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Research Article

COMFA ANALYSIS OF GALLIC ACID ANALOGS FOR ANTIOXIDANT ACTIVITIES

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ABSTRACT

Objective: The objective of the research is to study COMFA analysis of Gallic acid derivatives for antioxidant activities.

Methods: All molecular modeling techniques and COMFA studies were performed on silicon graphics. INDY R5000 workstation using the Sybyl 6.9 molecular modeling software package from Tripos

Results: By increasing more bulk groups near green, less bulk group near yellow, more positive charge near blue, more negative charge near red , we can still develop more active molecules.

Conclusion: The model developed by us is predictable and can be used for developing more active molecules

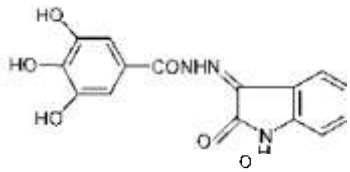
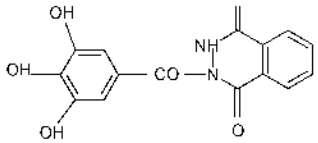
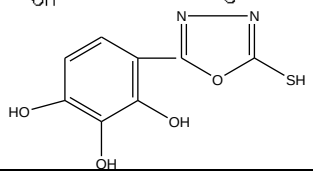
INTRODUCTION

Anti-oxidant capacity of gallate ester against hydroxyl, azide and superoxide radicals has also been reported .It is widespread in plant foods and beverages such as tea and wine and was proven to be one of the anticarcinogenic polyphenols present in green tea. The poly phenols were reported antioxidants [1]. It has shown phytotoxicity and antifungal activity and it is of great interest in arteriosclerosis prevention. It is found to posses various pharmacological activities like antioxidant [2] antimicrobial [3], analgesics [4], vasoconstrictorsresponse [5], antineoplastics [6], anti tyroniase activity [7]. We have already reported the synthesis of ten gallic acid derivatives and their antioxidant property [8]. In the present communication we report the QSAR activity of Gallic acid analogues for their antioxidant property.

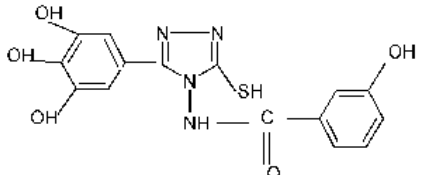
MATERIALS AND METHODS

All molecular modeling techniques and COMFA studies were performed on silicon graphics,INDY R5000 workstation using the Sybyl 6.9 molecular modeling software. 3D structures for all the compounds were drawn using Chem- Draw. Then conformational analysis was done. When no structure information is available, methods that investigate conformational space (e.g.: using stimulated annealing and cluster analysis) may find the best match between various ligands. The fragment libraries in SYBYL database were used as building blocks for the construction of most active molecules XX in training set. A preliminary minimization was performed to remove close atom contacts by 1000 cycles of minimization using standard **Tripos** force field (with 0.005 Kcal/mol energy gradient convergence criterion); and their charge were calculated by the **Gasteiger-Huckel** method. The structure was next subjected to molecular dynamic Simulation to heat the molecule at 2000 k fr 1000 fs followed by anneal the molecule to 200 K for 1000 fs. The lowest energy conformation was selected and the final minimization was carried out by 100 cycles. No significant conformational changes were observed during minimization process. All the remaining molecules were constructed using the same template and subjected to simple minimization and filled with **Gastiqer- Huckel** charge.After conformational analysis, pharmacophore alignment was done. Then model is developed. The activities for synthesized compounds are predicted and graph was drawn between predicted activity and actual activity. One compound was left graph is again drawn likewise the compounds were left randomly and graph was drawn until a linear line was obtained Here linear line was obtained by leaving compound 5 and 11.The nine compounds (III, I e, I a, I b, II b, I d, III a, II a, I c) were taken as training set and compounds 5 and 11 (III b, propyl gallate) all were taken as test set and model is build up. Structural alignment is done using this model.

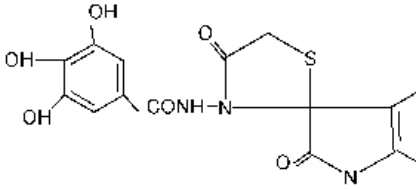
Table 1: List of compounds used in QSAR

S. No.	Structures
1(III)	
2(I d)	
3(I a)	

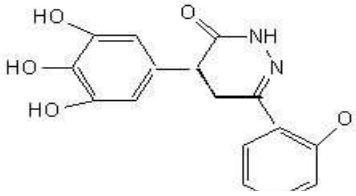
4(I b)



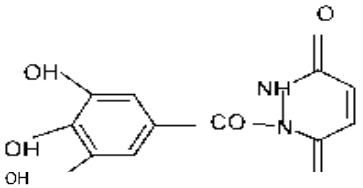
5(III b)



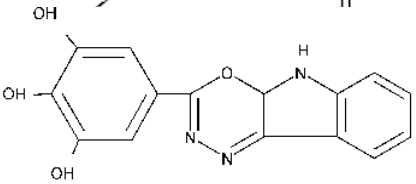
6 (II b)



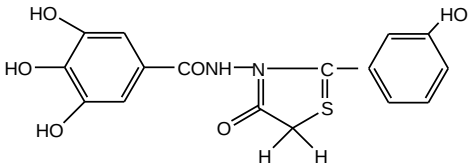
7 (I e)



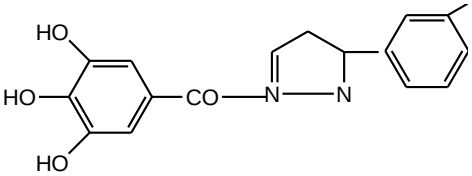
8 (IIIa)



9 (II a)



10 (I c)



11 (propyl gallate)

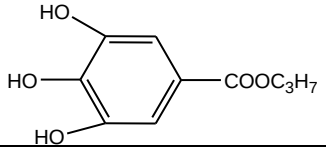


Table 2: Training Set Molecule

		Activity
1	MOLECULE_1	3.24
2	MOLECULE_2	3.45
3	MOLECULE_3	3.21
4	MOLECULE_4	3.29
5	MOLECULE_6	3.24
6	MOLECULE_7	3.49
7	MOLECULE_8	3.19
8	MOLECULE_9	3.21
9	MOLECULE_10	3.24

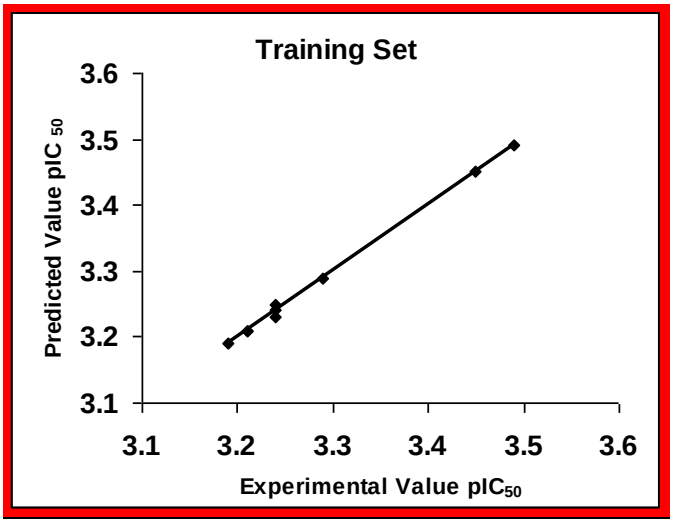


Fig. 1: Contours of the Steric map

Table 3: Regression Equations

		Activity
1	MOLECULE_1	3.24
2	MOLECULE_2	3.45
3	MOLECULE_3	3.21
4	MOLECULE_4	3.29
5	MOLECULE_5	3.41
6	MOLECULE_6	3.24
7	MOLECULE_7	3.49
8	MOLECULE_8	3.19
9	MOLECULE_9	3.21
10	MOLECULE_10	3.24
11	MOLECULE_11	3.43

Contribution of electronic and steric parameter were calculated using:

-log EC_{50} (PEC_{50}) = 0.719 (steric) + 0.281 (electronic)

n =9, r^2_{cv} = 0.523; r^2_{ncv} = 0.999; F= 1150.077.

Now the activities were predicted for test set (i.e. compound 5 and 11) using the model.

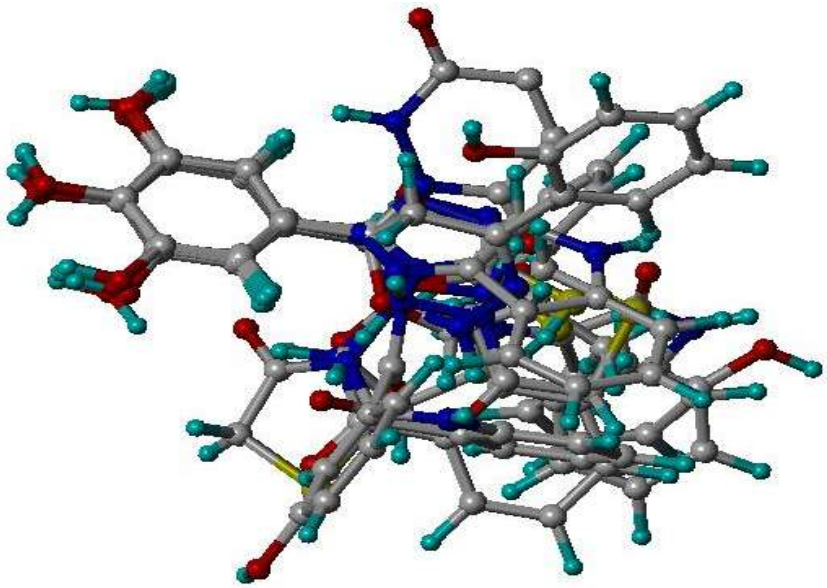


Fig. 2: bio-active measurement

The contours of the steric map are shown in yellow and green, and those of the electrostatic map are shown in red and blue (FIG – I). Greater values of "bio-active measurement" are correlated with: more bulk near green; less bulk near yellow; more positive charge near blue, and more negative charge near red. (FIG – II).There is also a graph of residuals, at each point representing a compound, with point in the upper right being the most active. (FIG –III)

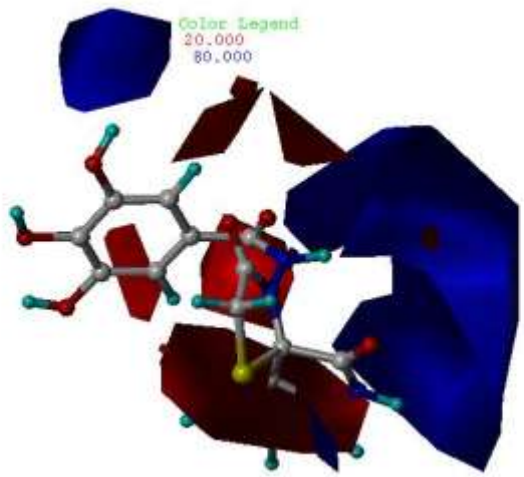
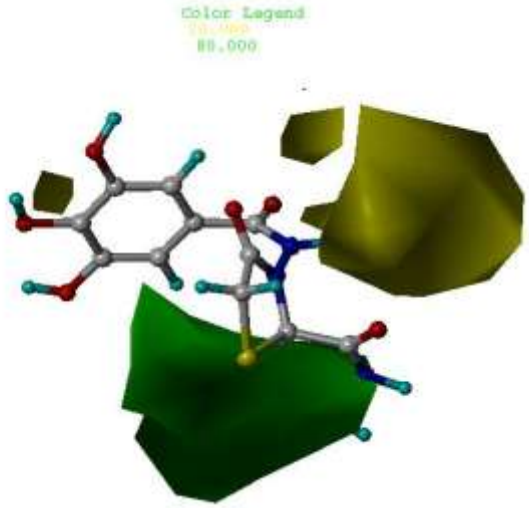


Fig. 3: Graph of residuals



RESULTS AND DISCUSSION

The predicted activities of test compounds are very close to the actual activities. R^2 value was less than 1. That shows that the model developed by us is predictable .By increasing more bulk groups near green, less bulk group near yellow, more positive charge near blue, more negative charge near red, we can still develop more active molecules.

PREDICTING MOLECULE _11 (M1) Test Set :-

Row 10 MOLECULE -11X Column #2 (COMFA2): COMFA ... predictionOf ACTIVITY FOR MOLECULE _ 11X: 3.2618

PREDICTING MOLECULE _ 5 (M2) Test Set:

Row 10 MOLECULE –5X Column # 2 (COMFA2): COFMA ...Prediction Of ACTIVITY for MOLECULE - 5X: 3.26606

Table 4: Predicted activity Vs Observed activity for test set compounds

Compounds	Predicted activity using COMFA	Observed activity
11	3.2618	3.43
5	3.26606	3.41

From the table we can observe that the predicted activity is closer to observed activity.

CONCLUSION

The statistical parameters for the developed model are significant. The predicted activity is closer to observed activity. So this model can be used for developing more active compounds.

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