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Design optimization through 3D QSAR of Malonyl-Coenzyme - A Decarboxylase inhibitors with the help of Comparative Molecular Field Analysis

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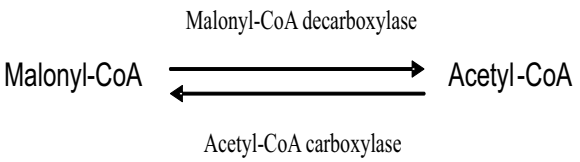
ABSTRACT

Malonyl CoA Decarboxylase, (MCD) plays a critical role in ischemic heart disease. During the past several years there have been extensive research in the identification and optimization of Malonyl CoA Decarboxylase Inhibitors (MCDIs) as a novel anti ischemic drugs. We analyzed the structure and biological activity data for 56 compounds from which 27 molecules were reverse amide based, 19 molecules were urea based and 9 were amide based. QSAR study was performed on comprehensive data set using PLS technique and created CoMFA model. A prediction and description of 3D-QSAR model was observed with r2-value of 0.98 and q2-value of 0.6. The confidence limit for a q^2 observed more than 95% as the value of q^2 is 0.6.

INTRODUCTION

Bioinformatics is a scientific discipline of discovering biological functions through analysis of series of different computer based model (Yadav et al., 2003; Atwood and Parry-Smith, 2001) Quantitative structure-activity relationship (QSAR) of a series of structural diverse malonyl-CoA decarboxylase (MCD) inhibitors has been investigated by using the predictive single model as well as the consensus analysis (Li et al., 2008). Quantitative correlation of the biological (ecological, toxicological or pharmacological) activity with the calculated properties from the structure of chemical compounds allows the prediction of the so-called "drug potency" of a structurally related compound. Drug discovery often involves the use of QSAR to identify chemical structures that could have good inhibitory effects on specific targets. Morales-Bayuelo et al., 2015 used the quantum similarity field as well as reactivity descriptors based on the density functional theory as a consistent approach to better understand the 3D-QSAR studies in drug design. 3D-QSAR analysis for MCD inhibitors was done using CoMFA and CoMSIA techniques by Pourbasheer et al., 2015. Calder et al., 1993 did CoMFA validation of the superposition of six classes of compounds which block GABA receptors non-competitively.Three methods were used to predict the toxicity effects of a given molecule. Technique of 3D-QSAR is a specialization concerned with three-dimensional quantitative structure activity relationships. This involves the three-dimensional properties of molecules. The idea underlying a Comparative Molecular Field Analysis (CoMFA) was that differences in a target property were often related to differences in the shapes of the non-covalent fields surrounding the tested molecules.

The enzyme malonyl-CoA decarboxylase (MCD, CoA = coenzyme A) catalyze the conversion of the malonyl-CoA to acetyl-CoA and thereby regulates malonyl-CoA levels (Cheng et al., 2006a).



MCD was first purified from the uropygial glands of water fowl and subsequently from a number of mammalians, plants, and bacteria (Cheng et al., 2006a). A single human MCD mRNA was observed by Northern-blot analysis. The highest mRNA expression levels were found in muscles and heart tissues, followed by liver, kidney and pancreas, with detectable amount found in many other tissues. Recent studies indicate that MCD exists in cytosolic, mitochondrial and peroxisomal compartments (Cheng et al., 2006a; Cheng et al., 2006b). Malonyl CoA Decarboxylase play a important role in two energy metabolisms in heart (Patel and Talele, 2007). Normally, the metabolism of fatty acids contributes about 60% to 80% of the heart's energy need (Jason et al., 2004; Noga et al., 2004). The malonyl-CoA decarboxylase (MCD) inhibition activity of derivatives of N-alkyl-N-(1,1,1,3,3,3-hexafluoro-2-hydroxypropylphenyl)amide has also been analyzed through combinatorial protocolin multiple linear regression (CP-MLR) using different topological descriptors obtained from Dragon software for the energy minimized 3D-structures of these molecules (Singh et al., 2009). In drug research, once a chemical class (lead) is focused for investigation, it is necessary to understand the physicochemical, topological features for optimum response, also to know the unexplored structural domains in the vicinity of the lead; and explore the scope and ways to proceed for further modification (Deshpande et al., 2010).

MATERIALS AND METHODS

Software used

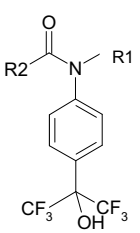
The CoMFA technique of the SYBYL software was used to create a 3D QSAR model of the MCD inhibitors. The 7.0 version of software was used.

Statistical technique

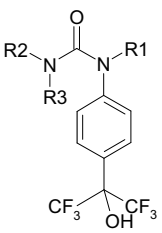
Partial Least Square (PLS) statistical technique was used for creating the correlation between the parameters and biological property of the molecules and developing a QSAR equation. The PLS regression includes the response variables y in the process of reduction of the variables. Because PLS was able to investigate complex structure activity problem, to analyze data in a more realistic way, and interpret how to molecular structure influences biological activity.

MCD inhibitors

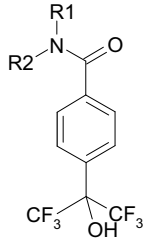
For creating a 3D QSAR model of MCD inhibitors we used Cheng et al., 2006a model in which three types of structures was given of MCD inhibitors as a reference.



i) Reverse amide based



ii) Urea based



iii) Amide based

Total numbers of molecules were 56, of which 27 molecules were reverse amide based, 19 molecules were urea based and 9 were amide based. The range of biological activity of the compounds is from 8 nM to 6626 nM [1].

Training set of the molecules

Total 39 molecules were taken in the training set to create a model, in which 16 molecules were reverse amide based, 15 molecules of urea based and 8 molecules of amide based structure has taken and range of biological activity in training set was from 8 nM to 6626 nM. Data is presented in the table1 as a summary of results.

Alignment

The alignment of the molecules submitted to the CoMFA procedure, which is the critical step of the analysis. In the alignment process the bonds of the molecules were rotating for superimposing the molecule over template and after changes the molecule must be minimized. The alignment of the molecules for the CoMFA analysis was obtained by superimposing each analogue on the template i.e., compound 5w which is the most potent molecule among the series of molecules chosen for developing the model (Fig. 1).

RESULTS AND DISCUSSION

Partial Least Square analysis

To obtaining the 3D QSAR equation, PLS analysis was performed using steric and electrostatic fields of CoMFA in combination (Geladi and Kowalsky, 1886; Wold et al., 2012). Results of analysis are shown in Table1. The present model gave the best statistical results. The model was thus chosen as the working CoMFA model, whose descriptivity and predictivity assessed by the r^2-value of 0.98 and q^2-value of 0.6. The confidence limit for a q^2 is more than 95% as the value of q^2 is 0.6.

Contour map of the model

The results of the CoMFA illustrated by plotting the iso-contour maps calculated from the QSAR equation expressing the non-cross-validated model. The iso-contour generated by CoMFA equation for the steric and electrostatic contribution is shown in figure 2. CoMFA contour plots are shown surrounding regions in the space around the template 5w. The steric contours are coloured green where addition of steric bulk increase the activity, and yellow where in increase steric bulk decreases the activity. The electrostatic contour are coloured blue where addition of electrostaticaly positively charged substituent increase the activity of the molecule and red where the addition of electrostaticaly negative charge substituent increase the activity of the molecule.

The part of steric effects, in particularly a green favorable contours are located in the position corresponding mostly to the R1 position of molecule and a yellow unfavorable contours are located in a position corresponding to the R2 position of molecule. The part of electrostatic effect in concerned of blue electrostatic positive charge favorable contour are located in a position surrounding mostly to R1 position of molecule and a red negative charge favorable contours are located in a position corresponding mostly to the R2 position of molecule.

Validation of the model

To get an objective validation of the QSAR model developed to describe the structure activity relationship of the MCD inhibitors, the activity of the test set molecules was predicted by using the model and determining the deviation between predicted and experimental values of the molecules. The test set predicted values and deviation of these from experimental are shown in Table 2. Most of the molecules of the test set were predicted well, the deviation between the predicted and experimental pIC50 values were less than 0.5, indicating that the reported CoMFA model was fairly significant from a statistical point of view. Calculated pIC50 value deviate from the corresponding experimental one by 1.31 for the compound 5r, thus strongly under predicted. The molecule 5r is a unique and this type of molecule was not present in the training set that is reason the molecule is under prediction. While many other molecules such as 11a, 5t, and 6r were predicted to be much different from the actual experimental values, but efforts to improve the derived model further for its better statistical accuracy were not put in. Our results are confirmation with the findings of Cheng et al., 2006a towards design optimization of 3D QSAR of Malonyl-Coenzyme through CoMFA model of MCD inhibitors.

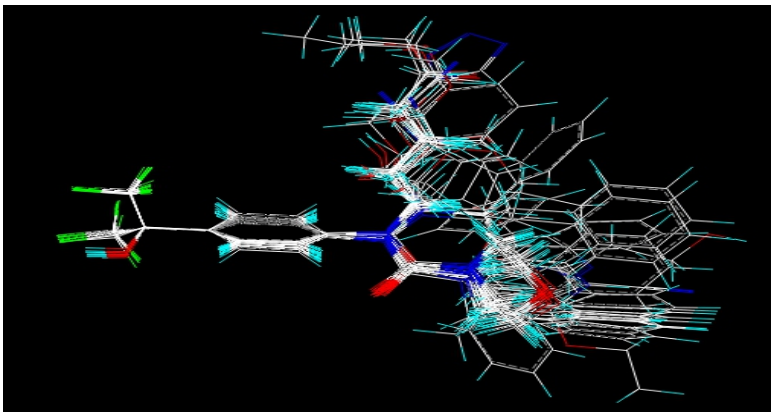


Figure 1: Alignment of the molecules.

Table 1: Summary of CoFMA results of the molecules.

Q^2	S_{cross}	R^2	S	F	N
0.60	0.5	0.98	0.09	571	5

Q2 - Cross validated r2, Scross – Standard Cross, R2 - Correlation Coefficient, S – Standard Deviation, F - F-value is ratio of the r2 to 1.0-r2

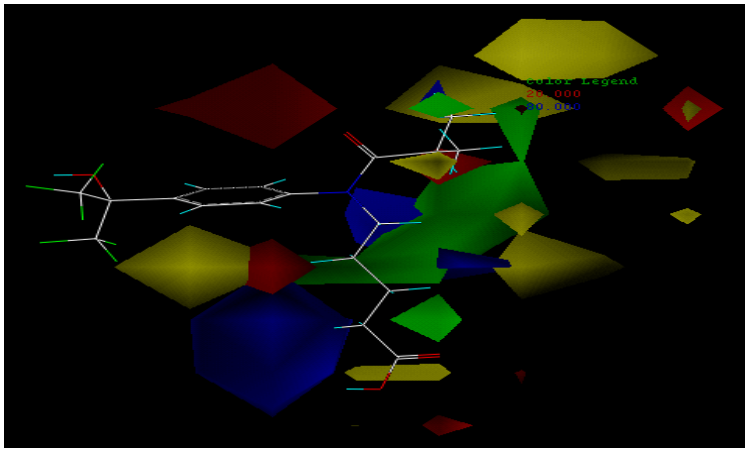


Figure 2: Alignment of the molecules.

Table 2. Test set of validation .

Name	pIC_{50} (experimental)	pIC_{50} (calculated)	Deviation
5w	8.1	8.0	0.1
5q	7.7	7.4	0.3
5y	7.7	7.2	0.5
5v	7.6	7.5	0.1
5p	7.6	7.2	0.4
5t	7.5	6.8	0.7
6t	7.4	7.1	0.3
5o	7.4	6.9	0.5
6l	7.1	6.9	0.2
6q	7.0	7.4	-0.4
5g	6.9	6.7	0.2
6o	6.8	7.1	-0.3
5e	6.7	7.1	-0.4
6r	6.6	7.2	-0.6
5u	6.2	6.7	-0.5
5r	5.9	7.2	-1.3
11a	5.8	5.1	0.7

CONCLUSION

In the present study we attempted to derive structure activity relationship (SAR) to summarize the effects of the introduction of substituents on the some positions of the lead compounds of malonyl CoA decarboxylase inhibitors. The derived CoMFA model of MCD inhibitors provided a satisfactory consistency with respect to the statistics and predictive ability of activity, and pointed following main SAR aspects of the amide based, urea based and reverse amide based structure of MCD inhibitors: a) High steric and positive electrostatic effect of the substituent at R1 position of compound. b) High negative electrostatic and less steric effect of the substituent at R2 position of the compound. The present model may also be used for predicting the activity of new designed molecules of the same series in the future.

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REFERENCES

1. Attwood, T.K. and Parry-Smith, D.J. (2001) Introduction to Bioinformatics. Pearson Education Ltd. Singapore. pp 261
2. Calder, J.A., Wyatt, J.A., Frenkel, D.A., Casida, J.E. (1993) CoMFA validation of the superposition of six classes of compounds which block GABA receptors non-competitively. *J Comput Aided Mol Des*. 7(1): 45-60
3. Cheng, J., Chen, M., Wallace D., Tith, S., Haramura, M., Liu B., Mak, C. C., Arrhenius T., Brown R. S., Thorn V., Harmon C., Rick B., Jason R. B. ,Gary D. L., and Nadzan A. M. (2006a). Synthesis and Structure-Activity Relationship of Small-Molecule Malonyl Coenzyme A Decarboxylase Inhibitors. *J. Med. Chem*. 49: 1517-1525
4. Cheng,J., Chen, M., Liu, B., Zheng H., Arrhenius, T., and Nadzan, A.M. (2006b) Design and synthesis of heterocyclic malonyl-CoA decarboxylase inhibitors. *Bioorganic & Medicinal Chemistry Lett*. 16: 695–700
5. Deshpande, S., Gupta, M. K., and Prabhakar,Y.S. (2010) Multi-Model Environment as a Rational Approach for Drug Design: An Experience with CP-MLR. *The IUP J Chem*. 3(1): -27
6. Geladi, P., Kowalsky, B. R. (1886) Partial Least Square: a tutorial. Anal Chem Acta. 185: 1-17
7. Jason, R.B., Cheng, D. J., Stanley, W.C., Barr, R., Chandler, M. P., Brown, S., Wallance, D., Arrhenius, T., Harmon, C., Yang, G., Nadzan, A. M. and Lopaschuk, G.D. (2004) Malonyl Coenzyme A Decarboxylase Inhibition protects the Ischemic Heart by Inhibiting Fatty Acid Oxidation and *Simulating Glucose Oxidation*. Circ. Res. 94;78-84.
8.Li J., Lei B., Liu H., Li S., Yao X., Liu M., Gramatica, P. (2008). QSAR study of malonyl CoA decarboxylase inhibitors using GA-MLR and a new strategy of consensus modeling. *J Comput Chem*. 29(16):2636-47
9.Morales-Bayuelo A., Matute R., A., Caballero, J. (2015) Understanding the comparative molecular field analysis (CoMFA) in terms of molecular quantum similarity and DFT-based reactivity descriptors. *J Mol Model*. 21(6):156
10. Noga, A.A., Dyck, J.R.B, Lopaschuk, G.D. (2004) Alterations in energy metabolism in acute coronary syndromes. *Heart Metab*. 23:3–4
11.Patel M.R., Talele T. T. (2007) 3D-QSAR studies on malonyl coenzyme A decarboxylase inhibitors. *Bioorg Med Chem*. 15(13):4470-81
12. Pourbasheer, E., Ebadi A. R., Ganjali, A., Mohammad R. (2015) 3D-QSAR analysis of MCD inhibitors by CoMFA and CoMSIA. *Combinatorial Chemistry & High Throughput Screening*. 18 (8), 751-766
13.Singh, P., Kumar, R. , Sharma, B. K. and Prabhakar, Y. S. (2009) Topological descriptors in modeling malonyl coenzyme A decarboxylase inhibitory activity: N-Alkyl-N-(1,1,1,3,3,3-hexafluoro-2 hydroxypropylphenyl)amide derivatives. *J Enz Inhibition and Med Chem*. 24(1): 77-85
14. Schleyer, P.R.; Allinger, N.L., Clark, T., Gasteiger, J., Kollman. P.A., Schaefer III, H.F., Screiner, P.R. (Eds.), (1998). Jhon Wiley and Sons Ltd.
15. Wold, S., Sjostron, M., Eriksson, L. (2012). Partial least square projections to latent structure (PLS) in chemistry. In Encyclopedia of Computational Chemistry; Vol.4.
16. Yadav, M. K. Tripathi, M.K., Yadav, S.L., Mishra, A., Gaur, A.K., Garg, G. K. and Mishra, D.P. (2003) Bioinformatics: New directions to know facts of life. *Bioinformatics India*. 1(3): 76-82