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Review Article

MOLECULAR MODELING, QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP AND PHARMACOPHORE STUDIES ON ANTI-VIRAL, ANTI-MALARIAL AND ANTI-INFLAMMATORY BIOACTIVE COMPOUNDS FROM MARINE SOURCES

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ABSTRACT

Methyltransferase, human dihydrofolate reductase, and acidic mammalian chitinase are the potential targets for the viral, malarial and inflammatory diseases, respectively. Hence, it is of interest to screen the natural compounds against these proteins using molecular docking. In this study, pharmacophore modeling was performed on marine compounds against these diseases using PHASE module. This resulted in the common pharmacophore hypothesis AADRR.7f, which might be responsible for the biological activity: Two acceptor (A) groups (−C=O), one donor (O-H) and two aromatic rings (R). The three-dimensional-quantitative structure activity relationship model obtained has the correlation coefficient values q^2=0.67; pred r^2=0.86. In addition, molecular docking studies were performed. The model developed may serve as a query tool for future virtual screening and drug designing for these targets. Marine compounds from the different marine sources such as alga, bacterium, sponges, soft corals, sea cucumber, and clam have been selected from the literature.

Keywords: Molecular modeling, Quantitative structure activity relationship, Pharmacophore, Methyltransferase, Human dihydrofolate reductase, Acidic mammalian chitinase, Absorption, distribution, metabolism and excretion, Docking, Structure based drug design.

INTRODUCTION

Investigation/research in the field of marine natural products have led to the finding of potent active agents which are considered for clinical application. Marine environment is an outstanding reservoir of bioactive natural products and many of which exhibit structural/ chemical features which are not found in terrestrial natural products [1]. Marine organisms play an important role in developing biochemical and physiological mechanisms that include generation of the bioactive compounds for such purpose of infection, reproduction, communication and competition [2]. Due to the physical and chemical conditions in the marine environment almost all classes of marine organism reveal variety of molecules with unique structural features.

Marine environment also provides wonderful biological diversity. From the original point of view of biodiversity the sea is far more diverse. Based on the literature survey, researchers have isolated more than 7000 marine natural products, in this 25% from algae, 33% from sponges, 24% from invertebrates such as tunicates, molluscs, starfish, sea cucumbers, and bryozoans (moss animals) and 18% from coelenterates (sea whips, sea fans and soft corals). Analysis of these data reveals that 10% of the drugs from marine sources in drug discovery progress in each year [3].

In fact, there are many marine derived drugs that resulted in several products are commercially available. In 1950s Bergmann *et al.* isolated some nucleosides from the Caribbean sponge *Tethya crypta* (Tethylidae). Two of these spongothymidine and spongouridine contain a arabinose sugar which is ubiquitous sugar in nucleosides. This invention led researches to synthesize some analogues, Ara-A (Vidarabine®, Vidarabin Thilo®) and Ara-C (Cytarabine, Alexan®, Udicil®), which improved antiviral activity. From the brown seaweeds, the phlorotannin was isolated and named as phlorofucofuroecol A which has anticancer activity. The secondary metabolites produced by marine bacteria have yielded pharmaceutical products such as novel anti-inflammatory agents (pseudopterosin A, topsentins, scytonemin, and manoalide), anticancer agents (bryostatins, discodermolide, eleutherobin, and sarcodictyin), and antibiotics (marinone)(Fig. 1). At present, these are some of the marine related compounds in clinical use and few other compounds are in clinical trials [4].

Anti-viral activity

The genus flavivirus belongs to the family of *Flaviviridae* and it is composed of more than 70 viruses [5]. Many of these viruses are naturally arthropod borne and cause human diseases. Dengue virus, yellow fever virus, West Nile virus (WNV), Japanese encephalitis virus and tick-borne encephalitis virus are classified as global emerging pathogens and are also National Institute of Allergy and Infectious Diseases priority pathogens [6]. The armamentarium contains nearly 40 substances, which are commercially available for flavivirus that have been officially approved already for clinical use [7]. Most of these existing drugs have been discovered in this century and at least half of them are used for the treatment of human immunodeficiency virus infections [8]. Taking this as a report, the significance of developing the new antiviral agents in order to increase the number of these available drugs becomes clear. The search for new antiviral agents from marine sources yielded several promising therapeutic drugs. The literature shows a great number of reports about different pharmacological activities of marine sponges. Many papers show the results of screening of marine organisms for antiviral activity and a wide range of active substances have been isolated and characterized from them [9-12]. For some of these substances, important antiviral activities were also reported.

Recent study explains that the N-terminal methyltransferase (MTase) domain of NS5 has a guanyltransferase activity, transferring the GMP moiety of GTP to the 5' end of ppA-RNA [13]. Compared to the cellular and many other viral MTases, flavivirus MTase is distinctive in that a single MTase domain catalyzes two methylation events, in the order of GpppA → m^7GpppA → m^7GpppAm [14]. Sinefungin (SIN), an AdoMet analog was shown to inhibit MTase as well as to inhibit WNV replication in the cell culture [15]. The crystal structure of the WNV MTase-SIN complex reveals the presence of a hydrophobic pocket extension of the AdoMet-binding pocket. This feature is conserved among the various

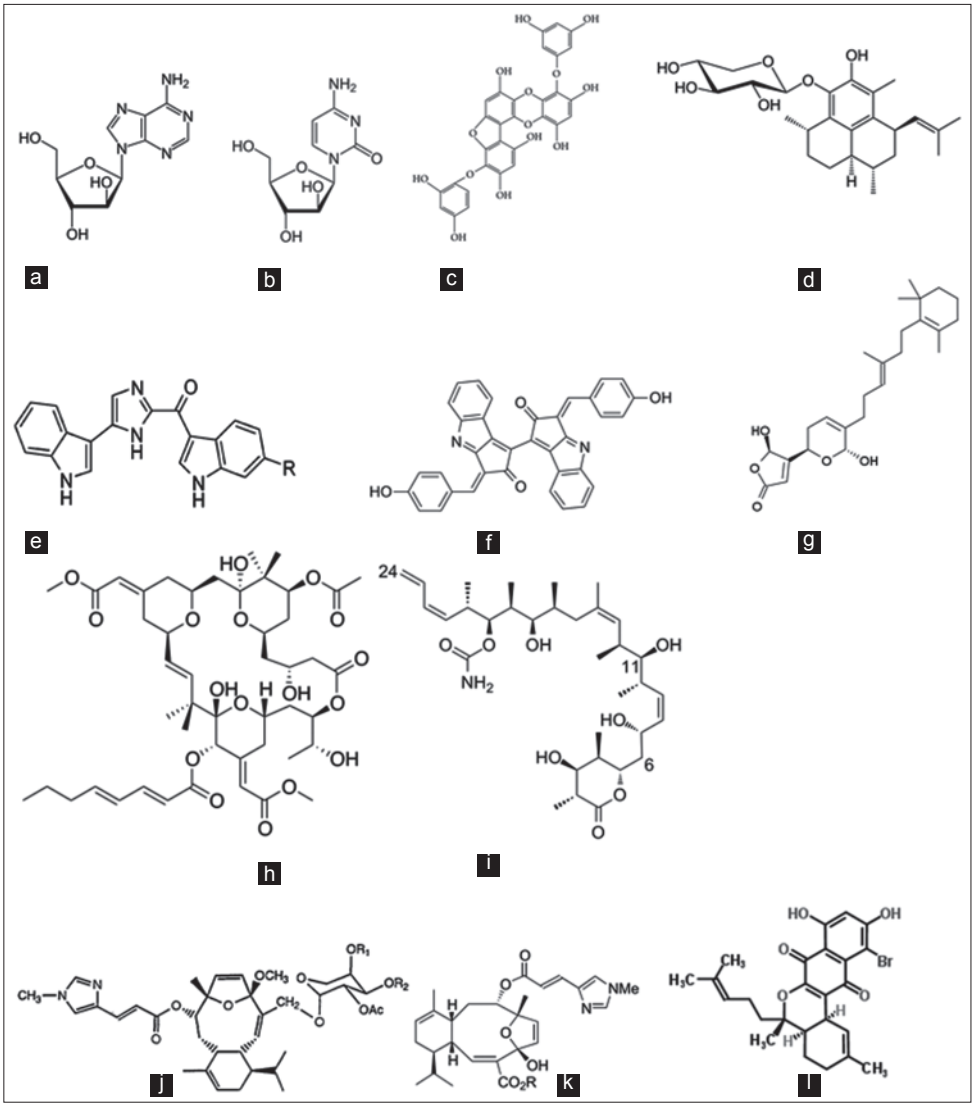

Fig. 1: Marine compounds with anti-cancer, anti-viral and anti-inflammatory activities, (a) Vidarabine®, (b) cytarabine®, (c) phlorofucofuroecol A, (d) pseudopterosin A, (e) topsentin, (f) scytonemin, (g) manoalide, (h) bryostatin, (i) discodermolide, (j) eleutherobin, (k) sarcodictyin, (l) marinone

flaviviruses. The residues within the pocket are very important in viral replication and that the N7 methylation efficiency correlates with the viral replication ability [16]. Therefore, modification of the SIN analog or some of the natural compounds is needed to inhibit the MTase activity.

Anti-malarial activity

Malaria is a serious public health issue in certain regions of Southeast Asia, South America, and Africa. Most of the malaria disease and deaths are mainly caused by the parasite *Plasmodium falciparum* [17]. Currently, *Plasmodium vivax* is the most widely distributed species which causes human malaria in the world. According to the latest estimates released in December 2013, there were nearly 207 million cases of malaria in 2012 and an estimated 6,27,000 deaths. The ability of this parasite to complete its sporogonic cycle at a temperature as low as 16°C, compared with 21°C for *P. falciparum*, has substantially contributed to its success in establishing stable foci of transmission in temperate zones [18]. Some of the new and effective drugs as anti-malarials have been achieved with novel small synthetic analogs of the artemisinin family of drugs [19].

Dihydrofolate reductase (DHFR) plays an important role in the formation of DNA by managing folate, an organic molecule that transports carbons to enzymes, which are needed for their reactions [20]. DHFR is present in all the organisms. Each organism makes a different version.

Anti-inflammatory activity

Inflammation is a complex of systematic or local host which is responsible to a wide range of tissue injury and infection. This is generally marked by increased levels of cytokines and its receptors, adhesion molecules, immune regulatory factors, and several mediators. Inflammation is a key etiological factor for several diseases such as hypersensitivity, asthma, inflammatory bowel disease, rheumatoid arthritis and many others. Most of the commercial therapeutic drugs are associated with adverse side effects and are not suitable for chronic therapies and so some of them were withdrawn from the markets. For instance, non-steroidal anti-inflammatory drugs are reported to have adverse drug interactions and hence are not prescribed along with warfarin, antihypertensives, and diuretics. Thus, treatment of these inflammatory disorders still remains a growing health concern and has become a major challenge to the health professionals [21].

Mammals contain two genes encoding active chitinases, chitotriosidase (CHIT1) and acidic mammalian chitinase (AMCase) that represent an ancient gene duplication event and show sequence homology to bacterial chitinases [22]. Initially, AMCase was described to be expressed in the gastrointestinal tract and lungs of rodents and humans [23]. Early exploration of mammalian chitinase function implicated in

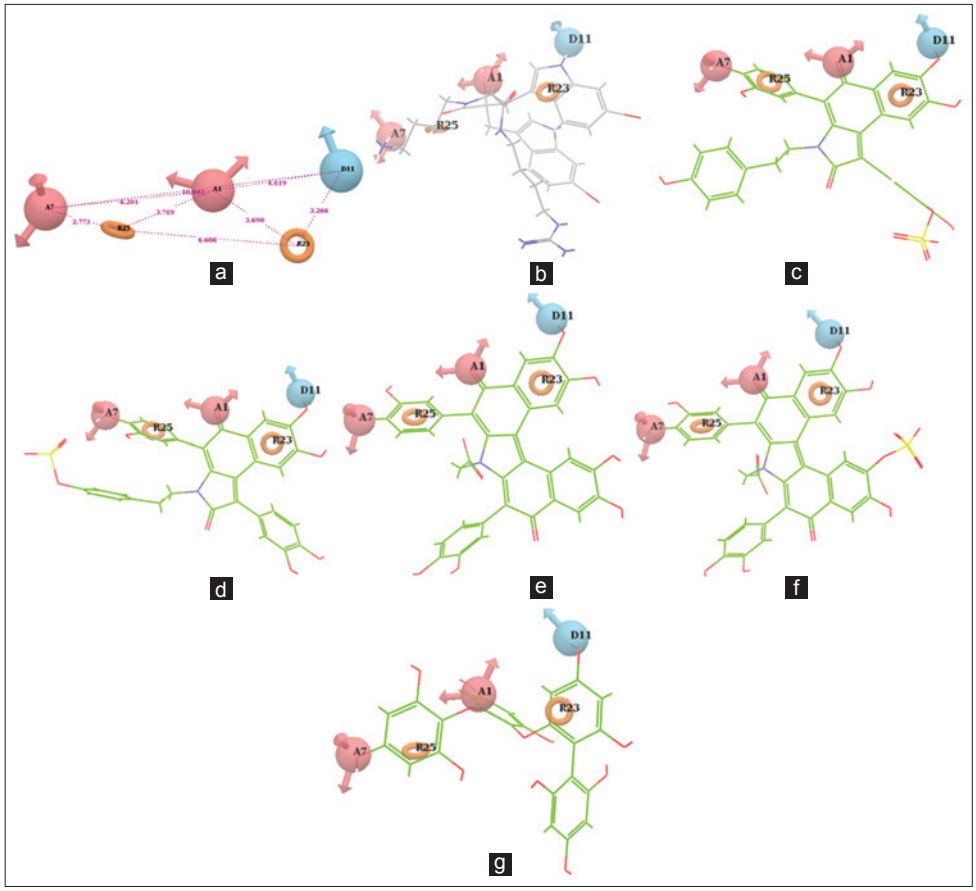

Fig. 2: AADRR.7 pharmacophore hypothesis and distance between pharmacophore sites. Common pharmaophore hypothesis (two hydrogen bond acceptors, two aromatic rings and one hydrogen bond donor) aligned with the active ligands of eusynstyelamide F, baculiferin I, baculiferin J, baculiferin L, baculiferin M and phlorotannin-3 is shown. Pharmacophoric feature A and D: Acceptor and donor appears as red and blue spheres centered on the atom with the long pair, the arrows are pointing in the direction of the lone pairs and the aromatic ring appears as brown in the plane of the ring. A: Hydrogen bond acceptor, D: Hydrogen bond donor, R: Aromatic ring, (a) QSAR model, (b) eusynstyelamide F, (c) baculiferin I, (d) baculiferin J, (e) baculiferin L, (f) baculiferin M, (g) phlorotannin 3

AMCase as a mediator of T-helper 2 cell (Th2) driven allergic airway diseases follow the use of the chitinase inhibitor allosamidin, a pseudotrisaccharide natural product derived from *Streptomyces* species in murine models [24,25]. Chitin is a surface element of parasites and insects and chitinases are induced in lower life forms during infections with these agents. Though chitin does not exist in humans, chitinase enzymes are present in the human genome. The expression of AMCase is associated with Th2-driven respiratory disorders. Allergic asthma was regarded for a long time as a characteristic example for Th2-mediated disease. Many studies have elegantly shown that numbers of Th2 cells are increased in the lung os patients with asthma and animal models [26]. This enzyme is characterized by an acidic isoelectric point and therefore named AMCase [23].

A pharmacophore model is an ensemble of electronic and steric features which is important to ensure the optimal interactions of molecules with a specific biological target or block its response [27]. Pharmacophore hypothesis assemble the common features distributed in the three-dimensional (3D) space representing groups in a molecule that participate in important interactions between the drug and the active site [28]. To continue this work in the development of pharmacophore and a 3D quantitative structure activity relationship (QSAR) for the several therapeutic agents, we report here studies on pharmacophore generation, QSAR model, docking studies for the marine compounds using in Schrodinger software [29].

The objective of this work was to generate the common pharmacophore model and to find the common features of the compounds responsible for the biological activity of inflammation, viral and malarial inhibitors.

EXPERIMENTAL SECTION

Materials

In this study, a set of 126 marine compounds was selected with their inhibition data from the literature [30,31]. The compounds were randomly divided into test set and training set by considering 70% of the total molecules in the training set and 30% in the test set. The training set was used to generate the 3D-QSAR model and the set was used to validate the feature of the model. All the biological activities of the compounds used in the present study were expressed as $pIC_{50} = -\log_{10}IC_{50}$, where IC_{50} is the micromolar concentration of the inhibitor producing 50% inhibition. In the pharmacophore model pIC_{50} values were used as dependent variables.

Preparation of protein and ligand

The targets flavivirus methyltransferase (protein data bank [PDB] id: 3LKZ) [16], human DHFR (PDB id: 1MVT)[32] and AMCase (PDB id: 2YBT)[33] at 2.0Å, 1.80Å and 2.2Å resolution respectively, have been selected from the PDB. A typical PDB structure contains heavy atoms, water molecules, metal, and may include co-crystal ligand. These proteins were prepared using the module protein preparation wizard under maestro [29]. The ligands were drawn using the software ChemSketch and converted into 3D structures. The impact energy minimization was performed for all 126 compounds individually for 1000 cycles of steepest descent and 5000 cycles of conjugate gradient methods with optimized potential for liquid simulations 2005 force field using Schrodinger suite [29].

Absorption, distribution, metabolism and excretion (ADME) property

ADME explains absorption, distribution, metabolism, and excretion. It plays an important role in the drug designing process. Due to the 60% failure of all drugs in the clinical phases, confirming the ADME property of these compounds is very much essential. ADME is an early phase application in the drug discovery field in order to remove the molecules with the poor ADME properties and also it is very useful in research and development costs [34]. The toxicity profile of the marine compounds is predicted using the QikProp module of Schrödinger suite (Table 1).

Common pharmacophore generation

A pharmacophore hypothesis is a spatial arrangement of chemical features which is common to two or more active ligands that are proposed to explain the key interactions involved in binding of a ligand with its receptor. PHASE module [29] generally provides standard pharmacophore features to describe the chemical features of ligand, i.e., a hydrogen bond acceptor (A), a hydrogen bond donor (D), aromatic ring (R), a hydrophobic group (H), a negatively ionizable (N) and positively ionizable (P) compound. The generation of hypotheses depends on the systematic variation of number of sites and number of matching active compounds. This common pharmacophore hypothesis was considered, which indicated at least five sites common to all the molecules used for the study.

Docking studies

GLIDE was used for the docking study [29]. The compounds from the marine sources were selected and subjected to the virtual screening and flexible docking studies. Virtual screening is the method to identify and rank the potential drugs from the set of compounds. The compounds were subjected to Glide based docking approach in which all the compounds were docked by three stages of the docking protocol, i.e., high throughput virtual screening (HTVS), standard precision (SP) and xtra precision (XP). In the first stage, HTVS screens the ligands, which are retrieved, and all the screened compounds are moved to the next stage of the SP docking. These compounds were docked using more accurate and computationally intensive XP mode. Based on the glide score and energy it gives the leads in XP descriptor.

Table 1: ADME properties of the selected marine compounds

Entry Id	Molecular weight	DonorHB	AccptHB	Qplogpo/w	Qplogs	% Human oral absorption
2	205.30	1	2.5	2.69	−2.90	100
7	308.30	2	4.25	2.14	−4.03	76.95
15	255.23	2	4.75	2.10	−3.17	74.97
17	348.42	4	5.5	1.64	−3.19	68.12
18	300.32	1	5	2.32	−3.88	90.55
19	316.32	2	5.75	1.63	−3.70	77.28
22	304.47	1	3.7	4.18	−4.65	100
23	478.92	2	4	3.46	−4.42	62.73
27	472.80	1	0.5	4.82	−5.74	100
28	422.90	2	1.5	3.97	−4.60	100
29	460.57	3	8.6	3.48	−5.89	92.47
30	291.15	1	1.75	3.59	−4.17	100
32	480.59	5	5.25	2.64	−5.20	76.91
33	184.15	1	5.25	-0.02	−1.19	70.3
34	339.10	2	3.5	1.67	−2.50	85.05
39	342.52	1	4	3.28	−4.90	88.85
40	316.39	2	5.5	3.38	−4.32	58.42
50	473.05	1	4.25	3.81	−3.14	95.69
51	351.98	2	4.5	1.70	−3.08	66.64
59	368.51	1	6.45	4.25	−4.3	87.90
60	310.15	5	4.5	1.19	−3.36	71.52
64	322.49	2	3.2	4.17	−4.83	100
66	363.46	2	2.7	4.7	−5.76	91.54
72	451.60	2	8.75	2.90	−5.21	62.12
74	236.35	2	2.45	2.76	−3.129	100
79	523.68	2	9.5	4.12	−6.23	41.36
80	523.68	2	9.5	3.96	−5.74	39.45
82	390.48	1	6.5	3.25	−4.50	95.96
83	392.49	2	7.45	2.95	−4.41	93.75
84	348.40	1	9.4	0.97	−2.53	78.60
89	344.45	3	5.2	3.62	−5.49	90.17
90	342.39	1	7.5	2.04	−3.88	86.41
91	165.15	3	6	−1.32	−1.47	50.11
93	346.42	1	3.75	4.24	−5.56	100
94	389.05	3	5.5	1.54	−3.63	83.75
95	343.47	2.5	5.75	2.45	−4.10	84.43
97	223.29	2	3.95	1.91	−2.64	95.31
98	498.40	5	8.5	1.28	−4.84	23.26
99	405.96	1	4.7	4.12	−4.40	100
103	398.54	1	5.2	4.73	−5.25	100
107	477.16	5	8.25	1.35	−5.25	56.48
109	404.55	1	5.7	4.73	−7.06	100
110	323.31	3	8	0.66	−3.55	67.04
114	167.16	2	5.25	-0.30	−1.35	64.71
115	328.50	1	3.5	3.77	−5.24	100
116	474.72	2	4.25	6.18	−7.40	100
117	246.35	2	3.4	2.78	−3.09	100
122	318.39	1	5.5	2.77	−4.05	100

Glide includes protein-ligand interaction energies, hydrophobic interactions, hydrogen bonds, internal energy and root mean square deviation and desolvation. Computational docking techniques are involved in the prediction of a ligand's conformation and orientation at the binding site of the target. Induced fit docking (IFD) has two powerful programs called prime (protein structure and side chain prediction) and Glide (rigid receptor docking). It is one of the most advanced docking programs which is particularly useful when a conformational change on both the receptor and ligand structure is induced during ligand-receptor binding [35].

RESULTS AND DISCUSSION

Structure based drug design provides a detailed knowledge of the binding sites of targets (proteins) associated with the corresponding disease. The activity or effectiveness of the compounds depends on the structural interaction with the receptor or the target molecule. Six different major chemical classes, namely, polyketides, terpenes, peptides, alkaloids, shikimates, and sugars were selected. These compounds have antibacterial, antiprotozoal, antimalarial, antituberculosis, anti-inflammatory, antifungal and antiviral activity. From this, only three corresponding targets (viral, malaria, inflammation) have been selected for the study. Totally, 126 compounds from various marine sources were selected and analyzed using Qikprop tool of Schrodinger software, among which major descriptors are required for predicting the drug-like properties of molecules such as molecular weight, octanol/water partition coefficient, aqueous solubility, cell permeability, brain/blood partition coefficient, and percent human oral absorption. 50 compounds have shown significant values for the properties analyzed (Table 1) and they exhibited drug-like characteristics based on Lipinski's rule of five. These compounds showed ADME properties in an acceptable range.

The default pharmacophore feature definitions were used for site generation. After site generation, the common pharmacophore was searched from the set of variants which was generated by a systematic variation of the number of sites. AADRR for which all the compounds were matched was searched to generate the best common pharmacophore hypothesis (AADRR) based on the survival score by PHASE. The survival score of hypothesis was determined by using the following formula: Survival score = (Vector)+ (Site)+ (Volume)+ (Selectivity)+ (Number of actives that match the hypothesis − 1)− (Reference-ligand relative conformational energy)+ (Reference-ligand activity).

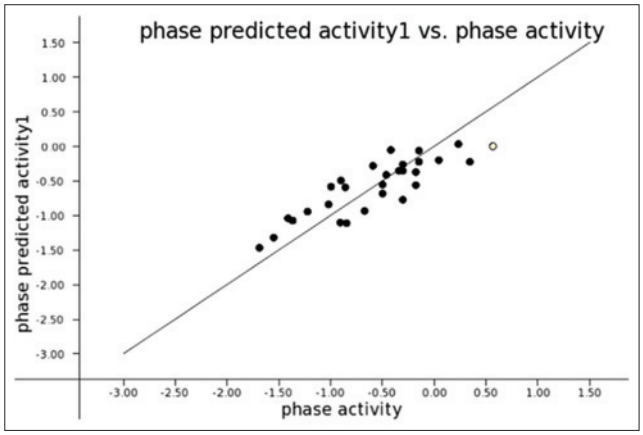

Fig. 3: Fitness graph between observed activity and predicted activity for the training set compounds

Hypothesis AADRR.7 was selected as the best hypothesis because it has a higher survival score (3.541)(Table 2). The highest survival score of the common pharmacophore hypothesis gives the best alignment of the active ligands. These alignments give the fitness to all the inhibitors. The best- aligned ligand shows the maximum fitness. The highest score hypothesis was then used to build 3D-QSAR model.

To obtain the desired pharmacophore of ligand molecules further study has been performed by pharmacophore modeling method. The method is very useful to select the active part of a set of drug molecules having potential to cure the diseases. The five featured common pharmacophore hypothesis was found for the compounds baculiferin M, baculiferin I, baculiferin L, baculiferin J, phlorotannin 3 and eusynstyelmaide F (Fig. 2). The 3D-QSAR model was generated using PHASE with 87 compounds as training and model was validated using 39 compounds as test set. The validity and predictive character of AADRR was further assessed by using the test set prediction. The predicted activity of training set molecules exhibited r^2==0.86 and the correlation coefficient value of q^2=0.67 using the model AADRR.7. The plot between the observed and predicted activities was generated for the training set (Fig. 3). The higher values of r^2 and q^2 in the training set are clearly indicated by the points lying near to the best fit line. High pred_r^2 value (pred_r^2=0.86) suggests a significant predictive ability of the QSAR model. In the present study, *in silico* docking studies were performed for the 126 compounds from the various marine sources with the crystal structure of three different targets such as methyltransferase, human DHFR and AMCase to know the binding mode of the ligands with these receptors. Active site residues were

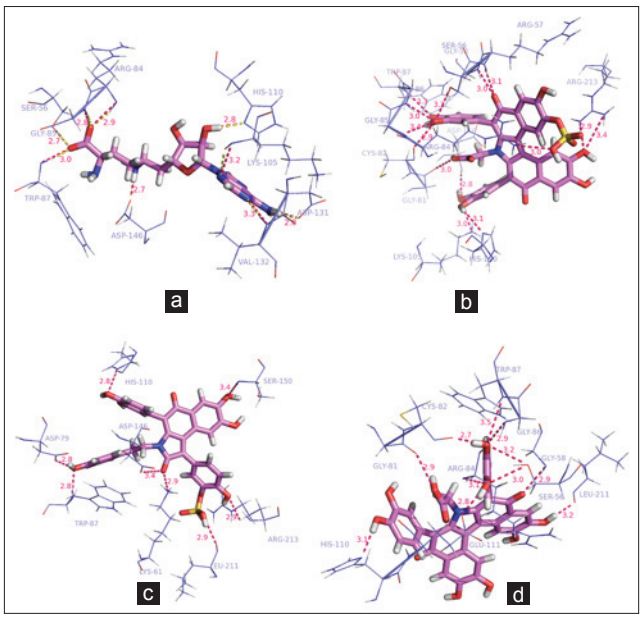

Fig. 4: Induced fit docking pictures of the selected compounds with methyltransferase. Interactions of the compounds (shown in pink color), (a) co-crystal ligand (SFG) (b) baculiferin M (c) baculiferin I and (d) baculiferin L are shown at the active site (shown in blue color). Hydrogen bond distances are in Å

Table 2: Score hypothesis

ID	Survival	Site	Vector	Volume	Selectivity	Matches	Energy	Activity
AADRR.7	3.54	0.98	1	0.78	1.73	75	0.3	8.53
AADRR.6	2.42	0.44	0.57	0.46	1.68	75	0.65	7.64
AADRR.1	2.21	0.34	0.63	0.4	1.71	75	0.86	7.18
AADRR.5	1.98	0.09	0.33	0.16	1.43	75	2.66	5.30

Table 3: Docking results of the marine compounds with methyltransferase

Compounds	H-bond Interactions (D-H…A)	Distance (Å)	GLIDE score	GLIDE energy (kcal/mol)
SFG (co-crystal)	(SER 56) N-H…O	2.8	−10.46	−81.11
	(ARG 84) N-H…O	2.9		
	(GLY 85) O-H…O	2.7		
	(TRP 87) N-H…O	3.0		
	(LYS 105) N-H…N	3.2		
	O-H…N (HIS 110)	2.8		
	N-H…O (ASP 131)	2.8		
	(VAL 132) N-H…N	3.3		
	N-H…O (ASP 146)	2.7		
Baculiferin M	(SER 56) O-H…O	3.2	−7.67	−83.42
	(ARG 57) N-H…O	3.1		
	(GLY 58) N-H…O	3.0		
	O-H…O (GLY 81)	3.0		
	O-H…O (CYS 82)	2.9		
	(ARG 84) N-H…O	3.0		
	(GLY 85) N-H…O	3.4		
	(GLY 86) N-H…O	3.0		
	(TRP 87) N-H…O	3.3		
	(LYS 105) N-H…O	3.0		
	O-H…N (HIS 110)	3.1		
	O-H…O (ASP 146)	2.8		
	(ARG 213) N-H…O	2.9		
	(ARG 213) N-H…O	3.4		
Baculiferin I	(LYS 61) N-H…O	2.9	−9.49	−83.03
	O-H…O (ASP 79)	2.8		
	(TRP 87) N-H…O	2.8		
	(HIS 110) N-H…O	2.8		
	(ASP 146) O-H…O	3.4		
	(SER 150) N-H…O	3.4		
	O-H…O (LEU 211)	2.9		
	(ARG 213) N-H…O	2.9		
Baculiferin L	(SER 56) O-H…O	3.2	−7.29	−81.67
	(SER 56) O-H…O	3.0		
	(GLY 58) N-H…O	2.9		
	O-H…O (GLY 81)	2.9		
	O-H…O (CYS 82)	2.7		
	(ARG 84) N-H…O	3.1		
	(GLY 86) N-H…O	2.9		
	(TRP 87) N-H…O	3.5		
	O-H…N (HIS 110)	3.1		
	O-H…O (GLU 111)	2.8		
	O-H…O (LEU 211)	3.2		

predicted through the volume occupied by the known ligand in the active site. The binding site was identified by analyzing the protein-ligand interactions from the co-crystal structures which were deposited in PDB. To confirm the active site residues, docking studies were carried out for the co-crystal also.

For the methyltransferase, baculiferin M, baculiferin I and baculiferin L showed good docking scores of −7.67, −9.49 and −7.29, glide energy of −83.42, −83.03 and −81.67 kcal/mol, respectively. The co-crystal SFG of this target showed the glide score of −10.46 and the glide energy of −81.11 kcal/mol. These compounds interact with the key residues such as ARG 84, SER 56, TRP 87, HIS110, LYS105, ASP 146, GLY 81 (Table 3 and Fig. 4).

For the human DHFR target, baculiferin M, baculiferin I, baculiferin J and phlorotannin 3 showed good docking scores of −12.76, −12.15, −9.88 and −9.09 and glide energy of −95.09, −86.75, −83.30 and −73.35 kcal/mol, respectively. The co-crystal ligand DTM of this target showed the docking score of −6.01 and glide energy of −46.69 kcal/mol. These

Table 4: Docking results of the marine compounds with the human DHFR

Compounds	H- bond interactions D-H…A	Distance (Å)	Glide score	Glide energy (kcal/mol)
DTM (Co-crystal)	N-H…O (ALA 9)	3.0	−6.01	−46.69
	N-H…O (ILE 16)	3.0		
	N-H…O (ILE 16)	3.2		
	(ASN 64) N-H…O	2.9		
	(ASN 64) N-H…O	3.2		
	N-H…O (VAL 115)	2.8		
Baculiferin M	O-H…O (ASP 21)	3.0	−12.76	−95.09
	(TRP 24) N-H…O	2.9		
	O-H…O (GLU 30)	2.8		
	O-H…O (GLU 30)	2.8		
	(GLN 35) N-H…O	3.4		
	(THR 56) O-H…O	3.2		
	O-H…O (ASN 64)	2.8		
Baculiferin I	O-H…O (ILE 16)	2.9	−12.15	−86.75
	O-H…O (ASP 21)	2.5		
	(ARG 28) N-H…O	2.8		
	O-H…O (PHE 31)	2.8		
	O-H…O (VAL 115)	2.8		
	O-H…O (TYR 121)	2.9		
Baculiferin J	O-H…O (ASP 21)	3.0	−9.88	−83.30
	(ARG 28) N-H…O	2.9		
	(GLN 35) N-H…O	2.8		
	(THR 56) O-H…O	3.1		
	O-H…O (VAL 115)	2.9		
	O-H…O (VAL 115)	2.7		
	(SER 118) N-H…O	3.0		
Phlorotannin 3	O-H…O (ASP 21)	2.8	−9.09	−73.35
	O-H…O (GLU 30)	2.4		
	(GLN 35) N-H…O	3.1		
	O-H…O (THR 56)	3.3		
	O-H…O (SER 59)	2.8		
	O-H…O (ASN 64)	2.8		

DHFR: Dihydrofolate reductase

Table 5: Docking of the marine compounds with AMCase

Compound name	H-bond interactions (D-H…A)	Distance (Å)	Glide score	Glide energy (kcal/mol)
DW0 (co-crystal)	(TRP 99) N-H…O	3.4	−5.29	−55.41
	(ASN 100) N-H…O	3.1		
	(TYR 212) O-H…N	2.8		
Baculiferin M	(TRP 99) N-H…O	3.25	−12.10	−88.78
	(TYR 212) O-H…N	2.77		
Eusynstyelamide F	(TRP 99) N-H…O	3.2	−9.59	−79.55
	(GLU 140) O-H…O	3.2		
	(TYR 212) O-H…N	2.8		
Baculiferin J	(TRP 99) N-H…O	3.4	−11.40	−75.80
	(GLU 140) O-H…O	3.0		
	(TYR 212) O-H…N	2.7		
Phlorotannin 3	(TRP 99) N-H…O	3.2	−6.06	−66.62
	(TYR 212) O-H…N	2.8		

AMCase: Acidic mammalian chitinase

compounds reveal the major interactions with the active site residues, namely, ASN 64, VAL 115 and ASP 21 (Table 4 and Fig. 5).

For the AMCase, baculiferin M, eusynstyelmaide F, baculiferin J and phlorotannin 3 showed good interactions with the glide score of −12.10, −9.59, −11.40 and −6.06 and glide energy of −88.78, −79.55, −75.80 and −66.62 kcal/mol, respectively. The co-crystal ligand bisdionin (DW0) of this target showed the docking score of −5.29 and the glide energy

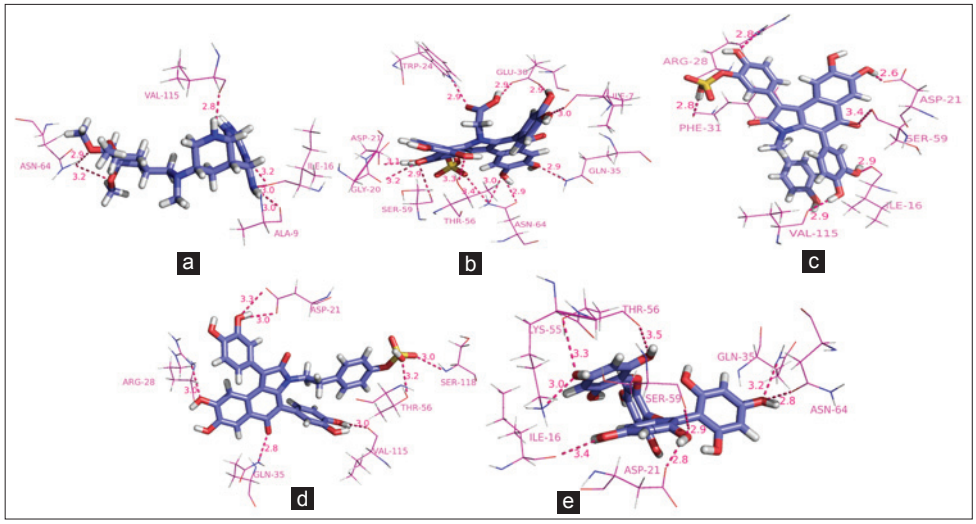

Fig. 5: Induced fit docking pictures of the compounds with the human dihydrofolate reductase. Interactions of the compounds (shown in blue color), (a) DTM (co-crystal) (b) baculiferin M (c) Baculiferin I (d) baculiferin J and (e) pholorotannin 3 are shown at the active site (shown in pink color). Hydrogen bond distances are in Å

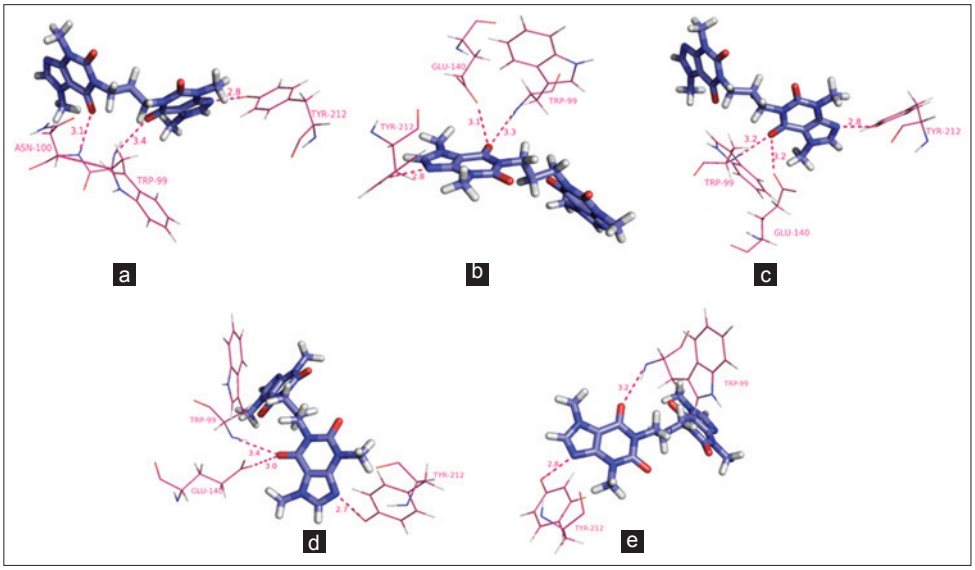

Fig. 6: Induced fit docking pictures of the compounds with the acidic mammalian chitinase. Interactions of the compounds (shown in blue color), (a) Bisdionin (co-crystal) (b) baculiferin M (c) eusynstyelamide F (d) baculiferin J and (e) phlorotannin 3 are shown at the active site (shown in pink color). Hydrogen bond distances are in Å

of −55.41 kcal/mol. These compounds interact with the active site residues, TYR 212, TRP 99, ASN 100, GLU 140 (Table 5 and Fig. 6). The docking results are presented in the following Tables 1-5 and Figs. 1-6.

CONCLUSIONS

The compounds selected from the marine sources have antiviral, antimalarial and anti-inflammatory activities. In order to predict the druggability of these compounds, the QSAR, pharmacophore and docking studies have been carried out. The five point pharmoacophore model was generated using a ligand-based approach for the marine compounds to understand the importance of steric and electronic feature of the ligand for binding with their targets and how these compounds are responsible for their activity. The common pharmacophore model was obtained for some of the compounds. The highly predictive 3D-QSAR model was generated using a set of molecules containing five point pharmacophore (AADRR) i.e., two hydrogen bond acceptors (A), one hydrogen bond donor (D) and two aromatic ring features (R). Based on the top ranking pharmacophore hypotheses and their feature composition, the AADRR.7 hypothesis was selected.

10 ligands were filtered through the virtual screening from the 126 compounds for each target. All the 10 compounds were subjected to the IFD studies with their corresponding targets. Among the 10 ligands, three ligands showed comparable docking score and energy with the co-crystal ligand (SFG) of the methyltransferse. Among these three ligands, baculiferin M shows the best glide energy and more interactions at the active site. Except the two interactions observed for the co-crystal, all the other interactions are maintained. Four ligands showed good docking score and glide energy than the co-crystal ligand (DTM) of the human DHFR. Among the four ligands, baculiferin M shows the best glide energy and ASN 64 maintains the common interaction. For the AMCase, four compounds showed good docking score and glide energy than the co-crystal ligand (DW0). Baculiferin M has the least glide energy and the two interactions at the active site matched with the co-crystal ligand. The above findings also suggest that baculiferin M seems to be a common inhibitor for methyltransferase, human DHFR and AMCase which are related to viral, malarial and inflammatory action, respectively. Therefore, the results of 3D-QSAR model and the docking studies may help in designing derivatives or analogs for synthesis with

better activity, which may be potent inhibitors for the viral, malarial, and inflammatory diseases.

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AUTHOR CONTRIBUTIONS

Karthiga Devi and Velmurugan designed the study. Karthiga Devi performed data analysis. Karthiga Devi and Velmurugan wrote the manuscript.

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