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COMPUTER AIDED DRUG DESIGN OF ANTIMALARIAL COMPOUNDS FOR THE DEVELOPMENT OF SIGNIFICANT MODELS

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ABSTRACT

The increasing emergence of drug-resistant *Plasmodium falciparum* strains has emphasized the need for the development of novel antimalarial agents. The present study employed computer-aided drug design (CADD) and quantitative structure–activity relationship (QSAR) techniques to develop predictive models for antimalarial quinazoline derivatives. A dataset of 100 quinazoline-based compounds with reported antiplasmodial activity (IC_{50} values) was compiled from published literature. Molecular structures were generated using ChemDraw Ultra 8.0, while molecular descriptors including surface area, volume, hydration energy, logP, refractivity, polarizability, and energy parameters were calculated using HyperChem 7.0 and Chem3D Ultra 8.0. Least-squares linear regression analysis was performed to establish relationships between molecular descriptors and biological activity. The developed QSAR models demonstrated good agreement between experimental and predicted biological activities for the majority of compounds, with only a limited number of outliers. The study identified key physicochemical and structural parameters governing antimalarial activity, providing valuable insights for the rational design and optimization of quinazoline-based antimalarial agents. These findings highlight the usefulness of QSAR modeling as a rapid and cost-effective approach for virtual screening and lead optimization in antimalarial drug discovery.

KEYWORDS: Computer-Aided Drug Design (CADD), Quantitative Structure–Activity Relationship (QSAR), Antimalarial agents, Quinazoline derivatives, HyperChem, Chem3D Ultra.

1. INTRODUCTION

1.1. Quantitative Structure Activity Relationship

Drug design is an iterative process, which begins with a compound that displays an interesting biological profile and ends with optimizing both the activity profile for the molecule and its chemical synthesis. The information feeding the drug design effort is increasingly quantitative, building upon recent developments in molecular structure description, combinatorial mathematics, statistics, and computer simulations. Collectively these areas have led to a new paradigm in drug design, which has been referred to as quantitative information analysis. Traditionally, the process of drug development has revolved around a screening approach, as nobody knows which compound or approach could serve as a drug or therapy. Such almost blind screening approach is very time-consuming and laborious. The alternative to this labour-intensive approach to compound optimization is to develop a theory that quantitatively relates variations in biological activity to changes in molecular descriptors, which can easily be obtained for each compound. Such approach is referred to as QSAR. A Quantitative Structure Activity Relationship (QSAR) represents an attempt to correlate structural or property descriptors of compounds, quantitatively with biological activities [1,2].

1.2. Early Developments

QSAR initially started in 19^{th} century. Crum-Brown published an equation, which is considered to be the first general equation of QSAR. It was not before 1893 that Richet followed this clue by showing that the toxicities in a series of simple compounds (alcohol, ethers and ketone) were inversely related to water solubility. The importance of these finding could not fully be understood before correct relationship between lipophilic behavior and solubility were established. It was Richet who has cleared up the first relationship between toxicity and lipophilicity. Bertholot and Jungfleish did the first systematic investigation on the distribution of compound between two immiscible liquids in 1872. The contribution of Nerst to this subject acquired much more attention, however and it is Nerst name that became undetectably connected with distribution and partition [3,4].

1.3. Quantitative Models

1.3.1. The Extra Thermodynamic Approach (Hansch Analysis)

Hansch analysis includes biological activity values with physicochemical properties. Thus Hansch analysis is property relationship model. As practically all parameters used in Hansch analysis are linear free energy-related values (i.e., derived from rate or equilibrium

constants), the terms “linear free energy-related approach” or “extra thermodynamic approach” are used as synonyms for Hansch analysis [5].

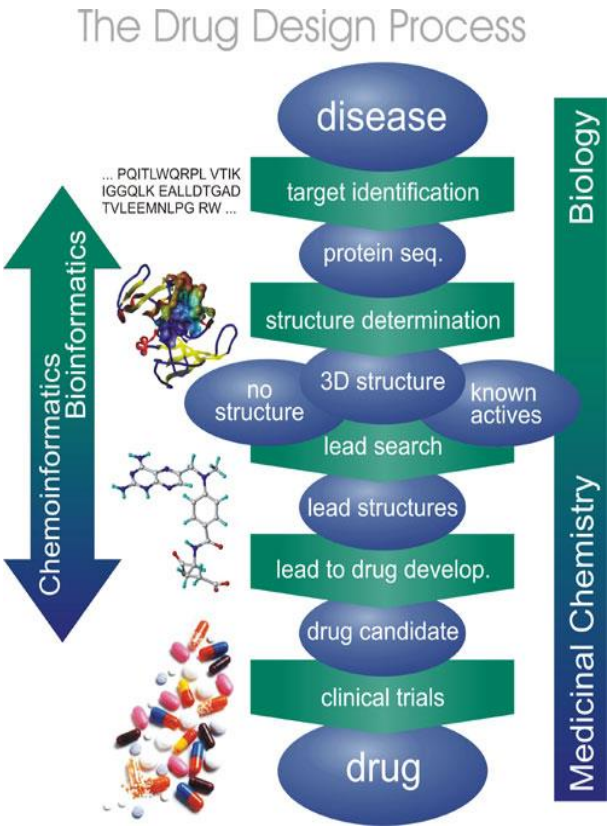


Fig 1: Drug Design Process.

1.4. MALARIA

Malaria causes 3-4 million deaths each year worldwide among about 250 million people suffering from this major parasitic infection, according to the W.H.O. Because of the emergence of parasites which have developed resistance to the most frequently used drug-compounds, in particular chloroquine, the fight against malaria, regarding the treatment level of action, requires the discovery of new efficient molecules with new mechanism of action, as recommended by the W.H.O. Plasmodium falciparum, the protozoan agent responsible for cerebral malaria, is the most worrying species, in particular with chloroquine- and multi-resistant strains such as W2. Effectively, its chemosensitivity appears nowadays as nearly limited to the single artemisin-based combination therapies. In such a context, medicinal chemists must investigate new pharmacophores in order to put forward new drug candidates presenting low costs of production which could significantly contribute to improve the sanitary situation of many developing countries. Among the different heterocyclic structures

which have been studied for their antiplasmodial properties, quinazoline has quite recently showed increasing interest [6-8].

Quinazoline is a versatile pharmacophore which exhibits wide variety of biological activities like antimalarial, antimicrobial, antiproliferative, analgesic, anti-leishmanial, antitumor, antifungal, DNA-ligand, antiinflammatory, antitoxoplasmosis, and PDE5-inhibitors, when it is substituted with different groups at various positions [9,10].

2. MATERIALS AND METHODS

A database of 100 antimalarial compounds has been built up from articles selected in European Journal of Medicinal Chemistry with the following criteria:

- The compounds included in all the series were quinazoline derivatives (i.e possessed same basic moiety).
- All the series included compounds with substitution at positions 2, 4 or 6.
- Each drug was identified by chemical structure and characterized by IC_{50} expressed in micromolar concentration.

The structures of all the compounds were drawn using the software ChemDraw Ultra 8.0.

The Software (HyperChem7.0, Computer Aided Chemistry)

HyperChem 7.0 is a sophisticated molecular modelling environment that is known for its quality, flexibility, and ease of use. Uniting 3D visualization and animation with quantum chemical calculations, molecular mechanics, and dynamics.

Significance of HyperChem 7.0 Software:

1) Structure Input and Manipulation

- Building a molecule
- Select, rotate, translate, and resize structures with convenient mouse controlled tools. Modify settings to control operation of tools.
- Convert rough sketches into 3D structures with HyperChem's model builder.
- Apply builder constraints easily: specify bond lengths, bond angles, torsion angles, or the bonding geometry about a selected atom.

2) Molecular Display

- Display structures using ball and stick, fused CPK spheres, sticks, van der Waals dots, and sticks; switch easily between rendering styles.

- Highlight potential hydrogen bond interactions.
- Display dipole moment vectors and gradient vectors.

3) Computational Chemistry

HyperChem is used to explore quantum or classical model potential energy surfaces with single point, geometry optimization, or transition state search calculations.

4) Conformational Search

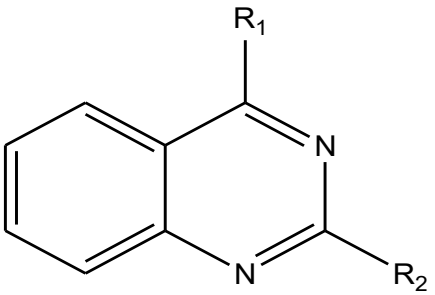
The conformational Search module is a tool for finding and saving stable structures of molecules, using stochastic approaches based on modification of torsion angles.

5) QSAR Properties

QSAR properties allow calculation and estimation of a variety of molecular descriptors commonly used in Quantitative Structure Activity Relationship studies.

Table 1: Diaryl-1, 2, 4 Quinazoline Derivatives with their Biological Activities

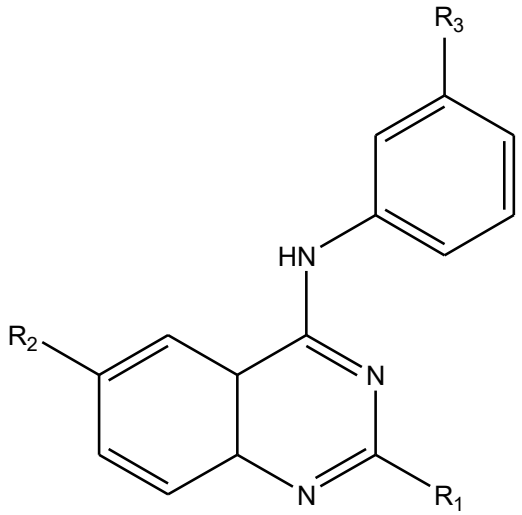
SERIES 1



MOLECULE	R_1	R_2	$IC_{50}(\mu M)$
Q1	n-Butyl-NH-	$-CCl_3$	14.3
Q2	Cycloheptyl-NH-	$-CCl_3$	5.1
Q3	Benzyl-NH-	$-CCl_3$	6.9
Q4	N-Morpholinyl-	$-CCl_3$	14.9
Q5	N-Pyrrolidinyl-	$-CCl_3$	41.5
Q6	4-CH_3-piperazin-1-yl-	$-CCl_3$	5.6
Q7	Ph-NH-	$-CCl_3$	11
Q8	4-F-Ph-NH-	$-CCl_3$	5.4
Q9	3-Cl-Ph-NH-	$-CCl_3$	1.7
Q10	2-NO_2pPh-NH-	$-CCl_3$	3
Q11	2-Cl-Ph-NH-	$-CCl_3$	4.6
Q12	4-Cl-Ph-NH-	$-CCl_3$	3
Q13	2-F-Ph-NH-	$-CCl_3$	9
Q14	3-F-Ph-NH-	$-CCl_3$	4
Q15	3-NO_2-Ph-NH-	$-CCl_3$	3

Q16	**4-NO_2-Ph-NH-**	**-CCl_3**	**2.8**
Q17	**2-Br-Ph-NH-**	**-CCl_3**	**3**
Q18	**3-Br-Ph-NH-**	**-CCl_3**	**2.2**
Q19	**4-Br-Ph-NH-**	**-CCl_3**	**1.5**
Q20	**2-CF_3-Ph-NH-**	**-CCl_3**	**7.4**
Q21	**3-CF_3-Ph-NH-**	**-CCl_3**	**1.8**
Q22	**4-CF_3-Ph-NH-**	**-CCl_3**	**1.6**
Q23	**2-OCH_3-Ph-NH-**	**-CCl_3**	**6**
Q24	**3-OCH_3-Ph-NH-**	**-CCl_3**	**4**
Q25	**4-OCH_3-Ph-NH-**	**-CCl_3**	**6**
Q26	**2-CH_3-Ph-NH-**	**-CCl_3**	**7**
Q27	**3-CH_3-Ph-NH-**	**-CCl_3**	**2.3**
Q28	**4-CH_3-Ph-NH-**	**-CCl_3**	**2.4**
Q29	**3,4-Di-Cl-Ph-NH-**	**-CCl_3**	**5**
Q30	**2,3-Di-Cl-Ph-NH-**	**-CCl_3**	**14**
Q31	**2,6-Di-Cl-Ph-NH-**	**-CCl_3**	**21.9**
Q32	**2,4-Di-Cl-Ph-NH-**	**-CCl_3**	**0.4**
Q33	**3,5-Di-Cl-Ph-NH-**	**-CCl_3**	**4**
Q34	**2,5-Di-Cl-Ph-NH-**	**-CCl_3**	**1.7**
Q35	**3,5-Di-CF_3-Ph-NH-**	**-CCl_3**	**3**
Q36	**4-OCF_3-Ph-NH-**	**-CCl_3**	**2.9**
Q37	**1-Naphthyl-NH-**	**-CCl_3**	**6**
Q38	**3-Cl-Ph-NH-**	**-CH_3**	**55**
Q39	**3-CF_3-Ph-NH-**	**-CH_3**	**42.5**
Q40	**2,4-Di-Cl-Ph-NH-**	**-CH_3**	**85**

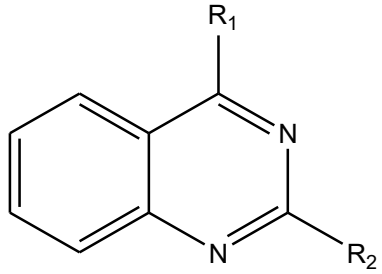
SERIES 2



MOLECULE	R_1	R_2	R_3	IC_{50}(µM)
R1	**(pCH_3)Ph-SO_2-CH_2-**	**H-**	**H-**	**-**
R2	**(pCH_3)Ph-SO_2-CH_2-**	**H-**	**CF_3-**	**15**
R3	**(pCH_3)Ph-SO_2-CH_2-**	**H-**	**4-F-**	**20**
R4	**(pCH_3)Ph-SO_2-CH_2-**	**H-**	**3-Br-**	**13**
R5	**(pCH_3)Ph-SO_2-CH_2-**	**H-**	**2-Cl-**	**14**

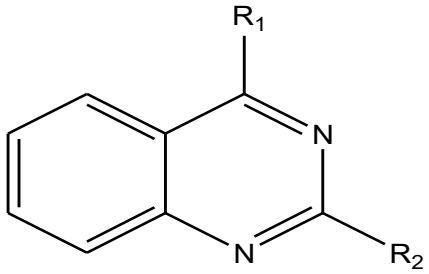
R6	$(CH_3)_2C=CH-$	NO_2-	H-	17
R7	$(CH_3)_2C=CH-$	NO_2-	3-CF_3-	3.2
R8	$(CH_3)_2C=CH-$	NO_2-	4-F-	5.6
R9	$(CH_3)_2C=CH-$	NO_2-	3-Br-	7.5
R10	(pCH_3)Ph-SO_2-CH_2-	NO_2-	H-	5
R11	(pCH_3)Ph-SO_2-CH_2-	NO_2-	3-CF_3-	0.95
R12	(pCH_3)Ph-SO_2-CH_2-	NO_2-	4-F-	2.2
R13	(pCH_3)Ph-SO_2-CH_2-	NO_2-	3-Br-	-
R14	(pCH_3)Ph-SO_2-CH_2-	NO_2-	3-Cl-	1.3

SERIES 3



MOLECULE	R_1	R_2	IC_{50}(µM)
S1	Cl-	-CCl_3	54.5
S2	HO-	-CCl_3	>50
S3	Ph-O-	-CCl_3	3.1
S4	1-Naphthyl-O-	-CCl_3	3.9
S5	2-Naphthyl-O-	-CCl_3	2.3
S6	3,4-Di-CH_3-Ph-O-	-CCl_3	3.3
S7	4-Cl-Ph-O-	-CCl_3	1.1
S8	3-Cl-Ph-O-	-CCl_3	2.4
S9	2-Cl-Ph-O-	-CCl_3	4.4
S10	4-F-Ph-O-	-CCl_3	2.4
S11	3-F-Ph-O-	-CCl_3	2.3
S12	2-F-Ph-O-	-CCl_3	5.0
S13	4-CF_3-Ph-O-	-CCl_3	1.8
S14	3-CF_3-Ph-O-	-CCl_3	2.3
S15	2-CF_3-Ph-O-	-CCl_3	3.3
S16	4-NO_2-Ph-O-	-CCl_3	3.5
S17	3- NO_2-Ph-O-	-CCl_3	3.0
S18	2- NO_2-Ph-O-	-CCl_3	4.9
S19	4-CH_3-Ph-O-	-CCl_3	3.2
S20	3-CH3-Ph-O-	-CCl_3	2.9
S21	2-CH_3-Ph-O-	-CCl_3	5.5
S22	4-OCH_3-Ph-O-	-CCl_3	2.9
S23	3-OCH_3-Ph-O-	-CCl_3	1.9
S24	2-OCH_3-Ph-O-	-CCl_3	6.0
S25	4-Cl-Ph-O-	-CH_3	28
S26	4-Cl-Ph-O-	-CF_3	68

SERIES 4



MOLECULE	R_1	R_2	$IC_{50}(\mu M)$
T1	Cl-	$-CCl_3$	55.0
T2	Ph-S-	$-CCl_3$	1.9
T3	2-Cl-Ph-S-	$-CCl_3$	2.8
T4	3-Cl-Ph-S-	$-CCl_3$	2.2
T5	4-Cl-Ph-S-	$-CCl_3$	0.9
T6	2-F-Ph-S-	$-CCl_3$	2.3
T7	3-F-Ph-S-	$-CCl_3$	1.9
T8	4-F-Ph-S-	$-CCl_3$	1.2
T9	2-CF_3-Ph-S-	$-CCl_3$	2.5
T10	3-CF_3-Ph-S-	$-CCl_3$	2.2
T11	4-CF_3-Ph-S-	$-CCl_3$	1.0
T12	2-CH_3-Ph-S-	$-CCl_3$	7.0
T13	3-CH_3-Ph-S-	$-CCl_3$	1.9
T14	4-CH_3-Ph-S-	$-CCl_3$	1.6
T15	2-OCH_3-Ph-S-	$-CCl_3$	3.9
T16	3-OCH_3-Ph-S-	$-CCl_3$	2.0
T17	4-OCH_3-Ph-S-	$-CCl_3$	2.5
T18	2,4-Di-Cl-Ph-S-	$-CCl_3$	1.5
T19	2-Cl-Ph-S-	-H	4.4
T20	2-Cl-Ph-S-	$-CF_3$	>15

Table.2: Properties Calculated for all the Series of Quinazoline Derivatives by HyperChem.

Mol	Surface Area Approx	Surface Area Grid	Volume	Hydration Energy	Log P	Refrac-tivity	Polari-zability	Mass
Q1	457.74	495.67	834.76	-2.41	3.06	85.27	31.51	318.63
Q2	468.46	545.98	941.73	-1.73	3.83	97.01	36.24	358.70
Q3	412.75	509.87	875.77	-4.36	2.86	100.15	35.66	352.65
Q4	448.91	522.72	868.31	-5.55	1.37	88.67	32.72	347.63
Q5	419.28	487.41	807.39	-1.17	2.54	84.23	30.73	316.62
Q6	468.94	521.34	889.64	-1.06	2.01	92.74	33.92	345.66
Q7	435.37	503.96	830.63	-5.61	2.48	96.28	33.83	338.62
Q8	449.49	511.33	842.90	-5.30	1.88	96.41	33.74	356.61
Q9	470.31	529.19	875.88	-5.20	2.26	100.99	35.76	373.07
Q10	456.06	547.08	924.83	-12.88	-1.69	102.33	36.12	384.63

Q11	460.76	522.11	870.84	-5.08	2.26	100.99	35.76	373.07
Q12	471.55	530.19	875.52	-5.25	2.26	100.99	35.76	373.07
Q13	441.34	508.18	840.80	-5.16	1.88	96.41	33.74	356.61
Q14	448.50	511.61	843.01	-5.27	1.88	96.41	33.74	356.61
Q15	488.78	553.49	923.11	-14.92	-1.69	102.33	36.12	384.63
Q16	488.94	558.54	927.67	-15.10	-1.69	102.33	36.12	384.63
Q17	468.35	529.66	886.23	-5.04	2.53	103.81	36.45	417.52
Q18	479.17	538.76	893.90	-5.18	2.53	103.81	36.45	417.52
Q19	480.39	539.53	894.42	-5.23	2.53	103.81	36.45	417.52
Q20	451.85	533.03	897.65	-3.54	3.05	101.49	35.39	406.62
Q21	498.81	548.41	910.18	-4.92	3.05	101.49	35.39	406.62
Q22	500.59	548.93	910.49	-4.99	3.05	101.49	35.39	406.62
Q23	481.53	558.61	935.41	-5.82	1.49	102.65	36.30	368.65
Q24	489.49	561.94	934.07	-6.90	1.49	102.65	36.30	368.65
Q25	496.17	560.53	934.07	-7.04	1.49	102.65	36.30	368.65
Q26	468.18	531.85	899.28	-4.13	2.63	100.56	35.66	352.65
Q27	474.85	541.39	907.28	-4.21	2.63	100.56	35.66	352.65
Q28	478.95	544.1	908.17	-4.24	2.63	100.56	35.66	352.65
Q29	504.12	550.79	917.13	-4.9	2.04	105.71	37.68	407.51
Q30	492.73	543.96	910.62	-4.73	2.04	105.71	37.68	407.51
Q31	465.01	519.22	882.9	-4.21	2.04	105.71	37.68	407.51
Q32	497.71	547.99	915.08	-4.75	2.04	105.71	37.68	407.51
Q33	499.06	548.4	916.5	-4.84	2.04	105.71	37.68	407.51
Q34	489.54	539.77	909.99	-4.71	2.04	105.71	37.68	407.51
Q35	543.73	574.98	976.43	-4.38	3.62	106.71	36.95	474.62
Q36	519.56	564.09	935.4	-7.17	3.42	103.76	36.03	422.62
Q37	122.16	315.61	545.08	-0.82	2.99	113.63	40.2	390.70
Q38	390.57	481.26	778.42	-5.23	0.59	85.48	29.97	269.73
Q39	416.88	513.23	825.29	-4.84	1.38	85.98	29.61	303.29
Q40	154.13	295.4	488.97	-1.01	0.36	90.2	31.9	304.18
R2	623.07	682.51	1160.52	-7.740	1.24	128.32	42.24	457.47
R3	573.55	645.71	1094.18	-8.130	0.07	123.24	40.59	407.46
R4	595.53	669.32	1145.57	-8.040	0.73	130.64	43.30	468.37
R5	584.84	656.80	1121.10	-7.900	0.45	127.82	42.61	423.92
R6	504.59	563.31	937.97	-13.610	-2.10	101.42	35.65	321.36
R7	567.05	623.66	1031.44	-12.820	-1.53	106.63	37.22	389.36
R8	518.31	571.20	950.07	-13.300	-2.70	101.54	35.56	339.35
R9	548.28	597.45	1001.47	-13.180	-2.05	108.95	38.28	400.25
R10	617.47	681.16	1161.95	-17.570	-3.49	129.16	42.97	435.48
R11	684.16	737.49	1249.28	-16.900	-2.92	134.37	44.54	503.48
R12	635.44	695.39	1178.21	-17.320	-4.09	129.16	42.88	453.47
R14	656.11	719.11	1211.45	-17.220	-3.72	133.87	44.90	469.92
S1	368.54	403.46	634.57	-2.64	2.61	68.14	24.74	281.96
S3	438.17	500.36	827.40	-5.13	2.66	94.03	33.11	339.61
S4	473.95	573.56	980.37	-4.00	3.17	111.38	39.49	391.68
S5	470.27	564.87	949.34	-5.06	2.73	112.23	39.30	389.67
S6	519.60	563.62	946.59	-2.84	2.96	102.60	36.78	367.66
S7	473.53	526.85	872.92	-4.78	2.44	98.75	35.04	374.05

S8	473.04	525.22	872.86	-4.74	2.44	98.75	35.04	374.05
S9	462.32	516.84	866.36	-4.52	2.44	98.75	35.04	374.05
S10	451.55	507.37	839.77	-4.83	2.06	94.16	33.02	357.60
S11	451.17	506.57	840.32	-4.80	2.06	94.16	33.02	357.60
S12	444.09	503.69	838.06	-4.64	2.06	94.16	33.02	357.60
S13	501.79	544.83	906.22	-4.52	3.23	99.25	34.68	407.61
S14	501.24	544.60	905.73	-4.46	3.23	99.25	34.68	407.61
S15	450.07	535.30	896.44	-3.42	3.23	99.25	34.68	407.61
S16	493.29	554.30	920.82	-14.75	-1.51	100.08	35.41	385.61
S17	492.04	553.64	921.43	-14.51	-1.51	100.08	35.41	385.61
S18	470.86	549.46	915.49	-12.84	-1.51	100.08	35.41	385.61
S19	480.33	528.38	878.26	-3.91	2.81	98.32	34.95	353.63
S20	478.72	529.01	877.89	-3.88	2.81	98.32	34.95	353.63
S21	461.16	522.71	871.66	-3.57	2.81	98.32	34.95	353.63
S22	489.97	544.32	906.27	-6.76	1.66	100.41	35.59	369.63
S23	488.94	546.73	903.88	-6.65	1.66	100.41	35.59	369.63
S24	470.32	527.41	887.30	-5.95	1.66	100.41	35.59	369.63
S25	402.03	476.56	770.16	-4.71	0.76	83.23	29.26	270.72
S26	418.10	493.61	799.95	-4.92	1.88	54.25	28.98	324.69
T1	368.54	403.46	634.57	-2.6	2.61	68.54	24.74	281.96
T2	453.93	516.29	862.27	-4.4	3.00	100.48	35.48	355.67
T3	504.17	550.02	913.81	-4.2	2.78	105.19	37.41	390.11
T4	490.5	550.77	909.73	-4.0	2.78	105.19	37.41	390.11
T5	513.94	553.05	912.22	-4.3	2.78	105.19	37.41	390.11
T6	462.71	552.68	872.55	-4.1	2.40	100.60	35.39	373.66
T7	466.29	523.71	874.64	-4.1	2.40	100.60	35.39	373.66
T8	466.98	523.53	874.08	-4.1	2.40	100.60	35.39	373.66
T9	457.99	551.29	919.35	-3.2	3.57	105.69	37.04	423.67
T10	514.74	558.55	940.53	-3.8	3.57	105.69	37.04	423.67
T11	514.73	559.75	939.28	-3.8	3.57	105.69	37.04	423.67
T12	494.38	551.86	923.87	-3.2	3.15	104.76	37.31	369.70
T13	504.54	555.43	929	-3.2	3.15	104.76	37.31	369.70
T14	506.4	556.12	929.38	-3.2	3.15	104.76	37.31	369.70
T15	504.88	557.05	930.9	-5.3	2.01	106.85	37.95	385.69
T16	510.18	562.53	934.62	-6.0	2.01	106.85	37.95	385.69
T17	552.33	582.49	955.49	-6.2	2.01	106.85	37.95	385.69
T18	519.34	566.75	949.55	-3.7	2.56	109.91	39.33	424.56
T19	378.65	467.93	749.76	-5.6	0.90	85.61	29.79	272.75

Table 3: Actual, Predicted and Residual B.A. of Quinazoline Derivatives.

Mol.	Actual BA	Predicted BA	Residual
Q1	-1.1553	-0.9829	-0.1724
Q2	-0.7076	-0.5764	-0.1312
Q3	-0.8388	-0.4922	-0.3466
Q4	-1.1732	-1.0320	-0.1412
Q5	-1.6180	-1.2723	-0.3458
Q6	-0.7482	-1.2277	0.4795
Q7	-1.0414	-0.5547	-0.4867

Q8	-0.7324	-0.7430	0.0106
Q9	-0.2304	-0.5463	0.3158
Q10	-0.4771	-0.7787	0.3016
Q11	-0.6628	-0.5586	-0.1042
Q12	-0.4771	-0.5412	0.0640
Q13	-0.9542	-0.7573	-0.1969
Q14	-0.6021	-0.7461	0.1440
Q15	-0.4771	-0.5697	0.0926
Q16	-0.4472	-0.5513	0.1041
Q17	-0.4771	-0.4257	-0.0514
Q18	-0.3424	-0.4113	0.0689
Q19	-0.1761	-0.4062	0.2301
Q20	-0.8692	-0.4947	-0.3745
Q21	-0.2553	-0.3534	0.0981
Q22	-0.2041	-0.3462	0.1421
Q23	-0.7782	-0.6491	-0.1290
Q24	-0.6021	-0.5385	-0.0636
Q25	-0.7782	-0.5241	-0.2540
Q26	-0.8451	-0.5675	-0.2776
Q27	-0.3617	-0.5593	0.1976
Q28	-0.3802	-0.5562	0.1760
Q29	-0.6990	-0.5264	-0.1726
Q30	-1.1461	-0.5438	-0.6023
Q31*	-1.3400	-	-
Q32*	0.3980	-	-
Q33	-0.6021	-0.5325	-0.0695
Q34	-0.2304	-0.5458	0.3154
Q35	-0.4771	-0.1364	-0.3407
Q36	-0.4624	0.0280	-0.4904
Q37	-0.7782	-0.5086	-0.2695
Q38	-1.7404	-1.3459	-0.3945
Q39	-1.6284	-1.1642	-0.4642
Q40	-1.9294	-1.7302	-0.1992
R1	n.a	-	-
R2*	-1.1760	-	-
R3*	-1.3010	-	-
R4*	-1.1140	-	-
R5*	-1.1460	-	-
R6	-1.2304	-0.8340	-0.3965
R7	-0.5051	-0.6429	0.1377
R8	-0.7482	-1.0225	0.2743
R9	-0.8751	-0.6906	-0.1845
R10	-0.6990	-0.1564	-0.5426
R11	0.0223	0.0470	-0.0247
R12	-0.3424	-0.3415	-0.0009
R13	n.a	-	-
R14	-0.1139	-0.1445	0.0305
S1	-1.7364	-1.4751	-0.2613

S2	n.a	-	-
S3	-0.4914	-0.6081	0.1167
S4	-0.5911	-0.1870	-0.4041
S5	-0.3617	-0.1757	-0.1860
S6	-0.5185	-0.5647	0.0462
S7	-0.0414	-0.5933	0.5519
S8	-0.3802	-0.5974	0.2171
S9	-0.6435	-0.6199	-0.0236
S10	-0.3802	-0.7953	0.4151
S11	-0.3617	-0.7984	0.4367
S12	-0.6990	-0.8148	0.1158
S13	-0.2553	-0.3983	0.1430
S14	-0.3617	-0.4044	0.0427
S15	-0.5185	-0.5110	-0.0075
S16	-0.5441	-0.5913	0.0472
S17	-0.4771	-0.6159	0.1388
S18	-0.6902	-0.7870	0.0968
S19	-0.5051	-0.5940	0.0888
S20	-0.4624	-0.5970	0.1346
S21	-0.7404	-0.6288	-0.1116
S22	-0.4624	-0.5594	0.0970
S23	-0.2788	-0.5707	0.2919
S24	-0.7782	-0.6424	-0.1358
S25	-1.4472	-1.4060	-0.0412
S26*	-1.8330	-	-
T1	-1.7404	-1.4700	-0.2704
T2	-0.2788	-0.4433	0.1645
T3	-0.4472	-0.4134	-0.0338
T4	-0.3424	-0.4338	0.0914
T5	0.0458	-0.4031	0.4489
T6	-0.3617	-0.6308	0.2690
T7	-0.2788	-0.6308	0.3520
T8	-0.0792	-0.6308	0.5516
T9	-0.3979	-0.2942	-0.1037
T10	-0.3424	-0.2327	-0.1097
T11	0.0000	-0.2327	0.2327
T12	-0.8451	-0.4274	-0.4177
T13	-0.2788	-0.4274	0.1486
T14	-0.2041	-0.4274	0.2233
T15	-0.5911	-0.4670	-0.1241
T16	-0.3010	-0.3953	0.0943
T17	-0.3979	-0.3748	-0.0231
T18	-0.1761	-0.4139	0.2378
T19	-0.6435	-1.2225	0.5791
T20	n.a	-	-

* Outlier (Value of residual activity >2× actual activity)

n.a - Values of biological activitiy not available

3. RESULTS & DISCUSSION

In pursuit compounds having improved antiplasmodial activity compared to the existing compounds, a quantitative structure-activity relationship analysis was performed by using modeling software HyperChem. Least square linear regression analysis resulted in significant QSAR models:

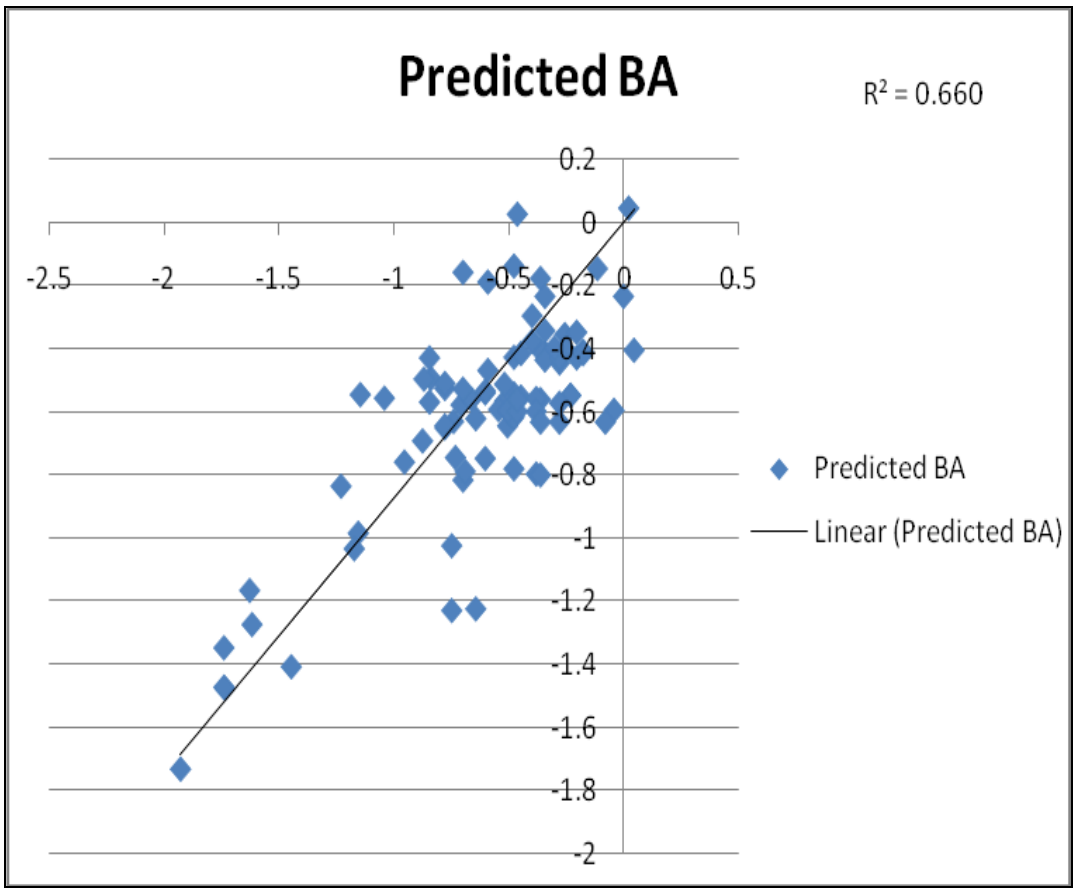


Figure 2: Plot between actual and predicted biological activity.

Table 4: Properties Calculated for all the Series of Quinazoline Derivatives by Chem3D Ultra 8.0.

Mol.	Eb	Ed	Ev	Stretch energy	Torsion energy	ET	E14
Q1	6.89638	4.40034	-3.73942	4.24901	4.39687	26.9993	10.6899
Q2	8.9283	4.35988	-4.23775	4.55454	12.2928	42.1259	16.1343
Q3	7.34046	3.99695	-4.61329	4.02477	-1.48504	21.188	11.7906
Q4	14.0585	4.67242	-5.28742	5.82354	10.3016	44.0871	13.8153
Q5	10.9758	3.89253	-2.2763	2.8696	21.3586	48.9416	11.9114
Q6	11.0001	3.88608	-4.36629	3.66304	18.9099	48.8469	15.3546
Q7	2.96888	4.84652	-3.71518	3.90846	4.24776	23.0763	10.7055
Q8	2.99969	5.01907	-3.72395	4.52103	4.46822	23.8497	10.4795
Q9	2.99619	5.05371	-3.96736	3.96522	5.11382	24.4808	11.2182
Q10	3.1735	4.87495	-3.29059	83.0574	-6.64949	91.0599	11.7838

Q11	2.99341	5.49824	-4.49111	3.97566	6.68949	26.2593	11.4948
Q12	2.98857	5.006	-3.87588	4.01761	4.39745	23.7931	11.1539
Q13	2.54528	5.99965	-3.44692	4.90039	20.2455	41.2672	10.9435
Q14	3.07474	5.07169	-3.79113	4.46233	4.8455	24.2192	10.4905
Q15	3.11524	4.85683	-3.05052	84.9127	-5.61559	95.6247	11.7983
Q16	3.05818	4.87887	-2.84891	84.8799	-5.94575	95.2281	11.6933
Q17	3.02728	5.40536	-4.65112	3.91878	6.47021	25.9476	11.666
Q18	3.01566	5.03557	-4.03705	3.88937	5.26183	24.5854	11.3195
Q19	3.06752	4.9966	-3.95093	3.91873	4.46259	23.847	11.2468
Q20	6.58402	4.97147	-4.35061	6.92317	9.50159	34.9444	11.1549
Q21	5.01018	5.01212	-3.86334	6.61663	9.33495	33.2937	11.0077
Q22	4.96735	4.97427	-3.86374	6.64211	8.38701	32.2478	10.9619
Q23	7.4607	4.99867	-3.55787	5.64265	23.9766	52.0899	13.5155
Q24	11.2798	4.96536	-2.73866	4.49288	4.75222	36.1481	13.299
Q25	10.938	4.92862	-2.94011	4.4921	6.09986	36.9509	13.3223
Q26	3.0018	4.70158	-4.20296	4.14432	6.27094	25.65	11.6363
Q27	3.02965	4.8074	-3.96597	4.00708	4.53265	24.0272	11.5039
Q28	3.04685	4.81608	-3.908	4.05087	3.76173	23.3473	11.4661
Q29	3.10515	7.77371	-4.09163	4.19796	3.39518	27.2032	12.7395
Q30	3.00627	8.30596	-4.63497	4.30492	4.99606	29.221	13.2628
Q31	3.12314	6.8172	-5.33832	4.24897	13.5524	34.7931	12.3075
Q32	3.03145	6.36678	-4.65086	4012241	6.43694	27.349	11.9509
Q33	3.00444	6.02113	-4.39007	4.08122	5.25505	25.8173	11.7467
Q34	2.99109	6.26848	-4.91032	4.09924	6.89558	27.4421	12.0038
Q35	6.67036	5.73738	-4.43983	9.29326	14.3042	43.2206	11.3877
Q36	11.4913	16.7719	-4.45347	5.68878	8.86567	50.7077	12.1723
Q37	4.64378	4.92012	-4.24839	3.9277	22.2659	46.142	14.5966
Q38	2.23325	-0.39759	-2.82567	3.78077	2.82692	15.4764	9.72006
Q39	4.26128	-0.45574	-2.88617	6.42341	8.32331	25.4026	9.5337
Q40	2.26116	0.85272	-3.6376	3.92319	5.37047	19.3605	10.4694
R2	6.3335	2.31318	-5.0499	17.6621	2.6056	40.3357	15.9704
R3	4.50204	2.55108	-5.08238	15.589	-3.36484	29.7574	15.2566
R4	4.56114	2.47205	-5.21794	14.8754	-1.58384	31.6655	16.1696
R5	4.37305	2.85144	-5.63627	14.9207	-0.11122	33.2329	16.419
R6	3.25443	-0.40023	-2.17508	93.7585	-4.61784	101.874	12.0886
R7	5.30718	-0.32174	-2.15348	96.0505	-0.12685	111.338	12.442
R8	3.31369	-0.32142	-2.14153	92.3298	-4.58195	100.439	11.8767
R9	3.34713	-0.28374	-2.32213	93.2187	-4.55166	101.968	12.7145
R10	2.31092	2.59905	-2.78099	87.3843	-17.9292	88.6128	16.3446
R11	6.4276	2.40395	-4.33088	96.5321	-12.8986	106.111	16.9834
R12	4.56408	2.5146	-4.25135	92.5945	-17.3682	95.0802	16.3241
R14	4.49703	2.44166	-4.39242	93.406	-17.2173	96.6376	17.1655
S1	2.22925	6.94455	-1.21498	2.03967	0.82818	19.1436	8.14771
S3	12.83	6.27756	-3.55979	3.42155	-3.59515	28.1919	12.8089
S4	18.7985	7.42264	38.6078	3.5102	10.4463	102.548	18.2551
S5	14.9972	7.66075	-2.05914	9.06366	-13.604	26.1212	15.554
S6	13.1126	6.31345	-2.9406	3.76616	-5.11319	29.6762	14.5202
S7	12.8171	6.43241	-3.70137	3.53114	-3.61032	28.748	13.2693

S8	12.9415	6.46403	-3.71832	3.52984	-3.62185	28.8495	13.253
S9	12.1026	6.90492	-4.22002	3.61431	-3.98349	27.7077	13.3055
S10	12.7768	6.44057	-3.57147	4.09029	-3.59678	28.6913	12.5802
S11	13.0333	6.47678	-3.55308	4.05846	-3.63165	28.9519	12.603
S12	12.5035	7.01085	-3.63688	3.97624	-3.61616	28.7913	12.5837
S13	14.9274	6.40264	-3.62733	6.10976	0.70785	37.718	13.1142
S14	14.6949	6.42847	-3.72448	6.11015	0.76146	37.4573	13.1045
S15	15.1939	7.42826	-1.35206	6.13353	-1.4009	39.0157	12.9356
S16	7.53582	7.21059	3.57704	11.1958	-1.92717	44.0432	16.0666
S17	12.9602	6.27391	-2.90144	25.264	-3.73313	51.9058	13.8748
S18	13.0165	6.27123	-1.78105	15.6275	-3.30353	43.7647	13.6813
S19	12.8526	6.24482	-3.73184	3.58871	-4.29921	28.2387	13.5715
S20	12.8866	6.23819	-3.77769	3.58773	-4.30361	28.232	13.5913
S21	12.741	6.13133	-3.18006	3.69371	-5.52303	27.4335	13.5864
S22	20.7729	6.3066.	-2.62052	4.09261	-3.54032	40.4147	15.408
S23	21.6457	6.75613	-1.88927	3.86693	-4.65183	41.1893	15.4396
S24	21.3538	6.40322	-0.8278	4.09944	-4.1857	42.076	15.2131
S25	12.1857	0.80952	-2.66477	3.29902	-5.08438	20.4035	11.8115
S26	13.9168	6.82644	-2.37215	6.27036	-4.27597	31.9577	11.2782
T1	2.2293	6.94459	-1.21497	2.04015	0.82906	19.1451	8.14769
T2	4.84976	5.33516	-1.7499	9.53603	-5.50513	24.0873	13.2426
T3	6.91028	7.18515	-0.90396	9.88882	-6.02019	31.7749	16.859
T4	4.8896	5.7091	-1.89841	9.53762	-5.5499	24.7996	13.7124
T5	5.03024	5.61843	-1.8327	9.69058	-5.54464	24.9926	13.6962
T6	4.26731	6.98764	-1.92015	10.103	-5.60777	25.3158	12.9685
T7	5.01276	5.74145	-1.68484	9.98405	-5.55135	24.8862	13.0203
T8	5.00638	5.62847	-1.71061	10.29	-5.5245	25.0268	13.0326
T9	6.73977	5.97537	-1.4385	11.6101	-1.22542	34.0244	13.6619
T10	10.2096	5.67269	-0.53408	12.5939	-1.73234	37.961	13.9859
T11	9.54435	5.60194	-0.90906	12.4511	-1.52477	36.9515	13.8878
T12	4.75937	4.994	-6.50034	9.51662	-6.42002	25.5204	14.3434
T13	4.88711	5.25682	-1.97217	9.65014	-6.20485	24.0129	14.0081
T14	7.40577	5.30088	-1.09235	10.1074	-6.20238	27.652	14.3169
T15	12.1522	6.04953	-0.70703	10.4757	-5.49696	37.0913	16.1252
T16	17.442	5.49003	0.86083	10.3591	-6.06961	42.0171	16.3834
T17	12.7529	5.35958	-0.95006	10.5054	-5.4475	36.418	15.8104
T18	4.9601	8.03784	-2.00117	9.87143	-5.85087	29.4046	16.0777
T19	3.88513	0.24090	7.93927	9.0085	-4.91669	18.2426	11.7805

Table 5: Actual, Predicted and Residual B.A of Quinazoline Derivatives.

Mol.	Actual BA	Predicted BA	Residual
Q1	-1.1553	-0.7571	-0.3983
Q2	-0.7076	-0.8681	0.16051
Q3	-0.8388	-0.7174	-0.1215
Q4	-1.1732	-0.8058	-0.3674
Q5	-1.618	-1.0438	-0.5742
Q6	-0.7482	-1.0084	0.26026
Q7	-1.0414	-0.7118	-0.3296

Q8	-0.7324	-0.6957	-0.0367
Q9	-0.2304	-0.7029	0.47243
Q10	-0.4771	-0.3092	-0.168
Q11	-0.6628	-0.6802	0.01749
Q12	-0.4771	-0.6977	0.22053
Q13	-0.9542	-0.8129	-0.1413
Q14	-0.6021	-0.6958	0.09379
Q15	-0.4771	-0.3192	-0.1579
Q16	-0.4472	-0.3126	-0.1345
Q17	-0.4771	-0.6867	0.20953
Q18	-0.3424	-0.7069	0.36452
Q19	-0.1761	-0.6998	0.5237
Q20	-0.8692	-0.7617	-0.1076
Q21	-0.2553	-0.7563	0.50106
Q22	-0.2041	-0.747	0.54292
Q23	-0.7782	-0.961	0.18282
Q24	-0.6021	-0.705	0.10297
Q25	-0.7782	-0.7271	-0.051
Q26	-0.8451	-0.7531	-0.092
Q27	-0.3617	-0.7193	0.35753
Q28	-0.3802	-0.7077	0.3275
Q29	-0.699	-0.4085	-0.2904
Q30*	-1.1461	-	-
Q31*	-1.3400	-	-
Q32*	0.3980	-	-
Q33	-0.6021	-0.6084	0.00631
Q34	-0.2304	-0.6062	0.37573
Q35	-0.4771	-0.7438	0.26666
Q36	-0.4624	0.41498	-0.8774
Q37	-0.7782	-0.9508	0.17266
Q38	-1.7404	-1.2135	-0.5268
Q39	-1.6284	-1.2861	-0.3423
Q40	-1.9294	-1.1237	-0.8057
R1	n.a	-	-
R2	-1.1761	-0.8973	-0.2788
R3	-1.301	-0.7986	-0.5024
R4	-1.1139	-0.8331	-0.2808
R5	-1.1461	-0.8154	-0.3307
R6	-1.2304	-0.8269	-0.4036
R7	-0.5051	-0.8732	0.3681
R8	-0.7482	-0.8241	0.0759
R9	-0.8751	-0.8179	-0.0571
R10	-0.699	-0.3672	-0.3318
R11	0.02228	-0.4264	0.44867
R12	-0.3424	-0.3668	0.02434
R13	n.a	-	-
R14	-0.1139	-0.3735	0.25955
S1	-1.7364	-	-

S2	n.a	-	-
S3	-0.4914	-0.464	-0.0274
S4	-0.5911	-0.542	-0.0491
S5	-0.3617	-0.1719	-0.1899
S6	-0.5185	-0.4386	-0.08
S7	-0.0414	-0.448	0.40664
S8	-0.3802	-0.4447	0.06453
S9	-0.6435	-0.3957	-0.2477
S10	-0.3802	-0.4456	0.06543
S11	-0.3617	-0.4417	0.07994
S12	-0.699	-0.3891	-0.3099
S13	-0.2553	-0.5019	0.2466
S14	-0.3617	-0.5000	0.13831
S15	-0.5185	-0.3711	-0.1474
S16	-0.5441	-0.3695	-0.1746
S17	-0.4771	-0.3932	-0.0839
S18	-0.6902	-0.4299	-0.2603
S19	-0.5051	-0.4571	-0.0481
S20	-0.4624	-0.4577	-0.0047
S21	-0.7404	-0.4513	-0.2891
S22	-0.4624	-0.4597	-0.0027
S23	-0.2788	-0.4006	0.12183
S24	-0.7782	-0.4413	-0.3369
S25	-1.4472	-0.987	-0.4601
S26*	-1.8330	-	-
T1*	-1.7404	-	-
T2	-0.2788	-0.5121	0.23331
T3	-0.4472	-0.3202	-0.127
T4	-0.3424	-0.4743	0.13189
T5	0.04576	-0.4829	0.52866
T6	-0.3617	-0.3448	-0.017
T7	-0.2788	-0.4697	0.19091
T8	-0.0792	-0.4803	0.4011
T9	-0.3979	-0.5004	0.1025
T10	-0.3424	-0.5204	0.17802
T11	0	-0.5308	0.53076
T12	-0.8451	-0.5335	-0.3116
T13	-0.2788	-0.5099	0.23116
T14	-0.2041	-0.5041	0.3
T15	-0.5911	-0.4383	-0.1528
T16	-0.301	-0.4864	0.18533
T17	-0.3979	-0.5074	0.10941
T18	-0.1761	-0.2379	0.06178
T19	-0.6435	-1.0277	0.38423
T20	n.a	-	-

*Outlier (Value of residual activity > 2× actual activity

n.a - Values of biological activitiy not available

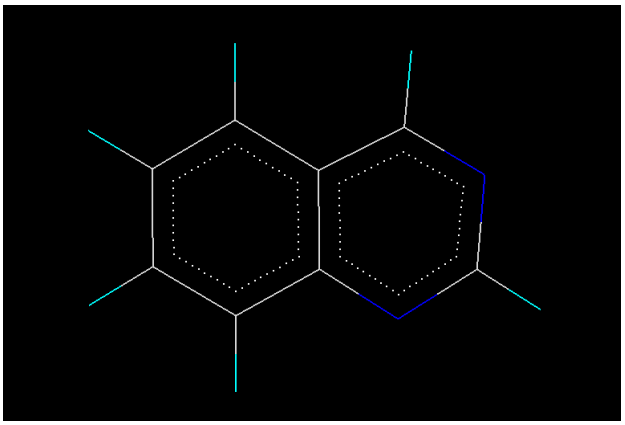


Fig 3: Template used for alignment of quinazoline molecules.

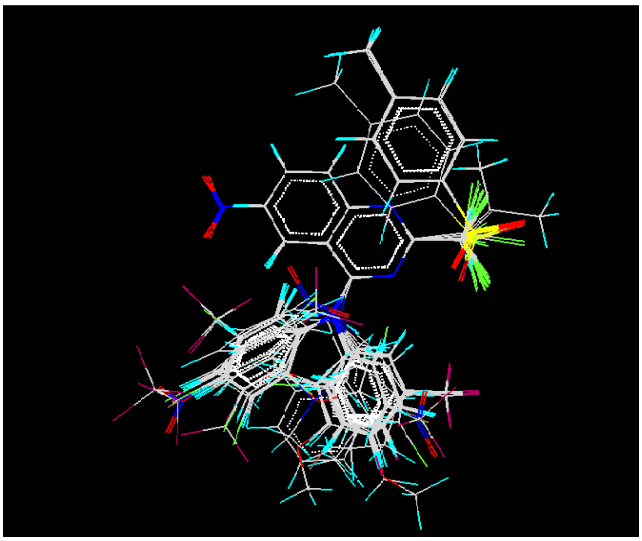


Fig 4: Aligned quinazoline molecules by template-based alignment.

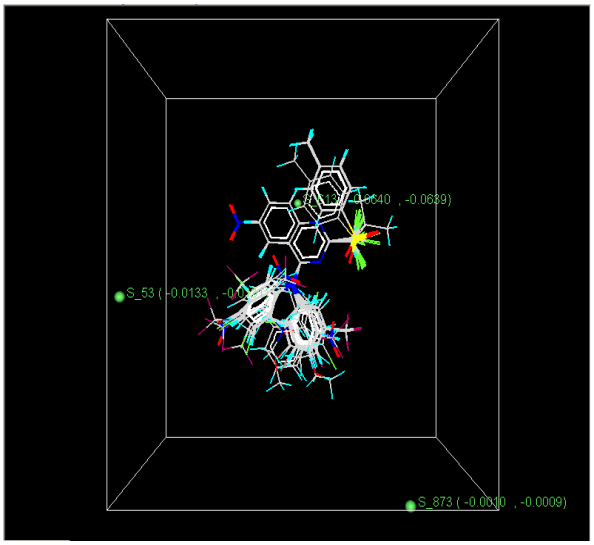


Fig 5: Model summary dialogue box generated by [(SW) kNN MFA] method in 3D QSAR model showing steric and electrostatic region.

- **Electrostatic region**
- **Steric region**

4. CONCLUSION: The present study successfully demonstrated the application of computer-aided drug design and QSAR methodologies for predicting the antimalarial activity of quinazoline derivatives. Molecular descriptors calculated using HyperChem and Chem3D software enabled the development of statistically significant predictive models capable of correlating structural characteristics with biological activity. The comparison between predicted and experimental activities indicated satisfactory predictive performance for most compounds, while a few compounds were identified as outliers. The results suggest that physicochemical properties such as lipophilicity, molecular surface area, molecular volume, refractivity, polarizability, and energy-related descriptors play important roles in determining antiplasmodial activity. Overall, the developed QSAR models provide a valuable framework for the rational design, virtual screening, and optimization of new quinazoline-based antimalarial compounds, thereby reducing the time and cost associated with conventional drug discovery. Future studies should incorporate external validation and advanced machine-learning approaches to improve model robustness and facilitate the identification of potent antimalarial drug candidates.

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