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Azaadamantane Benzamide 5-HT₄ Agonists: Gastrointestinal Prokinetic SC-54750

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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.

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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IBS in a phase III trial.¹⁰ Cisapride (PrepulsidTM) had been marketed for motility disorders¹¹ but was withdrawn due to potent hERG block and QT prolongation.¹² An excellent review of the 5-HT₄ receptor and key ligands was recently published.¹³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-52491**¹⁷, 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 alkylation²² 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(NH₃)/CHCl₃. 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-HT₄ agonism in the rat tunica muscularis mucosae (TMM) assay,²³ and the *anti*-isomer is an order of magnitude more potent in 5-HT₄ receptor binding²⁴ ($K_i = 57$ nM vs. > 500 nM). *Anti*-aminoazaadamantane **9b** is also substantially (37X) more potent than the *syn*-isomer in 5-HT₃ binding.²⁵ This greater potency for the 5-HT₃ receptor is also revealed in the Bezold-Jarisch reflex²⁶ 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 ($K_i = 25.4$ 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,²⁷ as are the other azaadamantane derivatives, as summarized in Table 2, with no affinity detected ($IC_{50} > 10,000$ nM) for serotonin 5-HT₁ or 5-HT₂ receptors, dopamine D₁ or D₂ receptors, α_1 or α_2 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 α_1 receptors, and is exceptionally potent for the 5-HT₂ receptor ($IC_{50} = 6.1$ nM).

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

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

Table 2. Receptor profiling of azaadamantane benzamides **9a-d** and cisapride: ED₅₀ [5-HT₄] or IC₅₀ [all others], nM

Entry	5-HT ₄	5-HT ₃	5-HT ₁	5-HT ₂	D ₁	D ₂	α ₁	α ₂	β
9a	538	672	>10K	1800	>10K	>10K	>10K	6400	>10K
9b	262	18	>10K	>10K	>10K	>10K	>10K	>10K	>10K
9c SC-54750	73.6	3.5	>10K	>10K	>10K	>10K	>10K	>10K	>10K
9d	545	11	ND	ND	ND	>10K	ND	ND	ND
SC-52491	51.3	2.3	>10K	>10K	>10K	>10K	>10K	>10K	>10K
Cisapride	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.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.

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