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Exploring QSAR with E-state index: selectivity requirements for COX-2 versus COX-1 binding of terphenyl methyl sulfones and sulfonamides☆

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Abstract—An attempt has been made to explore selectivity requirements for cyclooxygenase-2 (COX-2) versus cyclooxygenase-1 (COX-1) binding of terphenyl methyl sulfones and sulfonamides using electrotopological state (E-state) index and suitable indicator parameters. Multiple linear regression analyses produced statistically acceptable equations: the best relation based on 'all-possible-subsets regression' for COX-1 binding ($n=18$) showed predicted variance and explained variance of 0.675 and 0.777, respectively, while in case of the best equation for COX-2 binding ($n=38$), these values rose to 0.842 and 0.874, respectively. For the selectivity relation ($n=17$), predicted variance and explained variance values were 0.601 and 0.687, respectively. Based on the results of the analyses, three important sites have been suggested: sites A (methylsulfonyl or aminosulfonyl moiety), B (central phenyl ring), and C (terminal phenyl ring containing different substituents). All three sites are important for COX-2 binding while sites B and C are important for COX-1 binding. For COX-2 selectivity, only site C plays an important role. The study shows the utility of E-state index in developing statistically acceptable model having direct physicochemical significance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for occasional headache or fever or to reduce soreness and inflammation resulting from work or exercise, and in patients with rheumatoid arthritis and osteoarthritis. However, these drugs are associated with high risk of gastrointestinal and renal adverse effects.[1–3] NSAIDs exhibit their effect through inhibition of cyclooxygenase (COX) enzymes by blocking the synthesis of proinflammatory prostaglandins from arachidonic acid.[4,5] COX exists in two isoforms: the constitutive form (COX-1), which is expressed virtually in all tissues, and the inducible form (COX-2), which is largely restricted in brain and kidney. Inhibition of COX-1 is primarily responsible for the adverse gastrointestinal and renal effects of NSAIDs while the inhibition of COX-2 accounts for the therapeutic effects of NSAIDs.[6] Additionally COX-2 inhibitors are also useful in cancer prevention and delaying the progression the Alzheimer's disease.[6,7] COX-2 is a homodimeric, glycosylated, monotopic membrane protein with molecular weight of 72 kDa and having 17% larger central channel than COX-1. This difference in size is due to the exchange of valine in COX-2 at positions 434 and 523 in place of isoleucine in COX-1, which changes the chemical environment of the binding pocket (or nook) of NSAIDs and also preferentially reduces steric and ionic crowding by the charged Arg120 in COX-2 and thus preferentially increases binding of nonacidic NSAIDs.[8]

The present paper attempts to develop a statistically acceptable QSAR models for COX-2 and COX-1 binding of terphenyl methyl sulfones and sulfonamides[9] (Table 1; Fig. 1) and explore selectivity requirements for COX-2 versus COX-1 binding using electrotopological state (E-state) index, developed by Kier and Hall's group.[10,11] Estrada and co-workers[12,13] recently clarified the role of topological descriptors in chemistry, although use of such indices in QSAR has been criticized by some authors.[14] The present group of authors have

Keywords: QSAR; E-state index; Terphenyl methyl sulfones and sulfonamides; COX-2 inhibitors.

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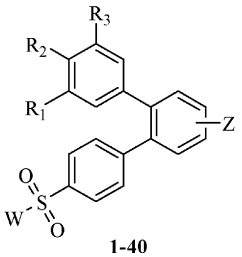
Table 1. Structural features, observed, calculated, and predicted human cyclooxygenase binding affinities of 1-(substituted phenyl)-2-(4-aminosulfonyl/methylsulfonyl)-substituted benzenes



1-40

Sl. no.	Substituents					Biological activity [−log IC_{50}(M)]								
	R_1	R_2	R_3	W	Z	COX-1 binding affinity			COX-2 binding affinity			COX-2/COX-1 selectivity		
						Obs.[a]	Calc.[b]	Pred.[b]	Obs.[a]	Calc.[c]	Pred.[c]	Obs.[a]	Calc.[d]	Pred.[d]
1	H	F	H	CH_3	4,5-F_2	—	—	—	7.85	8.06	8.08	—	—	—
2	H	F	H	NH_2	4,5-F_2	5.24	5.38	5.42	8.40	8.47	8.48	3.16	3.22	3.23
3	H	F	Cl	CH_3	4,5-F_2	—	—	—	8.00	8.06	8.06	—	—	—
4	H	F	Cl	NH_2	4,5-F_2	5.26	5.29	5.30	8.70	8.47	8.45	3.44	3.36	3.32
5	H	F	CH_3	CH_3	4,5-F_2	—	—	—	8.30	8.06	8.03	—	—	—
6	H	F	CH_3	NH_2	4,5-F_2	5.43	5.40	5.40	8.70	8.47	8.45	3.27	3.17	3.15
7	H	OCH_3	F	CH_3	4,5-F_2	—	—	—	7.68	7.47	7.45	—	—	—
8	H	OCH_3	F	NH_2	4,5-F_2	4.65	4.49	4.41	7.89	7.89	7.89	3.24	3.47	3.61
9	H	OCH_3	Cl	CH_3	4,5-F_2	—	—	—	7.72	7.47	7.44	—	—	—
10	H	OCH_3	Cl	NH_2	4,5-F_2	4.72	4.70	4.69	7.89	7.89	7.89	3.17	3.13	3.12
11	Cl	OCH_3	Cl	NH_2	4,5-F_2	—	—	—	7.68	7.89	7.91	—	—	—
12	H	OCH_3	CH_3	CH_3	4,5-F_2	—	—	—	7.89	7.47	7.42	—	—	—
13	H	OCH_3	CH_3	NH_2	4,5-F_2	4.96	4.81	4.78	8.30	7.89	7.84	3.34	2.95	2.85
14	H	OCH_3	OCH_3	CH_3	4,5-F_2	—	—	—	6.47	6.89	7.09	—	—	—
15	H	OCH_3	OCH_3	NH_2	4,5-F_2	—	—	—	7.19	7.30	7.36	—	—	—
16	H	OCH_2O		CH_3	4,5-F_2	—	—	—	7.92	8.06	8.07	—	—	—
17	H	OCH_2O		NH_2	4,5-F_2	5.77	5.73	5.72	8.40	8.47	8.48	2.63	2.64	2.65
18	H	CH_3	H	CH_3	4,5-F_2	—	—	—	8.16	8.06	8.05	—	—	—
19	H	CH_3	H	NH_2	4,5-F_2	4.77	4.94	4.99	8.40	8.47	8.48	3.63	3.55	3.51
20	H	CH_3	Cl	CH_3	4,5-F_2	—	—	—	7.89	8.06	8.07	—	—	—
21	H	CH_3	Cl	NH_2	4,5-F_2	4.78	4.83	4.84	8.52	8.47	8.47	3.74	3.74	3.73
22	H	CH_3	CH_3	CH_3	4,5-F_2	—	—	—	7.64	8.06	8.10	—	—	—
23	H	CH_3	CH_3	NH_2	4,5-F_2	4.83	4.94	4.97	8.30	8.47	8.49	3.47	3.55	3.59
24	H	Cl	CH_3	CH_3	4,5-F_2	—	—	—	8.22	8.06	8.04	—	—	—
25	H	Cl	CH_3	NH_2	4,5-F_2	5.41	5.74	5.83	8.52	8.47	8.47	3.11	2.64	2.56
26	H	$N(CH_3)_2$	Cl	CH_3	4,5-F_2	—	—	—	8.10	8.06	8.05	—	—	—
27	H	$N(CH_3)_2$	Cl	NH_2	4,5-F_2	6.23	5.80	5.64	8.22	8.47	8.50	1.99	2.54	2.66
28	H	OCH_2CH_2O		CH_3	4,5-F_2	—	—	—	6.47	6.67	6.71	—	—	—
29	H	OCH_2CH_2O		NH_2	4,5-F_2	4.75	4.89	4.92	7.49	7.53	7.55	2.74	2.60	2.57
30	H	F	H	CH_3	H	—	—	—	6.58	6.67	6.69	—	—	—
31	H	F	H	NH_2	H	4.72	4.87	4.91	7.21	7.53	7.62	2.49	2.63	2.66
32	Cl	F	H	CH_3	H	—	—	—	6.44	6.67	6.72	—	—	—
33	Cl	F	H	NH_2	H	5.03	4.78	4.71	7.77	7.53	7.48	2.74	2.77	2.78
34	H	Cl	H	CH_3	H	—	—	—	6.85	6.67	6.64	—	—	—
35	H	Cl	H	NH_2	H	5.40	5.20	5.13	—	—	—	—	—	—
36	F	OCH_3	H	NH_2	H	4.88	4.95	4.97	7.48	7.53	7.55	2.60	2.89	2.96
37	Cl	OCH_3	H	CH_3	H	—	—	—	—	—	—	—	—	—
38	Cl	OCH_3	H	NH_2	H	5.09	5.16	5.19	7.72	7.53	7.49	2.63	2.55	2.50
39	H	F	H	CH_3	4,5-Cl_2	—	—	—	6.62	6.67	6.68	—	—	—
40	H	F	H	CH_3	4-OCH_2O-5	—	—	—	7.08	6.67	6.59	—	—	—

Obs. = observed, Calc. = calculated, Pred. = predicted.

[a] Observed values are taken from Ref. 9.

[b] From Eq. 1.

[c] From Eq. 3.

[d] From Eq. 6.

used E-state index to explore QSARs of ligands acting on pharmacologically relevant targets of contemporary interest.[15–20] In continuation of such efforts, the present communication will show here the utility of E-state index in QSAR studies by modeling COX-2 and COX-1 binding of terphenyls using E-state index.

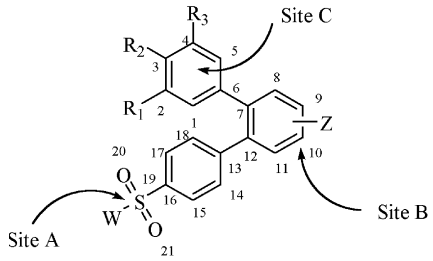


Figure 1. General structure of terphenyl methyl sulfones and sulfonamides: the common atoms are numbered 1–21 and important interaction sites for COX-1/COX-2 binding are indicated with arrows.

The E-state index is an atom level descriptor[10,11] encoding both electronic character and topological environment of each skeletal atom in a molecule. It has two basic components: (i) intrinsic electrotopological state of an atom, (ii) effect of the environment influencing the atom (perturbation), considering differences in the intrinsic electrotopological states of different atoms and topological distance among them. The E-state index has been shown to have power to identify atoms or fragments in the molecules that are important for the biological activity.[11]

All compounds considered in the present study contain 21 common atoms (excluding hydrogens), which were numbered arbitrarily as shown in Figure 1. The E-state values were calculated using ELECTRO1 program[21] according to the original references.[10,11] We have tried to include appropriate indicator and integer variables (listed in Table 2) in the relations based on intuitive judgement. The program AUTOREG[21] was used to relate biological activity with E-state index of different atoms and different combinations of them in addition to indicator and integer variables to find out the best multivariate relations. For this purpose, all-possible-subsets regression was used with a restriction that predictor variables used in an equation are not much intercorrelated ($r^2 < 0.5$). Using the program RRR98,[21] regression coefficients with corresponding standard errors and various statistical parameters reflecting quality[22] of the equations (like explained variance R^2_a, correlation coefficient R, standard error of estimate s, variance ratio F, and average absolute residual AVRES) were found out. Leave-one-out cross-validation[23] was performed using the programs KRPRES1 and KRPRES2,[21] which generate predicted variance (Q^2), predicted residual sum of squares (PRESS), standard deviation of error of prediction (SDEP) and average absolute predicted residual ($\mathrm{Pres_{av}}$). The 95% confidence intervals of the regression coefficients have been mentioned within parentheses in the presented equations.

Table 3 shows the results of all-possible-subsets regression for the COX-1 ($\mathrm{pC_1}$), COX-2 ($\mathrm{pC_2}$) and selectivity data ($\mathrm{pC_2 - pC_1}$) modeling.

While modeling COX-1 data, indicator variable $I'_{\mathrm{OMe\text{–}Me}}$ emerged as single best parameter explaining 26.3% of the variance. When bivariate relations were tried, $I_{9,10\text{-F2}}$ along with $I'_{\mathrm{OMe\text{–}Me}}$ could explain 58.9% of the variance. Among the trivariate relations, the best one involves E-state value of atom $\mathrm{C_5}$ (S_5) along with $I'_{\mathrm{OMe\text{–}Me}}$ and $I_{9,10\text{-F2}}$ as predictor variables.

$$\begin{aligned}\mathrm{pC_1} &= 1.365(\pm 0.794)S_5 - 0.974(\pm 0.274)I'_{\mathrm{OMe\text{–}Me}} \\ &\quad + 0.870(\pm 0.300)I_{9,10\text{-F2}} + 2.532(\pm 1.362)\\ n &= 18,\ Q^2 = 0.675,\ R^2_a = 0.777,\ R^2 = 0.816,\\ R &= 0.903,\ F = 20.7(\mathrm{df}3, 14),\ s = 0.200,\\ \mathrm{AVRES} &= 0.141,\ \mathrm{SDEP} = 0.234,\ S_{\mathrm{PRESS}} = 0.265,\\ \mathrm{PRESS} &= 0.985,\ \mathrm{Pres_{av}} = 0.184\end{aligned} \quad (1)$$

Eq. 1 shows predicted variance of 67.5% and explained variance of 77.7%. The standard error of estimate of Eq. 1 is 0.200 while the predicted standard error is 0.234. Eq. 1 is closely followed (explained variance of 74.8%) in statistical quality by the equation where S_5 in Eq. 1 is replaced by S_4 (vide Table 2). As S_5 and S_4 are highly intercorrelated ($r^2 = 0.810$), a new variable S_{4+5} is defined as sum of S_4 and S_5 values and the resultant Eq. 2 shows comparable quality to Eq. 1.

$$\begin{aligned}\mathrm{pC_1} &= 0.485(\pm 0.303)S_{4+5} - 0.975(\pm 0.286)I'_{\mathrm{OMe\text{–}Me}} \\ &\quad + 0.759(\pm 0.280)I_{9,10\text{-F2}} + 3.327(\pm 1.015)\\ n &= 18,\ Q^2 = 0.654,\ R^2_a = 0.761,\ R^2 = 0.803,\\ R &= 0.896,\ F = 19.1(\mathrm{df}3, 14),\ s = 0.207,\\ \mathrm{AVRES} &= 0.145,\ \mathrm{SDEP} = 0.242,\ S_{\mathrm{PRESS}} = 0.274,\\ \mathrm{PRESS} &= 1.050,\ \mathrm{Pres_{av}} = 0.189\end{aligned} \quad (2)$$

Table 2. Definitions of different variables

Variable	Definition
$I'_{\mathrm{OMe\text{–}Me}}$	Indicator variable having value 1 to denote presence of methoxy or methyl group at $\mathrm{R_2}$ in presence of fluoro substitution on $\mathrm{C_9}$ and $\mathrm{C_{10}}$, value 0 otherwise
$I_{9,10\text{-F2}}$	Indicator variable having value 1 in presence of fluoro substitution on $\mathrm{C_9}$ and $\mathrm{C_{10}}$, value 0 otherwise
I_{OMe}	Indicator variable having value 1 to denote presence of methoxy group at $\mathrm{R_2}$, value 0 otherwise
I_{Me}	Indicator variable having value 1 to denote presence of methyl group at $\mathrm{R_2}$, value 0 otherwise
N'_{OMe}	Number of methoxy group at the phenyl ring (R positions) in presence of fluoro substitution on $\mathrm{C_9}$ and $\mathrm{C_{10}}$
I_{W1}	Indicator variable having value 1 to denote presence of amino group at W in presence of fluoro substitution on $\mathrm{C_9}$ and $\mathrm{C_{10}}$, value 0 otherwise
I_{W2}	Indicator variable having value 1 to denote presence of amino group at W in absence of fluoro substitution on $\mathrm{C_9}$ and $\mathrm{C_{10}}$, value 0 otherwise
S_{X}	E-state value of atom X

Table 3. Results of all-possible-subsets regression[a]

Activity	No. of predictor variables	Combination of variables	Statistics			
			R_a^2	R	F	s
COX-1 binding	1	I'_{OMe-Me}	0.263	0.554	7.1	0.363
	2	I'_{OMe-Me}, $I_{9,10-F2}$	0.589	0.798	13.2	0.271
	3	I'_{OMe-Me}, $I_{9,10-F2}$, S_5	0.777	0.903	20.7	0.200
		I'_{OMe-Me}, $I_{9,10-F2}$, S_4	0.748	0.890	17.8	0.212
		I'_{OMe-Me}, $I_{9,10-F2}$, S_{4+5}	0.761	0.896	19.1	0.207
COX-2 binding	1	$I_{9,10-F2}$	0.453	0.684	31.6	0.483
		S_{15}	0.450	0.682	31.3	0.484
	2	$I_{9,10-F2}$, N'_{OMe}	0.668	0.828	38.3	0.376
		$I_{9,10-F2}$, S_{20}	0.646	0.816	34.8	0.388
	3	$I_{9,10-F2}$, N'_{OMe}, S_{19}	0.846	0.926	68.5	0.256
		$I_{9,10-F2}$, N'_{OMe}, S_{20}	0.839	0.923	65.0	0.262
	4	$I_{9,10-F2}$, N'_{OMe}, I_{W1}, I_{W2}	0.874	0.942	65.3	0.231
		$I_{9,10-F2}$, N'_{OMe}, S_{19}, I_{W2}	0.871	0.941	63.5	0.234
		$I_{9,10-F2}$, N'_{OMe}, S_{20}, I_{W2}	0.866	0.938	60.8	0.239
		$I_{9,10-F2}$, N'_{OMe}, S_{19-20}, I_{W2}	0.859	0.935	57.2	0.245
Selectivity	1	I_{Me}	0.319	0.601	8.5	0.387
	2	I_{Me}, S_5	0.571	0.790	11.6	0.307
	3	I_{Me}, S_5, I_{OMe}	0.687	0.864	12.7	0.262

[a] Cutoff intercorrelation (r^2) among predictor variables was set to 0.5.

The calculated and predicted COX-1 binding data according to Eq. 1 are given in Table 1. Interestingly, for the compound with least COX-1 binding affinity (**8**), the calculated and predicted values (4.49 and 4.41, respectively) are close to the observed one (4.65). The intercorrelation (r^2) matrix for Eq. 1 is given in Table 4.

The positive coefficients of the variable $I_{9,10-F2}$ in Eqs. 1 and 2 indicate that presence of fluoro substitution on C_9 and C_{10} of the central phenyl ring is conducive to the COX-1 binding affinity while negative coefficients of I'_{OMe-Me} indicate that presence of methoxy or methyl substituent at R_2 position of the terminal phenyl ring in presence of fluoro substitution at C_9 and C_{10} is detrimental for the binding affinity. Again, the variables S_5 and S_{4+5} indicate the importance of electron density distribution in the terminal phenyl ring containing different substituents.

Table 3 shows that $I_{9,10-F2}$ appeared as single best descriptor (explaining 45.3% of the variance), which is closely followed by E-state value of atom 15 (S_{15}). The best bivariate relation involving $I_{9,10-F2}$ and N'_{OMe} could explain 66.8% variance of COX-2 binding. On using S_{20} instead of I'_{OMe} in the bivariate relation, 64.6% of the variance was explained. The best trivariate relation explaining 84.6% of the variance involves $I_{9,10-F2}$, N'_{OMe} and S_{19} as predictor variables. The best tetravariate relation involving $I_{9,10-F2}$, N'_{OMe}, I_{W1} and I_{W2} as predictor variables shows excellent statistical quality (87.4% explained variance, 84.2% predicted variance), which is closely followed in quality by the relations where S_{19} or S_{20} replaces I_{W1} (vide Table 3).

$$\begin{aligned} pC_2 &= 0.414(\pm 0.181)I_{W1} + 0.861(\pm 0.285)I_{W2} \\ &\quad - 0.584(\pm 0.145)N'_{OMe} + 1.385(\pm 0.239)I_{9,10\text{-}F2} \\ &\quad + 6.673(\pm 0.206) \\ n &= 38,\ Q^2 = 0.842,\ R_a^2 = 0.874,\ R^2 = 0.888, \\ R &= 0.942,\ F = 65.3(df4, 33),\ s = 0.231, \\ AVRES &= 0.178,\ SDEP = 0.256,\ S_{PRESS} = 0.274, \\ PRESS &= 2.485,\ Pres_{av} = 0.208 \end{aligned} \tag{3}$$

$$\begin{aligned} pC_2 &= -0.799(\pm 0.362)S_{19} + 0.464(\pm 0.340)I_{W2} \\ &\quad - 0.592(\pm 0.147)N'_{OMe} + 1.316(\pm 0.257)I_{9,10\text{-}F2} \\ &\quad + 4.075(\pm 1.314) \\ n &= 38,\ Q^2 = 0.837,\ R_a^2 = 0.871,\ R^2 = 0.885, \\ R &= 0.941,\ F = 63.5(df4, 33),\ s = 0.234, \\ AVRES &= 0.182,\ SDEP = 0.260,\ S_{PRESS} = 0.279, \\ PRESS &= 2.561,\ Pres_{av} = 0.214 \end{aligned} \tag{4}$$

Table 4. Intercorrelation (r^2) matrix for COX-1 data modeling (Eq. 1)

	I'_{OMe-Me}	$I_{9,10-F2}$	S_5
I'_{OMe-Me}	1	0.250	0.016
$I_{9,10-F2}$		1	0.178
S_5			1

As S_{19} and S_{20} are highly intercorrelated ($r^2 = 0.711$), a new variable S_{19-20} was defined as signed difference between the values of S_{19} and S_{20}.

$$\begin{aligned} \mathrm{pC_2} &= -1.212(\pm 0.626)S_{19-20} + 0.532(\pm 0.347)I_{\mathrm{W2}} \\ &\quad - 0.625(\pm 0.156)N'_{\mathrm{OMe}} + 1.321(\pm 0.273)I_{9,10\text{-F2}} \\ &\quad - 11.346(\pm 9.444) \end{aligned}$$

$$n = 38,\ Q^2 = 0.820,\ R_a^2 = 0.859,\ R^2 = 0.874,$$

$$R = 0.935,\ F = 57.2(\mathrm{df}4, 33),\ s = 0.245,$$

$$\mathrm{AVRES} = 0.191,\ \mathrm{SDEP} = 0.273,\ S_{\mathrm{PRESS}} = 0.293,$$

$$\mathrm{PRESS} = 2.828,\ \mathrm{Pres_{av}} = 0.224 \qquad (5)$$

The calculated and predicted COX-2 binding data according to Eq. 3 are given in Table 1. Interestingly, for the compounds with highest COX-2 binding affinity (**4** and **6**), the calculated and predicted values (8.47 and 8.45) are close to the observed one (8.70). The intercorrelation (r^2) matrix for Eq. 3 is given in Table 5.

The positive coefficients of the variable $I_{9,10\text{-F2}}$ in Eqs. (3)–(5) indicate that presence of fluoro substitution on C_9 and C_{10} of the central phenyl ring is conducive to the COX-2 binding affinity while negative coefficients of N'_{OMe} indicate that presence of methoxy substituent at *R* positions of the terminal phenyl ring in presence of fluoro substitution at C_9 and C_{10} is detrimental for the binding affinity. Again the variables I_{W1} and I_{W2} indicate the importance of amino group (which contributes positively) at W position in presence and absence, respectively, of fluoro substitution at C_9 and C_{10}. The variables S_{19} and S_{20} indicate the importance of the sulfonyl moiety. The variable S_{19-20} in Eq. 5 indicates that difference of E-state values of sulfonyl sulfur and sulfonyl oxygen may play an important role in COX-2 binding.

While exploring selectivity, I_{Me} emerged as single best predictor variable explaining 31.9% of the variance. The best bivariate relation involved I_{Me} and S_5 (57.1% explained variance) and the best trivariate relation (Eq. 6 explaining 68.7% of the variance) involved I_{Me}, S_5, and I_{OMe} as predictor variables.

$$\begin{aligned} \mathrm{pC_2} - \mathrm{pC_1} &= -2.184(\pm 1.096)S_5 + 0.389(\pm 0.337)I_{\mathrm{OMe}} \\ &\quad + 1.200(\pm 0.434)I_{\mathrm{Me}} + 6.375(\pm 1.857) \end{aligned}$$

$$n = 17,\ Q^2 = 0.601,\ R_a^2 = 0.687,\ R^2 = 0.746,$$

$$R = 0.864,\ F = 12.7(\mathrm{df}3, 13),\ s = 0.262,$$

$$\mathrm{AVRES} = 0.164,\ \mathrm{SDEP} = 0.287,\ S_{\mathrm{PRESS}} = 0.328,$$

$$\mathrm{PRESS} = 1.402,\ \mathrm{Pres_{av}} = 0.210 \qquad (6)$$

Table 5. Intercorrelation (r^2) matrix for COX-2 data modeling (Eq. 3)

	$I_{9,10\text{-F2}}$	I_{OMe}	I_{W1}	I_{W2}
$I_{9,10\text{-F2}}$	1	0.110	0.238	0.372
N'_{OMe}		1	0.036	0.041
I_{W1}			1	0.088
I_{W2}				1

Table 6. Intercorrelation (r^2) matrix for COX-1/COX-2 selectivity data modeling (Eq. 6)

	I_{OMe}	I_{Me}	S_5
I_{OMe}	1	0.089	0.033
I_{Me}		1	0.168
S_5			1

The calculated and predicted selectivity data obtained from Eq. 6 are given in Table 1. Interestingly, for the compound with highest selectivity value (**21**), the calculated and predicted values (3.74 and 3.73, respectively) are almost same as the observed one (3.74). The intercorrelation (r^2) matrix for Eq. 6 is given in Table 6. Compound **27** acts as a marginal outlier for this equation.

The positive coefficients of I_{OMe} and I_{Me} in Eq. 6 indicate that COX-2 selectivity increases in presence of methoxy and methyl groups at R_2 position of the terminal phenyl ring. Again, negative contribution of S_5 indicates that the E-state value of C_5 should be less for higher COX-2 selectivity.

Based on the results of the analyses, three important sites are suggested: sites A (methylsulfonyl or aminosulfonyl moiety), B (central phenyl ring), and C (terminal phenyl ring containing different substituents). All three sites are important for COX-2 binding while sites B and C are important for COX-1 binding. For COX-2 selectivity, only site C plays an important role. Furthermore, presence of fluoro substitution at C_9 and C_{10} of the central phenyl ring significantly modulates the effects of substitutions in the other two rings on COX binding affinities.

The present QSAR study could throw some light on the selectivity requirements of terphenyls for binding with COX-2. The study also shows the utility of E-state index in developing statistically acceptable model having direct physicochemical significance. However, more data points covering wider features of substitution pattern need to be considered to reach a conclusion.

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