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2-(ARYLOXYMETHYL) AZACYCLIC ANALOGUES AS NOVEL NICOTINIC ACETYLCHOLINE RECEPTOR (nAChR) LIGANDS

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Abstract: A series of 2-(aryloxymethyl) azetidine and pyrrolidine nAChR ligands in which the 3-pyridyl moiety of a previously described series[1] was replaced by a substituted phenyl group was explored. Aromatic substitution afforded analogues with K_i values ranging from 3 to >10,000 nM. Generally, substitution at the *ortho-* and *para-*position was unfavorable, whereas electron-withdrawing groups at the *meta*-position improved the K_i values.

There is considerable evidence suggesting that selective neuronal nicotinic acetylcholine receptor (neuronal nAChR) ligands may have therapeutic potential in a number of CNS diseases and disorders, including Alzheimer's disease (AD), neuroprotection, smoking cessation, schizophrenia, and anxiety disorders.[2-5] Much of this evidence is based on studies using (-)-nicotine, a prototypical but nonselective nicotinic agonist. However, nicotine's poor pharmacokinetics, unfavorable GI and cardiovascular effects, propensity to cause sleep disturbances, and addiction liabilities make it unlikely that (-)-nicotine will be a therapeutic agent of choice.[6] The emerging diversity of nAChR subtypes[7-12] supports the possibility of developing receptor subtype selective therapeutic agents that lack or have substantially attenuated side-effects.[13,14]

There is mounting evidence suggesting that a nicotinic agent may be therapeutically useful in ameliorating the cognitive decline that occurs in AD. Postmortum examination of the brains affected by AD consistently shows a substantial decrease in nicotinic receptors,[15,16] whereas changes in other receptors, including muscarinic receptors, is more variable and often less pronounced. Furthermore, the cognitive enhancement of nicotine and neuronal nAChR agonists has been well documented in rodents, [17-23] nonhuman primates,[24,25] as well as AD patients. [26-28]

We have had a continuing interest in the development of novel and selective nAChR ligands as potential cognition enhancers to treat AD. We previously reported on 2-pyrrolidinyl isoxazoles (exemplified by **ABT-418**)[29-32] which were shown to be potent and selective neuronal nAChR ligands with cognition enhancing properties. Subsequently, a 3-(2-pyrrolidenylmethoxy)pyridine class of nAChR ligands **I**[1] (Figure 1) was demonstrated to have very high affinity for neuronal nAChR's. Previous SAR studies of various nAChR ligands have shown that in certain cases substituted phenyl rings can bioisosterically substitute for heteroaromatic rings, as was found for a series of 2-phenyl pyrrolidine analogues **II**.[33] We therefore decided to explore analogues of **I**

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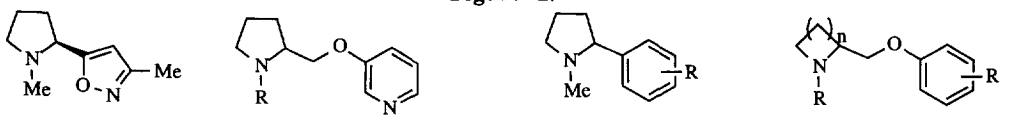
in which the 3-pyridyl ring has been bioisosterically replaced with substituted aryl rings, and herein report on a class of phenyl ether analogues **III** that possess high affinity for the neuronal nAChR.

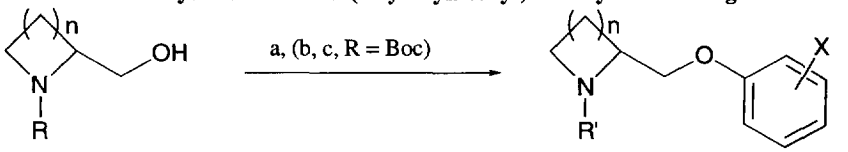
Figure 1.



ABT-418 **I** **II** **III** (n = 1,2)

Methods: The synthesis of the 2-(aryloxymethyl) azacyclic analogues is outlined in Scheme 1. In the case of the pyrrolidine analogues, protection of the nitrogen of either (*R*)- or (*S*)-proline with a *t*-butoxycarbonyl (Boc) group followed by borane reduction afforded the *N*-Boc-protected amino alcohols in good yield. In certain cases the commercially available (*S*)-*N*-Me alcohol (Aldrich) was directly coupled with the phenol under Mitsunobu conditions to afford the final product. Removal of the Boc protecting group afforded the desired secondary amines, and subsequent *N*-methylation using Eschweiler-Clarke conditions yielded the desired tertiary amines. In some cases the *N*-Boc analogues were directly converted to the *N*-methyl analogue using Eschweiler-Clarke conditions. The *N*-Et analogue **5** was synthesized via reductive amination ($NaCNBH_3$/MeCHO) of the secondary amine, and the *N*-cyanomethyl analogue **6** was made via *N*-alkylation with bromoacetonitrile. The thioether analogues **44** and **45** were synthesized similarly using Mitsunobu couplings, and the anilino analogue **46** was commercially available (Aldrich). The azetidine analogues **40-43** were synthesized analogously to the pyrrolidine compounds, starting with the commercially available (*S*)-azetidine carboxylic acid (Aldrich). The analogues were tested for nicotinic binding using [^{3}H]-(-)-cytisine following the procedure of Pabreza [34] using a whole rat brain preparation. Compounds were evaluated for cognitive-enhancing properties in mouse using the inhibitory avoidance paradigm as previously described.[32]

Scheme 1. Synthesis of 2-(Aryloxymethyl) Azacyclic Analogues.



R = Boc or CH_3

R' = H, Me
n = 1, 2

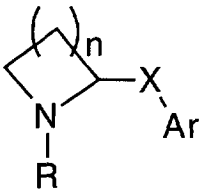
(a) ArOH/Mitsunobu conditions (b) TFA/CH_2Cl_2 (c) HCOOH/aq formalin, reflux

Results and Discussion: The binding affinity of these phenyl ether analogues for the neuronal nAChR varied widely, with the K_i values ranging from 3 nM to >10,000 nM (Table 1). The SAR of the unsubstituted phenyl

ether analogues **1-6** reveals that the tertiary (*S*)-*N*-Me analogue **2** is more potent than the corresponding *N*-H analogue **1**, whereas the (*R*)-*N*-H analogue **3** is more potent than the (*R*)-*N*-Me analogue **4**. Generally, the 2-(*S*) stereochemistry was preferred for nearly all of the pyrrolidine phenyl ether analogues (*vida infra*), although there were some exceptions (e.g., **16** and **17**, **33** and **34**) . The reverse was observed for the few analogues evaluated having the (*R*)-stereochemistry (e.g., **3** and **4**, **13** and **14**). These results are in contrast with the related pyrrolidine 3-pyridyl ethers, where the (*S*)-*N*-H, (*S*)-*N*-Me, and (*R*)-*N*-H were equipotent, and the (*R*)-*N*-Me analogue was over 100-fold less potent.[1] Replacement of the *N*-methyl group of **2** with the larger ethyl (**5**) or cyanomethyl (**6**) group led to a precipitous loss in binding affinity, hence further SAR studies focused on *N*-H and *N*-Me analogues.

Subsequent SAR studies within the pyrrolidine series explored the effect of aromatic substitution on nAChR binding. Compounds having substituents at the 2-position (e.g., **7**, **8**, **9**, and **10**) uniformly demonstrated poor receptor binding affinity, although analogues with fluorine at both the 2- and 3-position (e.g., **24** and **25**) demonstrated moderate binding affinity. The most potent compounds were those containing an electron-withdrawing group (e.g., F, Cl, CN; compounds **11-17**) at the 3-position of the phenyl ring; the larger 3-acetamido analogue (**18**) and 3-trifluoromethyl compounds (**19** and **20**) were significantly less effective. A second electron-withdrawing group at the 2-, 4-, or 5-position (e.g., **24-30**) gave no further enhancement in the K_i values. The 4-chloro analogue **23** likewise had poor receptor binding, and further substitution of the aromatic ring with electron-withdrawing groups (e.g., the pentafluoro analogues **33** and **34**) caused a dramatic loss of binding affinity. It was also found that fusion of a second aromatic ring onto the phenyl ring was detrimental to activity, as demonstrated by analogues **35-38**. In addition, replacement of the oxygen atom with either sulfur (**44** and **45**) or nitrogen (**46**) led to a dramatic increase in the K_i values. Only a limited number of 2-(*S*)-azetidine analogues were evaluated as nicotinic ligands (**40-43**), and were found to generally have binding affinities in the same range as their pyrrolidine counterparts, although the *N*-H analogues were 2-5 times more potent than the corresponding *N*-Me analogues. The *N*-H azetidine analogue **42** was the most potent of all the compounds evaluated. Two compounds (**2** and **31**) evaluated in the mouse inhibitory avoidance paradigm were found to have no positive cognitive effect.

Table 1. Analytical Data and Neuronal nAChR Binding of 2-(Aryloxymethyl) Azacyclic Analogues



Compd	n	R	X	Ar	Mass Spectrum[a]	Ki (nM)[b]
1	2	H	(*S*)-CH_2O	phenyl	178 (M+H), 195 ($M+NH_4$)	195 ± 16.9
2	2	Me	(*S*)-CH_2O	phenyl	192 (M+H)	42 ± 1.45

3	2	H	(*R*)-CH_2O	phenyl	178 (M+H), 195 ($M+NH_4$)	107 ± 1
4	2	Me	(*R*)-CH_2O	phenyl	192 (M+H)	204 ± 32
5	2	Et	(*S*)-CH_2O	phenyl	206 (M+H)	5166 ± 1521
6	2	CH_2CN	(*S*)-CH_2O	phenyl	217 (M+H), 234 ($M+NH_4$)	1059 ± 207
7	2	Me	(*S*)-CH_2O	2-fluorophenyl	210 (M+H)	304 ± 59
8	2	H	(*S*)-CH_2O	2-trifluoromethylphenyl	246 (M+H), 263 ($M+NH_4$)	>10,000 (3)
9	2	Me	(*S*)-CH_2O	2-trifluoromethylphenyl	260 (M+H)	2,433 ± 875
10	2	Me	(*S*)-CH_2O	2-acetylphenyl	234 (M+H)	3333 ± 286
11	2	H	(*S*)-CH_2O	3-fluorophenyl	196 (M+H), 213 ($M+NH_4$)	14.3 ± 3
12	2	Me	(*S*)-CH_2O	3-fluorophenyl	210 (M+H), 227 ($M+NH_4$)	5 ± 0.8
13	2	H	(*R*)-CH_2O	3-fluorophenyl	196 (M+H), 213 ($M+NH_4$)	13 ± 3.2
14	2	Me	(*R*)-CH_2O	3-fluorophenyl	210 (M+H)	78 ± 14
15	2	Me	(*S*)-CH_2O	3-chlorophenyl	226 (M+H)	37 ± 0.8
16	2	H	(*S*)-CH_2O	3-cyanophenyl	203 (M+H), 220 ($M+NH_4$)	18 ± 0.9
17	2	Me	(*S*)-CH_2O	3-cyanophenyl	217 (M+H)	51 ± 4
18	2	H	(*S*)-CH_2O	3-acetamidophenyl	235 (M+H)	136 ± 3
19	2	H	(*S*)-CH_2O	3-trifluoromethylphenyl	246 (M+H), 263 ($M+NH_4$)	523 ± 148
20	2	Me	(*S*)-CH_2O	3-trifluoromethylphenyl	260 (M+H)	557 ± 64
21	2	H	(*S*)-CH_2O	3-methoxyphenyl	208 (M+H)	468 ± 87
22	2	Me	(*S*)-CH_2O	3-methoxyphenyl	222 (M+H)	175 ±10
23	2	Me	(*S*)-CH_2O	4-chlorophenyl	226 (M+H)	603 ± 24
24	2	H	(*S*)-CH_2O	2,3-difluorophenyl	214 (M+H), 231 ($M+NH_4$)	77 ± 6
25	2	Me	(*S*)-CH_2O	2,3-difluorophenyl	228 (M+H)	69 ± 7
26	2	H	(*S*)-CH_2O	3,4-difluorophenyl	214 (M+H), 231 ($M+NH_4$)	17.3 ± 1.6
27	2	Me	(*S*)-CH_2O	3,4-difluorophenyl	228 (M+H)[c]	17.6 ± 3
28	2	H	(*S*)-CH_2O	3,5-difluorophenyl	214 (M+H), 231 ($M+NH_4$)[d]	18 ± 2.7
29	2	Me	(*S*)-CH_2O	3,5-difluorophenyl	228 (M+H)	19.3 ± 3
30	2	Me	(*S*)-CH_2O	3,4-dichlorophenyl	260 (M+H)	112 ± 6
31	2	Me	(*S*)-CH_2O	3,4-methylenedioxyphenyl	236 (M+H)	169 ± 21
32	2	Me	(*S*)-CH_2O	6-(1,3-benzoxathiol-2-one)	266 (M+H)	339 ± 87
33	2	H	(*S*)-CH_2O	pentafluorophenyl	268 (M+H), 285 ($M+NH_4$)	3067 ± 1149
34	2	Me	(*S*)-CH_2O	pentafluorophenyl	282 (M+H)	>10,000 (3)
35	2	Me	(*S*)-CH_2O	7-quinolyl	243 ((M+H)	5000 (3)

36	2	H	(*S*)-CH_2O	1-naphthyl	228 (M+H), 245 ($M+NH_4$)	2890 ± 590
37	2	Me	(*S*)-CH_2O	1-naphthyl	242 (M+H)	592 ± 111
38	2	H	(*S*)-CH_2O	2-naphthyl	228 (M+H)	6889 ± 1439
39	2	Me	(*S*)-CH_2O	4-(7-chloroindanyl)	266 (M+H)	1866 ± 641
40	1	H	(*S*)-CH_2O	phenyl	164 (M+H), 181 ($M+NH_4$)	52 ± 4.3
41	1	Me	(*S*)-CH_2O	phenyl	178 (M+H)	101 ± 9.2
42	1	H	(*S*)-CH_2O	3-fluorophenyl	182 (M+H), 199 ($M+NH_4$)	3.1 ± 0.08
43	1	Me	(*S*)-CH_2O	3-fluorophenyl	196 (M+H)	14.4 ± 0.9
44	2	H	(*S*)-CH_2S	3-fluorophenyl	212 (M+H)[d]	5406 ± 1550
45	2	Me	(*S*)-CH_2S	3-fluorophenyl	226 (M+H)	1191 ± 384
46	2	H	(*S*)-CH_2NH	phenyl	177 (M+H)	5086 ± 988

[a] All final compounds were fully characterized by ^{1}H-NMR and MS, with elemental analyses within ±0.4% of theoretical values. [b] The compounds were tested for nAChR binding in a whole rat brain preparation using [^{3}H]-cytisine following a modification of the procedure of Pabreza et al. as described.[34] [c] Anal. calcd for $C_{12}H_{16}ClF_2NO \cdot 1.85\ H_2O$: C, 48.52; H, 6.40; N, 4.72; Found: C, 48.50; H, 5.40; N, 4.07. [d] elemental analyses within ±0.6% of theoretical values.

A key feature of the classical Beers-Reich[35] pharmacophore model for nAChR binding is hydrogen bond interactions between the pyridyl nitrogen of nicotine and the receptor. The improved binding observed upon substituting a 3-fluorine atom for the hydrogen atom in this series may be due to the H-bonding capacity of the fluorine atom, although it is not possible to rule out electronic effects. Conceivably, the ether oxygen atom might also be involved in H-bonding interactions with the nAChR, although computer modeling efforts to overlay the lone pair electrons of the oxygen with the nitrogen lone pair of nicotine were inconclusive. Perhaps the receptor can tolerate several vectors of approach for potential hydrogen-bond acceptors, or it can accommodate different ligands via alternate binding modes. Other components may also contribute to the binding of these phenyl-substituted ether analogues, including aromatic-aromatic interactions and favorable hydrophobic interactions. Interestingly, the 3,4-methylenedioxyphenyl moiety (see compound **31**), which was the best bioisosteric replacement for the 3-pyridyl ring in a different previously reported series,[33] was only moderately active in this series. It is unknown why the two compounds evaluated in the mouse inhibitory avoidance paradigm were inactive, although it may be that these analogues lacked key pharmacophore(s) for good intrinsic agonist activity.

In conclusion, we have demonstrated that in terms of neuronal nAChR binding affinity substituted phenyl rings can bioisosterically substitute for the 3-pyridyl ring in a series of 2-(aryloxymethyl)pyrrolidinyl- and 2-(aryloxymethyl)azetidinyl analogues. Substitution of the aromatic ring afforded compounds with K_i values for nAChR binding ranging from 3 to >10,000 nM, with the most potent analogues having electron-withdrawing groups at the *meta*-position. Two compounds evaluated in mouse inhibitory avoidance paradigm showed no activity.

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