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Original article

Synthesis and serotonin receptor activity of the arylpiperazine alkyl/propoxy derivatives of new azatricycloundecanes

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Abstract

A set of 36 arylpiperazine derivatives with two novel complex terminal imide fragments, 8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate and 1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione, were synthesized and tested for their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. The Fujita–Ban analysis showed that the influence of structural modifications on the affinity for both receptor subtypes is additive and that the activity of similar compounds could be predicted with high accuracy. Compounds **46**, **48** and **18** out of 14 screened in a functional model of anxiety and depression demonstrated antidepressant activity in the forced swimming tests in mice, and were devoid of neurotoxic effects (chimney test in mice).

Keywords: Arylpiperazine; Azatricycloundecane; 5-HT$_{1A}$ receptor; 5-HT$_{2A}$ receptor; Fujita–Ban analysis; Antidepressant activity

1. Introduction

The serotonergic system has been consistently implicated in the pathophysiology of a number of psychiatric disorders including depression and anxiety [1]. Of the 13 different serotonin receptors belonging to GPCR superfamily [2], the 5-HT$_{1A}$ and 5-HT$_{2A}$ subtypes are most frequently considered to be the targets for anxiolytic and antidepressant drugs [3]. Indeed, 5-HT$_{1A}$ agonists and partial agonists (e.g. buspirone (**1**) and tandospirone) [4], as well as 5-HT$_{2A}$ antagonists (e.g. ritanserin and mirtazapine) [5] demonstrate clinical effectiveness in the treatment of either disorder. However, development of agents of this type is still a topical subject of investigations and lies within the area of our interest. In the group of previously investigated compounds, several *o*-methoxyphenylpiperazines (**2**–**4**) showing a similar 5-HT$_{1A}$/5-HT$_{2A}$ binding profile as buspirone (Fig. 1) exhibit anxiolytic- and/or antidepressant-like activity in some behavioral models in rats [6–8]. On the basis of their structures, we synthesized a series of new arylpiperazine derivatives with two novel complex terminal imide fragments: 8,11-dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]undec-8-en-1-yl acetate and 1,11-dimethyl-4-azatricyclo[5.2.2.0^{2,6}]undecane-3,5,8-trione.

Besides pyrimidynyl and *o*–OCH$_3$–phenyl, 5 other classic aryl groups, as well as such standard linkers as: propyl, butyl and propoxyl were used (Table 1). In addition, benzylpiperazine derivatives were also investigated, since for some close analogs a high 5-HT$_{1A}$ receptor affinity was reported [9,10]. Of the 36 new compounds, 25 were tested for their affinity for 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors. The influence of structural modifications on serotonin activity was analyzed using a non-parameter Fujita–Ban method [11], and the binding constants of the remaining 11 derivatives were predicted on the basis of derived equations. In addition, the pharmacological properties of several selected compounds were evaluated in one anxiety test and one "behavioral despair" test.

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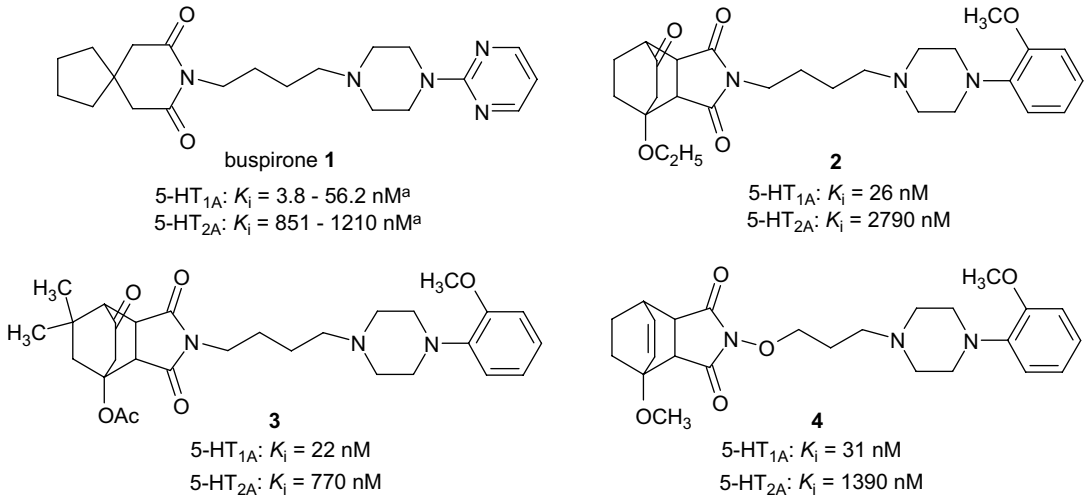

Fig. 1. Structure and affinity data for buspirone (**1**) and compounds **2**–**4**. [a]Range of K_i values taken from PDSB K_i Database (http://pdsp.med.unc.edu/kidb.php).

2. Chemistry

The synthesis of the target compounds **18**–**53** started with the preparation of appropriate imides in the Diels–Alder reaction. Imides **5** and **7** were obtained in a reaction of 3,5-dimethylcyclohex-2-en-1-one with 1*H*-pyrrole-2,5-dione, *p*-toluenosulphonic acid and isopropenyl acetate followed by hydrolysis (Scheme 1). The *N*-hydroxyimides **10** and **11** were initially prepared by an analogous method using 1-hydroxy-substituted 1*H*-pyrrole-2,5-dione (Scheme 2). Unfortunately, targeted imides were obtained in low yield, and, additionally, two by-products (**8** and **9**) were identified. Therefore an alternative substrate, i.e. furan-2,5-dione, was used, and the obtained two anhydrides were subsequently condensed with hydroxylamine, giving *N*-hydroxyimides **10** and **11** with good yield (Scheme 3). The standard alkylation procedure of intermediates **5**, **7**, **10** and **11** with 1,4-dibromobutane or 1,3-dibromopropane led to 4-bromobutyl (**12**, **13**), 3-bromopropyl (**14**, **15**) or 3-bromopropoxy (**16**, **17**) derivatives which were then condensed with appropriate amines to yield the final compounds **18**–**53** (Scheme 4).

3. Pharmacology

The 5-HT_{1A} and 5-HT_{2A} receptor affinities were determined for 25 compounds (**18**–**30**, **33**, **36**, **39**, **42**–**44**, **46**–**48**, **50** and **52**–**53**) in *in vitro* studies on the basis of their ability to displace [^{3}H]-8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino)tetraline] and [^{3}H]-ketanserin [3-{2-[4-(4-fluorobenzoyl)piperidino]ethyl}quinazoline-2,4(1*H*,3*H*)-dione], respectively. The results are presented in Table 1.

The neurotoxic effects of compounds showing significant affinity for 5-HT_{1A} receptors ($K_i < 130$ nM) were quantified by the Boissier chimney test [12]. Next, potential anxiolytic and antidepressant activities were evaluated by a four-plate test [13] and a forced swimming test [14] in mice, respectively. The effect of active compounds on the spontaneous locomotor activity of mice was also tested.

4. Results and discussion

In general, the tested compounds were more active for 5-HT_{1A} receptors ($K_i = 10$–2730 nM) than for 5-HT_{2A} ones ($K_i = 102$–9720 nM). Eleven ligands showed 5-HT_{1A} affinity below 100 nM, but benzyl and pyrimidinyl derivatives were practically inactive. The highest K_i value was found for the *o*-methoxyphenylpiperazine derivative **18**, which was also the most selective 5-HT_{1A}/5-HT_{2A} ligand (K_i ratio 5-HT_{2A}/5-$HT_{1A} = 74$). As regards to 5-HT_{2A} receptors, only four compounds displayed K_i values below 200 nM, and among them derivative **53** could be classified as a dual 5-HT_{1A}/5-HT_{2A} agent of moderate activity.

A qualitative data analysis indicated that the affinities of the investigated compounds strongly and systematically depended on the 13 structural variables applied (eight aryl substituents, three linkers and two imide terminals). To quantitatively determine that relationship, we applied a Fujita–Ban analysis [11] – a simple QSAR technique that directly relates structural features to biological activity [15]. Using that non-parameter method, compound affinity was expressed in a logarithmic scale (pK_i) as a sum of the calculated theoretical activity of the arbitrarily chosen reference derivative **33** (μ) and activity contributions of the respective structural fragments (α_{Ar}, α_{spacer} and α_{imide}).

$$pK_i = \mu + \alpha_{Ar} + \alpha_{spacer} + \alpha_{imide}$$

As shown in Table 2, the results of the Fujita–Ban analysis indicated that the effect of structural modifications on the affinity for both receptor subtypes is additive and the majority of activity contributions α are significant at a 95% confidence level (*t*-test). The most negative values were obtained for α_{Bz} and $\alpha_{pyrimidinyl}$ (from -0.554 to -0.705), which reflected the above-mentioned, and confirmed previously observed [16,17], poor affinity of benzyl and pyrimidinyl derivatives. The contributions of pyridyl substituent were also negative ($\alpha_{pyridyl}$[5-HT_{1A}] $= -0.145$ and $\alpha_{pyridyl}$[5-HT_{2A}] $= -0.346$) when compared to the reference phenyl fragment ($\alpha_{Ph} = 0$).