FMO/EDA study of 1-hexyl-4-(2-methoxyphenyl)piperazines as ligands of serotonin receptors

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Background

Long-chain arylpiperazines (LCAP) are one of the commonly studied classes of bioactive compounds due to their potential therapeutic effects caused by interactions with different subtypes of serotonin receptors. A number of studies have been aimed at examining the impact of LCAP structure modifications on the affinity, selectivity and function at a given receptor protein [1].

[1] Kowalski P. et al., Arch. Pharm. Chem. Life Sci. 346 (2013) 339–348

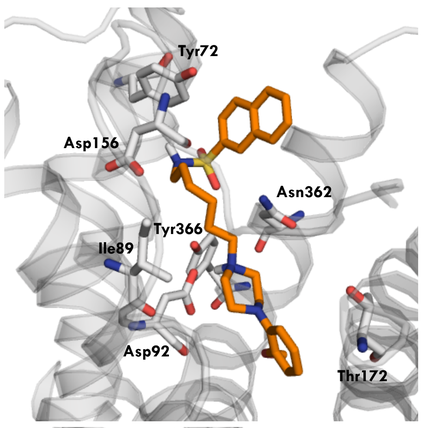
Methodology

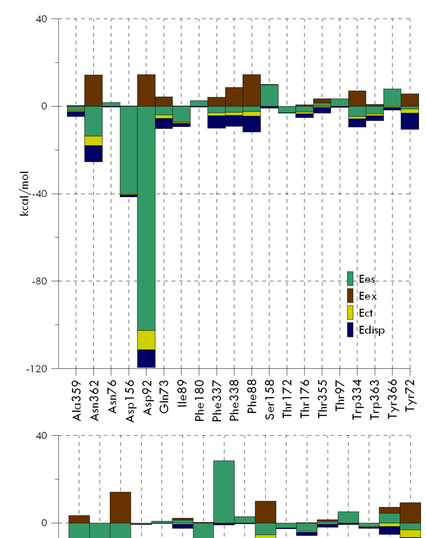
The structure of five derivatives of 1-hexyl-4-(2-methoxypneyl)piperazine complexed with two serotonin receptor homology models (5-HT_{1A}R, 5-HT_7R) were investigated by means of quantum mechanical methods: ONIOM (Our own N-layered Integrated molecular Orbital and molecular Mechanics: M06/6-31G*:AMBER) and FMO (Fragment Molecular Orbitals Method): MP2/6-31G*, water (PCM).

Firstly, compounds were docked to 5-HT_{1A}R and 5-HT_7R (Homology models based on 5-HT_{1B}R template). The missing hydrogens were added and than structures were fully optimized with ONIOM approach. Consecutively the ligand's stabilization energy was calculated with the FMO/EDA method.

5-HT_{1A} Receptor

1





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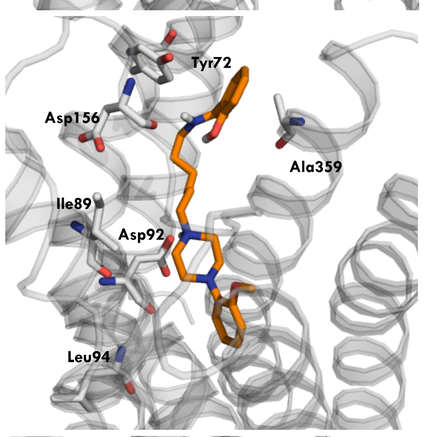

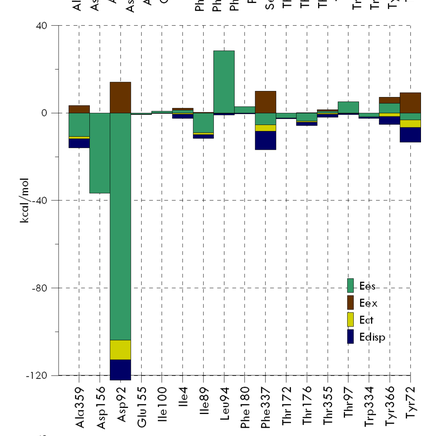

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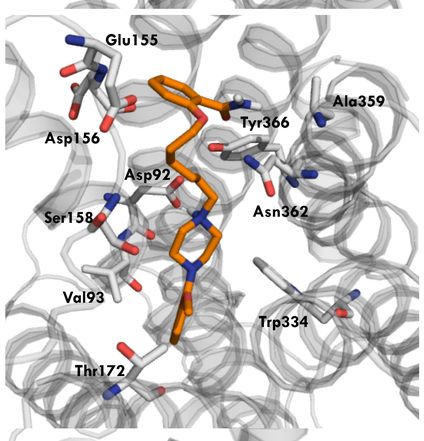

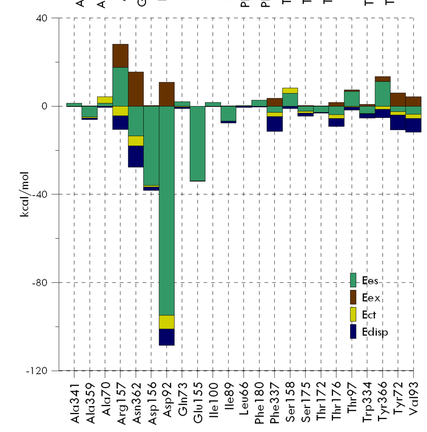

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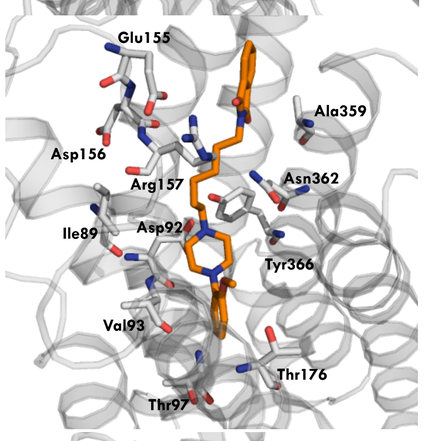

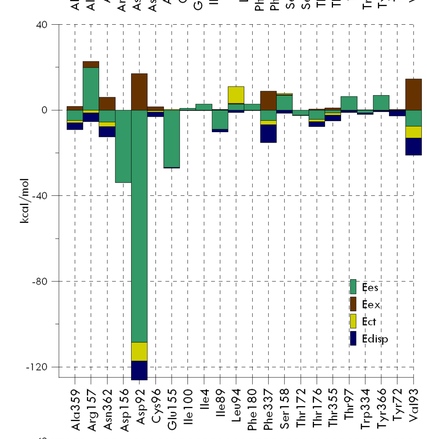

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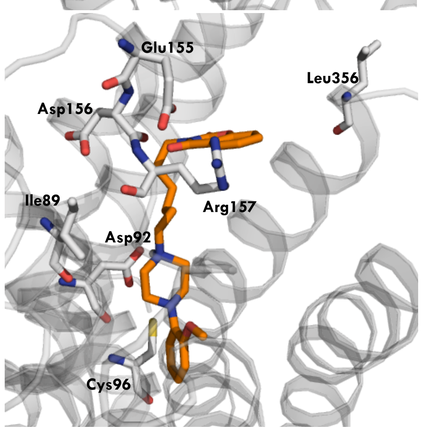

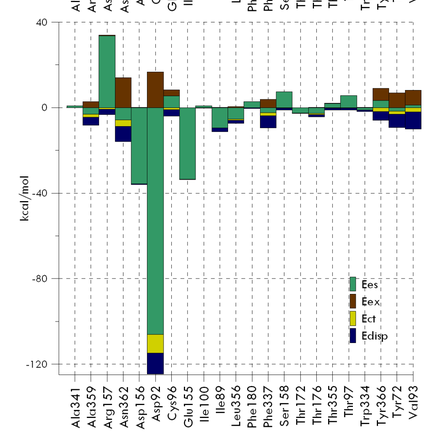

5-HT_7 Receptor

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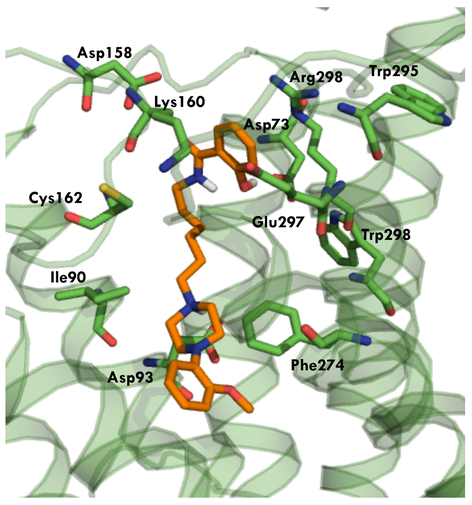

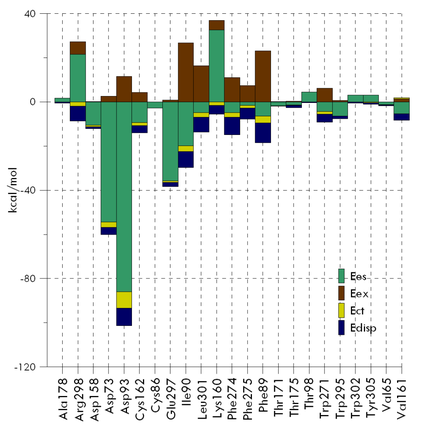

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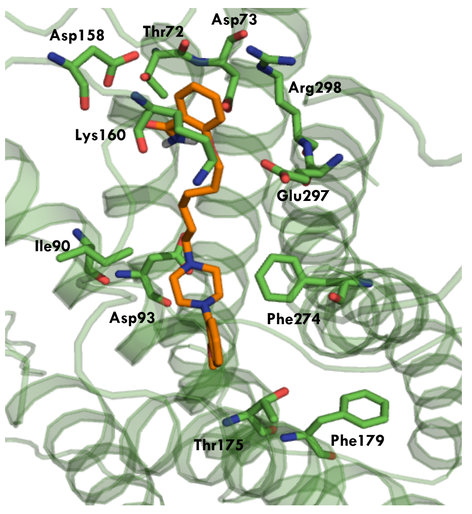

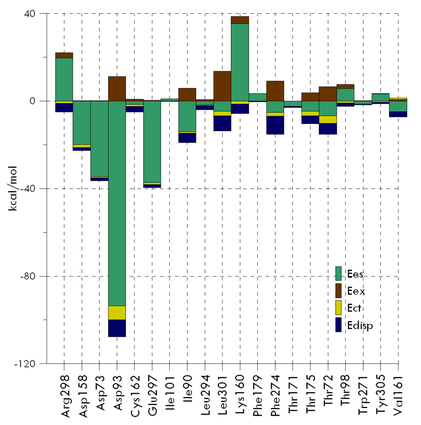

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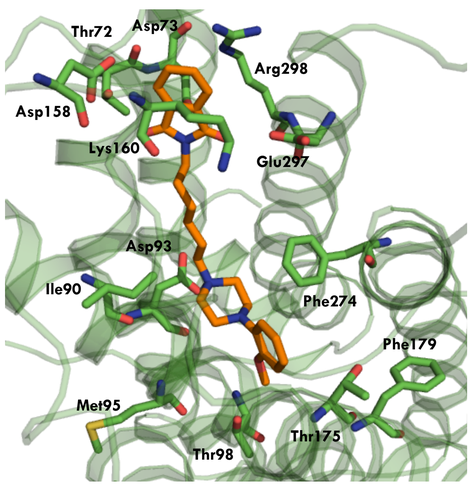

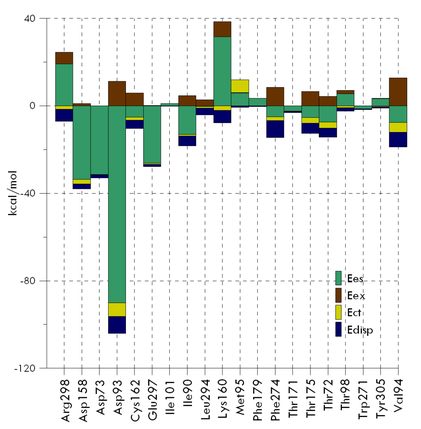

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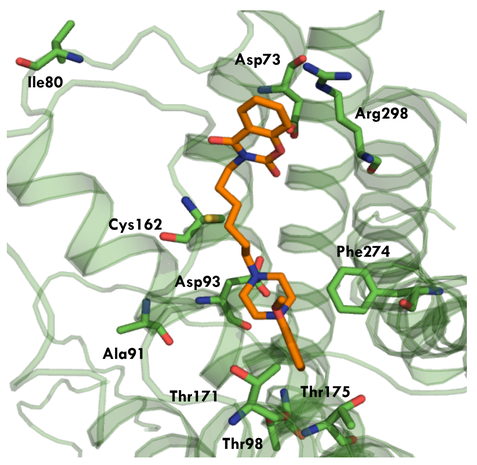

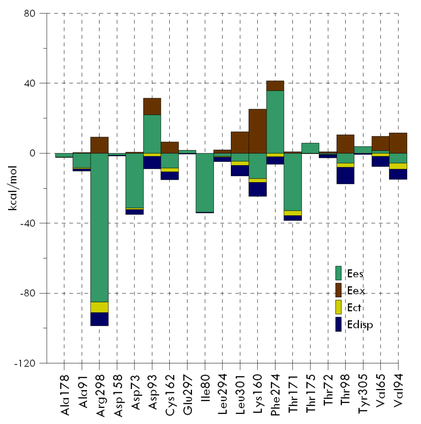

Conclusions

The FMO/EDA analysis showed that the 2-(piperazin-1-yl)-methoxybenzene moiety of considered ligands forms very strong salt bridge between the protonated nitrogen atom of piperazine and Asp3.32 (Asp92 or Asp93 on Figures). However, the hydrophobic interaction of the methoxybenzene ring with the aromatic cluster of TMH6 (Phe274 on Figure), were observed only for 5-HT_7R. The performed calculations are helpful in the interpretation of the experimental affinity of the compound to receptors, as well as they provide the reasonable binding energies and binding patterns of ligand-protein interactions.

Acknowledgements

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