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Structure–activity relationships of N-substituted ligands for the α7 nicotinic acetylcholine receptor

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ABSTRACT

A series of α7 neuronal nicotinic acetylcholine receptor ligands were designed based on a structural combination of a potent, but non-selective ligand, epibatidine, with a selective lead structure, **2**. Three series of compounds in which aryl moieties were attached via a linker to different positions on the core structure were studied. A potent and functionally efficacious analog, (3a*R*,6a*S*)-2-(6-phenylpyridazin-3-yl)-5-(pyridin-3-ylmethyl)octahydropyrrolo[3,4-*c*]pyrrole (**3a**), was identified.

Neuronal nicotinic acetylcholine receptors (nAChRs) are of great interest as therapeutic targets for the treatment of pain and cognitive disorders, and for smoking cessation.[1] Different subtypes in this receptor family have been shown to mediate different effects, and compounds that are selective among the subtypes have the potential to target particular diseases.[2] Agonists selective for the α7 receptor subtype have been shown to have beneficial effects on cognition,[3] offering the potential to treat diseases such as Alzheimer's disease and schizophrenia.[4] Several groups have reported agonists based on the quinuclidine pharmacophore.[3] We sought to design α7 ligands with a unique core structure. The natural product epibatidine (**1**), isolated from the skin of an Ecuadorian tree frog, is very potent at the α7 receptor (K_i = 2.7 nM), but also binds to other subtypes including α4β2 (0.1 nM), α3β4 (0.3 nM) and ganglionic and neuromuscular nAChRs.[5] By combining elements from epibatidine with structures that were selective for α7, our research program aimed to produce compounds with improved potency and selectivity for the α7 nAChR.

Compound **2** (A-582941) is a nAChR agonist discovered in our laboratories with activity across a range of cognition models.[6] It binds to the α7 receptor with a potency of 11 nM, and it is selective for α7 over other subtypes (α4β2 K_i >100 μM, α3β4 K_i = 4700 nM). Ligands for nAChRs bind in a highly conserved 'aromatic box' of amino acid sidechains.[7] The amine portion of the ligand is held in the binding site through a hydrogen bond or a cation-pi interaction. Inspection of simple 3D models in which the basic nitrogen of **1** and **2** were overlapped led to the hypothesis that the aromatic moiety of epibatidine was oriented differently in the binding pocket than the biaryl group of **2**. We therefore conjectured that addition of a substituent to compound **2** might offer an additional binding interaction that would enhance potency. This hypothesis suggested analogs **3**, **4** and **5** with substituents on the pyrrolidine ring that combined elements of epibatidine **1** with **2** (Fig. 1).

To explore possible substituents, we sought to quickly generate N-substituted analogs. As shown in Scheme 1, bicyclic diamine analogs **3a–f** were generated from precursor **6**[8] by reaction with alkyl or arylmethyl halides. Aminopyrrolidine analogs were synthesized by a coupling of racemic *tert*-butyl pyrrolidin-3-ylcarbamate and 3-chloro-6-phenylpyridazine using excess diisopropylethylamine in DMSO. The carbamate nitrogen was reacted with various alkyl or arylmethyl halides and the Boc group was removed by treatment with acid. Reductive methylation gave the tertiary amine analogs **4a–f**.

As shown in Table 1, in the bicyclic diamine series (**3**), the substituent on the nitrogen had a substantial effect on binding of the ligand to the rat α7 receptor. Compound **2**, with a methyl substituent, bound potently with a K_i of 11 nM. Larger substituents (Et or Bn) brought a 30- or 40-fold drop in potency. Among the pyridylmethyl substituted analogs, the position of the pyridyl nitrogen impacted potency. The 2- and 4-pyridylmethyl substituted analogs were about 50-fold less potent than **2**, comparable to the benzyl analog. In contrast, the 3-pyridylmethyl analog **3e** had a K_i of 3.6 nM. The 3-pyridyl isomer in **3e** corresponds to the position of

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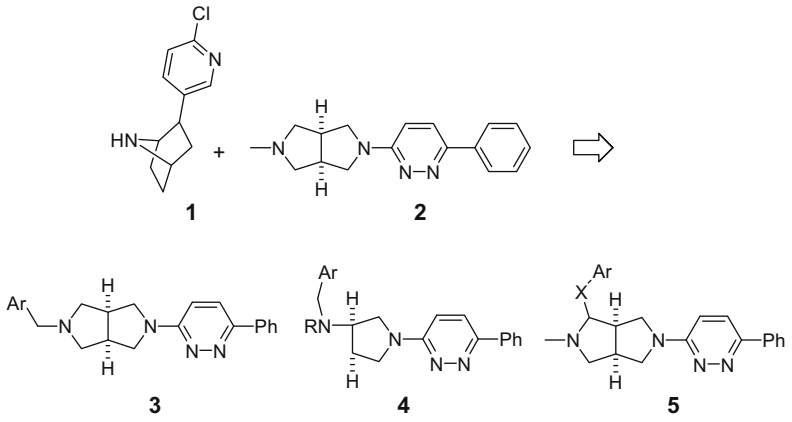
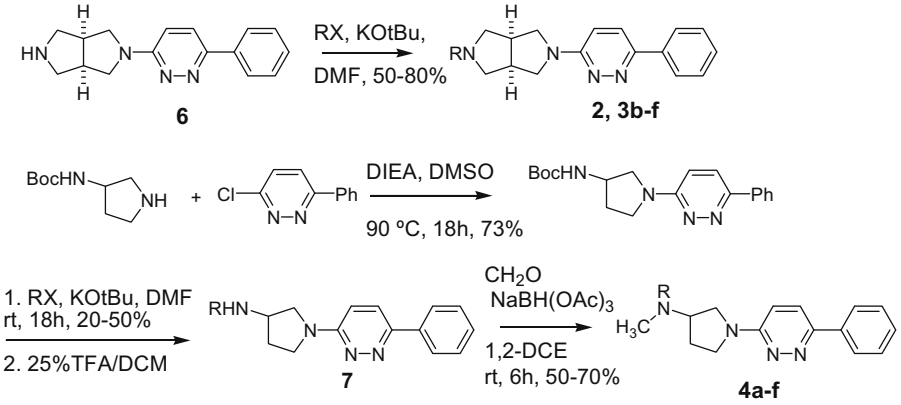
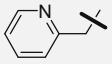
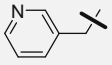
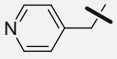
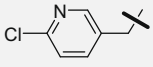


Figure 1. Proposed analogs.



Scheme 1. Preparation of N-substituted derivatives.

Table 1
α7 nAChR binding of N-substituted derivatives[10]

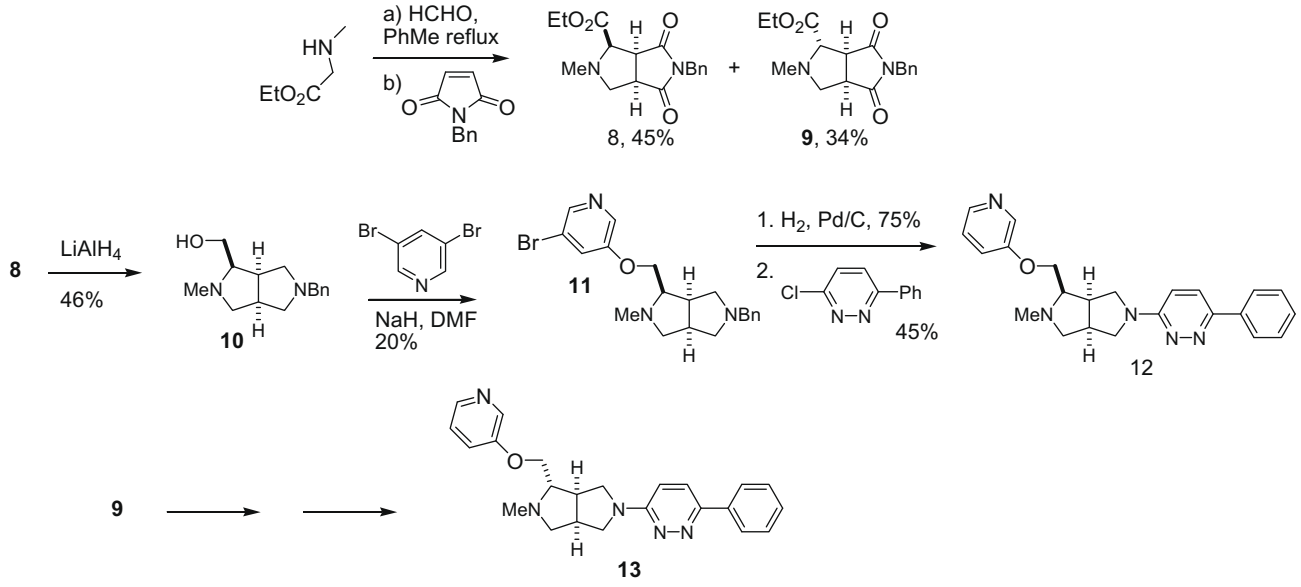
Compd	R	Series **3** α7 nAChR binding[a] K_i (nM)	Series **4** α7 nAChR binding[a,b] K_i (nM)
2	CH_3	11	
4a			478
3b	Et	331	
4b			746
3c	Bn	476	
4c			$>10^4$
3d		533	
4d			$>10^4$
3e		3.6	
4e			$>10^4$
3f		541	
4f			$>10^4$
3g		102	
4g			$>10^4$
6	H	17.5	
7	CH_3		$>10^4$
C-Linked analogs			
12	NA	320	
13	NA	42	

[a] Displacement of [^{3}H]-A-585539 from rat brain.[10] Kis reported are the mean of three determinations; SEM versus p$K_i \leqslant 0.08$.
[b] Analogs are racemic.

the nitrogen in the 2-chloropyrid-5-yl substituent in epibatidine. Compound **3g**, bearing a chloropyridyl group like epibatidine, was also superior to the analogs containing other pyridyl isomers, but it was 28-fold less potent than analog **3e**. Compound **6**, the NH analog of the lead compound **2**, bound potently to the α7 receptor, with a K_i of 17.5 nM. But compound **6** was somewhat less selective, binding the α4β2 nAChR subtype with a K_i of 5.3 μM. All other compounds tested in series **3**, **4** or **5** did not bind to the α4β2 receptor at concentrations up to 10 μM.[9]

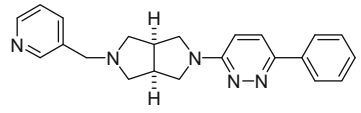
Compounds containing an aminopyrrolidine group (series **4**) bound less potently to the α7 receptor than the bicyclic diamine compounds **3**. Dimethylaminopyrrolidine **4a** had a K_i of 478 nM. The ethyl analog **4b** was about twofold less potent, and larger substituents, including 3-pyridylmethyl, abolished binding up to 10 μM. All compounds in the aminopyrrolidine series with a secondary amine, that is, **7** had K_is >10 μM.

Compounds related to **5** were synthesized as shown in Scheme 2. The fused [3.3.0] ring system was accessed by a [3+2] cycloaddition.[11] The azomethine ylide was formed in situ and reacted with *N*-benzylmaleimide to give cis isomer **8** and its epimer **9** in approximately a 1:1 ratio.[12] The imide was reduced with lithium aluminum hydride to amino alcohol **10**. Attachment of the pendant pyridyl ring was achieved by nucleophilic aromatic substitution to give intermediate **11**. Hydrogenation over palladium on carbon removed the aromatic bromide and the benzyl group. Coupling of the resulting amine with 3-chloro-6-phenylpyridazine gave compound **12**. The relative stereochemistry of **12** was established by



Scheme 2. Preparation of diamine analogs.

Table 2
Functional efficacy of lead compounds[a]



3e

Compd	EC_{50} (μM)	Maximal response[a] (%)
2	4.26	52
3e	9.36	84
3g	11.77	13
12	>100	—
13	12.90	44

[a] Normalized to the maximal response of ACh (10 mM) in Xenopus oocytes expressing human α7 receptors.[13]

2D NMR and is consistent with literature.[12] Compound **13** was synthesized similarly from compound **9**.

Based on previous observations, series **5** compounds were designed with a pendant 3-pyridyl group. The addition of the substituent in compound **12** gave a 30-fold loss in potency relative to **2** (K_i = 320 nM, Table 1). However, the epimeric compound **13** largely retained its ability to bind α7, with a K_i of 42 nM. Although **13** is slightly less potent than **2**, the binding site is able to accommodate the addition of this substituent.

The stereochemistry and attachment of the pyridyl substituent also had a dramatic effect on the ability of the ligands to activate the receptor. The α7 nAChR is a ligand-gated ion channel. Activation of the receptor by an agonist opens the channel to allow the flow of ions across a membrane. Five compounds were tested for their ability to evoke Ca^{2+} currents in Xenopus oocytes expressing recombinant human α7 nicotinic receptor (Table 2).[13] The maximal response was calculated as a percent of the response evoked by 10 mM acetylcholine. Compound **2** is a partial agonist at human α7 with an EC_{50} of 4.3 μM. N-Substituted compound **3e** is about twofold less potent, but closer in efficacy to ACh. Compound **13** is a partial agonist, threefold less potent than **2**. But compound **12** shows no efficacy up to 100 μM. While compounds bearing a non-optimal substituent might lose binding potency, ligands **3g**, **12** and **13** suffered a loss in functional potency and efficacy, suggesting they were less able to catalyze the conformational change leading to channel opening.

Previous approaches to designing ligands for nAChRs based on epibatidine have produced compounds that are selective for the α4β2 receptor subtype over α7.[14] Successful designs for α7 receptor ligands have employed specific amine pharmacophores such as quinuclidine[3] or other amine groups[15] linked to an aromatic or bisaromatic moiety to give a linear core. In addition, a few α7 ligands have been reported that contain a 3-pyridyl group as one of two aromatic substituents branching from the amine pharmacophore, notably the anabaseine derivative GTS-21.[16] The quinuclidine pharmacophore has been combined with a 3-pyridylmethyl substituent to give very potent α7 agonists.[17] These observations suggested that the α7 binding site could accommodate a branched ligand displaying two distinct aromatic groups linked to the alkylamine headgroup.

In the present study, arylmethyl substituents were attached at different positions to a diamine-containing core. Consistent with previous results, we found that a 3-pyridyl group was preferred over other pyridine isomers or aromatic groups. The most potent analog discovered was (3a*R*,6a*S*)-2-(6-phenylpyridazin-3-yl)-5-(pyridin-3-ylmethyl)octahydropyrrolo[3,4-*c*]pyrrole, **3e**, in which a 3-pyridyl group was attached by a linker to the terminal nitrogen. This result was somewhat surprising, given that the substituted nitrogen binds in a well-defined pocket, and the change from a methyl to ethyl in **3b** caused a 30-fold drop in potency. The nitrogen of the quinuclidine analogs, by contrast, occupies a bridgehead position that minimizes steric demand. This suggests the basic amine binding site has the flexibility to accommodate an appropriate substituent. The binding energy available from the correctly placed pyridyl group enhanced the potency of **3e**, and the substituent also increased its effectiveness as an agonist compared to the parent compound, **2**.

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