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3-(4-Aminobutyn-1-yl)pyridines: binding at α4β2 nicotinic cholinergic receptors☆

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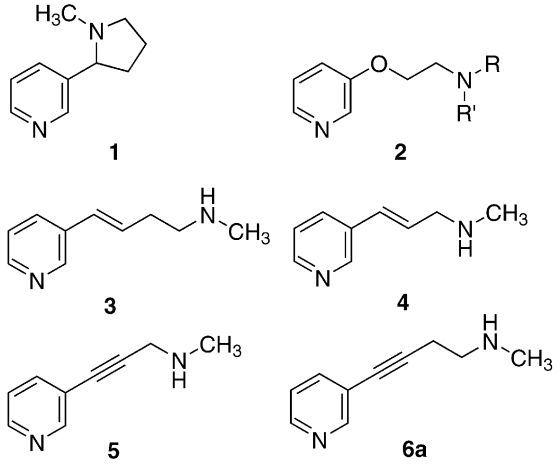
Abstract—The binding of a series pyridylbutynylamines **6** was examined at α4β2 nACh receptors. Structural modifications, comparing **6** with pyridyl ethers **2**, did not consistently result in parallel effects on receptor affinity, suggesting possible differences in their modes of binding. Furthermore, the binding of amine **6a** seemed to be accounted for by the newer vector pharmacophore models.

Nicotine (**1**) produces many of its effects via interaction with nicotinic cholinergic (nACh) receptors.[1,2] Several populations of nACh receptors have been identified, but the most prevalent population in mammalian brain are α4β2 receptors.[1] Novel structure types with 'extended' side chains have been shown to bind at α4β2 receptors including pyridyl ethers **2**, and a metabolite of **1**: *trans*-metanicotine (also known as RJR-2403, TC-2403, or simply as 'metanicotine', **3**).[3,4] Shortening the length of the alkyl chain of **3** (K_i ca. 25 nM)[5,6] by one methylene unit results in dramatically decreased affinity (**4**; K_i ≈6000 nM).[7] Alkyne **5** (K_i = 2285 nM) also binds in the micromolar range.[7] Chain extension of **5** results in **6a** (K_i = 58 nM) which binds with higher affinity than **5**, and with an affinity comparable to **3**.[6]

The purpose of this investigation was several fold. Compound **6a** has been reported (as its free base and fumarate salt) only in an abstract[5] and in the patent literature;[6] its structure–affinity requirements have not been studied in detail. Because tertiary amines of **1** and **2** are typically favored over secondary amines for α4β2 receptor binding,[8] it was of interest to determine how variation of the terminal amine substituents of **6a** would influence affinity. Also, because introduction of halogen at the 6-position of either **1** or **2** has little effect on nACh receptor affinity whereas introduction of a methoxy group and replacement of the pyridine nitrogen atom by CH are not well tolerated,[8] we examined the 6-chloro, 6-methoxy, and de-aza derivatives of **6a**. Another reason to examine analogues of **6a** is from a theoretical perspective. That is, several pharmacophore models have been proposed for nicotinic action. In one model, an internitrogen (N–N) distance of 4.8 Å is suggested to be important.[9] Nicotine (**1**) possesses such a distance. However, compound **2**, although longer in length relative to nicotine (**1**), is much more con-



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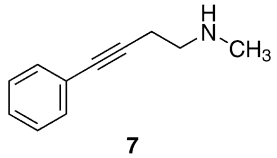
formationally flexible and a number of low-energy conformations with varying N–N distances are possible.[10] Compound **6a**, although still conformationally flexible, possesses a certain amount of constraint due to the presence of the *sp*-hybridized carbon atoms in the side chain. It is unlikely that **6a** can achieve an N–N distance of 4.8 Å. More recent pharmacophore models place less importance on N–N distance.[11–13] Thus, an examination of analogues of **6a** also allows this concept to be addressed.

Several derivatives of **6a** were prepared and examined (Table 1).[14] Physicochemical and spectral data for **6a** were similar to that in the literature, and its nACh receptor affinity ($K_i = 113$ nM) was not inconsistent with what was reported earlier ($K_i = 58$ nM).[6]

The novel *N,N*-dimethyl and *N*-ethyl-*N*-methyl derivatives **6b** and **6c** ($K_i = 510$ and 1770 nM, respectively) displayed 5- and 15-fold lower affinity than the secondary amine **6a**. The pyrrolidinyl analogue **6d** lacked affinity whereas the *N,N,N*-trimethyl quaternary amine **6e** ($K_i = 470$ nM) displayed an affinity comparable to that of **6b**. Introduction of a 6-chloro group had little impact on affinity (i.e., **6f** $K_i = 154$ nM) whereas a methoxy group at this position was not tolerated (i.e., **6g** $K_i > 10{,}000$ nM).

Compound **7**[16] ($K_i > 10{,}000$ nM), the de-aza counterpart of **6a**, lacked affinity for nACh receptors.



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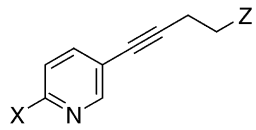
The influence of the 6-position substituents on affinity generally follows that seen with nicotine and pyridyl ether **2**;[17] that is, halogen has little effect but a methoxy group decreases affinity. The presence of the pyridyl nitrogen atom is important for the binding of **6a** (as seen with **7**) as it is for the binding of nicotine and the pyridyl ethers.[10] However, amine substituents seem to influence these ligands differently. Demethylation of nicotine to its corresponding secondary amine, nornicotine, decreases affinity by approximately 15-fold.[8] Table 2 compares the influence of amine substituents on **6a** relative to **2** and a series of ring-opened analogues of nicotine: 3-(aminomethyl)pyridines. The *N*-monomethyl, *N,N*-dimethyl and *N*-ethyl-*N*-methyl analogues of **2** bind with comparable affinity ($K_i = 21$–35 nM). With the aminomethylpyridines (see ***B***, Table 2) optimal affinity is associated with the *N*-ethyl-*N*-methyl and pyrrolidinyl derivatives. In contrast, the highest affinity analogue of **6** is associated with the secondary amine **6a**; the affinities of the tertiary amines are somewhat lower. Also, the pyrrolidinyl analogue of **2** binds with low affinity whereas that of **6** (i.e., **6d**) lacks affinity. One of the most striking differences is seen upon quaternization. Quaternization (via methylation) of nicotine has little effect on affinity[18] whereas quaternization of the *N,N*-dimethyl analogue of **2** increased affinity by about 40-fold.[19] In the present study, *N*-methylation of **6b** had essentially no effect on affinity. Although additional compounds might need to be studied, a general conclusion that can be tentatively reached is that alteration of the terminal amine group of **6**-series compounds, more so than alterations in the pyridyl portion, results in greater disparity of results when compared with the pyridyl ether (i.e., **2**-) series (or the aminomethylpyridine series) of compounds.

Table 1. Physicochemical properties and α4β2 nACh receptor binding affinities for pyridylbutynylamines **6a–g**



	Z	X	Mp (°C)	Empirical formula[a]	K_i, nM[b]
6a	–NH–CH_3	–H	156–157	$C_{10}H_{12}N_2 \cdot C_2H_2O_4$	113 (16)
6b	–$N(CH_3)_2$	–H	152–153	$C_{11}H_{14}N_2 \cdot C_2H_2O_4$	510 (50)
6c	–$N(CH_3)C_2H_5$	–H	90–91	$C_{12}H_{16}N_2 \cdot 1.5C_2H_2O_4$	1770 (900)
6d		–H	141–142	$C_{13}H_{16}N_2 \cdot C_2H_2O_4$	>10,000
6e	–$N(CH_3)_3^+$	–H	177	$C_{12}H_{17}IN_2$	470 (110)
6f	–NH–CH_3	–Cl	196–197	$C_{10}H_{11}ClN_2 \cdot C_2H_2O_4$	154 (40)
6g	–NH–CH_3	–OMe	177–178	$C_{11}H_{14}N_2O \cdot C_2H_2O_4$	>10,000

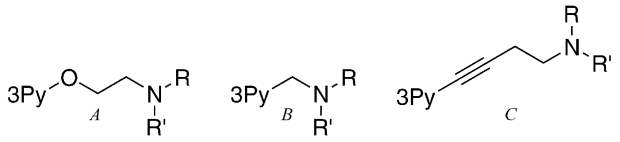
[a] Compounds, isolated as their oxalate salts except for **6e** iodide, analyzed within 0.4% of theory. Compounds were recrystallized from absolute EtOH except for **6a** (MeOH), **6c** (acetone/hexane), **6d**, **6e** (acetone).

[b] K_i values were determined at least in triplicate using [^{3}H](−)nicotine as radioligand and are followed, except where $K_i > 10{,}000$ nM, by ±SEM in parentheses.[15] For reference, the K_i value for (−)nicotine = 2.1 nM.

Do pyridylbutynylamines **6** meet the requirements of any of the three currently prevailing nicotinic pharmacophore models? The Sheridan et al.[9] model requires an N–N distance of 4.8 Å. Molecular modeling studies performed on **6a** identified numerous low-energy conformers typically displaying N–N distances of >7.7 Å.[20] The shortest possible N–N distance achievable is 5.7 Å (energy within 0.3 kcal/mol of the lowest-energy conformer: 2.9 kcal/mol). On this basis, it is unlikely, as might have been expected, that **6a** can meet the Sheridan et al.[9] pharmacophore N–N distance requirement of 4.8 Å.

Olesen and co-workers[11] have proposed that the distance between two points, *a* and *b*, at the ends of vectors (each 2.9 Å in length) drawn in the direction of the lone-pair electrons of nicotinic ligands, should be between 7 and 8 Å. In a second study where a 2.9-Å vector was attached to each nitrogen atom of **6a** and calculations were repeated using an *a–b* constraint of 7–8 Å, about 24 low-energy conformers (E≈3.35 kcal/mol; N–N distance ≈7.2 Å) with an *a–b* distance of about 7.8 Å were identified (Fig. 1). Thus, **6a** seemingly meets the vector pharmacophore requirements.

Table 2. Comparison of α4β2 affinities for several series of 3 -pyridyl-substituted ligands[a]



–NRR′	K_i (nM)[b]		
	A	*B*	*C*
–NH–CH_3	35	> 10,000	113
–N(CH_3)$_2$	21	540	510
–N(CH_3)C_2H_5	22	28	1770
	212	30	> 10,000
–N(CH_3^+)$_3$	0.5	110	470

[a] Data for the pyridyl compounds ***A*** and ***B*** have been previously reported;[7,10] data for pyridylalkynes ***C*** are from Table 1. 3-Py = 3-pyridyl.

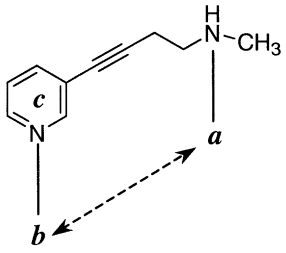


Figure 1. Computational studies with **6a** revealed that it meets the 7–8 Å *a–b* distance requirement of the vector pharmacophore model where *a* and *b* are hypothetical receptor points located 2.9 Å from each of the two nitrogen atoms.

Olesen and co-workers[12,13] have also proposed a modification of their vector model by introducing an aryl centroid feature *c*. In the modified vector pharmacophore, optimal affinity is associated with an *a–b* distance of 7.3–8.0 Å, an *a–c* distance of 6.5–7.4 Å, and a *b–a–c* angle of 30.4–35.8°. Several conformers of **6a** were identified with an *a–b* distance of about 7.9 Å, an *a–c* distance of about 6.6 Å, and a *b–a–c* angle of 32.6–32.9°; however, these conformers possessed energies (≈8.1 kcal/mol) about 5 kcal/mol above the lowest energy conformer. Thus, it is possible, at least in theory, for **6a** to meet the modified pharmacophore requirements, and the higher energy associated with the necessary conformers might offer an explanation for the reduced affinity of **6a** relative to nicotine.

The results of the present investigation confirm that pyridylbutynylamine **6a** binds at nACh receptors. Furthermore, it was found that a 6-chloro group but not a 6-methoxy group is tolerated, that the *N*-methyl secondary amine (i.e., **6a**) binds with higher affinity than simple tertiary amine analogues, that quaternization has little effect on affinity, and that the pyridine nitrogen atom is important for binding. Evidence is presented that analogues **6** may not bind in a manner that parallels that of the pyridyl ethers **2** because different terminal amine substituents have a different effect on the binding of members of the two series. Perhaps the pyridylbutynylamines utilize the same pyridine binding site as **2** (or **1**), but different terminal amine sites; alternatively, if a common amine site is used, the amine substituents must be oriented differently to account for the lack of parallel affinity shifts between members of the series. Compound **6a** was shown to be too long to conform to the internitrogen distance requirements of the Sheridan et al.[9] pharmacophore model but, seemingly, might meet the requirements of the newer vector-based pharmacophore models proposed by Olesen and colleagues.[11–13]

Acknowledgements

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14. The appropriate 3-bromopyridine was allowed to react with 3-butynol in the presence of bis(triphenylphosphine)$PdCl_2$/CuI, the resultant alcohol was converted to its mesylate derivative, and the mesylate was allowed to react with the requisite amine at room temperature in a manner similar to that reported by Caldwell et al.[5] Physicochemical data are shown in Table 1.
15. K_i values were obtained as previously described, using rat brain homogenates minus cerebellum, in: Dukat, M.; Damaj, I. M.; Young, R.; Vann, R.; Collins, A. C.; Marks, M. J.; Martin, B. R.; Glennon, R. A. *Eur. J. Pharmacol.* **2002**, *435*, 171 using [^{3}H](−)nicotine as radioligand.
16. Compound 7 as its oxalate salt (MeOH; mp 156–157 °C) analyzed within 0.4% of theory for C, H, and N.
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20. Modeling studies. Studies were conducted using SYBYL (*SYBYL Molecular Modeling Package*, Version 6.8; Tripos Inc.: St. Louis, MO, USA, 2001). The structure of **6a** was built using standard bond lengths and angles within the BUILD/SKETCH molecule command followed by molecular mechanics minimization (MINIMIZE) and calculation of charges by the Gasteiger-Huckel algorithm. Conformational search was performed using the SYSTEMATIC SEARCH command; the four rotatable bonds were rotated in 30°-increments starting at 0°. For evaluation of vector models, an *a*–*b* distance constraint of 7–8 Å was introduced. Results were ANALYZED with the SYSTEMATIC SEARCH command. A total of 791 conformers were identified, of which only the 24 lowest energy conformers were considered.