Scoring Functions and Modeling of Structure-Activity Relationships for Cannabinoid Receptors

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Abstract—Computer-aided drug design could help much in the field of bioinformatics and biomedical engineering if there is a good model of CB1 and CB2 receptors and a suitable algorithm for the obtained ligand-receptor complex. The purpose of this article is to find the most appropriate scoring function and model for docking between cannabinoid ligands and cannabinoid receptors that correlate well with the data from biological activity of the compounds. The analysis of the obtained results indicates that the values of the ChemScore function correlate with the biological activity data at the highest degree and obtained correlation has a biological sense. This combination will allow us to test virtually a large number of potential cannabinoid ligands.

Keywords—Scoring functions; CB1; CB2; computer modeling; structure-activity relationships.

1 Introduction

An important task in the drug design is to find a bioactive conformation of a particular molecule defined as suitable to dock to the receptor binding site and to elicit a biological response. Finding a correlation between the structure and biological activity of cannabinoid receptors and their ligands is of interest to many researchers. To obtain a significant correlation, it is essential that appropriate descriptors are employed. Many of these descriptors reflect simple molecular properties and can provide insight into the physicochemical nature of the investigated compounds. The biological activity can be described by some known mathematical function, F: Biological activity = F [structure (parameters)] and it can be any measure of the parameters describing structural and physicochemical properties such as K_A, IC_{50}, EC_{50}, e_{rel}, E_m^T [1]. The structure-activity relationship is a mathematical expression derived by statistical or related techniques.

In the current investigation, we present a study of cannabinoid receptors and cannabinoid ligands. Cannabinoid receptor type 1 (CBR2) and cannabinoid receptor type 2 (CBR2) are attractive targets for many researchers in the field of bioinformatics and biomedical engineering [2-4]. The cannabinoids activate special receptors in the human body to produce a pharmacological action, particularly in the central nervous system and the immune system. Cannabinoids could be useful for treating side effects in cancer [5-9].

Docking experiments with these receptors and cannabinoid ligands were performed and evaluated with scoring functions embedded in the software GOLD 5.2. The results are presented in the following articles [10-12].

The main purpose of this article is to determine the correct way of ligand binding to the receptor in order to find a complex with a minimal energy. Our goal is to find the most appropriate scoring function and model for docking between cannabinoid ligands and cannabinoid receptors that correlate well with the data from biological activity of the compounds. This is important for determining the structure-activity activity relationship (SAR) by using molecular docking.

2 Materials and Methods

We apply an optimization algorithm for selecting potent cannabinoid ligands using the results of docking performed by genetic algorithm software GOLD 5.2 [13]. The docking is a computational method which predicts the preferred orientation of one molecule to other when bound to each other to form a stable ligand-receptor complex. If we know the preferred orientation of the molecules, we may be to predict the binding affinity between ligand and receptor using scoring functions. These functions are fast approximate mathematical methods used to predict the binding affinity between investigated compounds (in our case cannabinoid receptors and cannabinoid ligands) after they have been docked. We used four scoring functions provided with GOLD 5.2 (GoldScore, ChemScore, ChemPLP, ASP) which are described in Table 1 [13-18].

Table 1. Scoring functions used in docking experiments

Scoring functions	
$GoldScore = S_{hb_{ext}} + S_{vdw\_ext} + S_{hb\_int} + S_{vdw\_int}$	S_{hb_ext} - protein-ligand energy of H-bond S_{vdw_ext} - protein-ligand energy of Van der Waals S_{hb_int} (*internal H-bond*) S_{vdw_int} (*internal vdw*)
$ChemScore = \Delta G_{binding} + E_{clash} + E_{int} + E_{cov}$	$\Delta G_{binding}$ - free binding energy E_{clash} - clash energy E_{int} - internal energy E_{cov} - covalent bonding energy
$f_{CHEMPLP} = f_{PLP} - (f_{chem-hb} + f_{chem-cho} + f_{chem-met})$	f_{PLP} - Piecewise Linear Potential $f_{chem-hb}$ - H-bond, depending on the distance $f_{chem-cho}$- H-bonds, depending on the angles $f_{chem-met}$ - metal-bonds, depending on the distance
$ASP = -C_s S(map) - c_{int}E_{int} - c_{clash}E_{clash}$	$S(map)$ - total state score, all combinations of protein atoms *p* and ligands atoms *l*; C_s - scaling factor; E_{int} - internal energy; E_{clash} - clash coefficients.

Ligands used in the current investigation and their values of biological activity (K_A) from *in vitro* experiments are presented in Table 2 [18].

Table 2. Biological activity of the cannabinoid ligands used in the studies

Ligands	Values of biological activity
Anandamide	78 nM
N-Arachidonoyl dopamine	-
2-Arachidonoylglycerol	-
2-Arachidonyl glyceryl ether	21 nM
Δ-9-Tetrahydrocannabinol	10 nM
EGCG(Epigallocatechin Gallate)	33,6 μM
Yangonin	0,72 μM
UR-144	150 nM

3 Results and Discussion

For the human cannabinoid receptor type 1 three structures were used: the first two are models, obtained by algorithms for homology modelling (HM) in different software: MOE and Chimera, and the third is the crystal structure of the CBR1, obtained by Protein Data Bank (PDBid: 5tgz) (https://www.rcsb.org/). For the human cannabinoid receptor type 2 was used a model of the receptor, obtained by HM in Swiss-Model [10,11] (Figure 1).

According to Shim et al. [19] it is known that the binding site for CBR1 is asparagine residue around the receptor. In our investigation of the three models of CBR1 this residue is Asp366. The binding site for CBR2 is known from the literature as the cysteine residue in transmembrane helix 6 of the receptor homologous to C6.47 (355) in the CB1 receptor with which the NCS moiety of AM-841 interacts [20]. In the docking experiments between cannabinoid ligands and cannabinoid receptors the binding site was defined as residues within 10 Å radius of Asp 366 for CBR1 and 10 Å radius of Cys257 for CBR2.

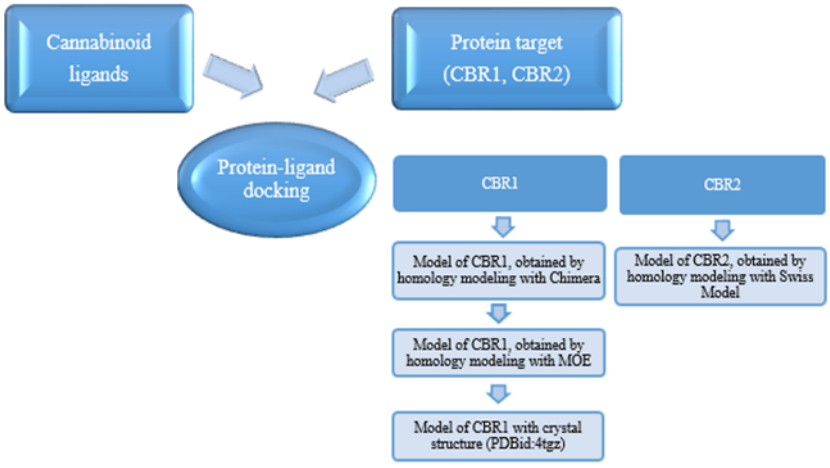

Fig. 1. Protein-ligand docking for cannabinoid receptors and cannabinoid ligands.

For protein target – in our case the models of the CBR1 and CBR2, molecular docking with software GOLD 5.2 generates several probable ligand binding conformations at the active sites around the receptors. The scoring functions from software for docking–ASP, ChemPLP, ChemScore, GoldScore were used to rank the ligand conformations by evaluating the binding density of each of the probable ligand-receptor complexes.

There are significant correlations between the values of ChemScore function (docking results) and the values of affinity of the ligands (biological activity) for CBR1 and CBR2. The obtained results are presented in Table 3 and Figure 2.

Table 3. Pearson correlation coefficient for CBR.

Functions	CB1			CB2
	CB1 (MOE)	***CB1 (Chimera)***	***CB1 (PDBid:5tgz)***	***CB2 (Swiss-Model)***
ASP	0,963	0,923	0,881	-0,1343
ChemPLP	-0,176	-0,472	-0,502	-0,511
ChemScore	-0,994	-0,924	-0,831	-0,9456
GoldScore	0,065	-0,341	-0,4393	-0,342

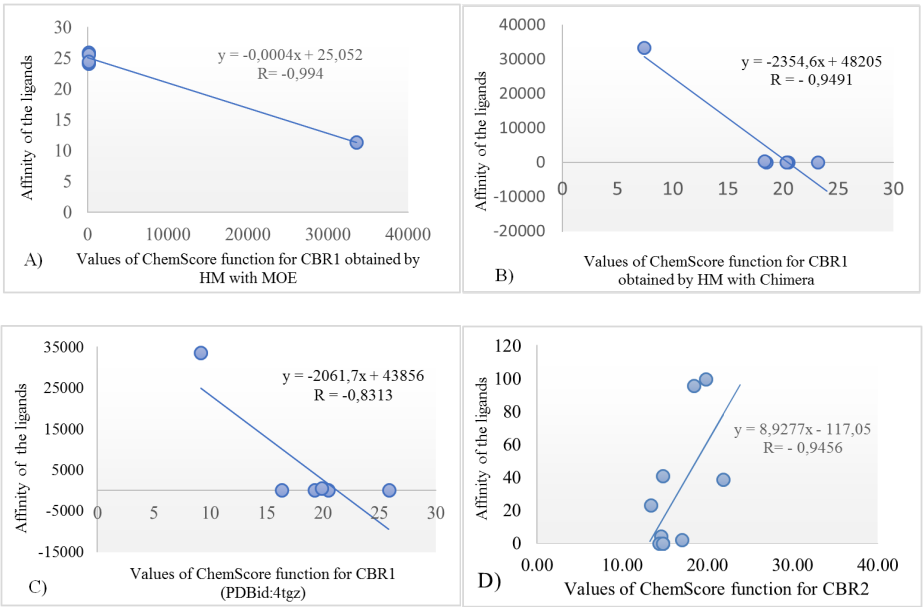

Fig. 2. Relationship between the values of the biological activity of cannabinoid ligands and the values of the ChemScore function for models of CBR1 and CBR2: A) CBR1 (model obtained by HM in MOE); B) CBR1 (model obtained by HM in Chimera); C) CBR1 (crystal structure, PDBid:5tgz); D) CBR2 (model obtained by HM in Swiss-Model).

As can be seen from Table 3 the values of correlations are higher with ChemScore function: CBR1 (model obtained by HM in MOE, R= -0,994); CBR1 (model obtained by HM in Chimera), R = -0,924; CBR1 (crystal structure, PDBid:5tgz), R=-0.831; and CBR2 (model obtained by HM in Swiss-Model), R = -0.924. The results are presented in Figure 3.

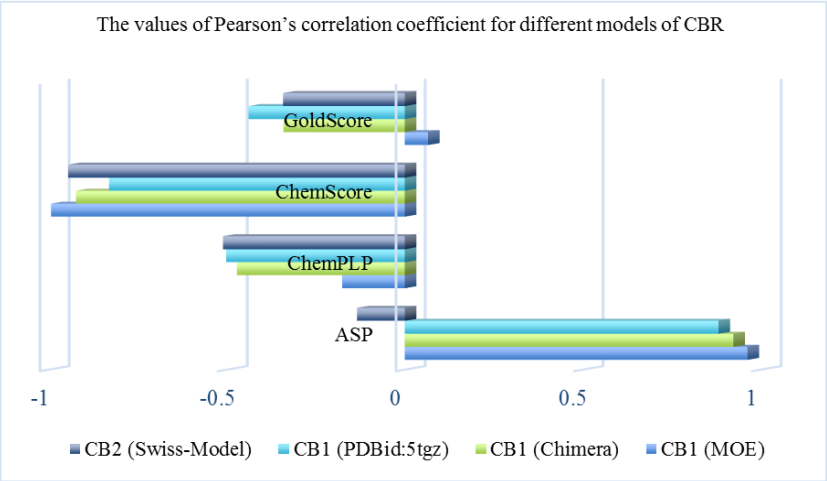

Fig. 3. The values of Pearson's correlation coefficient between biological activity of cannabinoid compounds and the four scoring functions of GOLD 5.2 for different models of CBR

A negative correlation between the values of ChemScore scoring function for models of CBR1 and CBR2 and the values of the affinity of the cannabinoid ligands was established. It is known that as lower the value of the affinity constant is the biological effect of the ligands is the stronger [21-26]. Dependence that best describes the biological effects using the docking is between ChemScore function and K_A.

4 Conclusion

The research community focused mostly on improving scoring predictions, because in common opinion, calculating a ligand *in vitro* activity is very difficult task. Therefore, typical strategy is to gather data from diverse set of scoring functions representing different approaches to create new function using simple linear regression technique.

The analysis of the obtained results indicates that the values of the objective function, named ChemScore function correlate with the data for biological activity of the cannabinoid ligands at the highest degree and obtained correlation has a biological sense. This combination will allow us to test virtually a large number of potential cannabinoid ligands.

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