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Laboratory note

Synthesis and binding of 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*d*]azepine and related ring-opened analogs at central nicotinic receptors

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Abstract – 6,7,8,9-Tetrahydro-5*H*-pyrido[3,4-*d*]azepine (**5a**) and its N_7-methyl derivative **5b** were synthesized and evaluated as potential nicotinic acetylcholinergic receptor (nAChR) ligands. On the basis that 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*c*]azepine (**4a**), which binds at nAChRs with low affinity (K_i = 1100 nM), possesses an internitrogen distance (4.6 Å) that may be less than optimal, we designed compound **5a** due to its similar shape but longer internitrogen distance (5.5 Å). Compound **5a** (K_i = 46 nM) was found to bind with enhanced affinity. However, unlike what is seen with nornicotine/nicotine, N-methylation of **5a** reduced affinity (**5b**; K_i = 268 nM) rather than enhancing it. The results suggest that **5** may interact at nicotine receptors in a manner that is somewhat different from that of nicotine. Ring-opening of the pyrido[3,4-*d*]azepine ring led to a series of 3-(2-aminoethyl)pyridines **21** that retained the affinity of the cyclic compound. Subsequent modification, including further chain lengthening (e.g. aminopropylpyridines **22**) and introduction of unsaturation, ultimately led to the development of a series of 3-(2-aminethoxy)pyridines **27**. Simple N-substituted derivatives of **27** were found to bind with K_i values of 20 to 35 nM. Because parallel structural changes in several series of related compounds did not result in parallel shifts in nAChR affinity, it is unlikely that all the investigated compounds bind in a similar fashion at these receptors. Nevertheless, some of these compounds represent novel classes of nAChR ligands. © Elsevier, Paris

nicotine receptors / nicotinic cholinergic receptors / pyrido[3,4-*c*]azepines / pyrido[3,4-*d*]azepines / 3-(2-aminoethyl)pyridines / 3-(2-aminoethoxy)pyridines

1. Introduction

Our laboratory is currently examining nicotine acetylcholinergic receptor (nAChR) ligands in an attempt to exploit their therapeutic potential. nAChRs have been implicated as playing roles in, for example, anxiety, appetite control, pain and various cognitive and neurological disorders [1], and novel nicotinic cholinergic agents may be of practical therapeutic benefit in their treatment. We began our investigation by excising and abbreviating the pyrrolidine portion of nicotine (**1**) in order to determine the minimal structural requirements for the binding of this agent at nAChRs [2]. It was found that the intact pyrrolidine ring, although seemingly optimal, was not essential in order for these compounds to bind at nAChRs. For example, the simple aminomethylpyridine (AMP) **2** where R = R' = $–CH_3$ (i.e., **2b**, K_i = 540 nM) binds, albeit with modest affinity, at nAChRs. However, **2a** (where R = R' = –H) is devoid of affinity (i.e., K_i > 10000 nM) whereas **2** (where R = $–CH_3$, R' = $–C_2H_5$; K_i = 28 nM) binds with significantly higher affinity and with only 10-fold lower affinity than (–)-nicotine ((–)-**1**) itself (K_i = 2.3 nM) [2]. Apparently, amine substituents can significantly influence affinity. We have also examined several conformationally-constrained aminomethylpyridines including naphthyridine derivatives such as **3** and pyrido[3,4-*c*]azepines such as **4** [2]. Compound **3b** (**3** where R = $–CH_3$) binds at nicotine receptors with high affinity (K_i = 18 nM); interestingly and surprisingly, the affinities of both **4a** (K_i = 1100 nM) and **4b** (K_i = 780 nM) were significantly lower [2].

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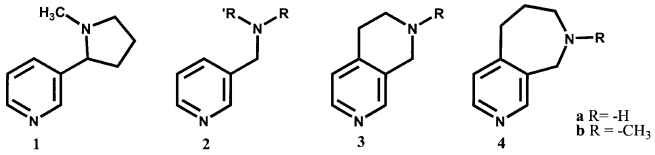
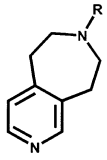


1 2 3 4

In an effort to gain an understanding of how these agents might bind at nicotine receptors, one purpose of the present study was to determine why the affinity of **4b** was so low relative to **3b**. There are several possible explanations: (a) the internitrogen distance in **4b** might be too short, (b) the receptors might not tolerate the added bulk of the larger (i.e., 7-membered) ring of **4**, and/or (c) the structure of **4** might not have been correctly assigned (it should be noted that **4b** was synthesized from **4a**). We set out to test these possibilities.

We have previously suggested that an internitrogen distance of 5.1 to 5.5 Å may be optimal for nAChR binding [3]. The calculated internitrogen distances for **1** and **3** are about 4.8 Å [3]. However, the calculated internitrogen distance in **4** is only 4.6 Å [3]; it might be this shorter distance that accounts, at least in part, for the reduced affinity of **4**. We reasoned that shifting the nitrogen atom of **4** by one position, to afford the pyrido[3,4-*d*]azepine system **5**, should increase the internitrogen distance, and that **5**, although no longer an aminomethylpyridine, might bind with enhanced affinity. We calculated the internitrogen distance in **5** and found it to be 5.5 Å. The second factor to be considered was that of steric bulk. For example, **2** binds with low affinity at nAChRs when R' = $–CH_2CH_2CH_3$, (where R = H, K_i = 2470 nM; where R = $–CH_3$, K_i = 1140 nM) [2]; thus, the low affinity of **4** might simply reflect the lack of bulk tolerance associated with the amine binding site at nicotinic receptors. Compound **5**, because it shares the bulk character of **4**, might be expected to bind with low affinity if its bulk is not tolerated; on the other hand, if **5** binds, it would suggest that internitrogen distance may be an overriding factor. Consequently, we undertook the synthesis and evaluation of compound **5a** and its N-methyl derivative **5b**. And finally, because **4b** was synthesized from **4a**, we also wished to develop a second, independent synthesis of compound **4a** in order to confirm the structure of this ring system.



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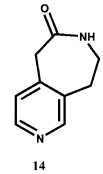
Preliminary radioligand binding data indicated that **5a** binds at nAChRs with higher affinity than **4**. Consequently, we prepared several conformationally-flexible (i.e., ring-opened) analogs of this compound to further explore the role of internitrogen distance on nAChR affinity. This investigation also involved exploration of various N-substituents in the ring-opened analogs.

2. Chemistry

We have previously prepared compound **4a** via synthesis and subsequent $LiAlH_4$ reduction of 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*c*]azepine-9-one [2]. To confirm the structure of this compound, we synthesized **4a** via an independent route taking advantage of a ring-opening/rearrangement reaction reported by Kao [4]. Treatment of 7-hydroxy-8-nitrosoisoquinoline (**6**) with tosyl chloride in basic aqueous acetone gave an acrylic acid, **7,** as previously described [4]. Compound **7** was catalytically reduced to 3-(2-aminomethylpyrid-4-yl)propionic acid (**8**) which was not characterized but immediately converted to 6,7,8,9-tetrahydro-5H-pyrido[3,4-*c*]azepine-7-one (**9**) by heating in the presence of Al_2O_3 to effect cyclization. Compound **9** was reduced using $LiAlH_4$ to give **4a** that was identical to that which we previously reported [2].

We attempted to synthesize compound **5a** using a somewhat analogous approach, i.e., by reduction of the corresponding azepinone **14**. Ethyl (3-pyridyl)acetate (**10**) was converted to ethyl 3-[(3-carbethoxymethyl)pyrid-4-yl]propionate (**11**) as previously reported [5]; cyclization of **11** to **12** followed by hydrolysis and decarboxylation afforded 5,6-dihydro-7(8H)-isoquinolin-7-one (**13**). However, all attempts to convert **13** to azepinone **14** were unsuccessful.



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A somewhat different approach to the synthesis of **5a** is shown in *figure 1*. 2-(3-Pyridinyl)ethanol (**15**, R = H) [6] was treated with *t*-butyldimethylsilyl (*t*-BDMS) chloride in the presence of imidazole to give the protected alcohol in 90% yield. The protected alcohol was reacted with ethyl chloroformate and the resultant pyridinium salt was next reacted with a cuprate reagent ($IZnCH_2CH_2COOEt/Li_2CuCNCl_2$), followed by oxidation, to give ester **16** in about 30% yield. The ester was converted to amide **17** (71% yield) by treatment with an aluminum-

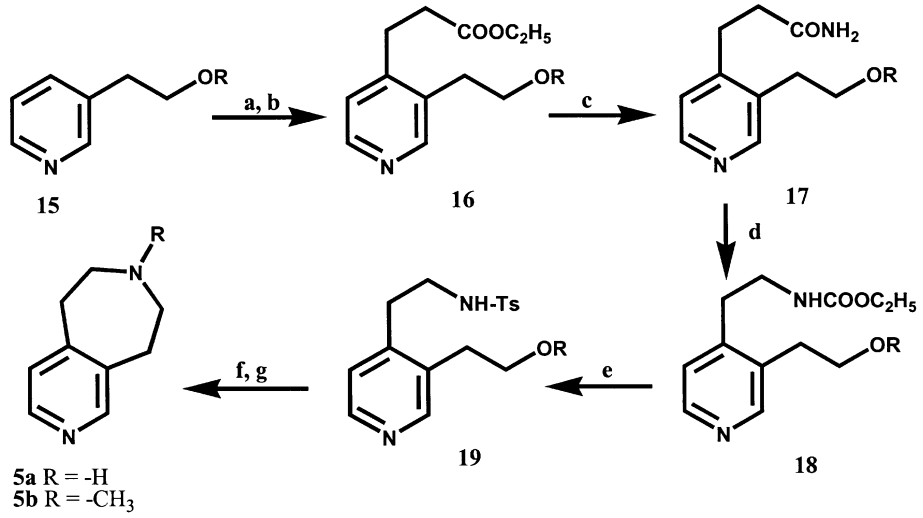


Figure 1. Conditions: (a) *t*-BDMS Cl, imidazole, DMF; (b) 1: ClCOOEt, THF, –78 °C → 0 °C, 2: $IZnCH_2CH_2COOEt$, CuCN/LiCl, –78 °C, 3: xylene, S, Δ; (c) NH_4Cl, $AlMe_3$; (d) Br_2/NaOMe, MeOH; (e) 1: 35% HCl, Δ, 2: TsCl, $NaHCO_3$, THF/H_2O; (f) Ph_3P, DEAD, THF, room temperature; (g) 33% HBr, HOAc, phenol. Compound **5a** was converted to **5b** using $(CH_2O)_n$, $NaBH_3CN$ in MeOH.

amine complex [7, 8], and Hoffmann rearrangement of **17** to **18** was accomplished using Br_2/NaOMe [9]; carbamate **18** was hydrolyzed and tosylated to afford **19**. Treatment of **19** with Ph_3P and diethyl azidodicarboxylate (DEAD) [10] gave the tosylated azepine (**5**, R = tosyl) in 85% yield. To our knowledge, this is the first example of the use of an intramolecular Mitsunobu reaction to construct a medium-sized ring system. The tosyl group was removed [11] by reaction with phenol and 33% HBr in acetic acid to give **5a** in 78% yield. Compound **5a** was methylated by reductive alkylation using sodium cyanoborohydride and paraformaldehyde *(figure 1)*.

The free bases of compounds **21a,b** and **22a,b** are known [12] and were prepared according to a literature procedure and converted to their hydrochloride or oxalate salts *(table I)*. Tertiary amines **21c,d** and **22d** were obtained by reductive amination of **21a** and **22a** and the appropriate aldehyde. Compounds **22c** was prepared by amination of ethyl 3-(3-pyridyl)propionate [13, 14] with N-ethylmethylamine in the presence of trimethylaluminum, followed by reduction of the corresponding amide with alane. The 6-chloro derivative of **21c** (i.e., **23**) was prepared in a similar manner from the known (6-chloropyridin-3-yl)acetic acid [15]; following formation of the amide using N,N'-dicyclohexylcarbodiimide (DCC) and N-ethylmethylamine, reduction was accomplished with alane. Targets **24a**–**e** *(table I)* were obtained by conversion of 3-(3-pyridyl)-2-propen-1-ol (**31**) [16] to its corresponding chloro derivative by reaction with $SOCl_2$ followed by amination with the requisite amine. This is shown in *figure 2* for compound **24c**. The 2-*Z* propenyl analogs **25b**–**d** were synthesized in several steps

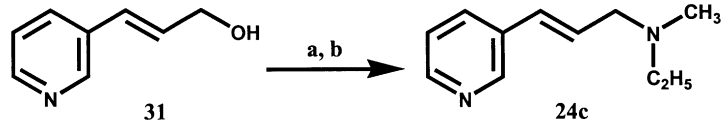


Figure 2. Conditions: (a) $SOCl_2$; (b) CH_3–NH–C_2H_5.

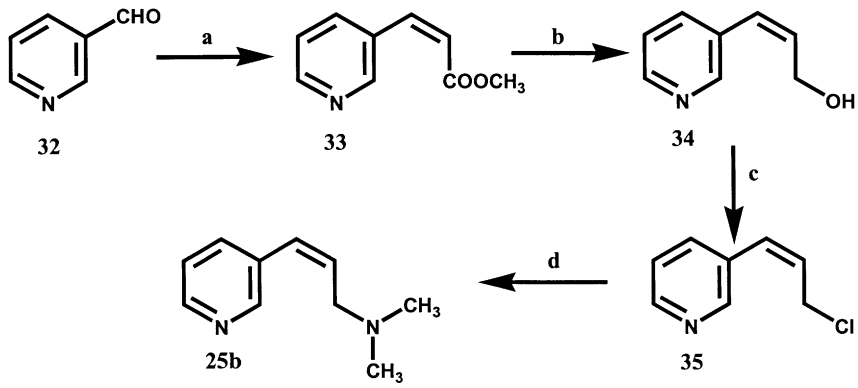


Figure 3. Conditions: (a) KHMDS, THF, –78 °C/$(CF_3CH_2O)_2POCH_2COOCH_3$, 18-crown-6/MeCN complex; (b) DiBALH, toluene; (c) $SOCl_2$; (d) $(CH_3)_2NH/H_2O$.

(figure 3). Methyl 3-(3-pyridyl)-*Z*-acrylate (**33**) was prepared by the reaction of pyridine-3-carboxaldehyde (**32**) and *bis*-(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphonate [17] in the presence of 18-crown-6/acetonitrile complex [18]; hydride reduction of the ester afforded the alcohol **34** which was converted to the corresponding chloro compound **35** and allowed to react with the appropriate amine (exemplified for **25b** in *figure 3*). Compound **25a** was prepared, using a similar strategy, from the known 3-(3-pyridyl)-2-propyn-1-ol [19]; the alkynol was catalytically (Lindlar's catalyst) reduced to the corresponding 2-*Z*-propenol which was then converted to its chloro derivative by reaction with $SOCl_2$, followed by amination with methylamine to give **25a**. It might be noted that the intermediate alcohol in the preparation of **25a** (i.e., **34**) is identical to the intermediate used in the synthesis of analogs **25b**–**d**. The 2-propynyl derivatives **26a,b,d** were obtained by amination of the chloro compound **37** obtained from the reaction of 3-(3-pyridyl)-2-propyn-1-ol (**36**) [19] with $SOCl_2$ *(figure 4)*. Compound **26c** was prepared in a similar manner from 3-(3-pyridyl)-propyn-1-yl bromide hydrobromide [20] and N-ethylmethylamine.

Compounds **27a**–**e** were prepared in a manner similar to that used for the synthesis of **22c**; amination of ethyl 2-[(3-pyridyl)oxy]acetate (**38**) [14] with the appropriate amine in the presence of trimethylaluminum afforded amides **39**, which were reduced by alane (shown for **27e** in *figure 5*).

Analog **28**, a positional isomer of **27a**, was synthesized from 2-chloropyridine by nucleophilic displacement of halogen with the sodium salt of N-benzyl-N-methyl-ethanolamine, followed by catalytic debenzylation.

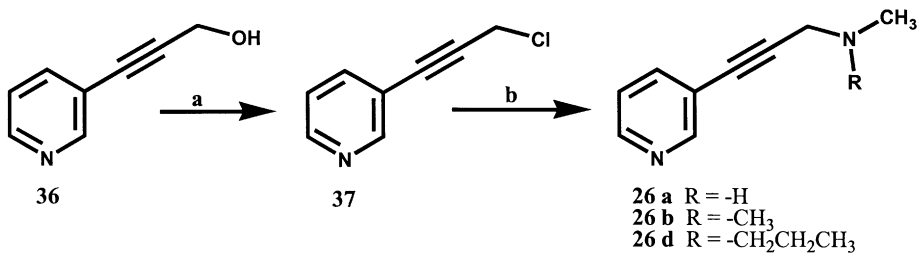
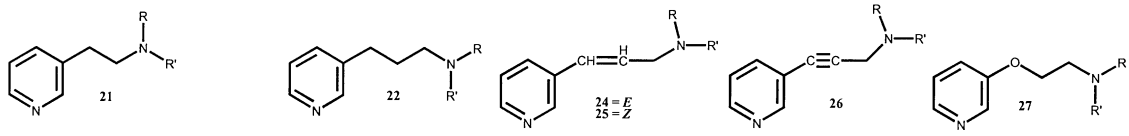


Figure 4. Conditions: (a) $SOCl_2$; (b) $(CH_3)_2NH$.

Table I. Physicochemical properties of aminoalkyl-, aminopropenyl-, aminopropynyl- and aminoethoxypyridines.



	Method [a]	R	R'	Yield	M.p. (°C)	Recrystallization solvent	Empirical formula [b]
21a	[c]	–H	$–CH_3$	83 %	188–189	iPrOH–MeOH	$C_8H_{12}N_2·2C_2H_2O_4$
21b	[c]	$–CH_3$	$–CH_3$	67 %	205–206	iPrOH	$C_9H_{14}N_2·2HCl$
21c	A	$–CH_3$	$–C_2H_5$	61 %	135–136	iPrOH	$C_{10}H_{16}N_2·2C_2H_2O_4$ [d]
21d	A	$–CH_3$	$–C_3H_7$	61 %	156–158	iPrOH	$C_{11}H_{18}N_2·2.5C_2H_2O_4$
22a	[c]	–H	$–CH_3$	83 %	151–152	MeOH–EtOH	$C_9H_{14}N_2·2C_2H_2O_4$
22b	[c]	$–CH_3$	$–CH_3$	71 %	138–140	EtOH	$C_{10}H_{16}N_2·2C_2H_2O_4$
22c	B	$–CH_3$	$–C_2H_5$	49 %	89–90	iPrOH–acetone	$C_{11}H_{18}N_2·2C_2H_2O_4$
22d	A	$–CH_3$	$–C_3H_7$	80 %	155–157	iPrOH–EtOH	$C_{12}H_{20}N_2·2C_2H_2O_4$
24a	C	–H	$–CH_3$	76 %	125–127	EtOH	$C_9H_{12}N_2·2C_2H_2O_4$
24b	C	$–CH_3$	$–CH_3$	71 %	156–157	EtOH	$C_{10}H_{14}N_2·2C_2H_2O_4$ [e]
24c	C	$–CH_3$	$–C_2H_5$	56 %	120–122	iPrOH	$C_{11}H_{16}N_2·2.5C_2H_2O_4$
24d	C	$–CH_3$	$–C_3H_7$	74 %	145–147	EtOH	$C_{12}H_{18}N_2·2C_2H_2O_4$ [f]
24e	C	$–CH_2CH_2CH_2CH_2–$		50 %	128–130	iPrOH	$C_{12}H_{16}N_2·2C_2H_2O_4$
25a	D	–H	$–CH_3$	39 %	164–166 (decomp.)	iPrOH–Et_2O	$C_9H_{12}N_2·1.4C_2H_2O_4$
25b	E	$–CH_3$	$–CH_3$	51 %	142–143	iPrOH–Et_2O	$C_{10}H_{14}N_2·2C_2H_2O_4$
25c	E	$–CH_3$	$–C_2H_5$	63 %	135–137	iPrOH	$C_{11}H_{16}N_2·2C_2H_2O_4$ [d]
25d	E	$–CH_3$	$–C_3H_7$	24 %	128–130 (decomp.)	iPrOH–Et_2O	$C_{12}H_{18}N_2·2C_2H_2O_4$
26a	F	–H	$–CH_3$	62 %	107–110	iPrOH–Et_2O	$C_9H_{10}N_2·C_2H_2O_4$
26b	F	$–CH_3$	$–CH_3$	20 %	149–152 (decomp.)	iPrOH–Et_2O	$C_{10}H_{12}N_2·1.8C_2H_2O_4$
26c	G	$–CH_3$	$–C_2H_5$	60 %	120–122	iPrOH	$C_{11}H_{14}N_2·1.5C_2H_2O_4$ [g]
26d	F	$–CH_3$	$–C_3H_7$	80 %	129–130 (decomp.)	iPrOH–Et_2O	$C_{12}H_{16}N_2·2C_2H_2O_4$
27a	B	–H	$–CH_3$	50 %	154–155	MeOH	$C_8H_{12}N_2O·2C_2H_2O_4$
27b	B	$–CH_3$	$–CH_3$	83 %	148–150	iPrOH–MeOH	$C_9H_{14}N_2O·2C_2H_2O_4$
27c	B	$–CH_3$	$–C_2H_5$	54 %	116–118	iPrOH–MeOH	$C_{10}H_{16}N_2O·2C_2H_2O_4$ [f]
27d	B	$–CH_3$	$–C_3H_7$	53 %	135–136	iPrOH–MeOH	$C_{11}H_{18}N_2O·2C_2H_2O_4$
27e	B	$–CH_2CH_2CH_2CH_2–$		80 %	145–146	iPrOH–MeOH	$C_{11}H_{16}N_2O·2C_2H_2O_4$

[a] Method: A representative example is provided in the Experimental section for each method listed. [b] All compounds analyzed within 0.4% of theory for C, H and N. [c] The free bases of **21a**, **21b**, **22a** and **22b** were prepared following a known literature procedure [12] and converted to HCl or oxalate salts. [d] Crystallized with 0.25 mol H_2O. [e] Crystallized with 0.4 mol H_2O. [f] Crystallized with 0.5 mol H_2O. [g] Crystallized with 1.0 mol H_2O.

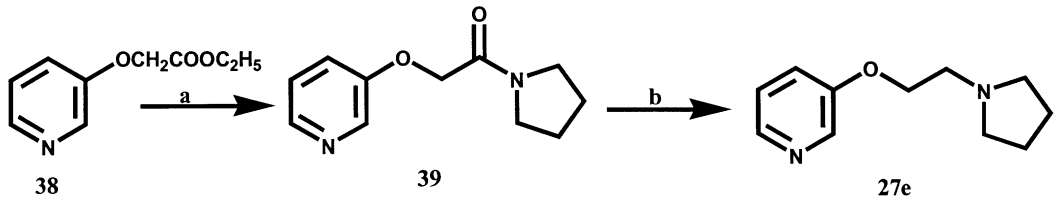


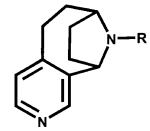
Figure 5. Conditions: (a) pyrrolidine, $(CH_3)_3Al$, CH_2Cl_2; (b) AlH_3, THF.

3. Results and discussion

3.1. Pyridoazepine analogs

The identity of **4a** was confirmed by a new method of synthesis. Consequently, the low affinity reported earlier for **4** [2] cannot be due to incorrect structural assignment. Both **5a** and **5b** were also successfully prepared, and radioligand binding data were obtained for both. The affinity of **5a** (K_i = 46 ± 7 nM) was significantly higher than that of the structurally-related aminomethylpyridine **2** where R' = $–CH_2CH_2CH_3$ (K_i = 2470 nM [2]). Thus, it would seem that the low affinity of **4** cannot be explained simply by the presence of the added bulk. The affinity of **5a** was also higher than that of the corresponding pyridoazepine **4a** (K_i = 1100 nM). The difference in affinity between the two structurally-related compounds (i.e., **4a** and **5a**) may be related to the longer internitrogen distance of **5a**.

N-Monomethylation of nicotinic ligands can increase, decrease, or have little influence on affinity depending upon the particular series of agents being investigated [2, 3]. The affinity of the N-methyl derivative **5b** (K_i = 268 ± 44 nM) was nearly six times lower than that of **5a**. Demethylation of nicotine to nornicotine typically results in a 10- to 20-fold decrease in affinity whereas demethylation of **3b** to **3a** (K_i = 12330 nM), results in a 685-fold decrease in affinity [2, 21]. Demethylation of **4b** has essentially no (i.e., less than 2-fold) effect on affinity [2]. Thus, the trend of decreasing affinity upon demethylation seen with nicotine, **2** (where R = R' = $–CH_3$), and **3b** seems to end with **4**, and is reversed in **5**. This unusual affinity-enhancing effect seen upon demethylation has been noticed before; for example, demethylation of the N-methyl pyridohomotropane **20**, where R = $–CH_3$ (IC_{50} = 1000 nM), results in a 200-fold increase in affinity [22]. We have previously suggested, given the observed differences in affinity between various N-methyl and N-desmethyl derivatives, that these compounds may not be binding in exactly the same manner at nAChRs [2, 3]; that is, the compounds may not utilize identical receptor binding features and/or the amine nitrogen (or its substituents) are oriented somewhat differently upon interaction with the receptor. This latter possibility is particularly reinforced by the difference in affinity of **4a** (K_i = 1100 nM) and its more conformationally-constrained counterpart **20** where R = H (IC_{50} = 5 nM) [22] which is simply a bridged analog of **4a**.



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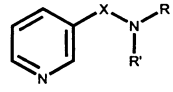
3.2. Conformationally-flexible analogs

3.2.1. Aminoalkylpyridines

Due to the higher affinity of **5a** (K_i = 46 nM) over **4a** (K_i = 1100 nM) we examined several ring-opened, more flexible, analogs of **5**. If the aminomethylpyridines (AMPs, **2**) are viewed as ring-opened analogs of **4**, then the aminoethylpyridines(AEPs, **21**) may be viewed as the corresponding ring-opened analogs of **5**. The aminopropylpyridines (APPs, **22**) represent chain-extended analogs of **21**. Binding data for **21** and **22** derivatives, relative to **2**, are shown in *table II*.

Table II. Nicotine receptor affinities of 3-substituted pyridine analogs; K_i values, nM (SEM).

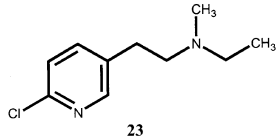


	X	a	b	c	d	e
	–NRR'=	$–N(CH_3)H$	$–N(CH_3)_2$	$–N(CH_3)C_2H_5$	$–N(CH_3)C_3H_7$	1-Pyrrolidinyl
2	$–CH_2–$	> 10000 [a]	540 [a]	28 [a]	1140 [a]	30 [a]
21	$–CH_2–CH_2–$	289 (± 17)	47 (± 2)	18 (± 1)	427 (± 46)	– [b]
22	$–CH_2–CH_2–CH_2–$	> 10000	> 10000	> 10000	> 10000	– [b]
24	–CH=CH–CH_2– (*trans*)	6055 (± 960)	2775 (± 714)	> 10000	> 10000	5035 (± 6)
25	–CH=CH–CH_2– (*cis*)	2870 (± 440)	2100 (± 400)	> 10000	> 10000	– [b]
26	$–C≡C–CH_2–$	2285 (± 630)	2165(± 580)	900 (± 95)	2240 (± 200)	– [b]
27	$–O–CH_2–CH_2–$	35 (± 10)	21 (± 17)	22 (± 1)	138 (± 16)	212 (± 7)

[a] Data previously reported [2].
[b] Data unavailable; compound not prepared.

In general, analogs of the aminoethylpyridine (i.e., **21**) series were found to bind with higher affinity than the corresponding members of the aminomethylpyridine (i.e., **2**) series, whereas members of the aminopropylpyridine (i.e., **22**) series were essentially inactive (K_i > 10000 nM). Although the lack of affinity of the aminopropylpyridine series of compounds might be attributable to an excessive chain length (calculated internitrogen distance ≈ 6.9 Å), the enhanced affinity of the aminoethylpyridine series (calculated internitrogen distance ≈ 5.9 Å) cannot be accounted for solely on the basis of internitrogen distance. That is, this internitrogen distance is longer than that thought to be optimal [2]. Comparing **2a**–**d** with **21a**–**d** *(table II)* it is obvious that parallel changes in the terminal amine substituents did not result in parallel changes in affinity. That is, increasing the alkyl chain length of the aminomethylpyridines by one methylene group variously enhanced affinity by 2-fold to more than 30-fold depending upon the nature of the terminal amine. This provides evidence that members of the two series may not be binding in exactly the same manner. Nevertheless, in both instances, the N-ethyl-N-methyl analogs (i.e., **2c** and **21c**) bind with the highest affinity.

If two series of compounds are binding in the same manner, parallel structural changes should result in parallel shifts in affinity. We previously have reported that incorporation of a 6-chloro substituent has relatively little effect on the affinity of **2c** (**2c** K_i = 28 nM; 6-chloro **2c** K_i = 41 nM) [2]. Consequently, we prepared and examined the 6-chloro derivative of **21c** (i.e., **23**). Although **23** (K_i = 71 ± 10 nM) binds with 4-fold lower affinity than **21c** itself (K_i = 18 nM), the change in affinity was not sufficiently large to draw any definitive conclusions.



23

3.2.2. Aminopropenylpyridines and aminopropynylpyridines

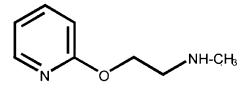
Increasing chain length by a single methylene group (**21** → **22**) had a rather dramatic effect on nicotinic receptor affinity. In an attempt to slightly shorten chain length and to limit conformational flexibility in the aminopropylpyridine series, unsaturation was introduced into the chain. The first member of the series to be examined, **24b** (K_i = 2775 nM; *table II*), offered some encouragement because, although it did not bind with as high an affinity as **21b**, its affinity was higher than that of the corresponding aminopropylpyridine **22b** (K_i > 10000 nM). However, the remaining members of the series, **24a**, **24c**, **24d**, were essentially inactive *(table II)*. Interestingly, stereochemistry did not seem critical; that is, the *trans* compound **24b** and its *cis* isomer **25b** bind with nearly identical affinity (K_i = 2775 and 2100 nM, respectively). The alkynyl derivative **26c** (K_i = 900 nM) *(table II)* was found to bind with higher affinity than its corresponding alkyl or alkenyl counterparts (i.e., **22c** and **24c**, K_i > 10000 nM). Although compounds **26** generally bind with low affinity, unsaturation again seems to contribute to binding.

Introduction of a double or triple bond certainly influences internitrogen distance. But, it also introduces an electronic character to the side chain that is absent in the aminopropylpyridine series. To examine further a possible electronic contribution to binding we prepared a series of aminopropylpyridines where the aromatic methylene group was replaced by an ether oxygen atom (i.e., aminoethoxypyridines).

3.2.3. Aminoethoxypyridines

Data for the aminoethoxypyridines are shown in *table II*. Some members of the pyridyl ether series, **27a**–**d**, were found to bind with more than 500-fold higher affinity than the corresponding members of the aminopropylpyridine (**22**) series. Interestingly, and in contrast to what was seen with the AMP (**2**) series, terminal amine substitution seemed to play a less significant role; that is, compounds **27a**–**c** (K_i = 35 nM, 21 nM and 22 nM, respectively) where one of the amine substituents is varied from H to methyl to ethyl, bind with relatively similar affinity. This provides some additional evidence that members of the different series of compounds are not binding in an identical manner.

In order to determine whether the introduction of the ether oxygen atom increases affinity by a specific receptor interaction or whether it was more of a nonspecific effect, such as its influence on the electronic character of the pyridyl ring, we examined **28**, a positional isomer of **27a**. Compound **28** was found to lack affinity for nicotinic receptors (K_i > 10000 nM).

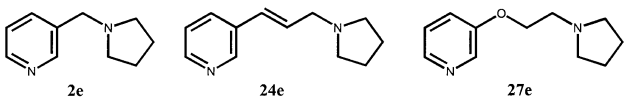


28

3.2.4. Pyrrolidine analogs

Cyclization of the terminal dimethyl groups of **2b** to a pyrrolidine ring (i.e., **2e**; K_i = 30 nM) results in about a 20-fold increase in affinity, and in a compound that binds with affinity comparable to **2c** (K_i = 28 nM; *table II*), the

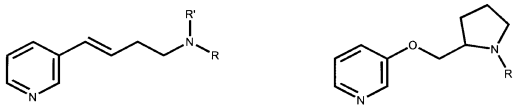
highest affinity member of the series [2]. This offered another opportunity to compare several series of compounds. Thus, we examined a pyrrolidinyl analog in the *trans* olefinic series (i.e., **24e**) and one in the pyridyl ether series (i.e., **27e**).



2e **24e** **27e**

Compound **24e** (K_i = 5035 nM; *table II*) binds with half the affinity of its corresponding N,N-dimethyl counterpart **24b** and did not represent the highest affinity member of the series. Likewise, **27e** (K_i = 212 nM; *table II*) binds with 10-fold lower affinity than its N,N-dimethyl counterpart **27b** and represents the lowest affinity member of the series. On the basis of these results, it is probably safe to conclude that these agents are not binding in an identical manner at nAChRs.

While our studies were nearing completion several reports appeared in the literature that have a direct bearing on our results. Caldwell et al. [23] reported that RJR-2043 (**29**; R = H, R' = $-CH_3$), a homolog of **24a**, binds at nAChRs with high affinity (K_i = 26 nM). Abreo and co-workers also reported on a series pyridyl ethers [24]. For example, A-84543 (**30**, R = $-CH_3$, *S*-(–)-isomer; K_i = 0.15 nM) and its *R*-(+)-enantiomer (K_i = 19.7 nM) bind at nAChRs with high affinity [24].



29 **30**

4. Conclusion

The chief difference between the structures of **4** and **5** is the distance between the two nitrogen atoms. Consequently, **4** and **5** offer a unique set of compounds to investigate interatom distances. The lower affinity **4** possesses an internitrogen distance of 4.6 Å whereas that in **5** is 5.5 Å. On this basis, it was expected that derivatives of **5** might bind with higher affinity than derivatives of **4**. This was found to be the case; compound **5a** (K_i = 47 nM) binds with higher affinity than **4a** (K_i = 1100 nM). Although N-monomethylation of **4a** to **4b** had very little effect on affinity, it was found that N-methylation of **5a** to **5b** decreased affinity by nearly 6-fold.

The increased affinity of **5** over **4** led to an examination of chain-extended analogs of the aminomethylpyridines (**2**). The aminoethylpyridine series compounds (i.e., **21**) were found to bind with enhanced affinity relative to the aminomethylpyridines and represent a novel class of nicotinic ligands. The longer aminopropylpyridine series compounds (i.e., **22**) were, however, inactive. Introduction of unsaturation (e.g. **24**/**25**/**26**) suggested possible electronic involvement of a side chain atom, and this ultimately led to the development of a series of pyridyl ethers **27**. The pyridyl ethers were generally found to bind with enhanced affinity relative to the aminoalkyl analogs (i.e., **2**, **21**, **22**). This work supports the recent independent claim by Abbott Laboratories that pyridyl ethers represent high affinity nicotinic cholinergic receptor ligands [24]. It is also quite interesting that although A-85380 is quite similar in structure to, for example, **27a**, it binds with more than 650-fold higher affinity than the latter.

Continued investigation of compounds such as those described herein is certain to lead to interesting agents. However, on the basis of the data presented above, as well as on the results of studies by Glennon et al. [3], Caldwell et al. [23] and Abreo et al. [24], it would appear that parallel structural changes do not consistently lead to parallel shifts in affinity suggesting that the different series of compounds, or perhaps individual members within various series, may not be binding in similar manner at nicotinic cholinergic receptors. Results of these same studies also indicate that agents with internitrogen distances of > 4.8 Å represent worthwhile targets as novel nAChR ligands.

5. Experimental protocols

5.1. Chemistry

Melting points were determined with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained using a Nicolet 5ZDX spectrophotometer and proton NMR were recorded on a Gemini-300 instrument. Spectral data are consistent with the assigned structures. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Microanalysis was performed by Atlantic Microlab and determined values are within ±0.4% of theory. Column chromatography employed 70–230 mesh SiO_2.

*5.1.1. 6,7,8,9-Tetrahydro-5H-pyrido[3,4-c]azepine oxalate **4a***

Lithium aluminum hydride (0.25 g, 6.6 mmol) was added to a solution of **9** (0.25 g, 1.5 mmol) in dry THF (10 mL) at 0 °C; the reaction mixture was allowed to stir at room temperature for 1 h, after which H_2O (0.3 mL),

10% NaOH (0.4 mL) and H_2O (0.5 mL) were successively added at 0 °C. The precipitate was collected by filtration, washed with THF (10 mL), and the combined solution was evaporated to an oily residue. The residue in 95% EtOH (5 mL) was treated with HCl and the entire reaction mixture was evaporated to dryness. The crude material was triturated with Et_2O to afford a hygroscopic hydrochloride salt. The salt was converted to its free base and treated with a solution of oxalic acid in anhydrous Et_2O to yield 0.24 g (70%) of the desired product as its *bis* oxalate salt, m.p. 203–205 °C (lit. [2] 202–205 °C).

*5.1.2. 6,7,8,9-Tetrahydro-5H-pyrido[3,4-d]azepine hydrobromide **5a***

Triphenyl phosphine (0.29 g, 1.10 mmol) and 90% DEAD (0.19 g, 0.96 mmol) were added to a stirred solution of **19** (0.25 g, 0.78 mmol) in THF (100 mL) under N_2 at room temperature. The reaction mixture was allowed to stir at room temperature for 2 h and was then heated at reflux for 15 min. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography using SiO_2 (eluent: EtOAc/petroleum ether 1:3) to give 0.20 g (85%) of **5** where R = tosyl, m.p. 121–124 °C. A solution of this material (0.10 g, 0.35 mmol) and phenol (0.30 g, 3.20 mmol) in 33% HBr in HOAc (6 mL) was allowed to stir at room temperature for 24 h. The HOAc was evaporated under reduced pressure and the residue was triturated with EtOAc (10 mL). The solvent was decanted and the resulting solid was recrystallized from MeOH/EtOAc to give 0.06 g (58%) of **5a**, m.p. 268–270 °C (decomp.).^{1}H-NMR (DMSO-d_6) δ: 3.25 (m, 8H), 7.78 (d, 1H), 8.61 (m, 2H). Anal. ($C_9H_{12}N_2$•2HBr) C, H, N.

*5.1.3. N-Methyl-6,7,8,9-tetrahydro-5H-pyrido[3,4-d] azepine oxalate **5b***

Paraformaldehyde (28 mg, 1 mmol) and $NaBH_3CN$ (63 mg, 1 mmol) were added to a stirred solution of **5a** (28 mg, 0.09 mmol) in MeOH (10 mL) at room temperature. This was followed by the addition of 2.5 M HCl in MeOH (0.1 mL). The reaction mixture was allowed to stir at room temperature for 48 h; the MeOH was evaporated under reduced pressure and the residue was dissolved in Et_2O (30 mL). The ethereal solution was washed with saturated $NaHCO_3$ (5 mL), dried (K_2CO_3) and evaporated in vacuo to give an oil which was purified by column chromatography on SiO_2 (eluent: EtOAc/MeOH 10:1) to give 14 mg (96%) of **5b** as the free base. The free base was converted to **5b** by treatment with oxalic acid in Et_2O to give 15 mg of product, m.p. 125–127 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (s, 3H), 2.60 (m, 4H), 2.90 (m, 4H), 7.00 (d, 1H), 8.25 (s, 1H), 8.35 (d, 1H). Anal. ($C_{10}H_{14}N_2$•2$C_2H_4O_8$) C, H, N.

*5.1.4. 6,7,8,9-Tetrahydro-5H-pyrido[3,4-c]azepine-7-one **9***

7-Hydroxy-8-nitrosoisoquinoline (**6**) was prepared and converted to acrylic acid **7** as described by Kao [4]; 5% Pd/C (0.06 g) was added to a suspension of the acid (0.42 g, 2.4 mmol) in HOAc (60 mL) and the mixture was shaken on a Parr hydrogenator (57 psi H_2) for 48 h. The mixture was filtered, and the solid material was washed with HOAc (2 × 10 mL). The combined HOAc portion was evaporated under reduced pressure to afford 0.72 g of a yellow oil, which was used without further purification or characterization. The oily residue was neutralized by the addition of 10% NaOH; toluene (30 mL) and Al_2O_3 (4.8 g) were added with stirring. The two-phase system was heated at reflux for 20 h using a Dean–Stark water trap. The resulting suspension was filtered, the residue was washed with CH_2Cl_2/MeOH (9:1), and the combined solutions were filtered through a pad of SiO_2. Evaporation of the solvent gave 0.10 g of **9** as a crystalline solid, m.p. 111–113 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.77 (t, 2H, *J* = 7 Hz), 3.05 (t, 2H, *J* = 7 Hz), 4.32 (d, 2H, *J* = 6 Hz), 7.01 (d, 1H, *J* = 5 Hz), 7.23 (br s, 1H), 8.25 (s, 1H), 8.36 (d, 1H, *J* = 5 Hz). Anal. ($C_9H_{10}N_2O$•H_2O) C, H, N.

*5.1.5. 5,6-Dihydro-7(8H)-isoquinolin-7-one **13***

The known compound ethyl 3-(3-carbethoxy-methylpyrid-4-yl)propionate (**11**) was prepared from ethyl 2-(3-pyridyl)acetate (**10**) by treatment with ClCOOEt and $IZnCH_2CH_2COOEt$ as previously reported by Shiao et al. [5]. Sodium hydride (60%; 0.91 g, 22.4 mmol) was added to a solution of di-ester **11** (2.0 g, 7.5 mmol) in dry THF (100 mL) under N_2. The resulting reaction mixture was heated at reflux for 6 h under N_2, allowed to cool to room temperature, and 4 N HCl (5 mL) was carefully added. THF was removed by evaporation under reduced pressure, and the crude residue was dissolved in 6 N HCl (30 mL); the solution was heated at reflux for 12 h, allowed to cool to room temperature, neutralized with solid KOH and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extract was dried ($MgSO_4$) and evaporated to dryness to give a crude product; purification was achieved by column chromatography on SiO_2 (eluent: EtOAc/petroleum ether, 4:1) to give 0.45 g (41%) of **13**, m.p. 70–72 °C. Anal. (C_9H_9NO) C, H, N.

*5.1.6. Ethyl 3-[2-(t-butyldimethylsilyloxyethyl)pyridin-4-yl]propionate **16***

Imidazole (2.81 g, 41.4 mmol) and *t*-butyldimethylsilyl chloride (4.97 g, 33.1 mmol) were added to a stirred solution of 2-(3-pyridyl)ethanol [6] (**15**, R = H; 3.41 g, 27.6 mmol) in DMF (50 mL). The reaction mixture was allowed to stir at room temperature overnight and was poured into ice water (100 mL). The aqueous mixture was extracted with petroleum ether (2 × 200 mL), and the combined organic portion was washed well with brine, dried ($MgSO_4$) and evaporated in vacuo to give 5.90 g (90%) of crude **15** where R = *t*-butyldimethylsilyl.

Ethyl 3-iodopropionate (8.0 g, 22.0 mmol) in THF (20 mL) was added in a dropwise manner to a suspension of freshly activated Zn powder (2.6 g, 40.0 mmol) in THF (10 mL) at 45 °C. The reaction mixture was allowed to stir at this temperature overnight. This solution was then added to a stirred solution of CuCN (2.3 g, 25.0 mmol) and LiCl (2.3 g, 50.0 mmol) in THF (50 mL) at –40 °C. The resultant solution was allowed to slowly warm to 0 °C and was then cooled to –78 °C. The solution was added to a suspension of the pyridinium salt [prepared from **15** (4.1 g, 15 mmol) and ethyl chloroformate (2.2 g, 20 mmol) in THF (60 mL) at –25 °C for 30 min] at –78 °C. The solution was then allowed to warm to room temperature and was quenched by the addition of 5% NH_4OH solution (100 mL). The organic portion was separated, dried ($MgSO_4$), and the solvent was removed in vacuo to give an intermediate which was oxidized by boiling with sulfur (0.8 g) in xylene (25 mL) for 12 h. The reaction mixture was filtered, the xylene was evaporated, and the crude product was distilled (Kugelrohr, 150–160 °C/0.05 mmHg) to give 1.7 g (30%) of **16** as a pale-yellow oil. Infrared (film): 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 6H), 0.90 (s, 9H), 1.28 (t, 3H), 2.67 (t, 2H), 2.92 (t, 2H), 3.15 (t, 2H), 3.81 (t, 2H), 4.18 (q, 2H), 7.12 (d, 1H), 8.40 (d, 1H), 8.45 (s, 1H). Anal. ($C_{18}H_{31}NO_3Si$) C, H, N.

*5.1.7. 3-[2-(t-Butyldimethylsilyloxyethyl)pyridin-4-yl] propionamide **17***

A solution of $AlMe_3$ (2M, 10 mL, 20.0 mmol) in hexane (10 mL) was added in a dropwise manner to a stirred suspension of NH_4Cl (1.1 g, 20.0 mmol) in dry benzene (25 mL) at ice-bath temperature. After the addition was complete, the mixture was allowed to stir at room temperature for 30 min. A solution of **16** (1.0 g, 3.0 mmol) in benzene (5 mL) was added; the reaction mixture was allowed to stir at 50 °C for 15 h and was subsequently cooled to room temperature, treated carefully with 10% HCl (2 mL), and the benzene portion decanted. The residue was washed with EtOAc (2 × 50 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to dryness to give a residue that was purified by column chromatography (SiO_2; eluent: EtOAc/MeOH 2:1) to give 0.65 g (71%) of the desired product, m.p. 82–84 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 6H), 0.90 (s, 9H), 2.55 (t, 2H), 2.95 (t, 2H), 3.05 (t, 2H), 3.85 (t, 2H), 5.85 (br s, 2H), 7.15 (br s, 1H), 8.40 (m, 2H). Anal. ($C_{16}H_{28}N_2O_2Si$) C, H, N.

*5.1.8. N-Tosyl-2-[3-(2-hydroxyethyl)pyridin-4-yl]-ethylamine **19***

Compound **17** (0.62 g, 2.0 mmol) was added to a stirred solution of NaOMe (prepared by dissolving 0.18 g of Na metal in 12 mL of MeOH) at room temperature. After solution was complete, Br_2 (0.64 g, 4.0 mmol) in MeOH (3 mL) was added at one time. The resultant solution was allowed to stir at room temperature for 30 min and was then heated at reflux for 30 min. The MeOH was evaporated under reduced pressure, and the residue dissolved in EtOAc (50 mL), and the solution washed with brine (2 × 10 mL). The EtOAc solution was dried ($MgSO_4$) and evaporated in vacuo to give 0.73 g of crude product, which was purified by column chromatography (SiO_2; eluent: MeOH/EtOAc 1:9) to give 0.43 g (67%) of **18** and 0.15 g of **17**. The above reaction was repeated to obtain additional **18**. A solution of **18** (0.50 g, 1.5 mmol) in concentrated HCl (15 mL) was heated at reflux under N_2 for 5 h. The reaction mixture was evaporated to dryness under reduced pressure, a saturated solution of $NaHCO_3$ was added to adjust the pH to 8, and again the solvent was removed by evaporation. The residue was dissolved in absolute EtOH, and the undissolved material was removed by filtration. The ethanolic solution was evaporated under reduced pressure to give a residue (0.3 g) which was then dissolved in wet THF (20 mL). Solid $NaHCO_3$ (0.22 g, 2.7 mmol) and TsCl (0.32 g, 1.8 mmol) were added to this residue and the resultant mixture was allowed to stir at room temperature for 1 h. The mixture was diluted by the addition of EtOAc (100 mL) and the aqueous phase was separated. The organic portion was dried ($MgSO_4$) and evaporated under reduced pressure to give 0.35 g (74%) of the desired compound, m.p. 116–118 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (s, 3H), 2.85 (m, 4H), 3.20 (m, 2H), 3.86 (t, 2H), 5.80 (br s, 1H), 6.95 (d, 1H), 7.18 (d, 2H), 7.64 (d, 2H), 8.20 (d, 1H), 8.34 (s, 1H). Anal. ($C_{16}H_{20}N_2O_3S$) C, H, N.

*5.1.9. N-Methyl-N-n-propyl-2-(3-pyridyl)ethylamine oxalate **21d** [Method A]*

Propionaldehyde (0.8 mL, 11 mmol) and then $NaBH_3CN$ (252 mg, 4 mmol) was added to a stirred

solution of **21a** (free base; 500 mg, 3.67 mmol) in absolute EtOH (30 mL) at room temperature. Subsequently, 2.5 N HCl in MeOH (0.8 mL) was added in a dropwise fashion. When the reaction was complete the solvent was evaporated in vacuo and the residue was dissolved in Et_2O (100 mL), and the ethereal solution was washed with saturated $NaHCO_3$ (3 × 20 mL) and excess brine. The ethereal solution was dried (K_2CO_3) and solvent was evaporated in vacuo to give approximately 1 g of a residue which on Kugelrohr distillation gave 400 mg (61%) of the desired free base. Treatment of the free base with an ethereal solution of oxalic acid afforded **21d** after recrystallization from iPrOH, m.p. 156–158 °C. ^{1}H-NMR (D_2O) δ: 0.95 (s, 3H), 1.85 (m, 2H), 2.95 (s, 3H), 3.15–3.60 (m, 6H), 8.05 (m, 1H), 8.55 (d, 1H), 8.70 (d, 1H), 8.75 (s, 1H). Anal. ($C_{11}H_{18}N_2$•2.5$C_2H_2O_4$) C, H, N.

*5.1.10. N-Ethyl-N-Methyl-3-(3-pyridyl)propylamine oxalate **22c** [Method B]*

A solution of 2 M $AlMe_3$ (7 mL, 14 mmol) in hexane was added in a dropwise manner under N_2 to a solution of N-ethylmethylamine (0.83 g, 14 mmol) in benzene (40 mL) at ice-bath temperature. The reaction mixture was allowed to stir at room temperature for 30 min before ethyl 3-(3-pyridyl)propionate [13] (1.79 g, 10 mmol) was added. The resultant reaction mixture was heated at reflux for 48 h, allowed to cool to room temperature, treated with 10% HCl (2 mL) and diluted with CH_2Cl_2 (60 mL). The precipitate was collected by filtration and washed with CH_2Cl_2 (20 mL). The combined organic solution was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give a light-yellow oil which on Kugelrohr distillation (130–140 °C, 0.06 mm) gave 0.95 g (50%) of the amide.

A solution of 1 M AlH_3 (8 mL, 8 mmol) in THF was added under N_2 to a solution of the above amide (0.95 g, 4.9 mmol) in THF (30 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1 h, and then 10% NaOH (2 mL) was added to destroy excess AlH_3. The THF solution was diluted with Et_2O (100 mL), washed with saturated $NaHCO_3$, dried (Na_2SO_4), and solvent was evaporated in vacuo to give a light-yellow oil. The oil was purified by column chromatography (SiO_2 with MeOH–EtOAc 1:12 as eluent) to give 0.43 g (49%) of the desired product as the free base. The free base was converted into an oxalate salt and recrystallized from iPrOH/acetone, m.p. 89–90 °C. ^{1}H-NMR (D_2O) δ: 1.27 (t, 3H, *J* = 7.4 Hz), 2.12 (m, 2H), 2.82 (s, 3H), 2.94 (t, 2H, *J* = 7.7 Hz), 3.17 (m, 2H), 3.23 (m, 2H), 8.00 (m, 1H), 8.51 (d, 1H, *J* = 8.2 Hz), 8.65 (d, 1H, *J* = 5.9 Hz), 8.68 (s, 1H). Anal. ($C_{11}H_{18}N_2$•2$C_2H_2O_4$) C, H, N.

*5.1.11. N-Ethyl-N-methyl-(6-chloropyridin-3-yl)ethylamine oxalate **23***

A mixture of DCC (618 mg, 3.0 mmol), (6-chloropyridin-3-yl)acetic acid [15] (439 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was allowed to stir for 5 min at room temperature; N-ethylmethylamine (240 mg, 4.0 mmol) was added and the reaction mixture was allowed to stir for an additional 48 h. The precipitated material was removed by filtration and the filtrate was washed with 5% HCl and then dilute $NaHCO_3$ solution. The filtrate was dried (Na_2SO_4) and the solvent was removed in vacuo to give 500 mg of oil. Alane (1 M, 3 mL, 3.0 mmol) was added to a solution of the crude amide (200 mg) in THF (10 mL) at 0 °C and the reaction mixture was allowed to stir for 1 h. Water was carefully added at 0 °C in a dropwise manner until evolution of H_2 ceased. The mixture was diluted with Et_2O (75 mL) and washed with 5% KOH (2 × 5 mL) and saturated NaCl solution (10 mL). The organic portion was dried (K_2CO_3) and evaporated to dryness in vacuo to give a crude product. The product was purified by column chromatography (30 g silica gel, Et_2O/MeOH 12:1) to give 150 mg (85%) of the target compound as its free base. The free base was converted to its oxalate salt and recrystallized from iPrOH to give **23** as a white solid, m.p. 125–127 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (m, 3H), 2.95 (s, 3H), 3.10–3.60 (m, 6H), 7.52 (d, 1H, *J* = 5.6 Hz), 7.84 (d, 1H, *J* = 5.6 Hz), 8.32 (s, 1H). Anal. ($C_{10}H_{15}ClN_2$•$C_2H_2O_4$) C, H, N.

*5.1.12. (E)-N-Ethyl-N-methyl-3-(3-pyridyl)-2-propenylamine oxalate **24c** [Method C]*

Thionyl chloride (1 mL) was added to (*E*)-3-(3-pyridyl)propen-1-ol (**31**) [16] (150 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the resultant solution was heated at reflux for 1 h. Solvent and excess $SOCl_2$ were removed by evaporated in vacuo. The residue was dissolved in H_2O (5 mL) and N-ethylmethylamine (304 mg, 5.15 mmol) was added; the solution was allowed to stir at room temperature for 1 h and was then heated at reflux for 1 h. Once the reaction mixture had attained room temperature, it was extracted with Et_2O (2 × 50 mL); the combined ethereal extracts were dried (K_2CO_3) and solvent was evaporated in vacuo to give a yellow oil (108 mg, 56%) which was converted to an oxalate salt and recrystallized from iPrOH, m.p. 120–122 °C. ^{1}H-NMR (D_2O) δ: 1.58 (t, 3H, *J* = 7.26 Hz), 3.12 (s, 3H), 3.53 (m, 2H), 4.23 (m, 2H), 6.90 (dt, 1H, *J* = 7.38 Hz, 15.45 Hz), 7.30 (d, 1H, *J* = 15.05 Hz), 8.28 (m, 1H), 8.95 (d, 2H, *J* = 6.00 Hz), 9.11 (s, 1H). Anal. ($C_{11}H_{16}N_2$•2.5$C_2H_2O_4$) C, H, N.

5.1.13. (Z)-N-Methyl-3-(3-pyridyl)-2-propenylamine oxalate ***25a*** *[Method D]*

Lindlar's catalyst (76 mg) was added to a solution of 3-(3-pyridyl)-2-propyn-1-ol [19] (756 mg, 5.7 mmol) and quinoline (76 mg, 0.6 mmol) in MeOH (70 mL) and the reaction mixture was hydrogenated in a Parr apparatus at atmospheric pressure for 18 h. The mixture was filtered through a Celite pad and the filtrate was evaporated to dryness in vacuo. The crude product was purified by column chromatography (60 g silica gel, petroleum ether/EtOAc 1:4) to yield 600 mg of an oil which was further purified by Kugelrohr distillation (125 °C, 0.08 mm) to give 370 mg of a product that was homogeneous by thin-layer chromatography.

Thionyl chloride (1.07 g, 8.96 mmol) was added in a dropwise manner to a stirred solution of the above alkene (303 mg, 2.24 mmol) in $CHCl_3$ (20 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was allowed to stir at room temperature for 3 h and the solvent and excess $SOCl_2$ were removed by evaporation in vacuo. The white hydrochloride salt of 1-chloro-3-(3-pyridyl)-*Z*-2-propene was used without further purification. An aqueous solution of methylamine (40%, 3 mL, 19 mmol) was added to a portion of the crude salt (360 mg, 1.9 mmol). After stirring at 70 °C for 1 h the pale yellow reaction mixture was extracted with Et_2O (10 × 30 mL) and the combined ethereal extract was dried (K_2CO_3) and the solvent was removed in vacuo to give 300 mg of a pale orange oil. The oil was purified by column chromatography (30 g silica gel, EtOAc/MeOH/diisopropylamine 120:60:1) to yield 190 mg of the desired product as its free base. The base was converted to its oxalate salt and recrystallized from iPrOH/Et_2O to afford 210 mg (39%) of **25a** as a white powder, m.p. 164–166 °C. ^{1}H-NMR (D_2O) δ: 2.70 (s, 3H), 3.95 (dd, 2H, *J* = 1.7 Hz, 6.9 Hz), 6.15 (dt, 1H, *J* = 6.9 Hz, 11.8 Hz), 6.99 (d, 1H, *J* = 11.8 Hz), 8.04 (dd, 1H, *J* = 6.0 Hz, 8.1 Hz), 8.42 (d, 1H, *J* = 8.1 Hz), 8.72–8.73 (m, 2H). Anal. ($C_9H_{12}N_2$•1.4$C_2H_2O_4$) C, H, N.

5.1.14. (Z)-N,N-Dimethyl-3-(3-pyridyl)-2-propenylamine oxalate ***25b*** *[Method E]*

Bis(2,2,2-trifluoroethyl)methoxycarbonylmethyl) phosphonate [17] (3.50 g, 11.0 mmol) was added to a solution of 18-crown-6/acetonitrile complex [18] (9.08 g, 27.7 mmol) in anhydrous THF (300 mL) under an N_2 atmosphere. The reaction mixture was cooled to –70 °C and a 0.5 M toluene solution of KHMDS (22 mL, 11.0 mmol) was added in a dropwise manner. The reaction mixture was allowed to stir for an additional 20 min and a solution of pyridine-3-carboxaldehyde (**32**) (1.12 g, 10.5 mmol) in dry THF (40 mL) was added in a dropwise manner. The reaction mixture was allowed to stir for 45 min at –70 to –65 °C, and the yellow-orange mixture was poured into saturated NH_4Cl solution (100 mL) and extracted with Et_2O (5 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness in vacuo to give an orange oil. The oil was purified by column chromatography (SiO_2 with petroleum ether/EtOAc 1:1 as eluent) to yield 1.26 g (74%) of ester **33** as a light-orange oil. R_f (hexanes/EtOAc) 0.3. A solution of this acrylate ester (0.83 g, 5.1 mmol) in dry toluene (20 mL) was added in a dropwise manner to a hexane solution (1.0M) of DIBALH (10.7 mL, 10.7 mmol) under N_2 at 0 °C. The reaction mixture was allowed to stir at this temperature for 4.5 h and an additional quantity of DIBALH (1 mL) was added. After an additional 2 h, a solution of toluene (1 mL) and MeOH (1 mL) was slowly added, followed by 2 M HCl (1 mL). The solid aluminum salts were collected by filtration and extracted with CH_2Cl_2 (10 × 50 mL). The combined organic extracts were dried (K_2CO_3) and solvent was evaporated in vacuo to give an orange oil which was purified by column chromatography (SiO_2 with petroleum ether/EtOAc 3:8 as eluent) to yield 0.29 g (41%) of the alcohols an oil. The alcohol was further purified by Kugelrohr distillation (b.p. 125 °C, 0.09 mmHg). R_f (petroleum ether/EtOAc 3:8) = 0.16.

Thionyl chloride (0.93 g, 7.8 mmol) was added in a dropwise fashion to a stirred solution of alcohol **34** (0.16 g, 1.2 mmol) in anhydrous Et_2O (20 mL) under N_2 at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h and was heated at reflux for 2 h. Solvent and excess $SOCl_2$ were removed by evaporation in vacuo. The light-brown hydrochloride salt was isolated and used without further purification or characterization. An aqueous solution (40 wt.%) of $NHMe_2$ (0.27 g, 6.0 mmol) was added in a dropwise manner to a solution of the HCl salt in H_2O (4 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature overnight and was extracted with Et_2O (5 × 25 mL). The combined ethereal extract was dried ($MgSO_4$) and evaporated to dryness in vacuo to yield 0.16 g of an oil. The oil was purified by column chromatography (SiO_2 with petroleum ether/EtOAc/NEt_3 10:100:1 as eluent) to afford about 0.1 g of product. The oxalate salt was prepared and recrystallized from iPrOH/Et_2O to give 0.13 g (51%) of **25b** as a white powder, m.p. 142–143 °C. ^{1}H-NMR (D_2O) δ: 2.71 (s, 6H), 3.89 (dd, 2H, *J* = 1.6 Hz, 7.0 Hz), 6.05 (dt, 1H, *J* = 7.0 Hz, 11.7 Hz), 6.92 (d, 1H, *J* = 11.7 Hz), 7.95 (dd, 1H, *J* = 5.9 Hz, 8.2 Hz), 8.33 (d, 1H, *J* = 8.2 Hz), 8.60 (m, 2H). Anal. ($C_{10}H_{14}N_2$•2$C_2H_2O_4$) C, H, N.

*5.1.15. N-Methyl-N-n-propyl-3-(3-pyridyl)-2-propyn-1-ylamine oxalate **26d** [Method F]*

Thionyl chloride (1.34 g, 11.3 mmol) was added in a dropwise manner to a stirred solution of 3-(3-pyridyl)-2-propyn-1-ol (**36**) [19] (0.50 g, 3.8 mmol) in $CHCl_3$ (30 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was allowed to stir overnight at room temperature and the solvent and excess $SOCl_2$ were removed by evaporation in vacuo. The white hydrochloride salt was used in the next step without further purification.

N-Methyl-*n*-propylamine (2.74 g, 37.5 mmol) was added in a dropwise manner to a stirred solution of the above salt in H_2O (15 mL) at 0 °C. The reaction mixture was allowed to stir at 40 °C for 1.5 h and the mixture was extracted with Et_2O (5 × 40 mL). The combined ethereal extracts were dried (K_2CO_3) and solvent was removed in vacuo to yield the free base as an orange oil. The oil was purified by Kugelrohr distillation (70–80 °C, 0.05 mm), converted to the oxalate salt and recrystallized from iPrOH/Et_2O to give 0.96 g (80%) of **26d** as a white powder, m.p. 129–130 °C. ^{1}H-NMR (D_2O) δ: 0.95 (dt, 3H, *J* = 7.3 Hz, 3.0 Hz), 1.76 (m, 2H), 2.99 (s, 3H), 3.19–3.32 (m, 2H), 4.35 (s, 2H), 8.02 (dd, 1H, *J* = 8.1 Hz, 5.5 Hz), 8.68 (d, 1H, *J* = 8.1 Hz), 8.77 (d, 1H, *J* = 5.5 Hz), 8.92 (s, 1H). Anal. ($C_{16}H_{18}N_2$•$2C_2H_2O_4$) C, H, N.

*5.1.16. N-Ethyl-N-methyl-3-(3-pyridyl)-2-propyn-1-ylamine oxalate **26c** [Method G]*

N-Ethylmethylamine (308 mg, 5.2 mmol) was added to a solution of 3-(3-pyridyl)-2-propyn-1-yl bromide hydrobromide [20] (263 mg, 1 mmol) in H_2O (5 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 h and was then extracted with Et_2O (2 × 50 mL). The combined ethereal solution was dried (K_2CO_3) and evaporated to dryness in vacuo to give 104 mg (60%) of crude product. The free base was converted to the oxalate salt and recrystallized from iPrOH, m.p. 120–122 °C. ^{1}H-NMR (CD_3OD) δ: 1.44 (t, 3H, *J* = 7.29 Hz), 3.15 (s, 3H), 3.40 (q, 2H, *J* = 7.29 Hz), 4.42 (s, 2H), 7.54 (dd, 1H, *J* = 4.95 Hz, 7.89 Hz), 8.04 (dd, 1H, *J* = 1.87 Hz, 7.89 Hz), 8.63 (dd, 1H, *J* = 1.59 Hz, 4.95 Hz), 8.76 (s, 1H). Anal. ($C_{11}H_{14}N_2$•$1.5C_2H_2O_4$•H_2O) C, H, N.

*5.1.17. N-Methyl-O-(2-pyridyl)aminoethanol **28***

A solution of N-benzyl-N-methyl-2-(aminoethanol) (3.5 g, 21 mmol) in THF (5 mL) was added to a refluxing suspension of petroleum ether-washed 60% NaH (0.92 g, 23 mmol) in THF (40 mL) under N_2. The reaction mixture was heated at reflux for 3 h, and 2-chloropyridine (2.4 g, 21 mmol) was added. The resultant solution was heated under reflux for an additional 14 h and allowed to stir at room temperature for another 24 h. The precipitated NaCl was collected by filtration and the filtrate was evaporated in vacuo to give a light yellow oil which, upon Kugelrohr distillation (125–130 °C, 0.05 mm), gave 2.8 g (57%) of the desired target pyridylethylamine. A solution of this amine (1.5 g, 6.2 mmol) in MeOH (40 mL) was hydrogenated at 50 psi in the presence of 20% Pd/C (0.2 g) for 12 h in order to remove the benzyl group. The Pd/C was removed by filtration with the aid of Celite. Solvent was evaporated in vacuo to give 0.8 g (85%) of the desired compound as its free base. The free base was converted into an oxalate salt and recrystallized from an iPrOH/MeOH mixture, m.p. 169–170 °C. ^{1}H-NMR (D_2O) δ: 2.79 (s, 3H), 3.50 (t, 2H, *J* = 5.0 Hz), 4.53 (t, 2H, *J* = 5.0 Hz), 7.00 (d, 1H, *J* = 8.8 Hz), 7.13 (m, 1H), 7.87 (m, 1H), 8.12 (d, 1H, *J* = 5.1 Hz). Anal. ($C_8H_{12}N_2O$•$C_2H_2O_4$) C, H, N.

5.2. Radioligand binding

The receptor binding assay was conducted as previously reported in greater detail [2, 25]. In brief, rat brain without cerebellum was homogenized in 10 volumes of ice-cold 0.05 M sodium potassium phosphate buffer (pH 7.4) and centrifuged at 17500 g (4 °C) for 30 min. The pellet was resuspended in 20 volumes of ice-cold glass-distilled water and allowed to incubate on ice for 60 min prior to centrifugation as described above. The final pellet was resuspended (40 mg/mL) in buffer; [^{3}H]nicotine was incubated with 0.5 mL of tissue homogenate (final volume 1 mL) for 2 h at 4 °C, and samples were rapidly filtered through Whatman GF/C filters. Specific binding was defined as the difference in the amount of binding in the presence and absence of 100 μM (–)-nicotine tartrate. Following buffer wash, the filters were air-dried, placed in scintillation vials, and radioactivity was quantified. Following transformation of the data by the Scatchard method, the K_D and B_{max} values were determined using the program LIGAND [26]. Displacement of [^{3}H]nicotine binding at 1 nM was determined in the presence of increasing concentrations of test compound and converted to percent displacement of specific binding. IC_{50} values were determined from a plot of the log concentration versus percent displacement and converted to K_i values by the method of Cheng and Prusoff [27]. K_i values were determined at least in triplicate.

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