3D QSAR Pharmacophore Based Virtual Screening, ADME Analysis and Estimation of MM/GBSA binding Free Energies of Azoles as a Potential Inhibitor of DprE1 for Mycobacterium Tuberculosis

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Abstract

Decaprenylphosphoryl - D - ribose - 2 -epimerase (DprE1) is a promising drug target to identify new anti- TB drugs against drug resistant tuberculosis. DprE1 helps in cell wall biosynthesis through Decaprenyl-phosphoryl d-arabinose pathway. Inhibition of DprE1 results in blocking of cell wall biosynthesis, causing death of mycobacterium tuberculosis. In current studies, a set of thirty triazole molecules having antitubercular activity were selected for pharmacophore 3D QSAR studies. The generated common pharmacophore hypothesis (AHRRR.172) consists of one acceptor (A), one hydrophobic (H), and three aromatic rings (R). The resulted pharmacophore model recorded with good statistical results, $R^2 = 0.71$, $Q^2 = 0.54$ and other parameters $F = 45$, $RMSE = 0.41$. This model further investigated to identify pharmacophoric features which are crucial for biological activity. The resultant pharmacophore model was used to screen ZINC chemical database molecules to identify potent lead molecules against DprE1 enzyme. The resultant hit molecules were recorded with dihydroquinonolin 2-one and Pyrazolo [1, 5] pyrimidin 5-one scaffold and this information could be helpful to design new potent anti-tuberculosis agent. Further, these molecules along with co-crystal ligand were utilized for the estimation of physicochemical properties and followed by binding mode analysis.

1. Introduction

Tuberculosis is commonly known as TB, it is one of the top killed diseases today and caused by *M.tuberculosis* [1–2]. As per WHO report, nearly 10 million people infected and 1.4 million people died from tuberculosis in the year of 2019 [3]. India is the highest TB burden country accounting for more than 1/4 global incidence [4–5].

A six months therapy (DOT) was introduced by WHO to treat tuberculosis, which includes administration of four first line drugs (Isoniazid, rifampicin, ethambutol, pyrazinamide) for 2 months, accompanied by administration of two drugs (Isoniazid and rifampicin) for 4 months. This long term treatment of combination of drugs with toxic side effects and poor adherence of patients leads to *M. tuberculosis* resistant to anti TB drugs called drug resistant TB such as Multi Drug Resistance (MDR) and Extensively Drug Resistance (XDR) TB [6–9]. Multi Drug Resistance TB is form of a drug resistant TB that does no longer replies to at least any one of the first line drugs (especially rifampicin and isoniazid). MDR-TB is treated with administration of second line drugs [10], but this treatment is limited and also expensive. Sometimes additional severe MDR-TB may changes to XDR-TB. According to WHO report, India is one of the countries in the world, which has the highest burden of both tuberculosis and drug resistant tuberculosis. It is reported that nearly 0.5 million people are affected by DR-TB. Therefore, there is a great need to develop novel and effective drugs against tuberculosis [11].

Mycobacterium tuberculosis is unique among prokaryotes. Unlike other prokaryotes, the cell wall is made up of lipids, peptidoglycan and arabinogalactan complex (PAM) [12]. This specific property of the cell wall lead to a realization that enzymes involved in the biosynthesis of this structure become attractive potential drug targets to design novel anti TB drugs [13–14]. The D-arabinofuranose is one of the

important constituent of cell wall biosynthesis. DprE(Decaprenylphosphoryl - D – ribose – 2 - epimerase) is essential for the conversion of ADP to DPA which is precursor of arabinogalactan synthesis in cell wall [15–16]. DprE1 is the enzyme FAD-dependent oxido-reductase while the other enzyme DprE2 depends on NADH reductase. The previous studies suggest that some of the molecules such as benzthiazinones against DprE1 have antibacterial activity without exhibiting TB resistance [17]. This indirectly confirms that enzyme DprE1 is a promising drug target to design new anti- TB drugs [18–22].

In recent years *M. tuberculosis* has attained elevated resistance across drugs [23–28]. Hence, there is a need to establish novel, fast acting and potent anti- microbial drugs with reduced toxicity. The development of novel drugs with XDR-TB, MDR-TB, and latent TB is a primary concern and will help to cut down the chemotherapy [29]. Thereby in this present study, a set of triazole derivatives, which are found to be highly effective for anti-tubercular activity were selected for 3D QSAR and pharmacophore based virtual screening. The resultant pharmacophore model reveals that the pharmacophoric features, which are crucial significant functions for ligand binding.

2. Materials And Methods

2.1 Data set selection and preparation for analysis

For the computational analysis, a total of thirty-one triazole derivatives' against *M. tuberculosis* were selected from literature by considering a wide range of activity (supplementary table S1)[30]. The pharmacological activity of these compounds was expressed in IC_{50} value. To generate a QSAR model, the reported IC_{50} values were transformed into corresponding pIC_{50} value by using $pIC_{50} = -\log IC_{50}$.

The chemical structures of all the data set molecules were drawn by using 2D sketcher. All the 2D chemical structures converted into 3D chemical structures during creating a new entry into the project file. The energy optimizations of 3D structures were carried out by using Ligprep module, employing OPLS_2005 force field [33]. It includes generation of stereoisomer, neutralization of optical structures and generation of most credible ionization states at target pH 7.0 ± 2.0 [31]. The molecules were then subjected to ConfGen with OPLS_2005 force field to get various conformations for each molecule.

2.2 Generation of Pharmacophore sites

The energy minimized chemical structures along with biological activity (i.e. pIC_{50}) are imported into PHASE module to get a validated 3D QSAR model. PHASE module makes available inbuilt generation of pharmacophores, such as Acceptor - A, Donor -D, Hydrophobic - H, Positive and Negative - P/N and Aromatic Rings - R. In order to find common pharmacophores for all active ligands “Develop Common Pharmacophore Hypothesis” was used by selecting a maximum number of pharmacophore sites five. Consequently, nine variant pharmacophores have appeared. Basically, the resulting pharmacophore hypothesis are scored to get the best alignment pharmacophore hypothesis by using automatic default parameter such as vector, site and volume scores above 1.0 and RMSD value under $1.7 \text{ \AA}$ in the Phase

module. The quality of pharmacophore model depends on the highest survival score or survival-inactive score. The survival score exhibited as in the following equation

$$S = W_{\text{site}} S_{\text{site}} + W_{\text{vec}} S_{\text{vec}} + W_{\text{vo1}} S_{\text{vo1}} + W_{\text{se1}} S_{\text{se1}} + W_{\text{rew}}^m$$

Where, W and S symbolize volume and score; S_{site} imply alignment score; S_{vec} represents vector score; S_{vo1} imply volume score; S_{se1} represents selectivity score and W_{rew}^m = reward weights defined by m-l (where, m outline the number of actives that suite to hypothesis) [32].

PHASE is a highly flexible system, it provides two alternatives for the 3D QSAR model development i.e., Pharmacophore based QSAR model, whereas another one is Atom based QSAR model. During this work, we have chosen atom based 3D QSAR model which is more suitable for explaining the structural activity relationship of database ligands having similar scaffolds. In this method each atom of the molecule is assigned as a particular molecular feature such as hydrogen-bond donors (D), hydrogen bond acceptors (A), negative and positive ionic (N/P), electron withdrawing (w) and miscellaneous (X). The atom based QSAR model was generated by applying a statistical technique called partial least squares (PLS) analysis value five and grid space $1\text{\AA}^0$. The obtained atom based pharmacophore model was further evaluated via flowing some statistical measures i.e. R^2 = correlation coefficient; Q^2 = predicted activities; SD = standard deviation; F = overall significance of Model; RMSE = root mean square error; Pearson R value; number of PLS factors and stability. Further the PLS factor with low RMSE value was selected among all the PLS factors.

2.3 Evaluation of model generation

The development of 3D QSAR model is a crucial step to establish a statistical significant relationship between the target property and descriptors. QSAR model was generated by using the partial least square method (PLS) to escape false outcomes. The fined common pharmacophore among the active ligands, a set of desired variant list selected with the option create site as default in Phase module [34]. As a result two variants with maximum hypothesis AHRRR, AAHRR are formed from list of nine variant combinations i.e., AAAHH, AAAHR, AAARR, AAHHR, AAHRR, AARRR, AHHRR and AHRRR, HHRRR. To get best pharmacophore model, all nine variants are scored by applying the automatic default parameter of PHASE module. The resulted best hypothesis (AHRRR) is associated with one hydrogen bond acceptor; A (*displayed with a pink color sphere*), one hydrophobic; H (*displayed with green color sphere*) and three aromatic groups; R (*displayed with an orange color sphere*) (Fig. 2). The angle and distances between the spheres of common hypotheses are arranged in Table 1.

Table 1
The distance and angle between spheres of common
pharmacophore

Angle between the common pharmacophore sites				
Entries	Site-1	Site-2	Site-3	Angle in A ⁰
1	H4	A3	R6	168.4
2	H4	A3	R7	1.0
3	H4	A3	R8	153.6
4	R6	A3	R7	167.4
5	R6	A3	R8	21.9
6	R7	A3	R8	153.0
7	A3	H4	R6	4.2
8	A3	H4	R7	0.9
9	A3	H4	R8	14.8
10	R6	H4	R7	3.3
11	R6	H4	R8	12.9
12	R7	H4	R8	14.3
13	A3	R6	H4	7.4
14	A3	R6	R7	5.7
15	A3	R6	R8	141.8
16	H4	R6	R7	1.7
17	H4	R6	R8	140.0
18	R7	R6	R8	140.5
19	A3	R7	H4	178.0
20	A3	R7	R6	6.9
21	A3	R7	R8	19.7
22	H4	R7	R6	175.0
23	H4	R7	R8	161.3
24	R6	R7	R8	16.6
25	A3	R8	H4	11.6

Angle between the common pharmacophore sites				
26	A3	R8	R6	16.3
27	A3	R8	R7	7.2
28	H4	R8	R6	27.2
29	H4	R8	R7	4.4
30	R6	R8	R7	22.9
Distance between the common pharmacophore sites				
Entries	Site-1	Site-2	Distance in A ⁰	
1	A3	H4	5.936	
2	A3	R6	3.405	
3	A3	R7	2.799	
4	A3	R8	7.503	
5	H4	R6	9.26	
6	H4	R7	3.138	
7	H4	R8	13.089	
8	R6	R7	6.166	
9	R6	R7	4.526	
10	R7	R8	10.078	

Table 2
The various parameters of the training and test set ligands.

C.N	Exp. A (pIC50)	QSAR set	Pre. A (pIC50)	F. Score	Pharm Set
M1	5.769	training	5.25	2.05	moderate
M2	5.619	training	5.59	2.42	moderate
M3	5.455	test	5.64	2.53	moderate
M4	5.619	test	5.3	2.28	moderate
M5	5.494	training	5.62	2.53	moderate
M6	5.958	training	5.78	2.87	moderate
M7	5.619	test	5.7	2.8	moderate
M8	5.6	training	5.21	2.25	moderate
M9	5.52	test	5.71	2.88	moderate
M10	5.1	training	5.2	2.25	moderate
M11	5.443	training	5.87	2.95	moderate
M12	5.585	training	5.5	2.65	moderate
M13	6.154	test	5.8	3	active
M14	5.537	training	5.74	2.96	moderate
M15	6.301	test	5.79	2.99	active
M16	4	training	4.03	2.02	inactive
M17	5.08	training	5.22	2.35	moderate
M18	4.27	test	5.12	2	inactive
M19	4.575	training	5.22	2.41	inactive
M20	4.364	test	5.12	2	inactive
M21	6.096	training	6.02	2.92	active
M22	5.657	training	5.82	2.85	moderate
M23	6.698	training	5.96	2.97	active
M24	5.619	training	5.93	2.96	moderate
M25	5.657	test	5.59	2.22	moderate
M26	5.585	training	5.72	2.39	moderate
M27	6.096	training	5.83	2.47	active

C.N	Exp. A (pIC50)	QSAR set	Pre. A (pIC50)	F. Score	Pharm Set
M28	5.657	test	5.71	2.44	moderate
M29	6.04	test	5.83	2.46	active
M30	5.585	training	5.69	2.08	moderate
M31	4.602	training	4.49	2.17	inactive
C.N: Compound Name; Exp. A: Experimental Activity (pIC50); Pre. A: Predicted Activity (pIC50); F. Score: Fitness Score					

2.4 Virtual Screening

Virtual screening is the largest source of novel lead over the last fifteen years, which is mainly in terms of cost effect less and probability of finding the most appropriate novel hits. The virtual screening workflow utilizes the “Glide module” to search best fit molecule (best pose) [35–36]. Glide allows the scientist to screen the dataset molecule in three different ways of the docking protocol, namely High throughput virtual screening (HTVS), Standard precision (SP) and Extra precision (XP) mode [37–39]. The force field employed during docking stimulations is OPLS_2005.

2.5 Protein Preparation

In order to use protein for docking, the structure file of DprE1 in a complex with CT319 was downloaded from the protein data bank with resolution 2.4 Å (PDB ID 4FDO) [52]. The first step in keeping with the requirement, the protein is prepared by using Protein Preparation Wizard workflow [40–41]. The preparation includes adding hydrogen in physiological pH value, removal of water molecules beyond 5 Å⁰ from the group that are not concerned in ligand binding, preprocessing and energy minimization in the selected force field (OPLS2005 and RMSD of 0.30 Å). After the energy minimization, the receptor active sites are identified by choosing a co-crystal ligand.

2.6 Grid generation

Grid generation is a very crucial step in molecular docking to expect the ligand binds. The Grid was generated by selecting the co-crystal ligand in ligand binding domain, which generates the grid containers and changed it with the studied ligands in the course of the method of docking [42].

2.7 MM/GBSA calculations

The binding free energies of a docked complex were determined by using Prime MM/GBSA (Molecular Mechanics/ Generalized Born Surface Area) method [43–49]. This comprises OPLS-2005 force field and rotamer search algorithm. The change in the binding free energy of docked complex i.e. ΔG_{bind} can be calculated with the following equation

$$\Delta G_{\text{bind}} = E_{\text{complex}} - (E_{\text{protein}} + E_{\text{ligand}})$$

Here, the term ΔG_{bind} defines ligand binding energy with receptor; E_{complex} define energy of complex after docking; E_{protein} defines energy of receptor before docking; E_{ligand} defines energy of ligand.

3. Results And Discussion

A set of thirty-one data set molecules having triazole moiety was selected and divided into two training and test set consisting of twenty-one and nine molecules respectively to get the best alignment pharmacophore model by using a default parameter “maximum number of sites” 5 and “minimum number of sites” 3. The ligand molecules are divide into active and inactive molecules based on an activity threshold value, the molecules which has pIC_{50} more than 6.0 considered as an active molecule, on the other hand, the molecules which has pIC_{50} less than or equal to 4.8 considered as inactive molecules and the molecules which has pIC_{50} in-between 6.0 to 4.8 is considered as moderate to get best pharmacophore model. The generated model is validated by different statistical parameters such as R^2 , Q^2 , RMSE, SD, F and Pearson R value. These are measured to inspect the strength of the pharmacophore model and the model with PLS value identified to be best. The best hypothesis associates with a Low Root Mean Square Error (RMSE) value of 0.418, higher the stability value of (S) 0.3628, higher the value of (F) 45 and lower the value of P (2.743e-006). The model AHRRR 1 also recorded with high predictive correlation value of 0.5492 (Q^2), a good correlation coefficient value of 0.712(R^2) along a high Pearson R value of 0.8899 specifies that there is a correlation between actual and predicted biological activity. The difference between correlation coefficient R^2 and predictive correlation value Q^2 is less than 0.3 ($R^2 - Q^2 = 0.165$), this low value suggested that the obtained model is accurate and reliable [50–51](Table 3). Figure 2 illustrated that the hydrogen bond acceptor A3 (pink color sphere) mapped with oxygen atom which is located between triazole and benzene ring, whereas the hydrophobic H4 (green color sphere) mapped with an atom at para position of benzene ring present on the fourth position of triazole. The aromatic rings R6, R7 and R8 (orange color sphere) are mapped with all three rings of ligand molecules. The graph of experimental v’s predicted biological activity (in terms of pIC_{50}) of anti-tubercular inhibitors is given in Fig. 1. All the active and inactive molecules are aligned to map common pharmacophoric features which is a crucial step in the development of pharmacophore model. The alignment of a fittest molecule to map common pharmacophore is shown in Fig. 2. Further, these are treated to generate 3D QSAR model through applying test and training set molecules (Table-2).

Table 3
Summary of phase statistical model

S.N.	R^2	F	Q^2	SD	P	RMSE	Pearson R
AHRRR.172	0.7142	45	0.5496	0.3277	2.43e.006	0.417	0.8899
R^2 = correlation coefficient; Q^2 = predicted activities; SD = standard deviation; F = overall significance of Model; RMSE = root mean square error; Pearson son R value; number of PLS factors and stability.							

Due to technical limitations, table 4 is only available as a download in the Supplemental Files section.

Table 5
Docking results of top 15 molecules.

Compound	Docking Score	XP Score	Glide emodel	B.A kcal/mole
S1	-9.4	-11.4	-91.9	-49.7
S2	-9.3	-11.2	-85.1	-70.2
S3	-10.2	-11.2	-89.6	-46.7
S4	-10.0	-11.2	-81.9	-67.8
S5	-9.5	-11.0	-90.8	-81.9
S6	-10.3	-11.0	-101.8	-73.7
S7	-10.7	-10.9	-58.2	-78.7
S8	-10.2	-10.6	-91.4	-75.9
S9	-10.5	-11.5	-85.4	-80.3
S10	-10.4	-11.1	-91.3	-74.9
S11	-9.3	-10.5	-71.3	-70.3
S12	-9.7	-10.5	-64.8	-66.3
S13	-9.7	-10.4	-86.9	-91.4
S14	-10.12	-10.2	-86.8	-79.0
S15	-10.3	-10.3	-63.4	-75.7
Co-crystal	-7.7	-7.7	-56.2	-48.3

3.1 Visual inspection of Atom-based 3D QSAR model

The results of 3D QSAR model were visually inspected to identify ligand features that contribute to enhance or diminish the activity. These features are crucial for the interaction of the ligand molecule and its target enzyme. According to the sign of their co-efficient value, the regression map are color coded. The blue color indicates that most favorable significant biological activity and the red color indicates the unfavorable biological activity. The blue color cubes suggest that increase in activity while red color cube indicates a decrease in activity. In order to identify the chemical features of ligand molecules, whether they are enhance or diminish the biological activity determined by visual inspection of 3D QSAR model. This information provides a piece of evidence for convince and non-convince groups at a specific position on ligand molecule.

3.2 Visualization of an active molecule

The 3D visualization of compound M15 (active; 5.79) and compound M16 (inactive; 4.03) were carried out to attempt more insight into Structural Activity Relationship (SAR) to describe a biological activity. The pictorial representation of molecule M15 and M16 is displayed in Fig. 3. The hydrophobicity feature of molecule M15 and molecule M16, which is obtained by 3D QSAR model, is represented in Fig. 3. It reveals that the presence of blue color cubes around hydrophobic feature at para position to benzene reveals more favorable for activity. Similarly, the presence of hydrophobic groups except for para position on benzene reveals that unfavorable for activity. It advises that as the hydrophobic substituent is added to the phenyl ring and inhibitory activity of the ligand increases.

The electron withdrawing field prediction that had been obtained from atom based QSAR model applied most active (M15) and inactive ligands (M16). The pictorial representation of Fig. 3 demonstrates that the presence of red color cubes around the group 'NO₂' indicates the unfavorable for biological activity. The presence of electron withdrawing substituents indicates a decrease in biological activity.

3.4 Virtual Screening

The resulted 3D QSAR model (AHRRR) was employed as a 3D quarry to screen ZINC database molecules to identify novel lead molecules [53]. The screening resulted in 22,271 molecules and utilized for virtual screening workflow. It includes HTVS (high throughput virtual screening), SP (standard precision) and XP (extra precision) modes. Initially, these molecules were screened by utilizing high throughput virtual screening (HTVS) against the DprE1 enzyme with a default parameter without any constraints. Further, these molecules were exposed to Glide SP mode followed by Glide XP mode. As a result, 31 molecules with a good Glide score were recorded. The obtained virtual hits are subjected to further analysis. The GLIDE (Glide-Based Ligand Docking with Energetics) is an automated docking program, which is used to explore the interaction between the ligand and receptor molecule. The ligand interaction tool of Schrödinger was utilized to investigate the intermolecular interaction between the ligand and receptor molecule.

3.5. Binding free energy estimation

The docked complexes obtained as virtual hits along with receptor co-crystal ligand were exposed to MM/GBSA calculations to estimate relative binding free energy. The binding energy values are ranging from -46.27 to -91.45 kcal/mole. The binding free energy of co-crystal ligand with a receptor is -52.67 kcal/mole. The binding affinity of a co-crystal ligand is fixed as a cutoff value to screen the compound. As a result, fifteen molecules having good binding free energy and these molecules are utilized for further analysis. The molecules which are recorded above the cutoff value and their estimated binding energies

are depicted in **Table- 5**. **Table-5** pointed out that they all resulted in fifteen molecules comprising hydroquinoline – 2-one and pyrimidine 5-one moiety.

3.6 ADME properties

The estimation of ADME properties is an important indicator for the development of novel drug molecules. All the Unfavorable properties help to eliminate the drug molecule in the process of drug development. The molecules which are resulted from virtual screening are screened by utilizing QuickProp module of the Schrodinger suit. The calculated physicochemical properties such as H-donors, H-acceptors, molecular weight, Plog S, QplogPoct, number of violations related to Lipinski rule of five and three [54] are listed in **Table-4**. The QuickProp results indicate that the molecules S3-S10 and S14 were recorded with desirable physicochemical properties; however the molecules S8 and S14 were recorded with 100% human oral absorption value. The molecules S1, S2, S11 to S13 and S15 were recorded with good binding affinity even though they are recorded undesirable physicochemical properties. The molecules which are recorded with desirable physicochemical properties were selected for further analysis.

3.7 Binding mode investigation

In the current study, determination of active site was carried by choosing co-crystal ligand and the residues which are present at the active site were shown in **figure-4**. The co-crystal ligand within the protein molecule was extracted and re-docked to get awareness into on binding pattern of ligand at the active site. For the validation of docking accuracy, the RMSD value is calculated between the experimental conformation and re-docked conformation of co-crystal ligand at the active site of the target protein. The co-crystal ligand forms two H-bonds with amino acid residues Gly117 and Tyr60 with a bond distance of $2.14 \text{ \AA}$, $1.681 \text{ \AA}$ respectively. Based on knowledge of Glide energy, binding affinity, hydrogen bond interactions and physicochemical properties, four molecules were selected as hit molecules and utilized for binding mode analysis. The binding mode analysis of all four hit molecules are shown in Fig. 5. Results of binding mode analysis indicate that the molecule S8 (ZINC44890235) forms H-bonding interactions between the O atom of methoxy-methyl group and -NH of Gly117, O atom of carboxamide and -OH group of Tyr60 with a bond distance $1.96 \text{ \AA}$ and $2.17 \text{ \AA}$ respectively same as co-crystal ligand. In addition to this, the molecule S8 also forms H-bond interaction with amino acid Arg58 and Pi-Pi interactions amino acid Lys418 with a bond distance of $2.36 \text{ \AA}$ and $5.01 \text{ \AA}$ respectively. The molecule S9 (ZINC58156954) forms three H-bond interactions with active site amino acids His136, Tyr415 and Lys418 with bond distance $2.10 \text{ \AA}$, $1.85 \text{ \AA}$ and $1.96 \text{ \AA}$ respectively. The **figure-6** indicates the binding mode of molecule S14 (ZINC35685029). The binding mode analysis of molecule S10 (ZINC44920132) is similar to molecule S8. The molecule S10 forms three hydrogen bonds with amino acids Gly117, Arg58 and Tyr60 with bond distances $1.93 \text{ \AA}$, $2.40 \text{ \AA}$ and $2.20 \text{ \AA}$ respectively. The molecule S10 also forms Pi-Pi interactions with amino acid Lys418 $\text{\AA}$. However, the molecule S14 recorded with three H-bonds between the O atoms of methoxy group with amino acid Cys 129 with bond distance $2.02 \text{ \AA}$, the O atom of the pyrimidine 5- one and amino acid Arg 58 with bond distance $2.05 \text{ \AA}$. In addition to this, it also forms H-

bond with amino acid Tyr60 with bond distance $2.15\text{\AA}$ and Pi-Pi interactions with Lys418. The binding mode analysis of all top hit molecules along with co-crystal ligand at the active site shows in Fig. 6. The binding mode analysis of compounds S3 to S7 shown in supplementary **figure S1**.

4. Conclusion

Mycobacterium tuberculosis has attained elevated resistance across drugs. Hence there is a need to develop potent anti-microbial drugs with reduced toxicity. In the current study, 3D QSAR model was developed to investigate the pharmacophoric features which are crucial for biological activity. The generated common pharmacophore hypothesis (AHRRR.172) consists of one acceptor-A, one hydrophobic-H and three aromatic rings -R. These are essential features for ligand binding. The generated 3D QSAR model was found to be recorded with good statistical results with $R^2 = 0.71$, $Q^2 = 0.54$ and other parameters $F = 45$, $RMSE = 0.41$. The difference between R^2 and Q^2 is very low and this indicates that the obtained model is accurate and reliable. Visual examination of resulted 3D QSAR model, within the context of the foremost active and least active molecule, explains the structural features responsible for biological activity against DprE1 enzyme. The obtained five-point pharmacophore model was used to screen zinc chemical database molecules to identify potent lead molecules against DprE1 enzyme. The resultant molecules recorded with dihydroquinonolin 2-one and Pyrazolo[1,5] pyrimidin 5-one scaffold are utilized for the estimation of physicochemical properties and followed by binding mode analysis. The QuikProp study reveals that all hit molecules are associated with good pharmacokinetic properties and considered as prospective drug candidates for future research.

Declarations

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Conflicts of interest The authors declare that there is no competing of interests.

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Figures

Figure 1

A correlation graph of experimental vs. predicted biological activity of both training and test set molecules.

Figure 2

Alignment of best fit molecule with pharmacophoric features, where A is acceptor; H is hydrophobic; R is aromatic ring.

Figure 3

QSAR model visualization of inactive (M16) and active (M15) molecule (Presence of blue color cubes depicts positive potential and red color cubes depicts negative potential). (a) Visualization of electron withdrawing feature of molecule-M16. (b) Visualization of electron withdrawing feature of molecule-M15. (c) Visualization of hydrophobic feature of molecule – M16. (d) Visualization of hydrophobic feature of molecule – M15.

Figure 4

The residues present at active site of protein (Tyr60, Val121, Lys417, Gly117, Thr118, Pro116, Gly321, Arg58, Ser59 and Cys387).

Figure 5

(a) Binding mode analysis of molecule S8 (ZINC44890235), (b) Binding mode analysis of molecule S9 (ZINC58156954), (c) Binding mode analysis of molecule S10 (ZINC44920132), (d) Binding mode analysis of molecule S14 (ZINC35685029). The violet color bonds indicates H-bonds, red color bonds indicates that Pi-Pi staking interactions.

Figure 6

Binding mode analysis of all four hit molecules along with co-crystal ligand (blue).

Supplementary Files

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