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Synthesis and biological evaluation of a series of novel pyridinecarboxamides as potential multi-receptor antipsychotic drugs

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ABSTRACT

In previous study, a series of benzamides was identified as potent antipsychotic agents. As a continuation of the program to discover novel antipsychotics, herein we reported the evaluation of a series of pyridinecarboxamide derivatives. The most promising compound **7h** not only held good activities on dopamine D_2, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, but also exhibited low potency for α_{1A}, H_1 and 5-HT_{2C} receptors, indicating a low propensity of side effects like orthostatic hypotension and weight gain. Furthermore, **7h** exhibited more potent antipsychotic-like effect than aripiprazole in behavioral studies. The preliminary results were promising enough for further research around this scaffold.

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Schizophrenia is one of the most common public health issues, influencing about 1% of the world's population.[1] It is a complex psychiatric disorder characterized by impairments in multiple domains, including perception, affect, and cognition. The symptoms of schizophrenia are categorized into positive symptoms (delusions, hallucinations and thought disorder), negative symptoms (alogia, affective flattening, anhedonia, avolition and apathy) and cognitive dysfunction.[2] Typical antipsychotics like chlorpromazine and haloperidol were effective in alleviating positive symptoms through blocking dopamine D_2 receptors in mesolimbic dopamine pathway.[3] Whereas inevitable inhibition of other dopamine pathways leads to some serious adverse effects, such as extrapyramidal symptoms (EPS), tardive dyskinesia (TD)[4] and hyperprolactinemia,[5] which weaken medication adherence of patients. Introduction of clozapine marked the era of atypical antipsychotics (e.g., risperidone, ziprasidone and aripiprazole), which block both serotonin 5-HT_{2A} and dopamine D_2 receptors at clinically effective doses. Consequently, incidence of EPS and TD side effect reduced substantially, and safety profile got greatly improved. However, their effects on negative symptoms and cognitive dysfunction were still far from ideal. Moreover, there were also safety concerns over atypical antipsychotics, with the occurrence of some other adverse effects like weight gain, hyperlipidemia and sexual dysfunction.[6,7] Hence, development of novel antipsychotics as a more effective, side-effect-free therapy is of great significance.

As schizophrenia is a complex psychiatric disorder with many different symptoms, developing multi-target drugs with polypharmacological profile has become an effective approach.[8] Among the receptors involved in atypical antipsychotics, D_2 and 5-HT_{2A} receptors appeared to be the most important, as inhibition of these two receptors was the common feature of all atypical antipsychotics.[9] 5-HT_{2A} receptor antagonistic activity had been suggested to be responsible for reducing EPS. Antagonism of 5-HT_{2A} receptor counteracted the effect of D_2 receptor blockade in striatum, thus decreases the risk of EPS.[10] On the other side, as a widely distributed 5-HT receptor subtype in central nervous system (CNS), 5-HT_{1A} receptor also played an important role in CNS disorders, such as schizophrenia,[11,12] major depressive disorder[13] and anxiety.[14] Beneficial effects of 5-HT_{1A} receptor mainly lay in three aspects. First, partial agonism of 5-HT_{1A} receptor ameliorated positive symptoms.[15] Second, stimulation of 5-HT_{1A} receptor promoted dopamine release in medial prefrontal cortex (mPFC), thus might improve negative symptoms and cognitive impairment.[10,16]

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Last but not least, activation of 5-HT_{1A} receptor could alleviate the EPS side effect of antipsychotics by activating 5-HT_{1A}R located in primary motor cortex and dorsolateral striatum regions.[17–19] Thus, new compounds targeting D_2/5-HT_{1A}/5-HT_{2A} receptors might not only retain antipsychotic efficacy, but also have the potential to alleviate negative symptoms and cognitive dysfunction with fewer side effect. Additionally, upon modulation of the central 5-HT_{1A}R-mediated neurotransmission, these compounds might also exhibit certain anxiolytic and/or antidepressant effects.

In the previous study, our group had reported a class of benzamide derivatives (represented by compounds **1** and **2**, Fig. 1) with potent antipsychotic effects.[20] While further evaluation of compounds **1** and **2** was underway, we sought to identify additional novel, potent and multireceptor antipsychotic candidates. Based on bioisosterism approach, a series of pyridinecarboxamide derivatives with D_2, 5-HT_{1A} and 5-HT_{2A} receptor activities was designed and synthesized. Among compounds synthesized, **7h** with unique pharmacological profile was identified as potential candidate for development of novel antipsychotics.

The synthesis of compounds **7a**–**7i** was depicted in Scheme 1. As shown in Scheme 1, reaction of commercially available 4-hydroxypicolinic acid **3** with methanol in the presence of concentrated sulfuric acid provided ester **4**. Treatment of **4** with 1,4-dibromobutane afforded mono-substituted compound **5**, which then coupled with corresponding arylpiperazine or arylpiperidine in the presence of K_2CO_3 and KI in CH_3CN to give intermediates **6a**–**6e**. Compounds **7a**–**7i** were obtained by aminolysis of **6a**–**6e** with corresponding amine in alcohol in a sealed tube.

Compounds **12a**–**12d**, **17a**–**17d**, **22a**–**22e** could be prepared in a similar fashion as the procedure for synthesizing compounds **7a**–**7i**.

Taking compounds **1** and **2** with excellent receptor activity profiles as lead compounds, we synthesized compounds **7a** and **7d** at the beginning of our work (Table 1). Compared with compound **1**, **7a** exhibited higher potency for 5-HT_{1A} receptor (EC_{50}, 9 nM vs 13 nM), whereas lower potency for D_2 and 5-HT_{2A} receptors. In contrast, compound **7d** showed comparable potency for D_2R and 5-HT_{1A}R while higher potency for 5-HT_{2A}R compared with **2**.

To investigate the influence of the relative position between pyridine N atom and amide group, compounds **12a**, **17a** and **22a** were synthesized. Shifting pyridine N atom from 2-position (**7a**) to 6-positon (**22a**) resulted in significant improvement in antagonistic activities on D_2R and 5-HT_{2A}R. However, changing pyridine N atom from 2-position (**7a**) to 3-positon (**12a**) or 4-positon (**17a**) led to stronger potency for 5-HT_{2A}R while weaker potency for D_2R. Disappointingly, compounds **12a**, **17a** and **22a** were all devoid of 5-HT_{1A}R agonistic activity with EC_{50} > 100 μM. Consequently, we presumed that pyridine-2-carboxamide fragment (as in **Y1**, **Y5** and **Y6**) might be superior to other pyridinecarboxamide fragments (**Y2**, **Y3**, **Y4**, **Y7** and **Y8**). This presumption was further confirmed with data of compounds **12b**, **12c**, **17b** and **17c**, which also displayed no agonistic activities on 5-HT_{1A}R as well. Our previous paper showed that modifying substituent on amide moiety had a direct impact on receptor functional activities.[20] According to present study results, replacement of *N*-methyl substituent on amide with larger ethyl or cyclopropyl substituent led to somewhat reduced activity for 5-HT_{1A}R (**7b** and **7c** vs **7a**). With regard to D_2R and 5-HT_{2A}R, compound **7b** with ethyl substituent, compounds **12c** and **17c** with cyclopropyl substituent exhibited optimal activities in their respective groups (**7b** vs **7a** and **7c**; **12c** vs **12a** and **12b**; **17c** vs **17a** and **17b**). It can be concluded that for the series of compounds bearing (6-fluorobenzo-[d]isoxazol-3-yl)

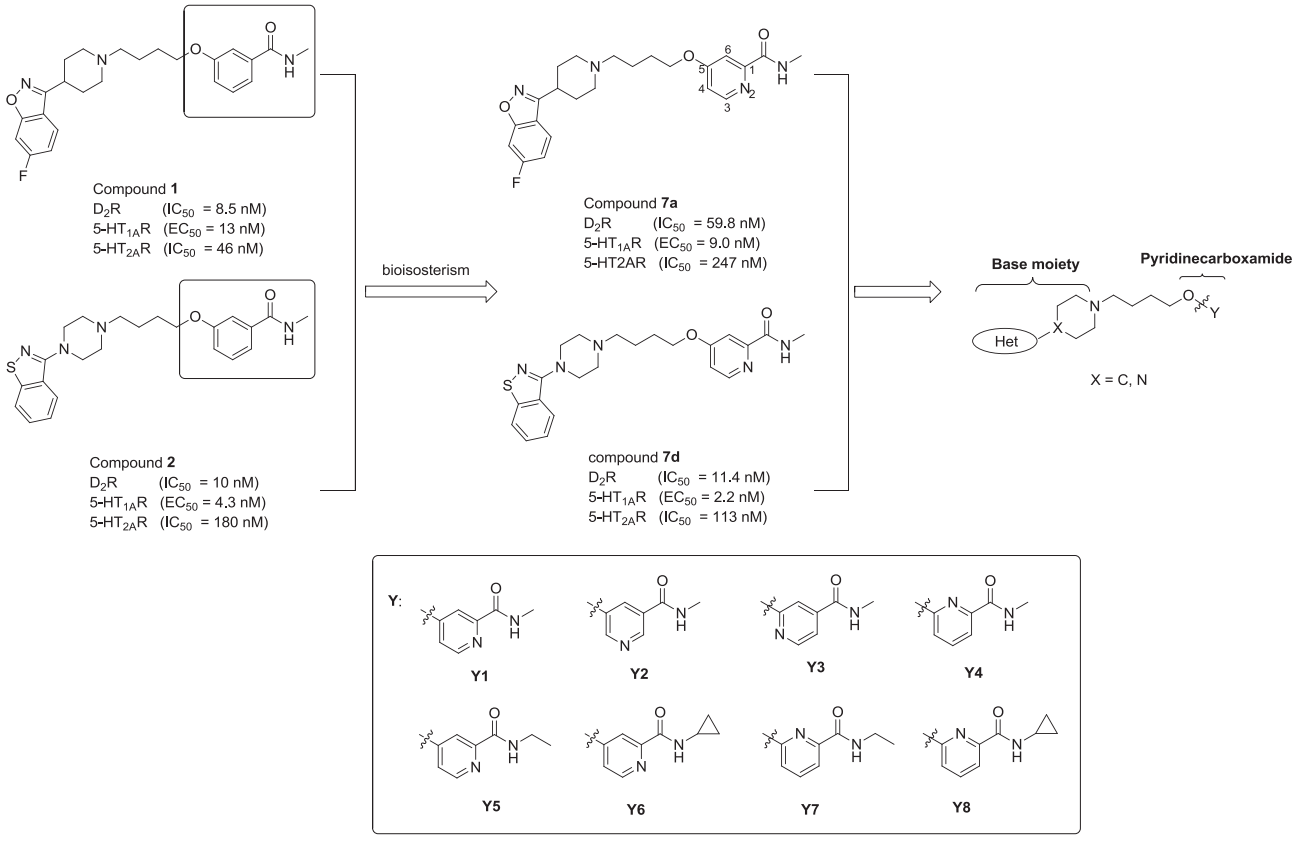

Fig. 1. Design of pyridinecarboxamide derivatives.

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