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 azacycle I₆a,7 for the preparation of SC-52491, which contains four contiguous asymmetric centers. 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 C₅ 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 (+)-aristolochic acid. 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**

![Structural diagrams of azanoradamantanes I and II](image)

The aminomethylazanoradamantane Ia was prepared as shown in Scheme I. Reduction of 1,\(^7\) 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 aminomethyl azanoradamantane Ib (Scheme II).

**Scheme I**

![Reactions and products for Scheme I](image)

**Scheme II**

![Reactions and products for Scheme II](image)

The isomeric endo- and exo-aminoazanoradamantanes of type II were prepared from azanoradamantanone 4\(^8\) by reduction of the O-benzoxime 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-azaadamantan-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...
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-NH$_2$) 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-HT$_4$ agonist activities are summarized in Table I, and SC-52491 (8a) is included as a reference standard. The endo derivative 8b showed modest 5-HT$_4$ agonist activity in the rat tunica muscularis mucosae assay with an EC$_{50}$ of 712 nM, but the exo isomer 8b was twice as potent with an EC$_{50}$ of 382 nM. We observed that epimeric homologation increases the potency in the azaadamantane series. However, the 5-HT$_4$ 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-HT$_4$ activity. The acetamide 8f did exhibit rather weak 5-HT$_4$ 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-HT$_4$ antagonist activity.
The derivative 8i was the most potent meso-azanoradamantane examined in this study, exhibiting an EC$_{50}$ of 217 nM. The homolog 8j was almost an order of magnitude less potent.

Azanoradamantane 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)azanoradamantane 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>
<thead>
<tr>
<th>Compound</th>
<th>Z</th>
<th>R</th>
<th>5-HT₄ Agonism EC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>H</td>
<td></td>
<td>51.3 (6.6)</td>
</tr>
<tr>
<td>SC-52491</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>H</td>
<td></td>
<td>711.6 (83.7)</td>
</tr>
<tr>
<td>8c</td>
<td>H</td>
<td></td>
<td>382.0 (24.1)</td>
</tr>
<tr>
<td>8d</td>
<td>H</td>
<td></td>
<td>420.7 (87.2)</td>
</tr>
<tr>
<td>8e</td>
<td>H</td>
<td></td>
<td>660 (126.3)</td>
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<tr>
<td>8f</td>
<td>Ac</td>
<td></td>
<td>3335 (225)</td>
</tr>
<tr>
<td>8g</td>
<td>Ac</td>
<td></td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8h</td>
<td>Ac</td>
<td></td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8i</td>
<td>H</td>
<td></td>
<td>216.8</td>
</tr>
<tr>
<td>8j</td>
<td>H</td>
<td></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)


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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.