Available online on 25.12.2017 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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CoMFA and CoMSIA Studies on 6, 8-Dibromo–4(3H)-Quinazolinone Derivatives for Anti-Bacterial Activity against *Salmonella typhimurium*

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ABSTRACT

In order to explore the structure – activity relationship of quinazolinone moiety for anti-bacterial activity against *Salmonella typhimurium*, a series of 4(3H) – quinazolinone derivatives were subjected to Comparative molecular field analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) methods. The best models for CoMFA and CoMSIA had correlation coefficient of 0.905 & 0.868 and cross-validated correlation coefficient of 0.501 & 0.592 respectively. The information obtained from the above models might be useful in designing of quinazolinone moiety as potent anti-bacterial agents.

Cite this article as: Dixit R, Soni LK, Sharma R, CoMFA and CoMSIA Studies on 6, 8-Dibromo–4(3H)-Quinazolinone Derivatives for Anti-Bacterial Activity against Salmonella typhimurium, Journal of Drug Delivery and Therapeutics. 2017; 7(7):93-96

INTRODUCTION:

Bacterial infections are becoming untreatable due to development of resistance in bacteria against the presently available anti – bacterial agents. This condition presents an immense need to search a new agent which could be effective against the bacteria. Quinazoline and quinazolinone derivatives have been widely studied for its diverse pharmacological activities. Of these, studies reveals 4- (3H)- quinazolinone derivatives as a potential moiety for anti – bacterial activity. There are three main positions (R_1, R_2, R_3) which can be varied in quinazolinone nucleus for variation in biological activity (Fig.1). Literatures also reveal that the variationat R_1position bring changes in anti – bacterial activity gram negative bacteria[1].

MATERIALS AND METHODS:

The antibacterial activities of 4 (3H) – quinazolinone derivatives (Table 1) against *Salmonella typhimurium* were taken from the work of Mohamed et al.[2]. The activities reported as zone of inhibition (ZOI) were converted to natural logarithm of zone of inhibition (lnZOI) (Table 2).

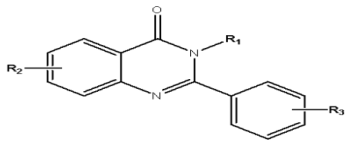


Figure 1: 4- (3H) quinazolinone moiety

The predictive power of QSAR was analysed by dividing the dataset into training set and test set.

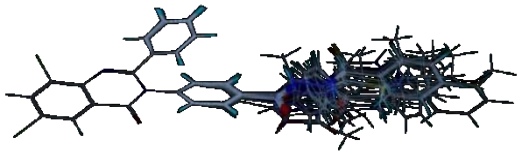


Figure 2: Structure alignment of molecules of 6, 8-dibromo-4(3H) quinazolinone derivatives (training)

Structural Alignment: The molecules taken in training set were aligned on the common template of quinazolinone.

CoMFA: Steric (S) and Electrostatic (E) fields were calculated using sp^3 hybridised carbon atom with +1 charge at each lattice of 2 Ansgstrom and the default energy cut off of 30 kCal/mol. Gasteiger, Gasteiger-Huckel, MMFF_94, DelRe and Pullman charges were used to generate the partial charges on the molecules under study and generated models were explored models for the best models.

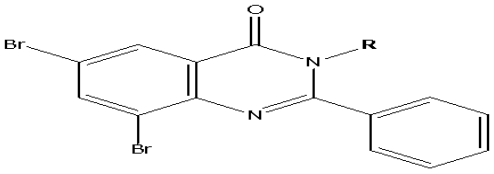
CoMSIA: CoMSIA descriptors i.e. Steric (S), Electrostatic (E), Hydrophobic (H), Hydrogen bond donor (D) and Hydrogen bond acceptor (A), were generated using a sp^3 hybridized carbon atom with +1 charge; the attenuation factor was set to 0.3 and a Vanderwaals radius of 1.4 Angstrom.

Partial Least Square and Predictive r^2 analysis: Leave one out (LOO) validation method was used to calculate optimum number of components while no validation approach was adopted for the predictability of the developed model. R^2_{pred} value is calculated for test set molecules and can be mathematically represented as;

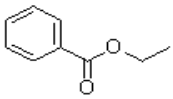
$$R^2_{pred} = 1- (PRESS/SD)$$

where SD is the sum of squared deviation between the biological activities of the test set molecules to the mean activity of the training set molecules, while PRESS is the sum of squared deviations between the observed the predicted activities of the test molecules.

Table 1 : Structures of the molecules considered for QSAR studies



Template



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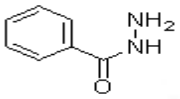

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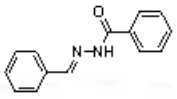

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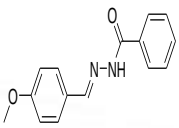

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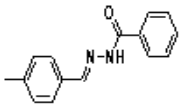

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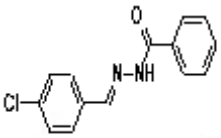

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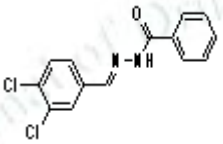

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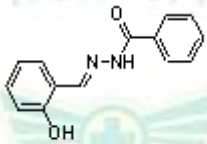

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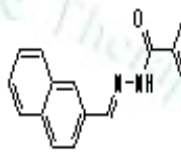

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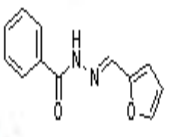

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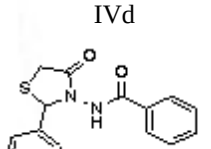

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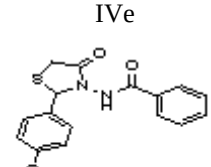

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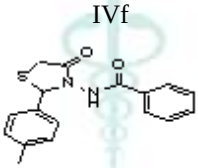

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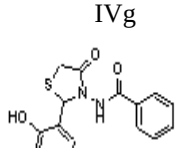

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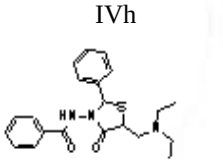

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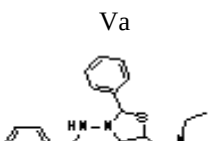

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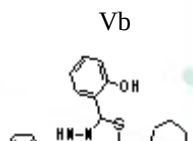

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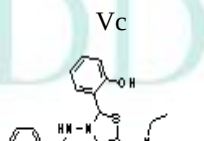

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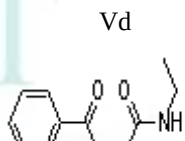

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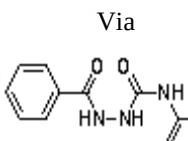

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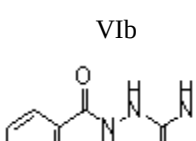

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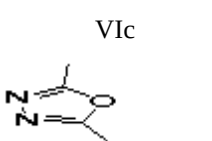

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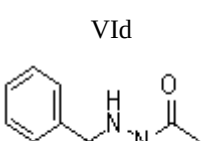

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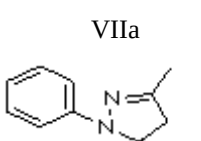


X

XI

Table 2: Experimental and predicted activities of 6,8-dibromo-4 (3H) quinazolinone derivatives with ZOI and lnZOI values of bacteria *Salmonella typhimurium*

XII			XIII			XIV		
Comp.	**ZOI (mm)**	**lnZOI**	**Comp.**	**ZOI (mm)**	**lnZOI**	**Comp.**	**ZOI (mm)**	**lnZOI**
Training								
II	16	2.7726	**IVg**	12	2.4849	**VIII**	12	2.4849
III	11	2.3979	**IVh**	16	2.7726	**IX**	14	2.6391
IVb	10	2.3026	**Vb**	12	2.4849	**X**	14	2.6391
IVc	15	2.7081	**VIa**	11	2.3979	**XI**	14	2.6391
IVd	10	2.3026	**VIb**	10	2.3026	**XIII**	17	2.8332
IVe	11	2.3979	**VIIb**	16	2.7726	**XIV**	11	2.3979
IVf	13	2.5649	**VIIc**	12	2.4849	**XV**	18	2.8904
Test								
IVa	10	2.3026	**Vd**	12	2.4849	**VIIa**	16	2.7726
Va	16	2.7726	**VIc**	15	2.7081	**XII**	12	2.4849
Vc	15	2.7081	**VId**	18	2.8904			

RESULTS AND DISCUSSION:

The best model was screened out on the basis of Q^2 (Crossvalidated R^2) ≥ 0.5 and R^2 > 0.6 (Table 3). The model was validated plotting the graph between observed biological activity versus predicted CoMFA and CoMSIA activity (Table 4). This revealed that the model is validated and contain proper training and test sets for further study.

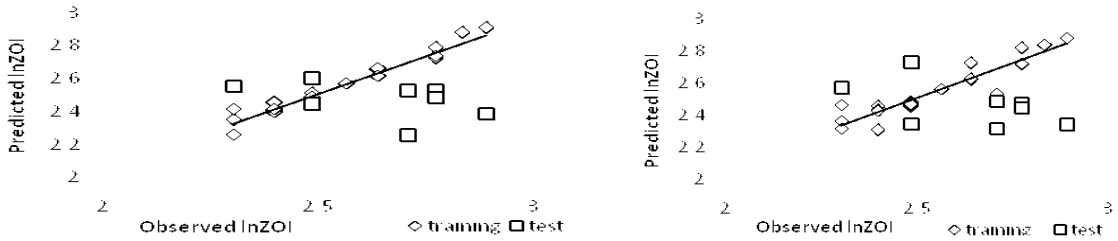
Table 3: CoMFA and CoMSIA statistical results and field contribution of training sets of 6,8-dibromo – 4 (3H) quinazolinone derivatives with for bacteria *Salmonella typhimurium* (Charge: MMFF_94)

Parameters	**CoMFA**	**CoMSIA**	**Parameters**	**CoMFA**	**CoMSIA**
Q^2(Crossvalidated R^2)	0.501	0.592	Steric field	0.407	0.223
R^2	0.905	0.868	Electrostatic field	0.593	0.777
F value	38.218	37.274	(N_1, N_2) for F	4,16	3,17
SEE	0.064	0.073	R^2_{pred}	0.494	0.513
No. of components	4	3			

Table 4: CoMFA and CoMSIA predicted activities of 6,8- dibromo-4(3H)quinazolinone series for bacteria *Salmonella typhimurium*

Comp	**CoMFA**		**CoMSIA**		**Comp**	**CoMFA**		**CoMSIA**	
	Predicted	**Residual**	**Predicted**	**Residual**		**Predicted**	**Residual**	**Predicted**	**Residual**
Training									
II	2.7231	0.0495	2.7224	0.0502	**VIb**	2.2586	0.044	2.314	-0.0114
III	2.4083	-0.0104	2.453	-0.0551	**VIIb**	2.7372	0.0354	2.82	-0.0474
IVb	2.3496	-0.047	2.3632	-0.0606	**VIIc**	2.4493	0.0356	2.4765	0.0084
IVc	2.5231	0.185	2.5345	0.1736	**VIII**	2.4905	-0.0056	2.4654	0.0195
IVd	2.4163	-0.1137	2.4628	-0.1602	**IX**	2.654	-0.0149	2.6223	0.0168
IVe	2.3976	0.0003	2.4301	-0.0322	**X**	2.6626	-0.0235	2.7264	-0.0873
IVf	2.5718	-0.0069	2.5638	0.0011	**XI**	2.6157	0.0234	2.6258	0.0133
IVg	2.5106	-0.0257	2.4552	0.0297	**XIII**	2.8787	-0.0455	2.8399	-0.0067
IVh	2.7853	-0.0127	2.7229	0.0497	**XIV**	2.4157	-0.0178	2.3062	0.0917
Vb	2.4612	0.0237	2.4561	0.0288	**XV**	2.9076	-0.0172	2.8825	0.0079
VIa	2.4541	-0.0562	2.4277	-0.0298					
Test									
IVa	2.5532	-0.2506	2.5722	-0.2696	**VIc**	2.2569	0.4512	2.3145	0.3936
Va	2.5271	0.2455	2.4747	0.2979	**VId**	2.3866	0.5038	2.3424	0.548
Vc	2.5283	0.1798	2.4856	0.2225	**VIIa**	2.4847	0.2879	2.4453	0.3273
Vd	2.4456	0.0393	2.3438	0.1411	**XII**	2.6019	-0.117	2.7322	-0.2473

Graphs:



Contour maps: In steric contour map, yellow colours shows steric group is unfavourable while green colour shows steric group is favourable. In electrostatic contour map, red colour shows electronegative group while blue group favours electropostive group.

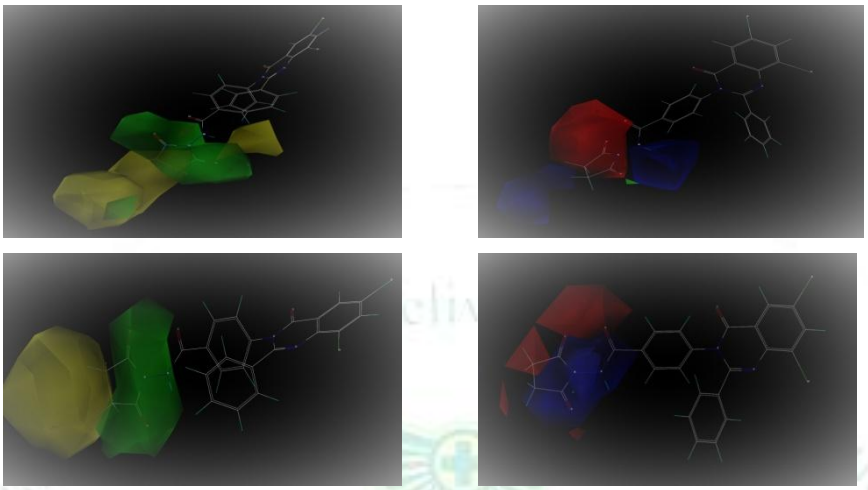
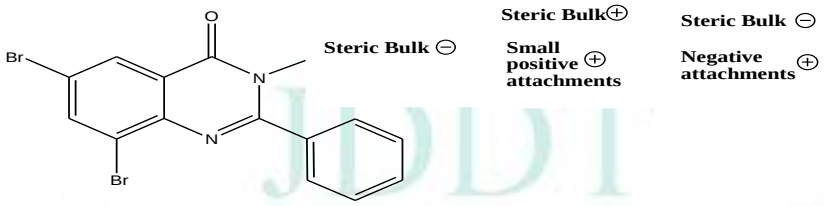


Figure 3: a) CoMFA–Steric b) CoMFA–Electrostatic c) CoMSIA– Steric d) CoMSIA –Electrostatic

Figure 4: Structure activity relationship on the basis of QSAR studies



Region_1: Non steric group with small positive charge attachments on it may be good for activity.
Region_2: Steric group with small hydrophobic and positive attachment may improve the activity.
Region_3: Less bulky group with negative substituents may be beneficial for anti-bacterial activity.

CONCLUSION:

3D-QSAR models developed in our present study are quite reliable based on appropriate statistical parameters and proper validation of test set. Though CoMFA method afforded slightly better predictability, models from both CoMFA and CoMSIA were utilized in development of SAR. The designed model could serve as a guideline for further study or development of novel anti-bacterial agent against *Salmonella typhimurium*.

Acknowledgement: The authors would like to acknowledge AICTE and UGC for the work carried out in DAVV.

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