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## Discovery of 2-substituted benzoxazole carboxamides as 5-HT<sub>3</sub> receptor antagonists

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### ABSTRACT

A new class of 2-substituted benzoxazole carboxamides are presented as potent functional 5-HT<sub>3</sub> receptor antagonists. The chemical series possesses nanomolar in vitro activity against human 5-HT<sub>3</sub>A receptors. A chemistry optimization program was conducted and identified 2-aminobenzoxazoles as orally active 5-HT<sub>3</sub> 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<sub>3</sub> receptor function, especially diarrhea predominant irritable bowel syndrome (IBS-D).

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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.<sup>1</sup> Effective pharmacological treatment of this disorder has been elusive.

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 This first-in-class drug was voluntarily withdrawn from the market shortly following its launch due to the appearance of rare incidents of ischemic colitis, a life-threatening ailment of the gastrointestinal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

Strong patient advocacy helped return alosetron to the marketplace, albeit with severe use restrictions.<sup>4</sup> 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<sub>3</sub> blockers have safely and effectively been used to treat chemotherapy-induced nausea and vomiting (CINV) for years with no reports of ischemic colitis.<sup>5</sup> To this point, a re-purposed CINV agent, ramosetron hydrochloride, was approved in 2008 for the treatment of IBS-D in Japan.<sup>6</sup> No reports of ischemic colitis have appeared for this 5-HT<sub>3</sub> receptor antagonist suggesting that new 5-HT<sub>3</sub> 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.<sup>7</sup> Indeed, alosetron is contraindicated for patients with severe hepatic impairment. Studies conducted with radiolabelled alosetron identified 28 discrete metabolites.<sup>8</sup> At least 13 alosetron metabolites have been identified in humans, several of which are active at the 5-HT<sub>3</sub> receptor.<sup>9</sup> The pharmacodynamic and toxicological effects of alosetron's metabolites are not fully understood.

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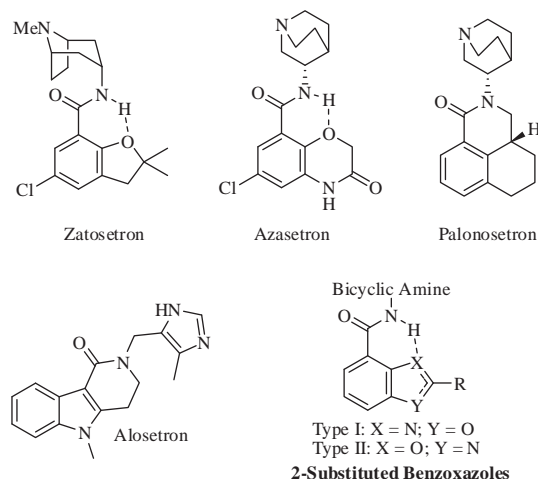


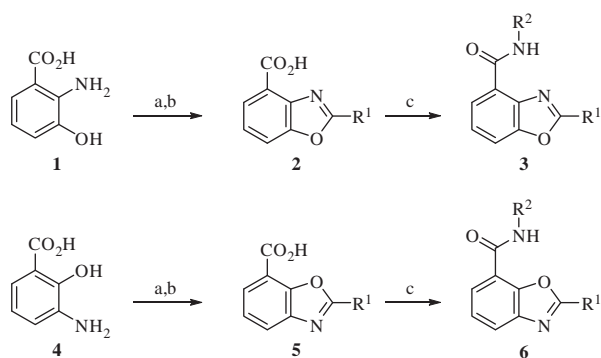
Figure 1. Type I and type II 2-substituted benzoxazoles.

New structural types of 5-HT<sub>3</sub> receptor modulators with improved metabolic profiles are needed. Herein, we report early findings in support of our goal to identify improved 5-HT<sub>3</sub> receptor modulators for IBS.

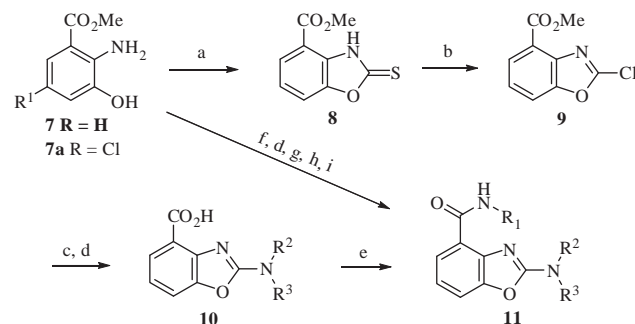
The benzoxazole scaffold depicted in Figure 1 was conceived through the hypothesis that a potential hydrogen bonding interaction between the carboxamide NH and the ring heteroatom of the core heterocycle may be important for a preferred binding configuration.<sup>10</sup> This feature may be operating for certain potent 5-HT<sub>3</sub> receptor antagonists (e.g., zatosetron<sup>11</sup> and azasetron<sup>12</sup>) and mimics the constrained geometry of the second generation anti-emetic palonosetron.<sup>10b</sup> The carboxamide benzoxazole scaffold had not been previously explored as a 5-HT<sub>3</sub> receptor ligand and therefore the benzoxazole platform was of interest to us as a starting point.<sup>13</sup> 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<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub>, rt; (b) *p*-TsOH, toluene, reflux; (c) R<sup>2</sup>NH<sub>2</sub>, EDC-HCl, HOBt, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt.



Scheme 2. General synthesis of 2-aminobenzoxazole carboxamides. Reagents and conditions: (a) EtOCS<sub>2</sub>K, pyridine, reflux; (b) POCl<sub>3</sub>, PCl<sub>5</sub>, 95 °C; (c) R<sup>2</sup>NHR<sup>3</sup>, THF; (d) 2 N NaOH, THF, rt; (e) R<sup>1</sup>NH<sub>2</sub>, EDC-HCl, HOBt, Et<sub>3</sub>N, DMF, rt. For R<sup>2</sup> = R<sup>3</sup> = H: (f) di(1*H*-imidazol-1-yl)methanimine, THF; (g) Boc<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; (h) R<sup>1</sup>NH<sub>2</sub>, EDC-HCl, HOBt, Et<sub>3</sub>N, DMF; (i) TFA, CH<sub>2</sub>Cl<sub>2</sub>.

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<sub>2</sub> substituted benzoxazoles (R<sup>2</sup> = R<sup>3</sup> = H), methyl 2-amino-3-hydroxybenzoate or methyl-2-amino-5-chloro-3-hydroxybenzoate were treated with di(1*H*-imidazol-1-yl)methanimine<sup>14</sup> followed by ester saponification and amidation.

Initially, type I and type II 2-aryl benzoxazole 5-HT<sub>3</sub> receptor SAR was examined to determine whether a preference existed for either of the heterocyclic isomers (Table 1). The 5-HT<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> receptor antagonists. In addition, oral

Table 1  
Type I versus type II 2-aryl benzoxazoles

Comp.	Type		
		Ar	K <sub>i</sub> <sup>a</sup> (nM)
<b>12</b>	I	Ph	15.1 ± 4.9
<b>13</b>	I	4'-F-Ph	16.3 ± 1.5
<b>14</b>	I	4'-Cl-Ph	18.0 ± 12.7
<b>15</b>	I	4'-OMe-Ph	18.8 ± 7.3
<b>16</b>	II	Ph	40.4 ± 9.4
<b>17</b>	II	4'-F-Ph	94.9 ± 48.4
<b>18</b>	II	4'-Cl-Ph	73.8 ± 30.8
<b>19</b>	II	4'-OMe-Ph	58.5 ± 6.5

<sup>a</sup> h5-HT<sub>3A</sub> (n ≥ 3).<sup>18</sup>

**Table 2**  
Profile data for representative 2-substituted benzoxazoles

	Bicyclic amine <sup>a</sup> , 2-R group	K <sub>i</sub> <sup>b</sup>	3A4 <sup>c</sup>	CL <sub>int</sub> <sup>d</sup>	hERG <sup>e</sup>	% <sup>f</sup>
<b>20</b>	G, morph.	40.0 ± 5.5	>50	1.0	1.4	35
<b>21</b>	Q, morph.	165 ± 25	>100	0.6	3.2	100
<b>22</b>	Q, 2'-OMePh	47.3 ± 14.8	>50	10.1	0.2	100
<b>23</b>	G, 2'-OMePh	14.9 ± 6.4	1.1	2.8	0.4	44
<b>24</b>	Q, <i>c</i> -C <sub>3</sub> H <sub>5</sub>	32.7 ± 18.8	>100	4.5	0.7	13
<b>25</b>	G, <i>c</i> -C <sub>3</sub> H <sub>5</sub>	8.3 ± 4.0	>50	23.5	0.2	32
	Ondansetron	3.4 ± 1.7	11	5.8	0.4	21
	Alosetron	0.5 ± 0.1	0.6	3.0	2.3	100

<sup>a</sup> Type I 2-benzoxazole (see Fig. 1), Q = (*S*)-quinuclidinyl, G = *endo*-granisyl, morph = morpholine.

<sup>b</sup> h5-HT<sub>3A</sub> (nM), *n* ≥ 3.

<sup>c</sup> Human CYP 3A4 inhibition IC<sub>50</sub> (μM).<sup>19</sup>

<sup>d</sup> Compounds were incubated with human liver microsomes; data reported in μL/min/mg.<sup>20</sup>

<sup>e</sup> 5-point IC<sub>50</sub> (μM) reported from HEK cells stably expressing the hERG potassium channel by the patch clamp technique on a Molecular Devices Patch Express 7000 (MDS).<sup>21</sup>

<sup>f</sup> Data from rats (*n* = 3 per group) dosed either 10 mg/kg po or 1 mg/kg iv.

activity was confirmed for all compounds at 30 mg/kg po as demonstrated by inhibition of the 5-HT induced bradycardia reflex in mice, the so-called Bezold–Jarisch model.<sup>15</sup> 2-Aminobenzoxazoles **20** and **21** exhibited the best starting profile for a hit to lead optimization campaign. For example, compound **20** has excellent in vitro metabolic stability and CYP inhibition properties. The initial low intrinsic clearance (CL<sub>int</sub>) in human liver microsomes was attractive. No significant inhibition (>50% inhibition at 1 μM) for off-target receptors<sup>16</sup> was observed in a 68-membered panel. The compound was neither mutagenic nor cytotoxic in a mini Ames screen (TA98 and TA100 ± S9) up to 100 μM.<sup>17</sup> Increasing the binding affinity for the 5-HT<sub>3</sub> receptor was an area for initial improvement.

The initial SAR study in the 2-amino series focused on preparing alkyl substituted morpholines as shown in Table 3. 5-HT<sub>3</sub> receptor binding is sensitive to the position and stereochemistry of alkyl substituents on the cyclic amine. An (*S*)-substituent is preferred

**Table 3**  
In vitro 5-HT<sub>3</sub> receptor binding data: cyclic amine SAR

Compd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	X	K <sub>i</sub> <sup>a</sup> (nM)
<b>20</b>	G	H	H	H	H	O	40.0 ± 5.5
<b>21</b>	( <i>S</i> )-Q	H	H	H	H	O	165 ± 25
<b>26</b>	G	H	( <i>S</i> )-Me	H	H	O	12.9 ± 3.7
<b>27</b>	G	H	( <i>R</i> )-Me	H	H	O	92.6 ± 13.7
<b>28</b>	G	H	( <i>S</i> )-Et	H	H	O	4.6 ± 1.6
<b>29</b>	G	H	( <i>S</i> )- <i>n</i> -Pr	H	H	O	3.9 ± 0.8
<b>30</b>	G	H	( <i>S</i> )- <i>i</i> -Pr	H	H	O	5.0 ± 1.1
<b>31</b>	G	H	( <i>S</i> )- <i>i</i> -Bu	H	H	O	3.5 ± 0.9
<b>32</b>	G	H	( <i>S</i> )- <i>t</i> -Bu	H	H	O	2.0 ± 0.3
<b>33</b>	G	( <i>S</i> )-Me	( <i>S</i> )-Me	H	H	O	0.6 ± 0.3
<b>34</b>	( <i>S</i> )-Q	( <i>S</i> )-Me	( <i>S</i> )-Me	H	H	O	6.8 ± 6.4
<b>35</b>	G	( <i>S</i> )-Me	( <i>S</i> )-Et	H	H	O	1.0 ± 0.2
<b>36</b>	G	H	H	( <i>R</i> )-Me	( <i>S</i> )-Me	O	35.3 ± 18.1
<b>37</b>	G	H	H	H	H	NH	72.2 ± 4.0
<b>38</b>	G	H	( <i>S</i> )-Me	H	H	NH	16.5 ± 8.7
<b>39</b>	G	cis-Me	Me	H	H	NH	37.3 ± 21.0
<b>40</b>	G	( <i>R</i> )-Me	( <i>R</i> )-Me	H	H	NH	59.4 ± 24.1
<b>41</b>	G	( <i>S</i> )-Me	( <i>S</i> )-Me	H	H	NH	2.4 ± 0.6

<sup>a</sup> h5-HT<sub>3A</sub> (*n* ≥ 3).

**Table 4**  
Acyclic 2-amino benzoxazoles

Compd	Amine	R	K <sub>i</sub> <sup>a</sup>
<b>42</b>	Q	NEt <sub>2</sub>	12.4 ± 7.3
<b>43</b>	Q	<i>i</i> -PrNMe	66.5 ± 32.8
<b>44</b>	Q	NMe <sub>2</sub>	18.2 ± 4.5
<b>45</b>	Q	NHEt	36.4 ± 20.3
<b>46</b>	Q	NHMe	36.4 ± 19.2
<b>47</b>	Q	NH <sub>2</sub>	13.8 ± 4.2
<b>48</b>	Q	6-Cl, NH <sub>2</sub>	4.7 ± 1.7

<sup>a</sup> h5-HT<sub>3A</sub> (*n* ≥ 3).

**Table 5**  
Profile of compounds **41**, **47** and **48**

Compd	K <sub>i</sub> <sup>a</sup>	CYP <sup>b</sup>	CL <sub>int</sub> <sup>c</sup>	hERG <sup>d</sup>	Bezold–Jarisch <sup>e</sup>
<b>41</b>	2.4 ± 0.6	1.4, 2C19	<2	6.4	0.85
<b>47</b>	13.8 ± 4.2	>100	<2	>30	1.08
<b>48</b>	4.7 ± 1.7	>30	3	4.8	0.40
Ondansetron	3.4 ± 1.7	9.3, 3A4	5	0.4	0.54
Alosetron	0.5 ± 0.1	0.6, 3A4	3	2.3	0.02

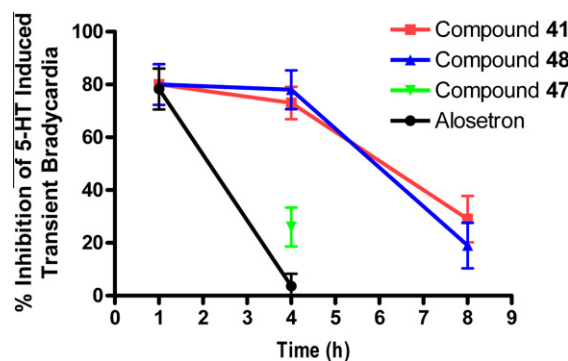
<sup>a</sup> h5-HT<sub>3A</sub> (nM, *n* ≥ 3).

<sup>b</sup> Human CYP inhibition IC<sub>50</sub> (μM). CYP isoforms tested: 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, CYP isoforms showing IC<sub>50</sub> <10 μM are specified.

<sup>c</sup> Compounds were incubated with human liver microsomes; data reported in μL/min/mg.

<sup>d</sup> 5-point IC<sub>50</sub> (μM) reported from HEK cells stably expressing the hERG potassium channel by the patch clamp technique on a Molecular Devices Patch Express 7000.

<sup>e</sup> Compounds were dosed po to mice one hour prior to 0.1 mg/kg 5-HT challenge. ED<sub>50</sub> determined by 4-point dose–response, *n* = 5 mice per dose.

**Figure 2.** Duration of action in mice. Compounds were compared at ED<sub>80</sub> po doses (1.9 mg/kg **41**, 1.3 mg/kg **47**, 0.56 mg/kg **48**, 0.05 mg/kg alosetron) for the ability to inhibit 5-HT induced bradycardia in mice.

over an (*R*)-substituent at the R<sup>3</sup> position (compare **26** and **27**). Larger alkyl groups at R<sup>3</sup> improve the binding affinity (**28–32**). An additional (*S*)-substituent at R<sup>2</sup> further increased affinity for the 5-HT<sub>3</sub> receptor (**33–35**), but there was no obvious advantage for substituents at R<sup>4</sup> and R<sup>5</sup> (**36**). Application of the morpholine SAR trends to piperazine analogues gave similar results. For example, (2*S*,6*S*)-dimethyl substitution on the piperazine ring (**41**) increased potency for the 5-HT<sub>3</sub> receptor 30-fold compared to the unsubstituted parent piperazine, **37**. The cis-2,6-disubstituted piperazine **39** was not more potent than the singly substituted compound **38**. The (2*R*,6*R*)-dimethyl piperazine **40** was also a much weaker binder than **41**, highlighting the stereochemical preference.

Considering the success in optimizing cyclic amines, simple acyclic amines were prepared and tested for 5-HT<sub>3</sub> receptor activity (Table 4).<sup>18</sup> Compared to the cyclic starting point morpholine **20**, alicyclic side chains gave 5-HT<sub>3</sub> receptor binding potencies

similar in magnitude to that of singly methyl-substituted morpholine **26** or piperazine **38**. For compound **44**, it was observed that, following incubation with mammalian microsomes for 4 h, products resulting from N-demethylation, including di-N-demethylation for some species, were detected by LC/MS. In total, eight metabolites were detected in vitro for this compound. Since one goal of the project was to deliver an end product with a simple metabolite profile, the 2-amino analogs, **47** and **48**, were prepared to eliminate the dealkylation pathway.<sup>22</sup> A subsequent metabolism study using human liver microsomes confirmed that only 2 and 3 metabolites were now detected by LC/MS for **47** and **48**, respectively. In a similar study, piperazine **41** gave three human metabolites.

Compounds **41**, **47** and **48**, had a balance of desirable in vitro properties such as improved 5-HT<sub>3</sub> receptor binding, low CYP inhibition, low intrinsic clearance in human liver microsomes, and 1000-fold or greater separation from hERG functional activity that resulted in their selection for further in vivo testing (Table 5).

To assess in vivo functional activity, the compounds were measured for efficacy and duration of action in the murine von Bezold-Jarisch reflex assay.<sup>23</sup> The compounds are able to block 5-HT induced transient bradycardia when dosed orally and exhibit efficacy similar to ondansetron. The duration of action study compared AMRI compounds to alosetron (Fig. 2), each at their respective ED<sub>80</sub> oral doses. The duration study indicated that all three compounds were longer acting than alosetron. Compounds **41** and **48** exhibited long duration of action in that they were able to inhibit 5-HT induced transient bradycardia up to 8 h after oral dosing.

2-Aminobenzoxazole carboxamides **41**, **47** and **48** were identified as potent 5-HT<sub>3</sub> receptor antagonists in a hit to lead optimization campaign. Early profiling suggests these 2-aminobenzoxazole carboxamides have drug-like properties. The compounds are active by the oral route in mice, blocking 5-HT induced transient bradycardia. Compounds **41** and **48** show extended duration of action in the mouse. The findings demonstrate the series can produce compounds with oral efficacy, long duration of action and a reduced number of metabolites relative to alosetron.

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22. The NH<sub>2</sub> group may be viewed as a metabolic liability or potential toxicophore. In this case, the NH<sub>2</sub> functionality has a calculated pK<sub>a</sub> of 14.0 and is therefore predicted to be amide-like. No reactive metabolites were detected using three trapping agents (glutathione, semicarbazide and KCN) for either **47** or **48** at 100 μM in incubations with human liver microsomes. In addition, these compounds were neither mutagenic nor cytotoxic in a mini Ames screen (TA98 and TA100 ± S9) up to 100 μM.
23. Animal data was obtained at MDS Pharma according to: Saxena, P. R.; Lawang, A. *Arch. Int. Pharmacodyn. Ther.* **1985**, *277*, 235.