European Journal of Medicinal Chemistry 74 (2014) 427–439

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and evaluation of new coumarin derivatives as potential atypical antipsychotics

Yin Chen [a,b], Yu Lan [a], Songlin Wang [a], Heng Zhang [a], Xiangqing Xu [b], Xin Liu [a], Minquan Yu [b], Bi-Feng Liu [a], Guisen Zhang [a,b,*]

[a] Systems Biology Theme, Department of Biomedical Engineering, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China
[b] Jiangsu Nhwa Pharmaceutical Co., Ltd., 69 Democratic South Road, Xuzhou, Jiangsu 221116, China

ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form
7 January 2014
Accepted 8 January 2014
Available online 15 January 2014

Keywords:
Coumarin
Dopamine
Serotonin
Atypical antipsychotics

ABSTRACT

In this paper, we report the synthesis of novel, potential antipsychotic coumarin derivatives combining potent dopamine D_2, D_3 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors properties. We describe the structure activity relationship that leads us to the promising derivative: 7-(4-(4-(6-fluorobenzo[*d*]isoxazol-3-yl) piperidin-1-yl)butoxy)-6-methyl-2,3-dihydrocyclopenta[*c*]chromen-4(1*H*)-one **27**. The unique pharmacological features of compound **27** are a high affinity for dopamine D_2, D_3 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors, together with a low affinity for H_1 receptor (to reduce the risk of obesity under chronic treatment). In animal models, compound **27** inhibited apomorphine-induced climbing and MK-801-induced hyperactivity without observable catalepsy at the highest dose tested. In particular, compound **27** was more potent than clozapine.

1. Introduction

Schizophrenia is a chronic incapacitating syndrome that affects 1% of the population [1]. First generation anti-psychotic drugs (APs) are dopamine 2 (D_2) receptor antagonists. While effective in reducing positive symptoms, these drugs are ineffective in treating negative symptoms and cognitive dysfunction and commonly cause extrapyramidal syndrome (EPS) [2–4]. Second generation APs (*e.g.*, clozapine, ziprasidone and risperidone, Fig. 1) target the D_2 receptor, as well as other receptors and have a lower incidence of EPS [5]. However, a major issue with many atypical antipsychotics is their association with numerous side effects, including substantial weight gain and QT interval prolongation [6–9]. Therefore, there is a tremendous unmet need for new antipsychotic medications that effectively treat all aspects of the disease, while possessing a side-effect profile that poses little challenge to compliance.

During the past decade, experimental evidence suggested that a complex binding profile is linked to the clinical efficacy of antipsychotic drugs. Indeed, the importance of designing multi-target G-protein-coupled receptors to deal with schizophrenia has been pointed out by many studies [10–12]. The serotoninergic system plays a variety of roles in the regulation of the prefrontal cortex (PFC) and is highly associated with emotional control, sleep, mood, cognitive behavior and memory [13,14]. The pyramidal neurons of the PFC possess numerous serotoninergic receptors, including 5-HT_{1A} and 5-HT_{2A} receptors [15]. Several studies have shown that activation of 5-HT_{1A} receptor increases dopamine release in the frontal cortex, which may improve negative symptoms and cognitive deficits in schizophrenia [16]. Serotonin acting at 5-HT_{2A} receptor, inhibits neuronal activity in the substantia nigra and ventral tegmental areas. A growing number of studies have reported that 5-HT_{2A} receptor antagonists increase the activity of nigrostriatal DA-containing neurons following moderate D_2 receptor blockade associated with antipsychotic drugs [17,18]. The blockade of 5-HT_{2A} receptors has been implicated in both the enhanced efficacy against negative schizophrenic symptoms and improved EPS profile of the atypical antipsychotics [19]. Dopamine plays important roles in behavior and cognition in the central nervous system (CNS) [20]. Blockade of mesolimbic D_2 receptor increases the efficacy of atypical antipsychotics against positive symptoms associated with schizophrenia [21]. The role of D_3 receptor in antipsychotic therapy is currently unknown; however, D_3 antagonists may enhance acetylcholine release in the frontal cortex, thereby improving cognitive deficits. A growing number of preclinical studies suggest

* Corresponding author. Systems Biology Theme, Department of Biomedical Engineering, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China. Tel.: +86 27 87792235; fax: +86 27 87792170.
E-mail address: gszhang@mail.hust.edu.cn (G. Zhang).

0223-5234/$ – see front matter © 2014 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2014.01.012

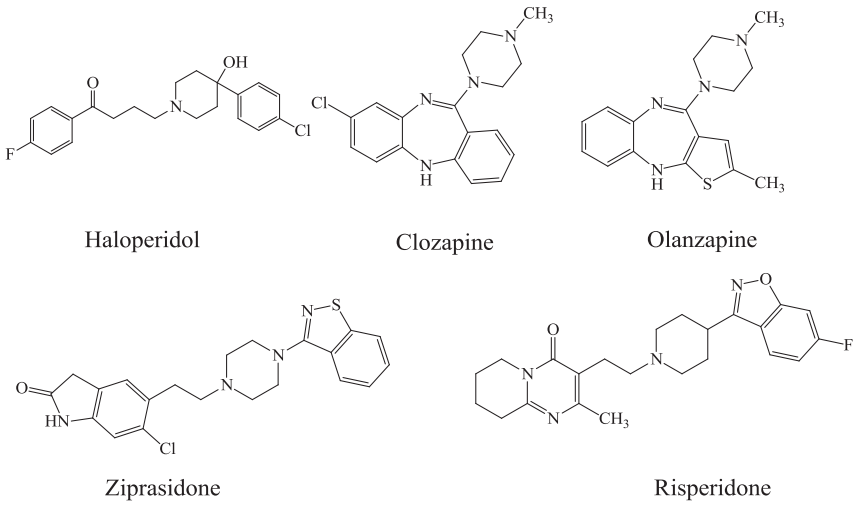

Fig. 1. Structures of a typical (haloperidol) and some atypical antipsychotics.

that the D_3 receptor may be a useful target for amelioration of the negative and cognitive symptoms associated with schizophrenia and substance abuse disorders [22–25]. Moreover, H_1 receptor may be involved in the weight gain associated with the treatment of schizophrenia *via* atypical antipsychotic drugs [26,27]. Thus, the aim of our work is to develop a novel antipsychotics that acts on dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors with a low affinity for the H_1 receptor, so that it could effectively cure positive symptoms, negative symptoms and cognitive impairment without the weight gain side-effect.

In our previous study, coumarin derivatives showed obviously antipsychotic activity. Compound **1** possesses high affinity for dopamine D_2, D_3 and serotonin 5-HT_{1A}, 5-HT_{2A} receptors, and it possesses low affinity for H_1 receptor (to reduce the risk of obesity associated with chronic treatment) [28]. Furthermore, compound **1** exhibited obviously antipsychotic without observable catalepsy in animal models. In order to expand the structure–activity relationships of coumarin derivatives, the present study focused on the synthesis and pharmacological evaluation of a new class of antipsychotic agents which connect 3-position and 4-position into ring derivatives (Fig. 2). The target compounds were subjected to preliminary pharmacological evaluation to determine their affinity for D_2, D_3, 5-HT_{1A}, 5-HT_{2A} and H_1 receptors. The appropriate compounds have to be chosen here for the basic behavioral screening of their atypical antipsychotic potency.

2. Chemistry

The synthesis of the novel coumarin derivatives was performed according to the reaction pathways illustrated in Schemes 1 and 2. The 2-carboalkoxcyclohexanone derivatives (**4**) were synthesized, exploiting the Dieckmann condensation of the corresponding pimelic esters (**3**) (Scheme 1) by treatment with $AlCl_3$ and triethylamine; this provided a good yield [29]. Subsequently, 2-carboalkoxcyclohexanone derivatives (**4**) reacted with substituted resorcinol *via* the Pechmann reaction to give 7-hydroxycoumarin intermediates (**5**) [30]. The standard alkylation procedure of intermediates **5** with 1,4-dibromobutane, 1,3-dibromopropane or 1,5-dibromopentane led to derivatives **6** which were then condensed with appropriate amines to yield the target compounds **7**–**30** (Scheme 1, Tables 1–3).

Finally, 3-hydroxy-6*H*-benzo[*c*]chromen-6-one (**32**) was conveniently prepared by the condensation of the 2-bromobenzoic acid with resorcinol [31]. Subsequently, 3-hydroxy-6*H*-benzo[*c*]chromen-6-one (**32**) reacted with 1,4-dibromobutane or 1,3-dibromopropane led to derivatives **33**, which were then condensed with appropriate amines to yield compounds **34**, **35** (Scheme 2, Table 3).

3. Pharmacology

3.1. In vitro studies

All the new compounds were dissolved in 5% DMSO. The following specific radioligands and tissue sources were used: (a) serotonin 5-HT_{1A} receptor, [^{3}H]8-OH-DPAT, rat brain cortex; (b) serotonin 5-HT_{2A} receptor, [^{3}H]ketanserin, rat brain cortex; (c) serotonin 5-HT_{2C} receptor, [^{3}H]mesulergine, rat brain cortex; (d) dopamine D_2 receptor, [^{3}H]spiperone, rat striatum; (e) dopamine D_3 receptor, [^{3}H] 7-OH-DPAT, rat olfactory tubercle; (f) histamine H_1 receptor, [^{3}H]mepyramine, guinea pig cerebellum;

Total binding was determined in the absence of no-specific binding and compounds. Specific binding was determined in the presence of compounds. Non-specific binding was determined as the difference between total and specific binding.

$$\text{Percentage of inhibition } (\%) = (\text{total binding} - \text{specific binding}) \times 100\%/(\text{total binding} - \text{nonspecific binding})$$

Blank experiments were carried out to determine the effect of 5% DMSO on the binding and no effects were observed. Compounds were tested at least three times over a 6 concentration range (10^{-5} M to 10^{-12} M), IC_{50} values were determined by nonlinear regression analysis using Hill equation curve fitting. K_i values were calculated based on the Cheng and Prussoff equation: $K_i = IC_{50}/(1 + C/K_d)$ where C represents the concentration of the hot ligand used and K_d its receptor dissociation constant were calculated for each labeled ligand. Mean K_i values and SEM are reported for at least three independent experiments. Binding affinities were expressed as K_i values in Tables 1–4.

3.2. In vivo studies

Selected compounds were further evaluated in *vivo* animal models, including the apomorphine-induced climbing, MK801-induced hyperactivity and catalepsy models.