Experimental and theoretical studies on conformations of arylpiperazines with pyrimido[5,4-*c*]quinolin-4(3*H*)-one terminal

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Introduction

Bioactive conformation of a ligand can be experimentally determined by X-ray crystallography of the ligand-receptor complex. In the absence of target crystal structures, it has to be studied theoretically using various molecular modeling methods. The main problem that is frequently recognized by medicinal chemists in a prediction of reliable bioactive conformations, is structural flexibility of many biologically active compounds. In this study we focused on the group of pyrimido[5,4-*c*]quinolin4(3*H*)-ones, 5-HT_{1A} receptor ligands, which structure is characterized by flexible alkyl chain segment. Their active conformations were predicted in binding pocket of 5-HT_{1A} receptor model and obtained geometries were compared with results of conformational analysis and crystallographic data.

Methods

Conformational analysis of selected set of 4 ligands (with determined crystallographic structures) from a larger group was performed using Systematic Search method delivered with SYBYL 8.0 package (Tripos). All rotatable bonds were changed by 120 degrees per iteration. To avoid sterical bumps, total number of initial set of conformations was reduced to 48 for lew4, 43 for lew5 and 19 for both, lew16 and lew19. Each set of structures was used as an input for OpenMopac 2007 to perform geometry optimization. Semiempirical methods were chosen due to their calculation speed and accuracy higher than molecular mechanic methods. OpenMopac calculations were performed for both vacuum and solvent environment (COSMO algorhitm). PM6 hamiltonian was used for all the OpenMopac jobs. Flexible docking for 100 5-HT_{1A} receptor models [1] was performed using FlexX 2.0.3 program (BioSolveIT), and received data were scored using Cscore module of SYBYL 8.0. Top result for each docked ligand was then fit to optimized conformers and the closest structure has been chosen using RMSD criteria.

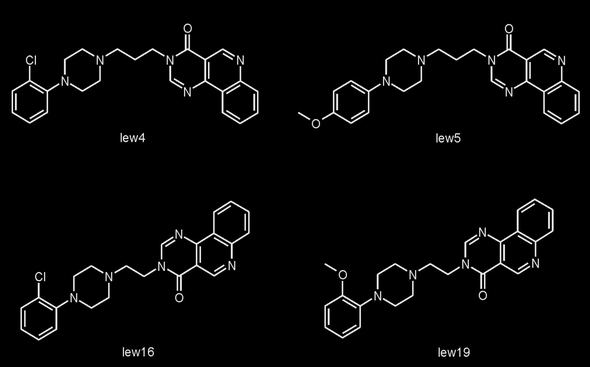

Figure 1. Arylpiperazines with three and two carbon spacers used in research

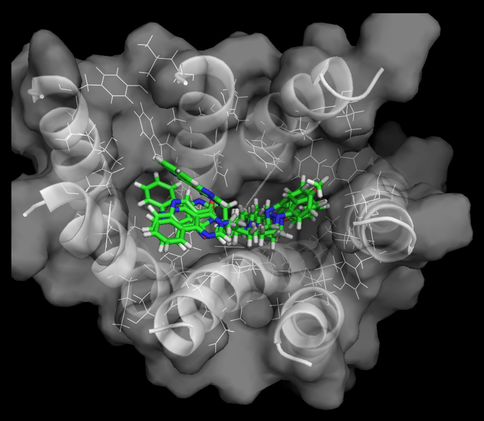

Figure 2. Top scored ligands bound into 5-HT_{1A} active site

Results and conclusions

A distance between nitrogen atoms at both ends of a linker represented simplified spacer geometry. The results of conformational analysis show that solvent simulation (COSMO algorithm) usually prefers extended conformations, whereas in vacuum, bent geometries dominated (Fig. 5).

In the case of crystal structure of lew5 an axial position of *p*-OMe-phenyl substituent was determined. Since for arylpiperazine derivatives it is rather rare situation we have decided to compare both, axial and equatorial variants of lew5 in docking studies. It was found that the first geometry does not fit well into binding pocket of 5-HT_{1A}R (Fig. 4), so further analysis was limited to isomer with equatorial arrangement.

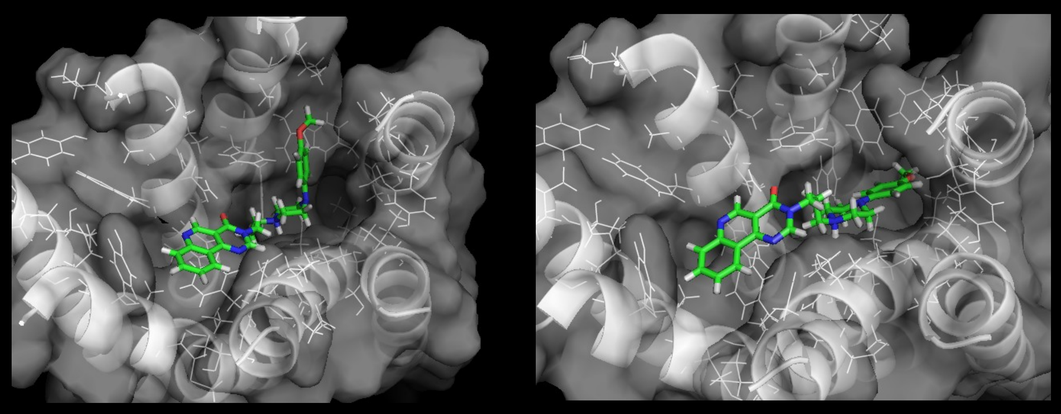

Figure 4. Lew5, with phenyl in axial (left) and equatorial (right) position in relation to piperazine, bound into 5-HT_{1A} receptor. Axial geometry makes the ligand structure difficult to fit into the binding pocket.

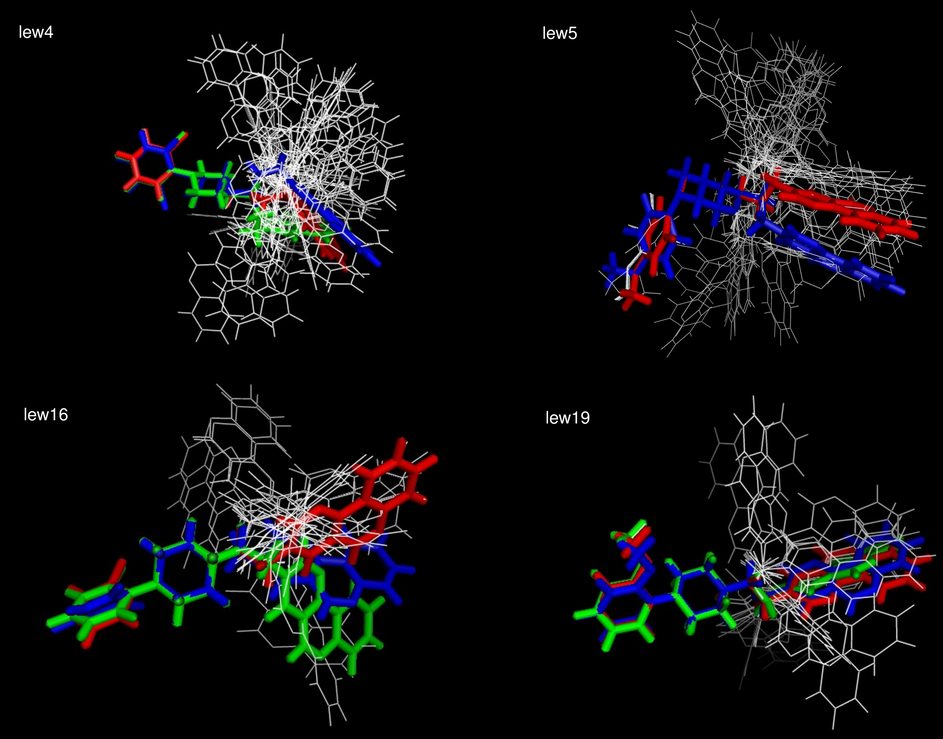

Figure 3. Conformations received after geometry optimization with COSMO algorithm. Crystal is in red, top score ligand received from docking process in blue, the closest conformer corresponding to dock hit in terms of RMSD value is in green

All other compounds bind into receptor models in a way similar to that described previously [1]. Phenyl substituent interacts with phenylalanine buried deep in binding pocket (Phe6.52), protonated piperazine nitrogen is anchored by aspartic acid (Asp3.32) and terminal part interacts with phenylalanine and/or tyrosine (Phe3.28, Tyr7.43) residues.

As can be seen on Fig. 5. crystal structures belong to group of extended conformations. In terms of NN distance for compounds with two methylene spacer docking hit and crystal geometry seem alike (Fig. 5), but in fact the corresponding RMSD values are above 3Å. Despite about 1Å difference between NN distance in crystal and docking hit their RMSD is significantly lower (1.8Å).

In general, it seems that for arylipierazines studied, both crystal structures or low energy conformers from optimization in water environment may be regarded as close to bioactive conformations as found in molecular docking studies.

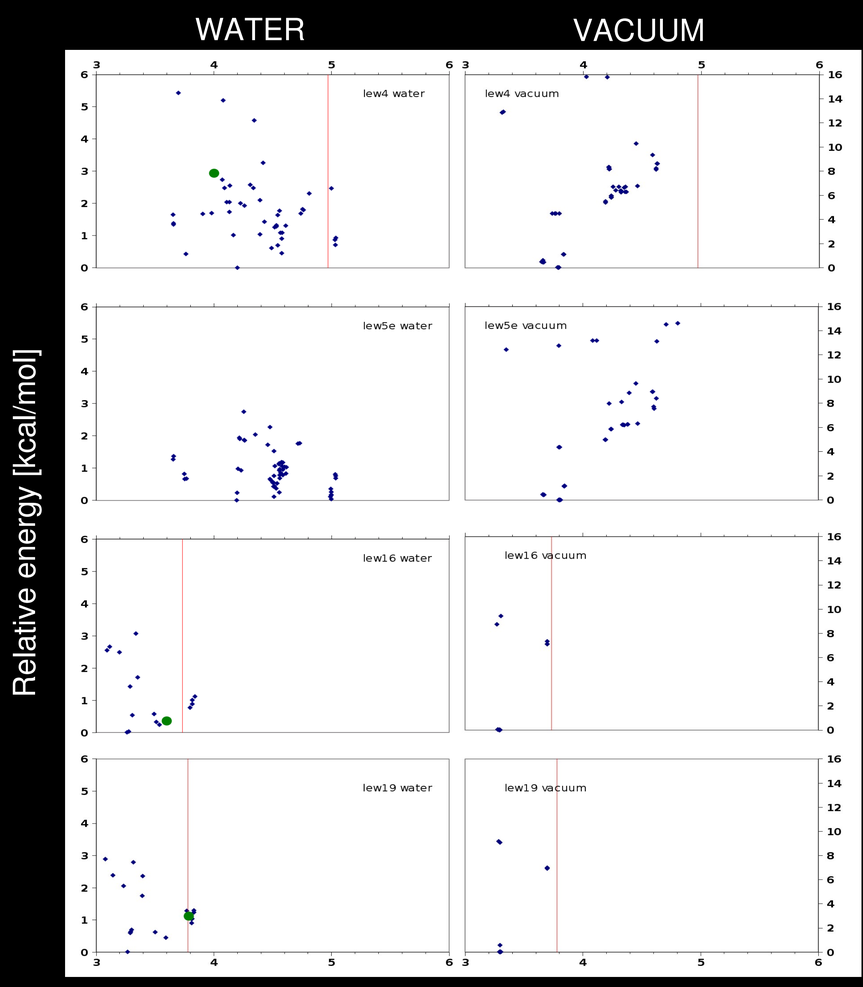

Figure 5. Graphs represent the relation between conformational energy and NN distance. Red lines indicate NN distance in crystal structures. Green dots highlight conformers which are the most similar to the top docking results.

References

[1] Nowak M. Kołaczkowski M. Pawłowski M. Bojarski J. A. J. Med. Chem. 2006, 49, 205-214