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Qsar Study for Antimicrobial Activity of Quinoline Based Quinazolinone -4- Thiazolidinone Heterocycles

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ABSTRACT: In an attempt to find new pharmacologically active molecules, we report here the synthesis and in vitro antimicrobial activity of various 2-(2-chloro-6-methyl(3-quinolyl))- 3-[2-(4-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]-5-[(aryl)methylene]-1,3-thiazolidin-4-ones. Results of statistical analysis found with value of Variance as 0.7622, Cross validated regression coefficient and Fisher- value as 0.6881 and 11.221 respectivelywhich 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 antitumor agents in future.

Key words: QSAR,Quinazoline, antimicrobial activity.

I. INTRODUCTION

Quinazoline derivatives are one of the maximum energy guides of compounds with a broad organic recreational spectrum. They are widely used in prescription drugs and agrochemicals; for example - Fungicide fluquinconazole for the management of agricultural diseases.[1-5] Many reviews have been posted on the biological preferences of quinazoline derivatives including their bactericidal, natural and antitumor preferences. Their synthesis is therefore a remarkable pastime in the generation of bioenergetic heterocyclic compounds. Recently, several quinazolines have been suggested to have excellent antibacterial activity (Desai &Dodiya, 2011). Motivated by these findings, the existing paper describes the synthesis of an expanded collection of 3-substituent-2-phenylquinazolin-4(3H)-on derivatives and testing in antimicrobial preferences of them.[6-11]

Quinoline is known to inhibit DNA synthesis by promoting the cleavage of bacterial DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death. Several entirely quinolinebased pills, including doxorubicin and mitoxantrone, have been heralded as one of today's simplest cancer retailer's scientific manuals with software that extends to multiple treatments.[12-15]leukaemia and lymphomas as well as in mixed chemotherapy of aggressive tumours. The potent antitumor activity beyond certain toxic consequences for these Compounds is generally attributed to, at least, 2 main mechanisms: one, protein binding, involving entrainment of protein enzyme cleavable DNA intermediates, while the other, which is not protein related, is involved in the redox process of quinoline radicals, generating destructive free radicals.[16-20]

II. PRESENTATION OF DATA

In present study table1 represents the structure of 3-substituted-2-phenylquinazolin-4(3H)-one derivatives, while table 2 shows the calculated topological&2-D matrix descriptors with antimicrobial activity of quinazoline derivatives; table 3 represents the correlation matrix between different topological&2-D matrix descriptors.
Table 4 represents the residual report from best model of topological&2-D matrix descriptors. Table 5 represents the Cross validation of best models.

TABLE 1: Structures of 3-substituted-2-phenylquinazolin-4(3H)-one

Com. No.	Structure of Compounds	Com. No.	Structure of Compounds

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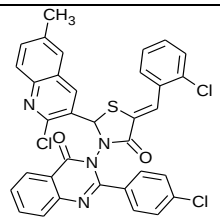
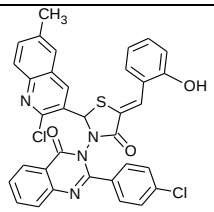
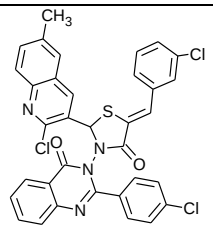
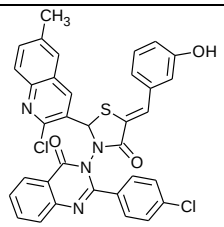
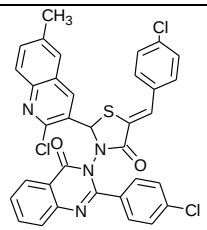
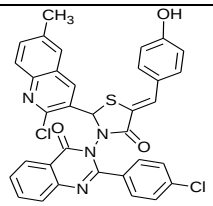
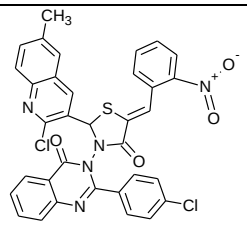
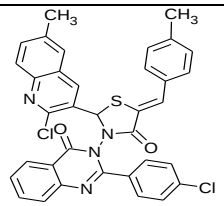
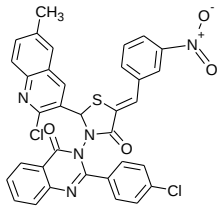
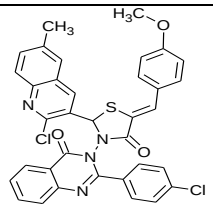
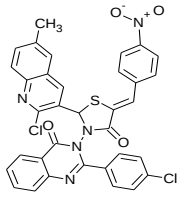
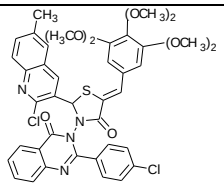
Com. 1		Com. 7	
Com. 2		Com. 8	
Com. 3		Com. 9	
Com. 4		Com. 10	
Com. 5		Com. 11	
Com. 6		Com. 12	

III. RESULTS AND DISCUSSION

QSAR study of a series of 3-substituted-2-phenylquinazolin-4(3H)-one derivativeswas per-formed by using dragon software. In this study, antimicrobial activity (E.coli) as dependent and various topological &2-D matrix 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 12 compounds that the antimicrobial activities of all 12 compounds gave maximum and minimum value range of antimicrobial activities.

In order to understand experimental antimicrobial activity data of 12, 3-substituted-2-phenylquinazolin-4(3H)-one Compound on theoretical basis, we established a QSAR study between antimicrobial activity and descriptor for

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topological &2-D matrix properties of the molecules under consideration 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 descriptors have to be considered.

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

The different molecular descriptors independent variables like topological& 2-D matrix indices **(Chi_X, ChiA_X, J_X, MSD, SMTI, SMTIV)**are calculated for compounds 3-substituted-2-phenylquinazolin-4(3H)-one presented in table 2.

Preliminary analysis was carried out in terms of correlation analysis (table 4.10.3). In general high co-linearity (r>70) was observed between different parameters.

It is clear from these table that topological &2-D matrix parameters are strongly correlated with antimicrobial activity with value of correlation coefficient more than 0.7 i.e. with Chi_Xand J_X strong auto correlation is also exist between Chi_X and J_X etc. so correlation matrix indicated the predominance of topological &2-D matrix parameter in describing the antimicrobial activity heterocyclic compounds 3-substituted-2-phenylquinazolin-4(3H)-one.

The data presented in table 3 demonstrated the low co-linearity between the parameters (r<70) indicated that these parameter could be combined to get multiples regression (MLR) models. The analysis of matrix disclosedtopological&2-D matrix descriptors for the development of (MLR) models.

The regression analysis gave mono parametric models. Out of which one contain **mean square distance index (Balaban) (MSD)** was found to give good results, the model obtained is as follows:

Antim. Act. = -3681.6232+526.4962(±263.5359)MSD [1]

N=12, √MSE=146.0584, R^2=0.2853, AR^2=0.2138, Q-VALUE= 0.0036

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. From above mono parametric model it is clear that **mean square distance index (Balaban) (MSD)** has a positive correlation influence on toxicity suggest that toxicity as expressed by E.coli decreases with increase in magnitude of **mean square distance index (Balaban) (MSD)**.

Bi parametric correlations involves the **Randic-like index from chi matrix (Chi_X) andBalaban-like index from chi matrix (J_X)** as:

Antim. Act. = -848408.0829+33239.9163(±9102.9594)Chi_X-2596.2302(±712.2809)J_XD [2]

N=12, √MSE=108.3826, R^2=0.6458, AR^2=0.5686, Q-VALUE=0.0074

In this model molecular refractivity shows also a negative influence on antimicrobial activity and increase from 0.2853 to 0.6458 in variance is observed.

After deleted Compound no 3 and 8 the best bi parametric correlation involves the **Randic-like index from chi matrix (Chi_X)** and**Balaban-like index from chi matrix (J_X)** as follows:

Antim. Act. =-895682.5236+ 35122.6496(±7678.5986)Chi_X - 2745.6498(±600.9110)J_X [3]

N=10, √MSE=90.6402, R^2=0.7622, AR^2=0.6943, Q-VALUE=0.0096

Finally in order to confirm out of the proposed models which is the most appropriated for modeling the antimicrobial 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.3 as 0.0096. So Eq. 3 is the best model for modeling antimicrobial activity with topological & 2-D matrix parameters and a graph (fig. 1 & 2) are plotted between observed vs. predicted values of antimicrobial activity from Eq. 3.

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

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data presented in Table 5 indicate that model no. 3 proposed are significant. Finally in order to confirm our finding, antimicrobial 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 antimicrobial activity.

According the result of antimicrobial screening summary of 3-substituted-2-phenylquinazolin-4(3H)-one derivatives graph is plotted between observed and predicted E.coli (Fig. 1), further a bar graph is also obtained to show the reliability of selected model between observed antimicrobial activity and residuals (Fig. 2).

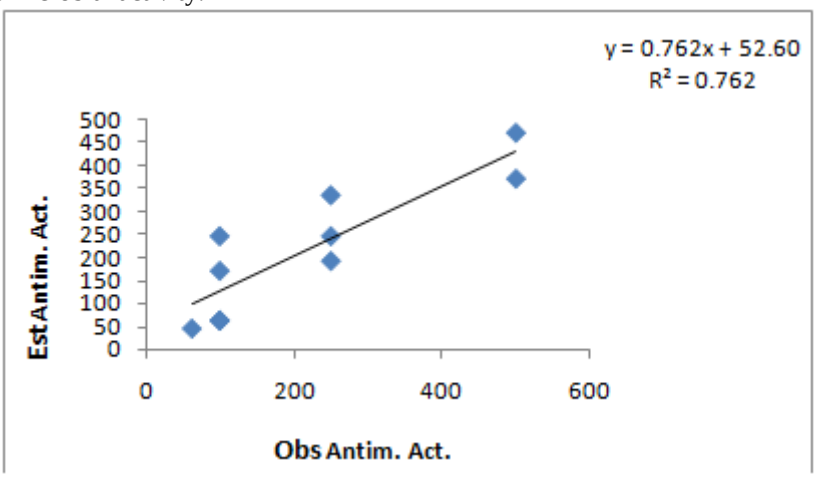

Fig. 1: Plot of observed Antim. Act. versus experimentally Antim. Act.

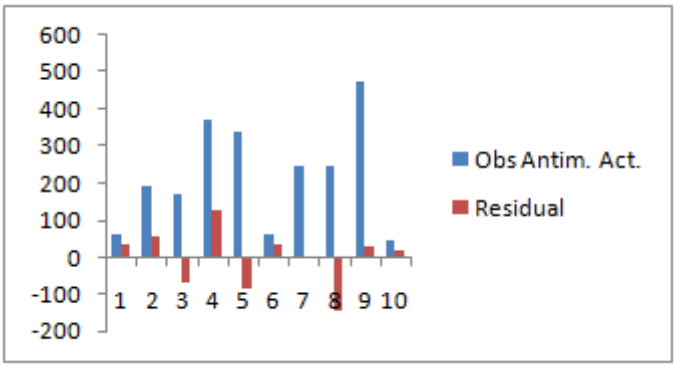

Fig. 2: Plot of Estimated Antim. Act. versus Residual.

TABLE2: Calculated topological, 2-D matrix descriptors and antimicrobial activity of Compound

Com. No.	Antim. Act.	Chi_X	ChiA_X	J_X	MSD	SMTI	SMTIV
1	100	49.868	0.997	311.675	7.173	27179	54999
2	250	49.875	0.997	311.7173	7.225	27338	55422
3	50	49.878	0.998	311.736	7.281	27498	55845
4	100	51.856	0.997	337.0663	7.394	30421	62491
5	500	51.867	0.997	337.1339	7.539	30900	63612
6	250	51.865	0.997	337.1214	7.696	31380	64733
7	100	49.868	0.997	311.675	7.173	27179	54649
8	25	49.875	0.997	311.7173	7.225	27338	55035
9	250	49.878	0.998	311.736	7.281	27498	55421
10	100	49.878	0.998	311.736	7.281	27498	54573
11	500	50.863	0.997	324.2542	7.502	29435	59344

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12	62.5	51.848	0.997	337.0098	7.487	30716	61119

Detailed Name of Descriptors

S. No.	Name of Descriptors	Detailed Name of Descriptors
1	**Chi_X**	Randic-like index from chi matrix
2	**ChiA_X**	Average Randic-like index from chi matrix
3	**J_X**	Balaban-like index from chi matrix
4	**MSD**	Mean square distance index (Balaban)
5	**SMTI**	Schultz Molecular Topological Index (MTI)
6	**SMTIV**	Schultz Molecular Topological Index by valence vertex degrees

TABLE 3: Correlation matrix

	Antim. Act.	Chi_X	ChiA_X	J_X	MSD	SMTI	SMTIV
Antim. Act.	1	0.6808	0.6505	0.6794	0.6822	0.6828	0.6886
Chi_X		1	0.9473	0.9996	0.9936	0.9991	0.999
ChiA_X			1	0.952	0.9093	0.9522	0.9521
J_X				1	0.9912	0.9998	0.9997
MSD					1	0.9903	0.9903
SMTI						1	0.9999
SMTIV							1

TABLE 5: Residual Report

Com. No.	ObsAntim. Act.	Est Antim. Act.	Residual
1	63.379	100	36.621
2	193.096	250	56.904
3	171.589	100	-71.589
4	372.333	500	127.667
5	336.408	250	-86.408
6	63.379	100	36.621
7	247.121	250	2.879
8	247.121	100	-147.121
9	472.338	500	27.662
10	45.737	62.5	16.763

TABLE6: Result of Cross Validation

Model No.	N	PRESS	SSY	PRESS/ SSY	R^2	R^2_{CV}	PSE	S_{PRESS}
1	12	213330.6	85145.96	2.5054	0.2853	0.00	34.7397	146.0584
2	12	105721.1	192755.4	0.5484	0.6458	0.4516	27.0956	108.3825
3	10	57509.55	184381.1	0.3119	0.7622	0.6881	23.9811	90.6402

IV. CONCLUSION

The followingconclusions are obtained from this analysis:

(1) Topological and 2-D matrix parameters are more effective in this QSAR study.

(2) **Chi_X, ChiA_X, J_X, MSD, SMTI, SMTIV**parameters is useful for this study.

(3) The highest value R^2 = 0.7622 are obtained in QSAR models.

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