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DESIGN OF NEW PEROXISOME PROLIFERATORS GAMMA ACTIVATED RECEPTOR AGONISTS (PPARγ) VIA *QSAR* BASED MODELING

Tripathi RB[1]*, Jain J[1], Siddiqui AW[2]

[1]RamEesh Institute of Vocational & Technical Education, Greater Noida, Uttar Pradesh-201310
[2]School of Pharmacy, Lloyd Institute of Management and Technology, Greater Noida, Uttar Pradesh-201310.

ABSTRACT

Introduction: The Peroxisome proliferators-activated receptors (PPARs) are one of the nuclear fatty acid receptors, which contain a type II zinc finger DNA binding pattern and a hydrophobic ligand binding pocket. These receptors are thought to play an essential role in metabolic diseases such as obesity, insulin resistance, and coronary artery disease. Therefore Peroxisome Proliferators-Activated Receptor (PPARγ) activators have drawn great recent attention in the clinical management of type 2 diabetes mellitus, prompting several attempts to discover and optimize new PPARγ activators. **Objective:** The aim of the study was to finding new selective human PPARγ (PPARγ) modulators that are able to improve glucose homeostasis with reduced side effects compared with TZDs and identify the specific molecular descriptor and structural constraint to improve the agonist activity of PPARγ analogs. **Material and Method**: Software's that was used for this study include S.P. Gupta QSAR software (QSAR analysis), Valstat (Comparative QSAR analysis and calculation of L-O-O, Q^2, r^2, S_{press}), BILIN (Comparative QSAR analysis and calculation of Q^2, r, S, S_{press}, and F), etc., allowing directly performing statistical analysis. Then multiple linear regression based *QSAR* software (received from BITS-Pilani, India) generates QSAR equations. **Result and Discussion:** In this study, we explored the quantitative structure–activity relationship (QSAR) study of a series of meta-substituted Phenyl-propanoic acids as Peroxisome Proliferators Gamma activated receptor agonists (PPARγ).
The activities of meta-substituted Phenyl-propanoic acids derivatives correlated with various physicochemical, electronic and steric parameters. **Conclusion:** The identified QSAR models highlighted the significance of molar refractivity and hydrophobicity to the biological activity.

Keywords: PPARγ agonist, Diabetes, QSAR, TZDs, Multiple regressions.

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Correspondence:
Dr. Ram Babu Tripathi, Associate Professor, Ram-Eesh Institute of Vocational & Technical Education, Greater Noida (UP), India.
Phone: 8744085833.
Email: tripathi2011@gmail.com

INTRODUCTION

The peroxisome proliferator-activated receptor ((PPARγ)) is one of the nuclear receptor mostly found in liver and adipose tissue.[1, 1, 3] PPARγ is mainly focused as a molecular target for the thiazolidinedione class of anti-diabetic drugs, as it plays a key role in the generation and development of diabetes mellitus.[4,5] Modern studies have shown that PPAR agonists, including rosiglitazone and pioglitazone may be used as insulin sensitizers in target tissues to lower glucose, as well as fatty acid levels in T2D patients.[6] However, both rosiglitazone and pioglitazone has been introvert from the market because of major hepatotoxicity, weight gain and development of cancer.[7] Hence, there is an urgent necessitate for the development of safer and effective PPAR modulating non thiazolidinedione derivative drugs. One severe side-effect of known PPAR agonists, involves sodium and water retention, which may be dangerous for patients suffering from congestive heart conditions.[8] Recently, various new non thiazolidinedione compounds have been shown to act as PPAR agonists that, not only lowered blood pressure and reduced systemic glucose, triglycerides, and free fatty acid levels, but have also been shown to maintain water and electrolyte homeostasis.[9] Therefore, a variety of non thiazolidinedione compounds have been identified as safer PPAR modulators for the treatment of T2D.The foundation of QSAR was laid by Crum-Brown and Fraser by proposing the idea that biological response is a function of chemical structure of the molecules. A set of extra-thermodynamically derived and computationally based descriptors is employed to correlate *in vitro* or *in vivo* biological activity of a set of molecules. Generally such descriptors are lipophilic, electronic, steric or topologic in nature.[10]

Correlating these parameters with biological activity of a set of molecules provides valuable insight into molecular mechanism of binding interaction.

However, choice of parameters is very important, as their availability has become quite handy. Numerous irrelevant parameters and their values are made available at the press of a key, which could not provide any information as to how a molecule is interacting with receptor. A stroke of chance could result in a statistically significant equation with one or other parameter. Although quite important, statistics alone could not discount the doubt and risk involved in a standalone QSAR equation. [11]

Some basic requirements are essential for the development of best QSAR model to predict the biological activity. Out of which some of them are mentioned below. [12]

- All analogues belong to a congeneric series (classical QSAR studies) exerting the same mechanism of action
- The set of compounds have same mechanism of action
- Biological response should be distributed over a wide range
- Biological activity should be in specific units (concentration in molar units or IC50 or percentage inhibition)

Approaches in QSAR Studies

There are different widely used approaches in QSAR studies. Following are the commonly used ones. [13]

- Hansch analysis (linear free energy relationship or extra thermodynamic approach)
- Free and Wilson analysis
- Pattern recognisation
- Quantum mechanical methods

Molecular Descriptors or Parameters

Molecular descriptors can be defined as a numerical representation of chemical information encoded within a molecular structure via mathematical procedure. They can be both experimental physico-chemical properties of molecules and theoretical indexes calculated by mathematical formulas or computational algorithms. Thus, molecular descriptors, which are closely connected to the concept of molecular structure, play a fundamental role drug designing process**.** Following are the commonly used descriptors. [14, 15, 16]

Lipophilic descriptors

Lipophilic descriptors are commonly used to relate drug absorption and distribution with biological activity like Partition coefficient (log P) and Distribution coefficient (log D).

Electronic descriptors

The distribution of the electrons in a drug molecule influence to reach its target, drug normally has to pass through a number of biological membranes. As a general rule, non-polar and polar drugs in their unionized form are usually more readily transported through membranes than polar drugs and drugs in their ionized forms e.g. Hammett , Taft's inductive (polar) constant.

Stearic descriptors

Drug bind effectively to its target site the size of the pharmacophore must be matching to the target site. So that size of molecule play importance role in drug receptor interactions likes. Taft's steric parameter (Es), Molar refraction (MR), Van der waals radius.

MATERIALS AND METHODS

Data Set

Multiple regression analysis was performed to carry out QSAR analysis with Hansch approach on Meta-substituted Phenyl-propanoic acids as Peroxisome Proliferator-Activated Receptor Gamma Agonists. [17] The biological activity EC_{50} of the compounds was collected from the literature and converted into molar concentrations. Biological activity EC_{50} were converted into a negative logarithm of biological activity that provide better correlations with physicochemical parameters and avoid clustering of data points; –logIC50 therefore becomes dependent variable in subsequent equations. The data table depicts various biological activities viz. observed by experimentation (Obs.), calculated by equation (Cal.), and externally predicted (Ext. Pred.).

Parameter Calculation

Physicochemical parameters for different types of substituent's for unionized molecules like Clog*P*, CMR and Verloop's sterimol L1 was obtained from *MMP plus*(www.norgwyn.com), *Marvin Sketch* and *ChemDraw*.[18] An interesting aspect of MR is its dependency on combined effect of molecular volume and polarizability represented by *MW*. However the effect of polarizability is less as for most compounds. It is assumed that MR is a much better parameter than molecular volume. [19]

Chemometric Tools and Technique

A multiple linear regression based software *QSAR* (received from BITS-Pilani, India) generates QSAR equations and provides correlation coefficient (*r*), standard deviation (*s*), and ratio between variance of calculated and observed activites (*F*); $F = fr2/[(1 - r2)m]$, where f is degree of freedom, m is number of variables, $f = n - (m + 1)$, where n is number of data points. *F* value indicates true relationship or level of significance of QSAR equation.

In equations, the figure in parentheses is 95% confidence intervals and *F* value in parenthesis is critical 99% confidence intervals. The software also provides intercorrelation matrix between descriptors.

Compounds were deemed to be outliers on the basis of their difference between observed and calculated activities, which should be greater than 2*s*. Biological activity of outliers was calculated from the final equation. Applicability domains of QSAR models were estimated wherever necessary by software *AMBIT*. [20]

RESULTS AND DISCUSSION

The activities of meta-substituted Phenyl-propanoic acids derivatives (Table 1) and (Figure 1) were correlated with various physicochemical, electronic and steric parameters. After many trials Equation (1) was found to be promising.

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

S.NO	X	EC50 (µM)
1	H	0.121
2	F	0.139
3	Cl	0.028
4	Br	0.036
5	I	0.04
6	CH_3	0.046
7	OH	2.94
8	OMs	1.61
9	OMe	0.175
10	t-Bu	0.279

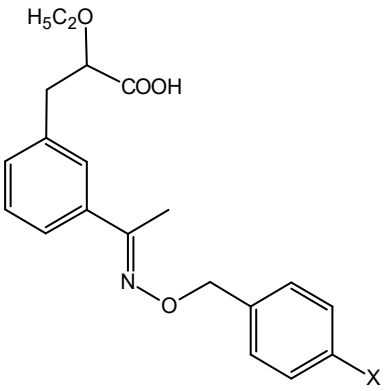

Figure 1: Nucleus of m-Phenyl-propanoic acid

-logEC50= 0.833(0.460) logp -0.340(0.435) MR +6.792(4.690)

n = 10, r = 0.857, s = 0.357, F = 9.689 **(Equation 1)**

For detecting the outliers, standard deviation was multiplied by factor 2. It was observed that amongst 10 data points, two data point (7, 10) were having calculated residual value outside 2*s* range. This indicated that two outliers were present in this model. After removing them a new equation was generated with the same parameters.

The resultant equation 2 is as follows:

-logEC50 = 0.814(0.206) logp -0.218(0.194) MR +5.750(2.455)

n = 8, r = 0.982, s = 0.108, F = 67.76, R^2= 0.90, RMSE = 0.383, Q2= 0.807

(Equation 2)

Interpretation of QSAR Result

In equation 2, the positive contribution of lipophilic parameter (*logp*) indicated the presence of lipophilic group at this position which was involved in the interaction with the receptor. Thus, the new substituents at this position should be high lipophilic groups. While contribution of van der Waal's volume (R2*Vw*), is negative, thus to avoid the steric hindrance with the receptor, the substituent should be small with molar refractivity (*MR*).

CONCLUSION

To explore the structural requirements of PPAR agonists, 2D (QSAR) quantitative structure–activity relationship analysis was performed on a series of Meta-substituted Phenyl-propanoic acids. QSAR equation (2) gives some evidence that during the synthesis of new molecules of peroxisome proliferator-activated receptor ((PPARγ)) agonist select such substituent's to facilitate have higher lipophilic properties and lower molar refractivity.

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CONFLICT OF INTERESTS

Authors do not have any conflict of interests.

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