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Molecular docking and druggability studies of terpenoid-derived metabolites from marine sponges as IL-17A inhibitors

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Abstract

In this study, physicochemical properties of 49 compounds, extracted from anti-inflammatory sponge species with the aim of ADMET test and Lipinski rule of five, have been determined. Fourteen compounds, which showed the best results, were subjected to molecular docking studies with IL-17. Among these compounds, four compounds with low binding energy were obtained. These compounds; namely, frondosins C, frondosins D, methylpourewate B, and Cadlinolide C, have shown promising ADMET properties and strong interactions in the active site of IL-17. The ROC curve with the acceptable area under the curve of 0.853 was used for validation of the docking protocol. If the efficacy of these compounds is proven by biochemical tests, the molecules will be potentially important inhibitors of IL-17A and used as a basis for the further development of anti-inflammatory and anti-psoriasis agents.

Keywords: Molecular docking; druggability; interleukin 17-A, psoriasis; marine sponge.

Introduction

The IL-17A is a major cytokine produced by the stimulation of the Th17 cell line. In addition to T cells, mast cells and neutrophils have also been identified as the source of IL-17 in psoriasis and numerous immune diseases [1]. IL-17A receptors are expressed at the level of keratinocyte cells, making these cells the main cause of psoriasis disease. After being bound to IL-17A, the expression of multiple chemical keratinocytes (including CCL20, CXCL1 and CXCL8) increased which played an important role in the absorption of inflammatory cells into skin lesions and stimulated the intrinsic immune system. This complex interaction ultimately resulted in an excessive growth of the epidermis layer and impaired dermatological activity as an important factor in the pathogenesis of psoriasis [2]. In psoriasis, the expression of mRNA,

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related to IL-17 in the damaged skin, is more than healthy skin [3]. A cohort study showed that the level of IL-17A in Psoriasis patients with a Psoriasis Area and Severity Index (PASI) of more than 10 in comparison to patients with a PASI of less than 10, is triple[4]. Through the conducted research, IL-17 inhibition reduces the proliferation of keratinocytes, the penetration of T-cells into the dermis and the expression of mRNA as the key developers of the disease[5]. Therefore, there is considerable information on the central role of IL-17 in the pathogenesis of psoriasis and the importance of the targeted biological treatment of IL-17 in the treatment of the moderate to severe psoriasis. Several clinical trials support the benefits of inhibiting the IL-17 [6].

Marine sponges are a valuable source of bioactive metabolites important for their chemical protection against predators [7]. About 5,300 natural products have been isolated from marine sponges and their associated microorganisms, so the marine sponge can be regarded as a rich source of various compounds [8]. In this study, 49 terpenoid-derived metabolites from marine sponge with anti-inflammatory properties were selected for this study (Table 1) [9].

In the beginning, they were analyzed for pharmacological properties, adsorption, distribution, metabolism, excretion, and poisoning (ADMET) (pharmacokinetic analysis) and, then, the screened terpenoids were examined for docking with IL-17A.

Experimental

In this study, molecular docking was performed using Autodock 4.2. Chimera 1.13 and Plip online web software were applied to visualize the interactions. For the similarity of pharmaceutical compounds, the latest DruLiTo version was used. Using admetSAR which is online web software, ADMET profile was created. ChemBioDraw (Ultra 14.0) and Hyperchem 8.0 were used to draw the ligand structure. In this sense, Hyperchem software was used to optimize the energy of the compounds, respectively.

Selection of the ligand: 49 terpenoids compounds extracted from marine sponges and having significant anti-inflammatory effects were selected as candidate compounds. The structure of these compounds was drawn using ChemBioDraw (Ultra 14.0). Subsequently, using Hyperchem software and based on the Polak-Ribiere algorithm, they were optimized for energy[13].

Pharmacokinetic analysis: The prediction of ADMET properties in drug studies is used to evaluate the appropriateness of long-term potential therapeutic molecule[14]. In this study, the admetSAR predictive tool was used. **(http://lmmd.ecust.edu.cn:8000/).**

Human Intestinal Absorption (HIA) is a process in which oral drugs are absorbed through the intestine and then they enter the bloodstream. The blood-brain barrier (BBB) is an impediment that blocks the entry of many compounds from the blood into the brain.

Cytochrome P450 2D6 (CYP2D6): CYP2D6 is responsible for the metabolism of a wide range of metabolites in the liver.

To evaluate the efficacy of these compounds as potential therapeutic molecules, these 49 terpenoids compounds were initially analyzed for their pharmacokinetic properties through Lipinski rule (drug similarity) analysis using DruLiTo software. The four parameters of H-donor, H-

acceptor, molecular weight and logP were considered in drug similarity evaluation.

Receptor selection: The crystallographic x-ray structure of IL-17A (PDB ID: 5HI3) was retrieved from the Protein Data bank (http://www.rcsb.org/pdb/home/home.do).

Molecular docking: Based on the Lamarckian Genetic Algorithm (LGA) method, the Docking analysis of modeled protein (IL-17A) and terpenoids (ligand) were performed using the AutoDock 4.2.1 [14-15]. The preparation of the protein was done using AutoDock Tools 4, which is a GUI for AutoDock 4.2.1. It was conducted by adding a polar hydrogen atom to the macromolecule and then calculating the load of each macromolecule atoms. The LGA method was used to search for ligand interaction[16]. The active protein region of the target has been selected based on the previous studies[17]. The interaction of the protein-ligand was evaluated using Chimera 1.13 software and online web-based Plip software. The binding site on 5hi3 was defined by a grid system of (x, y, z) = (45, 49, 51-point) with a grid Spacing of 0.375 Å that was originated at the center of the grid box. Finally, docking simulations were carried out via Autodock4 with a rigid receptor structure, which allowed for flexibility in the ligand structure using a Lamarckian Genetic Algorithm (LGA). The Lamarckian genetic algorithm was applied to the following protocol: trials of 100 runs, energy evaluations of 5,000,000, a maximum number of generations of 30,000, a population size of 200, a mutation rate of 0.02, a crossover rate of 0.8, and an elitism value of 1. The docking results were evaluated by sorting the docking energy predicted by docking conformations.

Docking protocol validation: To confirm the docking protocol, the ligands whose position was empirically determined in the target protein structure by crystallography were separated from the receptor and redocking with the receptor [18].

For the validation of docking, co-crystal ligand (N-(4-{2-[({1-[2-(dimethylamino)-2-xoethyl]cyclopentyl}acetyl)amino]ethyl}phenyl)-2-fluoro-Nalpha-[(1-methyl-1H-pyrazol-5-yl)carbonyl]-L-phenylalaninamide), inside the PDB file of IL-17A (5HI3), was extracted using a viewer and treated as other ligands. As a part of the molecular docking validation, by searching on the CHEMBLsite (https://www.ebi.ac.uk/chembl/) and through the compounds tested on the target ligand, some compounds were selected [19]. Based on the half maximal inhibitory concentration, (IC50) values were divided into two groups of active compounds and Decoy compounds and, then, after redocking, based on the same conditions to the investigated ligands of this study, their results were drawn by the docking analysis curve indicating the function of the system. Finally, the surface area below the chart was measured.

Results and discussion

Before the docking process of sponge terpenoids, 49 terpenoids were monitored through ADMET and Lapinsky Law using the DruLiTo software and admetSAR website. It should be noted that among the 49 selected terpenoids, only 14 of these compounds had the ADMET and Lapinsky rules. Table 2 shows the various ADMET and with Lipinski rules parameters.

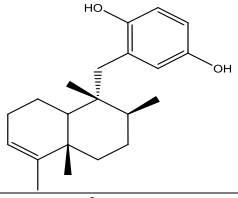
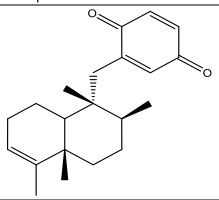
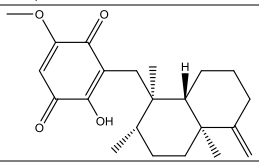
Pharmacokinetics: The ADMET properties obtained from the admetSAR server show that most compounds have a higher HIA than the control molecule. Penetration from blood–brain barrier (BBB) was greater for most compounds than control molecules. In this regard, Frondosins C compound was significantly higher than the control molecule (0.9 and 0.5). Regarding metabolism, we found that none of the studied terpenoids compounds had an inhibitory effect and metabolism using CYP2D6. The lack of inhibition of CYP2D6 means that the molecule does not inhibit the biotransformation of the drugs metabolized by the CYP2D6 enzyme [20]. AMES Toxicity Test is used to determine whether a compound has been mutated or not. Like control, all the tested ligands showed negative AMES toxicity test which means that ligands are non-mutagenic agents. Also, the characteristics of the carcinogenicity of the compounds showed that none of the ligands was carcinogenic. One of the most important information obtained from the admetSAR server is how to calculate the LD50 dose in the wild rat model.

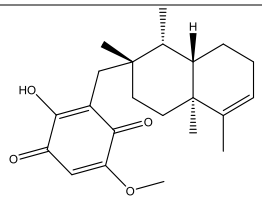
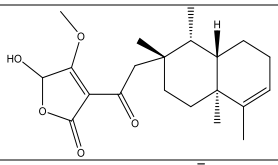
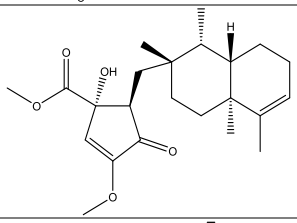
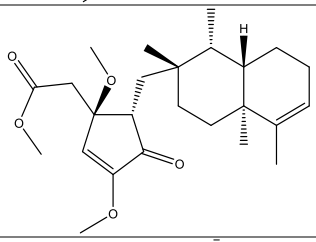
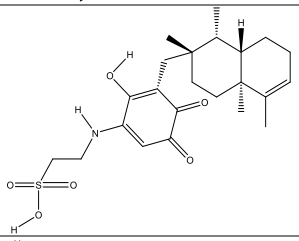
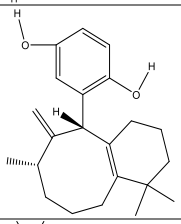
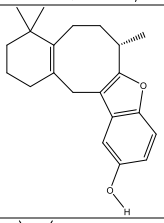
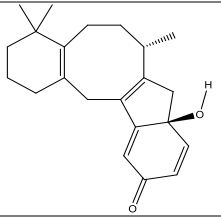
LD50 ("lethal dose, 50%") is a measure of the lethal dose of a toxin, radiation, or pathogen. The value of LD50 for a substance is the dose required to kill half the members of a tested population after a specified test duration.

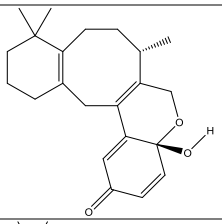
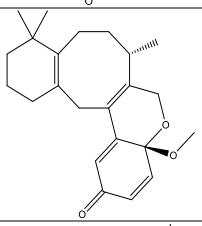
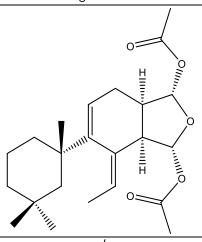
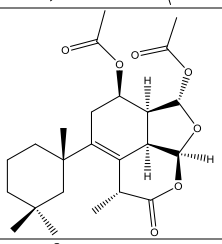
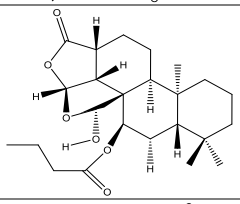
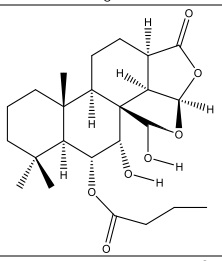
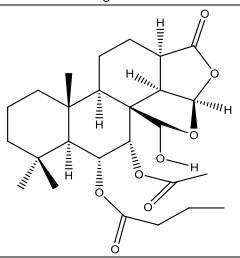
To compare the dose of LD50, the compound with a lower dose is more fatal than the compound with a higher dose of LD50 [20]. Among ligands, Frondosins D with LD50 of 1.5763 was the most toxic.

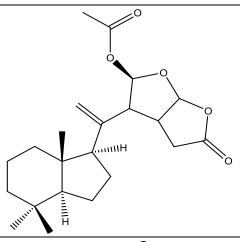
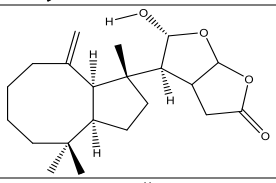
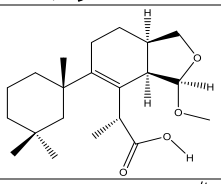
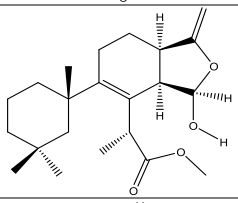
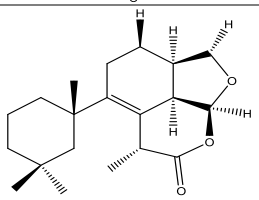
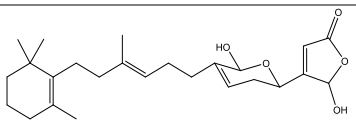
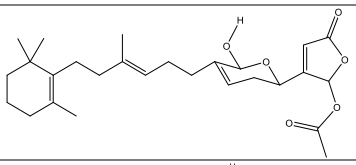
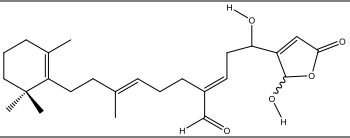
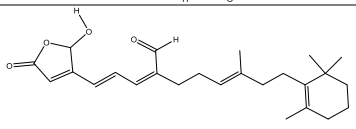
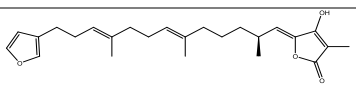
Docking: The binding energy is one of the most important data from molecular docking that can detect the power of binding between the ligand and receptor. The more binding energy, the weaker bond and conversely [20].

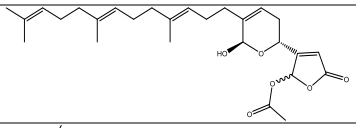
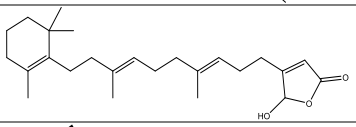
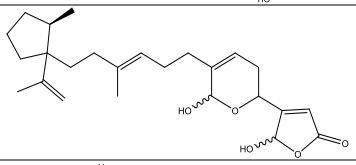
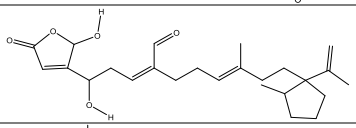
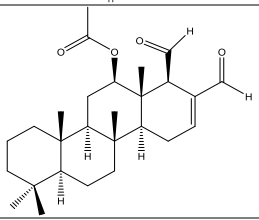
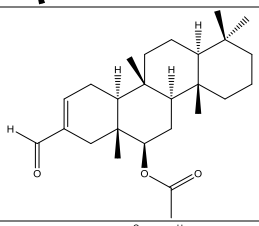
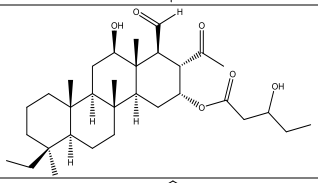
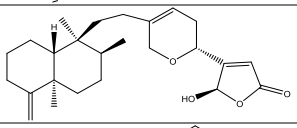
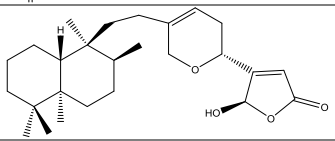
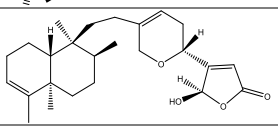
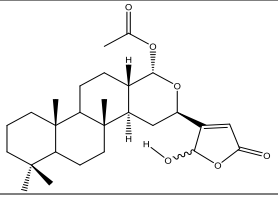
Table 1. Structures and origin of selected compounds [19]. All of these compounds have anti-inflammatory properties

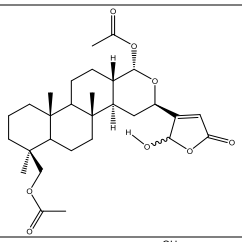
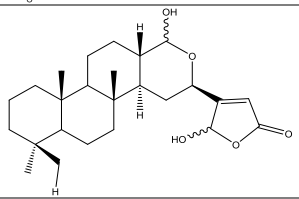
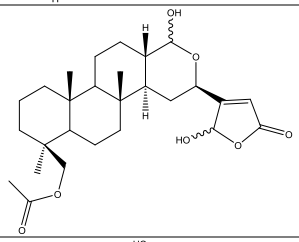
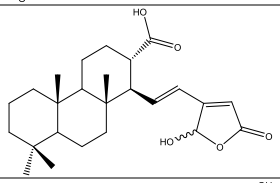
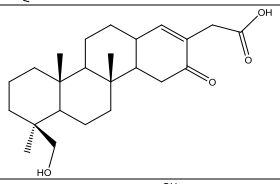
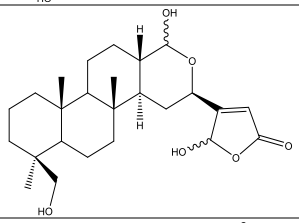
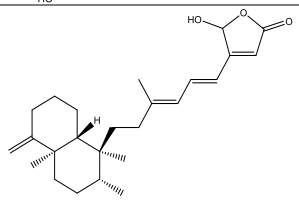
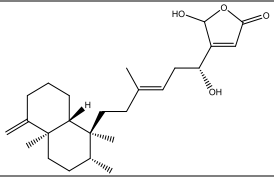
Entry	Compound	Structures	Origin
1	Avarol		Dysidea avara
2	Avarone		Dysidea avara
3	Ilimaquinone		Hippospongia metachromia

4	Bolinaquinone		Dysidea sp
5	dysidotronic acid		Dysidea sp
6	dysidenones A		Dysidea sp
7	dysidenones B		Dysidea sp
8	Dysidine		Dysidea sp
9	frondosins A		Dysidea frondosa
10	frondosins B		Dysidea frondosa
11	frondosins C		Dysidea frondosa

12	frondosins D		Dysidea frondos
13	frondosins E		Dysidea frondosa
14	Gracilin A		Californian Aplysilla sp
15	12- acetoxytetrahydroaplysulfurin-1		Californian Aplysilla s
16	aplyroseols-1		Aplysilla rosea
17	aplyroseols-5		Aplysilla rosea
18	aplyroseols-6		Aplysilla rosea

19	Norrisolide		Dendrilla membranosa
20	dendrillolide A		Dendrilla membranosa
21	pourewic acid A		Chelonaplysilla violacea
22	methylpourewate B		Chelonaplysilla violacea
23	Cadlinolide C		Chelonaplysilla violacea
24	Manoalide		Luffariella variabilis
25	manoalide monoacetate		Thorectandra excavates
26	secomanoalide		Luffariella variabilis
27	4E,6E-dehydromanoalide		Luffariella variabilis
28	Variabilin		Ircinia variabilis

29	thorectolide monoacetate		Hyrtios sp
30	Luffariellolide		Luffariella sp
31	luffariellins A		Luffariella variabilis
32	luffariellins B		Luffariella variabilis
33	Scalaradial		Cacospongia mollior
34	Hyrtial		Hyrtios erecta
35	Foliaspongin		Phyllospongia foliascens
36	Cacospongionolide B		Fasciospongia cavernosa
37	Cacospongionolide		Fasciospongia cavernosa
38	cacospongionolide E		Fasciospongia cavernosa
39	petrosaspongionolides M		Petrosaspongia nigra

40	petrosaspongionolides N		Petrosaspongia nigra
41	petrosaspongionolides P		Petrosaspongia nigra
42	petrosaspongionolides Q		Petrosaspongia nigra
43	petrosaspongionolides R		Petrosaspongia nigra
44	21-Hydroxypetrosaspongiolide K		Petrosaspongia nigra
45	21-hydroxypetrosaspongiolide P		Petrosaspongia nigra
46	Palauolide		Fascaplysinopsis sp
47	Palauolol		Fascaplysinopsis sp

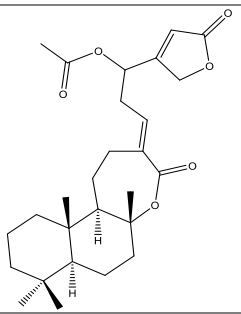
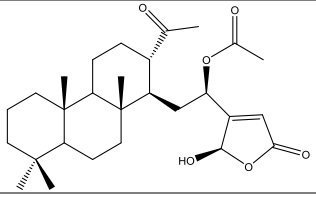
48	Luffalactone		Luffariella variabilis
49	Luffolide		Luffariella sp

Table 2. Analyzing the medicinal properties of eligible terpenoids with Lipinski rules and ADMET

Compound	MW	HIA	BBB	HBA	HBD	CYP2D6	Log P	AMES toxicity	Carcinogenicity	LD50 in rat
Dysidine	451.2	0.949	0.6563	7	3	Non-substrate	3.05	Non	Non	2.4358
frondosins B	310.19	1	0.9371	2	1	Non-substrate	4.547	Non	Non	2.0669
frondosins C	324.21	1	0.9651	2	1	Non-substrate	3.791	Non	Non	2.2435
frondosins D	340.2	0.993	0.8628	3	1	Non-substrate	3.369	Non	Non	1.5763
frondosins E	354.22	0.996	0.8226	3	0	Non-substrate	3.888	Non	Non	1.8993
12-acetoxytetrahydroaplysulfurin-1	434.23	1	0.8778	7	0	Non-substrate	4.365	Non	Non	3.3926
aplyroseols-5	436.25	0.89	0.7405	7	2	Non-substrate	4.402	Non	Non	3.1661
pourewic acid A	350.25	0.996	0.5172	4	1	Non-substrate	4.571	Non	Non	2.9188
methylpourewate B	362.25	0.983	0.5736	4	1	Non-substrate	4.881	Non	Non	3.3727
Cadlinolide C	318.22	1	0.9094	3	0	Non-substrate	4.872	Non	Non	2.6747
Manoalide	416.26	0.971	0.6157	5	2	Non-substrate	4.415	Non	Non	4.2679
secomanoalide	416.26	0.794	0.7713	5	2	Non-substrate	4.802	Non	Non	3.5754
petrosaspongionolides P	418.27	0.993	0.5227	5	2	Non-substrate	7.161	Non	Non	4.2943
21-hydroxypetrosaspongiolide P	434.27	0.99	0.7589	6	3	Non-substrate	4.974	Non	Non	4.1
Cocrystal	604.71	0.978	0.5389	6	3	Non-substrate	3.70	Non	Non	2.5767

Among 14 terpenoids compounds, 4 compounds named frondosins C, frondosins D, methylpourewate B and Cadlinolide C showed the best docking results (having minimum binding energy) on IL-17A. Among these

compounds, frondosins C is the strongest inhibitor of IL-17A with the least binding energy (-6.84 kcal/mol). The results of docking analysis including free binding energy and all interactions are presented in Table 3. IL-17A complexes with the best-connected terpenoids are shown in Figure 1. The interaction of frondosins C with the target protein in the docking region was analyzed which in turn contained nine interactions of hydrophobic interactions with ILE96A, VAL98A and LEU112A amino acids. Also, it contains hydrogen bound with LEU97A amino acid at the active site of the target protein (Figure 2).

Table 3. Summary of the results of the binding of the selected terpenoids with IL-17A

Compounds	Binding Energy (kcal/mol)	(Hydrogen Bonds)	(Hydrophobic Interactions)	Salt Bridges
Dysidine	-6.54	GLU 95A LEU 97A	TYR 62A- PRO 63A- ILE 96A- LEU99A	_
Frondosins B	-6.2	TYR 62A LEU 97A	TYR 62A- ILE 96A- LEU 97A- VAL 98A- LEU 99A- LEU 112A	-
frondosins C	-6.84	LEU97A	66A ILE- 96A ILE- 96A ILE- 98A VAL- 112A LEU	-
frondosins D	-6.64	97A LEU	62A TYR - 62A TYR- 96A ILE- 97A LEU- 98A VAL- 99A LEU- 112A LEU	-
frondosins E	-6.37	97A LEU	62A TYR -63A PRO-96A ILE - 97A LEU- 98A VAL- 112A LEU	-
12-acetoxytetrahydroaplysulfurin-1	-6.17	97A LEU	9I LEU- 62A TYR-62A TYR-63A PRO-97A LEU- 99A LEU	-
aplyroseols-5	-5.95	97A LEU 99A LEU	62A TYR-63A PRO-96A ILE	-
pourewic acid A	-5.72	97A LEU	62A TYR- 63A PRO-98A VAL-99A LEU	-
methylpourewate B	-6.8	97A LEU 99A LEU	9I LEU- 62A TYR- 62A TYR- 96A ILE- 97A LEU- 99A LEU- 112A LEU	-
Cadlinolide C	-6.64	non hydrogen bond	62A TYR -96A ILE -98A VAL- 99A LEU- 112A LEU	-
Manoalide	-6.3	97A LEU	6I PRO-9I LEU-62A TYR-62A TYR-96A ILE-98A VAL- 99A LEU- 112A LEU	-
secomanoalide	-5.7	94A GLN 95A GLU	62A TYR-62A TYR-96A ILE- 97A LEU-98A VAL- 99A LEU-112A LEU	114A LYS
petrosaspongionolides P	-6.35	95A GLU	96A ILE - 97A LEU	114A LYS
21-hydroxypetrosaspongiolide P	-6.02	95A GLU 97A LEU	95A GLU-96A ILE-97A LEU	-
Cocrystal	-6.38	97A LEU	62A TYR-94A GLN 96A ILE-96A ILE-97A LEU 99A LEU-112A LEU	-

Alignment with RMSD of Reference ligand: After performing the docking process and predicting the interactions and docking state, Co-

crystal molecule which had the experimental mode of interaction with the active site of the target protein, was redocked to evaluate the accuracy of docking [22]. After redocking, it was found that the co-crystalline ligand interacts with LEU97A amino acid in the active site of IL-A7. Frondosins C was also showed this type of interaction by hydrogen bonding. Some hydrophobic interactions, with LEU112A and ILE96A residues, were also observed for co-crystalline ligand and Frondosins C. The obtained RMSD values was 0.79 Å. RMSD value less than 2 Å indicating validated docking protocol [23-25].

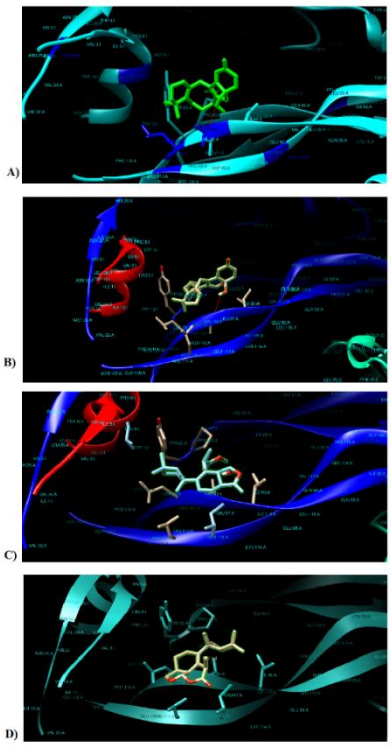


Figure 1. The structure of the three-dimensional complex of tropenoid compounds with IL-17A A: Frondosin C B: Frondosin D C: Methylpourewate B D: Cadlinolide C

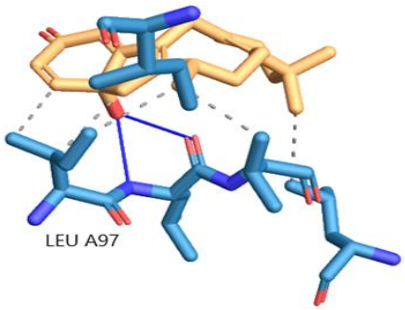


Figure 2. Hydrogen bond and Hydrophobic Interactions of Frondosins C with IL-17A active site amino acids

Analysis of receiver operating characteristics (ROC)

The area under the curve of receiver operating characteristics is an acceptable evaluation system for evaluating the ability of a docking model to distinguish the docking of active and inactive ligands [26]. The ROC curve provides a graphical diagram of the overall performance of docking to detect active and decoy ligands during the screening on the desired receptor [27]. When the surface below the ROC chart is close to one, the model's ability to differentiate the active and inactive ligands is higher and when it is close to zero, it indicates the inability of the model to create a distinction [26]. If the surface below the chart equals to 1, it means that the system can detect false and correct docked states without error. The value of 0.5 means the poor ability to predict random choice and the value of less than 0.7 represents a moderate distinction [28].

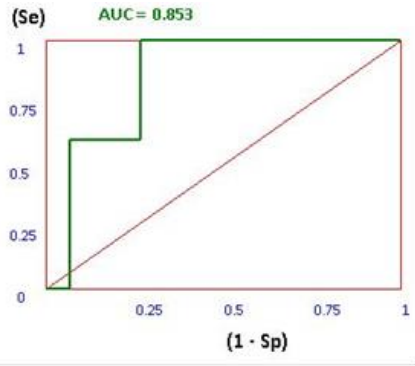


Figure 3. The ROC curve for validation of the docking protocol

The value for the surface below the chart of ROC curve for active ligands and 110 inactive ligands on IL-17A is 0.853 (Figure 3). The value for the surface below the chart between 0.8 and 0.9 is considered good and reasonable, and values between 0.7 and 0.8 are acceptable [29-30].

Conclusion

The results of the docking studies on IL-17A corroborate to the findings that the most suitable Druggability properties are possessed by frondosins C, frondosins D, methylpourewate B and Cadlinolide C. This provides evidence of how marine sponges can be a source of potential anti-inflammatory agent. If the efficacy of these compounds is proven by biochemical tests, these molecules can be important inhibitors of IL-17A which play a significant role in the mechanism of psoriasis.

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