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Synthesis and Structure–Activity Relationship of Novel Pyridyl Ethers for the Nicotinic Acetylcholine Receptor

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Abstract—The preparation of novel pyridyl ethers as ligands for the nicotinic acetylcholine receptor (nAChR) is described. Variations of the ring size of the azacycle and substitution on the pyridine had dramatic effects on receptor binding affinity with IC_{50}s at the $\alpha_4\beta_2$ nAChR ranging from 22 to >10,000 nM. The most potent molecule was (*R*)-2-chloro-3-(4-cyanophenyl)-5-((3-pyrrolidinyl)oxy)pyridine **27f** with an IC_{50} of 22 nM.

The discovery of compounds that can safely treat both acute and chronic pain without the side effect of drug dependency would be an important advance in pain management. The discovery of epibatidine **1**, a nAChR modulator, suggested that it might be possible to obtain an analgesic compound that is devoid of opioid-related side effects.[1] But the narrow therapeutic index of epibatidine prohibited further development of the compound as an analgesic.[2] The discovery of ABT-594 fueled further investigation of the therapeutic potential of ligands that bind to the nAChR.[3] ABT-594 was shown to be at least 20 times more potent than morphine as an analgesic.[3a] Furthermore, the initial findings suggested that the compound did not elicit the drug dependency associated with morphine. To this end, we now report the discovery of novel pyridyl ethers as potent ligands for the $\alpha_4\beta_2$ nAChR subtype.

Our program focused on using natural product ligands such as epibatidine **1** and nicotine **2** as starting points for analogue design as shown in Figure 1. We retained the pyridyl group as a part of the novel ligands. The only criteria left on the molecule was to place nitrogen in an optimal distance from the 3 position of the pyridine. Numerous models have been suggested in the literature regarding the location and angle of the nitrogen in respect to the pyridine.[4] As part of our structure–activity program, we identified the pyridyl ethers **3** as potent ligands that bound to the $\alpha_4\beta_2$ nAChR subtype.

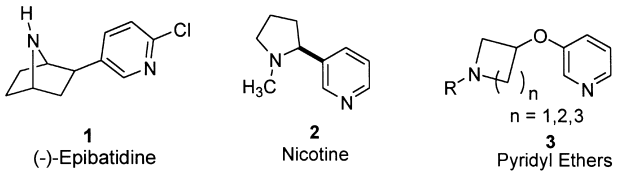

Figure 1. Ligands for nAChR.

Chemistry

The nitrogen of 3-pyrrolidinol **4a**[5] was first protected with a Boc group as shown in Scheme 1. The Boc-protected pyrrolidinol **5** ($n=1$) was then coupled with 3-hydroxypyridine under Mitsunobu conditions.[6] The pyridyl ether **6** ($n=1$) was then treated with a solution of trifluoroacetic acid (TFA) and methylene chloride (1:1) to obtain 3-((3-pyrrolidinyl)oxy)pyridine (**7**). 3-((4-Piperidinyl)oxy)pyridine (**8**) was obtained from 4-piperidinol[5] by a similar route as described above. *N*-Methyl, -ethyl, -isopropyl analogues **3** ($n=2$, $R=CH_3$, CH_2CH_3, $CH(CH_3)_2$) were prepared from *N*-methyl, -ethyl, -isopropyl-3-pyrrolidinols[5] as shown in Scheme 1 without the Boc-protecting group. The chiral 3-pyrrolidinols[5] were used to prepare the corresponding enantiomers as shown in Scheme 1.

The azetidine analogue was prepared as shown in Scheme 2. The hydrogenation of 1-(diphenylmethyl)-3-hydroxyazetidine[5] under H_2, Pd/C and protection of the reduced nitrogen with a Boc group resulted in the Boc-

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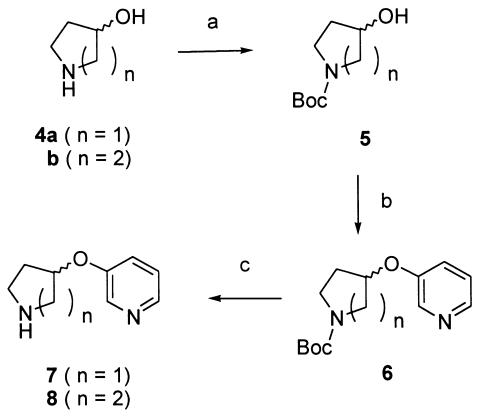
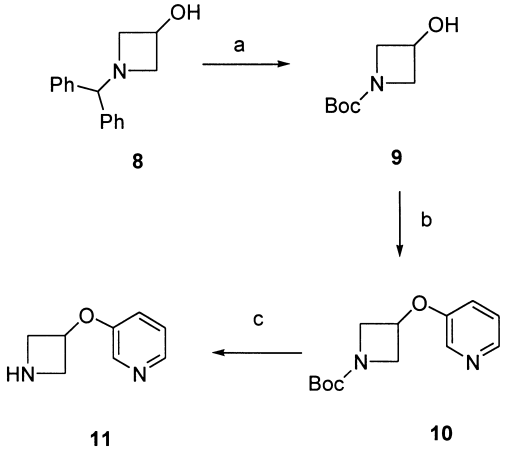


Scheme 1. (a) Boc_2O, DIEA, Dioxane:H_2O (1:1); (b) 3-Hydroxypyridine, PPh_3, DEAD, THF; (c) TFA:CH_2Cl_2 (1:1).

protected 3-hydroxyazetidine **9**. Mitsunobu coupling between **9** and 3-hydroxypyridine gave the protected pyridyl ether **10**. Subsequent de-protection of the Boc group with a solution of TFA and methylene chloride (1:1) resulted in the desired 3-((3-azetidinyl)oxy)pyridine (**11**).

To prepare 5-substituted pyridyl ethers, the Boc-protected (*S*)-3-pyrrolidinol (**12**) was first coupled with either 3-bromo-5-hydroxypyridine or 2-chloro-3-bromo-5-hydroxypyridine (**13**) under Mitsunobu conditions to obtain the desired ether **14** as shown in Scheme 3. Addition of trimethylsilylacetylene to **14** under Sonogashira conditions[7] provided the aryl acetylenes **15**. The trimethylsilyl group was subsequently removed to obtain **16**. The pyridyl ether **17** was obtained from **16** after treating the compound with a solution of TFA:CH_2Cl_2 (1:1). Using a Stille coupling reaction,[8] the vinyl analogue **19** was prepared from the aryl bromide **14**. The methyl analogue **21** was obtained from Mitsunobu coupling between **12** and 2-chloro-3-methyl-5-hydroxypyridine.

3-Aryl substituted pyridyl ethers were prepared according to Scheme 4. *p*-Nitrophenylcarbonate Wang resin was allowed to react with (*S*)-3-pyrrolidinol in the presence of DIEA and DMF. Mitsunobu coupling between the resin bound pyrrolidinol **23** and either 3-bromo-5-hydroxypyridine or 2-chloro-3-bromo-5-hydroxypyridine provided the resin bound core structure **24**. Suzuki coupling between **24** and arylboronic acids, followed by cleavage of the coupled products from the resin provided the desired compounds **27**.



Scheme 2. (a) (i) H_2, Pd/C, (ii) Boc_2O, DIEA, Dioxane:H_2O (1:1); (b) 3-Hydroxypyridine, PPh_3, DEAD, THF; (c) TFA:CH_2Cl_2 (1:1).

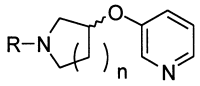
Results and Discussion

To elucidate the structure–activity relationship of the pyridyl ethers, the ring size of the azacycle of the pyridyl ethers was initially examined. The binding affinities of these initial compounds are shown in Table 1. As shown in Table 1, both 5- and 6-membered pyridyl ethers **7** and **8** showed a similar binding affinity toward the $\alpha_4\beta_2$ nAChR subtype (209 and 205 nM, respectively). The azetidine analogue **11** did not show any binding affinity toward the receptor subtype. Then substitution at the nitrogen of the pyrrolidine was examined. The *N*-methyl analogue **3a** showed more than a 2-fold increase in the binding affinity compared with des-methyl analogue **7**, with an IC_{50} of 92 nM. Substitution with either *N*-ethyl or -isopropyl groups (**3b**,**c**) resulted in the loss of the binding activity.

Since **7** was a racemic compound, the corresponding enantiomers were prepared to evaluate the binding activities of each enantiomer. As shown in Table 1, the (*R*)-isomer (***R*)-7** was about 4-fold more active than **7** with an IC_{50} of 45 nM. On the other side, the (*S*)-isomer (***S*)-7** was more than 2-fold less active than **7**. These results indicated that (*R*)-isomer was considerably more active than the (*S*)-isomer.[9] We then explored the structure–activity relationships of the pyridine portion of the core structure and the results are shown in Table 2.

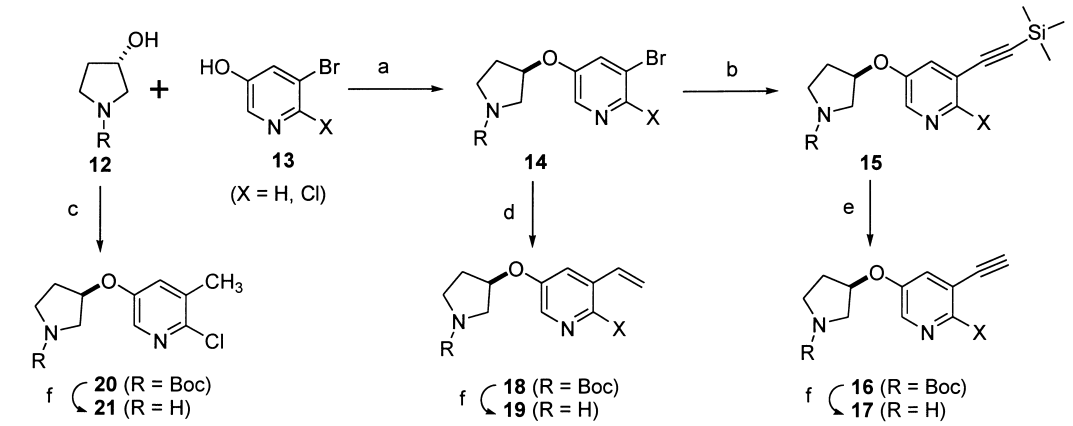
A general trend was observed. In all cases, substitution of a chloride at the 2 position of the pyridine analogues resulted in an increase of the binding affinity (ex. **17b** versus **17a** and **19b** versus **19a**). When nonaromatic alkyl groups were added at the 5 position of the pyridine ring, the acetylene substitution **17a**,**b** resulted in the highest binding activity (62 and 46 nM for the deschloro and chloro analogues, respectively), followed by the methyl **21**, and vinyl **19a**,**b** analogues. We then

Table 1. The $\alpha_4\beta_2$ nAChR binding data on pyridyl ethers[10]

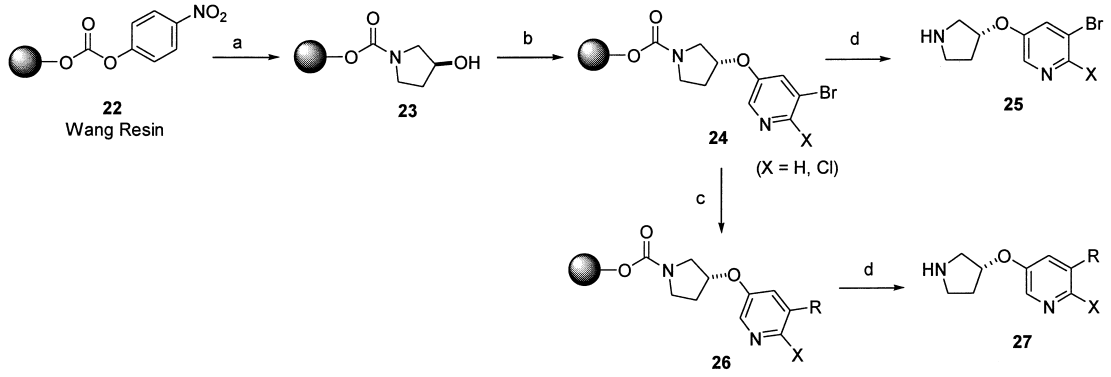


Entry	*n*	R	IC_{50} (nM)
7	1	H	209 (157–278)[a]
8	2	H	204 (132–314)
11	0	H	>10,000
3a	1	CH_3	92 (61–138)
3b	1	CH_2CH_3	>10,000
3c	1	$CH(CH_3)_2$	>10,000
(*R*)-7	1	H	45 (21–99)
(*S*)-7	1	H	449 (118–1720)

[a]The values in the parenthesis represent 95% confidence limits.



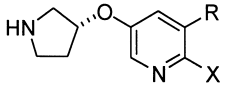
Scheme 3. (a) PPh_3, DEAD, THF; (b) Trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, Et_3N, THF; (c) 2-chloro-3-methyl-5-hydroxypyridine, PPh_3, DEAD, THF; (d) *n*-$Bu_3SnCH=CH_2$, $Pd(PPh_3)_4$, Toluene; (e) TBAF, THF; (f) TFA:CH_2Cl_2 (1:1).



Scheme 4. (a) (*S*)-3-pyrrolidinol, DIEA, DMF; (b) PPh_3, DEAD, 3-bromo-5-hydroxypyridine or 2-chloro-3-bromo-5-hydroxypyridine, THF; (c) Arylboronic acid, LiCl, $Pd(PPh_3)_4$, Na_2CO_3, Toluene, EtOH; (d) 95% TFA/H_2O.

explored aromatic substitution on the 5 position of the pyridine ring. The addition of a phenyl ring at the position (**27b**) was well tolerated with an IC_{50} of 75 nM. When substituted phenyls were examined, 4-cyano phenyl substitution (**27f**) gave the most potent binding activity with an IC_{50} of 22 nM. Generally, *para* substitution (**27f**) gave better binding activity than the *meta*-isomers (e.g., **27d**,**j**). The binding activity of the pyridine substituted analogue **27h** was similar to the one observed with the phenyl analogue **27b** (65, and 75 nM respectively).

Table 2. The $\alpha_4\beta_2$ nAChR binding data on pyridyl ethers[10]



Entry	R	X	IC_{50} (nM)
17a	CCH	H	62 (44–89)[a]
17b	CCH	Cl	46 (18–114)
19a	$CHCH_2$	H	883 (408–1900)
19b	$CHCH_2$	Cl	140 (111–1760)
21	CH_3	Cl	64 (26–160)
25	Br	Cl	94 (55–159)
27a	Ph	H	1820 (560–5990)
27b	Ph	Cl	75 (25–226)
27c	3-OMe-Ph	H	1120 (760–1650)
27d	3-OMe-Ph	Cl	58 (38–88)
27e	4-CN-Ph	H	544 (67–4400)
27f	4-CN-Ph	Cl	22 (13–38)
27g	4-Pyr	H	571 (188–1740)
27h	4-Pyr	Cl	65 (33–126)
27i	3-Cl-Ph	H	940 (380–2320)
27j	3-Cl-Ph	Cl	103 (50–205)

[a]The values in the parenthesis represent 95% confidence limits.

In summary, we prepared novel pyridyl ethers as ligands for the $\alpha_4\beta_2$ nAChR subtype. Variation of the size of the azacycle and substitution on the pyridine had dramatic effects on receptor binding affinity with IC_{50} ranging from 22 to >10,000 nM. The optimum binding affinity was observed when the ring size was a 5-membered ring. A clear separation of the binding affinity was observed with enantiomers (***R*)-7** and (***S*)-7**. Increase in the binding activity was observed when the 2 position of the pyridine was substituted with a chloride. Additional binding activity was gained when the 3 position of the pyridine was substituted with a 4-cyanophenyl group. The in vivo analgesic activities of the novel pyridyl ethers will be reported in due course.

Acknowledgement

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