3D-QSAR Analysis of Human Immunodeficiency Virus Entry -1 Inhibitors by CoMFA and CoMSIA

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Abstract

3D-QSAR studies namely CoMFA, CoMFA region focusing for optimizing the region for the final PLS analysis and CoMSIA have been carried out on a series (36 compounds) of HIV-1 entry inhibitors. An alignment rule for the compounds was defined using Distill in SYBYL 7.3. Models were validated using a data set obtained by dividing the data set into a training set and test set using hierarchical clustering, based on the CoMFA fields and biological activities (pIC_{50}). The best predictions were obtained with a CoMFA region focusing model ($q^2 = 0.719$, $r^2_{pred} = 0.911$), CoMFA standard model ($q^2 = 0.660$, $r^2_{pred} = 0.890$), and CoMSIA (steric and hydrophobic) model ($q^2 = 0.521$, $r^2_{pred} = 0.794$). The statistical parameters from the models indicate that the data are well fitted and have high predictive ability. Moreover, the resulting 3D CoMFA/CoMSIA contour maps provide useful guidance for designing highly active ligands.

Introduction

The human immunodeficiency virus type 1 (HIV-1) is the etiologic agent of the globally epidemic disease named acquired immunodeficiency syndrome (AIDS). A highly active antiretroviral therapy (HAART), by controlling viral load and disease progression has provided an effective healing means of HIV-1. However, HAART has important limitations, including incomplete efficacy, and emergence of resistant virus. HIV-1 entry is a dynamic process beginning with viral attachment to the host cell via interactions between the viral gp120 and CD4 which is the primary receptor for HIV-1. Changing the conformation in the gp120 glycoprotein is the major function of CD4 binding. The change of conformation makes the binding site to be exposed and facilitate the binding of gp120 to the co-receptors CCR5 or CXCR4 [1].

Comparative molecular field analysis (CoMFA) is a versatile and powerful tool in rational drug design and related applications. CoMFA samples the steric and elrctrostatic fields surrounding a set of ligands and constructs a 3D QSAR model by correlating these 3D steric and electrostatic fields with the corresponding observed activities via PLS regression. A similar approach to the computation of molecular potential fields has been described as the comparative molecular similarity indices analysis (CoMSIA), in which a probe atom is used to calculate similarity indices, at regularly spaced grid points, for the pre-aligned molecules. A 3D-QSAR model was built to reveal the stereoelectronic parameters that govern the inhibitory activity of HIV-1 entry inhibitors. The results provide insights into the effect of substitution and show that conformation does to some extent affect activity, And may prove generally useful in the optimization of lead structures against HIV-1.

Materials & Methods

All the molecular modeling studies were performed using SYBYL7.3 molecular modeling software from Tripos, Inc., St. Louis, MO. The 3D structures of these compounds were constructed and partial atomic charges were calculated by the Gasteiger Hückel method and energy minimizations were performed using the Tripos force field with a distance-dependent dielectric and the Powell conjugate gradient algorithm (convergence criterion of 0.01 kcal/mol Å).

Rong-Jian Lu et al [2] reported several novel small molecular HIV-1 attachment inhibitors which prevent the virus access to host cells by inhibiting the gp120–CD4 interaction that used as dataset in this study. The template molecule was chosen based on highest activity and all other compounds were aligned on the basis of the common structure. Rigid body alignment of molecules in a Mol2 database was performed using maximum common substructures defined by Distill (without including bond types in rings.

The chemometric technique of hierarchical cluster analysis (HCA) was the approach used to remove outliers and then select the training and test sets based on structural similarities, CoMFA steric and electrostatic fields and biological activity data (expressed as pIC_{50}).

Results

The best results of CoMFA modeling was obtained from CoMFA region focusing approach: q^2 of 0.719 with five components, F = 109.184, r^2_{ncv}=0.975 and a standard error of estimation of 0.158. In CoMSIA analysis the highest q^2 of 0.521 was obtained with five components at a column filtering of 1 kcal/mol, grid spacing of 2 Å, F = 24.288, non-cross-validated r^2 of 0.841, and SEE = 0.342, for both steric and hydrophobic fields. CoMSIA models with hydrogen-bond donor, hydrogen-bond acceptor, and electrostatic fields were statistically poor.

The contour maps of CoMFA show contribution for favorable and unfavorable interactions with the receptor in terms of steric (80% green, 20% yellow) and electrostatic (80% blue and 20% red). Greater values of bio-activity are correlated with more bulk near green, less bulk near yellow more positive charge near blue and more negative charge near red.

Contour maps of CoMSIA (steric) are nearly similar to the corresponding CoMFA and/or CoMFA region focusing contour maps. In the hydrophobic contour map of CoMSIA , yellow polyhedra regions and white polyhedra regions indicate the areas where hydrophobic and hydrophilic properties are preferred, respectively. Fig. 1 shows the steric and electrostatic contour maps based on one of the most active compounds in the set

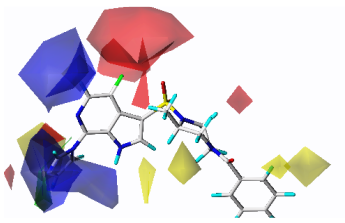

Fig. 1;CoMFA contour maps

Conclusions

The QSAR models gave good statistical results in terms of q^2 and r^2 values, and have been validated using a test set, obtained from the hierarchical clustering. The CoMFA region focusing model provided the most significant correlation of steric and electrostatic fields with the biological activities. Totally, the CoMFA models provided better statistical results than CoMSIA, which shows the significance of steric and electrostatic fields in the selectivity and activity of these compounds.

References

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