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Bioorganic & Medicinal Chemistry Letters 16 (2006) 5493–5497
Bioorganic & Medicinal Chemistry Letters

Epibatidine isomers and analogues: Structure–activity relationships

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Received 6 July 2006; revised 9 August 2006; accepted 9 August 2006
Available online 28 August 2006

Abstract—Binding affinities for a range of epibatidine isomers and analogues at the α4β2 and α3β4 nAChR subtypes are reported; compounds having similar N–N distances to epibatidine show similar, high potencies.

The remarkable affinity of epibatidine (**1**) for the nicotinic acetylcholine receptor (nAChR) is now well known.[1] Epibatidine is a potent but non-selective agonist, its pharmacological effects probably being mediated by a variety of nAChR subtypes including α7, α4β2, α3β4 and the α1β1γδ receptor at the neuromuscular junction.[2] The recognition of a wide variety of receptor subtypes has encouraged the exploration of epibatidine analogues in the hope of developing subtype-selective therapeutic compounds.[2] These compounds could then be employed as treatments for several neurological and psychiatric disorders including Parkinson's and Alzheimer's diseases, schizophrenia, chronic pain and tobacco dependence.[2] Greater subtype selectivity is likely to be associated with lower toxicity and fewer undesirable side effects.[2] The α4β2 nAChR is absent from the periphery but widely expressed within the CNS and may be a useful therapeutic target in several of the disorders described above. In contrast, activity at either the neuromuscular junction or the α3β4 ganglionic nAChR might be expected to lead to undesirable side effects. Work on defining the full role of each of the nAChR subtypes is highly dependent on the availability of subtype-specific ligands.[2]

We designed our target compounds to include: a bicyclic secondary nitrogen centre (the source of the quaternary nitrogen which is essential for binding); a freely rotating heterocyclic substituent; a rigid bicyclic framework which is capable of providing an appropriate N–N distance in one or both of the minimum-energy conformations (based on rotation about the C-pyridyl bond).[3] Our earlier work with tropanes (8-azabicyclo[3.2.1]octanes) and with 2- and 7-azabicyclo[2.2.1]heptanes (2- and 7-azanorbornanes)[4] has led us to synthesize a range of analogues and isomers based on these azabicyclic frameworks (Fig. 1). These include homoepibatidine (**2**),[5] dihomoepibatidine (**3**)[5] and isoepibatidine (**4**)[6] in which the positions of the bicyclic nitrogen and the heterocycle have been reversed. The epibatidine isomers **5** and **6**,[7] in which the bicyclic nitrogen is now in the 2-position and the 5- (or 6-)heterocyclic substituents are *endo*-, produce a calculated N–N distance in the appropriate range (Table 3).

The *exo*-isomers **7** and **8**,[7] having greater N–N distances, were included in these studies for comparison and contrast. In addition, the *syn*- and *anti*-isoepiboxidines **10** and **11**,[8] in which the chloropyridyl substituent of **4** has been replaced by a methylisoxazole ring, were synthesized in the hope of retaining potency but with lower toxicity (as reported for epiboxidine (**9**)).[9]

The synthesis and spectroscopic properties of these compounds have been published but full experimental details for *syn*-isoepibatidine (**4**) are recorded at the end of this letter since our very recent report[6] gave only a general procedure.

Activity data at the α4β2 and α3β4 receptors are listed in Table 1. Some previously published α4β2 and α7 binding data for selected compounds[7a] are included for

Keywords: Epibatidine analogues; Epibatidine isomers; nAChR affinity; Nicotinic receptor subtypes; Structure–activity relationships.
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doi:10.1016/j.bmcl.2006.08.049

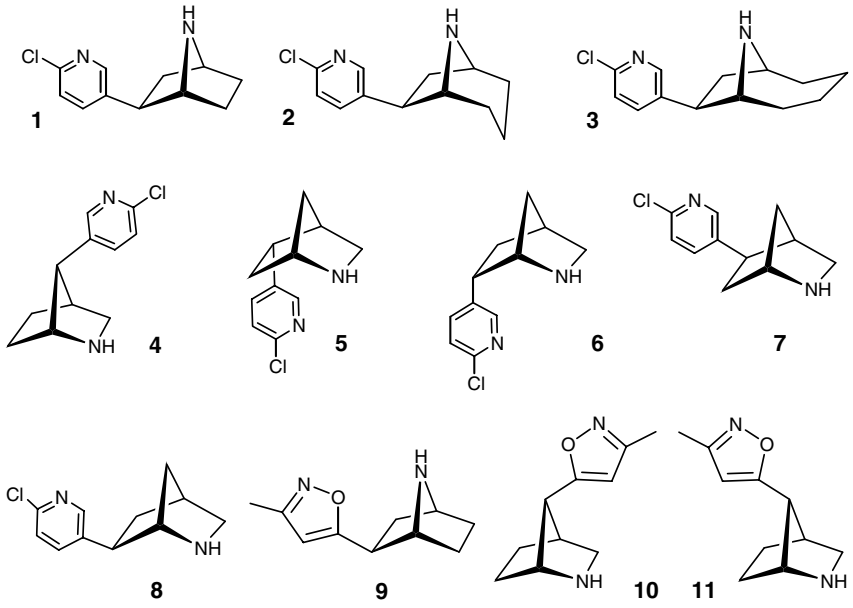


Figure 1. Epibatidine isomers and analogues.

Table 1. Inhibition of binding at human recombinant nicotinic receptors for compounds **1**,**2**, **4**–**7**,**10** and **11**

Compound	K_i[a] (nM)		α3β4/α4β2
	α4β2	α3β4	
(±)-**1**	0.0558 (±0.0056)	0.191 (±0.0075)	3.42
(+)-**2**	0.127 (±0.011)	0.925 (±0.032)	7.28
(−)-**2**	0.343 (±0.026)	0.527 (±0.053)	1.54
(±)-**4**	0.0785 (±0.00617)	0.16 (±0.00189)	2.05
(+)-**5**	0.182 (±0.33)	0.944 (±0.058)	5.19
(−)-**5**	1.23 (±0.025)	8.73 (±0.179)	7.1
(±)-**6**	0.771 (±0.067)	2.35 (±0.122)	3.05
(±)-**7**	ne at 1000 nM	ne at 1000 nM	
(±)-**10**	0.763 (±0.092)	9.51 (±0.428)	12.5
(±)-**11**	ne at 1000 nM	ne at 1000 nM	
Cytisine	2.59 (±0.202)	525 (±6.32)	203

Preliminary data have been reported earlier.[10]

[a] Values are geometric means of at least three experiments, standard error is given in parentheses (ne = no effect).

comparison (Table 2). Differences between the K_i binding constants in Tables 1 and 2 (and early data recorded in Ref. 5) may be due to the fact that in Table 1, binding was at human recombinant nAChR, whereas the nAChR used to generate the values in Table 2 were from native rat tissue. These native receptors may be subtly different from the human recombinant nAChR in terms of their unit stoichiometry (ratio of α4 and β2 subunits) and composition (inclusion of other subunits, for example, α5).[11]

Table 2. Inhibition of binding at native rat nicotinic receptors for compounds **1**, **2** and **5**–**8**[7a]

Compound	α4β2 K_i[a] (nM)	α7 K_i[b] (nM)	α7/α4β2
1	(+)0.019	4.9 (±0.7) (n = 3)	258
	(−)0.020	7.0 (±1.8) (n = 4)	350
(±)-**2**	0.23	13 (n = 2)	56.5
(±)-**5**	0.056	6.3	112.5
(±)-**6**	0.045	3.9	86.7
(±)-**7**	ca. 40	3300	<87
(±)-**8**	ca. 40	1600	<42

[a] [^{3}H]Nicotine binding to rat cortical membranes.

[b] [^{125}I-α]Bungarotoxin binding to rat hippocampal membranes.

The most significant result is that isoepibatidine (**4**) is almost as potent as epibatidine ((±)-**1**). It shows similar activity to (±)-**1** at both the α4β2 and α3β4 receptors. This confirms earlier indications[5] that the unusual chemical properties[4b] of the nitrogen atom in the 7-azanorbornane ring system are not an essential factor in the unusual biological properties of **1**. Earlier results for homoepibatidine (**2**) have shown that incorporation of an extra methylene group into the 2-carbon bridge has little effect on binding affinity[5,12] (see also Table 2); thus the 7-azanorbornane system is not a pre-requisite for high activity although we have demonstrated that insertion of a second additional methylene group in dihomoepibatidine (**3**) leads to an order of magnitude reduction in activity, presumably because of the substantially greater bulk of the tetramethylene portion.[5] The new data for the enantiomers of **2** (Table 1) confirm the high

potency; the two enantiomers shows similar α4β2 selectivity.

Of the other 2-azanorbornane isomers, the *endo*-5-substituted compound **5** shows an almost 10-fold difference in the binding ability of the two enantiomers at both the α4β2 and α3β4 subtypes (Table 1), with the values for the (+)-enantiomer at the α4β2 being only 3-fold more than those for epibatidine ((±)-**1**). The enantiomers of **5** show little subtype selectivity. The K_i values for the racemic *endo*-6-substituted compound **6** are close to the average values for the enantiomers of **5** despite the difference in position of the heterocycle.

The previously accepted 'ideal' N–N distance of ca. 5.5 Å has been revised; recent X-ray studies suggest a value of 4.4–4.5 Å for the active conformation.[3b] This is in agreement with calculations for the compounds in Table 3. Interestingly, the methylisoxazole-substituted **10** is the only isomer which shows N–N distances close to the 'ideal' in both minimum energy conformations. Whatever the minor structural differences between the epibatidine isomers **1**, **4**, **5** and **6**, they all retain the key pre-requisites, including a broadly similar N–N distance, and show high potency. Significant changes are only observed when the two nitrogen centres are widely separated, as in the *exo*-isomers **7** and **8**. The *exo*-compounds are essentially inactive; the α4β2 and α3β4 data for **7** in Table 1 augment the earlier α4β2 and α7 results (Table 2).[7a]

Variation of the heterocyclic substituent has been widely investigated as a means of modifying the properties of nicotinic agonists.[2b] One of the more successful bioisosteric replacements for the chloropyridyl ring is the methylisoxazole ring, introduced by Daly in epiboxidine (**9**)[9] and, more recently, in the higher homologue homoepiboxidine.[13] We have recently reported the synthesis of the isoepiboxidine isomers **10** and **11** based on the 2-azanorbornane framework.[8] The *syn*-isomer (**10**) has approximately 13-fold weaker affinity than epibatidine at the α4β2 receptor (Table 1); this modest reduction mirrors that reported for epiboxidine (**9**).[9] The potency of **10** at the α3β4 receptor is lower but the discrimination is modest. The inactivity of the anti-isomer **11**, even at 1000 nM, is not surprising given the distance between the secondary nitrogen and the heterocycle (Table 3).

Table 3. Calculated N–N distances for amines[a]

Compound (unprotonated)	Minimum energy conformation (Å)	After 180° rotation about the C-heterocycle bond (Å)
1	4.5	5.5
2	4.6	5.6
4	4.5	5.2
5	4.8	5.9
6	4.3	5.3
7	6.4	6.6
8	5.7	6.1
10	4.4	4.8
11	5.6	5.8

[a] Calculated using Spartan Pro; equilibrium geometry by Hartree–Fock, 6-31G*.

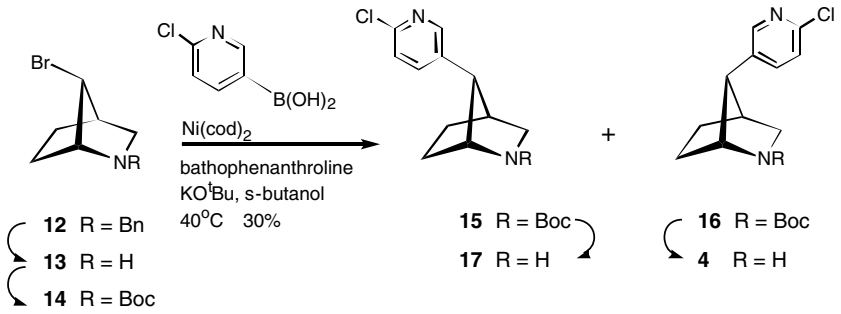
We recognise that calculated minimum energy N–N distances are a crude, indirect measure of the efficiency of interaction between the ligand and receptor and that many other factors are involved which are not yet fully understood.[3] Nevertheless, our work shows good correlations between calculated N–N distances and binding affinities for a homologue (**2**) of epibatidine, for epibatidine isomers (**4**–**6**) and for a variant (**10**) in which methylisoxazole replaces chloropyridine. Whilst the new compounds show similar high potency to epibatidine, there is no increase in selectivity between the α4β2 and α3β4 receptor subtypes.

Membrane preparation. Cell pastes from large-scale production of HEK-293 cells expressing cloned human α4β2 or α3β4 nAChR were homogenized in 4 volumes of buffer (50 mM Tris–HCl, 150 mM NaCl and 5 mM KCl, pH 7.4). The homogenate was centrifuged twice (40,000*g*, 10 min, 4 °C) and the pellets re-suspended in 4 volumes of Tris–HCl buffer after the first spin and 8 volumes after the second spin. The re-suspended homogenate was centrifuged (100*g*, 10 min, 4 °C) and the supernatant kept and re-centrifuged (40,000*g*, 20 min, 4 °C). The pellet was re-suspended in Tris–HCl buffer supplemented with 10% w/v sucrose. The membrane preparation was stored in 1 ml aliquots at −80 °C until required. The protein concentration of the membrane preparation was determined using a BCA protein assay reagent kit.

Nicotinic receptor radioligand binding scintillation proximity assay (SPA). SPA radioligand binding assays were performed in 96-well plates in a final volume of 250 μl Tris–HCl buffer (50 mM Tris–HCl, 150 mM NaCl, 5 mM KCl, pH 7.4) using the following conditions: [^{3}H]epibatidine (53 Ci/mmol; Amersham)-α4β2 = 1 nM, α3β4 = 2 nM; WGA-coated PVT SPA beads (Amersham)-α4β2 = 1 mg/well, α3β4 = 1.5 mg/well; membrane protein = 30 μg/well for both assay types. Non-specific binding (<10% for both assay types) was determined using 10 μM epibatidine. Reactions were allowed to equilibrate for 2–4 h at room temperature prior to reading on a Trilux Scintillation counter (Perkin Elmer). Data were analyzed using a standard 4-parameter logistic equation (Multicalc, Perkin Elmer) to provide IC_{50} values that were converted to K_i values using the Cheng–Prusoff equation.[15]

Synthesis of isoepibatidine **4**

anti-7-Bromo-2-azabicyclo[2.2.1]heptane (**13**). *anti*-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane **12**[6] (2.80 g, 0.012 mol) in dry MeOH (60 ml) was hydrogenolyzed using a standard procedure;[8] flash chromatography (Et_2O/MeOH; 9:1) gave **13** as a white crystalline solid (32%). δ_H (300 MHz, $CDCl_3$) 1.42–1.63 (m, 2H, H_{5n}, H_{6n}), 1.97–2.17 (m, 2H, H_{5x}, H_{6x}), 2.40 (dd, 3.8, 3.8 Hz, 1H, H_4), 2.68 (d, 9.7 Hz, 1H, H_{3n}), 3.00 (ddd, $J \approx 9.7$, 3.4, 3.4 Hz, 1H, H_{3x}), 3.37 (dd, $J = 3.1$, 3.1 Hz, 1H, H_1), 4.04 (dd, 1.5, 1.5 Hz, 1H, H_7). δ_C (75.5 MHz, $CDCl_3$) 26.5, 29.3 (C_5, C_6), 42.3 (C_4), 49.9 (C_3), 55.0 (C_7), 60.2 (C_1). ν_{max} 2976s, 2524 m, 1636 s, 1522m, 1421s cm^{-1}. *m/z* 176/178 (MH^+). $C_6H_{11}NBr$ [MH^+] requires 176.00749; observed 176.00751.



anti-2-Boc-7-bromo-2-azabicyclo[2.2.1]heptane (**14**). The procedure described for compounds **19** and **23** in Ref. 8 was followed using the *anti*-isomer **13** (344 mg, 1.95 mmol), Boc_2O (694 mg, 3.18 mmol), $NaHCO_3$ (595 mg, 6.77 mmol), THF (4 ml) and H_2O (12 ml). After reaction at rt for 72 h, **14** was obtained as a white crystalline solid (448 mg, 1.62 mmol, 83%) R_f (Et_2O/petrol; 1:1) 0.57. δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N–CO rotation (ratio ~ 45:55), the minor rotamer signal is shown in italics.] 1.45 (br s, 9H, Boc), 1.04–1.88, 2.02–2.23 (2× m, 4H, H_5, H_6), 2.57 (br s, 1H, H_4), *3.05*, 3.10 (2× d, J = 9.6 Hz, 1H, H_{3n}), 3.34 (ddd, $J \approx 9.6$, 3.1, 3.1 Hz, 1H, H_{3x}), 4.05 (br s, 1H, H_7), 4.05, *4.25* (2× br s, 1H, H_1). δ_C (75.5 MHz, $CDCl_3$) 25.6, 28.1 (C_5, C_6), 28.4 (Boc CH_3), 43.0, *43.5* (C_4), 51.9 (C_7), 51.3, *52.1* (C_3), *59.7*, 60.8 (C_1), 79.7 (Boc C), 153.9 (Boc CO). ν_{max} 2977s, 1692s, 1398s, 1331m, 1304m, 1246m, 1155s, 1111s cm^{-1}. *m/z* 276/278 (MH^+). $C_{11}H_{19}NO_2Br$ [MH^+] requires 276.05992; observed 276.05987.

anti- and *syn*-2-Boc-7-(6-chloro-pyridin-3-yl)-2-azabicyclo[2.2.1]heptane (**15** and **16**). Procedure adapted from Ref. 14. In a glove box, $Ni(cod)_2$ (95 mg, 0.35 mmol) was placed in a two-necked flask. Bathophenanthroline (228 mg, 0.69 mmol), 4-chloro-3-pyridyl boronic acid (148 mg, 0.94 mmol) and ^{t}BuOK (136 mg, 1.22 mmol) were added, the reaction vessel was evacuated and refilled with N_2 thrice. Dry *s*-BuOH (10 ml) was added and the mixture stirred for 10 min at rt under N_2; the colour changed to deep-purple, indicating the formation of the active complex. A solution of *anti*-**14** (210 mg, 0.76 mmol) in *s*-BuOH (2 ml) was added and the resulting mixture stirred under N_2 at 40 °C for 24 h, then cooled and passed through a short pad of silica. Solvents were removed in vacuo. Flash chromatography (Et_2O) of the crude residue gave a mixture of **15** and **16** as a pale yellow oil (~25:75; *anti*-:*syn*-) (69 mg, 0.22 mmol, 30%) R_f 0.49. δ_H [300 MHz, $CDCl_3$; signals corresponding to the minor (*anti*-) epimer are underlined; where there is signal duplication because of slow N–CO rotation (ratio ~ 45:55), the minor rotamer signal is shown in italics.] 1.39, 1.48, <u>1.50</u> (3× br s, 9H, Boc), 1.44–2.04 (m, 4H, H_5, H_6), 2.69, <u>2.91</u> (2× br s, 1H, H_4), 2.95, 3.02, <u>3.13–3.25</u>, <u>3.44–3.53</u> (br s, br s, m, m, 3H, H_{3x}, H_{3n}), <u>4.45</u>, *4.48*, 4.61 (4× br s, 1H, H_1), 7.22–7.33 (m, 1H, $H_{5'}$), 7.47–7.60 (m, 1H, $H_{4'}$), 8.23–8.32 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 28.1, 28.2, *30.6*, 31.0 (C_5, C_6), 28.3, 28.5 (Boc CH_3), <u>*39.0*</u>, <u>39.4</u>, 41.5, *42.4* (C_4), 49.1, *49.5* (C_7), <u>53.3</u>, <u>*53.8*</u>, *49.4*, 50.0 (C_3), 57.2, <u>*58.0*</u>, *58.4*, <u>59.0</u> (C_1), 79.3, 79.5 (Boc C), 123.8, 123.9, 124.0 (C_5), 132.5, 132.8, 132.9 ($C_{3'}$), 138.0, 138.2 ($C_{4'}$), 148.8 ($C_{6'}$), 149.3, 149.4 ($C_{2'}$), 154.2, 154.3 (Boc CO). Further chromatographic separation (Et_2O) allowed the isolation of a sample of the major (*syn*-) epimer **16** as a yellow oil: δ_H [300 MHz, $CDCl_3$; signal descriptors as described above (rotamer ratio ~ 45:55).] 1.41, 1.50 (2× br s, 9H, Boc), 1.61–2.04 (m, 4H, H_5, H_6), 2.69 (br s 1H, H_4), 2.95, 3.02 (br s, m, 3H, H_{3x}, H_{3n}, H_7), *4.48*, 4.61 (2× br s, 1H, H_1), 7.25 (m, 1H, $H_{5'}$), 7.54 (m, 1H, $H_{4'}$), 8.31 (m, 1H, $H_{2'}$). δ_C (75.5 MHz, $CDCl_3$) 28.1, 28.2, 30.6, *31.0* (C_5, C_6), 28.3, *28.5* (Boc CH_3), 41.6, *42.4* (C_4), 49.1, *49.5* (C_7), *49.4*, 50.0 (C_3), 57.3, *58.4* (C_1), *79.3*, 79.5 (Boc C), *123.8*, 123.9 ($C_{5'}$), *138.0*, 138.2 ($C_{5'}$), 149.3, *149.4* ($C_{2'}$), 132.9, *133.0* ($C_{3'}$), 154.2 (Boc CO). ν_{max} 2970s, 2934s, 1696s, 1606m, 1488s, 1406s, 1284s cm^{-1}. *m/z* 309 (MH^+). $C_{16}H_{22}N_2O_2$ [MH^+] requires 309.13698; observed 309.13692.

syn-7-(6-Chloro-pyridin-3-yl)-2-azabicyclo[2.2.1]heptane (*syn*-isoepibatidine) (**4**). A 75:25 mixture of epimers **15** and **16** (476 mg, 1.54 mmol) was dissolved in EtOAc (50 ml); EtOH (10.4 ml) and CH_3COCl (8.6 ml) were added with cooling in ice and the reaction mixture was allowed to reach rt and stirred for 4 h before being evaporated to dryness. The crude mixture of epimers of isoepibatidine–HCl salts was triturated with CH_2Cl_2 to give a sample of pure **4** (94 mg) and a sample containing **17** and **4** (2:1, 107 mg) (53% total yield). Data for free amine **4**: δ_H (300 MHz, $CDCl_3$) 1.24–1.50, 1.50–1.72, 1.72–1.93 (3× m, 4H, H_5, H_6), 2.63 (br s, 1H, H_4), 2.68 (d, J = 10.1 Hz, 1H, H_{3n}), 2.76 (ddd, $J \approx 10.1$, 2.9, 2.9 Hz, 1H, H_{3x}), 3.71 (br s, 1H, H_1), 2.89 (br s, 1H, H_7), 7.26 (s, 1H, $H_{2'}$), 7.69 (dd, J = 3.1, 0.5 Hz, 1H, $H_{4'}$), 8.36 (d, J = 2.4 Hz, 1H, $H_{5'}$). δ_C (75.5 MHz, $CDCl_3$) 29.1, 32.9 (C_5, C_6), 40.7 (C_4), 48.9 (C_3), 49.8 (C_7), 58.4 (C_1), 124.0, 138.5, 149.4 (pyridyl). *m/z* 209/211 (MH^+). ν_{max} 2970s, 2750w, 2706w, 1622m, 1588w, 1561w cm^{-1}. *m/z* 209 (MH^+). $C_{11}H_{14}N_2Cl$ [MH^+] requires 209.08455; observed 209.08454. Tosic acid salt of **4**: mp 186–190 °C. Analysis: $C_{18}H_{21}N_2O_3SCl$ requires: C, 56.76; H, 5.56; N, 7.35; observed: C, 56.82; H, 5.46; N, 7.26.

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