

TITLE: 3D-QSAR AND MOLECULAR DOCKING OF INDOLO[3,2-C] QUINOLONE ANALOGUES FOR ANTIPLASMODIAL ACTIVITY

Running Title: Antiplasmodial activity of Indolo quinolone analogues

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Abstract:

As per the 2020 World Malaria Report, an approximate of 429000 fatalities worldwide were attributed to malaria. In order to treat the various underlying deficiencies of the pathology of malaria and to overcome the limitations of monotherapy, contemporary medications are being utilized as useful adjuncts to dietary therapeutic strategies, either alone or in combination. In recent times, heterocyclic compounds have become increasingly significant due to their pharmacological properties. *in silico* virtual screening and molecular docking are valuable techniques in drug discovery and development. These methods leverage computational approaches to analyze and predict the interactions between small molecules (ligands) and biological macromolecules, such as proteins. As a result, this research effort uses a contemporary *in silico* virtual screening technique to prioritize unique One hundred twenty-five compounds were proposed as antimalarials based on the reported structure-activity relationship of Indolo[3,2-c] quinolone analogues as well as QSAR research using CoMFA, CoMSIA, HQSAR, and Molecular modeling (Docking) studies. To get more models, QSAR research have also been carried out. The time, money, and human resources required to get the medication to patients are reduced by QSAR.

Key words: QSAR, CoMFA, CoMSIA, HQSAR, *in silico* virtual screening, β -haematin inhibitory activity, antiplasmodiam activity.

INTRODUCTION:

The female Anopheles mosquito transmits malariaan infectious condition caused by a blood-borne Plasmodium protozoan (P). The apical complex, a particular organelle that allows parasites to infiltrate their intended host cells, is what makes this genus a member of the phylum Apicomplexa. The genus Plasmodium consists of various species of parasites, and some of them can infect humans, causing malaria. The five species of the Plasmodium parasite that commonly infect humans are:-Plasmodium Falciparum, **vivax, malariae knowlesi, Plasmodium ovale.** This species is responsible for the majority of malaria cases and is often associated with severe and potentially fatal infections. ¹

Reports from ancient China's medical records date the symptoms of malaria to approximately 2700 BC.² Many years later, in 1847, German physician Meckel identified significant amounts of dark colored patches from the blood, liver, and spleen of a mentally ill patient that he dubbed "melanin," but he was unable to correlate this unusual Initially.² It was thought that the body created this pigment in an effort to fight off the infection.³ But in 1880, while analyzing recently tainted blood from a patient suffering from malaria, French army surgeon Charles Laveran discovered the missing link between this pigment and the protozoan parasite that was causing it.⁴ Decades later, pathologists still utilize this pigment, now known as "hemozoin" (Hz), as a critical component in the diagnosis of this illness.⁵⁻⁶

QSAR

Quantitative Structure-Activity Relationship (QSAR) is a powerful analytical tool used in medicinal chemistry and drug design to establish a quantitative relationship between the structural features of molecules and their biological activities. QSAR models help predict the activity of new compounds based on their chemical structure, enabling researchers to prioritize and design molecules with desired properties. QSAR is a modeling technique that correlates the "physio chemical properties or structural features of a compound with its biological activity. It is widely employed in biological, environmental, medical, physical organic, and agricultural research and is regarded as a major technique of chemical research worldwide today ⁷. When attempting to explain the connections between chemical structure and experimental results, QSAR is a very useful tool. The quality of the observed data, the statistical techniques employed, and the numerical descriptors that convert a chemical structure into mathematical variables are important components of the methodology. ⁸

Inter molecular forces and various analyses, such as Hansch analysis, Free Wilson analysis, and CoMFA, play a crucial role in understanding how medications interact with biological equivalents (CoMFA). ⁹ quantitative structure-activity relationships (QSAR) derive models that describe the structural dependence of biological activities.

Drugs that interact with specific targets, such as enzymes, receptors, ion channels, nucleic acids, or other biological macro molecules, play a crucial role in medicine. Here are some examples of drugs that target specific biological molecules: to produce biological effects, need to have a three-dimensional structure that is roughly complementary to a binding site in terms of both surface properties and functional group arrangement ¹⁰. As a first approximation, the following can be

said: a drug's affinity and potential biological activity will increase with improved steric fit and complementation of its surface qualities to its binding site.

Quantitative Structure-Activity Relationship (QSAR) equations. QSAR equations mathematically express the quantitative relationship between the biological activity of a molecule and various structural or physicochemical descriptors. The general form of a QSAR equation is: Biological Activity= f (parameters)

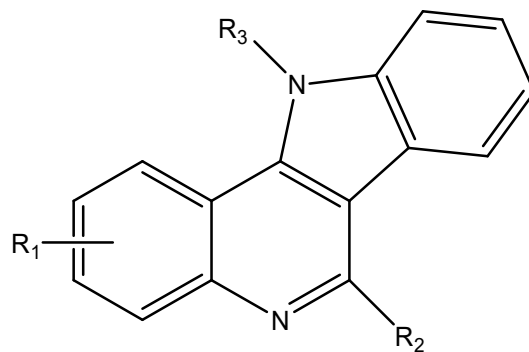
which often expresses the activity as $\log[1/(\text{concentration term})]$, where C is the minimal concentration needed to elicit a certain biological reaction.¹¹ Other factors must be more crucial to the drug's action in cases where there is a weak association between the values of that parameter and the drug's activity.

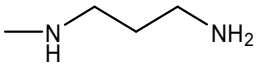
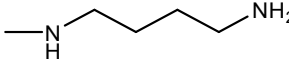
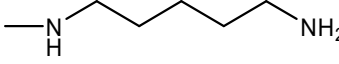
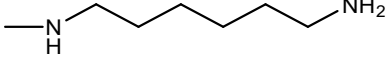
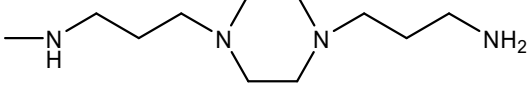
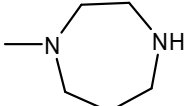
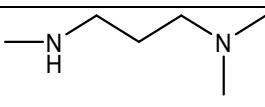
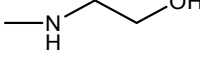
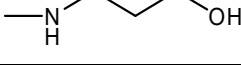
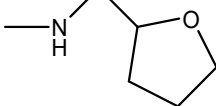
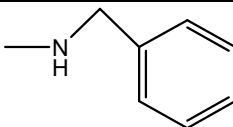
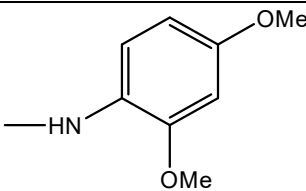
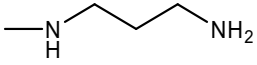
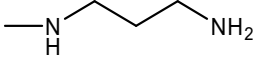
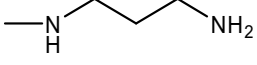
Docking studies When docking the ligand to protein the process undergoes a search of different position and confirmation with in the protein.¹²


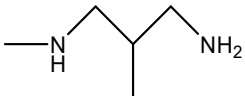
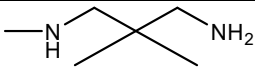
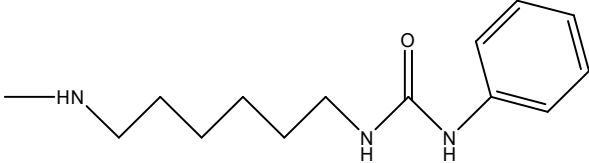
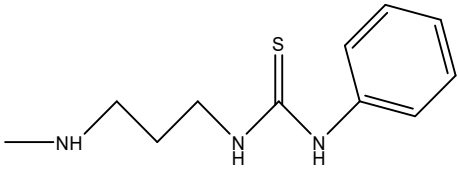
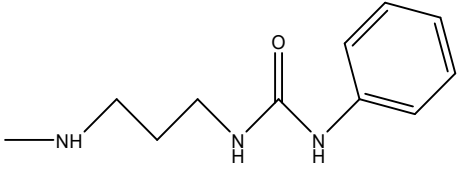
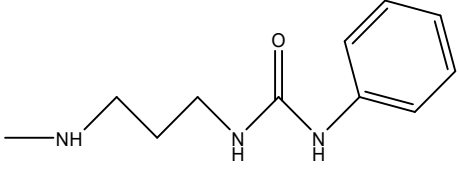
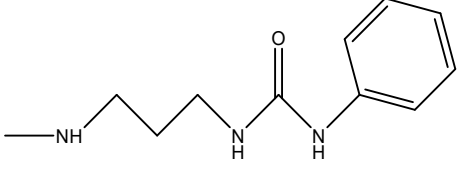
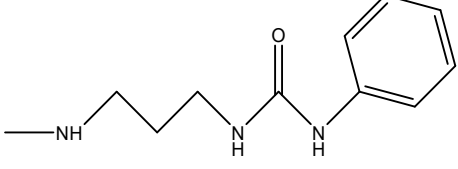
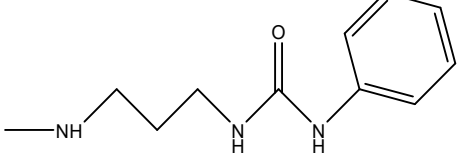
MATERIALS AND METHODS:

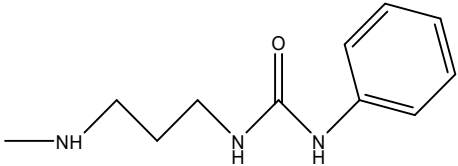
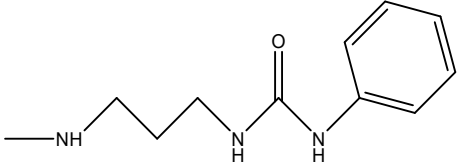
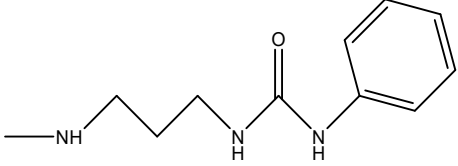
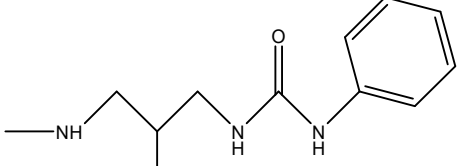
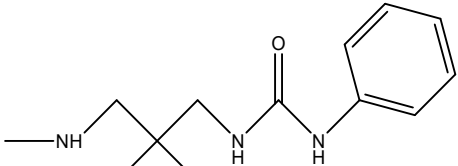
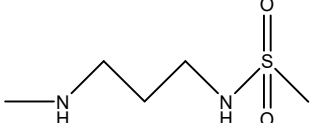
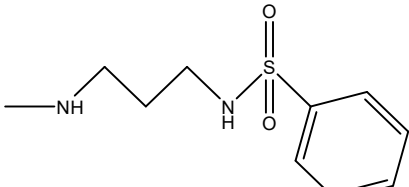
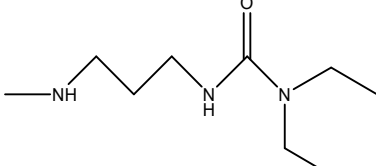
a specific study conducted by N. Wang and colleagues in 2014. In this study, the researchers investigated Isocryptolepine analogues and their biological activities, specifically focusing on their Antiplasmodial activity and β -haematin inhibitory activity. Isocryptolepine is an indoloquinoline alkaloid known for its potential antiplasmodial (antimalarial) properties.¹³ [BHIA] against *P. falciparum* (CQS, NF54 strain), cytotoxicity towards L6 cells, and both.¹⁴⁻¹⁵ The datasets were split into training and test sets, each with 10 compounds, using the random method to add QSAR modeling, achieving quantitative structure-activity relationship (QSAR) models and computational drug discovery in general—namely, the importance of structural diversity and a comprehensive representation of biological activities in the dataset. This allowed researchers to assess The predictive power of Quantitative Structure-Activity Relationship (QSAR) models is a crucial aspect in their utility for drug discovery and design. pIC_{50} was created using the IC_{50} values to provide numerically greater data values.¹⁶

Table 1: Indolo[3,2-c] quinoline analogues with different substitution on R₁, R₂ and R₃



SN	R ₁	R ₂	R ₃
1	H	Cl	H
2	H		H
3	H		H
4*	H		H
5	H		H
6	H		H
7	H		H
8	H		H
9	H		H
10	H		H
11	H		H
12	H		H
13	H		H
14*	2-F		H
15	2-Br		H
16	2-Me		H

17*	2-Cl		H
18	2-Cl		H
19	2-Cl		H
20	H		H
21*	H		H
22	H		H
23	2-F		H
24*	1-Br		H
25	2-Br		H
26	2-Me		H

27	2-MeO		H
28	2-NO ₂		H
29	2-Cl		H
30	2-Cl		H
31	2-Cl		H
32*	H		H
33	H		H
34*	H		H

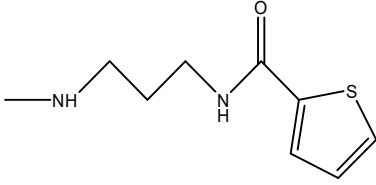
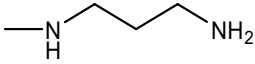
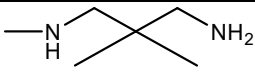
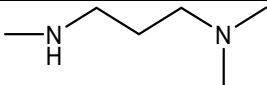

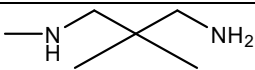
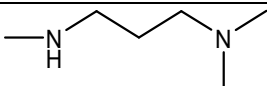
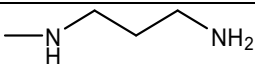
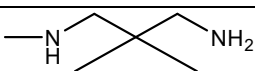
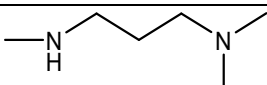
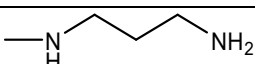


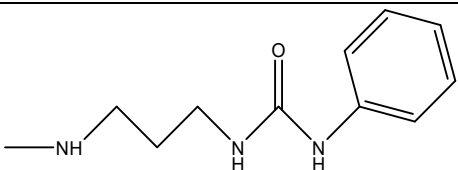
35	H		H
36	H	Cl	Me
37	H		Me
38*	H		Me
39	H		Me
40	2-Br		Me
41	2-Br		Me
42	2-Br		Me
43	2-Cl		Me
44	2-Cl		Me
45	2-Cl		Me
46	2-F		Me
47	2-Me		Me
48*	2-MeO		Me
49*	H		Me
	*test set		

Table 2: Isocryptolepine analogues with their different biological activity

S N	IC ₅₀ NF54(nM)	pIC ₅₀ (NF54)	IC ₅₀ L6(nM)	pIC ₅₀ (L6)	SI (L6/NF54)	pIC ₅₀ (SI)	βHI IC ₅₀ (uM)	βHI pIC ₅₀
1	10209.7	4.991	192956. 1	3.7145	18.9	7.7235	-	-
2	13.7	7.8633	626.8	6.2029	45.8	7.3391	116.3	3.9344
3	36.1	7.4425	739.1	6.1313	20.5	7.6882	62	4.2076
4	12.6	7.8996	816.5	6.088	64.8	7.1884	81	4.0915
5	15	7.8239	1182.1	5.9273	78.8	7.1035	49.6	4.3045
6	26.4	7.5784	1776.4	5.7505	67.3	7.172	62.4	4.2048
7	63.2	7.1993	4108.7	5.3863	65	7.1871	171	3.767
8	9.4	8.0269	606.1	6.2175	64.3	7.1918	83.6	4.0778
9	140.6	6.852	890.6	6.0503	6.3	8.2007	200	3.699
10	226.5	6.6449	717.4	6.1442	3.2	8.4948	286.7	3.5426
11	113.4	6.9454	2051.1	5.688	18.1	7.7423	147.8	3.8303
12	18.6	7.7305	2934.5	5.5325	157.8	6.8019	30.6	4.5143
13	316.7	6.4994	15213	4.8178	48	7.3188	44.1	4.3556
14	13	7.8861	638.9	6.1946	49.1	7.3089	14.3	4.8447
15	8.1	8.0915	891	6.0501	110	6.9586	19.4	4.7122
S N	IC ₅₀ NF54(nM)	pIC ₅₀ (NF54)	IC ₅₀ L6(nM)	pIC ₅₀ (L6)	SI (L6/NF54)	pIC ₅₀ (SI)	βHI IC ₅₀ (uM)	βHI pIC ₅₀
16	36.1	7.4425	322	6.4921	8.9	8.0506	60.9	4.2154
17	6.2	8.2076	1120.7	5.9505	180.8	6.7428	12.4	4.9066
18	29.5	7.5302	1918.4	5.7171	65	7.1871	12.7	4.8962
19	25.5	7.5935	1839.3	5.7353	72.1	7.1421	20.7	4.684
20	22.1	7.6556	861.5	6.0647	39	7.4089	16.2	4.7905
21	23.5	7.6289	249.1	6.6036	10.6	7.9747	18.5	4.7328
22	2.4	8.6198	1152.6	5.9383	480.3	6.3185	23.9	4.6216
23	25.7	7.5901	1504.2	5.8227	58.5	7.2328	22.7	4.644
24	288.7	6.5396	3624.2	5.4408	12.6	7.8996	22	4.6576
25	22.5	7.6478	1281.1	5.8924	56.9	7.2449	13.9	4.857
26	23.6	7.6271	965.7	6.0152	40.9	7.3883	17.2	4.7645
27	17.1	7.767	1517.8	5.8188	88.8	7.0516	14.8	4.8297
28	24.2	7.6162	4642.7	5.3332	191.8	6.7172	15.2	4.8182
29	27	7.5686	2568	5.5904	95.1	7.0218	14.4	4.8416
30	10.9	7.9626	4105.3	5.3867	376.6	6.4241	14.6	4.8356
31	10.6	7.9747	4004.4	5.3975	377.8	6.4227	11.7	4.9318
32	54.3	7.2652	1063.9	5.7043	19.6	7.7077	118.5	3.9263

33	72	7.1427	810.6	6.0912	11.3	7.9469	24.2	4.6162
34	41.1	7.3862	3568.8	5.4475	86.8	7.0615	39.2	4.4067
35	72.4	7.1403	3495.6	5.4565	48.3	7.3161	24.1	4.618
36	7386	5.1316	17284	4.7624	2.3	8.6383	-	-
37	72.3	7.1409	279.2	6.5541	3.9	8.4089	24.2	4.6162
38	273.7	6.5627	258.7	6.5872	0.9	9.0458	-	-
39	93.2	7.0306	700.8	6.1544	7.5	8.1249	-	-
40	31.3	7.5045	824.5	6.0838	26.3	7.58	26.6	4.5751
41	58.3	7.2343	576.2	6.2394	9.9	8.0044	41.2	4.3851
42	48.6	7.3134	457	6.3401	9.4	8.0269	39.9	4.399
43	35.4	7.451	619.8	6.2077	17.5	7.757	28	4.5528
44	95.4	7.0205	425.2	6.3714	4.5	8.3468	38.4	4.4157
45	40.9	7.3883	313.4	6.5039	7.7	8.1135	25.9	4.5867
46	52.7	7.2782	291.6	6.5352	5.5	8.2596	25.8	4.5884
47	31.4	7.5031	191.6	6.7176	6.1	8.2147	29.5	4.5302
48	32.9	7.4828	137.6	6.8614	4.2	8.3768	56.9	4.2449
49	7.3	8.1367	107.7	6.9678	14.8	7.8297	22.7	4.644

RESULT AND DISCUSSION:

A molecular modeling study conducted using the SYBYL X2.0 software on a workstation with a Core-2 Duo Intel processor. The molecules that were to be analyzed were lined up on a suitable template, which is thought to be standard substructure.

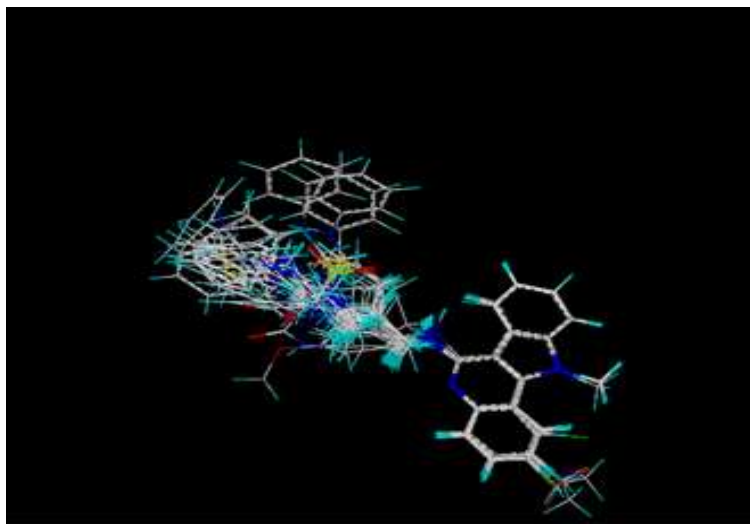


Fig.1. Structure alignment of Isocryptolepine analogues

CoMFA

Comparative Molecular Field Analysis (CoMFA) in your computational chemistry and quantitative structure-activity relationship (QSAR) studies. Additionally, you've used various methods, such as Gasteiger, Gasteiger–Hückel, MMFF, Del-Re, and Pullman charges, to calculate partial charges on the molecules and models.¹⁷

CoMSIA (Comparative Molecular Similarity Indices Analysis), which is another widely used method in computational chemistry, particularly in the field of quantitative structure-activity relationship (QSAR) studies. CoMSIA is an extension of CoMFA and includes additional descriptors to further enhance the understanding of molecular interactions.^{18,19}

HQSAR

Utilizing specialized fragment fingerprints as predictive variables of biological activity, HQSAR is a novel 2D-QSAR approach. Three parameters affect hologram production in HQSAR: hologram length, hologram size, and fragment distinction. Additionally, 3D alignment is not necessary for the production of models. The pieces that are distinct are the atoms (A), bonds (B), connections (C), hydrogen atoms (H), chirality (Ch), and donor (D)²⁰. First, several models were created with various components and the 4–7 fragment size as the default.

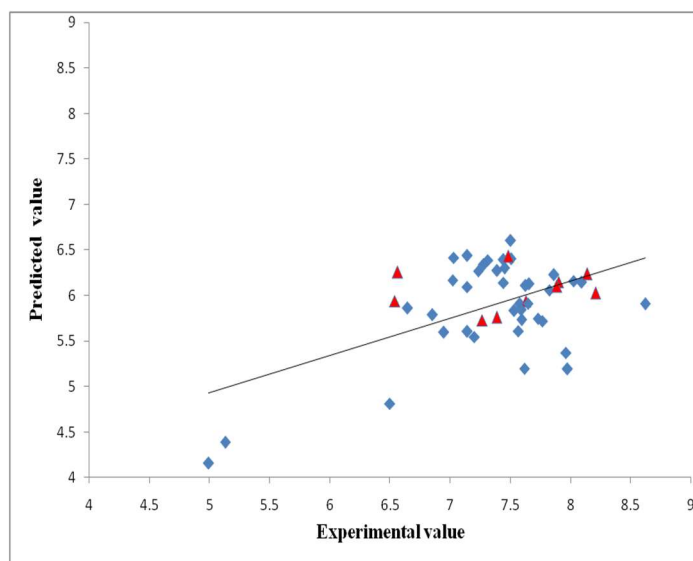


Fig.-2. Correlation graph between experimental and predicted activities of training set and test set molecules based on CoMFA model.

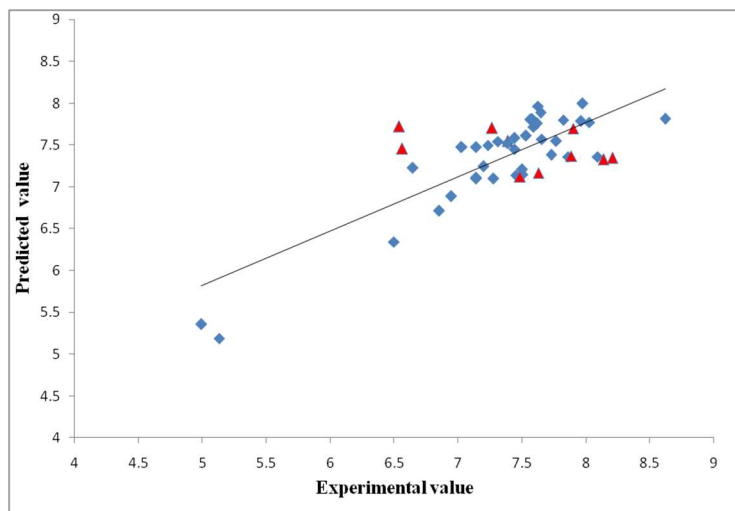


Fig. 3. Correlation graph between experimental and predicted activities of training set and test set molecules based on CoMSIA model.

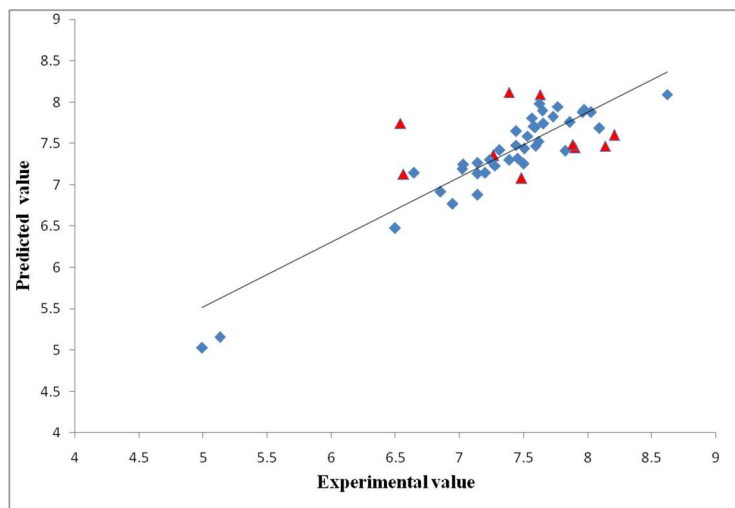


Fig.4. Correlation graph between experimental and predicted activities of training set and test set molecules based on HQSAR model.

Docking Analysis

docking studies using the Surflex Dock module in SYBYL X2.0 software and utilized protein structures from the RCSB Protein Data Bank with the PDB entry codes 3DGA and 3QG2. Molecular docking is a computational technique used to predict the preferred orientation of one molecule (the ligand) when bound to another molecule (the target or receptor) to form a stable complex.). Energy minimization and charge calculation were applied to the protein structure (AMBER7FF99). Following that, the docking methodology was examined and validated using the known complex protein structure. Every ligand and water molecule was eliminated. For the creation of protomol, the bloat values were set to 1 and the threshold values to 0.5, and the positioEnergy minimization and charge calculation are common steps in preparing a protein

structure for molecular docking studies. Energy minimization and charge calculation are common steps in preparing a protein structure for molecular docking studies.²⁰

Table 3: Comparison of Docking score of Compounds on 3DGA and 3QG2 PDB

3DGA			3QG2		
SN	COMPOUND NO.	TOTAL SCORE	SN	COMPOUND NO.	TOTAL SCORE
1	5	8.55	1	25	7.78
2	23	8.49	2	32	7.76
3	48	8.26	3	18	7.29
4	38	8.11	4	37	7.05
5	47	8.01	5	2	7.04
6	40	7.89	6	23	7.01
7	20	7.76	7	3	7
8	37	7.74	8	38	6.95
9	3	7.67	9	22	6.92
10	33	7.59	10	6	6.84
11	49	7.5	11	16	6.79
12	26	7.49	12	5	6.63
13	41	7.28	13	40	6.51
14	15	7.22	14	45	6.46
SN	COMPOUND NO.	TOTAL SCORE	SN	COMPOUND NO.	TOTAL SCORE
15	25	7.13	15	17	6.31
16	4	7.11	16	4	6.25
17	10	7.06	17	26	6.24
18	2	7.04	18	46	6.21
19	6	6.94	19	47	6.13
20	30	6.91	20	33	6.11
21	27	6.84	21	27	5.97
22	28	6.77	22	15	5.95
23	32	6.69	23	49	5.94
24	22	6.54	24	20	5.83

25	19	6.36	25	48	5.73
26	43	6.36	26	10	5.52
27	17	6.27	27	39	5.52
28	8	6.16	28	9	5.5
29	18	6.04	29	19	5.48
30	14	6.03	30	24	5.31
31	31	5.94	31	30	5.3
32	34	5.91	32	12	5.16
33	29	5.76	33	28	5.12
34	45	5.67	34	8	5.09
35	46	5.62	35	41	5.03
36	16	5.62	36	29	4.98
37	35	5.61	37	43	4.97
38	42	5.55	38	14	4.89
SN	COMPOUND NO.	TOTAL SCORE	SN	COMPOUND NO.	TOTAL SCORE
39	39	5.39	39	35	4.88
40	44	5.3	40	21	4.86
41	11	5.08	41	34	4.7
42	24	5.06	42	44	4.66
43	7	5	43	42	4.45
44	21	4.71	44	13	4.28
45	13	4.62	45	11	4.09
46	9	4.24	46	31	3.78
47	12	3.85	47	7	3.6
48	36	2.58	48	36	2.18

CONCLUSION:

The CoMFA, CoMSIA and For isocryptolepine derivatives, HQSAR models demonstrated significant statistical significance in internal validation (q^2), external validation (r^2), and anticipated r^2 (10 test set). The three-layered QSAR technique produced models with easy-to-use, correlative, and predictive capabilities. Hierarchical Quantitative Structure-Activity Relationship (HQSAR), Comparative Molecular Field Analysis (CoMFA), and Comparative Molecular Similarity Indices Analysis (CoMSIA) are all computational methods used in the field of

cheminformatics and computational chemistry to understand the relationship between chemical structure and biological activity of compounds. Sufficient information was disclosed by the CoMFA, CoMSIA, and HQSAR contour maps to comprehend the structure-activity relationship (SAR) and identify structural elements impacting inhibitory activity. One hundred and twenty-five new antimalarials were successfully created, with good projected activities in all three applicable computational techniques, based on the SAR research produced by molecular modeling analysis.

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