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# Modified Quercetin Derivatives as Potent Anti Diabetic Agents: A QSAR Approach

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## ABSTRACT

A 3D QSAR model has been developed from a series of 17 synthesized congeners of quercetin as *α-amylase* inhibitors. Physico-chemical parameters and *α- amylase* inhibitory activity were taken as independent and dependent variables respectively. The multiple regression analysis was carried out using a compute program VALSTAT. All the possible combinations of parameters were considered for the QSAR study. The best model was selected on the basis of various statistical parameters. This study indicates that, lumo energy, shape attribute and total connectivity were important for the inhibition of *α- amylase* enzyme and contributes positively to anti diabetic activity. The information generated from the present study may be useful in the design of more potent structural motifs of quercetin as *α- amylase* inhibitors.

**Keywords** - QSAR, Quercetin, α- *Amylase*.

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## INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by a congenital (type I insulin dependent diabetes mellitus/IDDM) or acquired (type II noninsulin-dependent diabetes mellitus/ NIDDM) inability to transport glucose from the bloodstream into cells [1]. At present it is estimated that 150 million people, worldwide, have diabetes and that it may increases to 220 million by 2012 and 300 million by 2025. Globally, type II diabetes afflicts approximately 90% of all diabetes. So there is a need for potent anti-diabetic agent. Quercetin belongs to flavonoid group of polyphenols, reported in onion, apple, citrus fruits and red grapes etc [2]. It exhibits a wide range of biological activities such as antibacterial, antioxidant, antidiabetic, anticancer, anti-inflammatory etc. So the main objective of the present work is to synthesize potent modified derivatives of quercetin having anti-diabetic activity. *α- amylase* is one of the enzyme that catalyses the breakdown of starch to maltose and finally to glucose, which is the only sugar that can be utilized by the body. The inhibition of these enzymes leads to a decrease in blood glucose level [3].

The purpose of this study is to gain insight into the structural features related to *α-amylase* inhibitory activity of the compound from the quercetin congeners by applying the QSAR methodology and also to suggest a new substituent to enhance the anti-diabetic activity. The QSAR study is a useful tool for retinal search of bioactive compounds and it describes a definite role in quantitative term of structural feature in a molecule with a definite contribution to the activity of a particular physicochemical property of the structural feature [4]. Thus it provides a deeper insight into the drug receptor interaction. We therefore report here a QSAR study on quercetin derivatives for *in vitro α- amylase* inhibitory activity to explore their physicochemical properties required for inhibition and thus may be helpful in designing new molecules [5].


**1-10** **11-17**

**Fig.1 Skeletan structures of Quercetin analogues**

## MATERIALS AND METHODS

A set of 17 derivatives of quercetin (Fig.1) were synthesized and taken for the present QSAR study. The evaluated biological data ($IC_{50}$ in µg/ml) was converted into negative logarithmic dose in moles ($_PIC_{50}$) for quantitative structure activity relationship analysis. This is done to eliminate more clustering and rendering more suitable for QSAR analysis [6]. All the molecules were constructed using Chem. Office 12 version 8.0 Cambridge software and it was saved as template structure. For every compound the template structure was suitably changed considering its structural feature, copied on 3D model and finally the model was cleaned up and subjected to energy minimization using Molecular Mechanics ($MM_2$). The minimization was

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executed until the Root Mean Square (RMS) gradient value reaches a value smaller than 0.1kcal/mol. The energy minimized molecules were subjected to re-optimization via Austin model-1 method until RMS gradient attains a value smaller than 0.0001 kcal/mol $A^o$ using MOPAC. The variables used as descriptors in analysis are thermodynamic, electronic and steric parameters [7]. The descriptor values for all the molecules were calculated using compute properties module of the programme and tabulated in Table1. The data was transferred to the statistical programme in order to establish a correlation between physico-chemical parameters as independent variable and $pIC_{50}$ as dependent variable. The multiple regression analysis was carried out using a compute program VALSTAT. All the possible combinations of parameters were considered for the QSAR study.

## RESULTS AND DISCUSSION

Among the various models generated, model 1 to 3 were chosen for further analysis based on statistical parameters.. [8] Various QSAR equations generated are

**Model -1** BA= [2.23(± 0.214)] +LUMO [1.877(± 5.34)] +Shp A [1.015(± 1.28)] + TC [4.01]
n=11, r=0.9386, $r^2$=0.881, $Q^2$=35, Std=0.247, F= 0.955, PRESS= 0.0036, Variance=0.061, chance =< 0.551

**Model -2** BA= [2.28(± 0.22)] +Ovality [-4.64(± 1.57)] +Shp A [-9.21] +TC [3.35(± 9.588)]
n=11, r=0.7153, $r^2$=0.5172, $Q^2$=37, Std=0.250, F= 0.815, PRESS= 0.0441, Variance=0.062, chance =< 0.589

**Model-3** BA= [2.27(± 0.244)] +$P_X$ [-4.13] +$P_Z$ [9.6609(± 3.177)] +$E_S$ [6.2621]
n=11, r=0.5522, $r^2$=0.3047, $Q^2$=0.998, Std=0.275, F= 0.433, PRESS= 0.0004, Variance=0.075, chance =< 0.99

**Table 1: Descriptors used in present QSAR**

| S.No | Descriptors | Type |
|---|---|---|
| 1. | Log P | Thermodynamic |
| 2. | Molar refractivity(MR) | Thermodynamic |
| 3. | Connolly accessible area(CAS) | Steric |
| 4. | Connolly molecular area(CMA) | Steric |
| 5. | Connolly solvent excluded volume(CSEV) | Steric |
| 6. | Ovality | Steric |
| 7. | Principal moment of inertia x($x_p$) | Steric |
| 8. | Principal moment of inertia y($y_p$) | Steric |
| 9. | Principal moment of inertia z($z_p$) | Steric |
| 10. | Bend energy | Thermodynamic |
| 11. | Non 1,4-VDW energy($E_v$) | Thermodynamic |
| 12. | Stretch energy($E_s$) | Thermodynamic |
| 13. | Stretch bend energy($E_{sb}$) | Thermodynamic |
| 14. | Torsion energy | Thermodynamic |
| 15. | VDW 1,4 energy | Thermodynamic |
| 16. | Lumo energy | Electronic |

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| | | |
|---|---|---|
| 17. | Balban index(BAI) | Steric |
| 18. | Shape attribute | Steric |
| 19. | Shape coefficient | Steric |
| 20. | Sum of degrees(SD) | Steric |
| 21. | Total connectivity(TC) | Steric |

**Table 2: LOO predicted values**

| Comp.No | R -Substituents | Obs value* | Pred value* | Res value |
|---|---|---|---|---|
| 1 | 2,4-Dimethyl Phenyl | 2.255 | 2.250 | -0.005 |
| 2 | 2-Chloro Phenyl | 2.113 | 2.233 | -0.119 |
| 3 | 2-Nitro Phenyl | 2.431 | 2.310 | 0.120 |
| 4 | 4-Bromo Phenyl | 2.000 | 2.450 | -0.450 |
| 5 | 3-Phenyl CarboxylicAcid | 2.518 | 2.508 | 0.010 |
| 6 | 4- Phenyl CarboxylicAcid | 2.414 | 2.236 | 0.178 |
| 7 | 2- Pyridinyl | 2.301 | 2.233 | 0.067 |
| 8 | 1-Naphthyl | 2.204 | 2.234 | -0.030 |
| 9 | 2-Mercapto Phenyl | 2.079 | 2.233 | -0.154 |
| 10 | 4-Hydroxy Phenyl | 2.278 | 2.233 | 0.045 |
| 11 | 2- Pyridinyl | 2.309 | 2.234 | 0.075 |
| 12 | 4-Bromo Phenyl | 2.260 | 2.229 | 0.031 |
| 13 | 1-Phenyl Piperidin -4-yl | 2.150 | 2.236 | -0.086 |
| 14 | Morpholinyl | 2.460 | 2.233 | 0.226 |
| 15 | Dimethyl | 2.750 | 2.559 | 0.191 |
| 16 | Diethyl | 2.090 | 2.250 | -0.160 |
| 17 | 1-Benztriazolyl | 1.890 | 2.203 | -0.313 |

* Obs value-Observed value * Pred value-Predicted Value

The regression analysis study of anti-diabetic activity and physico-chemical descriptors has given a significant equation in model-1 with better correlation coefficient(r=0.938648) which accounted for more than 93.8% variance in activity. The data showed overall internal significance level better than 99.9%. The equation was further subjected to cross validation method to confirm internal consistency [9]. The predictive powers of the equations were validated by Leave-One-Out (LOO) cross validation method and given in Table 2. Predicted residual sum of square (PRESS), cross-validated $Q^2$ and standard deviation were considered for the validation of these models. The result from cross-validated analysis was expressed as the cross-validated squared correlation coefficient ($Q^2$). The $Q^2$ is defined as

$$Q^2 = 1-\sum (Y_{pred}-Y_{act})^2/(Y_{act}-Y_{mean})^2$$

Where $Y_{pred}$, $Y_{act}$, $Y_{mean}$ are predicted, actual and mean values of the target property (-log $IC_{50}$) respectively. $\sum (Y_{pred}-Y_{act})^2$ is the Predictive Residual Error Sum of Squares (PRESS).PRESS is an important cross validation parameter as it is a good approximation of the real predictive error of the model. The cross validated squared coefficient ($Q^2$=35) suggested good correlation between physico-chemical parameters and anti-diabetic activity [10]. All the descriptors LUMO energy, shape attribute and total connectivity positively contribute to the equation. The electronic parameter LUMO which denotes energy of the lowest unoccupied molecular orbital

bears a positive coefficient in the equation. The energy of LUMO is directly related to the electron affinity and characterizes the susceptibility of the molecule towards attack by nucleophiles. The positive coefficient of the LUMO energy indicates that increasing of LUMO energy will increase the magnitude of *α-amylase* inhibitory activity. Energy of LUMO can be increased by electron withdrawing substituents. Positive contribution of steric parameters, shape attribute and total connectivity shows that increase in these values will increase the magnitude of *α- amylase* inhibitory activity.

## CONCLUSION

QSAR analysis was performed on 17 synthesized derivatives of quercetin as anti-diabetic agents against *α-amylase* enzyme. All the molecules were constructed using Chem. Office 12 version 8.0 Cambridge software and multiple regression analysis was carried out using a compute program VALSTAT. Among the various models generated the best model was selected on the basis of various statistical parameters. It may be concluded that steric parameters are important for *α-amylase* inhibition and this data can be used to provide more potent congeners of quercetin as anti diabetic agents.

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