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Original Research Paper

DESIGNING POTENT ANTITRYPANOSOMAL AGENTS USING 3D QSAR, PHARMACOPHORE MODELLING, VIRTUAL SCREENING AND MOLECULAR DOCKING STUDIES

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ABSTRACT

The last twenty years have seen noteworthy success in efforts to control HAT (Human African Trypanosomiasis) in Africa. HAT is a neglected tropical disease with major public health and economic effects in sub-Saharan Africa, and its effects on livestock productivity and development are considered major constraints to alleviating poverty in this region. The identification of important chemical features using the existing molecules will be helpful to discover the potent candidate to treat HAT. The development of novel HAT inhibitors is done using pharmacophore based virtual screening and docking study. The 3D-QSAR was also performed to determine the predicted biological activity. The best hypothesis from PHASE, gave the five point pharmacophore hypothesis, AAPRR.687 with two hydrogen bond acceptors (A), two aromatic rings (R) and one charged group (P). Amongst them the pharmacophore hypothesis yielded a statistically significant 3D-QSAR model with 0.9521 as coefficient of determination (r2), a Pearson coefficient of 0.8796 and good F value and was considered to be the best pharmacophore hypothesis. The developed pharmacophore based 3D-QSAR model was validated by predicting the activity of test set molecules. The squared predictive correlation coefficient (q^2) of 0.7359 was observed between experimental and predicted activity values of test set molecules. The developed pharmacophore was used to screen the chemical database. Subsequently the screened compounds were filtered by molecular docking. Finally five compounds were obtained as novel lead against human African trypanosomiasis.

Keywords: 3D-QSAR, Pharmacophore, Virtual screening, Docking.

INTRODUCTION

Human African Trypanosomiasis is a neglected disease since the people most affected by it are the poorest residing in remote, rural areas, urban slums or conflict zones. The conditions under which the neglected diseases persist are those of poverty and mainly affect impoverished populations of the developing world.[1,2] Benzyl phenyl ether diamidine derivatives were synthesized and evaluated for their antiprotozoal activities.[3] Current treatments include drugs such as Pafuramidine, Pentamidine, Furamidine, (figure 1) suramin, eflornithine, melarsoprol whose availability is not a problem but they suffer from a number of disadvantages such as the need for long periods of medication, renal disruption or other side effects, the emergence of resistance, toxicity and high costs, parenteral administration is required by pentamidine and suramin and they have adverse effects, eflornithine must be administered in high doses over long periods.[4]

There is lack of a guaranteed supply and increasing incidences of treatment failure and the need for well-tolerated, orally active and economically feasible drug persists. Thus, the search for new and more effective chemotherapeutic agents against HAT with fewer or no side effects motivated us to design and develop the new chemical entities with good biological activity and fewer side effects. To better understand the structural features of benzyl phenyl ether diamidine derivatives as inhibitors of Trypanosoma brucei rhodesiense, PHASE program was used for building the pharmacophore hypothesis.[5] Pharmacophore modelling is one of the proven approaches to quantitatively investigate common chemical features among a considerable number of structures and a qualified pharmacophore model could also be used as a query for searching chemical databases to find new chemical entities. Pharmacophore modeling acts as a link between activities and the spatial arrangement of various chemical features. Pharmacophore mapping and quantitative structure-activity relationship exemplify ligand-based drug design and can be used in drug discovery in several ways, e.g. rationalization of activity trends in molecules under study, prediction of the activity of novel compounds, database search for new hits and to identify important features for activity. In the present research paper, a robust ligand-based pharmacophore, 3D-QSAR, virtual screening and docking study is described for the development of new HAT inhibitors.

Computational Details

The PHASE software was employed for developing the 3D-QSAR pharmacophore model. Given a set of molecules with affinity for a specific target, PHASE employs fine-grained conformational sampling and a plethora of scoring techniques to identify the common pharmacophore hypothesis. This common pharmacophore hypothesis brings forth those characteristics of 3D chemical structures that are important for binding. Aligned conformations follow each hypothesis which is suggestive of the relative fashion in which the molecules would most possibly bind to the receptor. A standard set of six pharmacophore features is provided by PHASE, namely, hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionizable (N), positively ionizable (P) and aromatic ring (R).

The Glide software package was employed for the docking procedure. It assists in high-throughput screening of potential ligands on the basis of binding mode and affinity towards a particular receptor molecule. 3 different levels of docking precision are provided by Glide; high-throughput virtual screening, standard precision and extra precision.[6-9]

EXPERIMENTAL

- **Selection of Dataset**
- **Ligand Preparation**
- **Pharmacophore Modelling**
- **3D QSAR**
- **Virtual Screening**
- **Docking**

Selection of Dataset

In the computerized pharmacophore generation process an accurate choice of the training set is a key issue. The developed pharmacophore hypothesis is dependent on the input data information. The criteria for the selection of the dataset are as follows:

- All compounds should bind in the same fashion with the same nucleotide.
- The data should be well populated so that we can differentiate active from inactive compounds.
- The most active compound should most certainly be included in the training set.
- All the biological data should be obtained from the same procedure.

Every individual feature in the hypothesis will have certain contribution that is proportional to its relative contribution to biological activity. By taking into consideration the above criteria we chose the dataset of 62 compounds[10] having antitrypanosomal activity from the literature resources. The biological activity was reported in terms of IC_{50}. The whole dataset was divided into

training set (44 compounds) and test set (18 compounds) randomly. The training set was used to construct the 3D-QSAR model. The dataset comprised of some active, some inactive and some highly active compounds.[11-13]

Ligand Preparation

Pharmacophore modelling studies start with ligand preparation. The chemical structures of all the 62 compounds were drawn in Maestro and geometrically refined using Ligprep module. *LigPrep* is a robust tool designed to prepare high quality structures for large numbers of drug-like molecules, starting with the 2D or 3D structures in SD or Maestro format. The simplest use of LigPrep produces a single, low-energy, 3D structure with correct chiralities for each successfully proposed input structure. While performing this step, chiralities were determined from 3D structure and original states of ionization were retained. Conformers were generated using MacroModel method discarding current conformers. The conformations were generated by the Monte Carlo (MCMM) method as implemented in MacroModel version 9.6 using a maximum of 2,000 steps with a distance-dependent dielectric solvent model and an OPLS-2005 force field. All the conformers were subsequently minimized using truncated Newton conjugate gradient (TNCG) minimization up to 500 iterations. For each molecule, a set of conformers with a maximum energy difference of 30 kcal/mol relative to the global energy minimum conformer was retained. The conformational searches were done for aqueous solution using the generalized born/solvent accessible surface (GB/SA) continuum solvation model.[13]

Pharmacophore Modelling

It was accomplished by the generation of twenty hypotheses with imperative statistical parameters using PHASE module of Schrodinger Inc. The generation of hypothesis was done using a systematic variation of the number of sites (n_{sites}) and the number of matching active compounds (n_{act}).[14-17] The pharmacophoric sites were created for all 62 ligands. In the present study, an initial analysis revealed that two chemical feature types i.e., hydrogen-bond acceptor (A), and aromatic ring (R) could effectively map all critical chemical features of all molecules in the data set. The minimum and maximum sites for all the features were kept 3 and 5 respectively. These features were selected and used to build a series of hypothesis. For searching the common pharmacophore, all conformations of the ligands in the data set were examined and clustered using complete clustering protocol. Identification of common pharmacophores was done using a tree - based partitioning technique that groups together the similar pharmacophores according to the distances between pairs of sites in the pharmacophore.

The hypotheses were scored using scoring function to examine the common pharmacophore hypotheses in order to yield the best alignment of the active ligands using an overall maximum root mean square deviation (RMSD) value of 1.2 Å for distance tolerance. Survival score was employed to measure the quality of alignment. The scoring protocol involved a ranking of different hypotheses to choose the most appropriate pharmoacophore further investigation. The inactive molecules were also scored so as to observe the alignment of these molecules with respect to the different pharmacophore hypotheses in order to select the best one. The 3D-QSAR Model was generated by dividing ligands into training (70%) and test sets (30%). PHASE helps in building 3D QSAR models for a set of ligands that are aligned to a selected hypothesis. The space occupied by the ligands is partitioned into a cubic grid by the Phase 3D QSAR model. The regression was done by constructing a series of models with an increasing number of PLS factors. In the present case, the pharmacophore based model was generated by keeping 1Å grid spacing and 3 as the maximum number of PLS factors. Selected hypothesis was used to build an atom based QSAR model derived from a regular grid of cubic volume elements that span the space occupied by the training set of ligands by keeping 1Å grid spacing. The activity was predicted for a

maximum number of 3 PLS factors. Predicted activities of test and training set compounds were plotted against their experimental activities, and the relevant statistics were computed. The goodness of the model was measured in terms of correlation coefficient (r^2) and cross-validated correlation coefficient, q^2 (or cross-validated r^2; also written as r^2_{cv}). The validation of the pharmacophore model constitutes an important aspect of pharmacophore design, particularly when the model is built for the purpose of predicting activities of compounds in external test series. The predictability of a model can be judged based on external validation which is considered to be a conclusive proof of the same. Development of QSAR models was a priority. The model developed in such that the output model will be statistically robust both internally as well as externally. The pharmacophore model developed by us was tested for its validity by predicting the activity of test set molecules and correlation between the experimental and predicted activities of the test set molecules.

The quality of alignment is measured in three ways: the alignment score, the vector score and the volume score. The following equation has been used for the final survival scoring process.

A site score for each alignment is then computed based on the alignment score $S_{align(i)}$ and the cutoff C_{align} by

$$S_{site(i)} = 1 - S_{align(i)} / C_{align}$$

This score is always between 0 and 1 because alignments with $S_{align(i)} > C_{align}$ are eliminated.

$$S = W_{site} S_{site} + W_{vec} S_{vec} + W_{vol} S_{vol} + W_{sel} S_{sel} + W^{m}_{rew} - W \Delta E + W_{act} A$$

Where W's indicate weights and S's indicate scores. Additionally, an adjusted survival score is derived using the following equation using a weight of 1.0 for the inactive scores.

$$S_{adj} = S_{actives} - W_{inactives} S_{inactives}$$

The goodness of the model was measured in terms of correlation coefficient (r^2) and cross-validated correlation coefficient, q^2 (or 'cross-validated r^2; also written as r^2_{cv}).

$$r^2 = 1 - [\sum (Y_{pred} - Y_{obs})^2 / \sum (Y_{obs} - Y_{mean})^2]$$

Where, Y_{pred}, Y_{obs} and Y_{mean} indicate the predicted, observed and mean biological activity values.

$$q^2 = [1 - \sum (Y)_i - (\hat{Y}_i)^2] / \sum (Y)_i - (\bar{Y}_i)^2$$

Where, q^2 = cross-validated correlation coefficient

($\hat{Y}_i$) is the observed response (training set), ($\bar{Y}_i$) is the predicted response of the training set molecules [18-21]

Virtual Screening

Methodology

The best pharmacophore generated was subjected to virtual screen the compounds in the database. For searching the matches in the database thorough sampling technique was used with varying amide bond confirmation and keeping relative energy window 10 kcal/mol. The matching criteria was set with intersite distance matching tolerance 2 Å. The hit treatment was done using QSAR model with fitness and vector score 1. The compounds were rejected with vector score less than 1.

Molecular Docking

Nucleotide Structure Preparation

The X-ray crystal structure of the nucleotide (PDB ID: 1VZK), obtained from RCSB Protein Data Bank (PDB) was used in order to model the nucleotide structure in the docking study. Water molecules of crystallization were kept upto 3Å distance from the nucleotide. The nucleotide was prepared for docking using the protein preparation and refinement utility provided by Schrödinger LLC.

Docking Protocol

All docking calculations were performed using the ''Standard Precision'' (SP) mode of Glide program and the 2001 implementation of the OPLS-AA force field. A short description on the methodology used by Glide is provided below. The binding site, for which the various energy grids were calculated and stored, is defined in terms of two concentric cubes: the bounding box, which must contain the center of any acceptable ligand pose, and the enclosing box, which must contain all ligand atoms of an acceptable pose. Cubes with an edge length of 12 Å and centered

at the midpoint of the longest atom–atom distance in the respective co-crystallized ligand defined the bounding box in the protein. The larger enclosing box was also defined in terms of the co-crystallized ligand: an edge length of 30 Å was used. Poses with an RMSD of less than 0.5 Å and a maximum atomic displacement of less than 1.3 Å were eliminated as redundant in order to increase diversity in the retained ligand poses. The scale factor for Van Der Waals radii was applied to those atoms with absolute partial charges less than or equal to 0.15 (scale factor of 0.8) and 0.25 (scale factor of 1.0) electrons for ligand and protein, respectively. The *maxkeep* variable which sets the maximum number of poses generated during the initial phase of the docking calculation were set to 5000 and the keep best variable which sets the number of poses per ligand that enters the energy minimization was set to 1000. Energy minimization protocol includes dielectric constant of 4.0 and 1000 steps of conjugate gradient. Upon completion of each docking calculation, at most 100 poses per ligand were generated. The best docked structure was chosen using a Glidescore (G-score) function. The G-score is a modified and extended version of the empirically based Chemscore function. Another scoring function used by Glide is E-model, which itself is derived from a combination of the G-score, Coulombic, van der Waals and the strain energy of the ligand. All computations were carried out on a Dell Precision T5600 dual processor with the Linux OS (Red Hat Enterprise WS 6.2).[22-25] The ligands were docked on the nucleotide along with the phase matches obtained from the database. Molecular docking was performed with PDB: 1VZK and the ligands.

RESULTS AND DISCUSSION

To find the common pharmacophore hypothesis the dataset was divided into active and inactive sets (Table 4) Molecules with IC_{50} are converted to pIC_{50}. The pIC_{50} less than 4.3 are taken into inactive set and pIC_{50} values higher than 7.6 are considered to be active. The compounds with pIC_{50} values less than 7.6 and more than 4.3 are considered to be moderately active. By using this data, sixty pharmacophore hypotheses were identified. Out of which twenty hypotheses survived with different phases of PHASE scoring procedure (survival, survival inactive, post- hoc score). All twenty pharmacophore were subjected to QSAR. For QSAR model generation the data set was divided into test and training set. 70 percent ligands were taken into training set. The best pharmacophore model resulted AAPRR687 with 3.286 post hoc score (Table 5). The distance and angle geometry of the pharmacophore containing A, A, P, R and R is shown in Figure 2 and Table 1, 2. An atom based 3D QSAR analysis was derived one the basis of standard phase parameter. Table No. 3 shows all statistical parameters derived zinc phase methodology. The correlation coefficients are statistically acceptable (R^2 0.95 and Q^2 0.73), supporting the robustness of statistical model. Moreover high Pearson R value (0.87) also indicates close correlation between predicted and actual values. The 3D QSAR results are also visualized using 3D plots of pharmacophore regions- In Figure 3 the blue cubes refers to ligand region in which specific feature (hydrogen bond donor substituent) is important for good activity whereas substitution in red cube refers decrease in activity of same ligand. Similarly, Figure 4 and 5 shows 3D QSAR results for hydrophobic, electron withdrawing field prediction. The plots of predicted versus actual pIC_{50} training and test sets are reported in Figure 10 and 11. On the basis of the statistical parameters we finalized AAPRR687 hypotheses for virtual screening. Eight lakhs compounds were taken from Schrödinger provided database. Top 1000 ligands were extracted from the database, having good fitness score with the query hypotheses. To identify top hits, the ligands were docked on 1VZK nucleotide. For validating the docking procedure, the compound embedded with nucleotide in x-ray crystallographic structure was removed and redocked to see the binding site of 1VZK. We found that very good agreement between the localization of inhibitor upon docking and from the crystal structure. The top hits were selected based on G-Score and E-Model which is depicted in Table no 7. Compound

number a-e showed good binding affinity towards the nucleotide. Compound a showed a docking score -10.926 and G-score 10.939 and G-Model -123.889, which is better than the active compounds in the series (Table 6). Carbon number 13 of ligand 1 is exposed to the solvent molecule while DA6, DA5, DG16, DA17, DG10, DT8, DT20 and DT7 are found in vicinity of ligand molecule (Figure 7). The ligand no. 1 forms hydrogen bond with DC9 residue (-H---O-, d=2.01 Å, Figure 6). It has been observed that the ligand is located in the solvent exposed pocket of 1VZK. Being exposed to the solvent this ligand may offer a good handle for improving the pharmacokinetic profile of the ligand. The ligand number 1-5 showed nearly similar docking pose with compound number 55, (Figure 8 and 9).

The designed pharmacophore and 3D QSAR study on recently synthesized benzyl phenyl ether derivatives as trypanosomal inhibitors along with the molecular docking study provides an excellent platform for rational design and development of potent and selective antitrypanosomal agents.

LIST OF ABBREVIATIONS

- HAT : Human African trypanosomiasis
- SMARTS – Smiles arbitrary target specification
- PLS – Partial least squares
- OPLS – Optimized potentials for orthogonal liquid simulations

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest associated with this article.

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Table 1: Distances between the sites of the model

Entry	Site1	Site2	Distance
AAPRR.687	A1	A3	6.431
	A1	P10	9.457
	A1	R13	3.718
	A1	R14	7.489
	A3	P10	6.475
	A3	R13	2.786
	A3	R14	3.712
	P10	R13	7.442
	P10	R14	3.713
	R13	R14	4.69

Table 2: Angles between different sites of the model

Entry	Site1	Site2	Site3	Angle
AAPRR.687	A3	A1	P10	43.1
	A3	A1	R13	7.4
	A3	A1	R14	29.7
	P10	A1	R13	47.1
	P10	A1	R14	21.6
	R13	A1	R14	30.6
	A1	A3	P10	94.2

	A1	A3	R13	9.9
	A1	A3	R14	91.1
	P10	A3	R13	99.1
	P10	A3	R14	29.3
	R13	A3	R14	91.3
	A1	P10	A3	42.7
	A1	P10	R13	21.5
	A1	P10	R14	47.8
	A3	P10	R13	21.7
	A3	P10	R14	29.3
	R13	P10	R14	31.4
	A1	R13	A3	162.7
	A1	R13	P10	111.4
	A1	R13	R14	125.6
	A3	R13	P10	59.2
	A3	R13	R14	52.3
	P10	R13	R14	24.3
	A1	R14	A3	59.1
	A1	R14	P10	110.6
	A1	R14	R13	23.8
	A3	R14	P10	121.4
	A3	R14	R13	36.4
	P10	R14	R13	124.3

Table 3: Summary of the PLS of the common pharmacophore hypotheses

ID	# Factors	SD	R-squared	F	P	Stability	RMSE	Q-squared	Pearson-R
AAPRR.687	1	0.8972	0.7485	125	3.61e-14	0.8003	0.5521	0.5701	0.8189
	2	0.6237	0.8814	152.3	1.047e-19	0.793	0.4443	0.7216	0.9031
	3	0.4014	0.9521	264.8	2.057e-26	0.791	0.4328	0.7359	0.8796

Table 4: Alignments for the common pharmacophore hypotheses

Ligand	QSAR	Activity	Factors	Predicted	Pharm Set	Fitness
16	training	3.623	1,2,3	4.63 4.87 4.45	inactive	1.78
17	training	3.65	1,2,3	3.21 3.51 3.77	inactive	1.75
29	training	3.793	1,2,3	4.50 3.41 3.84	inactive	1.21
59	training	3.804	1,2,3	4.08 4.32 3.80	inactive	1.6
30	training	3.889	1,2,3	2.88 3.34 3.85	inactive	1.44
60	training	3.963	1,2,3	2.78 3.16 3.25	inactive	1.83
53	training	4.056	1,2,3	4.22 4.77 4.26	inactive	1.83
54	training	4.089	1,2,3	5.19 4.51 4.33	inactive	2.39
38	training	4.102	1,2,3	5.29 4.83 4.63	inactive	2.36

57	training	4.124	1,2,3	5.50 4.76 4.12	inactive	2.42
45	training	4.221	1,2,3	4.64 3.31 3.82	inactive	1.2
24	training	4.298	1,2,3	3.18 3.56 3.90	inactive	1.74
40	training	4.299	1,2,3	4.71 4.90 4.42	inactive	2.19
34	test	4.308	1,2,3	4.85 5.09 4.70	*	2.19
56	test	4.412	1,2,3	4.63 4.85 4.36	*	2.06
41	training	4.46	1,2,3	4.64 4.53 4.63	*	2.38
44	test	4.578	1,2,3	5.65 5.00 5.29	*	1.06
51	training	4.58	1,2,3	5.90 4.39 4.22	*	2.23
35	training	4.583	1,2,3	4.87 4.81 4.94	*	2.35
23	test	4.588	1,2,3	4.94 5.36 4.88	*	1.74
20	test	4.62	1,2,3	4.54 5.24 5.42	*	1.85
21	training	4.726	1,2,3	3.53 3.85 4.35	*	1.9
37	test	4.833	1,2,3	4.17 4.36 4.07	*	2.14
50	training	4.866	1,2,3	7.06 6.00 5.90	*	2.37
4	test	5.031	1,2,3	5.85 5.57 5.50	*	1.89
13	training	5.138	1,2,3	6.14 5.56 5.15	*	1.96
48	test	5.157	1,2,3	6.07 5.02 4.70	*	2.13
47	training	5.162	1,2,3	6.55 5.39 5.02	*	1.69
7	test	5.356	1,2,3	6.04 6.09 5.32	*	1.73
10	training	5.403	1,2,3	6.25 6.47 5.49	*	1.76
6	test	5.431	1,2,3	5.75 5.69 5.61	*	1.84
11	training	5.523	1,2,3	5.71 5.70 5.66	*	1.84
8	test	5.567	1,2,3	5.73 5.64 5.55	*	1.84
3	training	5.575	1,2,3	7.10 6.14 5.53	*	2.13
12	test	5.674	1,2,3	5.78 5.66 5.46	*	1.92
2	training	5.721	1,2,3	6.34 5.81 5.40	*	1.85
1	test	5.735	1,2,3	6.15 5.77 5.46	*	1.87
15	test	5.87	1,2,3	5.41 6.21 6.32	*	1.73
9	training	5.889	1,2,3	5.38 6.40 6.49	*	1.81
5	test	6.318	1,2,3	6.43 6.23 5.96	*	1.84
58	test	6.738	1,2,3	7.43 7.28 7.35	*	2.11
27	training	6.914	1,2,3	7.14 7.38 7.22	*	2.14
28	test	6.959	1,2,3	6.68 6.80 6.69	*	2.02
62	training	7.013	1,2,3	6.42 6.37 6.91	*	1.91
14	test	7.041	1,2,3	6.43 6.99 7.24	*	1.77
32	training	7.469	1,2,3	6.83 7.81 8.25	*	2.42
61	training	7.553	1,2,3	6.59 6.54 7.35	*	1.88
25	training	7.62	1,2,3	7.06 7.40 7.32	active	2.1
31	training	7.62	1,2,3	7.27 7.94 8.22	active	2.35
18	training	7.658	1,2,3	7.26 8.06 7.30	active	1.84
42	training	7.721	1,2,3	7.20 7.45 7.30	active	2.5
22	training	7.77	1,2,3	7.37 8.17 7.37	active	1.83
26	training	7.77	1,2,3	7.12 7.45 7.36	active	2.12

19	training	7.796	1,2,3	7.35 8.16 7.37	active	1.84
43	training	8	1,2,3	7.93 7.72 8.27	active	2.41
33	training	8.155	1,2,3	6.87 7.61 8.11	active	2.43
36	training	8.301	1,2,3	7.41 7.88 8.00	active	2.36
39	training	8.301	1,2,3	6.92 7.57 8.00	active	2.44
52	training	8.301	1,2,3	8.09 7.91 8.46	active	2.97
46	training	8.398	1,2,3	7.82 7.84 8.33	active	2.47
49	training	8.523	1,2,3	7.92 7.52 8.10	active	2.42
55	training	8.523	1,2,3	8.11 7.87 8.44	active	3

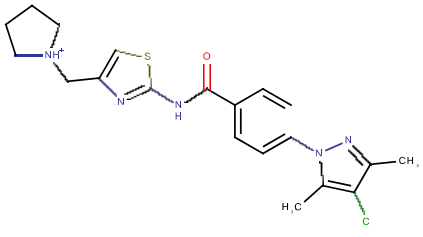
Table 5: Best pharmacophore hypothesis

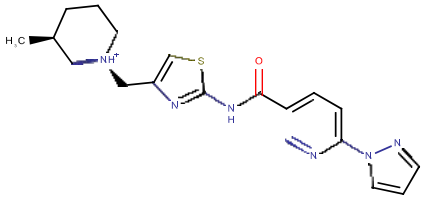
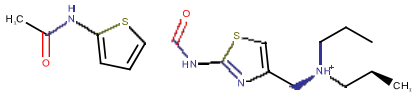
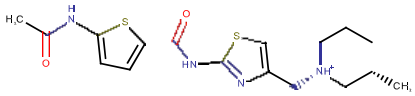
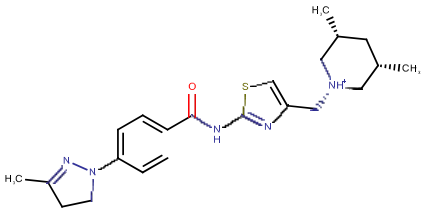
ID	Survival	Survival - inactive	Post - hoc
AAPRR.687	3.286	1.459	3.286

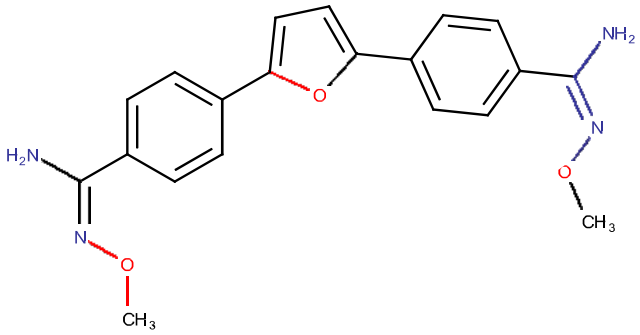
Table 6: Ligands with docking score

Title	Docking score	Glide Gscore	Glide Emodel
33	-10.849	-10.849	-126.527
36	-10.670	-10.670	-126.302
31	-10.598	-10.598	-119.240
42	-10.512	-10.512	-116.183
32	-10.468	-10.468	-118.528
61	-10.446	-10.446	-109.465
9	-10.429	-10.429	-122.974
39	-10.041	-10.041	-113.930
62	-9.517	-9.517	-106.098
37	-9.470	-9.477	-96.283
19	-9.407	-9.407	-99.511
14	-9.385	-9.385	-98.541
15	-9.383	-9.383	-116.632
35	-9.352	-9.352	-93.823
18	-9.268	-9.268	-97.559
34	-9.258	-9.272	-90.379
41	-9.091	-9.097	-92.741

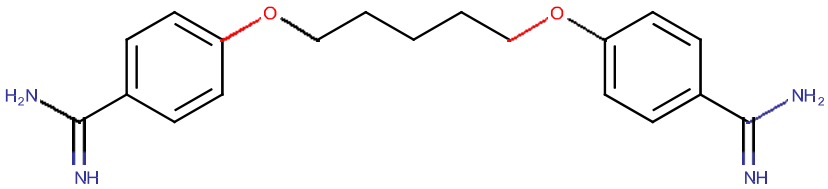
Table 7: Phase matches with their docking score

Compound Number	Title	Docking score	Glide Gscore	Glide Emodel
a		-10.926	-10.939	-123.889

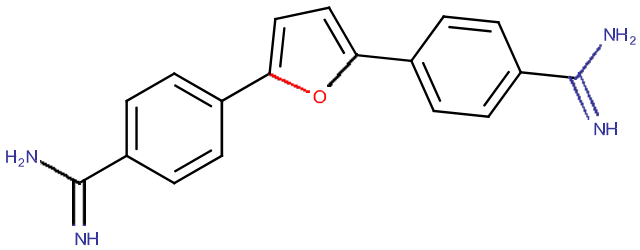
b		-10.466	-10.513	-112.253
c		-10.261	-10.277	-116.513
d		-10.205	-10.218	-97.366
e		-9.961	-10.033	-110.021



Pafuramidine



Pentamidine



Furamidine

Figure 1: clinically used antitrypanosomal drugs

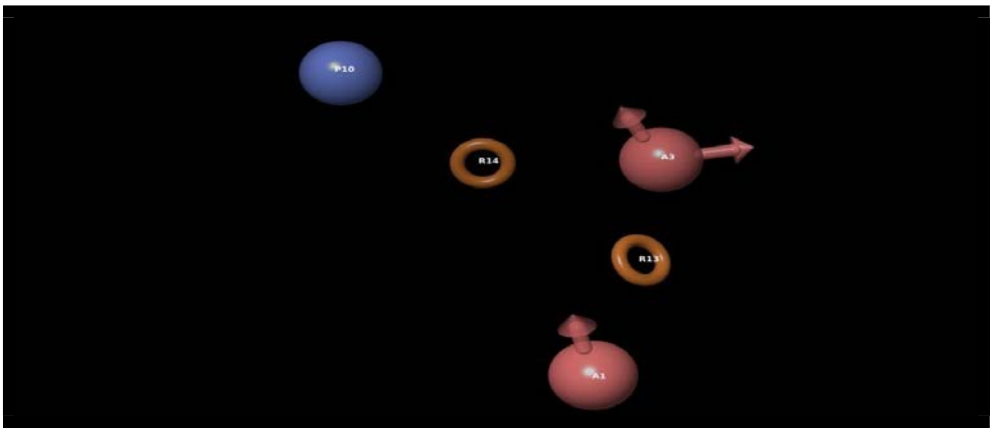


Figure 2: Ligand-based pharmacophore model

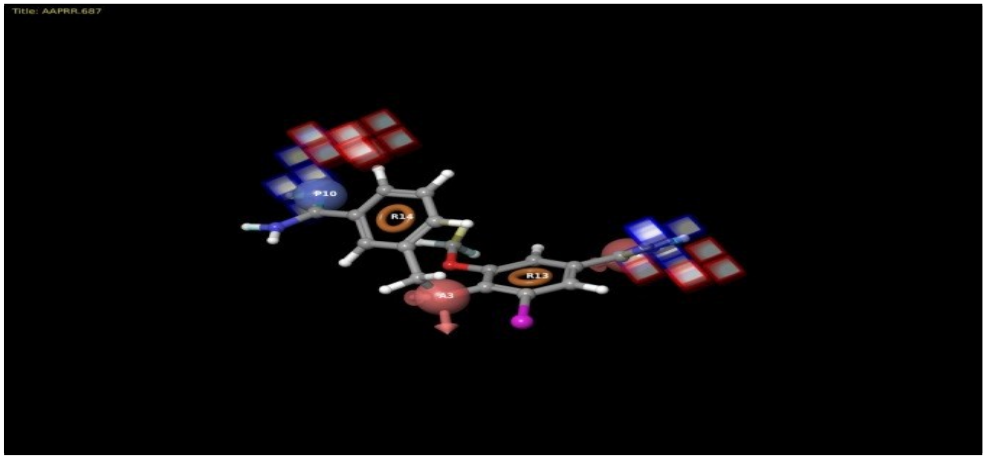


Figure 3: Hydrogen bond donor field prediction

The blue cubes suggest that substitutions having hydrogen bond donor property favour the antiprotozoal activity. The region with red cubes suggests that groups having hydrogen bond donor property do not favour the antiprotozoal action.

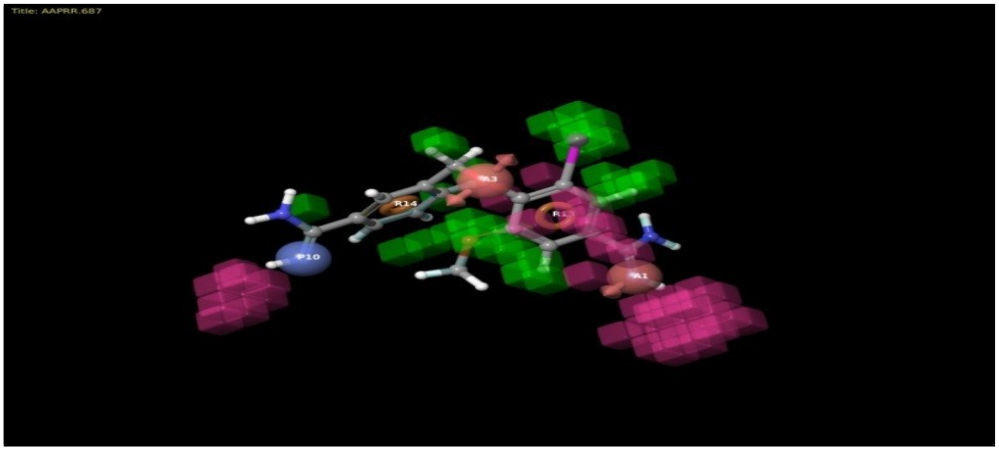


Figure 4: Hydrophobicity field prediction

Substitutions which fall in the green region will favour the antiprotozoal activity. Pink region indicates that groups having more hydrophobic property do not favour antiprotozoal activity.

Electron Withdrawing Field Prediction

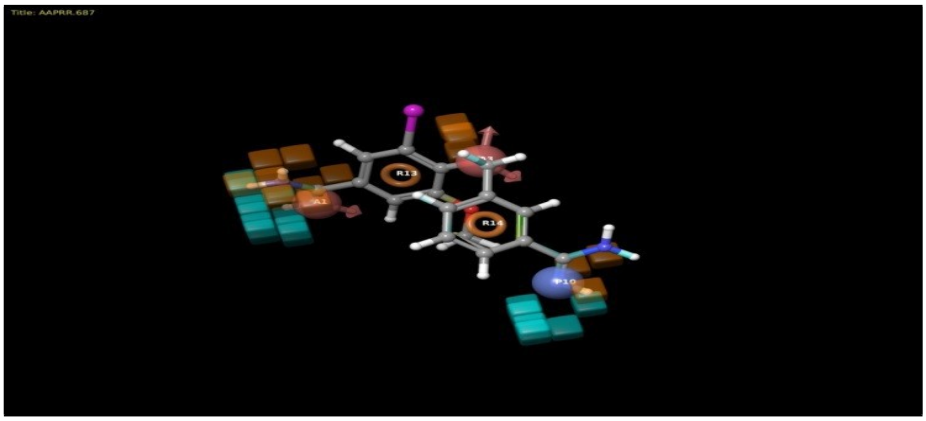


Figure 5: Electron withdrawing field prediction

Orange cubes in the pharmacophore indicate that substitution at this site will increase antitrypanosomal activity of benzyl phenyl ether diamidine derivatives and favour the biological activity. Whereas cyan cubes indicate negative effect which shows that electron withdrawing group at these regions will be responsible for decreasing the activity of benzyl phenyl ether diamidine derivatives.

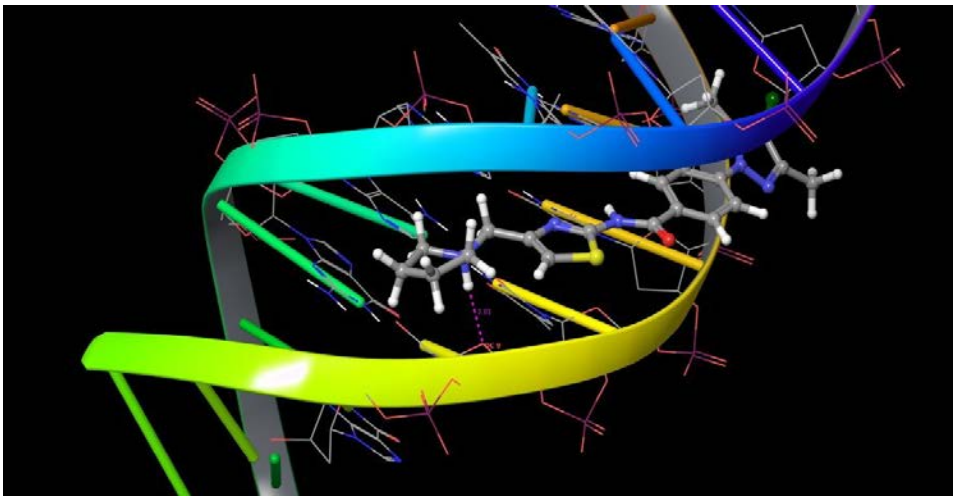


Figure 6: Docking pose for phase match CACPD2011a-0000959689

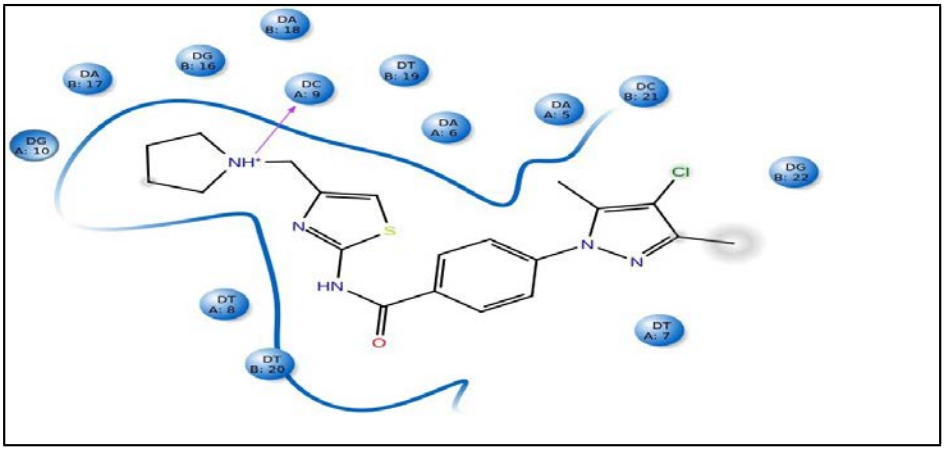


Figure 7: Nucleotide and ligand interaction in 2D for phase match CACPD2011a-0000959689

The pose of the most active ligand is shown in the figure below. The hydrogen bonding and all other bonds are shown in the nucleotide in the figure given below.

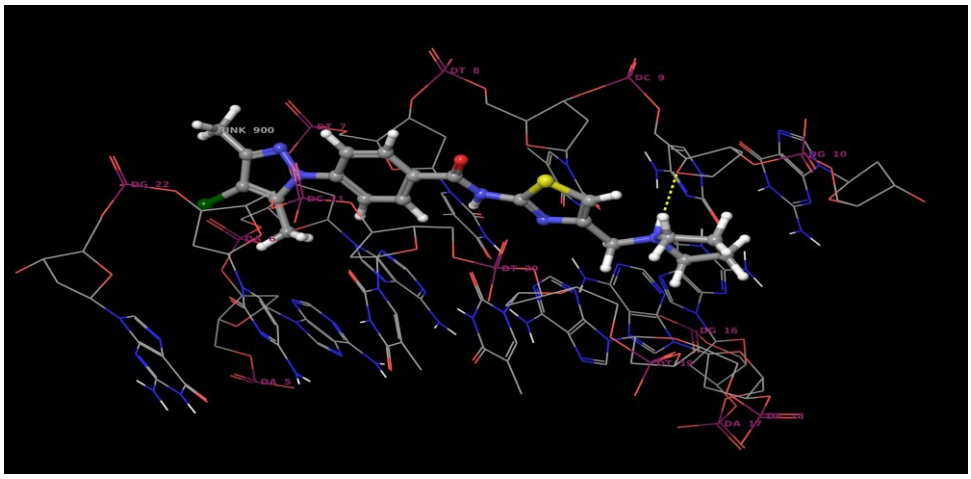


Figure 8: Nucleotide and ligand interaction for ligand molecule 33 of the dataset

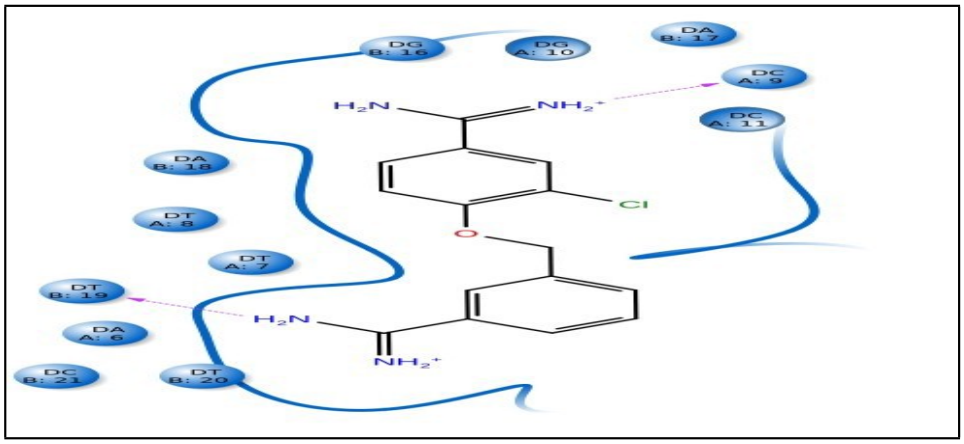


Figure 9: Nucleotide and ligand interaction for ligand molecule 33 of the dataset in 2D

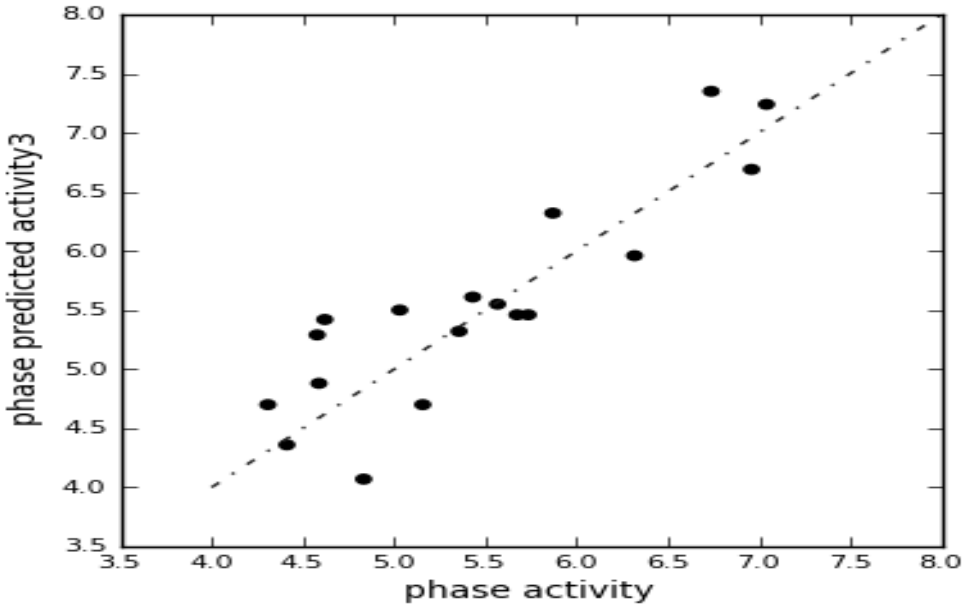


Figure 10: Plot of activity versus predicted activity for the test set ligand

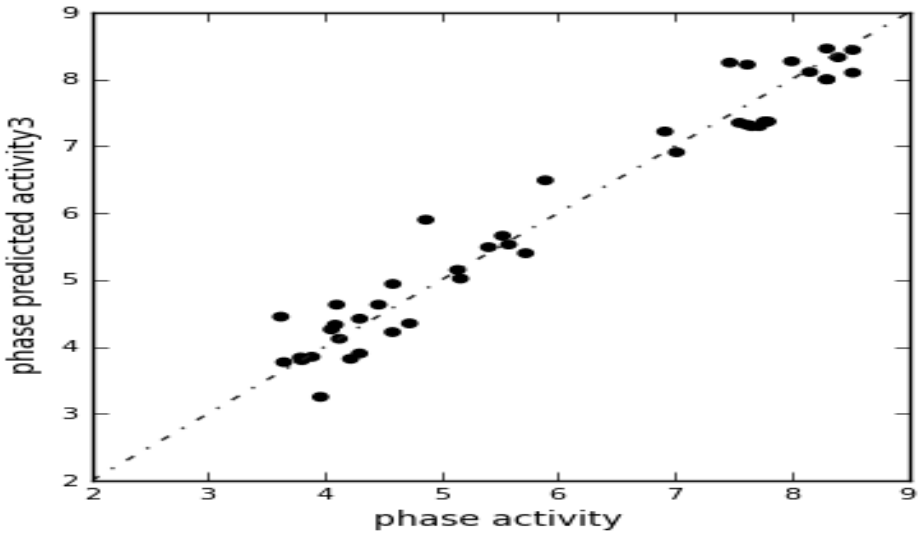


Figure 11: Plot of activity versus predicted activity for the training set ligand

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