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

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*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 $\alpha_1$ receptors. All compounds with a benzimidazole group had a 5-$HT_{2A}$/$D_2$ receptors binding ratio characteristic for atypical neuroleptics (>1, p$K_i$ 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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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: $\delta$ 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: $\delta$ 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: $\delta$ 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: $\delta$ 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: $\delta$ 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: $\delta$ 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-$d_6$): $\delta$ 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-$d_6$): $\delta$ 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-$d_6$): $\delta$ 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-$d_6$): $\delta$ 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:

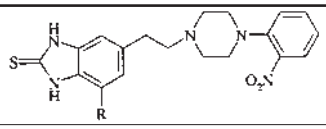
*m/e* 352 (100) (M+1); $C_{19}H_{21}N_5O_2$. (**7b**): Yield: 85 %; m.p. 86 °C; IR ($cm^{-1}$): 1345, 1519, 1604, 2833, 3432; $^1$H NMR (DMSO-$d_6$): $\delta$ 2.82 (*s*, 6H), 2.93 (*s*, 2H), 3.10 (*s*, 4H), 7.12–7.20 (*m*, 2H, ArH), 7.33–7.42 (*m*, 2H, ArH), 7.57–7.65 (*m*, 1H, ArH), 7.82 (*dd*, 1H, $J$ = 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-$d_6$): $\delta$ 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*

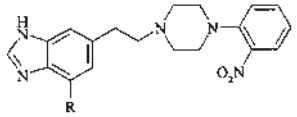
Specific binding affinities ($pK_i$, values, Table I) of several newly synthesized (2-nitrophenyl)piperazines and clozapine were determined exactly as described previously[9] by measuring the extent of displacement of $^3$H-labelled specific ligands purchased from Amersham Buchles GmbH ([$^3$H]spiperone for $D_2$, [$^3$H]8-OH-DPAT for $5HT_{1A}$, [$^3$H]ketanserin for $5HT_{2A}$ and [$^3$H]prazosine for $\alpha_1$ 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 ($\alpha_1$). 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

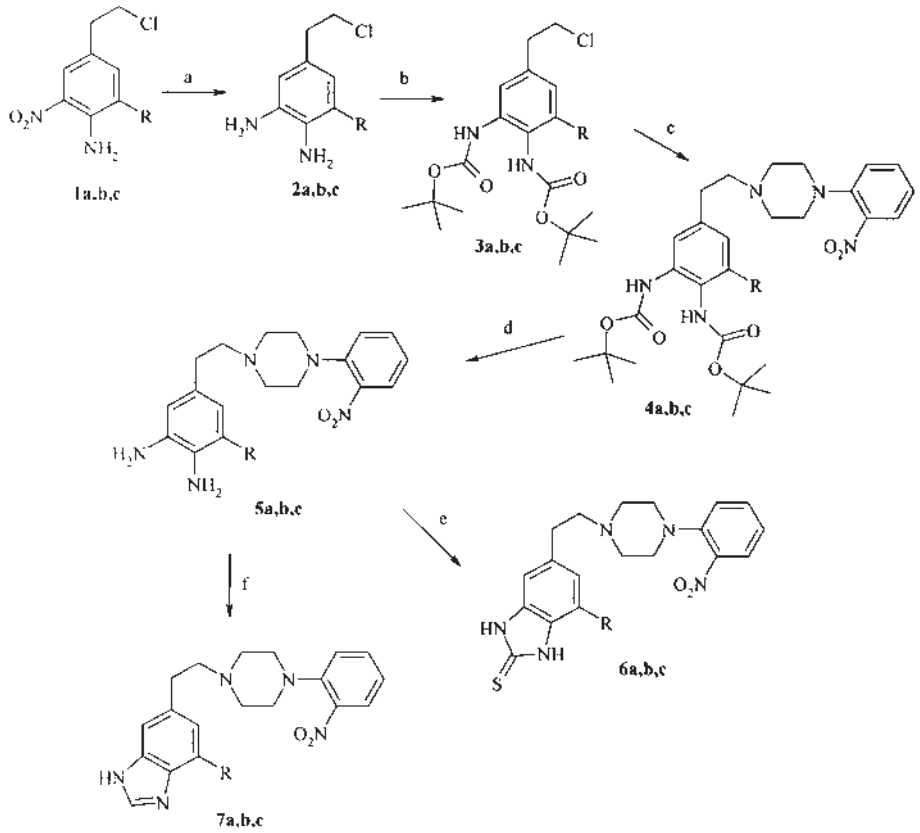


| No | R | $pK_i$ ± SEM | | | | $5HT_{2A}/D_2$ binding ratio |
|---|---|---|---|---|---|---|
| | | $D_2$ | $5HT_{1A}$ | $5HT_{2A}$ | $\alpha_1$ | |
| **6a** | H | 7.55±0.20 | 6.76±0.18 | 7.09±0.06 | 7.45±0.11 | 0.94 |
| **6b** | Cl | 7.08±0.05 | 6.74±0.08 | 6.83±0.05 | 7.23±0.07 | 0.97 |
| **6c** | Br | 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 |
|---|---|---|---|---|---|---|
| | | $D_2$ | $5HT_{1A}$ | $5HT_{2A}$ | $\alpha_1$ | |
| **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 ($\alpha_1$).




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 $\alpha_1$-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 $\alpha_1$-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 [p$K_i$ ($K_i$) 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, p$K_i$ 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, p$K_i$ value) and showed all prerogatives characteristic for atypical neuroleptics and suggests this compound to be a good pretender for further *in vivo* testing.

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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 $\alpha_1$ рецепторима. Сва једињења са бензимидазолским групама су показала $5\text{-}HT_{1A}/D_2$ однос везивања карактеристичан за атипичне неуролептике (>1, p$K_i$ 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.

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