Understanding the structural requirements of triarylethane analogues towards PDE-IV inhibitors: A molecular modeling study

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A three-dimensional quantitative structure activity relationship study has been performed on a series of 44 triarylethanes to determine the structural requirements for phosphodiesterase-IV (PDE-IV) enzyme inhibition. Considering the stereochemistry of the data set molecules and the varied types of alignments available, a total of seven models are presented. While most models were optimized to yield satisfactory \( r^2 \) and \( q^2 \) values, the best model was obtained with 29 molecules including all the \( R \) conformation with \( r^2 \) 0.996, \( q^2 \) 0.510 and \( \text{F}^2 \) 0.744. A complementary molecular docking analysis is carried out considering the 29 stereochemically characterized set of molecules. The CoMFA maps and the docking studies were used to understand the structural requirements for the PDE-IV inhibition. These studies are expected to provide useful insights into the roles of various substitution patterns on the triarylethane skeleton and also help to design more potent compounds.

The phosphodiesterases (PDEs) constitute a large divergent family of 11 isoenzymes and more than 60 mRNA splicing isoforms have been detected in various human tissues\(^1\). This family of enzymes catalyzes the hydrolysis of cyclic adenosine 3', 5'-monophosphate (cAMP) and cyclic guanosine 3', 5'-monophosphate (cGMP) into the corresponding 5'-nucleotide (AMP and GMP). Cyclic AMP and cyclic GMP are second intracellular messengers, mediating the response of cells to a wide variety of hormones and neurotransmitters in signal transduction pathways\(^2\). The consequence of increasing levels of cAMP has been associated with the airway smooth muscle relaxation and decreased inflammatory cell activation. Thus, inhibition of PDE activity can potentially be utilized as bronchodilators as well as anti-inflammatory agents\(^3\). PDE-IV, a cAMP specific PDE, has become an attractive target for asthma in the recent years, not only because of its distribution in most immune and inflammatory cells, but also due to the crucial role it plays in a range of biological disorders (such as asthma, chronic obstructive pulmonary disease (COPD) and various inflammatory diseases)\(^4\). The utility of first generation PDE-IV inhibitors (Rolipram) has been severely reduced due to the dose limiting side effects, such as nausea, vomiting, psychotropic activity, and increase in gastric secretion\(^5\). Thus, there is considerable interest to develop novel, potent and selective PDE-IV inhibitors, which were devoid of these side effects\(^6\). A set of 44 triarylethane compounds was reported in this direction in the year 2002 which were the analogues of CDP840, a potent PDE-IV inhibitor\(^7\). In order to increase the potency and metabolic stability of the compound CDP840, Alexander et al.\(^8\) group synthesized this series of triarylethanes.

In this study, we present Comparative Molecular Field Analysis (CoMFA)\(^9\) and docking studies on a series of triarylethanes as PDE-IV inhibitors. CoMFA, an important three-dimensional quantitative structure activity relationship (3D QSAR) tool in rational drug design, has been selected because of the robustness of the model it produces for biological activity prediction. In addition to the QSAR studies, docking calculations were also done using three different protocols on all the stereochemically characterized molecules. Using these molecular modeling approaches, the study further delves on the structural requirements of this class of compounds towards PDE-IV enzyme inhibition by comparing the CoMFA maps with the docking studies on the most and least active compounds of the series.

**Computational Details**

**Data set for analysis**

In *vitro* data of a set of 44 triarylethane analogues reported by Alexander *et al.*\(^8\) was considered in the current study (Fig. 1). Based on their stereo selectivity...
Fig. 1—The dataset considered in the present study. The experimental activities (IC₅₀ in nM) are given in parentheses.
the initial set was divided into two sets. The set whose stereo selectivity was not known was considered as set A (14 molecules) and the other set whose stereo selectivity was known was considered as set B (30 molecules). The inhibitor activities (IC50) against yeast cells were converted into pIC50 according to the formula, pIC50 = -log IC50.

Molecular modeling

All the calculations were performed on SYBYL 6.513 installed on a Silicon Graphics Octane workstation. Powell's conjugate gradient method was used until a convergence gradient of 0.001 kcal/mol was reached. Thus, while the most active compound 35 was used for building the data set conformations, the Rolipram co-crystal conformation (1OYN)1 was used as a template to CoMFA models. Tripos force field with distance dependent dielectric constant and Gastieger-Hückel partial atomic charges were employed on the minimum energy conformations of all the 44 compounds considered. Conformations were optimized so as to obtain better statistical fits. Alignment of structures was perhaps the most subjective and vital step in a CoMFA study, mainly because the 3D QSAR model built was often sensitive to a particular alignment scheme. The CoMFA models are in general sensitive to the change in orientation of the superimposed molecules in the lattice space. Therefore, we made a systematic study of the available alignment options by employing database alignment, RMS fit and MULTIFIT alignments as implemented in SYBYL. The substructure used for superposition is shown in (I) and the aligned molecules are shown in Fig. 2 (A).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{(A) Database alignment of the dataset molecules, and, (B) CoMFA steric and electrostatic STDEV^2COLFF contour maps for model IV. Green contour indicates where bulky group increases activity, whereas yellow color contour indicates region where bulky group decreases activity. Blue contour indicates region where positive charge increases activity, whereas red contour indicates region where negative charge increases activity.}
\end{figure}

Generation of CoMFA fields

The aligned molecules were positioned in a 3D cubic lattice with a grid spacing of 2.0 Å in x, y and z directions. The steric (Lennard-Jones, 6-12 potential) and electrostatic (Coulombic with 1/r dielectric) fields were calculated at each lattice point using Tripos force field and a distance dependent dielectric constant of 1.0. An sp^3-hybridised carbon with a +1.0 charge was used as a probe atom. To avoid too high and unrealistic energy values inside the molecule, a 30 kcal/mol energy cutoff was applied, and the electrostatic fields were ignored at the lattice points with maximal steric interactions.

Partial least square analysis

Partial least square method was used to derive a linear correlation between the CoMFA fields
(independent variables) and the inhibitory activity values (dependent variables). The cross-validation analysis was performed using Leave-One-Out (LOO) method in which one compound was removed from the dataset and its activity was predicted using the model built from rest of the dataset. The cross-validation run returns the optimum number of components for which it has maximum cross-validated $r^2$ ($q^2$) and minimum standard error of prediction (SEP). In order to overcome the over-fitting problem, no-validation run was performed using the same optimum number of components that resulted from the cross-validation run. Equal weights were assigned to steric and electrostatic fields using CoMFA-standard scaling option. To speed up the analysis and to reduce the noise, a minimum filter value ($\sigma$) of 2.00 kcal/mol was used.

Docking

Three different procedures, Genetic Optimization for Ligand Docking (GOLD) Version 2.1,14,15 FlexX16 method as implemented in Sybyl 6.9 version and Automated Docking (AutoDock) Version 3.0.5,17 were adopted for docking studies. For the present docking study recently reported crystal structure of a complex of human phosphodiesterase4D2 (PDB entry 1OYN) with (R, S)-Rolipram from the Brookhaven Protein Data Bank (PDB) was downloaded. The crystal structure was a tetramer of a catalytic domain. Initially, for the purpose of docking studies only chain A was considered without the ligand and water molecules. The protein structure thus obtained was minimized using Tripos force field and Kollman-All partial atomic charges, where the two Zn atoms were assigned +2 charge each, by fixing the backbone structure. Powell’s conjugate gradient method was used until a convergence gradient of 0.01 kcal/mol Å was reached and the energy minimized structure was used for further docking analysis. For the docking calculations using GOLD program, the default parameters (population size 100, selection-pressure 1.1, number of operations 100000, number of islands 5, niche size 2 and operator weights for migrate, mutate and crossover are 10, 95 and 95) were applied. The active site with 15 Å radius sphere from the atom 669 is defined and the GOLD scoring function, which includes van der Waals, hydrogen bonding and torsional strain energy terms. In FlexX the active site comprise a 9 Å sphere from the Zn atom to the residue Gln369, and following the FlexX score the top 30 conformations were saved. The default AutoGrid settings with $60 \times 60 \times 60$ grid size and a grid spacing of 0.375 Å centered on the ligand were used for preparing the grid. Step sizes were set to 0.2 for translation and 5.0 for quaternion and torsion. In the Lamarckian genetic algorithm procedure in the AutoDock 3.0.5, we employed the default values, which were set to 250000 energy evaluations and 27000 generations. The zinc parameters were taken from the recent literature values of Hu et al.18 The best-docked conformations in each of the case were taken to unravel the disparities in binding between the most and least active compounds 35 and 39 respectively.

Results and Discussion

In this section, we start with a description on how various models are arrived at. This is followed by the presentation of CoMFA results and analysis. The dataset was grouped into the following models for CoMFA studies. Models I and II were developed based on the entire set (except compound 1)19 with database alignment and atom fit alignment respectively. A separate model, model III was developed for the 14 compounds of unknown stereochirality with set A, where molecules with only R stereochemistry were considered, as the remaining 29 most active compounds (set B) all have R stereochemistry. As set B with 29 compounds consists of the most important subgroup, we have dealt this in more detail. Compound 16 was excluded as it has ‘S’ stereochemistry where the rest are all with ‘R’ stereochemistry. Here database and multifit alignment protocols were employed in generating four models (model IV, model V, model VI and model VII) where, in all cases, 24 molecules were considered randomly as training set and the remaining 5 molecules placed in the test set. This is followed by a discussion of the docking studies.

QSAR models

Model I showed a correlation coefficient ($r^2$) of 0.954 and ($q^2$) of 0.660 with minimum standard error of prediction and 5 optimum number of components. The steric and electrostatic contributions are in the ratio of 48:52 respectively. Model II generated from atom-based alignment, has a slightly improved correlation with a $q^2$ value of 0.666 with six components and $r^2$ of 0.972. In this model, the steric and electrostatic contributions are in the ratio of 49:51 respectively. Model III, generated for the 14 racemic mixtures considered in the study, yields a good $r^2$ of
A linear alignment procedure was applied, giving a linear correlation coefficient value of 0.996, 0.998 and 0.997 with a satisfactory standard error of estimate (SEE) values of 0.049, 0.035 and 0.042 respectively, giving a linear correlation between the observed and computed affinities of the compounds in the training set. By going to MULTIFIT alignment procedure we obtained model VII that yields an $r^2$ of 0.996 and $q^2$ value of 0.517. A comparison of the model VII with earlier models indicates that it is equally good compared to those models obtained through database alignment. Table 1 reveals that the best among the seven models is model IV, with a PRESS value of 0.250 and predicted $r^2$ ($r^2_{pred}$) of 0.744, which was considered for further analysis of CoMFA maps. The PLS statistics for CoMFA studies are shown in Table 1. The actual, predicted and residual values of model III is given in Table 2 and the actual, predicted and residual values of training set and test set for models IV and VII are given in Tables 3 and 4 respectively. A graph of predicted versus actual activity for training and test set for the model IV is illustrated in (Fig. 3).
Table 3—Experimental and predicted inhibitory activities ($pIC_{50}$) and residuals of model IV and model VII training set

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Table 4—Experimental and predicted inhibitory activities ($pIC_{50}$) and residuals of model IV and model VII test set

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Contour maps are generated as scalar product of coefficients and standard deviations associated with each CoMFA column. The 3D QSAR contour map revealing the contribution of CoMFA fields is shown in Fig. 2(B). The CoMFA steric maps are represented by green and yellow color contours while electrostatic interactions are represented by red and blue contours.

Analysis of CoMFA maps

The red and green contours around pyridine N atom as well as near the amide side chain suggest that the bulkier electronegative atom or groups will improve the activity. More electronegative atoms like oxygen or N-O in place of pyridine nitrogen is more favorable. This is in turn complementary with the positive binuclear metal center in the active site of PDE-IV and is also supported by the experimental

Fig. 3—Graph of actual versus predicted inhibitor activities of training set (○) and test set (▼) for CoMFA.
Compounds 15 and 17, which are lacking a side chain analogue, are surrounded by sterically favorable green and electrostatic red contours, signifying that there is a definite necessity for a suitable side chain. Green contour near heterocycle rings in 18 and 19 explains the more potent nature of 19 in which the thiophene ring is present in place of furan ring of 18. The red and green contours near the amide side chain suggest that compound 22, has both bulkier and electronegative groups, which explains why it is more active than 20 and 21. The inferior activity of 23 with two SO₂Me side chains, compared to the related compounds with only one SO₂R side chain, 22, 24 and 25, may be easily accounted for by examining the CoMFA contour maps depicted in Fig. 2(B). As can be seen, the substitution in the series 21-24 is in the para-position in contrast to that in the most active compound 35, where the substituent is in the meta-position. The CoMFA contour map clearly indicates that activity may be increased only when one sterically bulky substituent is attached in the para-position of the aryl-R in that series. The analysis of CoMFA for the compounds, where the substitution is at meta-position, starting from compound 33 onwards indicate that steric bulk seems to play a very critical role. Notice that the contour maps display a large green region followed by yellow strips beyond them. Such a disposition clearly indicates that moderate steric bulk is required to obtain the optimal activity. This is exactly what has been observed. Compound 33, which has only hydrogens as substituents, is less active. As the steric bulk of the substituents increases in compounds 34 and 35 the activity increases reaching a maxima, further increases in the size of the substituents in compound 36 to n-Pr drastically reduces the activity. Expectedly increase in the R group size to n-Bu results in drastic reduction in the activity in compound 37. The compounds 40, 41, and 42, where both the amide hydrogens are replaced by medium sized substituents (Me, Et) show reasonable activity. Substitution of the bulkiest tert-butyl group makes compound 39 the least active compound among the 29 compounds considered.

Docking studies

In the present study, we performed docking calculations on 29 stereochemically active molecules using GOLD, Sybyl (FlexX module) and AutoDock suits of programs. Although no correlation has been observed between docked score and the activities, docking calculations are expected to further improve our understanding on the structural requirements for binding to the PDE-IV enzyme. In the GOLD calculations, only hydrogen bonding interactions and
van der Waals interactions were evaluated and the electrostatic interactions were not considered, whereas FlexX and AutoDock include both steric as well as electrostatic interactions. A quick perusal of the docked structures indicate that the dialkoxypheynyl skeleton (I) is very similar in all the molecules, which further substantiates that choosing that motif as a skeleton for the 3D-QSAR studies is a good choice. A hydrophobic pocket formed by the amino acid residues Ile336, Phe372, Tyr159 and Asn321 wrap around the phenyldioxy ring. The methoxy group was deeply buried in a pocket, where Thr333, Trp332, Pro322 and Asn321 form the sides of the pocket and Gln369, Tyr159 forms the bottom of the pocket. Cyclopentoxy group makes some moderately weak hydrophobic interactions with Ile336, Phe372, Met337 and Phe340 and the ethyl side chain analogue of the ligand was oriented towards the binuclear metal center. In all the docked ligands (except 44 and 23 in FlexX) the side-chain amine hydrogens of Gln369 exhibit hydrogen-bonding interactions with the methoxy and cyclopent oxy oxygen atoms. A critical examination of the three docking procedures indicate that the results obtained with the GOLD and FlexX methods are in good agreement with the experimental observations regarding the active site residues.1-3

Similar to the pyrrolidinone group of Rolipram,2 two different orientations are possible to the pyridine ring of the ligand, either pointing towards the metal center or towards the solvent. In GOLD where the orientation of the pyridine ring is towards the metal ion, the pyridine ring of most active compound 35 is stacked in between the metal and Met273 and is oriented within a distance of 3.97 Å and 5.17 Å from the metal atoms. Even if the pyridine ring of least active compound 39 is equidistant (3.84 Å and 3.97 Å) from the two metal atoms, the other phenyl side chain of 39 is oriented in such away that the urea group lacks the hydrophilic interactions with His160, which is apparently a key residue in cAMP hydrolysis as well as for the hydrophilic interactions with Rolipram, whereas the orientation of phenyl side chain of 35 favors these hydrophilic interactions. The distance between imidazole N of His160 and oxygen atom of urea group of 35 is 3.23 Å (Fig. 4). However, in FlexX where the orientation of the pyridine rings is towards the solvent (except 15, 19, 20, 27, 28 and 29) the pyridine ring is stacked in between phenyl ring of Phe340 and side chain of Ile376 and Met273. In the absence of the X-ray structural evidence it will be difficult to validate the correct orientation, but considering the fact that Rolipram itself was crystalized in two different orientations both possibilities seem to be probable. Thus, in the conformation where the pyridine group is oriented towards the solvent, the para substituted compounds, specifically from 21-32, more or less the N atom of the amide side chain is forming hydrogen bonds with Asp318, His164. In the meta-substituted compounds particularly from 33-39 the N atom of the amide side chain is forming hydrogen bond preferably with Thr271 and Asp201. As most compounds have very similar hydrogen bonding interactions with the active site residues, the binding of the alkyl group of the side chain essentially controls the binding affinity (Fig. 5).

Therefore, the structures from 33-39 bind quite similarly forming virtually identical hydrogen bonding interaction, and 35 with the optimum steric component (with the ethyl substituents) turned out to be the most active compound. However, increasing the bulk further in the series leads to a reduced activity, as evidenced for 36 (i-propyl group), 37 (n-butyl group), 38 (i-propyl group) and 39 (t-butyl group). Ethyl is adjudged to provide the optimal steric bulk, as the less bulky substituents, 33 (hydrogens as substituents) and 34 (methyl group), also leads to reduced activity. Unambiguous support for the foregoing reasoning was also evident from the analysis of steric CoMFA maps as discussed earlier (Fig. 2(B)). His160, His204, Glu339, Ser208, Asn209, Leu229, Ser274, Glu230 and Asn209 surround the phenyl side chain of 35, justifying the presence of the hydrophobic favorable red contour and moderately steric favorable green and yellow contours around the phenyl side chain in CoMFA, while in 39, the tertiary butyl group may diminish the additional hydrophilic interactions essential for formation of a stronger complex between the ligand and the protein. However, both the most active as well as least active compounds have similar urea side chains, but the appropriate orientation of this side chain along with accompanying requirements are compulsory for potent ligand activity.

The steric favorable green and yellow contours and negative charge favorable red contours are clearly supported by the docking studies, where the hydrophilic as well as hydrophobic residues around the amide side chain. It indicates that to exhibit the PDE-IV inhibiting activity both electron negative and moderate steric groups should be present rather than...
electropositive and less bulky groups. In the CoMFA study, the red contour near the oxygen and nitrogen atoms of amide side chain and the location of polar amino acids like His 160, His 204, Glu 339, Ser 208, Asn 209, Leu 229, Ser 274, Glu 230 and Asn 209, signify the requirement of electron rich compounds capable of participating in hydrogen bonding.

Conclusions

The present study attempts a 3D-QSAR study on triarylethene analogues. The critical analysis reveals that as the observed biological activity depends on the configuration (R or S) of the putative ligand and structure based approaches are necessary to build reliable model. However, CoMFA analysis has been successfully applied to the set, including all R configurations. Excellent $r^2$ and $q^2$ values have been obtained for the 3D-QSAR employed, indicating that the model constructed has a good correlative and predictive property. Both the steric and electrostatic fields contribute considerably to the biological activity. The reported compound L-791, 943 also supports the red electrostatic region around the pyridine N. Predictive power of CoMFA model has been evaluated by the test set and good predictive $r^2$ value has been obtained. The docking analysis provides a qualitative representation of ligand and protein interactions, which not only correlate with the reported experimental results but also complementary with the CoMFA maps. The CoMFA and docking studies indicate that substitution of electron-rich compounds (so as to be able to donate or accept the hydrogen bonds in the position of amide side chain associated with enhanced electronegativity at pyridine nitrogen) may lead to improved biological activity of triarylethene derivatives. Experimental efforts in this direction may prove to be rewarding.

Acknowledgements

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References

13. SYBYL 65 Tripos Associates Inc, USA.
14. GOLD 21 Cambridge Crystallographic Data Center, Cambridge, UK.
17. AutoDock 10550 North Torrey Pines Road La Jolla CA 92037-1000 U.S.A.
19. Compound I being a mixture of compound 15 and 16 could not be included in the models.