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Article

ANALYSIS AND VISUALIZATION OF MOLECULAR DOCKING 2HI4 PROTEIN

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Abstract: The crystal structure of the human microsomal complex P450 1A2 with alpha-naphthoflavone, a cytochrome P450 (CYP) enzyme is particularly important, as it is abundant in the human liver and alters a more diverse xenobiotic array than any other group of metabolic enzymes. CYP1A2 is abundantly found in the liver and involved in the metabolism of about 10% of clinically used drugs metabolized by CYP enzymes. The current drug discovery and development mostly uses high-throughput screening (HTS). However, this regular method is time-consuming and costly. To address the issue, an advanced drug discovery and development method namely chemical compound database screening through computational methods used in this study as a promising method for chemical compound identification. Molecular docking predicts the conformation and orientation of the ligand in the binding site of the target protein. The results of molecular bonding of 2hi4 protein with 15 chemical compounds showed that three chemical compounds, benzo(a)pyrene, pteryxine, and quinine had satisfactory binding energy levels. A comparison of amino acids seen from 2D visualization shows that there are 7 amino acids in common, namely ALA317, GLY316, ASP313, ASP320, PHE260, PHE226, and THR118.

Keywords: Molecular docking, 2hi4

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1. Introduction

Protein 2hi4 consists of one type of cytochrome CYP1A2, cytochrome P450 superfamily (CYP)5, that plays a pivotal role in detoxifying foreign compounds and the biosynthesis of endogenous compounds, such assteroid hormones, bile acids, and cholesterol. CYP1A2 is highly expressed in and contributes significantly to the drug metabolism in the liver, such as flutamide, lidocaine, olanzapine, tacrine, theophylline, triamterene, and zolmitriptan. Therefore, protein 2hi4 is a common drug target in drug discovery.

In silico approach for drug discovery allows the virtual screening of millions of compounds in a short period, thereby reducing the initial costs of compound identification and increasing the probability to discovering promising drug candidates. Currently, various molecular modeling techniques are available to facilitate drug discovery, mostly classified based on their structure and ligand-based approaches.

One of the most popular *in silico* methods for drug discovery is molecular tethering. This method could predict the interactions between molecules and biological targets. The process could be achieved by predicting the molecular orientation of the ligand in the receptor, followed by estimating the replacement of the ligand in the receptor using a scoring function.

2. Results and Discussion

The first stage of molecular docking is initialized with sample preparation by removing hydrogen bonds and separating CYP1A2 form the native ligand, namely BHF800. After that, the molecular anchoring between CYP1A2 and the native ligand was validated by looking at the RMSD comparison between different grid boxes. In this experiment, it was tested with grid boxes 40, 50, and 60.

Table 1. Model validation analysis

	40×40×40	**50×50×50**	**60×60×60**
Binding Energy	-10.28	-10.27	-10.27
Grid Center	3.648	3.647	3.647
x =	15.883	15.880	15.886
y =	21.922	21.924	21.923
z =			
RMSD	0.76 Å	0.76 Å	0.76 Å
Inhibition Constant	29.39 nM	29.39 nM	29.41 nM

The result of model validation analysis (Table 1) showed that each grid box had the same RMSD value. The best grid box was determined based on the binding energy, -10.28 on a 40x40x40 grid box.

After that molecular anchoring was carried out with 15 chemical compounds using autodock. 12 compounds came from screening with the herbalDB omit 1 database, while 3 chemical compounds came from a literature search on the drug bank database. The results (Table 2) indicated that Benzo(a)pyrene, Pteryxine, and Quinine were the chemical compounds that have the best binding energy. Those three chemical compounds were visualized in 2D using ligplot and 3D using autodock (Figure 2.2 -2.4).

Table 2. Chemical compunds

Compound	**Binding Energy**	**Inhibit Constant**	**Hydrogen Bond**
Native	-10.28	29.39 nM	-
Clozapine	-9.33	145.51 nM	4
Dihydroxybergamottin	-8.22	950.87	2
Methoxyresorufin	-7.08	6.49 μM	1
Pentachlorobipheny	-7.5	3.2 μM	-
Ethoxyresorufin	-7.36	4.04 μM	2
BENZO(a)PYRENE	-10.05	43.29 nM	3
Amitriptyline	-8.11	1,14 μM	5
Naringenin	-7.08	6.51 μM	3
Phaseol	-9.14	201.02 μM	-
Bidwillol A	-9.12	208.05 nM	2
Dehydrocycloguanandin	-9.11	210.69 nM	2
Pteryxin	-9.69	78.95 nM	2
Curcumene	-7.64	2.49 μM	2
Quinine	-9.49	111.37 nM	4
Turmerone	-7.53	3.04 μM	2

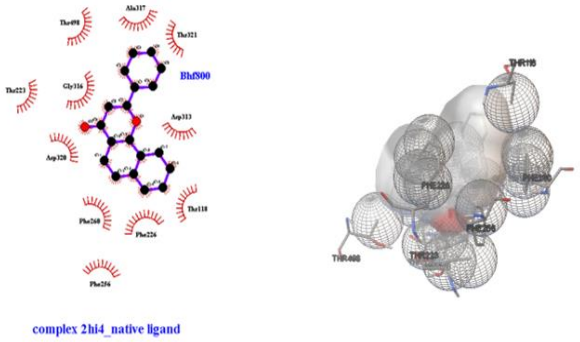

Figure 2.1 Molecular Docking Visualization on Native Ligands

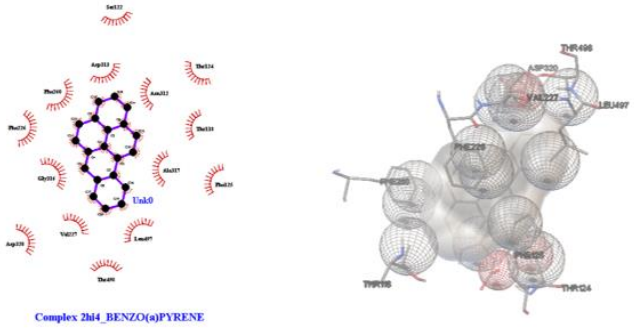

Figure 2.2 Molecular Docking Visualization on Benzo(a)pyrene

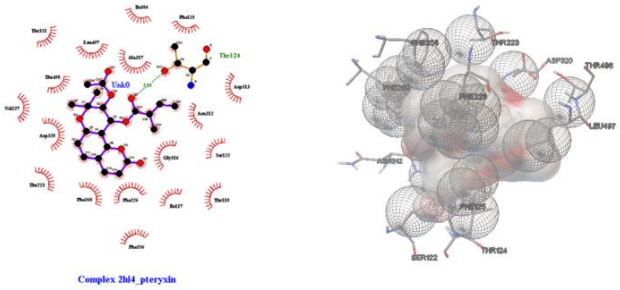

Figure 2.3 Molecular Docking Visualization on Pteryxine

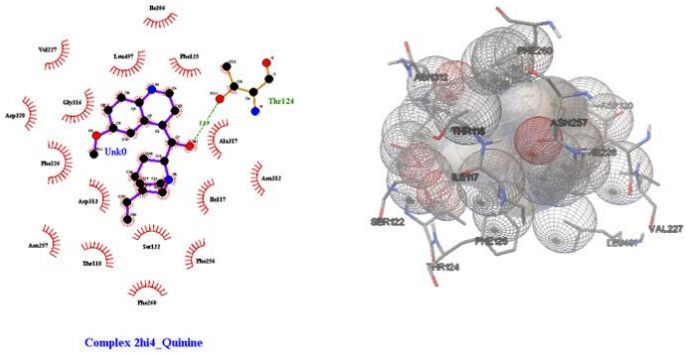

Figure 2.4 Molecular Docking Visualization on Quinine

2D visualization using ligplot simplify the observation of amino acids that had been successfully formed from the molecular bonding. Table 3 indicated that 7 amino acids were shared by the four ligands, namely ALA317, GLY316, ASP313, ASP320, PHE260, PHE226, and THR118. Moreover, Pteryxine ligand had all the same amino acids as the native ligand. This evidence indicated that Pteryxine could excellently bind to CYP1A2.

Table 3. The comparison of amino acids among various ligands

Amino Acid	**Native Ligand**	**Benzo(a)pyrene**	**Pteryxine**	**Quinine**
ALA317	V	V	V	V
THR498	V	V	V	-
THR321	V	-	V	-
THR223	V	-	V	-
GLY316	V	V	V	V
ASP313	V	V	V	V
ASP320	V	V	V	V
PHE260	V	V	V	V
PHE226	V	V	V	V
PHE256	V	-	V	V
THR118	V	V	V	V
SER122	-	V	V	V
ASN312	-	V	V	V
THR124	-	V	V 2.85Å	V 2.69Å
PHE125	-	V	V	V
LEU497	-	V	V	V
VAL227	-	V	V	V
ILE386	-	-	V	V
ILE117	-	-	V	V
ASN257	-	-	-	V

Table 4. Admetox Analysis

Ligands	**Druglikeness**					**Pharmacokinetics**						**Toxicities**	
	MW (g/mol)	HBA	HBD	LogP	GI Abs	Inhibitor CYP					AMES	Carcino-genesis	AOT
						CYP1A 2	CYP2C 19	CYP2C 9	CYP2D 6	CYP3A 4			
Benzo(a) pyrine	252.31	0	0	5.33	Low	Yes	No	no	no	No	+	-	III
Pteryxine	386.40	7	0	3.08	High	No	Yes	Yes	No	Yes	-	-	III
Quinine	324.42	4	1	2.81	high	no	no	no	yes	No	-	-	II

For more than a decade, the ADME-Tox properties of compounds have represented the cornerstone of drug development and discovery in silico prediction. Early assessment of ADME-Tox properties could shorten screening and testing time and reduce costs by identifying the strongest candidates for development and rejecting those with a low probability of success. In silico methods could be applied for predicting preclinical toxicological endpoints and clinical side effects.[7]

Solubility is considered as fundamental properties of drug absorption and plays critical role in the drugs that administered orally. Lipophilicity is the effective solubility of a compound into a non-aqueous medium and is correlated with various models of drug properties such as adsorption, distribution, metabolism, and toxicity. A molecule is more soluble if the consensus log P-value is more negative8 than Benzo(a)pyrenethat its molecular weight five times higher as compared to Pteryxine and Quinine, then Quinine is the most soluble molecule than the others, but belongs to AOT category II. Therefore, pteryxine was selected as a drug candidate compound by being a CYP1A2 ligand.

3. Materials and Methods

3.1. Finding Compound Target

Compound Target for 2hi4 proteins used LigandScout 4.3 and HerbalDB

3.2. Preparation of 2hi4 targets

Preparation of macromolecules downloaded from the PDB (Protein Data Bank) database. Separation of ligands from molecular complexes

3.3. Preparation of Ligand

The two-dimensional structure of compound target from herbalDB and Drugbank were withdrawn using Marvin Sketch.

3.4. Molecular Docking

Molecular docking compound targeted from herbalDB and Drugbank to see the activity of the compound on the site of BHF400 ligand (native ligand of 2hi4) used autodock software.

3.5. Analysis

Molecular docking of 15 target compounds from herbalDB and Drugbank analysis which compound had the highest RMSD (Root Mean Square Deviation) and condition of hydrogen bonds.

4. Conclusions

The best molecular binding of 2hi4 protein on a 40x40x40 grid with binding energy at -10.28. The results of molecular bonding of 2hi4 protein with 15 chemical compounds showed that three chemical compounds, benzo(a)pyrene, pteryxine, and quinine, had the best binding energy levels. A comparison of amino acids seen from 2D visualization shows that there are 7 amino acids in common, those were ALA317, GLY316, ASP313, ASP320, PHE260, PHE226, and THR118. Pteryxine had amino acid similarities to the native ligand. Admetox analysis of chemical compounds showed that pteryxine was better than other chemical compounds, because it was hydrophilic, and categorized as AOT III.

References

1. Sansen S, Yano JK, Reynald RL, et al. Adaptations for the oxidation of polycyclic aromatic hydrocarbons exhibited by the structure of human P450 1A2. *Journal of Biological Chemistry*. 2007;282(19):14348-14355. doi:10.1074/jbc.M611692200
2. Pinzi L, Rastelli G. Molecular docking: Shifting paradigms in drug discovery. *International Journal of Molecular Sciences*. 2019;20(18). doi:10.3390/ijms20184331
3. Juvonen RO, Jokinen EM, Javaid A, Lehtonen M, Raunio H, Pentikäinen OT. Inhibition of human CYP1 enzymes by a classical inhibitor α-naphthoflavone and a novel inhibitor N-(3, 5-dichlorophenyl)cyclopropanecarboxamide: An in vitro and in silico study. *Chemical Biology and Drug Design*. 2020;95(5):520-533. doi:10.1111/cbdd.13669
4. Tornio A, Backman JT. Cytochrome P450 in Pharmacogenetics: An Update. In: *Advances in Pharmacology*. Vol 83. Academic Press Inc.; 2018:3-32. doi:10.1016/bs.apha.2018.04.007
5. Batool M, Ahmad B, Choi S. A structure-based drug discovery paradigm. *International Journal of Molecular Sciences*. 2019;20(11). doi:10.3390/ijms20112783
6. Kumar A, Zhang KYJ. Application of Shape Similarity in Pose Selection and Virtual Screening in CSARdock2014 Exercise. *Journal of Chemical Information and Modeling*. 2016;56(6):965-973. doi:10.1021/acs.jcim.5b00279
7. Alqahtani S. In silico ADME-Tox modeling: progress and prospects. *Expert Opinion on Drug Metabolism and Toxicology*. 2017;13(11):1147-1158. doi:10.1080/17425255.2017.1389897
8. Ortiz CLD, Completo GC, Nacario RC, Nellas RB. Potential Inhibitors of Galactofuranosyltransferase 2 (GlfT2): Molecular Docking, 3D-QSAR, and In Silico ADMETox Studies. *Scientific Reports*. 2019;9(1). doi:10.1038/s41598-019-52764-8