Novel Pyridyl Ring C5 Substituted Analogues of Epibatidine and 3-(1-Methyl-2(*S*)-pyrrolidinylmethoxy)pyridine (A-84543) as Highly Selective Agents for Neuronal Nicotinic Acetylcholine Receptors Containing β2 Subunits

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Abstract: Introduction of a hydrophobic or hydrogen-bonding alkynyl group into the C5 position of the pyridyl ring of epibatidine and A-84543 significantly increased the selectivity for neuronal nicotinic acetylcholine receptors (nAChRs) containing β2 subunits over nAChRs containing β4 subunits (K_i ratio up to 92000-fold). Our data indicate that the extracellular domains of the nAChRs are sufficiently different to allow for the design of novel ligands with high affinity and selectivity for the nAChR subtypes.

Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels.[1] These receptors hold considerable promise as therapeutic targets for the treatment of disorders of the central nervous system (CNS) and peripheral nervous system.[2] Most nAChRs are heteromeric pentamers. The subunits that comprise the receptors have a common general structure consisting of a large extracellular N-terminal domain that contains the binding sites for acetylcholine, nicotine, and other ligands, four membrane-spanning hydrophobic segments, and a large intracellular domain between the third and the fourth membrane-spanning segments.[3] Twelve neuronal nAChR subunits (α2−α10 and β2−β4) have been identified in vertebrates, and different combinations of these subunits define nAChR subtypes.[4]

Subtype selectivity is a critical issue for the effectiveness and safety of drugs. To selectively affect different physiological functions pharmacologically, it is very important to have drugs that preferentially act on specific receptor subtypes. Similarly, nAChR subtype-selective ligands may prove useful in the diagnosis of brain pathology by means of positron emission tomography (PET) imaging.[5] However, finding compounds that discriminate among nAChR subtypes has proven to be difficult because of the large number of potential receptor subtypes and the relatively subtle differences in their structures. There are a large number of nicotinic agonists and noncompetitive antagonists (channel blockers), but very few of these nicotinic compounds are subtype-selective.[6]

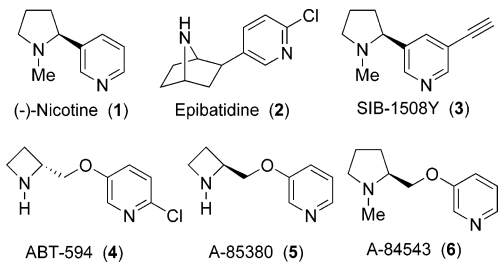

Figure 1.

Development of selective agonists or antagonists may therefore result in new and potentially useful therapeutic agents. One of the important targets for selective drugs is the α4β2 nAChR subtype, which is the most abundant nAChRs in the brain. Nicotine (**1**) and epibatidine (**2**), as naturally occurring agonists of nAChRs, have attracted interest as starting points for modification leading to structures with improved pharmacological properties.[6−8] In particular, within the past several years, a series of pyridyl ether compounds, including ABT-594 (**4**), A-85380 (**5**), and A-84543 (**6**), were synthesized as high-affinity chain-extended analogues of nicotine (**1**) (Figure 1).[9] Although some of these compounds are selective, their discrimination among receptor subtypes is generally about 1 or 2 orders of magnitude.[10] Among the new nicotinic compounds developed in recent years, A-85380 and one of its analogue, 5-iodo-A-85380, showed the highest selectivities between the α4β2 subtype and α3β4 subtype, the main ganglionic nAChR population.[11] We found previously that some modifications at the C5 position of the pyridyl ring of **5** significantly enhanced the selectivity to 4 orders of magnitude between α4β2 and α3β4 subtypes.[12] In continuation of our efforts to find selective neuronal nAChR ligands,[13] we report here our discovery that introduction of hydrophobic or hydrogen-bonding alkynyl substituents at the C5 position of the pyridyl ring of **6** and dechloroepibatidine imparts very high selectivity for receptors containing β2 subunits over receptors containing β4 subunits.

The C5 position of the pyridyl moiety of A-84543 tolerated sterically bulky substituents without losing its binding affinity at α4β2 nAChR.[9] Our aim therefore was to investigate the effects of C5 substituents of the pyridine ring on the binding affinity and subtype selectivity at neuronal nAChRs caused by steric factors and the hydrophobicity of the newly introduced group. Introduction of an ethynyl substituent at the C5 position of the pyridyl ring of **1** led to SIB-1508Y (**3**) with altered subtype selectivity for neuronal nAChRs.[14] Thus, 5-alkynyl-substituted A-84543 analogues **8**−**15** were prepared (Scheme 1) and evaluated by binding assays at six heterologously expressed nAChR subtypes (α2β2, α2β4, α3β2, α3β4, α4β2, and α4β4). In particular, we compared the affinities of these ligands at the α3β4 subtype with their affinities at the α4β2 subtype. The

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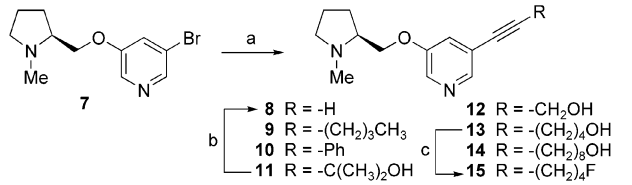
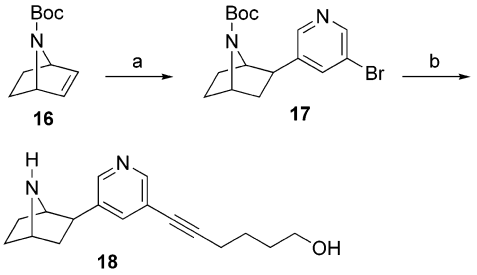
Scheme 1[a]



[a] Reagents: (a) alkyne, 10% Pd−C (cat.), CuI (cat.), K_2CO_3, DME, H_2O, reflux, 72 h, 55−95%; (b) NaH (cat.), toluene, 120 °C, 1 h, 99%; (c) (i) I_2, PPh_3, imidazole, CH_2Cl_2, 92%; (ii) AgF, acetonitrile, 10 h, 57%.

Scheme 2[a]



[a] Reagents: (a) 3,5-dibromopyridine, $Pd(PPh_3)_4$ (cat.), piperidine, HCO_2H, DMF, 80 °C, 72 h, 61%; (b) (i) 6-[(*tert*-butyldimethylsilyl)oxy]-1-hexyne, $Pd(PPh_3)_2Cl_2$ (cat.), CuI (cat.), Bu_4NI, Et_3N, DMF, reflux, 48 h, 93%; (ii) CF_3CO_2H, CH_2Cl_2, 90%.

results are summarized in Table 1. The α3β4 subtype is found in many sympathetic ganglia, while the α4β2 subtype is the predominant nAChR in the forebrain; therefore, the affinity ratios of drugs at these subtypes can help to predict the likelihood of autonomic nervous system side effects of drugs aimed at the predominant receptor subtype in the forebrain.[11] Neither nicotine (**1**) nor epibatidine (**2**) shows significant selectivity among the six nAChR subtypes (<45-fold). A-84543 (**6**) possesses very high affinity for all three nAChR subtypes containing β2 subunits but much lower affinity for the subtypes containing β4 counterparts, although the highest selectivity among the six nAChR subtypes is still less than 750-fold. The improved selectivity suggests the possibility of developing subtype-selective ligands. Introduction of additional substituent groups at the C5 position of the pyridyl ring of **6** resulting in **8**−**15** did not cause marked differences in the binding affinities at the α4β2-containing subtype (within ∼4-fold). However, it is noteworthy that introduction of a 5-alkynyl group decreased the affinities of **8**−**15** at the α3β4 subtype, in some cases markedly, resulting in improved selectivity between the nAChR subtypes. As expected, introduction of an ethynyl substituent at the C5 position of the pyridyl ring of **6** led to **8** with improved nAChR subtype selectivity between α4β2 and α3β4 (>4000-fold). Extension of the ethynyl substituent with hydrophobic groups or hydrogen-bonding groups improved the selectivity (as shown by **9**−**14**). The 6-hydroxy-1-hexynyl substituent at the C5 position of the pyridine ring of **13** is a preferred group for attaining the expected high binding affinity at the α4β2 receptor (0.85 nM) and very high subtype-selectivity (>74000-fold). Similarly the fluoride-containing analogue **15** possesses much higher affinities at receptors composed of an α subunit in combination with the β2 subunit than with the β4 subunit.

If epibatidine **2** and the 3-pyridyl ether **6** bind at each nAChR in a common manner, then the significant improvement of the subtype selectivity of **13** that is achieved by introducing a 6-hydroxy-1-hexynyl group at the C5 position of the pyridyl ring should also apply to the corresponding epibatidine analogues. A very recent study reveals that introduction of a bulky phenyl group at the C5 position of the pyridyl ring of epibatidine results in ligands that are antagonists at nAChRs.[15] On the other hand, it has been shown that dechloroepibatidine binds with similar affinity as epibatidine at the α4β2 nAChR subtype.[16] Thus, 5-(6-hydroxy-1-hexynyl)-substituted dechloroepibatidine analogue **18** was prepared by using the reductive Heck reaction of **16**[16a] with 3,5-dibromopyridine followed by the Sonogashira reaction as the key steps (Scheme 2). As shown in Table 1, **18** also possesses subnanomolar affinities at the β2-containing subtypes, although its affinities are 2- to 8-fold lower than those of epibatidine at each of the β2-containing subtype. It is noteworthy that **18** was quite selective for an α subunit paired with the β2 versus the β4 subunit. Thus, the α3β4/α4β2 affinity ratio of **18** was >2385, while epibatidine, which itself binds to most nAChR subtypes with picomolar affinity, displays a ratio of only ∼9.

To further explore the binding modes of these ligands at different nicotinic receptor subtypes and to uncover the underlying mechanism for the observed selectivity,

Table 1. Binding Affinities of (−)-Nicotine (**1**), (±)-Epibatidine (**2**), A-84543 (**6**), **8**−**15**, and **18** at Six nAChR Subtypes[a]

	binding affinity K_i (nM)						selectivity	
ligand	α2β2	α2β4	α3β2	α3β4	α4β2	α4β4	α3β4/α4β2	cLogP[b]
1	12 ± 2	112 ± 21	47 ± 11	443 ± 60	10 ± 2	40 ± 6	44	0.88
2	0.025 ± 0.001	0.095 ± 0.017	0.035 ± 0.011	0.57 ± 0.12	0.061 ± 0.009	0.16 ± 0.01	9	1.55
6	2.5 ± 1.3	320 ± 60	7.7 ± 0.7	1400 ± 400	1.9 ± 0.7	220 ± 70	737	1.83
8	2.5 ± 1.7	750 ± 200	8.2 ± 1.3	6800 ± 2300	1.6 ± 0.7	710 ± 190	4250	2.10
9	9.4 ± 3.8	1900 ± 200	21 ± 1	40000 ± 30000	1.4 ± 0.6	1900 ± 600	28571	4.08
10	4.4 ± 1.9	500 ± 70	8.6 ± 2.1	8100 ± 5700	0.51 ± 0.21	530 ± 160	15882	4.47
11	1.9 ± 0.1	8400 ± 1300	23 ± 2	61000 ± 21000	2.9 ± 1.5	7000 ± 1200	21034	1.35
12	3.4 ± 2.1	1900 ± 100	7.1 ± 0.3	23000 ± 6000	0.93 ± 0.22	1300 ± 300	24731	0.64
13	1.9 ± 0.7	3600 ± 300	13 ± 3	63000 ± 12000	0.85 ± 0.19	1200 ± 100	74118	2.23
14	22 ± 8	6,200 ± 800	48 ± 3	66,000 ± 7,000	6.1 ± 0.5	2,400 ± 600	10,820	4.34
15	4.2 ± 2.2	3,700 ± 700	14 ± 1	88,000 ± 58,000	0.95 ± 0.57	2,000 ± 1,100	92,632	3.49
18	0.19 ± 0.09	28 ± 9	0.23 ± 0.09	310 ± 60	0.13 ± 0.03	10 ± 3	2,385	1.15

[a] The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.02 for α2β2, 0.08 for α2β4, 0.03 for α3β2, 0.30 for α3β4, 0.04 for α4β2, and 0.09 for α4β4.[11] The K_i values of (−)-nicotine (**1**) and (±)-epibatidine (**2**) were published previously[11] and are shown here for comparison. The K_i values of **6**, **8**−**15**, and **18** shown are the mean of three independent measurements. [b] http://www.daylight.com/daycgi/clogp.

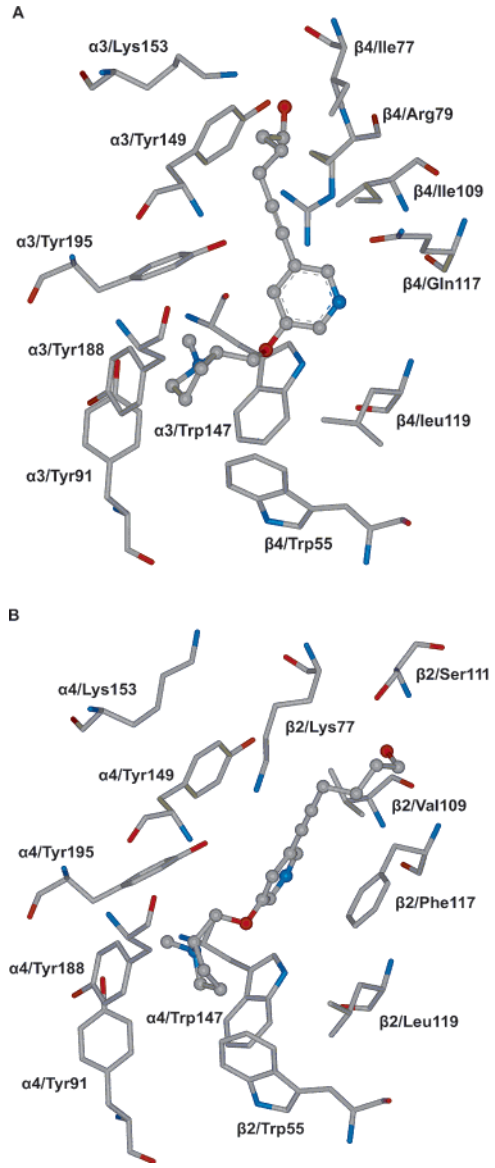


Figure 2. Difference in the binding modes of ligand **13** docked to the models of α3β4 (A) and α4β2 (B) nAChR receptors.

we used the program Autodock3.0[17] to dock these ligands in the rat nicotinic receptor models α3β4 (1OLJ) and α4β2 (1OLE),[18] which are based on the X-ray structure (1I9B) of the acetylcholine-binding protein (AChBP).[19] The Phe^{117} in the β2 subunit protein may be involved in the high-affinity binding of nicotine.[18,20] The docking results confirm that the pyridyl ring and the 5-substitued hydrophobic group of ligand **13** have π−π and strong hydrophobic interactions with the phenyl ring of Phe^{117} in the α4β2 protein (Figure 2B), whereas similar lipophilic interactions are not possible with the polar side chain of Gln^{117} in the α3β4 nicotinic receptor (Figure 2A) and other β4-containing receptors. According to the docking experiment, the pyridyl ring of ligand **13** tends to rotate about 90° to avoid unfavorable interactions with the polar side chain of Gln^{117}. This spatial reorganization does not lead to formation of new hydrogen bonds; thus, the loss of hydrophobic interactions is not balanced, which ultimately leads to weaker binding of ligand **13** in this series to the receptors containing the β4 subunits. Overall, this difference in the binding modes may explain the fact that ligands **8**−**15** in general have much higher affinities for the β2-containing receptors than for the β4-containing receptors.

On the basis of their binding affinities and the results from modeling, we conclude that nicotine, epibatidine, and the 3-pyridyl ether analogues bind in a similar fashion at each nAChR subtype. These selective analogues containing appropriately functionalized side chain appendages are quite interesting because, in addition to their general use as pharmacological tools, they may be used in creating fluorescent probes and affinity columns for certain nAChR subtypes. In addition, if labeled with ^{11}C or ^{18}F, some of these selective ligands could be useful as PET imaging probes.[21] We have begun studies of the pharmacological actions of some of these ligands at nAChR subtypes to determine whether they are agonists, partial agonists, or antagonists. Moreover, in light of the high affinity and selectivity found for some of these ligands (e.g., **11**−**13** and **15**), efforts to explore them in brain PET studies are underway.

In summary, we have synthesized high-affinity nAChR ligands that display selectivity for nAChRs containing the β2 subunit in general and the α4β2 subtype in particular. These studies thus show that the extracellular domains of the nAChRs are sufficiently different to allow for the design of novel ligands with high affinity and selectivity for the nAChR subtypes. Because of the recent advance in solving the structure of the molluscan AChBP[19] and the resulting homology modeling of the extracellular domains of some nAChRs,[18,20,22] strategies for developing new subtype-selective ligands should become more rational.

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Supporting Information Available: Detailed experimental procedures with spectroscopic data and table of combustion data. This material is available free of charge via the Internet at http://pubs.acs.org.

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