2D-QSAR Study of Indomethacin Ester Derivatives as Cyclooxygenase-2- Inhibitors

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Cyclooxygenase-2 inhibitors of indomethacin ester derivative series were subjected to quantitative structure activity relationship analysis with an attempt to derive and understand a correlation between the biological activity as dependent variable and various descriptors as independent variables. Several statistical regression expressions were obtained using multiple linear regression analysis. The analysis resulted in the following 2-D equation, which suggests that, BA = (0.8098) MR + (–0.0385) FR(–0.7764) F(–5.8964), n = 20, r = 0.912, r^2 = 0.831, f = 7.133, t = 2.671, std = 0.64. The cyclooxygenase-2 inhibition by ester derivatives of indomethacin is highly correlated with the thermodynamic (MR) and sterimol (B5, L) parameters, which in turn describes the importance of steric effect, indicating that a lipophilic bulkier group width-wise is required for good biological activity. This study can help in rational drug design and synthesis of new selective cyclooxygenase-2 inhibitors with predetermined affinity.

Novel categories of nonsteroidal antiinflammatory drugs (NSAIDs) are being developed based on the new mechanism of action and pathogenesis of inflammation. The discovery of cyclooxygenase-2 (COX-2) isoform has opened a new way for the development of antiinflammatory and analgesic agents with minimum gastric side effects of traditional nonsteroidal antiinflammatory drugs[1]. Numerous agents that inhibit this isoform can also delay or prevent certain forms of cancer and are reported to be beneficial in Alzheimer's disease[2]. Co-crystallization and site-directed mutagenesis studies have revealed that ion pairing of carboxylic group of NSAIDs and arachidonic acid with positively charged arginine 120 residue of cyclooxegenase-1 (COX-1) is necessary for both inhibition and catalyses, while such ion pairing is not necessary for the catalysis in case of COX-2[3,4]. Based on these observations, Kalgutkar *et al.* have found that derivatization of carboxylic acid moiety of NSAIDs would eliminate the inhibition of COX-1 without significantly affecting their COX-2 inhibitory properties. They proposed a general strategy for the conversion of conventional nonselective NSAIDs to selective COX-2 inhibitors and thus have taken the advantage of structural class with well-established safely profile. Analogue-based QSAR analysis of these facile conversions of carboxylic acid containing NSAIDs may provide some structural insight of COX-2 to develop more selective inhibitors.

In the present study, we have performed QSAR analysis of a series of ester derivatives of indomethacin by multiple linear regression technique. A data set of 22 molecules was taken from Kalgutkar *et al.*[5], and the IC_{50} values of molecules were converted to - log concentration for positive values. We have used software SMIRAILS[6] for multiple parameter regression analysis, which is developed and standardized on the known set at our own lab. The structures of the compounds in the series were built in Table 1 by using the molecular sketching facility provided in the modelling environment of the software. The thermodynamic parameters describe free energy change during drug receptor complex formation; they include log of partition coefficient (Log P) and molecular refractivity (MR). Sterimol parameters describe the bulk of substituent; they include length of substituent (L), width of substituent (B1, B5) orthogonal to length, having angle of 90° to each other and are used for QSAR[7,8] analysis. Statistical measures used in stepwise multiple regression analysis are, (n) - number of samples in the regression; (r) - coefficient of correlation; (r^2) - coefficient of determination; (std) - standard deviation; (t) - test for statistical significance and correlation matrix to show mutual correlation among the parameters. (Values of only those descriptors which were found to be relevant in the equation are given in Table 2).

TABLE 1: COX-2 INHIBITION DATA OF INDOMETHACIN ESTER DERIVATIVES ALONG WITH PREDICTED BIOLOGICAL ACTIVITY FROM EQUATIONS

*R	IC_{50} [a]	E IC_{50} [b]	pIC_{50} [c] Eq-1	pIC_{50} [c] Eq-2	PIC_{50} [c] Eq-3
H	0.75	5.87506	5.82	5.98	5.87
CH_3	0.25	5.39794	5.35	5.44	5.36
C_2H_5	0.10	5.0000	5.25	5.29	5.25
i-C_3H_7	0.25	5.39794	5.18	5.38	5.20
C_4H_9	0.050	4.6989	5.17	5.11	5.12
C_5H_{11}	0.050	4.6989	5.17	5.19	5012
C_6H_{13}	0.06	5.77815	5.17	5.88	5.51
cyc C_6H_{11}	0.12	5.07918	5.14	5.12	5008
$(CH_2)_2$ *cyc*-C_6H_{11}	1.0	6.000	5.18	5.11	5.10
C_7H_{15}	0.04	4.60205	5.18	5.22	5.11
$(CH_2)_2$ O $(CH_2)_3$ CH_3	0.060	5.39794	4.94	†	†
H_2CCH=CH $(CH_2)_3$ CH_3	0.050	5.0000	5.03	5.01	5.02
HC (CH_3) $CCCH_2CH_3$	0.25	5.07918	5.02	5.12	5.28
C_8H_{17}	0.12	4.95424	5.17	5.21	5.16
$(H_2C)_2$-N(R)-OO-C$(CH_3)_3$	0.090	4.653212	4.70	†	†
C_6H_5	0.40	5.60205	5.05	5.02	5.00
$(CH_2)_2C_6H_5$	0.404	4.60205	5.06	5.08	5.06
C_6H_4 (4-SCH_3)	0.30	5.47712	5.05	5.00	5.01
C_6H_4(2-SCH_3)	0.060	4.77815	5.05	4.88	4.78
C_6H_4(4-OCH_3)	0.040	4.60205	4.83	4088	4.69
C_6H_4(4-$NHCOCH_3$)	0.050	4.69897	4.68	4.71	4.69
C_6H_4(4-F)	0.075	4.87506	5.05	5.02	5.06

*Substituted groups. IC_{50} [a] = Dose in micro molar (mM) required to produce 50% inhibition (ref). E IC_{50} [b] = Experimental log molar dose. pIC_{50} [c] = predicted calculated values obtained by using Eqns. 1, 2 and 3. †Outlier compounds in deriving equations

QSAR analysis from the eight various descriptors,

TABLE 2: CALCULATED VALUES OF DESCRIPTORS FOR THE GIVEN SERIES OF COMPOUNDS

*FR	**Log MR	***F	#L	‡B5
0.23	0.0128	0.0	0.00	0.00
0.77	0.752	-0.04	0.1818	0.3096
1.43	1.128	-0.05	0.1818	0.5011
1.84	1.1749	-0.06	0.1818	0.5428
2.51	1.2926	-0.06	0.1818	0.6571
3.10	1.3848	-0.06	0.3096	0.7466
3.64	1.46029	-0.1	0.4082	0.8502
3.18	1.4281	-0.1	0.0755	0.5378
4.38	1.5571	-0.15	0.4698	0.7427
4.18	1.524	-0.14	0.4886	0.8842
1.65	1.4862	-0.03	0.6551	0.8722
2.83	1.4976	0.09	0.7160	0.8921
2.83	1.4966	0.02	0.8248	0.9425
5.07	1.6921	-0.12	0.5563	0.9395
0.42	1.5845	0.04	0.7474	0.9484
1.90	1.4041	0.08	0.0682	0.4928
2.98	1.5390	0.00	0.3096	0.8488
1.65	1.575	1.00	0.3820	0.7300
1.65	1.575	1.00	0.3820	0.7300
0.13	1.5005	0.34	0.3139	0.7143
-0.27	1.58024	0.36	0.3139	0.7574
1.29	1.4044	0.51	0.3139	0.5391

*Fragment substituent at R, **Log of molecular refractivity, ***field effect at R, #length of substituent at R, ‡Maximum width of substituents at R

many equations were generated. Using the 12 generated equations, not all the 22 analogues showed a significant cross correlation. Equation given below showed 72.9% of variance in the biological activity. BA = 0.6955MR1 - 0.1115Hdor1 - 0.1666F -5.7987 (1), n = 22, r = 0.729, r^2 = 0.537, f = 3.693, t = 1.922 and std = 0.337. If we see Table 1, we find that the IC_{50} is reduced by introduction of an electronegative atom (N, O) between ester chains in the substituents. Step by step, compounds 11 and 15 were eliminated as outliers by leave-one-out method to check the validity of model for significant correlation coefficient. BA = 0.8098 MR +-0.0385FR - 0.7764F - 5.8964 (2), n = 20, r = 0.912, r^2 = 0.831, f = 7.133, t = 2.671 and std = 0.64. The above-obtained equation, Eqn. 2, was found to be highly predictive and statistically significant, showing a positive value of MR at R, indicating good binding dispersion force between the analogues and the receptor. Table 1 shows the observed and the predictive values of biological activities after removal of outliers. In addition, the correlation coefficient 'r' accounts for 91.2% of variance in the biological activity, which is evident in Table 3, indicating that the biological activity would increase with increase in polarisability and steric bulk of the compounds within the series. For further investigation of MR at R, as it is positive, additional Sterimol parameters (B1, B5 and L) were subjected to QSAR analysis. The equation obtained was BA = 0.4664L + 0.9387B5 + 1.2162B1 - 5.9012 (3), n = 20, r = 0.874, r^2 = 0.764, f-test = 10.780, t-test = 3.283 and std = 0.214. The above equation is statistically significant, having good coefficient of determination; it indicates that the overall value of B5 (maximum width of substituent) is more contributive than L (length of substituent) along the axis of the parent skeleton - Table 4. From all the above observations, it is concluded that COX-2 inhibition by ester derivatives of indomethacin is highly correlated with the thermodynamic (MR) and Sterimol (B5, L) parameters, which indicates the importance of steric effect on the indomethacin substituents. Hence Eqns. 2 and 3 indicate that a lipophilic bulkier group width-wise is required for good biological activity. The above QSAR studies may throw some light on the substitutional requirement for further development and optimization of existing selective COX-2 inhibitors of this class of compounds for more potent activity.

TABLE 3: CORRELATION MATRIX OF VARIOUS PARAMETERS IN EQUATION 2

	*BA	#MR	†F	‡FR
BA	1	0.863	0.229	0.226
B1		1	0.241	0.486
L			1	0.357
B5				1

*Biological activity, †Field effect, #Molecular refractivity, ‡Fragment substituents

TABLE 4: CORRELATION MATRIX OF VARIOUS PARAMETERS IN EQUATION 3

	*BA	**B1	#L	†B5
BA	1	0.620	0.833	0.868
B1		1	0.162	0.221
L			1	0.211
B5				1

*Biological activity, **Width of substituents, #Length of substituents at R2, †Maximum width of substituents

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