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Original Article

3D QSAR AND DOCKING STUDIES OF A SERIES OF HAMAMELITANNIN DERIVATIVES AS POTENTIAL PBP4 INHIBITORS

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ABSTRACT

Objective: Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most dangerous pathogen and has emerged as a serious threat to public health world wide. Penicillin binding protein (PBP4) is essential for the beta-lactam struggle in Methicillin resistance strains (MRSA). The objective of this study was to develop Hamamelitannin derivatives and to study the inhibitory effects of the derivatives in order to find out the PBP4-3HUM protein interaction studies.

Method: 14 Hamamelitannin derivatives were taken from databases. The 3D-QSAR analysis was performed on 14 complexes combining the training and test sets using Discovery Studio. These derivatives were used to dock with Penicillin binding protein (3HUM) using the docking software Hex.

Results: The energy values of 14 compounds obtained were ranged from –178.68 to–317.38 Kcal. mol^{-1}. The coded compounds Comp-11, Comp-13 and Comp-14 exhibited better affinity towards the receptor 3HUM. The 3D-QSAR study demonstrated significant statistical values.

Conclusion: The Docking and QSAR study of the compounds yielded three compounds of interest. Therefore derivatives of these complexes may further be generated and would provide ample opportunities for further studies.

Keywords: *Staphylococcus aureus*, 3D-QSAR, Docking, PBP4, Methicillin.

INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) is widespread in India. It is one of the dangerous pathogen for hospital acquired infections. A study was conducted in 15 Indian tertiary care centers during a two year period from January 2008 to December 2009 to find out the prevalence of MRSA and susceptibility pattern of *S. aureus* isolates in India [1].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most essential nosocomial pathogens. It has emerged as a severe problem to public health all over the world [2]. Because of its multiresistance properties and its intrinsic resistance to all β-lactam antibiotics, there remain limited choices of antimicrobial agents to treat different severe life-threatening infections caused by MRSA, which lead to prolonged stay of such patients in the ICUs and hospitals, and increased cost of care. The emergence of resistant strains the represents a significant response to selective pressures imposed by antimicrobial chemotherapy and once is recognized, they are difficult to control and eliminate. The knowledge of occurrence of MRSA and its antibiotic sensitivity outline in any environment becomes essential for selection of appropriate treatment for these patients.

In the recent years the increasing resistance of *Staphylococcus aureus* have witnessed to many antimicrobial agents. The most remarkable example is the emergence of Methicillin-resistant *Staphylococcus aureus* (MRSA), which was reported immediately one year after the launch of methicillin. The ecological niches of the *S. aureus* strains are the anterior names. The identification of *Staphylococcus aureus* by using a proper antibiogram and the detection of methicillin resistant *Staphylococcus aureus* wholly contribute towards the successful treatment of the patients.

Almost 70% methicillin resistance has reported from hospitals in various parts of Indian hospitals like Banglore, South India etc [3]. The prevalence of methicillin (oxacillin)-resistant *S. aureus* are diverse greatly by region, site of infections and whether the infection was nosocomial or community onset. The increase in multidrug resistance amongst staphylococci and the possible emergence of vancomycin-resistant strains, global strategies are in need to control the emergence and spread of multiple resistant staphylococci [4]. *S. aureus* infection are prevalent in the wounds of skin, burns, intravenous (IV) sites, respiratory tract, urinary tract, bones, heart,blood and eyes. It also causes blood &skin infection. Causing serious complication in bloodstream, joints and pneumonia which may further cause organ failure and death [5-7].The MRSA strain of *S. aureus* is now becoming resistant to other antibiotics i.e. Oxacilin, Penicilin, amoxicillin and cephalosporin [8].

Penicillin binding protein, PBP4 is essential for the beta-lactam struggle in Methicillin resistance strains (MRSA). This is responsible for peptidoglycan cell wall biosynthesis of *S. aureus*. So, it is one of the foremost drug rediscovery of staphylococcal infection. To obtain new potent inhibitors for MRSA, we perform molecular docking and QSAR studies of Hamamelitannin derivatives [9]. Hamamelitannin is a natural product found in the bark and the leaves of *Hamamelis virginiana* (witch hazel), a deciduous shrub native to damp woods in eastern North America and Canada [10].

MATERIALS AND METHODS

Materials

A set of 14 Hamamelitannin derivative compounds were taken from the Pub Chem database. MDL ISIS draw2.5 was used for the sketching of molecules. The sketched 2D structures were transformed into 3D structures using the module Chem3D Ultra 8.0 of Chem Office and further minimization of energy of reported structures was carried out. The software used with the sources and their utilities are presented in Table 1.

IC_{50} for each compound was calculated using nonlinear regression (curve fit) using Graph Pad Prism 5.0 (Graph Pad Software, La Jolla, CA [11]. Discovery Studio2.5 package was used for QSAR equation..Discovery Studio contains a suite of applications for optimizing the drug discovery process. It has applications for properties examination, leads identification and candidate optimization. For example, other than structure-based design, simulation, QSAR and library design tools, it also contains the predictive ability [12].

Table 1: **Software used in this study, source and their utilities**

Software	Source	Utility
ISIS draw	Open source for limited period	Drawing of 2D structure of ligands.
Chem office	Paid software from	Chem3D generates 3D models. Chem Finder is a chemically-intelligent personal database system
UCSF Chimera	Cambridge soft	used to organize the compounds and to search and correlate structures with properties.
Graph Pad Prism 5.0	Under Academic license	Viewing of docking results. A powerful combination of biostatistics, curve fitting (nonlinear regression) and scientific
Discovery Studio 2.5 package	Commercial	graphing. Advanced software solutions for life science researchers and is easy to use, a graphical interface for powerful drug design and protein modeling, sequence analysis.
Argus Lab (4.0.1)	Open source	The Argus Lab contains tools for building and visualizing molecules as well as looking at the output from calculations.
SPDBV	Open source	Swiss-Pdb Viewer is an application that provides a user friendly interface allowing analyzing several proteins at the same time.
Hex (version 6.3)	Free for academic use	Docking software.

Methods

Structural assessment of the protein

The Ramchandran plot was generated using Pdbsum database.

Docking Studies

As the structures of more potential drug target are elucidated the opportunity for computers to perform initial binding studies is increasing. By computationally docking a ligand to a protein, one limits concerns about assay complication such as compound solubility and the needs to maintain extensive physical compound libraries. The objective of computational docking is to determine how to molecules of known structure will interact. The molecule may bind to receptor and modify their function [13].The docking studies was performed between receptor (3HUM) and ligands by using Hex (version 6.3). 3 HUM (Fig 1), retrieved from RCSB and prepared by UCSF Chimera.

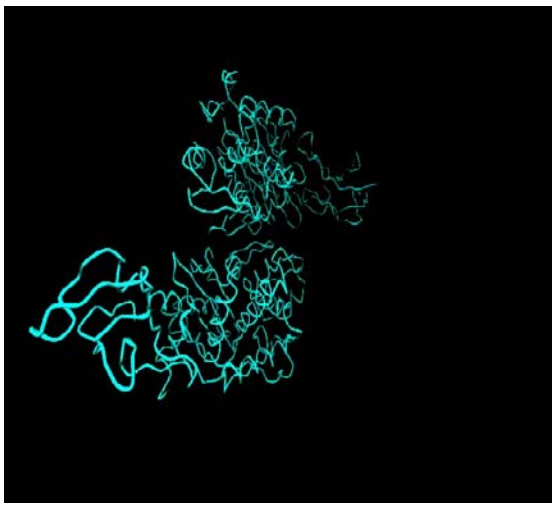

Fig. 1: Structure of 3HUM'

Calculation of descriptor and QSAR studies

QSAR is a broadly used tool for developing relationships between the effects (e.g. activities and properties of interest) of a series of molecules with their structural properties [14-15]. Descriptors values were calculated using DS 2.5.

Data Set

In the present study a data set of (2', 5-di-O-galloyl-D-hamamelose), Hamamelitannin derivatives (14 molecules) has been taken from the literature for QSAR studies reported in table 2.

Data selection

In order to evaluate the QSAR model externally, data set was divided into training and test set with random method using Discovery Studio. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive effectiveness of the model which is not included in model generation [16].

RESULTS AND DISCUSSION

Assessment of the Structural protein

The Ramachandran plot analysis is presented in Fig 2.The Ramachandran Plot statistics and G-factors are presented in Table 2 and Table 3. The G factor provides a measure of how unusual, or out-of-the-ordinary, a property is. The values of G factor below-0.5 indicates, unusual; and values below-1.0 indicate highly unusual. In this study, the value of G factor was found to be-0.14.

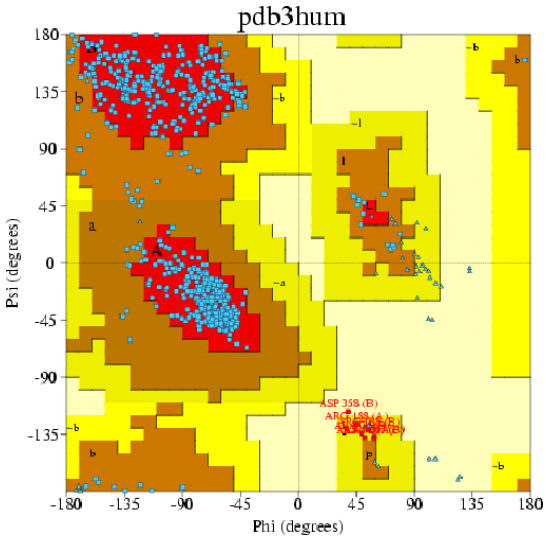

Fig. 2: Ramchandran Plot of 3HUM receptor

Docking studies

The derivatives of Hamamelitann in were docked to the receptor 3HUM and the energy values were computed using Hex. The outcome of docking studies and Lipinski's properties are presented in Table 4. The energy values obtained were ranged from-178.68 to-317.38 Kcal.mol^{-1}.The results indicate that comp11, comp13 and comp14 exhibited promising inhibitory activity in comparison to other compounds which are presented in Fig 3, Fig 4 and Fig 5 respectively.

Table 2: Ramachandran Plot statistics

	No. of residues	Percentage
Most favoured regions[A,B,L]	558	86.9%*
Additional allowed regions[a,b,l,p]	77	12.0%
Generously allowed regions[~a,~b,~l,~p]	6	0.9%
Disallowed regions [XX]	1	0.2%*
Non-glycine and non-proline residues	642	100.0%
End-residues (excl. Gly and Pro)	4	
Glycine residues	42	
Proline residues	28	
Total number of residues	715	

Table 3: The G-Factors

Parameter	Score	Average Score
Dihedral angles:-		
Phi-psi distribution	-0.27	
Chi1-chi2 distribution	-0.11	
Chi1 only	-0.08	
Chi3 & chi4	0.26	
Omega	-0.77*	
		-0.32
Main-chain covalent forces:-		
Main-chain bond lengths	0.22	
Main-chain bond angles	0.09	
		0.14
Overall Average		-0.14

Table 4: Chemical features and binding energy values

Compounds	Compound ID	M Wt (g/mol)	XLogP3	HBD	HBA	RB	TSA	IC_{50}	-E value (Kcal.mol^{-1})
comp1	71259968	296.35876	3.9	1	5	10	65	0.15	229.27
comp2	71254455	300.3044	0.8	2	7	8	94.4	0.01	229.14
comp3	71219047	226.22586	2	3	5	5	87	0.05	201.41
comp4	71231464	340.36826	2.4	0	7	7	72.4	0.04	235.29
comp5	71162008	280.35936	4.7	0	4	9	44.8	0.23	217.4
comp6	71140862	344.40156	4.3	0	5	9	54	0.19	254.93
comp7	71293744	226.22586	2.2	3	5	3	87	0.04	178.68
comp8	71293637	226.22586	2.5	3	5	5	87	0.06	194
comp9	71041179	274.26866	3.1	2	5	5	76	0.09	224.87
comp10	71259993	424.44316	4.3	1	7	10	83.4	0.19	246.25
comp11	71260017	412.407643	4.4	1	7	9	74.2	0.2	268.84
comp12	71260014	650.71362	7.5	0	9	17	90.9	0.6	242.21
comp13	71259994	412.407643	4.4	1	7	9	74.2	0.2	317.38
comp14	71262430	352.286266	4.1	1	8	8	82.1	0.17	274.11

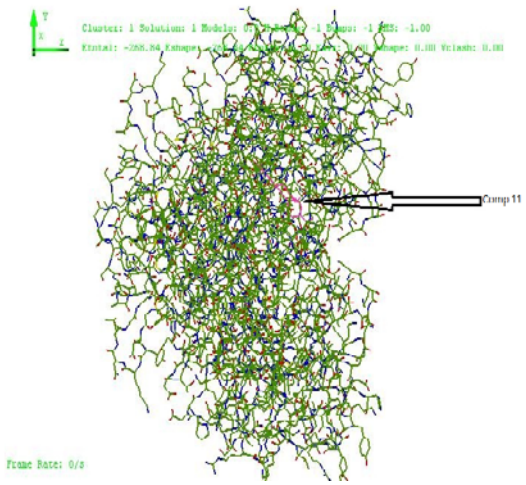

Fig. 3: Interaction and binding energy (compound 11)

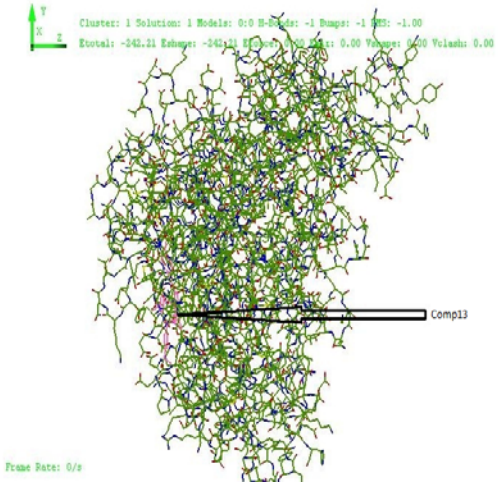

Fig. 4: Interaction and binding energy (compound 13)

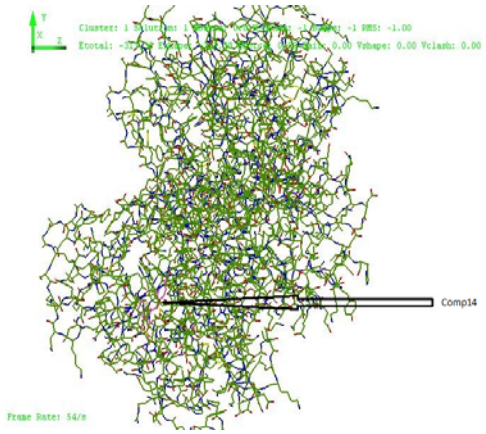

Fig. 5: Interaction and binding energy (compound 14)

Calculation of descriptor and QSAR studies

QSAR analysis was applied to 14 candidates of the Hamamelitannin derivatives using a combination of various physicochemical, steric, electronic, structural, molecular, constitutional descriptors and lipophilic parameters. Descriptors are calculated using Discovery Studio2.5. QSAR models were derived and validated to judge the reliability of models (Fig 6, Fig 7, Fig 8). Statistical significance of the generated best QSAR model was analyzed by cross validation. The best QSAR model obtained for activity was validated by dividing the data set of 14 Hamamelitannin derivatives into training set of11 compounds and test set of 3 compounds. Distribution of compounds into two sets was done randomly. Internal validity of the best QSAR model was checked by correlating the observed and predicted biological activities of the training set compounds and external validity was checked by correlating the observed and predicted biological activities of the test set compounds.

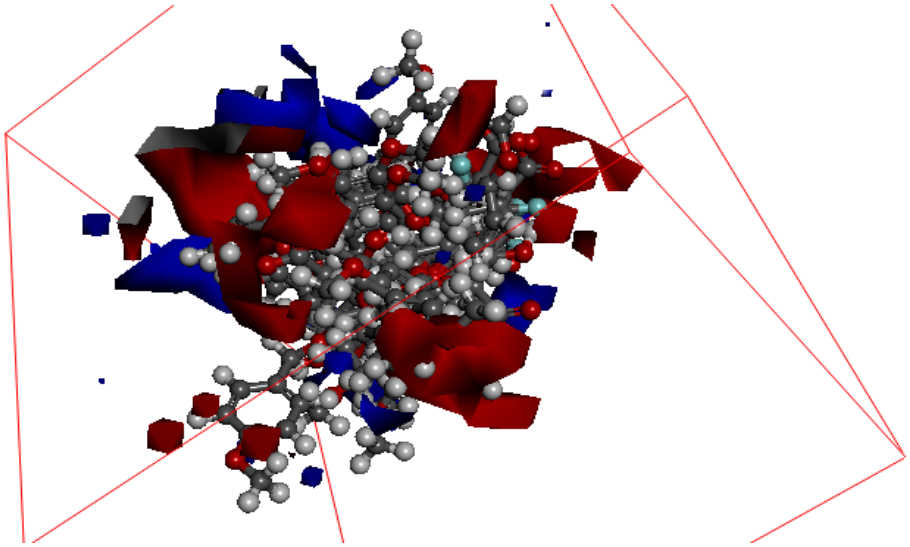

Fig. 6: Grid Model

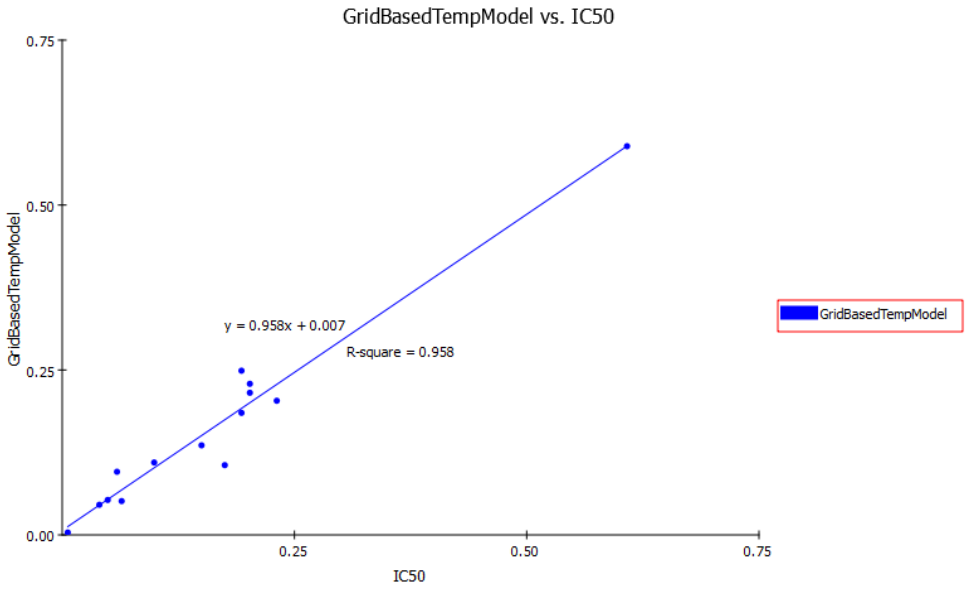

Fig. 7: Fitness plot using grid Based

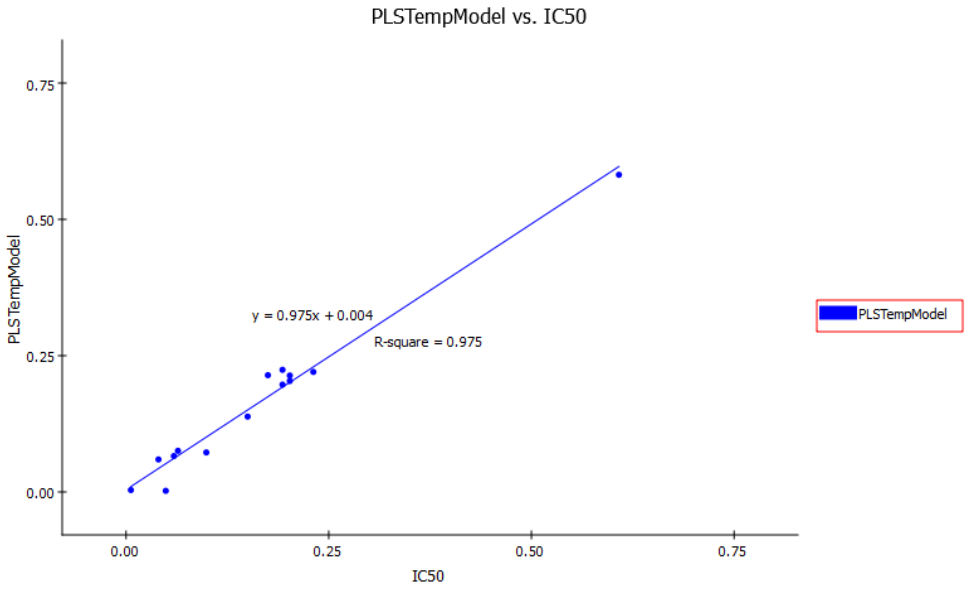

Fig. 8: Fitness plot using PLS

CONCLUSION

In this studies, docking of 14 Hamamelitannin derivatives was carried out and three derivatives namely, comp11,comp 13 and comp14 exhibited minimum energy value sand also followed all criteria of Lipinski's properties.. 3D-QSAR models have good r^2 values, suggesting a good predictive ability. The results of the QSAR and docking studies were supportive to the possibilities for development of novel molecule against pbp4.

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