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# 6′-Methylpyrido[3,4-*b*]norhomotropane: synthesis and outstanding potency in relation to the α4β2 nicotinic receptor pharmacophore model

David B. Kanne,[a] Motohiro Tomizawa,[a] Kathleen A. Durkin[b] and John E. Casida[a,*]

[a]*Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy and Management, University of California, Berkeley, CA 94720-3112, USA*
[b]*Molecular Graphics Facility, College of Chemistry, University of California, Berkeley, CA 94720-1460, USA*

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**Abstract**—6′-Methylpyrido[3,4-*b*]norhomotropane [synthesis as the racemate reported here] is more potent at the α4β2 nicotinic receptor than any previous bridged nicotinoid. The two nitrogens and 6′-methyl substituent are superimposable on the two nitrogens and 6-chloro substituent of epibatidine, with the best fit on comparing the chair conformer of the (1*R*)-pyridonorhomotropane with natural (1*R*)-epibatidine. In this pharmacophore model, the 6′-methyl substituent may be equivalent to the acetyl methyl of acetylcholine.


Nicotinic acetylcholine (ACh) receptor (nAChR) ligands are of interest in the treatment of cognitive and attention deficits, Parkinson's disease, schizophrenia and depression, and in nicotinically mediated analgesia.[1,2] The diversity of neuronal nAChRs (e.g., α4β2 and α7) provides the potential for developing subtype-selective therapeutic agents with reduced adverse side effect liabilities.[3,4] These goals are facilitated by successful pharmacophore mapping, which requires optimized probes of high potency and defined or predictable conformations. Studies on the α4β2 nicotinic receptor were based initially on nicotine (**1**) and nornicotine (**2**) and later on the exquisitely potent epibatidine (**3**),[5] all with two critically positioned nitrogens and free rotation of the pyridyl substituent (Fig. 1). Conformationally restricted ligands, for example, bridged nicotinoids,[6] facilitate further differentiation of the steric and electronic requirements of a receptor target. (±)-Pyrido[3,4-*b*]norhomotropane (**4**)[7,8] was the first bridged nicotinoid with affinity rivaling or surpassing the conformationally free analogs **1** and **2**, and it is therefore an excellent probe for further refinement of pharmacophore models.[9–11]

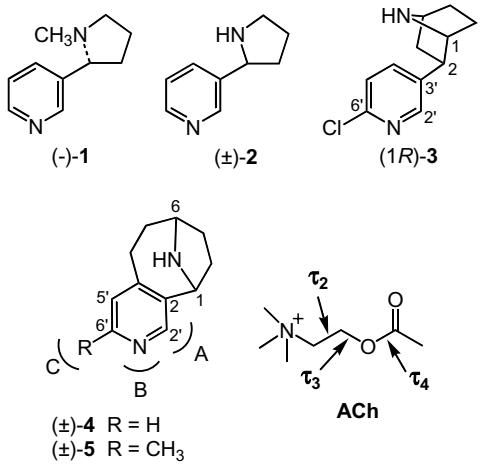


**Figure 1.** Structures of the non-protonated forms of standard nicotinoids [(−)-**1**, (±)-**2**, and (1*R*)-**3**] and (±)-pyrido[3,4-*b*]norhomotropanes [(±)-**4** and (±)-**5**] compared with ACh.

A 6-chloro or 6-methyl substituent is tolerated without major potency loss or even with a potency increase for **1**, **2**, and **3**.[12–14] This approach was therefore used here for **4** by adding a 6′-methyl substituent (**5**) to facilitate molecular comparisons between the conformationally flexible and restricted series (Fig. 1).

*Keywords*: Nicotinic receptor; Pharmacophore model; Pyridonorhomotropane; Epibatidine; Bridged nicotinoid.
* Corresponding author. Tel.: +1 510 642 5424; fax: +1 510 642 6497; e-mail: ectl@nature.berkeley.edu

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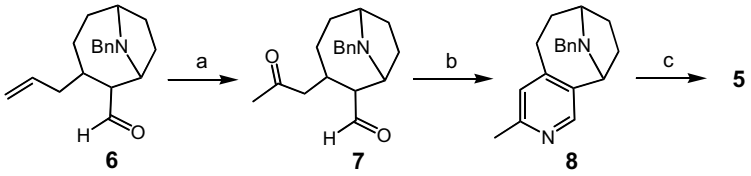


**Scheme 1.** Reagents and conditions: (a) $Na_2PdCl_4$, 0.5 M HCl, EtOAc, benzoquinone; (b) $NH_2OH{\cdot}HCl$, gl HOAc; (c) $Pd(OH)_2/C$, $H_2$.

*N*-Benzyl-3-allyl-2-formyl-9-azabicyclo[4.2.1]nonane (**6**), an intermediate in the synthesis of (±)-**4** prepared as reported earlier,[7,8] served as the starting material for the three-step conversion to (±)-**5** (Scheme 1). Wacker oxidation ($Na_2PdCl_4$, benzoquinone)[15] transformed **6** to *N*-benzyl-2-formyl-3-(2-oxopropyl)-9-azabicyclo[4.2.1]-nonane (**7**). Ring synthesis proceeded from **7** using $NH_2OH{\cdot}HCl$ in refluxing acetic acid to generate *N*-benzyl-6′-methylpyrido[3,4-*b*]norhomotropane (**8**)[16] which after hydrogenolysis with $Pd(OH)_2$ on carbon (Pearlman's catalyst) yielded **5**.[17] Compound **4** was prepared as previously described,[7,18] and *N*-methyl-**4** was available from our earlier study[8] and subjected to rechromatography.[18]

The binding affinities of the standard nicotinoids [(−)-**1**, (±)-**2**, and (±)-**3**] and pyridonorhomotropanes [(±)-**4** and (±)-**5**] were determined to both α4β2 and α7 nAChRs using (−)-[$^3$H]nicotine and [$^{125}$I]-α-bungarotoxin, respectively, as the radioligands (Table 1).[19–21] The α7 nAChR is much less sensitive than the α4β2 to all of the ligands with the highest selectivity factor for (±)-**4** and (±)-**5**. Most importantly, the affinity of (±)-**5** for the α4β2 receptor was 3-fold greater than that of (±)-**4** and 36-fold greater than (±)-**2**, making **5** the most potent bridged nicotinoid reported for the nicotinic receptor. The enhancing effect of the 6′-methyl group is in sharp contrast to the 600- to 700-fold loss in affinity resulting from a *N*-methyl or 2′-methyl substituent.[8,25]

**Table 1.** Binding affinities of standard nicotinoids and (±)-pyrido[3,4-*b*]norhomotropanes to the α4β2 and α7 nicotinic acetylcholine receptors

| Compound | $K_i$ (nM ± SD, $n$ = 3)[a] | |
|---|---|---|
| | α4β2 | α7 |
| *Standard nicotinoids* | | |
| (−)-**1** | 2.5 ± 0.3 | 7200 ± 220 |
| (±)-**2** | 14 ± 2 | 138,000 ± 17,000 |
| (±)-**3**[b] | 0.035 ± 0.004 | 10 ± 1 |
| (±)-*Pyrido[3,4-b]norhomotropanes* | | |
| (±)-**4** | 1.3 ± 0.2 | >100,000 (31%)[c] |
| (±)-**5** | 0.39 ± 0.04 | ~100,000 (52%)[c] |

[a] α4β2 subtype was immunoisolated by monoclonal antibody (mAb) 270 from mouse fibroblast M10 cells and assayed with 7 nM [$^3$H]nicotine binding. In the same manner, α7 subtype was immunoisolated by mAb 306 from human neuroblastoma SH-SY5Y cells and assayed with 1 nM [$^{125}$I]α-BGT binding. $K_i$ Values are calculated with the equation of Cheng and Prusoff,[22] $K_i = IC_{50}/(1 + [L]/K_D)$, with $K_D$ values of 3.8 and 1.06 nM for the α4β2 and α7 subtypes, respectively.[23,24]

[b] Data from Zhang et al.[21]

[c] Percent inhibition at the indicated concentration.

The diminished activity on *N*-methylation is also seen in other 9-azabicyclo[4.2.1]nonane systems such as anatoxin-a.[26] The loss in activity of 2′-Me-**4**[27] may result from unfavorable steric interactions with the receptor rather than from conformational perturbations; this proposal is based on the observation that each of 2′-Me-**4**, **4**, and **5** favor the chair conformation over the boat by 4.6, 3.8, and 4.8 kcal/mol, respectively (see Table 1 and Supplemental Table).[28]

The high potency of the conformationally restricted, bridged nicotinoid **5** makes it an ideal model to predict the bioactive conformations of more flexible ligands such as **3** and ACh. In considering possible molecular overlays, the (1*R*)-enantiomer of **5** was used based on analogy with the known stereochemistry of the more potent enantiomer of the related (+)-anatoxin,[8,10,29] an analogy supported by the observation that both **4** and (+)-anatoxin undergo major potency loss on *N*-methylation.[26] The natural (1*R*)-**3** (which is equipotent with its enantiomer)[14] was used in all comparisons.

Conformational analysis on protonated **3**, using a molecular mechanics calculation followed by further optimization at B3LYP/6-31G**++,[30] revealed minima with dihedral angles (C1–C2–C3′–C2′) of roughly +15°, +90°, and −90° (Table 2) in accord with a previ-

**Table 2.** Conformational analysis on protonated **3**, chair and boat conformers of protonated **5**, and ACh as distances, dihedral angles and relative Δ*G* for each set of calculated minima (all values as Gibbs free energies with zero point energy corrections included)

| Compound and conformation | N–N distance (Å) | Dihedral angle (°) | | | Relative Δ*G* (kcal/mol) |
|---|---|---|---|---|---|
| **3** | | C1, C2, C3′, C2′ | | | |
| | 4.56 | 84 | | | 0 |
| | 5.29 | −89 | | | 1.03 |
| | 4.63 | 14.7 | | | 0.67 |
| **5** | | C1–H, C1, C3′, C2′ | | | |
| Chair | 4.69 | −2.1 | | | 0 |
| Boat | 4.86 | −31 | | | 4.83 |
| ACh | N–O (carbonyl) distance (Å) | $\tau_2$ | $\tau_3$ | $\tau_4$[a] | |
| *gauche* | 5.06 | 65 | 166 | −179 | 0 |
| *trans* | 5.14 | 180 | 180 | 180 | 1.49 |
| other | 4.28 | 68 | 80 | −126 | 0.27 |
| other | 3.88 | −158 | 80 | 175 | 0.62 |
| other | 3.59 | 80 | −110 | −167 | 0.53 |

[a] $\tau_4$: C–O-C(O)–C.

ous report.[31] The barrier to rotation is small and **3** exists as a mixture of the minima with significant contributions from other conformers. Similar calculations on the two possible conformations of protonated **5** establish that the chair is more stable than the boat by ~5 kcal (Table 2). A systematic search for the optimal superpositioning of conformationally mobile (1*R*)-**3** and chair (1*R*)-**5** focused on four key overlay elements: (1) position and directionality (as indicated by projection of $NH_2^+$) of the charged ammoniums; (2) position and lone pair electron directionality of the $sp^2$ nitrogens; (3) position of 6′-substituents; and (4) position of carbon skeletons. An excellent overlay (Fig. 2) is obtained when **3** adopts a dihedral angle of −12° (i.e., close to one of the conformational minima) with the pyridine rings very close to coplanar.[32] The N–N distance for (1*R*)-**3** in this conformation is 4.50 Å compared to 4.69 Å for chair (1*R*)-**5**.

In a similar fashion, chair (1*R*)-**5** gives an excellent fit with the conformationally mobile ACh in a '*trans*' arrangement (see Fig. 3a and Table 2). This superposition allows overlap of the charged ammoniums, the H-bond acceptor, and the corresponding methyl groups. In this view the 6′-methyl group of **5** is equivalent to the acetyl methyl of ACh. The superposition with *gauche* ACh also provides a good fit with the ACh methyl positioned mid-way between C-5′ and C-6′ of **5** (Fig. 3b and Table 2).

An electrostatic potential map of chair (1*R*)-**5** is shown in Figure 4 with three designated regions (**A**, **B**, and **C**) for comparison with Figure 1. The dramatically enhanced affinity of 6′-Me-**4** (i.e., compound **5**) compared to 2′-methyl-**4** suggests that close approach to the receptor is required at C-2′ (region **A**) in order to achieve the H-bond receptor contact by the adjacent $sp^2$ nitrogen (shown in blue) (region **B**). In this model a C-2′ methyl prevents high affinity binding via an unfavorable steric interaction with the receptor while the C-6′ methyl resides in a region where such groups are well accommodated (region **C**). The onium site (protonated $sp^3$ nitrogen shown in red) of the ligand will interact with the π-electron-rich subsite formed by aromatic amino acids (Trp, Tyr) via a cation-π contact or through hydrogen bonding with a carboxyl oxygen of aspartic or glutamic acid as a complementary contributor.[33–35]

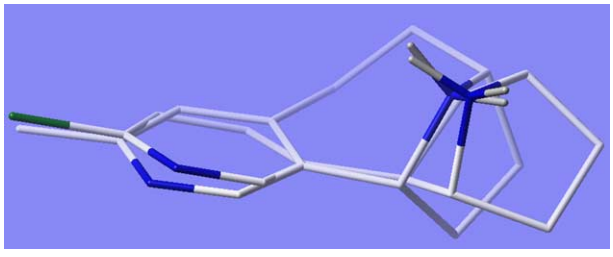

**Figure 2.** Superposition of the putative pharmacophoric elements of chair (1*R*)-**5** and (1*R*)-**3** having dihedral angle (C1, C2, C3′, C2′) of −12°. The N–N interatomic distances are 4.69 Å for (1*R*)-**5** and 4.50 Å (close to 4.63 Å from conformational analysis) for (1*R*)-**3** (Table 2). Hydrogens are shown on $sp^3$ nitrogens of **3** and **5**.

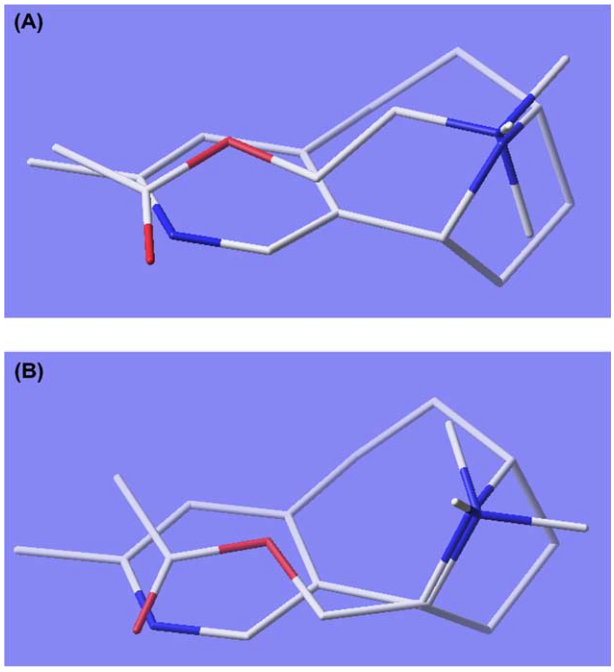


**Figure 3.** Superposition of the putative pharmacophoric elements of chair (1*R*)-**5** with the *trans* (**A**) and *gauche* (**B**) conformations of ACh. Three other low energy conformers of ACh (Table 2) provide less optimal or poor overlays with (1*R*)-**5**. Hydrogens are not shown on $sp^3$ nitrogen of **5**.

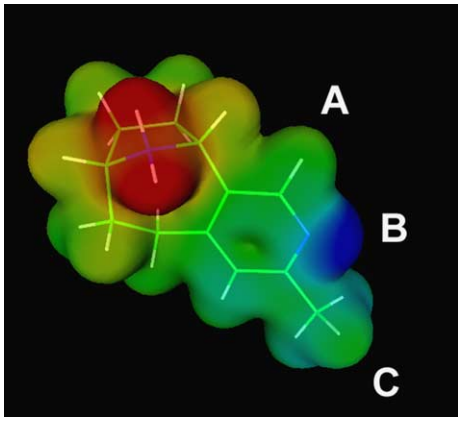


**Figure 4.** Electrostatic potential map of chair (1*R*)-**5**. Key regions of interaction with the receptor are discussed in the text. Blue ($sp^2$ pyridine nitrogen) is more negative and red ($sp^3$ protonated nitrogen) is more positive. This figure was generated with gOpenMol (www.csc.fi/gopenmol) from a Jaguar calculation.[30]

The bicyclic skeletons of **3** and **5** are accommodated by a lipophilic pocket of the receptor.

The combination of subnanomolar affinity and conformational rigidity makes **5** an excellent reference template for the pharmacophoric elements of other more flexible ligands. This exceptionally potent bridged nicotinoid establishes an important role of the 6′-methyl substituent in the pyrido[3,4-*b*]norhomotropane series, and serves as a useful model in the design of therapeutic agents targeted at the α4β2 nAChR.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.12.069.

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16. Compond **8**: The starting material was compound **6**.[7] $^1$H NMR (400 MHz, $CDCl_3$, 7.26 ppm): $\delta$ 9.3 (s, 1H), 7.1–7.7 (m, 5H), 5.3–5.8 (m, 1H), 4.9–5.3 (m, 2H), 3.5–3.7 (m, 4H), 1.2–2.5 (m, 12H). HRMS: calculated for $C_{16}H_{20}NO$ ($M^+-C_3H_5$): 242.1545. Observed: 242.1526. To **6** (87 mg, 0.307 mmol) dissolved in 0.5 M HCl (0.76 mL) was added ethyl acetate (0.42 mL), $Na_2PdCl_4$ (22 mg, 0.0748 mmol), and benzoquinone (11.4 mg, 0.105 mmol). The reaction (monitored by GC/MS) was complete after 24 h at 20 °C. Aqueous HCl (6 M, 2 mL) was added to the cooled (5 °C) reaction mixture, which was stirred for 5 min, and then partitioned between ether and an aqueous (pH = 13) solution saturated with NaCl. The organic layers from three extractions were dried ($Na_2SO_4$), and evaporated in vacuo to yield 58 mg of the crude product. To the 1,5-dicarbonyl compound **7** (without purification) was added a suspension of $NH_2OH{\cdot}HCl$ (60 mg, 0.86 mmol) in glacial acetic acid (1.0 mL), and the mixture was heated at reflux for 1.5 h. Workup by ether extraction and solvent evaporation as above gave an amber oil (42 mg). This material was chromatographed on silica with $CH_2Cl_2$/MeOH (95:5) as eluent to yield 20 mg of **8** as a colorless oil. $^1$H NMR (400 MHz, $CDC1_3$, 7.26 ppm): $\delta$ 7.93 (s, H-2′), 7.18–7.38 (m, 5H), 6.97 (s, H-5′), 4.08 (dd, H-1), 3.38–3.54 (m, 3H, $CH_2$ of *N*-benzyl overlaps multiplet of H-6 bridgehead), 3.0–3.1 (m, 1H), 2.6 (m, 1H), 2.50 (s, 3H), 2.45–2.55 (m, 1H), 1.6–2.3 (m, 4H), 1.5 (m, 1H). GC/MS: $M^+$ = 278, purity by GC = 100%.
17. Compound **5**: To a solution of **8** (6 mg, 0.0216 mmol) in 100 μL of MeOH/glacial acetic acid (4:1) was added 1 mg of Pearlman's catalyst. The mixture was shaken in a Paar apparatus and hydrogenated at 50 psi until a GC (after mini work-up) indicated completion of the reaction. Catalyst was removed by filtration through Celite and the pad was washed thoroughly ($CH_2Cl_2$/MeOH 10:1). Most of the solvent was evaporated with a stream of nitrogen and the residue was partitioned between $CH_2Cl_2$ and an aqueous (pH = 13) solution saturated with NaCl. The combined organic phase was dried ($Na_2SO_4$), and concentrated in vacuo to yield 4 mg of an amber oil. Chromatography on silica with $CH_2Cl_2$/MeOH (92.5:7.5) as eluent afforded 2.1 mg of **5** as a clear viscous oil. In a separate preparation, using 200 μL of solvent and 2.5 mg of catalyst, 12.0 mg of **8** gave after chromatography 3.2 mg of **5** and 1.8 mg of unreacted **8**. $^1$H NMR (400 MHz, $CDCl_3$, 7.26 ppm): $\delta$ 8.18 (s, H-2′), 6.94 (s, H-5′), 4.33 (dd, H1), 3.79 (dddd, H6), 3.05 (ddd, H4α), 2.64 (ddd, H4β), 2.46 (s, 6′-methyl), 2.42 (dddd, H8β), 2.0–2.5 (m, 2H), 1.5–1.9 (m, 4H), 2.13 (dddd, H7β), 1.8 (m, H5α, H7α, H8α), 1.6 (m, H8α). GC/MS: $M^+$ = 188, purity by GC = 100%. HRMS: calculated for $C_{12}H_{17}N_2$ ($MH^+$): 189.1392. Observed: 189.1373.
18. Compound **4** gave satisfactory GC/MS,[7] HRMS,[7] and $^1$H NMR (see Supplemental data). *N*-Me-**4** was chromatographed on silica with $CH_2Cl_2$/MeOH (97:3) as eluent and gave satisfactory LC, HRMS, and $^1$H NMR.[8]
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