Academic Sciences

International Journal of Chemistry Research

ISSN- 0976-5689 Vol 3, Issue 1, 2012

Research Article

QSAR STUDY OF INDANE-URIEDO-THIOISOBUTYRIC ACIDS AS A PPARα AGONISTS

DHARMESH SISODIYA,*KAMLESH DASHORA AND POORNIMA PANDEY

Institute of pharmacy, Vikram University Ujjain, (M.P) 456001, India. Email: dsresearch@rediffmail.com

Received: 4 Nov 2011, Revised and Accepted: 3 Jan 2012

ABSTRACT

In pursuit of better a PPARα agonist agent, QSAR studies were performed on a series of indane-uriedo-thioisobutyric acids analogues. Stepwise multiple linear regression analysis was performed to derive QSAR models which were further evaluated for statistical significance and predictive power by internal and external validation. The best QSAR model was selected, having correlation coefficient (r) = 0.9155, standard error of estimation (SEE) = 0.368 and cross validated squared correlation coefficient (q^2) = = 0.8067. Standard error of squared correlation coefficient (r^2se) = 0.2777.The predictive ability of the selected model was also confirmed by leave one out cross validation. The QSAR model indicates that the dielectric energy, connectivity index 1, dipole vector Y, dipole vector Z, and HOMO energy play an important role for the A1 receptor antagonist activities. The results of the present study may be useful on the designing of more indane-uriedo-thioisobutyric acids analogues; PPARα agonists analogues as an antidibetic agents.

Keywords: QSAR; Indane-uriedo-thioisobutyric acids analogues; Peroxisome proliferator-activated receptor-α (PPARα)

INTRODUCTION

Peroxisome proliferator-activated receptor (PPARα**)** agonist**s** comprise a wide variety of compounds. It is antidibetic agent and including pharmaceuticals, industrial chemicals, endogenous fatty acids and eicosanoids. PPARα plays a central role in the uptake and ß-oxidation of fatty acids, especially in the liver Stimulation of the PPARα receptor causes an increase in the transcription of genes related to fatty acid transport across the cell membrane, intracellular lipid trafficking, mitochondrial and peroxisomal fatty acid uptake, and both mitochondrial and peroxisomal fatty acid ß-oxidation which produces many important biological functions by activation of G protein coupled receptors that are classified in to alpha, beta and gamma are subtypes. Administration of these agents to rats and mice typically causes hepatic peroxisome proliferation, hypertrophy, hyperplasia and eventually hepatocarcinogenesis. importantly primates are relatively refractory to these effects The mechanism of PPARα-induced rat and mouse hepatocarcinogenesis is not completely understood but several hypothesis is have been put forth and mainly fall into two camps, one relating to increased oxidative stress caused by peroxisomal proliferation and the other centering on alteration in apoptosis.

Mandard *et al*.,expressed N_9 and C-8 position for increase Peroxisome proliferator-activated receptor-α (PPARα) agonist**s** affinity, small substituent at the 2-position of PPARα agonist only have limited effects on PPAR gamma receptor affinity.

Computational chemistry has developed into an important contributor to rational drug design. Quantitative structure activity relationship (QSAR) modeling results in a quantitative correlation between chemical structure and biological activity.

MATERIAL AND METHOD

Win Cache 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan), Molecular modeling pro 6.1.0 (trial version, Cambridge software Corp.), STATISTICA version 6 (Stat Soft, Inc., Tulsa, USA).

A data set of 38 compounds for (PPARα) -receptor agonist**s'** activity was used for the present QSAR study. The molar concentrations of the compounds required to produce binding at receptor site (in nm) converted to free energy related negative logarithmic values for undertaking the QSAR study.

All 38 compounds' structure were built on workspace of Win Cache 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan) and energy minimization of the molecules was done using Aligner's MM2 force field followed by semi empirical PM3 method available in MOPAC module until the root mean square gradient value becomes smaller than 0.001 kcal/mol Å. Most stable structure for each compound was generated and used for calculating various physico-chemical descriptors like thermodynamic, steric and electronic values of descriptors.

Descriptors calculation, QSAR models development and validation

In present study the calculated descriptors were conformational minimum energies (CME), Zero-order connectivity index (CI0), First-order connectivity index (CI1), Second-order connectivity index (CI2), dipole moment (DM), total energy at its current geometry after optimization of structure (TE), heat of formation at its current geometry after optimization of structure (HF), highest occupied molecular orbital energies(HOMO), lowest unoccupied molecular orbital energies(LUMO), octanol-water partition coefficient(LOGP), molar refractivity(MR), shape index order 1 (SI1), shape index order 2 (SI2), shape index order 3 (SI3), Zero-order valance connectivity index (VCI0), First-order valance connectivity index (VCI1), Second-order valance connectivity index (VCI2). Some of important descriptor which is present in model is shown in Table 2

All the calculated descriptors (50 descriptors calculated by Win Cache 6.1 and Molecular modeling pro 6.1.0, the complete descriptors data set of all compounds will be provided on request) were considered as independent variable and biological activity as dependent variable. STATISTICA version 6 (Stat Soft, Inc., Tulsa, USA) software was used to generate QSAR models by stepwise multiple linear regression analysis. Statistical measures used were n-number of compounds in regression, r-correlation coefficient, r^2-squared correlation coefficient, F- test (Fischer's value) for statistical significance, SEE- standard error of estimation, q^2- cross validated correlation coefficient and correlation matrix to show correlation among the parameters.

The squared correlation coefficient (or coefficient of multiple determination) r^2 is a relative measure of fit by the regression equation. Correspondingly, it represents the part of the variation in the observed data that is explained by the regression. The correlation coefficient values closer to 1.0 represent the better fit of the regression. The F-test reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. Standard deviation is measured by the error mean square, which expresses the variation of the residuals or the variation about the regression line. Thus standard deviation is an absolute measure of quality of fit and should have a low value for the regression to be significant.

The predictive ability of the generated correlations was evaluated by cross validation method employing a 'leave-one-out' scheme.

Validation parameters considered were cross validated r^2 or q^2, standard deviation based on predicted residual sum of squares (S_{PRESS}) and standard error of prediction (SDEP). The predictive ability of the selected model was also confirmed by external r^2CVext.

$$r^2CVext = 1 - \frac{\sum_{i=1}^{test}(y_{exp} - y_{pred})^2}{\sum_{i=1}^{test}(y_{exp} - \bar{y}_{tr})^2}$$

The robustness of a QSAR model was checked by Y – randomization test. In this technique, new QSAR models were developed by shuffling the dependent variable vector randomly and keeping the original independent variable as such. The new QSAR models are expected to have low r^2 and q^2 values. If the opposite happens then an acceptable QSAR model cannot be obtained for the specific modeling method and data.

RESULTS AND DISCUSSION

PPARs' are a popular target for the research chemists these days and substantial amount of work has been carried out in this direction. In the similar subject, a series of compounds belonging to class of indane-uriedo-thioisobutyric acids have been synthesized as novel potential PPAR-α agonists by and had been taken for present QSAR study.

Various physico-chemical parameters and inhibitory activity was taken as independent and dependent variables respectively. Correlations were established between the biological activity data and calculated molecular descriptors viz empirical, functional group, constitutional, topological etc. through sequential regression analysis. Among several QSAR, equations generated, best QSAR models were selected on the basis of various statistical parameters such as correlation coefficient (r> 0.9), r^2 is squared correlation coefficient (r^2 > 0.8), standard error of estimate and F-test values at 99% significance level.

The best correlation selected for modeling indane-uriedo-thioisobutyric acids as a PPARα agonists along with the statistical measures are summarized below.

Model no 1

$-\log EC_{50}$ =6.420 + [0.2878] R_2-chiV0 + [0.3344] R_1chi2 + [-0.5510] R_3 Carbons Count

Statistics

Optimum Components = 1, n = 38, r = 0.9155, r^2 = 0.8382, q^2 = 0.8067, F test = 139.8269, r^2 se = 0.2777, q^2 se = 0.3035, pred_r^2 = 0.6600,Pred_r^2se = 0.3211

In the above QSAR models,

n is the number of data points,

r is the correlation coefficient,

r^2 is squared correlation coefficient,

F represents Fischer ratio between the variances of calculated and observed activities,

q^2 is cross-validated squared correlation coefficient,

r^2se is standard error of squared correlation coefficient,

q^2se is standard error Squared cross-correlation co-efficient,

pred r^2 is predicted squared regression and

predr^2se standard error of predicted squared regression.

The equation contains three descriptors, i.e. chiV0, chi2 and Carbons Count.

A. R_2 chiV0

This descriptor signifies atomic valence connectivity index (order 0). In this equation this descriptor contributes positively and thus it can be stated that the presence of a Polar hetero atom at the position R_2 of the nucleus would increase the activity of the nucleus.

B. R_1 chi2

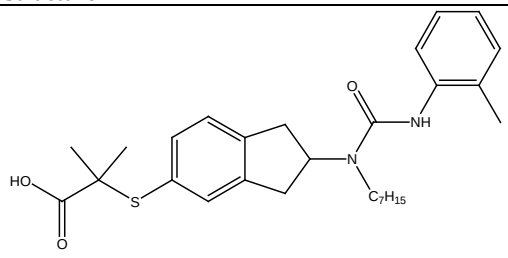
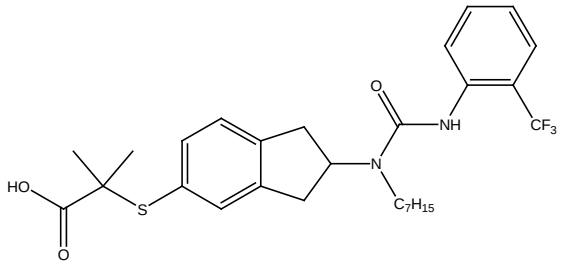
This descriptor signifies a connectivity index (second order) derived directly from gradient retention times. In the equation, this descriptor contributes negatively and thus it can be stated that the substitution of a ethyl group at the position R_1 of the nucleus decrease the activity.

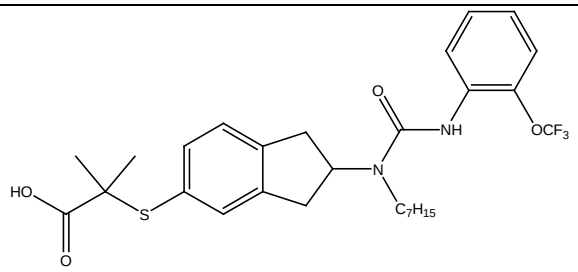
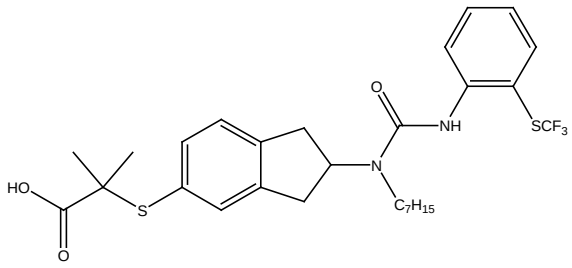
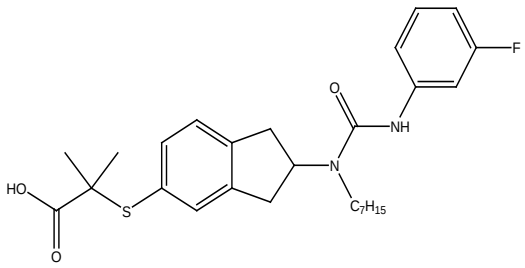
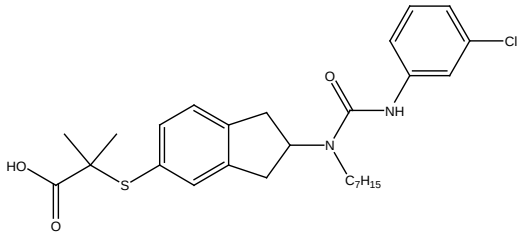
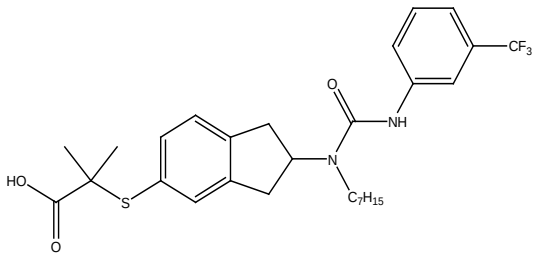
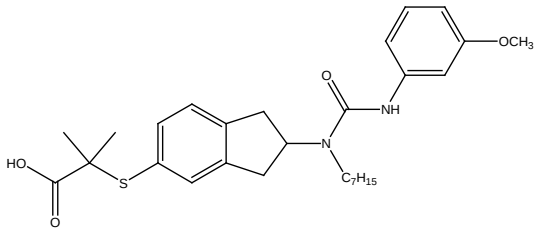
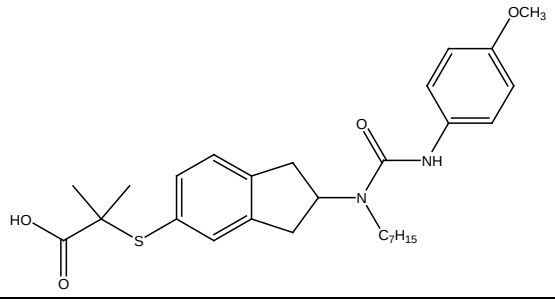
C. R_3 Carbons Count

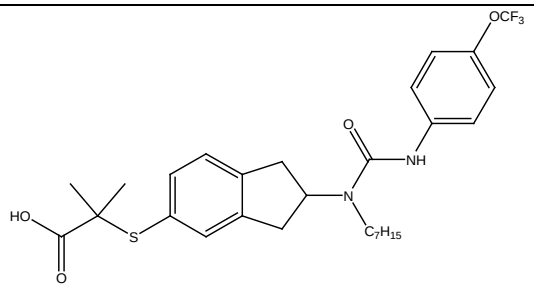
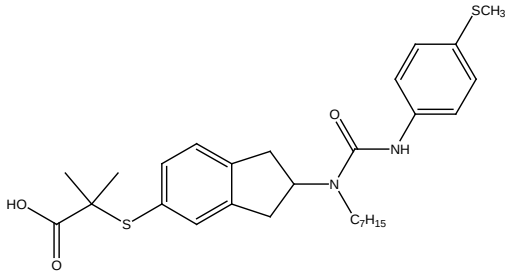
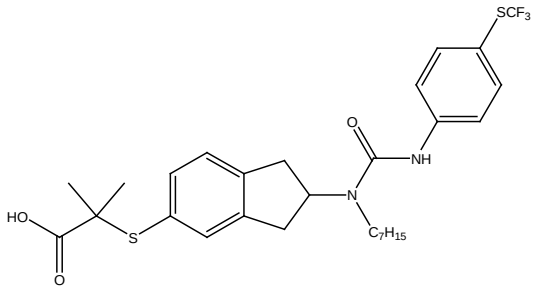
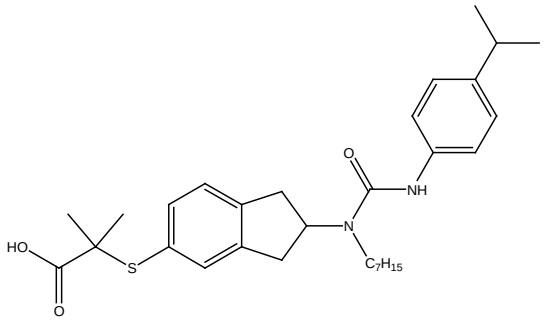
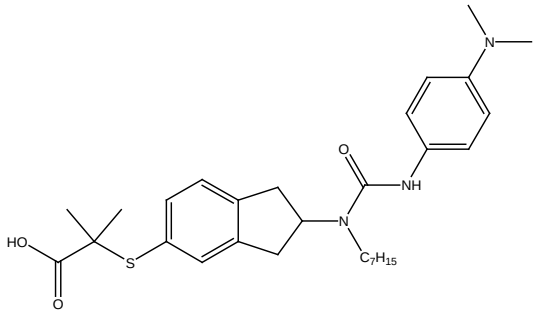
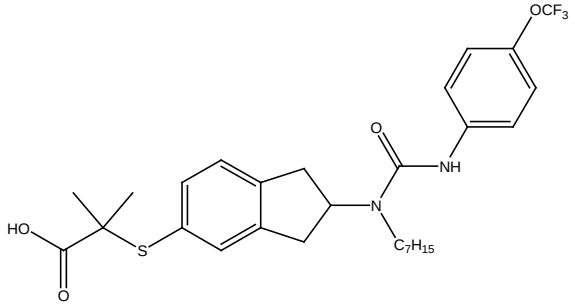
This descriptor signifies number of carbon atoms in a compound. In this equation, this descriptor contributes negatively and thus it can be said that any substitution increasing the number of carbons at the position R_3 of the nucleus will decrease the activity.

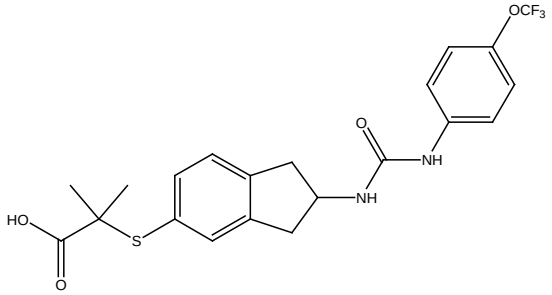
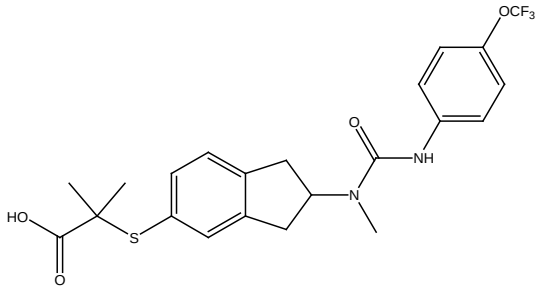
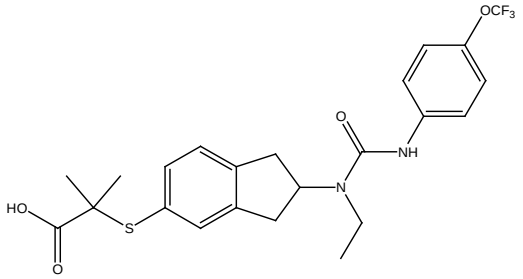
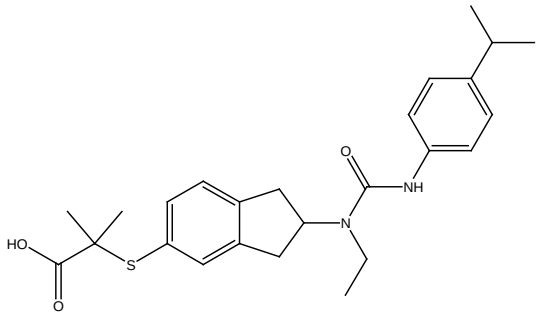
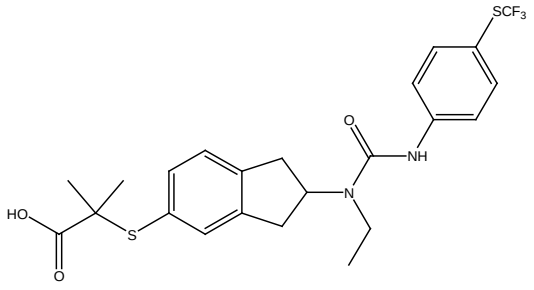
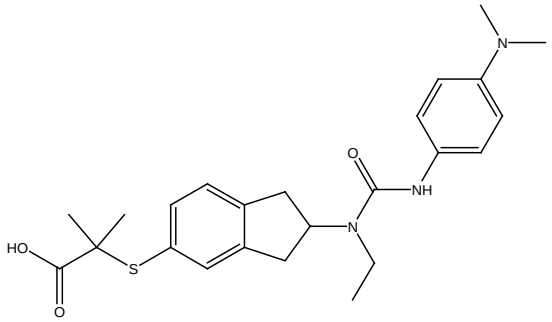
All the QSAR models are significant at 99% level, which is shown by their greater calculated value in comparison to the tabulated one. Accuracy in the analysis is shown by low values of standard error of estimate. Absence of co linearity is confirmed by calculation of inter correlation matrix for the predictor variables used in the models. Interco relation coefficients, so obtained indicate non-dependency of the descriptors on each other. High q^2 in each model reflect their good predictive potential.

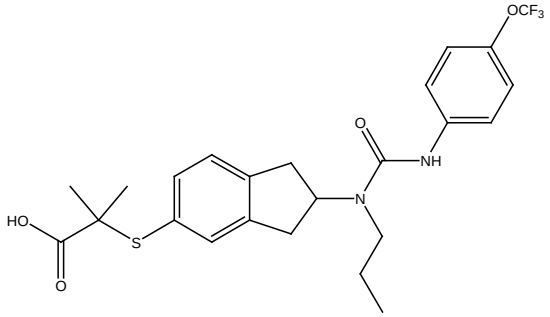
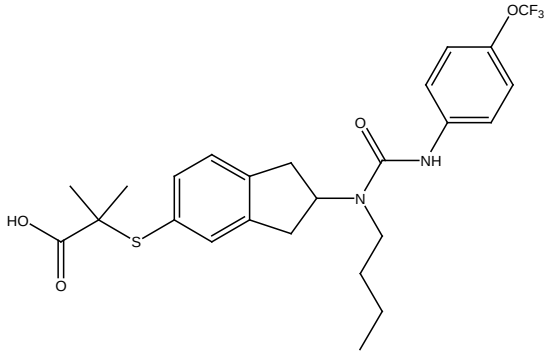
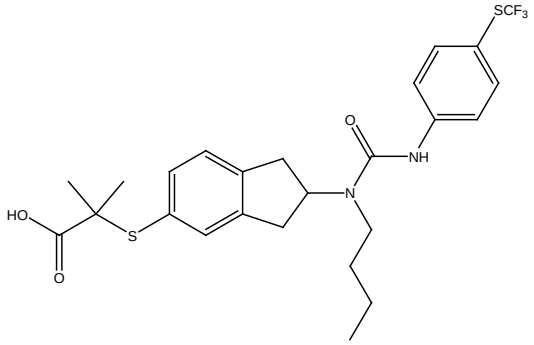
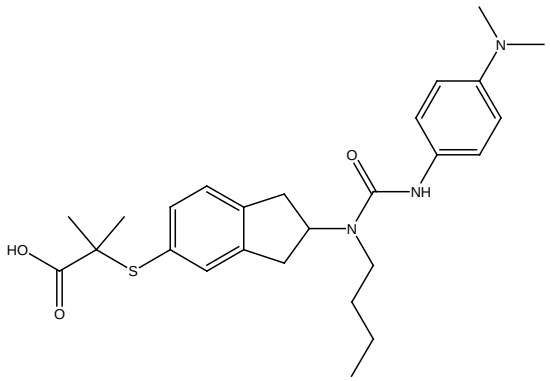
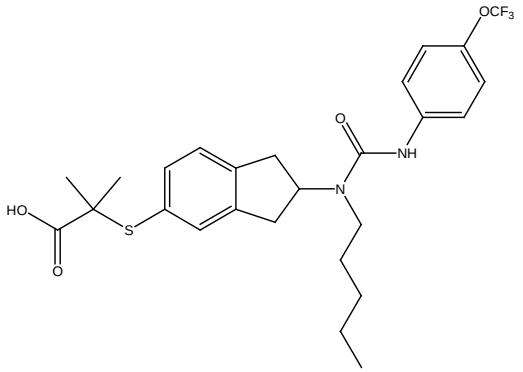
Table 1: Structures, biological activity of the Indane-uriedo-thioisobutyric acid analogues

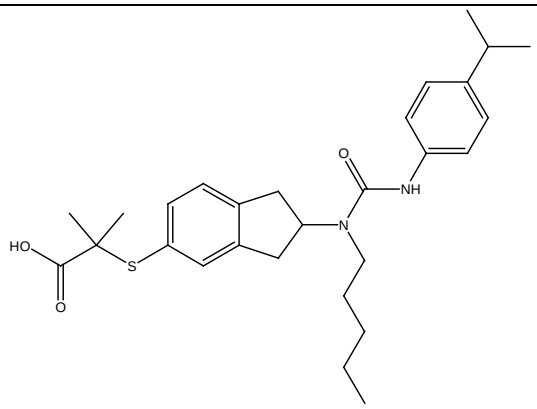
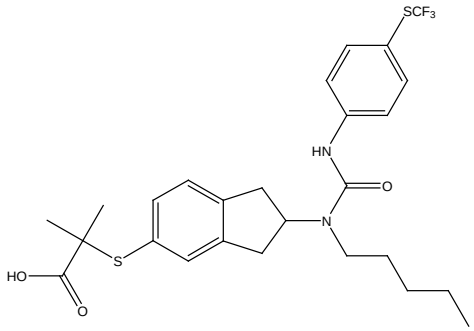
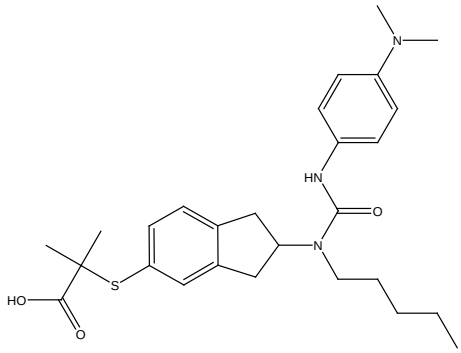
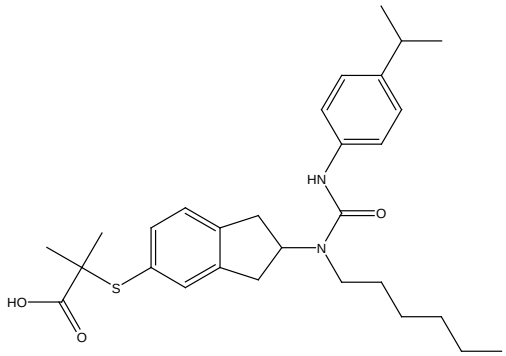
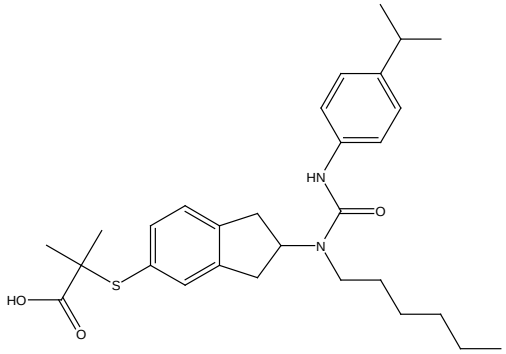
S. No	Name Assigne	Structure	EC_{50} (M)	log1/ EC_{50}
1	D1		7.54	5.122696
2	D2		6.39	5.194499

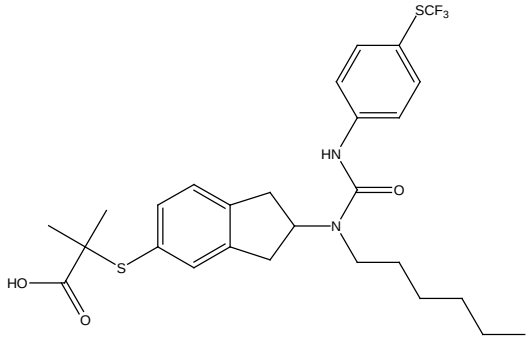
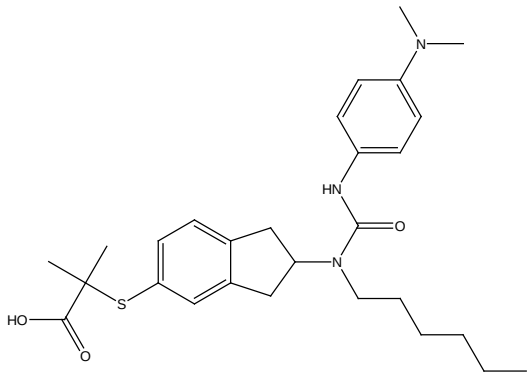
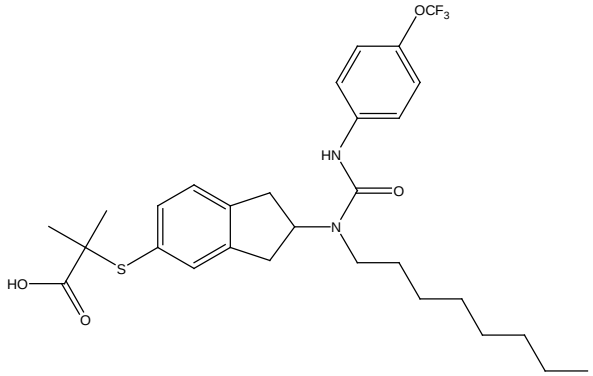
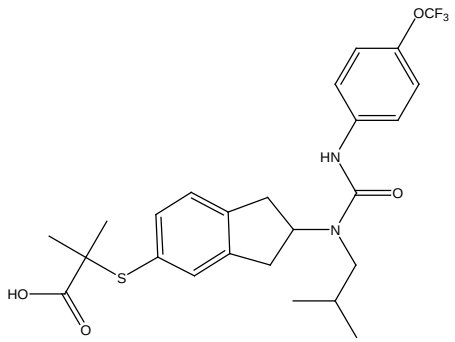
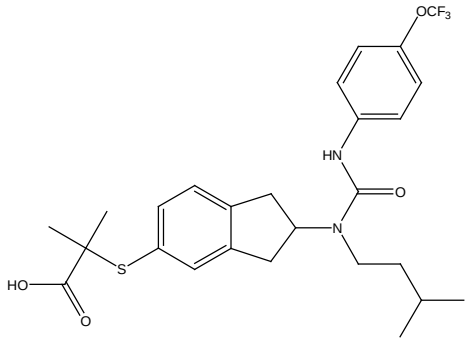
3	D3		4.99	5.301899
4	D4		1.96	5.707744
5	D5		2.67	5.573489
6	D6		2.09	5.679854
7	D7		2.73	5.563837
8	D8		1.11	5.954677
9	D9		0.0910	6.040959

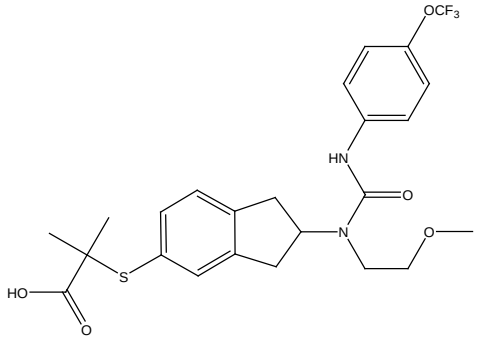
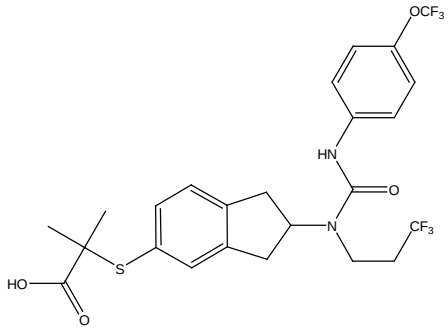
10	D10		1.27	5.896196
11	D11		0.419	6.377786
12	D12		0.210	6.677781
13	D13		0.229	6.640165
14	D14		0.252	6.598599
15	D15		0.294	6.531653

16	D16		0.096	7.017729
17	D17		2.85	6.545155
18	D18		0.033	7.481486
19	D19		0.032	7.49485
20	D20		0.023	7.638272
21	D21		0.117	6.931814

22	D22		0.158	6.801343
23	D23		0.196	6.709965
24	D24		0.160	6.79588
25	D25		0.561	6.251037
26	D26		0.105	6.978811

27	D27		0.159	6.798603
28	D28		0.046	7.337242
29	D29		0.141	6.850781
30	D30		0.166	6.779892
31	D31		0.180	6.744727

32	D32		0.249	6.603801
33	D33		0.219	6.659556
34	D34		1.03	5.987163
35	D35		2.34	5.630784
36	D36		0.386	6.413413

37	D37		0.425	6.371611
38	D38		0.707	6.150581

The Compounds in the series were sketched using Win Cache 6.1 (molecular modeling software, a product of Fujitsu private limited, Japan), Molecular modeling pro 6.1.0 (trial version, Cambridge software Corp.), STATISTICA version 6 (Stat Soft, Inc., Tulsa, USA. Energy minimized by applying the force field of the MDS and then these structures were used for the calculation of molecular descriptors available in QSAR module of Win Cache 6.1. Molecular and Electro topological descriptors for all molecules were calculated using QSAR module of Win Cache 6.1 and correlation between the biological activity and molecular descriptors was found through Partial Least Square Regression (forward stepwise). 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 degenerated and difficult to interpret. A correlation analysis was performed between inhibitory activities and remaining descriptors and the descriptors those were showing very low correlations with inhibitory activity were also removed.

Considering Anti-diabetic activity data as dependent variable and the reduced descriptor set as predictor variables, the data set was subjected to Partial Least Square Regression (stepwise forward). Statistical parameters were calculated subsequently for each step in the process so that the significance of the added parameter could be verified. Various QSAR models were generated by employing this technique. The statistical quality of the generated models was gauged by the parameters like correlation co-efficient (r), squared correlation co-efficient (r^2), which is relative measure of quality of fit, standard error (r^2se) representing absolute measure of quality of fit and Fischer's value (F), which represents F-ratio between the variance of calculated and observed activity. Best models were selected on the basis of their statistical significance. The orthogonality of descriptors in the selected QSAR models was checked by the calculation of overall correlation matrix. The selected models were validated by leave one out (LOO) cross validation method and test and training set method, which furnished squared cross correlation co-efficient (r^2or q^2), standard error of squared regression (r2 se), standard error Squared cross-correlation co-efficient (q2 se), predicted squared regression (pred r^2) and standard error of predicted squared regression (pred r^2 se) to estimate the predictive potential of models respectively.

The best correlations selected for modeling indane-uriedo-thioisobutyric acids as a PPARα agonists along with the statistical measures are summarized below.

$-\log EC_{50}$ =6.420 + [0.2878] R_2-chiV0 + [0.3344] R_1chi2 + [-0.5510] R_3 Carbons count

Table 2: Statistical parameters of indane-uriedo-thioisobutyric acids as a PPARα agonists

Model	N	r	S	F	r^2	q^2
1	38	0.9155	0..2777	139.82	0.8382	0.8067

No. of compounds (n) = 38

Std. Error of Regression (s) = 0.446

Calculated F-Ratio = 139.8269

Multiple Correlation Coefficient = 0.8382

Variance in Y explained by the Regression = 83.8%

Standard error Squared cross-correlation co-efficient q^2 se = 0.3035

Predicted squared regression pred_r^2 = 0.6600,

Standard error of predicted squared regression.pred_r^2se = 0.3211

The equation contains three descriptors, i.e. chiV0, chi2 and Carbons Count.

A. R_2-chiV0

This descriptor signifies atomic valence connectivity index (order 0).

B. R_1-chi2

This descriptor signifies a connectivity index (second order) derived directly from gradient retention times.

C. R_3-CarbonsCount

This descriptor signifies number of carbon atoms in a compound.

The above QSAR model shows high predictivity as indicated by high cross validated squared correlation coefficient (q^2) which is 0.8067 that shows high predictivity of the model. Another highly more robust method by dividing the all compounds into training set (N=27) and test set (N= 11) which gives high pred_r2= 0.6600 that represents the high predictivity of the model.

All the values of the selected descriptors in QSAR model of all the compounds are given in the table 3.

Table 3: Values of Descriptors used in the Selected QSAR Models

Serial no.	R2-chiV0	R1-chi2	R3-CarbonsCount
1	0	2.06066	1
2	0	2.06066	1
3	0	2.06066	1
4	0	2.06066	1
5	0	2.06066	0
6	0	2.06066	0
7	0	2.06066	0
8	0	2.06066	0
9	1.447214	2.06066	0
10	1.711244	2.06066	0
11	2.341641	2.06066	0
12	2.975534	2.06066	0
13	2.707107	2.06066	0
14	2.5	2.06066	0
15	2.081107	2.06066	0
16	2.081107	0	0
17	2.081107	0	0
18	2.081107	0	0
19	2.707107	0	0
20	2.975534	0	0
21	2.5	0	0
22	2.081107	0.707107	0
23	2.081107	1	0
24	2.975534	1	0
25	2.5	1	0
26	2.081107	1	0
27	2.707107	1.353553	0
28	2.975534	1.353553	0
29	2.5	1.353553	0
30	2.081107	1.707107	0
31	2.707107	1.707107	0
32	2.975534	1.707107	0
33	2.5	1.707107	0
34	2.081107	2.414214	0
35	2.081107	1.732051	0
36	2.081107	1.802095	0
37	2.081107	1	0
38	2.081107	2.914214	0

Table 4: Observed and Predicted Activity for Training Set compounds

Serial no.	Compound no.	Observed Activity	Predicated Activity
1	D4	6.64016	6.5233
2	D14	5.3019	5.51891
3	D8	7.49485	7.40388
4	D7	6.79588	6.88512
5	D13	5.98716	6.16981
6	D3	6.04096	6.01135
7	D18	5.12263	5.51891
8	D19	6.41341	6.17353
9	D25	6.80134	6.88492
10	D35	6.77989	6.47136
11	D9	5.63078	6.09754
12	D1	6.25104	6.89077
13	D37	5.1945	5.51891
14	D22	6.53165	6.28523
15	D31	6.54516	7.19288
16	D36	7.63827	7.35783
17	D26	6.6038	6.57235
18	D2	6.65956	6.58912
19	D15	5.57349	5.51891
20	D20	6.97881	6.76087
21	D16	6.74473	6.67434
22	D34	6.64016	6.5233
23	D5	5.3019	5.51891
24	D19	7.48149	7.18533
25	D27	7.49485	7.40388
26	D32	6.79588	6.88512
27	D24	5.98716	6.16981

Table 5: Observed and predicted Activity for Test Set Compounds

Serial No.	Compound no	Observed Activity	Predicted Activity
1	D06	5.67985	5.51891
2	D10	5.8962	6.1669
3	D11	6.37779	6.13207
4	D12	6.67778	6.44536
5	D17	7.01773	7.14768
6	D21	6.93181	7.31828
7	D23	6.58503	6.97667
8	D28	6.7986	6.82475
9	D29	7.33724	6.78571
10	D33	6.85078	6.73969
11	D38	6.37161	6.77511

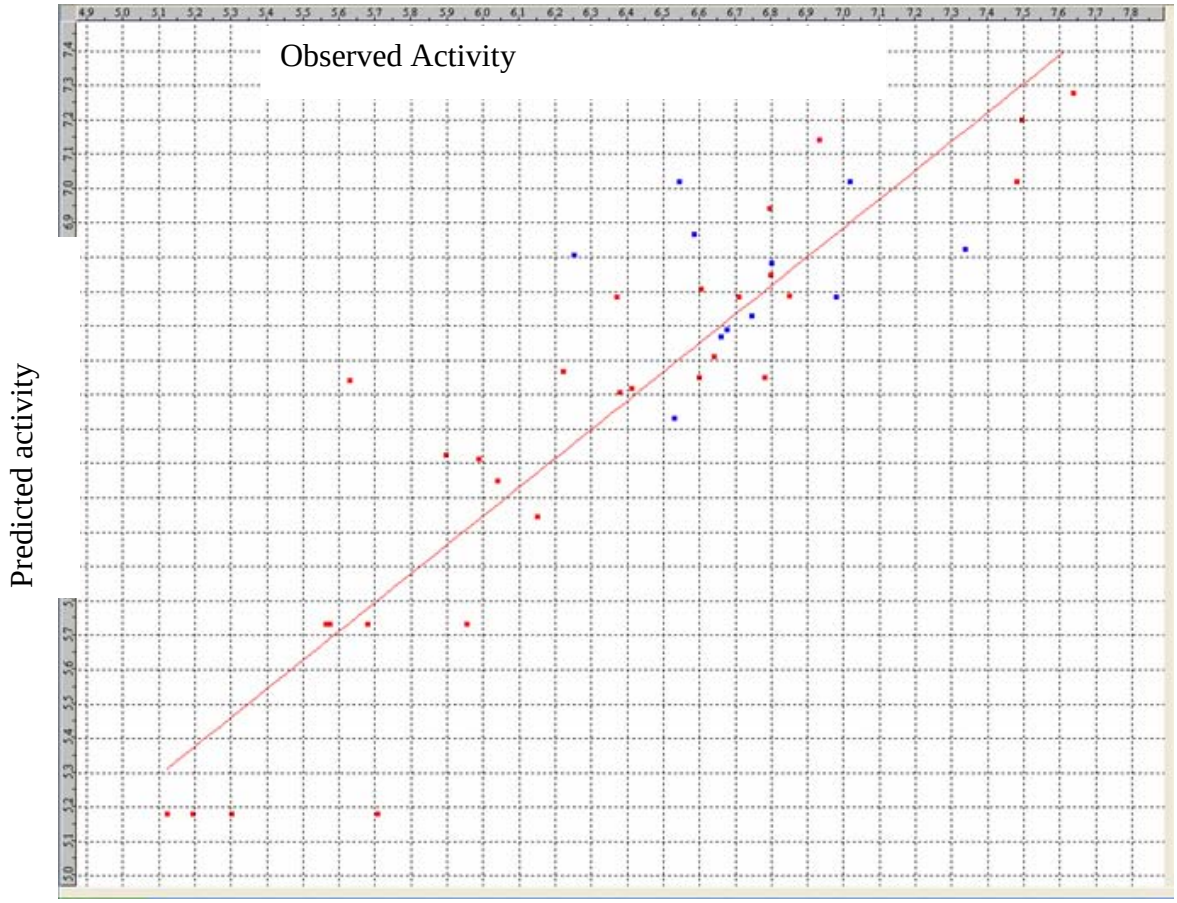


Fig. 1: Scatter Plot between the Observed and Predicted Activities. [Training Set (red spots) and test set (blue spots)]

The predictive ability of model-1s was also confirmed by external r^2CVext. The robustness of the selected model was checked by Y – randomization test. The low r^2 and q^2 values indicate (data not shown) that the good results in our original model are not due to a chance correlation or structural dependency of the training set. The predictive ability of this model was also confirmed by external cross validation (equation 3). The selected model was externally validated by randomly making training set of 27 compounds and test set of 10 compounds (06, 10, 11, 12, 17, 21, 23, 28, 29 and 33) (Table 5). QSAR was performed for training set and a model 3 was developed. This model was used to predict the biological activities of test set of compound.

pKi = 11.289 (± 1.609) DE – 0.391 (± 0.075) CI1 – 0.267 (± 0.116) DVZ + 0.500 (± 0.088) DVY + 3.166 (± 0.793) HE + 34.972 (± 7.850)…….. (3)

n = 38, r = 0.884, r^2 = 0.781, r^2_{adj} = 0.729, F = 14.96, SEE = 0.3632, P < 0.001.

The variables used in the selected model have no mutual correlation. This model showed good correlation coefficient (r) of 0.884 between descriptors Dielectric energy, Connectivity index 1, Diploe vector Y, and HE and Squared correlation coefficient (r^2) of 0.781 explains 78.1% variance in biological activity.

The positive contribution of dielectric energy, and dipole vector Y on the biological activity showed that the increase in the values of these parameters lead to better (PPARα) -receptor agonist**s** activity. The negative coefficient of connectivity index 1 indicated that the increase of CI1 is detrimental to biological activity and the negative coefficient of dipole vector Z is conducive to activity. Based on the developed QSAR model, new (PPARα) -receptor agonist**s** activity derivatives can be designed with caution.

ACKNOWLEDGEMENT

One of the authors Mr. Dharmesh sisodiya is grateful to A.I.C.T.E. for providing fellowship for this work.

REFERENCES

1. P.T Gund, Maggiora, G.; and Synder, J.P., In Guide Book on Molecular Modeling, Academic Press, London, 1996, 216-22.
2. R. E Christoffersen, Marr J.J.; and Wolff, M.E., In Burger's Medicinal Chemistry and Drug Discovery, fifth edition, Vol.1, Principles and Practice, John Wiley and sons, Inc. New York. 1989, 305.
3. S.Borman, Chemical & Engineering News, 1992, 18, 70.
4. T. J Perun; and Propst, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker, Inc, New York, 1989, 2.
5. R Leach, In Molecular Modeling, Principles & Application, Person Education Limited, 1996, 701.
6. P Willett., In Annual reports in Medicinal chemistry, Academic press, New York, 1998, 33, 337-348.
7. N.C Cohen, Blaney, J.M.; Humblet, C.; Gund, P.; and Barry, D.C., J. Med. Chem. 1990, .33, 883.
8. D.J Abraham,., In Computer Aided Drug Design Method & Application, Marcel Dekker Inc., New York, 1988, 93, 104.
9. J.T Gerig, In NMR in Drug Design, CRC Press, 1994, 15.
10. T.J Perun; and Propst, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker Inc., New York, 1989, 12.
11. T.J Perun, and Props, C.L., In Computer Aided Drug Design, Method & Applications, Marcel Dekker, Inc, New York, 1989, 156.
12. L. Ferrarini, C. Mori, C. Manera, A. Martinelli, F. Mori, G. Saccomanni, P. L. Barili, L. Betti, Giannaccini, L. Trincavelli, A. Lucacchini, J. Med. Chem. 43, 2814 (2000).
13. T. Katsushima, L. Nieves, N. Wells, J. Med. Chem. 33, 1906 (1990).
14. S. Kuroda, A. Akahane, H. Itani, S. Nishimura, K. Durkin, T. Kinoshita, Y. Tenda, K. Sakane,
15. Muller, Expert Opin. The. Pat. 5, 419 (1997).
16. P. L. Martin, R. J. Wysocki, R. J. Barrett, J. M. May, J. Linden, J. Pharmacol. Exp. 276, 490 (1996).
17. R. Volpini, S. Costanzi, C. Lambertucci, S. Vittori, A. Lorenzen, K. N. Klotz, G. Cristalli, Bioorg. Med. Chem. Lett. 11, 1931 (2001).
18. V. Ravichandran, R. K. Agrawal, Bioorg. Med. Chem. Lett. 17, 2197 (2007).
19. Ravichandran, V. K. Mourya, R. K. Agrawal, Arkivoc XIV, 204 (2007).
20. K. K. Sahu, V. Ravichandran, V. K. Mourya, R. K. Agrawal, Med. Chem. Res. 15, 418 (2007).
21. K. K. Sahu, V. Ravichandran, P. K. Jain, S. Sharma, V. K. Mourya, R. K. Agrawal, Acta Chim.Slov. (Inpress) (2007).
22. S. Sharma, V. Ravichandran, P. K. Jain, V. K. Mourya, R. K. Agrawal, J. Enzym. Inhib. Med. Chem. (In press) (2007).
23. H. K. Jain, R. K. Agrawal, Inter. Elect. J. Mol. Design 5, 224 (2006)
24. H. K. Jain, R. K. Agrawal, Inter. Elect. J. Mol. Design (In press) (2007).
25. P. L. Ferrarini, C. Mori, C. Manera, A. Martinelli, F. Mori, G. Saccomanni, P. L. Barili, L. Betti, G. Giannaccini, L. Trincavelli, A. Lucacchini, J. Med. Chem. 43, 2814 (2000).
26. T. Katsushima, L. Nieves, N. Wells, J. Med. Chem. 33, 1906 (1990).
27. S. Kuroda, A. Akahane, H. Itani, S. Nishimura, K. Durkin, T. Kinoshita, Y. Tenda, K. Sakane, Bioorg. Med. Chem. Lett. 9, 1979 (1999).
28. Muller, Expert Opin. Ther. Pat. 5, 419 (1997).
29. Rianne, D. Ligt, A. M. Pieter, V. D. Klein, K. Jacobien, F. Drabbe Kunzel, A. Lorenzen, F. A. Maate, S. Fujikawa, R. V. Westhoven, T. V. D. Hoven, J. Brussee, P. Ijzerman, Bioorg. Med. Chem.12, 139 (2004).
30. P. L. Martin, R. J. Wysocki, R. J. Barrett, J. M. May, J. Linden, J. Pharmacology. Exp. 276, 490 (1996).
31. R. Volpini, S. Costanzi, C. Lambertucci, S. Vittori, A. Lorenzen, K. N. Klotz, G. Cristalli, Bioorg. Med. Chem. Lett. 11, 1931 (2001).
32. V. Ravichandran, R. K. Agrawal, Bioorg. Med. Chem. Lett. 17, 2197 (2007).
33. V. Ravichandran, V. K. Mourya, R. K. Agrawal, Arkivoc XIV, 204 (2007).
34. K. K. Sahu, V. Ravichandran, V. K. Mourya, R. K. Agrawal, Med. Chem. Res. 15, 418 (2007).
35. K. K. Sahu, V. Ravichandran, P. K. Jain, S. Sharma, V. K. Mourya, R. K. Agrawal, Acta Chim. Slav. (In press) (2007)
36. S. Sharma, V. Ravichandran, P. K. Jain, V. K. Mourya, R. K. Agrawal, J. Enzyme. Inhibition. Med. Chem. (In press) (2007).
37. H. K. Jain, R. K. Agrawal, Inter. Elect. J. Mol. Design 5, 224 (2006).
38. H. K. Jain, R. K. Agrawal, Inter. Elect. J. Mol. Design (In press) (2007).