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N-[4-(Arylpiperazin-1-yl)butyl]bicyclo[2.2.1]hept-5-ene-*endo*-2,*endo*-3-dicarboximides and Their Epoxy Derivatives. Synthesis and Affinity for 5-HT_{1a} Receptors

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Abstract—New ligands for 5-HT_{1A} serotonin receptors, *N*-[4-(4-arylpiperazin-1-yl)butyl]bicyclo[2.2.1]hept-5-ene-*endo*-2,*endo*-3-dicarboximides and their epoxy derivatives, were synthesized, and their affinity for 5-HT_{1A} receptors was estimated at 16.2±2.0 to 0.60±0.08 nM.

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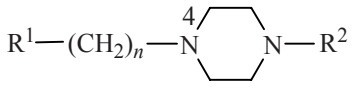
Ligands for serotonin and dopamine receptors were found among aryl(hetaryl)piperazine derivatives like **I**, and they showed anxiolytic, antidepressant, and neuroleptic properties [1–3].



I

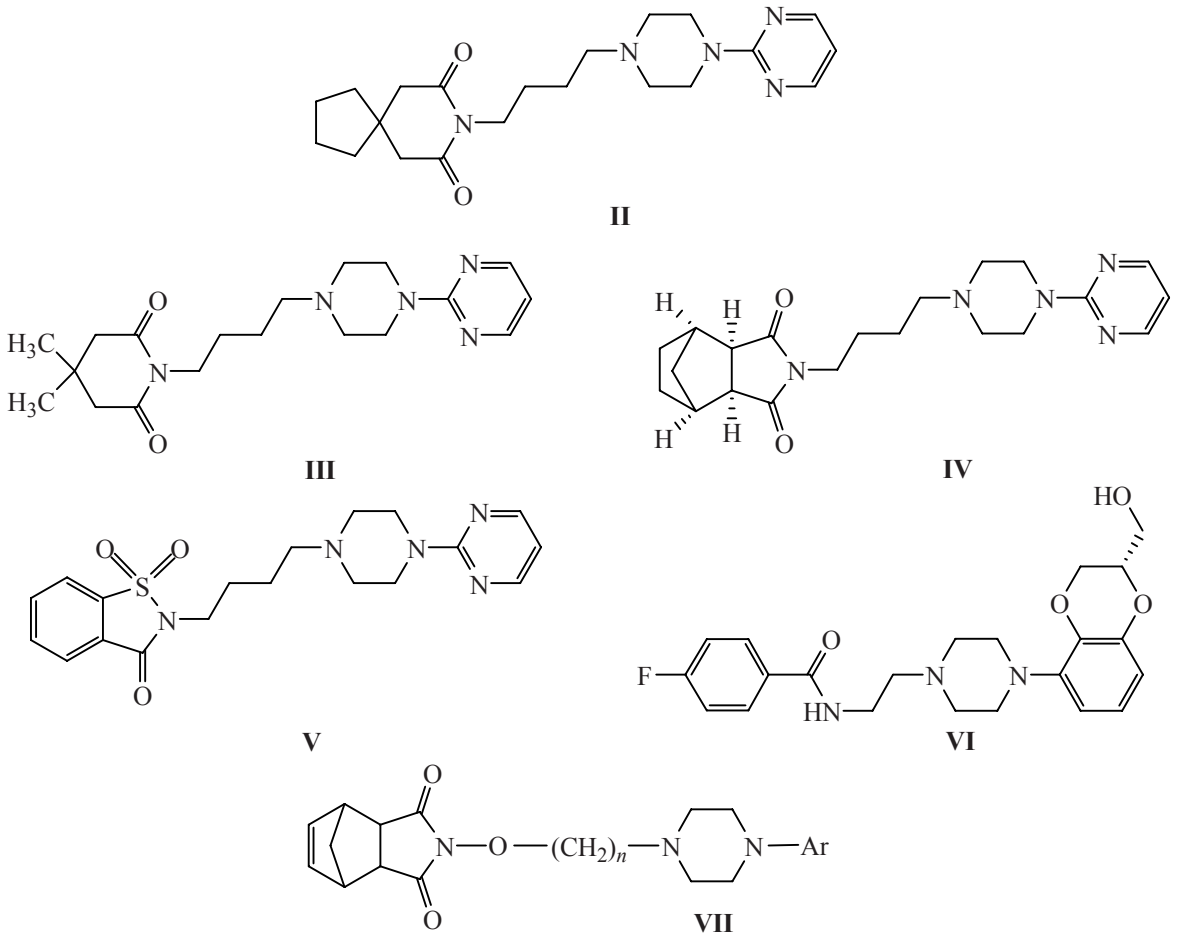
R^1 is imide or amide terminal fragment; n = 2–6; R^2 is aryl or getaryl fragment.

Buspirone (**II**) and related compounds, in particular gepirone (**III**), tandospirone (**IV**), ipsapirone (**V**), and flesinoxan (**VI**), exhibit high affinity for 5-HT_{1A} serotonin receptors (5-HT_{1A}R) and were the subjects of numerous studies in the field of medicinal chemistry, neuropharmacology, and clinical testing of neurotropic agents [4–7]. Buspirone and tandospirone are used in the treatment of anxiety and depressions [8, 9]. Arylpiperazine derivatives **VII** containing a norbornenedicarboximide moiety as terminal fragment were shown to be highly selective and potent ligands for 5-HT_{1A}R [10].

Neuropharmacological action of arylpiperazines **I** originates from formation of a supramolecular ligand **I**–5-HT_{1A}R complex. On the basis of QSAR analysis and molecular docking studies, hypothetical models have been proposed for the ligand–receptor interactions. It is believed that the ligand–receptor binding is determined by the ability of protonated N^4 atom in the piperazine ring to form hydrogen bond (whose strength approaches the strength of a ionic bond) with the aspartic acid residue which is located in the third transmembrane domain of the receptor (Asp 3.32) [11–15]. The second important structural fragment of the ligand, which is directly involved in ligand–receptor interaction, is aromatic ring R^2; it is responsible for CH–π interaction with the phenylalanine residue in the sixth domain of the receptor (Phe 6.52) [15]. An important role in ligand **I** binding to 5-HT_{1A}R is played by the terminal fragment R^1 which is capable of forming hydrogen bonds with the amino acid residues in the second and seventh domains of 5-HT_{1A}R [14, 15].

With a view to examine the structure–molecular mechanism of action–pharmacological properties relationships for ligands selective for 5-HT_{1A} receptors we synthesized new arylpiperazine derivatives of type **I**, which contained bicyclo[2.2.1]hept-5-ene- or 5,6-epoxybicyclo[2.2.1]heptane-*endo*-2,*endo*-3-dicarboximide

† Deceased.



II

III

IV

V

VI

VII

n = 2, 3.

moiety as terminal fragment (R^1), and determined their affinity for 5-HT_{1A}R. The synthesized compounds seem to be also interesting as new derivatives of cage-like systems exhibiting versatile pharmacological activity [16–21].

By reaction of endic acid imide **IX** or its epoxy derivative **X** with 1-aryl-4-(4-bromobutyl)piperazine in boiling anhydrous toluene in the presence of potassium carbonate we obtained 4-{4-[4-(4-arylpiperazin-1-yl]-butyl}-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-diones **XI** and 4-{4-[4-(arylpiperazin-1-yl]butyl}-*exo*-8,9-epoxy-4-azatricyclo[5.2.1.$0^{2,6}$]decane-3,5-diones **XII**, respectively (Table 1), which were isolated as the corresponding hydrochlorides. As starting compound we used endic anhydride (**VIII**, bicyclo[2.2.1]hept-5-ene-*endo*-2,*endo*-3-dicarboxylic anhydride). Imide **IX** was synthesized by reaction of anhydride **VIII** with aqueous ammonia, followed by heating in glacial acetic acid according to the procedure described in [22]. Oxidation of imide **IX** with peroxyformic acid generated *in situ* from 98% formic acid and 50% aqueous hydrogen peroxide according to the procedure reported in [23] gave epoxide **X**.

The product structure was confirmed by their IR, ^{1}H NMR, and mass spectra. The IR spectra of **XI** and **XII** contained strong absorption bands due to symmetric and asymmetric stretching vibrations of the C=O bonds (1680–1699 and 1760–1763 cm^{-1}), C–H bonds in the methylene groups (2830–3000 cm^{-1}), and C–H bonds in unsaturated fragments (3054–3062 cm^{-1}). In addition, epoxynorbornane derivatives **XII** characteristically displayed absorption bands belonging to the oxirane fragment (850, 852 cm^{-1}). In the mass spectra of hydrochlorides **XI** and **XII** we observed molecular ion peaks of the corresponding bases, while the most abundant ions were those resulting from elimination of the arylpiperazine fragment from the molecular ion (Table 2). The ^{1}H NMR spectra of these compounds were consistent with the assumed structures (Table 2).

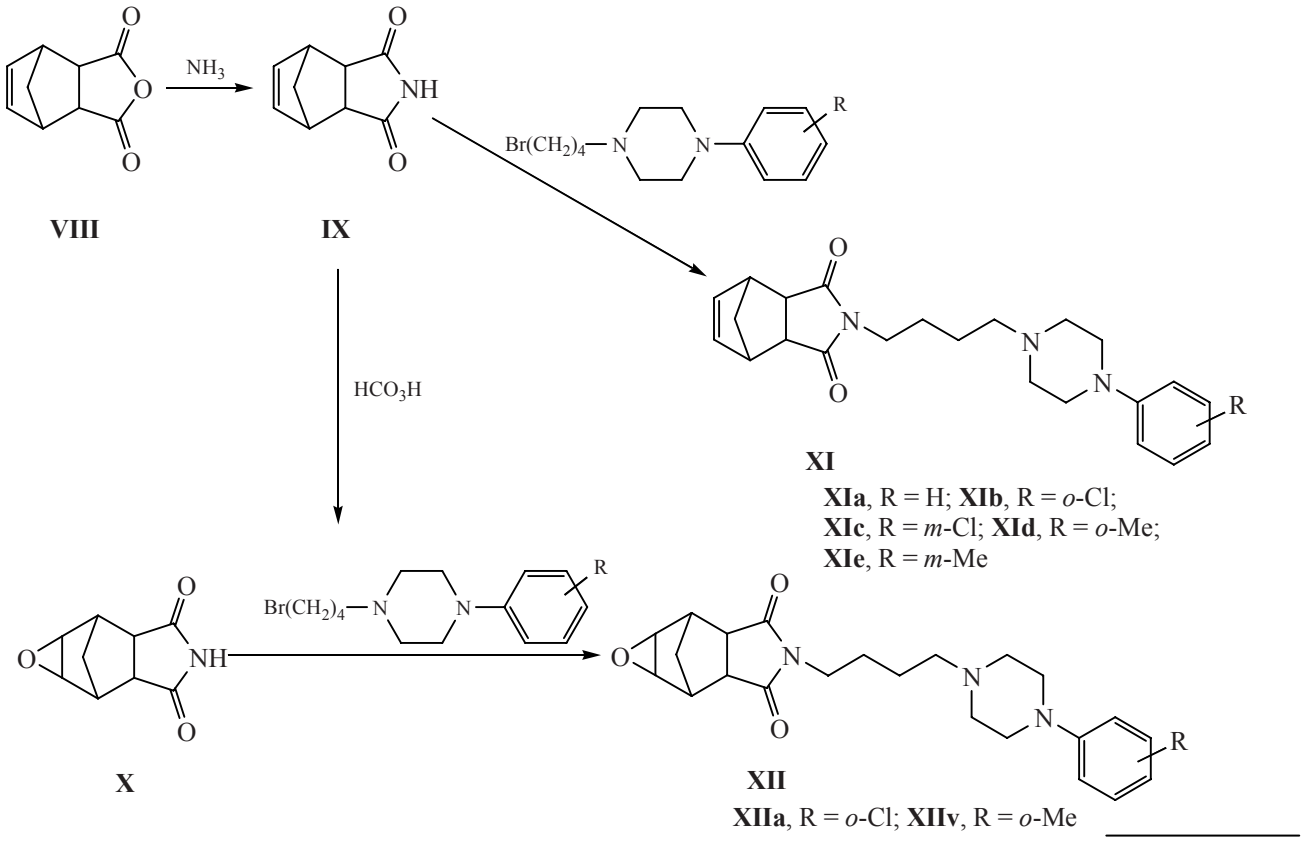
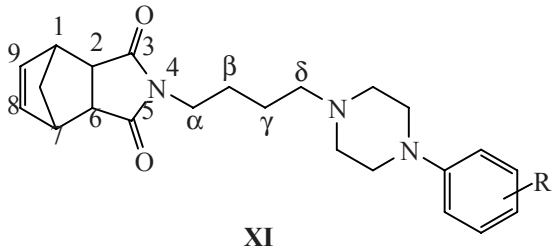
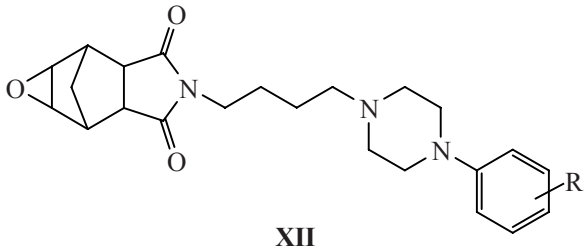


Table 1. Yields, melting points, elemental analyses, and affinities for 5-HT_{1A} receptors of *N*-[4-(4-arylpiperazin-1-yl)butyl] endic and -epoxyendic acid imides **XIa**–**XIe**, **XIIa**, and **XIIb**



XI



XII

Comp. no.	R	mp, °C	Yield, %	Calculated, %			Formula	Found, %			K_i, nM
				C	H	N		C	H	N	
XIa	H	190–192	66.0	66.4	7.0	10.1	$C_{23}H_{29}N_3O_2 \cdot HCl$	66.5	7.1	10.1	16.2±2.0
XIb	*o*-Cl	250–252	80.6	61.3	6.3	9.3	$C_{23}H_{28}ClN_3O_2 \cdot HCl$	61.4	6.3	9.4	0.60±0.08
XIc	*m*-Cl	198–200	53.4	61.3	6.3	9.3	$C_{23}H_{28}ClN_3O_2 \cdot HCl$	61.4	6.4	9.4	3.5±0.5
XId	*o*-CH_3	252–255	87.6	67.0	7.3	9.8	$C_{24}H_{31}N_3O_2 \cdot HCl$	67.0	7.3	9.7	8.3±0.9
XIe	*m*-CH_3	195–198	62.8	67.0	7.3	9.8	$C_{24}H_{31}N_3O_2 \cdot HCl$	67.1	7.4	9.8	3.6±0.5
XIIa	*o*-Cl	259–262	88.8	59.2	6.1	9.0	$C_{24}H_{28}ClN_3O_3 \cdot HCl$	59.3	6.1	9.1	0.70±0.08
XIIb	*o*-CH_3	257–258	65.8	64.6	7.0	9.4	$C_{24}H_{31}N_3O_3 \cdot HCl$	64.7	7.1	9.4	8.9±1.0
Buspirone 15.0±1.5											

Table 2. Mass and ^{1}H NMR spectra of compounds **XIa**–**XIe**, **XIIa**, and **XIIb**

Comp. no.	Mass spectrum,[a] *m*/*z*	^{1}H NMR spectrum, δ, ppm
XIa	379	1.38 m (2H, β-CH_2); 1.54 m (2H, H^{10s}, H^{10a}); 1.65 m (2H, γ-CH_2); 3.06 m (6H, H^1, H^7, $2CH_{2piper}$); 3.24 t (4H, $2CH_{2piper}$); 3.34 m (2H, H^2, H^6); 3.48 d (2H, δ-CH_2); 3.78 d (2H, α-CH_2); 6.11 m (2H, H^8, H^9); 6.84–7.29 m ($5H_{arom}$); 11.24 br.s (1H, $^+$NH)
XIb	413	1.39 m (2H, β-CH_2); 1.53 m (2H, H^{10s}, H^{10a}); 1.65 m (2H, γ-CH_2); 3.06–3.20 m (6H, H^1, H^7, $2CH_{2piper}$); 3.24 m (4H, H^2, H^6, δ-CH_2); 3.36–3.42 m (4H, $2CH_{2piper}$); 3.51 d (2H, α-CH_2); 6.12 m (2H, H^8, H^9); 7.09–7.46 m ($4H_{arom}$); 11.09 br.s (1H, NH)
XIc	413	1.39 m (2H, β-CH_2); 1.56 m (2H, H^{10s}, H^{10a}); 1.65 m (2H, γ-CH_2); 3.07 m (6H, H^1, H^7, $2CH_{2piper}$); 3.24 m (6H, H^2, H^6, $2CH_{2piper}$); 3.47 d (2H, δ-CH_2); 3.86 d (2H, α-CH_2); 6.12 m (2H, H^8, H^9); 6.86–7.26 m ($4H_{arom.}$); 11.02 br.s (1H, $^+$NH)
XId	393	1.39 m (2H, β-CH_2); 1.55 m (2H, H^{10s}, H^{10a}); 1.66 m (2H, γ-CH_2); 2.25 c (3H, CH_3); 3.09 m (2H, H^1, H^7); 3.14 br.s (8H, $4CH_{2piper}$); 3.25 m (4H, H^2, H^6, δ-CH_2); 3.46 t (2H, α-CH_2); 6.12 m (2H, H^8, H^9); 6.99–7.20 m ($4H_{arom}$); 11.09 br.s (1H, $^+$NH)
XIe	393	1.40 m (2H, β-CH_2); 1.55 m (2H, H^{10s}, H^{10a}); 1.66 m (2H, γ-CH_2); 2.27 c (3H, CH_3); 3.06 m (6H, H^1, H^7, $2CH_{2piper}$); 3.24 m (6H, H^2, H^6, $2CH_{2piper}$); 3.47 d (2H, δ-CH_2); 3.75 d (2H, α-CH_2); 6.11 m (2H, H^8, H^9); 6.86–7.16 m ($4H_{arom}$); 11.32 br.s (1H, $^+$NH)
XIIa	429	1.07 d (1H, H^{10a}); 1.36 d (1H, H^{10s}, $^2J_{10s,10a}$ 9.9 Hz); 1.49 m (2H, β-CH_2); 1.69 m (2H, γ-CH_2); 2.88 m (2H, H^1, H^7); 3.12 c (6H, H^8, H^9, $2CH_{2piper}$); 3.26 m (2H, H^2, H^6); 3.36 t (6H, δ-CH_2, 2-CH_{2piper}); 3.51 br.s (2H, α-CH_2); 7.11–7.44 m ($4H_{arom}$); 11.14 br.s (1H, $^+$NH)
XIIb	409	1.07 d (1H, H^{10a}); 1.36 d (1H, H^{10s}, $^2J_{10s,10a}$ 9.9 Hz); 1.50 m (2H, β-CH_2); 1.71 m (2H, γ-CH_2); 2.88 s (3H, $3CH_3$); 2.88 s (2H, H^1, H^7); 3.12 m (8H, H^8, H^9, δ-CH_2, $2CH_{2piper}$); 3.26 m (2H, H^2, H^6); 3.36 t (2H, α-CH_2); 3.47 s (4H, $2CH_{2piper}$); 6.98–7.20 m ($4H_{arom}$); 10.95 br.s (1H, $^+$NH)

[a] Given are *m*/*z* values for the free bases.

The affinity of compounds **XI** and **XII** for 5-HT_{1A} serotonin receptors were determined *in vitro* by radioligand assay. The ability of **XI** and **XII** to form supramolecular complexes with 5-HT_{1A}R was characterized by K_i values according to [24] (Table 1). As follows from the obtained data, all compounds **XI** and **XII** show high affinity for 5-HT_{1A}R. For example, the affinity of **XIa** approaches that typical of buspirone (K_i = 16.2±2.0 and 15.0±1.5 nM, respectively). Introduction of a chlorine atom into the *ortho* position of the benzene ring (compound **XIb**) gave rise to a subnanomolar affinity for 5□HT_{1A}R (K_i = 0.60±0.08 nM). *o*-Tolyl analog **XId** showed slightly lower affinity. Enhanced affinity was also found for *m*-chloro and *m*-methyl derivatives **XIc** and **XIe** as compared to unsubstituted ligand **XIa**. Our results are consistent with the conclusions drawn in [10], according to which high affinity for 5-HT_{1A} receptors is inherent to compounds containing an endic acid imide moiety as terminal fragment. As followed from the K_i values for compounds **XIIa** and **XIIb**, replacement of norbornene fragment by epoxynorbornane did not result in appreciable change of the affinity for 5-HT_{1A}R in comparison with **XIb** and **XId**.

EXPERIMENTAL

The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates using butanol–acetic acid–water (3:1:1) and chloroform–acetone (9:1) as eluent; spots were visualized under UV light or by treatment with a solution of potassium permanganate. The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1321 instrument (ion source temperature 200°C). The ^{1}H NMR spectra were measured on a Varian WXP-300 spectrometer (299.95 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference.

4-[4-(4-Phenylpiperazin-1-yl)butyl]-4-azatricyclo [5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione hydrochloride (XIa). A mixture of 0.247 g of imide **IX**, 0.446 g of 1-(4-bromobutyl)-1-phenylpiperazine, and 0.42 g of anhydrous potassium carbonate in 8 ml of anhydrous toluene

was heated for 30 h under reflux. The mixture was filtered while hot, and the precipitate of potassium carbonate was washed with boiling toluene. The filtrate was combined with the washings, the solvent was distilled off under reduced pressure, the residue was dissolved in anhydrous acetone, and the solution was acidified with a saturated solution of hydrogen chloride in alcohol. The precipitate was filtered off and washed with anhydrous acetone and diethyl ether. Yield 0.41g (66%).

Compounds **XIb**–**XIe**, **XIIa**, and **XIIb** were synthesized in a similar way.

The affinity of compounds **XI** and **XII** for 5-HT_{1A} receptors was determined according to the procedure described in [24] with the use of [^{3}H]-8-ON-DPAT as radioligand (Amersham, specific radioactivity 8470 TBq mol^{-1}). The assays were performed in outbred male rats with a weight of 180–200 g, which were maintained under standard vivarium conditions. All experimental procedures in animals were in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). The bound radioactivity was quantitated with the aid of a RackBeta-1219 (LKB) scintillation counter. The inhibitory concentration IC_{50} was determined by graphical method, and K_i values were calculated using the Cheng–Prusoff equation [25]. The results were processed using Statistica program.

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