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Azaadamanthane 1 was converted to a series of aminoaazaadamanthane benzanides 9a-d which were profiled for serotonin receptor activity. Aminomethylazaadamanthane SC-54750 is a potent 5-HT4 agonist and 5-HT3 antagonist with in vivo efficacy in gastroparesis models and also inhibits cisplatin-induced emesis.

\[
\text{SC-54750}
\]

\[
\begin{align*}
\text{5-HT4 TMM EC}_{50} &= 104.6 \text{ nM} \\
\text{5-HT3 IC}_{50} &= 3.5 \text{ nM} \\
\text{canine gastroparesis ED}_{80} &= 0.62 \text{ mpk ig} \\
\text{cisplatin emesis ID}_{50} &= 0.3 \text{ mpk iv}
\end{align*}
\]
Azaadamantane Benzamide 5-HT4 Agonists: Gastrointestinal Prokinetic SC-54750

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Abstract—Azaadamantanone 1 was converted to a series of aminoazaadamantane benzamides 9a-d which were profiled for serotonin receptor activity. Aminomethylazaadamantane SC-54750 is a potent 5-HT4 agonist and 5-HT3 antagonist with in vivo efficacy in gastroparesis models and also inhibits cisplatin-induced emesis.

Serotonin (5-hydroxytryptamine, 5-HT) functions as both a hormone and a neurotransmitter, controlling a host of central and peripheral effects via a number of receptors.1 The 5-HT4 receptor was discovered by Clark2 and Bockaert3 in the brain and gut, respectively, and is expressed in a wide variety of tissues including brain, heart, bladder, gut and kidney.4,5 Initial demonstration that renzapride and cisapride could enhance contractile activity at neuronal 5-HT4 receptors in the guinea pig ileum was made by Craig and Clarke.6 It was later demonstrated that 5-HT4 receptors mediate the relaxation of smooth muscle of the inner muscularis mucosae of rat esophagus7 and also the cholinergic stimulation of the ascending colon of the guinea pig.8 The 5-HT4 partial agonist tegaserod (SDZ HTF 919) was approved in 2002 for the treatment of constipation-predominant irritable bowel syndrome (IBS).9 Tegaserod showed a clear effect on the total colonic transit time in healthy subjects, and a significant improvement in patients with constipation-predominant IBS in a phase III trial.10 Cisapride (PrepulsidTM) had been marketed for motility disorders11 but was withdrawn due to potent hERG block and QT prolongation.12 An excellent review of the 5-HT4 receptor and key ligands was recently published.13

We have investigated a number of conformationally-constrained tertiary amine derivatives as serotonin 5-HT4 agonist and antagonists, and as 5-HT3 antagonists.14 We previously reported the 5-HT4 activity of pyrrolizidine SC-53116,15 the first selective 5-HT4 agonist, and SC-53606, a selective 5-HT4 antagonist.16 We have also reported the blended 5-HT3/5-HT4 activity of azanoradamantane SC-5249117, which is a mixed 5-HT4 agonist/5-HT3 antagonist, and of a series of meso-azanoradamantanes.18 Azaadamantanes are theoretically interesting molecules19 with many potential uses20 and have the advantage that they lack chirality. Herein we detail our investigation of aminoazaadamantane benzamides and disclose the aminomethylazaadamantane clinical candidate SC-54750, a selective 5-HT4 agonist with excellent in vivo pharmacology demonstrating utility as a gastrointestinal prokinetic agent.
We previously reported the synthesis of the individual syn and anti aminoazaadamantanes 2 and 3 via 1-azatricyclo[3.3.1.1^{3,7}]decan-4-one 1 (Scheme 1).\(^{21}\) Homologation of 1 was accomplished utilizing van Leusen’s reductive alkylation\(^{22}\) of 1 with tosylmethyl isocyanide (TosMIC) to give the nitriles 4 and 5 (Scheme 2), which were separated by chromatography on silica gel eluting with MeOH(NH\(_3\))/CHCl\(_3\). Reduction of the nitriles independently with lithium aluminum hydride gave the distillable amines 6 and 7, which suffered \(\leq 2\%\) epimerization in the reduction procedure. Benzamide coupling of the aminoazaadamantanes with 4-amino-5-chloro-2-methoxy benzoic acod 8 utilizing carbonyldiimidazole (CDI) as the coupling reagent gave the requisite aminoazaadamantane benzamides which were treated with hydrogen chloride to afford the crystalline monohydrochloride salts 9a-d (Scheme 3).
As seen in Table 1, *anti*-aminoazaadamantane 9b is twice as potent as the corresponding *syn*-isomer 9a in 5-HT₄ agonism in the rat tunica muscularis mucosae (TMM) assay, and the *anti*-isomer is an order of magnitude more potent in 5-HT₃ receptor binding (Ki = 57 nM vs. > 500 nM). *Anti*-aminoazaadamantane 9b is also substantially (37X) more potent than the syn-isomer in 5-HT₃ binding. This greater potency for the 5-HT₃ receptor is also revealed in the Bezold-Jarisch reflex in mice, where 9b affords > 50% inhibition down to 0.03 mpk ip, whereas 9a is inactive at 3 mpk. With the homologated aminomethylazaadamantanes, it is the *syn*-isomer that is more potent at both receptors. *Syn*-isomer 9c (SC-54750) is 5X more potent than anti-isomer 9d as an agonist at the 5-HT₄ receptor in the TMM assay (73.6 nM vs. 545 nM) and is 5X more potent in binding at the 5-HT₃ receptor (Ki = 25.4 nM vs. 143.7 nM). This differential in 5-HT₃ potency is reflected in the greater potency of inhibition of the 5-HT₃ receptor by SC-54750 in the von Bezold-Jarisch reflex assay, with 9c affording >50% inhibition down to 0.1 mpk versus 9d, which is inactive at 1 mpk.

Aminomethylazaadamantane SC-54750 is highly selective versus other monoamine receptors, as are the other azaadamantane derivatives, as summarized in Table 2, with no affinity detected (IC₅₀ > 10,000 nM) for serotonin 5-HT₁ or 5-HT₂ receptors, dopamine D₁ or D₂ receptors, α₁ or α₂ adrenergic receptors, or β-adrenergic receptors. SC-54750 is quite similar to SC-52491 in potency for both 5-HT₄ and 5-HT₃ receptors and possesses exquisite selectivity versus other monoamine receptors. Cisapride, in contrast, binds to D₂ and α₁ receptors, and is exceptionally potent for the 5-HT₂ receptor (IC₅₀ = 6.1 nM).
Table 1. In vitro serotonergic activity of aminoazaadamantane benzamides 9a-d

![Chemical structures of compounds 9a-d](image)

<table>
<thead>
<tr>
<th>Entry (stereo)</th>
<th>n</th>
<th>5-HT$_2$ Binding Ki, nM (SEM)</th>
<th>5-HT$_4$ agonism in rat TMM EC50 (nM)</th>
<th>5-HT$_3$ Binding Ki (nM)</th>
<th>Bezold-Jarisch Reflex, 5-HT$_3$ antagonism, % inhib at dose (mpk ip)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9a (syn)</strong></td>
<td>0</td>
<td>&gt; 500</td>
<td>538</td>
<td>336</td>
<td>85% at 10, 0% at 3</td>
</tr>
<tr>
<td><strong>9b (anti)</strong></td>
<td>0</td>
<td>57</td>
<td>262</td>
<td>9</td>
<td>86% at 10, 81% at 3, 75% at 1, 70% at 0.3, 64% at 0.1, 61% at 0.03</td>
</tr>
<tr>
<td><strong>9c (syn)</strong></td>
<td>1</td>
<td>51</td>
<td>73.6</td>
<td>25.4</td>
<td>88% at 10, 82% at 8, 82% at 1, 75% at 0.3, 60% at 0.1, 0% at 0.03</td>
</tr>
<tr>
<td><strong>9d (anti)</strong></td>
<td>1</td>
<td>ND</td>
<td>545</td>
<td>143.7</td>
<td>85% at 10, 82% at 3, 0% at 1</td>
</tr>
</tbody>
</table>
Table 2. Receptor profiling of azaadamantane benzamides 9a-d and cisapride: ED50 [5-HT₄] or IC₅₀ [all others], nM

<table>
<thead>
<tr>
<th>Entry</th>
<th>5-HT₄</th>
<th>5-HT₃</th>
<th>5-HT₁</th>
<th>5-HT₂</th>
<th>D₁</th>
<th>D₂</th>
<th>α₁</th>
<th>α₂</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>538</td>
<td>672</td>
<td>&gt;10K</td>
<td>1800</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
</tr>
<tr>
<td>9b</td>
<td>262</td>
<td>18</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
</tr>
<tr>
<td>SC-54750</td>
<td>73.6</td>
<td>3.5</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
</tr>
<tr>
<td>9d</td>
<td>545</td>
<td>11</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>&gt;10K</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>SC-52491</td>
<td>51.3</td>
<td>2.3</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
<td>&gt;10K</td>
</tr>
<tr>
<td>Cisapride</td>
<td>54.7</td>
<td>134</td>
<td>&gt;10K</td>
<td>6.1</td>
<td>1700</td>
<td>227</td>
<td>30</td>
<td>4500</td>
<td>&gt;10K</td>
</tr>
</tbody>
</table>
SC-54750 was selected for further study and was found to be a potent stimulator of gastric emptying in rats, with comparable activity that is observed for oral dosing when given at 3X the iv dose. SC-54750 is a potent stimulator of gastric contractile activity in fasted dogs that were surgically implanted with strain gauges.28 SC-54750 is comparable to cisapride in eliciting antral contractions, with intestinal myoelectric spike burst (contractile) activity that is stimulated in the same dose range.

The dosages responsible for eliciting gastric antral contractile responses in dogs corresponded well to the gastric emptying profiles. In a canine gastroparesis model of 5-HT₄ agonism²⁹ SC-54750 is potent and efficacious in restoring normal motility, exhibiting an EC₅₀ of 0.03 mg/kg iv and an ED₈₀ of 0.62 mg/kg, ig. The 5-HT₃ antagonism of SC-54750 gives rise to effective inhibition of cisplatin-induced emesis in dogs, with an ID₅₀ of 0.3 mg/kg, iv. The compound was orally active in this model as well.

SC-54750 is an achiral gastrointestinal prokinetic benzamide which compares quite favorably with cisapride and SC-52491. SC-54750 is a potent 5-HT₄ agonist and 5-HT₃ receptor antagonist with excellent selectivity. It is orally active in stimulating gastrointestinal motility and in blocking cisplatin-induced emesis.

References and Notes


23. Cumulative dose-response curves for agonists interacting with 5-HT4 receptors of rat TMM were done according to the method of Baxter, Craig and Clarke. See ref. 2. 

24. Serotonin 5-HT4 binding in guinea pig striatum was measured utilizing [3H]-GR113,808 and was performed by MDS Pharma Services [formerly Panlabs Taiwan] according to the literature method: Grossman, C. J.; Kilpatrick, G. J.; Bunce, K. T. Br. J. Pharmacol. 1993, 109, 618-624. 

25. The assay of Kilpatrick was employed for 5-HT3 binding using [3H]-GR65630 as the radioligand with male rat cortical tissue. See Kilpatrick, G. J.; Jones, B.J.; Tyers, M. B.; Nature, 1987, 330, 746. 

26. The von Bezold-Jarisch Reflex assay was performed according to the literature: P. R. Saxena and A. Lawang, Arch. Int. Pharmacodyn. 1985, 277, 235. 

27. Radioligands used for receptor profiling studies: [3H]-5-HT for 5-HT1-like receptors; [3H]-ketanserin for 5-HT2 receptors; [3H]-SCH23390 for D-1 receptors; [3H]-spiperone for D-2 receptors; [3H]-prazosin for alpha-1 adrenergic receptors. 
