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3D-QSAR and Molecular docking of Indolo[3,2-c] quinolone analogues for Antiplasmodial activity

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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.

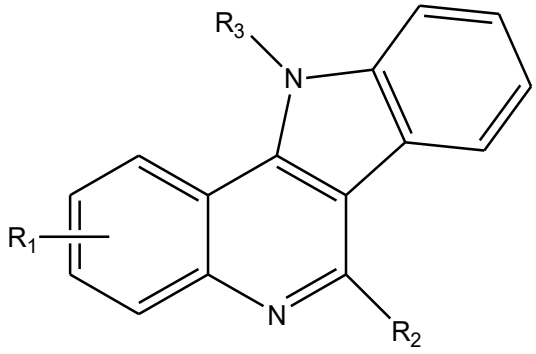
Quantitative Structure-Activity Relationship (QSAR) equations. QSAR equations mathematically express the quantitative relationship between the biological activity of a molecule and various structural or physicochemical descriptors. The general form of a QSAR equation is: Biological Activity=*f*(parameters) which often expresses the activity as log[1/(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 postion 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] [βHIA] 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 assessThe 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 IC50 values to provide numerically greater data values .[16]

Table 1: Indolo[3,2-c] quinoline analogues with different substitution on R_1, R_2 and R_3



SN	R_1	R_2	R_3
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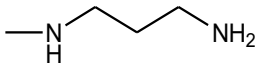
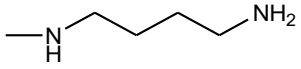
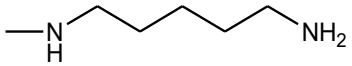
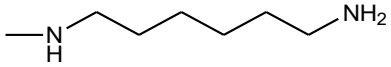
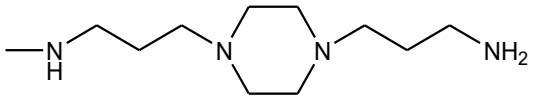
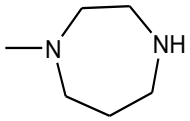
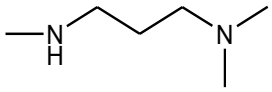
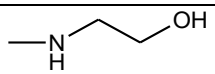
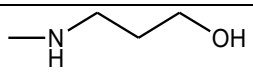
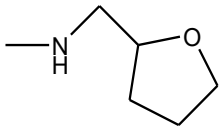
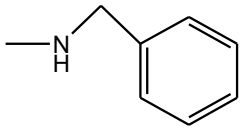
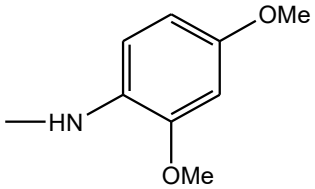
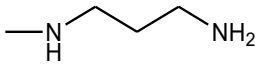
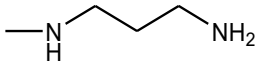
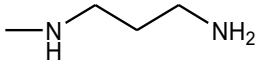
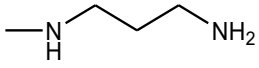
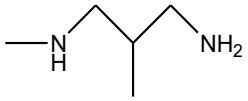
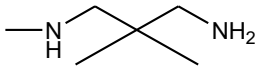
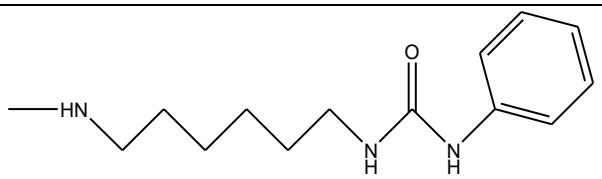
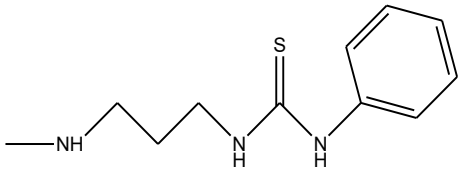
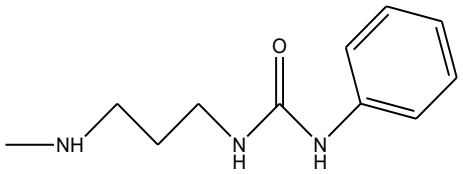
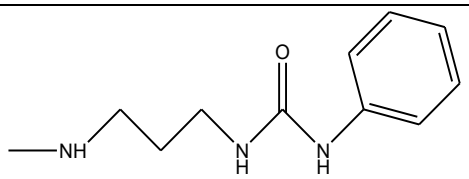
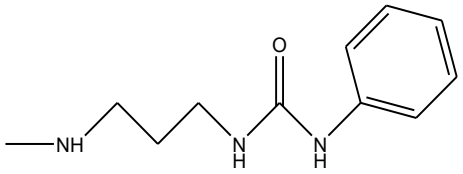
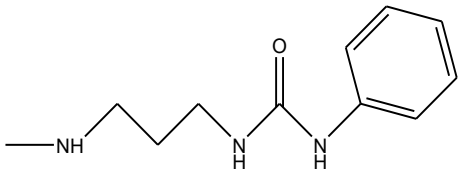
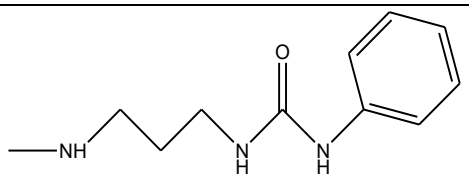
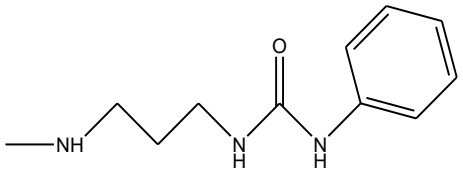
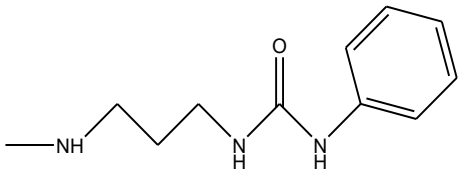
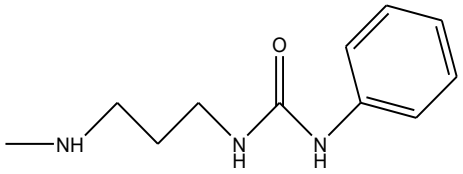
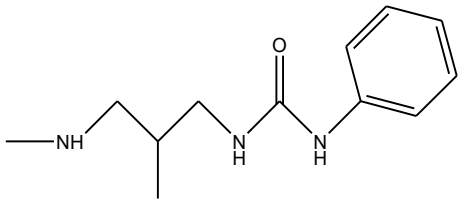
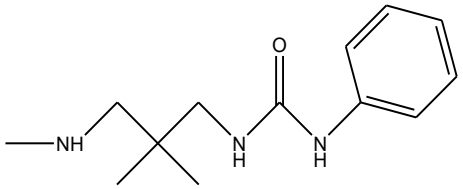
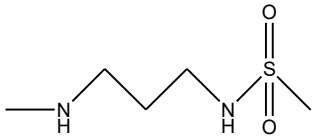
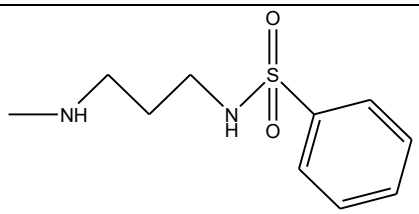
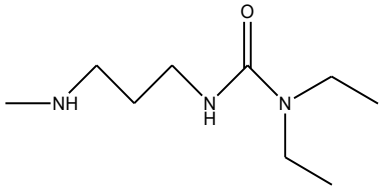
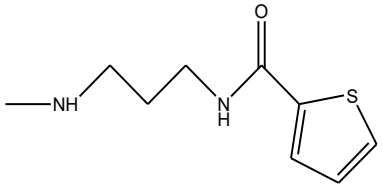
2	H		H
3	H		H
4*	H		H
5	H		H
6	H		H
7	H		H
8	H		H
9	H		H
10	H		H
11	H		H
12	H		H
13	H		H
14*	2-F		H
15	2-Br		H
16	2-Me		H
17*	2-Cl		H

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
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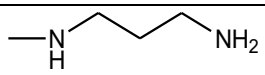
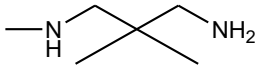
37	H		Me
38*	H		Me

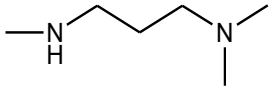
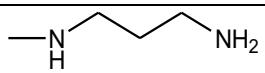
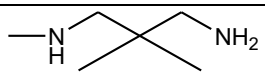
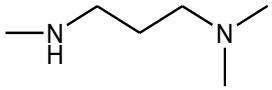
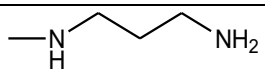
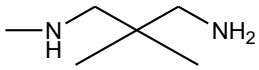
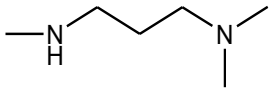
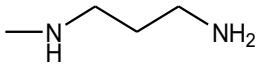
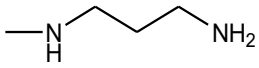
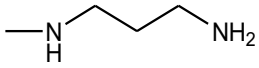
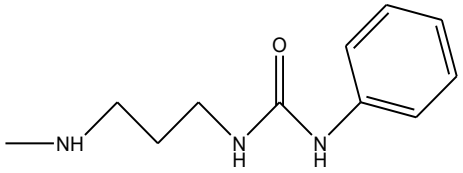
39	H		Me
40	2-Br		Me
41	2-Br		Me
42	2-Br		Me
43	2-Cl		Me
44	2-Cl		Me
45	2-Cl		Me
46	2-F		Me
47	2-Me		Me
48*	2-MeO		Me
49*	H		Me
	*test set		

Table 2: Isocryptolepine analogues with their different biological activity

SN	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
SN	**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.

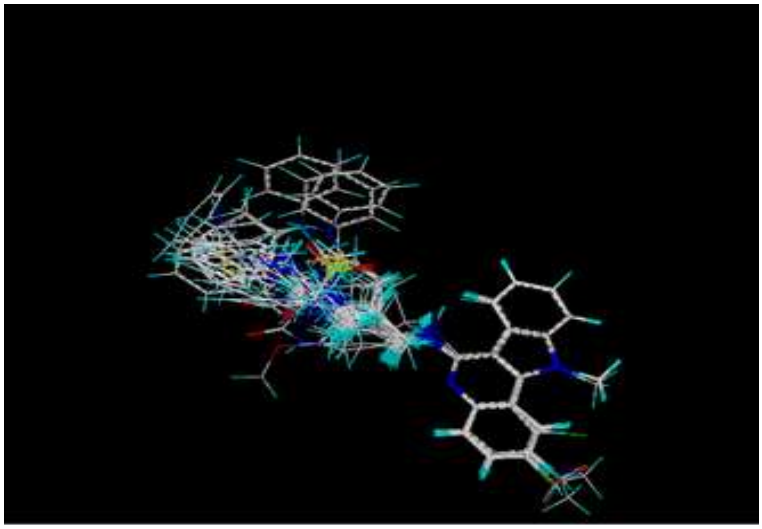


Fig.1.Structure alignment of Isocryptolepine analogues

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.

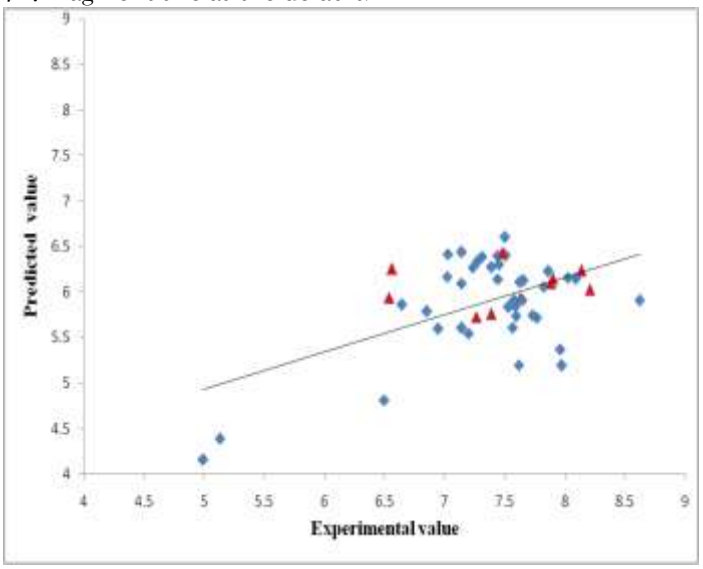


Fig.-2. Correlation graph between experimental and predicted activities of training set and test set molecules based on CoMFA model.

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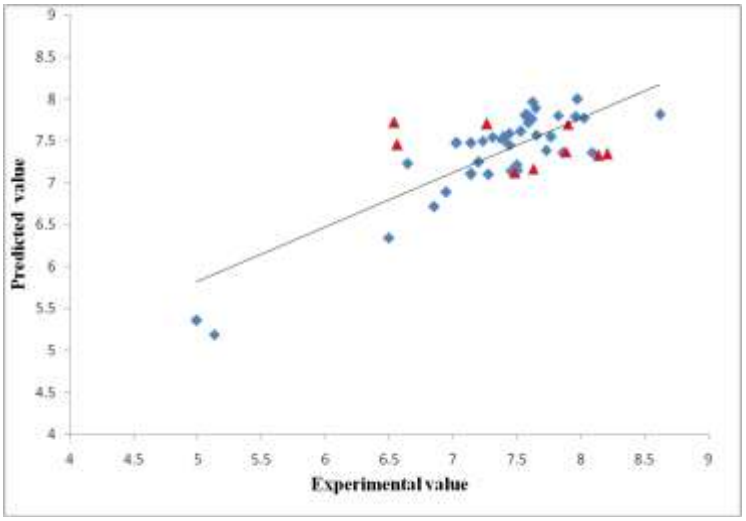

Fig. 3. Correlation graph between experimental and predicted activities of training set and test set molecules based on CoMSIA model.

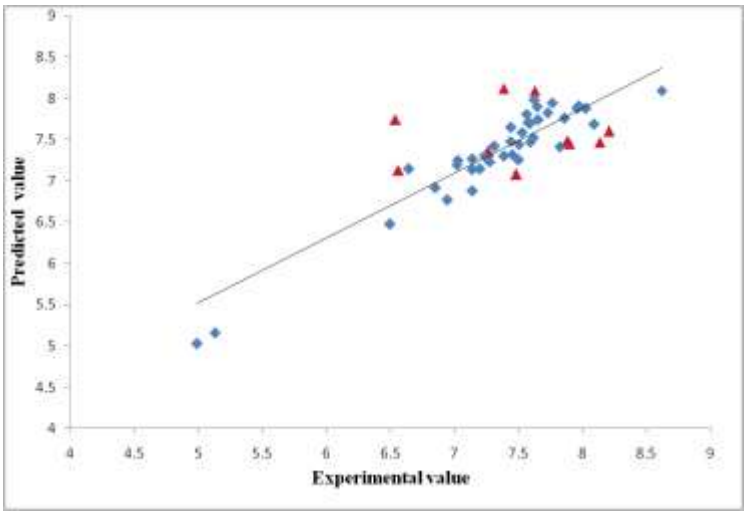

Fig.4. Correlation graph between experimental and predicted activities of training set and test set molecules based on HQSAR model.

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 (q2), external validation (r2), and anticipated r2 (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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