Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting information

Potential atypical antipsychotics: Synthesis, binding affinity and SAR of new heterocyclic bioisosteric butyrophenone analogues as multitarget ligands

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1. Chemistry general

All chemicals were purchased from commercial sources (e.g., Aldrich Chemical Co.) where available and used without further purification. When necessary, solvents were purified by distillation over an appropriate drying agent under an argon atmosphere and used immediately. Diazomethane solution was prepared according to Vogel.[43] 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}. NMR spectra were recorded on a Bruker WM AMX (300 MHz for ^{1}H NMR, and 75.5 MHz for ^{13}C NMR); chemical shifts (δ) were recorded in ppm downfield from tetramethylsilane (TMS) as internal reference; approximate coupling constants (*J*) are given in Hertz (Hz). All of the observed signals were consistent with the proposed structures; the following abbreviations were used for signal assignment: Bzi, benzoisoxazole; Bzt, benzothiazole; Bz, benzoyl; Idz, indazole; Ind, indole; Ph, phenyl; Pip, piperidine; Pyr, pyrrolidine; Thp, tetrahydropyridine; Ts, tosyl. Mass spectra were performed on a Kratos MS-50 or a Varian Mat-711 mass spectrometers by chemical ionization (CI) or by electron impact (EI) methods. 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, each purified compounds showed a single spot. Elemental combustion analyses were performed using a Perkin Elmer 240B apparatus. Unless otherwise stated, all reported values were within ± 0.4% of the theoretical compositions.

2. Procedures

2-[(Dimethylamino)methylen]-5-(methoxymethyl)-1,3-cyclohexanedione (2).

To a solution of diketone **1** (1.0 g, 6.4 mmol) in anhydrous THF (100 mL), cooled in an ice bath, was added DMFDMA (0.85 g, 7.1 mmol). The reaction mixture was stirred at room temperature for 1 h and refluxed for 12 h. After cooling, the solvent was evaporated under vacuum and the residue was purified by column chromatography using AcOEt as the eluent to give the title compound (1.28 g, 95%) as a yellowish solid, mp 84–85 °C. IR: 2929, 1660, 1631, 1584, 1106. ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H, =CH), 3.38 (s, 2H, CH_3OCH_2), 3.34 (s, 6H, $N(CH_3)_2$), 3.17 (s, 3H, OCH_3), 2.58–2.54 (m, 2H, $1H_4$ + $1H_6$), 2.39–2.26 (m, 3H, $1H_4$ + H_5 + $1H_6$). ^{13}C NMR ($CDCl_3$): δ 195.0 (2CO), 162.5 (=*C*H–$N(CH_3)_2$), 109.5 (C_2), 76.4 (CH_3OCH_2), 59.5 (OCH_3), 48.5 and 45.0 ($N(CH_3)_2$), 41.7 (C_4 + C_6), 32.6 (C_5). MS (CI) *m*/*z*: 211 $[M + H]^+$.

6,7-Dihydro-6-(methoxymethyl)indazol-4(5*H*)-one (3).

To a suspension of hydrazine hydrochloride (0.27 g, 2.56 mmol) in methanol (5 mL), a 2N aqueous solution of NaOH (3.84 mL, 7.68 mmol) was added. To this mixture enaminone **2** (0.54 g, 2.56 mmol) was added dropwise and the mixture was stirred at 80 °C for 4 h. Once cooled, the reaction mixture was neutralized with 10% HCl (2 mL) and concentrated to dryness. The residue was extracted at 50 °C with AcOEt, filtered and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography using AcOEt as the eluent gave the title compound (0.32 g, 70%) as a white solid, mp 98–100 °C. IR: 3200, 2926, 1662, 1510. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H, H_3), 3.46–3.39 (m, 2H, CH_3OCH_2), 3.36 (s, 3H, OCH_3), 3.07 (dd, 1H, *J* = 16.2, 4.3 Hz, H_5), 2.75 (dd, 1H, *J* = 16.1, 9.6 Hz, H_5), 2.62–2.53 (m, 2H, H_6 + H_7), 2.40 (dd, 1H, *J* = 17.1, 11.8 Hz, H_7). ^{13}C NMR ($CDCl_3$): δ 193.6 (C_4), 152.7 (C_{7a}), 134.6 (C_3), 119.0 (C_{3a}), 75.9 (CH_3OCH_2), 59.1 (OCH_3), 42.0 (C_5), 37.1 (C_6), 25.4 (C_7). MS (EI) *m*/*z*: 180 $[M]^+$. Anal. ($C_9H_{12}N_2O_2$): C, H, N.

6,7-Dihydro-6-(methoxymethyl)-1-methyl-1*H*-indazol-4(5*H*)-one (4).

To a stirred solution of enaminone **2** (0.54 g, 2.56 mmol) in methanol (5 mL), cooled in an ice bath, was added dropwise a solution of methylhydrazine (0.14 mL; 2.56 mmol) in methanol (3 mL). The reaction mixture was stirred at reflux temperature for 3 hours and then concentrated *in vacuo*, giving a residue which was purified by column chromatography eluting with AcOEt to give the title compound (0.35 g, 70%) as a white solid, mp 92–93 °C (2-propanol). IR: 2923, 1663, 1518, 1451, 1116. ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1H, H_3), 3.81 (s, 3H, NCH_3), 3.48–3.36 (m, 2H, CH_3OCH_2), 3.37 (s, 3H, OCH_3), 2.98 (dd, 1H, *J* = 15.1, 3.6 Hz, $1H_5$), 2.70–2.56 (m, 2H, $1H_5$, H_6), 2.51 (dd, 1H, *J* = 16.9, 3.1 Hz, $1H_7$), 2.34 (dd, 1H, *J* = 16.5, 11.3 Hz, $1H_7$). ^{13}C NMR ($CDCl_3$): δ 192.2 (C_4), 149.0 (C_{7a}), 137.4 (C_3), 119.5 (C_{3a}), 75.8 (CH_3OCH_2), 59.4 (OCH_3), 41.3 (C_5), 36.9 (CH_3), 36.5(C_6), 24.8 (C_7). MS (CI) *m*/*z*: 389 $[M + H]^+$. Anal. ($C_{10}H_{14}N_2O_2 \cdot 0.1H_2O$): C, H, N.

2-Acetyl-3-hydroxy-5-(methoxymethyl)-2-cyclohexenone (13).

To a solution of **1** (0.56 g, 3.57 mmol) in anhydrous $CHCl_3$ (10 mL), Et_3N (0.36 g, 3.57 mmol), Ac_2O (0.36 g, 3.50 mmol) and DMAP (catalytic) were added, and the mixture stirred at rt for 24 h. After evaporating the solvent under reduced pressure, the residue was purified by column chromatography with 1:3 AcOEt/hexane as the eluent to afford the title compound (0.52 g, 74%) as a colourless oil. IR: 2927, 1667, 1558, 1446. ^{1}H NMR ($CDCl_3$): δ 18.07 (s, 1H, OH), 3.36–3.26 (m, 2H, CH_3OCH_2), 3.32 (s, 3H, OCH_3), 2.74 (d, 1H, *J* = 4.3 Hz, $1H_6$), 2.69–2.47 (m, 2H, $1H_6$ + H_5), 2.57 (s, 3H, $COCH_3$), 2.37–2.30 (m, 2H, $2H_4$). ^{13}C NMR ($CDCl_3$): δ 203.1 ($COCH_3$), 198.4 (C_3),

195.1 (CO), 113.4 (C_2), 75.5 (CH_3OCH_2), 59.4 (OCH_3), 41.9 (C_6), 36.5 (C_4), 32.1 (C_5), 29.0 (CH_3CO). MS (EI) *m*/*z*: 198 $[M]^+$.

6,7-Dihydro-3-methyl-6-(methoxymethyl)benzo[*d*]isoxazol-4(5*H*)-one (14).

A solution of hydroxylamine was prepared by combining warm (60 °C) methanol solutions of hydroxylamine hydrochloride (0.17 g, 2.87 mmol, in 1 mL) and potassium hydroxide (0.16 g, 2.47 mmol, in 0.70 mL). After cooling to rt the solid precipitated (KCl) was filtered off, and the filtrated was added dropwise to a solution of **13** (0.33 g, 1.65 mmol) in anhydrous benzene (3.3 mL) at 0 °C. The mixture was stirred for 48 h at rt, then water (5 mL) was added and the mixture was extracted with ether (2 × 10 mL). The organic phase was washed with 10% Na_2CO_3 solution (2 × 10 mL), water (10 mL) and brine (12 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound as colourless oil. A second portion of this compound could be obtained from the aqueous phase by acidifying to pH 3 with 10% HCl and further extraction with Et_2O. Total yield: 0.23 g, 71%. IR: 2928, 1687, 1604, 1463, 1119. ^{1}H NMR ($CDCl_3$): δ 3.46–3.38 (m, 2H, CH_3OCH_2), 3.35 (s, 3H, OCH_3), 3.09 (dd, 1H, *J* = 17.6, 5.4 Hz, $1H_7$), 2.84 (dd, 1H, *J* = 17.6, 9.6 Hz, $1H_7$), 2.64–2.58 (m, 1H, H_6), 2.57–2.46 (m, 1H, $1H_5$), 2.45 (s, 3H, CH_3), 2.42–2.36 (m, 1H, $1H_5$). ^{13}C NMR ($CDCl_3$): δ 192.7 (C_4), 180.9 (C_{7a}), 157.7 (C_3), 115.4 (C_{3a}), 75.3 (CH_3OCH_2), 59.5 (OCH_3), 41.7 (C_5), 36.3 (C_6), 26.5(C_7), 11.1 (CH_3). MS (CI) *m*/*z*: 195 $[M + H]^+$.

2-Diazo-5-(methoxymethyl)-1,3-cyclohexanedione (18).

A solution of *p*-tosyl azide (0.37 g, 1.90 mmol) and triethylamine (0.26 mL, 1.90 mmol) in CH_2Cl_2 (1.10 mL) was added to a solution of diketone **1** (0.22 g, 1.43 mmol) in CH_2Cl_2 (6.60 mL). The mixture was protected from light and stirred at rt for 15 h. Then, the mixture was washed with 5% NaOH solution (2 × 2 mL) and water (2 × 4 mL), the organic phase was dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography with 2:3 Et_2O/hexane as the eluent to afford the title compound (0.21 g, 80%) as a colourless oil. IR: 2894, 2142, 1647, 1296, 1125. ^{1}H NMR ($CDCl_3$): δ 3.33–3.31 (m, 2H, CH_3OCH_2), 3.29 (s, 3H, OCH_3), 2.69 (dd, 2H, *J* = 13.0, 1.6 Hz, $1H_4 + 1H_6$), 2.55–2.37 (m, 3H, $1H_5 + 1H_4 + 1H_6$). ^{13}C NMR ($CDCl_3$): δ 190.1 (2CO), 75.3 (CH_3OCH_2), 59.4 (OCH_3), 40.4 ($C_4 + C_6$), 32.0 (C_5). MS (CI) *m*/*z*: 183 $[M + H]^+$.

6,7-Dihydro-2-methyl -6-(methoxymethyl)benzoxazol-4(5*H*)-one (19).

A solution of **18** (210 mg, 1.16 mmol) and $Rh_2(OAc)_4$ (10 mg, 0.02 mmol) in anhydrous acetonitrile (3.40 mL, 65 mmol) was stirred at 60 °C for 7 h. After cooling, the solvent was removed *in vacuo* and the residue was purified by column chromatography with 1:2 AcOEt/hexane as the eluent to

afford the title compound (136 mg, 60%) as a white solid, mp 34–36 °C. FTIR (KBr): 2930, 1691, 1613, 1397, 1201, 1115, 1053. ^{1}H-NMR ($CDCl_3$): δ 3.48–3.38 (m, 2H, CH_3OCH_2), 3.36 (s, 3H, OCH_3), 3.02 (dd, 1H, J = 17.4, 5.4 Hz, $1H_7$), 2.86–2.78 (m, 1H, $1H_7$), 2.65–2.49 (m, 2H, H_6, $1H_5$), 2.48 (s, 3H, CH_3), 2.45–2.39 (m, 1H, $1H_5$). ^{13}C NMR ($CDCl_3$): δ 190.7 (C_4), 163.9 (C_2), 162.3 (C_{7a}), 134.4 (C_{3a}), 75.4 (CH_3OCH_2), 59.4 (OCH_3), 41.2 (C_5), 36.1 (C_6), 25.6 (C_7), 14.2 (CH_3). MS (EI) *m*/*z*: 195 $[M + H]^+$.

2-Amino-5,6-dihydro-5-(methoxymethyl)benzothiazol-7(4*H*)-one (23).

A mixture of diketone **1** (220 mg, 1.43 mmol), thiourea (110 mg; 1.39 mmol), NBS (210 mg; 1.19 mmol) and benzoyl peroxide (catalytic) in anhydrous benzene (8 mL) was refluxed for 48 h. After cooling, the solvent was evaporated under vacuum, and the resultant residue was dissolved in water and basified with K_2CO_3 solution until pH 12. The aqueous solution was extracted with CH_2Cl_2, the organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow solid which was purified by column chromatography with 30:1 CH_2Cl_2/MeOH as the eluent to afford the title compound (180 mg, 70%) as a yellowish solid, mp 165–167 °C (benzene). IR: 3096, 1614, 1511, 1395, 1334. ^{1}H NMR (CD_3OD): δ 3.43 (d, 2H, J = 5.2 Hz, CH_3OCH_2), 3.37 (s, 3H, CH_3), 2.87 (d, 1H, J = 2.7 Hz, $1H_4$), 2.64–2.44 (m, 3H, $1H_4$, H_5, $1H_6$), 2.40–2.34 (m, 1H, $1H_6$). ^{13}C NMR (CD_3OD): δ 191.4 (C_7), 177.4 (C_2), 168.5 (C_{3a}), 118.8 (C_{7a}), 75.6 (CH_3OCH_2), 58.1 (OCH_3), 39.9 (C_6), 36.1 (C_4), 30.0 (C_5). MS (EI) *m*/*z*: 212 $[M]^+$. Anal. ($C_9H_{12}N_2O_2S·0.05C_6H_6$): C, H, N, S.

5,6-Dihydro-5-(methoxymethyl)-2-(pyrrolidin-1-yl)benzothiazol-7(4*H*)-one (24).

A solution of aminothiazole **23** (120 mg, 0.56 mmol) and 30% aqueous NaOH (0.15 mL; 1.1 mmol) in acetone (2 mL) was stirred at room temperature for 10 minutes. Then, 1,4-dibromobutane (70 □L, 0.56 mmol) was added and the mixture was refluxed for 7 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated. The residue was taken into water (5 mL), extracted with CH_2Cl_2 (3 × 4 mL), and the organic phase was dried (Na_2SO_4) and the solvent evaporated. Purification of the residue by column chromatography with CH_2Cl_2 as the eluent afforded the title compound (107 mg, 70%) as a yellow solid, mp 97–99 °C (cyclohexane). IR: 2870, 1628, 1554, 1386, 1249, 1113. ^{1}H NMR ($CDCl_3$): δ 3.43 (br s, 4H, $2H_2$ + $2H_5$ Pyr), 3.40 (d, 2H, J = 5.4 Hz, CH_3OCH_2), 3.35 (s, 3H, CH_3), 2.98 (dd, 1H, J = 16.6, 3.7 Hz, $1H_4$), 2.69–2.53 (m, 3H, $1H_4$, $1H_5$, $1H_6$), 2.42–2.33 (m, 1H, $1H_6$), 2.10–2.05 (m, 4H, $2H_3$ + $2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 198.6 (C_7), 171.3 (C_2), 167.6 (C_{3a}), 119.4 (C_{7a}), 75.8 (CH_3OCH_2), 58.9 (OCH_3), 49.9 (C_6), 40.2 (C_2 + C_5 Pyr), 35.9 (C_5), 30.7 (C_4), 25.6 (C_3 + C_4 Pyr). MS (EI) *m*/*z*: 266 $[M]^+$. Anal. ($C_{13}H_{18}N_2O_2S$): C, H, N, S.

General procedure for the methyl ether hydrolysis of compounds 3, 4, 14, 19, and 24

To a solution of the methyl ether (1.54 mmol) in anhydrous CH_2Cl_2 (6 mL) cooled at –40 °C, a 1M solution of BBr_3 in CH_2Cl_2 (1.85 mL, 1.85 mmol) was added. The mixture was stirred at –40 °C for 12 h and then at 0 °C for 12 h. After reaching room temperature, the mixture was basified until pH 8 by adding a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 3 mL) and AcOEt (6 × 3 mL). The organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the crude product was purified by column chromatography.

6,7-Dihydro-6-(hydroxymethyl)-1*H*-indazol-4(5*H*)-one (5).

Eluent: 1:2 toluene/acetone. White solid, mp 159–160 °C (2-propanol). Yield: 81%. IR: 3264, 1685, 1042. ^{1}H NMR (D_2O): δ 7.79 (s, 1H, H_3), 3.56–3.40 (m, 2H, C*H*$_2$OH), 2.85 (dd, 1H, *J* = 16.5, 3.8 Hz, 1H$_5$), 2.46 (dd, 1H, *J* = 16.5, 10.4 Hz, 1H$_5$), 2.50–2.17 (m, 3H, H_6, 2H$_7$). ^{13}C NMR (D_2O): δ 198.3 (C_4), 154.5 (C_{7a}), 134.8 (C_3), 117.6 (C_{3a}), 64.8 (CH_2OH), 40.7 (C_5), 38.5 (C_6), 24.0 (C_7). MS (EI) *m*/*z*: 166 [M]$^+$. Anal. ($C_8H_{10}N_2O_2$·0.1$C_4H_8O_2$·0.33H_2O): C, H, N.

6,7-Dihydro-6-(hydroxymethyl)-1-methyl-1*H*-indazol-4(5*H*)-one (6).

Eluent: 1:2 toluene/acetone. Beige solid, mp 109–110 °C (2-propanol). Yield: 40%. IR: 3406, 1656, 1514. ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H, H_3), 3.83 (s, 3H, CH_3), 3.79 (dd, 1H, *J* = 10.6, 4.7 Hz, *H*CHOH), 3.67 (dd, 1H, *J* = 10.6, 6.6 Hz, HC*H*OH), 3.01 (dd, 1H, *J* = 16.3, 4.7 Hz, 1H$_5$), 2.70 (dd, 1H, *J* = 16.3, 9.5 Hz, 1H$_5$), 2.57–2.50 (m, 2H, H_6, 1H$_7$), 2.36 (dd, 1H, *J* = 16.9, 12.0 Hz, 1H$_7$). ^{13}C NMR ($CDCl_3$): δ 192.6 (C_4), 149.2 (C_{7a}), 137.4 (C_3), 119.5 (C_{3a}), 65.8 (CH_2OH), 41.1 (C_5), 38.9 (CH_3), 36.5 (C_6), 24.4 (C_7). MS (CI) *m*/*z*: 181 [M + H]$^+$. Anal. ($C_9H_{12}N_2O_2$·0.25C_3H_8O·0.1H_2O): C, H, N.

6,7-Dihydro-6-(hydroxymethyl)-3-methylbenzo[*d*]isoxazol-4(5*H*)-one (15).

Eluent: 1:2 AcOEt/hexane. White solid, mp 57–58 °C (cyclohexane). Yield: 56%. IR: 3391, 1678, 1601, 1470. ^{1}H NMR ($CDCl_3$): δ 3.80–3.67 (m, 2H, C*H*$_2$OH), 3.14 (dd, 1H, *J* = 17.6, 5.0 Hz, 1H$_7$), 2.88 (dd, 1H, *J* = 17.5, 9.3 Hz, 1H$_7$), 2.63–2.49 (m, 2H, H_6, 1H$_5$), 2.47 (s, 3H, CH_3), 2.45–2.39 (m, 1H, 1H$_5$). ^{13}C NMR ($CDCl_3$): δ 192.9 (C_4), 181.0 (C_{7a}), 157.7 (C_3), 115.4 (C_{3a}), 65.4 (CH_2OH), 41.4 (C_5), 38.3 (C_6), 26.2 (C_7), 11.2 (CH_3). MS (EI) *m*/*z*: 181 [M]$^+$. Anal. ($C_9H_{11}NO_3$·0.05H_2O): C, H, N.

6,7-Dihydro-2-methyl -6-(hydroxymethyl)benzoxazol-4(5*H*)-one (20).

Eluent: AcOEt. White solid, mp 93–94 °C (2-propanol). Yield: 65%. IR: 1689, 1404, 1206, 1042. ^{1}H NMR ($CDCl_3$): δ 3.78-3.65 (m, 2H, C*H*$_2$OH), 3.05 (dd, 1H, *J* = 17.5, 5.3 Hz, 1H$_7$), 2.90–2.81 (m, 1H, 1H$_7$), 2.64–2.44 (m, 3H, H_6, H_5), 2.47 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 191.0 (C_4), 164.1 (C_2),

162.4 (C_{7a}), 134.5 (C_{3a}), 65.6 (CH_2OH), 41.1 (C_5), 38.3 (C_6), 25.3 (C_7), 14.3 (CH_3). MS (EI) *m*/*z*: 181 $[M]^+$. Anal. ($C_9H_{11}NO_3 \cdot 0.1C_3H_8O$): C, H, N.

5,6-Dihydro-5-(hydroxymethyl)-2-(pyrrolidin-1-yl)benzothiazol-7(4*H*)-one (25).

Eluent: 19:1 CH_2Cl_2/MeOH. Yellowish oil. Yield: 91%. IR: 2928, 1606, 1569, 1510, 1393. ^{1}H NMR ($CDCl_3$): δ 3.68 (d, 2H, *J* = 5.1 Hz, C*H*$_2$OH), 3.53 (br s, 4H, $2H_2$ + $2H_5$ Pyr), 3.00 (dd, 1H, *J* = 17.0, 3.9 Hz, $1H_4$), 2.71–2.34 (m, 4H, $1H_4$, H_5, $2H_6$), 2.10–2.05 (m, 4H, $2H_3$ +$2H_4$ Pyr), 1.71 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 189.8 (C_7), 171.4 (C_2), 167.7 (C_{3a}), 119.4 (C_{7a}), 65.7 (CH_2OH), 49.9 (C_6), 39.9 (C_2 + C_5 Pyr), 38.2 (C_5), 30.3 (C_4), 25.5 (C_3 + C_4 Pyr). MS (EI) *m*/*z*: 252 $[M]^+$.

General procedure for the preparation of tosylates 9, 10, 16, 21, and 26.

p-Toluenesulfonyl chloride (0.35 g, 1.83 mmol, 3 equiv) was added to a solution of the corresponding alcohol (0.61 mmol) in dry pyridine (5 mL) at 0 °C, and the mixture was stirred at room temperature for 12 hours. After addition of water (15 mL) and extraction with CH_2Cl_2, the organic layer was washed with water, dried (Na_2SO_4), concentrated to dryness, and the crude product was purified by column chromatography.

6,7-Dihydro-1-(tosyl)-6-(tosyloxymethyl)-1*H*-indazol-4(5*H*)-one (9).

The title compound was prepared using 7 equivalents of tosyl chloride. Eluent: 1:2 AcOEt/hexane. White solid, mp 140–142 °C. Yield: 50%. IR: 1694, 1562, 1375, 1184. ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H, H_3), 7.91 (d, 2H, *J* = 8.4 Hz, H_2 + H_6 NTs), 7.78 (d, 2H, *J* = 8.3 Hz, H_2 + H_6 OTs), 7.40–7.34 (m, 4H, H_3 + H_5 OTs, H_3 + H_5 NTs), 4.13–3.96 (m, 2H, CH_2OTs), 2.98 (d, 1H, *J* = 11.9 Hz, $1H_5$), 2.65–2.48 (m, 3H, $1H_6$, H_6, $1H_7$), 2.46 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.38–2.26 (m, 1H, $1H_7$). ^{13}C NMR ($CDCl_3$): δ 191.7 (C_4), 158.7 (C_{7a}), 147.3 (C_4 OTs + C_4 NTs), 145.7 (C_3), 133.3 (C_1 OTs), 132.9 (C_1 NTs), 131.5 (C_3 + C_5 OTs), 130.7 (C_3 + C_5 NTs), 129.0 (C_2 + C_6 OTs), 128.3 (C_2 + C_6 NTs), 120.52 (C_{3a}), 72.1 (*C*H_2OTs), 41.7 (C_5), 35.5 (C_6), 26.2 (C_7), 22.23 ($2CH_3$). MS (EI) *m*/*z*: 289 $[M - (CH_2OTs)]^+$. Anal. ($C_{22}H_{22}N_2O_6S_2 \cdot 0.2H_2O$): C, H, N, S.

6,7-Dihydro-1-methyl-6-(tosyloxymethyl)-1*H*-indazol-4(5*H*)-one (10).

Eluent: 1:1 toluene/acetone. White solid, mp 149–150 °C (2-propanol). Yield: 71%. IR: 3444, 1666, 1519, 1459, 1174. ^{1}H NMR ($CDCl_3$): δ 7.83 (s, 1H, H_3), 7.79 (d, 2H, *J* = 8.3 Hz, H_2 + H_6 Ts), 7.37 (d, 2H, *J* = 8.0 Hz, H_3 + H_5 Ts), 4.09–3.98 (m, 2H, CH_2OTs), 3.81 (s, 3H, NCH_3), 3.02–2.98 (m, 1H, $1H_5$), 2.71–2.66 (m, 2H, $1H_5$, H_6), 2.46 (s. 3H, CH_3Ph), 2.41–2.27 (m, 2H, $2H_7$). ^{13}C NMR ($CDCl_3$): δ 190.4 (CO), 147.8 (C_{7a}), 145.8 (C_4 Ts), 137.5 (C_3), 132.8 (C_1 Ts), 130.5 (C_3 + C_5 Ts), 128.3 (C_2 +

C_6 Ts), 119.3 (C_{3a}), 72.2 (CH_2OTs), 40.4 (C_5), 36.6 (NCH_3), 36.0 (C_6), 24.3 (C_7), 22.1 (CH_3Ph). MS (CI) *m*/*z*: 335 $[M + H]^+$. Anal. ($C_{16}H_{18}N_2O_4S$): C, H, N, S.

6,7-Dihydro-3-methyl-6-(tosyloxymethyl)benzo[*d*]isoxazol-4(5*H*)-one (16).

Eluent: 1:2 AcOEt/hexane. White solid, mp 109–110 °C (2-propanol). Yield: 61%. IR: 1687, 1601, 1417, 1173. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 2H, *J* = 8.3 Hz, H_2 + H_6 Ts), 7.38 (d, 2H, *J* = 8.1 Hz, H_3 + H_5 Ts), 4.14–4.01 (m, 2H, CH_2OTs), 3.12 (dd, 1H, *J* = 16.7, 4.2 Hz, $1H_7$), 2.81 (dd, 1H, *J* = 17.2, 10.1 Hz, $1H_7$), 2.75–2.68 (m, 1H, H_6), 2.56–2.46 (m, 1H, $1H_5$), 2.47 (s, 3H, CH_3), 2.44 (s, 3H, CH_3Ph), 2.43–2.32 (m, 1H, $1H_5$). ^{13}C NMR ($CDCl_3$): δ 190.4 (CO), 179.1 (C_{7a}), 157.3 (C_3), 145.4 (C_4 Ts), 132.3 (C_1 Ts), 130.5 (C_3 + C_5 Ts), 128.3 (C_2 + C_6 Ts), 115.0 (C_{3a}), 71.5 (CH_2OTs), 40.8 (C_5), 35.5 (C_6), 26.1 (C_7), 22.1 (CH_3Ph), 11.1 (CH_3). MS (EI) *m*/*z*: 335 $[M]^+$. Anal. ($C_{16}H_{17}NO_5S$): C, H, N, S.

6,7-Dihydro-2-methyl-6-(tosyloxymethyl)benzoxazol-4(5*H*)-one (21).

Eluent: AcOEt. White solid, mp 123–125 °C. Yield: 66%. IR: 2955, 1692, 1596, 1359, 1177, 1048. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, 2H, *J* = 8.3 Hz, H_2 + H_6 OTs), 7.37 (d, 2H, *J* = 8.1 Hz, H_3 + H_5 OTs), 4.15–3.99 (m, 2H, CH_2OTs), 3.06 (dd, 1H, *J* = 16.9, 4.8 Hz, $1H_7$), 2.88–2.54 (m, 2H, $1H_7$ + H_6), 2.48 (s, 3H, CH_3), 2.46 (s, 3H, CH_3Ph), 2.43–2.22 (m, 2H, $2H_5$). ^{13}C NMR ($CDCl_3$): δ 188.9 (C_4), 166.7 (C_2), 161.8 (C_{7a}), 145.8 (C_4 Ts), 133.7 (C_1 Ts), 132.8 (C_{3a}), 130.5 (C_3 + C_5 Ts), 128.3 (C_2 + C_6 Ts), 71.8 (CH_2OTs), 40.4 (C_5), 35.4 (C_6), 25.3 (C_7), 22.1 (CH_3Ph), 14.3 (CH_3). MS (EI) *m*/*z*: 335 $[M]^+$. Anal. ($C_{16}H_{17}NO_5S·0.15H_2O$): C, H, N, S.

5,6-Dihydro-2-(pyrrolidin-1-yl)-5-(tosyloxymethyl)benzothiazole-7(4*H*)-one (26).

Eluent: AcOEt. Yellow solid, mp 154–155 °C (2-propanol). Yield: 57%. IR: 1627, 1573, 1517, 1400, 1362, 1176, 1121. ^{1}H NMR ($CDCl_3$): δ 7.79 (d, 2H, *J* = 8.2 Hz, H_2 + H_6 Ph), 7.35 (d, 2H, *J* = 8.1 Hz, H_3 + H_5 Ph), 4.03 (d, 2H, *J* = 5.2 Hz, TsOC$\underline{H}_2$), 3.52 (sa, 4H, $2H_2$ + $2H_5$ Pyr), 3.02–2.92 (m, 1H, $1H_4$), 2.78–2.47 (m, 4H, $1H_4$ + $1H_5$ + $2H_6$), 2.45 (s, 3H, CH_3), 2.10–2.04 (m, 4H, $2H_3$ + $2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 187.7 (CO), 171.4 (C_2), 166.4 (C_{3a}), 145.0 (C_4 Ts), 132.6 (C_1 Ts), 129.9 (C_3 + C_5 Ts), 127.8 (C_2+C_6 Ts), 119.2 (C_{7a}), 72.1 ($\underline{C}H_2OTs$), 49.9 (C_6), 39.3 (C_2 + C_5 Pyr), 35.1 (C_5), 30.0 (C_4), 25.5 (C_3 + C_4 Pyr), 21.6 (CH_3). MS (EI) *m*/*z*: 406 $[M]^+$. Anal. Calcd ($C_{19}H_{22}N_2O_4S_2·0.25H_2O$): C, H, N, S.

General procedure for the preparation of the 4-(4-fluorobenzoyl)piperidine derivatives 11a, 12a, 17a, 22a, and 27a.

A mixture of the corresponding tosylate **9**, **10**, **16**, **21**, or **26** (0.42 mmol) and 4-(4-fluorobenzoyl)piperidine (170 mg, 0.84 mmol) in anhydrous solvent (3 mL) was stirred under reflux for 24–96 h. After cooling to room temperature, the precipitate was removed by filtration, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography.

6,7-Dihydro-6-[(4-(4-fluorobenzoyl)piperidin-1-yl)methyl]-1*H*-indazole-4(5*H*)-one (11a).

Reaction conditions: refluxing in benzene for 24 h. Eluent: 1:4 AcOEt/hexane. Colourless oil. Yield: 24%. IR: 3280, 2929, 1667, 1598. ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H, H_3), 7.97 (dd, 2H, *J* = 8.9, 5.4 Hz, H_2 + H_6 Bz), 7.14 (t, 2H, *J* = 17.2, 8.6 Hz, H_3 + H_5 Bz), 3.20–3.11 (m, 2H, CH_2–Pip), 2.99-2.85 (m, 2H, $2H_5$), 2.68-2.54 (m, 3H, $2H_4$ Pip + H_6 + $1H_7$), 2.46-2.04 (m, 5H, $1H_7$ + $2H_2$ Pip + $2H_6$ Pip), 1.87–1.78 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 201.6 (CO Bz), 193.9 (CO Idz), 166.1 (d, *J* = 254 Hz, C_4 Ph), 149.3 (C_{7a}), 134.8 (C_3), 132.7 (C_1 Ph), 131.2 (d, *J* = 9.1 Hz, C_2 + C_6 Ph), 119.5 (C_{3a}), 116.1 (d, *J* = 21.9 Hz, C_3 + C_5 Ph), 63.3 (CH_2-Pip), 54.6, 53.4 (C_2 + C_6 Pip), 43.9 (C_4 Pip), 43.7 (C_5), 34.5 (C_6), 29.2, 29.0 (C_3 + C_5 Pip), 26.7 (C_7). MS (EI) *m*/*z*: 355 $[M]^+$. Hydrochloride: mp 220–223 °C. Anal. Calcd ($C_{20}H_{22}FN_3O_2 \cdot 2HCl \cdot 0.5H_2O$): C, H, N.

6,7-Dihydro-1-methyl-6-[(4-(4-fluorobenzoyl)piperidin-1-yl)methyl]-1*H*-indazole-4(5*H*)-one (12a).

Reaction conditions: refluxing in acetonitrile for 96 h. Eluent: 1:1 toluene/acetone. White solid, mp 169–170 °C (AcOEt). Yield: 27%. IR: 1666, 1596, 1512, 1213. ^{1}H NMR ($CDCl_3$): δ 7.97 (dd, 2H, *J* = 8.8, 5.4 Hz, H_2 + H_6 Ph), 7.84 (s, 1H, H_3), 7.14 (t, 2H, *J* = 17.1, 8.6 Hz, H_3 + H_5 Ph), 3.83 (s, 3H, NCH_3), 3.22–3.10 (m, 2H, CH_2–Pip), 3.06–2.97 (m, 2H, $2H_5$), 2.89–2.86 (m, 1H, H_4 Pip), 2.63–2.35 (m, 4H, H_6 + $2H_7$ + $1H_2$ Pip), 2.28–2.04 (m, 1H, $1H_2$ Pip), 1.89–1.80 (m, 2H, $2H_3$ Pip). ^{13}C NMR ($CDCl_3$): δ 201.5 (CO Bz), 192.6 (CO Idz), 165.6 (d, *J* = 254.8 Hz, C_4 Ph), 149.3 (C_{7a}), 137.4 (C_3), 132.8 (C_1 Ph), 131.2 (d, *J* = 9.1 Hz, C_2 + C_6 Ph), 119.7 (C_{3a}), 116.2 (d, *J* = 21.9 Hz, C_3 + C_5 Ph), 63.3 (CH_2–Pip), 55.0, 53.1 (C_2 and C_6 Pip), 44.0 (C_4 Pip), 43.1 (C_5), 36.6 (NCH_3), 34.3 (C_6), 29.3, 29.1 (C_3 and C_5 Pip), 26.1 (C_7). MS (CI) *m*/*z*: 370 $[M + H]^+$. Anal. Calcd ($C_{21}H_{24}FN_3O_2 \cdot 0.08CHCl_3$): C, H, N.

6,7-Dihydro-6-[(4-(4-fluorobenzoyl)piperidin-1-yl)methyl]-3-methylbenzo[*d*]isoxazole-4(5*H*)-one (17a).

Reaction conditions: refluxing in acetonitrile for 31 h. Eluent: 1:1 AcOEt/hexane. White solid, mp 129–130 °C (2-propanol). Yield: 50%. IR: 2954, 1682, 1597. ^{1}H NMR ($CDCl_3$): δ 7.96 (dd, 2H, *J* = 8.8, 5.5 Hz, H_2 + H_6 Ph), 7.14 (t, 2H, *J* = 17.1, 8.5 Hz, H_3 + H_5 Ph), 3.25–3.15 (m, 2H, CH_2–Pip),

2.96–2.85 (m, 2H, $2H_7$), 2.76–2.61 (m, 3H, H_4 Pip + H_6 + $1H_5$), 2.46 (s, 3H, CH_3), 2.40 (d, 1H, *J* = 6.6 Hz, $1H_5$), 2.33–2.06 (m, 4H, $2H_2$ + $2H_6$ Pip), 1.85–1.83 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 201.3 (CO Bz), 193.0 (CO Bzi), 181.1 (C_{7a}), 166.0 (d, *J* = 254.5 Hz, C_4 Ph), 157.7 (C_3), 132.8 (C_1 Ph), 131.2 (d, *J* = 7.5 Hz, C_2 + C_6 Ph), 116.1 (d, *J* = 22.6 Hz, C_3 + C_5 Ph), 115.5 (C_{3a}), 62.9 (CH_2–Pip), 54.6, 53.5 (C_2 and C_6 Pip), 43.9 (C_4 Pip), 43.3 (C_5), 33.9 (C_6), 29.2, 29.1 (C_3 and C_5 Pip), 27.8 (C_7), 11.2 (CH_3). MS (CI) *m/z*: 371 $[M + H]^+$. Anal. Calcd ($C_{21}H_{23}FN_2O_3 \cdot 0.35H_2O$): C, H, N.

6,7-Dihydro-2-methyl-6-[(4-(4-fluorobenzoyl)piperidin-1-yl)methyl]benzoxazole-4(5*H*)-one (22a).

Reaction conditions: refluxing in acetonitrile for 24 h. Eluent: AcOEt. White solid, mp 150–152 °C (2-propanol). Yield: 50%. IR: 2935, 1684, 1594, 1200. ^{1}H NMR ($CDCl_3$): δ 7.95 (dd, 2H, *J* = 8.8, 5.3 Hz, H_2 + H_6 Bz), 7.13 (t, 2H, *J* = 17.1, 8.6 Hz, H_3 + H_5 Bz), 3.19–3.05 (m, 2H, CH_2–Pip), 2.96–2.84 (m, 2H, $2H_7$), 2.73–2.62 (m, 3H, H_4 Pip + H_6 + $1H_5$), 2.47 (s, 3H, CH_3), 2.46–2.32 (m, 1H, $1H_5$), 2.30–2.02 (m, 4H, $2H_2$ + $2H_6$ Pip), 1.86–1.77 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 201.4 (CO Bz), 191.0 (CO Bzi), 167.7 (C_2), 163.2 (d, *J* = 157.9 Hz, C_4 Bz), 164.2 (C_{7a}), 134.6 (C_1 Bz), 132.8 (C_{3a}), 131.2 (d, *J* = 9.1 Hz, C_2 and C_6 Bz), 116.1 (d, *J* = 21.9 Hz, C_3 and C_5 Bz), 63.0 (CH_2-Pip), 54.7, 53.2 (C_2 and C_6 Pip), 43.9 (C_4 Pip), 42.9 (C_5), 33.7 (C_6), 29.2, 29.0 (C_3 and C_5 Pip), 26.9 (C_7), 14.2 (-CH_3). MS (CI) *m/z*: 371 $[M + H]^+$. Anal. Calcd ($C_{21}H_{23}FN_2O_3 \cdot 0.2H_2O$): C, H, N.

5,6-Dihydro-5-[(4-(4-fluorobenzoyl)piperidin-1-yl)methyl]-2-(pyrrolidin-1-yl)benzothiazole-7(4*H*)-one (27a).

Reaction conditions: refluxing in acetonitrile for 24 h. Eluent: AcOEt. Yellow solid, mp 232–234 °C. Yield: 31%. IR: 2938, 1683, 1633, 1556, 1383. ^{1}H NMR ($CDCl_3$): δ 7.98–7.93 (m, 2H, H_2 + H_6 Ph), 7.16–7.10 (m, 2H, H_3 + H_5 Ph), 3.53 (br s, 4H, $2H_2$ + $2H_5$ Pyr), 3.22–2.84 (m, 4H, H_4 Pip + CH_2–Pip + $1H_4$ + $1H_6$), 2.74–2.17 (m, 11H, $1H_4$ + H_5 + $1H_6$ + $2H_2$ Pip + $2H_3$ Pip + $2H_5$ Pip + $2H_6$ Pip), 2.20–1.95 (m, 4H, $2H_3$ + $2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 201.0 (CO Bz), 190.0 (CO Bzt), 171.3 (C_2), 168.0 (C_{3a}), 165.5 (d, *J* = 254.9 Hz, C_4 Ph), 132.4 (C_1 Ph), 130.8 (d, *J* = 9.6 Hz, C_2 and C_6 Ph), 119.6 (C_{7a}), 115.6 (d, *J* = 21.9 Hz, C_3 and C_5 Ph), 63.2 (CH_2–Pip), 54.0 and 53.3 (C_2 and C_6 Pip), 49.9 (C_6), 43.6 (C_4 Pip), 41.9 (C_2 + C_5 Pyr), 35.5 (C_5), 32.3 (C_4), 28.8 and 28.7 (C_3 and C_5 Pip), 25.5 (C_3 + C_4 Pyr). MS (CI) *m/z*: 442 $[M + H]^+$. Anal. Calcd ($C_{24}H_{28}FN_3O_2S \cdot 0.45C_4H_8O_2 \cdot 0.9H_2O$): C, H, N, S.

General procedure for the preparation of the 4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidine derivatives 11b, 12b, 17b, 22b, and 27b.

A mixture of the corresponding tosylate **9**, **10**, **16**, **21,** or **26** (0.50 mmol) and 4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidine (220 mg, 1.00 mmol) in anhydrous solvent (3 mL) was stirred under reflux for 19–72 h. After cooling to room temperature, the precipitate was removed by filtration, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography.

6,7-Dihydro-6-[(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl]-1*H*-indazole-4(5*H*)-one (11b).

Reaction conditions: refluxing in benzene for 72 h. Eluent: 1:4 AcOEt/hexane. Yellowish oil. Yield: 44%. IR: 3216, 2929, 1665, 1616, 1123. ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H, H_3), 7.68 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Bzi), 7.23 (dd, 1H, *J* = 8.5, 2.0 Hz, H_7 Bzi), 7.06 (td, 1H, *J* = 8.8, 2.0 Hz, H_5 Bzi), 3.18–2.94 (m, 5H, $2H_5$ + CH_2–Pip + $2H_4$ Pip), 2.73–2.11 (m, 7H, H_6 + $2H_7$ + $2H_2$ + $2H_6$ Pip), 2.09–2.02 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 193.5 (CO), 164.4 (d, *J* = 226.4 Hz, C_6 Bzi), 163.3 (C_{7a} Bzi), 161.1 (C_3 Bzi), 149.3 (C_{7a}), 134.8 (C_3), 122.9 (d, *J* = 11.3 Hz, C_4 Bzi), 118.8 (C_{3a}), 117.2 (C_{3a} Bzi), 112.3 (d, *J* = 25.4 Hz, C_5 Bzi), 97.4 (d, *J* = 26.6 Hz, C_7 Bzi), 63.5 (CH_2–Pip), 54.8, 54.0 (C_2 and C_6 Pip), 43.7 (C_5), 34.8 (C_4 Pip), 34.6 (C_6), 31.0, 30.9 (C_3 + C_5 Pip), 26.5 (C_7). Hydrochloride: mp 204–207 °C. MS (EI) *m*/*z*: 368 $[M]^+$. Anal. Calcd ($C_{20}H_{21}FN_4O_2 \cdot 2HCl \cdot 2.9H_2O$): C, H, N.

6,7-Dihydro-6-[(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl]-1-methyl-1*H*-indazole-4(5*H*)-one (12b).

Reaction conditions: refluxing in acetonitrile for 19 h. Eluent: 2:1 toluene/acetone. White solid, mp 186–187 °C (2-propanol). Yield: 47%. IR: 2940, 2768, 1662, 1613, 1514, 1120. ^{1}H NMR ($CDCl_3$): δ 7.85 (s, 1H, H_3), 7.67 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Bzi), 7.25–7.22 (m, 1H, H_7 Bzi), 7.06 (dt, 1H, *J* = 8.8, 2.1 Hz, H_5 Bzi), 3.84 (s, 3H, NCH_3), 3.09–2.93 (m, 5H, $2CH_2$–Pip + $2H_5$ + H_4 Pip), 2.65–2.40 (m, 3H, H_6 + $2H_7$), 2.30–2.22 (m, 4H, $2H_2$ Pip + $2H_6$ Pip), 2.18–2.06 (m, 4H, $2H_3$ Pip + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 196.9 (CO), 165.1 (d, *J* = 211.3 Hz, C_6 Bzi), 163.9 (C_{7a} Bzi), 161.0 (C_3 Bzi), 149.2 (C_{7a}), 137.4 (C_3), 122.8 (d, *J* = 11.3 Hz, C_4 Bzi), 119.7 (C_{3a}), 117.4 (C_{3a} Bzi), 112.8 (d, *J* = 25.4 Hz, C_5 Bzi), 97.9 (d, *J* = 26.6 Hz, C_7 Bzi), 63.5 (CH_2–Pip), 54.8, 53.8 (C_2 and C_6 Pip), 43.1 (C_5), 36.6 (NCH_3), 34.3 (C_6), 31.1, 30.1 (C_3 and C_5 Pip), 26.2 (C_7). MS (EI) *m*/*z*: 382 $[M]^+$. Anal. Calcd ($C_{21}H_{23}FN_4O_2$): C, H, N. Hydrochloride: mp 220–221°C.

6,7-Dihydro-6-[(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl]-3-methylbenzo[*d*]isoxazole-4(5*H*)-one (17b).

Reaction conditions: refluxing in acetonitrile for 24 h. Eluent: 1:2→1:1 AcOEt/hexane. White solid, mp 135–137 °C (2-propanol). Yield: 50%. IR: 2933, 1683, 1129. ^{1}H NMR ($CDCl_3$): δ 7.67 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Bzi), 7.23 (dd, 1H, *J* = 8.5, 2.1 Hz, H_7 Bzi), 7.05 (td, 1H, *J* = 8.8, 2.1 Hz, H_5 Bzi), 3.20 (dd, 1H, *J* = 17.3, 4.6 Hz, HCH–Pip), 3.08–2.92 (m, 3H, HCH–Pip + $2H_7$), 2.77–2.61 (m, 3H, H_4 Pip + H_6 + $1H_5$), 2.45 (s, 3H, CH_3), 2.42 (d, 1H, *J* = 0.7 Hz, $1H_5$), 2.34–2.13 (m, 4H, $2H_2$ + $2H_6$ Pip), 2.09–2.00 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 190.0 (CO), 181.1 (C_{7a}), 164.5 (d, *J* = 250.6 Hz, C_6 Bzi), 164.3 (d, *J* = 14.3 Hz, C_{7a} Bzi), 159.54 (C_3), 122.9 (d, *J* = 10.6 Hz, C_4 Bzi), 117.6 (C_{3a} Bzi), 115.5 (C_{3a}), 112.8 (d, *J* = 24.9 Hz, C_5 Bzi), 97.9 (d, *J* = 27.2 Hz, C_7 Bzi), 63.0 (CH_2–Pip), 54.8, 53.9 (C_2 and C_6 Pip), 43.3 (C_5), 34.8 (C_4 Pip), 33.9 (C_6), 31.0, 30.9 (C_3 and C_5 Pip), 27.9 (C_7), 11.2 (CH_3). MS (EI) *m*/*z*: 383 $[M]^+$. Hydrochloride: mp 212–215 °C. Anal. Calcd ($C_{21}H_{22}FN_3O_3$·HCl·0.35H_2O): C, H, N.

6,7-Dihydro-2-methyl-6-[(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl]benzoxazole-4(5*H*)-one (22b).

Reaction conditions: refluxing in acetonitrile for 24 h. Eluent: AcOEt/hexane. Colourless oil. Yield: 20%. IR: 2924, 1686, 1612, 1458, 1119. ^{1}H NMR ($CDCl_3$): δ 7.68 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Bzi), 7.23 (dd, 1H, *J* = 8.6, 2.1 Hz, H_7 Bzi), 7.06 (td, 1H, *J* = 8.8, 2.0 Hz, H_5 Bzi), 3.14–2.92 (m, 4H, CH_2–Pip + $2H_7$), 2.76–2.68 (m, 3H, H_4 Pip + H_6 + $1H_5$), 2.49 (s, 3H, CH_3), 2.47–2.12 (m, 5H, $1H_5$ + $2H_2$ Pip + $2H_6$ Pip), 2.09–2.00 (m, 4H, $2H_3$ + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 191.0 (CO), 164.0 (d, *J* = 250.6 Hz, C_6 Bzi), 163.9 (C_2), 163.8 (C_{7a} Bzi), 161.8 (C_{7a}), 160.9 (C_3 Bzi), 134.7 (C_{3a}), 122.9 (d, *J* = 11.3 Hz, C_4 Bzi), 117.7 (C_{3a} Bzi), 112.8 (d, *J* = 24.9 Hz, C_5 Bzi), 97.8 (d, *J* = 26.41 Hz, C_7 Bzi), 63.1 (CH_2–Pip), 54.8, 53.8 (C_2 and C_6 Pip), 42.9 (C_5), 34.8 (C_4 Pip), 33.7 (C_6), 31.0, 30.9 (C_3 and C_5 Pip), 27.0 (C_7), 14.3 (CH_3). MS (CI) *m*/*z*: 384 $[M + H]^+$. Hydrochloride: mp 226–227 °C (Et_2O/MeOH). Anal. Calcd ($C_{21}H_{23}ClFN_3O_3$): C, H, N.

5,6-Dihydro-5-[(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl]-2-(pyrrolidin-1-yl)benzothiazole-7(4*H*)-one (27b).

Reaction conditions: refluxing in acetonitrile for 28 h. Eluent: AcOEt. White solid, mp 75–77 °C (cyclohexane). Yield: 46%. IR: 2926, 1632, 1551, 1385, 1298, 1122. ^{1}H NMR ($CDCl_3$): δ 7.70 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Bzi), 7.22 (d, 1H, *J* = 2.1 Hz, H_7 Bzi), 7.06 (td, 1H, *J* = 8.8, *J* = 2.2 Hz, H_5 Bzi), 3.53 (br s, 4H, $2H_2$ + $2H_5$ Pyr), 3.15–2.96 (m, 4H, H_4 Pip+ CH_2–Pip + $1H_4$), 2.71–2.41 (m, 4H, $1H_4$ + H_5 + $2H_6$), 2.33–2.02 (m, 12H, $2H_2$ Pip + $2H_3$ Pip + $2H_5$ Pip + $2H_6$ Pip + $2H_3$ Pyr + $2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 189.9 (CO), 171.3 (C_2), 167.9 (C_{3a}), 165.7 (C_{7a} Bzi), 162.5 (d, *J* = 210.4 Hz, C_6 Bzi), 122.6 (d, *J* = 10.3 Hz, C_4 Bzi), 119.6 (C_{7a}), 117.2 (C_{3a} Bzi), 112.2 (d, *J* = 24.5 Hz, C_5 Bzi),

97.3 (d, *J* = 27.1 Hz, C_7 Bzi), 63.2 (CH_2–Pip), 54.1 and 53.6 (C_2 and C_6 Pip), 49.9 (C_6), 41.9 (C_2 + C_5 Pyr), 34.5 (C_4 Pip), 33.5 (C_5), 32.3 (C_4), 30.6 and 29.1 (C_3 and C_5 Pip), 25.5 (C_3 + C_4 Pyr). MS (CI) *m*/*z*: 455 $[M + H]^+$. Anal. Calcd ($C_{24}H_{27}FN_4O_2S \cdot 0.05C_6H_{12} \cdot 0.65H_2O$): C, H, N, S.

General procedure for the preparation of the 4-(6-fluoro-1*H*-indol-3-yl)piperidine derivatives 17c, 22c, and 27c

A mixture of the corresponding tosylate **16**, **21,** or **26** (0.50 mmol) and 4-(6-fluoro-1*H*-indol-3-yl)piperidine (218 mg, 1.00 mmol) in anhydrous acetonitrile (3 mL) was stirred under reflux for 24 h. After cooling to room temperature, the precipitate was removed by filtration, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography.

6,7-Dihydro-6-[(4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl)methyl]-3-methylbenzo[*d*]isoxazole-4(5*H*)-one (17c).

Eluent: ethanol. White solid, mp 176–178 °C. Yield: 48%. IR: 2369, 1683, 1461, 1052. ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H, NH), 7.50 (dd, 1H, *J* = 8.6, 5.5 Hz, H_4 Ind), 7.01 (dd, 1H, *J* = 9.6, 2.1 Hz, H_5 Ind), 6.92 (d, *J* = 1.9 Hz, H_7 Ind), 6.85 (td, 1H, *J* = 9.1, 1.9 Hz, H_2 Ind), 3.18 (dd, 1H, *J* = 17.4, 3.2, HCH–Pip), 2.95–2.47 (m, 6H, HCH–Pip + $2H_7$ + H_4 Pip + H_6 + $1H_5$), 2.45 (s, 3H, CH_3), 2.40 (dd, 1H, *J* = 7.0, 2.7 Hz, $1H_5$), 2.32–2.11 (m, 4H, $2H_2$ + $2H_6$ Pip), 2.08–1.97 (m, 2H, $1H_3$ + $1H_5$ Pip), 1.81–1.68 (m, 2H, $1H_3$ + $1H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 192.8 (CO), 180.8 (C_{7a}), 159.2 (d, *J* = 284.2 Hz, C_6 Ind), 158.7 (C_3), 136.3 (C_{7a} Ind), 123.2 (C_{3a} Ind), 121.5 (C_3 Ind), 119.8 (C_2 Ind), 119.7 (d, *J* = 13.2 Hz, C_4 Ind), 115.1 (C_{3a}), 107.8 (d, *J* = 24.3 Hz, C_5 Ind), 97.4 (d, *J* = 26.1 Hz, C_7 Ind), 62.8 (CH_2–Pip), 55.3, 54.3 (C_2 and C_6 Pip), 43.0 (C_5), 33.6, 33.5 (C_4 Pip and C_6), 33.1, 33.0 (C_3 and C_5 Pip), 27.6 (C_7), 10.8 (CH_3). MS (CI) *m*/*z*: 382 $[M + H]^+$. HRMS (CI) calcd for $C_{22}H_{24}FN_3O_2$ $[M + H]^+$ 382.193081; found, 382.191574.

6,7-Dihydro--2-methyl-6-[(4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl)methyl]benzoxazole-4(5*H*)-one (22c).

Eluent: ethanol. White solid, mp 97–99 °C. Yield: 34%. IR: 2925, 2369, 1683, 1461, 1052. ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H, NH), 7.52 (dd, 1H, *J* = 9.0, 5.3 Hz, H_4 Ind), 7.04 (dd, 1H, *J* = 9.5, 2.0 Hz, H_7 Ind), 6.95 (d, 1H, *J* = 1.5 Hz, H_2 Ind), 6.86 (t, 1H, *J* = 9.1 Hz, H_5 Ind), 3.04 (dd, 1H, *J* = 4.4, 12.0 Hz, HCH–Pip), 2.90–2.78 (m, 2H, HCH–Pip + $1H_7$), 2.75–2.66 (m, 4H, $1H_7$ + H_4 Pip + H_6 + $1H_5$), 2.49 (s, 3H, CH_3), 2.46–1.99 (m, 5H, $1H_5$ + $2H_2$ Pip + $2H_6$ Pip), 1.82–1.73 (m, 4H, $2H_3$ Pip + $2H_5$ Pip). ^{13}C NMR ($CDCl_3$): δ 190.8 (CO), 163.8 (C_2), 161.8 (C_{7a}), 159.8 (d, *J* = 237.4 Hz, C_6 Ind), 136.3 (C_{7a} Ind), 134.2 (C_{3a}), 123.2 (C_{3a} Ind), 121.2 (C_3 Ind), 120.0 (C_2 Ind), 119.6 (d, *J* = 10.3 Hz, C_4 Ind), 107.7 (d, *J* = 24.5 Hz, C_5 Ind), 97.5 (d, *J* = 26.5 Hz, C_7 Ind), 62.9 (CH_2–Pip), 55.2, 54.2 (C_2 and C_6

Pip), 42.6 (C_5), 33.4 (C_4 Pip), 33.3 (C_6), 32.9 (C_3 and C_5 Pip), 26.7 (C_7), 13.8 (CH_3). MS (CI) *m*/*z*: 382 $[M + H]^+$. Anal. Calcd ($C_{22}H_{24}FN_3O_2 \cdot 0.7H_2O$): C, H, N.

5,6-Dihydro-5-[(4-(6-fluoro-1*H*-indol-3-yl)piperidin-1-yl)methyl]-2-(pyrrolidin-1-yl)benzothiazole-7(4*H*)-one (27c).

Eluent: AcOEt. Cream coloured solid, mp 220–222 °C. Yield: 31%. IR: 3419, 2929, 1627, 1552, 1386. ^{1}H NMR ($CDCl_3$): δ 7.96 (s, 1H, NH), 7.51 (dd, 1H, *J* = 8.6, 5.3 Hz, H_4 Ind), 7.01 (dd, 1H, *J* = 9.7, 2.3 Hz, H_7 Ind), 6.92 (d, 1H, *J* = 2.1 Hz, H_2 Ind), 6.84 (td, 1H, *J* = 9.1, 2.3 Hz, H_5 Ind), 3.51 (sa, 4H, $2H_2$ +$2H_5$ Pyr), 3.10–2.95 (m, 3H, -HCH-Pip + $1H_4$ + H_4 Pip), 2.79–2.41 (m, 5H, $1H_4$ + H_5 + $2H_6$ + HCH–Pip), 2.34–1.96 (m, 8H, $2H_2$ Pip + $2H_3$ Pip + $2H_5$ Pip + $2H_6$Pip), 1.89–1.69 (m, 4H, $2H_3$ + $2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 190.2 (CO), 171.4 (C_2), 168.1 (C_{3a}), 158.9 (d, *J* = 237.2 Hz, C_6 Ind), 136.4 (C_{7a} Ind), 123.2 (C_{3a} Ind), 121.3 (C_3 Ind), 120.0 (C_2 Ind), 119.6 (d, *J* = 13.0 Hz, C_4 Ind), 119.9 (C_{7a}), 107.5 (d, *J* = 24.3 Hz, C_5 Ind), 97.4 (d, *J* = 25.6 Hz, C_7 Ind), 63.3 (CH_2–Pip), 54.9, 54.5 (C_2 and C_6 Pip), 49.9 (C_6), 42.0 (C_2 +C_5 Pyr), 33.6 (C_5), 33.5 (C_4 Pip), 33.0 (C_3 and C_5 Pip), 32.4 (C_4), 25.5 (C_3 + C_4 Pyr). MS (CI) *m*/*z*: 453 $[M + H]^+$. Anal. Calcd ($C_{25}H_{29}FN_4OS \cdot 0.2C_4H_8O_2 \cdot 0.35H_2O$): C, H, N, S.

General procedure for the preparation of the 4-(6-fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridine derivatives 22d and 27d

A mixture 4-(6-fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydropyridine (216 mg, 1.0 mmol) in anhydrous acetonitrile (3 mL) was stirred under reflux for 24 h. After cooling to room temperature, the precipitate was removed by filtration, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography with AcOEt as the eluent.

6,7-Dihydro-2-methyl-6-[(4-(6-fluoro-1*H*-indol-3-yl)-1,2,5,6-tetrahydropyridin-1-yl)methyl]benzoxazole-4(5*H*)-one (22d).

Cream coloured solid, mp 85–86 °C. Yield: 10%. IR: 3365, 1683, 1458, 1049. ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H, NH), 7.77 (dd, 1H, *J* = 8.9, 5.4 Hz, H_4 Ind), 7.15 (d, 1H, *J* = 2.0 Hz, H_2 Ind), 7.05 (dd, 1H, *J* = 9.4, 2.3 Hz, H_7 Ind), 6.88 (td, 1H, *J* = 9.1, 2.3 Hz, H_5 Ind), 6.13 (s, 1H, H_3 Thp), 3.21–3.12 (m, 2H, H_2 Thp), 2.78–2.32 (m, 11H, $2H_5$ + $2H_6$ Thp, CH_2–Thp + $2H_7$ + H_6 + $2H_5$), 2.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 190.8 (CO), 163.9 (C_2), 161.9 (C_{7a}), 159.7 (d, *J* = 238.0 Hz, C_6 Ind), 136.9 (d, *J* = 12.0 Hz, C_{7a} Ind), 134.2 (C_{3a}), 129.6 (C_{3a} Ind), 121.7 (C_3 Ind), 121.5 (d, *J* = 41.4 Hz, C_4 Ind), 121.3 (C_2 Ind), 118.8 (C_3 Thp), 117.6 (C_4 Thp), 108.5 (d, *J* = 24.3 Hz, C_5 Ind), 97.6 (d, *J* = 25.6 Hz, C_7 Ind), 62.5 (CH_2–Thp), 53.6 (C_2 Thp), 50.6 (C_6 Thp), 42.5 (C_5), 33.4 (C_6), 28.9 (C_5 Thp), 26.6

(C_7), 13.8 (CH_3). MS (CI) *m/z*: 380 $[M + H]^+$. HRMS (CI) calcd for $C_{22}H_{22}FN_3O_2$ $[M + H]^+$ 380.178028; found, 380.177430.

5,6-Dihydro-5-[(4-(6-fluoro-1*H*-indol-3-yl)-1,2,5,6-tetrahydropyridin-1-yl)methyl]-2-(pyrrolidin-1-yl)benzothiazole-7(4*H*)-one (27d).

Yellow solid, mp 120–121 °C. Yield: 38%. IR: 2923, 1631, 1553, 1386, 1337. ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H, NH), 7.78 (dd, 1H, *J* = 8.7, 5.1 Hz, H_4 Ind), 7.13 (s, 1H, H_2 Ind), 7.05 (d, 1H, *J* = 9.3 Hz, H_7 Ind), 6.88 (t, 1H, *J* = 17.1, 9.3 Hz, H_5 Ind), 6.13 (s, 1H, H_3 Thp), 3.53 (br s, 4H, $2H_2$ + $2H_5$ Pyr), 3.21–3.08 (m, 3H, $2H_2$ Thp + $1H_4$), 2.73–2.28 (m, 10H, $1H_4$ + H_5 + $2H_6$, -CH_2–Thp, $2H_5$ + $2H_6$ Thp), 2.20–2.10 (m, 4H, $2H_3$ Pyr +$2H_4$ Pyr). ^{13}C NMR ($CDCl_3$): δ 190.2 (CO), 171.5 (C_2), 168.2 (C_{3a}), 159.6 (d, *J* = 237.4 Hz, C_6 Ind), 137.0 (d, *J* = 12.3, C_{7a} Ind), 129.6 (C_{3a} Ind), 121.6 (*J* = 38.7 Hz, C_4 Ind), 121.8 (C_3 Ind), 121.2 (C_2 Ind), 119.5 (C_{7a}), 118.8 (C_3 Thp), 117.6 (C_4 Thp), 108.3 (d, *J* = 23.9 Hz, C_5 Ind), 97.7 (d, *J* = 25.1 Hz, C_7 Ind), 62.8 (CH_2–Thp), 53.6 (C_2 Thp), 50.5 (C_6 Thp), 49.9 (C_6), 41.9 (C_2 + C_5 Pyr), 33.6 (C_5), 32.3 (C_4), 28.9 (C_5 Thp), 25.5 (C_3 + C_4 Pyr). MS (CI) *m/z*: 451 $[M + H]^+$. Anal. Calcd ($C_{25}H_{27}FN_4OS·0.7C_4H_8O_2·0.75H_2O$): C, H, N, S.

3. Receptor binding studies

The affinity of the new compounds for cloned human D_1, D_2, D_3, 5-HT_{2A} and 5-HT_{2C} receptors was evaluated by *in vitro* radioligand binding assays according to our previously described procedures.[2,3]

The affinity for cloned human 5-HT_{1A} receptors was evaluated by incubating 10 µg of membranes obtained from a HEK293 h5HT_{1A} cell line in assay buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, pH=7.4) with 2 nM [^{3}H]8-OH-DPAT for 120 min at 37 °C in a multiscreen GF/C plate (Millipore). Non-specific binding was defined with 10 µM 5-HT. After incubation time sample was filtered by using a multiscreen manifold (Millipore) and washed 4 times with ice-cold wash buffer (50 mM Tris-HCl, pH=7.4) and then scintillation cocktail (Universol, ICN Biomedicals) was added to each well and radioactivity was detected in a micoplate liquid scintillation detector (Microbeta Trilux, Perkin Elmer).

The affinity for cloned human 5-HT_6 receptors was evaluated by incubating 5 µg of membranes obtained from a HEK h5HT_6 cell line in assay buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 0.5 mM EDTA, pH=7.4) with 3 nM [^{3}H]LSD for 60 min at 37 °C in a multiscreen GF/C plate (Millipore). Non-specific binding was defined with 100 µM 5-HT. After incubation time sample was filtered by using a multiscreen manifold (Millipore) and washed 4 times with ice-cold wash buffer (50 mM Tris-HCl, pH=7.4) and then scintillation cocktail (Universol, ICN Biomedicals) was added to each

well and radioactivity was detected in a microplate liquid scintillation detector (Microbeta Trilux, Perkin Elmer).

K_i values (expressed as pK_i) were calculated according to the Cheng–Prusoff equation.[4]

4. References

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