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Qsar Studies of 4-Aminoquinoline Derived Thiazolidines as Antimalarial Agents

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ABSTRACT: The current study details the synthesis of a series of novel 4-aminoquinoline-derived thiazolidines and the evaluation of their antimalarial efficacy against Plasmodium falciparum NF-54 and Plasmodium yoelii N-67 strains in vitro and in vivo. Two compounds in the series, 2-(4-chloro-phenyl)-thiazolidine-4-carboxylic acid [2-(7-chloro-quinolin- 4-ylamino)-ethyl] and 2-(4-chloro-phenyl)-thiazolidine-4-carboxylic acid [2-(7-chloro-quinolin- 4-ylamino)-ethyl]-thiazolidine-4-carboxylic acid, the in vivo assay, -amide hydrochloride suppressed parasitaemia significantly. Results of statistical analysis found with value of Variance as 0.8033, Cross validated regression coefficient and Fisher-value as 0.7551 and 17.976 respectively which may be useful for (medicinal) chemists in selecting the most suitable substituent for the development of more potent, effective and selective Thiazolidine-2,4-dione based antimalarial agents in future.

Key words: QSAR, Thiazolidine-2,4-dione, 2D QSAR.

I. INTRODUCTION

Malaria is one of the most frequent infectious diseases in the world, and it poses a major health risk to humans. It is estimated that between 300 and 500 million clinical instances of protozoal infection occur each year. 1.5–2.5 million individuals die each year as a result of the lack of an appropriate treatment agent[1-3]. Due to their therapeutic efficacy, antimalarial medicine (CQ) and numerous aminoquinolines have been the cornerstones of protozoal infection therapy over the past four decades[4]. The emergence of resistance, on the other hand, has severely reduced the number of antiprotozoal medications now on the market. As a result, innovative chemotherapeutical drugs to treat protozoal infection are urgently needed. Researchers are focused on generating novel chemical entities or changing existing therapeutic agents to combat medicine resistance in order to attain this goal. Compounds formed by modifying the chain length square are more active, according to structure–activity relationship studies on CQ analogues[5-6].

Based on this finding, a number of research groups have created short chain analogues of 4-aminoquinoline derivatives that, in in vitro testing, proved to be much more effective than CQ against a CQ-resistant strain of Plasmodium falciparum. CQ and closely related 4-aminoquinolines form a complex with (Fe(III)FPIX) haematin, which is produced within the intraerythrocytic sporozoan's biological process cavum as a result of host hemoprotein's chemical activity. For sporozoans, free haematin is cytotoxic, and it is sequestered within the style of haemozoin. The drug–haematin interactions prevent the development of haemozoin crystals as well as the buildup of high concentrations of haematin, which is poisonous to the parasite and is thought to be the cause of the parasite's death. We've previously reported on the style, synthesis, and antimalarial drug activity of several aspect chain-modified 4-aminoquinolines in our efforts to produce effective antimalarial pharmacological agents.[7-12] we've positive that 4-aminoquinoline- deduced guanidine and tetramethylguanidine analogues with altered chain length parade promising exert ion against CQ-sensitive strains of P. falciparum NF-54 in vitro and CQ-resistant N-67 strain of Plasmodium yoelii in vivo[13]. Solomon et al. have shown that a series of short chain CQ derivations, on relief of the diethylamino perform with a spread of unrestricted chain negotiations toget

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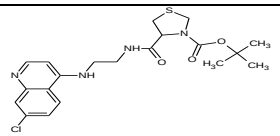
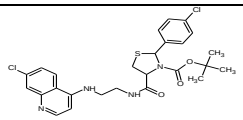
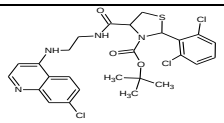
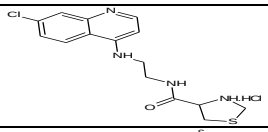
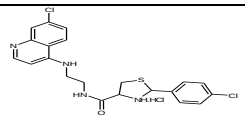
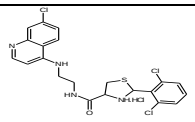
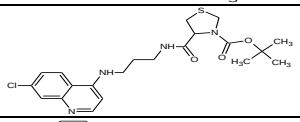
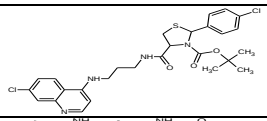
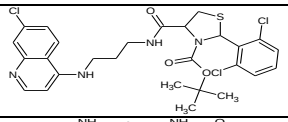
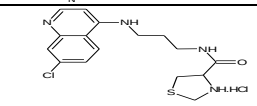
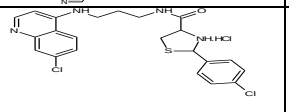
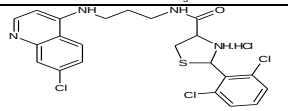
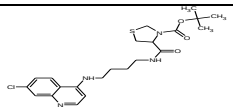
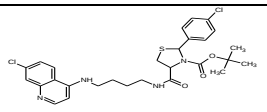
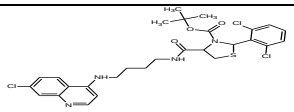
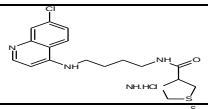
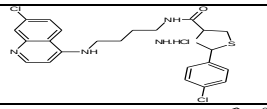
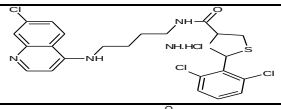
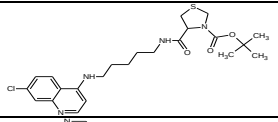
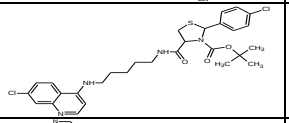
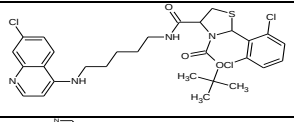
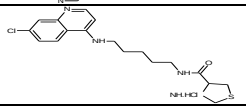
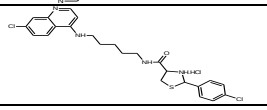
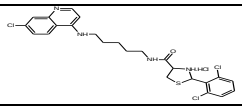
her with piperidinyl, pyrrolidinyl, morpholinyl and piperazinyl variations, affect in a considerable increase within the antimalarial medicine activity[14-17].

II. 2- PRESENTATION OF DATA

In present study table-1 represents the structure of 4-aminoquinoline derivatives, while table-2 shows the calculated topological and connectivity descriptors with biological activity of 4-aminoquinoline derivatives; table-3 represents the correlation matrix between different topological and connectivity descriptors.

Descriptor and biological activity are given in table-2, table-3 and table-4 represents the residual report from best model of topological and connectivity descriptors. Table-5 represent the Cross validation of best models. Ridge regression (fig-3) is representing the multicollinearity is not present in this study.

TABLE -1 – Structures of 4-aminoquinoline Derivatives of thiazolidine

Com	Structure	Com	Structure	Com	Structure
1		9		17	
2		10		18	
3		11		19	
4		12		20	
5		13		21	
6		14		22	
7		15		23	
8		16		24	

III. RESULT AND DISCUSSION

QSAR study of a series of 4-aminoquinoline derivatives was performed by using dragon software. In this study, biological activity (MIC) as dependent and various topological and connectivity descriptors taken as the independent variable and regression was established using MLR analysis. The models were selected on the basis of its statistical significance for further study. A data set of 24 compounds that the biological activities of all 24 compounds gave maximum and minimum value range of biological activities.

In order to understand experimental biological activity data of 24, 4-aminoquinoline compound on theoretical basis, we established a QSAR study between biological activity and descriptor for topological and connectivity properties of the molecules under consideration

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using multiple linear regressions describing by Hansch and Fojity.

Developing a QSAR model requires a diverse set of a data and thereby a large number of descriptor have to be considered.

Descriptors are numerical values that encode different structural features of the molecules selection of set of appropriate descriptor from a large number of them require a method, which is able to discrimination between parameters.

The different molecular descriptors independent variables like topological and connectivity indices (ZM^1, ZM^1V, ZM^2, χ^O, χ^1, χ^OA) are calculated for heterocyclic compounds 4-aminoquinoline presented in table-2.

Preliminary analysis was carried out in terms of correlation analysis (table-3). In general high co-linearity (r>80) was observed between different parameters.

It is clear from that topological and connectivity parameters are strongly correlated with biological activity with value of correlation coefficient more than 0.8 i.e. with ZM^1, ZM^1V, χ^O, and χ^0A strong auto correlation is also exist between ZM^1, ZM^1V, χ^O, and χ^1 etc. so correlation matrix indicated the predominance of topological and connectivity parameter in describing the biological activity heterocyclic compounds 4-aminoquinoline.

The data presented in table-3 demonstrated the low co-linearity between the parameters (r<81) indicated that these parameter could be combined to get multiples regression (MLR) models. The analysis of matrix disclosed topological and connectivity descriptors for the development of (MLR) models.

The topological and connectivity data was subjected to regression analysis and the best mono parametric model with connectivity descriptor is as follows.

The regression analysis gave mono -parametric models. Out of which one contain χ^1 was found to give good results, the model obtained is as follows-

MIC = 8.1771, -0.2869(±0.0473) χ^1

…… [1]

N=24, MSE=0.2942, R^2=0.6255, AR^2=0.6085, Q-VALUE= 2.6882

Here n is the number of compound, MSE is the means square error of estimation, R^2 is the regression coefficient, AR^2 Is the adjusted Regression coefficient and Q-value is the Quality factor.

MIC = 9.9266, 0.0904(±0.0422) ZM^1, -1.3745(±0.5093) χ^1 ……[2]

N=24, MSE=0.2529, R^2=0.6927, AR^2=0.6634, Q-VALUE=3.2909

MIC = -33.7641, -0.0415(±0.0127) ZM^1V, 0.1111(±0.0413) ZM^2, 6109643(±16.2567) χ^0A ….. [3]

N=24, MSE=0.2016, R^2=0.7666, AR^2=0.7316, Q-VALUE=4.343

MIC = 10.9409, -0.0371(±0.0117) ZM^1V, 0.1184(±0.0390) ZM^2, 1.1109(±0.2842) χ^0, -1.9720(±0.4605) χ^1 …. [4]

N=24, MSE= 0.1789, R^2= 0.8033, AR^2= 0.7619, Q-VALUE= 5.0098

Finally in order to confirm out of the proposed models which is the most appropriated for modeling the biological activity? We calculated the pogliani's quality factor Q which is Ratio of R and MSE (Means square error) among this Q value maximum value is found for Eq.4 as 5.0098. So Eq. 4 is the best model for modeling biological activity with topological and connectivity parameters and a graph (fig 1 & 2) are plotted between observed vs. predicted values of biological activity from Eq. 4.

We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

The various cross validation parameters, calculated for the proposed models, are presented on Table-5 and are discussed below.

PRESS is an important parameter for cross validation for account a good estimate of the real predictive error of the model. When its value is less than the SSY, the model predicts better than by chance alone, and can be considered statistically significant and are better that chance.

For the QSAR model to be considered reasonable, PRESS/SSY should be smaller than 0.4 and the data presented in Table-5 indicate that model no. 4 proposed are significant. Finally in order to confirm our finding, biological activity were compared with the corresponding values reported in Table-2 and comparisons are shown in Table-4. The values agree well within experimental error. The residual is the difference between observed and calculated biological activity.

According the result of biological screening summary of 4-aminoquinoline derivatives graph is plotted between observed and predicted MIC (Fig-1), further a bar graph is also obtained to show the reliability of selected model between observed biological activity and residuals

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(Fig-2). Ridge regression is more significant for analyzing best linear unbiased estimate in multiple linear regression analysis, value of variance inflation factor represents the effect of multicolinearity is admissible or not. Since all VIF's are less than 10, therefore multicollenerity is not a problem in present study.

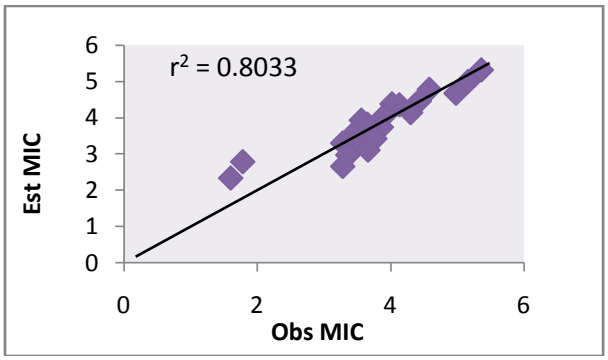

Fig. 1 - Plot of observed MIC versus experimentally MIC

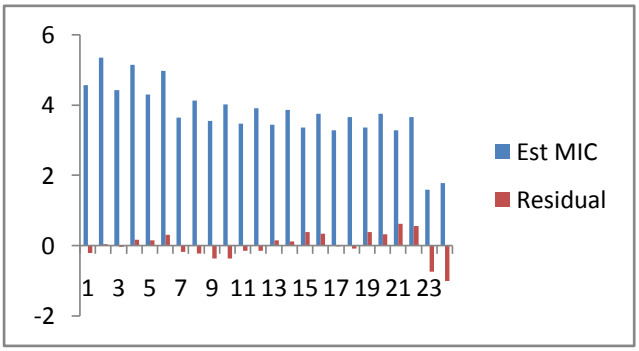

Fig. 2 - Plot of Estimated MIC versus Residual.

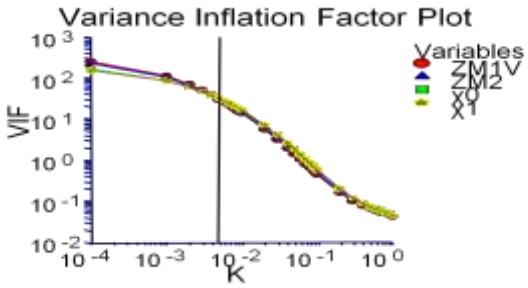

Fig. 3 - Ridge Regression Report.

TABLE- 2 – Calculated topological descriptors and biological activity of Compound

C. No.	MIC	ZM^1	ZM^1V	ZM^2	χ^0	χ^1	χ^0A
1	4.58	150	613	172	21.018	13.743	0.725
2	5.36	112	452	129	15.364	10.737	0.698
3	4.43	154	629	176	21.725	14.243	0.724
4	5.16	116	468	133	16.071	11.237	0.699
5	4.3	158	645	180	22.433	14.743	0.724
6	4.98	120	484	137	16.778	11.737	0.699

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7	3.65	162	661	184	23.14	15.243	0.723
8	4.13	124	500	141	17.485	12.237	0.699
9	3.56	190	758	221	25.872	17.12	0.719
10	4.02	152	597	177	20.217	14.097	0.697
11	3.47	194	774	225	26.579	17.62	0.718
12	3.91	156	613	181	20.924	14.597	0.697
13	3.44	198	790	229	27.286	18.12	0.718
14	3.86	160	629	185	21.631	15.097	0.698
15	3.36	202	806	233	27.993	18.62	0.718
16	3.76	164	645	189	22.338	15.597	0.698
17	3.28	196	807	230	26.742	17.548	0.723
18	3.66	158	646	186	21.087	14.525	0.703
19	3.36	200	823	234	27.449	18.048	0.722
20	3.76	162	662	190	21.794	15.025	0.703
21	3.28	204	839	238	28.156	18.548	0.722
22	3.66	166	678	194	22.501	15.525	0.703
23	1.6	208	855	242	28.863	19.048	0.722
24	1.78	170	694	198	23.209	16.025	0.703

ZM^1 = first Zagreb index, ZM^1V = first Zagreb index by valence vertex degrees.
ZM^2 = Second Zagreb index, χ^0 = connectivity index of order 0.
χ^1 = connectivity index of order 1 (Randic connectivity index).
χ^0A = average connectivity index of order 0.

TABLE -3- Correlation matrix

	MIC	ZM^1	ZM^1V	ZM^2	χ^0	χ^1	χ^0A
MIC	1						
ZM^1	-0.7655	1					
ZM^1V	-0.7725	0.9957	1				
ZM^2	-0.7704	0.9988	0.9953	1			
χ^0	-0.7536	0.9945	0.9938	0.9891	1		
χ^1	-0.7908	0.9962	0.9899	0.9935	0.9925	1	
χ^0A	-0.3006	0.6361	0.67	0.6144	0.697	0.6059	1

TABLE – 4 - Residual Report

C. No.	Obs MIC	Est MIC	Residual
1	4.785	4.58	-0.205
2	5.321	5.36	0.039
3	4.464	4.43	-0.034
4	5	5.16	0.16
5	4.144	4.3	0.156
6	4.678	4.98	0.302
7	3.823	3.65	-0.173
8	4.357	4.13	-0.227
9	3.934	3.56	-0.374
10	4.384	4.02	-0.364
11	3.613	3.47	-0.143
12	4.062	3.91	-0.152
13	3.292	3.44	0.148
14	3.741	3.86	0.119
15	2.97	3.36	0.39
16	3.42	3.76	0.34
17	3.302	3.28	-0.022
18	3.752	3.66	-0.092
19	2.981	3.36	0.379
20	3.431	3.76	0.329
21	2.66	3.28	0.62
22	3.109	3.66	0.551
23	2.339	1.6	-0.739
24	2.789	1.78	-1.009

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TABLE – 5 – Result of Cross Validation

Model No	N	PRESS	SSY	PRESS/SSY	R^2	R^2_{CV}	PSE	S_{press}
1	24	6.4726	10.8105	0.5987	0.6255	0.4013	0.1060	0.5424
2	24	5.3109	11.9722	0.4436	0.6927	0.5564	0.0960	0.5028
3	24	4.0336	13.2495	0.3044	0.7666	0.6956	0.0836	0.4489
4	24	3.3997	13.8835	0.2449	0.8033	0.7551	0.0768	0.4229

IV. CONCLUSION

The following conclusions are obtained from this analysis:

(1) Topological and connectivity parameters may be used for modeling of these compounds.

(2) Topological and connectivity parameters are more effective in this QSAR study.

(3) ZM^1, ZM^1V, ZM^2, χ^0, χ^1, χ^0A parameters is useful for this study.

(4) The highest value R^2 = 0.8033 are obtained in QSAR models.

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