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Topomer CoMFA Analysis of Xanthine Oxidase inhibitors

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Abstract

Xanthine Oxidase is an enzyme, which oxidizes hypoxanthine to xanthine, and xanthine to uric acid. It is widely distributed throughout various organs including the liver, gut, lungs, kidney, heart, brain and plasma. It is involved in gout pathogenesis. Hence, in the present study, topomer based Comparative Molecular Field Analysis (topomer CoMFA) was performed on a series of Xanthine oxidase antagonist named 2-(indol-5-yl) thiazole derivatives. The best topomer CoMFA model was obtained with significant cross-validated correlation coefficient (q^2 = 0.572) and non cross-validated correlation coefficients (r^2 = 0.937). The model was evaluated with six external test compounds and its r^2_{pred} was found to be 0.553. The steric and electrostatic contribution map show that presence of bulky and electropositive group in indole thiazole ring is necessary for improving the biological activities of the compounds. The generated topomer CoMFA model could be helpful for future design of novel and structurally related xanthine oxidase antagonists.

Keywords: Xanthine Oxidase, Topomer CoMFA

1. Introduction

Xanthine oxidase is an enzyme that generates reactive oxygen species. The enzyme oxidizes hypoxanthine to xanthine, and xanthine to uric acid, producing hydrogen peroxide. It is widely distributed throughout various organs such as the liver, gut, lung, kidney, heart, brain and plasma[1]. High level of XO secretion is found in the gut and the liver[2]. It is localized to the capillary endothelial cells, in the myocardium[3]. It is capable of catalyzing the formation of urate in man[4]. In gout, defective metabolism of uric acid causes arthritis, especially in the smaller bones of the feet and deposition of chalk-stones. This causes episodes of acute pain in patients. According to the Third National Health and Nutrition Examination Survey (1988-1994), gout is a prevalent disease with occurrence of >2% in men older than 30 years and in woman older than 50 years[5]. It occurs in individuals who have high serum uric acid levels, in response to precipitation of monosodium urate monohydate crystals in various tissues, followed by an inflammatory response. Typical symptoms include acute recurrent gouty arthritis, a tophinodular collection of monosodium urate crystals and uric acid urolithiasis[6]. XO also plays an important role in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure[7]. Xanthine oxidase inhibitor is any substance that inhibits the activity of xanthine oxidase. There are two kinds of Xanthine oxidase inhibitors: purine analogues and others. Purine analogues include allopurinol, oxypurinol, and tisopurine. Others include febuxostat, topiroxostat, and inositols (phytic acid and myo-inositol). These commercially available drugs have certain disadvantages[8-10]. Hence, the discovery of structurally diverse XO inhibitors and analyzing the important structural properties required for their biological activity becomes important.

In the present study, topomer CoMFA analysis has been performed on a series of Xanthine Oxidase antagonist named 2-(indol-5-yl) thiazole derivatives. A topomer is an invariant three-dimensional (3D) representation of molecular subunit generated from its two-dimensional (2D) topology by topomer alignment in topomer CoMFA. Topomer CoMFA includes alignment of structural fragments called topomers. Topomer CoMFA models were generated with different R1 and R2 fragments and its steric and electrostatic contribution map was analyzed to identify the important features of the compounds for

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improving the activity.

2. Materials and Methods

2.1. Data Set

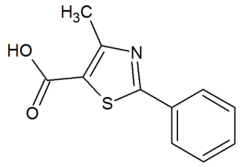
The structure of the 2-(indol-5-yl) thiazole derivatives and their biological activities of 21 compounds were taken from the literature[11]. Biological activities i.e. IC_{50} values of each inhibitor was converted into pIC_{50} (-log IC_{50}) and the dataset (26 compounds) were segregated into test (6 compounds) and training set (20 compounds). The training and test sets were classified to ensure that both sets could completely cover the whole range of biological activity and structural diversity. The structures and their activity values are displayed in Table 1.

2.2. Topomer CoMFA

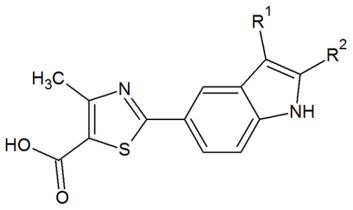
Topomer CoMFA, an alignment independent approach which merges the topomer technology and CoMFA was employed to overcome the alignment problem of CoMFA methodology[12,13]. A topomer is an invariant three-dimensional (3D) representation of molecular subunit generated from its two-dimensional (2D) topology[14]. In topomer CoMFA analysis, all molecules of dataset were divided into two fragments, shown as R1 (blue)

Table 1. Structures and biological activities (pIC_{50}) of xanthine oxidase inhibitors

The Xanthine Oxidase inhibitor scaffold

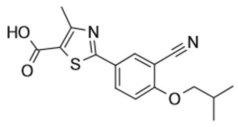


a) Compound 1-7

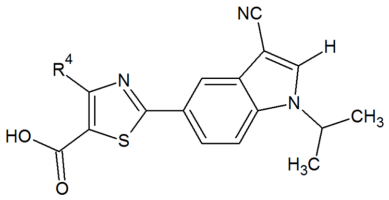


Compound	R^1	R^2	pIC50 values
1	H	H	6.9586
2	Cl	H	7.9706
3	Cl	H	8.5529
4	Cl	CH_3	8.0458
5	NO_2	H	7.9101
6	NO_2	H	8.2518
7	CN	H	8.2218

d) Febuxostat

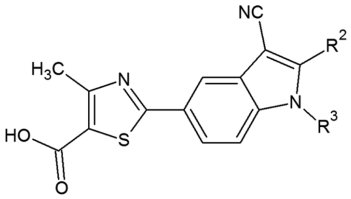
Compound	Structure	pIC50 values
21		8.2596

b) Compound 8-11



Compound	R^4	pIC50 values
8	H	8.4089
9	CF_3	8.0655
10	OCH_3	7.0457
11	CH_3	8.2441

c) Compound 12-21



Compound	R^2	R^3	pIC50 values
12	H	2-methylpropane	7.7959
13	CH_3	1-fluoro-2-methylpropane	8.3767
14	H	2-methylpropan-1-ol	7.9208
15	H	1-methoxy-2-methylpropane	8.2596
16	H	1-(methylsulfonyl)propane	8.3565
17	H	N-propylacetamide	6.0482
18	H	N-propylmethanesulfonamide	7.0458
19	H	ethylbenzene	8.4559
20	H	1-ethyl-2,4-difluorobenzene	8.320

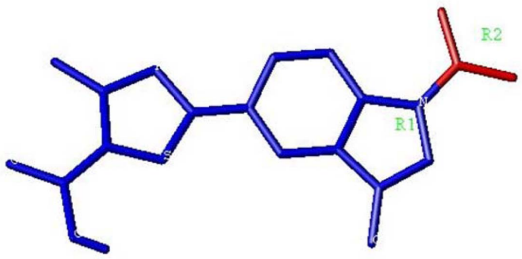


Fig. 1. Represents the Fragmentation pattern (R1 in blue and R2 in red) of highly active compound 03 obtained from topomer CoMFA analysis

and R2 (red) groups in Fig. 1. Each topomer fragment was applied with topomer alignment to make a 3D invariant representation[15]. During topomer CoMFA analysis, Gasteiger-Marsilli method was used to calculate the atomic charges and all molecules were divided into two fragments whose contribution was calculated by multiplying each grid point at a regular space grid of 2 Å.

2.3. Predictive Correlation Coefficient (r^2_{pred})

The predictive power of topomer CoMFA model was determined from six test molecules which were excluded during model development. The predictive correlation coefficient (r^2_{pred}) based on the test set molecules, is defined as:

$$r^2_{pred} = \frac{(SD - PRESS)}{SD}$$

where PRESS is the sum of the squared deviation between the predicted and actual activity of the test set molecules, and SD is defined as the sum of the square deviation between the biological activity of the test set compounds and the mean activity of the training set molecules[16].

3. Results and Discussion

3.1. Topomer CoMFA Analysis

In topomer CoMFA analysis, each of the training set molecules was split into two fragments (such as R1 and R2). This was accomplished by specifying acyclic single bond to cut within each complete structure. Here we have used the highly active compound as the template for splitting of fifteen training set molecules. The two fragments R1 and R2 is shown in the Fig. 1 where the blue color represents the R1 fragment and red color represents the R2 fragment. Once fragmentation was completed, topomers were generated. The model with good predictive ability in terms of $q^2 = 0.572$ and $r^2 = 0.937$ with 3 components was obtained. The summary of topomer CoMFA results was provided in Table 2. The predictive ability of the developed topomer CoMFA model has been assessed by predicting the activity of six test set compounds which were excluded during model generation. The predictive correlation coefficient r^2_{pred} for topomer CoMFA was 0.553 which indicates the developed model was more robust and reliable. The actual pIC_{50}, predicted pIC_{50} and residual values for test set (marked with *) and training set molecules were tabulated in Table 3 along with their R1 and R2 fragment contributions.

Table 2. Statistical results obtained from topomer CoMFA analysis

PLS Statistics	Topomer CoMFA
q^2	0.572
N	3
r^2	0.937
StdErr	0.470
SEE	0.180
intercept	8.25
r^2pred	0.553

q^2 = cross-validated correlation coefficient; N = number of statistical components; r^2 = non-cross validated correlation coefficient; SEE = standard estimated error; StdErr = standard error of prediction, F = Fisher value; $r^2_{predictive}$= predictive correlation coefficient for test set.

3.2. Contour Map Analysis

Topomer CoMFA steric and electrostatic contour maps for R1 and R2 fragments of the most active compound 03 are shown in Fig. 2. In case of steric contour map, the green contours denote favorable steric interactions and the yellow contours shows the region where the steric group was not favored. In Fig. 2(a), the green steric contour near the propanyl group indicates that bulkier substitutions are preferred at this position which shows the presence of bulky groups attached to indole thiazole ring makes the compound potent with higher activity. The blue colored regions show areas where more positively charged groups are favored, and red

Table 3. Experimental and predicted pIC_{50} values of training and test set compounds

Compound no	Actual pIC_{50}	Field Contribution		Topomer CoMFA	
		R1	R2	Predicted IC_{50}	Residual values
1*	6.959	-0.040	-0.049	6.165	-1.206
2	7.971	-0.050	-0.049	8.154	-0.183
3	8.553	-0.050	0.016	8.219	0.334
4	8.046	-0.047	-0.049	8.158	-0.112
5	7.910	-0.082	0.016	8.187	-0.277
6	8.252	-0.082	0.072	8.243	0.009
7	8.222	-0.101	-0.049	8.104	0.118
8	8.409	-0.020	0.016	8.250	0.159
9	8.065	-0.233	0.016	8.037	0.028
10*	7.046	-0.163	0.016	7.806	-1.060
11	8.244	-0.101	0.016	8.168	0.076
12*	7.796	-0.087	0.016	8.182	-0.386
13*	8.377	-0.101	-0.079	8.074	0.303
14	7.921	-0.101	-0.030	8.123	-0.202
15	8.260	-0.101	0.095	8.248	0.012
16	8.356	-0.101	0.239	8.392	-0.036
17	6.048	-0.101	-2.007	6.146	-0.098
18	7.046	-0.101	-1.188	6.965	0.081
19*	8.456	-0.101	0.035	8.187	0.269
20	8.320	-0.101	0.358	8.511	-0.191
21*	8.260	-0.101	0.348	8.421	-0.161

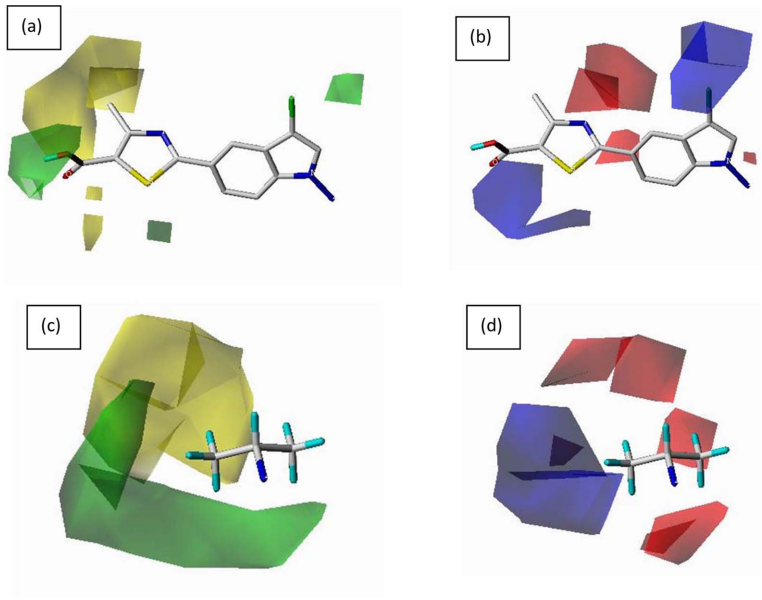


Fig. 2. Steric and electrostatic contour map for highly active compound 03 by topomer CoMFA analysis. (a) and (b) Steric and Electrostatic contour map for R1 fragment. (c) and (d) Steric and Electrostatic contour map for R2 fragment. Sterically favoured areas are shown in green and unfavoured areas are shown in yellow contour, while blue contour depicts the favourable sites for positively charged groups and red contour depicts the favourable sites for negatively charged groups.

region highlight areas where groups with more negative charges are favored in the electrostatic contour map. The blue colored region in electrostatic contour plot indicates the presence of electropositive groups around the indole thiazole ring makes it favorable for enhancing the biological activity.

4. Conclusion

In this study topomer CoMFA analysis was conducted on 2-(indol-5-yl) thiazole derivatives as xanthine oxidase inhibitors. The reliable topomer CoMFA model was generated and its predictive ability was determined using six test set compounds. The contour maps suggest the presence of bulky and electropositive group in indole thiazole ring will help in improving the activity of the compound. Hence, this study provides the useful information on structural and chemical features to discover of new antagonists for xanthine oxidase.

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