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3D-QSAR STUDIES OF MATRIX METALLOPROTEINASE-13 INHIBITORS

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ABSTRACT

A Three-dimensional quantitative structure-activity relationship models have been derived using molecule surface, electrostatic properties: positive and negative electrostatic fields, van der Waals effects and hydrophobic effects on a series of piperazine based analogs acting as matrix metalloproteinase-13 (MMP-13) inhibitors. Correlation and regression analysis performed on these series of MMP-13 inhibitors .The results are critically discussed on the basis of Correlation matrix and significant regression Coefficients(R^2=0.724). The obtained correlations also suggest that the presence of sulfonamide unit increase inhibitory activity of these molecules.

Keywords: *3D-QSAR; MMPs; Matrix Metalloprotinase-13 Inhibitors; Collagenases*

INTRODUCTION

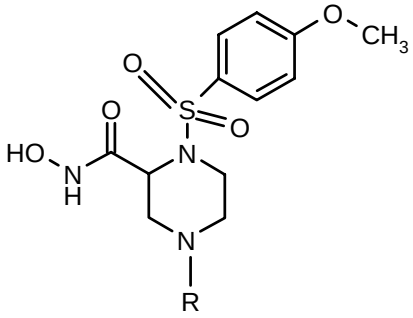
Matrix metalloproteinases (MMPs) constitute a family of zinc-dependent endoproteinases[1] that are involved in extracellular matrix[2] remodeling. The MMPs belong to a larger family of proteases known as the metzincin superfamily. Collectively they are capable of degrading all kinds of extracellular matrix proteins. They are known to be involved in the cleavage of cell surface receptors[3]. MMPs are also thought to play a major role on cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, angiogenesis, apoptosis and host defense. The family consists of 25+ members, which can be divided into general categories of collagenases (MMP-1, -8, -13), gelatinases(MMP-2, -9),, stromelysins (MMP-1, -10, -3), and membrane-type MMPs (MMP-14, -15, 16, 17) [4]. The process of angiogenesis, which is growth of new capillaries from pre-existing caprillaries, requires endothelial cell activation followed by proliferation, proteolysis, and migration through the encapsulating basement membrane into the interstitial matrix to form a new capillary connection [5,6].This process has been shown to involve MMPs in tumour–Induced angiogenesis and in angiogenesis induced by inflammation or wound healing [7].

The piperazine-based hydroxamic acid analog's acting as matrix metalloproteinase inhibitors[8]. hydroxamic acid as the zinc binding group because the hydroxamic acid has the high affinity for the catalytic zinc ion in the active site of MMPs [9]. A qsar studies has been carried out on a series of 28 piperazine based compounds based on molecule surface, electrostatic properties: positive and negative electrostatic fields, van der Waals effects and hydrophobic effects. It is aimed at explaining the observed results are correlated to biological activity and these studies also will help to develop potent inhibitors.

EXPERIMENTAL

Softwares: ***Molecular Modeling*** The structures of molecules were drawn using Hyperchem 7.0 software[10]. The final geometries were obtained with the semi-empirical AM1 method in Hyperchem program. The molecular structures were optimized using the Polak-Ribiere algorithm until the root mean square gradient was 0.01 kcal mol^{-1}.

Table-1: Biological activities and alignment scores of piperazine based MMP-13 Inhibitors.



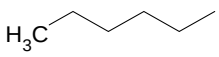
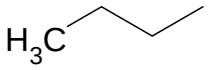
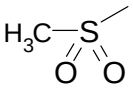
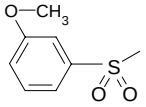
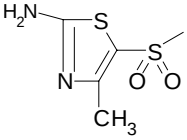
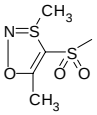
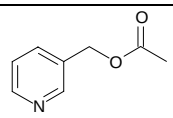
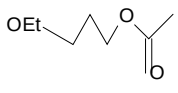
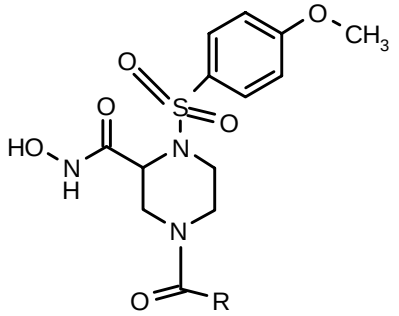
Compd. No	R	Similarity	IC50	Activity = LOG 1/IC50	Predicted activity
1.	H-	0.7390	1.7	0.76	0.66
2.		0.7400	4.2	0.33	0.65
3.		0.6800	8.0	0.08	0.49
4.		0.8260	1.0	1.0	.89
5.		0.7840	1.3	0.89	0.78
6.		0.7100	2.0	0.70	0.58
7.		0.7960	1.3	0.89	0.80
8.		0.8410	1.0	1.0	0.93
9.		1.0000	0.7	1.15	1.36

Table-2: Biological activities and alignment scores of piperazine based MMP-13 Inhibitors.



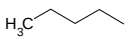
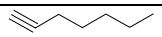
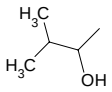
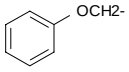
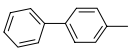
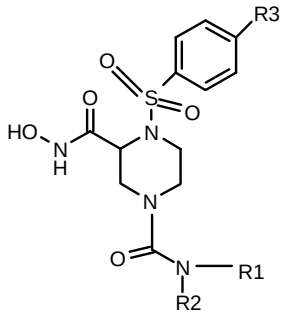
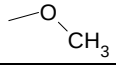
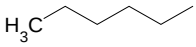
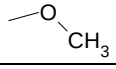
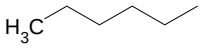
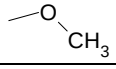
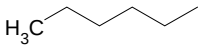
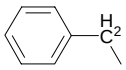
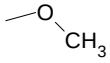
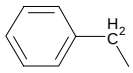
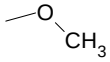
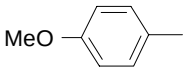
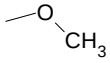
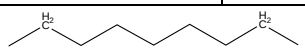
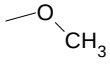
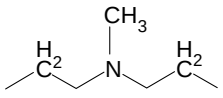
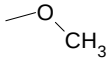
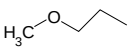
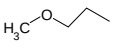
Compd. No	R	Similarity	IC50	Activity= LOG 1/IC50	Predicted Activity
10.		0.8260	1.0	1.0	0.89
11.		0.7900	1.7	0.76	0.79
12.		0.8210	1.5	0.81	0.87
13.		0.8160	1.0	1.0	0.87
14.		0.7540	2.1	.67	0.69
15.		0.6850	3.0	.52	0.51
16.		0.7930	1.9	.71	0.80
17.		0.7100	2.5	0.60	0.57
18.		0.8150	0.9	1.05	0.87

Table-3: Biological activities and alignment scores of piperazine based MMP-13 Inhibitors.



Compd. No	R1	R2	R3	Similarity	IC50	Activity =LOG 1/IC50	Predicted Activity
19.	H-	H-		0.6500	3.6	0.45	0.41
20.		. H-		0.8140	1.4	0.85	0.86
21.				0.7250	1.9	0.71	0.61
22			Br	0.6000	4.5	0.31	0.28
23.		H-		0.7300	2.4	0.62	0.63
24				0.7450	1.8	0.70	0.67
25.		H-		0.7100	2.8	0.55	0.57
26				0.7200	2.9	0.53	0.60
27.				0.625	4.1	0.39	0.34
28.			Br	0.6800	3.2	0.49	0.49

Alignment software Field Templater 2.1.1[11] is a tool for comparing molecules using their electrostatic, van der Waals effects and hydrophobic fields in order to find common patterns. When applied to several structurally-distinct molecules with a common activity, FieldTemplater can determine the bioactive conformations and relative alignments of these molecules**.** Similarity score is an average score of Field similarity and Volume similarity.

$$\text{Similarity} = \frac{\text{Field similarity} + \text{Volume similarity}}{2}$$

Field similarity: The total template similarity as measured using Cresset's field similarity metric Volume similarity: The total template volume (shape) similarity.

SPSS SPSS[12] Inc. is a leading worldwide provider of predictive analytics software and solutions.

Data Screening & Model Building

The selected descriptor (Similarity score) was calculated from the data of MMP-13[13] Inhibitors. The regression analysis was carried out using SPSS (version 17.0) software to derive the QSAR equations. Molecule structures, calculated similarity scores and molecules IC50 values were given in Table1, Table 2 and Table 3. Biologically highest activity molecule 9 taken as a template molecule to find alignment similarities with database molecules. A common substructure-based alignment similarity scores was adopted in the present study, the total similarity Score of molecules is in terms of their surface and electrostatic properties: positive and negative electrostatic fields, van der Waals effects and hydrophobic effects on and near the surface of a molecule.

Model building

The correlation matrix studies performed between biological activity (log1/IC50) and alignment similarity score are presented in Table 1,2,3.The correlation matrix table 4, that shows the strong correlation between activity and Similarity as indicated by values near 1(r=0.851) . The simple linear regression[14-16] method performs a standard linear regression calculation to generate QSAR equation. This method is good for exploring simple relationships between structure and activity. The present Similarity Score descriptor served as independent variable and activity (log1/Ic50) values as a dependent variable in regression analysis in deducing the 3D-QSAR[17-18] models. The significant equation with high correlation is listed below.

$$\textbf{Activity} = 2.698(0.327) * \text{similarity} + -1.338(0.248)$$

$$\textbf{N= 28 R= 0.851 } R^2 = 0.724 \quad \text{Adj } R^2 = 0.714 \quad \textbf{SEE=0.1372}$$

Table-4: Correlation Matrix between Activity and Similarity Score

		Activity	Similarity
Activity	Pearson Correlation	1	.851**
	Sig. (2-tailed)		.000
	N	28	28
Similarity	Pearson Correlation	0.851**	1
	Sig. (2-tailed)	0.000	
	N	28	28

**. Correlation is significant at the 0.01 level (2-tailed).

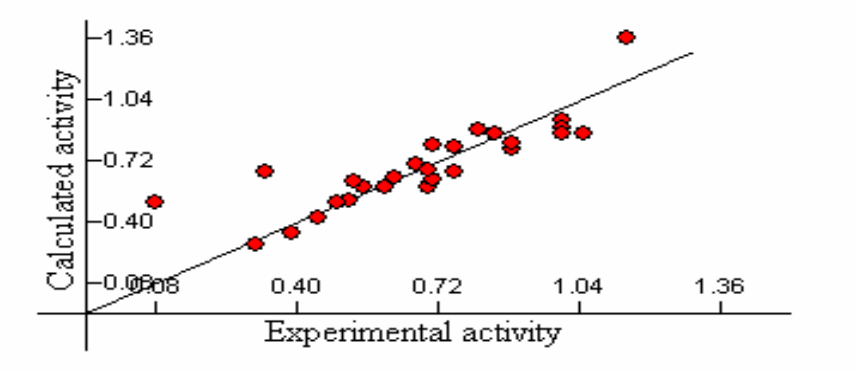


Fig.-1: Plot of observed versus predicted activity

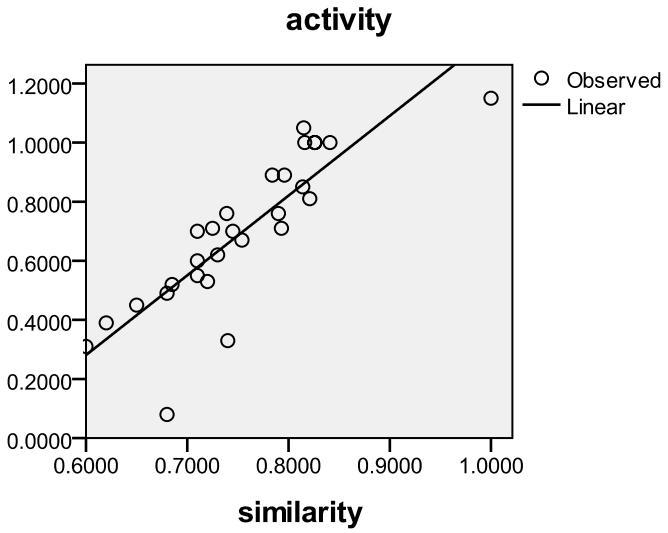


Fig.-2: Plot of activity versus similarity

Model validation

The performance of model was evaluted using the leave one out (LOO) cross--validation method. The corresponding squared cross-validated correlation coefficient[19] R^2_{cv} is calculated for the model, which is calculated automatically by the validation module implemented in CODESSA[20] PRO package. The cross-validated correlation coefficient R^2_{cv} 0.663 is pretty close to the correlation coefficient R^2(0.724) , that suggests a good predictive ability of the best linear model as shown in in figure 1. It can be easily observed that our linear regression equation is better in terms of stability and predictive ability with a lower difference R^2 _ R^2_{cv}.

RESULTS AND DISCUSSIONS

3D QSAR studies were performed using the Biological activity (log 1/IC50) data and similarity score (alignment) of molecules. The score of similarity of molecules taken in terms of their surface and electrostatic properties: positive and negative electrostatic fields, van der Waals effects and hydrophobic effects on and near the surface of a molecule. Experimental biologically highest activity molecule 9 taken as a template and compared molecular fields[21]of all molecules taken in tables 1,2,3. The hypothesis of

work relies is that two molecules which both bind to a common active site tend to make similar interactions with the protein, hence high score similarity molecules may show good binding with protein.

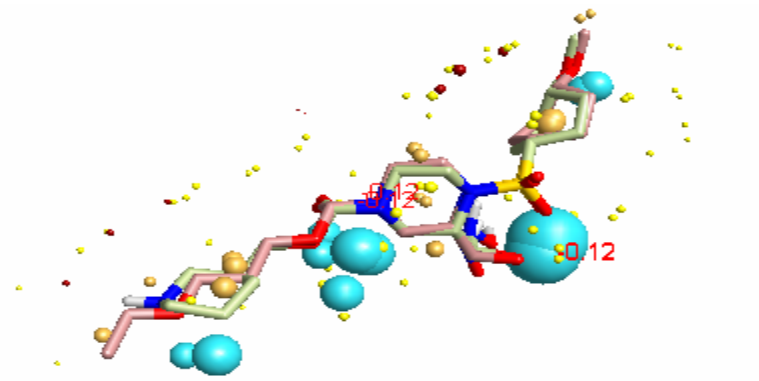


Fig.-4: Molecular algiments between template molecule and molecule 8
(Blue: Negative field points, Red: Positive field points, Yellow: van der Waals surface field points, Gold/Orange: Hydrophobic field points)

The statistics obtained from above Equation demonstrates the role of the alignment Score in the modeling of MMP-13 Inhibitors to explain binding affinity. The equation also shows the direct relationship between similarity score and its activity i.e., an increase in similarity score enhances the binding of MMP inhibitors. The best linear model as shown in in Figure 2 also explains relationship between activity and similarity. Molecules 4, 5, 6, 7, 8 and 9 from Table 1 showing high Similarity score with high Biological activity, this is due to van der walls effect of Bis-Sulfonamide ,one of the oxygen atom presented in sulfonaimde unit formed tight Hydrogen bonds and Hydrophobic interactions causes to increase potency of these molecules. Van der walls effect plays a key role in Molecules 10,11,12,13,14,116,18 .These molecules are also showing good similarity score with high Biological activities .Molecules 2,3,are showing high similarity with low biological activities due to increase of N-alkyl amines chain is causing to increase in alignment of molecular filed with template filed, but these molecules are not forms good interactions with in the active site with the absence of Hydrogen bondings and van der Walls effects . Molecules 19, 22, 25, 26, 27 and 28 are showing Moderate similarity score with low biological activities due to their molecular surfaces, with these effects molecules are not able to bind with proper interaction in the active site .

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