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International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN : 0974-4290
Vol.1, No.3 , pp 727-732, July-Sept 2009

3D-QSAR STUDIES OF N-ARYL-CHLOROETHYL UREAS

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ABSTRACT : A Three -dimensional quantitative structure activity relationship (3D-QSAR) studies were conducted on a series of 26 N-Aryl-3-(2-chloroethyl)ureas (CEUs) acting as potent cytotoxic and antineoplastic agents. The comsia analysis has been carried out to enhance the efficacy of N-Aryl-3-(2-chloroethyl)ureas by predicting important structural properties. The best predictions were obtained using regression analysis. The results are critically discussed on the basis of significant regression Coefficients (R^2=0.717). The obtained correlations also suggest that the presence of hydrophobic fields and little interference of van der walls effects are increasing inhibitory activity of these molecules.
Keywords: 3 D-QSAR, N-Aryl-3-(2-chloroethyl)ureas, comsia analysis , Antineoplastic agents

1. INTRODUCTION

N-Aryl-3-(2-chloroethyl)ureas (CEUs) are new agents that have shown promising cytotoxic and antineoplastic activities. The cytotoxicity of many CEUs was demonstrated on several tumor cell lines[1]. In addition, we also found that several CEUs were not mutagenic in the Ames test[2]. These ureas are belong to a new category of soft protein alkylating agents able to inhibit tumor cells growth, a capacity previously associated to ß-tubulin alkylation. ß-tubulin was one of the proteins putatively involved in the antimicrotubule effect observed when using tBCEU[3] .At first ,Structure Activity Relationship(SAR) identified a subset of chloro-ethyl ureas binding covalently to the colchin binding site[4] on tubulin through the acylation of glutamic acid -198 residue[5-6] and these drugs have also exhibited antiangiogenic properties in several in vitro models[7-9]. The SAR of the CEU derivatives showed that the unnitrosated derivatives were the only active ones; meanwhile, the exocyclic urea function and the 2-chloroethyl group were essential for activity.CEU's of the first generation are active anti-microtubule[10] agents on tumor cells having developed chemoresistance through mechanisms such as increased P-glycoprotien expression ,increased DNA repair , increased intracellular glutathione –S-transferase activity.

3D- QSAR studies have been performed on a series of 26 N-Aryl-3-(2-chloroethyl)ureas to evaluate the influence molecular fields with the biological activity. biologically highest activity molecule taken as a template and compared molecular fields of database molecules .The studies suggesting that , molecular alignment score is correlated with biological activity. i.e with increase in structure similarity, biological activity also increased.

2. EXPERIMENTAL

2.1 Softwares

2.1.1 Molecular Modeling

The structures of molecules were drawn using Hyperchem 7.0 software[11]. 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.

2.1.2 Alignment software

FieldTemplater 2.1.1[12] 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 .

2.1.3 SPSS

SPSS[13] Inc . is a leading worldwide provider of predictive analytics software and solutions.

2.2 Data Screening & Model Building:

The selected descriptor (Similarity score) was calculated from the data of 26 N-Aryl-3-(2-chloroethyl)ureas [14] Inhibitors and tabulated in table 1 . The regression analysis were 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. Biologically highest activity molecule 3 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.

2.3 Model building:
The correlation matrix studies performed between biological activity (log1/IC50) and alignment similarity score are presented in Table 1. The correlation matrix shows the strong correlation between activity and Similarity as indicated by values near 1(r=0.847) . The simple linear regression[15-17] 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[18-19] models. The significant equation with high correlation are listed below.

Activity (log1/IC50) = 6.434 * similarity + -4.15
N= 26 R= 0.847 R^2 = 0.716
Adj R^2 = 0.705 SEE= 0.223

2.4 Model validation

The performance of model was evaluted using the leave one out (LOO) cross--validation method. The corresponding squared cross-validated correlation coefficient[20] R^2_{cv} is calculated for the model, which is calculated automatically by the validation module implemented in CODESSA[21] PRO package. The cross-validated correlation coefficient R^2_{cv} 0.625 is pretty close to the correlation coefficient R^2(0.716) , that suggests a good predictive ability of the best linear model as shown in in Fig 4. 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}.

3. RESULTS AND DISCUSSIONS

3d qsar studies were performed using Comparative Molecular Similarity Indices Analysis(COMSIA) . The comsia analysis carried out using four descriptor fields: surface and electrostatic properties: positive and negative electrostatic fields, van der waals effects and hydrophobic effects on and near the surface of a molecule. The similarity score of molecules taken in terms of these four properties summarization. The comsia analysis explained using similarity score. experimental biologically highest activity molecule 3 taken as a template and compared molecular fields[22] and hydrophobic areas of all molecules taken in table 1 . 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 .
The statistics obtained from above Equation demonstrates the role of the alignment Score in the modeling of N-Aryl-3-(2-chloroethyl)ureas Inhibitors to explain binding affinity. The equation also shows the direct relationship between similarity score and it's activity i.e., an increase in similarity score enhances the binding of N-Aryl-3-(2-chloroethyl)ureas inhibitors. The best linear model(R^2 = 0.716) as shown in in Fig 5 also explains relationship between activity and similarity . As per the field alignment technology showing in fig 2 , substituted area is observed with gold colour field points, which are representing hydrophobic fields and little interference of van der walls effect(yellow colour field points) . This effect is observed in molecules 1,2,3,4,5,6 and these are also performed high biological activities. So, these properties are one of the important factors to decide biological activity . molecules(1,2,3,4,5,6) are substituted by cycloalkyl and aryl groups with single or bisubstituted fused rings causing to hydrophobicity and some van der walls effects Molecules 14,15,16,17,20,21,22,23 are showing low biological activites with low similarity scores .These molecules are also showing hydrophobicity . But high van der walls effect with increase in size of molecules are decreses it's activites as shown in fig3 .

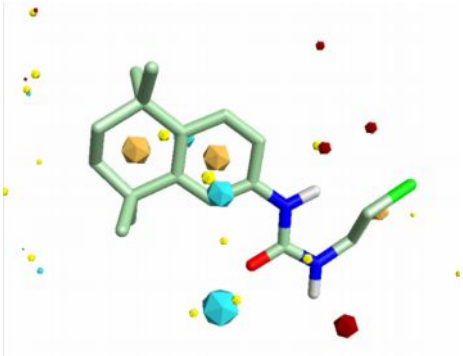


Fig 1 : Template molecule (molecule 3)

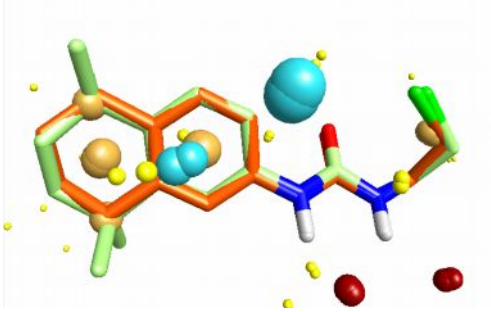


Fig 2: Molecular alignments between template molecule and molecule 2 (Blue: Negative field points, Red: Positive field points , Yellow: van der Waals surface field points , Gold/Orange: Hydrophobic field points)

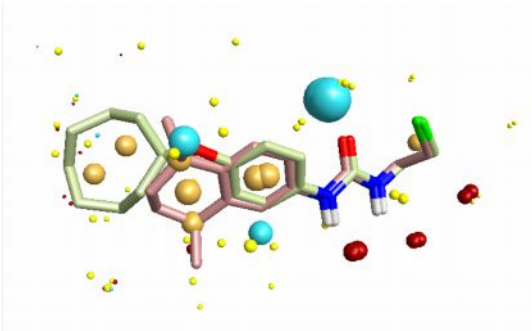


Fig 3 : Molecular alignments between template molecule and molecule 22

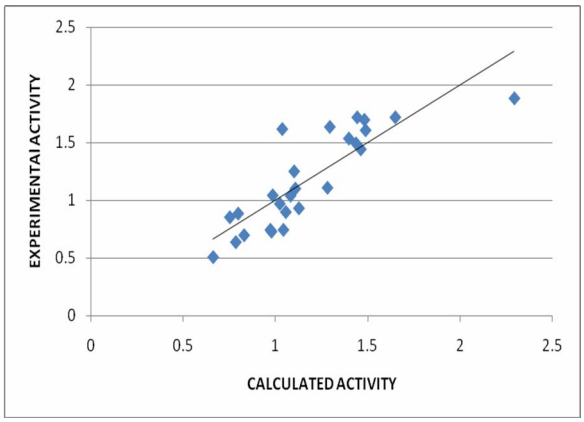


Fig 4 : Plot of observed versus predicted activity

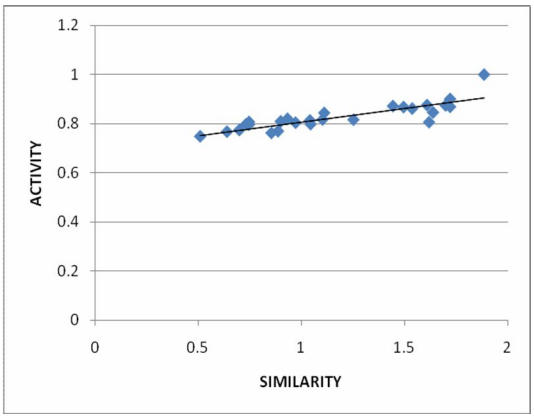
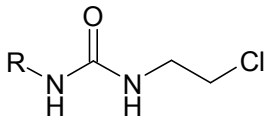
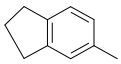
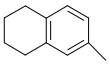
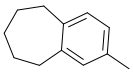
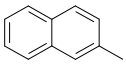
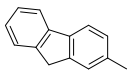
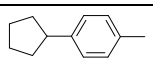
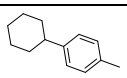
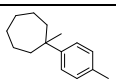
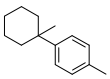
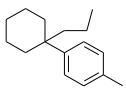
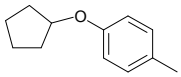
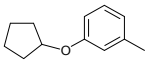
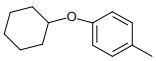
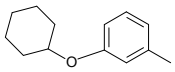
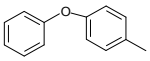
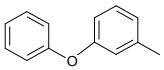
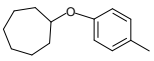
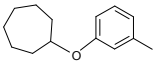
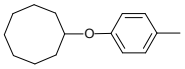
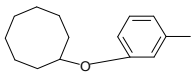
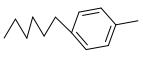


Fig 5 : Plot of activity versus similarity

Table 1 : Biological activities and alignment scores of N-Aryl-3-(2-chloroethyl)urea Inhibitors.



No	Structure	SIMILARITY	IC50	LOG 1/IC50	PREDICTED ACTIVITY	RESIDUAL VALUES
1		0.871	3.6	1.4437	1.4602	-0.0166
2		0.874	2.0	1.6989	1.4795	0.2193
3		1	1.3	1.886	2.2913	-0.4053
4		0.867	3.2	1.495	1.4344	0.0606
5		0.9	1.9	1.721	1.647	0.074
6		0.845	2.3	1.638	1.2926	0.3454
7		0.796	19	0.73	0.9769	-0.2469
8		0.806	18	0.745	1.0413	-0.2963
9		0.808	12.6	0.899	1.0542	-0.1552
10		0.819	11.7	0.932	1.1251	-0.1931
11		0.843	7.8	1.11	1.2797	-0.1697
12		0.812	9.1	1.041	1.08	-0.039

13		0.795	18	0.745	0.9705	-0.2255
14		0.747	31	0.508	0.6612	-0.1532
15		0.797	9.9	1.044	0.9834	0.0606
16		0.766	23	0.638	0.7836	-0.1456
17		0.816	7.9	1.102	1.1058	-0.0038
18		0.805	2.4	1.619	1.0349	0.5841
19		0.815	5.6	1.252	1.0993	0.1527
20		0.768	13	0.886	0.7965	0.0895
21		0.803	10.7	0.971	1.022	-0.051
22		0.761	14	0.854	0.7514	0.1026
23		0.773	20	0.698	0.8287	-0.1307
24		0.875	2.3	1.609	1.4859	0.1231
25		0.868	1.9	1.721	1.4408	0.2802
26		0.861	2.9	1.537	1.3957	0.1413

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