European Journal of Medicinal Chemistry 64 (2013) 629–637

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and pharmacological properties of a new hydrophilic and orally bioavailable 5-HT$_4$ antagonist

Bjarne Brudeli [a,d], Lise Román Moltzau [b,c], Cam H.T. Nguyen [b,c], Kjetil Wessel Andressen [b,c], Nils Olav Nilsen [a], Finn Olav Levy [b,c], Jo Klaveness [a,d,*]

[a] Drug Discovery Laboratory AS, Oslo Innovation Center, N-0349 Oslo, Norway
[b] Department of Pharmacology, Faculty of Medicine, University of Oslo and Oslo University Hospital, P.O. Box 1057, Blindern, N-0316 Oslo, Norway
[c] K.G. Jebsen Cardiac Research Centre and Center for Heart Failure Research, Faculty of Medicine, University of Oslo, N-0316 Oslo, Norway
[d] Department of Medicinal Chemistry, School of Pharmacy, University of Oslo, N-0316 Oslo, Norway

ARTICLE INFO

Article history:
Received 17 October 2012
Received in revised form
22 March 2013
Accepted 27 March 2013
Available online 9 April 2013

Keywords:
Bioavailability
hERG
5-HT$_4$ antagonist
Hydrophilic
Pharmacokinetic
Prodrug

ABSTRACT

5-HT$_4$ receptor antagonists have been suggested to have clinical potential in treatment of atrial fibrillation, diarrhea-prone irritable bowel syndrome and urinary incontinence. Recently, the use of 5-HT$_4$ antagonists has been suggested to have a therapeutic benefit in heart failure. Affinity for the hERG potassium ion channel and increased risk for prolonged QT intervals and arrhythmias has been observed for several 5-HT$_4$ ligands. Serotonin may also have beneficial effects in the central nervous system (CNS) through stimulation of the 5-HT$_4$ receptor, and reduced distribution of 5-HT$_4$ antagonists to the CNS may therefore be an advantage. Replacing the amide and *N*-butyl side chain of the 5-HT$_4$ receptor antagonist SB207266 with an ester and a benzyl dimethyl acetic acid group led to compound **9**; a hydrophilic 5-HT$_4$ antagonist with excellent receptor binding and low affinity for the hERG potassium ion channel. To increase oral bioavailability of carboxylic acid **9**, two different prodrug approaches were applied. The *tert*-butyl prodrug **11** did not improve bioavailability, and LC-MS analysis revealed unmetabolized prodrug in the systemic circulation. The medoxomil ester prodrug **10** showed complete conversion and sufficient bioavailability of **9** to advance into further preclinical testing for treatment of heart failure.

© 2013 Elsevier Masson SAS. All rights reserved.

1. Introduction

Serotonin (5-hydroxytryptamine; 5-HT) is a monoaminergic neurotransmitter in the central and peripheral nervous system. Today, 14 different human serotonin receptors are known, divided into 7 distinct families (5-HT$_{1-7}$) [1]. Pharmaceuticals acting on serotonin receptors play important roles in several pathological conditions. The first line treatment of migraine is triptans, a class of selective serotonin agonists that affect the 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors in cranial artery smooth muscle [2]. Nausea and emesis after chemotherapy are treated with e.g. ondansetron and tropisetron, selective serotonin antagonists that affect the 5-HT$_3$ receptor in the chemoreceptor trigger zone and the gastro-intestinal system.

Serotonin causes increased rate and force of contraction through 5-HT$_4$ receptors in human atria [3]. Recent investigations have revealed that the human cardiac ventricles show increased response to serotonin through 5-HT$_4$ receptors in infarcted and failing hearts [4]. Further, increased expression of the 5-HT$_4$ receptor may indicate a role of the serotonergic system in this condition. Recently, blocking of the 5-HT$_4$ receptor has been investigated in both experimental animals and humans, and the use of 5-HT$_4$ receptor antagonists may be a new therapeutic intervention in treatment of congestive heart failure [5,6].

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by abdominal pain, bloating and altered bowel habits. An increased understanding of the role of serotonin in regulation of GI motility, secretion and visceral sensitivity has led to the development of 5-HT receptor modulators for treatment of IBS [7]. Both the 5-HT$_3$ receptor antagonists alosetron and cilansetron and the 5-HT$_4$ agonists cisapride and tegaserod have been developed for treatment of diarrhea- and constipation-predominant forms of IBS, respectively. However, serious side effects have led to market withdrawal or suspension of these agents. Post market findings revealed that cisapride binds to the human *ether-à-go-go* related gene (hERG) potassium channel, an ion channel important for the cardiac action potential. High affinity for this channel can give rise to prolonged QT interval and cause fatal torsades des pointes arrhythmia [8].

* Corresponding author. School of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, N-0316 Oslo, Norway. Tel.: +47 22855043; fax: +47 22857975.
E-mail address: jo.klaveness@farmasi.uio.no (J. Klaveness).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.03.060

Increased focus on hERG has revealed strategies to avoid drug binding to this ion channel, and the incorporation of negatively-charged functional groups seems to be a feasible way to overcome hERG potassium channel-related side effects [9]. This strategy can also be used to avoid distribution of peripheral-acting drugs to the central nervous system, and it has been successfully introduced to second-generation antihistamine H_1-receptor antagonists. All second-generation anti-allergic drugs contain a carboxylic acid group, or they are metabolized to active metabolites with a carboxylic acid group [10]. Terfenadine, a H_1-receptor antagonist with a *tert*-butyl group, is extensively metabolized to the corresponding dimethyl acetic acid metabolite fexofenadine as outlined in Fig. 1. Fexofenadine, in contrast to terfenadine, does not bind to the hERG channel and has limited CNS distribution because of the negatively charged carboxylate group. However, reports of prolonged QT intervals and arrhythmias due to incomplete metabolic conversion of terfenadine to fexofenadine have led to market withdrawal of terfenadine. Only the carboxylic acid metabolite fexofenadine is used today in anti-allergic treatment. It has also been shown that the carboxylic acid group is important for antihistamine drugs to act as substrates for P-glycoproteins, and second generation antihistamines are actively transported out of the central nervous system [11].

We have previously reported the synthesis and pharmacological effects of some novel hydrophilic 5-HT_4 receptor antagonists [12]. Since 5-HT_4 agonists might have beneficial effects in the central nervous system, reduced distribution of 5-HT_4 antagonists to the CNS may be an advantage. Reducing the risk of cardiotoxic side effects like prolonged QT interval may be achieved by increasing the hydrophilicity of new therapeutic 5-HT_4 ligands, for example by incorporating a carboxylic acid moiety [9]. We have therefore prepared a new hydrophilic 5-HT_4 receptor antagonist **9** that has structural similarities with the second-generation H_1-antagonist fexofenadine as shown in Fig. 2. The dimethyl acetic acid antagonist **9** shows promising 5-HT_4 receptor binding and low affinity for the hERG potassium channel. The log $D_{Oct7.4}$ value also indicates low distribution to the central nervous system, a clinical benefit since reduced CNS side effects may be expected.

However, the hydrophilic carboxylic acid **9** showed limited oral bioavailability in a rat model. To increase oral bioavailability of the new antagonist, two different prodrug approaches were applied. First the corresponding *tert*-butyl prodrug **11** was synthesized and evaluated with respect to oral bioavailability. The *tert*-butyl derivative **11** did not improve bioavailability, and plasma analysis revealed incomplete metabolism to carboxylic acid **9**. Therefore, the corresponding medoxomil ester prodrug **10** was prepared. The medoxomil ester **10** showed both complete conversion to carboxylic acid **9** and satisfactory oral bioavailability and pharmacokinetics.

2. Chemistry

The hydrophilic carboxylic acid **9**, a derivative of the 5-HT_4 antagonist SB207266, and the corresponding prodrugs **10** and **11** are shown in Fig. 2.

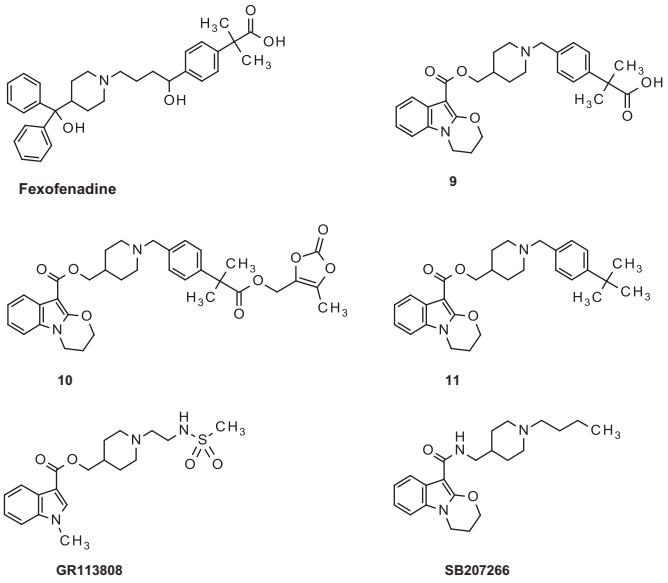

Fig. 2. Structures of fexofenadine, GR113808, SB207266 and the synthesized derivatives **9**–**11**.

The synthesis of benzyl-protected piperidine derivative **3** and the corresponding de-protected amine **4** is shown in Scheme 1. The synthesis of indole ester **1** and piperidine methanol derivative **2** has been described elsewhere [13,14]. The benzyl protected intermediate **3** was prepared by adding n-BuLi to a cooled solution of piperidine methanol derivative **2** in THF, followed by indole ester **1** and stirring to room temperature. Crystallization from EtOAc gave intermediate **3** in 89% yield. Hydrogenation of benzyl intermediate **3** using Pd/C at 5 bar in a mixture of glacial acetic acid and methanol at room temperature gave the de-protected amine **4** in 81% yield.

The synthesis of the bromide intermediate **7** is shown in Scheme 2. Alkylation of 2-(4-methylphenyl)propanoic acid with MeI in DMF in the presence of $NaHCO_3$ at room temperature gave the methyl ester **5** in 95% yield. Addition of **5** to a cooled suspension of NaH in n-hexane, followed by MeI and stirring at room temperature gave intermediate **6** in 49% yield. Addition of N-bromosuccinimide to a solution of **6** in dichloromethane followed by benzoyl peroxide and heating the mixture to reflux gave the bromo derivative **7** in 61% yield after filtration of the reaction mixture through a pad of silica.

The synthesis of carboxylic acid **9** and the corresponding prodrug ester **10** is shown in Scheme 3. Addition of bromo derivative **7** to a solution of amine **4** in acetone in the presence of K_2CO_3 and heating the mixture to reflux gave the methyl ester **8** in 45% yield after purification with column chromatography. Hydrolysis of methyl ester **8** with sodium hydroxide in a mixture of aqueous MeOH under reflux gave carboxylic acid **9** in 45% yield. Alkylation of carboxylic acid **9** with 4-chloromethyl-5-methyl-1,3-dioxol-2-one in DMA in the

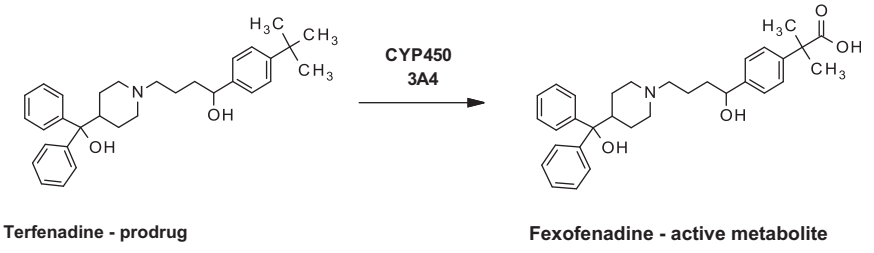

Fig. 1. First-pass metabolism of the second generation H_1 receptor antagonist terfenadine to the active metabolite fexofenadine.

Download English Version:

https://daneshyari.com/en/article/7802201

Download Persian Version:

https://daneshyari.com/article/7802201

Daneshyari.com