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Inhibitory mode of 2-acetoxyphenyl alkyl sulfides against COX-1 and COX-2: QSAR analyses

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Abstract—Selective inhibition of cyclooxygenase-2 (COX-2) inhibitors is an important strategy in design of potent anti-inflammatory compounds with significantly reduced side effects. Therefore, QSAR studies of 2-acetoxyphenyl alkyl sulfides were performed using Bioloom, CAChe 6.1, and Dragon 3.0 for the COX-2 and COX-1 inhibition. The analyses have produced good predictive and statistically significant QSAR models. These studies suggest that lipophilicity affects both COX-1 and COX-2 inhibition in different manner and indicator variables like presence of aromatic ring and triple bond play an important role in COX-2 selectivity. Branching in the molecule, higher path length 6 rich in polarizability, and lesser number of carbonyl groups would be favorable for COX-2 inhibition. Fourth highest eigenvalue of burden matrix corresponding to atomic mass would be favorable for COX-2 inhibition and sixth lowest eigenvalue of burden matrix corresponding to Sanderson electronegativities is conducive for COX-1 inhibition. Lower path length 3 rich in atomic mass and lesser degree of unsaturation in the molecule would be favorable for COX-1 inhibition.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of pain, pyrexia, inflammation, rheumatoid arthritis, and osteoarthritis. NSAIDs block biosynthesis of prostaglandins by inhibiting enzyme prostaglandin H_2 endoperoxide synthase (PGHS) or cyclooxygenase (COX).[1] COX enzyme exists as two related but distinct isoforms designated as COX-1 and COX-2.[2–4] COX-1 is a constitutive enzyme and produces 'housekeeping' prostaglandins critical to the maintenance of normal renal function, gastric mucosal integrity, vascular hemostasis, and the autocrine response to circulating hormones. On the other hand, COX-2 is the induced in response to inflammatory stimuli.[5] Selective inhibition of COX-2 provides a new class of anti-inflammatory and analgesic compounds with significantly reduced side effects such as gastrointestinal ulcer and renal dysfunction.[6] New therapeutic targets of COX-2 inhibitors are colon cancer and Alzheimer's disease.[2,7–9]

Several classes of compounds have been developed as selective COX-2 inhibitors: (1) diarylheterocycles such as celecoxib, Dup-697, and diarylisoxazoles, (2) acidic sulfonamides such as NS-398, and (3) modified NSAIDs (traditional) such as indomethacin analogues.[10–17] QSAR studies of meclofenamic acid analogues, oxazoles, pyrazoles, imidazole, thiophenes, and furanones as selective COX-2 inhibitors, have also been reported.[18–21] No QSAR work has been reported so far for 2-acetoxyphenyl alkyl sulfides.

In a series of 2-acetoxyphenyl alkyl sulfides, most potent compound selectively inactivates COX-2 by acetylating the same serine residue that aspirin acetylates and has ability to attenuate growth of COX-2 expressing colon cancer cells.[22] Therefore, quantitative structure–activity relationship (QSAR) studies have been done, in order to explore the substitutional requirement of *S*-alkyl chain and carbonyl moiety of 2-acetoxyphenyl alkyl sulfides. Structures of these compounds are presented in Table 1.

The COX-1 and COX-2 inhibition of 2-acetoxyphenyl alkyl sulfides has been reported in terms of 50% inhibitory concentration of enzyme (IC_{50} in μM). The enzyme inhibition data have been converted to negative logarithmic value (concentration in M) and then used for

Abbreviations: COX, cyclooxygenase; QSAR, quantitative structure–activity relationship; LOO, leave-one-out; SMILES, Simplified Molecular Input Line Entry Specification.

Keywords: QSAR; COX-1 and COX-2 inhibitor; Acetoxyphenyl alkyl sulfide.

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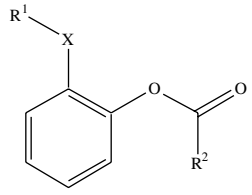
Table 1. Structural features of 2-acetoxyphenyl alkyl sulfide derivatives



01–29

Compound	R^{1a}	R^{2b}	X
01	CH_3	CH_3	S
02	CH_3	CF_3	S
03	CH_3	CH_2Cl	S
04	CH_3	CH_2Br	S
05	C_2H_5	CH_3	S
06	$(CH_2)_2CH_3$	CH_3	S
07	$(CH_2)_3CH_3$	CH_3	S
08	$(CH_2)_4CH_3$	CH_3	S
09	$(CH_2)_5CH_3$	CH_3	S
10	$(CH_2)_6CH_3$	CH_3	S
11	$(CH_2)_6CH_3$	CH_3	Se
12	$CH_2C_6H_5$	CH_3	S
13	$(CH_2)_2C_6H_5$	CH_3	S
14	$(CH_2)_6I$	CH_3	S
15	$(CH_2)_6Br$	CH_3	S
16	$(CH_2)_5Br$	CH_3	S
17	$(CH_2)_5COOH$	CH_3	S
18	$(CH_2)_5OCOCH_3$	CH_3	S
19	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	S
20	$CH_2CH{=}CH(CH_2)_3CH_3$	CH_3	S
21	$CH_2C{\equiv}CH$	CH_3	S
22	$CH_2C{\equiv}CCH_3$	CH_3	S
23	$CH_2C{\equiv}CCH_2CH_3$	CH_3	S
24	$CH_2C{\equiv}C(CH_2)_2CH_3$	CH_3	S
25	$CH_2C{\equiv}C(CH_2)_3CH_3$	CH_3	S
26	$(CH_2)_2C{\equiv}C(CH_2)_2CH_3$	CH_3	S
27	$CH(CH_3)C{\equiv}C(CH_2)_3CH_3$	CH_3	S
28	$CH_2C{\equiv}C(CH_2)_4CH_3$	CH_3	S
29	$CH_2C{\equiv}C(CH_2)_3CH_3$	CH_2Br	S

[a] *S*-Alkyl chain.
[b] Carbonyl moiety.

subsequent QSAR analyses as response variable. COX-2 inhibitory data have been available for 29 compounds and COX-1 inhibitory data have been available for 26 compounds. This compound set was first divided into two subsets based on hierarchical clustering of biological data to cover the whole activity range for training and test set. Models were constructed based on the training set and the generated models were then validated: internally (using the leave-one-out technique) and externally (predicting the activities of the test set). All of the Molecular Modeling studies, reported herein, and descriptors' calculation were performed running on a Pentium 4 processor (CPU 3.00 GHz HT) using Bioloom (BioByte Corporation),[23,27] CAChe 6.1 (Fujitsu Limited)[24,27] and Dragon 3.0 (Milano Chemometrics).[25–29] The descriptors present in the model along with definition are presented in Table 2.

The relationship between response variable (pC_1 and pC_2 as dependent variables for COX-1 and COX-2 inhibition, respectively) and various physicochemical and structural descriptors (as independent variables) is established by step-wise linear multiple regression analysis using Systat 10.2 and Valstat.[30,31] Significant descriptors were chosen on the basis of statistical data of analysis. Inter-correlation between these descriptors was checked for independence of the variables. The predictive power of equations was validated by leave-one-out (LOO) cross-validation method,[32] standard deviation based on predicted residual sum of squares (S_{PRESS}), and standard deviation of error of prediction (S_{DEP}).

The statistical quality of the developed equations was judged by the parameters like explained variance (%EV), correlation coefficient (r), standard error of estimate (s), variance ratio (F) at specified degrees of freedom (df), 95% confidence intervals of the regression coefficients, LOO cross-validation r^2 (Q^2), S_{PRESS}, and S_{DEP}. The number of developed equations was high, so further analysis was based on statistically significant parameters viz. r, s, Q^2, F, and inter-correlation among parameters used in the generation of an equation (|ICAP|). Among several generated models, six best QSAR models were selected for discussion, which are presented in Table 3, and their calculated and predicted biological activity are presented in Tables 4 and 5.

Here, we are reporting QSAR study of COX-1 and COX-2 inhibition using Hansch analysis and then mixed approach based on Hansch and Fujita-Ban anal-

Table 2. Definitions of molecular descriptors present in the models

Descriptors[a]	Definition (descriptor class)
CLOGP	Calculated logarithm of partition coefficient (lipophilicity)
SI2	a topological index that quantifies shape of the chemical sample (shape index)
DE	Dielectric energy is a portion of the total energy of a molecule embedded in a dielectric (energy)
I_1	Indicator variable having value 1 if aromatic ring is present at *S*-alkyl chain, value 0 otherwise
I_2	Indicator variable having value 1 if triple bond is present at *S*-alkyl chain, value 0 otherwise
X2A	Average connectivity index chi-2 (topological)
O-058	O = (atom-centered fragments)
BEHm4	Highest eigenvalue no. 4 of burden matrix/weighted by atomic masses (BCUT)
BELe6	Lowest eigenvalue no. 6 of burden matrix/weighted by atomic Sanderson electronegativities (BCUT)
Ui	Unsaturation index (empirical descriptors)
GATS3m	Geary autocorrelation-lag 3/weighted by atomic masses (2D autocorrelation)

[a] Refs. 23–25.

Table 3. The data of the statistically significant models[a,b, c]

No.	Equation statistics				Inter. valid.[d]		Exter. valid.[e]	
	n	*r*	*s*	*F*	Q^2	S_{PRESS}	*n*	r^2
COX-1 inhibition								
1	20	0.83	0.31	19.22	0.59	0.36	6	0.70
2	20	0.83	0.32	18.48	0.60	0.38	6	0.54
3	20	0.91	0.24	26.80	0.74	0.30	6	0.89
COX-2 inhibition								
4	22	0.93	0.34	25.35	0.76	0.43	7	0.72
5	22	0.93	0.32	28.22	0.79	0.41	7	0.53
6	22	0.93	0.31	39.13	0.69	0.36	7	0.90

[a] Chance < 0.001.
[b] Number of outliers = 0.
[c] $|ICAP| \leqslant 0.42$.
[d] Internal validation in the training set.
[e] External validation using test set.

Table 4. Observed, calculated, and predicted COX-1 inhibition of 2-acetoxyphenyl alkyl sulfides

Compound	Obs.[a,b]	Cal.[c]	Pred.[d]	Cal.[e].	Pred.[f]	Calc.[g]	Pred.[h]
02	3.59	3.83	—	4.16	—	3.56	—
03[i]	3.41	—	3.42		3.82	—	3.66
04	3.49	3.55	—	3.70	—	3.42	—
05	3.43	3.80	—	3.76	—	3.71	—
06	4.18	4.21	—	4.02	—	4.59	—
07[i]	4.40	—	4.53	—	4.32	—	4.87
08	5.30	4.74	—	4.76	—	4.97	—
09	5.10	4.87	—	4.81	—	4.98	—
10	5.22	4.89	—	5.23	—	5.00	—
11	4.92	4.82	—	4.92	—	5.00	—
14	4.15	4.81	—	4.60	—	4.04	—
15	4.60	4.84	—	4.80	—	4.60	—
16	4.47	4.69	—	4.35	—	4.59	—
17[i]	4.30	—	3.95	—	3.82	—	4.71
18	4.30	4.23	—	4.29	—	4.79	—
19[i]	4.66	—	4.29	—	4.74	—	4.99
20	4.66	4.89	—	4.94	—	4.72	—
21	4.40	3.86	—	3.96	—	4.01	—
22	4.46	4.26	—	4.14	—	4.54	—
23	4.70	4.56	—	4.34	—	4.73	—
24	4.85	4.77	—	4.70	—	4.77	—
25	4.77	4.87	—	4.86	—	4.77	—
26	4.74	4.76	—	4.94	—	4.71	—
27	4.82	4.89	—	4.86	—	4.67	—
28[i]	4.48	—	4.90	—	5.10	—	4.85
29[i]	4.70	—	4.90	—	4.97	—	4.71

[a] Negative logarithmic value of IC_{50} (in moles) [$pC_1 = -\log_{10}IC_{50}$ (for COX-1)].
[b] Ref. 22.
[c] Calculated (Cal.) from Eq. 1
[d] Predicted (Pred.) from Eq. 1.
[e] Calculated (Cal.). from Eq. 2
[f] Predicted (Pred.) from Eq. 2.
[g] Calculated (Cal.). from Eq. 3.
[h] Predicted (Pred.) from Eq. 3.
[i] Compounds of test set.

Table 5. Observed, calculated, and predicted COX-2 inhibition of 2-acetoxyphenyl alkyl sulfides

Compound	Obs.[a,b]	Cal.[c]	Pred.[d]	Cal.[e]	Pred.[f]	Cal.[g]	Pred.[h]
01[i]	3.60	—	3.15	—	3.35	—	3.48
02	3.59	3.88	—	3.86	—	3.51	—
03	3.44	3.32	—	3.67	—	3.10	—
04	3.29	3.51	—	3.58	—	3.45	—
05	3.70	3.84	—	3.62	—	3.84	—
06	4.18	4.40	—	3.97	—	4.42	—
07	4.47	4.81	—	4.34	—	4.78	—
08[i]	5.30	—	5.08	—	5.02	—	5.09
09	5.46	5.22	—	5.01	—	5.23	—
10	5.70	5.22	—	5.48	—	5.32	—
11[i]	4.92	—	5.08	—	5.26	—	5.32
12	3.60	3.66	—	3.69	—	3.80	—
13	4.00	3.94	—	3.91	—	3.96	—
14[i]	5.00	—	5.16	—	5.02	—	5.38
15	4.92	5.20	—	5.16	—	5.38	—
16	5.02	5.02	—	4.67	—	5.27	—
17	4.30	4.04	—	4.43	—	4.30	—
18[i]	4.30	—	4.41	—	4.94	—	4.38
19	5.15	4.49	—	5.12	—	5.32	—
20	4.96	5.22	—	5.27	—	5.32	—
21	4.60	4.30	—	4.39	—	4.44	—
22	4.70	4.84	—	4.68	—	4.79	—
23	5.30	5.23	—	4.98	—	5.08	—
24	5.52	5.49	—	5.41	—	5.22	—
25	6.10	5.61	—	5.68	—	5.32	—
26	5.19	5.48	—	5.74	—	5.32	—
27	5.15	5.61	—	5.68	—	5.18	—
28[i]	5.15	—	5.58	—	6.03	—	5.41
29[i]	4.59	—	5.61	—	5.93	—	4.69

[a] Negative logarithmic value of IC_{50} (in moles) [$pC_2 = -\log_{10}IC_{50}$ (for COX-2)].
[b] Ref. 22.
[c] Calculated (Cal.). from Eq. 4.
[d] Predicted (Pred.) from Eq. 4.
[e] Calculated (Cal.). from Eq. 5.
[f] Predicted (Pred.) from Eq. 5.
[g] Calculated (Cal.). from Eq. 6.
[h] Predicted (Pred.) from Eq. 6.
[i] Compounds of test set.

ysis. The statistically significant equation (Eq. 1), which contains calculated log of partition coefficient, is as follows.

$$pC_1 = 1.050(\pm 0.951) + 1.624(\pm 1.150)CLOGP - 0.171(\pm 0.160)(CLOGP)^2 \quad (1)$$

$n = 20$, $r = 0.83$, $s = 0.31$, $F = 19.22$, Chance < 0.001, $Q^2 = 0.59$, $S_{PRESS} = 0.36$, and $S_{DEP} = 0.33$

Eq. 1 is capable to predict 59.0% and explain 69.3% of variance of COX-1 inhibition. This model suggests that

there is a non-linear relationship with CLOGP, which is related to molecules' trend to partition into bilayers. It is most interesting and a well-known free energy related parameter.

When other relationships were searched with other descriptors obtained from CAChe, a significant Eq. 2 was developed that contains shape index (basic kappa, order 2) and dielectric energy, which is able to explain 81.0% of variance of COX-1 inhibition. This equation is having internal predictivity as shown by good Q^2 value of 0.54. The parameters used in the equation are almost independent [inter-correlation among the parameters (|ICAP|) $\leqslant$ 0.42].

$$pC_1 = 3.775(\pm1.019) + 0.278(\pm0.098)SI2 + 3.679(\pm2.275)DE \quad (2)$$

$n = 20$, $r = 0.83$, $s = 0.32$, $F = 18.48$, Chance < 0.001, $Q^2 = 0.54$, $S_{PRESS} = 0.38$, and $S_{DEP} = 0.35$

SI2 [shape index (basic kappa, order 2)] is a topological parameter. DE [dielectric energy] is a portion of the total energy of a molecule embedded in a dielectric. It is the energy of stabilization arising from the interaction of the charges in the solute with the induced charges on the solvent accessible surface (SAS) plus the electrostatic energy due to the charges on the SAS zinteracting with each other.

When other relationships were searched with the descriptors obtained from Dragon, a highly significant equation containing BELe6, GATS3m, and Ui was found, which is able to explain 83.4% of variance of COX-1 inhibition. This equation is having high internal predictivity as shown by good Q^2 value of 0.74. The parameters used in the equation are almost independent (|ICAP| $\leqslant$ 0.40).

$$pC_1 = 9.466(\pm5.197) + 2.573(\pm0.632)BELe6 - 62.753(\pm33.604)GATS3m - 1.961(\pm1.691)Ui \quad (3)$$

$n = 20$, $r = 0.91$, $s = 0.24$, $F = 26.80$, Chance < 0.001, $Q^2 = 0.74$, $S_{PRESS} = 0.30$, and $S_{DEP} = 0.27$

Sixth lowest eigenvalue of burden matrix corresponding to Sanderson electronegativities is conducive for COX-1 inhibition. Lower path length 3 rich in atomic mass and lower unsaturation index of the molecule would be favorable for COX-1 inhibition. Prediction of COX-1 inhibition of test set compounds using this equation shows the robustness of the models 1, 2, and 3 (Table 4)

The relationship of lipophilicity with COX-2 inhibition is different from COX-1 inhibition, as suggested by following model (Eq. 4). Eq. 4 is capable to predict 76.0% and explain 85.6% of variance of COX-2 inhibition.

$$pC_2 = 0.043(\pm0.20) + 2.265(\pm1.401)CLOGP - 0.247(\pm0.204)(CLOGP)^2 - 1.138(\pm0.587)I_1 + 0.377(\pm0.354)I_2 \quad (4)$$

$n = 22$, $r = 0.93$, $s = 0.34$, $F = 25.35$, Chance < 0.001, $Q^2 = 0.76$, $S_{PRESS} = 0.43$, and $S_{DEP} = 0.38$

This equation having significant values of coefficient of CLOGP, $(CLOGP)^2$, I_1, and I_2 suggests that as the value of CLOGP and I_2 increases COX-2 inhibition increases and the values of I_1 and $(CLOGP)^2$ increase COX-2 inhibition decreases. The parameters used in the equation are almost independent (|ICAP| $\leqslant$ 0.22). When other relationships were searched with other descriptors obtained from CAChe, a highly significant Eq. 5 containing shape index (basic kappa, order 2), dielectric energy, and indicator variables was found, which is able to explain 86.9% of variance of COX-2 inhibition. This equation is having high internal predictivity as shown by good Q^2 value of 0.79.

$$pC_2 = 2.600(\pm0.979) + 0.390(\pm0.097)SI2 + 2.739(\pm2.063)DE - 0.708(\pm0.517)I_1 + 0.475(\pm0.326)I_2 \quad (5)$$

$n = 22$, $r = 0.93$, $s = 0.32$, $F = 28.22$, Chance < 0.001, $Q^2 = 0.79$, $S_{PRESS} = 0.41$, and $S_{DEP} = 0.36$

Similar coefficients of SI2 and DE in the Eqs. (2) and (5) suggest that these parameters influence COX-1 and COX-2 inhibition, similarly.

This equation having significant values of coefficient of SI2, DE, I_1, and I_2 suggests that as the value of SI2, DE, and I_2 increases COX-2 inhibition increases and as the value of I_1 increases COX-2 inhibition decreases. Presence of triple bond at S alkyl chain is favorable for COX-2 inhibition. Presence of aromatic ring at *S* alkyl chain is not favorable for COX-2 inhibition. The parameters used in the equation are almost independent (|ICAP| $\leqslant$ 0.36). Models 4 and 5 suggest indicator variables (I_1 and I_2) account for selective COX-2 inhibition because lipophilicity, SI2, and DE also correlated with pC_1.

When other relationships were searched with other descriptors obtained from Dragon, a highly significant equation containing X2A, O-058, and BEHm4 was found, which is able to predict 69.3% and explain 92.7% variance of COX-2 inhibition. The parameters used in the equation are almost independent (|ICAP| $\leqslant$ 0.34).

$$pC_2 = -23.951(\pm5.878) + 75.897(\pm19.313)X2A - 1.561(\pm0.721)O\text{-}058 + 1.685(\pm0.886)BEHm4 \quad (6)$$

$n = 22$, $r = 0.93$, $s = 0.31$, $F = 39.13$, Chance < 0.001, $Q^2 = 0.693$, $S_{PRESS} = 0.364$, and $S_{DEP} = 0.353$

Correlation with X2A indicates that branching in the molecule would be better; O-058 indicates that lesser number of carbonyl groups is conducive for COX-2 inhibition. Fourth highest eigenvalue of burden matrix corresponding to atomic mass is conducive for COX-2 inhibition. These descriptors influence anti-inflammatory activity. Prediction of COX-2 inhibition of test set compounds using this equation shows the robustness of the models 4, 5, and 6 (Table 5).

The studies suggest that lipophilicity affects both COX-1 and COX-2 inhibition in different manner and indicator variables like aromatic ring and triple bond play an important role in COX-2 selectivity. Branching in the molecule, higher path length 6 rich in polarizability, and lesser number of carbonyl groups would be favorable for COX-2 inhibition. Fourth highest eigenvalue of burden matrix corresponding to atomic mass would be favorable for COX-2 inhibition and sixth lowest eigenvalue of burden matrix corresponding to Sanderson electronegativities is conducive for COX-1 inhibition. Lower path length 3 rich in atomic mass and lesser degree of unsaturation in the molecule would be favorable for COX-1 inhibition. These studies are promising for development of novel compounds, which are having potent anti-inflammatory activity devoid of side effects.

Supplementary data

SMILES notation of all compounds, Pearson correlation matrix, and other supplementary data associated with this article can be found in the online version. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.08.002.

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