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QSAR Study of 4-Benzylideneamino-Benzenesulfonamides & 4-Phenyliminomethyl-Benzenesulfonamides as Selective Cox-1 & Cox-2 Inhibitors

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ABSTRACT

A QSAR study on 4-benzylideneamino-benzenesulfonamide & 4-phenyliminomethyl-benzenesulfonamides derivatives as selective cyclooxygenase-2 (COX-2) & COX-1 inhibitors was performed with 21 (16 training + 5 test) compounds. Molecular modeling studies were performed using Chemoffice 6.0 supplied by cambridgesoft. The sketched structures were subjected to energy minimization and the lowest energy structure was used to calculate the physiochemical properties. The regression analysis was carried out using a computer program called VALSTAT. The best models were selected from the various statistically significant equations. The substitution Different monosubstituents preferably at the 3- or 4-position of the phenyl ring had the greatest influence on selectivity (COX-1 & COX-2). Replacement of the 4-hydroxy moiety with an electron withdrawing group such as 4-fluoro, 4-methoxycarbonyl, or 4-nitro substituents increased inhibitory potency and selectivity. However, 3-nitro substituent resulted in loss of inhibitory potency. On the other hand, the 4-N, N-dimethylamino substituent exhibited potent and selective inhibition of cyclooxygenase. Among these compounds with monosubstituted at the para-position, cyclooxygenase the inhibitory selectivity order was 4-F > 4-CO2Me > 4-NMe2 > 4-NO2 > 4-OH > unselective 3-NO2. The analysis resulted in QSAR equation, which suggests that, n=16, r=0.880, r^2=0.774, adjusted squared multiple R=0.713, Standard error of estimate(s) = 0.106 & validated r^2 (q^2) =0.671. This study can help in rational drug design of new cyclooxygenase-2 inhibitor with predetermined affinity.

Keywords: QSAR analysis, 4-benzylideneamino, 4-phenyliminomethyl-benzenesulfonamide, cyclooxygenase-2.

1. INTRODUCTION

The success of NSAIDs in treatment of various inflammatory disorders validated inhibition of COX enzyme as a highly suitable target in anti-inflammatory therapies. However, the gastrointestinal toxicities associated with widespread use of NSAIDs proved to be a major problem during long term therapy [1]. Although COX-2 is concerned to be the main isoenzyme related to inflammation, most NSAIDs in the market today block both forms of COX isoenzymes. Side effects such as gastrointestinal pain have been associated with NSAID use due to the inhibition of COX-1[2]. The non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly medications in the world. Their anti-inflammatory activity is due to inhibition of cyclooxygenases (COXs), which catalyze the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs). Prostaglandins such as PGE2 are produced in the cyclooxygenase pathway of the arachidonic acid cascade by the action of the isoenzymes COX-1 and COX-2[3]. Prostaglandins are among the most important mediators of inflammation. They promote blood vessel dilation and vascular permeability, causing the typical redness, heat and swelling phenomena involved in inflammation. Moreover, they promote pain transmission from nociceptors to the brain by increasing the sensitivity of the nerve endings. However, prostaglandins also play a cytoprotective role in the gastrointestinal tract and they are necessary for normal platelet aggregation and renal function [4].

The identification of cyclooxygenase-2 (COX-2) and the subsequent introduction of the COX-2 selective inhibitor NSAID drugs were thought to be a major breakthrough, with the Expectation of a significant reduction in gastrointestinal (GI) side effects. COX-2 is induced in response to proinflammatory conditions, while COX-1 is constitutive and responsible for the maintenance of physiological homeostasis, such as gastrointestinal integrity and renal function. Selective inhibition of COX-2 provides a new class of anti-inflammatory agents with significantly reduced side effects such as gastrointestinal ulcer and renal dysfunction. The initial postulate that a selective COX-2 inhibitor would reduce inflammation without causing gastric irritation was validated following the introduction of selective COX-2 inhibitors such as celecoxib and rofecoxib. However, it was subsequently observed that selective COX-2 inhibitors may alter the balance in the cyclooxygenase pathway resulting in a decrease in the level of the vasodilatory and anti-aggregatory prostacyclin (PGI2), relative to an increase in the level of the prothrombotic tromboxane A2 (TxA2), leading to increased incidences of an adverse cardiovascular thrombotic event [5]. The active sites of COX-1 and COX-2 are very similar. However, the COX-2 ligand binding domain has an additional hydrophobic pocket making it more spacious: Ile523 is exchanged for Val523 in COX-2. Furthermore, Ile434 and His513 from the second shell are exchanged for Val434 and Arg513 contributing to the enlargement of the ligand binding site. The presence of this small cavern allows for the design of specific inhibitors versus COX-2. Vice versa, no highly selective COX-1 inhibitor has been reported yet because all COX-1 inhibitors also fit well into the COX-2 active site [6-8]. The majority of selective COX-2 inhibitors belong to a class of tricyclic sulfone/sulfonamide compounds possessing 1,2-diaryl substitution on a central heterocyclic or carbocyclic ring system. Recently, a number of naturally occurring trans-stilbenoids have been reported as inhibitors of COX. For example, resveratrol (3,4,5-trihydroxy-trans-stilbene) is a phytoalexin present mainly in the skin of grapes and red wine. It has broad spectrum pharmacological activities (antioxidant, neuroprotective, anti-inflammatory, cardioprotective, cancer chemopreventive, etc.) and has been shown to exhibit moderate selective COX-1 inhibitory activity [9-10].

2. MATERIALS AND METHODS

2.1 Data Set

In QSAR analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model. The overall performance of the current method used for QSAR study is critically depends on the selection of compounds for series used to build the classifier model. The most critical aspect of the construction of the series is to warrant a great molecular diversity in this data set. The cyclooxygenase-2 inhibitors activity data of 4-benzylideneamino-benzenesulfonamide derivatives were taken from the reported work of Shwu-Jiuan Lin. 2008 [11]. The list of reported compounds with their IC_{50} values was reported in table 1. The biological activity data (IC_{50} in µM) was converted to negative logarithmic dose (IC_{50} in moles) for QSAR analysis. For the external validation of QSAR models, the molecules were rationally divided into training having 16 and test set having 5 compounds on the basis of structural diversity and cover the complete range of variations in inhibitory activity as the guidelines for dividing into training and test sets.

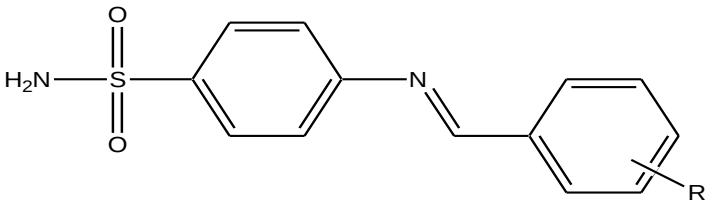
2.2 Molecular Structure Generation

The studies of 4-benzylideneamino-benzenesulfonamide & 4-phenyliminomethyl-benzenesulfonamides derivatives were performed using Chemoffice 2003 version 6.0 supplied by Cambridge Software Company, USA. All the molecules were sketched using ChemDraw Ultra module. The two-dimensional (2D) structures were transformed into three dimensional (3D) structures by using the Chem3D Ultra module. The resulting 3D structures were then subjected to an energy-minimization by using the molecular mechanics (MM2) method. The energy minimized molecules were re-optimizing using molecular orbital package (MOPAC). The numerical descriptors are responsible for encoding important features of the structure of the molecules and can be categorized as electronic, steric, and thermodynamic characters. The thermodynamic, spatial, electronic, and topological descriptors were calculated for QSAR analysis. The thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters were quantified for steric feature of drug molecules required for its complimentary fit with the receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and the receptor.

2.3 Division of Test and Training Set

It is proven that the only way to estimate the true predictive power of a model is to test it on a sufficiently large collection of compounds from an external test set. The test set includes five compounds, whose activities and structure must cover the range of activities and structures of compounds from the training set. This application is necessary for obtaining trustful statistics for comparison between the observed and predictive activities for these compounds. In this series 5 compounds were selected as a test set. This set used for the validation of model.

Table 1: Structure and Inhibitory activity of 4-benzylideneamino benzene sulfonamides using human whole blood assay



Compounds	R_1	IC_{50}	Cal B.A.
6	4-H	37.8	1.5775
7	4-F	71.5	1.8543
8	4-CO_2CH_3	67.3	1.8280
9	4-NO_2	47.1	1.6730
10	3-NO_2	15.6	1.1931
11	4-$N(CH_3)_2$	58.2	1.7649
12	4-OH	43.4	1.6375
13	4-CF_3	39.6	1.5977
14	4-CH_3	38.5	1.5855
15	4-OCH_3	31.8	1.5024
16	3-OCH_3	70.4	1.8476
17	4-OH	13.7	1.1367
18	3,4-$(OH)_2$	8.1	0.9085
19	3-OCH_3, 4-OH	26.5	1.4232
20	3-CO_2H, 4-OH	114.5	2.0588
21	3-OC_2H_5, 4-OH	13.0	1.1139
22	3-OH, 4-OCH_3	12.5	1.0969
23	3,4-$(OCH_3)_2$	35.6	1.5514
24	3,5-$(OCH_3)_2$	32.3	1.5092
25	3,4,5-$(OCH_3)_3$	57.0	1.7559
26	3,5-$(OCH_3)_2$, 4-OH	57.5	1.7597

2.4 Statistical Analysis

Statistical methods are an essential component of QSAR work. They help to build models, estimate a model's predictive abilities, and find relationships and correlations among variables and activities. The contribution of descriptors to biological activity (BA) was studied using simple linear regression analysis by VALSTAT Software [12]. The regression methods are used to build a model in the form of an equation that gives relationship between dependent variable (usually activity) and independent variable ("descriptors"). The model can then be used to predict activities for new molecules.

3. RESULTS AND DISCUSSION

When data set of 21 compounds was subjected to stepwise multiple linear regression analysis, in order to develop QSAR model, several model were obtained. The final set of equation was obtained using 16 compounds and the best equation was obtained by using the optimal combination of descriptors. Descriptors were selected for the final equation having intercorrelation coefficient below 0.5 were considered. The best QSAR model has characters of large F, low error S, low p-value, r^2 and q^2 value close to 1, as well as $P<0.001$. The large F means proposed regression model fits the data well. The low error means less standard deviation of the sampling distribution associated with the estimation method. The lower the p-value, more "significant" the result is, in the sense of statistical significance. The r^2 and q^2 value close to 1 means model explained well the activity variations in the compounds.

The stepwise development of model along with changes in statistical qualities on gradual addition of descriptors was done.

Model 1

BA = [1.84361(± 0.383094)] + SBE [0.0621601(± 0.0152692)] +NVDW [0.0766411(± 0.014639)] + PMZ [-0.350453(± 0.113786)] +Log P [-1.53434e-005(± 1.35159e-005)]

n = 16, r = 0.8874, r^2 = 0.7541, r^2adj = 0.71022, std = 0.160, F= 10.191

Model 1 explains only 75.40% variance in the cyclooxygenase inhibitory activity. It shows that descriptor non vanderwaals (NVDW) and Stretch-bend energy contribute positively; whereas Principal moment of inertia, Z (PMZ) and partition coefficient (Log P) contribute negatively towards cyclooxygenase inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 2

BA = [1.60468(± 0.571974)] + SBE [0.0584593(± 0.0162352)] + NVDW [0.0770918(± 0.014649)] CMA [0.00254067(± 0.00221303)] + PMZ [-0.331914(± 0.117384)]

n = 16, r = 0.88769, r^2 =0.7623, r^2adj = 0.710916, std = 0.1600, F=10.222

Model 2 explains only 76.2% variance in the cyclooxygenase inhibitory activity. It shows that descriptor non vanderwaals (NVDW) Connolly molecular surface area (CMA) and Stretch-bend energy (SBE) contribute positively; whereas Principal moment of inertia, Z (PMZ) contribute negatively towards cyclooxygenase inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 3

BA= [1.58993(±0.583526)] + SBE [0.0625449(±0.015174)] + NVDW [0.0761712(± 0.0146012)] +CSA [0.00198868(± 0.00173004)] + PMZ [-0.351771(± 0.113415)]

n = 16, r = 0.887729, r^2 = 0.7766, r^2adj = 0.71099, std = 0.160, F = 10.225

Model 3 explains only 77.6% variance in the cyclooxygenase inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance. In this equation non vanderwaals (NVDW), Connolly solvent excluded volume (CSA) and Stretch-bend energy (SBE) contribute positively, where as Principal moment of inertia, Z (PMZ) contribute negatively towards cyclooxygenase inhibitory activity.

Model 4

BA = [1.53157(± 0.628728)] + SBE [0.0581778(± 0.0163049)] + NVDW [0.0771068(± 0.0146384)] +CAA [0.0023326(± 0.00201764)] + PMZ [-0.329473(± 0.117875)]

n = 16, r = 0.887876, r^2 = 0.7883, r^2adj = 0.7113, std = 0.159, F= 10.241

Model 4 explains only 78.8% variance in the cyclooxygenase inhibitory activity. It is not satisfactory significant equation, therefore new model required for good explained variance. Eq. shows non vanderwaals (NVDW), Connolly solvent accessible surface area (CAA) and Stretch-bend energy (SBE) contribute positively; where as Principal moment of inertia, Z (PMZ) contribute negatively towards cyclooxygenase inhibitory activity.

Model 5

BA = [1.45418(± 0.63561)] + SBE [0.059027(±0.0156823)] + NVDW [0.0767263(± 0.0144517)] +MR [0.00137682(± 0.00108569)] + PMZ [-0.334962(± 0.114553)]

n = 16, r = 0.89044, r^2 = 0.79288, r^2adj = 0.7175, std = 0.158, F= 11.527

The r^2-value accounts for 79.2% variance in observed activity value. Therefore model 5 is the best equation in the QSAR study. The r^2 value can be easily increased by increasing the number of descriptors in the model, so cross validated correlation coefficient (q2) was used as a parameter to select the optimum number of descriptors.

Model shows that non van der Waals energy (NVDW), a thermodynamic property, denotes the sum of the angle-bending terms of the force-field equation, non van der waals energy (NVDW) is responsible for the stability of the compounds & it is positively correlated, the positive coefficients of this descriptor suggest the presence of bulky substituent oriented towards X-axis of the molecules will give better activity. Anything which can affect the bond properties and strength of the bonds in the molecule can affect the value of (NVDW) of that molecule of them, the number of atoms and number of the bonds and order of the bonds, and number of non-organic elements (heavy atoms) in a molecule directly affect on the value of NVDW . Number of atoms which are commonly existed in all molecules such as oxygen and fluorine atoms, and even heavy atoms affect NVDW of a molecule. Decrease in the number of these atoms in a molecule, increases NVDW of that molecule. Stretch bend energy (SBE), a thermodynamic property, denotes the sum of the angle-bending terms of the force-field equation, & it is positively correlated, which is indicative of deformation of the structure. Molar refractivity (MR) a steric property it Measure of the volume occupied by atoms or a group of atoms. In this equation Principal moment of inertia, Z is negatively correlated. The developed QSAR model can be utilized for the further designing of new compounds having cyclooxygenase-2 inhibitory activity.

4. CONCLUSION

It was observed from the selected QSAR models that biological activities of derivatives are governed by thermodynamic, electronic and steric properties of the molecules. The models also suggest about the groups that responsible to increase the activity. This information can be explored for the designing of new molecules having better cyclooxygenase inhibitor activity.

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