Bioorganic & Medicinal Chemistry Letters 20 (2010) 6538–6541

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Discovery of 2-substituted benzoxazole carboxamides as 5-HT$_3$ receptor antagonists

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ARTICLE INFO

Article history:
Received 23 August 2010
Revised 7 September 2010
Accepted 8 September 2010
Available online 16 September 2010

Keywords:
5-HT$_3$ receptor antagonist
Irritable bowel syndrome
IBS
Diarrhea
Alosetron
Ramosetron
Benzoxazole

ABSTRACT

A new class of 2-substituted benzoxazole carboxamides are presented as potent functional 5-HT$_3$ receptor antagonists. The chemical series possesses nanomolar in vitro activity against human 5-HT$_3$A receptors. A chemistry optimization program was conducted and identified 2-aminobenzoxazoles as orally active 5-HT$_3$ receptor antagonists with good metabolic stability. These novel analogues possess drug-like characteristics and have potential utility for the treatment of diseases attributable to improper 5-HT$_3$ receptor function, especially diarrhea predominant irritable bowel syndrome (IBS-D).

Diarrhea predominant irritable bowel syndrome (IBS-D) is a painful, debilitating disorder of the bowel that diminishes the quality of life for millions of men and women each day. The typical sufferer of IBS-D exhibits symptoms which include multiple daily diarrhea attacks and severe abdominal cramps. Secondary effects may include urgency, panic attacks, depression, withdrawal from social and family activities and malnutrition. It is estimated that IBS management in the US costs eight billion dollars in direct medical costs alone.[1] Effective pharmacological treatment of this disorder has been elusive.

One agent that has demonstrated relief for this population is Lotronex® (alosetron hydrochoride), a serotonin type 3 (5-HT$_3$) receptor antagonist.[2] This first-in-class drug was voluntarily withdrawn from the market shortly following its launch due to the appearance of rare incidents of ischemic colitis, a life-threatening ailment of the gastrointestinal tract.[3]

Strong patient advocacy helped return alosetron to the marketplace, albeit with severe use restrictions.[4] Such a reinstatement was a first in FDA's history and is a testimony to the drug's effectiveness for many patients and to the unmet need in IBS therapy. Alosetron remains unavailable to the majority of IBS patients.

The underlying cause of ischemic colitis in IBS patients is under much debate. A target-based explanation is not persuasive since a number of commercial 5-HT$_3$ blockers have safely and effectively been used to treat chemotherapy-induced nausea and vomiting (CINV) for years with no reports of ischemic colitis.[5] To this point, a re-purposed CINV agent, ramosetron hydrochloride, was approved in 2008 for the treatment of IBS-D in Japan.[6] No reports of ischemic colitis have appeared for this 5-HT$_3$ receptor antagonist suggesting that new 5-HT$_3$ receptor modulators may overcome the problems observed for alosetron.

One postulate for alosetron's failings may be linked to the compound's complex metabolic profile. Alosetron package labeling indicates the compound is heavily metabolized by the liver.[7] Indeed, alosetron is contraindicated for patients with severe hepatic impairment. Studies conducted with radiolabelled alosetron identified 28 discrete metabolites.[8] At least 13 alosetron metabolites have been identified in humans, several of which are active at the 5-HT$_3$ receptor.[9] The pharmacodynamic and toxicological effects of alosetron's metabolites are not fully understood.

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doi:10.1016/j.bmcl.2010.09.038

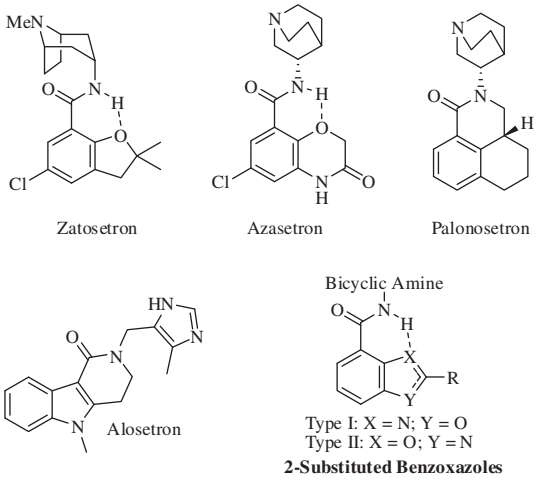


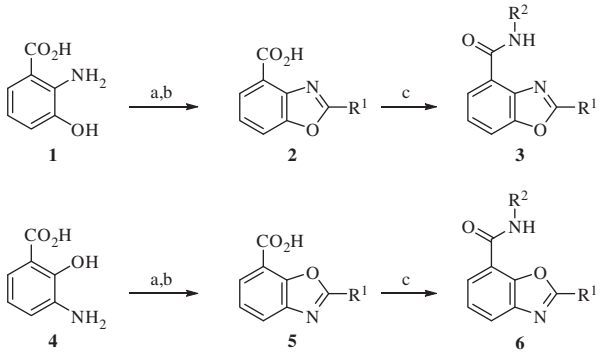
Figure 1. Type I and type II 2-substituted benzoxazoles.

New structural types of 5-HT_3 receptor modulators with improved metabolic profiles are needed. Herein, we report early findings in support of our goal to identify improved 5-HT_3 receptor modulators for IBS.

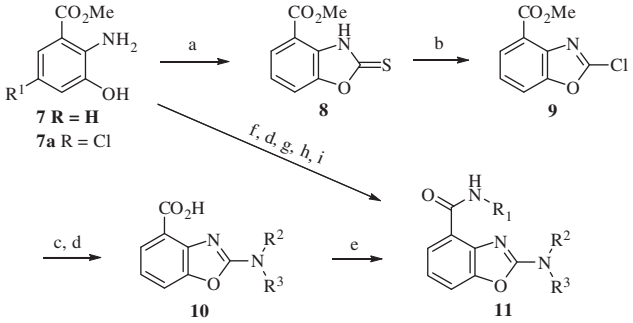
The benzoxazole scaffold depicted in Figure 1 was conceived through the hypothesis that a potential hydrogen bonding interaction between the carboxamide NH and the ring heteroatom of the core heterocycle may be important for a preferred binding configuration.[10] This feature may be operating for certain potent 5-HT_3 receptor antagonists (e.g., zatosetron[11] and azasetron[12]) and mimics the constrained geometry of the second generation anti-emetic palonosetron.[10b] The carboxamide benzoxazole scaffold had not been previously explored as a 5-HT_3 receptor ligand and therefore the benzoxazole platform was of interest to us as a starting point.[13] Additionally, the compound class is structurally distinct from alosetron, an element in line with our program objective.

The type I and type II isomers (Fig. 1) of the benzoxazole heterocycle were briefly investigated as well as three classes of 2-position substituents (R = alkyl, aryl or amino). 2-Substituted aryl and alkyl benzoxazoles were obtained in good yield by treatment of **1** or **4** with either an aryl or alkyl chloride in pyridine/CH_2Cl_2 followed by ring closure with *p*-toluene sulfonic acid in refluxing toluene (Scheme 1). The amide was prepared by condensation of an appropriate amine, either *endo*-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (G) or (*S*)-quinuclidin-3-amine (Q), with the carboxylic acid using a carbodiimide mediated coupling.

A general synthesis of 2-amino substituted benzoxazoles is described in Scheme 2.



Scheme 1. General synthesis of 2-aryl and 2-alkyl 2-aminobenzoxazole carboxamides. Reagents and conditions: (a) ArCOCl or alkylCOCl, pyridine, CH_2Cl_2, rt; (b) *p*-TsOH, toluene, reflux; (c) R^2NH_2, EDC·HCl, HOBt, Et_3N, CH_2Cl_2, rt.



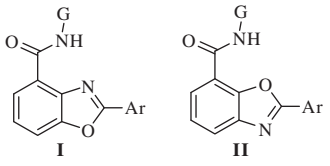
Scheme 2. General synthesis of 2-aminobenzoxazole carboxamides. Reagents and conditions: (a) $EtOCS_2K$, pyridine, reflux; (b) $POCl_3$, PCl_5, 95 °C; (c) R^2NHR^3, THF; (d) 2 N NaOH, THF, rt; (e) R^1NH_2, EDC·HCl, HOBt, Et_3N, DMF, rt. For $R^2 = R^3 = H$: (f) di(1*H*-imidazoyl-1-yl)methanimine, THF; (g) Boc_2O, CH_2Cl_2; (h) R^1NH_2, EDC·HCl, HOBt, Et_3N, DMF; (i) TFA, CH_2Cl_2.

2-Amino-3-hydroxybenzoic acid **7** was treated with potassium *O*-ethylxanthate to provide thione **8**. The thione was then converted to 2-chlorobenzoxazole **9** by reaction with phosphorus pentachloride in phosphorus oxychloride. Displacement of the chloride **9** with different amines followed by hydrolysis of the methyl ester yielded 2-aminobenzoxazoles **10**. EDC coupling of the acid **10** with the requisite G or Q amine in the presence of HOBT in DMF provided 2-aminobenzoxazole carboxamides **11**. For 2-NH_2 substituted benzoxazoles ($R^2 = R^3 = H$), methyl 2-amino-3-hydroxybenzoate or methyl-2-amino-5-chloro-3-hydroxybenzoate were treated with di(1*H*-imidazol-1-yl)methanimine[14] followed by ester saponification and amidation.

Initially, type I and type II 2-aryl benzoxazole 5-HT_3 receptor SAR was examined to determine whether a preference existed for either of the heterocyclic isomers (Table 1). The 5-HT_3 receptor binding data show a trend favoring the type I isomer. The type I benzoxazole was therefore selected for initial lead optimization. A subset of 2-aryl, 2-alkyl and 2-amino type I benzoxazoles were compared head-to-head for drug-like potential in a number of assessments to establish a preferred 2-substituent class. Key assessments included 5-HT_3 receptor affinity and selectivity, cardiovascular risk (hERG), cytochrome P450 inhibition, microsomal stability, mutagenicity potential (mini Ames), pharmacokinetic profile and confirmation of in vivo efficacy.

Table 2 summarizes select profiling data for G- and Q-derived compound pairs (**20**–**25**). Collectively, the three chemical series have overall good properties as starting points compared to the reference commercial 5-HT_3 receptor antagonists. In addition, oral

Table 1
Type I versus type II 2-aryl benzoxazoles



Comp.	Type	Ar	K_i[a] (nM)
12	I	Ph	15.1 ± 4.9
13	I	4′-F-Ph	16.3 ± 1.5
14	I	4′-Cl-Ph	18.0 ± 12.7
15	I	4′-OMe-Ph	18.8 ± 7.3
16	II	Ph	40.4 ± 9.4
17	II	4′-F-Ph	94.9 ± 48.4
18	II	4′-Cl-Ph	73.8 ± 30.8
19	II	4′-OMe-Ph	58.5 ± 6.5

[a] $h5\text{-}HT_{3A}$ ($n \geqslant 3$).[18]