Relevance of Accurate Molecular Docking Studies as First Step to Obtain Reliable CoMFA Model

Vázquez-Valadez Víctor H, Castillo-Sánchez Victor, Abrego Víctor H, Velázquez-Sánchez Ana Ma , Angeles Enrique R

Abstract: Computer aid drug design has become a powerful tool to develop new drugs and in drug repositioning. In our work we look to generate a QSAR (quantitative structure-activity relationship), more precisely a CoMFA model (Comparative Molecular-Field Analysis). We are looking to create and evaluate a computer model that will help us to analyze and predict antitumoral activity from a library with two hundred pre-synthesized compounds. This theoretical result in the future will be compared with in vivo or in vitro studies with analytical procedures. The most important step in CoMFA analysis is the alignment of structures. Many times, geometric optimization, with molecular mechanics or ab initio calculations are used, but the analysis requires the structure responsible of the biological activity. In order to improve the time for the analysis and avoid many procedure mistakes we performed molecular docking validating the complexes with molecular mechanics. This data will be used for molecular alignment, instead using in vivo data we decided to use molecular docking and molecular dynamics studies to obtain such structures and try to correlate all in silico data.

I. Experimental Procedure

Receptor: The protein with 3L3X code from Protein Data Bank PDB, without mutations. Resolution: 1.55Å; Rf: 0.206; Rw 0.179 and no Ramachandran outliers. The receptor was prepared with “Structure Preparation” protocol of MOE 2015 suite. Ligands: The ligands were obtained from ZINC database. They were selected because they have hAR pKi data and posteriorly these data are used as activity data. We obtained 74 compounds, of these 47 are steroid derivatives. The structures were analyzed to verify their molecular structure, and they used as is were obtained from database. Binding Site: It was defined by DHT position in crystal structure. Water molecules from the crystal structure were used, principally a water molecule that interact with Gln711 and Arg752 residues. Docking Protocol: Rotations in single bonds were allowed. Positioning was by Triangle Matcher protocol. Molecular Mechanics refinement was used in binding site, Amber10 force field was used and GBVI/WSA dG was used like final score function.

Vázquez-Valadez Víctor H is with Universidad Nacional Autónoma de México e-mail: hugounam83@me.com
Castillo-Sánchez Victor is with Universidad Nacional Autónoma de México e-mail: vcs_12@hotmail.com
Abrego Víctor H is with QSAR Analytics e-mail: victor.abrego@qsaranalytics.com.mx
Velázquez-Sánchez Ana Ma is with Universidad Nacional Autónoma de México e-mail: velzquezanamara@gmail.com
Angeles Enrique R is with Universidad Nacional Autónoma de México e-mail: angeles@unam.mx

II. Results and analysis

As first step, DHT docking was performed, and was compared with crystal structure to validate the docking protocol. Due to the most important step of CoMFA analysis is the alignment, we selected the structures that match with natural spatial orientation of DHT to generate the first training set. In the Fig 1 it can be observed the superposition of 26 compounds that show the same spatial orientation that DHT, they will be used has the first training set, Fig 2. Additionally, we observed that the 21 remaining compounds showed preferentially two orientations. One is resulting of a double reflection, and the other is perpendicular to DHT-plane orientation. This two sets will have analyzed posteriorly to obtain another activity prediction models.

III. Conclusions

We obtained the activity structure for 46 compounds steroid derived. From then, a 26 molecules training set was selected to generate a CoMFA activity predictive model. Additionally, we observe two orientations in the pocket, this will be used to obtain more predictive models with the purpose of have better and more complete description of interactions in the binding site.

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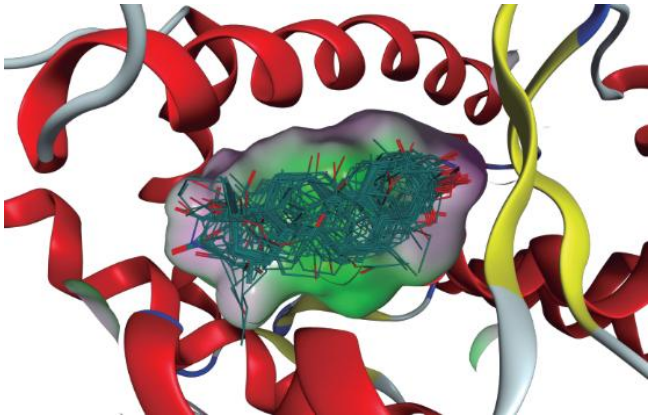

Fig 1. Superposition of 26 compounds used in the computational model CoMFA

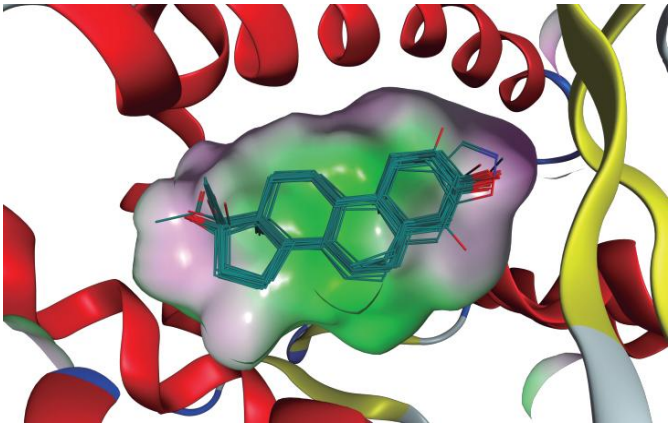

Fig 2. Training set representation of the molecules aligned after the molecular docking protocol and validated using molecular dynamics

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