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Synthesis, structure–activity relationships, and biological evaluation of a series of benzamides as potential multireceptor antipsychotics

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ABSTRACT

In the present study, a series of benzamides, endowed with potent dopamine D_2, serotonin 5-HT_{1A} and 5-HT_{2A} receptors properties, was synthesized and evaluated as potential antipsychotics. Among them, 3-(4-(4-(6-fluorobenzo[*d*]isoxazol-3-yl)-piperidin-1-yl)butoxy)-*N*-methylbenzamide (**21**) and its fluoro-substituted analogue (**22**) held the best pharmacological binding profiles. They not only presented potent activities for D_2, 5-HT_{1A}, and 5-HT_{2A} receptors, but were also endowed with low activities for 5-HT_{2C}, H_1 receptors and hERG channels, suggesting a low propensity of inducing weight gain and QT prolongation. In animal models, compounds **21** and **22** reduced phencyclidine-induced hyperactivity with a high threshold for catalepsy induction. It thus provides potential candidates for further preclinical studies.

Schizophrenia is among the most serious mental illness characterized by the coexistence of positive (e.g., hallucinations and delusions), negative (e.g., social withdrawal, anhedonia and poverty of thought and content of speech), and cognitive (e.g., impaired attention and learning) symptoms.[1] It affects approximately 1% of the world's population and has a considerable social and economic impact.[2]

The first-generation antipsychotics (e.g., chlorpromazine, **1** and haloperidol, **2**, Fig. 1) are dopamine D_2 receptor (D_2R) antagonists. However, their application is limited by the wide range of side effects (e.g., Parkinson-like extrapyramidal symptoms (EPS), prolactin release, weight gain, or even fatal cardiovascular events).[3] The second-generation antipsychotics (e.g., risperidone, **3** and ziprasidone, **4**, Fig. 1) have a broadened receptor-binding profile which results in their unique therapeutic properties for pharmacological treatment of neuropsychiatric disorders[4,5] and they are classified as 'atypical antipsychotics'.

The third-generation antipsychotics (e.g., cariprazine, **5**, aripiprazole, **6** and brexpiprazole, **7**, Fig. 1) are dopaminergic and serotoninergic modulators. Aripiprazole is characterized as a D_2R partial agonist with weak intrinsic activity (IA, 30%), 5-$HT_{2A}R$ antagonist and 5-$HT_{1A}R$ partial agonist according to the literature.[6] Besides, aripiprazole is also a β-arrestin-biased D_2R partial agonist which is well tolerated and does not significantly induce EPS, weight gain, QT prolongation or increase plasma prolactin levels.[6] Brexpiprazole, exhibiting similar pharmacological mechanism to aripiprazole, was also developed by Otsuka and is considered to be a successor of aripiprazole.[7]

Blockade of post-synaptic serotonin receptor subtype 2A (5-HT_{2A}) by atypical antipsychotics in substantia nigra neurons may elevate dopamine's level in axonal terminals. These antipsychotics are therefore able to compensate for the hypoactivity of dopamine in the nigrostriatal dopamine pathways to counteract D_2R-mediated EPS.[8] Likewise, the antagonism of serotonin 5-HT_{2A} receptors (5-$HT_{2A}R$) by atypical antipsychotics in the mesocortical dopamine pathway is responsible for balancing the dopamine activity deficiency and leading to an improvement of negative and cognitive symptoms of schizophrenia.[9,10]

Furthermore, the serotoninergic system plays an important role in the regulation of emotion, cognitive behavior, and working memory. Serotonin 5-HT_{1A} receptors (5-$HT_{1A}R$) are particularly dense in prefrontal cortex, hippocampus, and amygdala region.[11,12] Agonism of the 5-$HT_{1A}R$ increases dopamine release in the frontal cortex, which may reduce negative symptoms and cognitive deficits in patients with schizophrenia.[13] 5-$HT_{1A}R$ agonists and partial agonists have also demonstrated clinical effectiveness in the treatment of anxiety[14] and depression.[15,16] Recent preclinical and

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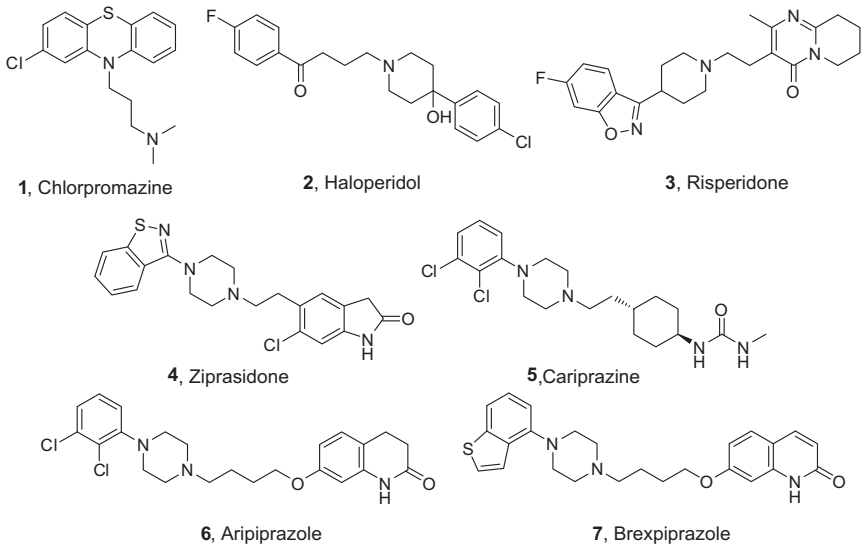
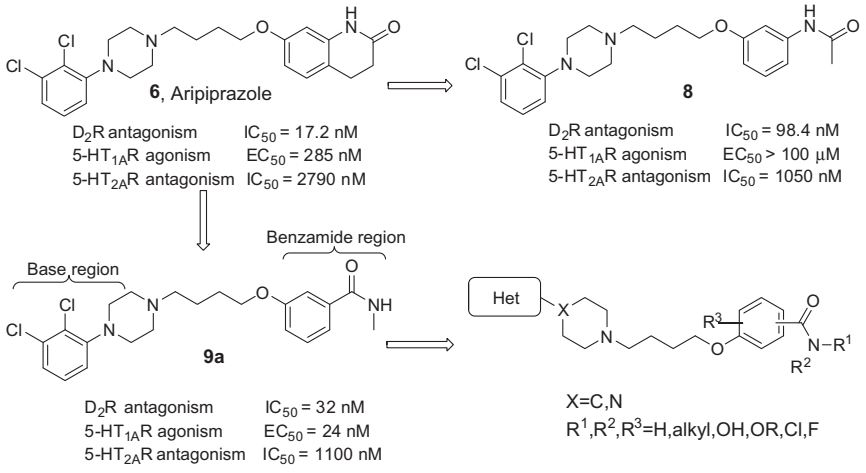


Figure 1. Representative typical and atypical antipsychotics.

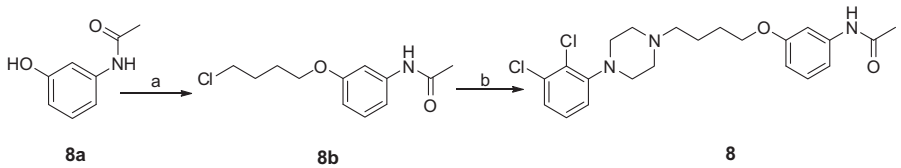
clinical studies also suggest that 5-HT_{1A}R agonists may be useful in treating dementia,[17] Parkinson's disease,[13,18] pain associated with spinal cord injuries,[19] ischemia,[20] and ADHD.[21] Thus, the aim of our work was to develop novel antipsychotics that act on dopaminergic and serotoninergic receptors with potent and balanced activities as well as with low activities for receptors associated with side effects. Our goal was to develop a pharmacological agent that could effectively address the positive symptoms, negative symptoms and cognitive deficits in schizophrenia with minimal side effects.

We selected the arylpiperazine system as a flexible scaffold for achieving a fine balancing of D_2R/5-HT_{2A}R antagonism and 5-HT_{1A}R agonism activities. Taking aripiprazole as a lead, we designed and synthesized compounds **8** and **9a** (Scheme 1). The synthesis route of compound **8** was shown in Scheme 2. Compound **8** exhibited a dramatic decrease in the activity of 5-HT_{1A}R agonism (Scheme 1), while compound **9a** had comparable activity to that of aripiprazole. Therefore, **9a** was selected for further structural optimizations to look for more favorable antipsychotics and also exploit the structural-activity relationships (SAR) especially in the benzamide and base regions.

SAR of the Benzamide Moiety. To investigate the effects of substituents (R^1 and R^2) in the benzamide region, we designed a series of compounds outlined in Figure 2. Compounds **9a**–**9d** with R^1 of



Scheme 1. Discovery of benzamide derivatives as potential multireceptor antipsychotics.



Scheme 2. Reagents and conditions: (a) 1-bromo-4-chlorobutane, K_2CO_3, DMF, rt, 5 h; (b) 1-(2,3-dichlorophenyl)piperazine hydrochloride, K_2CO_3, DMF/H_2O, 95 °C, 5 h.