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3-(2-Aminoethyl)pyridine analogs as α4β2 nicotinic cholinergic receptor ligands

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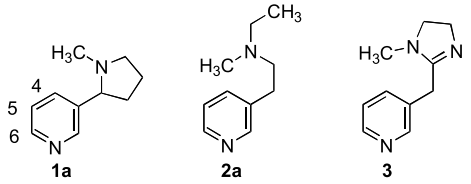
Abstract—An examination of several 3-(2-aminoethyl)pyridine analogs suggests that they likely orient at α4β2 nicotinic cholinergic receptors in a different fashion than their correspondingly substituted nicotine analogs.

The neurotransmitter acetylcholine produces many of its effects by interaction with muscarinic and nicotinic acetylcholinergic receptors. Nicotine (**1a**) displays selectivity for nicotinic cholinergic (nACh) receptors; however, these receptors can be classified as belonging to multiple subtypes depending upon their specific subunit composition.[1] The major population of neuronal nACh receptors are the α4β2 subtype. *S*(−)Nicotine (K_i ca. 2 nM) binds with high affinity at α4β2 nACh receptors; the aminoethylpyridine (i.e., AEP) **2a** (K_i = 18 nM), which was derived from nicotine in a systematic fashion,[2,3] retains affinity for this receptor population. Compound **2a** might also be viewed as a partial structure of the nACh receptor ligand homoazanicotine (**3**; K_i = 7.8 nM).[4]



On the basis that parallel substituent changes result in parallel shifts in affinity, we have concluded that analogs of **3** might bind at nACh receptors in a manner that mimics nicotine.[4] Because compound **2a** bears some structural resemblance both to **3** and nicotine (**1a**), it was of interest to determine if analogs of **2a** also bind in a similar fashion. Accordingly, we examined several ring-substituted analogs of **2a** for comparison with their corresponding nicotine analogs **1**.

1. Synthesis

Compounds (−)**1c** and (−)**1d**, the 4-methoxy and 4-amino analogs of nicotine, respectively, were prepared following a general approach described by Shibagaky et al.,[5] and Ochiai[6] using the nitrocotinine N-oxide **6** as a common intermediate (Scheme 1). Compound **6** was converted to methoxy analog **7** with sodium methoxide, and the N-oxide function was removed by treatment with PBr_3 to afford **8a**. Reduction of the carbonyl group using diborane afforded **1c**. The known free base[5] of 4-aminonicotine (**1d**) was prepared from **6** according to a literature procedure and converted to its oxalate salt (Scheme 1; Table 1).

Resolution of (±)5-bromonicotine (**1e**)[7] was accomplished using (−)L- and (+)D-di-*O*,*O*-*p*-toluoyltartaric acid to yield *S*(−)**1e** and *R*(+)**1e**. The latter two compounds have been previously characterized as their dibenzoyl-L-tartrate and di-*p*-toluoyl-D-tartrate salts, respectively.[8] The enantiomeric purity of the two isomers was monitored by ^{1}H NMR using the chiral shift reagent *S*(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, and optical rotations were determined on their maleate salts

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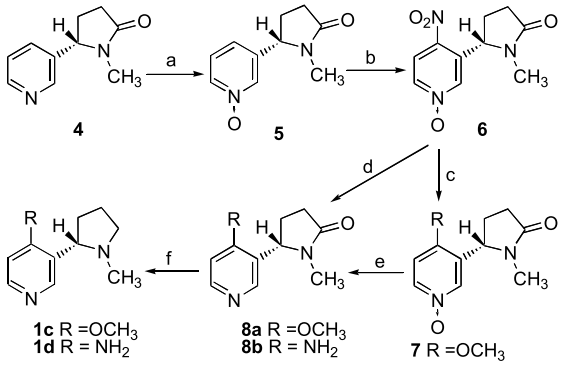
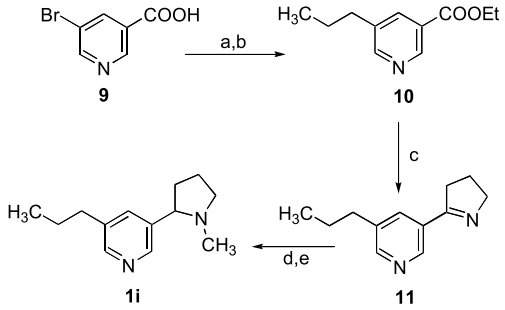


Scheme 1. Reagents: (a) H_2O_2 (30%), CH_3COOH; (b) HNO_3/H_2SO_4; (c) NaOMe, anhydrous MeOH; (d) H_2/Raney-Ni, MeOH; (e) PBr_3, $CHCl_3$; (f) BH_3/THF, dry THF.



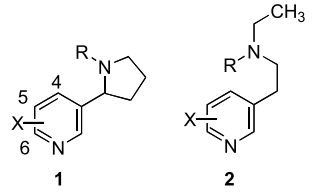
Scheme 2. Reagents: (a) i—$SOCl_2$, ii—absolute EtOH; (b) $(n\text{-Pr})_3Al$, dioxane, $Pd(Ph_3P)_4$; (c) *N*-vinylpyrrolidinone, NaH, toluene; (d) $NaBH_4$, MeOH; (e) $NaCNBH_3$, HCHO, CH_3CN.

(Table 1). Compound **1h** was prepared according to the procedure of Jacob et al.[9]

The 5-propyl analog **1i** (Scheme 2) was obtained by reaction of ethyl 5-bromonicotinate with $(n\text{-Pr})_3Al$ in the presence of $Pd(Ph_3P)_4$ using a procedure adapted from Bracher and Papke,[10] followed by formation of 5-*n*-propylnornicotine which was subsequently reductively methylated using the Borch and Hassid procedure.[11]

Several different procedures were used in the synthesis of the aminoethylpyridines **2**. Amines **2b**, **2e**, and **2l** were obtained as shown in Scheme 3 from commercially available pyridine acetic acid or 5-bromopyridine acetic acid; 6-bromopyridine acetic acid[12] was prepared in situ from (6-bromopyrid-3-yl)acetonitrile[13] according to a literature method. Acids **12** were converted to amides **13** using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), and reduced with diborane to the target amines. Treatment of **2e** with $(n\text{-Pr})_3Al$, as described above for **1i**, gave 5-propyl analog **2i**.

Table 1. Physicochemical properties of substituted nicotine analogs **1** and aminoethylpyridine analogs **2**



	X	R	Recrystallization solvent	Melting point (°C)	Empirical formula[a]
(−)**1c**	4-OCH_3[b]	Me	—[c]	78–80	$C_{11}H_{16}N_2$ 0.3H_2O
(−)**1d**	4-NH_2[d]	Me	EtOH/Et_2O	197–198	$C_{10}H_{15}N_2$ 2$C_2H_2O_4$
(−)**1e**	5-Br[e]	Me	2-PrOH/EtOH	100–102	$C_{10}H_{13}BrN_2$ $C_4H_4O_4$
(+)**1e**	5-Br[e]	Me	2-PrOH/EtOH	100–102	$C_{10}H_{13}BrN_2$ $C_4H_4O_4$
1h	5-CH_3	Me	MeOH/Et_2O	129–130	$C_{11}H_{16}N_2$
1i	5-$CH_2CH_2CH_3$	Me	2-PrOH	208–210	$C_{13}H_{20}N_2$ 2HCl 0.5 H_2O
2b	H	H	EtOH/Et_2O	79–83	$C_9H_{14}N_2$ 2$C_4H_4O_4$
2c	4-OCH_3	Me	EtOH/Et_2O	139–140	$C_{11}H_{18}N_2O$ 1.5$C_4H_4O_4$
2d	4-NH_2	Me	MeOH	203–205	$C_{10}H_{17}N_3$ 2.5$C_2H_2O_4$ 0.25H_2O
2e	5-Br	Me	EtOH/Et_2O	124–125	$C_{10}H_{15}BrN_2$ $C_2H_2O_4$
2f	5-Cl	Me	2-PrOH/EtOAc	125–127	$C_{10}H_{15}ClN_2$ $C_2H_2O_4$ 0.25H2O
2g	5-OCH_3	Me	EtOH/Et_2O	102–104	$C_{11}H_{18}N_2O$ 2$C_4H_4O_4$
2h	5-CH_3	Me	EtOH/Et_2O	97–98	$C_{11}H_{16}N_2O$ 2$C_2H_2O_4$
2i	5-$CH_2CH_2CH_3$	Me	EtOH/Et_2O	119–121	$C_{13}H_{22}N_2$ 2$C_2H_2O_4$ 0.25H_2O
2j	6-CH_3	Me	EtOH/Et_2O	71–74	$C_{11}H_{18}N_2$ 2$C_4H_4O_4$
2l	6-Br	Me	EtOH/Et_2O	74–75	$C_{10}H_{15}BrN_2$ $C_4H_4O_4$
2n	6-CH_2CH_2Ph(4-Cl)	Me	EtOH/Et_2O	137–141	$C_{18}H_{23}ClN_2$ 2$C_2H_2O_4$ 0.25H_2O
2o	6-CH_2CH_2Ph(4-OMe)	Me	EtOH/Et_2O	138–140	$C_{19}H_{26}N_2O$ 2$C_2H_2O_4$ H_2O

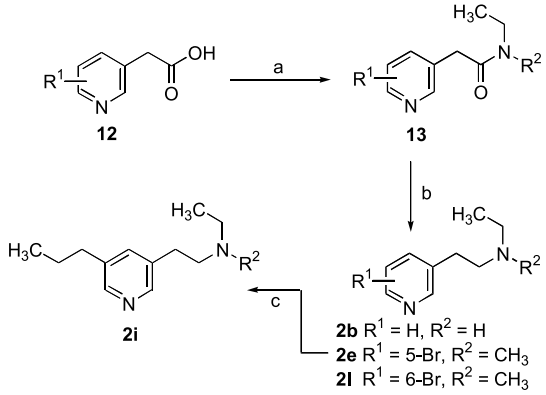
[a] Compounds analyzed within 0.4% of theory for C, H, and N. $C_4H_4O_4$ = maleate salt; $C_2H_2O_4$ = oxalate salt. All compounds were homogeneous as determined by thin-layer chromatographic analysis, and assigned structures are consistent with ^{1}H NMR spectra.

[b] Compound (−)**1c**: $[\alpha]_D = -140°$ (*c* = 1%, MeOH, 27 °C; free base).

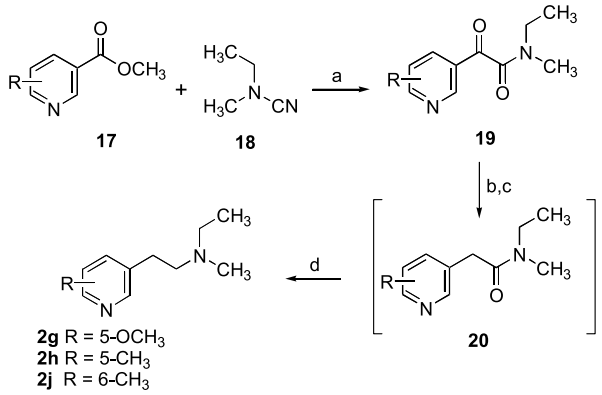
[c] Purified by silica gel column chromatography (eluent: CH_2Cl_2/MeOH, 8.5:1.5).

[d] Compound (−)**1d**: $[\alpha]_D = -87°$ (*c* = 0.7%, MeOH, 24 °C; free base).

[e] Compounds (−)- and (+)**1e**: $[\alpha]_D = -100°$ (*c* = 1.45%, EtOH, 24 °C); $[\alpha]_D = 97°$ (*c* = 1.45%, EtOH, 25 °C).



Scheme 3. Reagents and conditions: (a) EDCI, HOBT, CH_2Cl_2, rt and either $H_2NC_2H_5$ or CH_3-NH-C_2H_5; (b) BH_3/THF, Δ, dry THF; (c) $(n\text{-}Pr)_3Al$, dioxane, $Pd(Ph_3P)_4$.

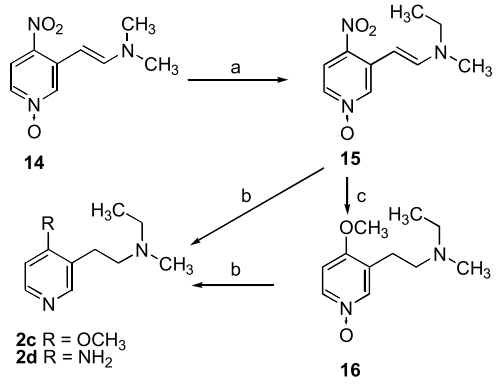


Scheme 5. Reagents: (a) NaHDMS; NaOCl, THF; (b) H_2, 10% Pd/C, MeOH; (c) i—$SOCl_2$, CH_2Cl_2; ii—H_2, 10% Pd/C, MeOH; (d) BH_3/THF, dry THF.

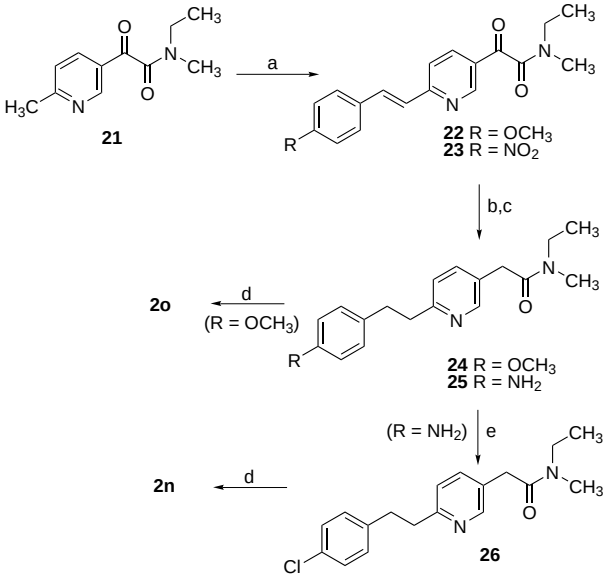
Modification of a procedure described by Dormoy and Heymes[14] was employed for the preparation of **2c** and **2d** (Scheme 4). The reported *N*,*N*-dimethyl-[2-(4-nitro-1-oxypyridin-3-yl)vinyl]amine[14] (**14**) was converted to its homologous amine **15**; using the procedure of Ochiai[6] the intermediate was treated with sodium methoxide to form **16**, and deprotection to **2c** was achieved using H_2/Raney-Ni. Compound **2d** was obtained directly from **15** by reduction with H_2/Raney-Ni.

For the synthesis of **2g**, **2h**, and **2j**, the appropriate 5- or 6-substituted methyl nicotinate was treated with *N*-methyl-*N*-ethylcyanamide[15] (**18**) to yield the corresponding glyoxylamides **19** (Scheme 5). Two-step reduction of **19** afforded the desired products. Intermediates **20** were occasionally isolated, but were not characterized. Methyl 5-methoxynicotinate[16] used in the preparation of **2g** was prepared from commercially available methyl 5-hydroxynicotinate by treatment with diazomethane.

The 6-phenylethyl derivatives **2o** and **2n** were prepared from compound **21**—an intermediate in the synthesis of **2j** (Scheme 6). Condensation of **21** with 4-methoxy- or 4-nitrobenzaldehyde afforded intermediates **22** and **23**, respectively. The remainder of the synthetic route was similar to that shown in Scheme 5 except that amine



Scheme 4. Reagents: (a) *N*-Methyl-*N*-ethylamine, DMF, 100 °C, 4 h; (b) H_2, Raney-Ni, MeOH; (c) NaOMe, anhydrous MeOH.



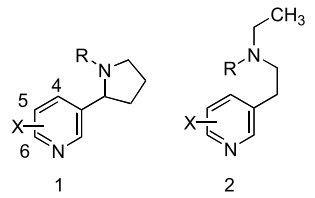
Scheme 6. Reagents: (a) (4-R)PhCHO, Ac_2O; (b) H_2, 10% Pd/C, MeOH; (c) i—$SOCl_2$, CH_2Cl_2; ii—H_2, 10% Pd/C, MeOH; (d) BH_3/THF, dry THF; (e) $NaNO_2$, HCl, $CuCl_2$.

25 was converted via a Sandmeyer-type reaction to its corresponding chloro analog **26** prior to reduction with diborane.

2. Pharmacology

The results of this investigation can be viewed from three perspectives. First, the binding data (Table 2) extend what is currently known about the structure–affinity relationships for the binding of nicotine analogs at α4β2 receptors and, in particular, for 4-substituted nicotine analogs—a position that has not previously received much attention. Second, they provide a structure–affinity assessment for the binding of aminoethylpyridine-type nicotinic ligands. And third, they allow comparisons to be made between the nicotine and aminoethylpyridine series. In studies aimed at pharmacophore elucidation, there is evidence that certain

Table 2. Binding of agents at nACh receptors[a]



X	R		nACh receptor affinity (K_i, nM ± SEM)[b]				
H	Me	(−)**1a**	1.8	(±0.4)	**2a**	18	
H	H	**1b**	30		**2b**	1780	(±100)
4-OCH_3	Me	(−)**1c**	2015	(±720)	**2c**	1840	(±460)
4-NH_2	Me	(−)**1d**	3150	(±1420)	**2d**	>10,000	
5-Br	Me	**1e**	6.9		**2e**	360	(±90)
	Me	(−)**1e**	5.4	(±0.5)		—	
	Me	(+)**1e**	270	(±50)		—	
5-Cl	Me		—		**2f**	310	(±30)
5-OCH_3	Me	**1g**	14		**2g**	19	(±4)
5-CH_3	Me	**1h**	1.8	(±0.2)	**2h**	370	(±40)
5-$CH_2CH_2CH_3$	Me	**1i**	2.1	(±0.4)	**2i**	52	(±3)
6-CH_3	Me	**1j**	1.8		**2j**	240	(±30)
6-Cl	Me	**1k**	0.6		**2k**	70	
6-Br	Me	**1l**	0.5		**2l**	83	(±4)
6-CH_2CH_2Ph	Me	**1m**	15		**2m**	>10,000	
6-CH_2CH_2Ph(4-Cl)	Me	**1n**	40		**2n**	>10,000	
6-CH_2CH_2Ph(4-OMe)	Me	**1o**	10		**2o**	>10,000	

[a] Radioligand binding assays performed as previously described.[24]
[b] K_i values previously reported for certain compounds and are included here for comparison: **1b**,[1] **1e**,[18] **1g**,[18] **1j–1l**,[19] **1m–1o**,[25] **2a**,[2] **2k**,[2] and **2m**.[25]

nicotinoids bind in a manner similar to that of nicotine, whereas others do not.[17] A comparison of aminoethylpyridine analogs with their similarly substituted nicotine analogs can provide information on how these two series bind relative to one another.

With regard to nicotine, it was found that introduction of polar substituents at the ring 4-position results in a >1000-fold reduction in affinity; i.e., the 4-methoxy and 4-amino analogs (−)**1c** and (−)**1d** (K_i = 2015 and 3150 nM, respectively) bind with substantially lower affinity than (−)nicotine (K_i = 1.8 nM). In contrast, the 5-position seems to tolerate a variety of substitutents including a methyl (**1h**; K_i = 1.8 nM) and an *n*-propyl (**1i**; K_i = 2.1 nM) group. We have previously examined the effect of a 5-bromo and 5-methoxy group on the affinity of nicotine,[18] as well as the influence of substituents at the 6-position.[19]

We have described in detail the pharmacology of (±)5-bromonicotine (**1e**).[18] Because (−)nicotine binds with at least 20-fold higher affinity than its (+)-enantiomer, and because the same stereochemical effect was observed with several other 6-substituted compounds,[1] it was felt important to make at least one enantiomeric potency comparison with a 5-substituted analog. Consequently, we resolved **1e**. *S*(−)5-Bromonicotine (K_i = 5.4 nM) was found to bind with 50-fold higher affinity than its (+)isomer (+)**1e** (K_i = 270 nM).[20]

Presented for the first time is the binding of variously substituted aminoethylpyridine (AEP; **2**) analogs. AEP **2a** binds with 10-fold lower affinity than nicotine (Table 2); although certain analogs, such as 5-methoxy AEP (**2g**; K_i = 19 nM compared with **1g**; K_i = 14 nM), bind with an affinity comparable to their nicotine counterparts, most AEP analogs bind with from about 50- to >200-fold lower affinity. In particular, the 6-phenylethyl substituted compound **2o** (K_i > 10,000 nM) binds with >1000-fold reduced affinity relative to **1o** (K_i = 10 nM).

In general, it would seem that the nicotine (i.e., **1**) and AEP (i.e., **2**) series are affected differently by substituent modifications. In fact, a plot of pK_i values for ten **2**-series compounds (**2a–c**, **2e**, **2g–l**) against the pK_i values of their corresponding nicotine analogs indicated only a very modest correlation (r = 0.604). It would appear that the AEP analogs **2** and nicotine analogs **1** might not orient similarly upon binding at α4β2 nACh receptors. This is perhaps most pronounced with the 6-phenylethyl-substituted compounds (**2m–o**—which could not be included in the correlation due to their indeterminate receptor affinities).

It is unknown how these ligands bind relative to one another. The AEP analogs **2** possess a longer internitrogen distance, and greater conformational flexibility, than the corresponding nicotine analogs.[21] Nevertheless, according to recent vector pharmacophore models for α4β2 binding that seemingly account for conformationally flexible agents with various internitrogen distances,[22,23] the binding of AEP analogs should not be excluded.[17,21] Indeed, many of the AEP analogs **2** bind at α4β2 receptors and probably share some receptor binding features with nicotine because binding is competitive. But, it is unlikely that binding occurs in a

manner where the pyridine nuclei of **1** and **2** are strictly superimposed. Consequently, parallel substituent changes might not necessarily result in parallel affinity shifts; this is supported by the present results. Compounds **2** also possess structural similarity to homoazanicotine **3** and, in fact, might be viewed as abridged, ring-open analogs of **3**. Yet, we have found that the homoazanicotine analogs seem to bind in a manner consistent with that of their corresponding nicotine counterparts.[4] One possibility we already suggested[4] to account for the binding of homoazanicotine analogs is that, upon protonation, the charge is dispersed over the entire amidine moiety; obviously, this is something that cannot occur with the AEP analogs because they lack this functionality.

In addition to providing new structure–affinity information on the binding of nicotine analogs **1** and 3-(2-aminoethyl)pyridine analogs **2** at α4β2 nACh receptors, the present results suggest that despite their structural similarity the two series likely orient differently upon interaction with the receptor.

Acknowledgments

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