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Comparative Molecular Field Analysis Study on Some 1,3,4-Thiadiazole Derivatives as Anti-inflammatory Agents

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ABSTRACT

Comparative molecular field analysis (CoMFA) which is a three-dimensional quantitative structure activity relationship (3D-QSAR) technique was performed on 1,3,4-thiadiazole derivatives having anti-inflammatory activity. This study was performed using 28 compounds, in which the CoMFA model was developed using a training set of 25 compounds. Three compounds (selected at randomly served as a test set), which were not used in model generation, were used to validate the CoMFA model. CoMFA derived QSAR model shows a good conventional squared correlation coefficient r^2 and cross validated correlation coefficient r^2cv 0.980 and 0.617 respectively. In this analysis steric and electrostatic field contribute to the QSAR equation by 71.7% and 28.3% respectively, suggesting that variation in biological activity of the compounds is dominated by differences in steric interactions.

Keywords: 3D-QSAR, CoMFA, 1,3,4-thiadiazole derivatives, Anti-inflammatory agents.

INTRODUCTION

Comparative Molecular Field Analysis (CoMFA) is a three-dimensional quantitative structure activity relationship (3D-QSAR) approach, introduced in 1988 by Cramer [1,2]. It was developed slowly. From the very first formulation of a lattice model to compare molecules by aligning them with a putative pharmacophore and by mapping their surrounding fields to a three-dimensional grid, CoMFA approach was an application of the dynamic lattice oriented molecular modeling system (DYLOMMS), as it was called till 1987. A real advance resulted in 1987, the method was still named DYLOMMS but now it used grids including several thousands of points,

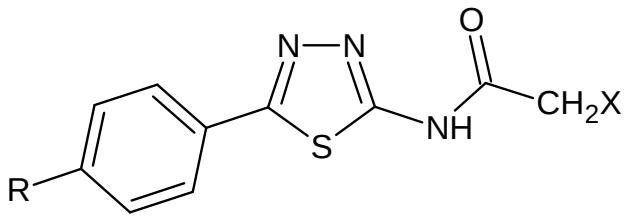
partial least squares (PLS) analysis and most important, a cross-validation procedure to check the predictive ability of different models. CoMFA is by far the most often employed receptor-independent (RI) 3D-QSAR approach, reflecting a novel, conceptually satisfying scientific approach reduced to practice as a well-written and versatile software package. In this method a relationship is established between the biological activities of a set of compounds and their steric and electrostatic properties [3-6].

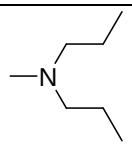
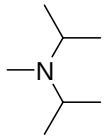
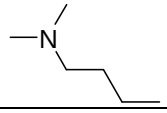
There are many reports in the literature of successful application of CoMFA that have not only led to predictive models within an analogue series of biologically active molecules, but also to insightful information on the general requirements for the expression of the activity [7-14]. For establishing relationship between structure and biological activities of the synthesized compounds [15-17] quantitatively, three-dimensional quantitative structure activity relationship (CoMFA) study was carried out.

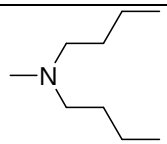
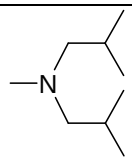
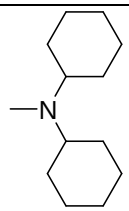
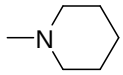
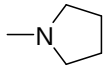
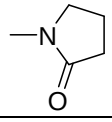
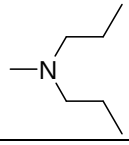
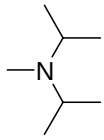
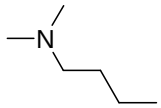
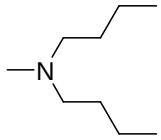
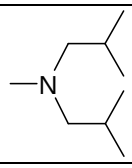
MATERIALS AND METHODS

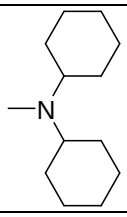
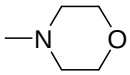
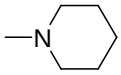
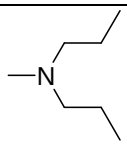
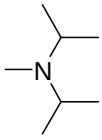
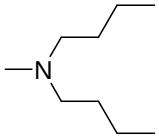
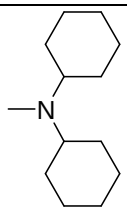
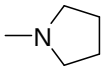
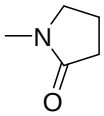
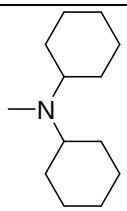
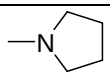
Data Set: A dataset of 28 molecules [15-17] synthesized earlier (1,3,4-thiadiazole derivatives) having anti-inflammatory activity has been taken for the present study (**Table-1**). Selected data set, their biological activity is shown in **Table-1** and **2** forming the training and test set respectively. For CoMFA studies, we have converted the percent paw oedema inhibition data to percent percent paw oedema inhibition per micromole of drug per kilogram of body weight (BA), then logarithmic value of biological activity (log BA) was taken [18].

Table-1: Structure and biological activities of training set molecules (25)



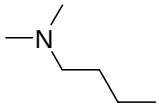
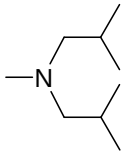
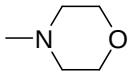
Compound S. No.	R	X	AA*	Mol. Wt.	BA**	log BA
1	H		48.57	318.44	0.1546	-0.81
2	H		25.71	318.44	0.0818	-1.09
3	H		45.71	304.41	0.1391	-0.86

4	H		37.14	346.49	0.1286	-0.89
5	H		31.42	346.49	0.1088	-0.96
6	H		28.57	398.57	0.1139	-0.94
7	H		25.71	302.42	0.0777	-1.11
8	H		42.85	288.37	0.1235	-0.91
9	H		14.28	302.35	0.04317	-1.36
10	CH_3O-		28.57	348.46	0.09935	-1.00
11	CH_3O-		8.57	348.46	0.02986	-1.52
12	CH_3O-		37.14	334.44	0.1242	-0.91
13	CH_3O-		28.57	376.52	0.1075	-0.97
14	CH_3O-		8.57	376.52	0.03226	-1.49

15	CH_3O-		17.14	428.59	0.07346	-1.13
16	CH_3O-		5.71	334.39	0.0191	-1.72
17	CH_3O-		14.28	332.42	0.04746	-1.32
18	CH_3		30.00	332.46	0.0997	-1.00
19	CH_3		14.28	332.46	0.0475	-1.32
20	CH_3		31.42	360.52	0.1132	-0.95
21	CH_3		22.85	412.59	0.0943	-1.02
22	CH_3		28.57	302.39	0.0864	-1.06
23	CH_3		05.71	316.38	0.0181	-1.74
24	Cl		08.57	433.01	0.0371	-1.43
25	Cl		31.42	322.81	0.1014	-0.99

* = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight orally.
** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

Table-2: Structure and biological activities of test set molecules (3)

Compound S. No.	R	X	AA	Mol. Wt.	BA	log(BA)
1	H		51.42	318.44	0.1637	-0.79
2	H		20.00	360.52	0.0721	-1.14
3	CH_3O-		14.28	318.39	0.0455	-1.34

* = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight orally.
** = Percent percent paw oedema inhibition per micromole of drug per kilogram of body weight.

Molecular Modeling

Molecular Modeling and CoMFA studies were performed on Silicon Graphics Octane computer using molecular modeling package SYBYL 6.5 using the standard TRIPOS force field. Structural manipulations were performed with molecular modeling package SYBYL 6.5 using the standard TRIPOS force field. Partial atomic charges of ligands were calculated using within MOPAC. The structures were then optimized by energy minimization using the Powell algorithm to a final root mean square gradient of 0.05 kcal / mol.

Alignment

The alignment, i.e. molecular conformation and orientation, is one of the sensitive inputs for CoMFA. One of the most active compounds used as a reference compound. The compounds were fitted to the active analogue compound.

GRID Size

Once the molecules are aligned a grid or lattice is established which surrounds the set of analogs in potential receptor space. CoMFA studies use grid resolution most often, 2 A^o. The choice of grid resolution represents a compromise between computational practicality and detailing of the fields. If the grid resolution is too small, the number of field–points (cells) becomes too large to perform a timely analysis. Moreover spatial information on field preference can be lost, through a ‘smearing out’ effect, if the cells become too small. The grid resolution in the 1 to 2 A^o range corresponds to, at best, differentiating single carbon-carbon (1.54 A^o) from one another.

CoMFA Interaction Energy

The steric and electrostatic (potential fields) energies were calculated at each lattice intersection of a regularly spaced grid box. The lattice spacing was set a value of 2.0 A^o. CoMFA region was defined automatically which extends the lattice walls beyond the dimensions of each structures by 4.0 A^o in all directions. The Lennard-Jones Potential and Coloumbic term which represent, steric and electrostatic fields respectively, were calculated using the TRIPOS force fields.

An sp^3 carbon atom with a van der Waals radius of 1.52 A^o and a +1.0 charge served as the probe atom to calculate steric and electrostatic fields. The default value of 30.0 kcal/mol was used as the maximum electrostatic and steric energy cutoff.

Partial least squares (PLS) and Cross-validation in CoMFA

The last step in a CoMFA is a partial least square analysis to determine the minimal set of grid points which is necessary to explain the biological activities of the compounds. Partial least–squares is an iterative procedure that applies two criteria to produce its solution. First, to extract a new component, the criterion is to maximize the degree of commonality between all of the structural parameter columns (independent variable) collectively and the experimental data (dependent variable). Second, in the evaluation phase of a PLS iteration, the criterion for acceptance of the principal component just generated is an improvement in the ability to predict, not to reproduce, the dependent variable.

The technique used in PLS to assess the predictive ability of a QSAR is cross-validation [19]. Cross-validation is based on the idea that the best way to assess predictive performance is to predict. When cross-validating, one pretends that one or more of the unknown experimental value is, infect, unknown. The analysis being cross-validated is repeated, excluding the temporarily 'unknown' compounds and then using the resulting equation to predict the experimental measurement of the omitted compound(s). The cross-validation cycle is repeated until each compound has been excluded and predicted exactly once. The results of cross-validation are the sum of the squared prediction errors, sometimes called the predicted residual sum of squares (PRESS). For evaluation of the overall analysis, the PRESS is commonly expressed as a cross-validated correlation coefficient r^2cv, or xv-r^2 value.

RESULTS AND DISCUSSSION

General structure of 1,3,4-thiadiazole derivatives is shown in **Figure-1**.

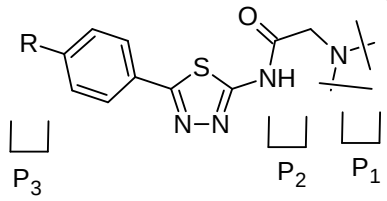


Figure-1: General structure of 1,3,4-thiadiazole derivatives

The results of the CoMFA studies are summarized in **Table-3**. From this table it is evident that the CoMFA derived QSAR shows a good cross validated r^2 (0.617) and conventional r^2 (0.980), therefore indicates a considerable predictive and correlative capacity of the model. In this analysis both steric and electrostatic field contribute to the QSAR equation by 71.7% and 28.3%, respectively, suggesting that variation in biological activity of compounds is dominated by differences in steric (van der Waals) interactions.

Table-3: Summary of CoMFA results

r^2 conventional	0.980
Standard error of estimate	0.045
F value	143.51
P value	0.000
r^2 cross-validated	0.617
Standard error of predictions	0.193
No. of components	6
Steric contribution	0.717
Electrostatic contribution	0.283

* Results from leave one out (LOO) cross validation analysis using six components.

The real test for model predictiveness is to predict the activity of ligands, which were not used in the model generation. Our test set has 3 ligands or compounds, which were randomly kept aside as a test set. The CoMFA model exhibited a good predictiveness on these ligands (**Table-4 and 5**).

Table-4: Data from PLS Cross- validated analysis (For Training Set)

Compound	Actual log (BA)	Calculated log (BA)	Residual
01	-0.81	-0.84	0.03
02	-1.09	-1.10	0.01
03	-0.86	-0.89	0.03
04	-0.89	-0.80	-0.09
05	-0.96	-0.95	-0.01
06	-0.94	-0.90	-0.04
07	-1.11	-1.09	-0.02
08	-0.91	-0.88	-0.03
09	-1.36	-1.45	0.08
10	-1.00	-0.97	-0.03
11	-1.52	-1.49	-0.03
12	-0.91	-0.91	0.00
13	-0.97	-1.04	0.07
14	-1.49	-1.48	-0.01
15	-1.13	-1.13	0.00
16	-1.72	-1.71	-0.01
17	-1.32	-1.37	0.04
18	-1.00	-1.02	0.02
19	-1.32	-1.28	-0.04
20	-0.95	-0.98	0.03
21	-1.03	-1.07	0.05
22	-1.06	-1.06	0.00
23	-1.74	-1.69	-0.05
24	-1.43	-1.44	0.01
25	-0.99	-0.99	0.00

BA = Biological Activity.

Table-5: Predicted biological activities of Test set molecules (From CoMFA Model)

Compound	Actual log (BA)	Calculated log (BA)	Residual
01	-0.79	-1.07	+0.28
02	-1.14	-1.13	-0.01
03	-1.34	-1.58	+0.24

To visualize the CoMFA steric and electrostatic fields from PLS analysis, contour maps of the product of the standard deviation associated with the CoMFA column and coefficient (SD × Coeff.) at each lattice point were generated. The contour maps are plotted as percentage contribution to the QSAR equation and are associated with the differences in biological activity.
In **Figure-2** the regions of high and low steric tolerance are shown in green and yellow polyhedral, respectively. The areas of high bulk tolerance (80% contribution) are observed near P1 position of the ligands (**Figure-1**). The active analogue (SM-1) shown in **Figure-2**, shows that propyl group embedded in the green region at P1' subsite. The anti-inflammatory activity shown by the compounds 3, 4, 5, 8, and 15 was due to the presence of bulky groups in P1 position surrounded by green contours in the steric field plot.

In the present sterically unfavored yellow regions were observed near the P3 position. The steric bulk in this region has a negative effect on the activity as represented by low activity of the compounds 14, 17, 26, 36 and 42. Sterically unfavored yellow contours are also present at P1 position, embedded in the surrounding green contours, suggesting that there is a definite requirement of a substructure with appropriate shape to exhibit high activity.

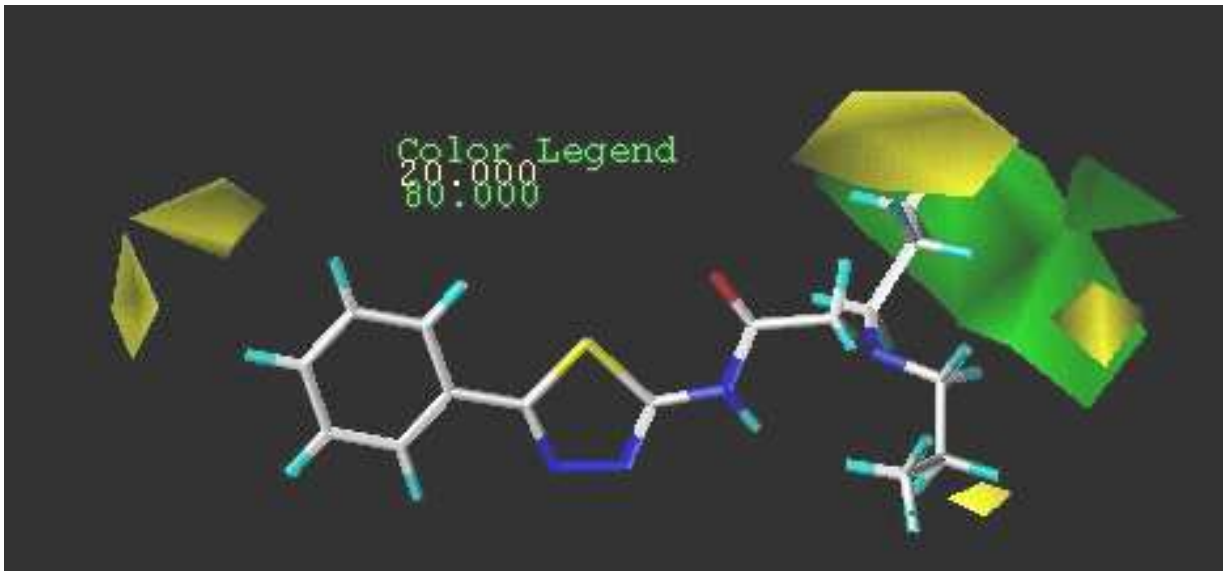


Figure-2: Steric contour plot: favored (contribution level 80%) and unfavored (contribution level 20%) areas are represented as green and yellow contours, respectively.

CoMFA electrostatic fields are shown as blue and red polyhedral in **Figure-3**. A low electron density within the molecules near blue and red polyhedral, respectively, increases or decreases

the activity and vice versa. Presence of a blue contour at P1' and P3 position suggesting that a low electron density in this area will have a positive effect on the biological activity and substructures with high electron density will reduce the activity. A predominant feature of the electrostatic field plot is the presence of red contours at P1", P2 and P3 position suggest that high electron density in this region increases the activity. Though the electrostatic field contributions are less, a small change in electrostatic interactions will have a considerable effect on the activity. Graph between actual and predicted biological activity for training and test is shown in **Figure-4**.

Figure-3: Electrostatic contour plot: positive (contribution level of 80%) and negative (contribution level of 20%) charge favoring areas are represented as blue and red contours, respectively.

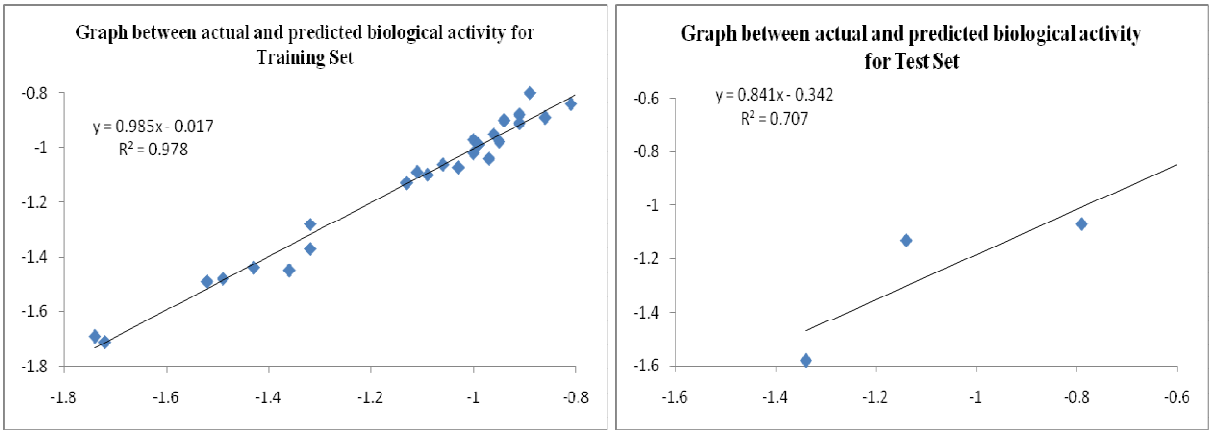


Figure-4: Graph between actual and predicted biological activity for Training set and Test set.

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