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RESEARCH ARTICLE

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

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ABSTRACT

A QSAR study on 4-benzylideneamino-benzenesulfonamide derivatives as selective cyclooxygenase-1 (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 COX-1 selectivity. Replacement of the 4-hydroxy moiety with an electron withdrawing group such as 4-fluoro, 4-methoxycarbonyl, or 4-nitro substituents increased COX-1 inhibitory potency and selectivity. However, 3-nitro substituent resulted in loss of COX-1 inhibitory potency. On the other hand, the 4-N, N-dimethylamino substituent exhibited potent and selective inhibition of COX-1. Among these compounds with monosubstituted at the para-position, the COX-1 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=0.850, r2=0.724, adjusted squared multiple R=0.713, Standard error of estimate(s) = 0.193 & validated r2 (q2) =0.618. This study can help in rational drug design of new cyclooxygenase-1 inhibitor with predetermined affinity.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. Traditional NSAIDs act as nonselective inhibitors of cyclooxygenase (COX) enzymes, which catalyze the formation of prostaglandins (PGs) from arachidonic acid. COX exists in at least two isoforms. COX-2 is induced in response to proinflammatory conditions, while COX-1 is constitutive and responsible for the maintenance of physiological homeostasis[1-2]. Cyclooxygenase exists in at least two isoforms, namely, the constitutive cyclooxygenase-1 (COX-1) and the inducible cyclooxygenase-2 (COX-2)[3]. Inhibition of COX-1 is responsible for the adverse gastrointestinal and renal effects of NSAIDs while the inhibition of COX-2 accounts for NSAIDs' therapeutic effects[4]. All classical NSAIDs, such as aspirin, ibuprofen, and indomethacin, can inhibit both COX-1 and COX-2, but bind more tightly to COX-1[5]. Selective COX-2 inhibitors have the same anti-inflammatory, anti-pyretic, and analgesic activities as do nonselective NSAIDs but without causing gastric ulceration, bleeding and perforation[6].

Since cyclooxygenase (COX) isozymes discovery, many papers and reviews have been published to describe the structural bases of COX inhibition, and to debate on the therapeutic and adverse effects of worldwide clinically used nonsteroidal anti-inflammatory drugs (NSAIDs), included COX-2 selective inhibitors (well known as Coxibs). COX-2 inhibition has been widely investigated, whereas the role of COX-1 in human pathophysiology is mostly not yet well ascertained. As time goes on, the cliché that the constitutively expressed isoform COX-1 is only involved in normal physiological functions, such as platelet aggregation, gastric mucosa protection and renal electrolyte homeostasis is going to be shattered. Low-dose aspirin, behaving as a preferential inhibitor of platelet COX-1, allowed enlightening the role exerted by this isoenzyme in many mammalian cell types. This review would elucidate the most recent findings on selective COX-1 inhibition and their relevance to human pathology such as

cancer, neuro-inflammation, cardioprotection, fever and pain. It would also focus on the design and development of new highly selective COX-1 inhibitors, useful tools in pharmacological studies aimed at gaining a deeper insight of the role of COX-1 in human health and disease. Among the traditional NSAIDs, other than aspirin and indomethacin, only few examples of selective COX-1 inhibitors (SC-560, FR122047, mofezolac, P6 and TFAP) have been so far identified. This review has also the scope to stimulate the development of novel drugs, which activity is COX-1 mediated[7-8].

Cyclooxygenase-1 (COX-1) inhibition has been one of the most widely investigated areas of research in the last decade due to its crucial role in relieving pain and other inflammatory conditions. Nonsteroidal anti-inflammatory drugs (NSAIDs) are profoundly used in the treatment of wide variety of inflammatory conditions including osteoarthritis and rheumatoid arthritis. However, these drugs are associated with high risk of gastrointestinal and renal adverse effects NSAIDs act by inhibition of cyclooxygenase (COX), the enzyme involved in the biosynthesis of prostaglandins, prostacyclins and thromboxanes from arachidonic acid[9].

EXPERIMENTAL SECTION

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-1 inhibitors activity data of 4-benzylideneamino-benzenesulfonamide derivatives were taken from the reported work of Shwu-Jiuan Lin. 2008[10]. 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 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.

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[11]. 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.

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= [1.73265(±0.651419)] +strE [-0.0600034(±0.0155109)] +NonVDW [0.059575(± 0.0192665)] +conMA [0.00355982(± 0.00292524)] +pmiz [-0.187892(± 0.0525032)]

n = 16, r = 0.825, r^2 = 0.681, r^2adj = 0.554, std = 0.207, F= 5.358

Model 1 explains only 68.1% variance in the cyclooxygenase-1 inhibitory activity. It shows that descriptor non vanderwaals (NonVDW) and Connolly molecular surface area (conMA) contribute positively; whereas Principal moment of inertia, Z (pmiz) and Stretch energy (strE) contribute negatively towards cyclooxygenase-1 inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 2

BA= [1.54645(±0.793777)] +strE [-0.0588695(±0.0156442)] +non VDW [0.0578437(± 0.0188597)] +MR [0.00185543(± 0.00150817)] +pmiz [-0.186656(± 0.0521314)]

n = 16, r = 0.826, r^2 =0.682, r^2adj =0.555, std = 0.207, F=5.380

Model 2 explains only 68.2% variance in the cyclooxygenase-1 inhibitory activity. It shows that descriptor molecular refractivity (MR) and non vanderwaals (NonVDW) contributes positively; whereas Principal moment of inertia, Z (pmiz) and Stretch energy (strE) contribute negatively towards cyclooxygenase-1 inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance.

Model 3

BA= [3.03881(± 0.304773)] +Str-Bnd [0.0413563(± 0.0140648)] +NonVDW [0.0330436(± 0.0166571)] + vdw [0.122362(± 0.0380394)] +TE [-0.0271009(± 0.00578538)]

n =16, r =0.8334, r^2 =0.6947, r^2adj =0.5726, std =0.103, F =5.689

Model 3 explains only 69.4% variance in the cyclooxygenase-1 inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance. In this equation torsional energy (TE) contribute negatively, where as Non-vander Waals Energy (Non VDW), Stretch-bend energy (Str-Bnd) and Vander Waals energy (1,4vdw) contribute positively towards cyclooxygenase-1 inhibitory activity.

Model 4

BA= [2.6951(± 0.208549)] +str-E [-0.0471051(± 0.0154463)] +NonVDW [0.0486007(± 0.0171434)] + vdw [0.0909265(± 0.0394272)] + MW [-0.0171033(± 0.00499935)]

n = 16, r = 0.839, r^2 = 0.705, r^2adj =0.587, std = 0.189, F= 5.97

Model 4 explains only 70.5% variance in the cyclooxygenase-1 inhibitory activity. It is not satisfactory significant equation, therefore new model required for good explained variance. Eq. shows vander Waals Energy (VDW) and Non-vander Waals Energy (Non VDW) contribute positively, where as Stretch energy & molecular weight (MW) contribute negatively towards cyclooxygenase-1 inhibitory activity.

Model 5

BA= [2.16557(± 0.222754)] + str E [-0.0554295(± 0.0148626)] + NonVDW [0.0669858(± 0.0189104)] + vdw [0.0498257 (± 0.0277195)] + pmiz [-0.280843(± 0.0773315)]

n = 16, r =0.850, r^2 =0.723, r^2adj = 0.613, std = 0.193, F= 12.5

The r^2-value accounts for 72.3% 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 (q^2) was used as a parameter to select the optimum number of descriptors. Model shows that van der Waals energy (VDW), a thermodynamic property, denotes the sum of the angle-bending terms of the force-field equation, van der waals energy (VDW) 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 (VDW) 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 VDW . Number of atoms which are commonly existed in all molecules such as oxygen and

fluorine atoms, and even heavy atoms affect VDW of a molecule. Decrease in the number of these atoms in a molecule, increases VDW of that molecule. The Stretch energy (str E) & Principal moment of inertia, Z (pmiz) is steric property which Representing the energy associated with distorting bonds from their optimal length & The moments of inertia when the Cartesian coordinate axes are the principal axes of the molecule & it is negatively correlated, which is indicative of deformation of the structure. The developed QSAR model can be utilized for the further designing of new compounds having cyclooxygenase-1 inhibitory activity.

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-1 inhibitor activity.

As a consequence, 16 novel inhibitors based on 4-benzylideneamino benzene sulfonamides family were designed. The calculated activity of these compounds exceeds the activity of the most potent known inhibitors to date. These fascinating results should prompt the synthesis of these compounds and the evaluation of their COX-1 inhibitory activity.

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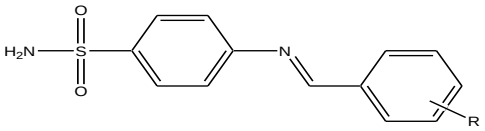
Table 1: Structure and Inhibitory activity of 4-benzylideneamino benzene sulfonamides using human whole blood assay



Compounds	**R_1**	**IC_{50}**	**Cal B.A.**
6	4-H	108.34	2.0348
7	4-F	159.07	2.2016
8	4-CO_2CH_3	183.50	2.2636
9	4-NO_2	141.25	2.1500
10	3-NO_2	105.63	2.0238
11	4-$N(CH_3)_2$	195.74	2.2917
12	4-OH	148.20	2.1708
13	4-CF_3	182.19	2.2605
14	4-CH_3	190.47	2.2798
15	4-OCH_3	313.83	2.4967
16	3-OCH_3	383.36	2.4967
17	4-OH	38.20	1.5821
18	3,4-$(OH)_2$	23.15	1.3646
19	3-OCH_3, 4-OH	78.20	1.8932
20	3-CO_2H, 4-OH	85.13	1.9301
21	3-OC_2H_5, 4-OH	47.91	1.6804
22	3-OH, 4-OCH_3	43.80	1.6415
23	3,4-$(OCH_3)_2$	110.27	2.0425
24	3,5-$(OCH_3)_2$	109.69	2.0402
25	3,4,5-$(OCH_3)_3$	167.09	2.2230
26	3,5-$(OCH_3)_2$, 4-OH	155.95	2.1930