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Highlight of New Phosphodiesterase 10A Inhibitors Using Molecular Docking

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Abstract: Phosphodiesterase 10A (PDE 10A) is an effective therapeutic approach for treatments of Schizophrenia (SCZ). In order to identify *in silico* new potent PDE 10A inhibitors, molecular docking approach was used. In this context, the compound S235 was predicted to exhibit a high potential PDE 10A inhibitory activity among 369 compounds tested. The predicted binding energy of this compound was improved from -10.28 to -13.80 Kcal/mol by structural replacements of its chemical grouping. Finally, the proposed compound was predicted to have good ADMET properties.

Keywords: Molecular Docking, AutoDock, Phosphodiesterase 10A, Binding Energy, Schizophrenia

Introduction

Many countries today have mental illness as a major public health issue. Among these diseases, Schizophrenia (SCZ) is the leading cause of severe and prolonged disability. In fact, in some countries, SCZ currently occupy more than half of psychiatric hospital beds. Since SCZ begins early in adulthood and does not significantly reduce life expectancy, not only are these patients removed from society to a period that should be that of their highest productivity. However, since they are often in good physical condition, their stay in hospital can last for very long years. It is therefore of the utmost importance to make every effort to prevent and treat this disease (Suzuki and Kimura, 2018). The main drugs used to treat symptoms of SCZ are antipsychotics. Although they are useful to most people with SCZ, antipsychotics can have serious side effects, let us take as examples: Motion disturbance, dizziness, cardiac arrhythmia, weight gain that increases the risk of diabetes and cardiovascular disease (Geddes *et al*., 2000). Among the various treatments of SCZ, Phosphodiesterase 10A (PDE 10A) inhibition appeared as a new and very effective therapeutic approach. PDE 10A inhibitors represent a new treatment for the negative, positive and the cognitive symptoms of SCZ, with a lower risk of side effects than conventional antipsychotics (Wagner *et al*., 2015).

Molecular docking is one of the most used computational methods in structure based drug design. It comprise two distinct tasks; the first being the prediction of favorable binding geometries for a small molecule in the binding site of a target protein and secondly, the estimation of the binding free energy of the complex so formed, also referred to as scoring (Kitchen and Decornez, 2004; Halperin *et al*., 2002).

The purpose of this work is to highlight new potent PDE 10A inhibitors using molecular docking method.

Materials and Methods

Target Preparation

The 3D structure of the PDE 10A; subject of our study, has been acquired from Protein Data Bank under the code 5UWF. This code corresponds to the 3D structure of the PDE 10A in complex with a co-crystallized inhibitor that has the code 8Q7. PDE 10A is a homodimeric enzyme; we have therefore eliminated one of its chain. This last was separated from its inhibitor (8Q7) in order to keep only the enzyme with free active site. Then, water molecules were also eliminated Afterwards, all the missing hydrogens are added and the partial loads of type "Kollman" are calculated with the Autodock Tools program. The prepared protein is stored in a *pdbqt* format file.

Ligand Preparation

The 3D structures of the PDE 10A inhibitors were drawn, minimized and exported as pdb files using Titan program. Then, all hydrogen atoms were added using Autodock Tools. This last program was also used in order to define aromatic carbons and rotatable bonds of each compound. The prepared ligands were exported as *pdbqt* files.

Docking Calculations

Molecular docking calculations were undertaken using the last version of AutoDock (Morris *et al*., 1998). The compound a is one of the best PDE 10A inhibitors (Tuttle and Kormos, 2014) with a value of IC_{50} of 0.4 nM. This compound was taken as starting structure for search of similar compounds. In this context, 396 similar compounds of a were downloaded from PubChem Database and prepared for docking calculations against active site of PDE 10A. According to docking's result, the structure of best similar compound was modified in order to define a new potent PDE 10A inhibitor.

Assessment of Docking Quality

The RMSD test represents the ability of a program to reproduce the experimental binding modes of a ligand. The RMSD value is equal to the average of the deviation of each of atoms compared to the original molecules. The best value of mean RMSD between the placing of the ligand calculated AutoDock and the conformation in the experimental complex was the smallest possible. The ratio accepted is 2Å beyond which the prediction is considered irrelevant. The current standars for evaluating the performance of a docking program is to make a test from hundreds of protein-ligand complexes crystallized. This test was performed on 100 complexes available in the PDB and the RMSD determined.

Drug Likeness Prediction

The pharmacokinetic parameters consisting of Blood-Brain Barrier (BBB) penetration, gastrointestinal absorption (GI), Cytochrome P450 (CYP) inhibition and Lipinski's rule of 5 of the best compound found in this word were predicted using Suissadme at http://www.swissadme.ch/index.php. Its toxicity was predicted using. PreADMET at https://preadmet.bmdrc.kr.

Results and Discussion

Validation of Docking Protocol

The performance of AutoDock was evaluated using 100 complexes Protein-Ligand available in the PDB. For each complex, the predicted binding mode was compared with the experimental binding conformation and a Root Mean Square Distance (RMSD) between the two models was calculated by AutoDock. A prediction of a binding mode was considered successful if the RMSD was below 2Å (Gabb *et al*., 1997). As shown in Fig. 1, the program AutoDock reproduced well the experimental data. Indeed, 71% of RMSD values are less than 2Å.

Virtual Screening of Similar Compounds Collection

The compound **a** is one of the best PDE 10A inhibitors (Tuttle and Kormos, 2014). Its experimental IC_{50} value is 0.4 nM. The binding energy between this compound and PDE 10A active site was predicted by molecular docking. The obtained value of binding energy (-10.28 Kcal/mol) showed a satisfactory agreement with the experimental data. In order to find new potent PDE 10A inhibitors, 369 similar compounds of a from PubChem database were docked into the active site of PDE 10A. It appears that the compound S235 was predicted as more potent PDE 10A inhibitor than the starting compound (a) since its binding was improved from -10.28 Kcal/mol to -11.95 Kcal/mol.

The binding mode of S235 into the active site of PDE10A was analyzed using the Maestro program. Figure 2 showed that S235 establish a hydrogen bond with Leu675.

Structural Modification of S235

In order to design new potent PDE10A inhibitor, the structure of S235 was modified. In this context, the cyclohexane ring of S235 was replaced by 1,4,5,6-tetrahydropyrimidine and its piperidine by a piperazine ring. The binding mode of the resulted compound, called a1, was predicted. Remarkably, the binding energy of this compound was improved from -11.95 Kcal/mol (S235) to -13.80 Kcal/mol. It should be noted that the improvement in the predicted binding energy is due to the setting up of new links and interactions because of the structural modifications performed. As shown in Fig. 3, a1 forms six hydrogen bonds with amino acids residues of PDE 10A active site.

Table1: The predicted pharmacokinetic and toxicity parameters of compound a1

Properties	Compound a1
BBB[a]	Yes
GI[b]	High
CYP[c] inhibitor	No
Lipinski's rule of 5	Suitable
Toxicity	CR[d]
	hERG[e] inhibition

[a]BBB: Blood-Brain Barrier. [b]GI: Gastrointestinal absorption. [c]CYP: Cytochrome P450. [d]CR: Carcinogenicity in Rat. [e]hERG: Human Ether-a-go-go Related Gene channel

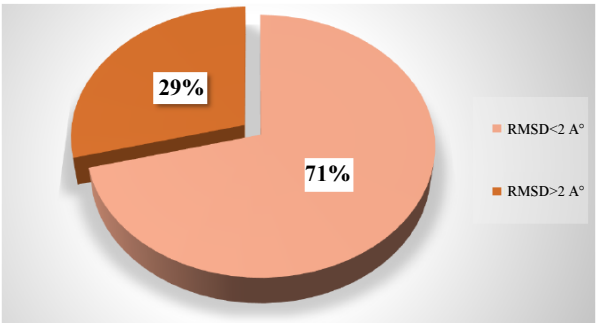

Fig. 1: Results in% obtained by AutoDock at two intervals of RMSD (Å)

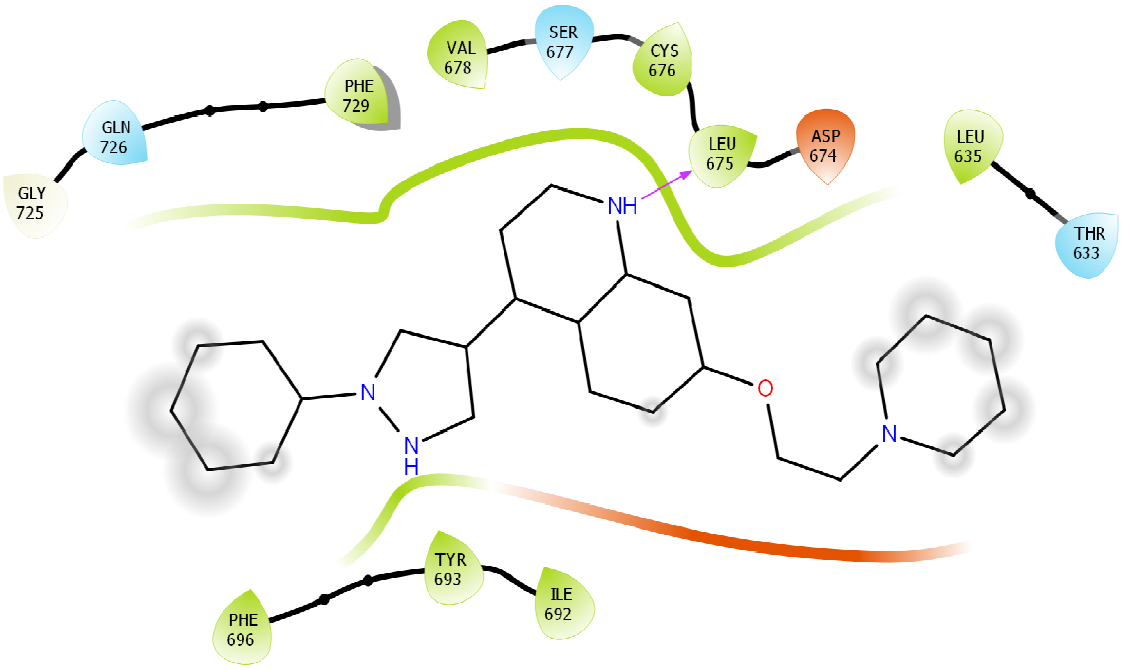

Fig. 2: Binding mode prediction of S235 into the PDE10A active pocket. Purple arrowhead from the donor to the acceptor of hydrogen bond. The images were done with the ligand interaction diagram script from the Schrçdinger suite

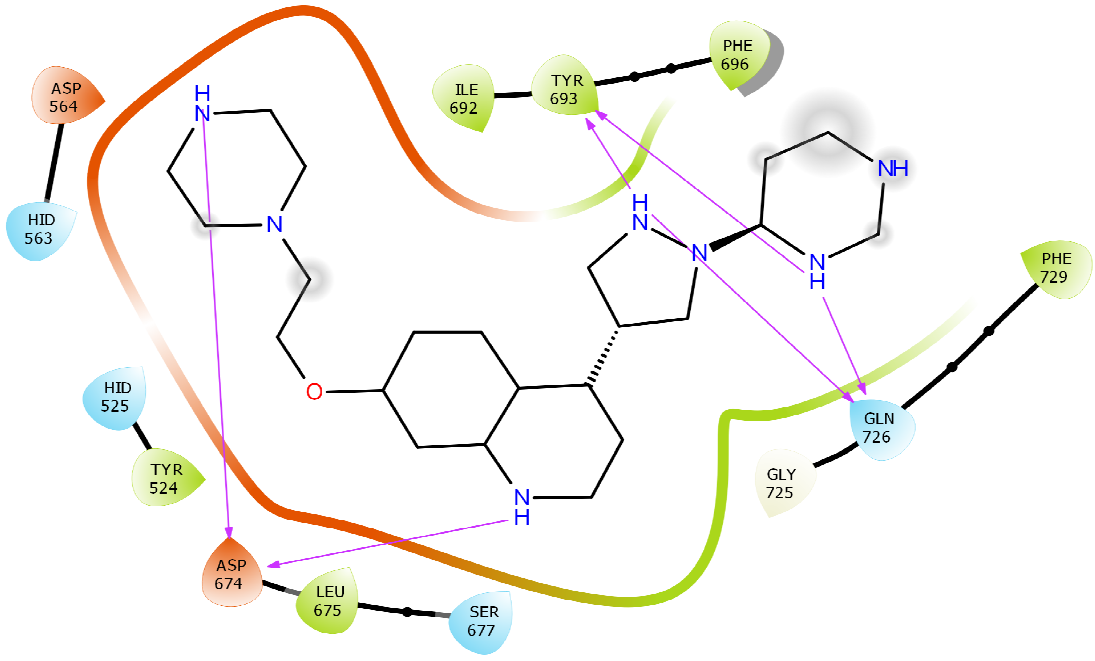

Fig. 3: Binding mode prediction of a1 into the PDE10A active pocket. Purple arrowhead from the donor to the acceptor of hydrogen bond. The images were done with the ligand interaction diagram script from the Schrçdinger suite

Drug Likeness Prediction

Finally, we predicted the pharmacokinetic and toxicity parameters of the most promising PDE10A inhibitor. As shown in Table 1, a1 had a high possibility in gastrointestinal absorption. Furthermore, this compound was not predicted to inhibit CYP (enzymes that should not be inhibited because they are essential for

the metabolism of many drugs in the liver). With no Lipinski's rule of 5 violation, a1 follows the criteria for orally available drugs. However, his toxicity problems including CR and hERG inhibition can be improved during its optimization.

Conclusion

In bref, this study showed that the AutoDock program can be used to predict enzyme-inhibitors interactions.

The strategy undertaken in this work, consisting of the docking of 369 compounds followed by a series of structural modifications allowed as identify a new potent PDE10A inhibitor. The binding mode of the most promising inhibitor was analyzed and showed that this compound cover the binding site of PDE10A in a rational orientation, where their hydrogen bonds with TYR693, GLN726, ASP674 seems to play an important role, leading to its high inhibitory potency. This new compound possess satisfying drug-like properties, indicating that it might be promising lead compound for further research.

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Author's Contributions

The first, the second and the last authors were participated in all experiments, coordinated the data-analysis and contributed to the writing of the manuscript, while the third author revised and modified the manuscript.

Ethics

This research was subjected to ethical clearance from the authrorities of University brother Mentouri Constantine 1, Algeria.

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Abbreviation and Units

3D	Three Dimensions
Å	Angstrom
ADMET	Absorption Distribution Metabolism Excretion Toxicity
IC_{50}	50% Inhibitory Concentration
KcaL/moL	Kilo calories/moL
nM	nanomolar
PDB	Protein Data Bank
PDE 10A	Phosphodiesterase 10A
RMSD	Root Mean Square Deviation
SCZ	Schizophrenia