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QSAR and Docking Studies of Indene N-Oxide Derivatives as PPARγ Agonists

Ganesh Prasad Mishra[1], Rajesh Sharma[2], Hemant M Joshi[1]

[1]Ujjain Institute of Pharmaceutical Sciences, Chandesara, Ujjain, Madhya, Pradesh, India –452 017

[2]School of Pharmacy, Devi Ahilya Vishwavidyalaya, Takshshila Campus, Indore, M. P., India-452 001

E-mail address: gmrdmishra@rediffmail.com

ABSTRACT

Indene N-oxide derivatives were used for docking and three dimensional quantitative structure activity relationship studies. Molecular docking and validation studies were carried out for all compounds on peroxisome proliferator activated receptor γ active site. The reliability of the docking results was acceptable with good root mean square deviation value (ranging from 0.96 to 2Å). The three dimensional quantitative structure activity relationship studies were also carried out by advanced technique (Stepwise forward-backward variable selection method) using training set of 19 compounds and test set of 7 compounds. A statistically reliable model with good predictive power (q2 = 0.8820, Pred r2= 0.7063) was achieved. Both above approaches illustrated insights into the structure activity relationship of these compounds which may helps in the design and development of potent indene N-oxide derivatives as PPARγ agonists.

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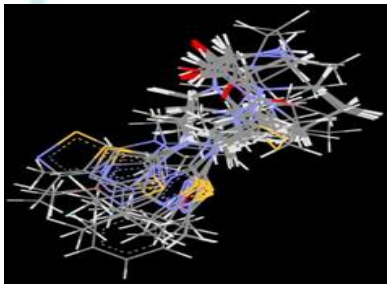
INTRODUCTION:

Type-2 diabetes has emerged as one of the biggest problems facing the world today. It is now forecasting that by the year 2025, 300 million people will suffer from diabetes worldwide, with 90% of these cases attributed to non-insulin dependent (type-2) diabetes[1]. Peroxisome proliferators-activated receptor gamma (PPARγ) is a nuclear receptor and transcription element that plays a crucial role in glucose homeostasis, insulin sensitization and lipid storage[2]. Currently, increasing interest on PPARγ research, a number of relevant quantitative structure-activity relationship (QSAR) studies were done. Most of them employed three dimensional QSAR field methodologies, such as Comparative Molecular Field Analysis and Comparative Molecular Similarity Indices Analysis[3]. In this paper, Non-TZDs (indene N-oxide derivatives) have been studied as PPARγ agonistic activity using docking and QSAR approach.

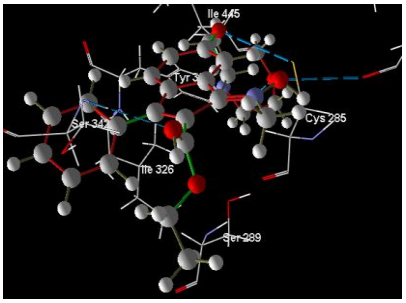
MATERIAL AND METHODS:

Dataset and molecular alignments

26 PPAR γ agonists were taken from the literature[4] and the reported EC_{50} values (µM) have been changed to the pEC_{50} for docking and QSAR study. The dataset was divided into a training set of 19 molecules and test set of 7 molecules as external set for validation of developed model using sphere exclusion methods. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive effectiveness of the model which is not included in model generation. Sphere exclusion algorithm was used for creation of training and test sets. The alignment of all the indene N-oxide derivatives is shown in Figure 1.



a.



b.

Figure 1: Structural alignment of indene N-oxide derivatives used to develop the 3D- QSAR models (a) and docking pose of most active compound 18 with 2xkw (b).

Molecular docking simulations

MOLDOCK program employed to simulate interaction of PPARγ receptor with selected molecules. The most promising poses returned when the docking run was completed and further analyzed in the Pose Organizer. Moreover selected poses were confirmed to be the most stable conformation of each molecule for the binding to the PPAR γ active site. All of the selected poses of the 26 analyzed molecules were visually inspected to demonstrate that they were able to establish the molecular interactions with receptor.

Generation of the three dimensional QSAR model

Here, we performed 3D-QSAR analysis using the Molecular Design Suit Vlife MDS software package, version 4.1; supplied by Vlife Sciences, Pune, India. Structures were sketched using CS Chem Office Version 11.0, Cambridge Soft Corporation, Software Publishers Association USA, the 2D draw application and converted to 3D structures. The sketched structures were subjected to energy minimization using molecular mechanics (MM2) until the root mean square (RMS) gradient value became smaller than 0.1 kcal/mol Å. The geometry optimization of the lowest energy structure was carried out using EF routine. K-Nearest neighbor molecular field analysis (kNN-MFA) is a novel methodology unlike conventional 3D-QSAR regression methods, this methodology can handle non-linear relationships of molecular field descriptors with biological activity by which it leads to improved models resulting in better predictive ability.

RESULTS AND DISCUSSION:

Molecular docking studies

26 compounds were docked into the crystal structure of PPARγ and the highest scoring pose was selected for each compound. The best docking poses are predicted to be the most stable conformation of each compound for binding to the PPAR γ receptor active site. Fig. 1 indicates that amino acid residue Ser289 and Cys285 were formed hydrogen bond with carboxylic part of the compound 18. A compound 18 with highest docking score has shown highest activity among indene N-oxide derivatives probably because of morpholine substituent fully interact with phenyl ring of Tyr 327 amino acid residue.

SW-kNN MFA studies In the development of 3D-QSAR model stepwise (SW) variable selection method was used. The compounds of both, training and test set were aligned using the indene N-oxide template (Fig. 1). Descriptor range for the selected model of the Series indicates that; phenyl alkyl substituent is essential for the effective binding with the hydrophobic pocket of the active site of receptor. The presence of electrostatic field with positive coefficient (E_1212) suggests that polar group must be favorable and forming H-bond with the head group of the active site. Moreover, acidic carboxylic moiety of the ligand also plays an important role in the ligand-receptor interactions. The descriptor S_4412 exhibiting range analogously negative suggests that steric descriptors are provided less contribution than the others. The positive hydrophobic potential is favorable for increase in activity and hence more hydrophobic substituent group is preferred in tail region. Among the indene N-oxide derivatives, compound 18 is most potent; reason could be an optimum mopholine alkyl group is substituted 3rd position of the indene N-oxide ring is fully accommodate the hydrophobic pocket of the receptor.

CONCLUSION:

In the present study, we have successfully established the use of computational approaches to identify indene N-oxide derivatives as PPARγ agonists. It was found that, SW-kNN-MFA 3D-QSAR model and the docking interactions between the agonists and the active site of PPARγ are complementary. Moreover, these models match well with the known features of the different parts of the PPARγ binding site and approved that the binding portion of the PPARγ receptor is essential for agonistic activity. These results provide crucial clues that the positive hydrophobic potential is favorable for increase in activity. Therefore hydrophobic groups might be suitable substituents for designing of PPARγ agonists.

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