Synthesis and structure activity relationships of new non-imidazole H\textsubscript{3} receptor antagonists

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The histamine H\textsubscript{3} receptor regulates, with a negative feed-back mechanism, the release of various neurotransmitters, including histamine, glutamate, norepinephrine, acetylcholine, dopamine and serotonin. Pharmacological studies show that improved levels of these neurotransmitters in the Central Nervous System (CNS) lead to procognitive effects. Therefore, H\textsubscript{3} receptors are an interesting drug target for the treatment of a variety of cognitive disorders, such as Alzheimer’s and Parkinson’s disease and also for narcolepsy and epilepsy. Starting from a class of non-imidazole H\textsubscript{3}-antagonists characterized by two basic fragments connected to a central biphenyl core through two methylene spacers, previously synthesized in our laboratory, two novel series of H\textsubscript{3}-antagonists were developed. In the first class, the role of basicity of the ending amino groups and the spacer length was investigated on the H\textsubscript{3} receptor affinity. In the second series, an additional substituent was introduced on one methylene spacer looking for supplementary interactions within the H\textsubscript{3} receptor, as suggested by molecular modeling studies. The newly synthesized derivates showed good affinity and antagonist potency values for both human and rat H\textsubscript{3} receptors.

1 Introduction

Histamine (1, Fig. 1) is a biogenic amine involved in a large variety of physiologic functions. It is produced by decarboxylation of L-histidine and it is metabolized by histamine N\textsuperscript{3}-methyltransferase (HMT) and mono- and diaminoxidases. It exerts its actions through four distinct G protein-coupled receptors, named H\textsubscript{1}, H\textsubscript{2}, H\textsubscript{3} and H\textsubscript{4} [1-2]. H\textsubscript{1} and H\textsubscript{2} receptor antagonists are well-known therapeutic agents and are in use for the treatment of allergic disease [3] and peptic ulcer [4-5], respectively. H\textsubscript{4} receptors are the less known. However, due to their preferred expression in T-cell, dendritic cells, monocytes and mast cell, ligands of these receptors could be effective in the regulation of the immune responses [6].

The histamine H\textsubscript{3} receptors (H3R) are predominantly expressed in CNS and they have been known since 1983 when were first characterized in rats by Arrang et al. [7]. At the beginning, H3R were identified as pre-synaptic autoreceptors able to control the biosynthesis and the release of histamine in the brain [8]. This finding was confirmed in 1987 by the discovery of the first selective H3R ligands, thioperamide (2, Fig. 1) and (R)-\textalpha-methylhistamine (3, Fig. 1). In addition, H3R can act as heteroreceptors able to modulate the release of various neurotransmitters, such as acetylcholine, serotonin, dopamine and norepinephrine [9-11]. In animal models, H3R antagonists, enhancing the release of these neurotransmitters, were able to improve attention [12] and cognition [12]; thus they may offer a novel therapeutic approach for the treatment of several cognitive disorders, including Alzheimer’s and Parkinson’s diseases, attention deficit hyperactivity disorder (ADHD) and also for dementia, narcolepsy, epilepsy and obesity [13-15].

The first generation of H\textsubscript{3}-antagonists were characterized by the presence of an imidazole ring as in histamine. These imidazole-based compounds could inhibit numerous mammalian CYP450 subtypes, causing potential drug-drug interactions. Moreover they showed poor brain penetration [16]. Thus, current efforts are focused on the development of non-imidazole H\textsubscript{3} receptor antagonists in order to obtain compounds with better pharmacokinetic and pharmacodynamic properties. In 1998 Ganellin et al. described first active compounds which the imidazole ring was substituted by piperidine and pyrrolidine [17]. Then, many classes of non-imidazole H\textsubscript{3}-antagonists with different structures were reported; these compounds
Fig. 1: Ligands of histamine H₁ receptors: histamine (1) agonist, thioperamide (2) antagonist and (R)-α-methylhistamine (RAMH) (3) agonist.

are usually characterized by three main portions: a basic amine linked to a central lipophilic region that could be connected to a second basic centre or a polar group or another lipophilic group, suggesting the pharmaphore model here reported (Fig. 2).

Fig. 2: Pharmacophore model proposed for non-imidazole H₁ receptor antagonists.

In a previous work, a series of non-imidazole H₁ receptor antagonists characterized by a central biphenyl core connected to two basic groups through a methylene spacer were described [18]. The most potent derivate (4, Fig. 3a) showed subnanomolar affinity for the human H₁ receptor (pKᵢ = 9.47).

For this series of compounds, docking studies inside the H₁ receptors model, validated in our laboratories [19], suggested two possible accommodations (Fig. 3b, 3c). A horizontal disposition where the basic centers interact with Asp114 and with Glu206 and a vertical pose where one piperidine interact with Asp114, while the compound is deeply inserted in a lipophilic pocket parallel to the helix bundle. The other piperidine can interact with Asn404.

Fig. 3: (a) lead compound (4), (b) horizontal disposition and (c) vertical disposition.

In order to explore and further extend the structure-activity relationships (SARs) of this class of H₁-antagonists, two new series of compounds were synthesized.

2 Design

Starting from the series previously described, during this PhD project two novel classes of non-imidazole H₁ receptor antagonists were prepared. These new compounds were characterized by two terminal fragments liked to a central biphenyl core through two alkyl spacers.

In the first series, the spacer length and the properties of the ending basic groups were varied. In particular, asymmetrical compounds carrying one piperidine and a variable second basic group with two methylene

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spacers were synthesized (7-14, Table 1) [20]. Moreover, symmetrical compounds having the same basic group and two ethylene linkers (20-21, Table 1) or one methylene and one ethylene spacers were prepared (22, Table 1) [20].

In the second series, an additional substituent was introduced on one methylene spacer. This substituent was introduced with the aim to investigate the presence of a hydrophobic pocket into the H₃ receptor as proposed by molecular modeling and docking studies. Structures, synthesis and pharmacological data obtained for these compounds cannot be reported.

The newly synthesized compounds were tested for their binding affinity and their H₃-antagonist behavior at the Dipartimento di Scienze Farmacologiche, Biologiche e Chimiche Applicate, Facoltà di Farmacia, Università degli Studi di Parma. H₃ receptor affinities, expressed as pKᵢ, for rat and human H₃ receptors and antagonist potency at human H₃ receptors, expressed as pKᵢ, are reported in Table 1.

3 Chemistry

The synthesis of compounds 7-14 is reported in Scheme 1. These derivates were obtained reacting the commercially available 4,4'-bis(chloromethyl)-biphenyl 5 with one equivalent of piperidine to achieve the monosubstituted intermediate 6. After isolation and purification, 6 was reacted with the appropriate amine to obtain the desired products.

Compounds 20-22 were synthesized following the efficient and simple procedure described in Scheme 2. Compounds 20 and 21 were prepared starting from 4,4'-bis(chloromethyl)-biphenyl 5, that was reacted with NaCN to obtain the dicyano derivate. Then hydrolysis of cyano groups and acidification, allowed to obtain the dicarboxylic acid 15. This was activated with CDI and reacted with piperidine to give the corresponding tertiary amide with general formula 19, that was finally reduced with RedAl® to the target diamino compounds. Compound 22 was synthesized starting from 4-iodophenylacetic acid, that was activated with CDI and reacted with piperidine to obtain the intermediate 17. This intermediate was reacted, via Suzuki coupling, with 4-carboxyphenyl boronic acid to obtain the biphenylcarboxy acid 18, that was activated with CDI and reacted with piperidine to give the intermediates with general formula 19. Finally, reduction with RedAl®, allowed to obtain the desired compound.

Fig. 4: Scheme 1 Reagents and conditions: (a) piperidine, Et₃N, CH₃CN, MW 150°C, 150 W, 120 psi, 5', 47.8%; (b) Amine, CH₃CN or THF, MW 150°C, 150 W, 120 psi, 5', 64.0-86.9%.

4 Results and discussions

Two new series of H₃ receptor antagonists were prepared with efficient and simple reactions; intermediates and final compounds were obtained in high yields. When possible, synthesis was performed by MAOS (Microwave Assisted Organic Synthesis) technology, thus reducing reaction times and avoiding purification of intermediates.

All compounds synthesized showed good affinity and antagonist potency for H₃ receptors. Compared to the reference compound 4, substitution of one piperidine with another basic group maintained good affinity values, suggesting a certain tolerance by H₃ receptor to variation of steric hydrance of one basic substituent. On the other hand, the presence of less-basic, such as a morpholine (10) or too hindered basic group, such as benzyl methyl amine (14), led to a significant drop in affinity and in antagonist potency for the H₃ receptor. Elongation of the methylene spacer (20-21) is tolerated for receptor binding, only producing a slight reduction of affinity compared to the corresponding shorter compounds [18]. The asymmetrical
Table 1: first series of compounds, values of rat and human H₃ receptor affinities (pKᵢ) and human H₃-antagonist potency (pKᵦ).  

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* Inhibition of [³H]RAMHA binding to rat brain experiments.

* Inhibition of [³H]RAMHA binding to SK-N-MC cells stably expressing the human histamine H₃ receptor.

* Antagonist potency at human histamine H₃-receptors expressed in SK-N-MC cells.

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Fig. 5: Scheme 2 Reagents and conditions: (a) NaCN, CH$_3$CN, MW 150˚C, 150 W, 120 psi, 5’, 92.0%; (b) 1) KOH, EtOH, MW 150˚C, 150 W, 120 psi, 5’; 2) HCl 1N, 99.0%; (c) 1) CDI, CH$_3$CN, MW 130˚C, 150 W, 120 psi, 5’; 2) Piperidine, CH$_3$CN, MW 130˚C, 150 W, 120 psi, 5’, 90.0%; (d) 4-carboxybenzen boronic acid, K$_2$CO$_3$, Pd(OAc)$_2$, Acetone, H$_2$O, 65˚C, 1h, 99.0%; (e) 1) CDI, THF, MW 130˚C, 150 W, 120 psi, 5’; 2) Amine, anhydrous THF, MW 150˚C, 200 W, 120 psi, 5’, 63.0-93.0%; (f) RedAl®, anhydrous Toluene or THF, 1 h rt, 3 h reflux, 74.0-90.0%.

compound 22 carrying two piperidine and methylene and ethylene spacers showed a moderate decrease in receptor affinity, compared to the shorter and the longer derivates [18], but it showed the highest potency on human H$_3$ receptors.

Introduction of an additional substituent led to a different behavior of the compounds, depending on the geometry and physico-chemical properties of the substituent. Some of them showed moderate H$_3$ receptor affinities, whereas most of them demonstrated a good binding profile, suggesting the possibility to be accommodated and to interact with an additional region of the H$_3$ receptor.

In conclusion, two novel series of non-imidazole H$_3$ receptor antagonists obtained from structure modification of a very potent lead compound 4 were prepared. Substitution of one piperidine with another basic group maintained good H$_3$-antagonists binding affinities. Introduction of a new substituent on one methylene spacer allowed to achieve interesting receptor affinities, suggesting the possibility of allocation and interaction between this substituent and the liphofilic pocket proposed in the H$_3$ receptor.

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References