Structural Insight into PRMT5 Inhibitors through Amalgamating Pharmacophore-Based Virtual Screening, ADME-Toxicity and Binding Energy Studies and Identify New Inhibitors by Molecular Docking.

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Abstract

Protein arginine methyltransferase 5 (PRMT5) is a member of the methyltransferases family, a type II arginine enzyme that is crucial for many cellular processes and is associated with many cancer diseases. In this study, pharmacophore-based 3D QSAR modeling, virtual screening and binding free energy studies were carried out from a set of 61 potent compounds reported being inhibitors of PRMT5 protein. A five-point pharmacophore model (AADHR) was generated and this model is used to generate an atom-based 3-Dimensional quantitative structure-activity relationship (3D-QSAR). The obtained 3D-QSAR model has high correlation coefficient ($R^2 = 0.91$), cross-validation coefficient ($Q^2 = 0.82$), F value (140.3), low RMSE (0.47) and pearson R-value (0.91). A library of 329825 molecules (ChEMBL database) is screened with pharmacophore model to retrieve hit molecules that are further subjected for molecular docking to identify best fit-active conformations binding at the receptor site of PRMT5 protein. Further, we are calculated ADME and toxicity properties using QikProp module and pkCSM server and finally prioritized the lead molecules by binding free energy prediction.

Introduction

Arginine methylation is the most widespread post-translational modification that regulates cellular processes, cell growth, proliferation and differentiation in a mammalian cell [1]. The reported nine human PRMTs (Protein arginine methyltransferases) were further divided into three types (Type-I, Type-II and Type-III) based on resulting methylated arginine. PRMT5 belongs to type-II PRMT which is the enzyme that catalyzes the transfer of methyl groups from S-adenosyl methionine (SAM) to guanidine nitrogen atoms of arginine residue on histone and non-histone proteins giving in symmetric dimethylarginine (DMA), monomethyl arginine (MMA) and S-adenosyl homocysteine (SAH) [2, 3]. The PRMT5 activity is a trademark associated with symmetrical dimethylarginine of histone and non-histone proteins. The PRMT5 protein was involved in various cellular processes, RNA processing, cell proliferation, metabolism and also transcription [4]. Overexpression of PRMT5 protein results in many human cancers such as breast cancer [5], lung cancer [6], lymphoma [7], colorectal cancer [8], multiple myeloma [9], glioblastoma [10] and hepatocellular carcinoma [11]. Therefore, PRMT5 protein was targeted for treating various cancers. Several lead PRMT5 inhibitors were reported earlier such as Sinefungin, JNJ-64619178, EPZ015666, GSK3326595, LLY-283 and A9145C were under clinical trial for the treatment of various cancer (Fig. 1) [12]. The present study involves developing ligand-based pharmacophore hypothesis and 3D QSAR model using the 61 ligand molecules with their biological activity as potent PRMT5 inhibitors. The best pharmacophore hypothesis was used for screening and identifying new lead molecules. Molecular docking based virtual screening was carried out using ChEMBL database. The final hit molecules were further optimized using glide score, Prime MM/GBSA and ADMET properties.

Materials And Methods

Data set

A set of 61 ligands were taken from the literature with the inhibitory activity of PRMT5 [13, 14]. IC₅₀ values are converted to pIC₅₀ values and those ligands are randomly selected in training set and test set [15, 16]. Phase module of Schrodinger suite used to generate similar pharmacophore and 3-D QSAR model [17].

Ligand preparation

The 3-Dimensional structures of all molecules were sketched in maestro build panel. The LigPrep module of Schrodinger suite was used to refine the structures geometrically, hydrogen atoms were added, neutralized the charged structures and finally possible lowest energy conformers were generated by applying (optimized potentials for liquid simulations) OPLS2005 forcefield [18, 19].

Prediction of common pharmacophore hypothesis

Each ligand molecule was symbolized by 3D space site points in which spatial arrange several chemical features that are proposed to explain the noncovalent binding interactions between ligand molecule and target receptor [20]. All the set of molecules defines by six pharmacophore features that are Hydrogen bond donor(D), hydrogen bond acceptor(A), positively ionizable(P), negatively ionizable(N) and aromatic ring(R). A common pharmacophore was identified from all ligand conformers with identical set of features consisting of intersite distance of 2 Å. A tree depth of 5 with a box size of initial set to 32Å and a final box size set to 1 Å was used. Hypotheses were produced by systematically changing the number of sites and number of matching active molecules [21].

Scoring pharmacophore hypothesis

The common pharmacophore is investigated by applying a scoring function to get the best alignment of active ligands. This Pharmacophore gives hypothesis, which is to define how the active ligand interacts with the receptor. The different hypotheses were ranked and scored using a scoring procedure to choose the best one. The scoring procedure is measured as alignment of site points, vector score, volume score, selectivity, number of ligands matched, relative conformational energy and activity [22].

3-D QSAR model generation

The 3D-QSAR model was developed using selected hypothesis by dividing the 61 molecules randomly into 43 training set molecules and 18 test set molecules. This 3D-QSAR model analyzes the relationship between Pharmacophore sites and activity of ligand molecules based on PLS (Partial least square) regression. It is acceptable for a set of independent binary variables. In atom-based 3-D QSAR model the structural features of actives were defined by van der waals models of the atoms in the ligands. To discriminate different atom types that occupy the same region of space atoms were classified as six features [23]. Each sphere is classified into six categories: H-bond donor (D), Hydrophobic or nonpolar (H), Negative ionic (N), Positive ionic (P), H-bond acceptor or electron-withdrawing groups (A), miscellaneous (M). The data set of ligand molecules were randomly divided into training set and test set in 70:30 ratio. The training set of ligand molecules was aligned for generating atom-based 3-D QSAR models using

selected AADHR hypothesis with three PLS factors and grid space occupying 1 Å. Validation of best 3D-QSAR model was done from internal training set and external test set ligands [24, 25].

3D database screened using pharmacophore model

The library of ChEMBL database consisting of 329825 ligand molecules which are bioactive drug-like molecules and are subjected to LigPrep module for generating lowest energy conformers by applying (optimized potentials for liquid simulations) OPLS2005 forcefield. The pharmacophore-based screening was carried out to identify new leads from screening a 3D database of ChEMBL library using best hypothesis and to estimate the predicted activity using 3D QSAR model [26].

Virtual screening and molecular docking

The crystal structure of PRMT5 protein (PDB id: 4GQB) was taken from Protein Data Bank. This protein was optimized using protein preparation wizard in maestro version (9.0.1.1.1) applying OPLS-2005 force field. The missing side chains and hydrogen atoms were added, deleting the water molecules, assigning partial charges and bond orders, alleviating steric clashes in protein. The minimization of PRMT5 protein was completed when it reaches maximum cut-off of an RMSD value is 0.30 Å. The receptor grid was generated using the receptor grid generation panel. The co-crystal ligand molecule was selected so that it could be excluded from grid generation and Van der Waals radius scaling is set to 0.9 [27]. Subsequently, top molecules retrieved from pharmacophore-based screening of ChEMBL database were subjected for filtering through HTVS, SP and XP docking mode at active site of PRMT5 protein using Glide module [28]. Final hit molecules were analyzed using QikProp module of Schrodinger suite to evaluate the ADME properties and binding free energies were calculated using Prime MM/GBSA [29, 30]. The toxicity parameters of the best hit molecules were determined using pkCSM server [31]. The binding interaction of final hit molecules was analyzed and visualized using XP Visualizer Tool.

Results And Discussion

The pharmacophore modeling and atom-based 3D QSAR model were developed on a set of PRMT5 inhibitors using PHASE module of Schrodinger suite. Experimentally reported 61 inhibitors were divided into active and inactive molecules (Table 1). The active inhibitors with a pIC₅₀ value greater than 7.64 and inactive inhibitors with a pIC₅₀ value less than 5.1 are assigned in the pharm set for creating pharmacophore site points. These active inhibitors can be used to derive better pharmacophore which defines the necessary structural characteristics of active molecules in order to effectively bind to target for its inhibition PRMT5 protein. The predicted activity of test set and training set molecules were calculated utilizing 3D-QSAR model provided in Table 2. Five minimum and maximum sites were used to generate optimum combinations with features of active compounds. The best common pharmacophore hypotheses were developed with different variant combinations that were showing best alignment of active ligands which were recognized by applying survival scores. The best pharmacophore hypothesis was chosen on the basis of survival inactive, volume and vector scores. site points, selectivity, number of ligands matched, relative conformational energy and activity. The generated five-point pharmacophore

hypotheses consisting of AADHR, AADRR, AADDR, ADHRR and ADDRR having H-Bond donor(D), hydrophobic(H), H-Bond acceptor(A) and aromatic ring (R) features and the pharmacophore hypotheses with AADHR descriptor was selected as the best one.

Table 1 Structures of different analogues reported as PRMT5 inhibitors.

Mol.	R	Mol.	R	Mol.	R
1	Benzy1	11	Tetrahydro-2H-pyran-4-yl	21	4-Acety1Benzoyl
2	Phenyl	12	Isocotinoyl	22	4-(Trifluoromethyl)benzoyl
3	1-Phenyl-ethyl	13	Furan-3-carbonyl	23	4-(tert-butyl) benzoyl
4	Phenylcarbonyl	14	Thiophen-3-carbonyl	24	4-Nitrobenzoyl
5	Phenylsulfonyl	15	2-Naphthyl	25	4-cynobenzoyl
6	Phenylacetyl	16	4-Methylbenzoyl	26	4-(Dimethylamino)benzoyl
7	Phenylloxy carbonyl	17	4-Methoxybenzoyl	27	4-(Aziridin-1-yl)benzoyl
8	Phenyl propanoyl	18	4-Fluorobenzoyl	28	3-Fluorobenzoyl
9	Propyl	19	4-Chlorobenzoyl	29	2-Fluorobenzoyl
10	Cyclohexyl	20	4-Bromobenzoyl

Mol.	R1	A			
30	Methyl
31	Methyl
32	Methyl
33	4-(Dimethyl amino) benzoyl
34	4-(Dimethyl amino) benzoyl
35	4-(Dimethyl amino) benzoyl
36	4-(Dimethyl amino) benzoyl
37	4-Methoxybenzoyl
38	4-Bromobenzoyl
Mol.	R2	R3	R4	Mol.	R2 Configuration
39	(4-Chlorobenzoyl) Oxy	H	OH	55	4-(Dimethylamino)benzoyl S
40	Benzoyloxy	Phenyl	OH	56	4-Methoxybenzoyl R
41	Pyridin-4-yl	Phenyl	OH	57	4-Methoxybenzoyl S
42	(4-Fluorobenzoyl) Oxy	Phenyl	OH	58	4-Bromobenzoyl S
43	(4-Chlorobenzoyl) Oxy	Phenyl	OH	59	4-Bromobenzoyl R
44	(4-Cyanobenzoyl) Oxy	Phenyl	OH	60
45	Benzoyloxy	Phenyl	H		
46	Benzoyloxy	Pyridin-2-yl	H		
47	Benzoyloxy	Indol-3-yl	H	61	
48	Benzoyloxy	Piperidin-1-yl	H		
49	Benzoyloxy	Morpholine-4-yl	H
50	Benzoyloxy	4-	H		
51	Benzoyloxy	4-Hydroxybenzyl	H		
52	Benzoyloxy	4-Methylbenzyl	H		
53	Benzoyloxy	4-Chlorobenzyl	H		
54	Benzoyloxy	3-Fluorobenzyl	H		

Table 2

Experimentally reported and predicted pIC50 values, Pharma set, Fitness score of PRMT5 inhibitors from PHASE and Glide score, binding free energy from molecular docking studies.

Mol.	Expt.pIC50	Pred.pIC50	Pharma set	Fitness Score	Glide Score	Binding Energy (Kcal/mol)
1	6.61	5.60		1.67	-7.13	-105.40
2	6.58	7.02		1.62	-10.59	-104.14
3*	7.22	5.57		1.74	-7.04	-93.92
4	7.40	7.45		2.87	-9.10	-109.35
5	7.04	6.92		1.38	-10.93	-84.33
6	7.30	7.69		1.65	-9.93	-112.33
7	7.30	7.16		1.91	-10.58	-110.69
8*	7.32	6.81		1.19	-10.29	-99.64
9*	5.95	6.32		1.54	-9.99	-107.93
10	6.88	6.32		1.51	-5.33	-139.22
11	6.33	6.32		1.52	-5.51	-135.83
12*	7.34	7.40		2.27	-10.76	-124.31
13	7.60	7.62		2.60	-9.50	-99.9
14*	7.43	7.44		2.68	-8.33	-112.70
15	7.65	7.47	Active	2.79	-7.46	-119.41
16	7.48	7.31		2.25	-5.81	-120.06
17	7.69	7.44	Active	2.29	-6.55	-122.92
18*	7.52	7.38		2.91	-8.89	-114.05
19	7.63	7.68		2.63	-7.73	-127.31
20	7.74	7.53	Active	2.50	-4.94	-116.99
21	7.72	7.58	Active	2.61	-7.44	-110.85
22	7.30	7.68		2.64	-4.81	-115.50
23	7.72	7.64	Active	2.70	-1.80	-
24	7.72	7.21	Active	3.00	-9.0	-115.33
*Test set molecules						

Mol.	Expt.pIC50	Pred.pIC50	Pharma set	Fitness Score	Glide Score	Binding Energy (Kcal/mol)
25	7.60	7.35		2.81	-6.74	-108.21
26	7.63	7.45		2.52	-3.72	-114.32
27	7.35	7.73		2.70	-2.76	-96.35
28	7.50	7.45		2.64	-11.87	-115.66
29	7.34	7.35		2.80	-9.05	-109.35
30*	7.32	5.75		1.53	-6.57	-83.77
31*	5.72	5.95		1.54	-9.39	-102.19
32	5.92	5.67		0.90	-8.09	-101.89
33	7.63	6.86		2.66	-7.13	-102.05
34	7.39	7.69		2.19	-5.16	-123.64
35	7.76	7.38	Active	1.50	-4.09	-88.02
36*	7.76	7.77	Active	1.95	-4.74	-78.97
37*	7.63	8.01		1.99	-6.84	-116.39
38*	7.95	7.36	Active	2.06	-8.78	-113.73
39	4.44	4.88	Inactive	1.50	-8.81	-99.33
40	5.52	5.33		0.92	-10.02	-88.61
41	5.07	5.33	Inactive	0.92	-10.07	-94.57
42*	5.04	6.23	Inactive	0.84	-9.91	-86.08
43	5.01	4.82	Inactive	0.97	-6.17	-100.19
44*	4.53	5.53	Inactive	0.54	-8.78	-95.33
45*	5.49	5.38		1.46	-8.63	-76.43
46	5.10	4.96		1.44	-9.72	-101.90
47	5.34	4.99		1.36	-8.99	-94.73
48	4.42	4.99		1.36	-8.56	-92.49
49	4.34	4.93	Inactive	1.37	-6.85	-88.00
*Test set molecules						

Mol.	Expt.pIC50	Pred.pIC50	Pharma set	Fitness Score	Glide Score	Binding Energy (Kcal/mol)
50	5.38	6.14		1.48	-9.16	-85.32
51*	5.19	5.29		1.45	-8.49	-77.39
52*	4.88	5.26	Inactive	0.84	-8.72	-91.70
53	4.60	4.69	Inactive	1.20	-9.47	-97.62
54	5.36	5.42		0.90	-9.10	-90.37
55	7.95	7.72		1.93	-4.74	-79.33
56*	7.48	7.99		2.04	-7.06	-100.11
57*	7.88	7.85	Active	1.94	-6.84	-116.48
58*	7.22	7.60		1.94	-8.78	-113.20
59	8.07	8.01	Active	1.96	-12.49	-103.34
60	7.32	7.73		0.85	-4.37	-114.32
61	4.60	4.75	Inactive	0.79	-10.20	-82.14
*Test set molecules						

The atom-based 3D-QSAR models were generated from five pharmacophore hypotheses by PLS regression with three PLS factors. Experimentally reported 61 ligands were divided randomly into 43 training sets of ligands and 18 ligands of test set. The structural diversity in both training set and test set was given as bias in order to form the standard 3:1 training to test set ratio. Among the five pharmacophore hypotheses (AADHR, AADRR, AADDR, ADHRR and ADDRR), AADHR model showed good statistical results: Low standard deviation (SD) = 0.34, high values of correlation coefficient (R^2) = 0.91, variance ratio (F) = 140.3, high value of cross-validation coefficient (Q^2) = 0.82, Pearson's R-value = 0.91 and low RMSE = 0.47 is shown in Table 3. The positive correlation between experimental and predicted biological activity of PRMT5 test and training ligands is shown in scatter plot in Fig. 2. Hence AADHR pharmacophore model is considered as robust and significant out of five pharmacophore hypotheses [32, 33]. Figure 3 shows the geometry of AADHR, two pink colored spheres representing hydrogen bond acceptor (A1, A2), blue colored sphere representing hydrogen bond donor (D5), green colored represents hydrophobic group (H6), orange colored represents aromatic ring (R9). The contour maps of the best pharmacophore hypothesis AADHR along with most active compound 59 was shown in Fig. 4. In Fig. 4a, b, c and d, dark blue, purple, pink and orange cubes areas represent favorable region whereas red, cyan, yellow and green cubes areas represent unfavorable regions for hydrogen bond acceptor, hydrogen bond

donor, hydrophobic and aromatic ring respectively. For molecule 59, hydrogen bond acceptor favored dark blue cubes were observed on the hydroxy group(Fig. 4a), hydrogen donor favored purple cubes was seen on NH group(Fig. 4b), hydrophobic group favored pink cubes are observed on tetrahydroisoquinoline ring(Fig. 4c), which should increase the inhibitory activity [34]. All the ligand molecules were docked at active site of PRMT5 protein using Glide module to identify potential inhibitors. The resulting inhibitors were further subjected to Prime MMGBSA to calculate the binding free energy of protein-ligand complexes and their interactions with PRMT5 protein. The glide score and binding free energy (ΔG) are shown in Table2. The best molecule 59 had a glide score of -12.49 kcal/mol with binding free energy of -103.34. Molecule 10 is showing effective binding free energy of -139.22 kcal/mol and glide score of -5.33 kcal/mol. The molecules 59 and 10 consist of similar N-(3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-hydroxypropyl) amide scaffolds.

Table 3
Statistical parameters of top five pharmacophore hypotheses developed from PHASE.

ID	SD	R ²	F	RMSE	Q ²	Pearson-R
AADHR	0.34	0.91	140.3	0.47	0.82	0.91
AADRR	0.37	0.90	121.4	0.51	0.79	0.90
AADDR	0.33	0.92	153	0.66	0.65	0.81
ADHRR	0.36	0.90	125.9	0.71	0.62	0.79
ADDRR	0.43	0.86	83.2	0.65	0.66	0.81

The ChEMBL database of 329825 ligand molecules was chosen for virtual screening which is bioactive and drug-like in nature. Initially, this database of small molecules was subjected to ligand preparation in Ligprep module of Schrodinger suite. which resulted 542356 3D low energy conformers as output. The lowest energy conformers of 542356 molecules were screened based on developed AADHR pharmacophore model. The top 5000 molecules were matched with five pharmacophore features. The top 5000 molecules were further subjected to molecular docking at the active site of PRMT5 protein. The molecular docking process is performed in Glide module through virtual screening workflow by using HTVS, SP and XP stages of screening. Initially, 50% of molecules were screened in HTVS mode which produced 2367 molecules. These 2367 molecules further were docked in 50% SP and 10% XP modes which produced 114 molecules [35, 36]. The binding free energy of 114 molecules was determined by Prime MM/GBSA. The top hit molecules have glide scores ranged between - 13.46 to -10.55 kcal/mol and binding free energy ranged from - 113.69 to -80.57 kcal/mol. The glide score, binding free energy and predicted pIC50 values were showed in Table 4. The predicted ADME properties of top hit molecules are showed in Table5 and their toxicity showed in Table6. The ChEMBL134525, ChEMBL298245 and ChEMBL61073 molecules have similar N²-N⁴-diphenyl-N⁶-(Pyridin-4-ylmethyl)-1,3,5-triazine-2,4,6-triamine core. It showed H-bonding interaction with Gly365, Glh444, Ser578, π - π interaction with Phe327, π -cation

interaction with Lys333, Lys393, Trp579, salt bridge with Glu435. The 3D and 2D binding interactions of best fit-conformation of top lead molecule ChEMBL134525, ChEMBL298245 and ChEMBL61073 with PRMT5 protein represented in Fig. 5. The ChEMBL134525, ChEMBL298245 and ChEMBL61073 molecules were obeying acceptable range of druglike properties that showed 100% human oral absorption, QlogP of n-octanol/water value (< 5), water solubility, cell membrane permeability and Lipinski rule of five. The toxicity properties of lead molecules are predicted using pkCSM server. All the top lead molecules showed negative test for mutagenic in AMES toxicity prediction including the final potential leads ChEMBL134525 and ChEMBL298245. The leads revealed high MRTD (maximum recommended tolerated dose) profile that is $\geq 0.477\log(\text{mg/kg/day})$ which are considered to be low toxic in nature. Drug-induced inhibition of the hERG channel may cause progression of acquiring long QT syndrome leading to arrhythmia. None of the lead molecules from the identified leads were showing hERG inhibitory activity and all of them were less toxic in terms of LD50 and also LOAEL (Lowest observed adverse effect). All the identified lead molecules were showing no or low toxicity profile considering it more druglike in properties. This toxicity profile from pkCSM server is utilized in optimizing potential leads against PRMT5. Based on all scoring functions and ADME-toxicity profile the leads ChEMBL134525, ChEMBL298245 and ChEMBL61073 are considered for further optimization in the discovery process as PRMT5 potential inhibitors.

Table 4
Glide score, binding free energy, predicted activity of top hit molecules obtained from molecular docking studies.

S. No	Molecule ID	Glide Score	Binding free energy	Predicted activity (PLS3)
1	ChEMBL134525	-13.46	-108.91	6.95
2	ChEMBL327952	-11.54	-113.69	6.06
3	ChEMBL298245	-11.53	-104.52	6.61
4	ChEMBL115698	-10.89	-85.88	6.06
5	ChEMBL283586	-10.85	-80.18	6.36
6	ChEMBL135416	-10.76	-113.01	7.47
7	ChEMBL67474	-10.55	-90.55	5.98
8	ChEMBL17629	-10.53	-86.90	6.98
9	ChEMBL260279	-10.50	-124.04	6.45
10	ChEMBL166874	-10.29	-67.18	7.28
11	ChEMBL61073	-10.23	-116.44	6.95
12	ChEMBL199847	-10.20	-83.02	6.13

Table 5
ADME properties of top hit molecules predicted from QikProp module of Schrodinger suite

Molecule ID	MW	logPo/w	logS	PCaco	PMDCK	#metab	%Human Oral Absorption	Rule Of Five
ChEMBL-134525	435.4	4.8	-6.6	1323.8	2239.7	2	100%	0
ChEMBL-327952	457.8	1.6	-4.3	185.7	262	2	77.3%	0
ChEMBL-298245	435.4	4.9	-6.7	1265.2	2148.1	3	100%	0
ChEMBL-115698	439.8	4.2	-7.4	150.5	851.8	2	90.57%	0
ChEMBL-283586	365.3	0.6	-3.2	170.3	266.3	8	70.60%	0
ChEMBL-135416	472.4	3.3	-5.6	326	706.2	7	91.47%	0
ChEMBL-67474	405.3	3.6	-6.7	162.9	533.3	3	87.9%	0
ChEMBL-17629	398.8	0.7	-4.0	219.4	294.4	4	73.4%	0
ChEMBL-260279	572.7	6.2	-9.5	670.7	10000	3	88.2%	2
ChEMBL-166874	313.3	2.9	-4.2	1016.7	780.1	4	100%	0
ChEMBL-61073	439.8	4.8	-7.2	1380.1	5793.2	1	100%	1
ChEMBL-199487	488.9	5.5	-7.6	770.1	1477.3	4	100%	1
Acceptable range for properties- {(350 ≤ MW ≤ 650), (-2.0 ≤ logPo/w ≤ 6.5), (-6.5 ≤ logS ≤ 0.5), (PCaco and PMDCK cell permeability: <25 poor, > 500 good), (Percent Human Oral Absorption > 80), (#metab: 1 to 8), Rule of five}								

Table 6
Toxicity parameters of top hit molecules obtained from pkCSM server.

Molecule ID	AMES toxicity	Max. tolerated dose (Human)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50)	Oral Rat Chronic toxicity (LOAEL)	Minnow toxicity
ChEMBL-134525	No	0.83	No	Yes	2.65	2.11	-3.39
ChEMBL-327952	No	0.40	No	No	3.09	1.12	1.77
ChEMBL-298245	No	0.83	No	Yes	2.71	2.14	-2.09
ChEMBL-115698	No	0.35	No	Yes	2.25	2.57	1
ChEMBL-283586	Yes	0.83	No	No	2.42	3.18	3.22
ChEMBL-135416	No	-0.15	No	Yes	2.48	1.21	3.77
ChEMBL-67474	Yes	0.34	No	Yes	2.26	2.65	1
ChEMBL-17629	No	0.09	No	No	2.38	2.76	2.72
ChEMBL-260279	Yes	0.17	No	Yes	2.46	1.13	-1
ChEMBL-166874	No	0.62	No	No	2.73	1.34	0.95
ChEMBL-61073	Yes	0.81	No	Yes	2.12	0.97	-1.02
ChEMBL-199487	Yes	0.48	No	Yes	2.92	-0.08	-1.35
(AMES toxicity (No (no mutagenic) Yes(mutagenic)) Max. tolerated dose (MRTD $\geq$ 0.477). Oral Rate Acute Toxicity (LD50) $\geq$ 1000 to 5000 mg/kg, Minnow toxicity: log LC50 > -0.3))							

Conclusion

The objective of this study is to identify common pharmacophore hypothesis and 3D-QSAR model. We have accomplished a molecular modeling study on 61 PRMT5 inhibitors using 3D-QSAR model, molecular docking and binding free energies. The highly predictive 3D-QSAR model generated using

active PRMT5 inhibitors consisting of five-point pharmacophore hypothesis AADHR. The accuracy of model is evident from their correlation coefficient ($R^2 = 0.91$) and cross-validation coefficient ($Q^2 = 0.82$). The generated 3D-QSAR model was used as query for screening of ChEMBL database of small molecules for design of new potential PRMT5 inhibitors. The new leads were identified using scoring functions glide score and binding free energies. The docking results revealed that the molecules containing N²-N⁴-diphenyl-N⁶-(Pyridin-4-ylmethyl)-1,3,5-triazine-2,4,6-triamine scaffold with prescribed pharmacophore features was showing consistent binding with Gly365, Glu444, Ser578 (H-bonding interaction), Phe327, Lys333, Lys393, Trp579 Glu435 (hydrophobic interactions) amino acid residues of PRMT5 protein and can act as potential PRMT5 inhibitors. Hence, we conclude that newly designed molecules ChEMBL134525, ChEMBL298245 and ChEMBL61073 having good glide scores, least binding free energy and falling in permissible range of ADME-Toxicity properties with the scaffold leads to identification of new PRMT5 inhibitors.

Declarations

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Conflict of interest

The authors declare no competing interests

Availability of data and material

No data

Code availability

Not applicable as no new code was used in this work

Authors contributions

Author Revanth Bathula has contributed to worked on the conception, design and written the first draft of manuscript. Author Sree kanth sivan, Gururaj Somadi and Sarita Rajender Potlapally corrected and commented the previous versions of the manuscript. Author Sarita Rajender Potlapally supervised the work and revised the study. All authors have read the paper and approved final version of manuscript.

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Figures

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Figure 1

Structures of representative PRMT5 inhibitors.

Figure 2

Scatter plot of experimental predicted pIC₅₀ values of training (yellow) and test (red) set molecules.

Figure 3

The representation of pharmacophore model AADHR where the pink sphere with vectors represents H-bond acceptor feature, blue sphere with vector represents H-bond donor feature, green sphere represents hydrophobic feature and orange ring represent aromatic ring features.

Figure 4

3D QSAR model visualization in connection with the best active molecule (59), illustrating the effect of 4a hydrogen bond acceptor, 4b hydrogen bond donar, 4c hydrophobic and 4d aromatic features.