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

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

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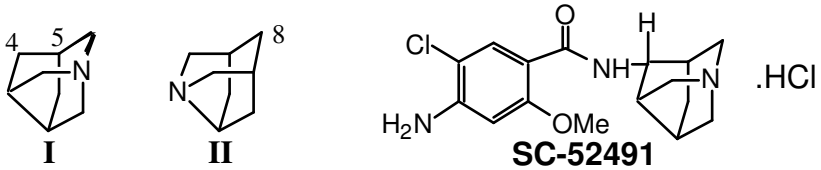
Abstract: A series of meso-amino(methyl)azanoradamantane benzamides have been prepared and evaluated for 5-HT_4 agonism activity in the rat tunica muscularis mucosae (TMM) assay. Compound **8i** is the most potent 5-HT_4 agonist in the series, with an EC_{50} of 217 nM.

The serotonin 5-HT_4 receptor has been identified in a variety of tissues and mediates an impressive array of functional responses.[1] The 5-HT_4 receptor was first described by Dumuis and Bockaert[2] in mouse embryo colliculi neurons and by Craig and Clarke[3] 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-HT_4 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-HT_4 receptor.[5]

In earlier communications[6] we disclosed a series of azaadamantane and azanoradamantane benzamides, including the potent 5-HT_4 agonist/5-HT_3 antagonist, SC-52491, which has an EC_{50} of 51 nM in the tunica muscularis mucosae assay and a K_i of 1.2 nM at the 5-HT_3 receptor. SC-52491 is also highly selective versus other monoamine receptors, with IC_{50}s >10,000 nM for serotonin 5-HT_1 and 5-HT_2 receptors; dopamine D_1 and D_2 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 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



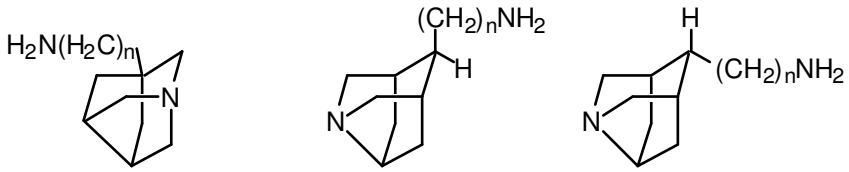
I **II** **SC-52491**

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 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 (+)-aristofruticosane.[9] 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

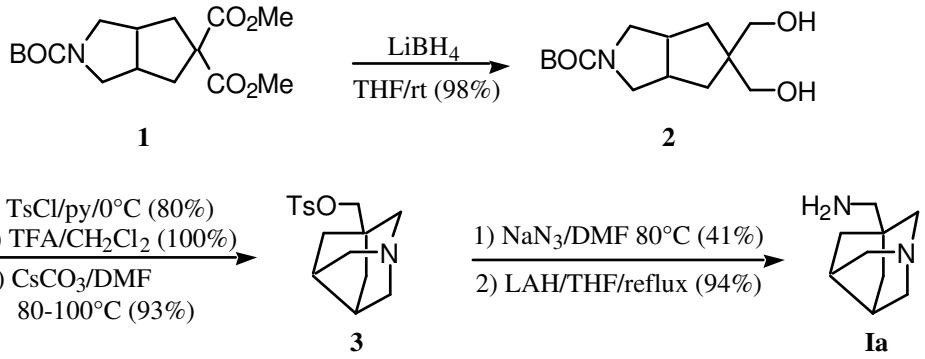


Ia (n = 1) **Ib** (n = 2) | ***endo*-IIa** (n = 0) ***endo*-IIb** (n = 1) | ***exo*-IIa** (n = 0) ***exo*-IIb** (n = 1)

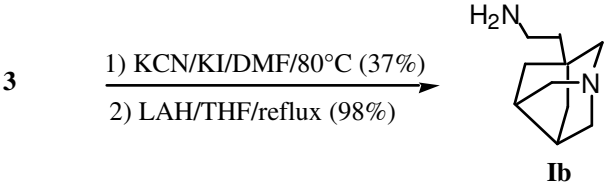
The aminomethylazanoradamantane **Ia** was prepared as shown in Scheme I. Reduction of **1**,[7] prepared by our tandem atom-transfer radical cyclization/ionic cyclization methodology, was reduced with lithium borohydride to give the diol **2**. Treatment with an excess of tosyl chloride gave the bis-tosylate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

Scheme I



Scheme II

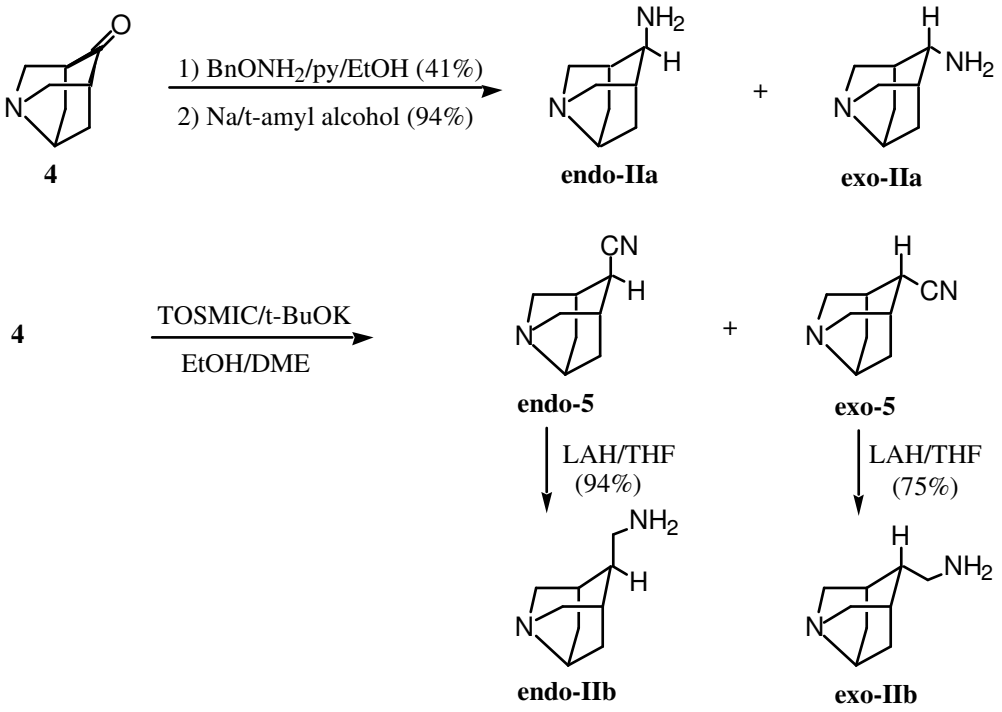


The isomeric endo- and exo-aminoazanoradamantanes of type **II** were prepared from azanoradamantanone **4**[8] by reduction of the O-benzyloxime to give **endo-**[10] and **exo-IIa**[10] as a 1:1 mixture (Scheme III). Alternatively, reductive homologation of azanoradamantone **4** with tosylmethyl isocyanide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

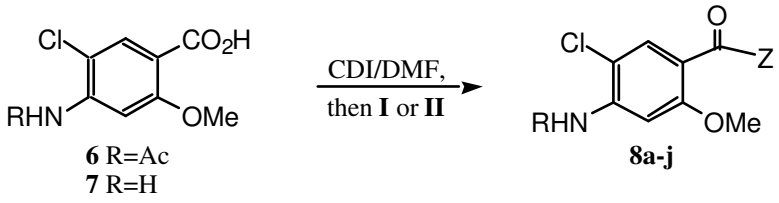
hydride on each nitrile isomer separately gave the corresponding aminoazaadamantanes **endo-IIb** and **exo-IIb**, respectively.

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 ($Z\text{-}NH_2$) 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[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 azaadamantane series.[12] However, the 5-HT_4 agonist potency was comparable for **8d** and **8c**.

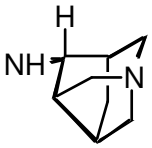
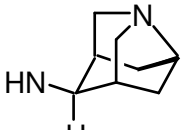
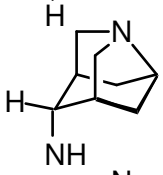
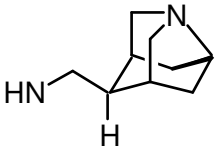
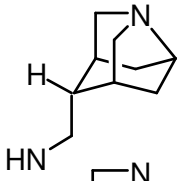
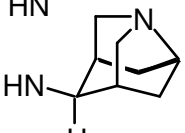
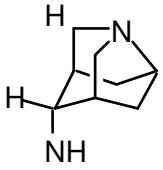
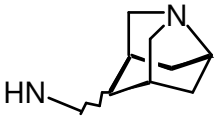
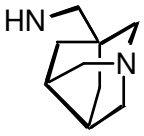
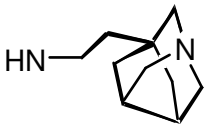
The corresponding acetamide derivatives **8f**, **8g**, and **8h** (1:1 epimeric mixture) were essentially devoid of 5-HT_4 activity. The acetamide **8f** did exhibit rather weak 5-HT_4 agonism (3.3 uM) and the unparallel slope observed for this compound suggested that this analog may have been acting 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_{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,[14] and exhibiting 70% inhibition of the serotonin 5-HT_3-mediated bradycardia in the Bezold-Jarisch reflex model[15] 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 I

Compound	Z	R	5-HT_4 Agonism EC50 (nM)
8a SC-52491		H	51.3 (6.6)
8b		H	711.6 (83.7)
8c		H	382.0 (24.1)
8d		H	420.7 (87.2)
8e		H	660 (126.3)
8f		Ac	3335 (225)
8g		Ac	>10,000
8h		Ac	>10,000
8i		H	216.8
8j		H	1658 (77)

References and Notes

1) a) Hoyer, D.; Clarke, D.E.; Fozard, J.R.; Hartig, P.R.; Martin, G.R.; Mylecharane, E.J.; Saxena, P.R., and Humphrey, P.P.A. *Pharmacol. Rev.* **1994**, *46*, 157-203. b) Ford, A.P.D.W. and Clarke, D.E., *Med. Res. Rev.* **1993**, *13*, 633-62. c) Bockaert, J.; Fozard, J.R.; Dumuis, A. and Clarke, D.E., *Trends Pharmacol. Sci.* **1992**, *13*, 141-5.d) Tonini, M.; Rizzi, C.A.; Manzo, L. and Onori, L., *Pharmacol. Res.* **1991**, *24*, 5-14. e) Turconi, M.; Schiantarelli, P.; Borsini, F.; Rizzi, C.A.; Ladinsky, H.; and Donetti, A. *Drugs of the Future* **1991**, *16*, 1011-26.

2) Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R. and Bockaert, *J. Mol. Pharmacol.* **1988**, *34*, 880-7.

3) a) Craig, D.A. and 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. and Clarke, D.E. *Br. J. Pharmacol.* **1991**, *102*, 563-4. c) Buchheit, K.-H. and Buhl, T. *Eur. J. Pharmacol.* **1991**, *205*, 203-8.

5) a) Our previous work resulted in SC-53116, the first selective 5-HT_4 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*, 1486-9. 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.; and 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*, 1613-8. 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", ed. D. Giardina et. al. , *Pharmacochemistry Library, Vol 24*, Elsevier Science B. V.: Amsterdam, **1996**, pp. 99-120.

7) Flynn, D.L.; Becker, D.P.; Nosal, R.; Zabrowski, D.L., *Tet. Lett.* **1992**, *33*, 7283-6.

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*, 3143-56. c) Bok, Th.R. and Speckamp, W.N., *Tetrahedron*, **1979**, *35*, 267-72.

9) Bick, I. C. R. and Hai, M. A. in "The Alkaloids", Ed. A. Brossi, Academic Press, 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) Oldenziel, 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, February 3, 1994.

13) Baxter, G.S.; Craig, D.A.; Clarke, D.E.; *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, *343*, 439-446.

14) The assay of Kilpatrick was employed using ^{3}H-GR65630 as the radioligand with male rat cortical tissue. Kilpatrick, G.J.; Jones, B.J.; Tyers, M.B.; *Nature*, **1987**, *330*, 746.

15) Saxena, P.R.; Lawang, A.; *Int. Pharmacodyn.* **1985**, *277*, 235.

Include in text or in references or at all??? NO

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)

6) b) Becker, D.P.; Gullikson, G.W.; Moummi, C.; Yang, D.-C., and Flynn, D.L.; *Bioorg. Med. Chem. Lett.* **1995**, *5*, XXXX-XX, preceding article in this issue.

Add current addresses of Gary and Chafiq? NO

7) 1-Azaadamantane and azanoradamantane II have been reported[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.