



SEROTONIN 5-HT₄ AGONIST ACTIVITY OF A SERIES OF MESO-AZANORADAMANTANE BENZAMIDES

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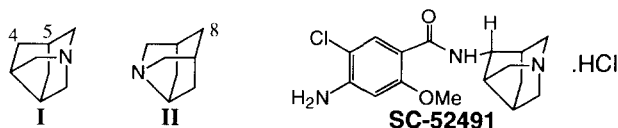
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Abstract: A series of *meso*-amino(methyl)azanoradamantane benzamides has been prepared and evaluated for 5-HT₄ agonism activity in the rat tunica muscularis mucosae (TMM) assay. Compound **8i** is the most potent 5-HT₄ agonist in the series, with an EC₅₀ of 217 nM. © 1997 Elsevier Science Ltd.

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, nonulcer dyspepsia (NUD) and possibly constipation-predominant 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 K_i 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 **I**^{6a,7} for the preparation of SC-52491, which contains four contiguous asymmetric centers. We subsequently focused 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 that exhibit a plane of symmetry. Benzamides produced from these scaffolds would obviate the need for either asymmetric synthesis or resolution.

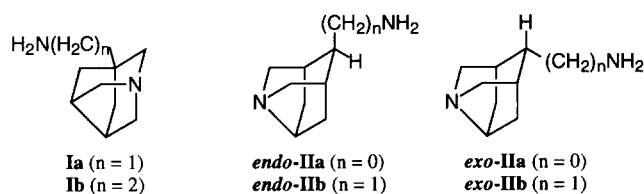
Figure 1



The noradamantane skeleton possesses two distinct 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 C_s 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**.

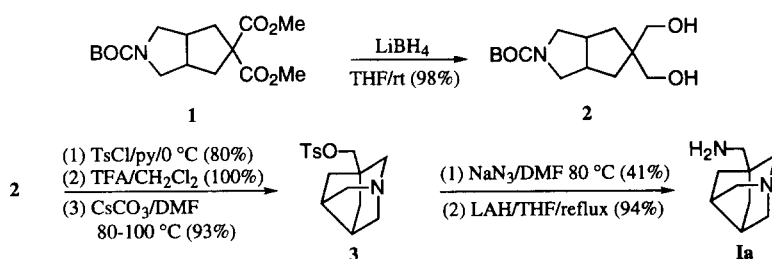
Compounds containing the *meso*-azanoradamantane skeleton of type **I** have not been reported in the literature. Azanoradamantanes of type **II** had previously been synthesized by Speckamp,⁸ and this skeleton is present in natural products, including (+)-aristofrutosane.⁹ Herein we describe the 5-HT₄ and 5-HT₃ 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



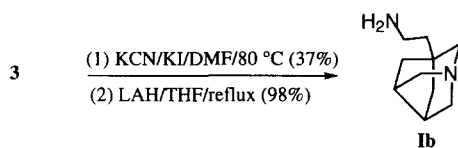
The aminomethylazanoradamantane **Ia** was prepared as shown in Scheme I. Reduction of **1**,⁷ prepared by our tandem atom-transfer radical cyclization/ionic cyclization methodology, was reduced with lithium borohydride to give the diol **2**. Treatment with an excess of tosyl chloride gave the bis-tosylate, 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**.

Scheme I



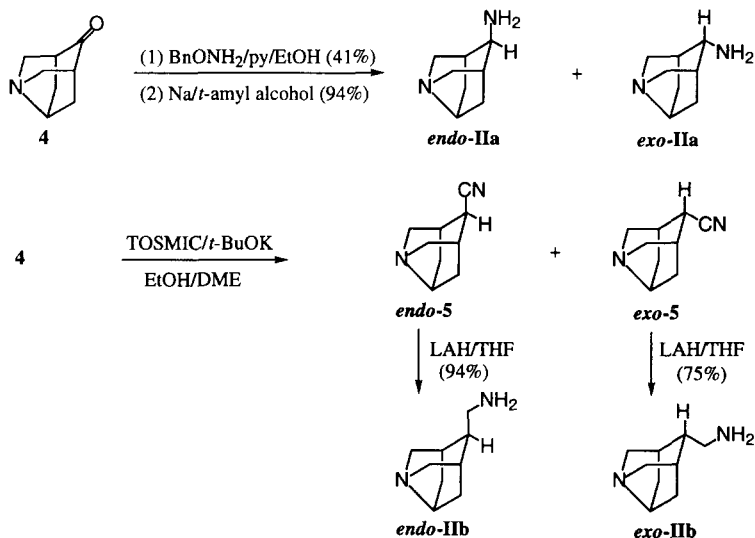
The homologated derivative **Ib** was prepared via treatment of the azanoradamantane tosylate **3** with potassium cyanide followed by reduction with lithium aluminum hydride to give the aminoethyl azanoradamantane **Ib** (Scheme II).

Scheme II



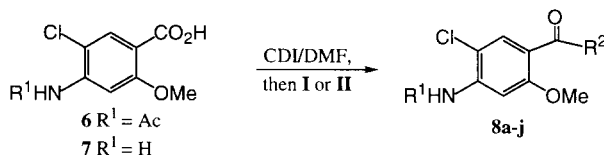
The isomeric *endo*- and *exo*-aminoazanoradamantanes of type **II** were prepared from azanoradamantanone **4**⁸ by reduction of the O-benzyloxime to give *endo*- and *exo*-**IIa**¹⁰ as a 1:1 mixture (Scheme III). Alternatively, reductive homologation of azanoradamantanone **4** with tosylmethyl isocyanide (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.

Scheme III



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 (R^2 amine) 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 IV



The 5-HT₄ agonist activities are summarized in Table I, and SC-52491 (**8a**) is included as a reference standard. The agonists shown in the table exhibited an efficacy of 85–90% relative to serotonin (5-hydroxytryptamine), which had an EC₅₀ of 8.5 nM in this assay. 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**.

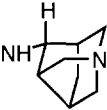
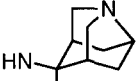
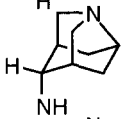
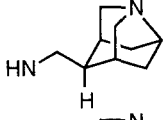
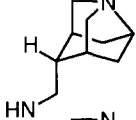
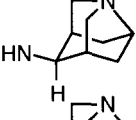
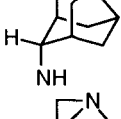
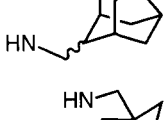
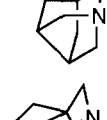
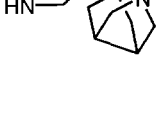
The corresponding acetamide derivatives **8f**, **8g**, and **8h** (1:1 epimeric mixture) were essentially devoid of 5-HT₄ activity. The acetamide **8f** did exhibit rather weak 5-HT₄ agonism (3.3 μM). It is not known if these compounds have 5-HT₄ antagonist activity.

The derivative **8i** was the most potent *meso*-azanoradamantane examined in this study, exhibiting an EC₅₀ 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-HT₄ agonist activity. The compound is also a potent 5-HT₃ antagonist, having a K_i of 5.0 (0.5) nM in the 5-HT₃ binding assay of Kilpatrick,¹⁴ and exhibiting 70% inhibition of the serotonin 5-HT₃-mediated bradycardia in the Bezold–Jarisch reflex model¹⁵ in mice at 1 mg/kg after ip administration. The compound was selective with respect to binding at the dopamine D₂ receptor (IC₅₀ >10,000 nM).

In summary, we have synthesized two new series of amino(alkyl)azanoradamantane benzamides that exhibit 5-HT₄ agonism as well as affinity for the 5-HT₃ receptor. SC-55387 was the most potent 5-HT₄ agonist in the present study with an IC₅₀ of 217 nM in the rat TMM assay and a K_i of 5.0 (0.5) nM at the 5-HT₃ 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-HT₄ agonist activity or 5-HT₃ antagonist activity.

Table I

Compound	R ¹	R ²	5-HT ₄ Agonism EC ₅₀ (nM); (SEM)
8a SC-52491	H		51 (7)
8b	H		712 (84)
8c	H		382 (24)
8d	H		421 (87)
8e	H		660 (126)
8f	Ac		3335 (225)
8g	Ac		>10,000
8h	Ac		>10,000
8i	H		217 (27)
8j	H		1658 (77)

References and Notes

- (a) Hoyer, D.; Clarke, D. E.; Fozard, J. R.; Hartig, P. R.; Martin, G. R.; Mylecharane, E. J.; Saxena, P. R.; Humphrey, P. P. A. *Pharmacol. Rev.* **1994**, *46*, 157. (b) Ford, A. P. D. W.; Clarke, D. E. *Med. Res. Rev.* **1993**, *13*, 633. (c) Bockaert, J.; Fozard, J. R.; Dumuis, A.; Clarke, D. E. *Trends Pharmacol. Sci.* **1992**, *13*,

141. (d) Tonini, M.; Rizzi, C. A.; Manzo, L. and Onori, L. *Pharmacol. Res.* **1991**, *24*, 5. (e) Turconi, M.; Schiantarelli, P.; Borsini, F.; Rizzi, C. A.; Ladinsky, H.; Donetti, A. *Drugs of the Future* **1991**, *16*, 1011.
2. Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R.; Bockaert, J. *J. Mol. Pharmacol.* **1988**, *34*, 880.
3. (a) Craig, D. A.; Clarke, D. E. *Br. J. Pharmacol.* **1989**, *96*, 247P. (b) Craig, D. A.; Clarke, D. E. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 1378.
4. (a) Dumuis, A.; Sebben, M.; Bockaert, J. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, *340*, 403. (b) Craig, D. A.; Clarke, D. E. *Br. J. Pharmacol.* **1991**, *102*, 563. (c) Buchheit, K.-H.; Buhl, T. *Eur. J. Pharmacol.* **1991**, *205*, 203.
5. (a) Our previous work resulted in SC-53116, the first selective 5-HT₄ agonist: Flynn, D. L.; Zabrowski, D. L.; Becker, D. P.; Nosal, R.; Villamil, C. I.; Gullikson, G. W.; Moummi, C.; Yang, D.-C. *J. Med. Chem.* **1992**, *35*, 1486. (b) King, F. D.; Hadley, M. S.; Joiner, K. T.; Martin, R. T.; Sanger, G. J.; Smith, D. M.; Smith, G. E.; Smith, P.; Turner, D. H.; Watts, E. A. *J. Med. Chem.* **1993**, *36*, 683. (c) Langlois, M.; Zhang, L.; Yang, D.; Bremont, B.; Shen, S.; Manara, L.; and Croci, T., *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1433.
6. (a) Flynn, D. L.; Becker, D. P.; Spangler, D. P.; Nosal, R.; Gullikson, G. W.; Moummi, C.; and Yang, D.-C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1613. (b) Becker, D. P.; Goldstin, B.; Gullikson, G. W.; Loeffler, R.; Moormann, A.; Moummi, C.; Nosal, R.; Spangler, D.; Villamil, C. I.; Yang, D. -C.; Zabrowski, D. L.; Flynn, D. L. In *Perspectives in Receptor Research*; Giardina, D.; Piergentili, A.; Pignini, M.; Ed.; *Pharmacochemistry Library*; Elsevier Science B. V.: Amsterdam, 1996; Vol 24, pp 99–120.
7. Flynn, D. L.; Becker, D. P.; Nosal, R.; Zabrowski, D. L. *Tetrahedron Lett.* **1992**, *33*, 7283.
8. (a) Bok, T. R.; Speckamp, W. N. *Heterocycles* **1979**, *12*, 343. (b) Speckamp, W. N.; Dujkink, J.; Dekkers, A. W. J. D.; Huisman, H. O. *Tetrahedron* **1971**, *27*, 3143. (c) Bok, Th. R.; Speckamp, W. N. *Tetrahedron*, **1979**, *35*, 267.
9. Bick, I. C. R.; Hai, M. A. In *The Alkaloids*; A. Brossi, Ed.; Academic: New York, 1985; Vol XXIV.
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.
11. Oldenzil, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
12. Flynn, D. L.; Shone, R. L.; U.S. Patent application serial number 07/919,679. WO 94/02482, 1994.
13. Baxter, G. S.; Craig, D. A.; Clarke, D. E. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, *343*, 439.
14. The assay of Kilpatrick was employed using ³H-GR65630 as the radioligand with male rat cortical tissue. Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. *Nature (London)* **1987**, *330*, 746.
15. Saxena, P. R.; Lawang, A.; *Int. Pharmacodyn.* **1985**, *277*, 235.

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