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6-[2-(4-Arylpiperazin-1-yl)ethyl]-4-halo-1,3-dihydro-2*H*--benzimidazole-2-thiones: synthesis and pharmacological evaluation

DEANA ANDRIĆ[1]*#, GORDANA TOVILOVIĆ[2], GORAN ROGLIĆ[1#], VUKIĆ ŠOŠKIĆ[3,4#], MIRKO TOMIĆ[2] and SLAĐANA KOSTIĆ–RAJAČIĆ[3]

[1]*Faculty of Chemistry, University of Belgrade, Studentski trg 16, 11000 Belgrade,* [2]*Department of Biochemistry, Institute for Biological Research, Bulevar Despota Stefana 142, 11060 Belgrade,* [3]*Center for Chemistry, Institute for Chemistry, Technology and Metallurgy, Njegoševa 12, 11000 Belgrade; Serbia and* [4]*Proteosys AG, Carl–Zeiss–Str. 51, 55129 Mainz, Germany*

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Abstract: Eight new compounds with halogen atom introduced into the benzimidazole-2-thione dopaminergic pharmacophore of 5-[2-(4-arylpiperazin-1-yl)ethyl]-1,3-dihydro-2*H*-benzimidazole-2-thiones with the arylpiperazine part of the molecule being selected according to known structure–affinity requirements, have been synthesized. All the new compounds were evaluated for the *in vitro* binding affinity at the dopamine (DA) D_1 and D_2 and serotonin 5-HT_{1A} receptors by the competitive radioassays, performed on synaptosomal membranes prepared from fresh bovine caudate nuclei and hippocampi. All the new compounds were strong competitors for the binding of the radioligands to the D_2 and 5-HT_{1A} receptors, with the most active of them having 34 and 170 time higher affinity than non-halogenated congeners in the D_2 DA receptor radioassays (compounds **9.1b** and **9.2b**, respectively). Divergently, these compounds were without significant affinities for the D_1 DA receptors.

Keywords: arylpiperazines, benzimidazole-2-thiones, dopamine receptors, serotonin receptors.

INTRODUCTION

For many years, the D_2 dopamine receptor (DAR) was a major target for neurobiological research and drug development, since DA antagonists have been proven to be efficient antipsychotics.[1] Since a great number of these compounds expressed undesirable side effects,[2,3] the need for new drugs is increasing. It took nearly four decades to make a breakthrough in this field of effort. These second-generation derivatives, named as atypical antipsychotics, combined D_2 and 5-HT_2 antagonism.[4] Newer atypical agents (*i.e.*, aripiprazole, bifeprunox, Fig. 1) differ

* Corresponding author. E-mail: deanad@chem.bg.ac.yu
# Serbian Chemical Society member.
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in that they act as partial agonists at D_2 and $5HT_{1A}$ receptors, although they also interact with an array of other CNS targets.[5] Such therapeutic strategy features the stabilization of dopamine function, instead of the inhibition of D_2 transmission caused by previous antipsychotic drugs.[5,6]

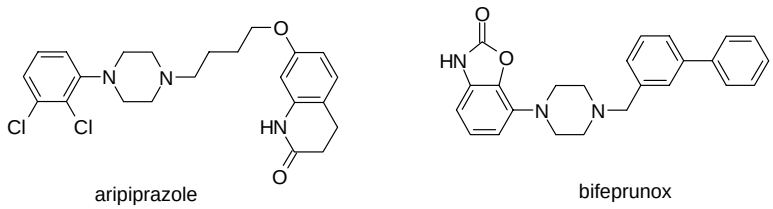


Fig. 1. Structures of aripiprazole and bifeprunox, atypical antipsychotics.

The work described herein presents the preparation of halogen derivatives of arylpiperazine-benzimidazole-2-thiones, ligands with mixed D_2/5-HT_{1A} activity. Arylpiperazines are a common structural motif included in various compounds for diverse pharmacological applications.[7] Certain groups of arylpiperazines express ligand property at the specific G-protein coupled receptors (GPCRs).[8,9] On the other hand, benzimidazole and their 2-substituted analogues possess a catechol moiety of biogenic catecholamine and are considered to be bioisosteres. Molecular modeling studies revealed that they both fit well into the binding pocket of D_2 DAR.[10,11] The interactions of 5-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-1*H*--benzimidazole (presented in Fig. 2) are realized at first by the salt bridge between protonated N1 of the piperazine ring with Asp86 in the binding pocket, and a mixture of hydrogen bonds, electronic and bulk interaction, which are all largely affected by the electrostatic surface potential (electron density distribution; ESP) in benzimidazole ring.

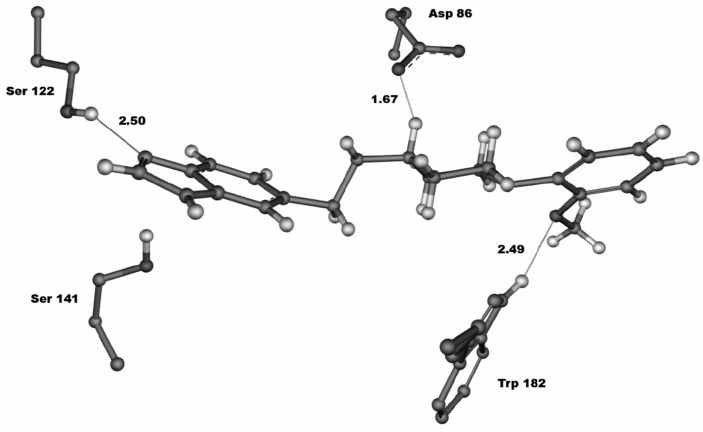


Fig. 2. Schematic representation of 5-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-1*H*-benzimidazole interaction with key amino acids in the binding site of the D_2 dopamine receptor.

In addition, ESP is influenced by the nature of substituents on the heterocyclic ring. This fact inspired us to insert halogen substituents into the benzimidazole pharmacophore, with the expectation that a mayor ESP perturbation will be achieved due to their large electron withdrawal effect. In recent publications, it was shown that high affinity D_2 DA/5HT_{1A} receptors ligands can be obtained by linking arylpiperazine and 2-substituted benzimidazole structural moieties through flexible linker.[10,12,13] The effect of various substituents on the stabilization of the ligand–D_2 complex through hydrogen bond formation, edge-to-face interactions and steric interactions with amino acid residues in the binding pocket of D_2 DAR receptors was investigated.[10]

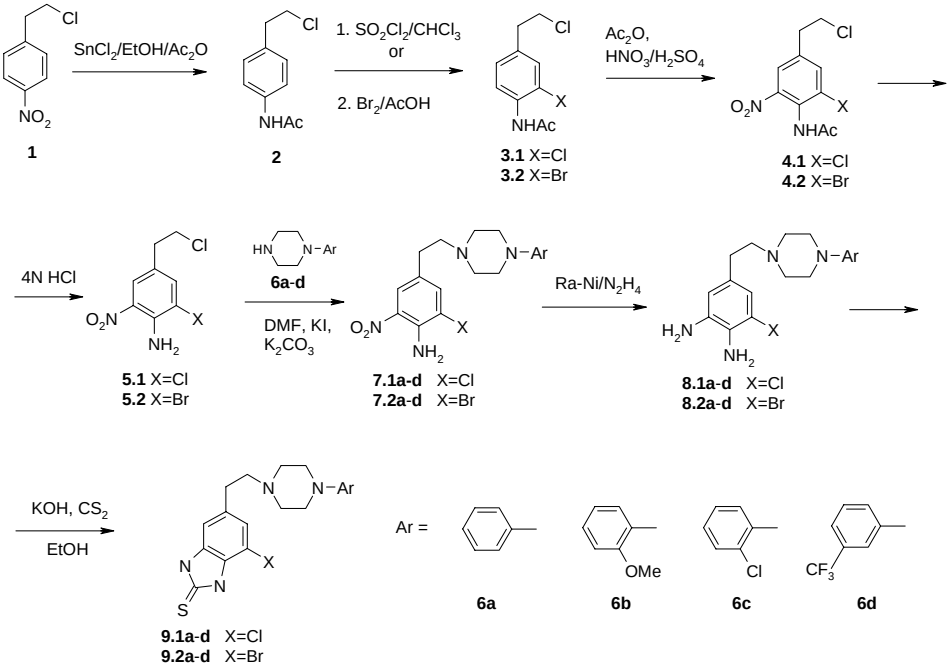
In this paper, the preparation of halogenated analogues together with their *in vitro* binding potencies at the D_1 and D_2 DAR and 5HT_{1A} receptors are presented. The effects of ligand halogenation on their dopaminergic/serotonergic activity are discussed.

RESULTS AND DISCUSSION

Eight new ligands, clasified as benzimidazole-2-thiones (compounds **9.1a–d – 9.2a–d**), were synthesized (as shown in Scheme 1). Shortly, compound **1** was reduced with stannous chloride in absolute ethanol[14] and the resulting amine was acylated without purification with acetanhydride to produce acetamide **2**. Compound **2** was converted either into corresponding halo-acetamides **3.1** or **3.2** using sulfuryl chloride[15] or bromine in acetic acid, respectively. Nitration of halo-acetamides **3.1** and **3.2** in acetanhydride with 100 % nitric acid/sulfuric acid afforded the corresponding compounds **4.1** and **4.2**. After hydrolysis of acetamido group in 4 N HCl, the resulting products **5.1** and **5.2** readily alkylated aryl-piperazines in the presence of potassium carbonate and potassium iodide in dimethylformamide. The obtained arylpiperazines **7.1a–d – 7.2a–d** were reduced with Ra-Ni/hydrazine[16] to produce corresponding diamines **8.1a–d – 8.2a–d**. Benzimidazole-2-thiones **9.1a–d – 9.2a–d** used as target ligands, were prepared by refluxing the diamines **8.1a–d – 8.2a–d** with carbon disulfide and KOH in ethanol.[17]

The affinities (K_i values, Table I) of the compounds towards DA (D_1 and D_2) and 5-HT (5-HT_{1A}) receptors were evaluated by *in vitro* binding assays. While none of the tested compounds were active displacers of [^{3}H]SCH 23390 at the D_1 DAR, they all showed significant affinities at the D_2 and 5-HT_{1A} receptors. Generally, all the newly synthesized compounds are stronger ligands at the D_2 receptors than the corresponding parent compounds **9a–d**. The most active of them (compounds **9.1b** and **9.2b**) have affinities in the low picomolar range and belong to the category of the most active hitherto described dopaminergic ligands. The phenyl derivatives (**9.1a** and **9.2a**) as well as the 2-chlorophenyl (**9.1c** and **9.2c**) and 3-(trifluoromethyl)phenyl derivative **9.1d** expressed affinity for binding at 5-HT_{1A} receptors similar to the affinities of the parent compounds. The 2-methoxy-

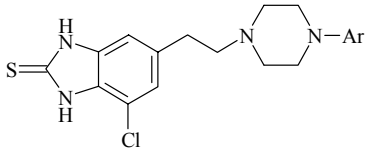
phenyl derivative **9.1b** was the strongest competitor in the [^{3}H]8-OH-DPAT binding assay too. The fact that the 3-(trifluoromethyl)phenyl ligand **9.1d** possesses greater affinity for the 5-HT$_{1A}$ than for the D$_2$ receptors was exceedingly manifested as a tendency in the case of the bromo derivative **9.2d**, which was the most selective 5-HT$_{1A}$ ligand.



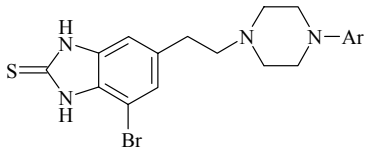
Scheme 1. Pathways for the synthesis of the ligands.

Taken together, these data confirm our previous observation that the affinity of the ligand for D$_2$ DA receptors depends both on the ESP of the benzimidazole pharmacophore[11] and on the choice of 1-arylpiperazine aryl groups. A positive ESP in the benzimidazole ring, induced by halogens and hydrogen bond acceptor groups (*e.g.* methoxy group) in the *ortho* position of 1-arylpiperazines, stabilizes the ligand–D$_2$ receptor complex.[10,18] These two factors additively contributed to the high affinity towards D$_2$ DA receptors in the compounds **9.1b** and **9.2b**. The influence on the affinity towards 5-HT$_{1A}$ receptors by the introduction of halogens into the benzimidazole pharmacophore of these ligands is diminished because the complete structure of the arylpiperazine part plays a predominant role. In conclusion, the here-presented fulfillment of the structural requirements for the DA and 5-HT ligand binding potency led to the expected rise of the affinity and selectivity for the tested compounds. Therefore, it seems that the binding characteristic of this kind of ligand can be predicted.

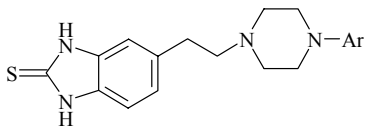
TABLE I. Chemical structure and K_i values* of the ligands



No	Ar	Formula	M.p. / °C	D_1 K_i / nM	D_2 K_i / nM	$5HT_{1A}$ K_i / nM
9.1a	Ph	$C_{19}H_{21}ClN_4S$	247	>1000	4.9±1.1	12.9±2.2
9.1b	2-MeOPh	$C_{20}H_{23}ClN_4OS$	246	>1000	0.054±0.003	0.36±0.04
9.1c	2-ClPh	$C_{19}H_{20}Cl_2N_4S$	257	>1000	11.9±2.4	36.1±1.3
9.1d	3-CF_3Ph	$C_{20}H_{20}ClF_3N_4S$	239	>1000	44.8±3.0	15.2±2.1



No	Ar	Formula	M.p. / °C	D_1 K_i / nM	D_2 K_i / nM	$5HT_{1A}$ K_i / nM
9.2a	Ph	$C_{19}H_{21}BrN_4S$	259	>1000	6.3±3.1	19.1±3.3
9.2b	2-MeOPh	$C_{20}H_{23}BrN_4OS$	236	>1000	0.01±0.005	1.7±0.2
9.2c	2-ClPh	$C_{19}H_{20}BrClN_4S$	254	>1000	7.1±1.5	76.5±5.7
9.2d	3-CF_3Ph	$C_{20}H_{20}BrF_3N_4S$	248	>1000	72.5±6.2	1.7±0.8



No	Ar	Formula	M.p. / °C	D_1 K_i / nM	D_2 K_i / nM	$5HT_{1A}$ K_i / nM
9a	Ph	$C_{19}H_{22}N_4S$	238	>1000	15.2±2.0	13.4±2.8
9b	2-MeOPh	$C_{20}H_{24}N_4OS$	250	ND	1.7±0.4	2.9±1.1
9c	2-ClPh	$C_{19}H_{21}N_4SCl$	236	ND	20.7±2.2	80.1±8.4
9d	3-CF_3Ph	$C_{20}H_{21}N_4SF_3$	265	>1000	134.0±15	10.7±3.2

*Values are the means ± S.E.M. of 3–4 indipendent experiments done in triplicate, performed at eight competing ligand concentrations (10^{-5}–10^{-9} M) and [^{3}H]SCH 23390 (D_1), [^{3}H]spiperone (D_2) and [^{3}H]8-OH-DPAT ($5HT_{1A}$).

EXPERIMENTAL

General

A Boetius PHMK apparatus (VEB Analytic, Dresden, Germany) was used to determine melting points, presented here as uncorrected. ^{1}H-NMR (at 200 MHz) and ^{13}C-NMR (at 50 MHz) spectra were recorded on a Gemini 2000 spectrometer (Varian, Palo Alto, CA, USA) with $CDCl_3$ as a solvent, unless otherwise stated, are reported in ppm using tetramethylsilane as the internal standard. The IR spectra were run on a Perkin Elmer 457 Grating FT Infrared Spectrophotometer (Perkin Elmer, Beaconsfield, UK). The mass spectra were determined by a Finnigan Mat 8230 mass spe-

ctrometer (Finnigan, Bremen, Germany). For analytical thin-layer chromatography Merck (Darmstadt, Germany) F-256 plastic-backed thin-layer silica gel plates were used. Chromatographic purifications were performed on Merck-60 silica gel columns, 230–400 mesh ASTM, under medium pressure (dry column flash chromatography). All reagents and solvents used in this work were obtained from Aldrich and were used without further purification. Solutions were routinely dried over anhydrous Na_2SO_4 prior to evaporation.

Chemistry

4-(2-Chloroethyl)-2-Halo-6-nitrophenylamines (**5.1** and **5.2**), 1,3-dihydro-5-[2-(4-phenylpiperazin-1-yl)ethyl]-2*H*-benzimidazole-2-thione **9a** and 5-[2-(4-arylpiperazin-1-yl)ethyl]-1,3-dihydro-2*H*--benzimidazole-2-thiones (**9b**–**c**) were prepared as previously described.[11,19,20]

General procedure for the synthesis of 4-[2-(4-arylpiperazin-1-yl)ethyl]2-halo-6-nitro-anilines ***7.1a–d – 7.2a–d***

To a solution of 10.0 mmol of either arylpiperazine in 50.0 ml DMF, 12.0 mmol of 4-(2-chloroethyl)-2-halo-nitroaniline (**5.1** or **5.2**), 6.0 g K_2CO_3 and 0.1 g of KI were added. The mixture was stirred at 80 °C for 12 h. After cooling, the precipitate was removed and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and obtained products purified by MPLC using CH_2Cl_2 as the eluent.

2-Chloro-6-nitro-4-[2-(4-phenylpiperazin-1-yl)ethyl]aniline (**7.1a**): Yield: 69 %; m.p. 104 °C; ^{1}H NMR: δ 2.57 – 2.80 (*m*, 8H), 3.20 – 3.25 (*m*, 4H), 6.45 (*s*, 2H, NH_2), 6.87 – 6.97 (*m*, 3H, ArH), 7.22 – 7.32 (*m*, 2H, ArH), 7.45 (*d*, 1H, J = 2.2 Hz, ArH), 7.97 (*d*, 1H, J = 2 Hz, ArH).

2-Bromo-6-nitro-4-[2-(4-phenylpiperazin-1-yl)ethyl]aniline (**7.2a**): Yield: 72 %; m.p. 110 °C; ^{1}H NMR: δ 2.57 – 2.80 (*m*, 8H), 3.20 – 3.25 (*m*, 4H), 6.51 (*s*, 2H, NH_2), 6.83 – 6.96 (*m*, 3H, ArH), 7.24 – 7.32 (*m*, 2H, ArH), 7.62 (*d*, 1H, J = 2 Hz, ArH), 8.01 (*d*, 1H, J = 2 Hz, ArH).

2-Chloro-4-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-6-nitroaniline (**7.1b**): Yield: 76 %; m.p. 97 °C; ^{1}H NMR: δ 2.59 – 2.81 (*m*, 8H), 3.10 – 3.21 (*m*, 4H), 3.87 (*s*, 3H, OCH_3), 6.45 (*s*, 2H, NH_2), 6.85 – 7.02 (*m*, 4H, ArH), 7.45 (*d*, 1H, J = 2 Hz, ArH), 7.97 (*d*, 1H, J = 2 Hz, ArH).

2-Bromo-4-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-6-nitroaniline (**7.2b**): Yield: 67 %; m.p. 95 °C; ^{1}H NMR: δ 2.58 – 2.79 (*m*, 8H), 3.12 (*s*, 4H), 3.87 (*s*, 3H, OCH_3), 6.51 (*s*, 2H, NH_2), 6.85 – 7.02 (*m*, 4H, ArH), 7.61 (*d*, 1H, J = 2 Hz, ArH), 8.00 (*d*, 1H, J = 2 Hz, ArH).

2-Chloro-4-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-6-nitroaniline (**71.c**): Yield: 79 %; m.p. 98 °C; ^{1}H NMR: δ 2.60 – 2.81 (*m*, 8H), 3.09 – 3.13 (*m*, 4H), 6.46 (*s*, 2H, NH_2), 6.93 – 7.09 (*m*, 2H, ArH), 7.19 – 7.27 (*m*, 1H, ArH), 7.36 (*dd*, 1H, J = 4 Hz, J = 2 Hz, ArH), 7.46 (*d*, 1H, J = 2 Hz, ArH), 7.98 (*d*, 1H, J = 2 Hz, ArH).

2-Bromo-4-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-6-nitroaniline (**7.2c**): Yield: 76 %; m.p. 128 °C; ^{1}H NMR: δ 2.60 – 2.80 (*m*, 8H), 3.08 – 3.13 (*m*, 4H), 6.52 (*s*, 2H, NH_2), 6.94 – 7.09 (*m*, 2H, ArH), 7.19 – 7.23 (*m*, 1H, ArH), 7.36 (*dd*, 1H, J = 6.2 Hz, J = 1.8 Hz, ArH), 7.62 (*d*, 1H, J = 2 Hz, ArH), 8.02 (*d*, 1H, J = 2 Hz, ArH).

2-Chloro-6-nitro-4-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)aniline (**7.1d**): Yield: 59 %; oil; ^{1}H NMR: δ 2.58 – 2.78 (*m*, 8H), 3.23 – 3.28 (*m*, 4H), 6.44 (*s*, 2H, NH_2), 7.08 – 7.21 (*m*, 3H, ArH), 7.42 (*t*, 1H, J = 8 Hz, ArH), 7.59 (*d*, 1H, J = 2 Hz, ArH), 7.97 (*d*, 1H, J = 2 Hz, ArH).

2-Bromo-6-nitro-4-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)aniline (**7.2d**): Yield: 64 %; oil; ^{1}H NMR: δ 2.58 – 2.71 (*m*, 8H), 3.24 – 3.29 (*m*, 4H), 6.52 (*s*, 2H, NH_2), 7.05 – 7.39 (*m*, 4H, ArH), 7.62 (*d*, 1H, J = 2 Hz, ArH), 8.04 (*d*, 1H, J = 2 Hz, ArH).

General procedure for the synthesis of 2-amino-5-[2-(4-arylpiperazin-1-yl)ethyl]3-halo-phenylamines ***8.1a–d – 8.2a–d***

Raney-Ni (0.06–0.08 g) was added in small portions to a stirred solution of 2 mmol of nitro compound (**7.1a–d–7.2a–d**) in 5 ml EtOH, 10 ml 1,2-dichloroethane and 0.9 ml hydrazine hydrate

at 30 °C. After the addition of Ra-Ni was completed, the mixture was heated in a water bath (50 °C, 60 min) and filtered through celite. The filtrate was evaporated *in vacuo* and crude products were used for further syntheses.

*Synthesis of 6-[2-(4-arylpiperazin-1-yl)ethyl]-4-chloro-1,3-dihydro-2*H*-benzimidazole-2-thiones (**9.1a–d**) and 6-[2-(4-arylpiperazin-1-yl)ethyl]-4-bromo-1,3-dihydro-2*H*-benzimidazole-2-thiones (**9.2a–d**)*

Carbon disulfide (0.24 ml, 4 mmol) and KOH (0.25 g in 0.6 ml water) were added to 2 mmol of diamine (**8.1a–d – 8.2a–d**) in 10 ml EtOH. After refluxing for 3 h, 0.3 ml of acetic acid in 3.3 ml water were added. The solvent was removed *in vacuo* and the residue chromatographed on silica gel.

*4-Chloro-1,3-dihydro-6-[2-(4-phenylpiperazin-1-yl)ethyl]-2*H*-benzimidazole-2-thione* (**9.1a**): Yield: 69 %; m.p. 247 °C; IR (cm^{-1}): 692, 1201, 1345, 1490, 1602, 2825; ^{1}H NMR (d_6DMSO): δ 2.65 (*s*, 6H), 2.84 (*t*, 2H, J = 8 Hz), 3.15 (*s*, 4H), 6.78 (*t*, 1H, J = 7.2 Hz, ArH), 6.92 – 7.00 (*m*, 3H, ArH), 7.12 (*s*, 1H, ArH), 7.17 – 7.25 (*m*, 2H, ArH), 12.75 (*s*, 1H, NH), 12.97 (*s*, 1H, NH). ^{13}C NMR (d_6DMSO): δ 32.31 (CH_2), 48.36 ($2CH_2$), 52.83 ($2CH_2$), 59.82 (CH_2), 108.48 (CH), 113.22 (C-Cl), 115.53 (2CH), 118.98 (CH), 122.78 (CH), 128.64 (C), 129.14 (2CH), 133.85 (C), 136.75 (C), 151.29 (C-N), 169.48 (C=S). MS: *m*/*e* (100) 372.0 (M+). $C_{19}H_{21}ClN_4S$.

*4-Bromo-1,3-dihydro-6-[2-(4-phenylpiperazin-1-yl)ethyl]-2*H*-benzimidazole-2-thione* (**9.2a**): Yield: 73 %; m.p. 259 °C; IR (cm^{-1}): 758, 1198, 1344, 1486, 1601, 2827, 2946, 3427; ^{1}H NMR (d_6DMSO): δ 2.55 – 2.59 (*m*, 6H), 2.81 (*t*, 2H, J = 7.8 Hz), 3.09 – 3.14 (*s*, 4H), 6.77 (*t*, 1H, J = 7.2 Hz, ArH), 6.91 – 6.95 (*m*, 2H, ArH), 7.02 (*s*, 1H, ArH), 7.17 – 7.25 (*m*, 3H, ArH), 12.79 (*s*, 2H, NH). ^{13}C NMR (d_6DMSO): δ 32.18 (CH_2), 48.31 ($2CH_2$), 52.79 ($2CH_2$), 59.78 (CH_2), 100.86 (C-Br), 108.89 (CH), 115.54 (2CH), 118.99 (CH), 125.73 (CH), 129.14 (2CH), 130.35 (C), 133.49 (C), 137.02 (C), 151.26 (C-N), 169.43 (C=S). MS: *m*/*e* (100) 415.9 (M–1). $C_{19}H_{21}BrN_4S$.

*4-Chloro-1,3-dihydro-6-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-2*H*-benzimidazole-2-thione* (**9.1b**): Yield: 75 %; m.p. 246 °C; IR (cm^{-1}): 650, 758, 1240, 1307, 1347, 1496, 2827; ^{1}H NMR (d_6DMSO): δ 2.63 (*s*, 6H), 2.82 (*t*, 2H, J = 7.8 Hz), 2.97 (*s*, 4H), 3.77 (*s*, 3H, OCH_3), 6.88 – 6.96 (*m*, 4H, ArH), 7.00 (*d*, 1H, J = 1 Hz, ArH), 7.10 (*d*, 1H, J = 1 Hz, ArH), 12.74 (*s*, 1H, NH), 12.94 (*s*, 1H, NH). ^{13}C NMR (d_6DMSO): δ 31.99 (CH_2), 49.97 (CH_3), 52.95 ($2CH_2$), 55.49 ($2CH_2$), 59.66 (CH_2), 108.54 (CH), 112.09 (CH), 113.22 (C-Cl), 118.22 (CH), 121.03 (CH), 122.63 (CH), 125.76 (CH), 128.59 (C), 133.80 (C), 136.53 (C), 141.32 (C-O), 152.17 (C-N), 169.47 (C=S). MS: *m*/*e* (100) 402.2 (M^+). $C_{20}H_{23}ClN_4OS$.

*4-Bromo-1,3-dihydro-6-{2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl}-2*H*-benzimida-zole-2-thione* (**9.2b**): Yield: 68 %; m.p. 236 °C; IR (cm^{-1}): 758, 1196, 1240, 1344, 1495, 1603, 2823, 3434; ^{1}H NMR (d_6DMSO): δ 2.66 (*s*, 6H), 2.83 (*t*, 2H, J = 7.8 Hz), 2.98 (*s*, 4H), 3.77 (*s*, 3H, OCH_3), 6.88 – 6.93 (*m*, 4H, ArH), 7.02 (*s*, 1H, ArH), 7.23 (*s*, 1H, ArH), 12.76 (*s*, 1H, NH), 12.85 (*s*, 1H, NH). ^{13}C NMR (d_6DMSO): δ 31.90 (CH_2), 49.97 (CH_3), 52.97 ($2CH_2$), 55.50 ($2CH_2$), 59.67 (CH_2), 100.87 (C-Br), 108.98 (CH), 112.09 (CH), 118.16 (CH), 121.05 (CH), 122.69 (CH), 125.73 (CH), 130.39 (C), 133.49 (C), 136.78 (C), 141.30 (C-O), 152.18 (C-N), 169.45 (C=S). MS: *m*/*e* (100) 447.4 (M^+). $C_{20}H_{23}BrN_4OS$.

*4-Chloro-6-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-1,3-dihydro-2*H*-benzimidazole-2-thione* (**9.1c**): Yield: 62 %; m.p. 257 °C; IR (cm^{-1}): 693, 933, 1348, 1485, 2937; ^{1}H NMR (d_6DMSO): δ 2.63 (*s*, 6H), 2.82 (*t*, 2H, J = 8 Hz), 2.98 (*s*, 4H), 6.99 – 7.17 (*m*, 4H, ArH), 7.25 – 7.42 (*m*, 2H, ArH), 12.73 (*s*, 1H, NH), 12.94 (*s*, 1H, NH). ^{13}C NMR (d_6DMSO): δ 32.16 (CH_2), 50.93 ($2CH_2$), 52.90 ($2CH_2$), 59.66 (CH_2), 108.54 (CH), 113.24 (C-Cl), 121.05 (CH), 122.80 (CH), 124.07 (C), 127.81 (CH), 128.30 (CH), 128.59 (C), 130.56 (CH), 133.82 (C), 136.64 (C), 149.20 (C-N), 169.48 (C=S). MS: *m*/*e* (100) 406.0 (M^+). $C_{19}H_{20}Cl_2N_4S$.

*4-Bromo-1,3-dihydro-6-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-2*H*-benzimidazole-2-thione* (**9.2c**): Yield: 72 %; m.p. 254 °C; IR (cm^{-1}): 760, 1191, 1344, 1483, 1603, 2819, 3097; ^{1}H NMR

(d_6DMSO): δ 2.62 (*s*, 6H), 2.81 (*t*, 2H, J = 8 Hz), 2.98 (*s*, 4H), 6.99 – 7.43 (*m*, 6H, ArH), 12.77 (*s*, 2H, NH). ^{13}C NMR (d_6DMSO): δ 32.16 (CH_2), 51.00 ($2CH_2$), 52.93 ($2CH_2$), 59.80 (CH_2), 100.86 (C-Br), 108.96 (CH), 121.05 (CH), 124.05 (C), 125.71 (CH), 127.80 (CH), 128.30 (CH), 130.35 (C), 130.55 (CH), 133.47 (C), 137.04 (C), 149.25 (C-N), 169.48 (C=S). MS: *m*/*e* (100) 451.8 (M^+). $C_{19}H_{20}BrClN_4S$.

*4-Chloro-1,3-dihydro-6-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-2*H*-benzimidazole-2-thione* (**9.1d**): Yield: 68 %; m.p. 239 °C; IR (cm^{-1}): 697, 953, 1123, 1451, 1490, 1611, 2952; ^{1}H NMR (d_6DMSO): δ 2.60 (*s*, 6H), 2.82 (*t*, 2H, J = 7.8 Hz), 3.23 (*s*, 4H), 6.99 – 7.24 (*m*, 5H, ArH), 7.42 (*t*, 1H, J = 8 Hz, ArH), 12.73 (*s*, 1H, NH), 12.95 (*s*, 1H, NH). ^{13}C NMR (d_6DMSO): δ 32.20 (CH_2), 47.69 ($2CH_2$), 52.54 ($2CH_2$), 59.60 (CH_2), 108.56 (CH), 110.97 (CH), 113.22 (C-Cl), 114.80 (CH), 118.90 (CH), 122.80 (CH), 128.59 (C), 129.77 (CH), 130.17 (CH), 130.40 (C), 133.82 (C), 136.62 (C), 151.44 (C-N), 169.47 (C=S). MS: *m*/*e* (100) 440.0 (M^+). $C_{20}H_{20}ClF_3N_4S$.

*4-Bromo-1,3-dihydro-6-(2-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-2*H*-benzimidazole-2-thione* (**9.2d**): Yield: 75 %; m.p. 248 °C; IR (cm^{-1}): 697, 952, 1314, 1348, 1451, 1487, 1607, 2947, 3049; ^{1}H NMR (d_6DMSO): δ 2.53 – 2.58 (*m*, 6H), 2.81 (*t*, 2H, J = 7.8 Hz), 3.20 (*s*, 4H), 7.02 – 7.24 (*m*, 5H, ArH), 7.42 (*t*, 1H, J = 8 Hz, ArH), 12.79 (*s*, 2H, NH). ^{13}C NMR (d_6DMSO): δ 32.22 (CH_2), 47.78 ($2CH_2$), 52.59 ($2CH_2$), 59.75 (CH_2), 100.88 (C-Br), 108.96 (CH), 110.94 (CH), 114.70 (CH), 118.88 (CH), 125.70 (CH), 128.55 (C), 129.77 (CH), 130.15 (C), 130.40 (C), 133.52 (C), 136.98 (C), 151.48 (C-N), 169.43 (C=S). MS: *m*/*e* (100) 484.0 (M–1). $C_{20}H_{20}BrF_3N_4S$.

Membrane preparation, binding assays and data analysis

Specific binding affinities (K_i values, Table I) of the thiones were determined exactly as described previously,[17,21] by measuring the extent of displacement of specific tritiated ligands ([^{3}H]SCH 23390 for D_1, CAS Number [87134–87–0], [^{3}H]spiperone for D_2, CAS Number [749–02–0], and [^{3}H]8-OH-DPAT for $5HT_{1A}$ receptors, CAS Number [80300–08–9]; products of Amersham Buchles GmbH, Germany) to fresh membrane preparations of bovine caudate nuclei and hippocampi. The competitive radioassays were performed in sample triplicates, with a range of concentrations (10^{-5}–10^{-9} M) of the selected compounds. Nonspecific binding was determined with the 1mM (+)-butaclamol (D_1 and D_2) and 10 μM serotonine ($5HT_{1A}$). The retained radioactivity was measured by introducing the dry filters into 5 ml toluene-based scintillation liquid and counting in a 1219 Rackbeta Wallac scintillation counter. Competition binding curves were constructed and analyzed by "GraphPad Prysm" (v. 4.0).

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И З В О Д

6-[2-(4-АРИЛПИПЕРАЗИН-1-ИЛ)ЕТИЛ]-4-ХАЛО-1,3-ДИХИДРО-2*H*-БЕНЗИМИДАЗОЛ-2--ТИОНИ: СИНТЕЗА И ФАРМАКОЛОШКО ИСПИТИВАЊЕ

ДЕАНА АНДРИЋ[1], ГОРДАНА ТОВИЛОВИЋ[2], ГОРАН РОГЛИЋ[1], ВУКИЋ ШОШКИЋ[3,4], МИРКО ТОМИЋ[2] и СЛАЂАНА КОСТИЋ-РАЈАЧИЋ[3]

[1]Хемијски факултет, Универзитет у Београду, Студентски трг 16, 11000 Београд, [2]Одсек за биохемију, Институт за биолошка истраживања "Синиша Станковић", Булевар Деспота Стефана 142, 11060 Београд, [3]Центар за хемију, ИХТМ, Његошева 12, 11000 Београд и [4]Proteosys AG, Carl–Zeiss-Str. 51, 55129 Mainz, Germany

Синтетисано је осам нових једињења код којих је атом халогена уведен у бензимидазол-2-тионску допаминергичку фармакофору 5-[2-(4-арилпиперазин-1-ил)етил]-1,3-дихидро--2*H*-бензимидазол-2-тиона са арилпиперазинским делом молекула изабраним сходно познатим захтевима о односу структуре и реактивности. За сва новосинтетисана једињења је одре-

ђен афинитет везивања за допаминске (D_1 и D_2) и 5-HT_{1A} рецепторе у *in vitro* експериментима компетиције са радиолигандима. Као извор допаминских и 5-HT_{1A} рецептора су коришћене синаптозомалне мембране изоловане из говеђег нуклеуса каудатуса и хипокампуса. Сва новосинтетисана једињења показала су се као јаки компетитори [^{3}H]спиперона и [^{3}H]8-OH-DPAT, од којих најактивнија (**9.1b** и **9.2b**) поседују 34 и 170 пута већи афинитет ка D_2 DA рецепторима од полазних, нехалогенованих једињења. Са друге стране, ова једињења не поседују значајан афинитет ка D_1 допаминским рецепторима.

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