Journal of Materials Science & Surface Engineering, 6(6): 895-898
ISSN (Online): 2348-8956; 10.jmsse/2348-8956/6-6.4

Computational Drug Discovery Based on Natural Products Against Acinetobacter *Baumannii*

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ABSTRACT

Antimicrobial resistance has been reported in opportunistic pathogenic bacteria *A. baumannii* with alarming rate. So far few drugs/inhibitors Carbapenem, Bedaquiline etc were developed as an effective treatment against the infection, but there efficacies have been found to be challenged in due course. Currently a potential drug target BfmR (PDB ID: 5HM6), a response regulator in signal transduction system (TCS), identified by scientific group in bacteria *A. baumannii* stain AB307-0294 is necessary for its survival. Natural products such as alkaloid, flavonoid, terpenes, have been reported effective antimicrobial treatments. In order to address the identified gaps in term of potential lead discovery, we proposed to perform the computational interaction study of the downloaded terpenes, alkaloid, phenols etc. available at drug bank database along with potential target BfmR. The docking experiments was carried out with control (Carbapenems, Bedequiline etc) as well as with test molecule (alkaloid) using Auto Dock Vina software. The obtained results revealed the binding energy -8.9 kcal/mol Ervacycline (control) Drugbank ID: DB12329 while the test sample 6,7,12,13-tetrahydro-5H-indolo [2,3-a] pyrrolo [3,4-c] carbazol-5-one having Drugbank Id:DB08036 an alkaloid molecule with binding energy -9.4 kcal/mol. Afterwards molecular dynamic simulation was performed on the best ligands to study the stability of interections. Hence this study supports the possible use of above ligand as alternative therapy against *A. baumannii* infection. The work can be enhanced with multiple drug target and taking into account other structure from other resources with large scale docking and simulations studies.

ARTICLE HISTORY
Received 06-04-2019
Revised 04-09-2019
Accepted 06-09-2019
Published 01-12-2019

KEYWORDS
A. Baumanni
BfmR
Natural product
Molecular Docking
DrugBank

Introduction

Acinetobacter baumannii, a gram negative bacilli has tremendously exhibited with Multidrug-resistant problem towards the currently used drugs and raised the challenges towards its effective treatment and control [10]. Pathogenic bacteria *A. baumannii* has been reported as antimicrobial resistance with alarming rate. So far few drugs/inhibitors like Carbapenem, Bedaquiline etc were developed as an effective treatment against the infection, but there efficacies have been found to be challenged in due course [1]. In this context, several reports have been broadly discussed and documented in literature [5][11]. *Acinetobacter baumannii* can survives in different environmental conditions for prolonged periods and reported to be associated with the organism causes outbreaks of infection and healthcare associated infections, including bacteraemia, pneumonia, meningitis, urinary tract infection, wound infection. The two-component systems regulate two function in *Acinetobacter baumannii* (i) Biofilm initiation and (ii) implementation of drug-resistance mechanisms. This system makes very attractive targets of these signal transduction modules for drug intervention. In two-component system of *Acinetobacter baumannii*, BfmR is responsible key regulator for biofilm initiation in and it can be used as a novel therapeutic target [8]. The carbapenem resistance in *Acinetobacter baumannii* is a matter of concern worldwide as it limits the boundary of therapeutic alternative. The MDR issues of *Acinetobacter baumannii* has put of the several challenges before any drug interaction and its affectivity in the treatment. An alternative apart from already known therapies should be aggressively explored. Currently a potential drug target BfmR (PDB ID: 5HM6), a response regulator in signal transduction system (TCS), identified by scientific group in bacteria *A. baumannii* stain AB307-0294 is necessary for its survival [3]. For structure-based drug discovery the molecular docking method is one of the most used methods, because of its ability to predict the proper receptor-ligand binding site [2]. Natural products such as alkaloid, flavonoid, terpenes, have been reported effective antimicrobial treatments [4]. Natural products are anything that is produced by a living organism found in nature. These are usually purified organic ompounds which may isolate from natural sources and produced by primary or secondary metabolite pathway. Example of natural products which are produced by nature like wood, silk, bioplastics, cornstarch, milk, plant exudates, soil, coal and other natural materials[9].

Experimental

Downloading the PDB structure

In this study we have taken protein BfmR, a biofilm regulator in *Acinetobacter baumannii.* It is a part of two-component system responsible for biofilm formation. We downloaded the structure of BfmR from Protein Data Bank (PDB) (https://www.rcsb.org/) having PDB ID: 5HM6.

Downloading the ligands

We downloaded the ligand structure for further molecular dockings studies on our receptor molecule i.e. 5HM6. All

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the ligands molecules taken into consideration in this study are downloaded from Drug Bank (https://www.drugbank.ca/) [15]. Drug Bank is a freely available database having detailed information of FDA approved drug and Experimental drug.
Experimental drugs are drugs which have been shown to bind experimentally with the protein in mammals, bacteria viruses, fungi or parasite, this includes those compounds that are Pre-Investigational New Drug Applications (Pre-IND or Discovery Phase compounds). From 12071 drug entries available in DrugBank we downloaded 437 molecules as ligands belonging to the drugs derived from natural products like alkaloids, terpenes, phenols, flavonoids etc. Structure of the compounds and antibiotics such as Carbapenems, Bedaquinone etc. are used against MDR [13]. *Acinetobacter baumannii* were also downloaded from Drug Bank and compound having less binding energy was considered as control.

Molecular Docking
Molecular docking studies was performed on the receptor molecule i.e. Protein molecule BfmR and downloaded ligands to find the protein-ligand complex with the minimum binding affinity [6]. We used freely available tools like AutoDock Vina and AutoDock Tools for molecular docking [7]. All the ligands were downloaded into SMILES format and then 3D optimised with the help of ChemSketch tool. First molecular docking of known ligands were performed on protein molecule BfmR having PDB ID 5HM6 and complex having minimum binding affinity was taken as control. Next molecular docking of 437 ligands obtained from Drug Bank database was performed. Ligand molecules having minimum binding affinity which is better than our control DB12329 (Binding affinity > -8.9 kcal/mol), were taken into consideration [12].

Druglikeness
Druglikeness is a term used to define the abilityof our ligand to display a drug like property. Lipinski Rule of Five is used for predicting the druglikeness.
We used freely available web tool (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) for calculating Lipinski Rule of Five of our ligand molecule.

Molecular Dynamics
Molecular Dynamics simulation of the protein-ligand complex was performed using GROMACS 5.1.2 at 10ns. MD simulation performed on the protein (PDB ID: 5HM6) with ligand (DB12329) complex was taken as control having binding affinity (-8.9 kcal/mol). Topology for the protein was created using the GROMOS96 43a1 force field was used to create the topology of the protein and ligand topologies was created using the PRODRG (http://davapc1.bioch.dundee. ac.uk). Energy minimization process was performed with the help of steepest descent algorithm at n steps=50000. After performing energy minimization equilibration of NVT at temperature of 300K and NPT was performed. This was followed by the final MD simulation of Protein-ligand complex at 10 ns.

Results and Discussion

Molecular Docking
Molecular docking studies were performed and ten potential lead molecules (DB05129, DB08036, DB12622, DB06746, DB13089, DB14037, DB00320, DB06743, DB01199, and DB05109) were identified. Druglikeness of the molecules was identified using Lipinski Rule of Five & ADME/Tox analysis of molecules displayed drug like criteria. DB05129 was not considered for further analysis as it was a antineoplastic agent. We selected novel lead molecule DB08036 (alkaloid) with best minimum binding energy of -9.4 kcal/mol and DB12622 having binding energy of -9.3 kcal/mol [16]. Binding energies of ligand molecules with our receptor having binding affinity better than our control DB12329 (i.e. -8.9 kcal/mol) is listed in Table 1

Table 1: Binding energies of ligand molecules with our receptor having binding affinity better than our control DB12329 (i.e. -8.9 kcal/mol)

Drugbank ID	docking energies(kcal/mol) >-8.9	Nature of molecule
DB05129	-9.9	coumarins
DB08036	-9.4	alkaloids
DB12622	-9.3	terpenes
DB06746	-9.1	terpenes
DB13089	-9.1	terpenes
DB14037	-9.1	terpenes
DB00320	-9.1	alkaloids
DB06743	-9	terpenes
DB01199	-9	alkaloids
DB05109	-9	alkaloids

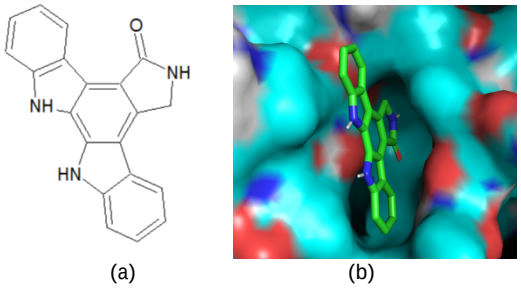
Lipinski Rule of Five: Lipinski's rule of five is also known as the Pfizer's rule of five to evaluate druglikeness. This rul have five key physiochemical parameters like lipophilicity, molecular weight, hydrogen bonding, polar surface area, and charge. For the drug's pharmacokinetics in human body the Molecular properties of Lipinski's rule of five is very crucial in which their absorption, distribution, metabolism, excretion ("ADME") and Toxicology is also include. The Lipinski rule is useful to discriminate the chemicals vrs possible drug molecules under the given rules.

Druglikeness:
Druglikeness was calculated with help of web server available at (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) and following result was obtained mentioned in table Table 2.

Table 2: Druglikeness properties of our ten best ligands

DrugBank ID	Mass	Hydrogen bond donor:	Hydrogen bond acceptors	logP	Molar Refractivity
DB05129	618.00	0	14	-0.517390	131.129974
DB08036	298.00	0	4	2.323710	84.531487
DB12622	380.00	0	1	0.923010	94.550972
DB06746	400.00	0	10	-2.409250	69.939499
DB13089	427.00	0	4	0.147310	100.311974
DB14037	459.00	0	6	0.00	0.00
DB00320	549.00	0	8	-0.442880	130.684372
DB06743	384.00	0	9	-2.128270	69.096497
DB01199	570.00	0	6	0.859200	137.796387

Molecular dynamics: Molecular Dynamics of the compounds having a good docking energy was performed using GROMACS 5.1.2. The protein ligand complex of the control was stable as seen in the fig 2. The RMSD of DB12622 was also relatively stable as seen in fig 3 as compared to DB08036 as seen in fig 4.



(a) (b)

Figure 1: (a): Structure of the compound DB08036 downloaded from DrugBank database. (b) Binding of the ligand DB08036 with the receptor molecule BfmR (PDB ID: 5HM6)

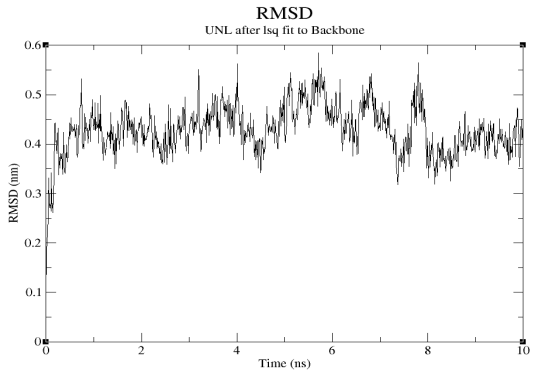


Figure 2: RMSD of DB12329 (control) calculated with the help of GROMACS 5.1.2

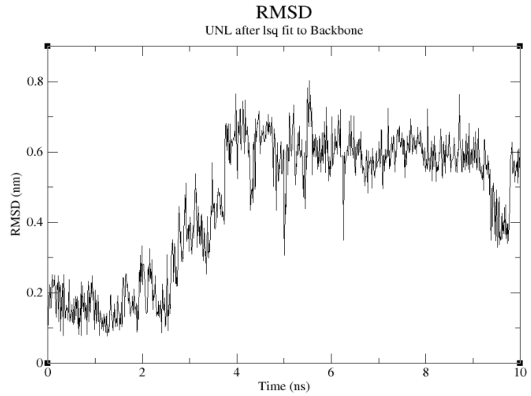


Figure 3: RMSD of DB12622 calculated with the help of GROMACS 5.1.2

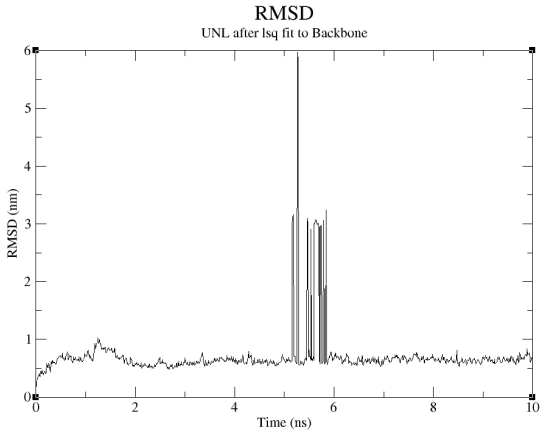


Figure 4: RMSD of DB08036 calculated with the help of GROMACS 5.1.2

Conclusions

In this study molecular docking was performed on potential drug target receptor BfmR protein a part of two component system responsible for biofilm formation in Acinetobacter baumannii. Drug like properties were predicted of the ten best ligands with Lipinski Rule of five and DB08036 which is an alkaloid has shown promising result. Further RMSD calculations performed showed DB12622 is relatively stable than DB08036. Further efforts can be made to study its antimicrobial activity of compounds DB12622 and DB08036 on variety of biological targets.

Acknowledgements

We are thankful to Department of Biotechnology, Jaypee Institute of Information Technology, Noida for providing necessary support.

References

1. Poirel L and Nordmann P, "Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology", Clinical Microbiology and Infection, 2006, 12:9, 826–836.
2. Sledz P and Caflisch A, "Protein structure-based drug design: from docking to molecular dynamics", Current Opinion in Structural Biology, 2018, 48:93–102.
3. Maragakis L and Perl T, "Acinetobacter baumannii: Epidemiology, Antimicrobial Resistance, and Treatment Options", Clinical Infectious Diseases, 2008, 46:1254–63.
4. Fishbain J and Peleg A, "Treatment of Acinetobacter Infections", Clinical Infectious Diseases 2010, 51(1):79–84.
5. Perez F, Hujer A et al. "Global Challenge of Multidrug-Resistant Acinetobacter baumannii", Antimicrobial Agents And Chemotherapy, 2007, 51:10 p. 3471–3484.
6. Ezeokonkwo M and Ogbonna O et al., "Angular Phenozaxine Ethers as Potent Multi microbial Targets Inhibitors: Design, Synthesis, and Molecular Docking Studies", Front. Chem. 2017, 5:107.
7. Chandrababu T and Siva Rajesh S, "Molecular docking, molecular dynamics simulation, biological evaluation and 2D QSAR analysis of flavonoids from Syzygium alternifolium as potent anti-Helicobacter pylori agents", RSC Adv., 2017, 7, 18277–18292.
8. Draughn L and Milton ME et al., "The structure of the biofilm-controlling response regulator BfmR from Acinetobacter baumannii reveals details of its DNA-binding mechanism", Journal of Molecular Biology, 2018, 430(6), 806-821.
9. Gupta PD and Birdi TJ., "Development of botanicals to combat antibiotic resistance", Journal of Ayurveda and Integrative Medicine, 2017, 1-10.
10. Fournier PE and Vallenet D., "Comparative Genomics of Multidrug Resistance in Acinetobacter baumannii", PLoS Genetics, 2006, 2(1), 62-72.
11. Amy B. Locke et al., "Urinary Tract Infection (UTI)", Integrative Approach to Disease, Chapter 22, 211-217.
12. R Priya and Rajendrarao S., "Molecular docking and molecular dynamics to identify a novel human immunodeficiency virus inhibitor from alkaloids of Toddalia asiatica", Pharmacogn Mag., 2015, 11 (44), 414-422.
13. French KE and Harvey J., "Targeted and Untargeted Metabolic Profiling of Wild Grassland Plants identifies Antibiotic and Anthelmintic Compounds Targeting Pathogen Physiology, Metabolism and Reproduction", nature scientific reports, 2018, 8:1695.
14. S. Skariyachan and M. Manjunath, "Screening of Potential Lead Molecules against Prioritized Targets of Multi-Drug Resistant Acinetobacter baumannii- Insights from molecular docking, molecular dynamic Simulations and in

Vitro Assays", Journal of Biomolecular Structure and Dynamics, 2019, 37(5), 1146-1169.
15. Wishart DS and Feunang YD et al., DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2017, 46:D1074–D1082.