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Two new phenylpiperazines with atypical antipsychotic potential

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Abstract—Two new series of substituted arylpiperazines with heterocyclic 3-propoxy-benzimidazole or 3-propoxy-benzimidazole-2-thione groups were synthesized and their in vitro binding affinities for the D_2, 5-HT_{1A}, 5-HT_{2A}, and α_1-adrenergic receptors determined. Among them, only two compounds with phenyl aryl-constituent (8a and 9a) showed 5-HT_{2A}/D_2 pK_i binding ratios proposed for atypical neuroleptics. As to their behavioral screening on rodents, both compounds exhibited a non-cataleptic action in rats and antagonized D-amphetamine-induced hyperlocomotion in mice, suggesting their possible atypical antipsychotic potency.

Schizophrenia is an overwhelming mental illness for which there is currently no ideal therapy. Classical antipsychotic drugs, exhibiting the mechanism of the central dopamine (DA) D_2 receptors blockade in the limbic forebrain, are useful for the treatment of the positive symptoms, but failed to manage the negative symptoms of schizophrenia.[1] Moreover, antipsychotics with prominent DA D_2 antagonist potency were shown to cause tardive dyskinesia and extrapyramidal side effects (EPS) in humans, presumably by simultaneous blockade of striatal DA receptors.[1,2] Limited efficacy and undesirable side effects of typical antipsychotics have driven the development of improved ''atypical'' antipsychotic agents, like the prototype antipsychotic drug—clozapine, which are in general effective for both positive and negative symptoms of schizophrenia, more efficacious than classical antipsychotics in treatment-refractory patients, and have a low incidence of extrapyramidal side effects.[1,2] A number of current approaches for the development of superior antipsychotic agents involve the mechanisms based on the reduction of the DA neurotransmission with partial D_2 agonists or DA autoreceptor agonists, together with antagonism at the central serotonin 5-HT_{2A} and partial agonism at 5-HT_{1A} receptors.[1–4] The blockade of 5-HT_{2A} receptors has been implicated in both the enhanced efficacy against negative symptoms of schizophrenia and improved EPS profile of the atypical antipsychotics,[3] while the 5-HT_{1A} receptor agonists are believed to attenuate some D_2 receptor-mediated side effects.[4] Thus, new compounds may retain antipsychotic efficacy, while having reduced liability for severe movement disorders often developed upon acute and long-term treatments, and could potentially alleviate certain negative schizophrenia-associated symptoms.[1,2] Additionally, upon modulation of the central 5-HT neurotransmission, these compounds may also exhibit certain anxiolytic and/or antidepressant effects.[1,5]

During the last decade, we have formulated the strategy on drug design and synthesis of mixed DA-/5-HT-ergic heterocyclic arylpiperazines, with different specific structure of heteroaryl-group that mimics catechol moiety of the dopamine,[6,7] and may exhibit atypical neuroleptic potential. In previous papers, we have presented some of the most appealing compounds upon alteration of heterocyclic and aryl groups.[7] Here, we present some selected newly synthesized ligands containing benzimidazole or benzimidazole-2-thione linked by propyloxy bridge to four different arylpiperazines, already characterized by improved interaction with the D_2 receptors.[7] Aryl parts of the ligands were chosen in accordance to their best pharmacological profiles[6–8] and our intention was also to further evaluate the influence of the propyloxy linker of the new ligands (instead of ethyloxy linker

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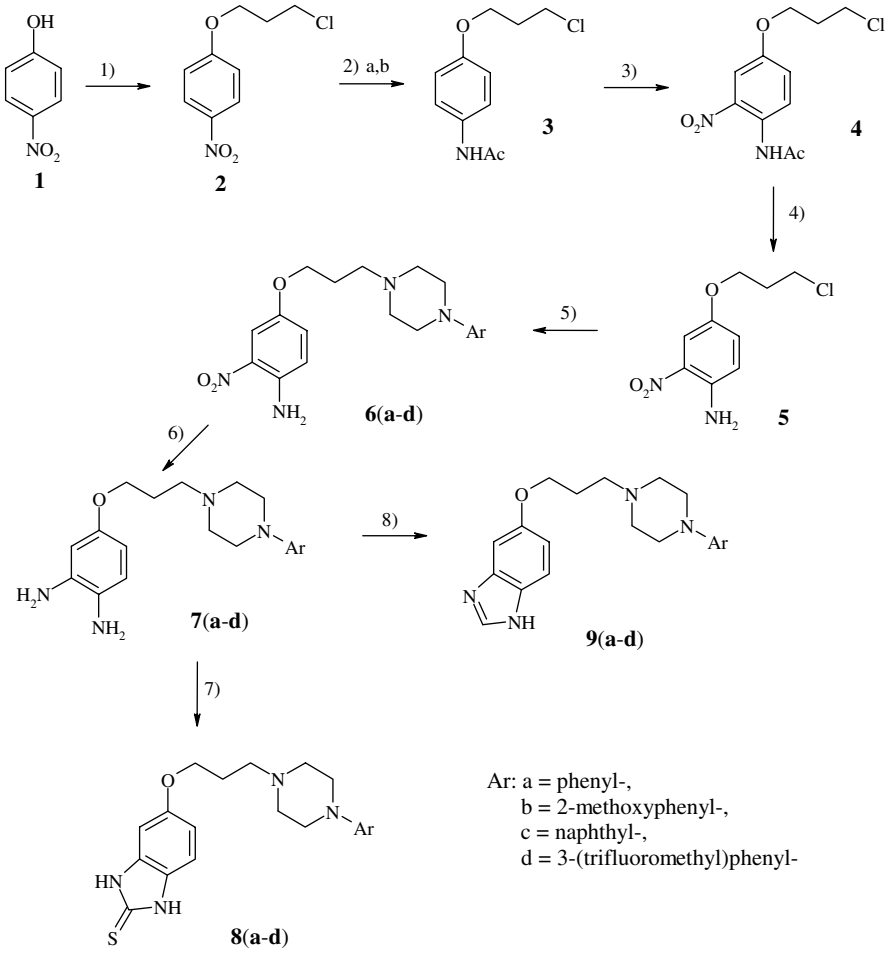
found in our previously synthesized compounds) on the receptor binding profiles.

Synthetic pathways, similar to previously described procedure,[8] of the two sets of ligands, 5-[3-(4-arylpiperazin-1-yl)propoxy]-1,3-dihydro-2*H*-benzimidazole-2-thiones (**8a–d)** and 6-[3-(4-arylpipera-zin-1-yl)propoxy]-1*H*-benzimidazoles (**9a–d)**, submitted to pharmacological exploration in the present study, are shown in Scheme 1. Yield and chemical characterization of the compounds **8a–d** and **9a–d** are given under Notes.[9,10]

Eight new compounds (**8a–d**, **9a–d**) and clozapine were initially evaluated for cytotoxicity by MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) colorimetric assay,[11] performed on the stable transfected CHO hD_2L cell line. Concentrations of the compounds killing 50% of the cells (EC_{50}) were estimated from the curves obtained with a series of ligand concentrations in culture media. The eight new ligands were also evaluated by in vitro assays for binding affinities at the specific DA (D_2), 5-HT (5-HT_{1A}, 5-HT_{2A}), and α_1-adrenergic receptors. These receptors were chosen concerning their anticipated role in the action of atypical antipsychotic drugs.[1–4] Specific binding affinities (pK_i, Table 1) of the new arylpiperazines and clozapine were determined by measuring the extent of displacement of ^{3}H-labeled specific ligands from rat striatal or cortical synaptosomes with a range of concentrations of selected compounds.[7,11] Based on their high pK_i's 5-HT_{2A}/D_2 receptor binding ratio, two of the compounds were selected to be assayed in simple animal behavioral models relevant to atypical antipsychotic activity. These compounds (**8a**, **9a**) were applied to rodents in 2–3 single doses (in the range 1–10 mg/kg bw; ip) and their possible cataleptic effects were evaluated in rats,[12] while their influence on spontaneous locomotion and amphetamine-induced hyperactivity was assessed in mice with an open-field test.[13]

The MTT assay revealed that all compounds had a low cytotoxic potential, mainly weaker than that of clozapine (EC_{50} = 56 μM). Compound **9c** expressed the highest cytotoxicity among the examined ligands (EC_{50} = 43 μM), while the EC_{50} values for the remaining ligands ranged from 139 to 859 μM. Binding affinities of arylpiperazines **8a–d**, **9a–d** for the D_2, 5-HT_{1A}, 5-HT_{2A}, and α_1–adrenergic receptors are listed in Table 1. The binding affinities of these new compounds appeared to be somewhat decreased for D_2 and 5-HT_{1A} receptors,



Scheme 1. Synthetic pathways of the new arylpiperazines. Reagents: (1) $Cl(CH_2)_3Br$, MEK, Na_2CO_3, 93%; (2) a—$SnCl_2$, $(CH_3)_2$ CHOH b—Ac_2O, $(CH_3)_2CHOH$, 94%; (3) Ac_2O, H_2SO_4/HNO_3, 68%; (4) 4 N HCl, 93%; (5) DMF, Na_2CO_3, arylpiperazine, 78–90%; (6) RaNi, N_2H_4; (7) CS_2, KOH; (8) 98% HCO_2H, 4 N HCl.