Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 631–633

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Structure–Activity Relationships of 5-Substituted Pyridine Analogues of 3-[2-((*S*)-Pyrrolidinyl)methoxy]pyridine, A-84543: A Potent Nicotinic Receptor Ligand

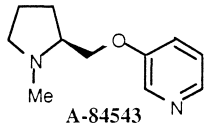
Nan-Horng Lin,* Yihong Li, Yun He, Mark W. Holladay, Theresa Kuntzweiler, David J. Anderson, Jeffrey E. Campbell and Stephen P. Arneric

Neurological and Urological Diseases Research, D-47W, Pharmaceutical Products Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3500, USA

Received 19 October 2000; accepted 18 December 2000

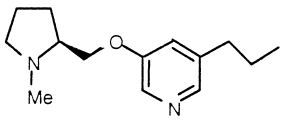
Abstract—In an effort to probe the steric influence of C5 substitution of the pyridine ring on CNS binding affinity, analogues of **1** substituted with a bulky moiety—such as phenyl, substituted phenyl, or heteroaryl—were synthesized and tested in vitro for neuronal nicotinic acetylcholine receptor binding affinity. The substituted analogues exhibited K_i values ranging from 0.055 to 0.69 nM compared to a K_i value of 0.15 nM for compound **1**. Assessment of functional activity at subtypes of neuronal nicotinic acetylcholine receptors led to identify several agonists and antagonists.

Recent evidence indicating the therapeutic potential of cholinergic channel modulators for the treatment of CNS disorders as well as the diversity of brain neuronal nicotinic acetylcholine receptor (nAChR) subtypes have suggested an opportunity to develop subtype-selective nAChR 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 cholinergic channel modulator.[5] Several compounds of this class were found to possess subnanomolar affinity for nAChRs and activate specific subtypes of neuronal nAChRs.[5] To explore the structural requirements for potent interaction with nAChRs, structural modifications of this compound were undertaken. Recently,[6] we demonstrated that subtype selectivity of agonists or antagonists could be achieved by varying the substituents on the pyridine ring. For example, compound **2**, which possesses a large alkyl group, exhibits a moderately selective antagonism of the α4β2 receptor subtype compared with **1**. In order to probe the effect of steric volume of substituents on the binding and functional potency, a large number of 5-substituted analogues of **1** have been prepared, including those with large substituents such as phenyl, substituted phenyl, substituted heteroaryl or heteroaryl groups.[6] These compounds have been screened in assays which measured binding affinity to central nAChRs and in vitro functional activity (ion flux). With regard to ion flux assays, a key focus was on functional activity in IMR-32 cells as a model for potential activity at human peripheral ganglionic receptors, which appear to at least partially mediate undesired cardiovascular and gastrointestinal effects of (*S*)-nicotine.[7,8] In this paper we describe SAR studies of 5-substituted analogues of **1**.



A-84543

1



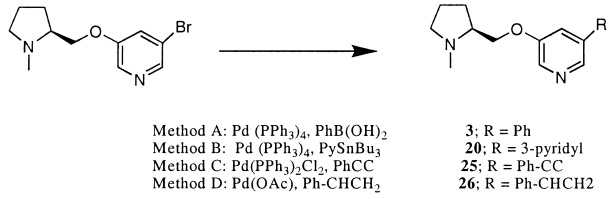
2

The pyridine substituted analogues of **1** were synthesized as outlined in Scheme 1. The 5-phenyl substituted pyridine analogues, as exemplified by the preparation of **3**, were synthesized employing the Suzuki reaction.[9] Thus, 5-bromopyridyl ether was heated with phenyl boronic acid employing tetrakis(triphenylphosphino)Pd(0) as catalyst to provide the corresponding

*Corresponding author. Fax: +1-847-938-5034; e-mail: nanhorng.lin@abbott.com

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00030-0

5-phenylpyridine compound. The 5-bromopyridine intermediate was prepared by treatment of 3,5-dibromopyridine with 1-methyl-2(*S*)-pyrrolidinylmethanol in the presence of sodium hydride. Employing Stille coupling reaction conditions (Method B), the 5-pyridyl and pyrimidinyl analogues were synthesized from the corresponding tributylstannanes as depicted in Scheme 1.[10] Treatment of 5-bromopyridine with phenylacetylene in the presence of palladium(II) catalyst furnished the 5-(2-phenyl-1-ethynyl)pyridine analogue **25** (Method C).[11] Employing Heck reaction conditions (method D),[12] 5-(*trans*-2-phenyl-1-vinyl)pyridine analogue **26** was prepared from 5-bromopyridine. It should be noted that only *trans* product was obtained from the coupling reaction. Hydrogenation of compound **26** provided the corresponding 5-(2-phenyl-1-ethyl)pyridine **27** in high yield.



Scheme 1.

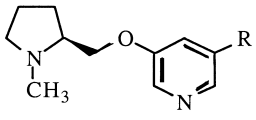
A major subtype of nAChR in the brain is labeled with high affinity by [^{3}H](−)-nicotine and [^{3}H](−)-cytisine and is composed of α4 and β2 subunits.[13] The effect of the substituents on binding affinity, as reflected by displacement of [^{3}H](−)-cytisine from rat brain membranes, are shown in Table 1. Replacement of the 3-pyridyl fragment of **1** with a 5-phenylpyridyl group (compound **3**) caused no reduction in binding affinity towards the [^{3}H]-cytisine binding site. However, a 10-fold reduction in binding affinity was observed in analogue **4** ($K_i = 1.1$ nM) having a 2-methylphenylpyridyl substituent. Replacement of methyl group with formyl group has a similar effect on binding affinity. When an electron-withdrawing group is incorporated into the phenyl ring to give 3-nitrophenyl analogue **6**, a 4-fold lower affinity than phenyl compound **3** is observed. Introduction of an electron-donating amino group (**7**) at the C3 position of the phenyl ring resulted in a 4-fold decrease in binding affinity. In general, compounds having substituents at C2 or C3 positions of the phenyl ring reduced receptor binding affinity.

To examine whether substituents at the C4 position of the phenyl ring have a similar effect on the nicotinic receptors as observed at the C2 or C3 positions, the corresponding 4-methyl analogue was evaluated for the nicotinic binding affinity. Table 1 reveals that C4 methyl (**11**) analogue was as potent as compound **3**. The OMe, CF_3, F and Cl moieties (compounds **8**, **9**, **10**, and **12**) were all well tolerated at this position. Introduction of an additional chlorine atom at either the C2 or C3 positions had only minor effect on the binding affinity (cf. **12** and **13**; **10** and **14**). In contrast, a 22-fold decrease ($K_i = 2.4$ nM) in binding potency was observed when trifluoromethyl group was introduced at both C3 and C5 positions (compound **15**).

To investigate the steric limitation of the C5 position, an additional ring was introduced to the phenyl moiety. Thus, introduction of a 2-naphthyl (**17**) group increased the K_i value to 0.33 nM (a 3-fold decrease compared to **3**), while replacement of phenyl ring with a 1-naphthyl group (i.e., **16**) resulted in a 38-fold decrease in binding potency. A 3-fold decrease in potency was observed when phenyl was replaced with 3-quinolyl (**18**) or 2-indolyl (**19**) group.

Although 3-pyridyl analogue (**20**) has a 2-fold decrease in binding potency when compared to **3**, no further reduction in binding potency was observed upon replacement with a five-membered heteroaryl moiety (cf. **21** and **22**). As observed previously, fusion of an additional phenyl ring to yield the benzofuran analogue **23** had little effect on binding potency. In addition, replacement of the pyridyl moiety with a pyrimidinyl group (**24**) resulted in little effect on the binding affinity.

Table 1. Binding data for pyridine substituted analogues



Compound	R	Method	[^{3}H]Cytisine binding K_i (nM)[a]
1	H	A	0.15±0.05
3	Ph	A	0.11±0.07
4	2-Me-Ph	A	1.1±0.1
5	2-CHO-Ph	A	0.56±0.13
6	3-NO_2-Ph	A	0.46±0.21
7	3-NH_2-Ph	A	0.43±0.05
8	4-OMe-Ph	A	0.32±0.21
9	4-CF_3-Ph	A	0.15±0.03
10	4-F-Ph	A	0.11±0.008
11	4-Me-Ph	A	0.13±0.02
12	4-Cl-Ph	A	0.082±0.022
13	2-Cl-4-Cl-Ph	A	0.16±0.03
14	3-Cl-4-F-Ph	A	0.055±0.007
15	3-CF_3-5-CF_3-Ph	A	2.4±0.7
16	1-Naphthyl	A	4.2±1.9
17	2-Naphthyl	A	0.33±0.11
18	3-Quinolyl	A	0.39±0.15
19	*N*-Me-2-indolyl	A	0.32±0.07
20	3-Pyridyl	A	0.27±0.08
21	2-Furyl	A	0.19±0.01
22	2-Thienyl	A	0.31±0.05
23	2-Benzofuryl	A	0.15±0.06
24	5-Pyrimidinyl	B	0.37±0.17
25	1-Ph-CC−	C	0.16±0.02
26	*trans*-1-Ph-CH=CH−	D	0.24±0.06
27	Ph-CH_2CH_2−	[b]	0.22±0.06
28	4-Me-Ph-CC−	C	0.31±0.13
29	4-Py-CH=CH−	D	0.12±0.03
30	4-Py-CH_2-CH_2−	[c]	0.064±0.012

[a]The ability of compound to displace [^{3}H](−)-cytisine binding to whole rat brain membranes was performed as described.[14] Values are the means±SEM; $n = 3$–4. In all cases, the Hill coefficient was close to unity indicative of an interaction with a single class of binding sites.
[b]Synthesized by hydrogenation of compound **25**.
[c]Synthesized by hydrogenation of compound **29**.

Table 2. Antagonist properties for pyridine substituted analogue[a]

Compound	R	Calcium dynamics in IMR32 Cells[15] IC_{50} (μM)[b]
3	Ph	5.1±0.9
4	2-Me-Ph	1.25±0.32
5	2-CHO-Ph	6.31±1.45
6	3-NO_2-Ph	2.33±0.94
7	3-NH_2-Ph	6.9±0.2
8	4-OMe-Ph	6.97±1.95
9	4-CF_3-Ph	5.71±1.65
10	4-F-Ph	6.48±1.57
11	4-Me-Ph	0.8±0.2
12	4-Cl-Ph	1.99±0.28
13	2-Cl-4-Cl-Ph	0.89±0.34
14	3-Cl-4-F-Ph	7.3±0.4
15	3-CF_3-5-CF_3-Ph	2.35±0.87
16	1-Naphthalyl	0.69±0.34
17	2-Naphthalyl	3.4±2.3
18	3-Quinolyl	5.1±0.7
19	*N*-Me-2-indolyl	6.1±0.5
20	3-Pyridyl	24.7±4.6
21	2-Furyl	7.9±0.9
22	2-Thienyl	1.7±0.6
23	2-Benzofuryl	2.9±1.3
24	5-Pyrimidinyl	[c]
25	1-Ph-CC−	0.79±0.14
26	*trans*-1-Ph-CH=CH−	4.8±0.9
27	Ph-CH_2CH_2−	1.1±0.6
28	4-Me-Ph-CC−	1.5±0.3
29	4-Py-CH=CH−	7.6±3.2
30	4-Py-CH_2-CH_2−	6.3±0.8

[a]Compounds were tested against 100 μM of (−)-nicotine.
[b]Values represent mean±SEM; $n=3$–5.
[c]EC_{50}: 32.4±8.1 μM; % Max: 38.9±14.7. % Max represents the maximal efficacy of the compounds relative to 100 μM nicotine.

The effect of phenyl substituents with longer aliphatic chains on the binding affinities was also examined. Changing the phenyl moiety to a phenylethynyl moiety (**25**) gave a compound possessing the same binding potency as **3**, while replacement of the phenyl moiety with a phenylethyl or phenylvinyl group (i.e., **27** or **26**) resulted in only little difference in binding potency. In general, introduction of a two-carbon chain between the phenyl and the C5 position of pyridine ring caused only a minor effect on binding potency regardless of the flexibility of the two-carbon moiety. Introduction of a nitrogen atom at the C4 position of the phenyl ring (**29**) resulted in a 2-fold decrease in binding potency compared with **26**. Interestingly, replacement of the phenyl group of **27** with a 4-pyridyl functionality caused a 3.5-fold decrease in binding potency (**27** vs **30**).

We conclude that the steric volume of substitutions at the C5 position of pyridine has little effect on nAChR binding affinity. Hence, the phenyl analogue **3** possesses similar binding activity as that of compound **1**. Introduction of an additional ring or aliphatic chain, such as 2-naphthyl (**17**) and phenylethyl analogue (**27**), resulted in only a 2- or 3-fold reduction in binding potency.

The ability of these analogues to activate nAChRs was investigated using a cell line that express the human ganglionic-like ($\alpha_3\beta_x$) nAChR (IMR 32 cells). With the exception of compound **24** (5-pyrimidinyl), all of analogues tested stimulated cation efflux with very low potency ($EC_{50}>1000$ μM) and efficacy (<20%) at human $\alpha_3\beta_x$ receptor subtypes (data not shown). In general, those 5-substituted phenyl analogues exhibited very low potency and efficacy at $\alpha_3\beta_x$ subtypes regardless of the position and functionality of substitution (Table 2).

Since most of the analogues displayed very low efficacy (<20%) at this subtype, they were then tested for their antagonist properties at $\alpha_3\beta_x$ receptor subtype. At the $\alpha_3\beta_x$ subtype, all of the analogues except compound **24**, which possesses EC_{50} value of 32 μM, antagonized cation efflux mediated by 100 μM (*S*)-nicotine with an IC_{50} value of 0.7–25 μM.

In summary, we have shown that varying the substituent pattern at the C5 position of the pyridyl moiety of A-84543 alters binding and particularly functional properties of compounds. The binding data in Table 1 indicated that large substituents are well tolerated at the C5 position. As demonstrated previously,[6] this study has also shown that preparation of agonists or antagonists could be achieved by varying the substituents on the pyridine ring. The 5-pyrimidinyl analogue **24** was identified as a $\alpha_3\beta_x$ partial agonist and several analogues (compounds **11**, **13**, **16**, and **25**) were identified as potent $\alpha_3\beta_x$ antagonist.

References

1. Holladay, M. W.; Lebold, S. A.; Lin, N.-H. *Drug Dev. Res.* **1995**, *35*, 191.
2. Arneric, S. P.; Sullivan, J. P.; Williams, M. In *Psychopharmacology: Fourth Generation of Progress*; Bloom, E., Kuper, D. J., Eds., Raven: New York, 1995; pp 95–110.
3. Meyer, E. M.; de Fiebre, C. M.; Hunter, B. E.; Simpkins, C. E.; Frauworth, N.; de Fiebre, N. E. C. *Drug Dev. Res.* **1994**, *31*, 127.
4. Garvey, D. S.; Carrera, G. M.; Arneric, S. P.; Shue, Y.-K.; Lin, N.-H.; He, E.; Lee, E.; Lebold, S. A. U.S. Patent 5 409 946, 1995.
5. Abreo, M. A.; Lin, N.-H.; Garvey, D. S.; Gunn, D. E.; Hettinger, A.-M.; Wasicak, J. T.; Pavlik, P. A.; Martin, Y. C.; Donnelly-Roberts, D. L.; Anderson, D. J.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817.
6. Lin, N.-H.; Gunn, D. E.; Li, Y.; He, Y.; Bai, H.; Ryther, K. B.; Kuntzweiler, T.; Donnelly-Roberts, D. L.; Anderson, D. J.; Campbell, J. E.; Sullivan, J.; Arneric, S. P.; Holladay, M. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 249.
7. McBride, P. E. *Med. Clin. N. Am.* **1992**, *76*, 333.
8. Carlson, G. M.; Ruddon, R. W.; Hug, C. C.; Schmiege, S. K., Jr.; Bass, P. *J. Pharmacol. Exp. Ther.* **1970**, *173*, 377.
9. Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.
10. Milstein, D.; Stille, K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
11. Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163.
12. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.
13. Flores, C. M.; Rogers, S. W.; Pabreza, L. A.; Wolfe, B. B.; Kellar, K. J. *Mol. Pharmacol.* **1991**, *41*, 31.
14. Pabreza, L. A.; Dhawan, S.; Kellar, K. J. *Mol. Pharmacol.* **1990**, *39*, 9.
15. Kuntzweiler, T. A.; Arneric, S. P.; Donnelly-Roberts, D. L. *Drug Dev. Res.* **1998**, *44*, 14.