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2-(Arylmethyl)-3-substituted quinuclidines as selective α7 nicotinic receptor ligands

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Abstract—A series of 2-(arylmethyl)-3-substituted quinuclidines was developed as α7 neuronal nicotinic acetylcholine receptor (nAChR) agonists based on a putative pharmacophore model. The series is highly selective for the α7 over other nAChRs (e.g., the α4β2 of the CNS, and the muscle and ganglionic subtypes) and is functionally tunable at α7. One member of the series, (+)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)benzo[*b*]furan-2-carboxamide (+)-**8l**), has potent agonistic activity for the α7 nAChR (EC_{50} = 33 nM, I_{max} = 1.0), at concentrations below those that result in desensitization.

The widely distributed and abundant, neuronal acetylcholine nicotinic receptors (nAChRs) are involved in a number of processes, including cognition, neuroprotection, sensory gating, inflammation, and nociceptive transmission. Thus, nAChRs are potential therapeutic targets for a variety of conditions and disorders, such as schizophrenia, chronic and neurophathic pain, neurodegenerative diseases, and cognitive deficits, many of which represent major unmet medical needs.[1] Nicotinic receptors in the CNS exist as several subtypes, the most common of which are the α4β2 and α7 subtypes. To create an effective nAChR-based R&D strategy, it is important to design ligands that selectively interact with specific receptor subtypes, thus maximizing the therapeutic effect and minimizing potentially adverse side effects. Examples of such selective ligands include the metanicotine and diazaspirocyclic classes identified by Targacept.[2] Recently, the full agonist AR-R 17779[3] (3*S*)-spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin]-2′-one, E_{max} = 96%, EC_{50} = 21 μM)[10] was shown to improve learning and memory in rats by activation of the α7 subtype.[3] In this paper, we describe 2-(arylmethyl)-3-substituted quinuclidines, a highly selective class of agonists at the α7 subtype.[15]

The synthesis of 2-(arylmethyl)-3-substituted quinuclidines is shown in Scheme 1. The key intermediate 2-(arylmethyl)quinuclidin-2-one was prepared by aldol condensation of quinuclidin-3-one (**1**) with an aromatic aldehyde, to afford the enone **2**, followed by catalytic hydrogenation. Further reduction of the ketone **3** with aluminum isopropoxide resulted in predominantly one diastereomer, *cis* alcohol **4**, presumably by selective hydride transfer to the least hindered face of the carbonyl.[12] The *cis* racemate was resolved by condensation with (*S*)-2-methoxy-2-phenylacetic acid to yield a pair of diastereomeric esters, which was separated by preparative HPLC and hydrolyzed into optically pure alcohols. The carbonyl moiety of ketone **3** was converted into amino group by reductive amination in the presence of a catalytic amount of zinc chloride.[13] Major *cis* amine **6** was separated from minor *trans*-diastereomer by HPLC. The racemic amine was then resolved by fractional crystallization of its *O*,*O*′-bis-*p*-toluoyltartrate salt. Addition of isocyanate to alcohol **4** or amine **6** produced carbamate **5** or urea **7**, respectively. Amine **6** was acylated to afford amide **8**[17] and treated with sulfonyl chloride to obtain sulfonamide **9**.

Quinuclidine is a well established pharmacophoric element, exemplified in both naturally occurring (e.g., quinine) and synthetic (e.g., azasetrone, benzoclidine) drugs. Its basic nitrogen, occupying a bridgehead position within an azabicyclic system, allocates maximal electrostatic interaction combined with minimal steric

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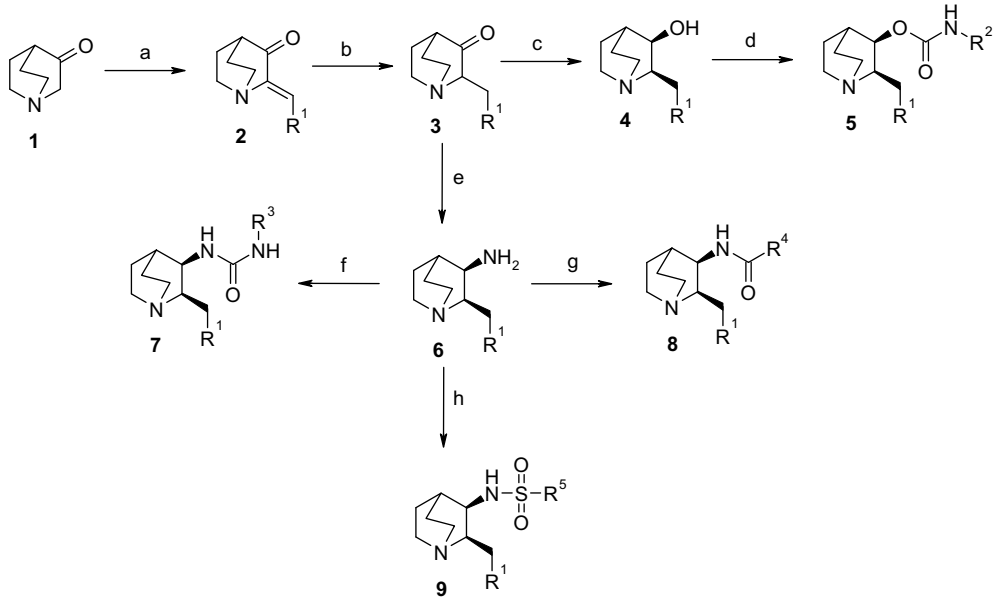
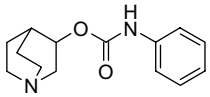
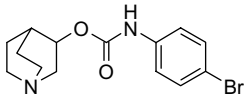
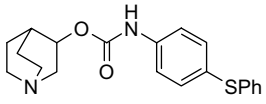
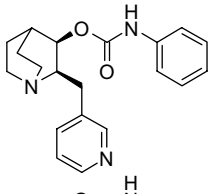
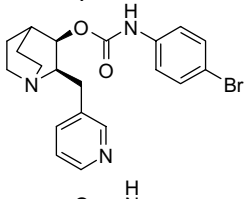
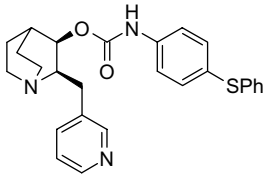


Scheme 1. (a) R^1CHO, KOH; (b) H_2, Pd/C; (c) $Al(O\text{-}i\text{-}Pr)_3$; (d) R^2NCO; (e) HCO_2NH_4, $ZnCl_2$, $NaCNBH_3$; (f) R^3NCO; (g) R^4CO_2H, Et_3N, $(PhO)_2P(O)Cl$; (h) R^5SO_2Cl, Et_3N.

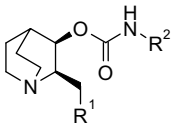
demand. Among the quinuclidine derivatives designed to interact with nAChRs are 2-(pyridylmethyl)quinuclidines[4] and 3-substituted 1-azabicyclo[2.2.2]octanes.[14] The former are moderately selective for α4β2 receptors (but have activity at α7 and peripheral sites as well), and the latter, especially 3-(*N*-arylcarbamoyl)quinuclidines,[5] interact with α7 nicotinic,[6] as well as muscarinic[7] and 5-HT_3[8] receptors. To further define pharmacophoric elements of the α7 binding site, we initiated virtual and synthetic diversification around a combination of 2-position and 3-position substitutions of the quinuclidine scaffold. The addition of substituents in position 3 of 2-(pyridylmethyl)quinuclidine produced compounds with decreased affinity for the α4β2 subtype and, in some cases, increased affinity for the α7. This effort relatively quickly revealed the presence, in certain derivatives, of three pharmacophoric elements: the cationic site (the quinuclidine nitrogen), a hydrogen bond acceptor at the 3-position, and another hydrogen bond acceptor at the 2-position (the pyridine ring). Evidence for this latter interaction can be seen by comparing derivatives with and without the pyridylmethyl group in position 2 (Table 1) and from comparison of the effect of various 2-position substituents within a 3-substituent series (e.g., the carbamates in Table 2). From Table 2, it is clear that, in position 2 of the quinuclidine, heteroarylmethyl groups are favored, over benzyl, and that steric constraints restrict substitution on the heteroaryl (pyridine) ring. The pharmacophoric element in position 3 was most amenable to diversification, resulting in the generation of four classes of ligands: carbamates (Table 3), ureas (Table 4), amides (Table 5), and sulfonamides (Table 6).[16] *cis*-Configuration is favorable for binding to the receptor, for example, *trans*-**5a** exhibits affinity with $K_i = 405$ nM. Within the 3-position substituents, comparison of aliphatic and aromatic (or heteroaromatic) groups (i.e., R^2, R^3, R^4, R^5) suggests that π-interaction may play a significant role in increasing affinity.

Table 1. Effect of 2-(pyridine-3-yl)methyl substituent on affinity

Compounds	α7 Affinity K_i (nM)
	120
	40
	53
	7
	5
	9

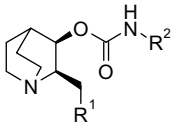
Many of synthesized compounds exhibited high affinity to the α7 nicotinic receptor subtype, as demonstrated by their inhibition of radiolabeled ^{3}H-methyllycaconitine binding to rat brain hippocampus receptors,[19] with

Table 2. Optimization of 2-arylmethyl moiety



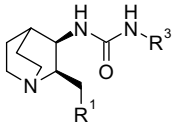
Compounds	R^1	R^2	α7 affinity K_i (nM)
5a	Pyridin-3-yl	4-Bromophenyl	5 ± 0.5
5b	2-Methoxy-pyridin-5-yl	4-Bromophenyl	29 ± 8
5c	2-Phenoxy-pyridin-5-yl	4-Bromophenyl	>10,000
5d	3-Methoxy-pyridin-5-yl	4-Bromophenyl	144
5e	3-Isopropoxy-pyridine-5-yl	4-Bromophenyl	7016
5f	Pyridin-2-yl	4-Bromophenyl	>10,000
5g	Pyrimidin-5-yl	4-Bromophenyl	40
5h	Quinolin-3-yl	4-Bromophenyl	10,000
5i	Phenyl	4-Bromophenyl	838
5j	4-Methoxyphenyl	4-Bromophenyl	>10,000
5k	4-(Dimethyl-amino)phenyl	4-Bromophenyl	1193 ± 74
5l	4-Fluorophenyl	4-Bromophenyl	263
5m	4-(Methylsulfonyl)-phenyl	4-Bromophenyl	6778
5n	Imidazol-1-yl	4-Bromophenyl	10
5o	Thien-3-yl	4-Bromophenyl	534
5p	Furan-2-yl	4-Bromophenyl	234
5q	Benzo[*b*]furan-2-yl	4-Bromophenyl	8388
(−)-Nicotine			1748 ± 597
Methyllycaconitine			2.3 ± 0.2

Table 3. Carbamates



Compounds	R^1	R^2	α7 Affinity K_i (nM)
5a	Pyridin-3-yl	4-Bromophenyl	5
5r	Pyridin-3-yl	4-Fluorophenyl	6
5s	Pyridin-3-yl	4-Methoxyphenyl	5
5t	Pyridin-3-yl	Phenyl	7
5u	Pyridin-3-yl	4-Phenoxyphenyl	50
5v	Pyridin-3-yl	4-Biphenyl	500
5w	Pyridin-3-yl	Benzyl	670
5x	Pyridin-3-yl	2-Phenylcyclopropyl	103

Table 4. Ureas

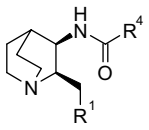


Compounds	R^1	R^3	α7 Affinity K_i (nM)
7a	Pyridin-3-yl	4-Bromophenyl	9
7b	Pyridin-3-yl	3-Bromophenyl	52
7c	Pyridin-3-yl	2-Methoxyphenyl	30
7d	Pyridin-3-yl	3-Methoxyphenyl	43
7e	Pyridin-3-yl	4-Methoxyphenyl	37
7f	Pyridin-3-yl	2,4-Dimethoxyphenyl	31
7g	Pyridin-3-yl	4-(Methylthio)phenyl	6
7h	Pyridin-3-yl	4-Fluorophenyl	74
7I	Pyridin-3-yl	3-Fluorophenyl	6
7j	Pyridin-3-yl	3,4-Dichlorophenyl	34
7k	Pyridin-3-yl	3-(Trifluoromethyl)-phenyl	91 ± 13
7l	Pyridin-3-yl	3-Cyanophenyl	170
7m	Pyridin-3-yl	4-(Dimethylamino)-phenyl	38
7n	Pyridin-3-yl	4-Phenoxyphenyl	16
7o	Pyridin-3-yl	4-Biphenyl	424 ± 105
7p	Pyridin-3-yl	Phenyl	16
7q	Pyridin-3-yl	4-Bromobenzyl	274 ± 131
7r	Pyridin-3-yl	2-Phenylcyclopropyl	104

equilibrium constant (K_i) values near or below 1 nM.[18] High throughput screening indicates that none of the compounds bound to α4β2 receptors[20] with any significant affinity (K_i values > 10 μM). Compounds show little or no evidence of agonist activity at concentration 100 μM in functional assays of muscle-type receptors (α1β1γδ subtype in human TE671/RD clonal cells), or ganglion-type receptors (α3β4 subtype in the Shooter subclone of rat pheochromocytoma PC12cells and in human SHSY-5Y clonal cells), generating only 1–12% (human muscle), 1–19% (rat ganglion), and 1–15% (human ganglion) of nicotine's response at these subtypes. These data indicate selectivity for CNS over PNS nAChRs. Since arylcarbamoyl quinuclidines had been described in the literature[8] as exhibiting muscarinic activity, representative compounds (**5a**,**s**,**t**, **8f**,**l**)) were evaluated for their ability to inhibit [^{3}H]-quinuclidinyl benzilate binding at muscarinic sites in the human clonal line TE671/RD.[21] None of the compounds was able to inhibit [^{3}H]-quinuclidinyl benzilate binding, indicating that these compounds do not bind to human M3 receptors.

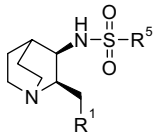
The α7 nAChR subtype is particularly susceptible to concentration dependent and rapid desensitization,

Table 5. Amides



Compounds	R^1	R^4	α7 Affinity K_i (nM)
8a	Pyridin-3-yl	4-Bromophenyl	7
8b	Pyridin-3-yl	3-Bromophenyl	64
8c	Pyridin-3-yl	Phenyl	52
8d	Pyridin-3-yl	4-Fluorophenyl	12
8e	Pyridin-3-yl	4-(Dimethylamino)-phenyl	134
8f	Pyridin-3-yl	4-(Phenylthio)phenyl	9
8g	Pyridin-3-yl	1-Methylpyrrol-2-yl	155
8h	Pyridin-3-yl	Thien-3-yl	790
8i	Pyridin-3-yl	5-Bromothien-2-yl	0.4
8j	Pyridin-3-yl	5-(Pyridin-2-yl)-thien-2-yl	0.7
8k	Pyridin-3-yl	5-Iodothien-2-yl	0.12 ± 0.03
8l	Pyridin-3-yl	Benzo[b]furan-2-yl	1
8m	Pyridin-3-yl	Indol-3-yl	8
8n	Pyridin-3-yl	1-Methylindol-3-yl	521
8o	Pyridin-3-yl	1-Hydroxynapht-2-yl	1
8p	Pyridin-3-yl	Styryl	0.6
8q	Pyridin-3-yl	α-Methylstyryl	5
8r	Pyridin-3-yl	β-Methylstyryl	87

Table 6. Sulfonamides



Compounds	R^1	R^5	α7 Affinity K_i (nM)
9a	Pyridin-3-yl	4-Bromophenyl	8088
9b	Pyridin-3-yl	Phenyl	418
9c	Pyridin-3-yl	4-Methoxyphenyl	8919
9d	Pyridin-3-yl	4-Acetamidophenyl	146
9e	Pyridin-3-yl	Benzyl	8839

which creates a special challenge for the pharmacological characterization of this receptor.[9] Potency and intrinsic activity values for carbamate (+)-**5s** (EC_{50} = 300 nM; I_{max} = 0.19) and amide (+)-**8l** (EC_{50} = 33 nM; I_{max} = 1.0) were determined by measuring current activation in *Xenopus* oocytes expressing rat nicotinic receptors. While carbamate (+)-**5s** is a partial agonist, amide (+)-**8l** is a potent full agonist for the α7 receptor, which significantly exceeds the potency of the known full agonist AR-R17779.[10] Higher concentrations of (+)-**8l** are required to produce residual inhibition (desensitization) than are required to activate the receptor. Since the ratio of IC_{50} to EC_{50} is approximately 6, an optimal dose might be found to exhibit in vivo efficacy of the α7 nicotinic full agonist. The nature of substituents in positions 2 and 3 of the described quinuclidine derivatives has an effect on the degree of both activation and desensitization of the receptor. Variation of diverse structural fragments allows the adjustment of functional activity and desensitization to optional levels.[11]

In summary, highly potent and selective ligands for the α7 subtype have been obtained by modification of 2-(pyridylmethyl)quinuclidine. Three key pharmacophoric elements have been identified: a basic nitrogen, a hydrogen-bond-accepting moiety and second polar region involved in interaction with the receptor via H-bonding. Electrophysiological data substantiate the therapeutic potential of amide (+)-**8l**.

Acknowledgements

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16. Affinity data are given for racemic compounds; some of compounds were resolved, however, absolute configuration has not been determined, for example, (+)-**8l** (K_i = 0.3 nM) and (−)-**8l** (K_i = 41.8 nM).
17. 1H NMR (300 MHz, CD_3OD): *cis*-**8l**, 1.98–2.42 (m, 5H), 3.40–3.87 (m, 6H), 4.32 (m, 1H), 4.55 (dd, 1H), 7.38 (m, 1H), 7.52 (m, 2H), 7.62 (m, 1H), 7.78 (d, 1H), 7.99 (m, 1H), 8.65 (d, 1H), 8.87 (d, 1H), 9.17 (s, 1H); *trans*-**8l**, 1.92–2.48 (m, 5H), 3.20–3.58 (m, 6H), 3.81 (m, 1H), 4.54 (dd, 1H), 7.39 (m, 1H), 7.55 (m, 3H), 7.72 (m, 2H), 8.00 (d, 1H), 8.47 (d, 1H), 8.6 (s, 1H).
18. K_i Values were determined from one to three competitive inhibition curves for each compound. Seven to eleven concentrations of each compound were utilized to define each inhibition curve with triplicate samples at each concentration. Where multiple competitive inhibition curves were available, SEM has been calculated and provided.
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