9-9-1997

Serotonin 5-HT4 Agonist Activity of a Series of Meso-Azanoradamantane Benzamides

Daniel Becker
Loyola University Chicago, dbecke3@luc.edu

Roger Nosal

Clara I. Villamil

Gary Gullikson

Author Manuscript
This is a pre-publication author manuscript of the final, published article.

Recommended Citation

This Article is brought to you for free and open access by the Faculty Publications at Loyola eCommons. It has been accepted for inclusion in Chemistry: Faculty Publications and Other Works by an authorized administrator of Loyola eCommons. For more information, please contact ecommons@luc.edu.

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 3.0 License.
© 1997 Elsevier
SEROTONIN 5-HT4 AGONIST ACTIVITY OF A SERIES OF MESO-AZANORADAMANTANE BENZAMIDES

Daniel P. Becker, Roger Nosal, Clara I. Villamil, Gary Gullikson, Chafiq Moummi, Dai-Chang Yang, and Daniel L. Flynn

Departments of Medicinal Chemistry and Pharmacology, Searle Research & Development, 4901 Searle Parkway, Skokie, IL 60077

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. The 5-HT4 receptor was first described by Dumuis and Bockaert in mouse embryo colliculi neurons and by Craig and Clarke 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. 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.

In earlier communications 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 6a,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, 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**

![Figure II](image)

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 aminooethyl azanoradamantane Ib (Scheme II).

**Scheme I**

![Scheme I](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-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 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 III](image)

**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$^{13}$ 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 azadamantane series.$^{12}$ 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<sub>50</sub> 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<sub>4</sub> agonist activity. The compound is also a potent 5-HT<sub>3</sub> antagonist, having a K<sub>i</sub> of 5.0 (0.5) nM in the 5-HT<sub>3</sub> binding assay of Kilpatrick, and exhibiting 70% inhibition of the serotonin 5-HT<sub>3</sub>-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<sub>2</sub> receptor (IC<sub>50</sub> >10,000 nM).

In summary, we have synthesized two new series of amino(alkyl)azanoradamantane benzamides which exhibit 5-HT<sub>4</sub> agonism as well as affinity for the 5-HT<sub>3</sub> receptor. SC-55387 was the most potent 5-HT<sub>4</sub> agonist in the present study with an IC<sub>50</sub> of 217 nM in the rat TMM assay and a K<sub>i</sub> of 5.0 (0.5) nM at the 5-HT<sub>3</sub> 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<sub>4</sub> agonist activity or 5-HT<sub>3</sub> antagonist activity.

### Table I
<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></td>
<td>H</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></td>
<td>H</td>
<td>711.6 (83.7)</td>
</tr>
<tr>
<td>8c</td>
<td></td>
<td>H</td>
<td>382.0 (24.1)</td>
</tr>
<tr>
<td>8d</td>
<td></td>
<td>H</td>
<td>420.7 (87.2)</td>
</tr>
<tr>
<td>8e</td>
<td></td>
<td>H</td>
<td>660 (126.3)</td>
</tr>
<tr>
<td>8f</td>
<td></td>
<td>Ac</td>
<td>3335 (225)</td>
</tr>
<tr>
<td>8g</td>
<td></td>
<td>Ac</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8h</td>
<td></td>
<td>Ac</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>8i</td>
<td></td>
<td>H</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\(^9\) to have pK\(_b\) values in water of 2.96 and 2.61, respectively, corresponding to pK\(_a\) values of 11.0 and 11.4 for the corresponding conjugate acids.