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Molecular Docking of Selected Compounds Against Cellular Components of Bacteria

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Abstract

Researchers are trying to develop new antibiotics by targeting cellular components due to the emergence of antibiotic resistance by microbes. In this study, three targets were chosen these are penicillin binding protein-4, cell division protein, FtsA and shikimate dehydrogenase enzyme. Their binding sites were predicted online by RaptorX and GalaxyWEB servers. Virtual screening was carried out using the AutoDock Vina tool for a total of 50 experimental and approved compounds selected from the Drug Bank database. The results were redocked again by iGEMDOCK and the online SWISS-DOCK server. The top ten compounds in AutoDock Vina were selected. In Pharcokinetics and pharmacodynamics study in silico, the highest three compounds in docking scores, Flunisolide, Doxazosin and Isradipine, showed high absorption by the gastrointestinal route and did not appear to cross blood blood-brain carrier, but the last two showed a probability of drug interaction via cytochrome. Hence, the study of pharmacokinetics and toxicities is crucial in the drug design approach. The use of more than one tool is preferred to obtain more reliable results.

Keywords: *Docking, Molecular Targets, Pharmacokinetics, Virtual Screening.*

Introduction

Bacteria are showing resistance to almost all currently used antibiotics via several mechanisms; therefore, researchers are investigating new alternative targets against which antibiotics may be developed, such as peptidoglycan synthesis, division machinery and shikimate biosynthetic pathway [1, 2].

Penicillin binding proteins (PBPs), sensitive to penicillin, are involved in peptidoglycan synthesis. These proteins catalyze polymerization of the glycan stand, which is composed of alternating N-acetylglucosamine and N-acetylmuramic acid through a transglycoslation reaction. Also, they are responsible for the cross-linking of the strands by transpeptidation. Some of these PBPs catalyse carboxypeptidation to bring about hydrolysis of the last amino acid of the pentapeptide and endopeptidation reaction, which is the hydrolysis of the bond that connects two strands of glycan [3-5].

FtsA is another molecular target. FtsA is a component of the cell division machinery called the divisome. One of the important divisome proteins on the inner side of the plasma membrane is FtsZ, which forms bundles of protofilaments organised later into the Z-ring assembly. FtsA anchors FtsZ to the membrane. FtsA acts to interfere with the lateral interactions between FtsZ protofilaments and may affect FtsZ's high-order structure and the function of the divisome [6-8].

The shikimate acid pathway is involved in aromatic amino acids synthesis in bacteria, fungi and plants. It is absent in humans, making its enzyme components a good target to design antibiotics. Shikimate dehydrogenase is responsible for the

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conversion of 3-dehydroshikimic acid into shikimate using NADPH [1]. In this study, virtual screening is performed to identify ligands from the Drug Bank database to inhibit three possible targets, namely PBP-4, FtsA and shikimate dehydrogenase, through a molecular docking approach.

Materials and Methods

Obtaining protein models and prediction of binding sites: Crystal structures of three targets were obtained from the Protein Data Bank database. The crystal structure of PBP-4 (dacB) has the PDB ID: 2EX8, the crystal structure of FtsA has PDB ID: 3WQU, and that of shikimate dehydrogenase has PDB ID: 1NYT. Binding sites were predicted by the RaptorX online server developed by Källberg *et al*. [9] at (http://raptorx.uchicago.edu/). GalaxyWEB web server [10] was also available at: (http://galaxy.seoklab.org/cgi-bin/submit.cgi?type=SITE).

Molecular docking: A total of 50 experimental and approved compounds from the Drug Bank database were selected [11]. It also shows the molecular descriptors of compounds. The controls were Penicllin G, ATP and shikimate for PBP-4, FtsA and shikimate dehydrogenase, respectively. Molecular docking was performed by three docking tools. AutoDock Vina [12] used an autogrid tool to pre-calculate a grid. This grid has a size of 60×60 × 60 and a box centre of 87.709, 4.765 and 45.407 for x, y and z, respectively, for the PBP-4 target. A box centre at -2.825, 25.163 and -32.295 for FtsA target was used and 57.345, 27.835 and 20.36 for shikimate dehydrogenase. Interactions between compounds and target models were visualized by LIGPLOT+ [13]. Results were subjected to docking with iGEMDOCK [14]. The online SWISS-DOCK was employed to dock the results again [15]. It is available at http://www.swissdock.ch/.

Pharmacokinetics and pharmacodynamics predictions: SwissADME online program was used to predict the pharmacokinetics and pharmdynamics of the experimental and approved compounds [16]. It can be accessed at: http://www.swissadme.ch/.

Results and Discussion

Three docking tools were used in the virtual screening of 50 experimental and approved chemical compounds obtained from the Drug Bank database, and the top ten compounds in docking scores were presented according to Autodock Vina. These ten compounds were re-docked twice by different tools to get more accurate results. The interaction between molecular targets and these ten ligands in terms of hydrogen bonds and hydrophobic interactions.

PBPs are classified into two main groups. High molecular weight PBPs are subdivided into Class A and B. These act in glycosylation and transpeptidation reactions involved in polymerisation of the peptidoglycan sacculus and its insertion into the preformed cell wall [17, 18]. There are seven low molecular weight PBPs, referred to as Class C, such as PBP4 and PBP7. These are endopeptidases that can cleave cross-linking between two strands of glycan, as in recycling, cell separation and peptidoglycan maturation [19].

The crystal structure of PBP-4 (dac) was used in this study [20]. PBP-4 consists of three domains. Two domains are inserted in the transpeptidase domain in the way of “matryoschka dolls”, where the third domain is inserted in the second domain, which is inserted in the penicillin-binding domain [4]. RaptorX predicted the binding residues as follows: A^{42}, S^{43}, K^{46}, F^{141}, S^{287}, N^{289}, G^{339}, L^{340}, K^{398}, T^{399} while GalaxyWEB sever: A^{42}, S^{43}, S^{287}, N^{289}, S^{388}, G^{339}, L^{340}, G^{400}, S^{401}, L^{402} (Table 1 and Table 2).

Table 1. Docking Scores (Kcal/mol) of PBP-4

Compound	AutoDock Vina	iGEMDOCK	SWISS-DOCK
PNG	-6.2	-54.28	-7.8
DB00177	-7.1	-82.7	-7.7
DB00180	-7.5	-74.6	-7.3
DB00243	-7.2	-76.5	-7.2
DB00270	-7.2	-75.4	7.9
DB00276	-7.3	-75.0	-7.4
DB00301	-7.2	-71.2	7.8
DB00443	-7.1	-73.1	-7.6
DB00485	-7.0	-67.5	-7.7
DB00494	-7.0	-79.8	-8.0
DB00522	-7.4	-77.3	-7.9

Table 2. Interaction of PBP-4 with Ligands

Compound	Hydrogen bonds	Hydrophobic interactions
PNG	S398	S62, F160, K305, S306, N308, L359, T418, G419, S420, L421
DB00177	N308	C159, F160, R171, K305, S306, D307, L359, S420, Q422
DB00180	S62, S240, S306	F160, R171, N308, L421
DB00243	-	F160, R171, K305, S306, D307, L359, S420, L421
DB00270	-	S62, F160, S306, N308, L359, S420, L421, Q422
DB00276	-	S62, F160, S306, D307, N308, R361, S420, L421, Q422
DB00301	-	S62, F160, R171, S306, D307, N308, L359, L421
DB00443	S306, T418, S420	S62, F160, K305, G419
DB00485	-	S62, F160, R171, S306, D307, N308, L359, L421
DB00494	-	S62, F160, R171, S306, D307, N308, L359, L421
DB00522	R171, R361, Q422	C159, F160, N308, L359, L421

The FtsA crystal structure in complex with an ATP molecule was used [21]. FtsA resembles actin in its structure and appears to consist of two domains with a common core, which makes a groove between these domains where the nucleotide binds. Each domain consists of two subdomains; A1 and A2 are large and composed of five β-sheets and three α-helices, while the other two are variable in the actin family [22]. RaptorX predicted the following amino acid residues in binding site: G^{28}, S^{29}, S^{30}, S^{31}, K^{33}, G^{224}, E^{225}, D^{226}, V^{227}, G^{248}, E^{267}, K^{270}, H^{271}, G^{340}, G^{341}, S^{342}, N^{344}, L^{345}, E^{374} while GalaxyWEB server predicted binding site as follows: G^{28}, S^{29}, S^{31}, K^{33}, G^{224}, E^{225}, D^{226}, V^{227}, K^{270}, H^{271}, G^{340}, G^{341}, S^{342}, N^{344}, L^{345}, E^{374} (Table 3 and Table 4).

Table 3. Docking Scores (Kcal/mol) of FtsA

Compound	AutoDock Vina	iGEMDOCK	SWISS-DOCK
ATP	-8.8	-61.3	-8.14
DB00197	-9.1	-61.2	-7.9
DB00243	-9.6	-78.8	-7.2

DB00301	-8.3	-69.4	-7.4
DB00341	-8.9	-85.3	-7.6
DB00346	-8.7	-70.1	-8.3
DB00384	-9.1	-93.7	-7.5
DB00436	-9.2	-86.1	-7.3
DB00469	-8.5	-96.4	-7.9
DB00507	-10.1	-87.8	-8.5
DB00590	-10.9	-79.9	-7.6

Table 4. Interaction of FtsA with Ligands

Compound	**Hydrogen bonds**	**Hydrophobic interactions**
ATP	S15	G12, S14, P79, G208, E209, V211, Q213, H225, K254, G325, S326, N328, L329
DB00197	D185	D10, G12, S14, K17, K77, T189, D206, G208, E209, V211, K254, H255, G325, S326, N328, E358, S361
DB00243	-	D10, G12, S13, S14, K17, K77, D206, G208, E209, V211, Q213, G325, S326, N328, G232, H255, E358
DB00301	D10, S14, E209, G325	G12, S15, K17, Q35, D206, G208, G324, S236, K254, H255, E358
DB00341	S14, E358	D10, G12, S13, S15, K17, Y37, D206, G208, E209, V211, G324, G325, E358, S361
DB00346	S15, K17, K77, D206, H255	D10, G12, S13, S14, G44, G208, V211, Q213, K254, G325, S326, N328, E358
DB00384	-	D10, G12, S14, K17, K77, D206, G208, E209, Q213, G324, G325, E358, S361
DB00436	S13, K17, K77, D206, G325	S14, P79, G208, E209, V211, Q213, G324, E358
DB00469	K17, E358	D10, G12, S13, S14, K77, D185, W189, D206, G208, E209, V211, Q213, G325, S361
DB00507	K77	S13, S14, K17, D206, G208, E209, V211, E213, G325, E358, S361
DB00590	-	D10, S13, S14, S15, K17, Q35, D206, G208, E209, Q213, K254, H255, G325, S326, N328, E358, S361

The Shikimate dehydrogenase crystal structure solved by Michel *et al*. [23] was used. Shikimate dehydrogenase contains two domains. The first catalytic domain possesses a twisted α/β motif. The second domain is a Rossmann fold in configuration and binds to NADPH [24]. According to RaptorX, the following residues are present in the binding site: V^{6}, S^{14}, S^{16}, N^{59}, V^{60}, T^{61}, K^{65}, N^{86}, D^{102}, L^{241}, Q^{244} while GalaxyWEB server shows the following: S^{16}, N^{59}, T^{61}, K^{65}, N^{86}, D^{102}, L^{241}, Q^{244} (Table 5 and Table 6).

Table 5. Docking Scores (Kcal/mol) of Shikimate Dehydrogenase

Compound	**AutoDock Vina**	**iGEMDOCK**	**SWISS-DOCK**
Shikimate	-6.5	-62.8	-6.4
DB00177	-9.2	-95.8	-9.3
DB00197	-9.8	-76.8	-8.5
DB00203	-9.2	-88.1	-8.9

DB00243	-9.4	-84.0	-8.3
DB00270	-10.3	-86.3	-8.6
DB00276	-9.4	-88.7	-8.9
DB00401	-9.8	-79.2	-8.5
DB00507	-9.3	-89.6	-7.8
DB00522	-10.0	-90.8	-8.2
DB00590	-9.5	-72.9	-8.8

Table 6. Interaction of Shikimate Dehydrogenase with Ligands

Compound	Hydrogen bonds	Hydrophobic interactions
Shikimate	S16, V60, T61, N86, D102	D59, K65, L241, Q244
DB00177	D102	V6, S16, N59, V60, T61, V62, K65, A187, T188, S189, M213, F214, W215, L241, Q244
DB00197	S16, N86, K65	V6, P10, N59, V60, T61, V62, D102, T188, S189, I192, M213, L241, Q244
DB00203	S14	V6, P10, S16, N59, T61, V62, D102, A130, A187, T188, S189, M213, F214, W215, L241, Q244
DB00243	-	V6, S14, S16, V60, T61, N86, A130, T188, S189, M213, F214, W215, L241, Q244
DB00270	-	T61, V62, K65, A130, A187, S189, M213, W215
DB00276	K65, A187	V62, P63, D102, G128, G129, A130, T188, S189, M213
DB00401	T61	P10, V62, D102, T188, S189, I192, M213, F214, W215, M240, L241
DB00507	S16, Q244	V6, S14, N59, T61, W215, L241
DB00522	W215	V62, P63, K65, G129, A130, A187, T188, S189, M213, F214
DB00590	-	S14, T61, V62, P63, K65, E66, G128, G129, A187, T188, S189, M213, F214, W215, L241

Flunisolide (DB00180) had the highest docking score in the virtual screening targeting PBP-4. It is a synthetic corticosteroid used in the treatment of asthma as an inhaler [25] (Table 7 and Figure 1).

Table 7. Molecular Descriptors of the Tested Compounds

Compound	Name	Molecular weight	logP	Hydrogen bond donors	Hydrogen bond acceptor
DB00177	Valsartan	435.519	3.68	2	6
DB00180	Flunisolide	434.498	2.20	2	6
DB00197	Troglitazone	441.540	4.16	2	5
DB00203	Revatio	474.576	2.35	1	8
DB00243	Ranolazine	427.536	2.08	2	6
DB00270	Isradipine	371.387	3.00	1	5
DB00276	Amsacrine	393.459	4.66	1	5
DB00301	Flucloxacillin	453.056	2.69	2	5
DB00341	Cetirizine	388.888	2.98	1	5

DB00346	Alfuzosin	389.449	2.02	2	8
DB00384	Triamterene	253.263	1.21	3	7
DB00401	Nisoldipine	388.414	3.63	1	5
DB00436	Bendroflumethiazide	421.415	1.83	3	5
DB00443	Betamethasone	392.461	1.93	3	5
DB00469	Tenoxicam	337.370	2.42	2	5
DB00485	Dicloxacillin	470.326	3.19	2	5
DB00494	Entacapone	305.286	2.50	2	6
DB00507	Nitazoxanide	307.282	2.14	1	5
DB00522	Bentiromide	404.415	2.99	4	5
DB00590	Doxazosin	451.475	2.53	5	9

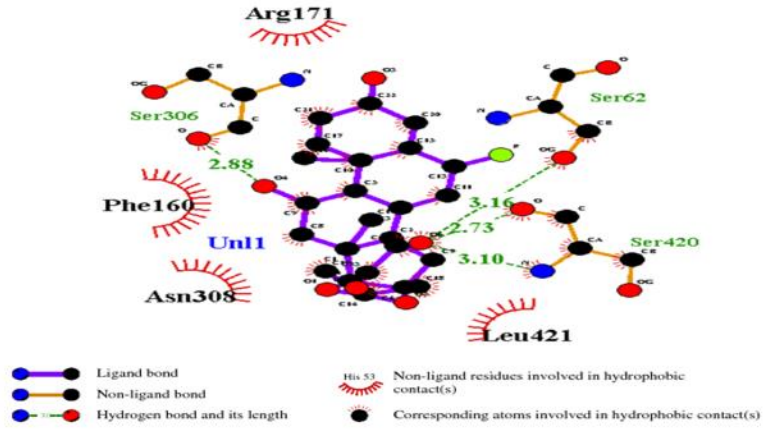

Figure 1. Interaction of PBP with DB00180

Doxazosin (DB00590) showed the highest docking score in AutoDock in the case of the FtsA target. It is an alpha1 blocker drug used in the treatment of benign prostatic hyperplasia [26]. Isradipine (DB00270), a calcium channel blocker used in the treatment of hypertension [27], showed the highest docking score against shikimate dehydrogenase. Molecular descriptors (Figure 2).

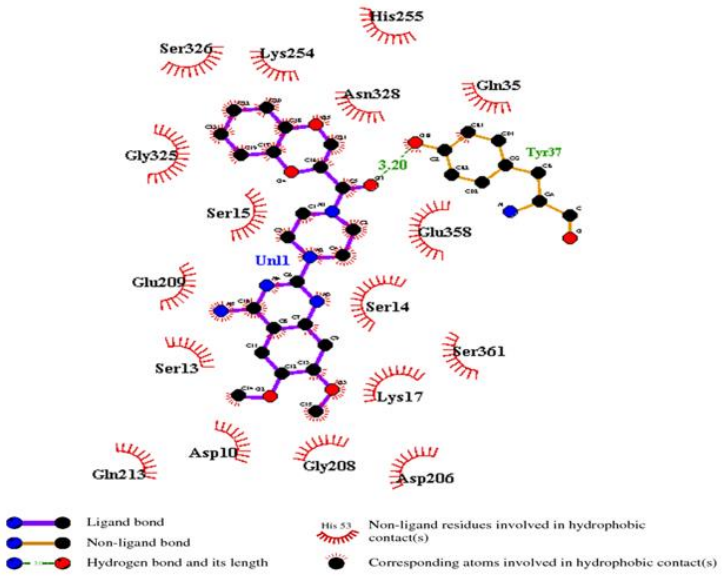

Figure 2. Interaction of FtsA with DB00590

José Alves et al. [28] used AutoDock 4 to measure the inhibition constant (Ki) of compounds found in mushrooms against PBP1a. Vanillic acid, gallic acid and protocatechuic acid have Ki values of 19.05, 19.02 and 18.2 µm, respectively. Kulanthaivel et al. [29] found that a compound which had ZINC database ID 95911396 gave a docking score of -10.12 among others, which was higher than previously reported ligands (3-bromopyruvate, 2-deoxyglucose, lonidamine, imatinib and oxythiamine). In addition, Isa et al. [30] used Autodock4 in virtual screening of a total of 13803 compounds against shikimate dehydrogenase (Figure 3). The study identified 26 compounds with binding energies ranged between -12.03 to -8.33 Kcal/mol. In further analyses, two compounds namely ZINC12135132 and ZINC08951370 were identified to have the best inhibitory actions.

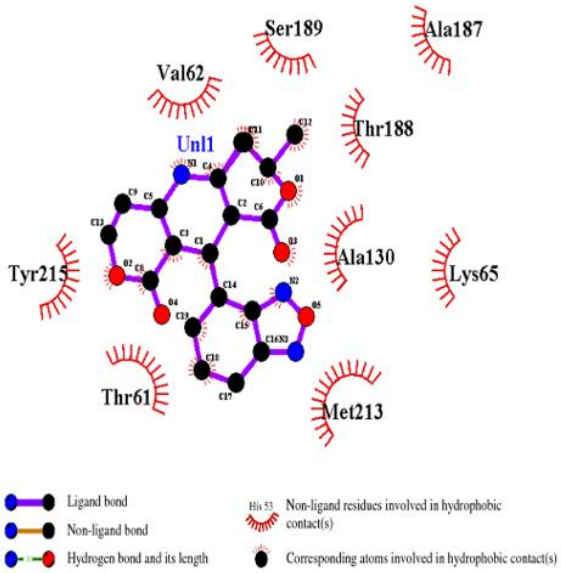

Figure 3. Interaction of Shikimate Dehydrogenase with DB00270

Table 8 shows some predictions of pharmacokinetics and pharmacodynamics for the experimental and approved compounds. Flunisolide, Doxazosin and Isradipine have high gastrointerstinal absorption and do not penetrate blood blood-brain barrier, so they can enter the body easily and do not have toxicity for the central nervous system [31]. However, both Doxazosin and Isradipine may inhibit cytochromes that are responsible for the oxidative stage of drug elimination from the human body [32], implying that toxicity from other drugs may result, i.e. drug interaction [33]. This green chemistry provides a valuable technique to control infection [34], even in the presence of multidrug-resistant bacteria [35] or associated chronic diseases [36].

Table 8. Pharmacokinetics and Pharmacodynamics of Tested Compounds

Compound	G.I.	BBB	P-gp	Cytochrome inhibition					D.L.
				1A2	2C19	2C9	2D6	3A4	
DB00177	High	No	No	No	Yes	Yes	No	Yes	Yes
DB00180	High	No	Yes	No	No	No	No	No	Yes
DB00197	High	No	Yes	No	Yes	Yes	No	Yes	Yes
DB00203	High	No	Yes	No	No	Yes	No	Yes	Yes
DB00243	High	No	Yes	No	No	No	Yes	No	Yes
DB00270	High	No	No	Yes	Yes	Yes	No	Yes	Yes
DB00276	High	No	No	Yes	Yes	Yes	Yes	Yes	Yes

DB00301	Low	No	Yes	No	Yes	No	No	Yes	Yes
DB00341	High	Yes	Yes	No	No	No	Yes	No	Yes
DB00346	High	No	Yes	No	No	No	No	No	Yes
DB00384	High	No	Yes	Yes	No	No	Yes	Yes	Yes
DB00401	High	No	No	Yes	Yes	Yes	Yes	Yes	Yes
DB00436	Low	No	Yes	No	No	No	No	No	Yes
DB00443	High	No	Yes	No	No	No	No	No	Yes
DB00469	High	No	No	No	No	No	No	No	Yes
DB00485	Low	No	Yes	No	Yes	No	No	Yes	Yes
DB00494	Low	No	Yes	No	Yes	No	No	Yes	Yes
DB00507	Low	No	No	No	Yes	No	No	No	Yes
DB00522	High	No	No	No	No	Yes	Yes	No	Yes
DB00590	High	No	No	No	No	Yes	Yes	Yes	Yes
G.I.: Gastrointestinal absorption, BBB: Blood brain barrier penetration, P-gp: Plasma glycoprotein substrate, D.L.: Lipinski´s drug likeness.									

Conclusion

The objective of the virtual screening approach is to select compounds for further *in vitro* experiments, where thousands of compounds are subjected to molecular docking against a given target and the top ten compounds in scored. However, negative and positive false results may occur. Using more than one docking tool can improve the process of getting more reliable results.

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Conflict of Interest

The authors declare no conflict of interest.

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