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Synthesis and Biological Evaluation of Pyridine-Modified Analogues of 3-(2-Aminoethoxy)pyridine as Novel Nicotinic Receptor Ligands

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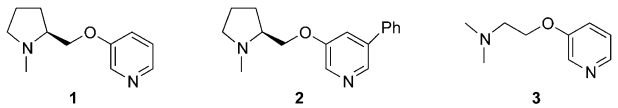
Abstract—Analogues of the potent nicotinic receptor agonist 3-(2-aminoethoxy)pyridine substituted at the 5′ and 6′-positions of the pyridine ring were synthesized and tested in vitro for nicotinic receptor binding activity (displacement of [^{3}H](−)cytisine from whole rat brain synaptic membranes). The substituted analogues exhibited K_i values ranging from 0.076 to 319 nM compared to a K_i value of 26 nM for compound **1**. Among the compounds tested, 5′-vinyl-6′-chloro substituted **1** was the most potent.

Recent evidence indicating the therapeutic potential of neuronal nicotinic receptor (NNR) ligands for the treatment of central nervous system (CNS) disorders as well as the diversity of brain NNR subtypes have suggested an opportunity to develop subtype-selective NNR ligands for the treatment of specific CNS disorders with reduced side effect liabilities.[1–4] We have recently identified A-84543 (**1**), a member of a novel series of 3-pyridyl ether compounds, as a potent neuronal nicotinic receptor ligand.[5] Several compounds of this class were found to possess sub-nanomolar affinity for NNR and activate specific subtypes of NNR.[5] To explore the structural requirements for potent interaction with NNR, structural modifications of this compound were undertaken. Recently,[6–8] we demonstrated that the binding affinity of analogues of A-84543 (**1**) can be modulated by varying the substituents on pyridine ring. For example, compound **2**, which possesses a large phenyl group when compared with A-84543, possesses similar binding potency compared with **1**. We have also identified compound **3**, an analogue lacking a cyclic ring structure but with potent binding activity. In order to probe the necessity of the heterocyclic ring on the binding and potency, a large number of N1-substituted analogues of **3** have been prepared, including those with mono- or dimethyl substituents, or unsubstituted amino groups. These compounds have been screened in assays that measured binding affinity to central NNR. In this paper we describe the structure–activity studies of N1-substituted analogues of **3**.



N1-substituted analogues were prepared based on the reaction sequences shown in Schemes 1–3. The starting chiral alcohol **3′** was prepared from the corresponding amino acid by reduction with borane. (Scheme 1) Formation of the pyridyl ether may be accomplished in two distinct ways. One involves the formation of a tosylate followed by displacement with a substituted hydroxypyridine under basic conditions. Alternatively, activation of an alcohol under Mitsunobu reaction conditions allows ether formation.

Scheme 2 illustrates how primary, secondary and tertiary amines can be obtained from a common Boc protected intermediate. Thus, alkylation of the Boc protected amine with methyl iodide provides the secondary amine after removal of the protecting group under acidic conditions. The dimethylamine analogue was prepared under Eschweiler–Clarke reaction conditions.

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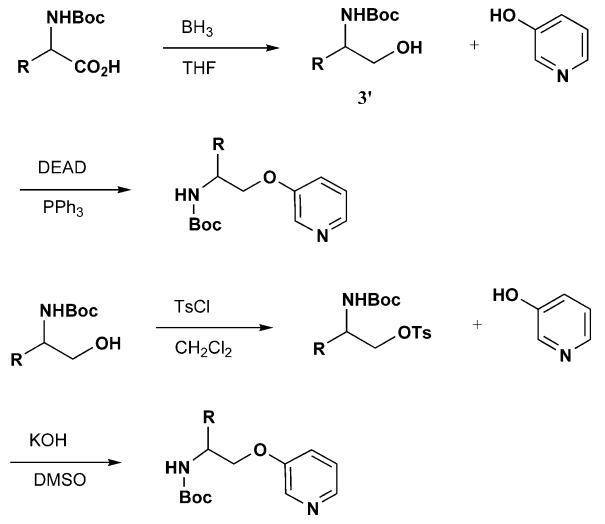
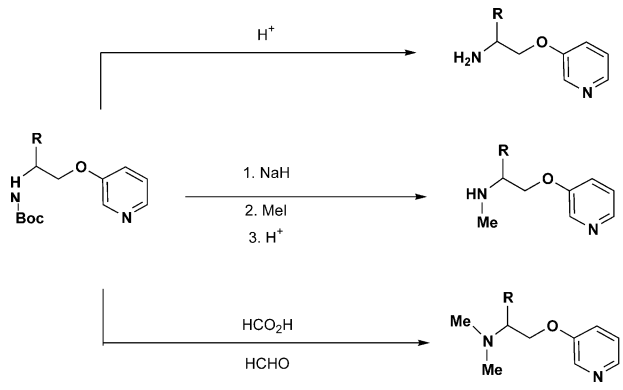
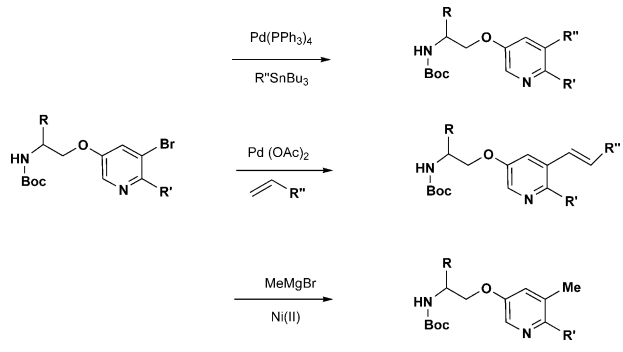


Scheme 1.



Scheme 2.

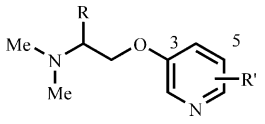


Scheme 3.

Further elaboration of the pyridine substituents may be accomplished after ether formation as illustrated in Scheme 3. It has been demonstrated previously[8] that a bromide may be activated with palladium catalyst to form aryl and vinyl compounds under Suzuki[9] and Heck[10] reaction conditions. The alkyl analogues may be prepared employing a nickel catalyst with the corresponding Grignard reagents.[11]

A major subtype of NNR in the brain is labeled with high affinity by [^{3}H](−)nicotine and [^{3}H](−)cytisine and is composed of α4 and β2 subunits.[12] The effect of the substituents on binding affinity, as reflected by displacement of [^{3}H](−)cytisine from rat brain membranes, is shown in Tables 1–3. We first examined the effect of the amino group on the binding potency. In general, compounds having a dimethylaminoethoxy group possess the weakest receptor binding affinity. The methylamino analogues have comparable binding potency to that of amino compounds (cf. **13**, **36** and **50**; **15**, **38** and **52**).

Table 1. Binding data for dimethylamino-pyridine substituted analogues

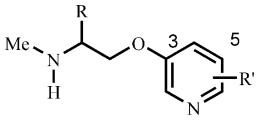


Compd	R	R′	[^{3}H](−)Cytisine binding K_i (nM)[a]
3	H	H	32.6±4.6
4	H	5-Cl	74±3
5	H	5-Br	50±9
6	H	5-CF_3	250±31
7	H	5-NO_2	260±79
8	H	6-Me	140±10
9	H	6-OMe	406±40
10	H	6-Cl	79±28
11	H	5-Cl, 6-Cl	16±16
12	H	5-Br, 6-Cl	7.1±2.3
13	(*R*)-Me	6-Cl	42±7.0
14	(*S*)-Me	6-Cl	42±5
15	(*R*)-Me	6-F	70±15
16	(*S*)-Me	6-F	100±45
17	(*R*)-Me	5-Br, 6-Cl	12±7.0
18	(*S*)-Me	5-Br, 6-Cl	31±9
19	(*R*)-Me	5-Me, 6-Cl	7.2±0.1
20	(*S*)-Me	5-Me, 6-Cl	9.6±1.1
21[b]	(*R*)-Me	5-(4-Py–CH=CH-), 6-Cl	0.10 ±0.02
22[b]	(*S*)-Me	5-(4-Py–CH=CH-), 6-Cl	0.37±0.06
23[b]	(*S*)-Et	5-(4-Py–CH=CH-), 6-Cl	3.6±0.7
24[b]	(*S*)-CH_2Ph	5-(4-Py–CH=CH-), 6-Cl	4.6±1.5
25	(*S*)-CH_2Ph	5-Br, 6-Cl	320±40
26	(*S*)-CH_2CH_2Cl	5-CF_3	5.5±3.2

[a]The ability of compounds to displace [3H](−)cytisine binding to whole rat brain membranes was performed as described.[13] Values are the means±SEM; $n=3$–4. In all cases, the Hill co-efficient was close to unity indicative of an interaction with a single class of binding sites.
[b]The geometry of the double bond is *trans*.

With this information in hand, we then investigated the effect of pyridyl substituents on the binding affinity. In the dimethylamino series, replacement of the 3-pyridyl moiety of **3** with either a 5-chloro or bromopyridyl group (**4** and **5**) caused only a 2-fold decrease in binding affinity towards the [^{3}H](−)cytisine binding site. In contrast, a dramatic decrease in binding affinity was observed for analogue **6** ($K_i=250$ nM) which has a 5-trifluoromethypyridyl substituent. Replacement of the CF_3 group with a nitro group has a similar effect on the binding affinity. With regard to the C6 position, when a chloro atom is incorporated, as in analogue **10**, a comparable affinity with the 5-chloro compound **4** is observed. Replacement of Cl with an electron-donating methoxy group (**9**) resulted in a 5-fold decrease in binding affinity. In contrast, a similar affinity is observed when the chloro was substituted with a methyl group.

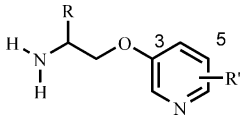
Table 2. Binding data for methylamino-pyridine substituted analogues[a]



Compd	R	R′	[^{3}H](−)Cytisine Binding K_i (nM)[a]
27	H	H	17±4
28	H	5-Cl	37±4
29	H	5-NH_2	27±4
30	H	5-NO_2	560±110
31	H	5-CF_3	1500±160
31	H	6-Me	43±10
32	H	6-OMe	620±5
33	H	6-Cl	22±5
34	H	5-Cl, 6-Cl	13±7
35	H	5-Br, 6-Cl	14.3±0.4
36	(*R*)-Me	6-Cl	5.9±1.8
37	(*S*)-Me	6-Cl	41.0±5.6
38	(*R*)-Me	6-F	11±3
39	(*S*)-Me	6-F	69±4
40	(*R*)-Me	5-Br, 6-Cl	1.5±0.3
41	(*S*)-Me	5-Br, 6-Cl	11.0±3.2
42	(*R*)-Me	5-Me, 6-Cl	0.57±0.15
43	(*S*)-Me	5-Me, 6-Cl	5.5±0.9
44[b]	(*R*)-Me	5-(4-Py–CH=CH–), 6-Cl	0.077±0.032
45[b]	(*S*)-CH_2Ph	5-(4-Py–CH=CH–), 6-Cl	2.6±2.1
46	(*S*)-CH_2Ph	5-Br, 6-Cl	85±38
47	(*S*)-CH_2Ph	H	690±29
48	(*S*)-Et	6-F	220±74

[a]The ability of compounds to displace [^{3}H](−)cytisine binding to whole rat brain membranes was performed as described.[13] Values are the means±SEM; n=3–4. In all cases, the Hill co-efficient was close to unity indicative of an interaction with a single class of binding sites.
[b]The geometry of the double bond is *trans*.

Table 3. Binding data for amino-pyridine substituted analogues[a]



Compd	R	R′	[^{3}H](−)Cytisine Binding K_i (nM)[a]
49	H	5-Cl	140±26
50	(*R*)-Me	6-Cl	5.3±1.7
51	(*S*)-Me	6-Cl	4.5±0.3
52	(*R*)-Me	6-F	6.6±2.5
53	(*S*)-Me	6-F	8.7±0.4
54	(*R*)-Me	5-Br, 6-Cl	1.5±0.3
55	(*S*)-Me	5-Br, 6-Cl	1.5±0.9
56	(*R*)-Me	5-Me, 6-Cl	0.98±0.17
57	(*S*)-Me	5-Me, 6-Cl	0.52±0.07
58[b]	(*R*)-Me	5-(4-Py–CH=CH–), 6-Cl	0.081±0.003
59[b]	(*S*)-Me	5-(4-Py–CH=CH–), 6-Cl	0.076±0.039
60[b]	(*S*)-Et	5-(4-Py–CH=CH–), 6-Cl	0.18±0.04
61[b]	(*S*)-CH_2Ph	5-(4-Py–CH=CH–), 6-Cl	9.9±0.9
62	(*S*)-Et	5-Br, 6-Cl	15±38
63	(*S*)-CH_2Ph	5-Br, 6-Cl	100±27
64	(*S*)-Et	6-F	39±7
65	(*S*)-Et	6-Cl	15.0±0.8

[a]The ability of compounds to displace [^{3}H](−)cytisine binding to whole rat brain membranes was performed as described.[13]Values are the means±SEM; n=3–4. In all cases, the Hill co-efficient was close to unity indicative of an interaction with a single class of binding sites.
[b]The geometry of the double bond is *trans*.

It is also interesting that compounds having halo substituents at both the C5 and C6 positions of the pyridyl ring increased receptor binding affinity (cf. **10** and **11**; **13** and **17**). A further increase in potency was observed when the C5 bromo atom was replaced with a 4-vinylpyridine moiety (cf. **18** and **22**; **17** and **21**). The binding potency at either the C5- or C6-position appears to be governed by both electronic and steric effects. A simple steric effect cannot account for the high affinity of the vinylpyridine analogue (**21**) that has a large group at the 5-position. It has been demonstrated that the OMe (**9**) substitution lead to weaker affinity than the Me (**8**) substitution, despite the larger size in volume. Therefore, it appears that electronic effects may play some role in determining binding affinity. The same SAR trend was also observed in the methylamino and amino series (Tables 2 and 3).

In general, Table 1 reveals that the 5-(4-Py–CH=CH–), 6-Cl analogue (**21**) is the most potent compound in the dimethylamino series. With the exception of the 5-NO_2, 5-CF_3 and 6-OMe groups, the F, Cl, Br and Me, moieties (**15**, **10**, **5**, and **8**) were tolerated at both C5 and C6-positions. With regard to the methylamino series, the most potent compound identified is the 5-(4-Py-CH =CH–), 6-Cl analogue (**44**) which possesses a K_i value of 0.077 nM. As shown in Table 3, 5-(4-Py–CH=CH–), 6-Cl analogue (**59**) is also the most potent compound in the amino series.

To examine whether substituents at the C2′ position of the ethoxy side chain have an effect on the nicotinic receptors, various 2′-substituted analogues were evaluated for their nicotinic binding affinity. We first investigated the dimethylamino series. Table 1 reveals that the C2′ methyl analogue (**18**) is 4-fold less potent than the corresponding parent analogue **12**. Another 10-fold decrease is observed when the C2′ methyl group was replaced with a benzyl functionality (**18** vs **25**). In the case of the 5-(4-vinylpyridyl), 6-Cl analogues, the order of binding potency of the C2′-substituted analogues is Me >Et >CH_2Ph. The same SAR trend is also observed in the amino series with the 5-Br, 6-Cl compound. In contrast to both the dimethylamino and amino series, no effect in binding potency is observed when a methyl group was introduced at the C2′ position (**35** vs **41**) in the methylamino series. However, replacing methyl with a benzyl group caused an 8-fold decrease in binding potency (**41** vs **46**).

With this information in hand, we then turned our attention to scrutinize the effect of chirality at the C2′ position on the binding potency. Examining the binding affinities of the Me analogue in the dimethylamino series, the configuration of the C2′ chiral center does not have much effect on the binding affinity. No significant difference in binding activity is observed when stereochemistry is changed from *R* to *S* (**13** vs **14**; **19** vs **20**). A similar trend is also observed in the amino series (**50** vs **51**; **54** vs **55**). In contrast to those results, the chirality at C2′ position shows a selected effect on the binding potency in the methylamino series. As indicated in Table 2, a 6-fold decrease in potency is observed when the stereochemistry is changed from *R* to *S* with the

fluoro analogues. In general, the *S*-enantiomer is 6–10 times more potent than the corresponding *R*-enantiomer in the methylamino series.

In summary, we have shown that varying the substituent pattern at the amino group of the aminoethoxy moiety of compound **3** alters the binding properties of these compounds. The binding affinities (Tables 1–3) indicate that large substituents are well tolerated at the C5 position of the pyridine ring. In general, the SAR of this series followed the trend as observed in the A-84543 series with only a few exceptions. This study has also shown that methylamino and amino compounds possess similar binding potency. The most potent analogue identified is compound **44** ($K_i = 0.077$ nM) that possesses a binding potency that is comparable with that of ABT-594 ($K_i = 0.05$ nM), a potent nicotinic receptor agonist.

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