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# QSAR Analysis of Amphipathic 3-Phenyl-7-propyl-benzisooxazoles as PPAR$_\gamma$, PPAR$_\delta$ and PPAR$_\alpha$ Agonist

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A quantitative structural activity relationship (QSAR) study on a series of analogs of amphipathic 3-phenyl-7-propylbenzisooxazoles with agonist activity on PPAR$_\gamma$, PPAR$_\delta$ and PPAR$_\alpha$ has been performed using combination of various thermodynamic, electronic and spatial descriptors. Several regression expressions are obtained using multiple linear regression analysis. The best QSAR is further validated by leave-one-out cross validation method. The study reveals that thermodynamic parameters were found to have overall significant correlationship with PPAR$_\gamma$, PPAR$_\delta$ and PPAR$_\alpha$ agonist activity. Thus QSAR brings important structural insight to aid the design of potent new molecules.

**Key Words: QSAR, 3-Phenyl-7-propyl-benzisooxazoles as PPAR$_\gamma$, PPAR$_\delta$ and PPAR$_\alpha$.**

## INTRODUCTION

Lifestyle interventions and pharmacological treatments of metabolic disturbance, collectively known as metabolic syndrome, are only partially efficient and new therapeutic approaches are urgently needed. Because of their wide range of actions on glucose homeostasis, lipid metabolism and vascular inflammation, peroxisome proliferator-activated receptors (PPARs) are promising targets for the development of new drugs for the treatment of metabolic disorders such as diabetes, dyslipidemia and atherosclerosis[1]. The peroxisome proliferator-activated receptors (PPAR) are lipid-activated transcription factors belonging to the nuclear receptor super family, which includes the receptors for steroid hormones, retinoids, thyroid hormone and Vitamin D[2,3]. Three different isoforms PPAR$_\alpha$, PPAR$_\gamma$, PPAR$_\delta$ of PPARs,

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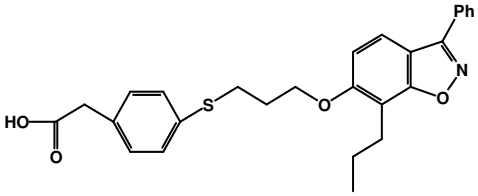
which differs by their target tissue and physiological functions[4,5]. The hypolipidemic fibrates and the insulin thiazolidinediones are believed to be acting through activation of the $PPAR_{\alpha}$[6,7] and $PPAR_{\gamma}$[8,9] subtypes, respectively. Several recent studies suggest that $PPAR_{\delta}$ emerged as a powerful metabolic regulation in diverse tissues including fat, skeletal muscle and the heart[10,11]. Its transcriptional program enhances fatty acid catabolism and energy uncoupling, resulting in decreased triglyceride stores, improved endurance performance and enhanced cardiac contractility respectively. Compounds that simultaneously activate the three peroxisome proliferator-activated receptor (PPAR) subtypes $\alpha$, $\gamma$ and $\delta$ hold potential to address the adverse metabolic and cardiovascular conditions associated with diabetes and the metabolic syndrome[12].

QSAR studies represent an attempt to correlate structural or property descriptors of compounds with activities. It explains the reasons of observed variations caused by the change of the substituents. Thus QSAR studies have predictive ability and simultaneously provide deeper insight into the mechanism of drug-receptor interactions[13] even before their synthesis. The aim of the present work is to study the QSAR of $PPAR_{\gamma}$, $PPAR_{\delta}$ and $PPAR_{\alpha}$ agonist and to optimize their physio-chemical properties. Thus may be helpful in designing new potent molecules.

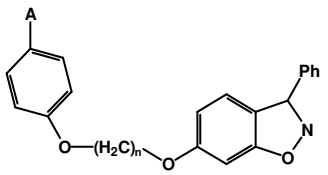
## EXPERIMENTAL

A series of amphipathic 3-phenyl-7-propylbenzisooxazoles (Table-1) as $PPAR_{\gamma}$, $PPAR_{\delta}$ and $PPAR_{\alpha}$ agonists were taken from literature[14] excluding compounds (ND = not run, max % at 3 μM) with biological activity numerically not well defined. The transactivation data $EC_{50}$ (nM) value was converted to negative logarithmic dose for QSAR analysis. Thus correlating the data linear to free energy change and reducing the skewness of the data set. The molecular modeling studies were carried out using CS Chem-Office[15] software version 6.0 (Cambridge soft) running on a P-IV processor. Structures of all the compounds were sketched using builder module of the program. Then the structure was subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value becomes smaller than 0.1 kcal/mol Å. Energy minimized molecule was subjected to re-optimization *via* Austin model-1[16] (AM1) method until the root mean square (RMS) gradient attains a value smaller than 0.0001 kcal/ mol Å using MOPAC. The geometry optimization of the lowest energy structure was carried out using Eigenvector following (EF) routine. The descriptor values for all the molecules were calculated using compute properties module of the program. The various structural and physio-chemical descriptors considered for 3D QSAR studies are given in Table-2.

TABLE-1
ANALOGS OF AMPHIPATHIC 3-PHENYL-7-PROPYLBENZISOOXAZOLE




Structure of compound **1**




Basic structure of compound **2-29**

| Compd. | A | Isomer | n | $EC_{50}$ (nM)* or MAX % (3 μM) | | |
|---|---|---|---|---|---|---|
| | | | | $PPAR_{\gamma}$ | $PPAR_{\delta}$ | $PPAR_{\alpha}$ |
| 1 | -COOH | *para* | 3 | 4 | 3 | 3 |
| 2 | -COOH | *para* | 4 | ND | ND | ND |
| 3 | -COOH | *meta* | 4 | 193 | 34% | 8 |
| 4 | $-CH_2$-COOH | *para* | 3 | 194 | 147 | 3 |
| 5 | $-CH_2$-COOH | *para* | 4 | 60 | 86% | 8 |
| 6 | $-C(CH_3)_2$-COOH | *para* | 4 | 10 | 59% | 2 |
| 7 | $-CH_2$-COOH | *meta* | 3 | ND | ND | ND |
| 8 | $-CH_2$-COOH | *meta* | 4 | 6 | 20 | 5 |
| 9 | $-C(CH_3)_2$-COOH | *meta* | 4 | 52 | 400 | 50 |
| 10 | $-CH_2$-COOH | *ortho* | 3 | ND | ND | ND |
| 11 | $-CH_2$-COOH | *ortho* | 4 | ND | ND | ND |
| 12 | $-CH_2-CH_2$-COOH | *para* | 2 | ND | ND | ND |
| 13 | $-CH_2-CH_2$-COOH | *para* | 3 | 99% | 74% | 42% |
| 14 | $-CH_2-CH_2$-COOH | *para* | 4 | 485 | 74% | 429 |
| 15 | $-C(CH_3)_2-CH_2$-COOH | *para* | 4 | 37 | 18% | 53 |
| 16 | $-CH_2-C-(CH_3)_2$-COOH | *para* | 4 | 20 | 860 | 4 |
| 17 | $-CH_2-CH_2$-COOH | *meta* | 3 | ND | ND | ND |
| 18 | $-CH_2-CH_2$-COOH | *meta* | 4 | ND | ND | ND |
| 19 | $-CH_2-CH_2$-COOH | *ortho* | 3 | ND | ND | ND |
| 20 | -CH=CH-COOH | *para* | 3 | 254 | 148 | 56% |
| 21 | -CH=CH-COOH | *para* | 4 | 29 | 640 | 13 |
| 22 | O-$CH_2$-COOH | *para* | 3 | 75 | 16 | 4 |
| 23 | O-$CH(CH_3)$-COOH | *para* | 3 | 27 | 13 | 2 |
| 24 | O-$CH(CH_3)$-COOH | *para* | 4 | 16 | 117% | 10 |
| 25 | O-$CH(CH_3)_2$-COOH | *para* | 4 | 2 | 172 | 2 |
| 26 | O-$CH_2$-COOH | *meta* | 4 | 87 | 127% | 248 |
| 27 | O-$CH(CH_3)_2$-COOH | *meta* | 4 | 100 | 85% | 92 |
| 28 | $-CH_2-CH_2-CH_2$-COOH | *para* | 2 | 72% | 69% | 33 |
| 29 | $-CH_2-CH_2-CH_2$-COOH | *para* | 3 | 156 | 183 | 3 |

A = Acid proximal structure, *$EC_{50}$ = The concentration yielding a 50 % response relative to the standard, ND = Not run.

TABLE-2
PHYSIOCHEMICAL DESCRIPTORS

| S. No. | Descriptors | Type | Descriptions |
|---|---|---|---|
| 1 | BP | Thermodynamic | Boiling point |
| 2 | CP | Thermodynamic | Critical pressure |
| 3 | CT | Thermodynamic | Critical temperature |
| 4 | HF | Thermodynamic | Heat of formation |
| 5 | HLC | Thermodynamic | Henry's law constant |
| 6 | IGTC | Thermodynamic | Ideal gas thermal capacity |
| 7 | log P | Thermodynamic | Logarithmic partition coefficient |
| 8 | MP | Thermodynamic | Melting point |
| 9 | MR | Thermodynamic | Molar refractivity |
| 10 | SGP | Thermodynamic | Standard Gibb's free energy |
| 11 | VDW-1,4 | Thermodynamic | Van der waals force |
| 12 | PARTCOFF | Thermodynamic | Partition coefficient for water/octanol |
| 13 | N-1,4-VDW | Thermodynamic | Non 1,4-Van der Waals force |
| 14 | STERG | Thermodynamic | Stretch energy |
| 15 | STBERG | Thermodynamic | Stretch bend energy |
| 16 | TORERG | Thermodynamic | Torsion energy |
| 17 | TOTERG | Thermodynamic | Total energy |
| 18 | CAA | Steric | Connolly accessible surface area |
| 19 | CMA | Steric | Connolly molecular surface area |
| 20 | CSEV | Steric | Connolly solvent-excluded volume |
| 21 | EM | Steric | Exact mass |
| 22 | MW | Steric | Molecular weight |
| 23 | OVAL | Steric | Ovality |
| 24 | PMI-X | Steric | Principal moments of inertia-X axis |
| 25 | PMI-Y | Steric | Principal moments of inertia-Y axis |
| 26 | PMI-Z | Steric | Principal moments of inertia-Z axis |
| 27 | DIPOLE-1 | Electronic | Dipole moment - X axis |
| 28 | DIPOLE-2 | Electronic | Dipole moment - Y axis |
| 29 | DIPOLE-3 | Electronic | Dipole moment - Z axis |
| 30 | DIPOLE-4 | Electronic | Resultant dipole moment |
| 31 | EERG | Electronic | Electronic energy |
| 32 | HOMO | Electronic | Energy of highest occupied molecular orbital |
| 33 | LUMO | Electronic | Energy of lowest unoccupied molecular orbital |
| 34 | REPLERG | Electronic | Repulsion energy |
| 35 | BENDERG | Electronic | Bending energy |
| 36 | DDERG | Electronic | Dipole-dipole energy |

Sequential multiple regression analysis method was used to perform QSAR analysis employing in-house VALSTAT[17] program. The auto-correlated parameters were eliminated depending on their individual correlation with the biological activity in order to avoid serious multicollinearity as well as the intercorrelation between the parameters with in acceptable range[18] have been selected for the study. Use of more than one variable in

the multivariate equation was justified by autocorrelation study. The statistical parameter *viz.*, correlation coefficient (r), standard error of estimate (s), sequential Fisher test (F) were considered to compare the generated QSAR models. The robustness and applicability of QSAR equation as best model, on the structural analogs was further confirmed, using various QSAR validation technique like leave-one-out (LOO) validated square correlation coefficient $Q^2$ ($r^2_{cv}$) using cross validation method[19], boot strapping square correlation coefficient ($r^2_{bs}$).

## RESULTS AND DISCUSSION

In the present study, an attempt has been made to find structural requirement for $PPAR_\gamma$, $PPAR_\delta$ and $PPAR_\alpha$ agonist activity using QSAR Hansch approach on amphipathic 3-phenyl-7-propylbenzisooxazole analogs and statistically significant equations were obtained after removal of few compounds as outlier, the reason for outlying behaviour is not immediately apparent. For PPARγ agonist, the statistically significant eqn. 1, with coefficient of correlation (r) = 0.736 and exclusion of compound **8** as outlier was considered as best model. The model showed overall internal statistical significance level better than 99 % as it exceeded the tabulated $F_{(2,15\ \alpha\ 0.001)}$ = 11.34. The selected model explains more than 76 % variance in the biological activity. The intercorrelation within the parameter (ICWP) is significantly low (less than 0.2) suggested the non-dependency of parameters on each other. The model was subjected to leave one out (LOO) cross validation method, the values of $Q^2 \geq 0.3$ in cross validation method corresponds to a confidence limit greater than 95 % which minimize the risk of finding significant explanatory equation for biological activity just by mere opportunity. The value of cross-validated squared correlation coefficient ($Q^2$ = 0.646), predictive residual sum of square ($S_{PRESS}$ = 0.486) and standard error of predictivity ($S_{DEP}$ = 0.443) suggested good predictive ability of the biological activity. The boot strapping $r^2$ ($r^2_{bs}$ = 0.748) is at par with conventional squared correlation coefficient indicating that no single compound much more or less contributed to the model.

$$BA = [58.878\ (\pm\ 19.101)] + HE\ [6.795\ (\pm\ 2.134)] + TOE\ [-0.057\ (\pm\ 0.0513)]$$
$$n = 18,\ r = 0.874,\ r^2 = 0.764,\ variance = 0.158,\ std = 0.397,$$
$$F = 24.271,\ ICWP < 0.2 \qquad (1)$$

From the above study, for the $PPAR_\gamma$ agonist activity HOMO energy contributing positively while Torsion energy (TOE) contributing negatively. HOMO energy is an electronic parameter. When a molecule acts as an electron pair donor, electron from its HOMO is supplied. The term indicates the importance of hydrogen bonding interactions. The positive contribution demonstrates that electron rich functional group may be favourable for

ligand receptor interaction. TOE is a thermodynamic parameter, which denotes the energy associated with deforming torsion angel in the molecule from their ideal value. The negative contribution suggested that bulky substituents are not favourable for activity. A plot of observed activity *vs.* calculated $pEC_{50}$ values of $PPAR^{\gamma}$ activity using eqn. 1 is given in Fig. 1.

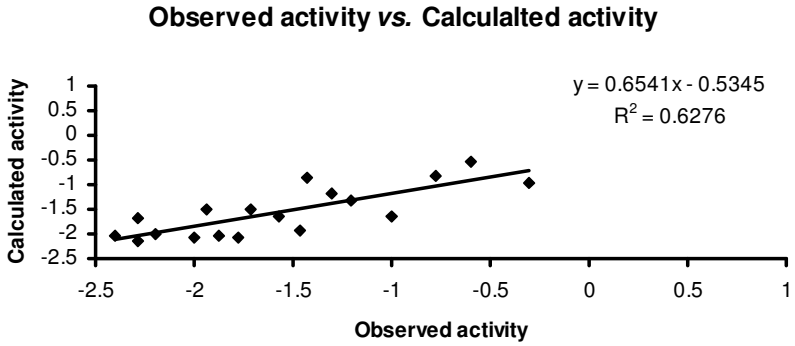



Fig. 1. A plot of observed *vs.* calculated $pEC_{50}$ values of $PPAR_{\gamma}$ activity using eqn. 1

For $PPAR_{\delta}$ agonist, the statistically significant eqn. 2 with coefficient of correlation (r) = 0.947 was considered as best model. The compound **8** was removed as outlier. The model showed overall internal statistical significance level better than 99 % as it exceeded the tabulated $F_{(2,7\,\alpha\,0.01)} = 12.25$. The selected model explains more than 90 % variance in the biological activity. The intercorrelation within the parameter (ICWP) is significantly low (less than 0.4). The value of cross-validated squared correlation coefficient ($Q^2 = 0.794$), predictive residual sum of square ($S_{PRESS} = 0.408$) and standard error of predictivity ($S_{DEP} = 0.341$) suggested good predictive ability of the biological activity. The boot strapping $r^2$ ($r^2_{bs} = 0.930$) is at par with conventional squared correlation coefficient.

$$BA = [-8.110\ (\pm\ 2.82109)] + CP\ [0.196\ (\pm\ 0.236] + SE\ [0.290\ (\pm\ 0.114)]$$
$$n = 10,\ r = 0.947,\ r^2 = 0.897,\ \text{variance} = 0.083,\ \text{std} = 0.288,$$
$$F = 30.587,\ ICWP < 0.4 \qquad (2)$$

From the eqn. 2, it is apparent that the thermodynamic properties are highly correlated with $PPAR_{\delta}$ agonist activity. Critical pressure (CP) is the minimum pressure that must be applied to liquefy the structure at the critical temperature. The positive contribution may facilitate attractive intermolecular forces in drug-receptor interaction. Stretch energy, the energy contribution associated with the deformation of a bond from its equilibrium bond length. The positive contribution reveals that the substituents, which increase the flexibility will increase the activity. A plot of observed activity *vs.* cal culated $pEC_{50}$ values of $PPAR_{\delta}$ activity using eqn. 2 is given iin Fig. 2.

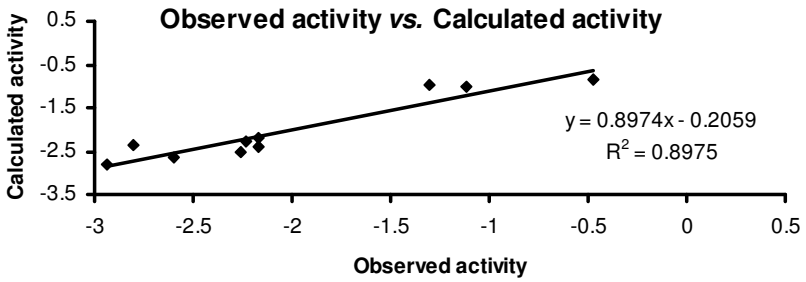



Fig. 4. A plot of observed *vs.* calculated $pEC_{50}$ values of $PPAR_{\delta}$ activity using eqn. 2

For $PPAR_{\alpha}$ agonist, among the various equations the statistically significant eqn. 3 with coefficient of correlation (r) = 0.852 was selected after removal of compound **5** and **8** as outlier. The model showed overall internal statistical significance level better than 99 % as it exceeded the tabulated $F_{(2,14\ \alpha\ 0.01)} = 6.51$. The selected model explains more than 73 % variance in the biological activity. The intercorrelation within the parameter (ICWP) is significantly low (less than 0.2). The value of cross-validated squared correlation coefficient ($Q^2 = 0.573$), predictive residual sum of square ($S_{PRESS} = 0.441$) and standard error of predictivity ($S_{DEP} = 0.400$) suggested good predictive ability of the biological activity. The boot strapping $r^2$ ($r^2_{bs} = 0.790$) is at par with conventional squared correlation coefficient.

$$\begin{aligned} BA = {} & [-2.391\ (\pm\ 3.648)] + CSEV\ [0.002\ (\pm\ 0.009)] + \\ & NVDE\ [-0.233\ (\pm\ 0.083)] \\ n = 17,\ r = 0.852,\ r^2 = 0.727,\ & variance = 0.125,\ std = 0.353, \\ F = 18.600,\ & ICWP < 0.2 \end{aligned} \quad (3)$$

The above eqn. 3 explains, for $PPAR_{\alpha}$ agonist activity (Fig. 3), connolly-solvent excluded volume a steric parameter contributes positively and non 1,4-vander Waals force a thermodynamic parameter contributes negatively.

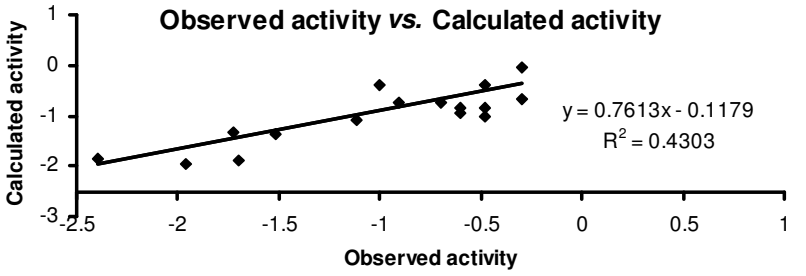



Fig. 5. A plot of observed *vs.* calculated $pEC_{50}$ values of $PPAR_{\alpha}$ activity using eqn. 3

TABLE-3
OBSERVED AND CALCULATED $pEC_{50}$ VALUES OF
PPARγ, PPARδ AND PPARα AGONISTS

| Compd. | $PPAR_{\gamma}$ | | $PPAR_{\delta}$ | | $PPAR_{\alpha}$ | |
|---|---|---|---|---|---|---|
| | Obs. | Calcd. | Obs. | Calcd. | Obs. | Calcd. |
| 1 | -0.602 | -0.546 | -0.477 | -0.851 | -0.4771 | -0.395 |
| 2 | ND | – | ND | – | ND | – |
| 3 | -2.286 | -1.679 | ND | – | -0.9031 | 1.046 |
| 4 | -2.288 | -2.156 | -2.167 | -2.212 | -0.4771 | -0.847 |
| 5 | -1.778 | -2.080 | ND | – | -0.9031 | -0.740 |
| 6 | -1.000 | -1.630 | ND | – | -0.3010 | Outlier |
| 7 | ND | – | ND | – | ND | – |
| 8 | -0.778 | -0.814 | -1.301 | -0.981 | -0.6989 | -0.744 |
| 9 | -1.716 | -1.513 | -2.602 | -2.649 | -1.6989 | -1.884 |
| 10 | ND | – | ND | – | ND | – |
| 11 | ND | – | ND | – | ND | – |
| 12 | ND | – | ND | – | ND | – |
| 13 | ND | – | ND | – | ND | – |
| 14 | -2.686 | Outlier | ND | – | -2.6325 | Outlier |
| 15 | -1.568 | 1.626 | ND | – | -1.7243 | -1.329 |
| 16 | -1.301 | -1.196 | -2.935 | -2.803 | -0.6021 | -0.838 |
| 17 | ND | – | ND | – | ND | – |
| 18 | ND | – | ND | – | ND | – |
| 19 | ND | – | ND | – | ND | – |
| 20 | -2.405 | -2.033 | -2.170 | -2.378 | ND | – |
| 21 | -1.462 | -1.938 | -2.806 | -2.370 | -1.1139 | -1.096 |
| 22 | -1.875 | -2.047 | -1.204 | Outlier | -0.6021 | -0.954 |
| 23 | -1.431 | -0.852 | -1.114 | -1.015 | -0.3010 | -0.653 |
| 24 | -1.204 | -1.339 | ND | – | -1.0000 | -0.393 |
| 25 | -0.301 | -0.981 | -2.236 | -2.282 | -0.3010 | -0.039 |
| 26 | -1.940 | -1.517 | ND | – | -2.3945 | -1.859 |
| 27 | -2.000 | -2.070 | ND | – | -1.9638 | -1.958 |
| 28 | ND | – | ND | – | -1.5185 | -1.351 |
| 29 | -2.193 | -2.002 | -2.263 | -2.529 | -0.4771 | -1.032 |

ND = $EC_{50}$ values are not well defined.

The positive contribution of connolly-solvent excluded volume suggests that bulky substituents can contact with large volume and it may facilitate drug receptor interaction. The non 1,4-vander Waals force refers the ability of molecules to interact with the receptor by non vander Waals force and hydrogen bonding during drug-receptor interaction. The negative contribution shows that the non-van der Waals interactions unfavourable for the activity.

The present study reveals important structural insight in designing new molecule for $PPAR_\gamma$, $PPAR_\delta$ and $PPAR_\alpha$ agonist activity. The statistically significant equations show that the thermodynamic parameters have good correlation with biological activity. For $PPAR_\gamma$ agonist activity nucleophilc non-bulkier substituents are favourable. For $PPAR_\delta$ agonist activity flexible conformer with attractive intermolecular force and for $PPAR_\alpha$ bulkier vander Waals bonding substituents are favourable for the activity. The study also shows that inverse relationship between $PPAR_\gamma$ and $PPAR_\alpha$ agonist activity.

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