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Research Article

3D-QSAR STUDIES OF SOME THIAZOLIDINESDIONES AS PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR$_\gamma$ (PPARγ) AGONIST

SATISH SAHU*, D V KOHLI AND LOPAMUDRA BANERJEE

Dept. of Pharm. Sciences, Dr. H. S. Gour University, Sagar (M.P.), India 469002. Email: satishbu@yahoo.co.in, drdvkohali@rediffmail.com

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ABSTRACT

A quantitative structure activity relationship (QSAR) study on a series of substituted thiazolidinediones with activity on PPARγ was made using various thermodynamic, electronic and spatial descriptors. Several statistical regression expressions were obtained using multiple regression analysis. Amongst them, two models was found to be best on various statistical criteria, involving the descriptor viz. steric parameters (Molar refractivity) and hydrophobic parameters (Hydrophobicity) with significant correlation coefficient.

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INTRODUCTION

Non-insulin dependent diabetes mellitus (NIDDM) is a complex, chronic metabolic disorder characterized by insulin resistance in liver and peripheral tissue, hyperglycemia and often hyperlipademia[1]. Untreated NIDDM leads to several chronic diseases such as neuropathy, nephropathy, retinopathy, premature atheroscerosis and cardiovascular diseases[2, 3]. The later lead to increase in mortality. At present, therapy for type II diabetes relies mainly on several approaches intended to reduce hyperglycemia itself: sulfonylureas, biaguanides, α-glucosidase inhibitors, insulin sensitizer and insulin secretagogues. Peroxisome proliferator activated receptors (PPARs) are orphan receptors belonging to steroid/retinoid receptor superfamily of ligand activated transcription factors. Three mammalian PPARs have been identified and are termed as PPAR-α, PPAR-δ, and PPAR-γ[4, 5, 6]. Thiazolidinediones (TZDs) is a novel class of oral antidiabetics. This series show no hypoglycemic effect. At submicromolar levels, TZD activates PPARγ and are used pharmaceutically as antidiabetic agents that increase insulin sensitivity of target tissues in animal models of NIDDM. *In vitro*, TZD promote adipocyte differentiation of preadipocyte and mesenchymal stem cell lines. TZD don't cause an insulin secretion or in the number or affinity of insulin receptor binding sites, suggesting that TZD amplify postreceptor events in the insulin signaling cascade[7]. PPARγ is the predominant molecular target for insulin-sensitizing TZD drugs. So scientists are trying to develop a drug which should be equipotent to that of TZD but devoid of any toxicity. Thiazolidinedione (TZD) is a novel class of oral antidiabetics is emerging and currently undergoing clinical trials. Pioglitazone, rosiglitazone, troglitazone, ciglitazone etc. of this class came into the market and other compounds had synthesized and evaluated but it was found that this class possesses severe side effects of liver toxicity. So scientists are trying to develop a drug which should be equipotent to that of TZD but devoid of any toxicity[8-12]. We therefore decided to study quantitative structure activity relationship (QSAR) of PPARγ receptor agonist. The aim of this work was therefore to identify the associated properties and exploit to optimize PPARγ agonist properties.

EXPERIMENTAL

The *in-vitro* transativation activity data of thiazolidinediones compounds were taken from reported work of Arakawa *et al* [13] (Table 1). The biological activity (EC_{50}) was converted to negative logarithm for QSAR analysis. For the present 3D-QSAR analysis Apex-3D expert system on a silicon graphics INDY-4000 was used. All molecular modeling and 3D-QSAR studies were performed on a silicon graphics INDY-4000 workstation employing molecular simulation software.

A series of 11 compounds were taken as a training set. The molecular structure of all compounds were constructed in 2D using the sketch program in the builder module of INSIGHT-II software and then converted to 3D for optimization of their geometry (net charge 0.0) by selecting the forcefield potential action and charge action as fixed. The molecules structures were finally minimized using the steepest descent, conjugate gradients and Newton Raphson's algorithm followed by Quasi-Newton-Raphson. Optimization techniques implemented in Discover module (version 2.9) by energy tolerance value of 0.001 Kcal/mol and maximum number of iteration set at 1000. A total of 89 conformers were generated for total molecules and lowest energy conformer of each cluster was selected by conformation clustering methodology. These conformations were subjected to different computational chemistry program including MOPAC 6.0 version (MNDO Hamiltonian) for the calculations of physicochemical parameters (π-population, atomic charges, electron donor and acceptor indexes, HOMO and LUMO coefficient and hydrophobicity and molar refractivity based on atomic contributions) and quantum chemical parameters.

The data was used by Apex-3D program for automated identification of biophores, superimposition of compounds and quantitative model building. Compounds present in the test have been predicted to check the validity of model. In addition to it "Leave One Out (LOO)" cross validation was also performed in which the objects were left out randomly but only once. On the basis of chance value, RMSA, RMSP, *R* and size, models have been selected which can be considered to be most robust model for the series.

RESULT AND DISCUSSION

Pharmacophore models with different size and arrangements were generated for the training set given in Table 2.

Among the different 3D models generated, those models with $R^2 > 0.70$, chance < 0.10, match value > 0.30 are listed in the Table 3. All of these models have three biophoric sites, two secondary sites in case of 11 compounds and one for 10 compounds. Among the two models 3 & 122 for 11 compounds and 4 & 101 for 10 compounds, one model for 11 compounds (Model No. 122) and one model for 10 compounds (Model No. 4) were chosen because of better statistics than the others in terms of correlation coefficient, match and/or chance values. Biophoric and secondary site features for the activity are given in the following Structure for Model No.122.

The 3D QSAR Model No.122 for 11 compounds describe three biophoric sites corresponding to sulphur atom of thiazolidinedione (site A), phenoxy oxygen (site B), and its oxygen lone pair (site C). Site A and B are electron rich sites capable of donating electrons by sulphur and oxygen atom respectively. The charge on the sites A and B are 0.154 and -0.300 respectively. Hence, site B may be involved in ionic bonding and/or electrostatic interactions. Site C which is an electronic cloud on oxygen atom is necessary for hydrogen bonding. All these properties of biophoric sites are given in Table 4. The mean interatomic distances between the biophoric sites A-B, B-C and A-C is 2.997, 7.864 and 6.447 A^0 respectively given in Table 5.

3D-QSAR equation for Model No. 122 is

- log (HA) = 19.387 (CHARGE) (±3.587) - 0.589 (REFRACTIVITY) (±0.208) - 2.830

n =11, R^2 = 0.81, R = 0.90, F (2, 8) = 16.64

Where, HA = Hypoglycaemic Activity

The equation was derived using these biophores as a template for superimposition. The variation in binding affinity with PPARγ receptor for these compounds is best described by two parameters, one being the charge at the biophore centre A corresponding to sulphur atom and other being the steric effect near to the aromatic carbon attached to phenoxy oxygen analyzed in terms of refractivity. Apart from acting as electron donor or nucleophilic centre, the biophoric centre A contributes positively for the activity. Therefore, the requirement of heteroatom at this position is essential for the activity.

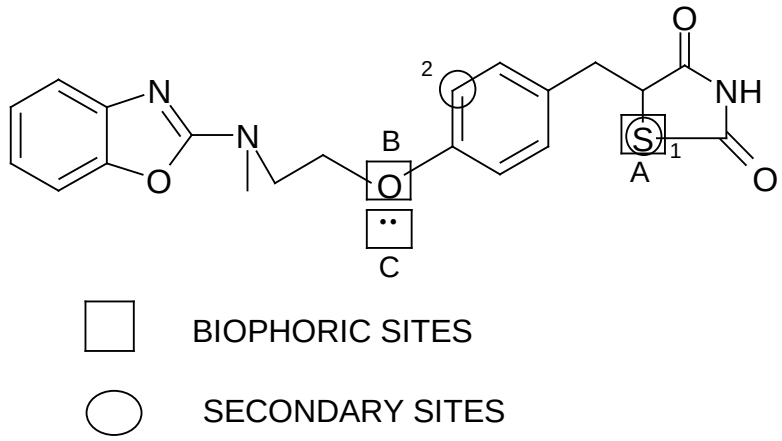


Fig. 1:

The other parameter explaining the variation in activity and contributing negatively as secondary site in steric effect described as refractivity at the vicinity of aromatic carbon atom attached to phenoxy oxygen. Therefore, the presence of bulky group at this site is not favourable for antidiabetic activity. The contribution by these two variables account for the variation in activity where a good correlation R = 0.90 between observed affinity and calculated affinity, of good statistical significance $F_{2,8}$ =16.64 is described with only 0.04 probability of chance correlation and reasonably low value of RMSA and RMSP. Structure activity data for Model No.122 are given in Table 6.

Biophoric and secondary site features important for the activity are given in the following Structure for Model No. 4

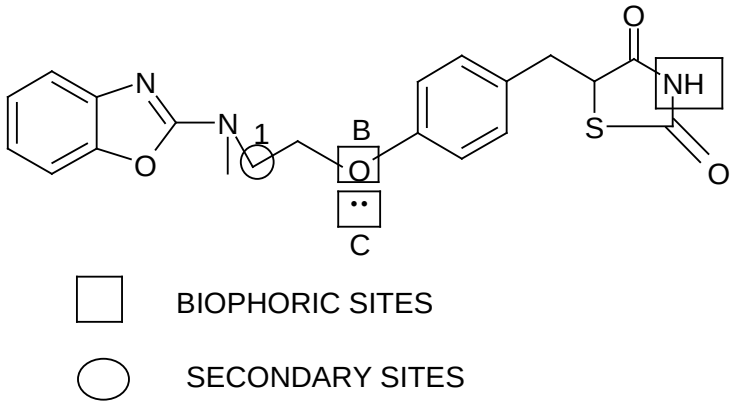


Fig.3:

The 3D QSAR Model No.4 for 10 compounds describe three biophoric sites corresponding to nitrogen atom of thiazolidinedione (site A), phenoxy oxygen (site B), and its oxygen lone pair (site C). Site A and B are electron rich sites capable of donating electrons by nitrogen and oxygen atom respectively. The charge on the sites A and B are 0.192 and -0.300 respectively. Hence, site B may be involved in ionic bonding and/or electrostatic interactions. Site C which has electronic cloud on oxygen atom is necessary for hydrogen bonding. All these property of biophoric sites are given in Table 7. The mean interatomic distances between the biophoric sites A-B, B-C and A-C is 8.679, 3.000 and 10.370 A^0 respectively. The Distance Matrix for Model No. 4 is given in Table 8.

3D-QSAR equation for Model No. 4 is

-log (HA) = -2.990 (HYDROPHOBICITY) (±0.582) - 1.480

n =10, R^2 = 0.77, R =0.877, F (1, 8) = 26.78

This equation was derived using these biophores as a template for superimposition. The variation in binding affinity with PPARγ receptor for these compounds is best described by the hydrophobic parameter analyzed in terms of hydrophobicity at the secondary site corresponding to the methylene unit attached to the phenoxy oxygen. It contributes negatively i.e. substitution by hydrophilic group at this site is favorable for antidiabetic activity. There is a good correlation (R = 0.877) between observed affinity and calculated affinity, of good statistical significance ($F_{1,8}$ = 26.78) and is described with only 0.04 probability of chance correlation.

Table 1: *In vitro* Activity Data of Series Thiazolidinediones

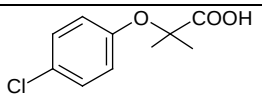
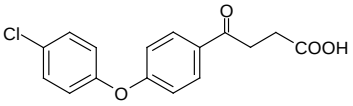
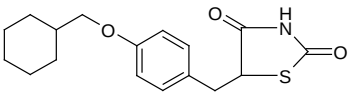
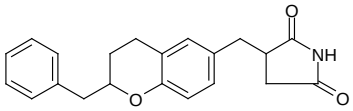
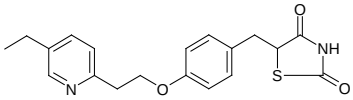
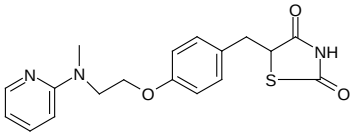
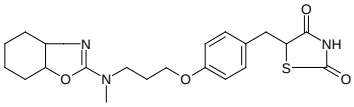
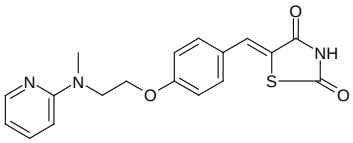
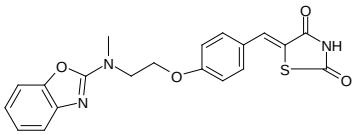
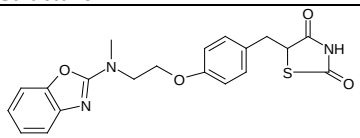
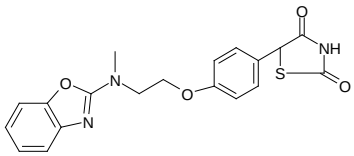
Compound No.	Structure	EC_{50}	-log EC_{50}
1		600	-2.7781
2		110	-2.0413
3		3.0	-0.4771
4		13.0	-1.1139
5		0.69	0.1615
6.		0.06	1.2218
7		1.0	0.0
8		0.19	0.7272
9		0.14	0.8538

Table 2: 3D-QSAR Pharmacophoric Models for Series Thiazolidinediones

Compound No.	Structure	EC_{50}	-log EC_{50}
10		**0.013**	**1.8860**
11		**10.0**	**1.0**

Model No.	RMSA	RMSP	R^2	Chance	Size	Match	Variable	No. of Compounds
3	0.58	0.60	0.87	0.09	3	0.32	2	11
4	0.61	0.68	0.77	0.04	3	0.47	1	10
101	0.69	0.75	0.70	0.03	3	0.38	1	10
122	0.55	0.58	0.81	0.04	3	0.35	2	11

Where,

RMSA - Root mean squared error of activity approximation.; RMSP - Root mean squared error of activity prediction

R - Correlation coefficient between experimental and approximated activity; Chance - Probability of chance correlation.

Size - Number of descriptor centers in biophore; Match - Quality of match for molecules having common biophores.

Variable - Number of variables in 3D-QSAR model.

Table 3: 3D-QSAR Model Describing Correlation and Statistical Reliability for Thiazolidinediones

Model No.	RMSA	RMSP	R^2	Chance	Size	Match	Variable	No. of Compounds
122	0.55	0.58	0.81	0.04	3	0.35	2	11
4	0.61	0.68	0.77	0.04	3	0.47	1	10

Table 4: Property Matrix for Model No. 122

Compound No.	Sites	Charge	Don_01	H-site
	A	-0.104	7.500	-
1	B	-0.266	8.312	-
	C	-	-	1.000
	A	-0.104	7.512	-
2	B	-0.240	8.611	-
	C	-	-	1.000
	A	0.154	6.453	-
3	B	-0.303	8.170	-
	C	-	-	1.000
	A	0.154	6.535	-
4	B	-0.292	8.245	-
	C	-	-	1.000
	A	0.155	6.600	-
5	B	-0.300	8.167	-
	C	-	-	1.000
	A	0.152	6.663	-
6	B	-0.301	8.296	-
	C	-	-	1.000
	A	0.154	6.664	-
7	B	-0.298	8.189	-
	C	-	-	1.000
	A	0.226	6.427	-
8	B	-0.300	8.229	-
	C	-	-	1.000
	A	0.228	6.417	-
9	B	-0.299	8.216	-
	C	-	-	1.000
	A	0.154	6.612	-
10	B	-0.300	8.192	-
	C	-	-	1.000
	A	0.153	6.442	-
11	B	-0.299	8.211	-
	C	-	-	1.000

Table 5: Distance Matrix for Model No. 122

Compound No.	A-B(A^0)	B-C(A^0)	A-C(A^0)
1	6.856	2.999	8.285
2	5.948	2.999	7.861
3	6.469	3.000	7.643
4	6.449	3.000	7.998
5	6.470	3.000	7.645
6	6.470	3.000	7.657
7	6.472	3.000	7.746
8	6.426	3.000	7.767
9	6.424	3.000	.672
10	6.508	2.999	8.512
11	6.680	3.000	7.818

Table 6: Structure Activity Data for Model No. 122

Compound No.	Experimental values	Calculated values	Calculated Error	Predicted values	Predicted Error
1	-2.78	-2.31	-0.47	-1.90	-0.88
2	-2.04	-2.31	0.27	-2.54	0.50
3	-0.48	-0.27	-0.21	-0.24	-0.24
4	-1.11	-0.53	-0.58	-0.40	-0.71
5	0.16	-0.27	0.43	-0.33	0.49
6	1.22	-0.27	0.43	-0.33	0.49
7	0.00	-0.27	1.49	-0.49	1.71
8	0.72	1.09	-0.37	1.18	0.46
9	0.85	1.09	-0.23	1.15	-0.29
10	1.89	1,76	0.12	1.11	0.77
11	-1.00	-0.27	-0.73	-0.16	-0.84

Table 7: Property Matrix for Model No. 4

Compound No.	Sites	Charge	DON_01	H-Site
	A	0.102	7.125	-
1	B	-0.266	8.312	-
	C	-	-	1.000
	A	0.103	7.132	-
2	B	-0.240	8.611	-
	C	-	-	1.000
	A	0.248	5.912	-
3	B	-0.303	8.170	-
	C	-	-	1.000
	A	0.248	5.978	-
4	B	-0.292	8.245	-
	C	-	-	1.000
	A	0.250	6.043	-
5	B	-0.300	8.167	-
	C	-	-	1.000
	A	0.246	6.712	-
6	B	-0.301	8.296	-
	C	-	-	1.000
	A	0.248	6.114	-
7	B	-0.298	8.189	-
	C	-	-	1.000
	A	0.342	5.875	-
8	B	-0.300	8.229	-
	C	-	-	1.000
	A	0.344	5.864	-
9	B	-0.299	8.216	-
	C	-	-	1.000
	A	0.248	6.074	-
10	B	-0.300	8.192	-
	C	-	-	1.000
	A	0.247	5.891	-
11	B	-0.299	8.211	-
	C	-	-	1.000

Table 8: Distance Matrix for Model No. 4

Compound No.	A-B(A^0)	B-C(A^0)	A-C(A^0)
1	9.056	2.999	10.794
2	8.227	2.999	10.370
3	8.740	3.000	10.151
4	8.775	3.000	10.503
5	8.752	3.000	10.154
6	8.752	3.000	10.161
7	8.755	3.000	10.156
8	8.661	3.000	10.278
9	8.657	3.000	10.180
10	8.786	2.999	10.998
11	8.953	3.000	10.328

Table 9: Structure Activity Data for Model No. 4

Compound No.	Experimental values	Calculated values	Calculated Error	Predicted values	Predicted Error
1	-2.78	-2.20	-0.58	-1.98	-0.82
2	-2.04	-1.49	-0.55	-1.22	-0.82
3	-0.48	-1.04	0.56	-1.19	0.72
4	-1.11	0.01	-1.12	0.13	-1.24
5	0.16	0.01	0.15	-0.01	0.17
6	1.22	1.05	0.17	1.01	0.21
7	0.00	0.01	-0.01	0.01	-0.01
8	0.72	1.05	-0.33	1.14	-0.42
9	0.85	1.05	-0.20	1.10	-0.25
10	1.89	1.05	0.83	0.84	1.05
11	-1.00	-1.49	0.49	-1.73	0.73

CONCLUSION

This study has resulted in the development of statistically significant and predictive QSAR equations for some thiazolidinediones using pharmacophoric mapping technique. Bearing the above biophoric patterns and the related properties in mind, several molecules can be designed and developed.

The field is further open for the study of these compounds with respect to other indirect drug design techniques as receptor surface

model generation, molecular shape analysis and comparative molecular field analysis.

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