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Quinazolinone Derivatives as Growth Hormone Secretagogue Receptor Inhibitors: 3D-QSAR study

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Abstract : The 3D-QSAR (CoMFA and CoMSIA) analyses has been performed on a series of Quinazolinone Derivatives in order to understand their Growth Hormone Secretagogue Receptor inhibitory activities. CoMFA and CoMSIA studies were also included in this study for the evaluation of 3D-QSAR model. In the present investigation, the CoMFA and CoMSIA methods were successfully employed for internal and external validation. Leave-one-out, no-validation, cross-validation and bootstrapping analysis were providing the most significant correlation between structural description and biological activity. Taking into account of 3D-QSAR and docking results, a series of new molecules with high predicted activities were designed.
Keywords: Quinazolinone Derivatives, 3D-QSAR, CoMFA, CoMSIA, Autodock.

Introduction

Heterocyclic compounds and their derivatives have attracted attention due to their different biological and pharmacological properties.[1] Heterocyclic compounds are the flexible compounds existing in all natural products and synthetic organic compounds.[2] Obesity is the key risk factor for type 2 diabetes. In developed countries around 90% of type 2 diabetes cases are due to increase in weight. Overweight issues in childhood and obesity are now leading to an arrival of premature type 2 diabetes. Type 1a growth hormone secretagogue receptor (GHS-R1a) is the only circulating appetite stimulant. Piperidine-substituted quinazolinone derivatives work as a new class of small molecule GHS-R1a antagonists.[1] Many anti-diabetic remedies are likely to increase body weight.[2] Diabetes mellitus is one of the major non communicable disease worldwide. It is the leading cause of death in developed countries. Diabetes mellitus belongs to heterogeneous group of disorders.[3]

Diabetes is a metabolic disorder characterized by hyperglycemia causing from defects in insulin secretion and insulin action. When Diabetes is not in it causes renal failure, neuropathy, cardiac arrest, heart attack and failure of blood vessels.[4] Diabetes Mellitus is a non-curable disease, which is characterized by several pathophysiologic deficiencies including progressive pancreatic β cell dysfunction, insulin resistance.[5] To our knowledge the present study is the application for 3D QSAR on quinazolinone derivatives as GHS-R1a inhibitors. The aim of current study is to analyze a correlation between the biological activity of molecules used in training set and their three dimensional structure. The importance of steric and electrostatic field characteristics is revealed by aligning structurally similar analogues using pharmacophoric features as structural superimposition guides.

CoMFA (Comparative molecular field analysis)[6] and CoMSIA (Comparative Molecular Similarity Indices Analysis)[7] methods are emerged as a very important methods in ligand based drug design strategies. Comparative molecular field analysis and comparative molecular similarity indices analysis has a combination of rational molecular descriptors, statistical analysis and graphical representation of results. Molecular structures are described with their interaction energies as steric and electrostatic fields surrounding the molecules, the statistics is computed by PLS[8] regression analysis and the output is displayed as contour maps superimposed on the molecules. The methodology of CoMFA predicts that a suitable sampling of steric and electrostatic fields surround a set of forty four aligned molecules provides all the information necessary for understanding their biological properties. The Comparative Molecular Similarity Indices Analysis methodology assumes that an appropriate sampling of hydrophobic, hydrogen bond donor and hydrogen bond acceptor along with steric and electrostatic fields.

Comparative Molecular Field Analysis is usually employed to increase the binding affinity. When used in a comparative investigation on the same series of molecules acting on multiple targets, such methodology is valuable in identifying the structural basis of the observed quantitative differences in the pharmaco toxicological properties. We developed the 3D QSAR CoMFA and CoMSIA models on Secretagogue receptor inhibitors in the expectation of getting a model that would account for the quantitative differences in biological activity seen in this series and to capitalize upon the insights to design ligands with strong inhibitory potency and selectivity.

Computational Studies

Dataset

The biological activity data of piperidine-substituted quinazolinone derivatives growth hormone secretagogue receptor inhibitors[9] were reported in IC_{50}. The IC_{50} values were converted into the corresponding pIC_{50} using the formula pIC_{50}=-logIC_{50}[13]. The logarithmic transformation helps to obtain a symmetrically distributed data which is apt for the PLS regression analysis.

The 3D-QSAR CoMFA and CoMSIA studies were carried out using piperidine-substituted quinazolinone derivatives growth hormone secretagogue receptor inhibitors. All the 25 compounds were partitioned into a test set of 7 and a training set of 18 compounds as 1:3 ratio (1 percent in test set is and 3 percent in training set) were selected randomly. The ligand-receptor interactions and statistically robust models were obtained from the CoMFA and CoMSIA studies.

Molecular Alignment

The MOPAC geometry optimized structures of piperidine-substituted quinazolinone derivatives have been aligned on the template molecule 5 by using the align database command on SYBYL, which is probably the most active molecule among the given set. Alignment of all the 25 compounds are shown in Fig.1

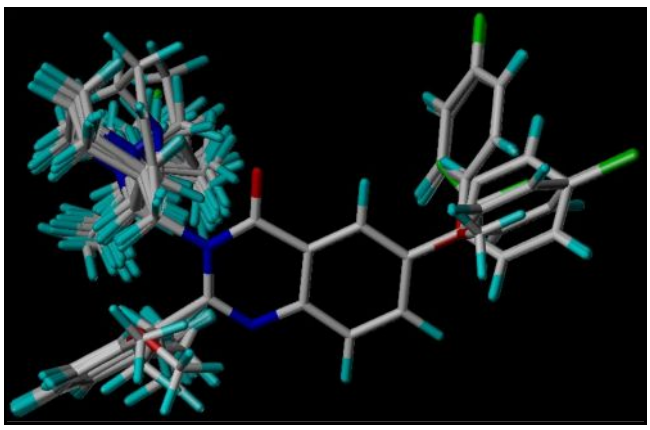


Fig.1 Conformations of piperidine-substituted quinazolinone derivatives superimposed on template compound 5

CoMFA Interaction Energies

The comparative molecular field analysis steric and electrostatic potential fields were calculated at each lattice intersection of a regularly spaced grid of 2.0. The vandar Waals potential and Columbic terms, these two signify steric and electrostatic fields respectively. A distance dependent dielectric constant of 1.00 was used[10]. A sp^3 hybridized carbon atom with +1 charge served as probe atom to calculate steric and electrostatic fields. +30.0 kcal/mol steric and electrostatic contributions were truncated. The cross-validation analysis was performed using leave-one-out method. The cross-validated q^2 that resulted in optimum number of components and lowest standard error of estimate was taken and also same weights for CoMFA were assigned to steric and electrostatic fields using CoMFA standard scaling option. To speed up the analysis a minimum column filtering value of 2.00 kcal/mol was used for the cross-validation. Further, final analysis was performed to calculate non cross-validated r^2 using the optimum number of components obtained from the leave one out cross validation analysis. To assess the robustness and statistical confidence we performed bootstrapping analysis by taking 100 runs.

Table.1: Statistical results of CoMFA, CoMSIA and PLS analysis

q^2	0.595		0.572	
r^2	0.985		0.984	
SEE	161.037		115.015	
F Value	0.141		0.153	
CV	0.602		0.609	
Bootstrap				
	Mean	Std.dev	Mean	Std.dev
SEE	0.085	0.069	0.089	0.074
r^2	0.994	0.004	0.994	0.005
Field Contribution (%)				
Steric	44.5		16.1	
Electrostatic	55.5		34.5	
Hydrophobic	-		01.1	
H Bond Donor	-		30.0	
H Bond Acceptor	-		18.3	

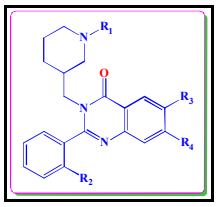
CoMSIA

In the present study, we analyze the nature of Piperidine-substituted quinazolinone derivatives using 3D-QSAR (Three-dimensional quantitative structure–activity relationship) analysis. (CoMSIA) Comparative molecular similarity indices analysis was used. In CoMSIA, changes in ligand affinities are directly related to changes in molecular properties.[11] CoMSIA method is good at describing the intermolecular interactions (steric, electrostatic, hydrophobic, hydrogen bond donor and acceptor) present at the molecular binding site. The method has been used to study the ligand–protein interactions before and has proved to be of good predictivity.

Partial Least Square (PLS)

The CoMFA and CoMSIA analyses were performed using the partial least square (PLS) method. PLS regression technique is useful in common cases where the number of descriptors is comparable to or greater than the number of compounds and / or there exist other factors leading to correlations between variables. Biological activity is used as dependent variable and molecular descriptors as independent variable. The column filtering was set to 2.0 kcal/mol, to improve the signal-to-noise ratio. q^2 (conventional r^2) were performed by the Leave-One-Out (LOO) procedure, for the calculation of optimum number of components (N). The cross-validated r^2 resulted in optimum number of components and lowest standard error of estimate was considered for further analysis. No-validation, cross-validation and finally bootstrapping analysis was performed to calculate conventional r^2 using the optimum number of components. Bootstrapping analysis for 100 runs was performed.

Table.2 a: Experimental and predicted residual values of piperidine-substituted quinazolinone derivatives growth hormone secretagogue receptor inhibitors used in training set



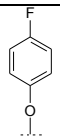
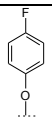
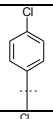
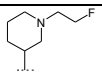
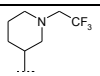
C. No	R_1	R_2	R_3	R_4	pIC 50	CoMFA		CoMSIA	
						Predicted	Residual	Predicted	Residual
2	Et	OM	OMe	H	6.04	6.51	-0.47	6.70	-0.66
3	Et	Me	OCF_3	H	7.62	7.84	-0.22	7.80	-0.18
4	H	Me		H	9.04	8.55	0.49	8.96	0.08
5	iPr	Me		H	9.33	8.94	0.39	9.69	-0.36
6	H	Me		H	8.15	8.46	-0.31	8.23	-0.08
7	Et	Me		H	8.74	8.21	0.53	8.33	0.41
9		Me	-	-	7.15	7.33	-0.18	7.39	-0.24
12		Me	-	-	8.40	8.28	0.12	8.21	0.19
13		Me	-	-	7.79	7.93	-0.14	7.72	0.07
14		Me	-	-	5.70	5.41	0.29	6.19	-0.49
16		Me	-	-	7.58	7.71	-0.13	7.29	0.29
18	iPr	iPr	-	-	7.40	7.14	0.26	7.38	0.02
19	iPr	iPr	-	-	7.34	7.21	0.13	7.36	-0.02
20	iPr	Me	-	-	6.96	6.58	0.38	6.86	0.10
21	iPr	H	-	-	6.35	6.69	-0.34	6.79	-0.44
23	iPr	iPr	-	-	8.40	8.56	-0.16	8.17	0.23
24	iPr	Me	-	-	7.77	8.27	-0.50	8.02	-0.25
25		Me	-	-	7.74	7.57	0.17	7.31	0.43

Table.2b: Experimental and predicted residual values of piperidine-substituted quinazolinone derivatives growth hormone secretagogue receptor inhibitors used in test set

C. No	R_1	R_2	R_3	R_4	pIC50	CoMFA		CoMSIA	
						Predicted	Residual	Predicted	Residual
1	iPr	Me	H	H	5.92	5.49	0.43	5.44	0.48
8		Me	-	-	8.77	8.06	0.71	8.31	0.46
10		Me	-	-	8.74	8.37	0.37	8.35	0.39
11		Me	-	-	8.60	7.93	0.67	7.96	0.64
15		Me	-	-	6.60	7.08	-0.48	7.16	-0.56
17	Et		-	-	8.70	7.99	0.71	8.97	-0.27
22	IPr		-	-	9.06	8.70	0.36	8.58	0.48

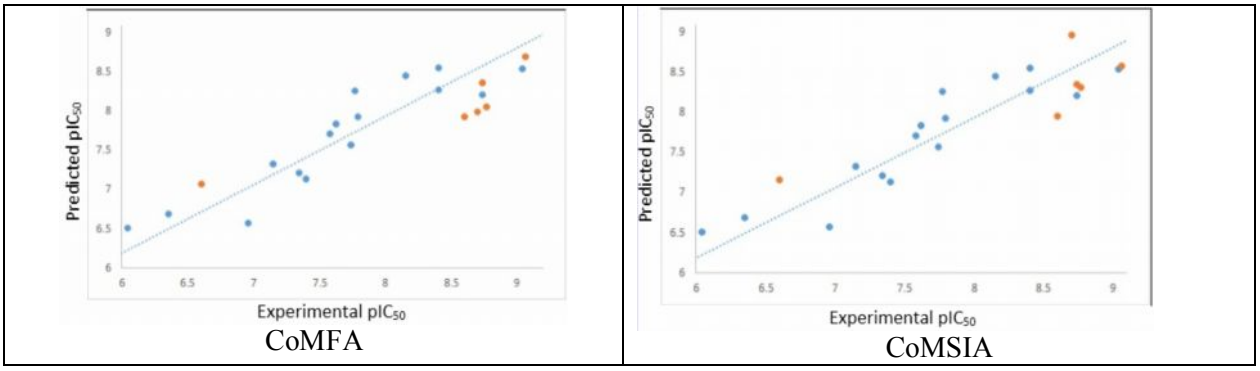


Fig.2 CoMFA, CoMSIA plots of experimental vs predicted pIC_{50}

Results and Discussion

The 3D-QSAR CoMFA and CoMSIA studies were carried out using Piperidine-substituted quinazolinone derivatives Growth Hormone Secretagogue Receptor Inhibitors, which are reported IC_{50} values on Growth Hormone Secretagogue Receptor. Quinazolinone derivatives were taken for the present study. All the 25 quinazolinone compounds were partitioned into a test set of seven and a training set of 18 compounds as 1:3 ratio (1 percent in test set is and 3 percent in training set) were selected randomly. The ambiguity of ligand-receptor interactions in general, statistically robust models were obtained from the CoMFA and CoMSIA models. Training set and test set Experimental and predicted activities are given in table 2 (a) and 2 (b).

The CoMFA and CoMSIA PLS analysis is summarized in Table 1. The cross-validated correlation co-efficient is used as a measure of goodness of prediction whereas the non-cross-validated conventional correlation co-efficient indicates goodness of fit of a QSAR model. F- value indicates for the degree of statistical confidence. A cross-validated correlation co-efficient q^2 of 0.595 was obtained using 5 as optimum number of components and 2.0 kcal/mol column filtering was used for the present model. The r^2cv obtained indicates a good internal predictive ability of the models. The models developed also exhibited a good non-cross validated correlation co-efficient r^2 of 0.985. The Test set compounds are used to evaluate the external predictive capabilities of QSAR models. 7 compounds were selected in test set randomly were set-aside during model development. Further, a bootstrapping analysis was done for 100 runs. The r^2bs value obtained 0.994 of bootstrapping by 100 runs which further supports the statistical validity of the developed models and absence of

chance correlation. The contributions of steric to electrostatic fields were found to be 44.5% for steric and 55.5% for electrostatic. Steric contribution is more than compared to electrostatic contribution.

The optimum CoMSIA model was derived with the combination of steric, electrostatic, hydrophobic, H-bond donor and H-bond acceptor field contribution using Gasteiger-Hückel charge with 2.0 Å grid space. Leave one out analysis gave the cross-validated q^2 of 0.572 with 6 components and column filtering was set to 1.0 kcal/mol. Non-cross-validated PLS analysis resulted in a correlation coefficient r^2 of 0.984, F= 0.153, with an standard error of estimate 115.015. Later we performed bootstrapping analyses to evaluate the robustness and statistical confidence of the final models (r^2 bootstrapping = 0.994, StdDev= 0.005). Statistical results obtained from the developed model verified the predictive ability of the model. The predictive ability of the developed CoMSIA model was assessed by the test set (7 molecules), were excluded during model generation. Predicted, experimental, residual values of all inhibitors are shown in Table 2 (b)

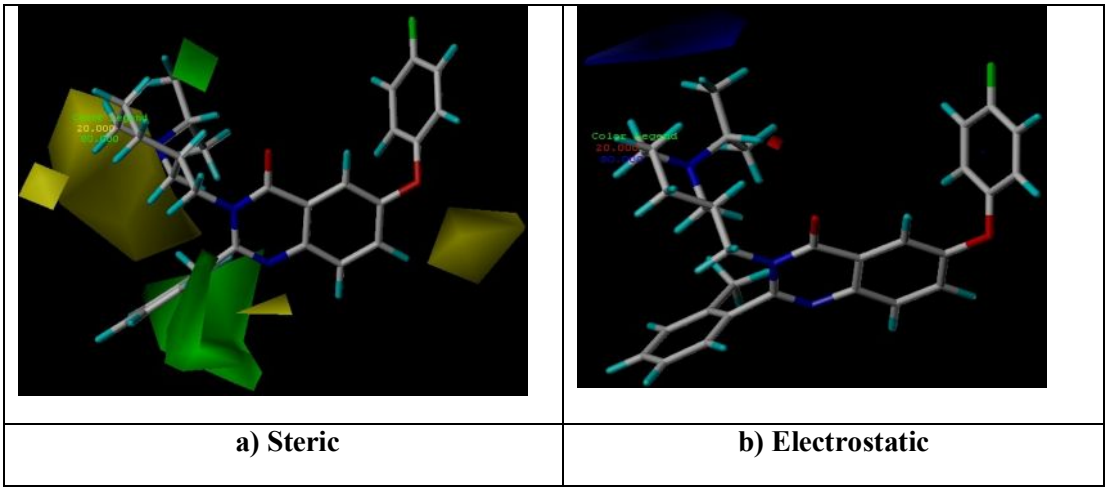
Contour Analysis

In SYBYL, steric interactions are displayed by green and yellow contours while electrostatic interactions are represented as red and blue contours. Green contours indicate where sterically bulkier groups are anticipated to increase the biological activity whereas the yellow contours are used to decrease the points where bulkier groups could lower the biological activity. The electrostatic red contours indicates where the presence of a negative charge is expected to increase the biological activity whereas the blue contours indicate where inserting positive charge is expected to better the experimental activity.

CoMFA Counter Analysis

In SYBYL, sterically favoured regions are representing in green colour contours (contribution level of 80%), unfavoured regions are shown in yellow colour contours (contribution level of 20%). Positive potential favoured regions are shown in blue colour contours (contribution level of 80%), Positive potential unfavoured regions are shown in red colour contours (contribution level of 20%). Colour polyhedra represent areas on or near the ligand where hydrogen bonding correlates strongly with binding affinity. Cyan colour indicates hydrogen-bond donors favoured; purple colour indicates hydrogen bond donors disfavoured; magenta colour indicates hydrogen-bond acceptors favoured; and red colour indicates hydrogen-bond acceptors disfavoured.

The CoMFA steric and electrostatic contour maps of piperidine-substituted quinazolinone derivatives for most active compound 5 in the data set is shown in Fig.3a & 3b. A big green counter near to R^2 position suggests sterically favourable regions where more bulky substituents are preferred to enhance the biological activity. Yellow polyhedron near to R^1 position reveals sterically unfavourable regions. In electrostatic counter maps a blue polyhedron present at R^1 position, which indicates more electron donating groups at blue region enhance the activity. A very small red polyhedron near to isopropyl group indicating more electron withdrawing groups at red region enhance the activity.



a) Steric	b) Electrostatic

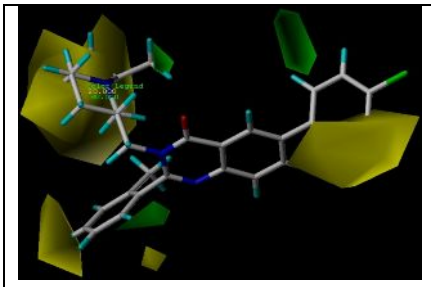
Fig. The CoMFA steric and electrostatic contour maps of piperidine-substituted quinazolinone derivatives

CoMSIA Counter Analysis

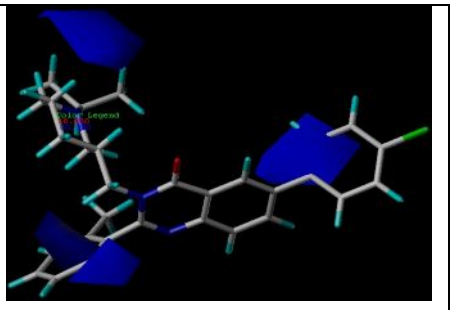
In CoMSIA, three green contours near to R^1, R^2 and R^3 positions suggested that more steric groups are favourable at this region and also a medium sized polyhedron at R^4 position and a small sized polyhedron present at R^2 position, indicating that bulky substituent's were preferred at this region. A big yellow polyhedron near R^1 position reveals that less steric groups are favourable. Electrostatic contours are displayed in blue and red color. In CoMSIA, three blue color contours are present at R^1, R^2, R^3 positions, which indicates electron donating groups at blue region increase the binding affinity. There is a no red contour present.

CoMSIA hydrophobic contour maps are represented by yellow and white colours. It shows a big and a medium sized contour near R^2 and R^3 positions indicates favourable for hydrophobic substitution increase activity. Two white polyhedron present at R^1 and R^4 positions which indicates disfavored conformation for hydrophobic substitution.

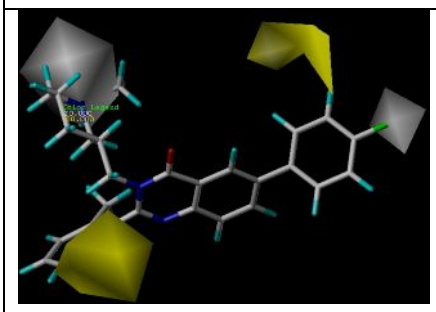
Colour contours represent areas on or near the ligand where hydrogen bonding correlates strongly with binding affinity. Cyan colour indicates hydrogen-bond donors favoured; purple colour indicates hydrogen bond donors disfavoured; magenta colour indicates hydrogen-bond acceptors favoured; and red colour indicates hydrogen-bond acceptors disfavoured. Hydrogen bond donor and acceptor explain the spacial arrangement of the favourable and disfavour able H-bond interactions to donor or acceptor groups of the target protein. Most active compound 5 shows a large purple colour contour at R^1 position. That indicates hydrogen bond donor disfavoured at this region. A medium sized magenta contour present at R^1 position, which indicates hydrogen bond acceptors are favoured.



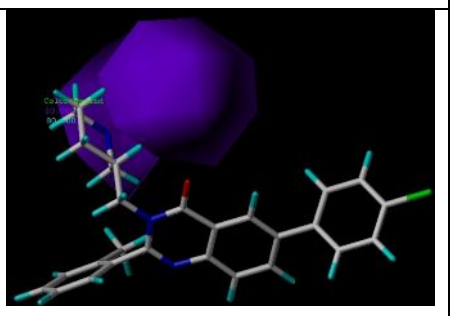
(a) **Steric**



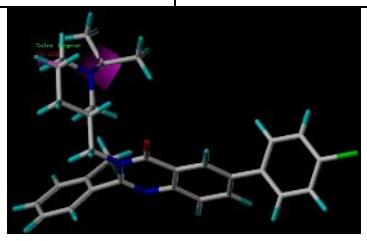
(b) **Electrostatic**



(c) **Hydrophobic**



(d) **Hydrogen-Bond Donor**



(e) **Hydrogen-Bond Acceptor**

Fig.4: CoMSIA steric, electrostatic, hydrophobic, hydrogen-bond donor and hydrogen-bond acceptor contour maps of piperidine-substituted quinazolinone derivatives

Conclusion

In the present work the 3D-QSAR CoMFA and CoMSIA technique have been effectively carried out on 25 piperidine-substituted quinazolinone derivatives. These derived models could be usefully employed to arrange chemicals for synthesis or in search of novel scaffolds from screening of chemical databases. The contour plots offer valuable insights into connections between structural description and inhibitory activity. Those features used to plan new lead compounds displaying better inhibitory activities.

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