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PharmTech

International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.4, pp 1992-1995, Oct-Dec 2011

# QSAR Analysis of Meta-substituted Phenyl propanoic acids as Peroxisome Proliferator-Activated Receptor Gamma Agonists as Antidiabetic agents

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**Abstract:** A Quantitative Structure Activity Relationship Study was conducted using a series of meta-substituted phenyl propanoic acids as peroxisome proliferator-activated receptor gamma agonists using V-Life MDS software. The significance of the quantitative correlation between the descriptor and the biological activity are expressed as correlation coefficient ($r^2$ = 0.9393), cross validated correlation coefficient ($q^2$= 0.8718) and $F_{test}$= 77.3249, etc.

## INTRODUCTION

Diabetes is most likely heterogeneous groups of disease sharing nothing more then a real/potential abnormality of glucose metabolism.There are two type of diabetes-Diabetes insipidus (DI) and Diabetes mellitus. Diabetes mellitus (DM) consists of a group of syndromes characterized by hyperglycemia; altered metabolism of lipids, carbohydrates, and proteins; and an increased risk of complications from vascular disease. Most patients can be classified clinically as having either type 1 or type 2 DM. Both type 1 and type 2 DM are increasing in frequency. Diabetes can cause many complications[1,2]. Acute complications (hypoglycemia, ketoacidosis or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease (doubled risk), chronic renal failure, diabetic retinopathy (which can lead to blindness), diabetic neuropathy i.e. nerve damage (of several kinds), and microvascular damage, which may cause erectile dysfunction and poor healing.

A sharp increase in the incidence of type 2 diabetes especially in the developed and fast developing countries is a matter of serious concern. It is predicted that the world's diabetic population will be doubled to 300 million before 2025. Non-insulin dependent diabetes mellitus or type 2 diabetes is a metabolism disorder that is primarily characterized by insulin resistance, relative insulin deficiency and hyperglycemia[3-7].

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors (NRs) that control many cellular and metabolic processes. These proteins are ligand-activated transcription factors and three isotypes called PPARα, PPARβ/δ and PPARγ have been identified in

lower vertebrates and mammals. They display differential tissue distribution and each of the three subtypes fulfills specific functions; however, all three PPARs affect energy homoeostasis and inflammatory responses. Since the identification of peroxisome proliferator activated receptors (PPAR α, γ, and δ) of the nuclear receptor superfamily, rapid progress has been made in understanding their functions. Besides sensitizing insulin receptors, it has been established that they play a central role in regulating the storage and catabolism of lipids, which is linked to the pathogenesis of diabetes[8-10].

## MATERIAL AND METHODS

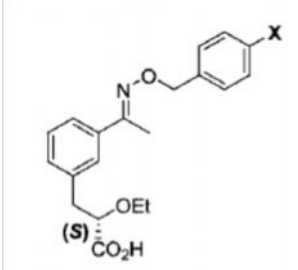
### 1. Data set

Experimental data set consist of 19 experimental biological activity [$IC_{50}$ (μM)] values were taken from Suh *at al*[11]. The sketched structures were subsequently energy minimized using universal force field.

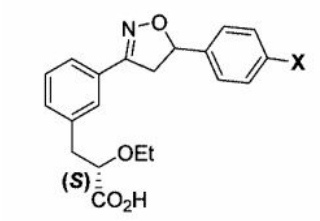
### 2. Computational approach

All the computational studies were performed on a HP Compaq PC running on Intel Pentium-D processor. The molecular structure of the training set and test were sketched using V-life MDS (Molecular Design Suite)™ 3.5[10,11] software supplied by V-life Sciences Technologies Pvt. Ltd., Pune, India 2006. Each compound was energy minimized and batch optimized by using Merck Molecular Force Field (MMFF) fixing Root Mean Square Gradients (RMS) to 0.01 Kcal/mol Å. The optimized batch of molecules was selected for calculation of the physiochemical descriptors. The descriptor pool was reduced by eliminating out the descriptors with constant and near constant values. Further reduction in the descriptor pool was done by ousting the descriptors that are highly degenerate and difficult to interpret. A correlation analysis was performed between biological data and remaining descriptors, most of which were molecular and electro-topological descriptors and the descriptors those were showing very low correlation with inhibitory activity were also removed.

**Table 1: Biological activity data and structures of the compounds in the series of meta-substituted phenyl propanoic acid.**




| Compound | X | $EC_{50}$ (μM) | -log $EC_{50}$ |
|---|---|---|---|
| 1 | H | 0.121 | 6.917215 |
| 2 | F | 0.139 | 6.856985 |
| 3 | Cl | 0.028 | 7.552842 |
| 4 | Br | 0.036 | 7.443697 |
| 5 | I | 0.04 | 7.39794 |
| 6 | CH3 | 0.046 | 7.337242 |
| 7 | OH | 2.94 | 5.531653 |
| 8 | OMs | 1.61 | 5.793174 |
| 9 | OMe | 0.175 | 6.756962 |
| 10 | t-Bu | 0.279 | 6.554396 |




| Compound | X | $EC_{50}$ (µM) | -log $EC_{50}$ |
|---|---|---|---|
| 11 | H | 0.22 | 6.657577 |
| 12 | F | 1.16 | 5.935542 |
| 13 | Cl | 0.816 | 6.08831 |
| 14 | Br | 0.74 | 6.130768 |
| 15 | I | 0.606 | 6.217527 |
| 16 | CH3 | 38.6 | 4.413413 |
| 17 | OH | 28.1 | 4.551294 |
| 18 | OMs | 3.19 | 5.496209 |
| 19 | OMe | 2.73 | 5.563837 |

## RESULTS AND DISCUSSION

The best QSAR model obtained for the selected data set is based on four variables and represented statistical parameter as follows:

$-\log IC_{50}$ = [11.3698] + [0.4002] SssCH2E-index + [-0.1471] SsOHE-index + [-2.0906] chiV4 + [0.5207] XlogP
n = 19, Degree of freedom = 15, r2 = 0.9393, q2 = 0.8718, F test = 77.3249, r2 se = 0.2473, q2 se = 0.3593, pred_r2 = 0.0000, pred_r2se = 0.0000.

In the QSAR model given above, n is the number of data points, $r^2$ is squared correlation coefficient, $r^2$se is standard error of estimate, F test represents Fischer ratio between the variances of calculated and observed activities. The statistical quantities $q^2$ and $q^2$ se are based on the leave-one-out method and correspond to cross-validated squared correlation coefficient, standard deviation of error of prediction respectively whereas pred_$r^2$ is the correlation coefficient for the external test set.

The negative coefficients of descriptors suggest that they are not favourable for the PPARγ agonistic activity. The significance of the quantitative correlation between the descriptor and the biological activity are expressed as correlation coefficient ($r^2$ = 0.9393), cross validated correlation coefficient ($q^2$= 0.8718) and $F_{test}$= 77.3249 etc. The significant equation obtained by partial least square regression (stepwise forward) analysis was validated by LOO training and test method.

## CONCLUSION

A QSAR model with reliable predictive power for has been successfully generated for the PPAR gamma agonistic activity exhibited by a series of meta-substituted phenyl propanoic acid. The good correlation between experimental and predicted biological activity for 19 compounds in the test set further highlights the reliability of the constructed QSAR model. The findings of the study will be helpful in the design of the potent PPARγ agonist.

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