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Aryloxyethylamines: Binding at α7 nicotinic acetylcholine receptors

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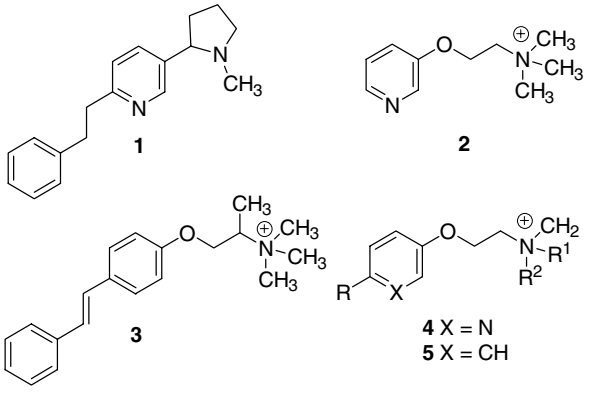
Abstract—Structure–affinity relationships for the binding of 3-[2-(*N*,*N*,*N*-trimethylammonium)ethoxy]pyridine (AXPQ) at α7 nACh receptors were investigated due to its close structural similarity to a known α7 antagonist.

Acetylcholine produces many of its effects by interaction with nicotinic acetylcholine (nACh) receptors, and the two most abundant receptor types in brain are the α4β2 and α7 nACh receptors. The medicinal chemistry of α4β2 receptors has been relatively well studied.[1] The latter population, about which much less is known, is of interest because of its possible role in certain central disorders such as cognitive and perceptual disturbances—especially those associated with schizophrenia.[2] There also is evidence that α7 nACh receptors are associated with the release of neurotransmitters that are involved in schizophrenia, depression, and anxiety, such as dopamine, norepinephrine, and serotonin.[3,4]

(±)6-(2-Phenylethyl)nicotine (6-PEN; **1**) is a nicotinic acetylcholine (nACh) receptor antagonist with reasonable selectivity for α4β2 (K_i = 0.015 μM) over other nACh receptors,[5] and AXPQ (**2**) is a high-affinity α4β2 agonist (K_i = 0.0005 μM).[6] Recently, Gotti et al.,[7] reported that choline ether F3 (**3**) is an α7-selective antagonist (α7 K_i = 0.057 μM) with little affinity (K_i = 39 μM) for β2-containing nACh receptors. As such, **3** might represent a novel template for further development of α7 ligands.

6-PEN (**1**), and even more so AXPQ (**2**), bear structural similarity to **3** but their binding at α7 receptors has not yet been examined. Furthermore, very little structure–affinity data are available for F3 (**3**). Due to this structural similarity, and because **3** is reportedly an α7-selective agent, it was of interest to determine the affinity of 6-PEN (**1**) and AXPQ (**2**) for α7 receptors, and to examine what common structural features might account for the affinity of **3**-related aryloxyalkylamines. For example, the presence and position of a pyridyl nitrogen atom is known to be a major determinant for high-affinity binding at α4β2 receptors;[1] compound **3** lacks this feature. If it could be verified that a pyridyl nitrogen atom is not required for α7 binding, this would provide a useful lead for further exploitation. Other issues needing to be addressed include the role of the ether oxygen atom, the nature of the amine, and the necessity of the phenylethenyl moiety for α7 binding. The present investigation was undertaken to address these issues.



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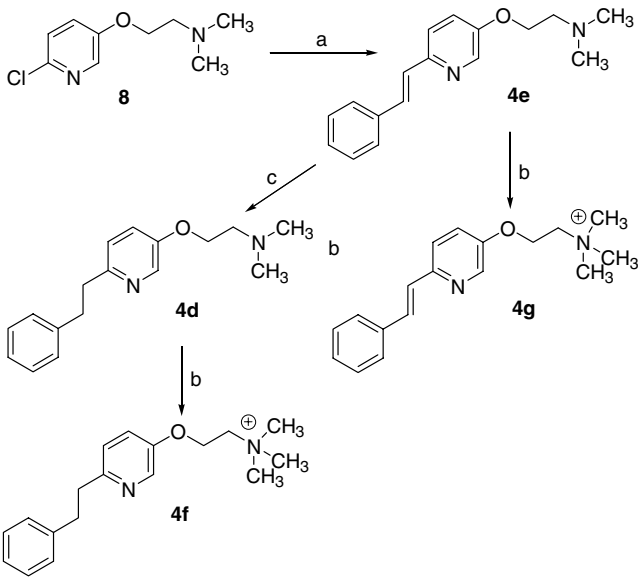
Specifically targeted were compounds **4** (where X = N) and **5** (where X = CH) where R^1 and/or R^2 are H or small alkyl groups, and R is either H, or a 2-phenylethyl or 2-phenylethenyl substituent as found in **1** and **3**, respectively. Also, examined, to determine the role of the ether oxygen atom, were a few derivatives where the ether oxygen was replaced by carbon (i.e., **6**), and an example of ether analog **2** where chain length was increased by one methylene unit (i.e., **7**).

Certain of the necessary compounds were available from studies previously conducted in our laboratories.[6,8,9] The physicochemical properties of the other target compounds are shown in Table 1.

Compound **4e** was prepared from halogenated aryl ether **8**[6] by a palladium-catalyzed reaction with potassium *trans*-styryltrifluoroborate[10] (Scheme 1). Careful quaternization of **4e** with MeI afforded **4g**.[11] Compound **4f** was obtained by catalytic reduction of **4e** followed by quaternization with MeI.[11]

Compounds **5a**[12] and **5d**[13] were prepared as their HCl salts according to literature procedures. The remaining analogs were prepared from **5d** in the same manner as shown in Scheme 1. That is, **5d** was quaternized to **5f**, or reduced to **5c**, and **5c** was quaternized to **5e**.

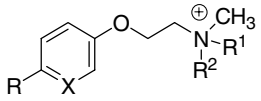
Although 6-PEN (**1**) bears some structural semblance to **3**, it was found to lack affinity for α7 receptors ($K_i > 10$ μM). The mere presence of the 6-position substituent in this molecule detracts from α7 binding when compared with (−)-nicotine ($K_i = 0.75$ μM).



Scheme 1. Reagents and conditions: (a) $PdCl_2(dppf)\cdot CH_2Cl_2$, potassium *trans*-styryltrifluoroborate, Et_3N, *i*PrOH:H_2O, 2:1; (b) MeI, CH_2Cl_2; (c) H_2, 10% Pd/C, EtOH.

The first issue to be addressed with regard to the aryloxyalkylamines was whether their carbon analogs bind at α7 receptors; the ethoxy group of several N-substituted 3-(2-aminoethoxy)pyridines was replaced by an *n*-propyl group (i.e., **6a** and **6b**),[8] and by a propenyl group (**6c**–**e**),[8] but none of the compounds displayed significant affinity (i.e., $K_i > 10$ μM). Initially, these

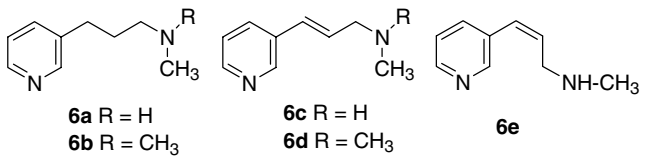
Table 1. Physicochemical properties and α7 nACh receptor binding affinities of target compounds



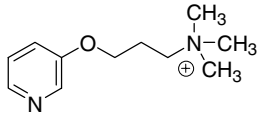
Compound	R	R^1	R^2	X	Recrystallization solvent	Mp (°C)	Empirical formula[a]	K_i[b] (μM)
4a[c]	–H	H	H	N	—	—	—	>10
4b[c]	–H	H	Me	N	—	—	—	>10
2[c]	–H	Me	Me	N	—	—	—	0.28
4c[c]	–H	H	Et	N	—	—	—	>10
5a	–H	H	Me	CH	*i*PrOH	163–164[d]	—	>10
5b	–H	Me	Me	CH	abs EtOH	164–165[e]	—	1.10
4d	$-CH_2-CH_2-Ph$	H	Me	N	abs EtOH/Et_2O	164–166	$C_{17}H_{22}N_2O\cdot 2C_2H_2O_4$	>10
5c	$-CH_2-CH_2-Ph$	H	Me	CH	abs EtOH	173–175	$C_{18}H_{23}NO\cdot HCl$	>10
4e	–CH=CH–Ph	H	Me	N	abs EtOH	219–221	$C_{17}H_{20}N_2O\cdot 1.25HCl$	>10
5d	–CH=CH–Ph	H	Me	CH	abs EtOH	238–240[f]	—	>10
4f	$-CH_2-CH_2-Ph$	Me	Me	N	MeOH/abs EtOH	210–212	$C_{18}H_{25}IN_2O$	4.32
5e	$-CH_2-CH_2-Ph$	Me	Me	CH	abs EtOH	208–210	$C_{19}H_{26}INO$	7.50
4g	–CH=CH–Ph	Me	Me	N	MeOH/abs EtOH	246–248	$C_{18}H_{23}IN_2O$	1.25
5f	–CH=CH–Ph	Me	Me	CH	MeCN	274–276	$C_{19}H_{24}INO$	2.17

[a] All compounds were homogeneous on thin-layer chromatography, analyzed within 0.4% of theory for C, H, and N, and ^1H NMR spectra were consistent with assigned structures. $C_2H_2O_4$ = oxalate salt.
[b] See Ref. 18 for assay conditions. For comparison, (−)-nicotine was found to bind with $K_i = 0.75$ μM.
[c] The synthesis of compounds **4a**,[8] **4b**,[8] **2**,[6] and **4c**[8] has been previously reported from this laboratory.
[d] Lit.,[12] mp = 163 °C for HCl salt.
[e] Lit.,[14] mp = 167–169 °C for bromide.
[f] Lit.,[13] mp = 238–240 °C for HCl salt.

compounds were of particular interest because of their known lack of affinity for α4β2 receptors[8] and, had they shown affinity, might have been selective for α7 receptors.



The simple secondary and tertiary (i.e., *N*-methyl and *N*,*N*-dimethyl) amine derivatives of AXPQ (**2**) also failed to bind at α7 receptors (**4a** and **4b**; $K_i > 10$ μM; Table 1). Extension of the *N*-methyl group of **4b** to an *N*-ethyl group likewise resulted in a compound with low affinity (i.e., **4c**; $K_i > 10$ μM). However, AXPQ itself (**2**; $K_i = 0.28$ μM) displayed twice the affinity of (−)-nicotine ($K_i = 0.75$ μM). Similar findings were obtained with phenyl counterparts **5a** and **5b**; that is, the *N*,*N*-dimethyl tertiary amine **5a** ($K_i > 10$ μM) failed to bind, whereas the quaternary amine **5b** displayed enhanced affinity ($K_i = 1.10$ μM). Evidently, higher affinity is associated with a quaternary amine in both series. Nevertheless, there must also be a chain-length requirement because the *n*-propoxy counterpart of **2** lacked appreciable affinity (**7**;[6] $K_i > 10$ μM).



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It might be noted that while our work was in progress Gündisch et al.[14] reported that **5b** binds at α7 receptors with $K_i \approx 0.2$ μM. Possible explanations for the nearly 6-fold difference in affinity are that the published study employed [^{3}H]MLA rather than [^{125}I]iodo-MLA as radioligand, and used rat forebrain rather than rat cerebral cortical homogenates.

Introduction of a 6-(2-phenylethyl) group had no apparent effect on the affinity of **4b** or **5a** (**4d** and **5c**, respectively; $K_i > 10$ μM). Likewise, their phenylethenyl counterparts **4e** and **5d** ($K_i > 10$ μM) lacked affinity for α7 receptors. Again, affinity seems to be associated only with the quaternary amines. The *N*,*N*,*N*-trimethyl quaternary amine counterpart of **4d** (i.e., **4f**; $K_i = 4.32$ μM) and **5b** (i.e., **5e**; $K_i = 7.50$ μM) showed enhanced affinity (Table 1). The corresponding phenylethenyl quaternary analogs **4g** ($K_i = 1.25$ μM) and **5f** ($K_i = 2.17$ μM) displayed about 3-fold enhanced affinity both in the pyridyl and phenyl series.

The results of this structure–affinity investigation indicate that the quaternary amine nature of both the pyridyl (i.e., **4**) and phenyl (i.e., **5**) series is a major determinant of affinity; *N*-methyl secondary amines and *N*,*N*-dimethyl tertiary amines bind with reduced affinity. The results also show that the phenylethenyl compounds **4g** and **5f** bind with about three times the affinity of their phenylethyl counterparts **4f** and **5e**, respectively. Furthermore, although the presence of the pyridyl nitrogen atom was found unnecessary for α7 binding, the pyridyl series seems to bind with 2- to 3-fold higher affinity than the phenyl series (compare **2** with **5b**, **4f** with **5e**, and **4g** with **5f**). Interestingly, neither the phenylethyl nor the phenylethenyl analogs of AXPQ (**2**), **4f** and **4g**, respectively, displayed higher affinity than AXPQ itself.

Compound **5f** differs in structure from choline ether F3 (**3**) only in that the latter possesses a methyl group α to the terminal amine, yet **5f** binds with >35-fold lower affinity than that reported for **3**. The affinity of **5f** at α7 receptors was re-determined and found ($K_i = 2.03 \pm 0.2$ μM) to be comparable to the result shown in Table 1. Evidently, the α-methyl group of **3** might play a major role in its higher affinity for α7 receptors. Consistent with this concept, Gotti et al.[7] have shown that moving this methyl group to the adjacent chain position is detrimental to binding. Future studies might wish to retain this substituent. In addition, it is rather interesting that AXPQ (**2**) binds with several-fold higher affinity at α7 receptors than either its phenylethyl or phenylethenyl counterparts **4f** and **4g**, respectively; because AXPQ binds with such high affinity at α4β2 receptors ($K_i = 0.0005$ μM; 560-fold α4β2 vs α7 selectivity), the phenylethenyl group of **3** might contribute to its selectivity for α7 receptors. Finally, although the 3-pyridyl substituted analogs tended to display several-fold higher affinity than their phenyl counterparts for α7 receptors, the presence of the pyridyl nitrogen atom is known to be important for α4β2 binding; hence, the absence of this feature in F3 (**3**) might additionally contribute to its selectivity for α7 versus α4β2 receptors, and it might be profitable to continue targeting phenyl rather than pyridyl analogs to achieve enhanced α7 selectivity.

Since this work was initiated, several investigative groups have identified novel α7 nACh receptor ligands that bind in the nanomolar range.[15–17] Nevertheless, we have extended the findings of Gotti et al.[7] on the binding of aryloxyalkylamines to α7 nACh receptors by providing additional structure–affinity data, and have shown that 6-PEN (**1**) and AXPQ (**2**) lack significant affinity for α7 nACh receptors relative to their affinity for α4β2 receptors.

Acknowledgments

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