QSAR Investigations on Benzylideneamino and Phenyliminomethyl Scaffolds for Selective COX-2 Inhibition: A Hansch Approach

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Abstract: Cyclooxygenase inhibitory and selectivity profile of a combined series of thirty one aryl sulphonamide compounds possessing 4-benzylideneamino or 4-phenyliminomethyl scaffolds were subjected to QSAR study using Hansch approach. The compounds in the selected series were characterized using classical aromatic substituent constants like hydrophobicity (π), molar refractivity (MR), Hammett electronic (σ), electronic field effect (F), resonance effect (R), and some indicator variables encoding molecular group contributions. Statistically significant QSAR models were generated using multiple regression analysis and cross-validation tools. The derived QSAR models demonstrated that the COX-2 selectivity over COX-1 is predominantly influenced by the central core –N=C- of the diaryl system. Further, the study also indicated that the electronic properties and structural variation in the para position of the phenyl ring (B) governs the COX-2 selectivity of the title compounds. The derived results reveal the important structural features significant for improved COX-2 inhibitory activity and selectivity of these novel aryl sulfonamides.

Key Words: QSAR, COX-1, COX-2, Selectivity, NSAIDs, 4-benzylideneamino, 4-phenyliminomethyl, Aryl sulfonamide.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most effective therapeutics for the treatment of pain, fever, acute and chronic inflammation diseases like rheumatoid arthritis, osteo arthritis, etc [1]. However, the clinical utility of these drugs is seriously limited by increased risk of peptic ulcers, renal insufficiency and cardiac toxicity. NSAIDs exhibit their therapeutic action by inhibiting the formation of prostaglandins in the arachidonic acid pathway [2]. The rate limiting step in the synthesis of prostaglandins and thromboxanes is the conversion of arachidonate to prostaglandin H_2 which is catalyzed by cyclooxygenase (COX) enzymes. The classical non-steroidal anti-inflammatory drugs (NSAIDs) inhibit both isoforms of prostaglandin synthase namely cyclooxygenase-1 and cyclooxygenase-2. COX-1 is constitutively expressed and is responsible for the maintenance of normal physiological functions whereas COX-2 is induced upon inflammatory stimuli and is responsible for the progression of inflammation [3]. Since the discovery of inducible isozyme COX-2 and the advent of several selective COX-2 inhibitors, selective inhibition of COX-2 over COX-1 continues to be an attractive target for anti-inflammatory therapy. Some of the selective COX-2 inhibitors with proven therapeutic utility for the treatment of inflammation include Celecoxib [4] (Celebrex®), rofecoxib [5] (Vioxx®) and valdecoxib [6] (Bextra®). Recently, Rofecoxib(Vioxx®) and valdecoxib (Bextra®) were withdrawn from the pharma market due to increased cardiac incidence associated with theses drugs.

Plentiful information regarding the diaryl substituted compounds as selective COX-2 inhibitors are found in literature. X-ray crystallographic studies [7, 8] suggest that it is a single amino acid difference that is primarily responsible for the selectivity of most selective COX-2 inhibitors: at position 523 is an isoleucine molecule in COX-1 and valine in COX-2. The amino acid valine, which is smaller than isoleucine by a single methyl group in COX-2, allows access to a side pocket, the binding site of most selective COX-2 inhibitors, Whereas the bulkier isoleucine in COX-1 blocks the access to the side pocket. Compounds with a central heterocyclic or carbocyclic core bearing two vicinal aryl rings have been studied in a greater extent for selective COX-2 inhibition [9, 10]. Substitution of one of the aromatic rings with a sulphonamido or methyl sulphonyl group is crucial for selective COX-2 inhibition. The central heterocyclic core is essential in properly orienting the aromatic rings in the COX binding site. However, a search of literature for novel anti-inflammatory compounds yielded a structurally distinct diaryl compounds possessing a central template as (–C=N-) and (–N=C-) for selective cyclooxygenase inhibition. Hence, we focused our attention in these interesting novel diaryl systems as a part of our on going research efforts [11-17]. In this communication, we report QSAR studies of a series of 4-benzylideneamino and 4-phenyliminomethyl aryl sulfonamides with classical 2D descriptors and some structural variables [18].

2. MATERIALS AND METHODS

A set of thirty one aryl sulfonamides comprising of 4-benzylideneamino and 4-phenyliminomethyl central core reported by S. J. Lin *et al.*, [18] were considered for exploring COX-2 selectivity requirements. The structures, biological activity and predicted activity data are given in Table **1**. The substitution pattern of these compounds in the parent nucleus prompted us to adopt a classical Hansch QSAR analysis. COX-1 and COX-2 inhibitory activity was reported as IC_{50} in μM units, where IC_{50} is the drug concentra-

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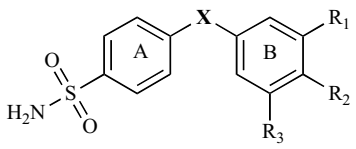
Table 1. Structure, Observed and Predicted Cyclooxygenase Inhibitory Activity and Selectivity Through Derived QSAR Models



Compd.	Structure				Observed Activity			Predicted Activity		
	R_1	R_2	R_3	X	$pIC_{50(COX-1)}$	$pIC_{50(COX-2)}$	$log_{(COX-1/COX-2)}$	COX-1[a]	COX-2[b]	Selectivity[c]
1	H	H	H	-N=C-	3.97	5.54	1.58	3.78	5.54	1.71
2	H	F	H	-N=C-	3.8	5.65	1.85	3.8	5.49	1.68
3	H	$COOCH_3$	H	-N=C-	3.74	5.56	1.83	3.8	5.54	1.69
4	H	NO_2	H	-N=C-	3.85	5.53	1.67	3.79	5.6	1.70
5*	NO_2	H	H	-N=C-	3.98	5.17	1.19	3.78	-	1.37
6	H	$N(CH_3)_2$	H	-N=C-	3.71	5.47	1.76	3.81	5.4	1.69
7	H	OH	H	-N=C-	3.83	5.47	1.64	3.79	5.49	1.70
8	H	CF_3	H	-N=C-	3.74	5.34	1.6	3.8	5.37	1.71
9	H	CH_3	H	-N=C-	3.72	5.31	1.59	3.8	5.45	1.71
10*	H	OCH_3	H	-N=C-	3.51	5.01	1.5	3.57	-	1.72
11	OCH_3	H	H	-N=C-	3.42	5.26	1.85	3.59	5.4	1.61
12	OH	H	H	-N=C-	4.42	5.56	1.14	4.23	5.49	1.01
13	OH	OH	H	-N=C-	4.64	5.55	0.91	4.7	5.64	1.12
14	OCH_3	OH	H	-N=C-	4.11	5.53	1.42	3.89	5.47	1.64
15*	COOH	OH	H	-N=C-	4.07	6.13	2.06	4.19	-	-
16*	OC_2H_5	OH	H	-N=C-	4.32	5.43	1.11	4.12	5.5	-
17	OH	OCH_3	H	-N=C-	4.36	5.46	1.1	4.48	5.48	1.03
18	OCH_3	OCH_3	H	-N=C-	3.96	5.51	1.55	3.92	5.48	1.63
19*	OCH_3	H	OCH_3	-N=C-	3.96	5.47	1.51	-	5.4	1.55
20	OCH_3	OCH_3	OCH_3	-N=C-	3.78	5.53	1.76	3.96	5.55	1.53
21	OCH_3	OH	OCH_3	-N=C-	3.81	5.57	1.76	3.95	5.52	1.53
22	H	H	H	-C=N-	4.2	5.51	1.31	4.28	5.5	1.13
23	H	F	H	-C=N-	4.1	5.36	1.26	4.29	5.38	1.13
24	H	CH_3	H	-C=N-	4.2	5.34	1.14	4.28	5.34	1.15
25	H	CF_3	H	-C=N-	4.36	5.18	0.83	4.26	5.23	1.18
26*	H	$N(CH_3)_2$	H	-C=N-	4.19	5.71	1.52	4.28	-	1.10
27*	H	OH	H	-C=N-	4.29	5.29	1.01	4.26	-	1.16
28	H	OCH_3	H	-C=N-	4.22	5.38	1.17	3.96	5.31	1.14

(Table 1. Contd….)

Compd.	Structure				Observed Activity			Predicted Activity		
	R_1	R_2	R_3	X	$pIC_{50(COX-1)}$	$pIC_{50(COX-2)}$	$log_{(COX-1/COX-2)}$	COX-1[a]	COX-2[b]	Selectivity[c]
29	OCH_3	OCH_3	H	-C=N-	4.5	5.37	0.86	4.36	5.47	1.10
30	$COOCH_3$	OH	H	-C=N-	4.62	5.5	0.89	4.64	5.43	0.93
31	H	$COOCH_3$	H	-C=N-	4.25	5.43	1.18	4.27	5.38	1.14

Note: [a]COX-1 inhibitory activity predicted through QSAR model-2.

[b]COX-2 inhibitory activity predicted through QSAR model-4.

[c]COX-2 inhibitory activity predicted through QSAR model-5.

*outlier compounds detected while deriving QSAR models.

tion required to inhibit 50% of the enzymes. For the present QSAR study the reported IC_{50} was converted to negative logarithm (pIC_{50}) in molar units. QSAR models for COX-2 selectivity over COX-1 were formulated by considering the log of reported selectivity ratios, *i.e.* log [COX-1/COX-2] as dependent variable. The various aromatic substituent constants used in the present study were derived from literature [19]. The predictor variables used for QSAR analysis include the hydrophobicity (π), molar refractivity (MR), Hammett electronic constant (σ), electronic field effect (F), resonance (R) effects and some structural variables or indicator variables encoding the group contribution of the title compounds. The physicochemical descriptors ClogP and CMR were calculated using ChemOffice 2001 molecular modeling software version 6.0, supplied by Cambridge Soft Corporation, USA. The physico-chemical descriptors and indicator variables calculated for the compounds are given in Table **2**.

QSAR models were built using the regression analysis module of Systat version 10.2. The correlation matrix was used to correlate the biological activity with various physicochemical and structural predictor variables. Descriptors with inter correlation above $|r|>0.5$ were not considered for formulation of QSAR models. The predictor variables with a "*p*" value greater than 0.05 were eliminated whilst deriving the QSAR models in order to assure their statistical reliability. The statistical significance of the derived QSAR models was gauged by the statistical parameters viz., correlation coefficient (r) or coefficient of determination (r^2), standard error of estimate (s), variance ratio (F) and student's t-distribution. Durbin-Watson (DW) test [20] was employed to check the serial correlation in residuals. A data point is considered as an outlier if it has a large magnitude (when the residual value exceeds twice the standard error of estimate of the model). Self-consistency of the derived models is ensured using the leave-one-out (loo) process and the predictability of each model was assessed by cross-validated r^2 or q^2. Standard predicted residual sum of squares (*Spress)* and standard deviation of error of prediction (*SDEP)* are the other supportive cross validation parameters calculated for each models.

3. RESULTS AND DISCUSSION

Several statistically significant QSAR models were developed considering pIC50(COX-2 HWB), pIC50(COX-1 HWB), log[COX-1/COX-2] as dependent variables and various aromatic substituent constants, indicator variables as independent variables. The individual QSAR models developed are discussed below:

$$pIC50_{(COX-1)} = 0.323(\pm0.058)\ I_{pm} + 0.506(\pm0.086)\ I_{mOH} - 0.185(\pm0.057)\ I_{OCH3}$$

$$-0.452(\pm0.054)\ I_{(-N=C-)} + 4.265(\pm0.044)$$

n= 31, r = 0.916, r^2_{Adj} = 0.814, s = 0.134, $F_{(4, 26)}$ = 33.866, p = 0.000, q2 = 0.764,

Spress = 0.162, SDEP = 0.148, DW=2.089. (Model 1)

The figures within the parentheses following the coefficient terms are the standard error of the regression terms and the constants. Model 1 is a tetra parametric model, which shows the contribution of various indicator variables for COX-1 inhibitory activity. Indicator variables are often used in QSAR models to explain the structural influence on the biological activity. An indicator variable takes the value of 1 for the presence/absence of a particular structure and 0 for others. The positive contribution of Ipm in this QSAR model shows the presence of any substitution on the phenyl ring "B" at both *meta* and *para* position enhances COX-1 inhibitory activity. The other indicator variables I_{mOH} and I_{OCH3} impart positive and negative contribution respectively; it suggests that the presence hydroxyl group at *meta* position and the absence of methoxy group in the aromatic ring "B" favours the COX-1 inhibitory activity. The negative coefficient for the term $I_{(-N=C-)}$ suggests that –N=C- as central core(X) in the aryl sulfonamides is detrimental for the COX-1 inhibitory activity. The structural variables alone in the model-1 explain 81.4% variance in COX-1 inhibitory activity.

$$pIC50_{(COX-1)} = 0.368(\pm0.052)\ I_{pm} + 0.511(\pm0.074)\ I_{mOH} - 0.240(\pm0.052)\ I_{OCH3} - 0.470(\pm0.047)\ I_{(-N=C-)} + 4.268(\pm0.038)$$

n= 30, r = 0.941, r^2_{Adj} = 0.867, s = 0.115, $F_{(4,25)}$ = 48.064, p = 0.000, q2 = 0.827,

Spress = 0.141, SDEP = 0.129, DW=2.042. (Model-2)

Model-2 is a tertaparametric equation developed for 30 compounds by omitting an outlier compound (**19**) with overall statistical significance. The model explains 86.7% variance in cyclooxygenase-1 inhibitory activity. The predictive ability of the model is also high as compared to the previous

Table 2. Predictor Variables for Cyclooxygenase Inhibitory Activity and Selectivity of Aryl Sulfonamides

Compd	Log *P*	$I_{(-N=C-)}$	I_{mono}	I_{pm}	I_{mOH}	I_{OCH3}	$I_{m-\sigma}$
1	1.23	1	1	0	0	0	0
2	1.37	1	1	0	0	0	0
3	1.2	1	1	0	0	0	0
4	0.97	1	1	0	0	0	0
5	0.97	1	1	0	0	0	0.71
6	1.91	1	1	0	0	0	0
7	1.46	1	1	0	0	0	0
8	2.11	1	1	0	0	0	0
9	1.73	1	1	0	0	0	0
10	1.57	1	1	0	0	1	0
11	1.57	1	1	0	0	1	0.12
12	1.46	1	1	0	1	0	0.12
13	1.13	1	1	1	1	0	0.12
14	1.32	1	0	1	0	0	0.12
15	2.04	1	0	1	0	0	0.37
16	1.85	1	0	1	0	0	0.1
17	1.32	1	0	1	1	1	0.12
18	1.32	1	0	1	0	1	0.12
19	1.68	1	0	0	0	1	0.24
20	0.97	1	0	1	0	1	0.24
21	1.07	1	0	1	0	1	0.24
22	1.76	0	0	0	0	0	0
23	2.07	0	1	0	0	0	0
24	2.26	0	1	0	0	0	0
25	2.94	0	1	0	0	0	0
26	1.93	0	1	0	0	0	0
27	1.09	0	1	0	0	0	0
28	1.78	0	1	0	0	1	0
29	1.44	0	0	1	0	1	0.12
30	2.05	0	0	1	0	0	0.37
31	2.04	0	1	0	0	0	0

model as established by high q^2 value (0.827). The correlation plot between the COX-1 observed and predicted activity by above QSAR model is shown in Fig. (**1**).

$pIC50_{(COX\text{-}2)}$ = -0.099(±0.059) log *P* - 0.172(±0.90) I_{ma} - 0.622(±0.170) I_{mOH}

+0.736(±0.146) m-HD + 5.595(±0.101)

n= 31, r = 0.736, r^2_{Adj} = 0.471, s = 0.141, $F_{(4,26)}$ = 7.668, p = 0.000, DW=2.007. (Model-3)

Model-3 is generated for COX-2 inhibitory activity of all 31 compounds in the series. Unfortunately the derived model is found unacceptable in all statistical respects. It explains only 47.1% variance in COX-2 inhibitory activity with four predicator variables namely log *P*, I_{ma}, $I_{m\text{-}OH}$ and m-HD. Above all, the variables in the model $I_{m\text{-}OH}$ and m-HD are highly inter-correlated as it is reflected from the Pearson correlation analysis value 0.850> 0.5. The t statistics and p statistics of the descriptor log *P* in the model is insignificant since the calculated t-value -1.668 is less than tabulated t-

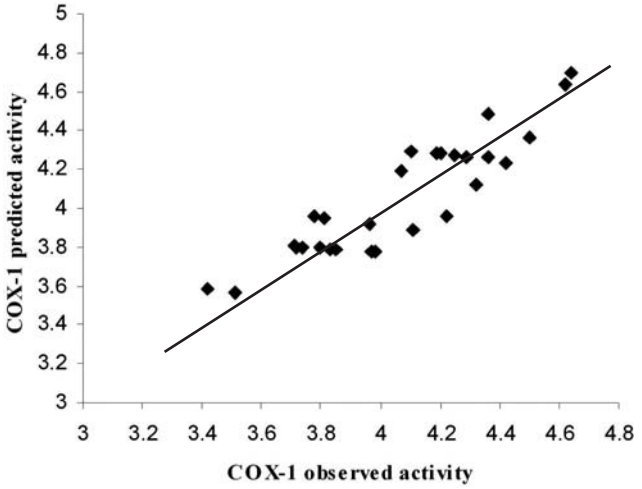


Fig. (1). Correlation between COX-1 observed and loo predicted activity through QSAR model-2.

value even at 95% confidence interval and the *P*-value is 0.107>0.05. furthermore, no good correlation could be obtained for COX-2 inhibitory activity by considering all the reported 31 compounds. In order to develop a statistically significant and good predictive COX-2 inhibitory model some of the data points were omitted.

$pIC50_{(COX\text{-}2)}$ = -0.191(±0.030) log *P* -0.064(±0.031) I_{mono} - 0.104(±0.033) I_{OCH3} + 5.836(±0.058)

n= 26, r = 0.825, r^2_{Adj} = 0.636, s = 0.066, $F_{(3,22)}$ = 15.588, p = 0.000, q2 = 0.555,

Spress = 0.078, SDEP = 0.072, DW=2.187. (Model-4)

Model-4 is a triparametric equation developed for COX-2 inhibitory activity after deleting five outlying data points from the original data set. Outliers were detected based on their high residual values. Model-4 explains 63.6% variance in COX-2 inhibitory activity. The correlation between the COX-2 observed and predicted activity by QSAR model-4 is shown in Fig. (**2**). The thermodynamic descriptor log *P* is a measure of hydrophobicity of whole molecules. The negative

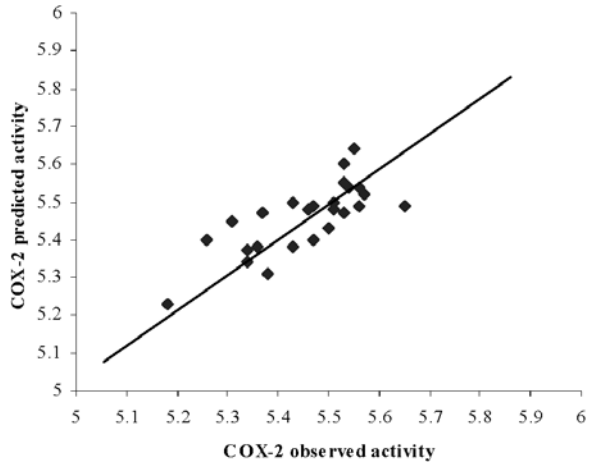


Fig. (2). Correlation between COX-2 observed and loo predicted activity through QSAR model-4.

contribution of log *P* suggests that increasing hydrophobicity of the molecules will decreases the COX-2 inhibitory activity. The negative coefficients of predictor variables I_{mono} and I_{OCH3} indicates that mono substitution pattern and presence of methoxy group at any position in the phenyl ring "B" decreases the COX-2 inhibitory activity.

$logIC50_{(COX\text{-}1/COX\text{-}2)}$ = - 0.574(±0.105) I_{mOH} - 0.618(±0.207) σ_m + 0.551(±0.068) $I_{(-N=C-)}$ + 1.147(±0.054)

n= 29, r = 0.875, r^2_{Adj} = 0.737, s = 0.166, $F_{(3,25)}$ = 27.122, p = 0.000, q2 = 0.695,

Spress = 0.189, SDEP = 0.176, DW=2.185. (Model-5)

Model-5 is generated to explore the COX-2 selectivity requirements of novel diaryl sulphonamide derivatives. The model explains 73.7% variance of COX-2 selectivity over COX-1. The negative coefficient of an indicator variable I_{mOH} suggests that presence of hydroxyl group at *meta* position of phenyl ring "B" decreases the COX-2 selectivity. The negative coefficient of physicochemical constant σ_m in the model implies that electron releasing substituents on meta position of the phenyl ring might impart COX-2 selectivity. The aryl sulfonamides possessing central core as –N=C- favours the COX-2 selectivity as evident from positive coefficient of the predictor variable $I_{(-N=C-)}$ in the above QSAR model. The correlation plot between the COX-1/COX-2 selectivity ratio and its predicted activity by above QSAR model-5 is shown in Fig. (**3**).

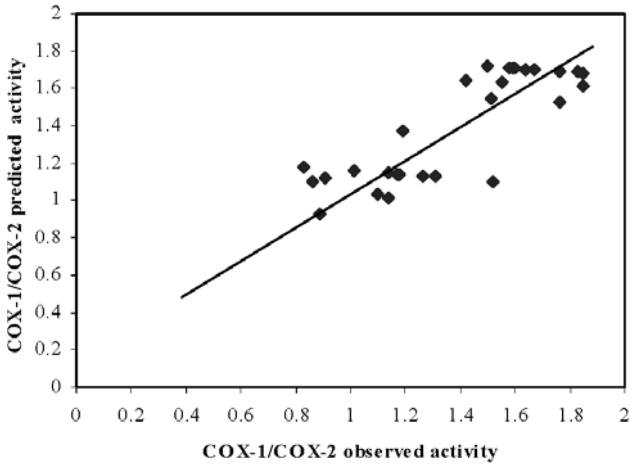


Fig. (3). Correlation between COX-1/COX-2 observed and loo predicted activity through QSAR model-5.

In the present study, a series of 4-benzylideneamino and 4-phenyliminomethyl aryl sulfonamides recently reported as selective cyclooxygenase inhibitors were analyzed quantitatively with various classical physicochemical descriptors and indicator variables using Hansch approach. The QSAR investigations revealed 4-benzylideneamino structure (the structural pattern –N=C- between the aryl rings) is essential for COX-2 selectivity and the same is detrimental to COX-1 inhibitory activity. The electronic influence and para substitution play a crucial role in governing the COX-2 selectivity. Substitutions like hydroxyl group at *meta* position of phenyl ring (B) has negative effect on COX-2 selectivity whereas

the same substituent has positive effect on COX-1 inhibitory activity. The electron donating group methoxy at both *meta* and *para* has a negative impact on COX-1 inhibitory activity. The derived results manifest the structural requirements for improved COX-2 inhibitory activity and selectivity of these novel lead compounds.

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