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NEW AZA(NOR)ADAMANTANES ARE AGONISTS AT THE NEWLY IDENTIFIED SEROTONIN 5-HT4 RECEPTOR AND ANTAGONISTS AT THE 5-HT3 RECEPTOR

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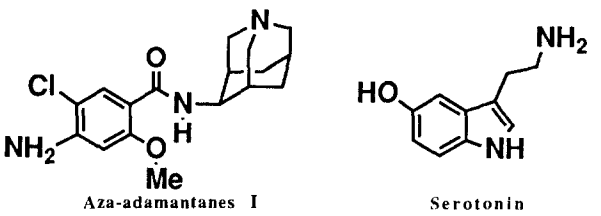
Abstract: New aza(nor)adamantanes **1A**, **1B**, and **1C** are described which exhibit properties of both 5-HT4 agonism and 5-HT3 antagonism. In particular, compound **1C** [SC-52491], an azanoradamantane, exhibits an EC_{50} of 51 nM in a functional model of 5-HT_4 agonism and potent antagonism, Ki = 1.2 nM, at the 5-HT_3 receptor.

Serotonin is a neurotransmitter, neuromodulator, and hormone which exhibits many pharmacological properties both in the central nervous system and in the periphery.[1] Among monoamine neurotransmitters, serotonin is unsurpassed in the number of receptor subtypes identified. Until recently, receptors have been subclassed into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_3.[2] However, some actions of serotonin have remained an enigma, producing effects which do not act via these classical receptors. For instance, the CNS hippocampal receptor positively coupled to adenylate cyclase and the enteric neuronal serotonin receptor mediating peristalsis do not share agonist or antagonist profiles which fit the above receptor classification.

Very recently, Bockaert[3] and Clarke[4] have independently characterized a new serotonin receptor subtype (5-HT_4) in brain hippocampal and gut neuronal tissues, respectively. Serotonin is quite potent (EC50 = 109 nM[3], 2.8 nM[4]) as an agonist at this new receptor, which is positively coupled to adenylate cyclase. Furthermore, the prokinetic activity of several agents, including metoclopramide, zacopride, cisapride, and renzapride, has been correlated with agonist activity at the 5-HT_4 receptor.[5] The search for new agents which act at serotonin 5-HT_4 receptors will aid in the further characterization of this new receptor subtype, as well as provide new therapies for both central nervous system and gastrointestinal diseases. In this regard, we report herein that (nor)azaadamantane substituted benzamides represent a new class of serotonin 5-HT_4 agonists.[6]

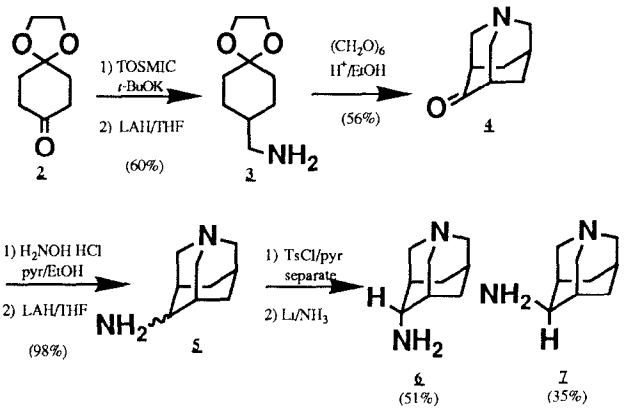
Our initial interest in azaadamantanes was generated by recognizing that 4-amino-1-azaadamantanes **I** might be useful mimics for the fully extended ethylamine side chain of serotonin, a conformation of serotonin not identified for agonism at 5-HT_1, 5-HT_2, or 5-HT_3 receptors (Figure 1). The benzamide portion of **I** is viewed as an indole isostere, wherein the virtual ring realized by intramolecular H-bonding gives the benzamide structure a fused heteroaromatic quality.



Aza-adamantanes I Serotonin

Figure 1

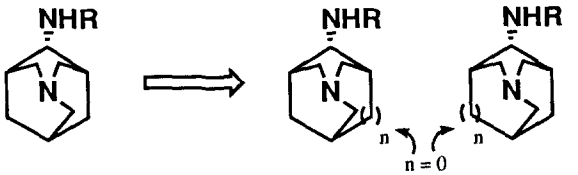
The requisite endo- and exo-4-amino-1-azaadamantanes needed for this investigation were prepared starting from commercially available cyclohexan-1,4-dione mono ketal **2** (Scheme 1).[7] Reductive homologation using tosylmethylisocyanide[8] (TOSMIC) afforded a nitrile which was reduced with lithium aluminum hydride/THF to give the aminomethyl substituted cyclohexane ketal **3** in 60% over-all yield. Double-Mannich condensation under acidic conditions (catalytic H_2SO_4/EtOH/ paraformaldehyde) then afforded 4-oxo-1-azaadamantane **4** directly in 56% isolated yield.[8b,9] Oximation and reduction (LAH/THF) gave the 4-amino-1-azaadamantanes 5 as an inseparable mixture of diastereomers (98% yield). The isomers were separated by conversion to their corresponding tosylamides, silica gel column chromatographic separation (3% ammonia saturated MeOH/97% $CHCl_3$), and reductive removal of the tosyl groups (Li/NH_3) to give the endo-4-amino-1-azaadamantane **6** (51% isolated yield) and exo-4-amino-1-azaadamantane **7** (35% isolated yield).



Scheme 1

The 4-amino-1-azaadamantanes **6** and **7** were coupled with 2-methoxy-4-amino-5-chlorobenzoic acid (CDI, DMF) to give the desired exo-amide 1A and endo-amide 1B (Figure 3) The Table illustrates the 5-

HT_4 agonist and 5-HT_3 antagonist properties of these compounds. Using the rat tunica muscularis mucosae (TMM) esophagus strip assay[10], we found that the exo-amide **1A** exhibited modest potency (EC50 = 538 nM) compared to renzapride (EC50 = 98 nM) and cisapride (55 nM). However, the endo-amide **1B** was approximately two-fold more potent (EC50 = 262 nM). A more pronounced difference in potency was seen regarding 5-HT_3 antagonism.[11] Again the endo-amide **1B** was more potent (Ki = 9 nM) than the exo-**1A** (Ki = 336 nM). This difference in 5-HT_3 binding potencies was reflected in in vivo testing. Amide **1B** exhibited significant inhibition of serotonin (5-HT_3-mediated) bradycardia in the Bezold-Jarisch reflex model (mice).[12] **1B** inhibited bradycardia by 61% even at 30 μg/kg IP (MED), whereas **1A** exhibited significant inhibition only at 10 mg/kg IP. The 5-HT_3 antagonist activity of **1B** compares very favorably with renzapride (MED = 0.25 mg/kg IP) and cisapride (MED = 5.0 mg/kg). It should be noted that **1B** (SC-51718), by virtue of possessing a plane of symmetry, does not exist as a racemic mixture of enantiomers. This obviates the issue of differing biochemical profiles and pharmacologic properties of enantiomeric pairs. Desiring to explore the basic azatricyclic system of the azaadamantanes more fully, we sought analogs wherein the shape of the azaadamantane was maintained but with less carbon-scaffolding. In particular, removal of one or the other enantiotopic methylene connectors, as illustrated with the azanoradamantane system (Figure 2), might remove a source of potential steric interference at the 5-HT_4 receptor and increase potency.



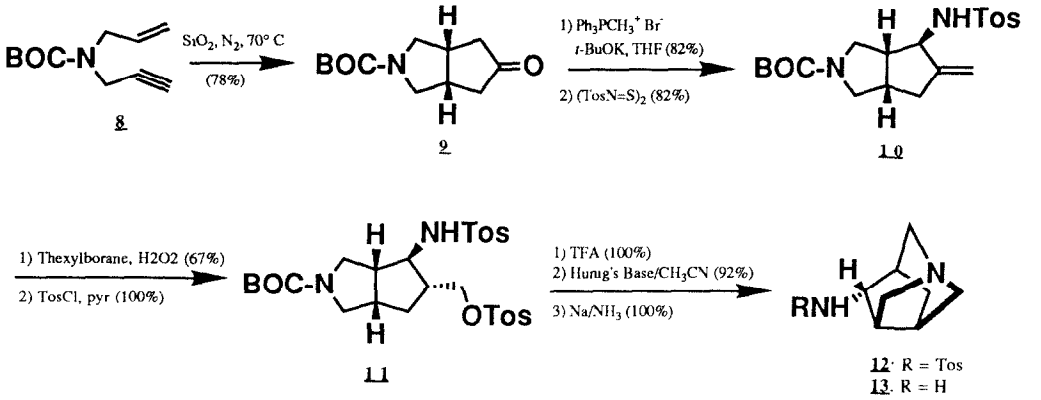
Azaadamantanes **Azanoradamantanes**

Figure 2

The azanoradamantane ring system **1C** represents a new ring system[13]. As illustrated in Scheme 2, entry into this series was initiated by utilizing a solid-phase Pauson-Khand double annulation reaction starting with N-BOC-allylpropargylamine **8**.[14] Noteworthy is the direct formation of the saturated ketone **9** rather than the enone product. We have found that the conjugately-reduced product **9** is routinely produced in high yield by performing the SiO_2-catalyzed reaction under nitrogen atmosphere. Wittig olefination, followed by allylic amination with tosylsulfodiimide[15] afforded the desired exo-allylamine **10** exclusively in 82% yield. Hydroboration/oxidation, followed by tosylation of the primary alcohol, then gave the fully functionalized annulation precursor **11**. Removal of the BOC group (TFA) and exposure to Hunig's base/acetonitrile/50° C afforded the norazaadamantane **12** in 92% isolated yield. Reductive removal of the tosylamide gave the amine **13** to be used in coupling experiments as described above for **6** and **7**.

Indeed, conversion of the azaadamantanes to the azanoradamantanes did result in a significant increase in potency. ***(R)*-1C**[16] [SC-52491, Figure 3] is a potent 5-HT_4 agonist, exhibiting an EC_{50} of 51.3 nM in the

rat TMM assay. This compound is significantly more potent than either azaadamantane **1A** or **1B**, (*S*)-zacopride, or renzapride; and is of comparable potency to cisapride. Additionally, SC-52491 is a very potent 5-HT_3 antagonist both in binding experiments (Ki = 1.2 nM) and in the Bezold-Jarisch reflex functional model (MED = 10 μg/kg IP). By comparison, the enantiomer **(*S*)-1C** is dramatically less active (EC_{50} = 3870 nM) in the 5-HT_4 assay, while being of comparable potency as a 5-HT_3 antagonist. Indeed, this antipode may be viewed as a more selective 5-HT_3 antagonist than any other 2-methoxy-4-amino-5-chloro substituted benzamide.



Scheme 2

Receptor profiling studies of SC-52491 reveal it to be very selective for its actions at 5-HT_4 and 5-HT_3 receptors. IC_{50} values > 10,000 nM (highest concentration tested) were found for its interactions at 5-HT_1-like, 5-HT_2, dopamine D_1 and D_2, alpha$_1$-, alpha$_2$-, and beta-adrenergic receptors. SC-52491 represents a very interesting drug candidate as a gastrointestinal prokinetic agent (5-HT_4 agonism) with the tandem property of potent 5-HT_3 antagonism. Details of pharmacological studies with this agent will be reported elsewhere.

TABLE

Compound	5-HT4 Agonism EC50, nM	5-HT3 Binding Ki, nM	Bezold-Jarisch Reflex MED, mg/kg IP
1A	538 (36)[a]	336 (28)[a]	10.0 [b]
1B [SC-51718]	262 (107)	9.0 (0.5)	0.03
(*R*)-1C [SC-52491]	51.3 (6.6)	1.2 (0.2)	0.01
(*S*)-1C	3870 (1061)	3.9 (0.3)	0.01
Cisapride	55.0 (8)	1500 (200)	5.0
Renzapride	98.0 (14)	5.6 (0.3)	0.25
(*S*)-Zacopride	203 (27)	0.23 (0.03)	0.3

[a], standard error mean; [b], minimum effective dose affording 50% inhibition of the serotonin-induced bradycardic response.

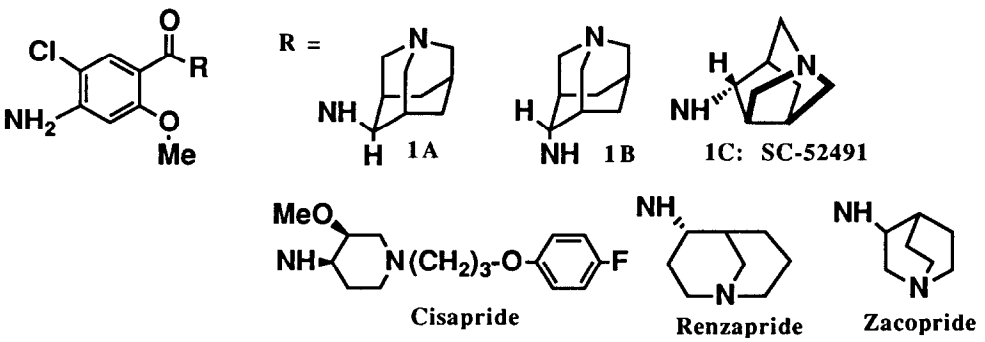


Figure 3
Structures of Benzamide Serotonin 5-HT4 Agonists

References

1. For a timely review, see: *Serotonin Receptor Subtypes: Basic and Clinical Aspects*; Stephen J. Peroutka, Editor; Wiley-Liss, Inc.: New York, 1991.
2. Peroutka, S.J.; The Molecular Pharmacology of 5-Hydroxytryptamine Receptor Subtypes. *Serotonin Receptors Subtypes: Basic and Clinical Aspects*; Stephen J. Peroutka, Editor; Wiley-Liss, Inc.; New York, 1991, pp 65-80.
3. Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R.; Bockaert, J.; *Mol. Pharmacol.* **1988**, *34*, 880.
4. Craig, D.A.; Clarke, D.E.; *J. Pharmacol. Exp. Ther.* **1990**, *252*, 1378.
5. Dumuis, A.; Sebben, M.; Bockaert, J.; *Naunyn-Schmeideberg's Arch. Pharmacol.* **1989**, *340*, 403.
6. This work was presented in part at the 202nd National American Chemical Society Meeting, August 25-30, 1991, New York. Becker, D.P.; Flynn, D.L.; Nosal, R.; "Synthetic Strategies for the Construction of Novel Azatricyclic Systems: Novel 5-HT3 and 5-HT4 Serotonergic Agents".
7. Aldrich Chemical Company, Milwaukee, Wisconsin.
8. a) Oldenziel, O.H.; van Leuson, D.; van Leuson, A.M.; *J. Org. Chem.* **1977**, *42*, 3114. b) Becker, D.P.; Flynn, D.L.; *Synthesis*, in press.
9. Black, R.M.; *Synthesis* **1981**, 829.
10. Baxter, G.S.; Craig, D.A.; Clarke, D.E.; *Naunyn-Schmeideberg's Arch. Pharmacol.* **1991**, *343*, 439.
11. The assay used is that of Kilpatrick. See Kilpatrick, G.J.; Jones, B.J.; Tyers, M.B.; *Nature*, **1987**, *330*, 746. ^{3}H-GR65630 was used as the radioligand in a binding assay using brain cortical tissue from male rats. Nonspecific binding was estimated in the presence of 1 μM ICS-205930.
12. Saxena, P.R.; Lawang, A.; *Int. Pharmacodyn.* **1985**, *277*, 235.
13. An isomeric 3-azanoradamantane system has been reported. Bok, T.R.; Speckamp, W.N.; *Heterocycles* **1979**, *12*, 343.

14. For a related study on cobalt-mediated annlulations of allylpropargylamines, see: Brown, S.W.; Pauson, P.L.; *J. Chem. Soc. Perkin Trans. I* **1990**, 1205.

15. Sharpless, K.B.; Hori, T.; *J. Org. Chem.* **1976**, *41*, 176.

16. Enantiopure (*R*)- and (*S*)-**1C** were prepared by resolution of diastereomeric ester intermediates **11** (Tos = (*R*)-O-methylmandelyl) utilizing chromatographic separation.

17. Spectroscopic and physical data for new compounds: **Compound 1A**: mp 234 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 7.75 (1H, s) 6.54 (1H, s), 4.23 (1 H, t, J = 2 Hz), 3.86 (3H, s), 3.62-3.56 (4H, m) 3.51 (2H, d, J = 18 Hz) 2.41 (2H, br s) 2.22-2.19 (3H, m), 2.10 (2H, d, J = 18 Hz); ^{13}CMR (100 MHz, CD_3OD) ∂ 166.3, 159.3, 150.4, 132.9, 111.5, 110.6, 98.8, 56.8, 56.4, 51.2, 49.0, 30.6, 28.7, 26.0; HRMS (EI) *m/e* calc for $C_{17}H_{22}N_3O_2Cl$ 335.1400, found 335.1404.

Compound 1B: mp 251 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 8.48 (1H, d, J = 6.6 Hz), 7.82 (1H, s), 6.56 (1H, s), 4.42 (1H, t, J = 3 Hz), 3.98 (3H, s), 3.69-3.61 (4H, m), 3.56 (2H, s), 2.35 (2H, br s), 2.21 (1H, br s), 2.11 (2H, d, J = 14 Hz), 2.02 (2H, d, J = 14 Hz). ^{13}CMR (100 MHz, CD_3OD) ∂ 167.1, 159.4, 150.5, 132.8, 111.5, 111.4, 98.5, 57.1, 56.9, 52.2, 51.9, 33.5, 31.0, 26.3. HRMS (EI) *m/e* calc for $C_{17}H_{22}N_3O_2Cl$ 335.1400, found 335.1395.

Compound 1C: ^{1}H NMR (300 MHz, $CDCl_3$) ∂ 8.09 (1H, s), 7.66 (1H, d, J = 6 Hz), 6.28 (1H, s), 4.37 (3H, m), 3.88 (3H, s), 3.21 (1H, dd, J = 11, 2.6 Hz), 3.05 (1H, dd, J = 11, 2.6 Hz), 3.0-2.8 (4H, m), 2.63 (1H, m), 2.56 (1H, m), 2.16 (1H, m), 2.1-1.97 (1H, m), 1.9 (1H, m). ^{13}CMR (100 MHz, $CDCl_3$): ∂ 163.3, 157.3, 146.5, 133.1, 112.8, 111.8, 97 8, 66.5, 65.0, 62.1, 57.4, 56.2, 45.6, 42.2, 39.2, 37.6. HRMS (EI) *m/e* calc for $C_{16}H_{20}N_3O_2Cl$ 321.1242, found 321.1242. *R*-1C: mp 241-242 °C; $[a]_D$ = +6.3° (c = 0.783, methanol). *S*-1C: mp 241-242 °C; $[a]_D$ = -6.3° (c = 0.795, methanol).