-2-pentyl-4,5,6,7-tetrahydrobenzothiophene **19** (0.5 g, 2.25 mmol) in dry THF (15 mL) was added dropwise. After stirring 1 h at –70 ºC, ethyl bromoacetate (0.37 g, 2.25 mmol) was added, and the mixture was stirred for 30 min at –70 ºC and then for 24 h at room temperature. The solvent

was removed in vacuo and the residue was dissolved in AcOEt, washed with water, 5% $NaHCO_3$ and 5% HCl. The organic extracts were dried (Na_2SO_4) and concentrated to give a residue that was purified by column chromatography (toluene/AcOEt 3:1) to yield ketoester **20** (0.36 g, 52%) as a pale yellow oil. IR: 1736, 1673. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, *J* = 6.8 Hz, 3H); 1.24 (t, *J* = 7.0 Hz, 3H); 1.28–1.33 (m, 4H); 1.58–1.64 (m, 2H); 1.98–2.08 (m, 1H); 2.23–2.37 (m, 2H); 2.68 (t, *J* = 7.4 Hz, 2H); 2.89–3.02 (m, 4H); 4.15 (q, *J* = 7.2 Hz, 2H); 6.99 (s, 1H). MS(CI, *m/z*): 309 (MH^+, 51%).

2-(4-Oxo-2-pentyl-4,5,6,7-tetrahydrobenzothiophen-5yl)acetic acid (21). A mixture of ethyl ester **20** (0.30 g, 0.97 mmol) and LiOH (0.20 g, 4.85 mmol) in 1:1 THF:H_2O (15 mL) was stirred at room temperature for 12 h, then acidified with 10% HCl, and extracted three times with AcOEt. The organic phase was washed with water, dried (Na_2SO_4) and concentrated in vacuo to give the ketoacid **21** (0.24 g, 86%) as a white crystalline solid, mp 81-82 °C (hexane). IR: 1693, 1666. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, *J* = 6.5 Hz, 3H); 1.24–1.37 (m, 4H); 1.57–1.67 (m, 2H); 1.96–2.11 (m, 1H); 2.27–2.45 (m, 2H); 2.70 (t, *J* = 7.5 Hz, 2H); 2.89–3.07 (m, 4H); 7.00 (s, 1H), 10.61 (s, 1H). MS (CI, *m/z*): 281 (MH^+, 96%).

1-[4-Oxo-2-pentyl-4,5,6,7-tetrahydrobenzo[b]thiophen-5-yl)acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (22): A solution of 4-(6-fluorobenzisoxazol-3-yl)piperidine (0.55 g, 2.5 mmol), 1-hydroxybenzotriazole (HOBt) (0.33 g, 2.5 mmol) and the acid **21** (0.70 g, 2.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred under argon at room temperature for 15 min and then cooled to 0 ºC. At this temperature, dicyclohexylcarbodiimide (DCC) (0.51 g, 2.5 mmol) was added and the reaction mixture was kept at 0-5 ºC for 1 h and then allowed to reach room temperature and left overnight. The precipitated dicyclohexylurea was filtered off, and the filtrate was washed several times with 5% $NaHCO_3$ and water, dried (Na_2SO_4) and condensed to dryness. The oily residue was purified by column chromatography (AcOEt/hexane 1:3) to give the amide **22** (0.89 g, 74%) as a white crystalline solid of mp 122-123 ºC (i-PrOH). IR: 1666, 1632. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H); 1.28–1.34 (m, 4H); 1.58–1.67 (m, 2H); 1.82–2.19 (m, 5H); 2.26–2.40 (m, 2H); 2.70 (t, *J* = 7.4 Hz, 2H); 2.82–

3.36 (m, 7H); 4.08–4.12 (m, 1H); 4.60–4.73 (m, 1H); 7.01 (s, 1H), 7.06 (dt, *J* = 8.8, 2.0 Hz, 1H); 7.23 (dd, *J* = 8.5, 2.0 Hz, 1H); 7.70 (ddd, *J* = 13.7, 8.6, 5.0 Hz, 1H). MS (EI, *m/z*): 482 (M^+, 2%).

1-[2-(4-Oxo-2-pentyl-4,5,6,7-tetrahydrobenzothiophen-5-yl)acetyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine, ethylene ketal (23). A stirred solution of amide **22** (0.85 g, 1.76 mmol), ethylene glycol (0.65 g, 10.47 mmol) and p-TsOH (20 mg) in anhydrous toluene (50 mL) was refluxed in a Dean-Stark apparatus for 5 days with azeotropic distillation of water. After cooling, the toluene solution was washed several times with 10% Na_2CO_3 and water and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting crude ketal **23** (0.90 g, 97%), an yellow oil with only one carbonyl band in its IR spectrum (at 1632 cm^{-1}), was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H); 1.31–1.33 (m, 4H); 1.61–1.63 (m, 2H); 1.83–2.16 (m, 5H); 2.20–2.28 (m, 2H); 2.60–2.96 (m, 7H); 3.18–3.36 (m, 2H); 4.01–4.28 (m, 5H); 4.64–4.74 (m, 1H); 6.56 (d, *J* = 7.1 Hz, 1H); 7.05 (dt, *J* = 8.5, 2.0 Hz, 1H); 7.26 (dd, *J* = 8.3, 2.1 Hz, 1H); 7.60-7.67 (m, 1H). MS (CI, *m/z*): 527 (MH^+, 100%).

1-[β-(4-Oxo-2-pentyl-4,5,6,7-tetrahydrobenzothiophen-5-yl)ethyl]-4-(6-fluorobenzisoxazol-3-yl)piperidine (24): A solution of ethylene ketal **23** (0.90 g, 1.71 mmol) in anhydrous ether (15 mL) was added dropwise under argon to a stirred suspension of $LiAlH_4$ (0.26 g, 6.86 mmol) in anhydrous ether (25 mL). The reaction mixture was heated at room temperature for 12 h, cooled to 0 ºC in an ice-bath, and then quenched by sequential dropwise addition of H_2O (1 mL), NaOH 10% (2 mL) and H_2O (4 mL). The coarse precipitate formed was filtered out and thoroughly washed with ether. The combined filtrates were treated with 10% HCl and heated under reflux for 1 h. On cooling, the aqueous phase was made alkaline with 20% NaOH and extracted with CH_2Cl_2 three times, the combined organic extracts were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1) to afford **24** (0.30 g, 86%) as brownish oil that crystallized on standing: mp 125–126 ºC (i-PrOH). IR: 1663, 1615. ^{1}H NMR ($CDCl_3$): δ 0.89 (t,

J = 6.8 Hz, 3H); 1.31-1.33 (m, 4H); 1.61–1.63 (m, 2H); 1.83–2.16 (m, 5H); 2.20–2.28 (m, 2H); 2.60–2.96 (m, 7H); 3.18–3.36 (m, 2H); 4.01–4.28 (m, 2H); 4.64–4.74 (m, 1H); 6.56 (d, *J* = 7.1 Hz, 1H); 7.05 (dt, *J* = 8.5, 2.0 Hz, 1H); 7.26 (dd, *J* = 8.3, 2.1 Hz, 1H); 7.60–7.67 (m, 1H). MS (CI, *m/z*): 469 (MH^+, 100%). *Hydrochloride*: mp 273-274 ºC (i-PrOH). Anal. ($C_{27}H_{33}FN_2O_2S$·HCl) C, H, N, S.