September 2007 Volume 3 Issue 3

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 3(3), 2007 [138-141]

Quantitative Structure Activity Relationship Studies Of Benzothiazolamine As Selective COX-2 Inhibitor

Kishor P.Bhusari[1], Ritesh P.Bhole[2*]

[1]Sharad Pawar College of Pharmacy,Wanadongri,Hingna Road, Nagpur- 441110, M.S. (INDIA)

[2]College of Pharmacy Neheru Vidyanager, Faizpur, M.S. 444205 (INDIA)

Phone : +91-02585-245574 ; Fax : 02585-245574

E-mail : ritesh.edu@gmail.com

Received: 22nd May, 2007 ; Accepted: 27th May, 2007

ABSTRACT

Selective COX-2 inhibitor have attracted much attention in recent times in design of non-steroidal anti-inflammatory agents(NSAID), which are devoid of the common side effects of classical NSAIDs. QSAR studies have been performed on a series of benzothiazolamines that acts as selective COX-2 inhibitor using a three dimensional QSAR. The studies were carried on twenty analogs. Various physicochemical parameter were calculated using Chem Office 2001 software.QSAR models were generated for cyclooxygenase inhibitor activity using stepwise multiple regression analysis. Statistically significant models were obtained gave r^2 value(square of correlation coefficient) as 0.8102 after per oral, 2h. The studies indicated that the anti-inflammatory activity is depend on spatial and thermodynamic descriptor. Cross validation was performed using the leave one out method. Obtained and validated models bring important structural insight to aid the design of novel selective COX-2 inhibitors prior to their synthesis.

KEYWORDS

Quantitative structure activity relationship;
COX inhibitor;
LOO model.

INTRODUCTION

The two major approaches for the design and synthesis of anti-inflammatory agents are based on inhibition of two enzymes[1] **(i)** Cyclooxegenase **(ii)**Lipooxygenase which is involved in the metabolism of arachidonic acid. Cyclooxegenase has been common target for most of anti-inflammatory drugs. New types of NSAID are being developed based on new understanding of their mechanism of action and the pathogenesis of inflammation[2] .NSAID have been of current interest[3] because their is no drug of choice for treatment of most of diseases like rheumatoid arthritis[4], allergic rhintis[5],psoriasis[6], ulcerative colitis and asthama[7].The new class of NSAID called selective cyclooxegenase -2(COX-2) inhibitors preserve the cyclooxegenase-1(COX-1) that is responsible for the the production of cytoprotective prostaglandins in stomach and selectively inhibit COX-2 resulting in the same analgesic and anti-inflammatory effect as the existing NSAID with less toxicity[8]. Uptill now, no QSAR studies have been attempted so far on

benzothiazolamine. Hence, it was worthwhile to carry out 3-D QSAR analysis for one of such reported series with COX-2 inhibiting activities, in order to identify the necessary structural and physicochemical requirement for binding with COX-2.

MATERIALS AND METHODS

Biological data

Bhusari et al reported a series of 20 benzothiazo lamine derivatives as a inhibitors of COX(TABLE 1). All the biological activity data (IC_{50}) have been converted to negative logarithmic molar dose. pIC_{50} in order to linearly relate free energy of the interaction of compounds with receptor and reduce the skewness of the data set.

Computer software

All computational work was performed on Pentium IV workstation-using softwares chem Office 2001, chem 3-D Ultra 6.0, chem Draw ultra 6.0 and chem finder (chem. SAR for excel).The structure of compounds were built using CS Chemdraw and transferred to chem. 3-D ultra software. The energy calculation was done using universal force field. The structures of newly synthesize compounds were energy minimized by standard minimizer algorithms. In the minimization process, the first steepest descent method was used to eliminate the unsuitable contacts, after which more accurate minimizing methods like conjugate gradient and truncated newton rapson method were used. The minimization terminates at which the root mean square for the molecule was less than 0.0001kcal/mol A^0.

Most stable conformation for each compound was generated and its analysis was performing using GRID method. These conformers were used for calculating other physicochemical parameters (descriptor). The semi empirical quantum mechanical calculations were performed using the modified neglected differential overlap(MINDO) method. The Austin model 1(AM1) and Hamiltonian of molecular orbital package(MOPAC) module was done by using calculating atomic charges and electron density on various atoms. The lowest energy conformation for each compound was found. The descriptor were calculated using the lowest energy conformations.

The physicochemical descriptors were calculated for 3-D QSAR study The values of only those descriptors which found place in equation and having significance in QSAR are given in TABLE 2.

TABLE 1 : Substituents and COX-2 inhibition data

Comp.no	R	IC_{50}	pIC_{50} calculated
1	CH_3	0.88	0.046
2	C_2H_5	0.85	0.055
3	C_6H_5	0.80	0.1241
4	$4NH_2C_6H_4$	0.58	0.2255
5	$4N(CH_3)C_6H_4$	0.73	0.2034
6	$4OCH_3C_6H_4$	0.53	0.2584
7	$2OCH_3C_6H_4$	0.51	0.2822
8	$4NO_2\ C_6H_4$	0.63	0.1887
9	$4OH\ C_6H_4$	0.53	0.2688
10	$4CH_3C_6H_5$	0.61	0.2126
11	CH_3	0.72	0.2126
12	C_2H_5	0.59	0.1348
13	C_6H_5	0.58	0.1562
14	$4NH_2C_6H_4$	0.47	0.2199
15	$4N(CH_3)C_6H_4$	0.49	0.3213
16	$4OCH_3C_6H_4$	0.42	0.2977
17	$2OCH_3C_6H_4$	0.41	0.3617
18	$4NO_2\ C_6H_4$	.51	0.4245
19	$4OH\ C_6H_4$	0.42	0.2784
20	$4CH_3C_6H_5$	0.49	0.3679

TABLE 2 : Descriptor contributing to COX inhibitory activity

Comp.no	R	PMIIZ	DX	E
1	CH_3	1173.79	-0.1595	-1869.51
2	C_2H_5	1555.68	-0.7193	-2025.3
3	C_6H_5	2384.88	3.5131	-536.04
4	$4NH_2C_6H_4$	2838.25	0.8039	-757.42
5	$4N(CH_3)C_6H_4$	3727.5	-.5794	-068.02
6	$4OCH_3C_6H_4$	3139.62	3.5364	-3011.85
7	$2OCH_3C_6H_4$	3068.59	2.6792	-3011.82
8	$4NO_2\ C_6H_4$	5444.38	0.3655	-4330.37
9	$4OH\ C_6H_4$	4281.35	-2.6402	-3820.16
10	$4CH_3C_6H_5$	4346.69	-1.8763	-3655.21
11	CH_3	2630.49	-1.8986	-2832.67
12	C_2H_5	2871.17	-1.8286	-2988.31
13	C_6H_5	3738.53	-1.8051	-3499.54
14	$4NH_2C_6H_4$	4284.89	-1.9321	-3720.61
15	$4N(CH_3)C_6H_4$	5386.26	-2.0096	-4031.22
16	$4OCH_3C_6H_4$	4928.11	-3.01	-3975.42
17	$2OCH_3C_6H_4$	4219.4	-2.937	-3975.38
18	$4NO_2\ C_6H_4$	5437.47	0.404	-4330.37
19	$4OH\ C_6H_4$	4283.93	-2.6423	-3820.16
20	$4CH_3C_6H_5$	4255.69	-1.7836	-3655.42

The correlations between the biological activity and the physicochemical parameter was found through stepwise multiple regression analysis using the method of least squares[stepwise predicted activity(SPA)].The 3-D QSAR equations were generated by stepwise multiple regression analysis. The cross correlation matrix for the -log (BA) (BA- biological activity) and the various physicochemical descriptions were calculated[9].The statistical parameters were calculated as correlation coefficient(r),

Full Paper

TABLE 3: Observed, calculated and predicted activity

Compound no	Observed activity	pIC_{50} calculated	pIC_{50} observed
1	0.88	0.046	-
2	0.85	0.055	0.11379
3	0.80	0.1241	0.02701
4	0.58	0.2255	0.0860
5	0.73	0.2034	0.24443
6	0.53	0.2584	0.23723
7	0.51	0.2822	0.24657
8	0.63	0.1887	0.18896
9	0.53	0.2688	0.21184
10	0.61	0.2126	0.24903
11	0.72	0.2126	0.18705
12	0.59	0.1348	0.22994
13	0.58	0.1562	0.14200
14	0.47	0.2199	0.28765
15	0.49	0.3213	0.29025
16	0.42	0.2977	0.31253
17	0.41	0.3617	0.33587
18	.51	0.4245	0.30416
19	0.42	0.2784	0.32431
20	0.49	0.3679	0.42133

squared correlation coefficient(r^2), Fisher's value(F), student's t-test and standard deviation (s).

Stepwise multiple regression analysis was used to generate QSAR equations. The statistical measures used were n-number of sample in the regression, r-correlation coefficient r^2 squared correlation coefficient (coefficient of determination), s-standard deviation, F-test(Fischer's value) for statistical significance and correlation-matrix to show mutual correlation among the parameters[12] TABLE 3.

RESULTS AND DISCUSSION

Initially, all the molecules were manually aligned to a molecule having highest potency and selectively towards COX-2 by considering the common structure. (Figure 1).The biological activities data for benzothiazolamines were taken from literature,[10]The IC_{50} values for COX-2 were transformed to -log[IC_{50}] i.e.pIC_{50}.Regression analysis was performed by taking pIC_{50} as dependent variables, Statistically significant equation 1 in which r>0.8, r^2>0.8, also F value is >literature F value, show positive relationship with molecular mass and negative correlation between repulsion energy.

Model

BA=[0.43173]+XMASS[0.000848639]+REP [0.19749]+E [1.643282000]

n=19 , r=0.9036 , r^2=0.81 F=22.26

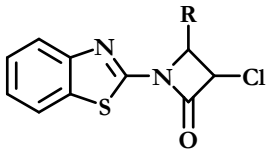

Figure 1 : Genral structure of benzothiazolamine analogues

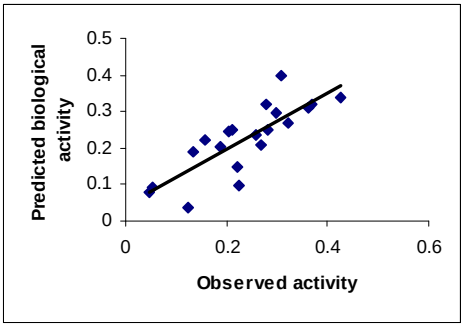

Figure 2 : Graph between experimental and predicted COX-2 inhibitor activity

The study revealed that steric, thermodynamic and electronic parameter are associates with anti-inflammatory activity. The above equation suggest that, Total mass of a molecule(XMass) & Repulsion energy(Rep) play an important role for biological activity. They contribute positively to the biological activity where as total Energy(E) also contribute positively to biological activity.

The equation (II) found to be as:

BA=[0.216548]+PMIZ (3.31130.05)+DX[2.5304 0.05]+E [0.002952]

n=19, r=0.90, r^2=0.81, F=21.35

The study reveled that all three parameters viz steric, thermodynamic & electronic are associated with anti-inflammatory activity.

The equation suggested that principle moment of inertia and dipole moment have better correlation with biological activity & have low value of standard deviation, The data showed overall significant level grater than a 99.9 as it exceeded the tabulated(11.5 F3.15)). The above equation was validated by leave one out cross validation method and boot strapping method which give statistically significant value, of internal validation where as Q^2 found to be greater that 0.5.

The absence of any serious multicollineaity between the descriptors present in the model was confirmed by calculation of correlation matrix(TABLE 5) and descriptors PMIZ, DX and E were reasonably orthogonal.

Principle moment of inertia(PMIX)is the steric

TABLE 4 : Correlation matrix

	PMIZ	DX	E
PMIZ	1	-	-
DX	0.079	1	-
E	0.2112	0.2232	1

parameter. The value of PMI depends on total mass of the molecule,mass distribution within the molecule and position of axis rotation of the molecules .Equation shows positive correlation of PMI of molecules on biological activity. This suggest that the substitution which does not facilitate the rotatory motion of the molecule around the principle axis, and increase steric bulk of compound within the series, produces the derivatives with better inhibition of COX-2.

Total energy (E) is the measure of polarizability and steric bulk of the molecules. Equation show positive correlation between biological activity and total energy. This infers that the biological activity would increases with increase in stability i.e. increase in the polarizability and steric bulk of the compounds within the series.

Dipole moment(DX) reflects the strength and orientation behavior of a molecule in electrostatic field. Equation reveals negative correlation of X components of dipole moment of the molecules, thereby electropositive substituents in the azetidin ring will increase the affinity of sulfonamide towards COX inhibition.

Although results obtained from equation(I)and(II) are not very significant statistically, these equation indicate that the steric and electronic effects of substituent might have a role to pay in determining the COX-2 inhibition. On the basis of these results, more advanced and accurate approach was further considered for these data set.

The statistical measures,r^2, s and F determine the estimation power of model for the same data from which it has been determine the prediction power for the data not included in deriving the model externally to avoid the chance correlation completely. It can be observed that the overall statistics of the equation generated are excellent and their prediction activity is also significant which is evident from their cross validated r^2_{cv} value.

CONCLUSION

On the basis of the above studies it can be concluded that selective COX-2 inhibition by the benzothiazolamines is strongly influenced by the steric and electrostatic nature of the substituents. Pattern of substitution can be extracted from the developed model. Consequently these studies may prove to be helpful in development and optimization of existing selective COX-2 inhibitors of these class of compounds.

ACKNOWLEDGEMENTS

Author wish to thank, Dr.Piyush Trivedi, Depatment of Pharmacy, S.G.S.I.T.S. Indore for providing software for study.

REFERENCES

[1] C.Hansch, P.G.Sammes, J.B.Taylor; In Comprihensive Medicinal Chemistry Enzymes and other Molecular Target, Peramon, New york, **2**, 147 **(1900)**
[2] G.Danhardt, W.Kiefer; Eur.J.Med.Chem., **36**, 109 **(2001)**.
[3] M.Arockia Babu, S.Neeraj, P.Prathipati, S.G. Kaskhedikar, A.K.Saxena; Bioorg.Med.Chem., **10**, 4035 **(2002)**.
[4] E.M.Davidson, S.A.Rae, M.J.H.Smith; Pharm. Pharmacol., **34**, 410 **(1982)**.
[5] S.D.Brain, R.D.Camp, S.Charleston, P.M.Dowd; Brit. J.Clin.Pharmacol., **17**, 650 **(1984)**.
[6] S.D.Brain, R.D.Camp, S.Charleston, P.M.Dowd; J. Invest.Derm., **83**, 70 **(1984)**.
[7] S.E.Wenzel; Pharmacotherapy, **35**, 117 **(1997)**.
[8] A.A.Shah, D.J.Fitzgerald, F.E.Murray; Irish J.Med.Sci., **168**, 242 **(1999)**.
[9] A.S.Kalgutkar, S.W.Rawlinson, L.J.Marnett; Bioorg. Med.Chem.Lett., **12**, 521 **(2002)**.
[10] K.P.Bhusari, P.B.Khedekar, S.N.Umathe, R.H. Bahekar, A.R.R.Rao; Arzneim-Forsch./Drug Res., **53(9)**, 640 **(2003)**.
[11] J.E.Lefflar, F.Grundwald; In 'Rates and Equlibrium Constant of Organic Reactions', John Wiley and Sons,New York, 445 **(1963)**.
[12] C.Hansch, A.Leo; 'Substituted Constants for Correlation Anlysis in Chemistry and Biology', John Wiley and Sons,New York, 5 **(1979)**.
[13] W.J.Dunn; J.Med.Chem., **12**, 109 **(1977)**.