Application of the 3D-QSAR methods for the development of novel more potent D_2 receptor antagonists.

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Introduction

Hallucinations, distortions in thinking, abnormal motor behavior- those are the symptoms of schizophrenia, a mental disease that affects around 20 million people worldwide. Although many medications are available for this condition, none of them can cure the disease or reduce its symptoms without causing significant side effects. Identification of a pharmacological gap in the treatment of schizophrenia became an incentive to thoughtfully examine the structure-activity relationship among a series of dopamine D_2 receptor antagonists

Methodology

The modeling set comprised of 176 compounds, divided into the training set (160 molecules) and 16 element test-set. Molecules were prepared with LigPrep and docked with Glide (Schrödinger software v. 2018-2) to the X-ray structure of the human dopamine D_2 receptor in the inactive state (**PDB ID**: 6CM4). Aligned poses had a protonated nitrogen atom that interacted with Asp (3.32) residue from the protein. The CoMFA model was constructed and validated in Sybyl-X v. .2.1. Later, the COMFA fields were mapped ontothe binding site of the dopamine D_2 receptor.

Content

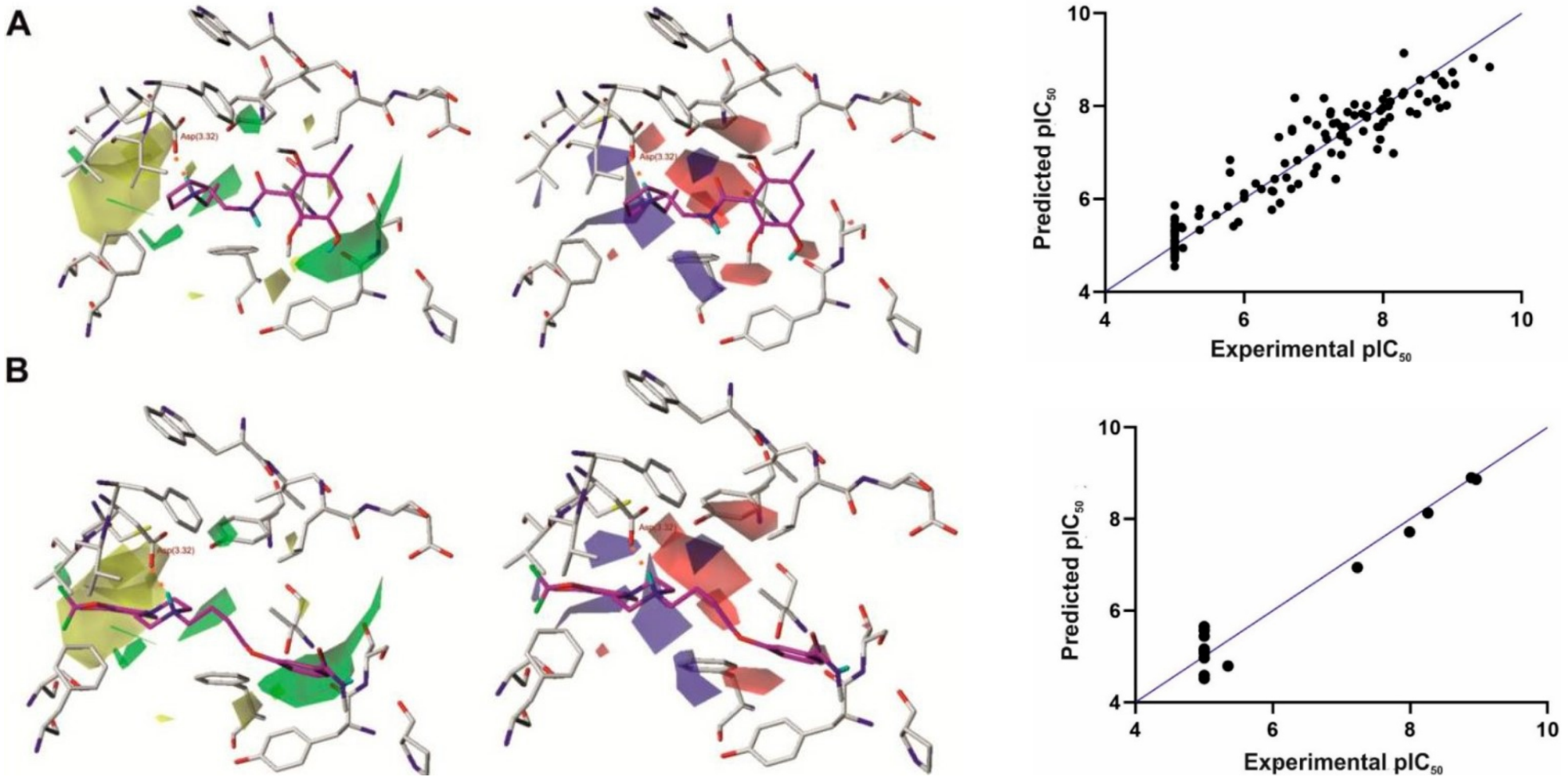

Fig 1. The CoMFA steric and electrostatic fields projected on the structure of dopamine D_2 receptor in complex with the most active (**A**) and the least active (**B**) of compounds.

Fig 2. The experimental versus predicted pIC_{50} values for the training set and test set.

Conclusion

The constructed universal 3D-QSAR CoMFA model was characterized by the following parameters: $\mathbf{R^2}$ of 0.92; $\mathbf{Q^2}$ of 0.76; **F-value** of 338.9; $\mathbf{r^2_{test\text{-}set}}$ of 0.95. The steric and electrostatic **field contributions** were 67.4% and 32.6% respectively. The results obtained in the procedure stand for a high statistical significance of the constructed CoMFA model, developed for a series of dopamine D_2 receptor antagonists. Analysis of contour plots provided us with structural requirements that may contribute to designing new antipsychotics. Moreover, it resulted in additional data that support suggestions regarding the presence of a common allosteric site in GPCRs.

References

Zięba, A.;Żuk, J.;Bartuzi, D.;Matosiuk, D.;Poso, A.;Kaczor, A.A. The Universal 3D QSAR Model for Dopamine D_2 Receptor Antagonists. *Int J Mol Sci* **2019**, *20*, doi:10.3390/ijms20184555