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QSAR modeling of benzoquinone derivatives as 5-lipoxygenase inhibitors

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ABSTRACT

The inhibitors of 5-LOX control the overproduction of pro-inflammatory mediators known as leukotrienes (LTs) and thus have therapeutic relevance in the treatment of various diseases like asthma, rheumatoid arthritis, inflammatory bowel disease and certain types of cancers. This has increased the search for efficient therapeutic agents for protein 5-LOX and this process is now primarily based on QSAR. In this study, we have developed four different quantitative structure and 5-LOX inhibition activity relationship models of benzoquinone derivative by exploiting CoMFA, RF, SVM, and MLR chemometric methods. Performance of the QSAR models was measured by using cross-validation technique as well as through the external test set prediction. RF model outperforms all other models. SVM and MLR models failed due to the poor performance of the external test set prediction. CoMFA model, which shows relatively good performance was used to explore the essential structural regions where the modification was necessary to design a novel scaffold with improved activity. Moreover, molecular docking of all the derivatives to the binding site of 5-LOX was done to show their binding mode and to identify critical interacting residues inside the active site of 5-LOX. The docking result confirms the stability and rationality of the CoMFA model.

1. Introduction

The biological properties of human 5-LOX have gained much attention from research because of its involvement in the pathogenesis of several diseases [1]. The 5-LOX pathway is the source of potent pro-inflammatory mediators known as leukotrienes (LTs). 5-LOX catalyzes the first two steps in leukotriene A4 (LTA4) biosynthesis, in which the one is the addition of molecular oxygen into 1, 4-cis–cis-pentadiene containing polyunsaturated fatty acids such as arachidonic acid and linoleic acid to give their hydroperoxy derivatives and the second step is the dehydration of this hydroperoxide to the key intermediate, short-lived epoxide leukotriene LTA4, which then converted to LTs [2]. These LTs are essential mediators of excessive and chronic inflammatory and allergic disorders such as Rheumatoid arthritis, Gastroesophageal reflux disease, Atherosclerosis, Inflammatory bowel disease, and Autoimmune, ulcerative colitis, asthma, psoriasis and allergic rhinitis [3]. Besides its important roles in inflammatory diseases, 5-LOX is also involved in the development and progression of numerous types of cancer such as such as leukemia, pancreas, prostate, and colon cancer [4–8]. Therefore, the pharmacological intervention of the 5-LOX pathway to control the formation of LTs is a promising therapeutic strategy for LT-related diseases.

A wide variety of inhibitors have been reported as active against 5-LOX invitro studies. These compounds include phenols, aromatic compounds containing heteroatoms, carboxamides, hydroxamic acids, flavonoids, chalcones, *etc.* Based on the nature of action, these inhibitors have been classified into four types such as redox inhibitors, iron-chelator agents and non-redox or competitive inhibitors and 5-Lipoxygenase activating protein (FLAP) inhibitors [9,10]. Despite all this intensive effort, Zileuton is the only orally active drug that has been approved as 5-LOX inhibitor used for the treatment of asthma [11]. However, zileuton itself has several side effects including liver toxicity and unfavorable pharmacokinetic profile [12]. So, the development of novel inhibitors having high inhibitory potency along with a favorable pharmacokinetic profile is the major challenge among the scientific community.

Drug discovery has been evolved from 'forward pharmacology' to rational drug design with the advancement of computational

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The polar OH- and C=O groups at the benzoquinone head portion interact with the polar amino acids of 5-LOX by forming hydrogen bonds with His 600, Gln 363 and Leu 420 residues and can be seen in green dotted line. This observation is compatible with CoMFA electrostatic contours found around benzoquinone head portion indicating these regions are favorable may be due to its interaction with polar amino acids of the target protein. This compound also forms hydrophobic interactions with the protein through its non-polar long alkyl part with residues like Leu 368, Ile 415, Phe 421, Phe 359, Leu 414, Leu 607, Phe 177. These findings again support the CoMFA result which has shown the importance of long, bulky alkyl group at the position 3 for a potentially active ligand.

4. Conclusions

Here, we report the systematic investigation of 2D and 3D-QSAR on benzoquinone derivatives as 5-LOX inhibitors. The 2D descriptors were obtained from e-Dragon, PowerMV and Gaussian 09 software packages. The most relevant descriptors were filtered with the help Correlation feature selection (CFS) technique. Different 2D-QSAR methods such as RF, SVM and MLR were employed to formulate a statistically reliable relationship between 5-LOX activity and the descriptors. The consistency of the developed 2D-QSAR models was verified using the Q^2 and R^2_{pred} values and the result shows that among the three models constructed, RF model gave the better predictive power with an R^2 value of 0.93, Q^2 (LMO) value of 0.51 and R^2_{pred} value of 0.71. The 3D-QSAR based on CoMFA methodology was also applied to the same set of benzoquinone derivatives. Reasonable Q^2, R^2 and R^2_{pred} values were obtained for the CoMFA indicating that the model constructed has an excellent internal predictive power and good external predictive ability. The contour maps extracted gives an idea of the effects of steric and electrostatic fields around the aligned molecules on their 5-LOX inhibitory activity. The lowest energy binding pose obtained from docking analysis provides a qualitative representation of ligand and protein interactions, which are Compactable with CoMFA maps and the 2D-QSAR model. Thus, both CoMFA and docking studies indicate the long, bulky alkyl residue at third position is very important for a potentially active ligand and the polar or hydrogen bonded interactions of benzoquinone's —OH group with polar amino acids of the target protein were also favorable for 5-LOX inhibition. 2D-QSAR also supports the results that the activity of the ligands was mainly depended on hydrogen bond donor/acceptor features and electron affinity values that might be responsible for its pharmacological action. Our findings would seem to show that RF and CoMFA models together could very profitable to uncover more 5-LOX active benzoquinone derivatives.

Conflict of interest

No conflict of interest to declare

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.fshw.2019.02.001.

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