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In Silico Molecular Docking & ADMET study of phycocomponents isolated from Padina tetrastromatica and Caulerpa peltata

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ABSTRACT

Brown algae, *P. tetrastromatica*and Green algae *C. peltata belong to the family* Dictyotaceae&Caulerpaceae. This present study was carried out by taking GC-MS data performed by M. Uma Maheswari et al.(2017) & K. Murugan and V. V. Iyer (2014). Phycocomponents were identified by them and its mechanism of action was identified through docking analysis. Most of the drugs currently used for the anti-bacterial treatments (for skin) produce side effects, and hence we focused on algae based compounds which exhibit the minimum toxic effects. Molecular docking, Binding energy, Absorption, Distribution, Metabolism, Excretion and Toxicity etc. were performed for phytocomponents to analyze as a drug molecule. Docking experiments were carried out between biocompounds from algae with 11 target proteins of well known skin pathogen *S. pyogenes* using PyRx. Compounds showed better activity in all parameters as tabulated. All the components can be further explored for structural modification and detailed investigation to arrive at possible newer potent agent with better therapeutic effects.

Key words: Algae, *C. peltata*, *P. tetrastromatica*, VEGA (Q)SAR, Molecular docking, ADMET

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INTRODUCTION

Recently, *in silico* procedure become a prominent tool for drug design and discovery. It is helpful to identify and discover new potential drugs from sets of compounds.[1, 2, 3] With the help of bioinformatics tools and techniques, the 3D structure of proteins, molecular modeling of gene, gene expression and gene sequence analysis can be studied. [4, 5, 6] This types of tools and techniques helpful to obtain, integrate and analyze data from diverse data sources. Other useful strategies include *in silico* drug design methods, drug repurposing by computational workflows, and network-based *in silico* screening for drug efficacy. [7, 8, 9]
The study of bioinformatics can assist a biologist to extract valuable information from biological data providing by various web- and/or computer-based tools, the majority of which are freely available.[10, 11] DDBJ, Uniprot, SWISS PROT, TAIR, Ensembl, Proteomics Identification Database, PubChem, HMDB etc. are the available databases for retrieving useful data.[12, 13, 14, 15] *In silico* study important in study related to the areas of biological research which can be greatly assisted by analyzing tools such as DNA and protein

sequence to identify various features, prediction of 3D structure of protein molecules, to study molecular interactions, and to perform simulations to imitate a biological problem to gain useful information from the data resources. [16, 17, 18]

Some popular drug target databases such as PDTD, DRUG BANK, TTD, TDR Target, MATADOR, DrugPort, ChEMBL etc. and other molecular dynamic simulation tests are Abalone, Ascalaph, Discovery studio, Molecular docking, Amber, FoldX etc. helpful to make prediction successful.[19, 20, 21] Among them, molecular docking is a key technique in structural molecular biology and computer-assisted drug design.[22, 23, 24] The aim of ligand protein docking is to study the superior binding mode(s) of a ligand with target protein. Molecular docking will produce binding energy, ligand protein interaction as well as its posing data as an output. Binding energy is released when a drug molecule binds with a target, leading to a lowering of the overall energy of the complex. [25, 26] The release binding energy also compensate for any transformation of the ligand from its energy minimum to its bound conformation. Thus, the greater the binding energy produce on binding of a ligand to the target protein, greater will be the affinity between them. [27, 28]

PyRx is a Virtual Screening valuable tool for Computational Drug Discovery to study docking interaction between ligands as well as target proteins that can be used to screen libraries of compounds against potential drug targets.[29, 30] It includes docking wizard with an easy-to-use user interface which makes it a benificial tool functionally and powerful for structure based drug design.[31, 32]

Another objective is to predict ADMET (stands for Absorption, Distribution, Metabolism, Excretion and Toxicity) property by using the VEGA (Q)SAR and DANISH (Q)SAR study.[33, 34, 35, 36] QSAR (Quantitative structure-activity relationship)model is helpful to study biological properties (such as boiling point, melting point, toxicity and certain molecular descriptions)ofchemical substancesbased on their structural characteristics. It can be assessed by *in silico* approach. The DANISH (Q)SAR database useful to predict physicochemical properties, ecotoxicity, ADME and toxicity properties of chemical substances based on similarity and structural difference. This platform developed by National Food Institute, Technical University of Denmark with the support of Danish Environmental Protection Agency, the Nordic Council of Ministers and the European Chemicals Agency.The main benefit behind ADMET properties prediction is to reduce risk of failures in different stages of drug discovery associated with the efficacy and safety deficiency. It also useful to reduce the amount of time wastage, resources as well as overall development process including clinical trial study. It is needful to minimize failures in the drug discovery process. [37, 38] The target bacterium *Streptococcus pyogenes*, or Group A streptococcus (GAS), is a facultative, Gram-positive coccus which grows in chains and causes numerous infections in humans including pharyngitis, tonsillitis, scarlet fever, cellulitis, erysipelas, rheumatic fever, post-streptococcal glomerulonephritis, necrotizing fasciitis, myonecrosis and lymphangitis etc.[39, 40] Virulence factors of group A streptococci include M protein and lipoteichoic acid; a hyaluronic acid capsule; Pyrogenic (erythrogenic) toxin; and Streptokinase, Streptodornase (DNase B), and Streptolysins etc.[41, 42, 43] There are many side effects of harmful chemical or synthetic drugs on human health such it creates toxicity, weaken the immune system, cause allergic reaction and make body less powerful to perform function as well as less fit with function life process. To overcome this disadvantages, natural resources are useful as a source of chemical constitutes in the process drug designing.

The aim of present study is to investigate the antibacterial efficacy of phycocomponents from extract of marine Brown algae, *Padinatetrastromatica* and Green algae *Caulerpapeltata*'s (belong to the family Dictyotaceae&Caulerpaceae, respectively) by an *in silico* procedure such as ADMET prediction and docking study.

MATERIALS AND METHODODLOGY

Selection of Phycocompounds

GC-MS is a Gas Chromatography-Mass Spectrometry is a combine technique to separate and quantify the compounds from any sample for characterization purpose.[44, 45, 46] This present study was carried out by taking GC-MS data performed by M. Uma Maheswari et al.(2017),[47] KavithaMurugan and Vidhya V. Iyer (2014). Phycocomponents were identified by them and tabulated below in table no.1. [48]

PubChem study

PubChem is an open chemistry database of chemical molecules and their biological activities. This database is maintained by NCBI (National Centre For Biotechnology Information).In the present study, Name of compounds, CAS number, Molecular formula. Molecular weight, Melting point (^{0}C) and Boiling point (^{0}C) are gained from this database. SDF(Smile Data Format) file of each phycocompounds downloaded from PubChem source that used as an input in further ADMET prediction as well as Docking study. (https://pubchem.ncbi.nlm.nih.gov/) [49, 50]

Target selection for docking study

Total 11 proteins of well known skin pathogen *S. pyogenes* targeted in following experiment to study the efficacy of phytocomponents as a drug molecule on it. Different bacterial proteins selected based on its virulence power as listed in table no. 2. PDB format file of target proteins 1Z0P, 2ESR, 2OTO, 1XF1, 4CMQ, 6N0A, 2YX2, 1B1Z, 6BZL, 3B2M and 2Q7A downloaded from PDB (Protein Data Bank) database. (https://www.rcsb.org/) [51, 52, 53]

Prediction of ADMET properties

Absorption, Distribution, Metabolism, Excretion and Toxicity study carried out by using VEGA (Q)SARand DANISH (Q)SAR models. In VEGA, different model are used to study such as Mutagenicity (Ames test) CONSENSUS model (version 1.0.2), Carcinogenicity model (CAESAR) (version 2.1.9), Developmental Toxicity model (CAESAR) (version 2.1.7), Developmental/Reproductive Toxicity library (PG) (version 1.0.0), Estrogen Receptor-mediated effect (IRFMN/CERAPP) (version 1.0.0), Skin Sensitization model (CAESAR) (version 2.1.6), Hepatotoxicity model (IRFMN) (version 1.0.0) and Persistence (water) model (IRFMN) (version 1.0.0).[54]

Docking analysis

This study was carried out by using PyRx software which was performed between phycocompounds (selected after ADMET study) with 11 target proteins of *S. pyogenes* as mentioned in target selection.[55, 56]

RESULTS AND DISCUSSION

The selected phycocompounds from two marine macro algae such as Brown algae *P. tetrastromatica* and Green alga *C. peltata* listed in table no. 1. Different properties such as CAS number, EC number, Molecular formula, Melting Point(^{0}C) and Boiling Point(^{0}C) obtained from PubChem database that expressed in table no. 3.

ADMET properties predicted by using two models: DANISH (Q)SAR and VEGA (Q)SAR. In VEGA(Q)SAR, different models such as Mutagenicity (Ames test) CONSENSUS model, Carcinogenicity model (CAESAR), Developmental Toxicity model (CAESAR), Developmental/Reproductive Toxicity library (PG), Sensitization model (CAESAR),

Hepatotoxicity model (IRFMN) and Persistence (water) model (IRFMN) used to predict different toxicity properties that noted in table no. 4. Whereas in DANISH (Q)SAR, different properties like Estimated Solubility Log Score, Estimated Solubility Class, Gastrointestinal Absorption 1 mg Dose(%), Skin Dermal Absorption, Blood Brain Barrier Penetration, Lipinski Violations, Toxicity, Carcinogenicity, Severe Skin Irritation In Rabit, Allergic Contact Dermatitis In Human, Respiratory Sensitization In Human, Mutagenicity Ames Test, In Vitro HGPRT Test are used to predict toxicity of selected phycocompounds.(Table no. 5 & 6)

According to VEGA (Q)SAR model, out of nine phycocomponents – 4 compounds such as Methyl oleate, Eicasanoic acid, Oleic acid, 5,8,11,14-eicosatetraenoic acid, methyl ester found Non mutagenic, Non carcinogenic, Non toxicant as well as Sensitizer in CAESAR model.Whereas in output of DANISH (Q)SAR model, same four compounds as mentioned in VEGA showed better predictability as a drug molecule. These four compounds reported No toxicity, No carcinogenicity, Better solubility, 100% Gastrointestinal absorption and significant skin dermal absorption. Another properties include Non tumorigenic, Non mutagenic, Non irritant and No reproductive Effect expressed by them. It also showed no allergic reaction as well as no respiratory sensitization. Whereas this obtained results suggested that this four compounds can be applicable as a drug molecule.

Target protein selection from skin pathogen *Streptococcus pyogenes*carried out from PDB (protein Data Bank). The PDB ID and its description enlisted in table no. 2. This significant compounds further proceed to study docking between ligand and proteins. PyRx data suggested Methyl oleate, Eicasanoic acid, Oleic acid, 5,8,11,14-eicosatetraenoic acid, methyl ester possessed lowest binding energy with 1B1Z(Streptococcal Pyrogenic Exotoxin A1).
This lowest binding energy gives more stable complex between drug and protein. Out of 4 compounds 5,8,11,14-eicosatetraenoic acid, methyl ester had most stable binding with 2ESR, 1XF1, 4CMQ, 1B1Z, 2Q7A, 6BZL, 6N0A, 3B2MC, 2Q7AA proteins. Methyl oleate and Eicasanoic acid showed most stable complex with 2YX2, 2Q7A A and 1Z0P, 3B2M B respectively. Lastly, oleic acid had better binding with 2OTO, 3B2M A, 3B2M C and 2Q7A B. Binding Interaction between target protein 1B1Zwith different ligands such asEicasanoic acid, Methyl oleate, Oleic acid, 5,8,11,14-eicosatetraenoic acid, methyl ester revealed in figure no. 1 - 4.

Advances in computational tools and techniques played important role in drug design and discovery process. To reduce the demerits of drug discovery such as cost, time and manpower etc, virtual screening procedures are routinely used. It utilizes docking and scoring of each phycocompounds from a datasets and predict the binding interaction between ligands and target proteins. Molecular docking techniques has helped important proceedings to drug discovery for a prolong time. It is helpful to study posing interaction as well as pose mode in binding pocket of a target protein and to predict binding property between them. All in all, this procedures will be lead to further pharmacological evaluation.

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Table: 1 Selection of marine algae and its phycocompounds for this study

COMPOUND NO.	NAME OF MOLECULE	SOURCE
	Brown algae*P. tetrastromatica*	
1	**Coumarin**	M. Uma Maheswari et al.(2017)
2	**Flavone**	
3	**7-Hydroxyflavone**	
4	**Methyl oleate**	
5	**Eicasanoic acid**	
6	**Oleic acid**	
	Green alga *C. peltata*	
7	**1-heptacosanol**	K. Murugan and V V. Iyer (2014)
8	**5,8,11,14-eicosatetraenoic acid, methyl ester**	
9	**Tetrahydro-6-nonyl-2H-pyran-2-one**	

Table: 2 Selection of target proteins with its description

NO.	PROTEIN ID	DESCRIPTION	SOURCE
1	1Z0P	Crystal structure of the Protein of Unknown Function SPY1572 from *Streptococcus pyogenes*	DOI: 10.2210/pdb1Z0P/pdb
2	2ESR	conserved hypothetical protein- *Streptococcus pyogenes*	DOI: 10.2210/pdb2ESR/pdb
3	2OTO	2OTO N-terminal fragment of *Streptococcus pyogenes* M1 protein	DOI: 10.2210/pdb2OTO/pdb
4	1XF1	Structure of C5a peptidase- a key virulence factor from Streptococcus	DOI: 10.2210/pdb1XF1/pdb
5	4CMQ	Crystal structure of Mn-bound *S.pyogenes* Cas9	DOI: 10.2210/pdb4CMQ/pdb
6	6N0A	Structure of the major pilin protein (T-18.1) from *Streptococcus pyogenes* serotype MGAS8232	DOI: 10.2210/pdb6N0A/pdb
7	2YX2	Crystal structure of cloned trimerichyluranidase from *Streptococcus pyogenes* at 2.8 A resolution	• DOI**:** 10.2210/pdb2YX2/pdb
8	1B1Z	*Streptococcal pyrogenic* EXOTOXIN A1	DOI: 10.2210/pdb1B1Z/pdb
9	6BZL	Solution structure of VEK75	DOI: 10.2210/pdb6BZL/pdbBMRB: 30391
10	3B2M	Crystal Structure of the Major Pilin from *Streptococcus pyogenes*	DOI: 10.2210/pdb3B2M/pdb
11	2Q7A	Crystal structure of the cell surface heme transfer protein Shp	DOI: 10.2210/pdb2Q7A/pdb

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Table: 3 Different properties of phycocompounds obtained from PubChem Database

No.	CAS Number	EC Number	Molecular Formula	Molecular Weight	Melting Point(^{0}C)	Boiling Point(^{0}C)
1.	**91-64-5**	202-086-7	C9H6O2	146.15	33.34	290.74
2.	**525-82-6**	208-383-8	C15H10O2	222.25	116.78	359.85
3.	**6665-86-7**	229-705-3	C15H10O3	238.24	151.33	394.69
4.	**112-62-9**	203-992-5	C19H36O2	296.5	80.09	352.56
5.	**506-30-9**	208-031-3	C20H40O2	312.54	149.51	405.25
6.	**112-80-1**	204-007-1	C18H34O2	282.47	132.66	385.62
7.	**2004-39-9**	217-906-9	C27H56O1	396.75	168.06	459.1
8.	**2566-89-4**	219-900-1	C2H34O2	318.5	84.46	386.49
9.	**2721-22-4**	220-334-2	C14H26O2	226.36	39.96	338.68

Table: 4 ADMET properties predicted by VEGA (Q)SAR

NO.	ID	SMILES	Mutagenicity (Ames test) CONSENSUS model	Carcinogenicity model (CAESAR)	Developmental Toxicity model (CAESAR)	Developmental/Reproductive Toxicity library (PG)	Skin Sensitization model (CAESAR)	Hepatotoxicity model (IRFMN)	Persistence (water) model (IRFMN)
1	520296	O=C1OC(CCC1)CCCCCCCCC	NON-Mutagenic 0.9	Carcinogen (LR)	NON-Toxicant (GR)	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (GR)
2	6421258	O=C(OC)CCCC=CCC=CCC=CCC=CCCCCC	NON-Mutagenic 0.75	NON-Carcinogen (GR)	NON-Toxicant (GR)	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (LR)
3.	323	O=C1Oc2ccccc2(C=C1)	Mutagenic 1	Carcinogen (MR)	Toxicant (EX)	Toxicant (EX)	NON-Sensitizer ((EX)	Unknown	nP (LR)
4.	10680	O=C1C=C(Oc2ccccc12)c3ccccc3	NON-Mutagenic 0.5	NON-Carcinogen (LR)	Toxicant (GR)	NON-Toxicant (LR)	Sensitizer (MR)	Unknown	nP (LR)
5.	5281894	O=C1C=C(Oc2cc(O)ccc12)c3ccccc3	NON-Mutagenic (0.5)	Carcinogen (LR)	Toxicant (GR)	Toxicant (MR)	Sensitizer(MR)	Toxic(LR)	nP (LR)
6.	10647	O=C(O)CCCCCCCCCCCCCCCCCCC	NON-Mutagenic (0.9)	NON-Carcinogen (LR)	NON-Toxicant (GR)	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (GR)
7.	5364509	O=C(OC)CCCCCCCC=CCCCCCCCC	NON-Mutagenic	NON-Carcinogen	NON-Toxicant	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (LR)

			(1)	(LR)	(MR)				
8.	445639	O=C(O)CCCCCCCC=CCCCCCCCC	NON-Mutagenic (1)	NON-Carcinogen (GR)	NON-Toxicant (GR)	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (MR)
9.	74822	OCCCCCCCCCCCCCCCCCCCCCCCCCC	NON-Mutagenic (0.67)	Carcinogen (LR)	Toxicant (LR)	NON-Toxicant (LR)	Sensitizer (GR)	Unknown	nP (GR)

GR: GOOD RELIABILITY, LR: LOW RELIABILITY, MR: MODERATE RELIABILITYEX: EXPERIMENTAL VALUE

Table: 5ADMET properties predicted by DANISH (Q)SAR

COMP.NO.	ESTIMATED SOLUBILITY Log SCORE	ESTIMATED SOLUBILITY CLASS	GASTROINTESTINAL ABSORPTION 1 mg DOSE(%)	SKIN DERMAL ABSORPTION	BLOOD BRAIN BARRIER PENETRATION	LIPINSKI VIOLATIONS	TOXICITY	CARCINOGENICITY
1	-2.37	Soluble	90	0.018	0.103	0	POS_IN	POS_IN
2	-3.74	Soluble	100	0.0081	0.503	0	POS_OUT	NEG_IN
3	-3.45	Soluble	100	0.00497	0.2047	0	POS_OUT	NEG_IN
4	-4.68	Soluble	100	7.91	1.405	1	NEG_IN	NEG_IN
5	-5.32	Soluble	100	6.39	1.477	1	NEG_IN	NEG_IN
6	-4.55	Soluble	100	0.000239	1.237	1	NEG_IN	NEG_IN
7	-7.23	Soluble	100	4.32	2.29897	1	NEG_IN	NEG_IN
8	-4.53	Soluble	100	3.44	1.471	1	NEG_IN	NEG_IN
9	-3.78	Soluble	100	0.001	0.707001	1	NEG_IN	NEG_IN

Table: 6 ADMET properties predicted by DANISH (Q)SAR

No.	Name of Molecule	Severe Skin Irritation In Rabit	Allergic Contact Dermatitis In Human	Respiratory Sensitization In Human	Mutagenicity Ames Test	In Vitro HGPRT Test	Other Effect
1.	**Coumarin**	NEG_OUT	POS_OUT	INC_OUT	INC_OUT	NEG_IN	T, R
2.	**Flavone**	NEG_IN	POS_IN	INC_OUT	NEG_IN	POS_IN	M
3.	**7 Hydroxyflavone**	NEG_IN	POS_IN	POS_IN	NEG_IN	INC_OUT	NT, NM, NI,NR
4.	**Methyl oleate**	POS_OUT	NEG_IN	NEG_IN	NEG_IN	NEG_IN	NT, NM, NI,NR
5.	**Eicasanoic acid**	NEG_IN	NEG_IN	INC_OUT	NEG_IN	NEG_IN	NT, NM, NI,NR

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6.	**Oleic acid**	POS_OUT	NEG_IN	INC_OUT	NEG_IN	NEG_IN	NT, NM, NI,NR
7.	**1-heptacosanol**	NEG_IN	NEG_IN	NEG_IN	NEG_IN	NEG_IN	I, NT, NM,NR
8.	**5,8,11,14-eicosatetraenoic acid, methyl ester**	NEG_IN	NEG_IN	NEG_IN	NEG_IN	NEG_IN	NT, NM, NI,NR
9.	**Tetrahydro-6-nonyl-2H-pyran-2-one**	NEG_OUT	NEG_IN	NEG_IN	NEG_IN	NEG_IN	NT, NM, NI,NR

NT: Non Tumorigenic, NM: Non Mutagenic, NI: Non Irritant, NR: No Reproductive Effect
T: Tumorigenic, M: Mutagenic, I: Irritant, R: Reproductive Effect

Table: 7 Binding energy predicted by PyRx software for different phycocompounds

Different Phycocompounds	1Z0P	2ESR	2OTO	1XF1	4CMQ	6N0A	2YX2	1B1Z	6BZL
5,8,11,14-eicosatetraenoic acid, methyl ester	-5.4	-5.0	-3.9	-5.4	-4.8	-5.6	-3.5	-7.0	-3.8
Methyl oleate	-5.1	-3.7	-4.2	-5.0	-3.7	-5.0	-3.9	-6.8	-3.2
Oleic acid	-5.3	-4.6	-4.8	-4.7	-4.5	-5.3	-3.6	-6.7	-2.8
Eicasonoic acid	-5.5	-4.3	-3.1	-5.0	-4.0	-5.1	-2.9	-6.8	-3.3

Table: 8 Binding energy predicted by PyRx software

Different Phycocompounds	3B2MA	3B2MB	3B2MC	2Q7A A	2Q7A B
5,8,11,14-eicosatetraenoic acid, methy ester	-3.5	-3.5	-3.5	-4.5	-3.7
Methyl oleate	-2.8	-2.8	-2.8	-4.5	-3.8
Oleic acid	-4.1	-3.5	-3.5	-4.1	-4.3
Eicasonoic acid	-3.7	-3.7	-2.8	-4.3	-4.0

Fig.1 Binding Interaction between Eicasanoic acid + 1B1Z

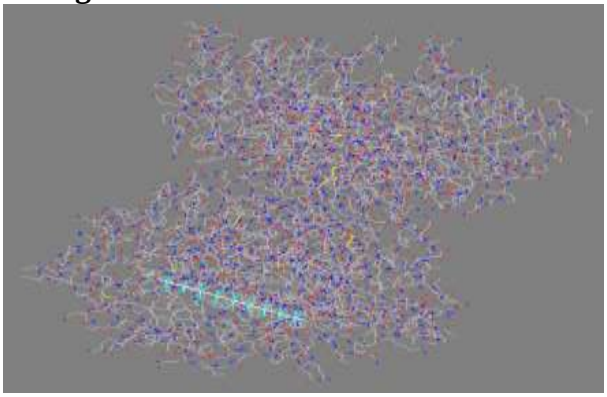


Fig.2 Binding Interaction between Methyl oleate+ 1B1Z

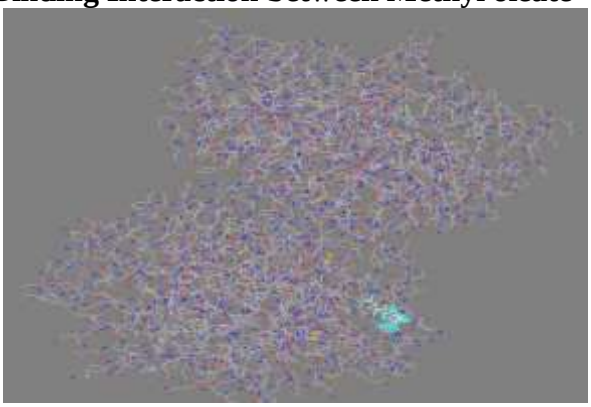


Fig.3 Binding Interaction between Oleic acid+ 1B1Z

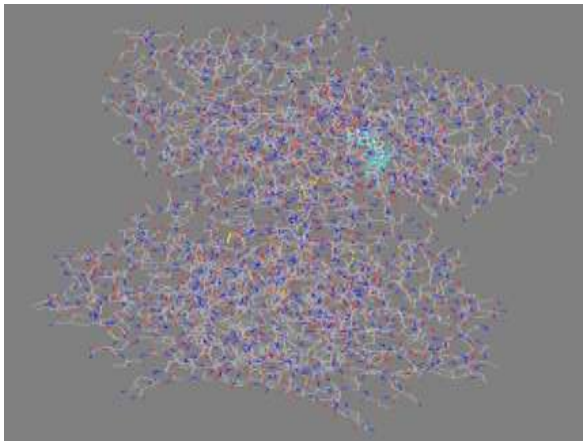
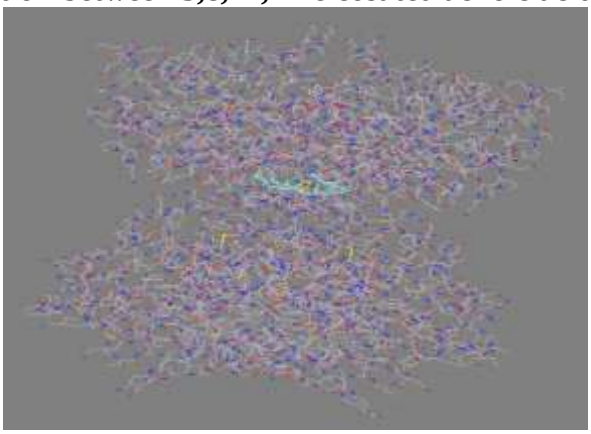


Fig.4 Binding Interaction between 5,8,11,14-eicosatetraenoic acid, methyl ester+ 1B1Z



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