Original Article

Screening of Inhibitors against Multidrug Resistant Protein 1 through Molecular Docking

Shiroli Dabbikar[1], Dipti Soni Jaipuriar[2], Sabitha Y[3,*]

[1]Department of Biochemistry, St. Francis College for Women, Hyderabad, Telangana, INDIA.
[2]Ex-Faculty, Department of Biochemistry, St. Francis College for Women, Hyderabad, Telangana, INDIA.
[3]Research Head, Ciencia Life Sciences, Kukatpally, Hyderabad, Telangana, INDIA.

Submission Date: 13-06-2021; Revision Date: 15-07-2021; Accepted Date: 25-08-2021

ABSTRACT

Multidrug Resistant Protein 1 (MRP1) has a significant role in the expulsion of substrates from the cancer cell. The over expression of MRP1 can be a reason for the unsuccessful attempt in chemotherapy. This study aims to find compounds that have an inhibitory role against MRP1 through Molecular Docking. Molecular Docking helps in visual analysis of the interactions between the ligand and a macromolecular target. The domain structure of MRP1 (PDB ID: 2CBZ) was retrieved from RCSB PDB and was visualized on UCSF Chimera. 58429 compounds were withdrawn from ChEBI and the ADMET parameters of 15178 selected compounds were evaluated by SwissADME predictor. The Primary and Secondary docking analysis was performed on Igemdock and AutoDock Vina respectively. Five compounds with low binding energies were selected from the results generated by Igemdock and they were subjected to secondary docking program on AutoDock Vina. From the binding energy and docking score outcomes of primary and secondary docking analysis we concluded that Acrivastine is the best candidate for targeting MRP1.

Key words: AutoDock Vina, Binding Affinity, Igemdock, Molecular Docking, Multidrug Resistant Protein 1.

Correspondence:
Dr. Sabitha Y,
Research Head, Ciencia Life Sciences, Kukatpally-500072, Hyderabad, Telangana, INDIA.
Phone no: +91 8247307129

Email: sabitha.kotra@gmail.com

INTRODUCTION

Chemotherapy is considered to be the most effective treatment for Cancer. However, it was observed in the past few years that the tumor cells are not responding to the drugs overtime due to the formation of multidrug resistance genes in the cancer cells.[1] The occurrence of multidrug resistance (MDR) initiated an effort to develop effective treatments to overcome the complications.[2] The MDRs work by expelling the accumulated drugs out of the cell. The ABC (ATP-Binding cassette) transporters are known as the largest protein family. It has two cytoplasmic domains that interact with ATP i.e. ATP- binding cassette and two trans-membrane domains (TMDs).[3] The multidrug resistant proteins belong to the ABC transporter superfamily. A majority of its entities are responsible for the transportation of compounds, including amino acids, ions and other xenobiotics across the cellular membranes. A famous study proposes that the drug molecule binds to a specific site in the lipid bilayer of the plasma membrane and transports the drug out of the cell using the energy released from ATP binding and hydrolysis.[4] The high expression of ABC transporters such as P-glycoprotein (Pgp) promoted decreased drug accumulation in tumor cells and later additional multidrug resistance proteins such as MRP1, MRP2, MRP3, and MRP4 were also discovered.[5] This paper aims to study the effect of compounds on MRP1 and contribute to therapeutic approaches in tackling MDR in tumor cells. The cloning of MRP1 was done from H69AR lung cancer cell lines in 1992. It is a 190k Daltons protein and is classified as a branch of the ABCC (ATP-Binding Cassette member C) subfamily in the ABC transporter superfamily.[6] There are 12 proteins within ABCC transporters of which 9 are collectively recognized as multidrug resistance

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DOI: 10.5530/ajbls.2021.10.53

proteins and MRP1 is found to have been encoded by ABCC1 gene. The ions being effluxed by ABCC1 encoded MRP1 are mostly conjugated to GSH (eg: leukotriene C_4). The increased efflux of compounds that block calcium channels (verapamil), high potency inhibitors (reserpine), antibiotics (puromycin) were tested for their action against Pgp-MDR. However, the reversal of multidrug resistance in tumor cells is a complicated process and the clinical studies are still being conducted in order to find ways to inhibit the activity of Pgp.[4] Although MRP1 and Pgp are structurally different, they do have a significant similarity in the phenotype of H69AR cells and the cells associated with Pgp.[5] Despite the clinical advances regarding the cancer treatments, the mutations that result in the multidrug resistance is causing a decline in the therapeutic preferences. Hence, in this paper, we will screen inhibitors against MRP1 using virtual screening which is carried out through Molecular Docking. Molecular docking is a computerized drug-designing method in which a target macromolecule like protein interacts with small molecules like ligands (drugs, enzymes, etc) at the target active site to form a stable complex and estimates the binding affinity of the two molecules.[6] It has become an important tool for discovering drugs and is widely used since the early 1980s. The discovery of compounds against MRP1 through Molecular Docking is not something new and multiple research groups have already used this approach to target MRP1 and the compounds showing favorable results were further analyzed *in vitro*.[5] X-ray crystallography, NMR spectroscopy has contributed to evaluating the structures of proteins and protein-ligand complexes. The traditional way for drug discovery is through High-throughput screening, but virtual screening has a relatively easier approach that is inexpensive yet shows effective screening.[7]

MATERIALS AND METHODS

Tools used: UniProt, PDB, UCSF Chimera, ChEBI, SwissADME, Igemdock, Autodock Vina.

Protein Retrieval

Uni Prot: Database was used to acquire data regarding the sequence length of MRP1 (ID: P33527) i.e. 1531 amino acids and its domain positions (325-608, 644-868, 975-1256, and 1293-1527).[8] The domain position with less resolution ($1.5A^0$) i.e. 642-871 is compatible for our docking study. The domain structure of MRP1 (ID: 2CBZ) was collected from RCSB PDB[9] and was visualized on UCSF Chimera.[10]

Determining the ADME Properties of Isolated Compounds

58429 compounds were isolated from Chemical Entities of Biological Interest (ChEBI) among which 15178 compounds were selected based on their molecular weights for our study.[11] SwissADME was employed to determine the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters of 15178 compounds by entering 500 compounds each time on the SMILES (Simplified Molecular-Input Line Entry System) submission.[12] 487 compounds were collected after filtering 15178 compounds based on their ADMET properties and were saved for further study.

Primary Docking

The IDs of 487 compounds were noted from ChEBI database and their 2D structures were downloaded in SDF format. The 2D structures of 487 ligands were then converted into 3D (as docking is only possible on a three-dimensional set up) and were saved as a PDB file.[13] In our study, Molecular Docking was performed twice, the primary docking program was processed on Igemdock, and AutoDock Vina with Chimera interphase was employed to carry out secondary docking analysis. Igemdock presents the binding energy values and the additional interaction observed in the protein-ligand complex and provides better binders for the secondary docking program. The PDB file of the protein of interest i.e. 2CBZ was entered at "prepare binding site" and 3D form of 487 compounds were submitted at "prepare compound" on Igemdock. The output pathway was set and the standard docking was allowed to run.[14] Subsequently, five candidate ligands were selected based on the binding energies acquired, for further docking studies.

Secondary Docking

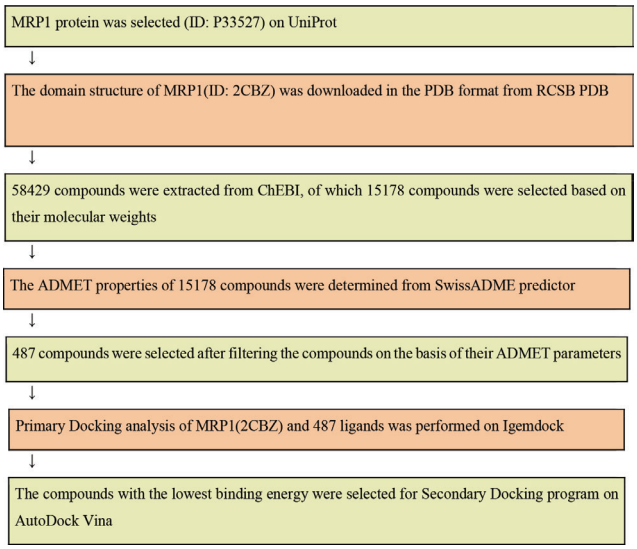
Autodock Vina was utilized for improved accuracy and efficiency in docking of compounds with the target protein. To perform secondary docking analysis, the addition of hydrogen bonds and deletion of water molecules that are co-crystallized with the protein of interest were done in order to examine the fidelity of all bonds. The target protein and ligands were dock-prepped by applying the "AMBER" force field prior to the start of secondary docking on UCSF Chimera. Next, the docking procedure begins by positioning an energy scoring-grid at the active binding site on the MRP1 receptor using AutoDock Vina. The dimensions of the grid box were set as, center: (-17.818 A°, 47.5959 A°, 4.25383A°), and size as (14.4669A°, 18.1667A°, 16.282A°). The grid box was fixed such that the target

binding site was enclosed by it. The residue sequence of 8A° was selected and deleted so as to let the ligand bind to the target binding site. A "score" scoring function with all docking parameters was set on default settings and the results were analyzed.[15]

Illustrations

Discovery studio version 4.0 was employed in order to generate images of the ligand structures, receptor, and their interactions.

METHODOLOGY FLOWCHART



RESULTS

The pharmacokinetic character and drug-likeness of a compound can be studied through ADMET parameters. To synthesize 15178 compounds, properties such as, molecular weight less than 500 g/mol, less than 8 hydrogen bond donors, less than 10 hydrogen bond donors were chosen as a criterion. A systematic result on lipophilicity and hydrophilicity of these 15178 compounds from the log P and log S prediction programs called ILOGP, XLOGP3, WLOGP, ESOL, and SILICOS-IT was generated by SwissADME. The Log *P* values account for the lipophilicity of a compound. It is the logarithm of the ratio of the concentration of drugs between two solvents in a unionized form. The lower the log *P* values of a compound, the higher is its lipophilicity. Log S is a 10-based logarithm of the solubility in mol/L and it measures the hydrophilicity of a molecule.[16] After assessing the ADMET properties, LIPINSKI RULE OF FIVE was applied for the filtration of compounds. It is a rule that examines the drug-likeness and determines if the compound has pharmacological activity, chemical, and physical properties to qualify as a potential drug for humans. Christopher. A. Lipinski formulated this rule based on the observation of comparatively small molecular weight and lipophilic character of orally administered drugs. This rule evaluates a compound's permeability and its solubility properties. An upper limit of 5 is set for filtering druggable compounds by Lipinski rule i.e. any compound that has more than 5 H-Bond donors, 10 H-Bond acceptors, molecular mass higher than 500 and log *P* value greater than 5 does not possess drug-like properties. The "Lipinski rule of 5" is relevant only if the said factors are either 5 or multiples of 5.[17]

After the primary docking analysis on Igemdock, ten compounds were selected on the basis of their binding energies (Table 1). Five compounds were eliminated from the ten candidates by formulating the lowest binding energy concept (lower the binding energy, better the ligand).[17] The ChEBI IDs of compounds with relatively lower binding energies are 59184, 31257, 83168, 125605, 132605 and their corresponding names are Bevantolol, Benzadac, Acrivastine, Thiorphan and Coronopilin respectively. The five compounds were docked against MRP1 individually, on AutoDock Vina for more accurate results of their binding capacity, interactions of ligand with the active site of the protein and, their potentiality in inactivating MRP1. The ADMET measures of the five hit compounds were also tabulated in order to study their pharmacokinetics and drug-like properties to correlate with the fact that they have the ability to inhibit MRP1 (Table 2).

The data obtained after secondary docking analysis on AutoDock Vina is displayed in Table 3. The score represents the binding affinity between a compound

Table 1: Interactions observed between MRP1 and ten candidate ligands showing its Binding Affinity, Van Der Waals forces, H-Bonds, and Electrostatic forces on Igemdock.

Compound (ChEBI ID)	Energy (Kcal/mole)	Van Der Waal's	H-Bonds	Electrostatic
59184	-106.83	-80.91	-25.92	0
28282	-100.80	-54.54	-43.67	-2.06
31257	-106.71	-69.04	-32.00	-5.67
63538	-101.38	-71.77	-24.50	-5.10
83168	-117.99	-86.10	-26.41	-5.47
86959	-102.51	-73.68	-28.83	0
125605	-109.38	-63.11	-38.78	-7.48
131715	-104.32	-69.50	-30.19	-4.61
132605	-106.87	-67.24	-34.38	-5.244
238698	-101.77	-78.70	-23.06	0

Table 2: ADME properties of final five candidate ligands.

Compound ChEBI ID	Molecular Weight	H-Bond Acceptors	H-Bond Donors	iLogP	ESOL LogS	G.I Absorption
59184	282.29	4	1	1.85	-3.72	High
31257	345.4	5	2	3.63	-3.57	High
83168	348.44	4	1	3.43	-2.97	High
125605	253.32	3	2	-0.22	-2.84	High
132605	264.32	4	1	1.44	-3.5	High

Table 3: Molecular Docking results of five selected compounds.

S. no	Compounds	Score (K cal/mol)	H-BONDS
1.	Bevantolol (ID:59184)	-6.4	5 (LYSA43, GLYA40, GLYA42, CYSA41, SERA44)
2.	Benzadac (ID:31257)	-7.0	5 (LYSA43, GLYA40, GLYA42, CYSA41, SERA44)
3.	Acrivastine (ID:83168)	-7.8	5 (LYSA43, GLYA40, GLYA42, CYSA41, SERA44)
4.	Thiorphan (ID:125605)	-6.2	4 (GLYA40, GLYA42, CYSA41, SERA44)
5.	Coronopilin (ID:132605)	-6.3	7 (SERA44, SERA45, SERA44, LYSA43, CYSA41, GLYA40, GLYA42)

and the target residues of the protein whereas the hydrogen bonds are characterized as the attractive forces existing between them. The potency of a compound to act against MRP1 is identified with the lowest docking score and maximum number of interactions. A low docking score indicates high binding affinity between a protein and the ligand. Therefore, the compound with high binding affinity is considered to be the best inhibitor against MRP1.[5] The scoring functions produce data regarding the binding affinities and conformations of the compounds as a compiled result on several parameters.

INTERACTIONS OBSERVED BETWEEN MRP1 AND THE FIVE CANDIDATE LIGANDS

The *in-silico* techniques depict the ligand binding to the key amino acids of the target protein with high affinity. The five candidate ligands showed successful binding and fit perfectly within the active site of the target macromolecule and the interactions observed were discussed individually.[5]

Bevantolol (1-[2-(3,4-dimethoxyphenyl)ethylamino]-3-(3-methylphenoxy)propan-2-ol) showed a docking score of -6.4 K cal/mole and formed five hydrogen bonds with the target residues, LYSA43, GLYA40, GLYA42, CYSA41, SERA44. The additional interactions seen between Bevantolol and the MRP1 receptor are Pi-Pi bond with TRPA12, alkyl bonds with HISA186, VALA39, TRPA12, VALA39; C-H bond with GLNA72, and a donor H-bond with GLYA42 (Figure 1).

Benzadac (2-(1-benzylindazol-3-yl) oxyacetic acid) is an anti-inflammatory indazole containing compound. It showed high binding affinity towards MRP1 with a docking score of -7.0 K cal/mol and formed five hydrogen bonds with the active site residues of MRP1 i.e. LYSA43, GLYA40, GLYA42, CYSA41, and SERA44. Additional interactions include a C-H bond with GLYA42, 2 attractive charges with LYSA43, MGA232, and two Pi-Pi bonds with TRPA12 (Figure 2).

Acrivastine ((E)-3-[6-[(E)-1-(4-methylphenyl) 3-pyrrolidin-1-ylprop-1-enyl] pyridine-2-yl]) is an antihistamine and showed

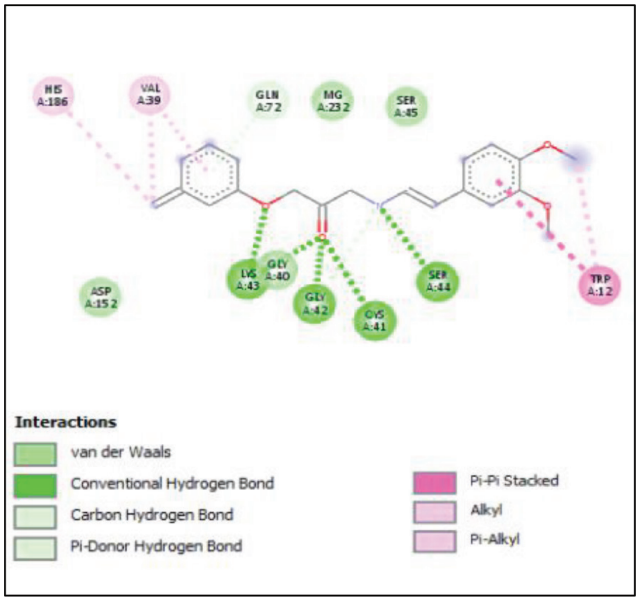


Figure 1: 2D Image of Bevantolol interactions with the protein.

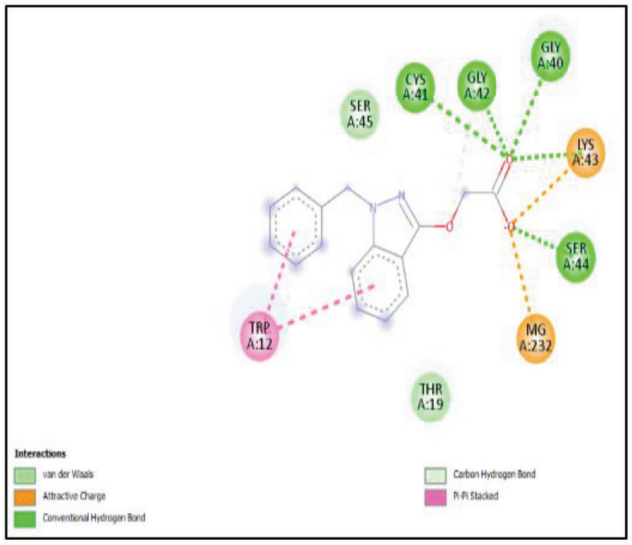


Figure 2: 2D Image of Benzadac interactions with the protein.

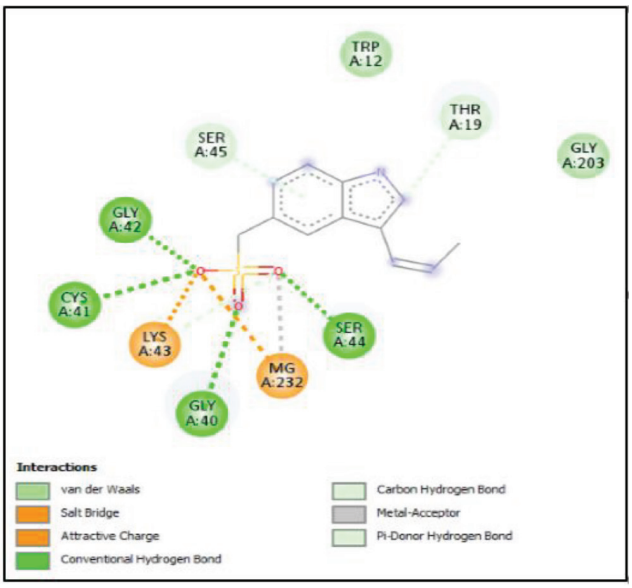


Figure 4: 2D Image of Thiorphan interactions with the protein.

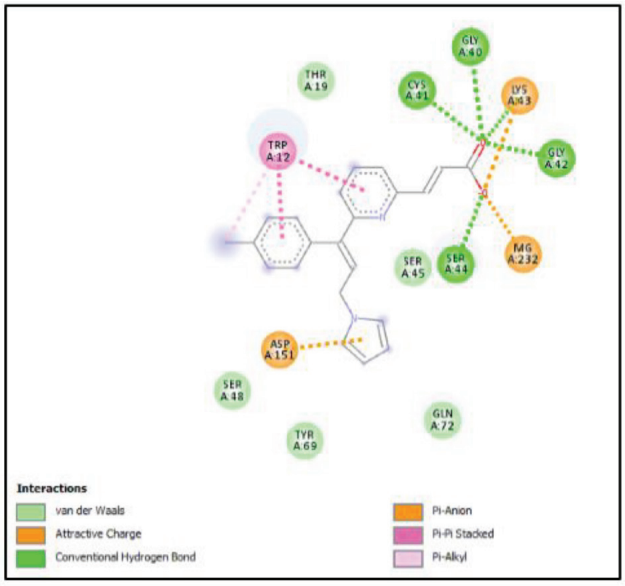


Figure 3: 2D Image of Acrivastine interactions with the protein.

the highest binding affinity towards the active site of MRP1 with a docking score of -7.8 K cal/mole. It also formed five hydrogen bonds with the protein residues, LYSA43, GLYA40, GLYA42, CYSA41, and SERA44. The additional interactions include, 2 pi-pi bonds with TRPA12; Pi-cation with ASPA151; 2 attractive charges with LYSA43, MGA232; an alkyl bond with TRPA12 (Figure 3).

Thiorphan (2-[(2-benzyl-3-sulfanylpropanoyl) amino] acetic acid) is a Neutral endopeptidase inhibitor. This compound showed docking score of -6.2 K cal/mole and it formed 4 H-bonds with GLYA40, GLYA42, CYSA41, and SERA44 residues of MRP1. A salt bridge with MGA232; an attractive charge with LYSA43; a donor H-Bond with SERA45 and a C-H bond with THRA19 were the additional interactions observed (Figure 4).

Coronopilin ((3aS, 6S, 6aR, 9As, 9bR)-6a-hydroxy-6,9a-dimethyl-3-methylidene-4,5,6,7,8,9 b-hexahydro-3a-azuleno [8,7-b] furane-2,9-dione) is a terpenoid lactone. It was stabilized with a docking score of -6.4 K cal/mole and formed 7 H-bonds with the target macromolecule residues i.e. SERA44, SERA45, SERA44, LYSA43, CYSA41, GLYA40, and GLYA42. Besides the H-bonds, coronopillin was also found to have shared 3 alkyl bonds with TRPA12; 2 attractive charges with LYSA43 and MGA232; a Pi-cation with MGA232 (Figure 5).

MRP1 was chosen as the target macromolecule and this study was conducted in order to search for compounds that have the potential to inhibit the MRP1 receptor. The compound with the lowest docking score and maximum number of interactions is considered favorable for inhibition. As previously mentioned, Acrivastine is the compound with the lowest docking score i.e. -7.8 K cal/mole having five H-Bonds, and Coronopilin has a docking score of -6.2 K cal/mole with maximum number of H-Bonds i.e. 7. However, the binding energies tabulated according to the outcome of primary docking analysis on Igemdock reveals that Acrivastine has a binding energy of -117.99 K cal/mole and the additional interactions such as Van Der Waal's forces, electrostatic forces, H-Bonds also play a key role in enhancing its binding energy. Therefore, it is established that Acrivastine is comparatively more stable than the rest of the compounds chosen

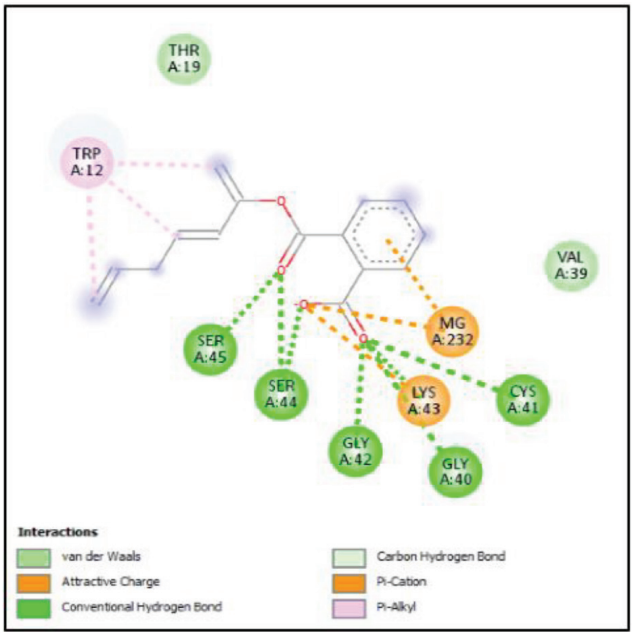


Figure 5: 2D Image of Coronopilin interactions with the protein.

in our study, which leads us to understand that this compound is capable of blocking the target amino acid residues of MRP1 and prevents the ATP binding and subsequent hydrolysis so, there would be no expulsion of drugs out of the cancer cell.[5]

The elevated levels of MRP1 induce the multidrug resistance in tumor cells. These complications cause the unsuccessful attempts of chemotherapeutic drugs that are employed to eradicate tumor cells and for this reason MRP1 was chosen as the ideal target to impede MDR in cancer cells. To inhibit MRP1 drug transport, a wide variety of compounds have been developed over the years. Besides the well-known inhibitor MK-571 which was originally developed to treat asthma, there are other drugs such as ONO-1078 and indomethacin which proved to inhibit the function of MRP1 but the *in vitro* and *in vivo* studies still lack promising results.[18,19] At present, researchers have been testing compounds that are capable of blocking the substrate translocation which prevents the decreased drug accumulation in tumor cells, they are also searching for inhibitors that create oxidative stress in MRP1 expressing cancer cells by boosting GSH efflux which reduces their antioxidant activity thereby, exposes the tumor cells to apoptosis. Other studies include, suppression of the elevated levels of MRP1 by targeting the mRNA of the protein.[5,20] From the molecular docking studies, we have studied that Acrivastine has the potential to target MRP1. It is an antihistamine and is used for the treatment of allergies. The H1 receptor antagonist functions by blocking the activity of histamines at the receptor.[21] A study conducted by Christensen, *et al.* proposed the successful inhibition of Pgp-MDR, one of the most important members of ABC transporter superfamily, by Acrivastine.[22] From the results obtained in our study, we can confirm that Acrivastine has the ability to bind to the active target site residues of MRP1 and acts as an inhibitor against it. The conventional wet lab experiments could further help in understanding the inhibiting potential of this compound. Our study was conducted on the knowledge of docking simulations which indicated that Acrivastine is the best candidate ligand against MRP1.

CONCLUSION

In this study, we have tried to find the best candidate inhibitor to target MRP1 among 15178 compounds by employing *in-silico* techniques. From the docking analysis, we conclude that Acrivastine is more stable as compared to all the compounds chosen in our study and therefore can be the lead compound in inhibiting MRP1. The predicted data of our experimental work could further aid in the development of Acrivastine as a drug to fight MDR in tumor cells.

ACKNOWLEDGEMENT

I would like to express my sincere gratitude to the Department of Biochemistry, St. Francis College for Women, Begumpet for their valuable guidance, constant supervision and for giving me the opportunity to write this paper. Secondly, I would like to thank my parents and my brother for their constant support, encouragement and for rendering all possible help required for the completion of my study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ADMET: Adsorption, Distribution, Metabolism, Excretion, Toxicity; **ChEBI:** Chemical Entities of Biological Interest; **MRP1:** Multidrug Resistant Protein 1; **MDR:** Multidrug resistance; **PDB:** Protein Data Bank.

SUMMARY

The high expression of ABCC1 encoded Multidrug Resistant Protein 1 causes multidrug resistance in cancer cells. Multidrug resistant proteins are a threat

to chemotherapy. This study aims to search for compounds that have the potential to inhibit the Multidrug Resistant Protein 1 through Molecular Docking. The inhibitory role of a compound was acknowledged from its binding affinity values and the additional interactions observed between the protein and the ligand. The compounds having the lowest binding affinity were chosen as the best candidates against target protein i.e MRP1.

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Cite this article: Shiroli D, Sabitha Y, Dipti SJ. Screening of Inhibitors against Multidrug Resistant Protein 1 through Molecular Docking. Asian J Biol Life Sci. 2021;10(2):400-6.