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Synthesis of 3,6-diazabicyclo[3.1.1]heptanes as novel ligands for neuronal nicotinic acetylcholine receptors

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ABSTRACT

A series of novel 3,6-diazabicyclo[3.1.1]heptane derivatives **4a–f** was synthesized and their affinity and selectivity towards α4β2 and α7 nAChR subtypes were evaluated. The results of the current study revealed a number of compounds (**4a**, **4b** and **4c**) having a very high affinity for α4β2 (K_i at α4β2 ranging from 0.023 to 0.056 nM) versus α7 nAChR subtypes; among these compounds, the 3-(6-bromopyridin-3-yl)-3,6-diazabicyclo[3.1.1]heptane **4c** was found to be the most α7α4β2 selective term in receptor binding assays (α7α4β2 = 1295). Moreover, compound **4d** also had high affinity for the α4β2 nAChR subtype (K_i = 1.2 nM) with considerably high selectivity (α7/α4β2 = 23300).

Inflammatory disease and neuropathic insults are often accompanied by severe pain states (physiological, inflammatory, and neuropathic) that can be treated with commonly prescribed analgesic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids.[1] Unfortunately, the therapeutic potential of these powerful drugs has been limited by safety concerns, as well as by unpleasant side effects with consequent poor patient compliance.[2–5]

Thus, the treatment of various form of pain is a hugely unmet medical need, and the search for novel and efficacious analgesics with improved therapeutic index receives considerable attention.[6,7]

Among a number of novel approaches to pain relief currently under investigation, nicotinic acetylcholine receptors (nAChRs) hold considerable potential as therapeutic targets for the development of analgesic drugs.[8,9] The neuronal nicotinic acethylcholine receptors are prototypic ligand-gated ion channel receptors that are widely expressed through the central and peripheral nervous system and mediate fast synaptic transmission.[8] Neuronal nAChRs are pentameric proteins comprising either combinations of two different types of subunit (α and β) or five copies of the same α subunit symmetrically arranged around a central ion pore.[10] Nine different types of α-subunit (α2−α10) and three kinds of β-subunits (β2−β4) have been cloned and characterized. The multiple nAChR subunits form a plethora of different receptor subtypes among which the most abundant in the CNS are the α4β2* and the α7* receptors (the asterisks indicate the potential presence of other subunits), whereas the α3β4 receptor is the predominant subtype at ganglionic synapses.[11,12]

The neuronal nAChRs are involved in a wide range of physiological and pathophysiological processes, and they have been proposed as potential therapeutic targets in a number of neurodegenerative and psychiatric disorders, in various form of pain, and in nicotinic addiction.[8,13–15]

The α4β2 receptor subtype has generated significant interest among academic and industrial researchers as a result of its role in pain reflexes.[16,17] Thus, the generation of potent α4β2 nAChR subtype selective ligands has been a goal for the advancement of novel nAChR-based analgesics with a minimum of side effects.[9]

The alkaloid epibatidine (**1**), the *exo*-2-(6-chloropyridin-3-yl)-7-azabicyclo[2.2.1]heptane, isolated from the skin of the ecuadorian poison frog *Epidobates tricolour*,[18] was identified as a potent ligand of α4β2 receptors having powerful analgesic activity.

Because of the identification of various adverse effects of **1** on CNS responses and respiratory, gastrointestinal and cardiovascular function, synthetic modifications of its structure have been performed in order to improve potency and selectivity while reducing the toxicity.

These endeavors, based upon examination of the two key structural elements of **1**, that is, the (i) azabicyclo amine moiety and the

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(ii) pyridine heterocycle, led to a number of promising substances, many of them closely related but also not related to epibatidine. For example, tebanicline (**2**) described as an azetidine bioisoster of **1** with (*R*)-absolute configuration, retained a potent nAChR agonism with moderate enhancement of α4β2 nAChR subtype selectivity as compared with **1**. Tebanicline showed analgesic action in a spectrum of acute and chronic nociceptive models as well as in neuropathic pain but with only a modest therapeutic index.[19–22]

Attempts to circumvent these problems induced W.H. Brunelle and coworkers to synthesize a series of *N*-(3-pyridinyl)-bridged bicyclic diamine derivatives as novel bridged nicotinoid, of which 2-(6-chloropyridin-3-yl)-2,5-diazabicyclo[2.2.1]heptane (**3**) is a representative term exhibiting exceptionally potent affinity for the α4β2 receptors but, unfortunately, inadequate pharmacokinetic properties (poor CNS penetration).[23] As a consequence compound **3** was not selected as a candidate for clinical evaluation. Nevertheless, the diazabcycle **3** could be assumed as a lead compound for the design of novel high-affinity α4β2 subtype-selective ligands.

In this context, the aim of this study was to investigate the effect of the variation of the 2,5-diazabicyclo[2.2.1]heptane scaffold of **3** with the 3,6-diazabicyclo[3.1.1]heptane skeleton synthesizing a range of isomers and analogues based on this diazabicyclic framework. This paper describes the synthesis of compounds **4** and the evaluation of their binding affinity at α4β2 and α7 nAChR subtypes (Fig. 1).

The synthetic route to the desired final compounds **4** is outlined in scheme 1. The sequence commenced with the addition of the monoprotected 3,6-diazabicyclo[3.1.1]heptane **5**[24] and haloazines **6** to a toluenic mixture of Pd-BINAP catalyst in the presence of a base (Cs_2CO_3 or NaO*t*Bu), resulting in coupling products **7a–d**. Synthesis of compound **7e** was accomplished by refluxing **5** with 3,6-dichoropiridazine in toluene and in the presence of TEA. Treatment of **7a–e** with HCOOH underwent smooth deprotection of the Boc group leading to **4a–e** in good-to-excellent yields (63–95%). Reaction of **4a** with HCOOH/HCHO produced the N_6-methylderivative **4f** in 72% yield.

The goal of this study was to prepare a series of 3,6-diazabicyclo[3.1.1]heptane analogues of the α4β2 nAChR subtype ligand, 2-(6-chloropyridin-3-yl)-2,5-diazabicycloheptane,[23] and to measure their affinity at α4β2 and α7 nAChR subtypes. The strategy of incorporating a novel diazabicycloheptane unit into the structure of **3** was expected to afford compounds with high affinity for α4β2 nAChR subtype. Modifications were principally made on the pyridine ring to investigate the effect of different variations on α4β2 and α7 nAChR subtype potency and selectivity.

Binding assays were performed on rat cortex tissues for α4β2 and α7 nAChR subtypes with [^{3}H]-epibatidine and [^{125}I]-α -bungarotoxin as radioligands, respectively.[25,26] The binding affinities (K_i values) for the new ligands,[27] as well as the reference compounds **3** and radioligands at α4β2 and α7 nAChR subtypes are shown in Table 1.

In general, results showed a spectrum of α4β2 nAChR subtype affinities ranging from 0.023 nM for compound **4a** to 1.2 nM for compound **4d**, with α7 nAChR subtype affinities ranging from 1.36 nM for compound **4b** to 28,000 for compound **4d**. Thus, the α7 nAChR affinities of all of the investigated 3,6-diazabicyclo[3.1.1]heptanes are lower than their α4β2 nAChR subtype affinities.

Compound **4a**, having a 3,6-diazabicyclo[3.1.1]heptane ring replacing the 2,5-diazabicyclo[2.1.1]heptane ring of **3**, had K_i values of 0.023 nM and 4.1 nM for α4β2 and α7 nAChR subtype, respectively, with a α7:α4β2 selectivity ratio of 178. Compound **4a** serves as a convenient benchmark for all of the others in term of presenting structure-binding affinity relationships.

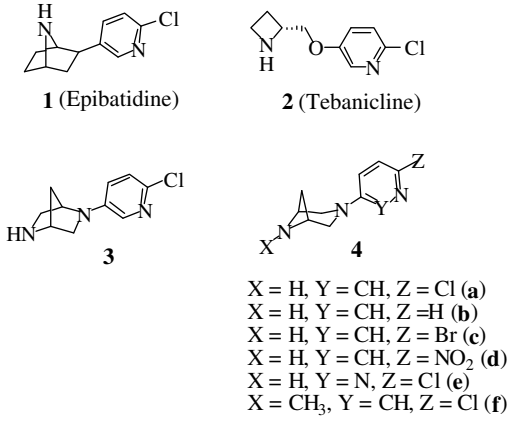
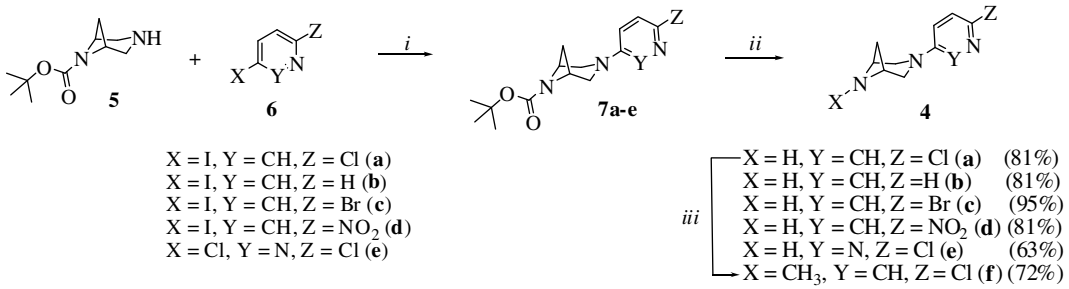


Figure 1. Epibatidine and related analogues.

Table 1
Binding affinity (K_i, nM)[a] of **4a–f** to α4β2 and α7 nAChR subtypes.

Compound	α4β2: [^{3}H-Epibatidine] (K_i, nM)	α7: [^{125}α-BgTx] (K_i, nM)	Selectivity K_i ratio α7/α4β2
4a	0.023 (34%)	4.1 (35%)	178
4b	0.056 (28%)	1.36 (42%)	24.3
4c	0.039 (36%)	50.5 (46%)	1295
4d	1.2 (45%)	28000 (52%)	23300
4e	0.168 (33%)	25 (48%)	149
4f	0.43 (34%)	20 (42%)	46.5
3	0.018[b]	—	—
^{3}H-Epibatidine	0.083	0.8	9.6
^{125}I-α-Bungarotoxin	—	0.9	—

[a] The K_i values shown were the mean (% coefficient of variation) of three independent measurements.
[b] Binding affinity of compound **3**[23] was determined by the inhibition of [^{3}H] cytosine binding in homogenates of rat striatum.



Scheme 1. Reagents and conditions: (i) $Pd_2(dba)_3$, rac-BINAP, Cs_2CO_3 or NaO*t*Bu, toluene, 100–110 °C, 22 h (for compounds **7a–d**); TEA, toluene, 120 °C, 24 h (for compound **7e**); (ii) HCOOH 99%, rt, 3.5 h; (iii) HCOOH 99%/HCHO 40%, 110 °C, 2.5 h.

De-chloro compound **4b** displayed 2.4-fold lower α4β2 nAChR subtype affinity than **4a** whereas the α7 nAChR subtype affinity was increased displaying 3-fold greater affinity.

The bromo-substituted compound **4c** had 1.7-fold and 12.3-fold lower affinity than **4a** for α4β2 and α7, respectively, and possessed a selectivity ratio of 1295.

Substitution with a nitro group, compound **4d**, resulted in a reduction, about 52-fold, of α4β2 receptor affinity and a much higher reduction of α7 receptor affinity with the highest selectivity ratio (23300).

These results indicate that factors such as electronics are likely involved in the binding of **4a** analogues.

Without doubts, the incorporation of a chlorine atom at C6′ position of the pyridine moiety as in **4a** is favourable for α4β2 affinity.

Compound **4e** has two basic nitrogen in the heteroaryl aromatic ring and is more hydrophilic than compound **4a**. This pyridazine derivative **4e** had 7.3-fold and 6.1-fold lower affinity than **4a** for α4β2 and α7 nACh receptor subtypes, respectively.

N_6-Methyl substitution of **4a** as in compound **4f** lowered affinities for both receptors with K_i values of 0.43 nM for α4β2 receptor and of 20 nM for α7 receptor.

The best compounds in the **4a–f** series show affinity for α4β2 nAChR in the same range as their diazabicyclo[2.2.1]heptane analogue **3** suggesting similar geometrical and conformational properties. Thus, we performed a modeling study on the protonated form of these compounds through optimizations within the density functional approach at the B3LYP/6-311+G(d,p) level.[28] The energy of the optimized structures were recalculated using a continuum solvent model (PCM)[29] as implemented in Gaussian 03[30] to take into account the effect of water on these highly polar molecules. The main degree of conformational freedom of compounds **3** and **4** is the rotation of the aryl group around the single bond that connects it to the diazabicyclic system. This rotation cannot be expected to be completely free as the orientation of the aromatic ring can be influenced by the resonance with the lone pair of the nitrogen atom to which it is connected, so that conformations that make possible this conjugation should be preferred. This nitrogen atom usually does not assume a completely planar geometry but shows a certain degree of pyramidalization that originates two possible 'configurations'. Finally, in **4** the piperazine ring can, in principle, assume either a chair or a boat conformation contrarily to **3** where the same ring is forced into a twisted boat geometry.

Several minimum energy conformations were located for each compound and in Table 2 are reported the gas-phase and the water-solvated energies of **3** and **4a** together with selected geometrical features including the distance between the protonated nitrogen and the pyridine nitrogen (A–B distance) or the center of the pyridine ring (A–C distance). The data in Table 2 and the three-dimensional plots, represented in Figure 2, show the very close similarity between **3** and **4a** that can justify the almost identical binding affinity to α4β2 nAChR. In fact, each conformation of **4a** shows energy and geometry data in strict analogy with the corresponding conformation of **3**. Moreover, in all the conformations the orientation of the chloropyridinyl group allows a good conjugation with the adjacent nitrogen atom (τ_2 always about 90 or −90°). It is worthy pointing out that both compounds show A–B distances of about 6 Å and A–C distances of 5.0–5.5 Å confirming that these long distances are compatible with affinity for α4β2 receptors in the subnanomolar range.[31]

The conformational behavior of **4b–f**, not reported in Table 2, are very similar to those of 4a. Thus, modulation of activity exerted by the substituent at C6′ (**4b–d**), the second nitrogen in the aromatic ring (**4e**), or the N6-methyl substitution (**4f**) seems to derive from specific interactions of these groups rather than from their influence on the conformation of the molecules.

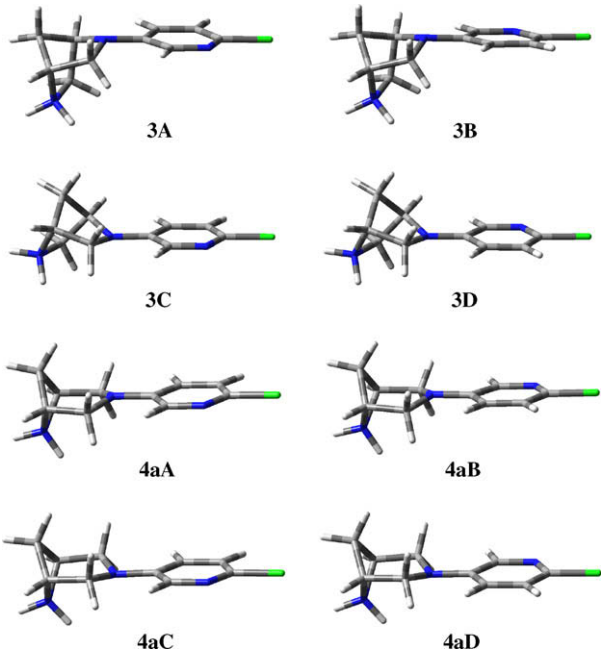


Figure 2. 3D plot of the most representative conformations of compounds **3** and **4a**.

Table 2
Relative energy and selected geometrical data of the B3LYP/6-311+G(d,p) calculated minimum energy conformations of compounds **3** and **4a**.[a]

Conformation	E_{rel} (gas-phase) (kcal/mol)	E_{rel} (water) (kcal/mol)	A–B[b](Å)	A–C[c](Å)	τ_1[d](°)	τ_2[e](°)	α[f] (°)
3A	0.34	0.00	5.78	5.00	−21	−94	8.8
3B	0.00	0.05	5.67	4.98	154	81	8.9
3C	1.28	1.09	6.31	5.48	8	−100	−5.9
3D	1.18	1.13	6.24	5.46	−177	75	−4.5
4aA	0.02	0.00	6.29	5.49	−9	−88	3.1
4aB[g]	0.02	0.00	6.29	5.49	169	88	3.1
4aC	0.00	1.42	6.14	5.32	11	−91	−4.6
4aD[h]	0.00	1.42	6.14	5.32	−167	91	−4.6

[a] Several other minimum energy conformation were located for **4a**, but they are not reported as their water-solvated energy is 5–7 kcal/mol higher than that of **4aA**.
[b] Distance between the protonated nitrogen and the pyridine nitrogen.
[c] Distance between the protonated nitrogen and the center of the pyridine ring.
[d] τ_1 is C3–N2–C3′–C2′ for **3** and C2–N3–C3′–C2′ for **4a**.
[e] τ_2 is the inproper torsional angle N^+–N2–C3′–C2′ for **3** and N^+–N3–C3′–C2′ for **4a**.
[f] Pyramidalization degree of the nitrogen atom bearing the aryl substituent defined as the difference between 360 and the sum of the three bond angles of the same atom, considered positive when it is pyramidalized in the direction of the methylene bridge and negative in the opposite case.
[g] Conformation enantiomeric to **4aA**.
[h] Conformation enantiomeric to **4aC**.

In summary, we have prepared ligands for α4β2 and α7 nAChR subtypes that combines a 3,6-diazabicyclo[3.1.1]heptane core with various pyridines and a pyridazine. Most of these ligands have very high affinity for α4β2 nAChR subtypes. The best, compound **4a**,[32] has a chloropyridine motif and binds 3.6 times better than epibatidine to α4β2 nAChR subtypes in the meantime maintaining similar α4β2 affinity respect to the lead **3**.

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32. Experimental procedure for the synthesis of compound **4a**. A round-bottom flask was charged with $Pd_2(dba)_3$ (0.92 g, 1.00 mmol) and BINAP (0.61 g, 1.00 mmol) in dry toluene (15 ml). The mixture was flushed with nitrogen for 10 min under magnetic stirring. In another round-bottom flask aryl iodide **6a** (0.61 g, 2.52 mmol), amine **5** (0.50 g, 2.52 mmol) and Cs_2CO_3 (3.29 g, 10.1 mmol) were mixed with an additional amount of toluene (10 mL). Then, the $Pd(OAc)_2$/BINAP solution was added and the mixture was refluxed for 22 h. After cooling, the residue was partitioned between diethyl ether and water. The organic phase was washed with water, dried (Na_2SO_4) and evaporated. The resulting crude product was purified by flash column chromatography (petroleum ether/Ethyl acetate 7:3) to give **7a** as a yellow solid (66%). R_f: 0.29; mp = 129–130 °C; ^{1}H NMR (200 MHz, $CDCl_3$, δ/ppm): 1.35 (s, 9H), 1.51 (d, 1H, *J* = 8.8 Hz); 2.58–2.78 (m, 1H); 3.26 (d, 2H, *J* = 10.6 Hz), 3.82–3.95 (m, 2H); 4.30 (d, 2H, *J* = 10.4 Hz) 6.97 (dd, 1H, *J* = 3.0 and 8.8 Hz); 7.17 (d, 1H, *J* = 8.8 Hz), 7.86 (d, 1H, *J* = 3.0 Hz). Anal. Calcd for $C_{15}H_{20}ClN_3O_2$: C, 58.16; H, 6.51; N, 18.56. Found: C, 58.20; H 6.40; N 18.60.A solution of **7a** (0.28 g, 0.90 mmol) in HCOOH 99% (5 ml) was stirred at room temperature for 3.5 h. The mixture was diluted with water and K_2CO_3 was added until neutral pH. The solution was extracted with CH_2Cl_2 dried (Na_2SO_4) and evaporated. The residue was triturated with diethyl ether to give the final compound **4a** as a white solid (81%). R_f: 0.21 (CH_2Cl_2/methanol 7:3); mp = 130–131 °C; ^{1}H NMR (200 MHz, $CDCl_3$, δ/ppm): 1.53 (br s, 1H), 1.62 (d, 1H, *J* = 8.8 Hz); 2.70–2.85 (m, 1H); 3.48–3.55 (m, 4H), 3.88–3.95 (m, 2H); 6.97 (dd, 1H, *J* = 2.8 and 8.8 Hz); 7.18 (d, 1H, *J* = 8.2 Hz), 7.87 (d, 1H, *J* = 3.2 Hz). Anal. Calcd for $C_{10}H_{12}ClN_3$: C, 57.28; H, 5.77; N, 20.04. Found: C, 57.16; H 5.74; N 19.90.