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J. Serb. Chem. Soc. 72 (5) 429–435 (2007)
JSCS–3573

UDC 542.913+547.822:615.214
Original scientific paper

Synthesis and pharmacological evaluation of several *N*-(2-nitrophenyl)piperazine derivatives

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(Received 7 April, revised 15 December 2006)

Abstract: Six newly synthesized heterocyclic (2-nitrophenyl)piperazines, with a specific structure of the heteroaryl group, which mimics the catechol moiety of dopamine (benzimidazoles and substituted benzimidazoles), were evaluated for their binding affinity to rat dopamine (DA), serotonin (5-HT) and α_1 receptors. All compounds with a benzimidazole group had a 5-HT_{2A}/D_2 receptors binding ratio characteristic for atypical neuroleptics (>1, pK_i values). Compound **7c**, 4-bromo-6-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}-1*H*-benzimidazole, expressed higher affinities for all receptor classes than clozapine. Also, it exhibited the best characteristic for atypical neuroleptics and presents a compound with the best profile for further *in vivo* investigations.

Keywords: arylpiperazines, benzimidazoles, dopamine receptors, serotonin receptors, atypical antipsychotic.

INTRODUCTION

One field of intensified research in the area of medicinal chemistry is focused on the design and synthesis of new antipsychotic drugs (APDs) which would express a higher therapeutic efficiency and a wider spectrum of action on schizophrenia symptoms, with minimized extrapyramidal side effects. Conventional APDs, acting by a common mechanism of the blocking of the central dopamine (DA) D_2 receptors, are generally considered to be effective in the treatment of schizophrenics with positive symptoms,[1] while a group of so-called atypical APDs, such as the prototype drug – clozapine, express increased effectiveness in negative affective symptoms, including efficacy in patients resistant to standard therapy.[2] The new genera-

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doi: 10.2298/JSC0705429A

tion of therapeutically successful atypical APDs act as both DA and 5-HT system stabilizers. They express partial agoinst activity at the 5-HT_{1A} receptors and stronger antagonism at the 5-HT_{2A} than at the D_2 receptors, which is also suggested in literature as a suitable model of interactions for some newly synthesized DA/5-HT ligands which are considered for their atypical neuroleptic potential.[2–4] Previous studies on benzimidazole type of dopaminergic/serotonergic ligands[5–7] showed that the affinity and DA/5-HT ratio can be fine tuned by small changes in the structure of the ligand. Following this approach, series of halogenated derivatives of benzimidazoles and benzimidazole-2-thiones, containing (2-nitrophenyl)piperazine moiety, which are expected to have APD-like properties, are presented.

EXPERIMENTAL

General

A Boetius PHMK apparatus (VEB Analytic, Dresden, Germany) was used to determine the melting points (uncorrected). The ^{1}H-NMR spectra were recorded on a Gemini 2000 spectrometer (Varian, Palo Alto, CA, USA), with $CDCl_3$ as the solvent unless otherwise stated and are reported in ppm downfield from the internal standard tetramethylsilane. The IR spectra were run on a Perkin Elmer 457 Grating Infrared Spectrophotometer (Perkin Elmer, Beaconsfield, UK). The mass spectra were determined using a Finnigan Mat 8230 mass spectrometer (Finnigan, Bremen, Germany). High-resolution mass spectra were aquired on a Bruker Biflex MALDI TOF (Bruker, 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 (MPLC). Solutions were routinely dried over anhydrous Na_2SO_4 prior to evaporation.

Chemistry

4-(2-Chloroethyl)-2-nitroaniline (**1a**),[8] 2-chloro-4-(2-chloroethyl)-6-nitroaniline (**1b**)[7]and 2-bromo-4-(2-chloroethyl)-6-nitroaniline (**1c**)[7] were prepared as previously described.

Synthesis of tert-*butyl 2*-[*(*tert-*butoxycarbonyl)amino*]-*4-(2-chloroethyl)phenylcarbamate (**3a**),* tert-*butyl 2*-[(tert-*butoxycarbonyl)amino*]-*3-chloro-5-(2-chloroethyl)phenylcarbamate (**3b**) and* tert-*butyl 2*-[*(*tert-*butoxycarbonyl)amino*]-*3-bromo-5-(2-chloroethyl)phenylcarbamate (**3c**).* Stannous chloride (47.5 g, 0.23 mol) was added to a solution of either 4-(2-chloroethyl)-2-nitroaniline (**1a**) or 2-halo-4-(2-chloroethyl)-6-nitroaniline (**1b,c**) (40 mmol) in absolute ethanol (85 mL). After 4 h at reflux, the solution was poured onto ice, made alkaline with 5 M NaOH and extracted with EtOAc. The extracts were dried and the solvent was removed *in vacuo*. The resulting diamine (**2a, 2b** or **2c**) was immediately used without further purification. The obtained diamine (**2a, 2b** or **2c**) (21 mmol) was dissolved at 0 °C in a mixture of dioxane (65 mL) and 1M NaOH (65 mL). To this solution, di-*tert*-butyl dicarbonate (6.9 g, 31.5 mmol) was added at 0 °C and after 2 h at this temperature, the reaction mixture was stirred overnight at room temperature. The excess solvent was evaporated *in vacuo* and the residue extracted with CH_2Cl_2. The obtained product was purified by MPLC using CH_2Cl_2 as the eluent. (**3a)**: Yield: 60%; oil; ^{1}H NMR: δ 1.51, (*s*, 18H), 3.01 (*t*, 2H, *J* = 7.6 Hz), 3.67 (*t*, 2H, *J* = 7.6 Hz), 6.61 (*s*, 1H, NH), 6.80 (*s*, 1H, NH), 6.96 (*dd*, 1H, *J* = 6.2 Hz, *J* = 2Hz, ArH), 7.35–7.43 (*m*, 2H, ArH). (**3b**): Yield: 88%; m.p. 112 °C; ^{1}H NMR: δ 1.52 (*s*, 18H), 2.93 (*t*, 2H, *J* = 7.4 Hz), 3.65 (*t*, 2H, *J* = 7.4 Hz), 6.24 (*s*, 2H, NH), 6.99 (*d*, 1H, *J* = 2 Hz, ArH), 7.17 (*s*, 1H, ArH). (**3c):** Yield: 96 %; m.p. 121 °C; ^{1}H NMR: δ 1.52 (*s*, 18H), 2.93 (*t*, 2H, *J* = 7.4 Hz), 3.65 (*t*, 2H, *J* = 7.6 Hz), 6.27 (*s*, 2H, NH), 7.14 (*d*, 1H, *J* = 2 Hz, ArH), 7.21 (s, 1H, ArH).

General procedure for the synthesis of tert-*butyl 2*-[(tert-*butoxycarbonyl)amino*]-*4-*{*2*-[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl*}*phenylcarbamate (**4a**) and* tert-*butyl 2*-[*(*tert-*butoxycarbonyl)ami -*

no]-*3-halo-5-{2-*[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}phenylcarbamates* (***4b,c***). To a solution of 10.0 mmol of 1-(2-nitrophenyl)piperazine in 50.0 mL DMF, 12.0 mmol of either *tert*-butyl 2-[(*tert*-butoxycarbonyl)amino]-4-(2-chloroethyl)phenylcarbamate (**3a**) or *tert*-butyl 2-[(*tert*-butoxycarbonyl)amino]-3-halo-5-(2-chloroethyl)phenylcarbamate (**3b,c**), 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 evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the obtained products purified by MPLC using CH_2Cl_2 as the eluent. (**4a)**: Yield: 58 %; oil; ^{1}H NMR: δ 1.52 (*s*, 18H, CH_3), 2.65–2.70 (*m*, 6H); 2.78–2.84 (*m*, 2H); 3.08–3.13 (*m*, 4H); 6.60 (*s*, 1H, NH); 6.76 (*s*, 1H, NH); 6.94–7.18 (*m*, 3H, ArH); 7.32–7.52 (*m*, 3H, ArH); 7.62 (*dd*, *J* = 6.4 Hz, *J* = 1.6 Hz, 1H, ArH). (**4b**): Yield: 72%; oil; ^{1}H NMR: δ 1.52 (*s*, 18H), 2.69–2.72 (*m*, 8H), 3.10–3.14 (*m*, 4H), 6.41 (*s*, 2H, NH), 6.98–7.18 (*m*, 4H, ArH), 7.44–7.53 (*m*, 1H, ArH), 7.77 (*dd*, 1H, *J* = 6.6 Hz, *J* = 1.6 Hz, ArH). (**4c**): Yield: 79%; oil; ^{1}H NMR: δ 1.52 (*s*, 18H), 2.64–2.69 (*m*, 8H), 3.08–3.13 (*m*, 4H), 6.24 (*s*, 2H, NH), 6.98–7.08 (*m*, 2H, ArH), 7.19–7.25 (*m*, 2H, ArH), 7.44–7.52 (*m*, 1H, ArH), 7.77 (*dd,* 1H, *J* = 6.6 Hz, *J* = 1.8 Hz, ArH).

General procedure for the synthesis of 2-amino-4-{2-[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}phenylamine* (***5a***) *and 2-amino-3-halo-5-{2-*[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}phenylamines* (***5b and 5c***)**.** Hydrochloric acid (37%, 10 mL) was added under stirring to a solution of either *tert*-butyl 2-[*(tert*-butoxycarbonyl)amino]-4-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}phenylcarbamate (**4a**) or *tert*-butyl 2-[(*tert*-butoxycarbonyl)amino]-3-halo-5-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}phenylcarbamate (**4b,c**) (5.0 mmol) in 20 ml EtOH at RT. After 60 min, the solvent was evaporated *in vacuo*. The residue was extracted with a mixture of 20 ml 10 % $NaHCO_3$ and 20 mL chloroform, the organic phase was separated, dried over Na_2SO_4, and evaporated *in vacuo*. The obtained products were used without further purification for the synthesis of compounds **6a–c** and **7a–c**.

Synthesis of 5-{2-[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}-1,3-dihydro*-2H-*benzimidazole-2-thione* (***6a***) *and 4-halo-6-{2-*[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}-1,3-dihydro*-2H-*benzimidazole-2-thi ones (**6b,c**).* Carbon disulfide (0.24 mL, 4 mmol) and KOH (0.25 g in 0.6 mL water) were added to 2 mmol of diamine (**5a,b** or **c**) 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 purified by silica gel column chromatography using a 0–5% MeOH gradient in CH_2Cl_2. (**6a):** Yield: 50 %; m.p.: 238–240 °C; IR (cm^{-1}): 1188, 1343, 1461, 1490, 1518, 1603, 2834, 2948, 3069; ^{1}H NMR (DMSO-d_6): δ 2.49–2.56 (*m*, 2H); 2.76–2.83 (*m*, 4H); 2.97–3.01 (*m*, 6H); 6.98–7.16 (*m*, 4H, ArH); 7.32 (*dd*, *J* = 7.2 Hz, *J* = 1 Hz, 1H, ArH); 7.58 (*t, J* = 2.6 Hz, 1H, ArH); 7.78 (*d*, *J* = 6.8 Hz, 1H, ArH); 12.47 (*s*, 2H, NH); MS *m/e* 384.142 (M+1); $C_{19}H_{21}N_5O_2S$. (**6b)**: Yield: 87 %; m.p. 249 °C; IR (cm^{-1}): 1196, 1348, 1488, 1515, 1607, 2829, 3446; ^{1}H NMR (DMSO-d_6): δ 2.50–2.56 (*m*, 6H), 2.80 (*t*, 2H, *J* = 8 Hz), 2.99 (*s*, 4H), 6.98 (*d*, 1H, *J* = 1.2 Hz, ArH), 7.09–7.16 (*m*, 2H, ArH), 7.29–7.33 (*m*, 1H, ArH), 7.58 (*t*, 1H, *J* = 7 Hz, ArH), 7.79 (*dd*, 1H, *J* = 8.6 Hz, *J* = 1.4 Hz, ArH), 12.82 (*s*, 2H, NH); MS: *m/e* 370.1 (100), 417.1 (M^+); $C_{19}H_{20}ClN_5O_2S$. (**6c**): Yield: 69 %; m.p. 256 °C; IR (cm^{-1}): 1196, 1343, 1485, 1518, 1604, 2826, 3035; ^{1}H NMR (DMSO-d_6): δ 2.49–2.56 (*m*, 6H), 2.80 (*t*, 2H, *J* = 7.8 Hz), 2.99 (*s*, 4H), 7.01 (*d*, 1H, *J* = 1.2 Hz, ArH), 7.12 (*t*, 1H, *J* = 7 Hz, ArH), 7.23 (*d*, 1H, *J* = 1.2 Hz, ArH), 7.31 (*d*, 1H, *J* = 8 Hz, ArH), 7.56 (*m*, 1H, ArH), 7.79 (*dd*, 1H, *J* = 9 Hz, *J* = 1.8 Hz, ArH), 12.79 (*s*, 2H, NH); MS: *m/e* 462.9 (100) (M+1); $C_{19}H_{20}BrN_5O_2S$.

Synthesis of 5-{2-[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}-1*H-*benzimidazole (**7a)** and 4-halo-6-{2-*[*4-(2-nitrophenyl)piperazin-1-yl*]*ethyl}-1*H-*benzimidazoles (**7b,c**).* 2 mmol of diamine (**5a,b** or **c**) and 0.44 mL (7.3 mmol) of 98% formic acid were heated in an oil bath at 100 °C for 2 h. After cooling to ambient temperature, 15 mL of 10% $NaHCO_3$ were added and the product extracted with CH_2Cl_2. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography using a 0–3% MeOH gradient in CH_2Cl_2. (**7a**): Yield: 88%; oil; IR (cm^{-1}): 1180, 1345, 1518, 1603, 2830, 3089; ^{1}H NMR (DMSO-d_6): δ 2.92–3.00 (*m*, 6H), 2.92–3.00 (*m*, 2H); 3.11 (*t*, 4H, *J* = 5 Hz), 7.00–7.08 (*m*, 1H, ArH), 7.11–7.17 (*m*, 2H, ArH), 7.43–7.52 (*m*, 2H, ArH), 7.60 (*d*, 1H, *J* = 8.4 Hz, ArH), 7.76 (*dd*, 1H, *J* = 1.6 Hz, *J* = 6.6 Hz, ArH), 8.08 (*s*, 1H, CH), 12.30 (*s*, 1H, NH); MS:

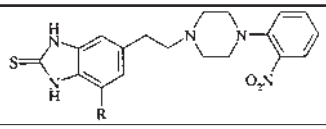
m/e 352 (100) (M+1); $C_{19}H_{21}N_5O_2$. (**7b**): Yield: 85 %; m.p. 86 °C; IR (cm^{-1}): 1345, 1519, 1604, 2833, 3432; ^{1}H NMR (DMSO-d_6): δ 2.82 (*s*, 6H), 2.93 (*s*, 2H), 3.10 (*s*, 4H), 7.12–7.20 (*m*, 2H, ArH), 7.33–7.42 (*m*, 2H, ArH), 7.57–7.65 (*m*, 1H, ArH), 7.82 (*dd*, 1H, J = 6.4 Hz, J = 1.6 Hz, ArH), 8.26 (*s*, 1H, CH), 12.75 (*s*, 1H, NH); MS: *m/e* 385.0 (100) (M^+); $C_{19}H_{20}ClN_5O_2$. (**7c**): Yield: 98 %; m.p. 82 °C; IR (cm^{-1}): 1197, 1345, 1486, 1518, 1603, 2825, 3094; ^{1}H NMR (DMSO-d_6): δ 2.58–2.65 (*m*, 6H), 2.87 (*t*, 2H, J = 8 Hz), 3.00 (*s*, 4H), 7.08–7.16 (*m*, 1H, ArH), 7.29–7.33 (*m*, 2H, ArH), 7.43 (*s*, 1H, ArH), 7.54–7.63 (*m*, 1H, ArH), 7.78 (*dd*, 1H, J = 6.8 Hz, J = 1.4 Hz, ArH), 8.24 (*s*, 1H, CH), 12.82 (*s*, 1H, NH); MS: *m/e* 430.9 (100) (M+1); $C_{19}H_{20}BrN_5O_2$.

Membrane preparation, binding assays and data analysis

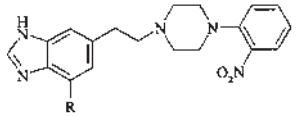
Specific binding affinities (pK_i, values, Table I) of several newly synthesized (2-nitrophenyl)piperazines and clozapine were determined exactly as described previously[9] by measuring the extent of displacement of ^{3}H-labelled specific ligands purchased from Amersham Buchles GmbH ([^{3}H]spiperone for D_2, [^{3}H]8-OH-DPAT for $5HT_{1A}$, [^{3}H]ketanserin for $5HT_{2A}$ and [^{3}H]prazosine for α_1 receptors) from rat striatal or cortical synaptosomes with a range of concentrations (10^{-5}–10^{-9} M) of the selected compound. Non-specific binding was measured in the presence of (+)-butaclamol (D_2), serotonine ($5HT_{1A}$), ketanserin ($5HT_{2A}$) and prazosine (α_1). The retained radioactivity was measured by introducing dry filters and 5 mL toluene-based scintillation liquid and counted in a 1219 Rackbeta Wallac scintillation counter.

Competition binding curves were constructed and analyzed by "GraphPad Prysm" (v. 4.0.).

TABLE I. Chemical structure and pK_i values of the ligands

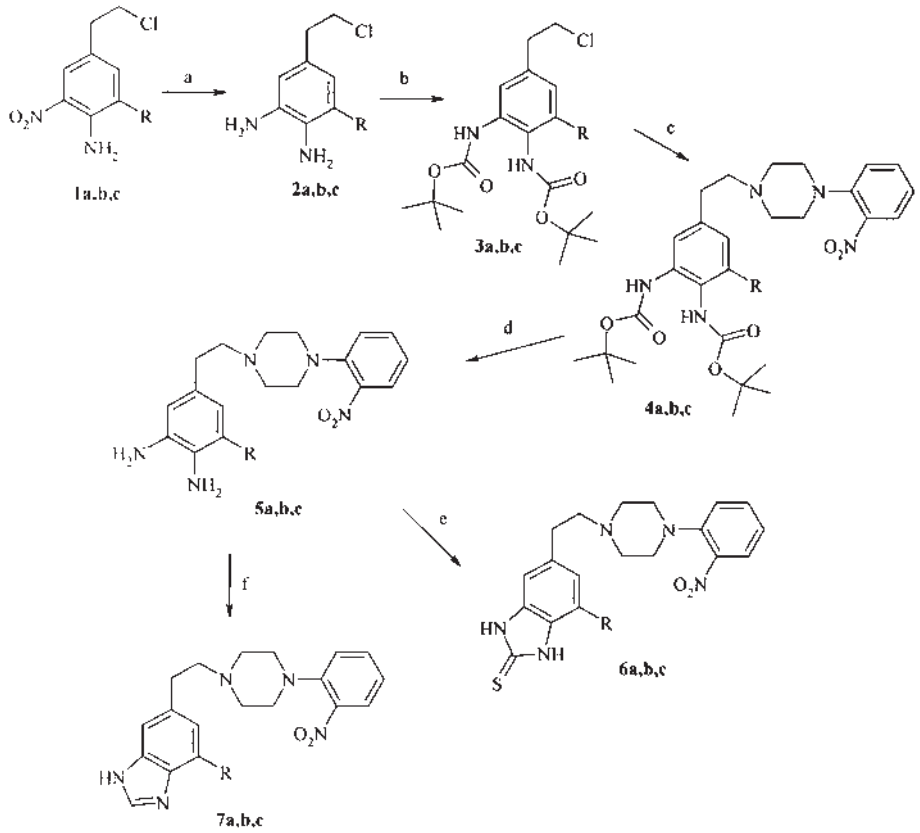


No	R	pK_i ± SEM				$5HT_{2A}/D_2$ binding ratio
		D_2	$5HT_{1A}$	$5HT_{2A}$	α_1	
6a	H	7.55±0.20	6.76±0.18	7.09±0.06	7.45±0.11	0.94
6b	Cl	7.08±0.05	6.74±0.08	6.83±0.05	7.23±0.07	0.97
6c	Br	6.94±0.09	6.68±0.05	6.84±0.11	7.64±0.09	0.99



No	R	pK_i ± SEM				$5HT_{2A}/D_2$ binding ratio
		D_2	$5HT_{1A}$	$5HT_{2A}$	α_1	
7a	H	7.71±0.05	6.37±0.14	7.79±0.10	7.94±0.06	1.01
7b	Cl	7.38±0.08	6.50±0.06	7.60±0.06	7.71±0.11	1.03
7c	Br	7.02±0.05	6.81±0.08	8.00±0.02	8.01±0.10	1.14
Clozapine		6.83±0.10	5.93±0.08	7.88±0.12	7.66±0.10	1.15

Values are the means of 3–4 independent experiments done in duplicate performed at five competing ligand concentrations (10^{-5}–10^{-9} M) with [^{3}H]spiperone (D_2), [^{3}H]8-OH-DPAT ($5HT_{1A}$), [^{3}H]ketanserin ($5HT_{2A}$) or [^{3}H]prazosine (α_1).



In all compounds labeled as **No. a.** the R substituent is H, in compounds labeled as **No. b.** the R substituent is Cl and in compounds labeled as **No. c.** the R substituent is Br.
a) $SnCl_2$, EtOH; b) 1M NaOH, $O(CO_2C(CH_3)_3)_2$; c) DMF, KI, K_2CO_3, 1-(2-nitrophenyl)piperazine; d) EtOH, 4M HCl, 60 °C; e) EtOH, KOH, CS_2; f) formic acid.

Scheme 1. Pathways for the synthesis of the ligands.

RESULTS AND DISCUSSION

Several new 5-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}-1,3-dihydro-2*H*-benzimidazole-2-thiones and 5-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}-1*H*-benzimidazoles (compounds **6a–c** and **7a–c**, respectively) were synthesized as shown in Scheme 1. In short, 4-(2-chloroethyl)-2-nitroaniline (**1a**) or 4-(2-chloroethyl)-2-halo-6-nitroaniline (**1b,c**) were reduced with stannous chloride in absolute ethanol, and the resulting diamines **2a–c** were converted into di-tBOC derivatives **3a–c**, using di-*tert*-butyl dicarbonate. The compounds readily alkylated 1-(2-nitrophenyl)piperazine in the presence of potassium carbonate and potassium iodide in DMF. Diamines **5a–c** were obtained by hydrolyzing the di-tBOC derivatives with 4M HCl in ethanol. Benzimidazole-2-thiones **6a–c** and benzimidazoles **7a–c** were synthesized from the corresponding diamines with CS_2/KOH in EtOH and formic acid, respectively.

The binding affinities were evaluated by specific *in vitro* assays for the DA (D_2), 5-HT (5-HT_{1A} and 5-HT_{2A}) and α_1-adrenergic receptors. These receptors were chosen in accordance to the serotonin–dopamine hypothesis of schizophrenia and with regards to their anticipated roles in the action of atypical APDs.[3,4] The significance of ligand interaction with adrenergic receptors was also suggested, as their blockage may stabilize dysregulated central dopaminergic systems in schizophrenia.[10] Specific binding affinities (pK_i values, Table I) of the newly synthesized compounds and clozapine, the prototype of atypical APD, were determined by measuring the extent of displacement of ^{3}H-labelled specific ligands from rat striatal or cortical synaptosomes with a range of concentrations of the compounds.[9,11]

In previous studies on ligand–D_2 dopamine receptor interactions, it was noticed that the binding affinity depends substantially on the structure of the arylpiperazine part of molecule.[6] In addition to general structural requirements, it was clearly shown that substituents able to participate in hydrogen bond formation (nitro or methoxy) in position 2 of the phenyl ring in the piperazine part of a ligand forming one more hydrogen bond, with Trp 182 (VI.48) (an amino acid highly conserved through the A class of the G protein-coupled receptor family), increase the binding affinities.[5] Additionally, a study of the effects of halogens on the electron density of the benzimidazole benzene ring raised the hypothesis that electron-withdrawing substituents have a strong influence on the electrostatic surface potential of a ligand, which is an important factor in the interaction with the receptors binding pocket.[7] Our leading idea was to combine those two effects by the synthesis of halogenated (2-nitrophenyl)piperazines and to compare their binding affinities with the parent, non-substituted (2-nitrophenyl)piperazines.

All compounds (parent, benzimidazole-2-thione and benzimidazole, and halogen substituted ligands) expressed a higher affinity for the D_2 and $5HT_{1A}$ receptors comparing to clozapine, while only benzimidazole series of the compounds showed increased affinity for the α_1-adrenergic receptor. Binding potency towards $5HT_{2A}$ receptors, similar to clozapine, were expressed only by (2-nitrophenyl)piperazines with the benzimidazole moiety, where compound **7c** showed a somewhat higher affinity for the $5HT_{2A}$ receptors than clozapine [pK_i (K_i) values of 8 (10 nM) and 7.88 (13.2 nM), respectively].

The results of the investigations justify our hypothesis that the introduction of a halogen atom in the heterocyclic, benzimidazole-like, part of the (2-nitrophenyl)piperazine molecule would result in a higher affinity for D_2 DAR. On the other hand, the benzimidazole series of the ligands showed a binding potency towards $5HT_{2A}$ receptors similar to that of clozapine and all of them showed a $5HT_{2A}/D_2$ binding ratio characteristic for atypical APDs (>1, pK_i values). Only in the case of compound **7c** the introduction of the halogen atom result in an increase of the selectivity towards $5HT_{2A}$ receptors.

Taking all this into account, 4-bromo-6-{2-[4-(2-nitrophenyl)piperazin-1-yl]ethyl}-1*H*-benzimidazole (**7c**) exhibited the most suitable $5HT_{2A}/D_2$ binding ratio (1.14, pK_i value) and showed all prerogatives characteristic for atypical neuroleptics and suggests this compound to be a good pretender for further *in vivo* testing.

Acknowledgments: This work was supported by the Ministry of Science, and Environmental Protection of Serbia, grants #142009 and #143032.

ИЗВОД

СИНТЕЗА И ФАРМАКОЛОШКО ИСПИТИВАЊЕ НОВИХ ДЕРИВАТА *N*-(2-НИТРОФЕНИЛ)ПИПЕРАЗИНА

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Синтетисано је шест хетероцикличних (2-нитрофенил)пиперазина са специфичном хетероарил групом, која подражава катехолску групу допамина (бензимидазоли и супституисани бензимидазоли), и испитан је њихов афинитет ка допаминским, серотонинским и α_1 рецепторима. Сва једињења са бензимидазолским групама су показала $5\text{-}HT_{1A}/D_2$ однос везивања карактеристичан за атипичне неуролептике (>1, pK_i вредности). Једињење **7c**, 4-бромо-6-{2-[4-(2-нитрофенил)пиперазин-1-ил]етил}-1*H*-бензимидазол, показало је израженији афинитет ка свим класама рецептора у поређењу са клозапином и такође представља једињење са најбољим карактеристикама за даља *in vivo* истраживања.

(Примљено 7. априла, ревидирано 15. децембра 2006)

REFERENCES

1. F.-A. Wiesel, *Br. J. Psychiat.* **164** (1994) 65
2. J. J. Sramek, N. R. Cutler, N. M. Kurtz, M. F. Murphy, A. Carta, in *Optimizing the Development of Antipsychotic Drugs*. J. J. Sramek, Ed., Wiley, Chichester, 1997, p. 7
3. H. Y. Meltzer, Y. Li, Y. Kaneda, J. Ichikawa, *Prog. Neuropsychopharmacol.* **27** (2003) 1159
4. A. R. Bantick, J. F. Deakin, P. M. Grasby, *J. Psychopharmacol.* **15** (2001) 37
5. V. Šukalović, M. Zlatović, D. Andrić, G. Roglić, S. Kostić-Rajačić. V. Šoškić, *Arch. Pharm. Pharm. Med. Chem.* **337** (2004) 502
6. V. Šukalović, M. Zlatović, D. Andrić, G. Roglić, S. Kostić-Rajačić, V. Šoškić, *Arzneim. Forsch./Drug. Res.* **55** (2005) 145
7. V. Šukalović, D. Andrić, G. Roglić, S. Kostić-Rajačić, V. Šoškić, *Arch. Pharm. Pharm. Med. Chem.* **337** (2004) 376
8. V. Šoškić, S. Dukić, D. Dragović, J. Joksimović, *Arzneim.-Forsch./Drug Res.* **46** (1996) 741
9. M. Tomić, M. Kundaković, B. Butorović, V. Vasilev, D. Dragović, G. Roglić, Đ. Ignjatović, V. Šoškić, S. Kostić-Rajačić, *Pharmazie* **58** (2003) 677
10. T. H. Swensson, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **27** (2003) 1145
11. G. H. Vogel, W. H. Vogel, Eds., *Drug Duscovery and Evaluation*, Springer-Verlag, Berlin, Heidelberg, 1997, p. 269.