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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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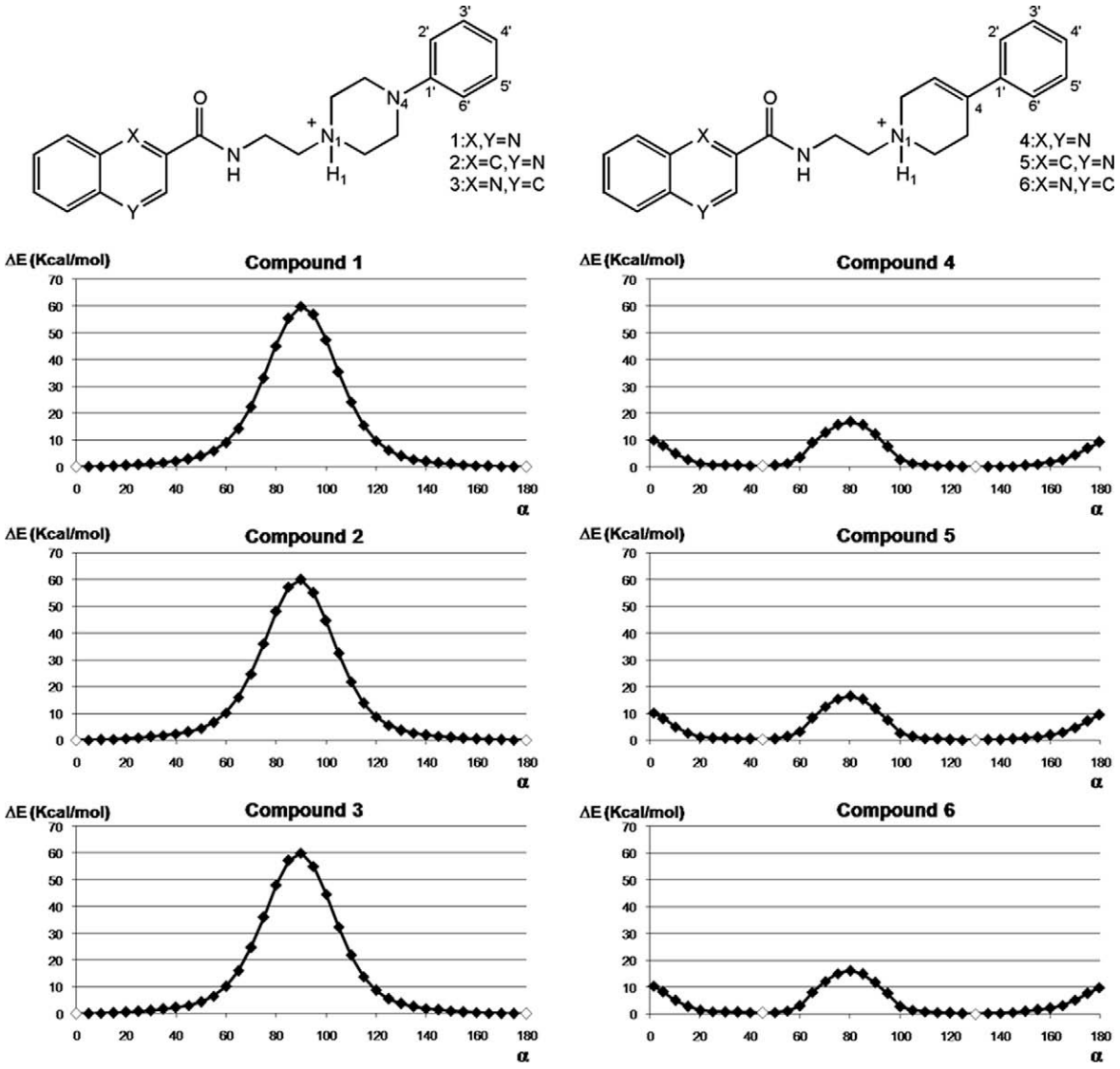

Figure 1. 4-Arylpiperazine-ethyl carboxamide derivatives in their protonated form: plots of the energy variation ΔE against the angle α for the phenylpiperazine compounds (left) and the 4-phenyl-1,2,3,6-tetrahydropyridine compounds (right). The energy minima are coloured in white.

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

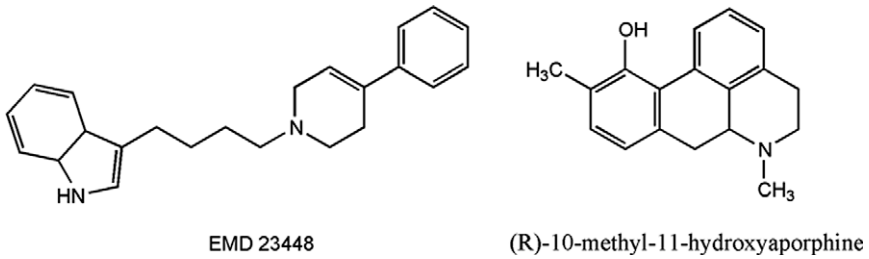

Figure 2. Chemical structures of EMD 23448 and (*R*)-10-methyl-11-hydroxyaporphine.

for $\alpha = 0$ or 180° (the plane of the phenyl ring parallel to the bond N1–H1).

With regard to the 4-phenylpiperazine family, very interesting observations can be made. Firstly, the three compounds show an identical plot profile indicating that the nature of the heteroaryl ring has no effect on the orientation of the 4-substituted phenyl ring. Secondly, the energy minima is found for $\alpha = 0$ or 180° demonstrating that the perpendicular orientation is the most energetically favourable conformation. Inversely, the strictly planar orientation appears to be impossible due to an energy barrier too high ($\Delta E \approx 60$ Kcal/mol). Intermediate conformations with α-values from 45° to 65° or from 115° to 135°, that could be called almost planar orientations, are considered as possible because their energy barrier is not critical ($\Delta E < 20$ Kcal/mol).

The plots of the 4-phenyl-1,2,3,6-tetrahydropyridine compounds exhibit a profile different than that of the 4-phenylpiperazine compounds. Indeed, the most energetically favourable conformation is found for $\alpha = 130°$. Moreover, a local energy minimum is detected for $\alpha = 45°$. These values relate to an almost planar orientation of the phenyl ring. On the other hand, the perpendicular orientation is much less favourable with an energy barrier close to 10 Kcal/mol. Finally, the strictly planar orientation appears to be the less appropriate conformation but not impossible ($\Delta E \approx 16$ Kcal/mol). Therefore, the rigidification of this part of the molecules with the replacement of the sp^3 nitrogen by a sp^2 carbon leads to a spatial constraint which seems to favour an almost planar orientation of the phenyl ring. This result is in agreement with a conformation of the indolyl-3-butyl analogue EMD 23448 (Fig. 2), a putative dopamine D2 agonist, found in crystals.[16]

As a result of these conformational explorations, the two different privileged positions of the phenyl ring in the 4-phenylpiperazine compounds and their 1,2,3,6-tetrahydropyridine analogues (Fig. 3) appear to be the key of the different affinities found in the in vitro binding experiments. These results seem to be consistent with some data from literature. Indeed, on the one hand, the favourable planar orientation must facilitate the interactions with the receptor, as described in previous works. Indeed, Nowak et al.[6] showed in the docking of 4-arylpiperazine analogues that this orientation helped the phenyl ring to make an edge-to-face CH–Π interaction with the Phe 6.52 residue. On the other hand, the almost planar orientation found in the 1,2,3,6-tetrahydropyridine compounds appear to be the closest conformation to the pharmacophore of the 5-HT_{1A} ligand recognition site defined by Hibert et al.[17] (Fig. 4). Indeed, the perpendicular orientation of the electron lone pair relative the plane of the aromatic ring is only found in the most stable conformation of the 1,2,3,6-tetrahydropyridine compounds (Fig. 5). Moreover, the distance between the aromatic ring and the basic nitrogen in 1,2,3,6-tetrahydropyridine compounds is close to the pharmacophore distance. Finally, another approach consisted in the comparison with the rigid and selective agonist (*R*)-10-methyl-11-hydroxyaporphine (Fig. 2).[18] The structure was minimized using the same conditions than that of other compounds. We considered, as references for the fit, the basic nitrogen and the substituted phenyl ring. In fact, Hedberg et al.[19] proved that these features were involved in the interaction with the 5-HT_{1A} receptor binding site. Compared to the perpendicular conformation found in 4-phenylpiperazine compounds, the planar one found in 1,2,3,6-tetrahydropyridine compounds allows to get a better fit of the phenyl rings. The superimposition of (*R*)-10-methyl-11-hydroxyaporphine with the low-energy conformations of compounds 1 and 4 are displayed in Figure 6.

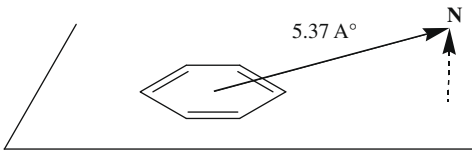

Figure 4. Pharmacophore of the 5-HT_{1A} agonist recognition site.

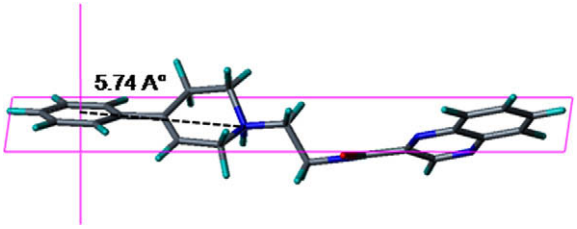

Figure 5. Favourable conformation in 1,2,3,6-tetrahydropyridine compounds.

Figure 3. The perpendicular orientation of the 4-substituted phenyl ring found in the conformational search of the 4-phenylpiperazine compounds (left). The almost planar orientation of 4-substituted phenyl ring found in the conformational search of the 4-phenyl-1,2,3,6-tetrahydropyridine compounds (right). The three compounds of each family were superimposed.

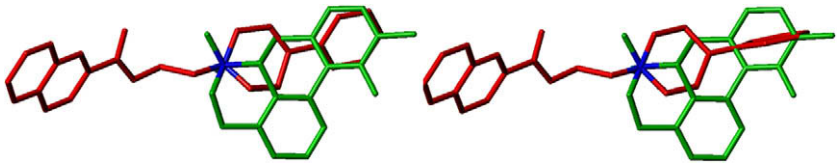

Figure 6. Superimposition of (*R*)-10-methyl-11-hydroxyaporphine (green and blue) with the low-energy conformation of compound **1** (red and blue) (left), and the low-energy conformation of compound **4** (red and blue) (right). The reference features for the fit are the basic nitrogen and the substituted phenyl ring.

In order to extend these observations, we explored other series and have found different molecules in the literature that could be further examined in this context.

The first one is a series of tetrahydrobenzindole derivatives[20] (Fig. 7) examined according to the same conformational analysis. This analysis leads to the same conclusion than that found with our molecules. Indeed, on the one hand, the two enantiomers of the 4-phenyl-1,2,3,6-tetrahydropyridine compound **8** (DR4004) preferentially adopt an almost planar orientation, whereas a perpendicular orientation is more energetically favourable for the two enantiomers of the 4-phenylpiperazine compound **7** (Fig. 7). On the other hand, Kikuchi et al.[20] showed that the 4-phenyl-1,2,3,6-tetrahydropyridine compound had also a higher affinity for the examined receptor, namely 5-HT_7 serotonergic receptor in this study, than the 4-phenylpiperazine compound (pK_i = 8.67 vs 8.48, respectively). These results correlate quite well with our hypothesis especially since Kołaczkowski et al.[21] demonstrated that the phenyl of DR4004 interacts with the receptor through an edge-to-face CH–Π interaction with the Phe 6.52 residue also found in the 5-HT_{1A} receptor.

The second one is composed of indolebutylamine analogues derived from EMD 23448 and described as selective 5-HT_{1A} agonists (Fig. 8).[22] Unlike our ligands, the 4-phenylpiperazine compounds **9** and **10** have the same 5-HT_{1A} affinity than the 1,2,3,6-tetrahydropyridine compounds **11** and **12** (IC_{50} = 0.8 and **20** nM, respectively). The comparison with other data is not so evident since these results are expressed in IC_{50} and not in K_i (pK_i). Nevertheless, in order to interpret these results, we explored the conformational space of these molecules. It turns out that all these structures favour a U-turn bringing the two aromatic systems of the opposite ends in close spatial neighbourhood (Fig. 9). This is not surprising since unlike our molecules these compounds appear to have a higher degree of freedom. This steric hindrance seems not to affect the favourable perpendicular orientation of the piperazine ring as shown in Figure 8 representing the plot of energy against the same angle α than that described for our ligands. However, the energy

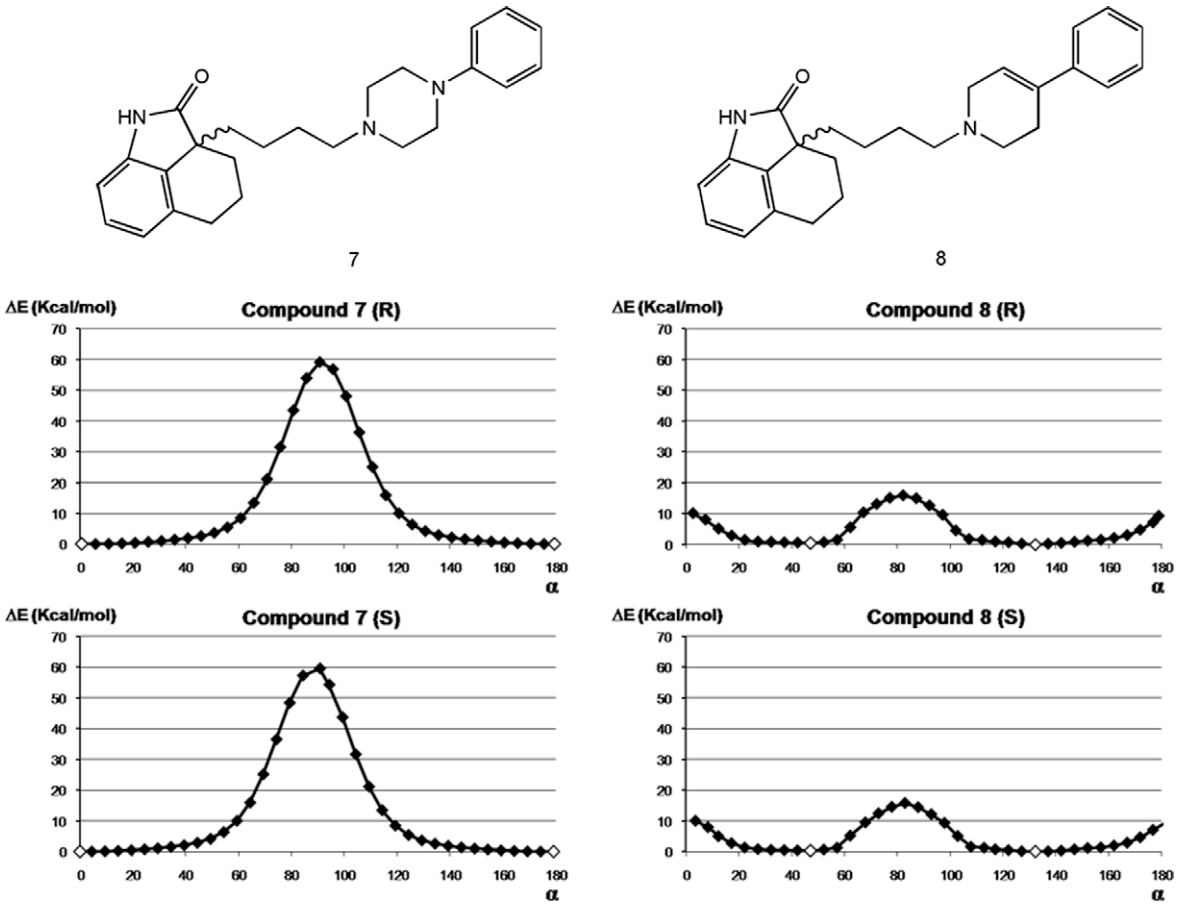

Figure 7. Tetrahydrobenzindole derivatives: plots of the energy variation ΔE against the angle α for the 4-phenylpiperazine compound (*R* and *S*) (left) and the 4-phenyl-1,2,3,6-tetrahydropyridine compound (*R* and *S*) (right). The energy minima are coloured white.

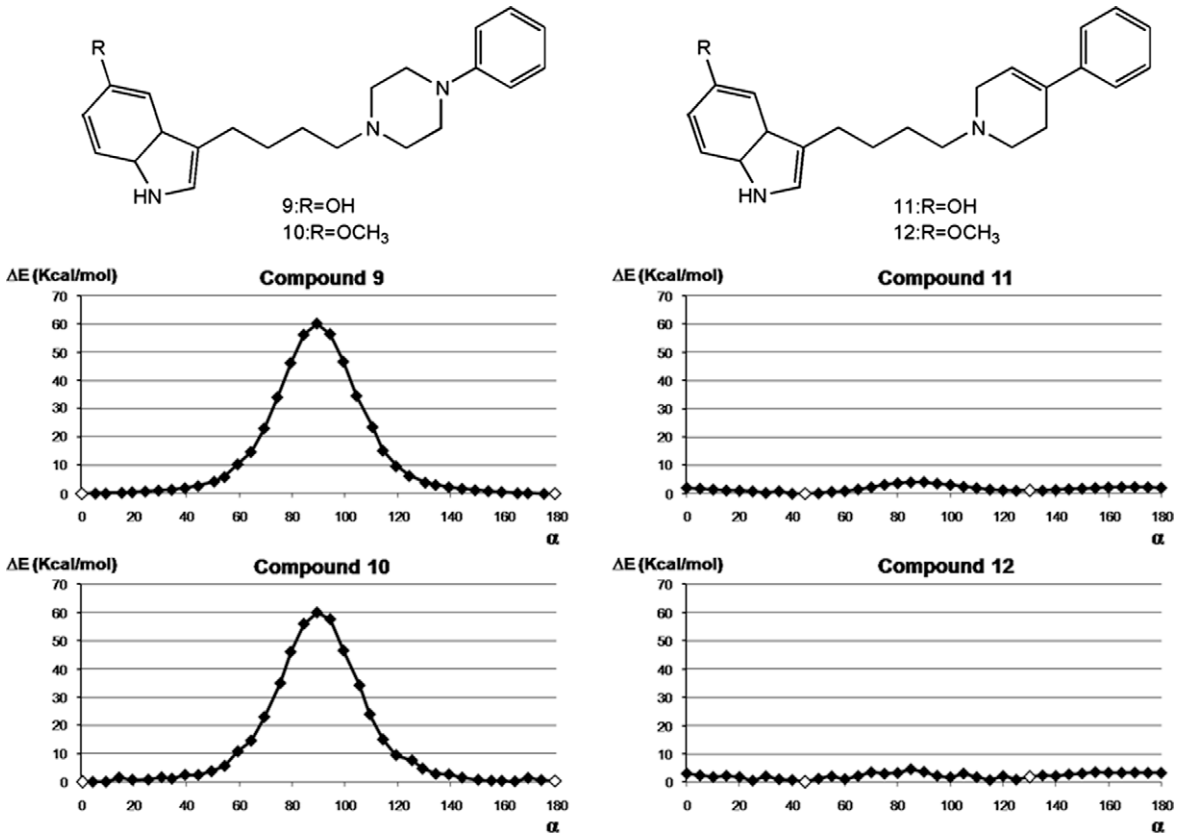

Figure 8. Indolebutylamine derivatives: plots of the energy variation ΔE against the angle α for the 4-phenylpiperazine compounds (left) and the 4-phenyl-1,2,3,6-tetrahydropyridine compounds (right). The energy minima are coloured white.

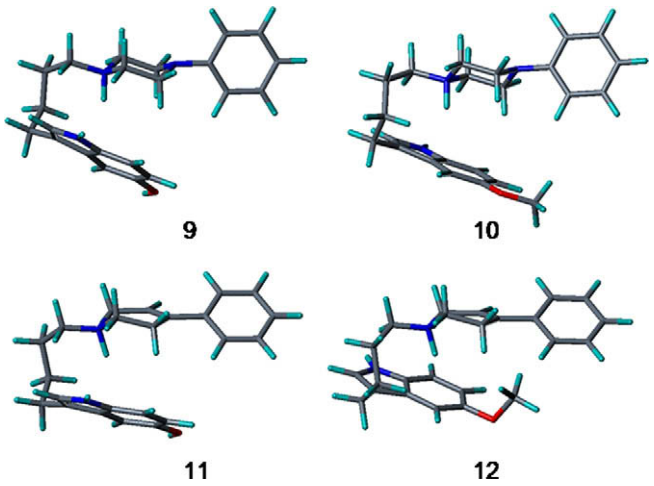

Figure 9. Favourable U-turn conformation in indolebutylamine compounds.

profile of the 1,2,3,6-tetrahydropyridine compounds completely differs from that of our series with a very small energy barrier ($\Delta E \approx 5$ Kcal/mol) (Fig 8). Thus, the almost planar orientation of these compounds is not so favourable and could explain the binding results mentioned above.

In summary, this molecular modeling investigation demonstrated that the favourable almost planar orientation found in the 4-phenyl-1,2,3,6-tetrahydropyridine compounds (**4**–**6**) appeared as an important spatial requirement for an optimal interaction with the 5-HT_{1A} receptor in the present series. This orientation should stabilize the ligand binding by an edge-to-face CH–Π interaction between the phenyl ring of the 4-phenyl-1,2,3,6-tetrahydropyridine compounds and the phenyl ring of the Phe 6.52 residue. This explains why the chemical modification of the piperazine ring into 1,2,3,6-tetrahydropyridine is favourable for receptor affinity. This finding could lead to new ideas in the design of high-affinity 5-HT_{1A} ligands.

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