Bioorganic & Medicinal Chemistry Letters 23 (2013) 3927–3934

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel nicotinic acetylcholine receptor agonists containing carbonyl moiety as a hydrogen bond acceptor

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ARTICLE INFO

Article history:
Received 21 February 2013
Revised 14 April 2013
Accepted 22 April 2013
Available online 1 May 2013

Keywords:
3-Azabicyclo[3.3.1]nonane
3-Azabicyclo[3.3.0]octane
3,7-Diazabicyclo[3.3.1]nonane
3,7-Diazabicyclo[3.3.0]octane
Hydrogen bond acceptor
Nicotinic acetylcholine receptor
Novel object recognition
Selective nAChR agonist

ABSTRACT

A novel series of α4β2 nAChR agonists lacking common pyridine or its bioisosteric heterocycle have been disclosed. Essential pharmacophoric elements of the series are exocyclic carbonyl moiety as a hydrogen bond acceptor and secondary amino group within diaza- or azabicyclic scaffold. Computer modeling studies suggested that molecular shape of the ligand also contributes to promotion of agonism. Proof of concept for improving working memory performance in a novel object recognition task has been demonstrated on a representative of the series, 3-propionyl-3,7-diazabicyclo[3.3.0]octane (**34**).

Nicotinic acetylcholine receptors (nAChRs) belong to a family of ligand-gated ion channels activated by neurotransmitters and are members of the Cys-loop superfamily of receptors. At least 16 different genes code for nAChR subunits, which can assemble as pentamers in distinctive combination to form diverse nAChR subtypes. nAChRs, which are extensively distributed throughout the central (CNS) and peripheral (PNS) nervous system, regulate neuronal function by modulating release of several neurotransmitters, including acetylcholine, dopamine, serotonin and GABA. The predominant α4β2 and α7 nAChR subtypes appear to play significant roles in cognitive function, neuronal degeneration, schizophrenia, and pain.[1] Subtype-selective ligands can differentially modify or regulate the activity of corresponding nAChRs. With this in mind, designing and targeting ligands to selectively interact with a distinct nAChR receptor subtype may increase therapeutic precision, with the potential to maximize benefit and minimize adverse effects.

The prevalence of α3β4 nAChRs in the autonomic ganglia supports the hypothesis that activation of this subtype contributes to gastrointestinal and cardiovascular effects of nonselective nicotinic ligands.[2] Despite certain progress, the discovery of potent α4β2 nAChR agonists with substantial functional selectivity over α3β4 nAChRs has been a major challenge. Clinical trials with nAChR agonist **1** (Fig. 1) were discontinued due to a narrow therapeutic index.[3] Compound **2** failed to demonstrate efficacy when tested at low doses in patients with diabetic neuropathic pain.[4] Peripheral and central adverse effects of the partial α4β2 nAChR agonist **3**, a smoking cessation medicine, may also be attributed to suboptimal subtype selectivity.[5]

Most known α4β2 nAChR agonists contain a 3-pyridinyl moiety, which is thought to be a key pharmacophoric element. Despite this belief, recently we described a selective α4β2 nAChR agonist AZD1446 (**4**)[6] which lacks a pyridinyl moiety. We discovered this selective α4β2 nAChR agonist by bioisosteric replacement of the hydrogen bond acceptor pyridine with a furoyl moiety in an diazabicyclo[3.3.0]octane series. To evaluate the effect of the electronic environment on the carbonyl group as a hydrogen bond acceptor, we obtained and characterized several series of amides, carbamates, and ketones (Tables 1–3)[7] based on diazabicyclic and azabicyclic scaffolds.

Commercially available N-Boc protected 3,7-diazabicyclo[3.3.0]octane and 3,7-diazabicyclo[3.3.1]nonane were coupled with corresponding carboxylic acids or methyl chloroformate followed by deprotection to provide amides **15**–**35** and carbamates **36** and **37**. The 3-azabicyclooctane scaffold **7** (Scheme 1) was produced by reaction of allyl iodomalonate **6** and N-Boc-protected allylamine in accordance with an adapted tandem radical annulation/ionic

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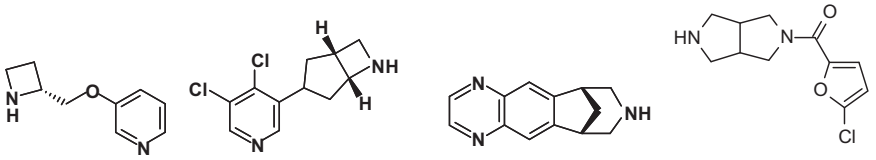
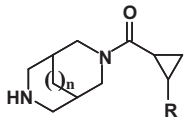
http://dx.doi.org/10.1016/j.bmcl.2013.04.058



tebanicline, 1 **ABT-894, 2** **varenicline, 3** **AZD1446, 4**

Figure 1. Selected α4β2 nAChR ligands.

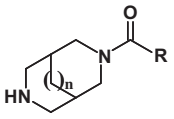
Table 1
Affinity and agonism of cyclopropyl carboxamides



Compd	*n*	R	Configuration	Affinity, K_i			Agonism			
				h α4β2 (nM)	*h* α3β4 (μM)	*h* α7 (μM)	*h* α4β2		*h* α3β4	
							EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
Nicotine				2 ± 0.2	0.4 ± 0.1	3 ± 0.4	3 ± 0.07	100	7 ± 0.1	100
4				30 ± 5	>10	6.7 ± 1.9	4.9 ± 0.7	120 ± 11	70 ± 12	10 ± 3
15	0	H	–	4 ± 1	0.67 ± 0.11	0.84 ± 0.16	0.47 ± 0.08	110 ± 2	4.9 ± 0.3	130 ± 3
16	0	F	1*S*,2*S*	17[a]	0.86[a]	6.9[a]	0.93 ± 0.34	120 ± 8	13[a]	88[a]
17	0	F	1*R*,2*R*	5[a]	0.38[a]	1.4[a]	1.0 ± 0.5	130 ± 15	24[a]	140[a]
18	0	F	1*R*,2*S*	30[a]	0.81[a]	2.7[a]	0.9 ± 0.1	140 ± 6	14 ± 4.6	90 ± 21
19	0	F	1*S*,2*R*	9 ± 3	0.42 ± 0.17	0.99 ± 0.39	0.19 ± 0.05	130 ± 8	8.4 ± 2.5	150 ± 12
20	0	Me	1*R*,2*S*	18[a]	2[a]	4.5[a]	19[a]	100[a]	10[a]	110[a]
21	0	Me	1*S*,2*R*	1[a]	0.28 ± 0.01	0.35[a]	1.2[a]	140[a]	1.4[a]	180[a]
22	0	Me	1*R*,2*R*	4[a]	0.36[a]	1.9[a]	1.7[a]	100[a]	14[a]	110[a]
23	0	Me	1*S*,2*S*	43[a]	13[a]	100[a]	5.6[a]	68[a]	34 ± 1.4	26 ± 2
24	1	H	–	1 ± 0	0.11 ± 0.05	0.02 ± 0.00	0.85 ± 0.14	46 ± 13	1.2 ± 0.3	160 ± 16
25	1	F	1*S*,2*S*	5.2[a]	1.2 ± 0.17	0.3[a]	0.4[a]	11[a]	11[a]	90[a]
26	1	F	1*R*,2*R*	1.4[a]	0.15[a]	0.1[a]	9.2[a]	7[a]	2.1[a]	130[a]
27	1	F	1*S*,2*R*	1[a]	0.036 ± 0.012	0.01[a]	0.43 ± 0.29	77 ± 12	0.39 ± 0.04	130 ± 6
28	1	F	1*R*,2*S*	7.3[a]	0.32[a]	0.4[a]	2.7 ± 1.6	84 ± 24	8.0 ± 4.7	210 ± 61
29	1	Me	1*R*,2*R*	1[a]	0.1[a]	0.03[a]	12[a]	23[a]	1.6[a]	120[a]
30	1	Me	1*S*,2*S*	28[a]	0.6[a]	0.3[a]	10[a]	21[a]	8.3[a]	89[a]
31	1	Me	1*S*,2*R*	0.2[a]	0.01[a]	0.005[a]	1.9[a]	5[a]	0.08[a]	160[a]
32	1	Me	1*R*,2*S*	2.9[a]	0.1[a]	0.1[a]	100[a]	0.5[a]	0.3[a]	140[a]

[a] *n* = 1.

Table 2
Affinity and agonism of aliphatic amides and carbamates



Compd	*n*	R	Affinity, K_i			Agonism			
			h α4β2 (nM)	*h* α3β4 (μM)	*h* α7 (μM)	*h* α4β2		*h* α3β4	
						EC_{50} (μM)	E_{max} (%)	EC_{50} (μM)	E_{max} (%)
33	0	Me	38[a]	14[a]	ND[b]	2.6[a]	110[a]	23[a]	36[a]
34	0	Et	12[a]	2.1[a]	4[a]	1.3 ± 0.4	120 ± 9	18 ± 2.5	130 ± 5
35	1	Me	20[a]	5.5[a]	3.3[a]	9.9 ± 0.6	34 ± 6	13[a]	110[a]
36	1	Et	8 ± 2	20[a]	1.6[a]	1.9 ± 0.1	83 ± 7	5.9 ± 4.5	130 ± 9
37	1	OMe	20[a]	ND	ND	5.2[a]	65[a]	ND	ND
38	0	OMe	23[a]	14[a]	ND	ND	ND	16 ± 6	85±11

[a] *n* = 1.
[b] ND = not determined.

cyclization sequence.[8] Halogen atom transfer annulation was performed in situ by an addition of triethylamine after iodine abstraction from **6** under nonreducing radical generating conditions and intermolecular addition to the acceptor olefin. Decarboxylation of **7** in refluxing hydrochloric acid followed by protection of the amino group provided 7-carboxy-3-azabicyclooctane **8** as a mixture of *cis*- and *trans*-isomers. Geometrical isomerism of the 7-substituted 3-azabicyclooctane is driven by a different orientation of the substituent and the fused pyrrolidine ring. Amino acid **8** was applied for the synthesis of ketones **39** and 4**0** via Weinreb amide **9**,[9]