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QM-polarized ligand docking accurately predicts the trend in binding affinity of a series of arylmethylene quinuclidine-like derivatives at the α4β2 and α3β4 nicotinic acetylcholine receptors (nAChRs)

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ABSTRACT

Compounds containing a quinuclidine scaffold are promising drug candidates for pharmacological management of the central nervous system (CNS) pathologies implicating nAChRs. We have carried out binding affinity and in-silico docking studies of arylmethylene quinuclidine-like derivatives at the α4β2 receptor using in-vitro receptor binding assay and comparative modeling, respectively. We found that introducing a hydrogen-bond acceptor into the 3-benzylidene quinuclidine derivative resulted in a 266-fold increase in binding affinity and confers agonism properties. By contrast, addition of a phenyl group to 3-benzylidene quinuclidine derivative only results in an 18-fold increase in binding affinity, without conferring agonism. We also found that docking into the orthosteric binding site of the α4β2 nAChR is consistent with the fact that the basic nitrogen atom donates a hydrogen-bond to the carbonyl group of the highly conserved Trp-149, as initially observed by Dougherty and co-workers.[1] The experimentally-observed trend in binding affinity at both α4β2 and α3β4 nAChRs was accurately and independently confirmed by quantum mechanics (QM)-polarized docking. The reduction in binding affinity to the α3β4 subtype primarily results from a dampening of both coulombic and cation–π interactions.

nAChRs are pentameric membrane proteins that are members of the Cys-loop ligand-gated ion channel superfamily. These receptors have been validated as drug targets for several CNS indications. Examples include but are not limited to schizophrenia, Parkinson's disease, Alzheimer's disease, major depression and drug addiction.[2–4]

Sixteen human genes encode for nAChR subunits, which can form homo- or hetero-pentamers with ubiquitous localization and differential expression in the brain and throughout the human body. Receptors composed of α4 and β2 subunits (the α4β2* subtypes) and those containing α7 subunits (the α7* subtypes) represent the predominant populations of neuronal nAChRs in the CNS. It should be noted that the α4β2*subtypes comprise the high sensitivity (HS) and the low sensitivity (LS) isoforms resulting from different stoichiometry of α4 and β2 subunits, and can also contain the structural α5, subunits as the fifth partners or the α6β3 interface, thus creating expanded structural diversity. Although it was long held that α7 subunits formed exclusively a homopentameric structure, some evidence for functional co-expression with β2 has been reported.[5,6] In addition, receptors containing various combinations of α2, α3, α5, α6, β3 or β4 subunits are also found in discrete CNS regions and very likely serve important physiological functions. In addition to discrete brain regions [e.g., nucleus tractus solitaris (NTS), the interpeduncular nucleus (IPN)], the α3β4* is expressed and may participate in the function of the hypothalamo-pituitary axis than can contribute to peripheral physiological manifestations (e.g., emesis). In autonomic and sensory ganglia and in the adrenal gland, nAChRs containing the α3 subunits in association with β2 and/or β4 subunits are predominant and mediate ganglionic transmission in sympathetic and parasympathetic systems. Therefore, it is important to minimize interaction with receptors mediating gastrointestinal and cardiovascular side effects (e.g., α3β4* receptors) and maximize the interactions resulting in beneficial effects in conditions such as Alzheimer's, Parkinson's disease, or schizophrenia (e.g., α4β2* and/or α7*).

Chantix, also known as varenicline, a drug primarily targeting human α4β2 and α3β4 nAChRs is marketed by Pfizer for smoking cessation.[7] EVP-6124, a novel α7 nAChR agonist discovered by

Abbreviations: ACHBP, acetylcholine-binding protein; Ach, acetylcholine; CNS, central nervous system; MEC, minimum-effective concentration; nAChR, nicotinic acetylcholine receptor; NIC, nicotine; Pdb, protein databank; rmsd, root-mean-squared-deviation; ROC, receiver operating characteristic curve; EF, enrichment factor; SP, standard precision; XP, extra precision; QPLD, quantum mechanics polarized ligand docking; QM, quantum-mechanics.

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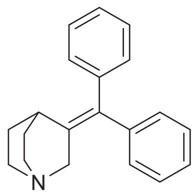

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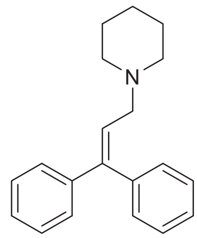

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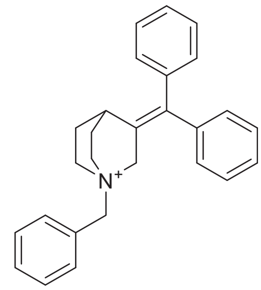

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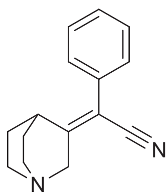

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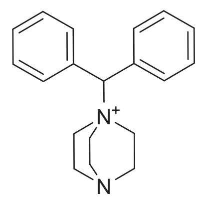

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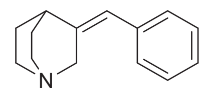

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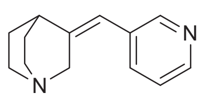

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Figure 1. 2D structures of the arylmethylene quinuclidine analogs.

Table 1
Binding affinity (K_i) of arylmethylene quinuclidine derivatives at human $\alpha 4\beta 2$ and $\alpha 3\beta 4$ nAChRs subtypes, respectively. Data are expressed as (mean ± SEM; with $n \geqslant 3$). $\alpha 3\beta 4$ Binding data were taken from Kombo et al.[25]

Compound	$\alpha 4\beta 2$ K_i (μM)	$\alpha 3\beta 4$ K_i (μM)
1	0.09 ± 0.01	1.50 ± 0.10
2	0.16 ± 0.06	2.20 ± 0.20
3	7.00 ± 3.20	2.30 ± 0.60
4	1.10 ± 0.40	2.10
5	>10	8.50 ± 1.60
6	1.60 ± 0.50	2.10 ± 0.50
7	0.006 ± 0.003	1.60 ± 0.50

Table 2
Efficacy and potency of arylmethylene quinuclidine derivatives to evoke functional response (Ca^{2+}-influx) in human SH-EP1-$\alpha 4\beta 2$ cells and human CHO-$\alpha 3\beta 4$ cells, respectively. Data are expressed as mean ± SEM; ($n \geqslant 3$). $\alpha 4\beta 2$ functional data were taken from Kombo et al.[25]

Compound	SH-EP1-$\alpha 4\beta 2$ cells		CHO-$\alpha 3\beta 4$ cells	
	E_{max} (% Nic)	EC_{50} (μM)	E_{max} (% Nic)	EC_{50} (μM)
1	6.00 ± 1.00	ND	14.00 ± 3.00	>10
2	9.00 ± 6.00	ND	31.00 ± 2.00	>10
3	<5	ND	10.00 ± 2.00	9.00 ± 4.00
4	<5	ND	<10	ND
5	<5	ND	<10	ND
6	11.00 ± 4.00	>10	25.00 ± 9.00	3.00 ± 1.00
7	18.00 ± 6.00	>10	31.00 ± 5.00	2.00 ± 0.30

EnVivo Pharmaceuticals, is currently advancing in clinical trials for cognitive disorders in schizophrenia.[8] Several candidate drugs developed by Targacept are in advanced clinical trials. Examples include a novel selective $\alpha 7$ nAChR agonist TC-5619 for schizophrenia, a novel selective $\alpha 4\beta 2$ nAChR agonist AZD-3480 for Alzheimer's disease, and a noncompetitive channel modulator TC-5214 for overactive bladder, thus illustrating the broad potential for nAChR-targeting therapeutics in largely unmet medical needs.

The three-dimensional structure of the acetylcholine-binding protein (AChBP), a water-soluble homolog of nAChRs, has been extensively characterized experimentally.[9–11] It has been widely used as a template to build homology models for the extracellular ligand-binding domain of nAChRs.[12–17] Furthermore, experimental physical chemistry and mutagenesis techniques have been extensively used to gain more insight into ligand–nAChR interactions.[18–21] In particular, Xiu et al.[1] have shown that binding of nicotine to brain $\alpha 4\beta 2$ receptors requires a strong cation–π interaction involving the ligand basic nitrogen atom, and a hydrogen-bond between the basic nitrogen and the carbonyl oxygen atom of a highly conserved key Trp residue.[19]

Recently, we have shown that the Glide docking software (Schrodinger, inc., Portland, Oregon) accurately reproduces the experimentally-observed binding mode of benzylidene anabaseine analogs into AChBP[13] that was experimentally-observed by Hibbs et al.[22] We have then been encouraged to extend our studies by docking spirodiazepine and spiroimidazoline quinuclidine analogs into rat $\alpha 7$ homology models.[13,14] Furthermore, we have used Glide to rationalize the binding affinity of the marine toxins