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Synthesis and SAR studies of 1,4-diazabicyclo[3.2.2]nonane phenyl carbamates – subtype selective, high affinity α7 nicotinic acetylcholine receptor agonists

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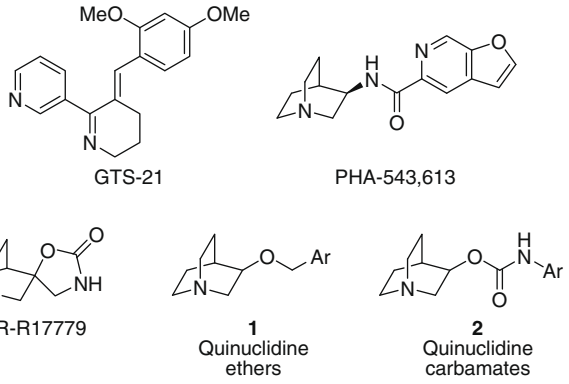
ABSTRACT

The synthesis and SAR studies about the bicyclic amine, carbamate linker and aromatic ring of a 1,4-diazabicyclo[3.2.2]nonane phenyl carbamate series of α7 nAChR agonists is described. The development of the medicinal chemistry strategy and SAR which led to the identification of **5** and **7aa** as subtype selective, high affinity α7 agonists as excellent leads for further evaluation is discussed, along with key physicochemical and pharmacokinetic data highlighting their lead potential.

Homomeric α7 nicotinic acetylcholine receptor (nAChR) agonists have been implicated as potential treatments for a variety of attention and cognitive disorders and could be used to treat the cognitive impairment associated with schizophrenia.[1,2] Interest in α7 nAChR agonists as a target has greatly expanded over the past decade, with a focus on identifying new ligands with improved selectivity over other nicotinic receptor subtypes.[1d] Most of the ligands described in the primary literature have evolved around the quinuclidine core structure and include quinuclidine amides (PHA-543,613),[3] spirooxazolidinones (AR-R17779),[4] as well as quinuclidine ethers[5] and quinuclidine carbamates (**1** and **2**, respectively).[6] However, despite the richness in chemical matter, there is still a need for novel α7 nAChR agonists as it has been reported that two of Pfizer's Phase I clinical candidates in the quinuclidine amide series (PHA-543,613 and PHA-568,487)[7] were discontinued due to cardiovascular findings.[8]

When we initiated efforts targeting novel α7 nAChR ligands, quinuclidine carbamate **3** was identified from our compound file (α7 K_i = 167 nM, 90% agonist activity (ag), Fig. 1).[9,10] In the interest of identifying novel chemical matter we utilized the following design criteria: (a) reverse the orientation of the carbamate to give **4** then (b) incorporate the nitrogen of the carbamate of **4** into a bicyclic ring system. These two design concepts were greatly enabled by our previous use of 1,4-diazabicyclo[3.2.2]nonane in a quinolone antibiotic program[11] and thus allowed us to quickly identify 1,4-diazabicyclo[3.2.2]nonane-(4-bromo)-phenyl carbamate **5** (α7 K_i = 38 nM, 158% ag) as a lead structure.[12,13] Herein we describe structure–activity relationship (SAR) studies about the diamine template, the carbamate linker and the aromatic ring. The results of these studies further elucidated the key aspects of the α7 nAChR pharmacophore and resulted in the identification of a selective, high affinity α7 nAChR agonist **7aa** with good pharmacokinetic properties and low hERG liability as an excellent tool with which to explore α7 pharmacology.



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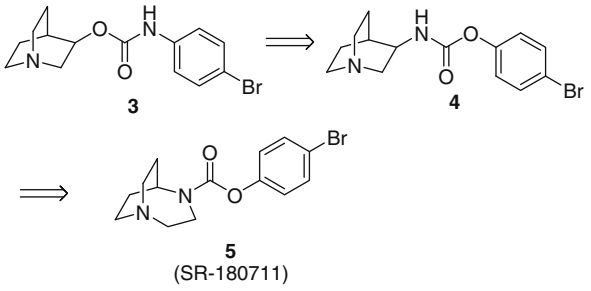
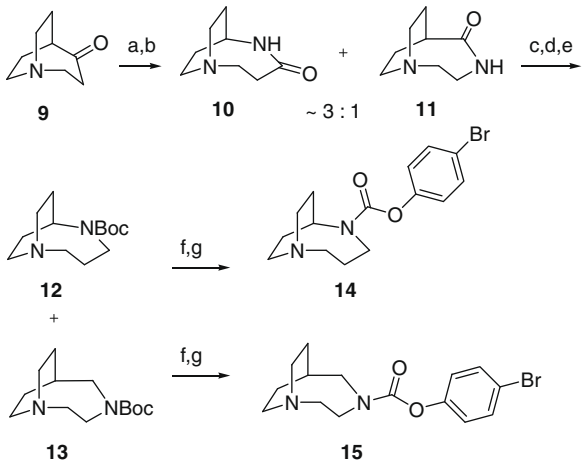


Figure 1. Approach used to discover the 1,4-diazabicyclo[3.2.2]nonane carbamate series.

The synthesis of 1,4-diazabicyclo[3.2.2]nonane carbamates is shown in Scheme 1. 1,4-Diazabicyclo[3.2.2]nonane[14] **6** was reacted with arylchloroformate in the presence of DMAP and pyridine to produce the desired carbamates **7**, typically in 60–70% yield. Many commercially available arylchloroformates were utilized to investigate the SAR in this series. In the instances where they were not available, the corresponding phenol was easily converted to the chloroformate by treatment with phosgene or triphosgene under standard reaction conditions. Expansion of the SAR in the *para*-position of the aromatic ring was accomplished starting with the 4-bromophenyl carbamate analog **5** and converting it to the pinacolato boronic ester **8** under Miyaura conditions in 49–64% yield.[15] The resulting aryl boronic ester could then be elaborated to biaryl analogs (**7o** and **s**–**u**) using standard Suzuki coupling conditions with the appropriate aryl bromide in 49–72% yield.[16]

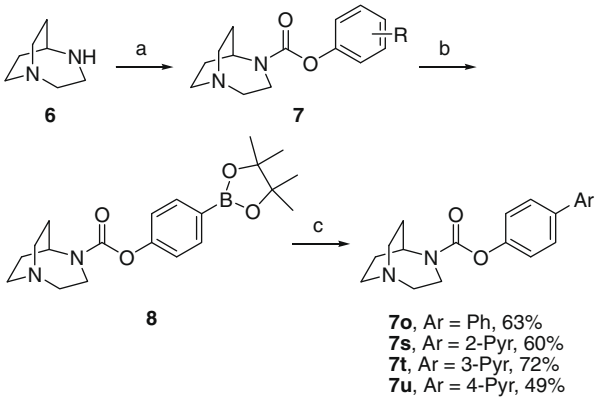
Synthesis of two novel diazabicyclic analogs, 1,5-diazabicyclo[4.2.2]decane carbamate **14** and 1,4-diazabicyclo[4.2.2]decane carbamate **15** are described in Scheme 2. 1-Aza-bicyclo[3.2.2]nonan-4-one[17] **9** was reacted with hydroxylamine and the resulting mixture of oxime isomers underwent Beckman rearrangement upon treatment with sulfuric acid (20% oleum) to give amides **10**/**11** in 53% yield over two steps, in ca. 3:1 ratio as determined by ^{13}C NMR peak heights. The mixture of amides was reduced with lithium aluminum hydride resulting in a 2.5:1 ratio as an inseparable mixture of bicyclic amines as determined by GC/MS. At this point, the major isomer was assigned as the isomer with nitrogen adjacent to the bridgehead.[18] Protection of the crude mixture of amines as their corresponding *tert*-butylcarbamates allowed for separation of the isomers via chromatography to afford **12** in 50% isolated yield and **13** in 14% yield (both over two steps). Removal of the Boc group using HCl in methanol followed by coupling of the resulting corresponding diamine with 4-bromophenyl chloroformate gave **14** and **15** in 54% and 56% yield, respectively, over two steps.



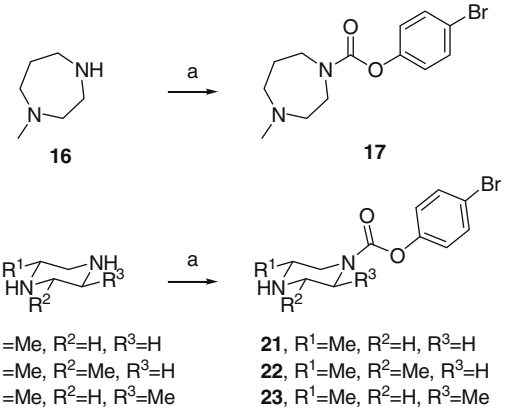
Scheme 2. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, Na_2CO_3, MeOH, 60 °C; (b) H_2SO_4, 100 °C, 53% for 2 steps; (c) $LiAlH_4$, THF, rt to ↑↓; (d) Boc_2O, NaOH, THF, H_2O; (e) chromatography, 50% **12**, 14% **13** (2 steps); (f) 1 M HCl, MeOH; (g) 4-bromophenyl chloroformate, DMAP, pyridine, CH_2Cl_2, 54% **14**, 56% **15** (2 steps).

Homopiperazine and piperazine analogs **17**, and **21**–**23** were prepared utilizing the same conditions as described to prepare carbamate analogs **7** (Scheme 3). Hence, 1-(4-bromophenyl)-4-methyl-1,4-diazepane-1-carboxylate **17** was prepared in 82% yield from methyl homopiperazine **16**. Piperazine analogs **21**–**23** were prepared from **18** to **20** in 57%, 20%, and 45% yield, respectively.

In vitro characterization data of the SAR studies about the bicyclic ring of **7** are described in Table 1. The modification of the bicyclic ring system from the 1,4-diazabicyclo[3.2.2]nonane system to the 1,5-diazabicyclo[4.2.2]decane system resulted in a 10-fold loss in α7 nAChR potency along with a substantial decrease in agonist activity (**5** vs **14**). Replacing the 1,4-diazabicyclo[3.2.2]nonane system with the 1,4-diazabicyclo[4.2.2]decane systems resulted in a 20-fold loss in potency (**5** vs **15**). Attempts to replace the 1,4-diazabicyclo[3.2.2]nonane ring system with diazamonocyclic ring systems resulted in complete loss of α7 nAChR binding affinity and functional activity (**5** vs **17** and **21**–**23**). This SAR highlights the importance of the direction of the nitrogen lone pair interaction with the α7 nAChR, as well as the relative position of this nitrogen lone pair to the aryl portion of the molecule in order to maintain good potency and functional activity.[19]



Scheme 1. Reagents and conditions: (a) aryl chloroformate, DMAP, pyridine, CH_2Cl_2, 60–70% (b) R = 4-Br, bis(pinacolato)diboron, $PdCl_2(dppf){\cdot}CH_2Cl_2$, dppf, KOAc, DMSO, 100 °C, 49–64% (c) ArBr, $PdCl_2(dppf){\cdot}CH_2Cl_2$, dppf, K_3PO_4, 1,4-dioxane, H_2O, 70 °C, 49–72%.



Scheme 3. Reagents and conditions: (a) 4-bromophenyl chloroformate, DMAP, pyridine, CH_2Cl_2, 82% for **17**, 57% for **21**, 20% for **22**, 45% for **23**.

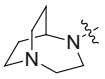
Table 1
In vitro SAR studies of different ring systems

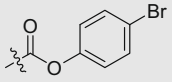
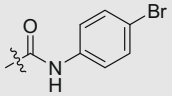
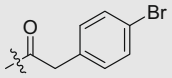
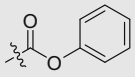
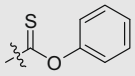
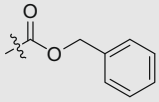
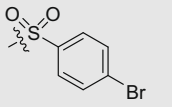
Compound	α7 K_i[a] (nM)	α7 agonist activity[b]	α4β2 IC_{50}[c] (nM)
5	38	158%	>5000
14	383	27%	>10,000
15	763	nd	>10,000
17	>5710	10%	>10,000
21	>5000	<0.1%	>10,000
22	>5000	<0.1%	>10,000
23	>5000	nd	>10,000

nd = not determined.
[a] GH_4C_1 cells binding assay, [^{125}I]-BTX, all values represent an average of a six point dose–response curve run in triplicate.[9]
[b] All test compounds were measured at 32 μM and are reported as a %control versus nicotine response at 50 μM.[10]
[c] Rat brain homogenate binding assay, [^{3}H]-Nic, all values represent an average of a six point dose–response curve run in triplicate.

The SAR studies about the carbamate linker of **7** are described in Table 2. Replacing the carbamate linker with a urea linker resulted in a 10-fold loss in potency (**5** vs **24**)[21] and replacing the carbamate linker with an amide resulted in a complete loss of α7 nAChR affinity (**25**).[22] The carbonyl oxygen may be replaced by sulfur without loss of α7 nAChR affinity; however this modification did result in a loss of functional activity (**7a** vs **26**).[23] Modifying the phenyl carbamate to a benzyl carbamate resulted in a 4.5× loss in potency (**7a** vs **27**)[24] and replacement of the carbamate linker with sulfonamide resulted in complete loss of α7 nAChR affinity (**28**).[25] These studies reveal some key elements to the α7 nAChR pharmacophore in that the heteroatoms of the carbamate are ideally suited for both α7 nAChR potency and functional activity.

Table 2
In vitro SAR studies about the carbamate linker



Compound	Substituent	α7 K_i[a] (nM)	α7 agonist activity[b]
5		38	158%
24		328	nd
25		>5000	1.7%
7a		739	99%
26		749	28%
27		3350	nd
28		>4720	nd

nd = not determined.
[a] GH_4C_1 cells binding assay, [^{125}I]-BTX, all values represent an average of a six point dose–response curve run in triplicate.[9]
[b] All test compounds were measured at 32 μM and are reported as a %control versus nicotine response at 50 μM.[10]

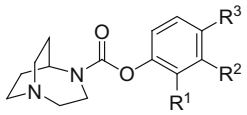
The SAR studies of a variety of mono-substituted analogs about the aromatic ring of the carbamate of **7** are described in Table 3. Substitution at the *para*-position of the aromatic ring in general resulted in the most functionally active compounds whereas substitution at the *meta*-position of the aromatic ring resulted in improved α7 nAChR potency with a concomitant loss of α7 nAChR functional activity (e.g., **7b** vs **7c**, **7d** vs **7e**, **5** vs **7g**, **7i** vs **7j**, **7k** vs **7l**, **7o** vs **7p**, **7q** vs **7r**). The only exception to this general trend was observed when the substituent was –C(O)Ph (**7m** vs **7n**) in that both potency and functional activity were improved in **7n**. Substitution at the *ortho*-position of the aromatic ring resulted in loss of α7 nAChR potency when compared to the same substituent in either the *meta*- or *para*-position (**7f** vs **7e** or **7d** and **7h** vs **7g** or **5**). In most cases where the α7 K_i < 100 nM the selectivity over the α4β2 nAChR was >50x (compounds **5**, **7a**–**n**, **7p**–**7r**). The only exception to this was observed with **7c** where the selectivity over the α4β2 nAChR was 30×. Interestingly, it appears as though *meta*-substitution began to illicit α4β2 nAChR affinity (**7e**, **7g**, and **7n**). Additionally, when the *para*-position of the aromatic ring was substituted with a phenyl ring (**7o**), modest potency, and good functional activity were maintained. However, while this modification resulted in good selectivity over the α4β2 nAChR, it did result in measurable α3β4 nAChR activity (IC_{50} = 3770 nM).[26] Replacing the 4-phenyl ring with pyridine heterocycles resulted in compounds with modest potency and good functional activity; however this modification did not result in improved selectivity over the α3β4 nAChR (α3β4 IC_{50}'s, **7s** = 4630 nM, **7t** = 3810 nM, **7u** = 2640 nM).

The SAR trends in Table 3 revealed that *meta*-substituted phenyl carbamate analogs were more potent at α7 nAChR then similarly substituted analogs at the *para*- or *ortho*-position, and *para*-substituted phenyl carbamate analogs had improved agonist activity over similarly substituted analogs at the *meta*- or *ortho*-position. Therefore we hypothesized that 3,4-disubstituted analogs would result in more potent and functionally active analogs. The SAR trends revealed that 3,4-disubstituted phenyl analogs were equipotent to the 3-phenyl substituted analogs but had similar functional activity to the 4-phenyl substituted analogs (Table 4). For example, the 4-bromo-3-chlorophenylcarbamate analog **7v** was equipotent to the 3-chlorophenylcarbamate analog **7e** and displayed similar functional activity as the 4-bromophenyl carbamate analog **5**. Similarly, **7z** was equipotent to **7n** with similar functional activity to **5**. All of the 3,4-disubstituted analogs displayed weak α4β2 and α3 nAChR affinity; however, they were still >50× selective for the α7 nAChR. The naphthyl carbamate analog **7aa** provided the best combined attributes of compounds within this series.

Selected physicochemical properties, selectivity, ADME, and pharmacokinetic data for compounds **5** and **7aa** are highlighted in Table 5. Both **5** and **7aa** displayed excellent aqueous solubility, good permeability, good/excellent in vitro metabolic stability and high selectivity versus the 5-HT_3 receptor.[19] One differentiating feature of the two compounds is highlighted by their affinity to the hERG ion channel, with **5** displaying greater inhibitory activity versus **7aa**. Both compounds displayed excellent brain penetration and CSF concentrations well above their α7 K_i. As such, both of the compounds would serve as excellent lead structures to explore in vivo α7 nAChR pharmacology.[13]

We have described the synthesis and detailed SAR of a series of 1,4-diazabicyclo[3.2.2]nonane phenyl carbamates that are

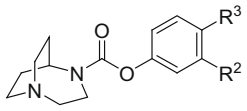
Table 3
In vitro SAR studies for compounds **5**, **7a**–**u**

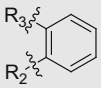


Compound	R^1	R^2	R^3	α7 K_i[a] (nM)	α7 agonist activity[b]	α4β2 IC_{50}[c] (nM)
7a	H	H	H	739	99%	1040
7b	H	H	F	537	100%	1780
7c	H	F	H	35	47%	1065
7d	H	H	Cl	79	145%	>5000
7e	H	Cl	H	32	77%	3505
7f	Cl	H	H	868	nd	>5000
5	H	H	Br	38	158%	>5000
7g	H	Br	H	9.5	70%	3935
7h	Br	H	H	725	nd	>5000
7i	H	H	Me	178	202%	>5000
7j	H	Me	H	25	46%	>5000
7k	H	H	OMe	201	126%	>5000
7l	H	OMe	H	79	26%	>5000
7m	H	H	C(O)Ph	95	35%	>5000
7n	H	C(O)Ph	H	11	98%	2615
7o	H	H	Ph	215	111%	>5000
7p	H	Ph	H	9	9%	>10,000
7q	H	H	OPh	212	241%	5030
7r	H	OPh	H	13	40%	>10,000
7s	H	H	2-Pyridyl	354	174%	>5000
7t	H	H	3-Pyridyl	203	189%	>5000
7u	H	H	4-Pyridyl	207	191%	>5000

nd = not determined.
[a] GH_4C_1 cells binding assay, [^{125}I]-BTX, all values represent an average of a six point dose–response curve run in triplicate.[9]
[b] All test compounds were measured at 32 μM and are reported as a %control versus nicotine response at 50 μM.[10]
[c] Rat brain homogenate binding assay, [^{3}H]-Nic, all values represent an average of a six point dose–response curve run in triplicate.[20]

Table 4
In vitro α7 binding and functional activity and α4β2 and α3β4 nAChR binding affinity for compounds **5**, **7v**–**aa**

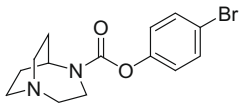


Compound	R^2	R^3	α7 K_i[a] (nM)	α7 agonist activity[b]	α4β2 IC_{50}[c] (nM)	α3 IC_{50}[d] (nM)
5	H	Br	36	158%	>5000	>6480
7v	Cl	Br	33	203%	7120	2090
7e	Cl	H	32	77%	3505	nd
7w	Me	Br	50	83%	7220	4020
7d	H	Cl	79	146%	>5000	>5000
7x	Cl	Cl	31	195%	4980	4750
7y	F	Cl	86	110%	6980	9960
7n	C(O)Ph	H	11	98%	2615	nd
7z[27]	C(O)Ph	Br	16	201%	2040	1390
7aa			23	175%	9880	4910

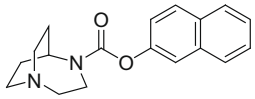
nd = not determined.
[a] GH_4C_1 cells binding assay, [^{125}I]-BTX, all values represent an average of a six point dose–response curve run in triplicate.[9]
[b] All test compounds were measured at 32 μM and are reported as a %control versus nicotine response at 50 μM.[10]
[c] Rat brain homogenate binding assay, [^{3}H]-Nic, all values represent an average of a six point dose–response curve run in triplicate.[20]
[d] IMR32 cells binding assay, [^{3}H]-Epibatidine, all values represent an average of a six point dose–response curve run in triplicate.[26]

subtype selective, high affinity agonists of the α7 nAChR. Optimization of the SAR resulted in the identification of **5** and **7aa**, which have excellent physical chemical properties and, as a result, display favorable in vitro and in vivo pharmacokinetic properties. Additionally, compound **7aa** was characterized by having the potential for an improved cardiosafety profile due to its low affinity for hERG. The data presented herein also serve to emphasize the many important elements of the α7 nAChR pharmacophore: the direction of the nitrogen lone pair; the situating of the oxygen atoms of the carbamate functional group for α7 nAChR potency and functional activity; and the simultaneous substitution at the *meta*- and *para*-position of the aromatic ring being optimal for potency and functional activity. These findings will prove useful in the discovery of additional subtype selective compounds suitable for clinical development.

Table 5
Selected physicochemical properties, ADME, and pharmacokinetic data for **5** and **7aa**



5



7aa

Compound	**5**	**7aa**
MW	325.21	296.37
*c*Log *P*	2.9	3.1
Log *D*[a]	2.1	2.3
TPSA	33	33
Aq Solubility (μg/ml)	>65	>65
Caco-2 AB/BA	10/26	12/48
hERG, %inh @ 10 μM[b]	46%	8%
5-HT_3 IC_{50}[c] (nM)	>3160	>3160
HLM Clint[d] (ml/min/kg)	<6.8	12.0
$T_{1/2}$ (min)	>105	61
Brain[e] (ng/g)	5461	5290
Plasma[e] (ng/ml)	648	463
Brain/plasma	9.1	11.6
CSF[e] (nM)	774	343

[a] Partition coefficient measured in 1-octanol/aqueous buffer @ pH 7.4.
[b] The percent inhibition of binding of [^{3}H]dofetilide to hERG stably expressed on HEK293 cells.
[c] HEK293 cells expressing h 5-HT_3 binding assay, [^{3}H]-LY278584, all values represent an average of a six point dose–response curve run in triplicate.[28]
[d] Determined using pooled liver microsomes in phosphate buffer @ pH 7.4 and 1 μM substrate concentration, with sampling made at the 30 min time point.
[e] Rat in vivo pharmacology: male Sprague-Dawley rats (n = 3) were treated with 5 mg/kg s.c. of test compound. Brain, Plasma, and CSF (cerebral spinal fluid) were assessed at 1 h post dose.

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21. Compound **24** was prepared by reacting 1,4-diazabicyclo[3.2.2]nonane with 4-bromophenylisocyanate in 14% yield.
22. Compound **25** was prepared by reacting 1,4-diazabicyclo[3.2.2]nonane with 2-(4-bromophenyl)acetyl chloride in 41% yield.
23. Compound **26** was prepared by reacting 1,4-diazabicyclo[3.2.2]nonane with phenylchlorothionocarbonate using the conditions to prepare **7** in 58% yield.
24. Compound **27** was prepared from benzylchloroformate using the conditions to prepare **7** in 15% yield.
25. Compound **28** was prepared by reacting 1,4-diazabicyclo[3.2.2]nonane with 4-bromophenylsulfonylchloride in 41% yield.
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