Bioorganic & Medicinal Chemistry Letters 26 (2016) 3010–3013

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Conformational analysis of 2-substituted piperazines

E. Adam Kallel [a,*], Colin Vangel [a], Daniel Elbaum [b]

[a] Retrophin, Inc. 12255 El Camino Real, Suite 250, San Diego, CA 92130, United States
[b] Retrophin, Inc, 301 Binney Street, Cambridge, MA 02142, United States

ARTICLE INFO

Article history:
Received 23 March 2016
Revised 6 May 2016
Accepted 7 May 2016
Available online 9 May 2016

The authors would like to dedicate this publication *to the occasion of Professor Stuart L. Schreiber's 60th birthday*

Keywords:
Piperazines
Conformational analysis
Computational chemistry

ABSTRACT

The unusual activity differences of carbon linked versus oxygen linked 2-substituted piperazines as α7 nicotinic acetylcholine receptor agonists led to a conformational study of several examples. The conformational preferences of which are absent from the literature. We report the first study and explanation of the conformational preference of 2-substiturted piperazines and show an example of how this preference controls binding in a pharmaceutically relevant case. In all cases the axial conformation for these 1-acyl and 1 aryl 2-substituted piperazines was found to be preferred. For the ether linked compounds, the axial conformation was found to be further stabilized by an intramolecular hydrogen bond. The axial orientation also places the basic and pyridyl nitrogens into a special orientation that closely mimics nicotine. Molecular modeling studies confirm that the *R* enantiomers of the compounds can bind to the α7 nicotinic acetylcholine receptor with the basic and pyridyl nitrogens colocalized with their counterparts in Epibatidine.

The α7 nicotinic acetylcholine receptor (nAChR) is a calcium permeable ligand gated ion channel that is implicated in a wide range of biological processes. As such, it has been prosecuted as a drug discovery target by numerous groups resulting in multiple agonists of various chemotypes.[1] The α7 nAChR was first recognized as a potential target for CNS diseases, particularly Alzheimer's and schizophrenia.[2] Although several compounds have advanced to clinical studies, to date no compound has been approved.

More recently, this receptor has been found on macrophages and shown to mediate an anti-inflammatory response.[3] This has led to several agonists being evaluated in animal models of sepsis, and arthritis.[4] In addition, a group in the Netherlands conducted a clinical study examining the efficacy of GTS-21 in LPS-induced endotoxemia.[4a] In this study, there was a dose-related reduction in pro-inflammatory mediators, however, the compound did not show statistically meaningful improvement in the efficacy endpoints. Targacept (now Catalyst Biosciences) also examined an α7 agonist, TC-5987, in a clinical trial aimed at treating asthma. The company has yet to fully disclose the results, although a press release was issued stating that the treated patients showed a statistically significant improvement in force expiratory volume in one second (FEV1).[5]

Several Letters regarding the discovery of a series of 2-((pyridine-3-yloxy)methyl)piperazines as agonist of the α7 nAChR have appeared in recent years. While the piperazine core is well represented in medicinal chemistry, this is the first Letter of this core being used in an α7 nAChR agonist.[4b,6] An examination of these compounds shows that, while similar to other classes of α7 nAChR agonists in that they possess both a basic nitrogen and a pyridine nitrogen, the through bond distance (8 bonds) between these two moieties was longer than any other example. This led us to question what the conformations of these compounds were and how they might bind to the receptor. Although it has been shown that 1-acyl-2-substituted piperidines show a preference for the 2-substituent to occupy the axial position,[7] we were unable to find any studies on the conformational preferences of 1-acyl or 1-aryl 2-substituted piperazines. Herein we detail our examination using quantum mechanical calculations that show that these compounds, like the piperidines, prefer to place the 2 substituent in the axial position, a finding absent from the medicinal chemical literature. We further explore how this conformation affects binding of the compounds to the α7 nAChR.

In our examination, the conformations of all six compounds were studied using the conformational import algorythm[8] in MOE[9] followed by optimization using the PM3 model Hammiltonian.[10] The lowest energy conformations for axial and equatorial orientation of the 2-position substituent were selected and optimized using Jaguar[11] at the B3LYP/6-31G** level of theory.

Abbreviations: nAChR, nicotinic acetylcholine receptor; B3LYP, Becke, three-parameter, Lee–Yang–Parr; D-PCM, dielectric polarizable continuum model.

* Corresponding author.

http://dx.doi.org/10.1016/j.bmcl.2016.05.022
0960-894X/

All structures were optimized to tight convergence criteria as defined in the respective manuals of the programs. The final calculated gas phase conformations are shown in Figures S1–S6. No imaginary frequencies were noted and stationary points were confirmed in all cases through vibrational frequency computation. Our initial examination of the low energy conformation of compound **1** indicated the presence of an intramolecular hydrogen bond. Given that our initial calculations were performed in the gas phase we recalculated the conformation using the dielectric polarizable continuum model (D-PCM)[12] as implemented in FIREFLY.[13] These calculations were run at the B3LYP/6-31G** level of theory as well. The relative energy of the axial and equatorial conformations are shown in Table 1.

For compound **1** (Fig. 1) the calculations show that the axial orientation is preferred by 9.6 kcal/mol. This conformation allows for the formation of an intramolecular hydrogen bond between the ether oxygen and the quaternary nitrogen.

While the addition of a solvent model does decrease the preference for the 2-substituent to occupy the axial orientation, it is still favored by 6.4 kcal/mol. This energy difference is sufficient to effectively lock the conformation of this compound with the 2-substituent in the axial position.

Table 1
Axial–equatorial energy differences in kcal/mol for compounds in Figure 1

Compd	ΔE B3LYP/6-31G**// B3LYP/6-31G**	ΔE D-PCM B3LYP/6-31G**//D-PCM B3LYP/6-31G**
1	−9.6	−6.4
2	−1.8	−3.4
3	−8.7	−2.5
4	−2.4	−0.32
5	−5.7	−3.8
6	−1	−0.5

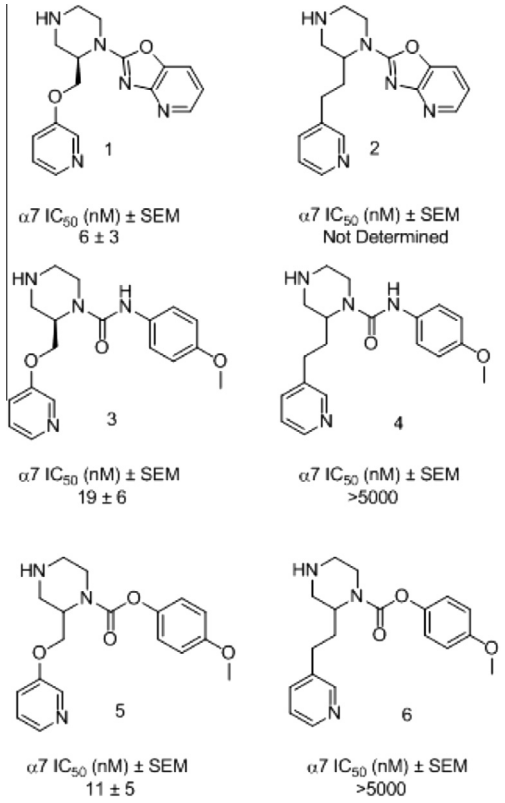

Figure 1. The pairs of 2-substituted piperazines highlighting the profound effect of replacing the ether with methylene.

For compound **2**, the axial conformation is still preferred, however, the energy difference in this case is only 1.8 kcal/mol in the gas phase. In contrast to compound **1**, addition of a solvent model increases the preference for the axial conformation to 3.4 kcal/mol.

The pair of compounds **3** and **4** present a similar picture. In compound **3**, the axial orientation is preferred by 8.7 kcal/mol in the gas phase. Inclusion of the D-PCM solvent model decreases the axial preference, but it remains 2.5 kcal/mol lower in energy that the equatorial conformation. Compound **4** has a preference for the axial orientation of 2.4 kcal/mol at B3LYP/6-31G**// B3LYP6-31G** which decreases to 0.32 kcal/mol with inclusion of solvation correction at D-PCM/B3LYP/6-31G**//D-PCM/B3LYP/6-31G**. While the axial orientation of the 2-substiuent is preferred in both cases, the ether linked compound, **3**, shows a much larger preference due to the presence of an intramolecular hydrogen bond. Although this preference is not as great as in the pair of compounds **1** and **2**. For compound **4**, the energetic difference between the axial and equatorial conformations is sufficiently low to allow interconversion, while the ether linkage in compound **3**, leads to pre-organization for binding with the 2-substituent in the axial conformation.

The calculations show that compounds **5** and **6** are conformationally similar to compounds **3** and **4**. For compound **5**, the axial orientation is preferred by 5.7 kcal/mol in the gas phase, inclusion of the D-PCM solvent model decreases the axial preference, but it remains 3.8 kcal/mol lower in energy that the equatorial conformation. Compound **6** has a preference for the axial orientation of

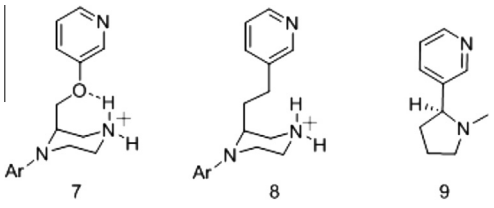

Figure 2. The aryl-ether is capable of forming an intramolecular hydrogen bond, mimicking nicotine while the aryl-ethyl is not.

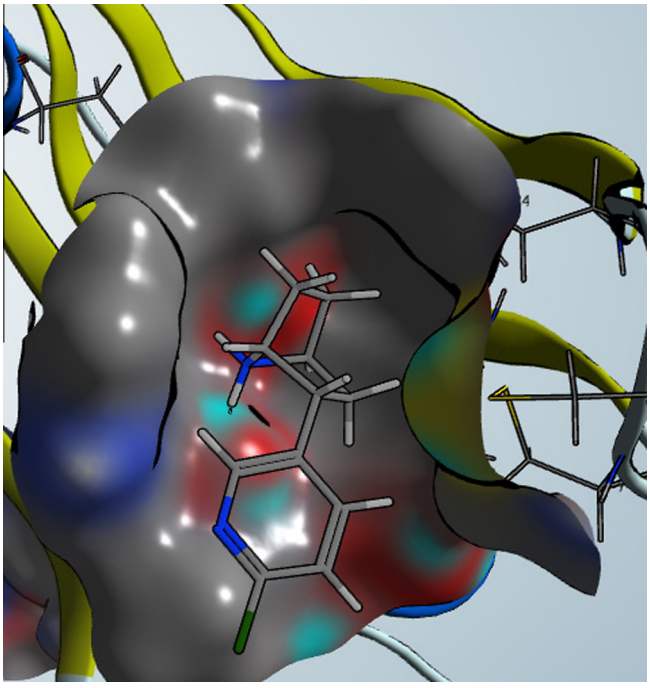

Figure 3. Epibatidine in the nicotine binding site of α7 nAChR from PDB file 3SQ6.