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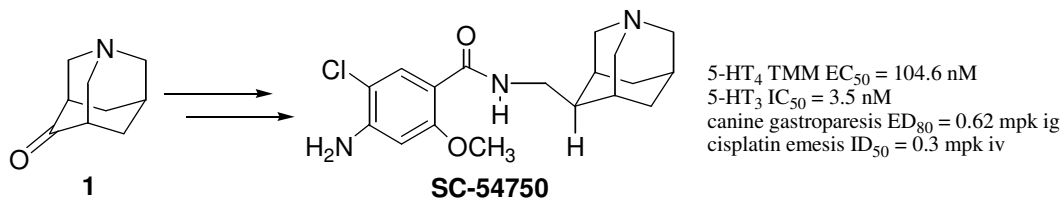
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## Azaadamantane Benzamide 5-HT<sub>4</sub> Agonists: Gastrointestinal Prokinetic SC-54750

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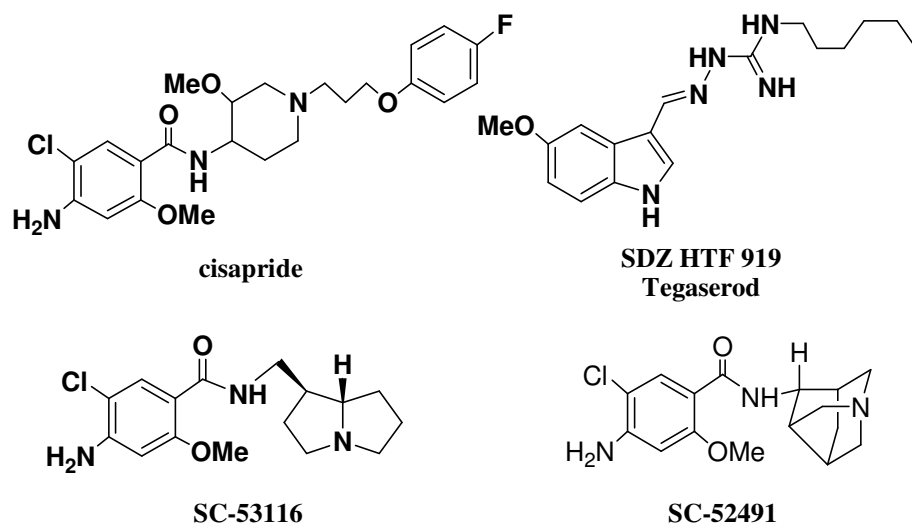
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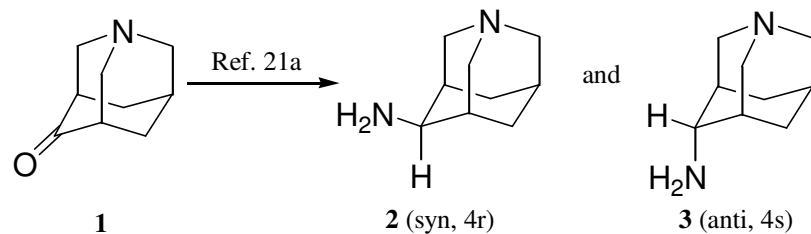
**Abstract**—Azaadamantanone **1** was converted to a series of aminoazaadamantane benzamides **9a-d** which were profiled for serotonin receptor activity. Aminomethylazaadamantane **SC-54750** is a potent 5-HT<sub>4</sub> agonist and 5-HT<sub>3</sub> antagonist with *in vivo* efficacy in gastroparesis 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.<sup>1</sup> The 5-HT<sub>4</sub> receptor was discovered by Clark<sup>2</sup> and Bockaert<sup>3</sup> in the brain and gut, respectively, and is expressed in a wide variety of tissues including brain, heart, bladder, gut and kidney.<sup>4,5</sup> Initial demonstration that renzapride and cisapride could enhance contractile activity at neuronal 5-HT<sub>4</sub> receptors in the guinea pig ileum was made by Craig and Clarke.<sup>6</sup> It was later demonstrated that 5-HT<sub>4</sub> receptors mediate the relaxation of smooth muscle of the inner muscularis mucosae of rat esophagus<sup>7</sup> and also the cholinergic stimulation of the ascending colon of the guinea pig.<sup>8</sup> The 5-HT<sub>4</sub> partial agonist tegaserod (SDZ HTF 919) was approved in 2002 for the treatment of constipation-predominant irritable bowel syndrome (IBS).<sup>9</sup> 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.<sup>10</sup> Cisapride (Prepulsid<sup>TM</sup>) had been marketed for motility disorders<sup>11</sup> but was withdrawn due to potent hERG block and QT prolongation.<sup>12</sup> An excellent review of the 5-HT<sub>4</sub> receptor and key ligands was recently published.<sup>13</sup>

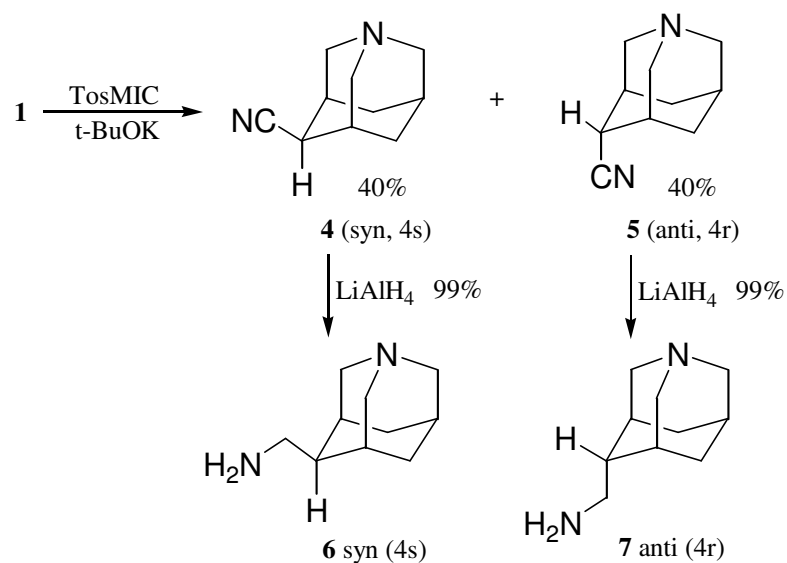
We have investigated a number of conformationally-constrained tertiary amine derivatives as serotonin 5-HT<sub>4</sub> agonist and antagonists, and as 5-HT<sub>3</sub> antagonists.<sup>14</sup> We previously reported the 5-HT<sub>4</sub> activity of pyrrolizidine **SC-53116**,<sup>15</sup> the first selective 5-HT<sub>4</sub> agonist, and **SC-53606**, a selective 5-HT<sub>4</sub> antagonist.<sup>16</sup> We have also reported the blended 5-HT<sub>3</sub>/5-HT<sub>4</sub> activity of azanoradamantane **SC-52491**<sup>17</sup>, which is a mixed 5-HT<sub>4</sub> agonist/5-HT<sub>3</sub> antagonist, and of a series of meso-azanoradamantanes.<sup>18</sup> Azaadamantanes are theoretically interesting molecules<sup>19</sup> with many potential uses<sup>20</sup> 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-HT<sub>4</sub> agonist with excellent *in vivo* pharmacology demonstrating utility as a gastrointestinal prokinetic agent.



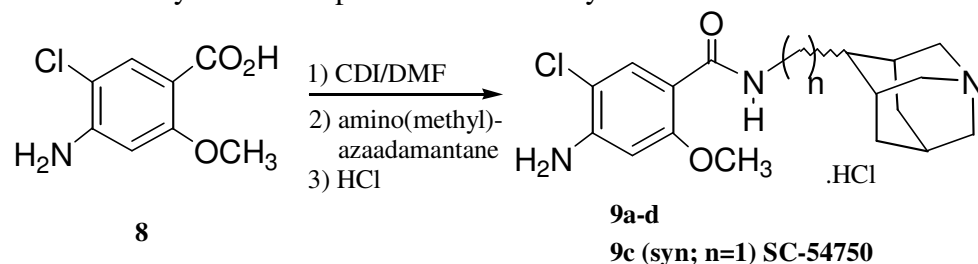
We previously reported the synthesis of the individual *syn* and *anti* aminoazaadamantanes **2** and **3** via 1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-4-one **1** (Scheme 1).<sup>21</sup> Homologation of **1** was accomplished utilizing van Leusen's reductive alkylation<sup>22</sup> of **1** with tosylmethyl isocyanide (TosMIC) to give the nitriles **4** and **5** (Scheme 2), which were separated by chromatography on silica gel eluting with MeOH(NH<sub>3</sub>)/CHCl<sub>3</sub>. 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 acid **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).



**Scheme 1.** Preparation of epimeric aminoazaadamantanes **2** and **3**.



**Scheme 2.** Synthesis of epimeric aminomethylazaadamantanes **6** and **7**.

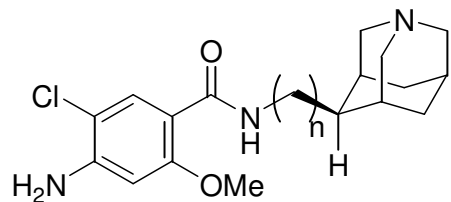


**Scheme 3.** Coupling procedure to afford aminoazaadamantane benzamides **9a-d**.

As seen in Table 1, *anti*-aminoazaadamantane **9b** is twice as potent as the corresponding *syn*-isomer **9a** in 5-HT<sub>4</sub> agonism in the rat tunica muscularis mucosae (TMM) assay,<sup>23</sup> and the *anti*-isomer is an order of magnitude more potent in 5-HT<sub>4</sub> receptor binding<sup>24</sup> (K<sub>i</sub> = 57 nM vs. > 500 nM). *Anti*-aminoazaadamantane **9b** is also substantially (37X) more potent than the *syn*-isomer in 5-HT<sub>3</sub> binding.<sup>25</sup> This greater potency for the 5-HT<sub>3</sub> receptor is also revealed in the Bezold-Jarisch reflex<sup>26</sup> 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-HT<sub>4</sub> receptor in the TMM assay (73.6 nM vs. 545 nM) and is 5X more potent in binding at the 5-HT<sub>3</sub> receptor (K<sub>i</sub> = 25.4 nM vs. 143.7 nM). This differential in 5-HT<sub>3</sub> potency is reflected in the greater potency of inhibition of the 5-HT<sub>3</sub> 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.

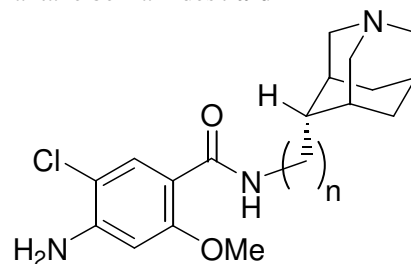
Aminomethylazaadamantane SC-54750 is highly selective versus other monoamine receptors,<sup>27</sup> as are the other azaadamantane derivatives, as summarized in Table 2, with no affinity detected (IC<sub>50</sub> > 10,000 nM) for serotonin 5-HT<sub>1</sub> or 5-HT<sub>2</sub> receptors, dopamine D<sub>1</sub> or D<sub>2</sub> receptors, α<sub>1</sub> or α<sub>2</sub> adrenergic receptors, or β-adrenergic receptors. SC-54750 is quite similar to SC-52491 in potency for both 5-HT<sub>4</sub> and 5-HT<sub>3</sub> receptors and possesses exquisite selectivity versus other monoamine receptors. Cisapride, in contrast, binds to D<sub>2</sub> and α<sub>1</sub> receptors, and is exceptionally potent for the 5-HT<sub>2</sub> receptor (IC<sub>50</sub> = 6.1 nM).

**Table 1.** In vitro serotonergic activity of aminozaadamantane benzamides **9a-d**



**9a** (n=0)

**9c** (n=1; SC-54750)



**9b** (n=0)

**9d** (n=1)

| Entry (stereo)                          | n | 5-HT <sub>4</sub> Binding Ki, nM (SEM) | 5-HT <sub>4</sub> agonism in rat TMM EC50 (nM) | 5-HT <sub>3</sub> Binding Ki (nM) | Bezold-Jarisch Reflex, 5-HT <sub>3</sub> antagonism, % inhib at dose (mpk ip) |
|---|---|--|--|-----------------------------------|---|
| <b>9a</b><br>( <i>syn</i> )             | 0 | > 500                                  | 538  | 336                               | 85% at 10<br>0% at 3  |
| <b>9b</b><br>( <i>anti</i> )            | 0 | 57                                     | 262  | 9                                 | 86% at 10<br>81% at 3<br>75% at 1<br>70% at 0.3<br>64% at 0.1<br>61% at 0.03  |
| <b>9c</b><br>( <i>syn</i> )<br>SC-54750 | 1 | 51                                     | 73.6   | 25.4                              | 88% at 10<br>82% at 8<br>82% at 1<br>75% at 0.3<br>60% at 0.1<br>0% at 0.03   |
| <b>9d</b><br>( <i>anti</i> )            | 1 | ND                                     | 545  | 143.7                             | 85% at 10<br>82% at 3<br>0% at 1  |

**Table 2.** Receptor profiling of azaadamantane benzamides **9a-d** and cisapride: ED<sub>50</sub> [5-HT<sub>4</sub>] or IC<sub>50</sub> [all others], nM

| <b>Entry</b>       | <b>5-HT<sub>4</sub></b> | <b>5-HT<sub>3</sub></b> | <b>5-HT<sub>1</sub></b> | <b>5-HT<sub>2</sub></b> | <b>D<sub>1</sub></b> | <b>D<sub>2</sub></b> | <b>α<sub>1</sub></b> | <b>α<sub>2</sub></b> | <b>β</b> |
|--------------------|-------------------------|-------------------------|-------------------------|-------------------------|----------------------|----------------------|----------------------|----------------------|----------|
| <b>9a</b>          | 538                     | 672                     | >10K                    | 1800                    | >10K                 | >10K                 | >10K                 | 6400                 | >10K     |
| <b>9b</b>          | 262                     | 18                      | >10K                    | >10K                    | >10K                 | >10K                 | >10K                 | >10K                 | >10K     |
| <b>9c SC-54750</b> | 73.6                    | 3.5                     | >10K                    | >10K                    | >10K                 | >10K                 | >10K                 | >10K                 | >10K     |
| <b>9d</b>          | 545                     | 11                      | ND                      | ND                      | ND                   | >10K                 | ND                   | ND                   | ND       |
| <b>SC-52491</b>    | 51.3                    | 2.3                     | >10K                    | >10K                    | >10K                 | >10K                 | >10K                 | >10K                 | >10K     |
| <b>Cisapride</b>   | 54.7                    | 134                     | >10K                    | 6.1                     | 1700                 | 227                  | 30                   | 4500                 | >10K     |

**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.<sup>28</sup> **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-HT<sub>4</sub> agonism<sup>29</sup> **SC-54750** is potent and efficacious in restoring normal motility, exhibiting an EC<sub>50</sub> of 0.03 mg/kg iv and an ED<sub>80</sub> of 0.62 mg/kg, ig. The 5-HT<sub>3</sub> antagonism of **SC-54750** gives rise to effective inhibition of cisplatin-induced emesis in dogs, with an ID<sub>50</sub> 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-HT<sub>4</sub> agonist and 5-HT<sub>3</sub> receptor antagonist with excellent selectivity. It is orally active in stimulating gastrointestinal motility and in blocking cisplatin-induced emesis.

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