Synthesis and structure evaluation of new complex butylarylpiperazin-1-yl derivatives

Daniel Szulczyk ∙ Anna Bielenica ∙ Michał A. Dobrowolski ∙ Łukasz Dobrzycki ∙ Mariola Krawiecka ∙ Bożena Kuran ∙ Marta Struga

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Abstract A series of arylpiperazine derivatives of 1,16-diphenyl-19-azahexacyclo-[14.5.1.0²,15.0³,8.0⁹,14.0¹⁷,2¹]docosa-2,3,5,7,8,9,11,13,14-nonane-18,20,22-trione and 4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione was synthesized. The pharmacological profile of compound 4 at the 5-HT₁A receptor was measured by binding assay. The title compounds were tested in cell-based assay against the human immunodeficiency virus type-1. The X-ray crystallographic studies of derivatives 2, 6, 7, 11, 19, and 20 were presented.

Keywords 5-HT₁A receptor ∙ Arylpiperazines ∙ X-ray crystallography ∙ Diels–Alder reaction

Introduction

The literature survey shows that many ligands of serotonin 5-HT₁A, 5-HT₂A, and 5-HT₇ receptors contain a flexible hydrocarbon chain of different lengths, attached to an arylpiperazine moiety that is the pharmacophore group (Fig. 1) (Lewgowd et al., 2011; Czopek et al., 2010; Bojarski, 2006; Leopoldo, 2004). The pharmacophore group is recognized not only by metabolotropic serotonin receptor binding sites, but also by those of D₂-dopaminergic (González-Gómez et al., 2003) and α₁-adrenergic receptors (Prandi et al., 2012).

Using quantitative structure–activity relationship analysis, the “rule of five” scheme was worked out for orally administrated drugs (Lipinski et al., 1997; Kern and Di, 2008). According to authors, the drugs that cross the blood–brain barrier are those of molecular mass lower than 450 u and of theoretical partition coefficient n-octanol/water (logP) being in the range of 1–4 or logD₇₄ 1–3. The biological barrier permeability is also determined by the following important parameters: numbers of hydrogen bond donors and acceptors in the potential medicine’s structure (HBD maximum 4 and HBA less than 6), polar surface area (PSA) correlated with them [expected value is less than 60–70 Å² (Oprea, 2002)], as well as compound’s solubility (logS greater than 60 log/cm³). Proper drug permeability makes it possible to cross the barrier and to reach the regions of a drug’s action.

In last two decades, a number of binding modes of long-chain arylpiperazine derivatives to 5-HT₁A (Lewgowd et al., 2011; Nowak et al., 2006), 5-HT₂A (Klabunde and Evers, 2005; Bronowska et al., 2001), and 5-HT₇ (Kim et al., 2012; López-Rodríguez et al., 2003) receptors have been proposed. The ionic interaction between the protonated nitrogen of the piperazine ring of a ligand and Asp3.32 residue of the receptor (Nowak et al., 2006; Vermeulen et al., 2003; Roth et al., 1997) constituted a main essential interaction. The hydrophobic terminal imide or amide group, the hydrocarbon linker, and an aromatic ring bound to the piperazine moiety are placed in a hydrophobic pocket composed of aromatic and/or aliphatic amino acids side chains (Kim et al., 2012; Varin et al., 2010; Lepailleur et al., 2005). The flexible chain of N-(4-arylpiperazin-1-yl-alkyl)substituted derivatives can adopt one of the two main conformations: extended or bent. The results of geometry optimization (Lewgowd et al., 2011) proved that conformers with extended spacer are...
preferred in a solution, whereas in vacuum bent geometries predominate. Theoretical calculations determine minimum energy for extended linker conformations also in solid state and for complexes with a receptor (Siracusa et al., 2008). According to pharmacophore model of the 5-HT1A receptor (Chilmonczyk et al., 1997; Bronowska et al., 2001), a folded conformer promotes high affinity for the 5-HT1A receptor. It is known that ligand binding can lead to a change in the conformation of the receptor protein, however, also in the ligand itself (Sylte et al., 2001). In addition, the role of the solvent molecules is quite difficult to explain— they can take part in a ligand—receptor H-bond formation, be involved in the process of a receptor activation or influence entropy effects (Pardo et al., 2007).

This paper reports synthesis and biological activity of compounds purposely designed to combine the bulky hydrophobic imide ring with alkyl linker bearing different substituents. The collected group of arylpiperazine derivatives can be used for further investigations concerning ligand-5-HT receptor interactions. For this reason X-ray crystallographic studies of derivatives 2, 6, 7, 11, 19, and 20 were described. The molecular descriptors for selected arylpiperazine derivatives were presented. The pharmacological profile of the compound 4 was evaluated for its affinity to the 5-HT1A receptor. It was reported, that cytotoxicity of aromatic, high-volume arylpiperazine derivatives is low (Filosa et al., 2007; Ananda Kumar et al., 2009), and they act as anti-HIV-1 agents (Yang et al., 2010), cytotoxicity and anti-HIV activity of selected derivatives were examined.

Materials and methods

Chemistry

All chemicals and solvents were purchased from Aldrich. Melting points were determined on an Electrothermal Digital Melting Point Apparatus and are uncorrected. The NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 300 MHz (1H NMR) and 75 MHz (13C NMR). The chemical shift values are expressed in ppm relative to TMS as an internal standard. Mass spectral electrospray ionization (ESI) measurements were carried out on a Mariner Perspective—Biosystem instrument with TOF detector. The spectra were obtained in the positive ion mode with a declustering potential 140–300 V. Elemental analyses were recorded on a CHN model 2400 Perkin-Elmer. TLC was carried out using silica gel 60 F254 with layer thickness of 0.25 mm (Merck) and the results were visualized using UV lamp at 254 nm. Column chromatography was carried out using silica gel 60 (200–400 mesh, Merck) and chloroform/methanol (19.5:0.5 vol) mixture as eluent.

1,16-Diphenyl-19-azahexacyclo[14.5.1.02,15.03,8.09,14.017,21]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20,22-trione (1)

The mixture of 2.14 g (0.004 mol) of 1,3-diphenyl-2H-cyclopental[1]phenanthren-2-one ("Phencyclone") was suspended in 75 ml of benzene and 0.48 g (0.005 mol) of maleimide was added. After refluxing time of 8 h the residue was evaporated, and the residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol). The combined fractions were condensed to dryness to give 1.86 g (87 %) of (1), m.p. 327–328 °C. 1H NMR (DMSO-d6) δ (ppm): 11.04 (s, 1H, NH), 8.85 (d, 2H, CH arom., J = 8.4 Hz), 8.24 (d, 2H, CH arom., J = 7.8 Hz), 7.73 (t, 2H, CH arom., J = 7.2 Hz), 7.59–7.51 (m, 4H, CH arom.), 7.41 (t, 2H, CH arom., J = 7.5 Hz), 7.22 (t, 2H, CH arom., J = 7.8 Hz), 7.14 (d, 2H, CH arom., J = 7.8 Hz), 7.04 (d, 2H, CH arom., J = 5.7 Hz), 4.65 (s, 2H, CH). 13C NMR (DMSO-d6) δ (ppm): 197.12, 173.09, 173.05, 134.03, 133.98, 133.48, 133.22, 133.76 (2C), 132.37, 132.12, 132.09, 132.06, 132.00, 131.83, 131.62, 131.47, 130.49, 130.21, 129.75, 129.68 (2C), 128.63, 128.54, 127.96, 126.84, 126.78, 122.35, 122.31, 63.65, 63.59, 45.25, 45.20. Anal. Calcd. for C33H21NO3: C, 82.45; H, 4.38; N, 2.92. Found: C, 82.40; H, 3.00; N, 4.40.
A mixture of imide (1) (1.41 g, 0.003 mol), 1,4-dibromobutane (0.7 ml, 0.006 mol), anhydrous K₂CO₃ (1.39 g), and catalytic amount of KI were refluxed in acetonitrile for 30 h. Then the mixture was filtered off and the oily residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol). The combined fractions were condensed to dryness to give 1.36 g (86 %) of (2), m.p. 286–289 °C. ¹H NMR (DMSO-d₆) δ (ppm): 8.84 (d, 2H, CH₆ arom., J = 9.0 Hz), 8.27 (d, 2H, CH₆ arom., J = 8.4 Hz), 7.75 (t, 2H, CH₆ arom., J = 8.1 Hz), 7.59–7.52 (m, 4H, CH₆ arom.), 7.43 (t, 2H, CH₆ arom., J = 8.7 Hz), 7.25–7.14 (m, 4H, CH₆ arom.), 7.01 (d, 2H, CH₆ arom., J = 7.5 Hz), 4.61 (s, 2H, CH₂), 2.87–2.78 (m, 2H, CH₂), 2.11–2.07 (m, 2H, CH₂), 1.24–1.21 (m, 2H, CH₂), 0.49–0.43 (m, 2H, CH₂). ¹³C NMR (DMSO-d₆) δ (ppm): 197.09, 173.12, 173.01, 134.11, 133.88, 133.51 (2C), 133.28, 133.39, 133.32, 132.17, 132.04, 132.00, 131.90, 131.87, 131.65, 131.36, 130.27, 129.19, 129.83, 129.69, 129.66, 128.52, 128.47, 127.89, 126.72, 126.68, 122.33, 122.30, 63.68, 63.61, 45.31, 45.28, 44.89, 32.79, 28.74, 28.53. ESI MS: m/z = 638.0 [M+H]⁺ (100 %).

General method for the preparation of arylpiperazine derivatives of 19-(4-bromobutyl)-1,16-diphenyl-19-azahexacyclo[14.5.1.0²⁺⁵.0³⁻⁷.0⁹⁻¹⁴.0¹⁷⁻²¹]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20,22-trione (3–9)

A mixture of derivative (2) (0.3 g, 0.002 mol) and the corresponding amine (0.004 mol), anhydrous K₂CO₃ (0.3 g), and catalytic amount of KI were refluxed in acetonitrile for 30 h. Then the mixture was filtered off and the solvent was evaporated. The gray residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol) and/or crystallized from methanol. Obtained compounds were converted into their hydrochlorides. The solid product was dissolved in methanol saturated with gaseous HCl. The hydrochloride was precipitated by addition of diethyl ether. The crude product was crystallized from an appropriate solvent.

1,16-Diphenyl-19-(4-(4-pyridin-2-yl)piperazin-1-yl)butyl)-19-azahexacyclo[14.5.1.0²⁻¹⁵.0³⁻⁸.0⁹⁻¹⁴.0¹⁷⁻²¹]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20,22-trione (3)

Yield: 67 %, m.p. 200–203 °C. ¹H NMR (DMSO-d₆) δ (ppm): 8.81 (d, 2H, CH₆ arom., J = 8.7 Hz), 8.27 (d, 2H, CH₆ arom., J = 8.1 Hz), 8.09–8.06 (m, 1H, CH₆ arom.), 7.74 (t, 2H, CH₆ arom., J = 7.8 Hz), 7.57–7.40 (m, 7H, CH₆ arom.), 7.36–7.14 (m, 4H, CH₆ arom.), 7.05 (d, 2H, CH₆ arom., J = 9.3 Hz), 6.75 (d, 1H, CH₆ arom., J = 8.7 Hz), 6.60 (d, 1H, CH₆ arom.), J = 5.1 Hz, J₂ = 5.4 Hz), 4.67 (s, 2H, CH₂), 3.78 (s, 1H, CH₂), 3.31–3.27 (m, 3H, CH₂), 3.05 (s, 1H, CH₂), 2.92 (s, 1H, CH₂), 2.05 (t, 4H, CH₂, J = 2.1 Hz), 1.44 (t, 2H, CH₂, J = 7.2 Hz), 1.24–1.22 (m, 1H, CH₂), 0.88–0.83 (m, 1H, CH₂), 0.33–0.23 (m, 2H, CH₂). ¹³C NMR (DMSO-d₆) δ (ppm): 197.17, 173.08, 173.02, 157.48, 147.68, 137.35, 134.24, 133.73, 133.68, 133.35, 133.30, 132.12 (3C), 132.07, 132.02, 132.00, 131.87, 131.69, 131.51, 130.31, 130.12, 129.99, 129.84, 129.73, 128.47, 128.32, 127.77, 126.58, 126.49, 122.41, 122.19, 119.83, 108.92, 63.75, 63.72, 50.87, 50.43, 48.58, 48.49, 45.34, 45.32, 44.86, 32.69, 28.81, 28.73. ESI MS: m/z = 697.1 [M+H]⁺ (100 %).
134.33, 133.82, 133.79, 133.41, 133.32, 132.17, 132.11, 132.06, 132.03, 131.92, 131.77 (2C), 131.58, 130.43, 130.18, 129.98, 129.89, 129.78 (2C), 128.51, 128.39, 127.81, 126.62, 126.53, 122.48, 122.22, 119.86, 115.37, 115.29, 63.81, 63.78, 50.90, 50.62, 48.64, 48.54, 45.48, 45.46, 44.93, 32.70, 28.84, 28.77. ESI MS: \( m/z = 696.2 \) [M+H]+ (100 %).

19-(4-(4-(4-Chlorophenyl)piperazin-1-yl)butyl)-1, 16-diphenyl-19-azahexacyclo-[14.5.1.0^{2,15}.0^{3,8}.0^{9,14}.0^{6,14}.0^{17,21}]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20-trione (8)

Yield: 77 %, m.p. 202–204 °C. \(^{1}H\) NMR (DMSO-\( d_{6} \)) \( \delta \) (ppm): 8.82 (d, 2H, CHarom., \( J = 8.1 \) Hz), 8.28 (d, 2H, CHarom., \( J = 7.8 \) Hz), 7.80–7.72 (m, 4H, CHarom.), 7.54 (t, 2H, CHarom., \( J = 7.2 \) Hz), 7.42 (t, 2H, CHarom., \( J = 7.5 \) Hz), 7.22 (t, 2H, CHarom., \( J = 7.8 \) Hz), 7.15 (d, 2H, CHarom., \( J = 7.8 \) Hz), 7.03 (d, 2H, CHarom., \( J = 8.1 \) Hz), 6.92 (d, 2H, CHarom., \( J = 9.3 \) Hz), 4.68 (s, 2H, CH2), 3.52–3.44 (m, 4H, CH2), 3.16 (t, 4H, CH2), 1.66 (m, 2H, CH2), 2.37–2.30 (m, 3H, CH2). \(^{13}C\) NMR (DMSO-\( d_{6} \)) \( \delta \) (ppm): 197.23, 186.59, 173.39, 173.37, 157.51, 147.59, 137.62, 134.57, 133.89, 133.85, 133.69, 133.57, 132.55, 132.34, 132.17, 132.11, 131.92, 131.85, 131.69, 131.57, 130.46, 130.38, 129.90, 129.83, 129.77, 129.72, 128.59, 128.30, 127.75, 126.61, 126.54, 122.47, 119.83, 115.39, 115.28, 63.80, 63.76, 50.91, 50.67, 48.68, 48.57, 45.42, 45.40, 44.96, 32.75, 28.86, 28.73. ESI MS: \( m/z = 738.6 \) [M+H]+ (100 %).

1,16-Diphenyl-19-(4-(4-(2-(trifluoromethyl)phenyl)phenyl)piperazin-1-yl)butyl)-19-azahexacyclo-[14.5.1.0^{2,15}.0^{3,8}.0^{9,14}.0^{17,21}]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20-trione (9)

Yield: 84 %, m.p. 205–207 °C. \(^{1}H\) NMR (DMSO-\( d_{6} \)) \( \delta \) (ppm): 8.78 (d, 2H, CHarom., \( J = 8.4 \) Hz), 8.30 (d, 2H, CHarom., \( J = 7.8 \) Hz), 7.74 (t, 2H, CHarom., \( J = 6.3 \) Hz), 7.69–7.60 (m, 3H, CHarom.), 7.54 (t, 3H, CHarom., \( J = 6.3 \) Hz), 7.48–7.40 (m, 4H, CHarom.), 7.18–7.14 (m, 2H, CHarom.), 4.48 (s, 2H, CH2), 3.95–3.91 (m, 3H, CH2), 3.61–3.37 (m, 10H, CH2), 3.22–3.17 (m, 3H, CH2), 3.01–2.92 (m, 4H, CH2). \(^{13}C\) NMR (DMSO-\( d_{6} \)) \( \delta \) (ppm): 197.19, 173.12, 173.05, 157.51, 147.74, 137.40, 134.36, 133.88, 133.77, 133.43, 133.37, 132.15, 132.10, 132.04, 132.01, 131.99, 131.78 (2C), 131.54, 130.48, 130.13, 129.92, 129.86, 129.71 (2C), 128.53, 128.37, 127.86, 126.66, 126.51, 123.92, 122.45, 119.83, 115.34, 115.28, 63.80, 63.70, 61.17, 50.92, 50.68, 48.62, 48.59, 45.45, 45.41, 44.97, 32.76, 31.28, 28.87, 28.73. ESI MS: \( m/z = 792.2 \) [M+H]+ (100 %).

The mixture of 2.06 g (0.006 mol) of 1,3-diphenylclopcenta[\(a\)]indene-2,8-dione (“Indanocyclone”) was suspended in 75 ml of benzene and 0.65 g (0.006 mol) of
maleimide was added. After refluxing time of 16 h the yellow residue was evaporated. Next it was purified by column chromatography (chloroform:methanol 9.5:0.5 vol). The combined fractions were condensed to dryness to give 1.50 g (73 %) of (10), m.p. 223–225 °C. 1H NMR (CDCl 3) δ (ppm): 7.60 (d, 2H, CH arom., J = 2.7 Hz), 7.59–7.58 (m, 2H, CH arom.), 7.32 (d, 2H, CH arom., J = 2.1 Hz), 7.51–7.49 (m, 2H, CH arom.), 7.45 (d, 2H, CH arom., J = 2.1 Hz), 7.44–7.40 (m, 4H, CH arom.). 13C NMR (CDCl 3) δ (ppm): 190.91, 165.89, 165.73, 149.69, 141.97, 139.37, 135.58, 135.52, 134.14, 134.24, 131.59, 130.57, 130.54, 129.87, 129.34, 129.28 (2C), 129.09 (3C), 128.59 (2C), 127.91 (2C), 124.59, 124.54. ESI MS: m/z = 424.4 [M+Na]⁺ (100 %).

2-(4-Bromobutyl)-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (11)

A mixture of imide (10) (2.64 g, 0.006 mol), 1,4-dibromobutane (1.5 ml, 0.012 mol), anhydrous K 2CO 3 (2.51 g), and catalytic amount of KI were refluxed in acetonitrile for 30 h. Then the mixture was filtered off and the yellow solid residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol). The combined fractions were condensed to dryness to give 1.50 g (73 %) of (10), m.p. 223–225 °C. 1H NMR (CDCl 3) δ (ppm): 7.60 (t, 3H, CH arom., J = 3.6 Hz), 7.56–7.44 (m, 8H, CH arom.), 7.40–7.31 (m, 2H, CH arom.), 7.28–7.23 (m, 2H, CH arom.), 6.98 (d, 2H, CH arom., J = 8.1 Hz), 6.86 (t, 1H, CH arom., J = 7.2 Hz), 6.23 (d, 2H, CH arom., J = 6.6 Hz), 3.76 (d, 2H, CH 2, J = 11.4 Hz), 3.49–3.42 (m, 4H, CH 2), 3.15–3.02 (m, 6H, CH 2), 1.72–1.69 (m, 2H, CH 2), 1.57–1.52 (m, 3H, CH 2). 13C NMR (CDCl 3) δ (ppm): 190.32, 165.58, 165.37, 149.52, 148.83, 141.58, 137.54, 135.13, 134.77, 134.39, 134.12, 133.94, 132.22, 130.47, 129.63 (2C), 129.41 (4C), 128.85 (2C), 128.49 (4C), 128.36 (2C), 127.24 (3C), 124.11, 123.53, 57.84, 57.65, 50.97, 50.86, 36.63, 34.50, 29.57, 26.48. ESI MS: m/z = 618.4 [M+H]⁺ (100 %).

A mixture of derivative (11) (0.3 g, 0.0005 mol) and the corresponding amine (0.001 mol), anhydrous K 2CO 3 (0.3 g), and catalytic amount of KI were refluxed in acetonitrile for 30 h. Then the mixture was filtered off and the yellow residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol) and/or crystallized from methanol. Obtained compounds were converted into their hydrochlorides. The solid product was dissolved in methanol saturated with gaseous HCl. The hydrochloride was precipitated by addition of diethyl ether. The crude product was crystallized from appropriate solvent.

A mixture of derivative (11) (0.3 g, 0.0005 mol) and the corresponding amine (0.001 mol), anhydrous K 2CO 3 (0.3 g), and catalytic amount of KI were refluxed in acetonitrile for 30 h. Then the mixture was filtered off and the solvent was evaporated. The yellow residue was purified by column chromatography (chloroform:methanol 9.5:0.5 vol) and/or crystallized from methanol. Obtained compounds were converted into their hydrochlorides. The solid product was dissolved in methanol saturated with gaseous HCl. The hydrochloride was precipitated by addition of diethyl ether. The crude product was crystallized from appropriate solvent.
2-[4-[4-(2-Fluorophenyl)piperazin-1-yl]butyl]-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (15)

Yield: 88 %, m.p. 245–247 °C. 1H NMR (DMSO-d6) δ (ppm): 7.61 (t, 3H, CH arom., J = 3.9 Hz), 7.56–7.44 (m, 8H, CH arom.), 7.41–7.30 (m, 2H, CH arom.), 7.21–7.00 (m, 4H, CH arom.), 6.23 (d, 1H, CH arom., J = 7.8 Hz), 5.30–3.37 (m, 8H, CH2), 3.21–3.08 (m, 4H, CH2), 1.70–1.68 (m, 2H, CH2), 1.58–1.53 (m, 2H, CH2). 13C NMR (CDCl3) δ (ppm): 191.47, 166.12, 165.97, 149.48, 148.57, 141.72, 137.16, 135.69, 134.38, 134.21, 134.09, 133.92, 132.46, 130.85 (2C), 129.36 (2C), 129.29 (3C), 128.63 (2C), 128.52 (3C), 128.47 (2C), 127.69 (4C), 124.82, 123.96, 57.06, 56.93, 50.46, 50.27, 36.12, 34.98, 29.58, 26.02. ESI MS: m/z = 636.4 [M+H]+ (100 %).

2-[4-[4-(Fluorophenyl)piperazin-1-yl]butyl]-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (16)

Yield: 93 %, m.p. 241–242 °C. 1H NMR (DMSO-d6) δ (ppm): 7.61 (t, 3H, CH arom., J = 3.9 Hz), 7.56–7.53 (m, 1H, CH arom.), 7.51–7.48 (m, 3H, CH arom.), 7.47–7.46 (m, 5H, CH arom.), 7.41–7.30 (m, 2H, CH arom.), 7.13–7.07 (m, 2H, CH arom.), 7.03–6.98 (m, 2H, CH arom.), 3.67 (d, 2H, CH2, J = 9.0 Hz), 3.47–3.42 (m, 4H, CH2), 3.06 (d, 6H, CH2, J = 8.4 Hz), 1.69–1.68 (m, 2H, CH2), 1.57–1.54 (m, 2H, CH2). 13C NMR (CDCl3) δ (ppm): 191.19, 166.58, 165.74, 149.53, 148.82, 141.13, 137.64, 135.97, 134.27, 134.09, 134.01, 133.84, 132.16, 130.76 (2C), 129.94 (3C), 129.59 (2C), 128.89 (3C), 128.72 (3C), 128.11 (2C), 127.75 (3C), 125.49, 123.52, 57.68, 57.51, 50.94, 50.00, 36.81, 34.86, 29.37, 26.97. ESI MS: m/z = 636.4 [M+H]+ (100 %).

2-[4-[4-(Chlorophenyl)piperazin-1-yl]butyl]-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (17)

Yield: 82 %, m.p. 248–249 °C. 1H NMR (DMSO-d6) δ (ppm): 7.61 (t, 3H, CH arom., J = 3.6 Hz), 7.56–7.53 (m, 1H, CH arom.), 7.51–7.48 (m, 2H, CH arom.), 7.47–7.45 (m, 5H, CH arom.), 7.40–7.30 (m, 2H, CH arom.), 7.31–7.27 (m, 2H, CH arom.), 7.00 (d, 2H, CH arom., J = 9.0 Hz), 6.23 (d, 1H, CH arom., J = 7.5 Hz), 3.77 (d, 2H, CH2, J = 10.8 Hz), 3.49–3.72 (m, 4H, CH2), 3.07–3.01 (m, 6H, CH2), 1.68–1.66 (m, 2H, CH2), 1.57–1.52 (m, 2H, CH2). 13C NMR (CDCl3) δ (ppm): 190.64, 165.27, 165.11, 149.82, 148.56, 141.93, 137.14, 135.70, 134.31, 134.27, 134.03, 133.91, 132.27 (2C), 130.39 (2C), 129.79 (2C), 129.51 (3C), 128.88 (3C), 128.68 (3C), 128.02 (2C), 127.57 (2C), 124.69, 123.24, 57.49, 57.33, 50.17, 50.06, 36.94, 34.42, 29.96, 26.76. ESI MS: m/z = 625.4 [M+H]+ (100 %).

3-[4-[4-(2-Metoxyphenyl)piperazin-1-yl]butyl]-3-azatricyclo[7.3.1.03,13]trideca-(12),5,7,9(13),10-pentaene-2,4-dione (20) was obtained according to method presented previously (Hackling et al., 2003).

Synthesis of 2-[4-[4-(2-Metoxyphenyl)piperazin-1-yl]butyl]-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (19)

Yield: 79 %, m.p. 245–246 °C. 1H NMR (DMSO-d6) δ (ppm): 7.61 (t, 3H, CH arom., J = 3.6 Hz), 7.56–7.44 (m, 8H, CH arom.), 7.41–7.31 (m, 2H, CH arom.), 7.05–6.87 (m, 4H, CH arom.), 6.23 (d, 1H, CH arom., J = 6.9 Hz), 3.79 (s, 3H, OCH3), 3.47–3.44 (m, 6H, CH2), 3.07–2.97 (m, 6H, CH2), 1.69–1.67 (m, 2H, CH2), 1.59–1.52 (m, 2H, CH2). 13C NMR (CDCl3) δ (ppm): 192.35, 165.07, 164.79, 149.81, 148.96, 141.13, 137.77, 135.42, 134.7, 134.26, 134.08, 133.11 (2C), 132.66 (2C), 130.72 (3C), 129.86, 129.72 (2C), 128.91 (3C), 128.54 (2C), 128.21 (3C), 127.75 (2C), 125.04, 123.59, 62.00, 58.84, 58.71, 52.97, 52.84, 35.06, 34.26, 29.59, 26.91. ESI MS: m/z = 648.3 [M+H]+ (100 %).
NMR (CDCl₃) δ (ppm): 165.72, 159.08, 158.97, 140.62, 134.22, 134.17, 134.09, 133.74, 132.25, 130.14, 129.64, 129.53, 128.47, 128.38, 128.09, 127.48, 124.02, 61.13, 60.95, 57.53, 51.27, 51.13, 41.37, 41.29, 26.96, 26.87. ESI MS: m/z = 344.6 [M+H]+ (100 %).

Biological assays

Cell-based assays

Cell-based assays were performed at Dipartimento di Scienze e Tecnologie Biomediche, Università di Cagliari, Monserrato, Italy.

Test compounds

Compounds were dissolved in DMSO at 100 mM and then diluted in culture medium.

Cells and viruses

Cell line and viruses were purchased from the American Type Culture Collection (ATCC). The absence of mycoplasma contamination was checked periodically by the Hoechst staining method. Cell line supporting the multiplication of human immunodeficiency virus type-1 (HIV-1) was the CD4+ human T-cells containing an integrated HTLV-1 genome (MT-4).

Cytotoxicity assays

Cytotoxicity assays were run in parallel with antiviral assays.

Exponentially growing MT-4 cells were seeded at an initial density of 1 × 10⁵ cells/ml in 96-well plates in RPMI-1640 medium, supplemented with 10 % fetal bovine serum (FBS), 100 units/ml penicillin G, and 100 μg/ml streptomycin. Cell cultures were then incubated at 37 °C in a humidified 5 % CO₂ atmosphere in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 h at 37 °C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method (Pauwels et al., 1988).

Antiviral assays

Compound’s activity against HIV-1 was based on inhibition of virus-induced cytopathogenicity in MT-4 cell acutely infected with a multiplicity of infection (m.o.i.) of 0.01. In brief, 50 μl of RPMI containing 1 × 10⁴ MT-4 cells were added to each well of flat-bottom microtitre trays, containing 50 μl of RPMI with or without serial dilutions of test compounds. Then, 20 μl of a HIV-1 suspension containing 100 CCID₅₀ was added. After a 4-day incubation at 37 °C, cell viability was determined by the MTT method (Pauwels et al., 1988).

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\text{Scheme 1 Synthesis of butylarylpyrazinyl derivatives of 1,16-diphenyl-19-azahexacyclo[14.5.1.0²,1⁵.0³,₈.0⁹,₁⁴.0¹⁷,₂₁]docosa-2,3,5,7,8,9,11,1₃,1₄-naene-1₈,2₀,2₂-trione (1)}
\]
In vitro ligand binding assays

Ligand studies with native 5-HT_1A receptor were conducted according to the methods previously described (Lewgowd et al., 2011).

X-ray structure determination

Suitable crystals were mounted for measurements. The X-ray measurements were performed at 100(2) K on a KUMA CCD k-axis diffractometer with graphite-monochromated Mo Kα radiation (0.71073 Å). The crystals were positioned at 62.25 mm from the KM4CCD camera. The data were corrected for Lorentz and polarization effects, additionally absorption corrections were applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław, Poland) programmes (Oxford Diffraction CrysAlis CCD and CrysAlis RED, 2001). The structures were solved by direct methods (Sheldrick, 1990) and refined by using SHELXL (Sheldrick, 1997). The refinement was based on \( F^2 \) for all reflections except for those with very negative \( F^2 \). The weighted \( R \) factor, \( wR \), and all goodness-of-fit \( S \) values are based on \( F^2 \). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from a difference map and were refined isotropically. The atomic scattering factors were taken from the International Tables (Wilson, 1992). Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 913714-913719. Copy of the data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (email: deposit@ccdc.cam.ac.uk).

**X-ray crystal data for 2**

\( \text{C}_{37}\text{H}_{39}\text{BrNO}_3 \), monoclinic space group \( P2_1/c \); \( a = 15.7066 \) (8), \( b = 7.9750(4) \), \( c = 23.0807(12) \) Å, \( \beta = 100.366(4) \); \( V = 2843.9(3) \) Å\(^3\), \( Z = 4 \), \( D_{\text{calc}} = 1.435 \text{ g/cm}^3 \); \( \mu = 1.485 \text{ mm}^{-1} \); \( F(000) = 1264 \). A total of 21,137 reflections

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**Scheme 2** 1,3-Diphenylcyclopenta[\( \alpha \)]indene-2,8-dione as starting material for new synthetic route of complex arylpiperazines

**Scheme 3** Synthesis of 3-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}3-azatricyclo[7.3.1.0\(^5\),13]trideca-(12),5,7,9(13),10-pentaene-2,4-dione (20)

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were integrated in the $\theta$-range of 2.71°–25.0° of which 5,007 were unique, leaving an overall R-merge of 0.041. For solution and refinement, 5,007 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.028$ for 3,431 reflections with $F > 4\sigma(F)$; $R1 = 0.050$ and $wR2 = 0.055$ for all the 5,007 data; GOF = 0.864. The residual electron density in the final difference Fourier does not show any feature above 0.33 e Å$^{-3}$ and below −0.32 e Å$^{-3}$.

**X-ray crystal data for 6**

C$_{47}$H$_{60}$Cl$_n$N$_3$O$_3$, monoclinic space group $P2_1/n$: $a = 11.8478$ (9), $b = 23.8155(18)$, $c = 13.0659(10)$ Å, $\beta = 101.732(6)$; $V = 3609.7(5)$ Å$^3$, $Z = 4$, $D_{calc} = 1.344$ g/cm$^3$; $\mu = 0.155$ mm$^{-1}$; $F(000) = 1536$. A total of 27,540 reflections were integrated in the $\theta$-range of 2.72°–25.0° of which 6,356 were unique, leaving an overall R-merge of 0.0653. For solution and refinement, 6,348 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.0339$ for 2,916 reflections with $F > 4\sigma(F)$; $R1 = 0.0935$ and $wR2 = 0.1195$ for all the 6348 data; GOF = 0.854. The residual electron density in the final difference Fourier does not show any feature above 0.22 e Å$^{-3}$ and below −0.22 e Å$^{-3}$.

**X-ray crystal data for 7**

C$_{47}$H$_{60}$FN$_3$O$_3$, monoclinic space group $P2_1/n$: $a = 11.8103$ (4), $b = 23.4267(5)$, $c = 13.2359(3)$ Å, $\beta = 96.196(2)$; $V = 3640.67(17)$ Å$^3$, $Z = 4$, $D_{calc} = 1.302$ g/cm$^3$; $\mu = 0.085$ mm$^{-1}$; $F(000) = 1504$. A total of 27,438 reflections were integrated in the $\theta$-range of 2.8°–25.0° of which 6,394 were unique, leaving an overall R-merge of 0.0104. For solution and refinement, 6,394 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.0323$ for 5,658 reflections with $F > 4\sigma(F)$; $R1 = 0.0365$ and $wR2 = 0.1276$ for all the 6,394 data; GOF = 1.144. The residual electron density in the final difference Fourier does not show any feature above 0.24 e Å$^{-3}$ and below −0.2 e Å$^{-3}$.

**X-ray crystal data for 11**

C$_{51}$H$_{32}$BrNO$_3$, monoclinic space group $P2_1$: $a = 9.3851$ (7), $b = 23.3058(14)$, $c = 11.4605(7)$ Å, $\beta = 106.711(7)$; $V = 2400.9(3)$ Å$^3$, $Z = 4$, $D_{calc} = 1.484$ g/cm$^3$; $\mu = 1.747$ mm$^{-1}$; $F(000) = 1,096$. A total of 9,877 reflections were integrated in the $\theta$-range of 2.86°–26.0° of which 6,914 were unique, leaving an overall R-merge of 0.0318. For solution and refinement, 4,835 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.0633$ for 4,665 reflections with $F > 4\sigma(F)$; $R1 = 0.1047$ and $wR2 = 0.1518$ for all the 6,914 data; GOF = 1.049. The residual electron density in the final difference Fourier does not show any feature above 1.05 e Å$^{-3}$ and below −0.96 e Å$^{-3}$.

**X-ray crystal data for 19**

C$_{47}$H$_{60}$Cl$_n$N$_3$O$_3$, triclinic space group $P-1$: $a = 11.4607(3)$, $b = 12.0127(3)$, $c = 13.7081(4)$ Å, $\alpha = 97.455(2)$, $\beta = 103.874(2)$, $\gamma = 105.357(2)$; $V = 1728.71(8)$ Å$^3$, $Z = 2$, $D_{calc} = 1.337$ g/cm$^3$; $\mu = 0.234$ mm$^{-1}$; $F(000) = 728$. A total of 19,541 reflections were integrated in the $\theta$-range of 3.01°–25.0° of which 6,084 were unique, leaving an overall R-merge of 0.0173. For solution and refinement, 6,084 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.0351$ for 4,789 reflections with $F > 4\sigma(F)$; $R1 = 0.0471$ and $wR2 = 0.0956$ for all the 6,084 data; GOF = 1.077. The residual electron density in the final difference Fourier does not show any feature above 0.29 e Å$^{-3}$ and below −0.25 e Å$^{-3}$.

**X-ray crystal data for 20**

C$_{27}$H$_{30}$Cl$_n$N$_3$O$_3$, triclinic space group $P-1$: $a = 7.66540$ (10), $b = 10.3318(2)$, $c = 16.0440(3)$ Å, $\alpha = 96.0230$ (10), $\beta = 93.910(2)$, $\gamma = 106.740(2)$; $V = 1203.60(4)$ Å$^3$,
Z = 2, $D_{\text{calc}} = 1.324 \text{ g/cm}^3, \mu = 0.193 \text{ mm}^{-1}; F(000) = 508$. A total of 13,968 reflections were integrated in the $\theta$-range of $2.94^\circ$–$25.0^\circ$ of which 4,235 were unique, leaving an overall $R$-merge of 0.0149. For solution and refinement, 4,235 were considered as unique after merging for Fourier. The final agreement factors were $R1 = 0.0267$ for 3,532 reflections with $F > 4\sigma(F)$; $R1 = 0.0327$ and $wR2 = 0.0758$ for all the 4,235 data; GOF = 1.068. The residual electron density in the final difference Fourier does not show any feature above 0.27 e Å$^{-3}$ and below −0.21 e Å$^{-3}$.

**Results and discussion**

**Chemistry**

**Synthesis of N-butylarylpiperazinyl derivatives**

Two synthetic lines of N-substituted arylpiperazine derivatives were prepared. In the first path (Scheme 1), commercially available 1,3-diphenyl-2H-cyclopenta[l]phenanthren-2-one (“Phencyclone”) and maleimide were condensed in Diels–Alder reaction, and toluene was used as a solvent. After addition of 1,4-dibromobutane, 1,16-diphenyl-19-azahexacyclo[14.5.1.0$^{2,15}$.0$^{3,8}$.0$^{9,14}$.0$^{17,21}$] docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20,22-trione was obtained (1). Finally, synthesized 19-(4-bromobutyl)-1,16-diphenyl-19-azahexacyclo[14.5.1.0$^{2,15}$.0$^{3,8}$.0$^{9,14}$.0$^{17,21}$]docosa-2,3,5,7,8,9,11,13,14-nonaene-18,20,22-trione (2) was used to obtain seven new complex arylpiperazines (3–9).

In the second synthetic path (Scheme 2), “Indanocyclone” and maleimide were refluxed to give 4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (10). This step of synthesis shows different approaches (decarbonylation) of the condensation reaction between dienes and dienophiles.

The 2-(4-bromobutyl)-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2-f]isoindole-1,3,5-trione (11) was obtained by condensation of 1,4-dibromobutane with above-mentioned complex imide in acetonitrile used as a solvent. The final step was to synthesize arylpiperazine derivatives by refluxing...
corresponding piperazines with 2-(4-bromobutyl)-4,10-diphenyl-1H,2H,3H,5H-indeno[1,2,3-f]isoindole-1,3,5-trione (11). Crude products (12–19) were purified and their hydrochlorides were made.

In addition, the synthesis of 3-[4-(2-metoxypheynyl)piperazin-1-yl]butyl]3-azatricyclo[7.3.1.05,13]tridec(12, 5,7,9(13),10-pentaene-2,4-dione (20) was carried out. The compound was the subject of previous biological (5-HTR affinity) investigations (Scheme 3), however, the X-ray crystal analysis of the compound has not been published yet.

All obtained compounds were purified by flash chromatography. Elemental analysis, mass spectrometry, 1H NMR and 13C NMR spectra confirmed the identity of the products. For compounds 2 and 11, also for hydrochlorides of 6, 7, 19, and 20 X-ray analyses were done.

Biology

Cytotoxicity and anti HIV-1 activity

Title compounds were tested in cell-based assay against the human immunodeficiency virus type-1 (HIV-1), using Efavirenz as reference inhibitor. The cytotoxicity was evaluated in parallel with the antiviral activity.

None of tested compounds showed selective antiviral activity against HIV-1. However compounds 10 and 14 turned out cytotoxic for exponentially growing MT4 cells in the low micromolar range (CC50 = 9 μM) (Table 1).

X-ray structural analyses

The crystal structures have been determined for three “phencyclone” derivatives 2, 6, and 7. Their main skeleton resembles buspirone, but have more bulky maleimide fragment and in the case of 2 there is no piperazine moiety (n-butyl chain is terminated by bromine atom). In structures 6 and 7, the aromatic fragment (p-chlorophenyl and o-fluorophenyl, respectively) is different from 2-piryimidinyl substituent in buspirone.

In all of these structures phenanthrene moiety forms a kind of “roof” over n-butyl chain, and phenyl rings are situated like “wings” directed outside (Fig. 2). In structures 6 and 7, the piperazine moiety adopts chair conformation. All compounds crystallize in monoclinic system without solvent with one molecule in an asymmetric unit. Unit cell contains 4 molecules related by inversion center (Fig. 3).

The crystal structure of 2 is stabilized by two kinds of short interactions between C–H⋯O and C–H⋯Br (Fig. 4). In 6 there are three types of C–H⋯O contacts. The oxygen atom from maleimide moiety contacts with piperazine and phenanthrene fragments. Second one interacts with phenyl ring (Fig. 5). The structure of 7 shows similar C–H⋯O interactions and there is an additional short C–H⋯F contact (Fig. 6).

Two crystal structures based on “Indanocyclone” 11 and 19 are disordered. Compound 11 crystallizes without solvent in monoclinic P21 space group with two molecules in an asymmetric unit. The structure is a racemic twin in which one molecule is disordered. The disorder occurs in the n-butyl chain together with bromine atom and in the first phenyl ring of Indanocyclone. Two side
phenyl rings are almost coplanar, the angle between mean best planes is 3.5°. There are three types of C–H···O interactions between maleimide oxygens and the n-butyl chain, as well as the side phenyl ring, and between oxygen from Indanocyclone moiety and the side phenyl ring (Fig. 7).

Compound 19 crystallizes as a hydrochloride with one molecule of water in triclinic P-1 space group with one molecule in an asymmetric unit. Disorder occurs in first Indanocyclone phenyl ring and gives rise to π···π stacking between disordered benzene and maleimide rings. Two side phenyl rings are tilted with respect to each other by 24.8° (Fig. 8). The n-butyl chain adopts cis conformation with dihedral angle N1-C28-C29-C30 equal to 55.6.

The structure is stabilized by a set of N′H···Cl− bonds between piperazine and chloride anions. There are two

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**Fig. 4** Short intermolecular contacts in crystal structure of 2

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**Fig. 5** Short intermolecular contacts in crystal structure of 6
Fig. 6 Short intermolecular contacts in crystal structure of 7

Fig. 7 Crystal packing and short intermolecular contacts in crystal structure of 11
types of interactions between oxygens from maleimide moiety and C–H from butyl chain and Indanocyclone phenyl ring. Water molecule forms C–H···O bonds with piperazine and Indanocyclone phenyl ring. There are also O–H···Cl− interactions (Fig. 9).

Compound 20, an analog of NAN-190, crystallizes in triclinic $P\bar{1}$ space group as a hydrochloride with one molecule in an asymmetric unit. The imide moiety is almost planar. The piperazine ring adopts chair conformation (Fig. 10). The crystal structure forms layers...
Fig. 10 Crystal structure of 20.
Thermal ellipsoids drawn at 50% probability level.

Fig. 11 Crystal packing of 20.
View along a axis.
along a axis comprising of alternating molecules (Fig. 11). The structure is stabilized by N–H...Cl− hydrogen bonds. In addition there are short contacts between chloride anion and C–H from the methoxy group, the butyl chain and the piperazine moiety. There are also interactions between oxygens from the imide fragment with C–H from piperazine and the methoxy-phenyl ring (Fig. 12).

Conclusions

Compounds 6, 7, 19, and 20 fit well to the three-point pharmacophore model for 5-HT1A receptor ligands (Chilmonczyk et al., 1997). Apart from an aromatic ring and the basic nitrogen of piperazine, localized in the distance of 5.2–5.7 Å from a centroid, authors have found the third point essential for a ligand–receptor interaction—the carbonyl oxygen, expected in the distance of 7.07 Å from the center of an aromatic ring and 4.3 Å from N4 piperazine atom. Intramolecular distances measured for a set of 5-HT1A receptor ligands by Chilmonczyk et al. were in the range of 7.93–12.37 Å (Centroid–O(1)), 3.95–7.16 Å (N(1)–O(1)), and 5.15–5.64 Å (Centroid–N(1)).

The values calculated for new arylpiperazine derivatives (6, 7, 19, and 20) are in agreement with the presented three-point pharmacophore model (Table 2, Fig. 13). The distance between the center of the phenyl group and the imide oxygen (O1) is in the range of 8.13–11.89 Å. The measured distance of the protonated nitrogen (N1) and O1 atom is in the range of 4.06–6.66 Å. The value of centroid – N1 length is in a narrow range between 5.67 and 5.71 Å. Presented results suggest that compounds 6, 7, 19, and 20 could serve as potential 5-HT1A receptor ligands. They also prove that similar molecular values can be estimated for the derivative 4. Although it is an exception from “the rule of five,” because of its high molecular weight, volume and logP, and low solubility logS (Table 3), the compound 4 possess moderate activity to the 5-HT1A receptor.

Table 2 Selected intramolecular distances (Å) for arylpiperazine derivatives 6, 7, 19, and 20

|                | 6   | 7   | 19  | 20  |
|----------------|-----|-----|-----|-----|
| Centroid–O(1)  | 10.78 | 10.7 | 8.13 | 11.89 |
| N(1)–O(1)      | 5.78 | 5.78 | 4.06 | 6.66 |
| Centroid–N(1)  | 5.69 | 5.71 | 5.67 | 5.68 |

Fig. 12 Short intermolecular contacts in crystal structure of 20

Fig. 13 Molecular geometric parameters (in Å) observed in solid state for the derivative 20

Table 3 Selected geometric parameters (Å) for arylpiperazine derivatives 6, 7, 19, and 20

|                | 6   | 7   | 19  | 20  |
|----------------|-----|-----|-----|-----|
| Centroid–O(1)  | 10.78 | 10.7 | 8.13 | 11.89 |
| N(1)–O(1)      | 5.78 | 5.78 | 4.06 | 6.66 |
| Centroid–N(1)  | 5.69 | 5.71 | 5.67 | 5.68 |

Fig. 13 Molecular geometric parameters (in Å) observed in solid state for the derivative 20

Table 3 Selected geometric parameters (Å) for arylpiperazine derivatives 6, 7, 19, and 20

|                | 6   | 7   | 19  | 20  |
|----------------|-----|-----|-----|-----|
| Centroid–O(1)  | 10.78 | 10.7 | 8.13 | 11.89 |
| N(1)–O(1)      | 5.78 | 5.78 | 4.06 | 6.66 |
| Centroid–N(1)  | 5.69 | 5.71 | 5.67 | 5.68 |
Table 3 Molecular descriptors calculated for representative 5-HT\(_{1A}\) receptor ligands and for selected synthesized derivatives (drug likeness prediction done via http://molsoft.com/mprop/)

| Compound    | Molecular weight (u) | Number of HBA | Number of HBD | logP | logS [log (moles/l)] | PSA (Å\(^2\)) | Volume (Å\(^3\)) |
|-------------|----------------------|---------------|---------------|------|----------------------|----------------|------------------|
| Buspirone   | 385.25               | 5             | 0             | 2.09 | −1.89                | 56.28          | 421.63           |
| BMY-7378    | 385.24               | 4             | 0             | 3.14 | −3.12                | 46.42          | 428.35           |
| NAN-190     | 393.21               | 4             | 0             | 3.08 | −4.16                | 44.93          | 415.76           |
| 4           | 725.33               | 5             | 0             | 6.82 | −10.82               | 58.07          | 758.15           |
| 6           | 729.28               | 4             | 0             | 7.91 | −11.22               | 49.46          | 769.80           |
| 7           | 713.31               | 4             | 0             | 7.33 | −11.12               | 49.96          | 758.17           |
| 19          | 651.23               | 4             | 0             | 7.74 | −10.79               | 49.75          | 646.73           |
| 20          | 443.22               | 4             | 0             | 4.25 | −5.74                | 44.30          | 466.09           |

Structural data obtained for a set of long-chain arylpiperazine derivatives can serve for further investigations concerning ligands activity to metabotropic 5-HT receptors.

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Conflict of interest None.

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