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Azaadamantane benzamide 5-HT4 agonists: gastrointestinal prokinetic SC-54750

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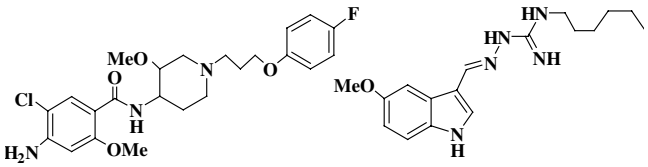
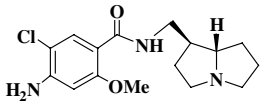
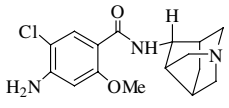
Abstract—Azaadamantanone **1** was converted to a series of aminoazaadamantane benzamides **9a–d**, which were profiled for serotonin receptor activity. Aminomethylazaadamantane **SC-54750** is a potent 5-HT_4 agonist and 5-HT_3 antagonist with in vivo efficacy in gastroparesis models and also inhibits 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-HT_4 receptor was discovered by Clark and co-workers[2] and Bockaert and co-workers[3] 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-HT_4 receptors in the guinea pig ileum was made by Craig and Clarke.[6] It was later demonstrated that 5-HT_4 receptors mediate the relaxation of smooth muscle of the inner muscularis mucosae of rat esophagus[7] and also the cholinergic stimulation of the ascending colon of the guinea pig.[8] The 5-HT_4 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 (Prepulsid™) had been marketed for motility disorders[11] but was withdrawn due to potent hERG block and QT prolongation.[12] An excellent review of the 5-HT_4 receptor and key ligands was recently published.[13]

We have investigated a number of conformationally-constrained tertiary amine derivatives as serotonin 5-HT_4 agonist and antagonists, and as 5-HT_3 antagonists.[14] We previously reported the 5-HT_4 activity of pyrrolizidine **SC-53116**,[15] the first selective 5-HT_4 agonist, and **SC-53606**, a selective 5-HT_4 antagonist.[16] We have also reported the blended 5-HT_3/5-HT_4 activity of azanoradamantane **SC-52491**[17], which is a mixed 5-HT_4 agonist/5-HT_3 antagonist, and of a series of *meso*-azanoradamantanes.[18] Azaadamantanes are theoretically interesting molecules[19] with many potential uses[20] 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_4







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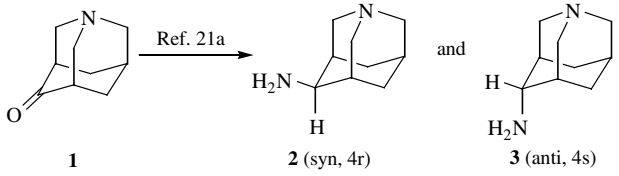
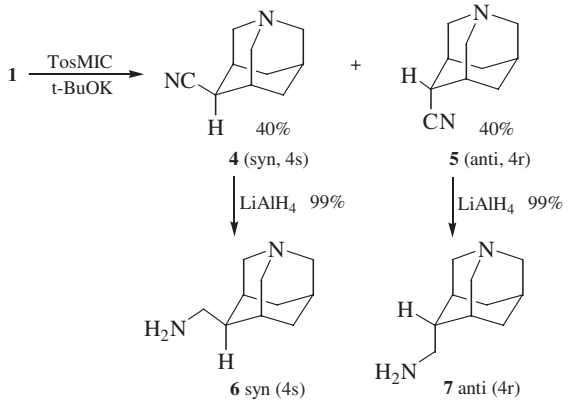
agonist with excellent in vivo pharmacology demonstrating utility as a gastrointestinal prokinetic agent.

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 $\leqslant$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).

As seen in Table 1, *anti*-aminoazaadamantane **9b** is twice as potent as the corresponding *syn*-isomer **9a** in 5-HT_4 agonism in the rat tunica muscularis mucosae (TMM) assay,[23] and the *anti*-isomer is an order of magnitude more potent in 5-HT_4 receptor binding[24] (K_i = 57 nM vs >500 nM). *anti*-Aminoazaadamantane **9b** is also substantially (37×) more potent than the *syn*-isomer in 5-HT_3 binding.[25] This greater potency for the 5-HT_3 receptor is also revealed in the Bezold–Jarisch reflex[26] 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 5× more potent than *anti*-isomer **9d** as an agonist at the 5-HT_4 receptor in the TMM assay (73.6 vs 545 nM) and is 5× more potent in binding at the 5-HT_3 receptor (K_i = 25.4 vs 143.7 nM). This differential in 5-HT_3 potency is reflected in the greater potency of inhibition of the 5-HT_3 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.



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

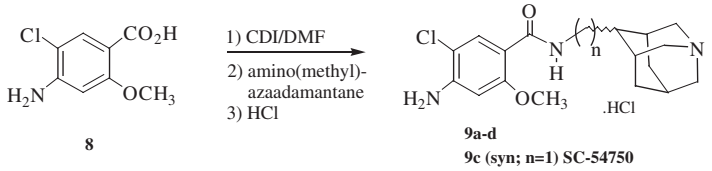


Scheme 2. Synthesis of epimeric aminomethylazaadamantanes **6** and **7**.

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-HT_1 or 5-HT_2 receptors, dopamine D_1 or D_2 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-HT_4 and 5-HT_3 receptors and possesses exquisite selectivity versus other monoamine receptors. Cisapride, in contrast, binds to D_2 and α_1 receptors, and is exceptionally potent for the 5-HT_2 receptor (IC_{50} = 6.1 nM).

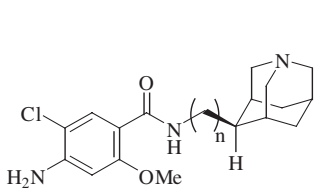
SC-54750 was selected for further study and was found to be a potent stimulator of gastric emptying in rats, with comparable activity that is observed for oral dosing when given at 3× the iv dose. **SC-54750** is a potent stimulator of gastric contractile activity in fasted dogs that were surgically 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-HT_4 agonism[29] **SC-54750** is potent and efficacious in restoring normal motility, exhibiting an EC_{50} of 0.03 mg/kg iv and an ED_{80} of 0.62 mg/kg, ig. The 5-HT_3 antagonism of **SC-54750** gives rise to effective inhibition of cisplatin-induced emesis in dogs, with an ID_{50} of 0.3 mg/kg, iv. The compound was orally active in this model as well.

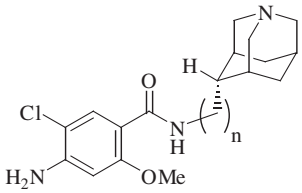


Scheme 3. Coupling procedure to afford aminoazaadamantane benzamides **9a–d**.

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



9a (n=0)
9c (n=1; SC-54750)



9b (n=0)
9d (n=1)

Entry (stereo)	*n*	5-HT_4 Binding K_i, nM (SEM)	5-HT_4 Agonism in rat TMM EC50 (nM)	5-HT_3 Binding K_i (nM)	Bezold–Jarisch reflex, 5-HT_3 antagonism, % inhib at dose (mpk ip)
9a (*syn*)	0	>500	538	336	85% at 10 0% at 3
9b (*anti*)	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 (*syn*) **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 (*anti*)	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: ED_{50} [5-HT_4] or IC_{50} [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 is an achiral gastrointestinal prokinetic benzamide, which compares quite favorably with cisapride and **SC-52491**. **SC-54750** is a potent 5-HT_4 agonist and 5-HT_3 receptor antagonist with excellent selectivity. It is orally active in stimulating gastrointestinal motility and in blocking cisplatin-induced emesis.

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