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Supporting Information

Arylsulfonamide derivatives of (aryloxy)ethylpiperidines as selective 5-HT$_7$ receptor antagonists and their psychotropic properties

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General chemical methods

Organic transformations were carried out at ambient temperature, unless indicated otherwise. Organic solvents used in this study (Chempur) were of reagent grade and were used without purification. All other commercially available reagents were of the highest purity (from Sigma-Aldrich, Alfa Aesar, Fluorochem).

All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel Merck 60 (70–230 mesh ASTM).

The purity of the compounds were confirmed by the thin layer chromatography (TLC) performed on Merck silica gel 60 F_{254} aluminum sheets (Merck, Darmstadt, Germany). Spots were detected by their absorption under UV light (λ = 254 nm).

Analytical HPLC analyses were run on an Alliance Waters 2695 Separations Module equipped with a Chromolith Speed ROD RP 18.5 µm column (4.6 × 50 mm). Standard conditions were as follows: eluent system A (water/0.1% TFA) and system B (MeCN/0.1% TFA). The column was maintained at 25°C. A flow rate of 5 mL/min with a gradient of (0–100)% B over 3 min was used. Detection was performed with a Waters 2998 Photodiode Array Detector. Spectra were analyzed in 200 – 600 nm range with 1.2 nm resolution and sampling rate 20 points/s.

The UPLC-MS/MS system consisted of a Waters ACQUITY® UPLC® (Waters Corporation, Milford, MA, USA) coupled to a Waters TQD mass spectrometer (electrospray ionization mode ESI-tandem quadrupole). Chromatographic separations were carried out using the Acquity UPLC BEH (bridged ethyl hybrid) C18 column; 2.1 × 100 mm, and 1.7 µm particle size, equipped with Acquity UPLC BEH C18 VanGuard pre-column; 2.1 × 5 mm, and 1.7 µm particle size. The column was maintained at 40°C, and eluted under gradient conditions from 95% to 0% of eluent A over 10 min, at a flow rate of 0.3 mL min-1. Eluent A: water/formic acid (0.1%, v/v); eluent B: acetonitrile/formic acid (0.1%, v/v).

Chromatograms were made using Waters eλ PDA detector. Spectra were analyzed in 200 – 700 nm range with 1.2nm resolution and sampling rate 20 points/s.

MS detection settings of Waters TQD mass spectrometer were as follows: source temperature 150 °C, desolvation temperature 350°C, desolvation gas flow rate 600 L h-1, cone gas flow 100 L h-1, capillary potential 3.00 kV, cone potential 40 V. Nitrogen was used for both nebulizing and drying gas. The data were obtained in a scan mode ranging from 50 to 2000 m/z in time 1.0 s intervals.

Collision activated dissociations (CAD) analyses were carried out with the energy of 60 eV and 70 eV, and all the fragmentations were observed in the source. Consequently, the ion spectra were obtained by scanning from 50 to 1100 m/z range. Data acquisition software was MassLynx V 4.1 (Waters).

^{1}H NMR and ^{13}C NMR spectra were obtained in Varian BB 200 spectrometer using TMS (0.00 ppm) as an internal standard in $CDCl_3$, and were recorded at 300 and 75 MHz, respectively. The *J* values are reported in Hertz (Hz), and the splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), ddd (doublet of doublet of doublets), m (multiplet), br s (broad signal).

Elemental analyses for C, H, N and S were carried out using the elemental Vario EI III Elemental Analyser (Hanau, Germany). All values are given as percentages.

General procedure for the alkylation with the ((aryloxy)ethyl)bromides of 4-(N-Boc-amino)piperidine (**5**–**6**)

Commercial 4-(Boc-*N*-amino)piperidine (0.015 mol) was dissolved in acetone (15 ml). Then K_2CO_3 (0.045 mol) and catalytic amount of KI were added followed by dropwise addition of (aryloxy)ethyl bromide (0.018 mol). The reaction was refluxed for 72 h. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel with DCM/MeOH as an eluting system.

Boc-deprotection protocol

TFA (4 ml) was added to the solution of Boc-protected alicyclic amine in DCM (2 ml) and stirred for 2 h at room temperature. The excess of reagent and solvent were removed under reduced pressure and left under vacuum overnight.

*General procedure for preparation of final compounds (**8**–**28**)*

A mixture of the appropriate (aryloxy)ethylpiperidine (0.38 mmol) in CH_2Cl_2 (3 mL), and TEA (1.14 mmol) was cooled down (ice bath), and alkyl/arylsulfonyl chloride (0.37 mmol) was added at 0°C in one portion. The reaction mixture was stirred for 2-6 hours under cooling. Then, the solvent was evaporated and the sulfonamides were purified using silica gel column with DCM/MeOH as an eluting system. Free bases were then converted into the hydrochloride salts by treatment of their solution in anhydrous ethanol with 1.25 M HCl in MeOH.

2. Characterization of final compounds

*2-Methylpropane--N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-sulfonamide (**8**)*

Yellow oil, 90 mg (83 % yield); LC/MS purity 98%, t_R = 4.87, $C_{20}H_{34}N_2O_3S$, MW 382.56, Monoisotopic Mass 382.23, $[M+H]^+$ 382.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J* = 5.87 Hz, 6H), 1.18 (d, *J* = 6.92 Hz, 6H), 1.42–1.56 (m, 2H), 1.79 (dd, *J* = 13.62, 3.08 Hz, 2H), 1.85–1.87 (m, 1H), 2.16–2.27 (m, 2H), 2.78 (t, *J* = 5.72 Hz, 2H), 2.82–2.90 (m, 2H), 3.20–3.34 (m, 2H), 3.56–3.58 (m, 2H), 4.05 (t, *J* = 5.71 Hz, 2H), 4.72 (br s, 1H), 6.79 (dd, *J* = 8.14, 0.83 Hz, 1H), 6.92 (td, *J* = 7.45, 0.93 Hz, 1H), 7.20 (dd, *J* = 7.50, 1.60 Hz, 1H), 7.46–7.54 (m, 1H).

*N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**9**)*

Yellow oil, 100 mg (85 % yield); LC/MS purity 97%, tR = 5.18. $C_{22}H_{30}N_2O_3S$, MW 402.55, Monoisotopic Mass 402.2, $[M+H]^+$ 403.1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.92 Hz, 6H), 1.44–1.55 (m, 2H), 1.75–1.81 (m, 2H), 2.16–2.26 (m, 2H), 2.78 (t, *J* = 5.74 Hz, 2H), 2.81–2.89 (m, 2H), 3.22–3.32 (m, 2H), 4.04 (t, *J* = 5.74 Hz, 2H), 4.61 (br s, 1H), 6.79 (dd, *J* = 8.14, 0.93 Hz, 1H), 6.88–6.94 (m, 1H), 7.12 (td, *J* = 7.76, 1.73 Hz, 1H), 7.20 (dd, *J* = 7.53, 1.67 Hz, 1H), 7.47–7.58 (m, 3H), 7.86–7.92 (m, 2H).

*3-Fluoro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**10**)*

Yellow oil, 140 mg (87 % yield); LC/MS purity 99%, t_R = 5.27, $C_{22}H_{29}FN_2O_3S$, MW 420.54, Monoisotopic Mass 420.19, $[M+H]^+$ 421.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.92 Hz, 6H), 1.42–1.56 (m, 2H), 1.79 (dd, *J* = 13.62, 3.08 Hz, 2H), 2.16–2.27 (m, 2H), 2.78 (t, *J* = 5.72 Hz, 2H), 2.82–2.90 (m, 2H), 3.20–3.34 (m, 2H), 4.05 (t, *J* = 5.71 Hz, 2H), 4.72 (br s, 1H), 6.79 (dd, *J* = 8.14, 0.83 Hz, 1H), 6.92 (td, *J* = 7.45, 0.93 Hz, 1H), 7.09–7.16 (m, 1H), 7.20 (dd, *J* = 7.50, 1.60 Hz, 1H), 7.23–7.31 (m, 1H), 7.46–7.54 (m, 1H), 7.59 (dt, *J* = 8.19, 2.08 Hz, 1H), 7.68 (dt, *J* = 7.81, 1.22 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.67, 26.74, 33.13, 50.83, 52.39, 57.14, 66.38, 111.23, 114.13, 114.45, 119.93, 120.77, 122.57, 122.62, 126.06, 128.16, 130.89, 130.99, 137.02, 143.40, 155.78, 160.75. Anal. calcd for $C_{22}H_{29}FN_2O_3S{\cdot}HCl$: C: 57.82, H: 6.62, N: 6.13, S: 7.02; Found C: 58.2, H: 5.41, N: 6.04, S: 6.80.

*3-Chloro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**11**)*

Yellow oil, 120 mg (72% yield); LC/MS purity 95%, t_R = 5.41, $C_{22}H_{29}ClN_2O_3S$, MW 437.00, Monoisotopic Mass 436.16, $[M+H]^+$ 437.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.18 (d, *J* = 6.96 Hz, 6H), 1.48–1.60 (m, 2H), 1.74–1.84 (m, 2H), 2.22 (t, *J* = 10.37 Hz, 2H), 2.79 (t, *J* = 5.69 Hz, 2H), 2.84–2.92 (m, 2H), 3.15–3.17 (m, 1H), 3.22–3.32 (m, 1H), 4.05 (t, *J* = 5.67 Hz, 2H), 5.14 (br s, 1H), 6.79 (dd, *J* = 8.13, 0.69 Hz, 1H), 6.89–6.95 (m, 1H), 7.12 (td, *J* = 7.76, 1.70 Hz, 1H), 7.20 (dd, *J* = 7.50, 1.60 Hz, 1H), 7.41–7.48 (m, 1H), 7.51-7.56 (m, 1H), 7.78 (dt, *J* = 7.72, 1.32 Hz, 1H), 7.89 (t, *J* = 1.84 Hz, 1H).

*3,4-Difluoro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**12**)*

Yellow oil, 120 mg (73% yield); LC/MS purity 98%, t_R = 5.45, $C_{22}H_{28}F_2N_2O_3S$, MW 438.53, Monoisotopic Mass 438.18, $[M+H]^+$ 439.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.92 Hz, 6H), 1.44–1.58 (m, 2H), 1.75–1.78 (m, 2H), 2.17–2.27 (m, 2H), 2.79 (t, *J* = 5.66 Hz, 2H), 2.85–2.88 (m, 2H), 3.15–3.21 (m, 1H), 3.22–3.32 (m, 1H), 4.05 (t, *J* = 5.66 Hz, 2H), 5.00 (br s, 1H), 6.79 (dd, *J* = 8.17, 0.93 Hz, 1H), 6.89–6.95 (m, 1H), 7.13 (td, *J* = 7.76, 1.73 Hz, 1H), 7.20 (dd, *J* = 7.53, 1.63 Hz, 1H), 7.30 (dt, *J* = 8.46, 1.11 Hz, 1H), 7.65–7.72 (m, 1H), 7.73–7.77 (m, 1H).

*2,5-Difluoro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**13**)*

Yellow oil, 130 mg (78% yield); LC/MS purity 99%, t_R = 5.19, $C_{22}H_{28}F_2N_2O_3S$, MW 438.53, Monoisotopic Mass 438.18, $[M+H]^+$ 439.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.92 Hz, 6H), 1.45–1.60 (m, 2H), 1.76–1.86 (m, 2H), 2.17–2.28 (m, 2H), 2.79 (t, *J* = 5.71 Hz, 2H), 2.83–2.92 (m, 2H), 3.27 (quin, *J* = 6.89 Hz, 2H), 4.05 (t, *J* = 5.71 Hz, 2H), 4.81 (br s, 1H), 6.79 (dd, *J* = 8.14, 0.96 Hz, 1H), 6.88–6.95 (m, 1H), 7.09–7.16 (m, 1H), 7.17–7.30 (m, 3H), 7.63 (ddd, *J* = 7.42, 5.47, 3.08 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 22.67, 26.74, 33.03, 51.08, 52.35, 57.13, 66.40, 111.22, 116.64, 117.00, 118.10, 118.20, 118.52, 120.77, 121.19, 121.40, 121.51, 126.07, 126.52, 137.02, 155.78. Anal. calcd for $C_{22}H_{28}F_2N_2O_3S{\cdot}HCl$: C: 55.63, H: 6.15, N: 5.90, S: 6.75; Found C: 56.43, H: 4.58, N: 5.63, S: 6.55.

*5-Chloro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-thiophene-2-sulfonamide (**14**)*

Yellow oil, 110 mg (65% yield); LC/MS purity 97%, t_R = 5.54, $C_{22}H_{27}ClN_2O_3S_2$, MW 443.02, Monoisotopic Mass 442.12, $[M+H]^+$ 443.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.92 Hz, 6H), 1.52–1.65 (m, 2H), 1.86-1.89 (m, 2H), 2.28 (t, *J* = 11.20 Hz, 2H), 2.83 (t, *J* = 5.64 Hz, 2H), 2.88–2.92 (m, 1H), 2.95–2.97 (m, 1H), 3.19–3.34 (m, 2H), 4.08 (t, *J* = 5.64 Hz, 2H), 6.78–6.82 (m, 1H), 6.90 (d, *J* = 3.98 Hz, 1H), 6.92–6.96 (m, 1H), 7.13 (td, *J* = 7.76, 1.70 Hz, 1H), 7.21 (dd, *J* = 7.53, 1.60 Hz, 1H), 7.41 (d, *J* = 4.01 Hz, 1H).

*1-Methyl-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-1H-pyrazole-4-sulfonamide (**15**)*

Yellow oil, 140 mg (89% yield); LC/MS purity 98%, t_R = 4.33, $C_{20}H_{30}N_4O_3S$, MW 406.54, Monoisotopic Mass 406.20, $[M+H]^+$ 407.5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.92 Hz, 6H), 1.46–1.60 (m, 2H), 1.81–1.97 (m, 3H), 2.18–2.28 (m, 2H), 2.79 (t, *J* = 5.71 Hz, 2H), 2.84–2.92 (m, 2H), 3.23–3.33 (m, 1H), 3.93 (s, 3H), 4.05 (t, *J* = 5.72 Hz, 2H), 4.76 (br s, 1H), 6.79 (dd, *J* = 8.16, 1.04 Hz, 1H), 6.92 (td, *J* = 7.45, 1.06 Hz, 1H), 7.09–7.16 (m, 1H), 7.20 (dd, *J* = 7.53, 1.67 Hz, 1H), 7.76 (d, *J* = 0.64 Hz, 1H), 7.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.68, 26.73, 33.11, 39.59, 50.62, 52.46, 57.19, 66.37, 111.20, 120.75, 123.56, 126.06, 126.53, 131.71, 137.00, 138.40, 155.77. Anal. calcd for $C_{20}H_{30}N_4O_3S{\cdot}HCl$: C: 54.22, H: 7,05, N: 12.65, S: 7.24; Found C: 52.64, H: 7.76, N: 11.19, S: 6.12.

*4-N-(1-{2-[(Propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-isoquinolinesulfonamide (**16**)*

Yellow oil, 140 mg (83% yield); LC/MS purity 100%, t_R = 4.93, $C_{25}H_{31}N_3O_3S$, MW 453.6, Monoisotopic Mass 453.21, $[M+H]^+$ 454.3. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.92 Hz, 6H), 1.39–1.53 (m, 2H), 1.67–1.77 (m, 2H), 2.09–2.19 (m, 2H), 2.73 (t, *J* = 5.69 Hz, 2H), 2.75–2.83 (m, 2H), 3.17–3.25 (m, 1H), 3.28–3.33 (m, 1H), 4.00 (t, *J* = 5.71 Hz, 2H), 5.40 (br s, 1H), 6.75 (dd, *J* = 8.13, 0.88 Hz, 1H), 6.86–6.93 (m, 1H), 7.06–7.13 (m, 1H), 7.18 (dd, *J* = 7.53, 1.63 Hz, 1H), 7.71–7.78 (m, 1H), 7.88 (ddd, *J* = 8.51, 7.07, 1.31 Hz, 1H), 8.10 (d, *J* = 8.01 Hz, 1H), 8.60 (dd, *J* = 8.58, 0.50 Hz, 1H), 9.18 (s, 1H), 9.43 (s, 1H).

*5-N-(1-{2-[(Propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-quinolinesulfonamide (**17**)*

Yellow oil, 150 mg (87% yield); LC/MS purity 99%, t_R = 4.74, $C_{25}H_{31}N_3O_3S$, MW 453.6, Monoisotopic Mass 453.21, $[M+H]^+$ 454.3. ^1H NMR (300 MHz, $CDCl_3$) δ 11.15 (d, *J* = 6.92 Hz, 6H), 1.36–1.51 (m, 2H), 1.64–1.71 (m, 2H), 2.08–2.19 (m, 2H), 2.74 (t, *J* = 5.66 Hz, 2H), 2.75–2.83 (m, 2H), 3.15–3.18 (m, 1H), 3.23–3.29 (m, 1H), 4.00 (t, *J* = 5.66 Hz, 2H), 5.31–5.38 (m, 1H), 6.75 (dd, *J* = 8.14, 1.03 Hz, 1H), 6.86–6.94 (m, 1H), 7.05–7.13 (m, 1H), 7.15–7.21 (m, 1H), 7.53 (dd, *J* = 8.69, 4.26 Hz, 1H), 7.77 (dd, *J* = 8.40, 7.50 Hz, 1H), 8.30–8.36 (m, 2H), 9.00 (td, *J* = 3.65, 1.59 Hz, 1H), 9.04 –9.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.66, 26.70, 33.14, 50.95, 52.44, 57.09, 66.31, 111.15, 120.74, 123.71, 126.03, 126.51, 128.52, 128.75, 128.90, 130.58, 130.73, 132.83, 136.96, 144.46, 155.73, 157.88. Anal. calcd for $C_{25}H_{31}N_3O_3S \cdot 2$ HCl: C: 57.03, H: 6.32, N: 7.98, S: 6.09; Found C: 54.59, H: 4.76, N: 6.71, S: 5.54.

*2-Methylpropane--N-{(1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-sulfonamide (**18**)*

Yellow oil, 80 mg (82 % yield); LC/MS purity 98%, t_R = 5.12, $C_{23}H_{32}N_2O_3S$, MW 416.58, Monoisotopic Mass 416.21, $[M+H]^+$ 417.4. ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J* = 5.87 Hz, 6H), 1.42–1.56 (m, 2H), 1.79 (dd, *J* = 13.62, 3.08 Hz, 2H), 1.85–1.87 (m, 1H), 2.16–2.27 (m, 2H), 2.78 (t, *J* = 5.72 Hz, 2H), 2.82–2.90 (m, 1H), 3.20–3.34 (m, 2H), 3.56–3.58 (m, 2H), 4.05 (t, *J* = 5.71 Hz, 2H), 4.72 (br s, 1H), 6.79 (dd, *J* = 8.14, 0.83 Hz, 1H), 6.92 (td, *J* = 7.45, 0.93 Hz, 1H), 7.20 (dd, *J* = 7.50, 1.60 Hz, 1H), 7.26–7.37 (m, 5H), 7.46–7.54 (m, 1H).

*N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**19**)*

Yellow oil, 110 mg following chromatographic purification over silica gel with CH_2Cl_2/MeOH (9/0.7); LC/MS purity 97%, t_R = 5.24. $C_{25}H_{28}N_2O_3S$, MW 436.57, Monoisotopic Mass 436.18, $[M+H]^+$ 437.1. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–1.46 (m, 2H), 1.63–1.72 (m, 2H), 2.00–2.10 (m, 2H), 2.66 (t, *J* = 5.61 Hz, 2H), 2.69–2.74 (m, 2H), 3.10–3.12 (m, 1H), 4.02 (t, *J* = 5.63 Hz, 2H), 4.49 (br s, 1H), 6.93(d, *J* = 8.21 Hz, 1H), 7.02 (td, *J* = 7.47, 1.09 Hz, 1H), 7.26–7.37 (m, 5H), 7.47–7.52 (m, 3H), 7.53–7.62 (m, 2H), 7.85–7.91 (m, 2H).

*4-Fluoro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**20**)*

Yellow oil, 120 mg (70% yield); LC/MS purity 95%, t_R = 5.25. $C_{25}H_{27}FN_2O_3S$, MW 454.56, Monoisotopic Mass 454.17, $[M+H]^+$ 455.3. ^1H NMR (300 MHz, $CDCl_3$) δ 1.37–1.48 (m, 2H),

1.67–1.73 (m, 2H), 1.99–2.10 (m, 2H), 2.64–2.74 (m, 4H), 3.10 (dd, *J* = 9.76, 3.93 Hz, 1H), 4.02 (t, *J* = 5.61 Hz, 2H), 4.87 (br s, 1H), 6.94 (d, *J* = 8.24 Hz, 1H), 6.99–7.06 (m, 1H), 7.14–7.22 (m, 2H), 7.25–7.38 (m, 5H), 7.47–7.52 (m, 2H), 7.86–7.93 (m, 2H).

*3-Fluoro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**21**)*

Yellow oil, 130 mg (75% yield); LC/MS purity 100%, t_R = 5.34. $C_{25}H_{27}FN_2O_3S$, MW 454.56, Monoisotopic Mass 454.17, $[M+H]^+$ 455.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.47 (m, 2H), 1.63–1.81 (m, 4H), 2.00–2.11 (m, 2H), 2.64–2.68 (m, 2H), 2.69–2.74 (m, 1H), 4.02 (t, *J* = 5.58 Hz, 2H), 4.51 (br s, 1H), 6.91–6.96 (m, 1H), 7.03 (td, *J* = 7.47, 1.09 Hz, 1H), 7.27–7.32 (m, 3H), 7.33–7.38 (m, 2H), 7.46–7.53 (m, 4H), 7.55–7.61 (m, 1H), 7.64–7.69 (m, 1H).

*3-Chloro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**22**)*

Yellow oil, 130 mg (73% yield); LC/MS purity 99%, t_R = 5.49. $C_{25}H_{27}ClN_2O_3S$, MW 471.01, Monoisotopic Mass 470.14, $[M+H]^+$ 471.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.49 (m, 2H), 1.67–1.73 (m, 2H), 2.01–2.10 (m, 2H), 2.63–2.68 (m, 2H), 2.71 (t, *J* = 3.61 Hz, 2H), 3.06–3.20 (m, 1H), 4.02 (t, *J* = 5.59 Hz, 2H), 4.98 (br s, 1H), 6.91–6.95 (m, 1H), 7.02 (td, *J* = 7.46, 1.07 Hz, 1H), 7.25–7.38 (m, 5H), 7.41–7.56 (m, 4H), 7.75–7.79 (m, 1H), 7.88 (t, *J* = 1.75 Hz, 1H). ^{13}C NMR (75 MHz $CDCl_3$) δ 15.30, 33.05, 50.74, 52.24, 56.76, 66.90, 112.63, 121.16, 124.94, 126.81, 126.99, 127.78, 128.58, 129.60, 130.44, 130.85, 131.13, 132.69, 135.24, 138.49, 143.08, 155.62. Anal. calcd for $C_{25}H_{27}ClN_2O_3S \cdot HCl$: C: 59.17, H: 5.56, N: 5.52, S: 6.32; Found C: 60.37, H: 5.01, N: 5.06, S: 5.59.

*2,5-Difluoro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**24**)*

Yellow oil, 140 mg (78% yield); LC/MS purity 98%, t_R = 5.35, $C_{25}H_{26}F_2N_2O_3S$, MW 472.55, Monoisotopic Mass 472.16, $[M+H]^+$ 473.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.50 (m, 2H), 1.64–1.75 (m, 2H), 2.01–2.11 (m, 2H), 2.64–2.69 (m, 2H), 2.71 (t, *J* = 3.49 Hz, 2H), 3.14–3.27 (m, 1H), 4.02 (t, *J* = 5.58 Hz, 2H), 6.99–7.05 (m, 1H), 7.20 (dd, *J* = 9.04, 4.14 Hz, 1H), 7.26–7.37 (m, 5H), 7.47–7.51 (m, 2H), 7.62–7.65 (m, 2H), 7.68–7.72 (m, 1H).

*5-Chloro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-thiophene-2-sulfonamide (**25**)*

Yellow oil, 120 mg (70% yield); LC/MS purity 99%, t_R = 5.35. $C_{23}H_{25}ClN_2O_3S_2$, MW 477.04, Monoisotopic Mass 476.1, $[M+H]^+$ 477.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.48 (m, 2H), 1.64–1.77 (m, 2H), 2.03–2.10 (m, 2H), 2.62–2.67 (m, 2H), 2.73 (t, *J* = 3.49 Hz, 2H), 3.15–3.27 (m, 1H), 4.05 (t, *J* = 5.58 Hz, 2H), 6.91–6.96 (m, 2H), 7.06 (td, *J* = 7.47, 1.03 Hz, 1H), 7.27–7.36 (m, 3H), 7.37–7.41 (m, 3H), 7.44–7.49 (m, 2H).

*1-Methyl-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-1H-pyrazole-4-sulfonamide (**26**)*

Yellow oil, 140 mg (83% yield); LC/MS purity 100%, t_R = 4.45, $C_{23}H_{28}N_4O_3S$, MW 440.56, Monoisotopic Mass 440.19, $[M+H]^+$ 441.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39–1.54 (m, 2H),

1.72–1.77 (m, 2H), 2.07 (t, *J* = 10.40 Hz, 2H), 2.67 (t, *J* = 5.64 Hz, 2H), 2.67–2.76 (m, 2H), 3.03–3.15 (m, 1H), 3.91 (s, 3H), 4.03 (t, *J* = 5.63 Hz, 2H), 5.14 (br s, 1H), 6.94 (d, *J* = 8.17 Hz, 1H), 7.02 (td, *J* = 7.46, 1.01 Hz, 1H), 7.27–7.32 (m, 3H), 7.33–7.40 (m, 2H), 7.48–7.52 (m, 2H), 7.75 (d, *J* = 0.55 Hz, 1H), 7.81 (s, 1H).

*4-N-{1-[2-(Biphenyl-2-yloxy)ethyl]piperidin-4-yl}-isoquinolinesulfonamide (**27**)*

Yellow oil, 140 mg (75% yield); LC/MS purity 100%, t_R = 4.94, $C_{28}H_{29}N_3O_3S$, MW 487.61, Monoisotopic Mass 487.19, $[M+H]^+$ 488.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.47 (m, 2H), 1.62 (d, *J* = 10.84 Hz, 2H), 1.98 (t, *J* = 10.71 Hz, 2H), 2.55–2.67 (m, 4H), 3.18–3.27 (m, 1H), 3.96 (t, *J* = 5.37 Hz, 2H), 5.47 (br s, 1H), 6.85–7.04 (m, 2H), 7.20–7.33 (m, 5H), 7.45 (d, *J* = 7.15 Hz, 2H), 7.70–7.91 (m, 2H), 8.10 (d, *J* = 8.05 Hz, 1H), 8.60 (d, *J* = 8.49 Hz, 1H), 9.17 (s, 1 H), 9.43 (s, 1H).

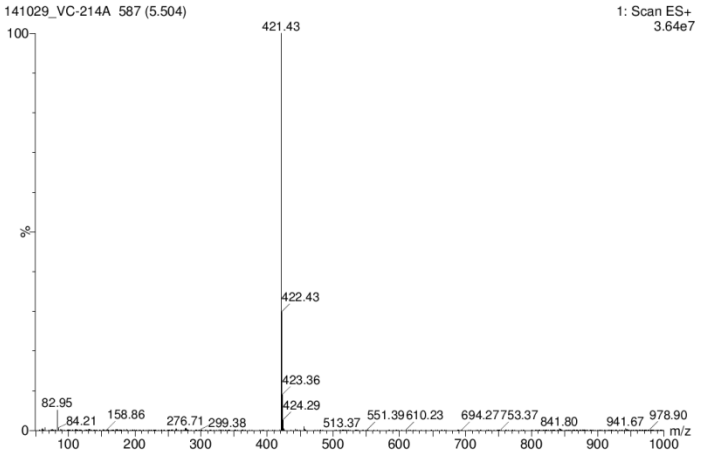
*5-N-{1-[2-(Biphenyl-2-yloxy)ethyl]piperidin-4-yl}-quinoline-sulfonamide (**28**)*

Yellow oil, 150 mg (81% yield); LC/MS purity 99%, t_R = 4.79, $C_{28}H_{29}N_3O_3S$, MW 487.61, Monoisotopic Mass 487.19, $[M+H]^+$ 488.4. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.45 (m, 2H), 1.57 (d, *J* = 10.13 Hz, 2H), 1.89–2.01 (m, 2H), 2.56–2.65 (m, 4H), 3.12–3.23 (m, 1H), 3.95 (t, *J* = 5.53 Hz, 2H), 5.60 (br s, 1H), 6.85–7.04 (m, 2H), 7.17–7.32 (m, 5H), 7.42–7.53 (m, 3H), 7.71–7.81 (m, 1H), 8.28–8.38 (m, 2H), 8.96–9.07 (m, 2H).

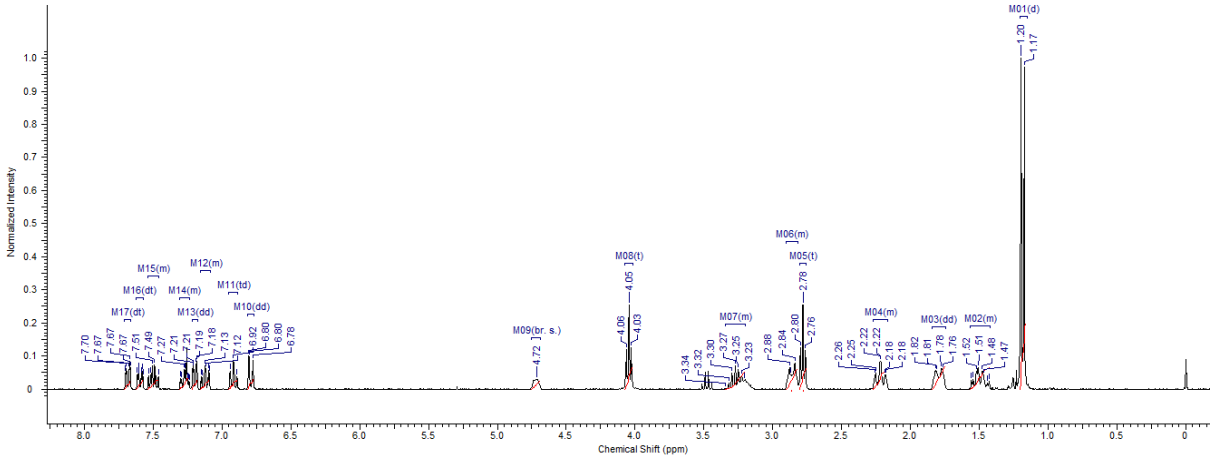
3. MS, ^{13}C NMR and ^{1}H NMR spectra of representative compounds

*3-Fluoro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**10**)*

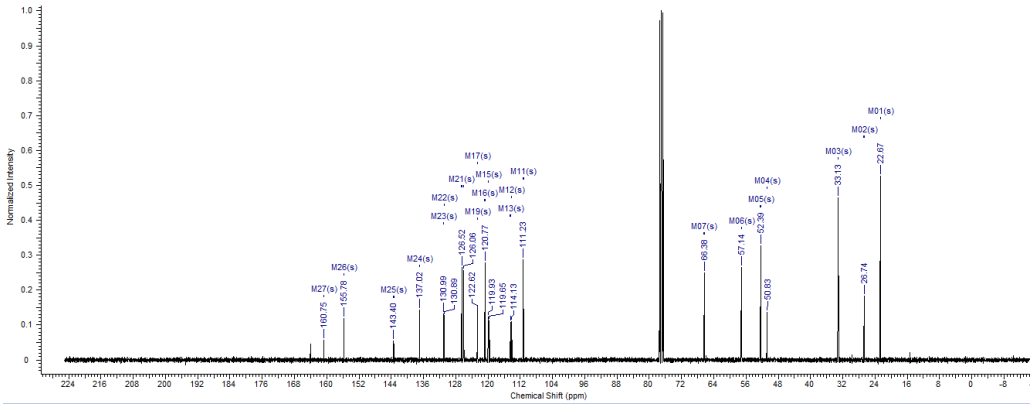
MS



^{1}H-NMR 300 MHz, $CDCl_3$

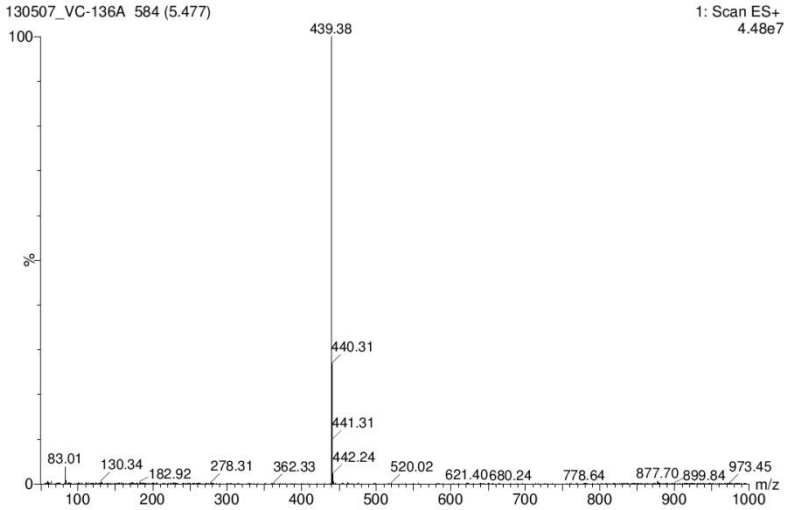


^{13}C-NMR 75 MHz, $CDCl_3$

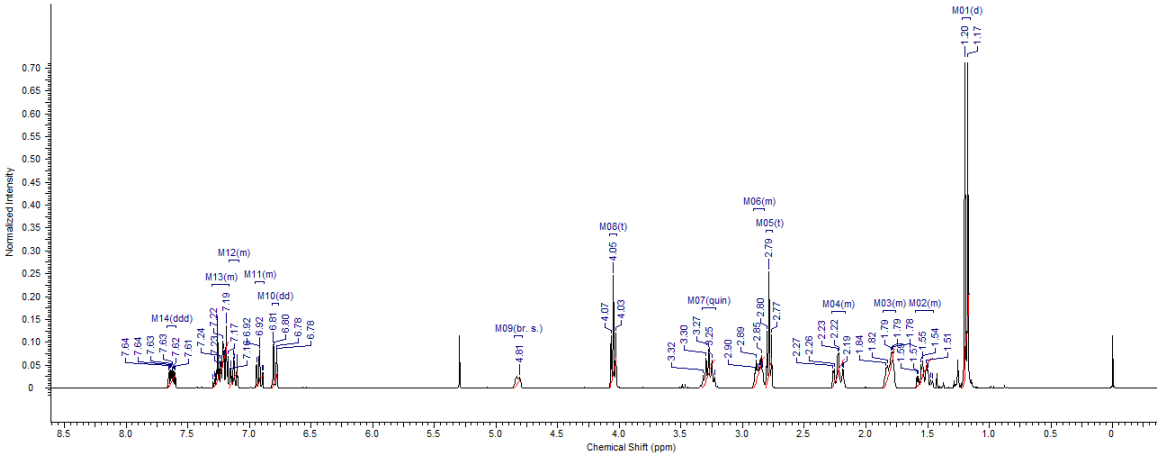


*2,5-Difluoro-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-benzenesulfonamide (**13**)*

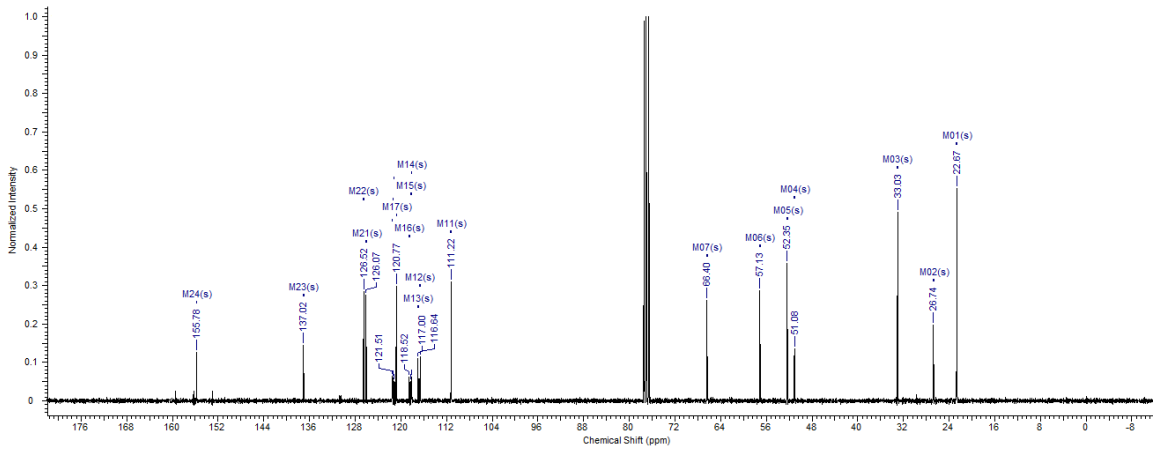
MS



^{1}H-NMR 300 MHz, $CDCl_3$

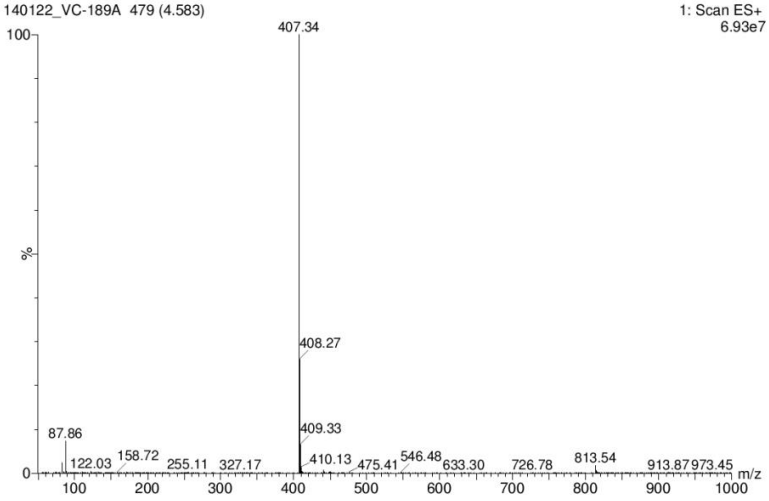


^{13}C-NMR 75 MHz, $CDCl_3$

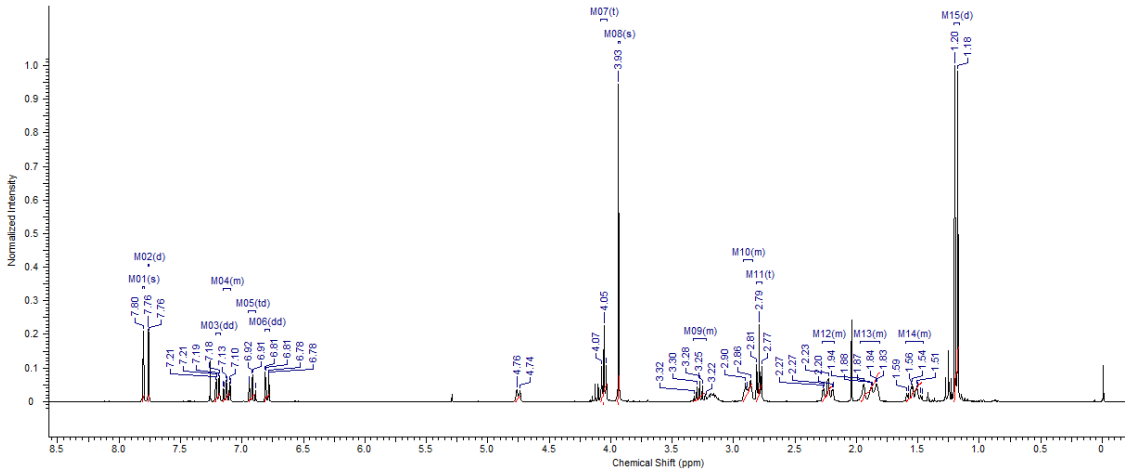


*1-Methyl-N-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-1H-pyrazole-4-sulfonamide (**13**)*

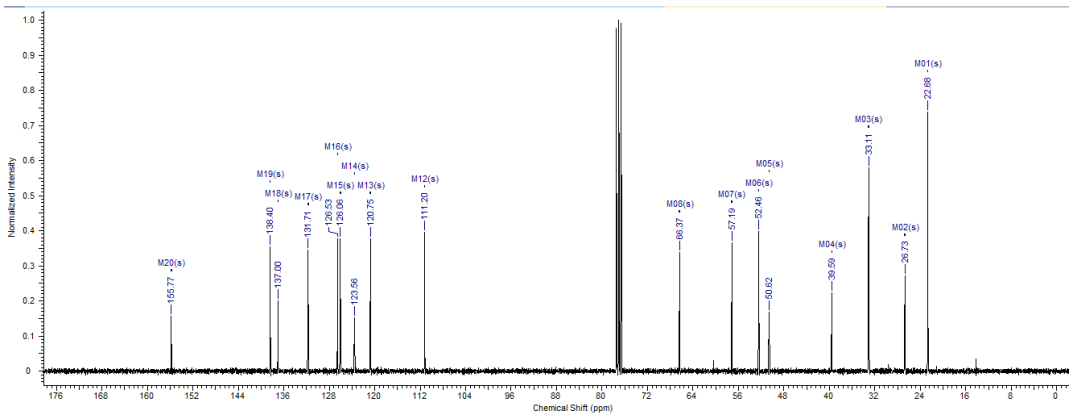
MS



^{1}H-NMR 300 MHz, $CDCl_3$

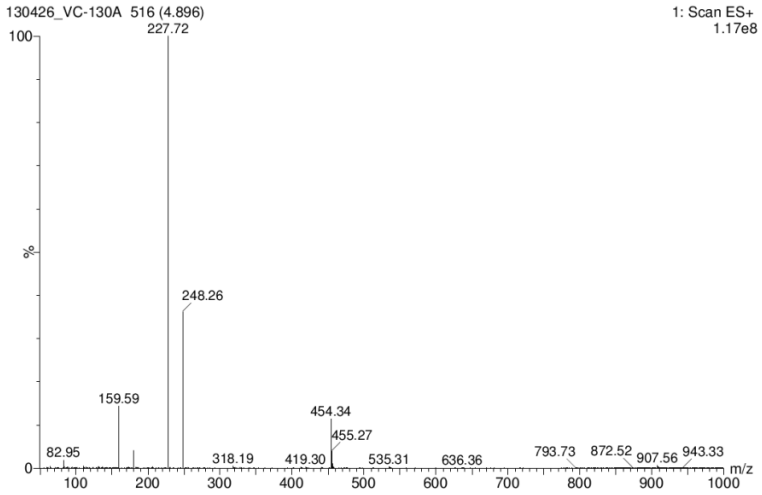


^{13}C-NMR 75 MHz, $CDCl_3$

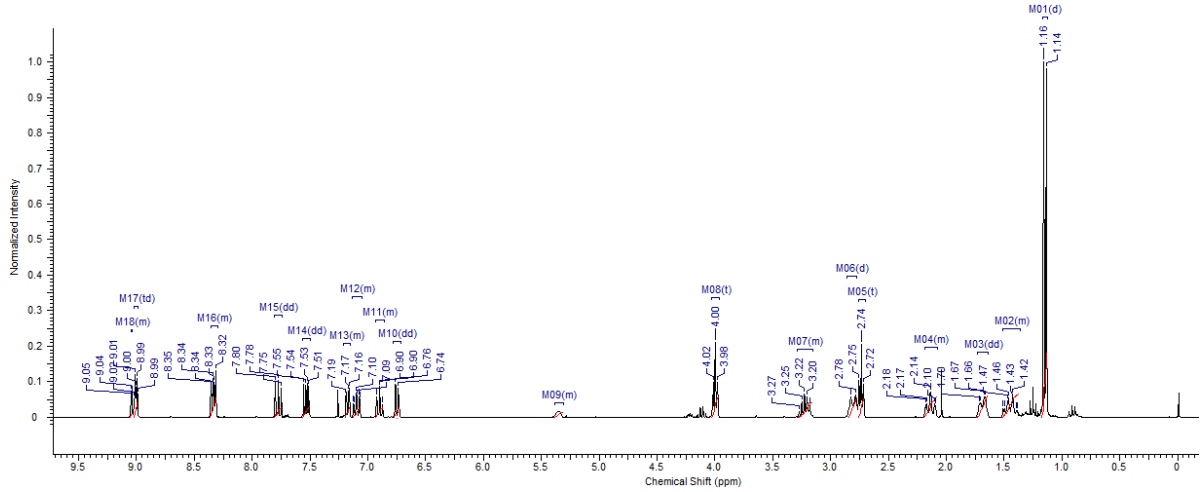


*5-N-(1-{2-[(Propan-2-yl)phenoxy]ethyl}piperidin-4-yl)-quinolinesulfonamide (**17**)*

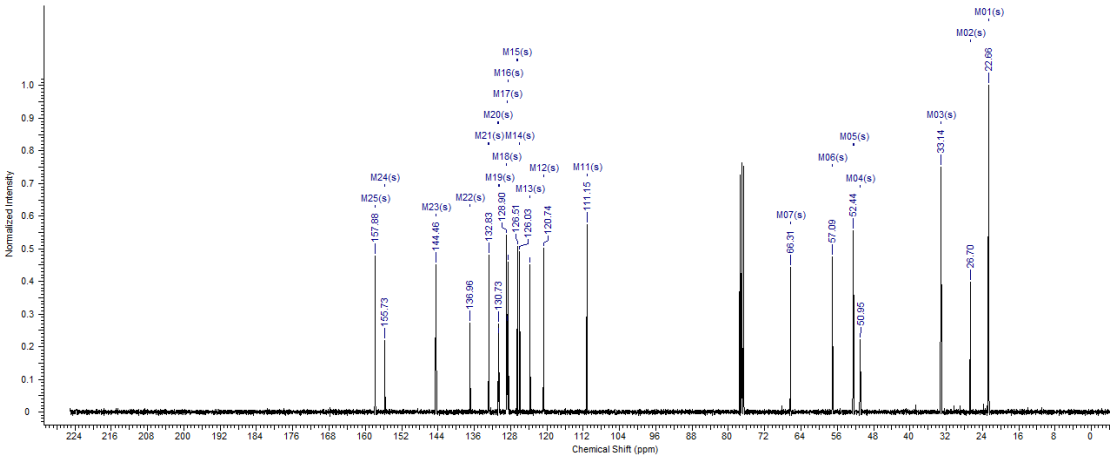
MS



^{1}H-NMR 300 MHz, $CDCl_3$

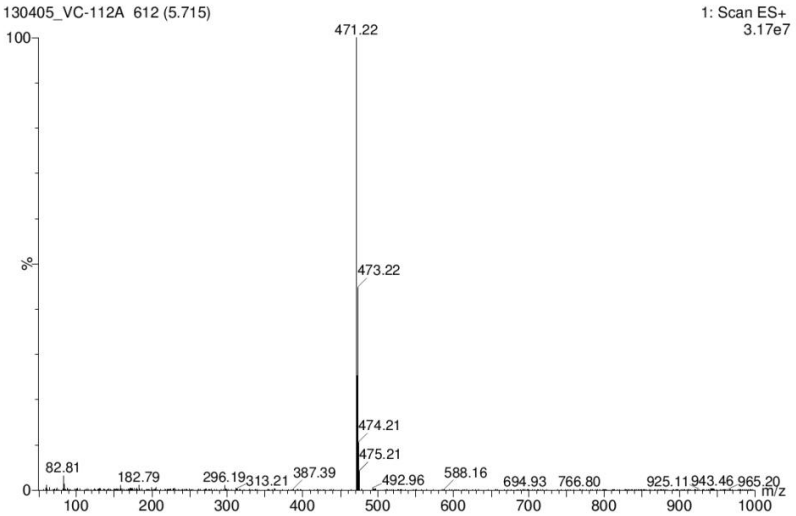


^{13}C-NMR 75 MHz, $CDCl_3$

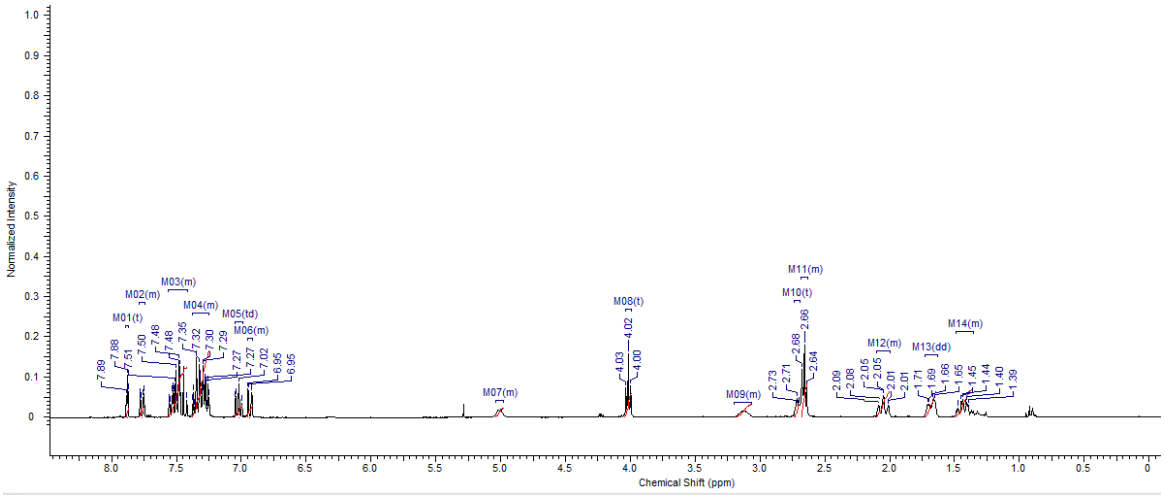


*3-Chloro-N-{1-[2-(biphenyl-2-yloxy)ethyl]piperidin-4-yl}-benzenesulfonamide (**22**)*

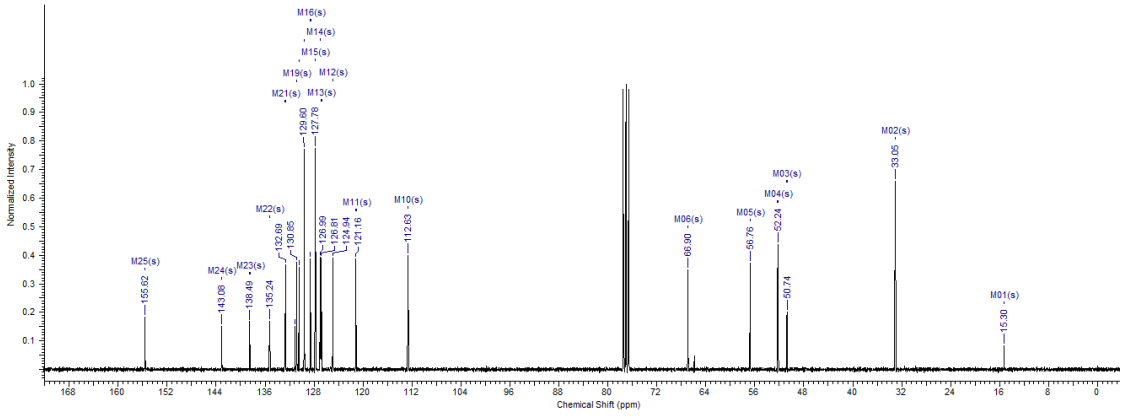
MS



^{1}H-NMR 300 MHz, $CDCl_3$



^{13}C-NMR 75 MHz, $CDCl_3$



4. Molecular modeling

To perform analysis of binding mode of the studied derivatives, we used the six different conformations of modified rhodopsin-based 5-HT_7R homology models,[1] successfully used in virtual screening of commercial databases[2] and selection of compounds to synthesize from virtual combinatorial library.[3] The 3-dimensional structures of the synthesized compounds were prepared using LigPrep ver. 3.2.and the appropriate ionization states at pH = 7.4 were assigned using Epik version 3.1.[4,5] The Protein Preparation Wizard was used to assign the bond orders, check the steric clashes, and assign appropriate amino acid ionization states. The receptor grids were generated (the OPLS_2005 force field) by centered the grid box of the size of 15Å on the Asp3.32. Automated docking was performed by using Glide version 6.6 at SP level with the flexible docking option turned on.[6] Final ranking scheme and post-docking filter were obtained by using previously reported procedures.[3]

5. Table 1.-SI. Calculated ADME parameters for final compounds using QikProp[7]

Compd	#rtvFG[a]	QPlogS[b]	QPPCaco[c]	QPlogBB[d]	MPO[e,8]
7 (PZ-766)	0	-3.08	392.73	-0.18	4.00
8	0	-3.19	479.68	-0.29	5.06
9	0	-2.84	374.00	-0.29	4.23
10	0	-3.04	392.93	-0.15	4.07
11	0	-3.51	376.37	-0.15	3.51
12	0	-3.40	375.99	-0.11	3.96
13	0	-3.38	401.42	-0.12	4.02
14	0	-3.19	356.83	-0.11	3.47
15	0	-2.40	265.95	-0.43	5.22
16	0	-3.10	281.92	-0.45	4.27
17	0	-3.39	317.62	-0.40	3.81
18	0	-3.27	514.89	-0.23	4.55
19	0	-3.14	395.15	-0.25	3.72
20	0	-3.54	395.01	-0.16	3.53
21	0	-3.15	393.66	-0.16	3.56
22	0	-3.90	396.46	-0.10	3.10
23	0	-3.85	400.49	-0.07	3.38
24	0	-4.96	442.43	-0.16	3.53
25	0	-3.50	376.83	-0.07	3.13
26	0	-2.84	273.48	-0.42	5.03
27	0	-4.68	274.49	-0.55	3.75
28	0	-4.04	320.91	-0.40	3.30

[a] number of reactive functional groups, recommended range: 0–2; [b] aqueous solubility (mole/liter), recommended range: -6.5–0.5; [c] gut-blood barrier (nm/s), recommended range: < 25 poor, > 500 great; [d] blood brain-barrier penetration coefficient, recommended range: -3.0–1.2; [e] multi-parameter optimization, MPO = Σ Score (clogP + clogD + PSA + MW + HBD + pKa), MPO_{max} = 6

6. *In vitro* pharmacology – radioligand binding assay protocol

Radioligand binding assays were employed to determine the affinity and selectivity profiles of the synthesized compounds in competition binding experiments for human serotonin 5-HT_{1A}, 5-HT_6, 5-HT_{7B} and D_{2L} receptors, which were all stably expressed in HEK293 cells. According to the previously published procedures,[3] the experiments were carried out using [^{3}H]-8-OH-DPAT (187 Ci/mmol), [^{3}H]-LSD (85.2 Ci/mmol), [^{3}H]-5-CT (39.2 Ci/mmol) and [^{3}H]-Raclopride (74.4 Ci/mmol) for 5-HT_{1A}, 5-HT_6, 5-HT_{7B} and D_2 receptors, respectively.

Cell pellets were thawed and homogenized in 20 volumes of assay buffer using an Ultra Turrax tissue homogenizer and centrifuged twice at 35 000 g for 20 min at 4°C, with incubation for 15 min at 37°C in between. The composition of the assay buffers was as follows: for 5-HT_{1A}R: 50 mM Tris–HCl, 0.1 mM EDTA, 4 mM $MgCl_2$, 10 mM pargyline and 0.1% ascorbate; for 5-HT_6R: 50 mM Tris–HCl, 0.5 mM EDTA and 4 mM $MgCl_2$, for 5-HT_{7b}R: 50 mM Tris–HCl, 4 mM $MgCl_2$, 10 mM pargyline and 0.1% ascorbate; for dopamine D_{2L}R: 50 mM Tris–HCl, 1 mM EDTA, 4 mM $MgCl_2$, 120 mM NaCl, 5 mM KCl, 1.5 mM $CaCl_2$ and 0.1% ascorbate.

All assays were incubated in a total volume of 200 µl in 96-well microtitre plates for 1 h at 37°C, except for 5-HT_{1A}R that was incubated for 1 h at room temperature. The process of equilibration is terminated by rapid filtration through Unifilter plates with a 96-well cell harvester and radioactivity retained on the filters was quantified on a Microbeta plate reader.

Non-specific binding is defined with10 µM of 5-HT in 5-HT_{1A}R and 5-HT_7R binding experiments, whereas10 µM of methiothepine or 1 µM of (+)butaclamol were used in 5-HT_6R and D_{2L} assays, respectively.

Each compound was tested in triplicate at 7–8 concentrations (10^{-11}–10^{-4} M). The inhibition constants (K_i) were calculated from the Cheng-Prusoff equation.[9] Results were expressed as means of at least three separate experiments.

Membrane preparation and general assay procedures for cloned receptors were adjusted to 96-microwell format based on described protocols.[10-12]

α_1-Adrenoceptor binding assays were carried out on the rat cerebral cortex. [^{3}H]-Prazosin (22 Ci/mmol) was used as ligand. The incubation mixture (final volume of 550 µl) consisted of 450 µl of membrane suspension, 50 µl of a [^{3}H]-Prazosin (0.6 nM) solution and 50 µl of buffer containing seven or eight concentrations (1 nM to 100 µM) of the investigated compounds. For measuring unspecific binding, phentolamine at a final concentration of 10 µM was present.

7. *In vitro* pharmacology – functional cAMP assay protocol

The functional properties of compounds **7** and **10** on 5-HT_7R were evaluated using their ability to inhibit cAMP production induced by 5-CT (10 nM) – a 5-HT_7R agonist, in ~~–a~~ HEK293 cells overexpressing the human 5-HT_{7b}R. Each compound was tested in triplicate at 8 concentrations (10^{-11}–10^{-4} M). The level of adenylyl cyclase activity was measured using recombinant HEK293 cells which stably expressing the human 5-HT_{7b} receptor. Cells (prepared with the use of Lipofectamine 2000) were maintained at 37 °C in a humidified atmosphere with 5% CO2 and were grown in Dulbeco's Modifier Eagle Medium containing 10% dialysed foetal bovine serum and 500 mg/mL G418 sulphate. For functional experiments, cells were subcultured in 25 cm diameter dishes, grown to 90% confluence, washed twice with prewarmed to 37 °C phosphate buffered saline (PBS) and were centrifuged for 5 min (160 × g). The supernatant was aspirated, the cell pellet was resuspended in stimulation buffer (1 × HBSS, 5 mM HEPES, 0.5 mM IBMX, 0.1% BSA). The cAMP level was measured using the LANCE cAMP detection kit (PerkinElmer), according to the manufacturer's directions. For the investigation of antagonist effect on 5-HT_7R, the agonist, 5-carboxyamidotryptamine (5-CT; EC_{50} = 1 nM) was used in submaximal concentration (6.2 nM) to stimulate cAMP production and cells (450 per well) were incubated with compound (1 µM) for 30 min at room temperature in 384-well white opaque microtiter plate. After incubation, the reaction was stopped and cells were lysed by the addition of 10 µL working solution (5 µL Eu-cAMP and 5 µL ULight-anti-cAMP). The assay plate was incubated for 1 hour at room temperature. Time-resolved fluorescence resonance energy transfer (TR-FRET) was detected by an Infinite M1000 Pro (Tecan) using instrument settings from LANCE cAMP detection kit manual.

8. *In vivo* pharmacology – forced swim test protocol

The experiments were performed on male Albino Swiss mice (22–28 g). The animals were kept at a room temperature of 20 ± 1°C, and had free access to food (standard laboratory pellets) and tap water before the experiment. All the experiments were conducted in the light phase between 9 a.m. and 2 p.m. All the experimental procedures were approved by the Local Ethics Commission for Animal Experiments of Jagiellonian University in Cracow. (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine (hydrochloride, SB-269970; Tocris, Cookson Ltd. UK) was suspended 1% aqueous solution of Tween 80. The investigated compounds were suspended in water or in a 1% aqueous solution of Tween 80. All the compounds were injected intraperitoneally (*i.p.*). The investigated compounds or vehicle were administered 60 min and SB-269970 30 min before the test. Each experimental group consisted of six to nine animals, and all the animals were used only once. The experiment was carried out according to the method of Porsolt *et al.*[13] Mice were individually placed in a glass cylinder (25 cm high; 10 cm in diameter) containing 6 cm of water maintained at 23–25°C, and were left there for 6 min. A mouse was regarded as immobile when it remained floating on the water, making only small movements to keep its head above it. The total duration of immobility was recorded during the last 4 min of a 6-min test session.

9. *In vivo* pharmacology – four plate test protocol

The experiments were performed on male Albino Swiss mice (22–28 g). The animals were kept at a room temperature of 20 ± 1°C, and had free access to food (standard laboratory pellets) and tap water before the experiment. All the experiments were conducted in the light phase between 9 a.m. and 2 p.m. All the experimental procedures were approved by the Local Ethics Commission for Animal Experiments of Jagiellonian University in Cracow. (2*R*)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine (hydrochloride, SB-269970; Tocris, Cookson Ltd. UK) was suspended 1% aqueous solution of Tween 80. The investigated compounds were suspended in water or in a 1% aqueous solution of Tween 80. All the compounds were injected intraperitoneally (*i.p.*). The investigated compounds or vehicle were administered 60 min and SB-269970 30 min before the test. Each experimental group consisted of six to nine animals, and all the animals were used only once.

The four-plate apparatus (BIOSEB) consists of a plastic cage (25 × 18 × 16 cm) floored by four identical rectangular metal plates (8 × 11 cm) separated from one another by a gap of 4 mm. The top of the cage is covered by a transparent Perspex lid that prevents escape behavior. The plates are connected to a device that can generate electric shocks. Following a 15-s habituation period, the animal's motivation to explore a novel environment was suppressed by an electric foot shock (0.8 mA, 0.5 s) every time it moves from one plate to another during a 1-min test session. This action is referred to as a 'punished crossing', and was followed by a 3 s shock interval, during which the animal can move across plates without receiving a shock.[14] The number of punished crossings received by an animal was recorded during the 60 s period.

Statistic for the forced swim test and four-plate test

All the data are presented as the mean ± SEM. The statistical significance of results was evaluated by a one-way analysis of variance (ANOVA) followed by Bonferroni's Comparison Test. $p<0.05$ was considered statistically significant.

10. *In vivo* pharmacology – spontaneous locomotor activity protocol

Locomotor activity was recorded with an Opto M3 multi-channel activity monitor (MultiDevice Software v.1.3, Columbus Instruments). Swiss albino mice were individually placed in plastic cages (22 × 12 × 13 cm) for 30 min habituation period, and then the ambulation were counted from 2 to 6 min or during 1 min 15 s that is the time equal to the observation period in the forced swim test and four plate test, respectively. The cages were cleaned up with 70% ethanol after each mouse. All the experimental procedures were approved by the Local Ethics Commission for Animal Experiments of Jagiellonian University in Cracow.

11. *In vivo* pharmacology – novel object recognition protocol

The experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee for Animal Experiments, Institute of Pharmacology.

Male Sprague–Dawley rats (Charles River, Germany) weighing ~250 g at the arrival were housed in the standard laboratory cages, under standard colony A/C controlled conditions: room temperature 21 ± 2°C, humidity (40–50 %), 12-hr light/dark cycle (lights on: 06:00) with ad libitum access to food and water. Rats were allowed to acclimatize for at least 7 days before the start of the experimental procedure. During this week animals were handled for at least 3 times. Behavioral testing was carried out during the light phase of the light/dark cycle. At least 1 h before the start of the experiment, rats were transferred to the experimental room for acclimation.

Rats were tested in a dimly lit (25 lx) "open field" apparatus made of a dull gray plastic (66 × 56 × 30 cm). After each measurement, the floor was cleaned and dried. The procedure lasting for 2 days consisted of the habituation to the test arena (without any objects) for 5 min. The test session comprising of two trials separated by an inter-trial interval (ITI) of 1 h was carried out on the next day. During the first trial (familiarization, T1) two identical objects (A1 and A2) were presented in the opposite corners of the open field, approximately 10 cm from the walls. During the second trial (recognition, T2) one of the A objects was replaced by a novel object B, so that the animals were presented with the A=familiar and B=novel objects. Both trials lasted for 3 min and the animals were returned to their home cages after T1. The objects used were the glass beakers filled with the gravel and the plastic bottles filled with the sand. The heights of the objects were comparable (~12 cm) and the objects were heavy enough not to be displaced by the animals. The sequence of presentations and the location of the objects was randomly assigned to each rat.

The animals explored the objects by looking, licking, sniffing or touching the object while sniffing, but not when leaning against, standing or sitting on the object. Any rat exploring the two objects for less than 5 s within 3 min of T1 or T2 was eliminated from the study. Exploration time of the objects and the distance traveled were measured using the Any-maze® video tracking system. Based on exploration time (E) of two objects during T2, discrimination index (DI) was calculated according to the formula: $DI = (E_B–E_A)/(E_A+A_B)$.

Phencyclidine (PCP), used to attenuate learning, was administered at the dose of 5 mg/kg (*i.p.*) 45 min before familiarization phase (T1). The compounds were administrated *i.p.* 1 hour and 15 min before T1.

Statistics for novel object recognition test

Data on exploratory preference were analyzed using three-way mixed-design ANOVAs with ketamine and the respective drug treatment as between-subject factors and object as a repeated measure; DI data were analyzed by two-way ANOVAs, and distance travelled was analyzed using mixed-design ANOVAs with ketamine and the respective drug treatment as between-subject factors and trial as a repeated measure.

12. Pharmacological effects of selected compounds in NOR test (Test 1 and Test 2)

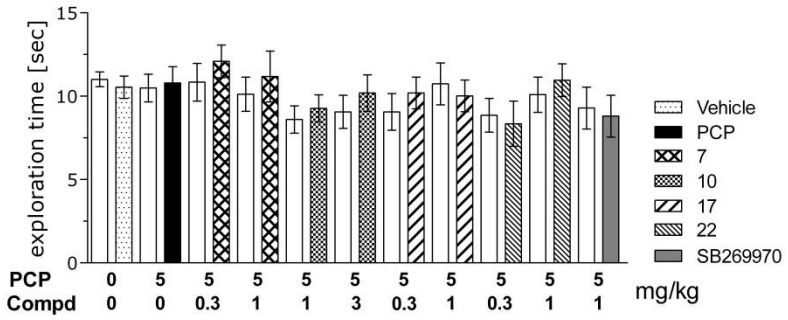


Figure 1-SI. Effects of the selected compounds on the exploration time of two identical object (Test 1)

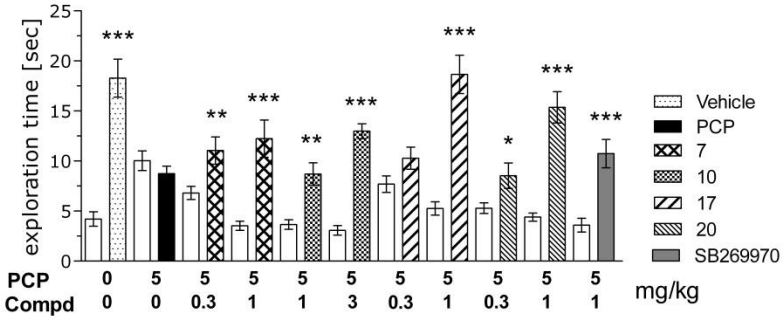


Figure 2-SI. Effects of the selected compounds on the exploration time of familiar *vs* novel objects (Test 2). *p<0.05 *vs* familiar, **p<0.01 *vs* familiar, ***p<0.001 *vs* familiar.

13. References

1 M. Kolaczkowski, M. Nowak, M. Pawłowski and A.J. Bojarski, *J. Med. Chem.* 2006, **49**, 6732–6741.

2 R. Kurczab, M. Nowak, Z. Chilmonczyk, I. Sylte and A.J. Bojarski, *Bioorg. Med. Chem. Lett.* 2010 **20**, 2465–2468.

3 P. Zajdel, R. Kurczab, K. Grychowska, G. Satała, M. Pawłowski and A.J. Bojarski, *Eur. J. Med. Chem.* 2012, **56**, 348–360.

4 LigPrep, version 3.2, Schrödinger, LLC, New York, NY, 2014.

5 Epik, version 3.1, Schrödinger, LLC, New York, NY, 2015.

6 Glide, version 6.6, Schrödinger, LLC, New York, NY, 2015.

7 QikProp, version 4.2, Schrödinger, LLC, New York, NY, 2014.

8 T.T. Wager, X. Hou, P.R. Verhoest and A. Villalobos, *ACS Chem. Neurosci.* 2010, **1**, 435–449.

9 Y. Cheng and W.H. Prusoff, W.H. *Biochem. Pharmacol*. 1973, **22**, 3099–3108.

10 A.J. Bojarski, M.T; Cegła, S. Charakchieva-Minol, M.J. Mokrosz, M. Maćkowiak, S. Misztal and J.L. Mokrosz, *Pharmazie*. 1993, **4**, 89–94.

11 M.H. Paluchowska, R. Bugno, B. Duszyńska, E. Tatarczyńska, A. Nikiforuk, T. Lenda and E. Chojnacka-Wójcik, *Bioorg. Med. Chem*. 2007, **15**, 7116–7125.

12 P. Zajdel, K. Marciniec, A. Maślankiewicz, G. Satała, B. Duszyńska, A.J. Bojarski, A. Partyka, M. Jastrzębska-Więsek, D. Wróbel, A. Wesołowska and M. Pawłowski, *Bioorg. Med. Chem.* 2012, **20**, 1545–1556

13 R.D. Porsolt, A. Bertin and M. Jalfre, *Arch. Int. Pharmacodyn. Ther.* 1977, **229**, 327–336.

14 C. Aron, P. Simon, C. Larousse and J.R. Boissier, *Neuropharmacology*. 1971, **10**, 459–469.