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3-D QSAR STUDY OF *p*-HYDROXYBENZOHYDRAZIDE DERIVATIVES AS ANTI *ESCHERICHIA COLI* AGENTS

RITESH P. BHOLE*, KISHORE P. BHUSARI
Department of Pharmaceutical Chemistry and Drug Discovery
Sharad Pawar College of Pharmacy, Wanadongri, Hingana Road
Nagpur, (MS), India-441110

In the present study 3-D QSAR analysis was performed on the previously synthesized and evaluated derivatives of N'-[-(3-substituted-alkyl/aryl)-4-(Substituted Aryl)-1,3-thiazolidin-2ylidene)]-4-hydroxybenzohydrazide and 4-hydroxy-*N*'- [-3-Substituted-4-oxo-1,3-thiazolidin-2-ylidene]benzohydrazides as a potent inhibitor of *E-coli* The novel Three-Dimensional QSAR (3D-QSAR) study based on the principle of the alignment of pharmacophoric features by PHASE module of Schrodinger suite has been carried out on the same set of inhibitors. Statistically significant 3-D (R^2=0.98) QSAR models were generated using 55 molecules in the training set. The predictive ability of both models was determined using a randomly chosen test set of eight molecules which gave predictive correlation coefficients (R^2_{pred}) of 0.80 for 3-D models, indicating good predictive power. PHASE pharmacophore hypothesis AHRRRR may correspond very closely to the interactions recorded in the active site of the ligand bound complex.

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Keywords: 3-D QSAR, PHASE, E-*coli*, *p*-hydroxy benzohydrazide.

1. Introduction

The deterioration of human population due to the enhance prevalence of infectious diseases is becoming a worldwide problem. Over the last few years, tuberculosis is retrieving its place among theses infectious diseases and today, nearly one-third of the world's population having gastrointestinal problem like food poisoning, diarrhea,etc caused by *gram -ve* bacteria especially *E –coli* [1,2]. *E. coli* and related bacteria possess the ability to transfer DNA via bacterial conjugation, transduction or transformation, which allows genetic material to spread horizontally through an existing population [3].

Discovering three-dimensional pharmacophores which can explain the activity of a series of ligands is one of the most significant contributions of computational chemistry to drug discovery.[4] Quantitative drug design embraces two major activities, the quantitative description of the structural differences among series of chemical compounds of biological interest, and the formulation of "QSAR" useful in the design of new and better therapeutic agents [5] .A QSAR is a mathematical relationship between a biological activity of a molecular system and its geometric and chemical characteristics.QSAR attempts to find consistent relationship between biological activity and molecular properties, so that these "rules" can be used to evaluate the activity of new compounds 3D models are more easily interpretable than 2D descriptor or fingerprint-based QSAR models, making it easier to suggest new compounds for synthesis. It should also be possible to make connections from such activity models to structure-based design, either to add more information to overlays for the construction of a pharmacophore model11 or to use a pharmacophore to assist in the refinement of protein homology models .[6]. In the present model

QSAR model has been developed for the prediction of *E-coli*. Inhibition. 3- D QSAR approach has been developed using PHASE module of Schrodinger suite. [7]

2. Experimental

2.1. Theory

We performed 3-D QSAR analysis on the previously synthesized and evaluated derivatives of 3-D QSAR study of N'-[-(3-substituted-alkyl/aryl)-4-(Substituted Aryl)- 1,3-thiazolidin-2ylidene)]- 4-hydroxybenzohydrazide and 4-hydroxy-*N*'- -3-Substituted-4-oxo-1,3-thiazolidin-2-ylidene]benzohydrazide derivatives against as a anti-*Escheria Coli* agents.

The software use for 3-D QSAR study is Schrodinger PHASE Module Workstation used are raster systems in which a computer with Linux as operating systems,180 giga bite space storage facility Intel Pentium IV as a processor and integrated with graphical display. PHASE module works as a following five staps as:

1. Selection of training set
2. Generating conformers
3. Find hypothesis for actives
4. Score hypothesis
5. Built QSAR model

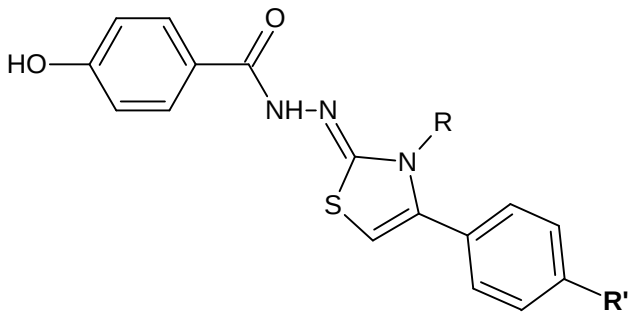
This 3D-QSAR approach involves the generation of a common pharmacophore

hypothesis built on the principle of identification and alignment of pharmacophoric features of the chemical structures. QSAR models are then developed for the pharmacophore hypothesis using the training set structures that match the pharmacophore on three or more sites, using Partial Least Square (PLS) statistical analysis. The volume occluded maps, generated for the pharmacophore hypothesis help in explaining the observed variation in activity by the variation in the structural features.

2.2 Dataset for analysis

A dataset comprising of 63 derivatives was used in the present study which is summarized in table 1. The dataset has been chosen by which covers the information about its biological activity ie anti-*e.coli*. The in vitro biological activity data was reported as IC_{50}. The IC_{50} values were converted to p_{IC50} The dataset consists of some highly active and inactive molecules, with very few molecules inbetween. Figure 1 represents the structures of the common scaffold p-hydroxybenzohydrazide and other derivatives employed in this study. Table 1 represents the pIC50 values for all the compounds involved in this study. A total of 63 molecules were available with p_{IC50} values, of which 55 molecules were randomly chosen for training set and 8 molecules were selected for test sets.

Antibacterial and antimycobacterial activity N'-[-(3-substituted-alkyl/aryl)-4-(Substituted Aryl)-1,3-thiazolidin-2ylidene)]- 4-hydroxybenzohydrazide



4-hydroxy-*N*'-[-3-Substituted-4-oxo-1,3-thiazolidin-2-ylidene]benzohydrazide

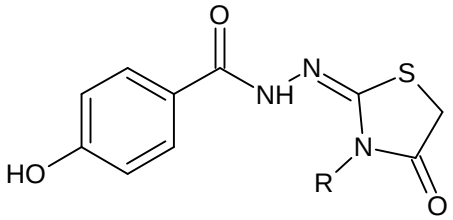


Table 1. Data set used for 3-D QSAR analysis with corresponding actual and predicted activities.

Compd. No	R	R'	*e-coli*		
			Actual PIC_{50}	Predicted PIC_{50}	Residuals
(6.a)	-Isoproyl	-	3.9	3.78	-0.12
(6.b)	-*n*-Butyl	-	3.1	3.72	0.62
(6.c)	-Phenyl	-	3.202	3.62	0.418
(6.d)	-4-Nitrophenyl	-	3.333	3.61	0.277
(6.e)	-4-Flurophenyl	-	4.108	3.62	-0.488
(6.f)*	-2,4-Dichlophenyl	-	3.899	3.59	-0.309
(6.g)	-2,6-Diflurophenyl	-	4.012	3.60	-0.412
(6.h)	-2,6-Dimethylphenyl	-	3.111	3.63	0.519
(6.i)	-2,4-Dimethoxyphenyl	-	3.81	3.56	-0.25
(7.a)	Isopropyl	H	3.98	4.24	0.26
(7.b)	n-butyl	H	4.44	4.40	-0.04
(7.c)	Phenyl	H	4.56	4.34	-0.22
(7.d)	4-nitrophenyl	H	4.20	4.53	0.33
(7.e)	4-flurophenyl	H	4.37	4.21	-0.16
(7.f)	2,4,-dichlorophenyl	H	4.22	4.45	0.23
(7.g)*	2,6-diflurophenyl	H	4.20	4.49	0.29
(7.h)	2,6-dimethylphenyl	H	4.46	4.39	-0.07
(7.i)	2,4-dimethoxyPhenyl	H	4.26	4.48	0.22
(8.a)	Isopropyl	4-Chloro	4.21	4.24	0.03
(8.b)*	n-Butyl	4-Chloro	4.56	4.43	-0.13
(8.c)*	Phenyl	4-Chloro	4.55	4.47	-0.08
(8.d)	4-nitrophenyl	4-Chloro	4.34	4.37	0.03
(8.e)	4-flurophenyl	4-Chloro	5.1	4.54	-0.56
(8.f)	2,4,-dichlorophenyl	4-Chloro	4.7	5.12	0.42
(8.g)*	2,6-diflurophenyl	4-Chloro	4.37	4.53	0.16
(8.h)	2,6-dimethylphenyl	4-Chloro	5.22	4.54	-0.68
(8.i)*	2,4-dimethoxyPhenyl	4-Chloro	4.1	4.50	0.4
(9.a)	Isopropyl	4- Bromo	4.19	4.27	0.08
(9.b)*	n-butyl	4- Bromo	4.26	4.43	0.17
(9.c)	Phenyl	4- Bromo	4.47	4.38	-0.09
(9.d)	4-nitrophenyl	4- Bromo	4.23	4.48	0.25
(9.e)	4-flurophenyl	4- Bromo	4.26	4.39	0.13
(9.f)	2,4,-dichlorophenyl	4- Bromo	4.31	4.51	0.2
(9.g)	2,6-diflurophenyl	4- Bromo	5.0	4.77	-0.23
(9.h)	2,6-dimethylphenyl	4- Bromo	4.60	4.53	-0.07
(9.i)	2,4-dimethoxyPhenyl	4- Bromo	4.00	4.50	0.5
(10.a)	Isopropyl	4-Methyl	4.26	4.31	0.05
(10.b)	n-butyl	4-Methyl	4.34	4.44	0.1
(10.c)*	Phenyl	4-Methyl	4.18	4.47	0.29
(10.d)	4-nitrophenyl	4-Methyl	4.56	4.49	-0.07
(10.e)	4-flurophenyl	4-Methyl	4.72	4.39	-0.33

(10.f)	2,4,-dichlorophenyl	4-Methyl	4.44	4.51	0.07
(10.g)	2,6-diflurophenyl	4-Methyl	4.49	4.69	0.2
(10.h)*	2,6-dimethylphenyl	4-Methyl	4.83	4.53	-0.3
(10.i)	2,4-dimethoxyPhenyl	4-Methyl	4.63	4.51	-0.12
(11.a)*	Isopropyl	4-Hydroxy	4.34	4.26	-0.08
(11.b)	n-Butyl	4-Hydroxy	4.44	4.39	-0.05
(11.c)	Phenyl	4-Hydroxy	4.25	4.46	0.21
(11.d)*	4-nitrophenyl	4-Hydroxy	4.34	4.47	0.13
(11.e)	4-flurophenyl	4-Hydroxy	4.10	4.39	0.29
(11.f)	2,4,-dichlorophenyl	4-Hydroxy	4.88	4.50	-0.38
(11.g)	2,6-diflurophenyl	4-Hydroxy	4.76	4.54	-0.22
(11.h)	2,6-dimethylphenyl	4-Hydroxy	4.46	4.52	0.06
(11.i)	2,4-dimethoxyPhenyl	4-Hydroxy	4.07	4.50	0.43
(12.a)	Isopropyl	4-Methoxy	4.53	4.27	-0.26
(12.b)*	n-Butyl	4-Methoxy	4.58	4.44	-0.14
(12.c)	Phenyl	4-Methoxy	4.23	4.50	0.27
(12.d)	4-nitrophenyl	4-Methoxy	4.48	4.29	-0.19
(12.e)	4-flurophenyl	4-Methoxy	4.22	4.03	-0.19
(12.f)	2,4,-dichlorophenyl	4-Methoxy	5.12	4.82	-0.3
(12.g)	2,6-diflurophenyl	4-Methoxy	4.76	4.79	0.03
(12.h)	2,6-dimethylphenyl	4-Methoxy	4.37	4.53	0.16
(12.i)*	2,4-dimethoxyPhenyl	4-Methoxy	5.22	4.82	-0.4

*testset molecules

2.3. Computational details for 3-D QSAR

In the 3D-QSAR approach, all molecular modeling and statistical analyses were performed using PHASE.[8] PHASE is a versatile product for pharmacophore perception, structural alignment, activity prediction, and 3-D database creation and searching. Given a set of molecules with affinity for a particular target, PHASE utilizes fine-grained conformational sampling and a range of scoring techniques to identify common pharmacophore hypothesis, which convey characteristics of 3-D chemical structures that are purported to be critical for binding. Each hypothesis is accompanied by a set of aligned conformations that suggest the relative manner in which the molecules are likely to bind to the receptor. Generated hypothesis with the aligned conformations may be combined with known activity data to create a 3D-QSAR model that identifies overall aspects of molecular structure that govern activity. PHASE 3D-QSAR model workflow consists of the following five steps

I. Preparing ligands

The 3-D conversion and minimization was performed using LigPrep [9] (MMFF force field) incorporated in PHASE. Developing a pharmacophore model requires all-atom 3-D structures that are realistic representations of the experimental molecular structure. Most ligands are flexible, so it is important to consider a range of thermally accessible conformational states in order to increase the chances of finding something close to the putative binding mode. For purpose of pharmacophore model development, PHASE provides two built-in approaches, both of which employ the MacroModel conformational search engine. Conformers were generated using a rapid torsion angle search approach followed by minimization of each generated structure using MMFF force field, with implicit distance dependent dielectric solvent model. A maximum of 100 conformers were generated per structure using a preprocess minimization of 100 steps and postprocess minimization of 50steps. Each minimized conformer was filtered through a relative energy window of 11.4 kCal/mol (50kJ/ mol) and a minimum atom deviation of 2.00 Å.

.II. Creating pharmacophore sites

The second step in developing a pharmacophore model is to use a set of pharmacophore features to create sites for all the ligands. Each ligand structure is represented by a set of points in 3-D space, which coincide with various chemical features that may facilitate noncovalent binding between the ligand and its target receptor. PHASE provides a built-in set of six pharmacophore features, hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic group (H), negatively ionizable (N), positively ionizable (P), and aromatic ring (R). The rules that are applied to map the positions of pharmacophore sites are known as feature definitions, and they are represented internally by a set of SMARTS patterns. Each pharmacophore feature is defined by a set of chemical structure patterns. All user-defined patterns are specified as SMARTS queries and assigned one of the three possible geometries, which define physical characteristic of the site:

(i) Point: the site is located on a single atom in the SMARTS query.

(ii) Vector: the site is located on a single atom in the SMARTS query, and it will be assigned directionality according to one or more vectors originating from the atom.

(iii) Group: the site is located at the centroid of a group of atoms in the SMARTS query. For aromatic rings, the site is assigned directionality defined by a vector that is normal to the plane of the ring. A default setting having acceptor (A), donor (D), hydrophobic (H), negative (N), positive (P), and aromatic ring (R) was used for the creation of pharmacophore sites. No user-defined feature was employed for the present study.

III. Finding a common pharmacophore

In the find common pharmacophore step, pharmacophores from all conformations of the ligand in the active site are examined, and those pharmacophores that contain identical sets of features with very similar spatial arrangements are grouped together. If a given group is found to contain at least one pharmacophore from each ligand, then this group gives rise to a common pharmacophore. Any single pharmacophore in the group ultimately become a common pharmacophore hypothesis which gives an explanation how ligands bind to the receptor. Common pharmacophores are identified using a treebased partitioning technique that groups together similar pharmacophores according to their intersite distances, i.e., the distances between pairs of sites in the pharmacophore. Active and inactive thresholds of P_{IC50} 4.1 and 4.5, respectively, were applied to the training set for developing the common pharmacophore hypotheses. After applying default feature definitions to each ligand, common pharmacophores containing six sites were generated using a terminal box size of 1 Å, and with requirement that all actives should match.

IV. Scoring Hypotheses

In the score hypotheses step, common pharmacophores are examined, and a scoring procedure is applied to identify the pharmacophore from each surviving n-dimensional box that yields the best alignment of the active set ligands. This pharmacophore provides a hypothesis to explain how the active molecules bind to the receptor. The scoring procedure provides a ranking of the different hypotheses, allowing making rational choices about which hypotheses are most appropriatefor further investigation. Scoring with respect to actives was conducted using default parameters for site, vector, and volume terms. Ligand activity, expressed as $-\log_{10}(IC50)$, was incorporated into the score with a weight of 1.0, and relative conformational energy (kJ/mol) was included with a weight of 0.01. Hypothesesthat emerged from this process were subsequently scored with respect to inactives, using a weight of 1.0. The inactive molecules were scored to observe the alignment of these molecules with respect to the pharmacophore hypothesis to enable making a decision on the selection of the hypothesis. Larger is the difference between the scores of active and inactives, better is the hypothesis at distinguishing the actives from inactives.

V. Building QSAR model

PHASE provides the means to build QSAR models using the activities of the ligands that match a given hypothesis. PHASE QSAR models are based on PLS regression, applied to a large

set of binary valued variables. The independent variables in the QSAR model are derived from a regular grid of cubic volume elements that span the space occupied by the training set ligands. Each ligand is represented by a set of bit values (0 or 1) that indicate which volume elements are occupied by a Vander Waals surface model of the ligand. To distinguish different atom types that occupy the same region of space, a given cube in the grid may be allocated as many as six bits, accounting for six different classes of atoms. The atoms classes are:
(i) D: hydrogen-bond donor
(ii) H: hydrophobic or nonpolar
(iii) N: negative ionic
(iv) P: positive ionic
(v) W: electron-withdrawing (includes hydrogen-bond acceptors)
(vi) X: miscellaneous (all other types).

PHASE QSAR models may be either atom-based or pharmacophore- based, the difference being whether all atoms are taken into account, or merely the pharmacophore sites that can be matched to the hypothesis. The choice of which type of model to create depends largely on whether or not the training set molecules are sufficiently rigid and congeneric. If the structures contain a relatively small number of rotatable bonds and some common structural framework, then an atom-based model may work quite well. Atom-based QSAR models were generated for AHRRRR hypothesis using the 55-member training set and a grid spacing of 1.0Å. QSAR models containing one to seven PLS factors were generated. A model with five PLS factors was considered as the best statistical model. This model was validated by predicting activities of test set molecules.

3. Results

The results were found as follows

Table.2 QSAR Hypothesis Score

ID	Survival	Survival – inactive	Post-hoc	Site	Vector	Volume
AARRRR.59	3.896	1.917	3.896	0.98	0.98	0.915
AARRRR.60	3.896	1.917	3.896	0.98	0.95	0.915
ADRRRR.83	3.896	1.938	3.896	0.98	0.96	0.915
ADRRRR.86	3.831	2.067	3.831	0.93	0.96	0.902
ADRRRR.84	3.83	2.162	3.83	0.92	0.92	0.906
ADHRRR.481	3.83	2.162	3.83	0.92	0.94	0.906
ADHRRR.727	3.83	1.93	3.83	0.94	0.95	0.895
AHRRRR.496	3.83	2.265	3.83	0.92	0.96	0.906
AHRRRR.494**	**3.829**	**2.086**	**3.829**	**0.92**	**0.98**	**0.906**

Selectivity	# Matches	Energy	Activity	Inactive
2.247	17	5.196	4.721	1.979
2.422	17	5.176	4.721	1.897
2.575	10	5.196	4.721	1.865
2.672	10	5.196	4.721	1.764
2.573	12	5.529	4.854	1.667
2.573	12	5.529	4.854	1.667
2.573	10	8.318	4.342	1.899
2.795	10	5.196	4.721	1.565
2.677	**10**	**5.196**	**4.721**	**1.742**

** Selected hypothesis

Table 3. QSAR model for Scheme II and Scheme III as anti Echeria Coli agents.

ID	# Factors	SD	R-squared	F
AARRRR.59	1 2 3 4	0.30 0.29 0.21 0.20	0.65 0.68 0.86 0.90	52.8 33.2 51 48.5
AARRRR.60	1 2 3 4	0.30 0.29 0.21 0.20	0.51 0.58 0.76 0.80	52.8 33.2 51 48.5
ADRRRR.83	1 2 3 4	0.29 0.28 0.19 0.18	0.65 0.70 0.91 0.95	60.4 37.4 67 62.9
ADRRRR.86	1 2 3 4	0.30 0.28 0.20 0.19	0.63 0.79 0.88 0.92	57 35.6 58.5 53.7
ADRRRR.84	1 2 3 4	0.30 0.28 0.20 0.19	0.63 0.75 0.88 0.92	57 35.6 58.5 53.7
ADHRRR.481	1 2 3 4	0.27 0.23 0.19 0.17	0.62 0.73 0.80 0.85	81.1 66.9 65.7 68.4
ADHRRR.727	1 2 3 4	0.30 0.29 0.23 0.19	0.52 0.58 0.72 0.81	54.4 33.4 41.4 52.2
AHRRRR.431	1 2 3 4	0.28 0.26 0.23 0.19	0.54 0.62 0.70 0.80	55.5 37.3 34.8 44.1
AHRRRR.496	1 2 3 4	0.28 0.26 0.23 0.19	0.54 0.62 0.70 0.80	55.5 37.3 34.8 44.1
AHRRRR.494* **	**1 2 3 4**	**0.26 0.24 0.18 0.17**	**0.74 0.79 0.82 0.98**	**87.9 55.8 75.5 70.5**

P	RMSE	Q-squared	Pearson-R
2.562e-09 8.975e-10 8.014e-15 6.102e-16	0.37 0.35 0.39 0.40	0.41 0.45 0.32 0.29	0.64 0.69 0.79 0.86
2.562e-09 8.975e-10 8.014e-15 6.102e-16	0.37 0.35 0.39 0.40	0.41 0.45 0.32 0.29	0.64 0.68 0.79 0.86
4.307e-10 1.602e-10 5.347e-17 4.52e-18	0.38 0.37 0.45 0.47	0.37 0.40 0.12 0.06	0.62 0.67 0.78 0.86
9.43e-10 3.263e-10 6.626e-16 9.304e-17	0.36 0.35 0.40 0.39	0.43 0.45 0.30 0.34	0.66 0.67 0.72 0.83
9.43e-10 3.263e-10 6.626e-16 9.304e-17	0.36 0.35 0.40 0.39	0.43 0.45 0.30 0.34	0.66 0.68 0.72 0.83
5.735e-12 1.302e-14 7.622e-17 9.027e-19	0.39 0.45 0.46 0.45	0.33 0.12 0.09 0.11	0.59 0.68 0.76 0.80
1.757e-09 8.091e-10 3.025e-13 1.594e-16	0.38 0.37 0.41 0.47	0.36 0.39 0.27 0.06	0.61 0. 63 0.78 0.87
1.938e-09 2.823e-10 1.116e-11 1.092e-14	0.36 0.35 0.36 0.32	0.43 0.45 0.43 0.54	0.66 0.68 0.76 0.88
1.938e-09 2.823e-10 1.116e-11 1.092e-14	0.36 0.35 0.36 0.32	0.43 0.45 0.43 0.54	0.66 0.68 0.76 0.88
1.623e-12 2.974e-13 5.364e-18 5.014e-19	**0.39 0.42 0.45 0.45**	**0.33 0.23 0.13 0.12**	**0.59 0.63 0.79 0.80**

*** selected model for QSAR

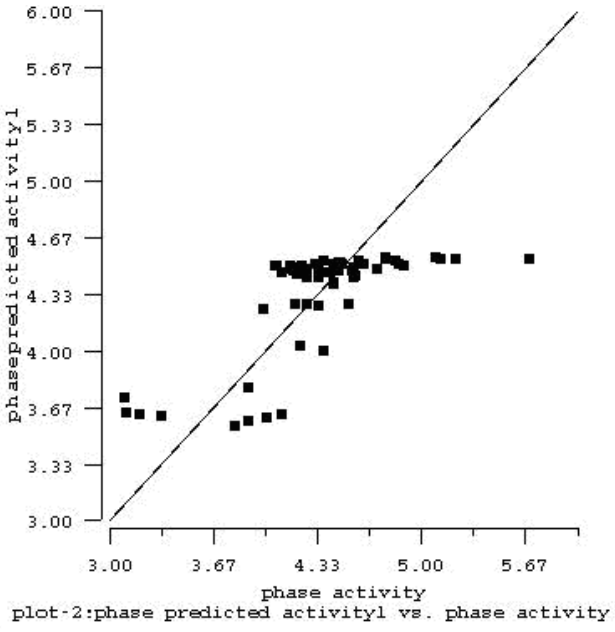
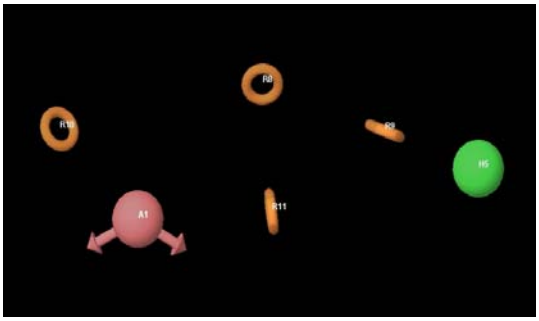
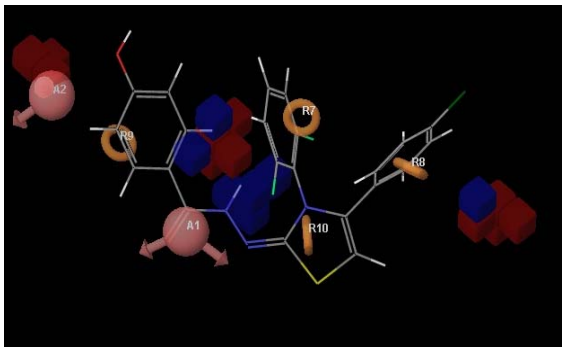


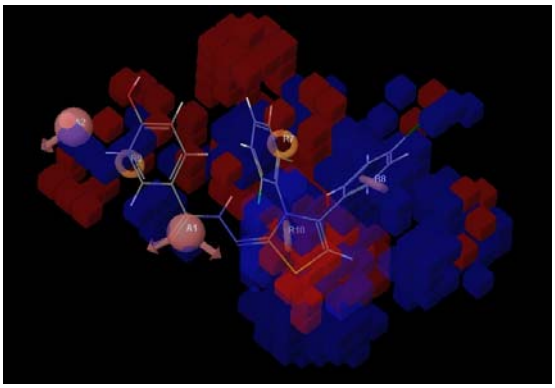
Fig. 1. Predicted versus Actual PIC_{50} of test set molecules for 3-D QSAR approach.



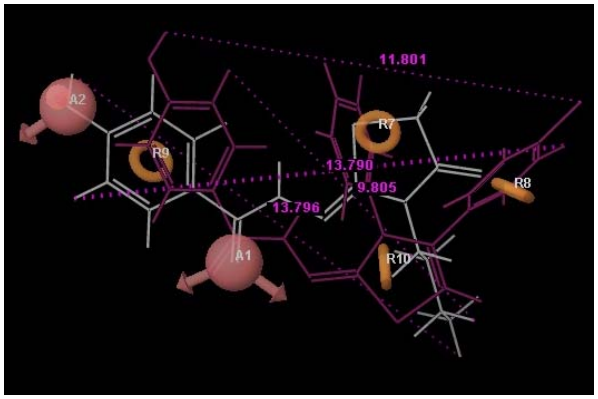
2.a) Phase Pharmacophore hypothesis (AHRRRR) with active molecules aligned that yielded the most predictive atom based model.



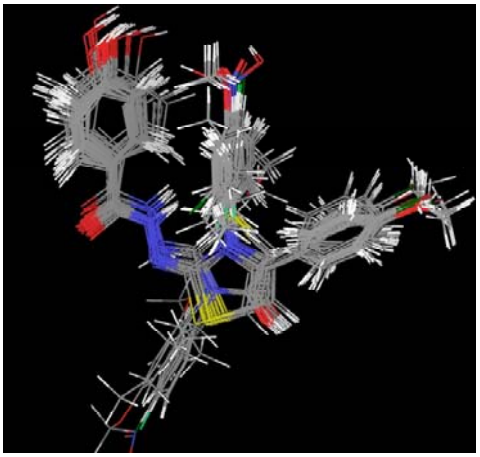
2.b) Active Ligand (9.g) hydrogen donor effect



2.c)Active Ligand (9.g) hydrophobic effect



2.d) Intermolecular distance in the active moiety



2.e)Structural alignment use

Fig. 2. Visual representation of atom-based PHASE QSAR.

4. Discussion

The 3D-QSAR studies for the set of benzohydrazide and their derivatives were carried out using PHASE module of Schrodinger molecular modeling package. For finding the common pharmacophore hypothesis, the dataset was divided into active and inactive sets. Molecules with pIC50 values more than 4.50 were considered to be active, and those with pIC50 values less than 4.10 were considered to be inactive, whereas those in-between were considered to be moderately active. A common pharmacophore model AHRRRR with two variants was generated after the creation and identification of pharmacophoric sites in all the molecules in the dataset. The variant with a site score 0.92, vector score 0.98, and volume score of 0.90 was chosen to be the common pharmacophore hypothesis. The pharmacophore hypothesis AHRRRR with all active molecules aligned to it is shown in Figure 2. All the molecules in the active set/modeled molecules matched with the hypothesis AHRRRR. This pharmacophore hypothesis was then used for the generation of QSAR model. For the QSAR model generation, nonmodeled (inactive or moderately active) molecules in the dataset were then aligned based on the matching with at least three of the pharmacophoric features. The dataset was randomly divided into a training set of 55 compounds and 08 in the test set with a bias given to the structural diversity in both the training and test set so as to form the standard 4 :1 training set to test set ratio for a QSAR study.

The PHASE statistical analysis for each of the test set selection methods is summarized in Table 2. The validity of each of the models was predicted from the calculated correlation coefficient for the randomly chosen test set comprising of diverse structures. The squared correlation for the test set (random selection (R^2 pred=0.98)) confirms the good predictability of the final QSAR model for the test set.

4.1. Analysis of Atom-Based PHASE 3D-QSAR Model

Figure 2 shows the volume occlusion maps for the atom-based PHASE 3D-QSAR model (donor, hydrophobic, and electronegative) represented by color codes. These maps represent the regions of favorable and unfavorable interactions. The volume occlusion maps of hydrogen bond donor (Figure 2.b) describe the spatial arrangement of favorable hydrogen bonding interactions to acceptor groups of the target protein.. Hydrophobic volume occlusion maps from PHASE 3-D QSAR model is shown in Figure 2.c. The map showed a big red colored region indicating that an increase in the hydrophobicity in this region is expected to improve the activity of the p-

hydroxybenzohydrazide like molecules. A blue color contour opposite to that of black disfavors the placement of hydrophobic groups.

5. Conclusion

3- D QSAR study was performed on the series of N'-[-(3-substituted-alkyl/aryl)-4-(substituted aryl)- 1, 3- thiazolidin-2ylidene)]- 4-hydroxybenzohydrazide and 4-hydroxy-*N*'- [-3-Substituted-4-oxo-1,3-thiazolidin-2-ylidene] benzohydrazide as a Anti *e.coli* agents by generating volume occupied maps,which demonstrated that the activity may be increased by substituting the doner groups the with the binding site of the receptor. Placement of the hydrophobic groups at the particular position of phenyl ring of the benzohydrazide may results in increase in the activity. Also demonstration of the pharmacophore hypothesis AAHRRR used for QSAR model to that of the binding mode of the benzohydrazide which validates the pharmacophore hypothesis.

This study can be further use for the synthesis of newer and may be more potent derivatives against infectious diseases.

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