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A novel series of [3.2.1] azabicyclic biaryl ethers as α3β4 and α6/4β4 nicotinic receptor agonists

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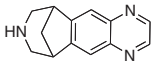
ABSTRACT

We report the synthesis of a series of [3.2.1]azabicyclic biaryl ethers as selective agonists of α3- and α6-containing nicotinic receptors. In particular, compound **17a** from this series is a potent α3β4 and α6/4β4 receptor agonist in terms of both binding and functional activity. Compound **17a** also shows potent in vivo activity in CNS-mediated animal models that are sensitive to antipsychotic drugs. Compound **17a** may thus be a useful tool for studying the role of α3β4 and α6/4β4 nicotinic receptors in CNS pharmacology.

Nicotinic acetylcholine receptors (nAChRs) are located in both the central and peripheral nervous systems and serve a wide variety of physiological functions.[1] Assigning any particular physiological response to activity at a specific nicotinic receptor, however, is challenging because of the complexity of the nAChR. The nAChR is a pentameric structure, and in the central nervous system (CNS) is comprised of various combinations of α(2–10) and β(2–4) subunits.[2] We have previously described our work on the smoking-cessation drug varenicline, (6,7,8,9-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-*h*][3]benzazepine), **1**, (Fig. 1), a potent and selective partial agonist at the α4β2 nicotinic receptor.[3] This compound allowed us to investigate the pharmacology of the α4β2 nicotinic receptor, which is the major nicotinic receptor subtype present in the CNS. In addition, we have reported the activity of positive effectors of α7 nAChRs, also present in the CNS.[4] As a follow-up to these studies, we became interested in the biology of other nicotinic receptor subtypes present in the CNS, in particular, the α3, α5, and α6 subunit-containing nAChRs.[2,5] Hence we began an investigation into finding selective ligands for these receptors to characterize their CNS pharmacology.

The starting point for our medicinal chemistry studies was the structure of varenicline, **1**, which, in addition to its potent activity at the α4β2 nicotinic receptor, we found to have weak affinity for the α3β4 and α6/4β4 nicotine receptors (see Table 1).[2] The [3.2.1] template present in **1** seemed like a potential starting point for exploring α3β4 and α6/4β4 nicotinic receptor SAR. In addition, the [3.2.1] template precursor compound **2** (see below) was readily available from our earlier SAR studies in this area. At the time we began the studies described herein, there were few literature reports examining α3* nicotinic receptor SAR,[6] and no literature reports that we were aware of describing α6* nicotinic receptor SAR. A recent report of α6β2* selective compounds is the first in this area.[7] In addition, high-throughput screening of our in-house compound collection for activity at α6/4β4 nAChRs failed to identify viable hits. So we initiated our work by exploring various derivatives of **2**, in particular extending the 'fused' type structure of **1** to a 'pendant' type of structure in which a linker would join the [3.2.1]azabicyclic template to an aromatic group. After exploring numerous combinations of linkers and aromatic groups, we discovered that an ether



1, Varenicline

Figure 1. Structure of varenicline, **1**.

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Table 1
In vitro activity of compounds **7**–**24**

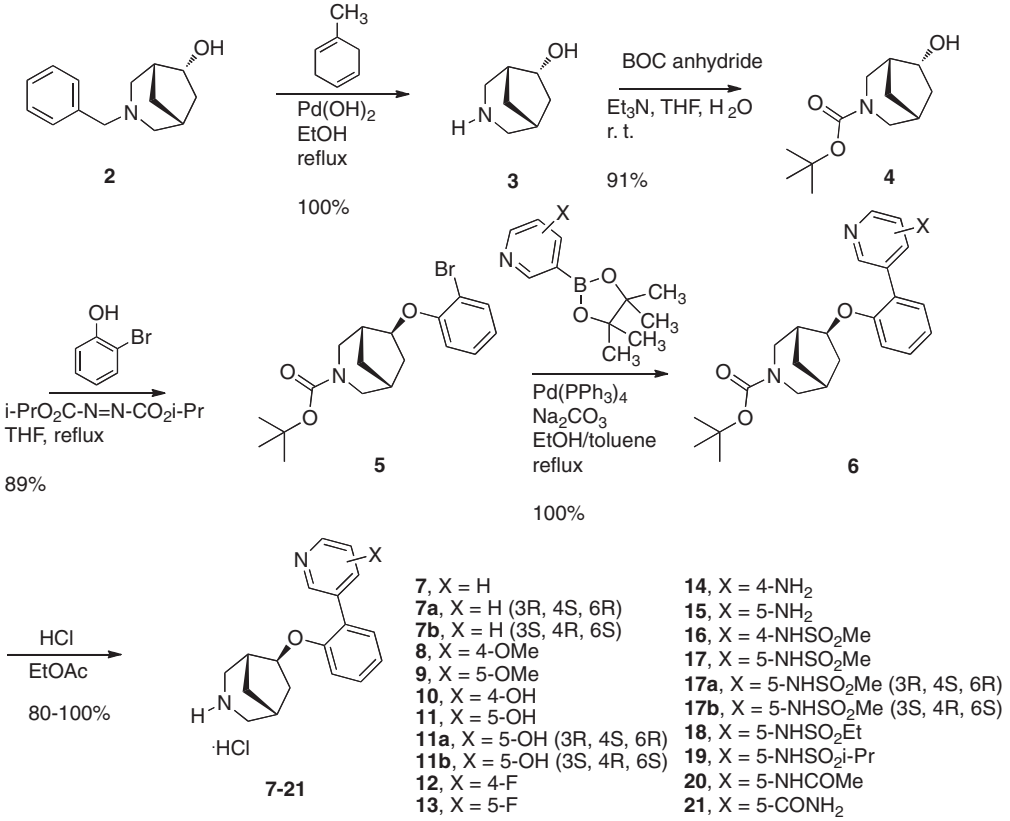
Compound	Binding K_i[a]					EC_{50}[c]	
	Alpha-1	Alpha-3	Alpha-4	Alpha-6	Alpha-7	Alpha-3	Alpha-6
7	NT	1.3 ± 0.33 (*n* = 5)	>1307 ± 194.6 (*n* = 4)	3.8 ± 0.505 (*n* = 5)	NT	57 (61.5%)	102 (32.5%)
7a	1020	1.21 ± 0.306 (*n* = 3)	>832 (*n* = 1)	2.15 ± 0.617 (*n* = 3)	3300	<100 (45%)	53 (35%)
7b	NT	16.9 ± 8.43 (*n* = 3)	>614 ± 270.53 (*n* = 3)	78.5 ± 27.5 (*n* = 3)	NT	NT	NT
8	NT	0.882 ± 0.376 (*n* = 4)	477 ± 202 (*n* = 4)	1.77 ± 0.782 (*n* = 4)	NT	<100 (46%)	126 (23%)
9	NT	94.1 ± 92.2 (*n* = 4)	>309 ± 205 (*n* = 2)	9.01 ± 2.21 (*n* = 4)	NT	32.7 (49%)	>30,000 (<20%)
10	>15,300	2.1 ± 0.62 (*n* = 5)	>419 ± 190 (*n* = 4)	3.15 ± 1.00 (*n* = 5)	>15,000	16.3 (11%)	28.9 (91%)
11	5000	0.186 ± 0.06 (*n* = 3)	255 ± 41.8 (*n* = 4)	0.425 ± 0.159 (*n* = 3)	1580	2.59 (82%)	5.00 (75%)
11a	1680	0.748 ± 0.557 (*n* = 5)	252 ± 57.9 (*n* = 6)	0.177 ± 0.040 (*n* = 5)	>13,500	2.99 (117%)	4.30 (230%)
11b	8320	2.02 ± 0.72 (*n* = 3)	149 ± 27.4 (*n* = 3)	7.16 ± 2.25 (*n* = 3)	>15,000	34.4 (118%)	279 (70%)
12	NT	0.856 (*n* = 1)	1860 (*n* = 1)	1.33 (*n* = 1)	NT	197 (52%)	NT
13	>16,900	2.17 ± 0.365 (*n* = 4)	>1503 ± 637.5 (*n* = 2)	10.1 ± 2.6 (*n* = 4)	>13,500	316 (65%)	625 (45%)
14	4430	0.957 ± 0.186 (*n* = 4)	>1040 (*n* = 1)	2.05 ± 0.754 (*n* = 4)	NT	33.6 (84.5%)	248 (61%)
15	>15,000	1.48 ± 0.553 (*n* = 4)	>575 ± 147 (*n* = 3)	5.83 ± 2.12 (*n* = 4)	>15,000	33.9 (97%)	265 (107%)
16	>15,000	0.382 ± 0.662 (*n* = 3)	250 ± 52.8 (*n* = 3)	5.21 ± 1.43 (*n* = 3)	7590	112 (80.5%)	64.4 (48%)
17	>13,500	0.243 ± 116 (*n* = 3)	>424 ± 225 (*n* = 3)	0.241 ± 0.038 (*n* = 4)	4750	2.99 (117%)	4.30 (230%)
17a	11,700	0.158 ± 0.04 (*n* = 6)	336 ± 22 (*n* = 6)	0.168 ± 0.030 (*n* = 6)	4780	3.06 (116%)	3.15 (148%)
17b	>15,000	1.33 ± 0.268 (*n* = 4)	2905 ± 835 (*n* = 2)	3.73 ± 1.17 (*n* = 4)	>15,000	2.92 (120%)	3.27 (182%)
18	>15,000	0.149 ± 0.07 (*n* = 4)	>604 ± 78 (*n* = 3)	0.313 ± 0.194 (*n* = 4)	9870	1.09 (122%)	2.27 (182%)
19	4240	0.126 ± 0.12 (*n* = 3)	745 ± 74.8 (*n* = 5)	0.202 ± 0.129 (*n* = 4)	14,600	0.16 (108%)	0.37 (160%)
20	530	9.53 ± 2.01 (*n* = 3)	>615.5 ± 150.5 (*n* = 2)	17.1 ± 3.32 (*n* = 3)	>15,000	252 (57%)	98.5 (51%)
21	>15,000	3.79 ± 1.03 (*n* = 3)	>962.5 ± 407.5 (*n* = 2)	12.5 (± 5.61 (*n* = 3)	>15,000	36.8 (100%)	35.4 (59.5%)
24	NT	496 ± 134 (*n* = 3)	NA	1130 ± 563 (*n* = 3)	NT	NA	NA
1	8200	74.7 ± 6.19 (*n* = 18)	0.295 ± 0.02 (*n* = 18)	89 ± 7.34 (*n* = 18)	125 ± 18[b]		
Nicotine	1480	394 ± 17.5 (*n* = 67)	9.46 ± 0.557 (*n* = 66)	168 ± 8.75 (*n* = 67)	2110 ± 852[b]		

NT—not tested; NA—not active.

[a] Binding K_i values given in nM units, ±s.e.m, and number of determinations, *n*, in parentheses, for the α1βγδ, α3β4, α4β2, α6/4β4, and α7 receptors respectively (see text). The numbers in italics indicate that one or more of the individual determinations did not give a K_i value since the required inhibition of binding could not be reached at the maximum concentration used in the assay. These values reflect only the determinations for which a K_i value could be determined, and are therefore underestimates of the actual binding potency.

[b] Values from Ref. 12.

[c] EC_{50} values for efficacy given in nM units, with the % efficacy in parentheses, results for a single determination.



Scheme 1. Preparation of [3.2.1] azabicyclic compounds.

linker and an ortho-substituted phenyl ring offered the best combination for potent α3β4 and α6/4β4 agonist activity. As we describe below, this effort led to the discovery of a highly potent and selective agonist of α3β4 and α6/4β4 nAChRs, **17a**.