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ORIGINAL ARTICLE

Computational analysis of benzyl vinylogous derivatives as potent PDE3B inhibitors

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Abstract Phosphodiesterases are a diverse family of enzymes that play a key role in regulating intracellular levels of the second messengers cAMP, cGMP and ultimate cell function. Selective PDE3B inhibitors were recognized to prevent oocyte maturation. In search of effective PDE3B inhibitors, the present study deals with 3D QSAR analysis on previously reported benzyl vinylogous derivative. The comparative molecular field analysis (CoMFA) studies resulted in reliable and remarkable computational models. The obtained CoMFA model showed high predictive ability with $q^2 = 0.556$, $r^2 = 0.936$ and standard error of estimation (SEE) = 0.231, explaining a majority of the variance in the data with four principal components. The result of the present study shows good correlation between descriptors and biological activity. On the basis of statistical significance of the generated model the results can be utilized in the design of new more potent benzyl vinylogous derivatives as PDE3B inhibitors.

1. Introduction

Phosphodiesterases (PDEs) are intracellular enzymes that specifically catalyze the hydrolysis of secondary messengers like cAMP and cGMP (Conti, 2000; Ahmad et al., 1999; Corbin and Francis, 1999; Schmidt et al., 1999). These secondary messengers contribute in the formation of AMP and GMP respectively, which plays a key role in a variety of functional responses to hormones and other cellular transmitters including vascular resistance, cardiac output, visceral motility, immune response, inflammation, neuroplasticity, vision and reproduction. PDEs comprise a large group of enzymes organized into 11 distinct families (PDE families PDE1–PDE11) based on their different gene families encoding for the structurally related, functionally distinct and highly regulated enzymes (Cortijo et al., 1993; Rabe et al., 1993; Hidaka and Endo, 1984).

PDE3 first named cAMP–PDE or cGMP-inhibited PDE that is characterized by its high affinity for cAMP and its capacity to hydrolyze both cAMP and cGMP. PDE3 has at least two different gene products: PDE3A and PDE3B are structurally similar but positions on different sites. PDE3A is mainly found in the oocyte, platelet, heart and vascular

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smooth muscle, whereas PDE3B is mainly associated to adipocytes, hepatocytes, spermatocytes, kidney, beta cells, T-lymphocytes and macrophages. A number of PDE3B inhibitors have been shown to successfully suppress oocyte nuclear maturation without affecting follicle rupture after gonadotropin stimulation in rats (Cruickshank, 1993; Degerman et al., 1997; Erherdt and Chou, 1991).

Quantitative structure activity relationship is an attempt to correlate structural or property descriptors of compounds quantitatively with biological activities (Ravichandran et al., 2007a,b). These physiochemical descriptors include parameters to account for hydrophobicity, topology, electronic properties and steric effects which are determined by computational methods, if such a relationship holds true an equation can be drawn up which quantifies the relationship and allow the medicinal chemist to say with some confidence that the property has an important role in the distribution or mechanism of the drug (Ravichandran et al., 2008a,b). Recent trends in 3D QSAR have focused on the development of procedures that allow selection of optimal variables from the available pool of descriptors of chemical structures i.e., ones that are most meaningful and statistically significant in terms of correlation with biological activity.

The most popular 3D QSAR methods are comparative molecular field analysis (CoMFA). The CoMFA methodology based on the genetic algorithm ultimately allows one to design and predict activities of molecules. The CoMFA method involves the generation of a common three dimensional lattice around a set of molecules and calculation of steric and electrostatic interaction energies at the lattice points (Vaidya et al., 2011; SYBYL, 2008; Prashanthakumar and Nanjan, 2010).

Herein, we used the structures of 29 benzyl vinylogous analogous and their PDE3B inhibitory activities to establish 3D QSAR model by CoMFA technique provided by SYBYL 6.9 molecular modeling software (Edmondson et al., 2003).

In conclusion of our earlier attempt to develop a predictive CoMFA model for designing new compounds, here we report CoMFA of benzyl vinylogous derivatives as potent PDE3B inhibitory agents.

2. Materials and methods

2.1. Data set

QSAR studies were performed on a series of benzyl vinylogous derivatives having twenty-nine compounds, out of these twenty-nine, fifteen have a dihydropyridazone ring and the fourteen having dimethylpyrazolones are listed below (Table 1).

2.2. Molecular structure optimization and alignment

Structures of the PDE3B inhibitors were built on the workspace of Silicon Graphics work station molecular modeling software SYBYL version 6.9. The geometry-optimization was carried out using the standard Tripos molecular mechanics force field with a distance-dependent ($1/r$) dielectric function and the Powell conjugate gradient algorithm with a convergence criterion of 0.001 kcal/mol. Partial charges for all the molecules were assigned using Gasteiger–Huckel method. After allocating the partial charge, molecules were submitted for a conformational search protocol using multi-search method with the following settings: maximum cycles 400, maximum conformers 100, energy cut-off 30 kcal/mol, number of hits 12, maximum rms gradient 3.0 and tolerance 0.40. The conformer of the most active compound with the lowest energy was then used.

For 3D QSAR alignment of molecules is the most subjective and critical step. In the present study, compound having highest $p\mathrm{IC}_{50}$ (compound No. 1e) served as a template, and all molecules were superimposed on the template via field fit alignment technique. Fig. 1 shows the field fit alignment of the molecules. Following alignment the molecules were placed within a lattice that extended 4 Å units beyond the aligned molecules in all directions with a grid step size of 2 Å, using a probe sp^3 hybridized carbon atom with +1 charge and Van der Waals radius of 1.52 Å was employed.

2.3. CoMFA analysis

For CoMFA analysis steric and electrostatic fields were generated with the distant-dependent dielectric constant using a cut-off of 30 kcal/mol to truncate both steric and electrostatic field energies. All models were generated using partial least square regression analysis (PLS) and cross validation was done with leave one out (LOO) method with 2.0 kcal/mol column filter. As for the modeling methods, the CoMFA energies fields were used as independent variables with the $p\mathrm{IC}_{50}$ activity value as a dependent variable. The statistical significance and predictive ability of resulting model was assessed using cross validated r^2, also called q^2. The conventional r^2 was considered as a measure of the predictive ability within the training set, while the q^2 has been considered as a measure of predictive ability outside the training set or test set.

3. Results and discussion

Three-dimensional structure building and all the modeling were performed by comparative molecular field analysis (CoMFA) on a Silicon Graphics work station using the SYBYL 6.9 molecular modeling software from Tripos Inc. (St. Louis, MO, USA).

CoMFA model with significant internal and external predictive ability was selected with a high q^2 value of 0.556 at the optimum number of components as four. The non-cross-validated r^2 (LOO) value was 0.936 with standard error of estimate (SEE) 0.231. This model also indicates statistical significance $>99.0\%$ with covariance ratio (F) of 62.78 (Table 2). The correlation between experimental and predicted activity with residual activity for both training and test set of compounds are shown in Table 1 and represented graphically in Fig. 2. These results authenticate the good prediction ability of the generated 3D QSAR model. The CoMFA contour plots show the generated steric and electrostatic fields around aligned molecules with 42.8% and 57.2% field contribution respectively (Fig. 3). The greater size of blue-red region than yellow-green region indicates a greater contribution of electrostatic fields (57.2%) than steric fields (42.8%) in the determination of biological activity. Greater values of "Bio-Activity Measurement" are correlated with more bulky near green, less bulky near yellow, more electronegative near red and less electronegative near blue.

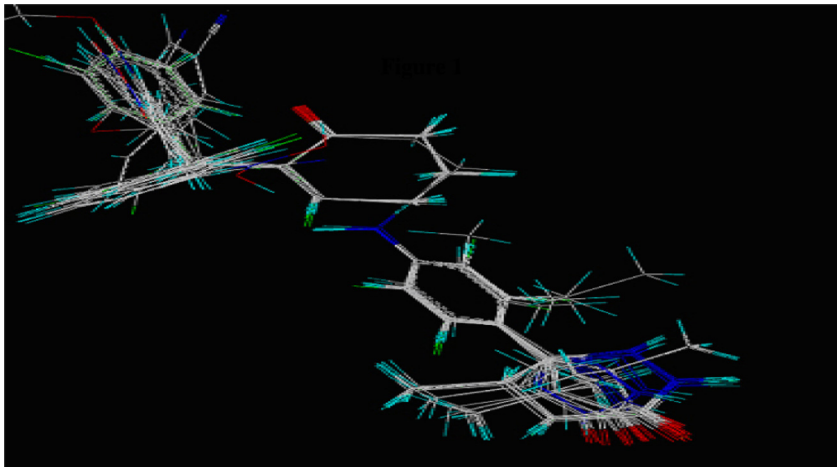

Figure 1 Field fit alignment of benzyl vinylogous derivatives.

Table 1 Structures of compounds used in the study with their biological activities.

Molecule	Ar	R	Actual pIC_{50}	CoMFA predicted pIC_{50}	CoMFA residual
1a	2-MeOPh	H	9.41	9.28	0.13
1b	2-CF_3Ph	H	9.08	9.21	−0.13
1c	3-FPh	H	7.55	7.6	−0.05
1d	3-BrPh	H	9.02	9.01	0.01
1e	3-IPh	H	9.48	9.48	0
1f	3-NO_2Ph	H	8.51	8.35	0.16
1g	4-MeOPh	H	8.64	8.73	0.09
1h	4-NO_2Ph	H	7.62	7.62	0
1i	Ph	2-Me	7.66	8.67	0.99
1j	Ph	3-Me	8.43	8.40	0.03
1k	Ph	2-Et	6.99	7.79	−0.8
1l	Ph	2-F	8.79	8.62	0.17
1m	Ph	3-F	8.92	9.07	−0.09
1n	Ph	2-Cl	7.33	8.35	−1.02
1o	Ph	2,5-DiF	8.79	8.85	−0.06
2a	Ph	H	7.27	8.06	0.79
2b	Ph	2-Me	7.42	7.24	0.18
2c	3-CNPh	2-Me	6.89	6.94	−0.05
2d	Ph	2-F	7.7	7.8	−0.1
2e	3-CNPh	2-F	7.16	7.21	−0.05
2f	3-NO_2Ph	2-F	6.82	7.42	−0.6
2g	2-ClPh	2-F	8.14	8.19	−0.05
2h	2,6-Cl_2Ph	2-F	7.66	7.32	0.34
2i	2-FPh	2-F	7.8	7.86	−0.06
2j	3-FPh	2-F	7.37	7.43	−0.06
2k	4-FPh	2-F	7.2	7.03	0.17
2l	3-NO_2Ph	2-Cl	6.26	6.44	−0.18
2m	2-ClPh	2-Cl	7.11	7.37	−0.26
2n	3-CNPh	2,3-F_2	8.12	8.12	0

Table 2 PLS statistics results of 3D QSAR model of CoMFA.

PLS statistics	CoMFA results
PC	4
q^2	0.556
r^2	0.936
SEE	0.231
F-value	62.78
Field contribution	
Steric	42.8%
Electrostatic	57.2%

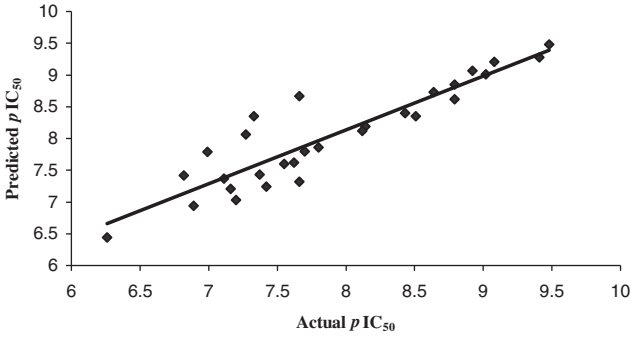

Figure 2 Correlation between the experimental and predicted activities of the developed CoMFA model.

A large green counter near fourth position substituted dihydropyridazinones or dimethylpyrazolones of benzyl ring indicates that the bulky substitutions favor the activity at the mentioned position therefore compounds of dihydropyridazinones derivatives (compound No. 1a–1o) showed greater activity as compared to dimethylpyrazolones derivatives (2a–2n). The yellow region near the 3rd position of benzyl ring derivatives suggests that biological activity will be decreased by introducing a bulky group at this position. Thus the presence of small group substitution or unsubstitution (such as the presence of methyl in compound 1j) enhances the biological activity.

Similarly, blue contour near 4-oxocyclohex-1ethylamino (Ar substitution) substitution indicates that substitution with less electronegative groups favors activity (3-IPh in compounds 1e). In spite of this red region near the 1st and 4th position substituted dihydropyridazinones or dimethylpyrazolones of benzyl ring favors more electronegative group substitution for improved biological activity.

4. Conclusion

The 3D QSAR studies of a set of recently synthesized vinylogous derivatives have been successfully performed using CoMFA method. The contour plots of CoMFA analysis provides many useful insights into the relationship between structural features and biological activity, and provides the information in designing novel compounds with increased PDE3B inhibition activity.

Declaration

Authors report no declaration of interest.

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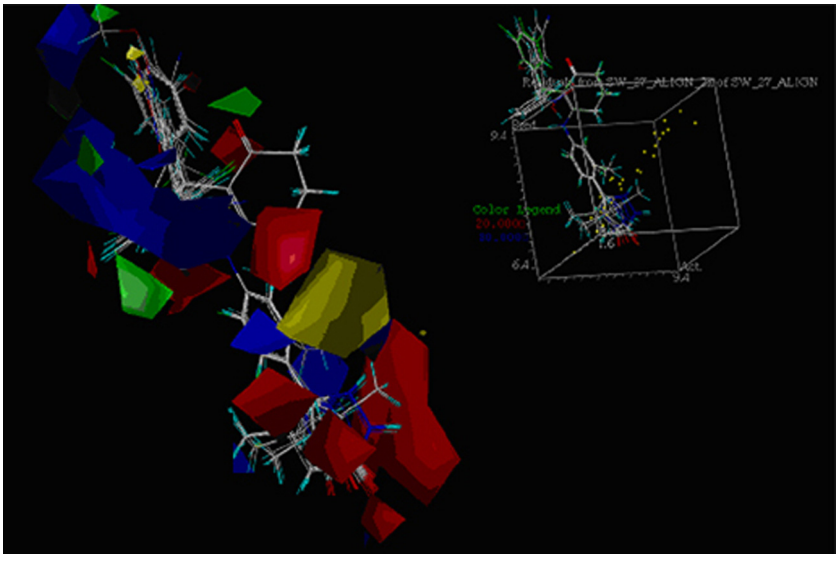

Figure 3 CoMFA contour plots for steric and electrostatic regions. Green counters indicate where bulky groups are required, whereas the yellow counter indicates those regions where bulky groups are not required. Red counters indicate the region needed electronegative contribution, whereas blue counters indicate the region where electropositive contribution is required.

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