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QSAR study of 4-benzylideneamino-benzenesulfonamides as selective cox-2 inhibitors

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ABSTRACT

A QSAR study on 4-benzylideneamino-benzenesulfonamide derivatives as selective cyclooxygenase-2 (COX-2) inhibitors was performed with 21 (16 training + 5 test) compounds. Molecular modeling studies were performed using Chemoffice 6.0 supplied by cambridgesoft. The regression analysis was carried out using a computer program called VALSTAT. The substitution Different monosubstituents preferably at the 3- or 4-position of the phenyl ring had the greatest influence on COX-2 selectivity. Replacement of the 4-hydroxy moiety with an electron withdrawing group such as 4-fluoro, 4-methoxycarbonyl, or 4-nitro substituents increased COX-2 inhibitory potency and selectivity. However, 3-nitro substituent resulted in loss of COX-2 inhibitory potency. On the other hand, the 4-N, N-dimethylamino substituent exhibited potent and selective inhibition of COX-2. Among these compounds with monosubstituted at the para-position, the COX-2 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.

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].

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. 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. As an alternative to convert a COX-1 selective compound into a COX-2 selective inhibitor, we have designed and modified the basic skeleton of trans-stilbene based on the concept of isosterism, which lacks a traditional central heterocyclic or carbocyclic ring template such as celecoxib (Celebrex)· It has broad spectrum pharmacological activities (anti- oxidant, neuro protective, anti-inflammatory, cardioprotective, cancer chemopreventive, etc.) and has been shown to exhibit moderate selective COX-1 inhibitory activity. 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. 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. 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 [2].

MATERIAL AND METHOD

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 molecularDiversity 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 (14). 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 [3].

Molecular Structure Generation

The studies of 4-benzylideneamino-benzenesulfonamide 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 [4].

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 [5].

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[15]. 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 [6].

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 [7].

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

Model 1

BA= [-0.886892(± 0.899574)] +NonVDW [-0.0357027 (± 0.0138358)] + Con AA [0.0071235 (± 0.00412361)] +MW [-0.00123455 (± 0.000505845)]

n=16, r=0.749634, r^2=0.561951, r^2adj=0.452439, std = 0.171138, F=5.1314

Model 1 explains only 56.0% variance in the cyclooxygenase-2 inhibitory activity. It shows that descriptor non vanderwaals (NonVDW) contribute negatively; whereas Connolly solvent accessible surface area (Con AA) and Molecular weight (MW) contribute positively towards cyclooxygenase-2 inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance [8].

Model 2

BA = [-1.36808 (± 1.06119)] + NonVDW [-0.0349211(± 0.0135501)] +MR [0.00471877 (± 0.00246204)] + MW [-0.00130095 (± 0.000495184)]

n = 16, r = 0.762373, r^2 = 0.581213, r^2adj = 0.476516, std = 0.167333, F=5.55139

Model 2 explains only 58.1% variance in the cyclooxygenase-2inhibitory activity. It shows that descriptor molecular refractivity (MR) contributes positively; whereas non-Van der Waals Energy (Non VDW) and molecular weight (MW) contribute negatively towards cyclooxygenase-2 inhibitory activity. It is not a very good significant equation, therefore new model required for good explained variance [9].

Model 3

BA = [1.10639 (± 0.24199)] + TE [0.0242804 (± 0.0115816)] + NonVDW [-0.0463719 (± 0.0126034)] + MW [-0.000845713 (± 0.000293203)]

n = 16, r = 0.774369, r^2 = 0.599648, r^2adj = 0.49956, std = 0.163608, F = 5.9912

Model 3 explains only 59.9% variance in the cyclooxygenase-2 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 positively, where as Non-vander Waals Energy (Non VDW) & molecular weight (MW) contribute negatively towards cyclooxygenase-2 inhibitory activity.

Model 4

BA = [0.485687 (± 0.131312)] + NonVDW [-0.0391849 (±0.0124222)] + VDW [0.041739 (± 0.0185722)] + MW [-0.000930017 (± 0.000306165)]

n = 16, r = 0.784246, r^2 = 0.615042, r^2adj = 0.518803, std = 0.160432, F=6.39075

Model 4 explains only 61.5% variance in the cyclooxygenase-2 inhibitory activity. It is not satisfactory significant equation, therefore new model required for good explained variance. Eq. shows vander Waals Energy (VDW) contribute positively, where as Non-vander Waals Energy (Non VDW) & molecular weight (MW) contribute negatively towards cyclooxygenase-2 inhibitory activity [10].

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

Compounds	R_1	IC_{50}	B.A.
6	4-H	2.87	0.4579
7	4-F	2.22	0.3464
8	4-CO_2CH_3	2.73	0.4362
9	4-NO_2	3	0.4771
10	3-NO_2	6.75	0.8293
11	4-$N(CH_3)_2$	3.36	0.5263
12	4-OH	3.42	0.5340
13	4-CF_3	4.6	0.6628
14	4-CH_3	4.94	0.6937
15	4-OCH_3	9.88	0.9948
16	3-OCH_3	5.45	0.7364
17	4-OH	2.78	0.4440
18	3,4-$(OH)_2$	2.85	0.4548
19	3-OCH_3, 4-OH	2.95	0.4698
20	3-CO_2H, 4-OH	0.74	-0.1308
21	3-OC_2H_5, 4-OH	3.69	0.5670
22	3-OH, 4-OCH_3	3.5	0.5441
23	3,4-$(OCH_3)_2$	3.09	0.4900
24	3,5-$(OCH_3)_2$	3.4	0.5315
25	3,4,5-$(OCH_3)_3$	2.93	0.4669
26	3,5-$(OCH_3)_2$, 4-OH	2.71	0.4330

Model 5

BA = [-0.262158 (± 0.225004)] + BE [-0.00891868 (± 0.00148603)] + StBE [-0.0845117 (± 0.0215898)] + VDW [0.0114337 (± 0.00307811)]

n = 16, r = 0.880246, r^2 = 0.774833, r^2adj = 0.713424, std = 0.106116, F= 12.6176

The r^2-value accounts for 77.4% 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 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 effect 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 bend energy (BE) & stretch bend energy (StBE), a thermodynamic property, denotes the sum of the angle-bending terms of the force-field equation, & 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-2 inhibitory activity [11].

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-2 inhibitor activity.

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REFERENCES

1. Xie W, Chipman JG, Robertson DL, 1991. Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing Proc. Natl Acad Sci. 88, Pages 2692-2702. Doi: 10.1073/pnas.88.7.2692.

2. Zarghi A, Zebardast T, Daraie B, 2009. Design and synthesis of new 1, 3- benzthiazinan-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors. Bioorg Med Chem. 17, Pages 5369–5373. Doi: 10.1016/j.bmc.2009.06.056.

3. Zarghi A, Ghodsi R, Azizi E, 2009. Synthesis and biological evaluation of new 4-carboxyl quinoline derivatives as cyclooxygenase-2 inhibitors. Bioorg Med Chem. 17, Pages 5312–5317. Doi: 10.1016/j.bmc.2009.05.084.

4. Schuhly W, Hufner A, Pferschy-Wenzig EM, 2009. Design and synthesis of ten biphenyl-neolignan derivatives and their in vitro inhibitory potency against cyclooxygenase-1/2 activity and 5-lipoxygenase-mediated LTB4-formation. Bioorg Med Chem. 17, Pages 4459–4465. Doi: 10.1016/j.bmc.2009.05.018.

5. Tally JJ, Oxford FD, 1999. A Synthesis of new imidazolyl acetic acid derivatives with anti-inflammatory and analgesic activities. Amsterdam. 36, Pages 201–234.

6. Jyoti M, Vihas TV, Ravikumar A, Sarita G, 2002. Glucose lowering effect of aqueous extract of Enicostemma Littorale Blume in diabetes: a possible mechanism of action. J. Ethnopharm. 81, 317-20. Doi: 10.1016/s0378-8741(02)00095-8

7. Thilahgavani Nagappan, Perumal R, 2011. Biological Activity of Carbazole Alkaloids and Essential Oil of Murraya koenigii Against Antibiotic Resistant Microbes and Cancer Cell Lines. Molecules. 16, Pages 9651-9664. Doi: 10.3390/molecules16119651.

8. Johannes Reisch, Olav Go, Anura Wickramasinghe, 2006. Induction of apoptosis by carbazole alkaloids isolated from Murraya koenigii. Phytomedicine. 13. Pages 359–365. Doi: https://doi.org/10.1016/j.phymed.2005.03.010.

9. Nykanen A, Haley B, Zamore PD, 2001. ATP requirements and small interfering RNA structure in the RNA interference pathway. Cell. 107, Pages 309-321. Doi: 10.1016/s0092-8674(01)00547-5.

10. Jang M, Cai L, Udeani G, 1997. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 41, Pages 275-218.

11. Sale S, Tunstall RG, Ruparelia KC, 2005. Comparison of the effects of the chemopreventive agent resveratrol and its synthetic analog trans 3,4,5,4 tetramethoxystilbene on adenoma development in the APC mouse and cox-2 in human derived colon cancer cells. Int J Cancer. 115, Pages 194-201. Doi: 10.1002/ijc.20884.