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Molecular modeling study of 4-phenylpiperazine and 4-phenyl-1,2,3,6-tetrahydropyridine derivatives: A new step towards the design of high-affinity 5-HT$_{1A}$ ligands

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ABSTRACT

The main feature of many drugs having a 5-HT$_{1A}$ affinity is the presence of an arylpiperazine moiety. Indeed, the protonated nitrogen and the aromatic ring of the arylpiperazine compounds are considered crucial for the interaction with the receptor. However, the replacement of the piperazine moiety by a 1,2,3,6-tetrahydropyridine ring in 4-arylpiperazine-ethyl carboxamide derivatives was recently shown to be highly favourable for 5-HT$_{1A}$ affinity. In order to better understand the favourable effect of this chemical modification, we performed a conformational analysis of these compounds mainly based on the position of the phenyl ring relative to the piperazine and tetrahydropyridine moiety. In the piperazine compounds, the phenyl ring preferentially adopts a perpendicular orientation, whereas an almost planar orientation seems to be the most favourable conformation for the tetrahydropyridine compounds. Therefore, this conformational difference appears as a key for a better interaction with the receptor binding site. This result will serve for the designing high-affinity 5-HT$_{1A}$ ligands.

For many years, serotonergic receptors have been widely studied due to their major role in a lot of physiological processes. Among the multiple subtypes, the 5-HT$_{1A}$ receptors represent a preferential target for pharmaceutical research owing to its involvement in pathologies such as anxiety,[1] depression,[2] sleep and memory disorders,[3,4] and schizophrenia.[5] Unfortunately, the lack of data about the three-dimensional structure of serotonergic receptors is a serious drawback to the determination of the binding mode of their ligands, and more precisely the 5-HT$_{1A}$ ligands. In this context, the ligand-based approach offers an appropriate alternative.

In this letter, we were interested in a series of 4-arylpiperazine compounds with significant 5-HT$_{1A}$ affinity. Two main interactions appear to be important for the receptor affinity.[6] Firstly, the protonated nitrogen atom of the piperazine ring was shown to form an ionic bond with the carboxyl oxygen of the Asp 3.32 side chain (Ballesteros–Weinstein nomenclature).[7] Secondly, the aromatic ring was demonstrated to stabilize the ligand binding by an edge-to-face CH–Π interaction with the Phe 6.52 residue (Ballesteros–Weinstein nomenclature). Interestingly, a recent study of our group revealed the presence of the 1,2,3,6-tetrahydropyridine instead of the piperazine moiety in 4-arylpiperazine-ethyl carboxamide derivatives was highly favourable for 5-HT$_{1A}$ affinity.[8] Indeed, compared to their 4-phenylpiperazine analogues (compounds **1**–**3**), the compounds **4**–**6** (Fig. 1) showed an affinity 7, 11, and 3 times higher, respectively. The favourable effect of this chemical modification could be explained by its impact on both previously described interactions. On the one hand, as the result of the pK_a values predicted by the SPARC on-line calculator[9] (Table 1), the nitrogen atom N1 appears to be more basic in the 1,2,3,6-tetrahydropyridine compounds. Therefore, the ionic interaction between these compounds and the Asp 3.32 residue should be stronger. On the other hand, the replacement of the sp^3 nitrogen by a sp^2 carbon is likely to affect the CH–Π interaction with the Phe 6.52 residue. In order to confirm this hypothesis, we performed a conformational search of these compounds (**1**–**6**) focusing on the orientation of the phenyl ring relative to the piperazine and 1,2,3,6-tetrahydropyridine rings.

First of all, models of the protonated compounds were built under the Sybyl 8.0 molecular modeling package (SYBYL 8.0, 2008, Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144-2913) running on HP xw6400 workstation and using standard fragments library. Their structure was then minimized using the Tripos force field,[10] the Gasteiger–Hückel charges,[11,12] and the method of Powell available in the Maximin2 procedure.[13] The conformational search was then performed for the six minimized compounds using the module Systematic Search of Sybyl. To explore the different possible conformations the rotatable bond of the 4-phenylpiperazine and 4-phenyl-1,2,3,6-tetrahydropyridine groups were incremented systematically by five degrees. Besides, two assumptions concerning the other part of the compounds were considered in order to limit the number of conformers. On the one hand, the

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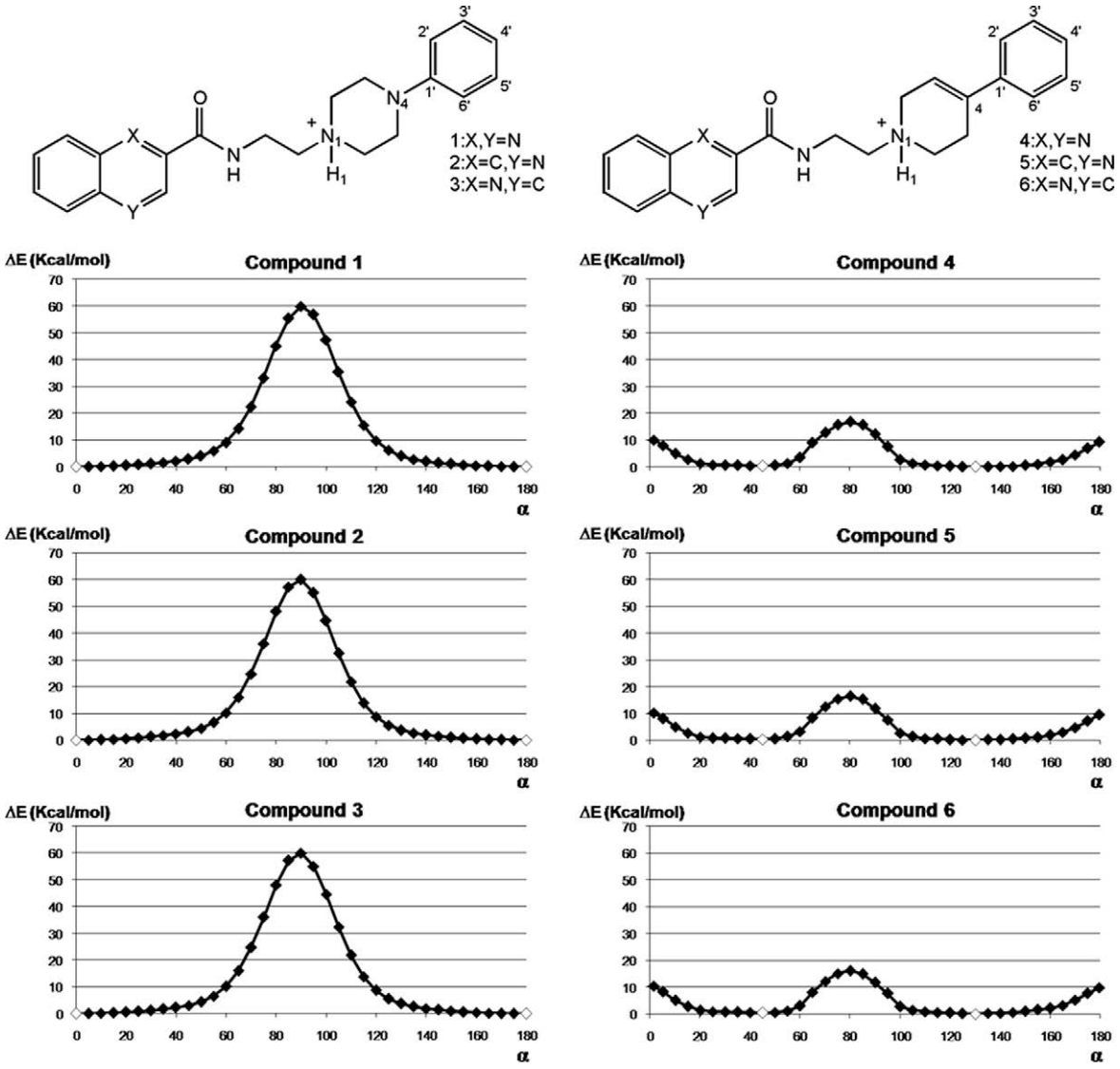

Figure 1. 4-Arylpiperazine-ethyl carboxamide derivatives in their protonated form: plots of the energy variation ΔE against the angle α for the phenylpiperazine compounds (left) and the 4-phenyl-1,2,3,6-tetrahydropyridine compounds (right). The energy minima are coloured in white.

Table 1
pK_a values predicted by the SPARC on-line calculator[9]

Piperazine compounds	Predicted pK_a	Tetrahydropyridine compounds	Predicted pK_a
1	7.07	4	7.90
2	7.21	5	8.04
3	7.16	6	7.99

Table 2
Energy difference ΔE between the lowest-energy chair conformations and the lowest-energy boat conformations

Compounds	ΔE (Kcal/mol)
1	17.60
2	17.44
3	17.59

piperazine ring of compounds **1**–**3** was fixed in a chair conformation. This conformation has been shown to be more energetically favourable than the boat conformation.[14] A conformational study focused on the piperazine ring was achieved with the program Random Search[15] of Sybyl® to confirm this assumption for the three compounds (Table 2). On the other hand, the ethyl-heteroaryl-carboxamide moiety was frozen in an extended conformation for the six compounds as suggested by a preliminary conformational analysis (data not shown). Under these conditions, 36 conformations were found for each compound.

Then, to determine the most stable conformations the energy of each conformer was calculated using the Tripos force field[10] and the Gasteiger–Hückel charges.[11,12]

Figure 1 displays the plots of the energy variation ΔE against the orientation of the phenyl ring relative to the piperazine and 1,2,3,6-tetrahydropyridine rings. This orientation was characterized by the angle α formed by the plane P_1 of the phenyl ring and the plane P_2 defined by the atoms N1, H1, and C1′ (Fig. 1). The orientation is considered planar for $\alpha = 90°$ (the plane of the phenyl ring perpendicular to the bond N1–H1) and perpendicular