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SEROTONIN 5-HT4 AGONIST ACTIVITY OF A SERIES OF Meso-Azanoradamantane Benzamides

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Abstract: A series of meso-amino(methyl)azanoradamantane benzamides have been prepared and evaluated for 5-HT4 agonism activity in the rat tunica muscularis mucosae (TMM) assay. Compound 8i is the most potent 5-HT4 agonist in the series, with an EC50 of 217 nM.

The serotonin 5-HT4 receptor has been identified in a variety of tissues and mediates an impressive array of functional responses.1 The 5-HT4 receptor was first described by Dumuis and Bockaert2 in mouse embryo colliculi neurons and by Craig and Clarke3 in guinea-pig ileum. Furthermore, agonist activity at this receptor has been correlated with gastrointestinal prokinetic activity of prokinetic benzamides, including metoclopramide, zacopride, cisapride and renzapride.4 Novel and potent 5-HT4 agonists have potential in treating gastrointestinal motility disorders including reflux esophagitis, non-ulcer dyspepsia (NUD) and the irritable bowel syndrome (IBS). Continuing efforts in this area have led to a number of potent agonists for the 5-HT4 receptor.5

In earlier communications6 we disclosed a series of azaadamantane and azanoradamantane benzamides, including the potent 5-HT4 agonist/5-HT3 antagonist, SC-52491, which has an EC50 of 51 nM in the tunica muscularis mucosae assay and a Ki of 1.2 nM at the 5-HT3 receptor. SC-52491 is also highly selective versus other monoamine receptors, with IC50s >10,000 nM for serotonin 5-HT1 and 5-HT2 receptors; dopamine D1 and D2 receptors; alpha-1, alpha-2 and beta adrenergic receptors; as well as muscarinic and substance P receptors. We previously described the synthesis of the anti-4(R)-amino derivative of azacycle I6a,7 for the preparation of SC-52491, which contains four contiguous asymmetric centers. We subsequently focussed our attention on a series of azanoradamantanes as serotonergics in order to capitalize on their conformationally rigid structure to produce analogs with high potency and selectivity. We were specifically attracted to achiral substituted azanoradamantane scaffolds which exhibit a plane of symmetry. Benzamides produced from these scaffolds would obviate the need for either asymmetric synthesis or resolution.

Figure I

The azanoradamantane skeleton possesses two nonequivalent bridgehead positions. Incorporation of a nitrogen atom at either of these two bridgehead positions leads to two isomeric azanoradamantanes, I and II (Figure I). Both I and II belong to the Cs symmetry group and as such are meso-structures. This symmetry is retained if substitution is made at the 5-position on azanoradamantane I or at the 8-position of azanoradamantane II.

Compounds containing the meso-azanoradamantane skeleton of type I have not been reported in the literature. Azanoradamantanes of type II had previously been synthesized by Speckamp,8 and this skeleton is
present in natural products, including (+)-aristofruticosane. Herein we describe the 5-HT$_4$ and 5-HT$_3$ properties of novel benzamide derivatives of amino(alkyl) derivatives of both isomeric meso-azanoradamantanes I and II. The requisite amino(alkyl)azanoradamantanes are shown in Figure II.

**Figure II**

![Chemical structures](image)

Ia (n = 1)
Ib (n = 2)
endo-IIa (n = 0)
endo-IIb (n = 1)
exo-IIa (n = 0)
exo-IIb (n = 1)

The aminomethylazanoradamantane Ia was prepared as shown in Scheme I. Reduction of 1, prepared by our tandem atom-transfer radical cyclization/ionic cyclization methodology, was reduced with lithium borohydride to give the diol 2. Treatment with an excess of tosyl chloride gave the bis-tosylate which was deprotected with trifluoroacetic acid and cyclized with cesium chloride to give the azanoradamantane tosylate 3 in excellent yield. Displacement of the neopentyl tosylate with azide followed by reduction with lithium aluminum hydride gave aminomethyl azanoradamantane Ia.

The homologated derivative Ib was prepared via treatment of the azanoradamantane tosylate 3 with potassium cyanide followed by reduction with lithium aluminum hydride to give the aminoethyl azanoradamantane Ib (Scheme II).

**Scheme I**

![Chemical reactions](image)

**Scheme II**

![Chemical reactions](image)

The isomeric endo- and exo-aminoazanoradamantanes of type II were prepared from azanoradamantanone 4 by reduction of the O-benzyloxime to give endo-10 and exo-IIa$^{10}$ as a 1:1 mixture (Scheme III). Alternatively, reductive homologation of azanoradamantone 4 with tosylmethyl isocyanide (TosMIC)$^{11}$ as we had done previously on 1-azaadamant-4-one,$^{12}$ gave the isomeric endo- and exo-nitriles 5 which were separable by flash chromatography on silica gel. Subsequent reduction with lithium aluminum
hydride on each nitrile isomer separately gave the corresponding aminoazaadamantanes endo-IIb and exo-IIb, respectively.

With the requisite amino(methyl)azanoradamantanes in hand, it remained to couple these amines with the appropriate benzoic acid derivative as shown in Scheme IV. 4-Acetamido-5-chloro-2-methoxybenzoic acid 6 was treated with 1,1'-carbonyldiimidazole (CDI) followed by the appropriate amino(alkyl)azanoradamantane (Z-NH₂) followed by deprotection with methanolic potassium hydroxide (except for 8f-h, which were tested as the acetamides). More conveniently, 4-amino-5-chloro-2-methoxybenzoic acid 7 can be treated directly with CDI followed by the appropriate amine to give the benzamide 8 (R=H).

Scheme III

Scheme IV

The 5-HT₄ agonist activities are summarized in Table I, and SC-52491 (8a) is included as a reference standard. The endo derivative 8b showed modest 5-HT₄ agonist activity in the rat tunica muscularis mucosae assay¹³ with an EC₅₀ of 712 nM, but the exo isomer 8b was twice as potent with an EC₅₀ of 382 nM. We observed that epimeric homologation increases the potency in the azaadamantane series.¹² However, the 5-HT₄ agonist potency was comparable for 8d and 8c.

The corresponding acetamide derivatives 8f, 8g, and 8h (1:1 epimeric mixture) were essentially devoid of 5-HT₄ activity. The acetamide 8f did exhibit rather weak 5-HT₄ agonism (3.3 uM) and the unparallel slope observed for this compound suggested that this analog may have been acting as a partial agonist. It is not known if these compounds have 5-HT₄ antagonist activity.
The derivative $8i$ was the most potent meso-azanoradantane examined in this study, exhibiting an EC$_{50}$ of 217 nM. The homolog $8j$ was almost an order of magnitude less potent.

Azanoradantane benzamide $8i$ was selected for further study on the basis of its more potent 5-HT$_4$ agonist activity. The compound is also a potent 5-HT$_3$ antagonist, having a K$_i$ of 5.0 (0.5) nM in the 5-HT$_3$ binding assay of Kilpatrick, and exhibiting 70% inhibition of the serotonin 5-HT$_3$-mediated bradycardia in the Bezold-Jarisch reflex model in mice at 1 mpk after I.P. administration. The compound was selective with respect to binding at the dopamine D$_2$ receptor (IC$_{50}$ >10,000 nM).

In summary, we have synthesized two new series of amino(alkyl)azanoradantane benzamides which exhibit 5-HT$_4$ agonism as well as affinity for the 5-HT$_3$ receptor. SC-55387 was the most potent 5-HT$_4$ agonist in the present study with an IC$_{50}$ of 217 nM in the rat TMM assay and a K$_i$ of 5.0 (0.5) nM at the 5-HT$_3$ receptor. These meso-compounds have the distinct advantage of being achiral, although the compounds of the present series were not as potent as SC-52491 in 5-HT$_4$ agonist activity or 5-HT$_3$ antagonist activity.

Table I
<table>
<thead>
<tr>
<th>Compound</th>
<th>Z</th>
<th>R</th>
<th>5-HT&lt;sub&gt;4&lt;/sub&gt; Agonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC-52491</td>
<td></td>
<td>H</td>
<td>51.3 (6.6)</td>
</tr>
<tr>
<td>8a</td>
<td></td>
<td>H</td>
<td>711.6 (83.7)</td>
</tr>
<tr>
<td>8b</td>
<td></td>
<td>H</td>
<td>382.0 (24.1)</td>
</tr>
<tr>
<td>8c</td>
<td></td>
<td>H</td>
<td>420.7 (87.2)</td>
</tr>
<tr>
<td>8d</td>
<td></td>
<td>H</td>
<td>660 (126.3)</td>
</tr>
<tr>
<td>8e</td>
<td></td>
<td>H</td>
<td>3335 (225)</td>
</tr>
<tr>
<td>8f</td>
<td>Ac</td>
<td>Ac</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8g</td>
<td>Ac</td>
<td>Ac</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8h</td>
<td>Ac</td>
<td>Ac</td>
<td>216.8</td>
</tr>
<tr>
<td>8j</td>
<td></td>
<td>H</td>
<td>1658 (77)</td>
</tr>
</tbody>
</table>

References and Notes


10) Endo and exo correspond to syn and anti, respectively (with respect to the ring nitrogen. Endo and exo also correspond to IUPAC designations of (r) and (s)-isomers, respectively, denoting the pseudoasymmetric centers of substitution: Nomenclature of Organic Chemistry, Sections A, B, D, E, F and H, 1979 Edition, section E-4.12, pp 482 and 489.


PanLabs IC50 @ 5-HT4

SC-55867  39% @ 500 nM
SC-56319  25% @ 500 nM
SC-55387  31% @ 500 nM
Cisapride   100 nM (Ki = 17 nM)
5HT        IC50 = 300 nM (Ki = 50 nM)
R,S-zac    IC50 = 1270 nM (Ki = 210 nM)


7) 1-Azaadamantane and azanoradamantane II have been reported\textsuperscript{9a} to have pKb values in water of 2.96 and 2.61, respectively, corresponding to pKa values of 11.0 and 11.4 for the corresponding conjugate acids.