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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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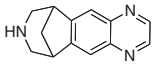
ABSTRACT

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**

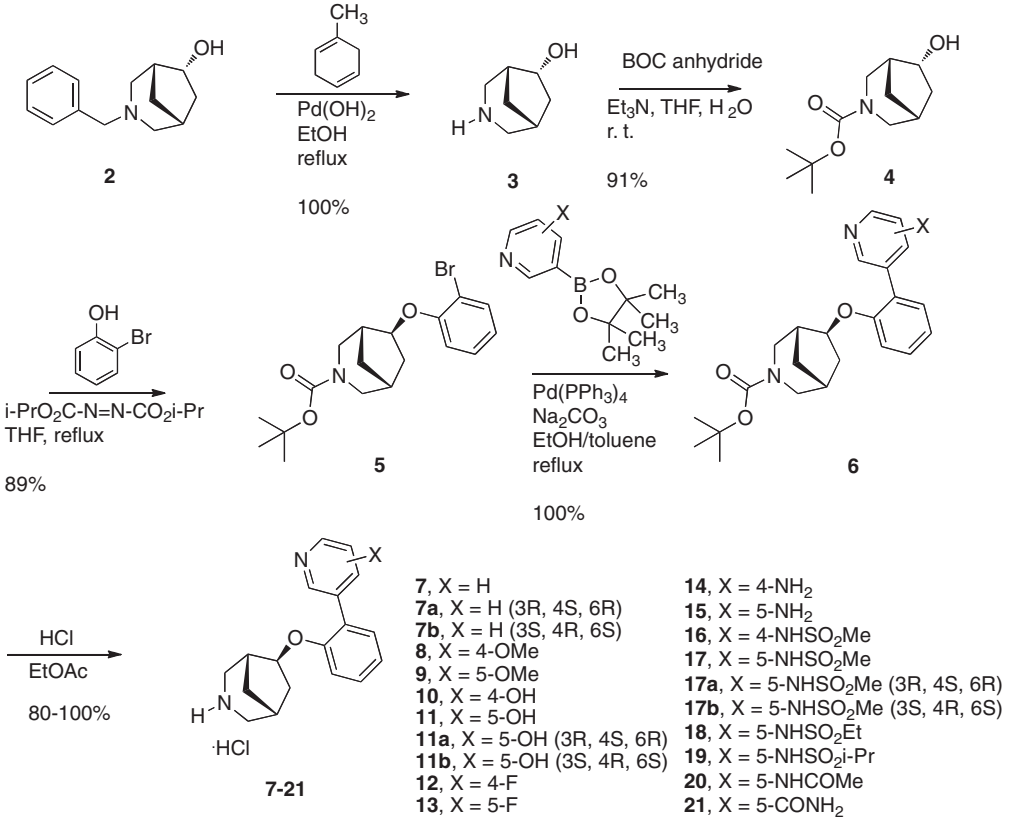
Compound	Binding K_i[a]					EC_{50}[c]	
	Alpha-1	Alpha-3	Alpha-4	Alpha-6	Alpha-7	Alpha-3	Alpha-6
7	NT	1.3 ± 0.33 (*n* = 5)	>1307 ± 194.6 (*n* = 4)	3.8 ± 0.505 (*n* = 5)	NT	57 (61.5%)	102 (32.5%)
7a	1020	1.21 ± 0.306 (*n* = 3)	>832 (*n* = 1)	2.15 ± 0.617 (*n* = 3)	3300	<100 (45%)	53 (35%)
7b	NT	16.9 ± 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**.

The synthesis of the compounds described in this work is summarized in Schemes 1 and 2. In Scheme 1, the known [3.2.1]azabicyclic intermediate **2**, readily prepared from acetoxynorbornene as previously described,[8] was converted to the free amine **3** and then re-protected as the *t*-butyl carbamate, **4**. The following two steps, Mitsunobu displacement[9] with 2-bromophenol to afford **5** and Suzuki coupling[10] with an aryl boronic acid to afford intermediate **6** followed the literature precedent. The known flexibility of these two extensively studied reactions and their adaptability to library chemistry affords a wide range of potential derivatives for SAR follow-up. Standard acid-catalyzed removal of the *t*-BOC group completed the synthesis, affording the target compounds **7**–**21**. In cases with a free OH group in the final product, a benzyl protecting group was used and was removed using palladium-mediated 1-methyl-1,4-cyclohexadiene reduction. Addition of the appropriate sulfonamide or acetamide function followed by deblocking completed the synthesis of compounds **16**–**20**.

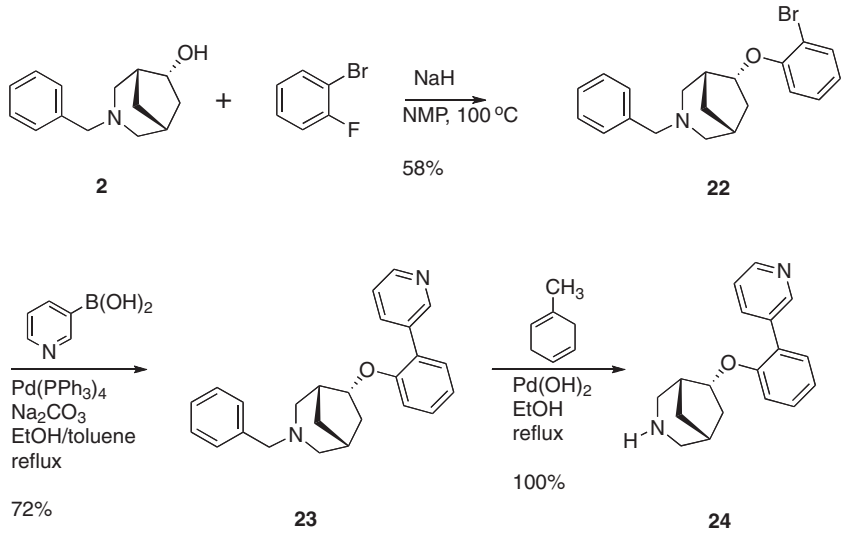
Since the *endo* alcohol **2** is the readily available stereoisomer starting from a mixture of acetoxynorbornene isomers, inversion of the stereochemistry in the Mitsunobu reaction gave exclusively the *exo* isomer of the aryl ether product **5**. X-ray structure determination of crystalline **5a**, the 1*R*,6*S*,5*R* enantiomer of **5**, established this stereochemistry unambiguously (see Supplementary data for details).[11] In order to prepare the corresponding *endo* isomer, nucleophilic aromatic displacement using 2-fluoro bromobenzene afforded the desired intermediate **22** as shown in Scheme 2. The remainder of the synthesis followed Scheme 1.

Table 1 summarizes the in vitro SAR results for compounds 7–**21** and **24**, and includes both binding and functional activity at nAChRs (see Supplementary data for detailed protocol for the assays). Binding displacement assays using tritiated epibatidine followed established literature protocols.[12] The α6/4β4 nAChR data, however, requires additional comment. This receptor is an artificial construct, using the extracellular, ligand-binding, domain of the α6 receptor and the transmembrane and intracellular domains of the α4 receptor, expressed with the β4 subunit, as described previously.[13] Positive controls nicotine and varenicline are included for comparative purposes. Results of functional testing, using a FLIPR (Fluorimetric Imaging Plate Reader) protocol, are given for the α3β4 and α6/4β4 nicotinic receptors only, because functional activity at the other nicotinic receptors was negligible.

Examining the SAR results in Table 1 shows that combining an ether linker from the [3.2.1] azabicyclic system to an ortho-substituted phenyl ring containing a 3-pyridyl ring affords potent binding activity with modest functional agonism as shown in compound **7**. The 3-substituted pyridine ring is reminiscent of the structure of nicotine, but attempts to overlap nicotine with compound **7** in molecular modeling studies were unrewarding. Given that the functional agonism of compound **7** is partial, unlike nicotine, this is not surprising. Finally, the *endo* isomer of compound **7**, compound **24**, afforded only weak activity in vitro.

In an effort to increase functional agonism, we next explored substitution on the pyridine ring. In the course of this effort, we serendipitously discovered that H-bond donating substituents at the 5-position of the pyridine ring have a marked effect on in vitro activity at nicotinic receptors, especially in terms of functional agonism. For example, compound **11** shows potent and nearly full functional agonist activity at both α3β4 and α6/4β4 nicotinic receptors, in contrast to close-in analogues **8**–**10**. This trend continues with compounds **12**–**15**. In addition, as these compounds demonstrate, a H-bond acceptor function is clearly not able to reproduce the activity afforded by a H-bond donor. Compound **17** in particular demonstrates that the strength of the H-bond donor is important, as it is much more potent as a functional α3β4 and α6/4β4 agonist than compound **15**, and very similar to compound **11**, its most similar compound in terms of H-bond donating ability (as an indication, calculated pK_a values for **11** = 8.08 and for **17** = 6.94). A small series of sulfonamides showed that this functionality is well tolerated, and compound **19** in particular demonstrated the most potent functional α3β4 and α6/4β4 agonism in this series. Finally, we examined two isosteres for the H-bond donating OH group, the *N*-acetyl and carboxamido groups, compounds **20** and **21**. These compounds proved surprisingly active, although far less active than compound **17**, and so may actually be serving as modestly effective isosteres in this case.

Table 2 summarizes the physical properties and in vitro ADME properties of selected compounds in this series. While the physical properties for these compounds are generally in the drug-able range, the requirement for a H-bond donor to achieve very potent binding and functional activity limits permeability. For example, compound **7** shows good permeability across MDCK cell membranes (MDCK AB Papp corrected = 30.3, with a value over 10 indicating generally good membrane permeability) and low liability for Pgp-mediated efflux (MDR ratio of 1.75 where a value below 2 indicates limited MDR liability and good brain penetration). Introduction of the H-bond donor functionality, however, markedly



Scheme 2. Preparation of endo diastereomer **24**.

Table 2
Physical properties of selected compounds

Compound	Mol wt	PSA	*c*Log *P*	hMic ER	MDCK Papp AB, corr	MDR ratio	Dofetilide K_i (nM)
7	281	34.1	2.28	0.5	30.3	1.75	2160
7a	281	34.1	2.28	NA	28.7	1.65	NA
9	311	43.4	2.69	NA	24.4	1.76	NA
11	297	54.4	2.57	0.35	4.05	5.84	1580
11a	297	54.4	2.57	<0.27	3.36	5.02	NA
11b	297	54.4	2.57	0.59	2.66	3.5	NA
12	299	34.1	2.5	0.47	13.3	1.26	1780
13	299	34.1	2.5	0.7	10	1.29	NA
17a	374	88.7	1.72	NA	1.17	4.38	NA
17b	374	88.7	1.72	<0.30	0.84	4.65	NA
18	388	88.7	2.24	<0.27	0.44	0.93	NA
19	402	88.7	2.55	<0.27	0.56	1.49	NA

Mol wt—molecular weight, PSA—polar surface area, *c*Log *P*—calculated lipophilicity, hMic ER—extraction ratio for clearance of compound from human microsomes in vitro, MDCK Papp AB, corr—corrected apparent permeability in MDCK cells, given in units of 10^{-6} cm/s, MDR ratio—ratio of the ratio of permeability in the BA direction over the AB direction in MDCK cells transfected with the human MDR gene versus the parent cell line, Dofetilide K_i, nM—binding affinity in nM units for the human ERG-encoded potassium channel, as determined by displacement of radiolabeled dofetilide.

reduces cell membrane permeability and increases MDR liability. For example, introduction of a 5-OH substituent, in compound **11**, affords a corrected MDCK AB Papp value of 4.05 and an MDR ratio of 5.84. For the sulfonamide compound **17a**, the values are 1.17 and 4.38. Given the necessity of the H-bond donor substituent for potent in vitro functional α3β4 and α6/4β4 agonism, the reduction of brain penetration it affords limits the developability of this class of compounds for CNS applications. However, although its CNS penetration is limited, it is nonetheless adequate for it to be used as a reagent for investigating central α3β4 and α6/4β4 nicotinic receptors, as described below.

In vivo testing was carried out in the prepulse inhibition (PPI) and mescaline-induced scratching (MIS) assays. PPI is a measure of sensorimotor gating, a form of information filtering that is deficient in patients with schizophrenia.[14] The MIS reflex is an inducible behavior that is sensitive to antipsychotic agents.[15] Both models are intended to develop pre-clinical evidence of potential therapeutic benefit in schizophrenia, and known antipsychotic drugs work in both assays. But for compounds with an untested mechanism of action in schizophrenia, these models suggest only that the compound acts in the CNS, but do not suggest what receptors may be involved in the response.

Based on its excellent in vitro potency, compound **17a** was selected for further evaluation in vivo. **17a** showed potent inhibition of both the MIS behavioral response in mice (ID_{50} = 0.66 mg/kg sc, 95% CI 0.24–1.64, with a minimal effective dose of 0.1 mg/kg sc) and the PPI model (MED = 3.2 mg/kg sc, where the antipsychotic drug risperidone shows an MED value of 1 mg/kg sc by comparison). Further details of the in vivo pharmacology of compound **17a** will be disclosed separately. In addition, the ADME profile of **17a** regarding permeability and brain penetration, to be published in detail separately, indicates it achieves free brain levels consistent with its in vitro activity at α3β4 and α6/4β4 receptors at doses producing the in vivo effects given above. Finally, given the in vitro profile of **17a**, the results suggest that these in vivo activities are not mediated by either α4β2 or α7 receptors.

In conclusion, compound **17a** represents an opportunity for the study of the pharmacology of α3-containing and α6-containing nAChRs. It shows potent activity in binding and functional assays for both these receptors, with little additional in vitro activity. **17a** was evaluated against a panel of 70 other receptors and in vitro targets, and showed no significant activity at 1.0 μM. In vivo, **17a** shows potent activity in two CNS-mediated animal models that are sensitive to antipsychotic agents, MIS and PPI. Given its potent α3β4 and α6/4β4 agonist activity without significant activity at α4β2 receptors as well as its potent in vivo activity, **17a** may complement selective α4β2 and α7 nicotinic receptor ligands as a useful tool for investigating nicotinic receptor pharmacology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.142.

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