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# 3D QSAR Analysis of PPAR-γ Agonist and PTPIB Antagonist as Anti-hyperglycemic Agents

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A quantitative structure activity relationship studies were observed on series of N-(2-benzoylphenyl)-L-tyrosine for Peroxisome Proliferator Activated Receptor (PPARγ) agonist and new azolidinediones for Protein Tyrosine Phosphatase 1B (PTP1B) antagonist. Various physicochemical parameters were calculated by chem 3D Ultra version 6.0. Several statistical regression expressions were obtained by using multiple regression analysis. Steric descriptor (PMI-X, Ovality, CMA, PMI-Z); electronic descriptor (DD, total energy); and thermodynamic descriptor (Gibb's energy, HF) were found to have significant correlation ship in both of the series. Value of correlation coefficient (r) in series 1 is found to be 0.799, statistical significance is 99 % and in series 2 r = 0.869, statistical significance is 99.9 %.

**Key Words: Antihyperglycemic, 3D-QSAR, PPAR-γ, PTP1B, PMI-X, Azolidinediones, N-(2-benzoylphenyl)-L-tyrosine.**

## INTRODUCTION

Diabetes mellitus[1] is a disorder of glucose metabolism classified under insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). By peripheral insulin resistance, β-cell dysfunction, hyperglycaemia and often hyperlipidemia is characteristic feature of NIDDM (Type-II)[2]. Insulin deficiency further leads to chronic diseases such as ketocidosis, retinopathy, nephropathy, neuropathy and cardiovascular disease[3].

Earlier, treatment of NIDDM done by bi-guanides, sulphonylureas, insulin secreatogogues, α-glucosides inhibitor, one novel class of anti-diabetic agent that appear to be effective as a treatment for diabetes are PPAR-γ agonist *viz.*, thiazolidinediones (TZDs) such as ciglitazone, englitazone, pioglitazone and rosiglitazone[4]. PPARs[5] are members of the nuclear hormone receptor super family of legend dependent transcription factors. PPARs play an important role in regulation of glucose metabolism, lipid metabolism and cell differentiation. Three PPAR isoforms have been identified PPARα, PPARγ and PPARβ. PPAR-γ[6] is mainly expressed in adipose tissue and plays an important role in insulin sensitivity. PPAR-γ receptor is attractive target for antidiabetic therapy. Thiazolidinediones were the first high affinity PPAR-γ agonist has been discovered in recent years,

but due to their unacceptable side effects TZDs have been dropped from development and market. Therefore, efforts were directed to develop antihyperglycemic agents without thiazolidinedione rings. It is decided to study QSAR such two series, which are having compounds devoid of TZD ring. Series 1 is N-(2-benzoylphenyl)-L-tyrosine[7], which possesses 5-600 fold greater affinities for PPARγ than corresponding TZDs. It reduce insulin resistance by lowering level of leptin and TNF-α[8] (Tumour necrosis factor).

Series-2 is new azolidinediones[9], which are potent antagonist against the recombinant rate and human PTP1B. PTPs[10] belong to growing family of enzymes, which are involved in regulation of cellular events. The role of PTP1B in diabetes has been more clearly defined as negative regulator of insulin signalling. Therefore, it was thought worthwhile to examine the structural features and physico-chemical parameters, which contribute to hypoglycaemic activity by inhibiting enzyme and by agonism of receptor. So the aim of present work is to utilize the data to predict the appropriate structures, which have more agonism and antagonism activity towards PPAR-γ receptor and PTP1B enzyme, respectively.

## EXPERIMENTAL

The $Ec_{50}$ μm values were converted into log $Ec_{50}$ from the reported *in vivo* data for the N-(2- benzoylphenyl)-L-tyrosine PPAR-γ agonist (Series-1 and Table-1). The $IC_{50}$ μm values were converted into log $IC_{50}$ from the reported *in vivo* data for the new azolidine- diones (Series-2 and Table-4).

All computational studies were performed by using chem. 3D Ultra6.0 software from Cambridge soft cam[11]. Energy minimization of molecules was done by fixing1000 iteration and RMS low energy derivative of 0.001 kcal/mol by $MM_2$ & MOPAC module. The descriptor value for all the molecules were calculated by using "compute properties module" of chem 3D version 6.0. Stepwise multiple regression analysis methods[12-14] were used to performed QSAR analysis. Following statistical parameter were considered to compare the generated QSAR models, correlation coefficient(r), standard deviation (s), $F_{test}$ (F) and tabulated F.

## RESULTS AND DISCUSSION

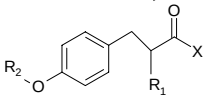
The two series are when, subjected to QSAR analysis, we obtained QSAR equations. However, on the basis of r, s and f values, the equations that are having more significance, are

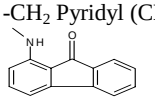
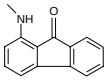
Series-1

$$-\log Ec_{50} = -0.000037 * PMI\text{-}X + 0.000003 * DD - 0.00100 * BP - 0.609587 \quad (1)$$

$n = 22$, $r = 0.747$, $r^2 = 0.558$, $s = 0.057$, $F = 5.074$, Tabulated $F_{(3, 18\ a\ 0.05)} = 3.16$

TABLE-1
PPARγ AGONIST ACTIVITY OF SUBSTITUTED
N-(2-BENZOYLPHENYL)-L-TYROSINE




| S. No | X | $R_1$ | $R_2$ | -log $EC_{50}$ |
|---|---|---|---|---|
| 1. | OH | -NHCH($CH_3$)$CH_2CO(C_6H_5)$ | $CH_2$-Ph | -0.8222 |
| 2. | $NH_2$ | -NHCH($CH_3$)$CH_2COC_6H_5$ | $CH_2$-Ph | -0.8001 |
| 3. | $OCH_3$ | -NHCH($CH_3$)$CH_2COC_6H_5$ | $CH_2$-Ph | -0.8202 |
| 4. | OH | H | $CH_2$-Ph | -0.7482 |
| 5. | OH | $-NHC_6H_8COC_6H_5$ | $CH_2$-Ph | -0.6981 |
| 6. | OH | -NH $C_6H_4COC_6H_5$ | $CH_2$-Ph | -0.6794 |
| 7. | OH | -NH $C_6H_4COC_6H_5$ | $CH_2$ ($CH_3$)$C_6H_{10}$ | -0.7931 |
| 8. | OH | -NH $C_6H_4COC_6H_5$ | -$CH_2$ Pyridyl ($CH_2$)$CH_3$ | -0.8633 |
| 9. | OH | $-NHC_6H_4COC_6H_5$ |  | -0.9053 |
| 10. | OH | $-NHC_6H_4COC_6H_5$ | 2-Aminomethylethyl pyridine | -0.9053 |
| 11 | OH | $-NHC_6H_7COC_6H_5$ | 2-Aminobenzooxazolemethyl ethyl | -0.9335 |
| 12. | OH | $-NHC_6H_7COC_6H_5$ | 2-(5-Methyl2phenyloxazole-4yl)ethyl | -0.9764 |
| 13 | OH | $-NHC_6H_7COC_6H_5$ | N-(2-benzooxazole)methyl ethyl | -0.8312 |
| 14 | OH | $-S-C_6H_4COC_6H_5$ | N-(2-benzooxazole)methyl ethyl | -0.7679 |
| 15 | OH | $-O-C_6H_4COC_6H_5$ | N-(2-benzooazxle)methyl ethyl | -0.7803 |
| 16 | OH |  | N-(2-benzooxazole)methyl ethyl | -0.8000 |
| 17 | OH | -N-(Napthyl-9,iodine) | N-(2-benzooxazole)methyl ethyl | -0.9191 |
| 18 | OH | $-NHC_6H_4CH_2CH_2C_6H_5$ | N-(2-benzooxazole)methyl ethyl | -0.8774 |
| 19 | OH | $-NHC_6H_4SO_2C_6H_5$ | N-(2-benzooxazole)methyl ethyl | -0.7589 |
| 20 | OH | $-NHC_6H_4OC_6H_5$ | N-(2-benzooxazole)methyl ethyl | -0.8432 |
| 21 | OH | $-NHC_6H_4C(OH)C_6H_5$ | 2-Pyridyl | -0.8028 |
| 22 | OH | $-NHC_6H_4-(C=N-NH_2)C_6H_5$ | 2-Pyridyl | -0.7832 |

$$-\log Ec_{50} = -0.000026*PMI\text{-}X - 0.353475*Ovality + 0.000144*HF + 0.000003*DD - 0.116282 \quad (2)$$

$n = 22$, $r = 0.799$, $r^2 = 0.638$, $s = 0.053$, $F = 5.280$, Tabulated $F_{(4, 17 \text{ a } 0.01)} = 4.67$

The correlation matrix for eqn. 2 is given in Table-2. The observed, calculated, predicated activity are summarized in Table-3.

F-value obtained from eqn. 1 is significant at 95 % level with $F_{(3, 18 \text{ a } 0.05)} = 3.16$. F-valued obtained for eqn. 2 is significant at 99 % level with $F_{(4, 17 \text{ a } 0.01)} = 4.67$.

Observation of models clearly indicated that parameters, PMI-X (principal moment of inertia at x axis), ovality (steric descriptor), HF (heat of formation, thermodynamic descriptor) and DD (dipole dipole moment, elec-

tronic descriptor) play an important role for biological activity of compounds. PMI-X and ovality negatively contribute to biological activity of compounds; HF and DD positively contribute to biological activity of compounds.

TABLE-2
CORRELATION MATRIX OF PARAMETERS

| | -log $EC_{50}$ | PMI-X | Ovality | HF | DD |
|---|---|---|---|---|---|
| -log $EC_{50}$ | 1.000 | – | – | – | – |
| PMI-X | 0.612 | 1.000 | – | – | – |
| Ovality | 0.523 | 0.573 | 1.000 | – | – |
| HF | 0.203 | 0.090 | 0.136 | 1.000 | – |
| DD | 0.425 | 0.166 | 0.041 | 0.009 | 1.000 |

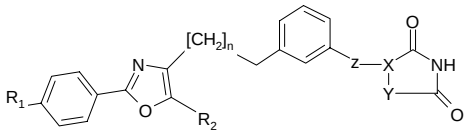
TABLE-3
OBSERVED, PREDICTED AND CALCULATED ACTIVITY OF N-(2-BENZOYLPHENYL)-L-TYROSINE

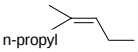
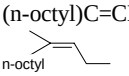
| Comp. No | Observed Activity | Predicted activity | Calculated Activity | O-P Residue | O-C Residue |
|---|---|---|---|---|---|
| 1 | -0.8222 | -0.8446 | -0.8473 | -0.0226 | 0.0251 |
| 2 | -0.8001 | -0.7951 | -0.7930 | 0.0050 | 0.0071 |
| 3 | -0.8220 | -0.8412 | -0.8471 | 0.0210 | 0.0269 |
| 4 | -0.7482 | -0.7057 | -0.6703 | 0.0425 | 0.0779 |
| 5 | -0.6981 | -0.7861 | -0.8058 | 0.0880 | 0.1077 |
| 6 | -0.6794 | -0.6794 | -0.8043 | 0.0000 | 0.1249 |
| 7 | -0.7931 | -0.8047 | -0.8065 | 0.0116 | 0.0134 |
| 8 | -0.8633 | -0.8585 | -0.8594 | 0.0048 | 0.0039 |
| 9 | -0.9053 | -0.90153 | -0.8969 | 0.0040 | 0.0084 |
| 10 | -0.9053 | -0.8514 | -0.8453 | 0.5390 | 0.0600 |
| 11 | -0.9335 | -0.8071 | -0.7987 | 0.1264 | 0.1348 |
| 12 | -0.9764 | -0.9095 | -0.8952 | 0.0713 | 0.0812 |
| 13 | -0.8312 | -0.8564 | -0.8603 | 0.0252 | 0.0291 |
| 14 | -0.7679 | -0.7902 | -0.8021 | 0.0223 | 0.0342 |
| 15 | -0.7803 | -0.8410 | -0.8995 | 0.0607 | 0.1193 |
| 16 | -0.8000 | -0.8035 | -0.8057 | 0.0035 | 0.0057 |
| 17 | -0.9191 | -0.9445 | -0.9458 | 0.0254 | 0.0267 |
| 18 | -0.8774 | -0.8454 | -0.8404 | 0.0320 | 0.0370 |
| 19 | -0.7589 | -0.7914 | -0.7954 | 0.0325 | 0.0365 |
| 20 | -0.8432 | -0.8483 | -0.8502 | 0.0052 | 0.0070 |
| 21 | -0.8028 | -0.8055 | -0.8056 | 0.0027 | 0.0028 |
| 22 | -0.7832 | -0.7813 | -0.7377 | 0.0019 | 0.0455 |

These equations and correlation matrix suggest that PMI-X (steric descriptor) is most important parameter influencing biological activity of compounds. It is having better correlation ($r = 0.612$) with $EC_{50}$ values. The correlation matrix shows that different independent variables (parameters) have very poor relation with each other as desired in QSAR analysis, on the

basis of high r-value (r = 0.799), low s-value (s = 0.053), high F-valued (F = 5.280) and statistical significance 99%, Equation 2 can be regarded as most suitable for predictability.

TABLE-4
PT1B ANTAGONIST ACTIVITY OF NEW AZOLIDINEDIONES




| S.N. | $R_1$ | $R_2$ | N | POA | X | Y | Z | -log $IC_{50}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | $CF_3O$ | $CH_3$ | 1 | 3 | CH | S | $H_3C$-C=$CHCH_2$- | -0.1761 |
| 2 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | $H_3C$-C=$CHCH_2$- | -0.2768 |
| 3 | $CF_3$ | $CH_3$ | 1 | 3 | N | S | $H_3C$-C=$CHCH_2$- | -0.5708 |
| 4 | $CF_3$ | $CH_3$ | 1 | 4 | N | O | $H_3C$-C=$CHCH_2$- | -0.6335 |
| 5 | $CF_3$ | $CH_3$ | 2 | 4 | N | O | $H_3C$-C=$CHCH_2$- | -0.2042 |
| 6 | $CF_3$ | $C_6H_5$ | 1 | 3 | N | O | $H_3C$-C=$CHCH_2$- | 0.5229 |
| 7 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | -$(CH_2)_3$- | -0.6335 |
| 8 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | -CH=CH-$CH(CH_3)$- | -0.8451 |
| 9 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | -$C_3H_3(CH_3)$-$CH_2$- | -0.0000 |
| 10 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (n-propyl)C=$CHCH_2$- | -0.3010 |
| 11 | $CF_3$ | $CH_3$ | 1 | 3 | N | O |  n-propyl | -0.2778 |
| 12 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (n-butyl)C=$CHCH_2$- | -0.1461 |
| 13 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (n-octyl)C=$CHCH_2$- | 0.3579 |
| 14 | $CF_3$ | $CH_3$ | 1 | 3 | N | O |  n-octyl | 0.5229 |
| 15 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (4-3butyl)C=$CHCH_2$- | 0.2118 |
| 16 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (I)C=$CHCH_2$- | -0.2553 |
| 17 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (Ph)C=$CHCH_2$- | -0.0414 |
| 18 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (benzyl)C=$CHCH_2$- | -0.0969 |
| 19 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (4-F-Ph)C=$CHCH_2$- | -0.0752 |
| 20 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | (4-Cl-Ph)C=$CHCH_2$- | -0.1461 |
| 21 | $CF_3$ | $CH_3$ | 1 | 3 | N | O | $(CH_3)$C=CHCH= $CHCH_2$- | -0.1461 |

For Series 2

$$-\log IC_{50} = 0.007317 * CMA - 0.000002 * PMI\text{-}Z - 3.3866668 \quad (3)$$

$n = 21$, $r = 0.869$, $r^2 = 0.738$, $s = 0.208$, $F = 15.049$, Tabulated $F_{(2,18a\ 0.001)} = 10.4$

$$-\log IC_{50} = 0.006849 * CMA - 0.000003 * PMI\text{-}Z - 0.000844 * Gibb's + 0.00014 * total\ E - 2.820657 \quad (4)$$

$n = 21$, $r = 0.864$, $r^2 = 0.782$, $s = 0.0203$, $F = 10.048$,

Tabulated $F(4,16\alpha 0.001) = 7.94$ from eqn. 4.

F-value obtained for eqn. 3 and 4 is significant at 99.9 % level with $F_{(2,\ 18\ a\ 0.01)} = 10.4$ and $F_{(4,16\ a\ 0.001)} = 7.94$ respectively.

Correlation matrix is given in Table-5. The observed and calculated, predicted activity are tabulated in Table-6.

TABLE-5
CORRELATION MATRIX OF PARAMETERS

| | -log $IC_{50}$ | PMI-Z | CMA |
|---|---|---|---|
| -log $IC_{50}$ | 1.000 | – | – |
| PMI-Z | 0.306 | 1.000 | – |
| CMA | 0.834 | 0.122 | 1.00 |

TABLE-6
OBSERVED, PREDICTED AND CALCULATED ACTIVITY
OF NEW AZOLIDINEDIONES

| Compd. | Observed Activity | Predicted Activity | Calculated Activity | O-P Residues | O-C Residues |
|---|---|---|---|---|---|
| 1 | -0.1761 | -0.2867 | -0.2959 | 0.1106 | 0.1198 |
| 2 | -0.2788 | -0.3920 | -0.4054 | 0.1132 | 0.1266 |
| 3 | -0.5789 | -0.6266 | -0.3308 | 0.0468 | 0.2490 |
| 4 | -0.6365 | -0.3414 | -0.3204 | 0.2921 | 0.3131 |
| 5 | -0.2042 | -0.2603 | -0.2626 | 0.0561 | 0.0584 |
| 6 | 0.5229 | 0.0509 | -0.0145 | 0.4720 | 0.5084 |
| 7 | -0.6335 | -0.4351 | -0.4089 | 0.1984 | 0.2249 |
| 8 | -0.8451 | -0.6668 | -0.6079 | 0.1783 | 0.2372 |
| 9 | 0.0000 | -0.2745 | -0.3005 | 0.2745 | 0.3005 |
| 10 | -0.3010 | -0.1807 | -0.1747 | 0.1203 | 0.1263 |
| 11 | -0.2788 | -0.2674 | -0.2740 | 0.0114 | 0.0077 |
| 12 | -0.1461 | 0.0086 | 0.0169 | 0.1375 | 0.1292 |
| 13 | 0.3979 | 0.5647 | 0.5985 | 0.1668 | 0.2006 |
| 14 | 0.5229 | 0.5647 | 0.5326 | 0.0418 | 0.0097 |
| 15 | 0.2218 | -0.0883 | -0.1077 | 0.1335 | 0.1147 |
| 16 | -0.2553 | -0.2876 | -0.2919 | 0.0323 | 0.0366 |
| 17 | -0.0414 | -0.0051 | -0.0042 | 0.0363 | 0.0372 |
| 18 | 0.0969 | 0.0561 | -0.0521 | 0.0408 | 0.0448 |
| 19 | -0.0792 | -0.5333 | -0.0527 | 0.4541 | 0.0265 |
| 20 | -0.1461 | 0.0494 | 0.0626 | 0.0967 | 0.0835 |
| 21 | -0.1461 | -0.1123 | -0.1119 | 0.0338 | 0.0342 |

Observations of equations indicated that parameters CMA (coonally molecular area) and PMI-Z (principle moment of inertia at z axis, steric descriptor); Gibb's energy (thermodynamic descriptor) and total energy (electronic descriptor) play an important role for biological activity of compounds (MA, Gibb's energy and total energy positively contributed to biological activity of compound and PMI-Z negatively contribute to biological activity. These equations and correlation matrix suggest that CMA (steric descriptor) is most important parameter and having better correlation (r = 0.834) with $IC_{50}$. The correlation matrix shows that the different independent variables (parameters) have very poor relation with each other as desired in QSAR analysis on the basis of high r-value (r = 0.869), low value

(s = 0.028), high F-value (F = 15.043), less number of parameters and statistical significance 99.9 %. Eqn. 3 can be regarded as most suitable for predictability.

Present studies revealed that in series-1, the compounds, which are having high PMI-X, value having more biological activity, hence more potent PPAR-γ agonist. It also shows that aminobenzophenone ($R_1$) is important for activity and substitution on $R_2$ by increasing 1 or 2 carbon atoms on side chain between the frame work of N-(2-benzoylphenyl-L-tyrosine increase the PMI-X value and hence increased the biological activity. In series-2, elongated spaces between the azolidinediones moiety and the central aromatic position at the molecule appeared to be very important to inhibitory activity large hydrophobic groups at the vicinity of this aromatic central region produce the most potent PTP1B antagonists. The octyl analogs were the best PTP1B antagonist CMA (Steric descriptor). The most important parameter for biological activities of compounds, which are having high value of CMA.

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