Bioorganic & Medicinal Chemistry Letters 19 (2009) 4747–4751

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

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

Christopher J. O'Donnell *, Langu Peng, Brian T. O'Neill, Eric P. Arnold, Robert J. Mather, Steven B. Sands, Alka Shrikhande, Lorraine A. Lebel, Douglas K. Spracklin, Frank M. Nedza

Neuroscience Medicinal Chemistry, Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340, United States

ARTICLE INFO

Article history:
Received 30 April 2009
Revised 10 June 2009
Accepted 15 June 2009
Available online 17 June 2009

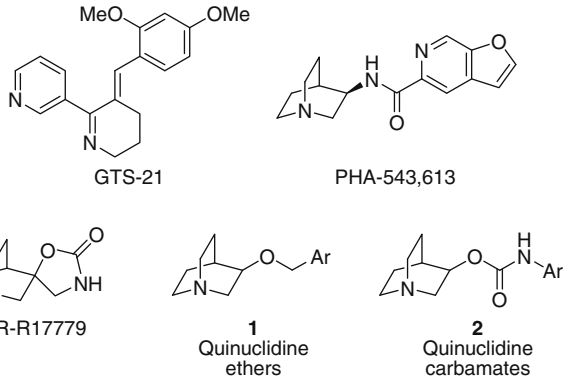
Keywords:
Alpha 7
Nicotinic acetylcholine receptor
nAChR
SAR
1,4-Diazabicyclo[3.2.2]nonane phenyl carbamate
Agonist

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.



* Corresponding author. Tel.: +1 860 715 4118; fax: +1 860 686 5158.
E-mail address: christopher.j.odonnell@pfizer.com (C.J. O'Donnell).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.06.059

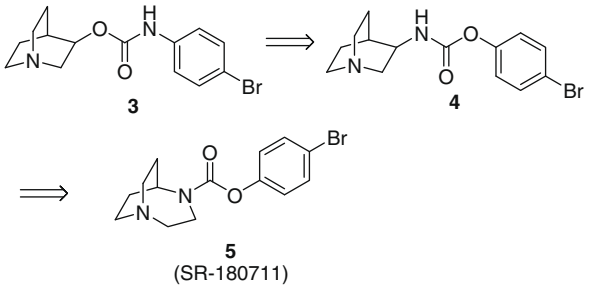
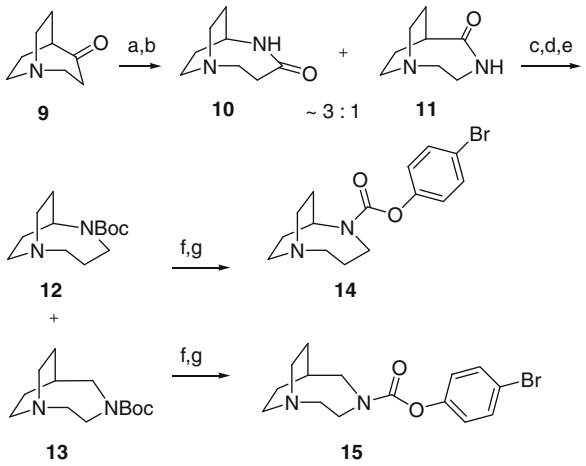


Figure 1. Approach used to discover the 1,4-diazabicyclo[3.2.2]nonane carbamate series.

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]

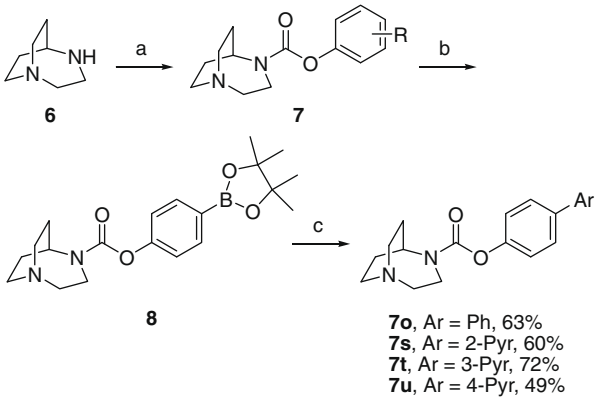
Synthesis of two novel diazabicyclic analogs, 1,5-diazabicyclo[4.2.2]decane carbamate **14** and 1,4-diazabicyclo[4.2.2]decane carbamate **15** are described in Scheme 2. 1-Aza-bicyclo[3.2.2]nonan-4-one[17] **9** was reacted with hydroxylamine and the resulting mixture of oxime isomers underwent Beckman 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.



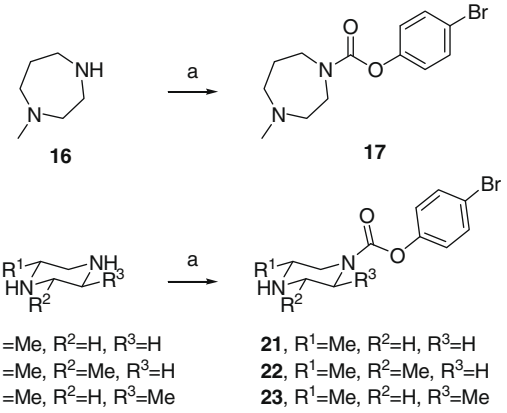
Scheme 2. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, Na_2CO_3, MeOH, 60 °C; (b) H_2SO_4, 100 °C, 53% for 2 steps; (c) $LiAlH_4$, THF, rt to ↑↓; (d) Boc_2O, NaOH, THF, H_2O; (e) chromatography, 50% **12**, 14% **13** (2 steps); (f) 1 M HCl, MeOH; (g) 4-bromophenyl chloroformate, DMAP, pyridine,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