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QSAR studies on structurally similar 2-(4-methanesulfonylphenyl)pyran-4-ones as selective COX-2 inhibitors: a Hansch approach

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Abstract—QSAR analysis based on classical Hansch approach was adopted on two recently reported novel series of 2-phenylpyran-4-ones as selective cyclooxygenase-2 (COX-2) inhibitors. The 6-methyl derivatives of title compounds bifurcate as 3-phenoxypyran-4-ones (subset A) and 3-phenylpyran-4-ones (subset B) among series 1. Series 2 consists of 5-chloro derivatives of title compounds. Various regression equations were derived to study the influence of phenoxy and phenyl ring substituents of series 1 compounds on COX-2, COX-1 and selective COX-2 over COX-1 inhibitory activity. The best triparametric equation derived for 36 compounds of series 1 explains the hydrophobic, electronic and steric requirements for improved COX-2 inhibitory activity. QSAR model derived to explore the selective COX-2 over COX-1 inhibition showed that selectivity could be influenced by size and lipophilicity of substituents. The size of the first atom of 2 substituents appears to have negative effect on selectivity, whereas highly polar 3 substituents at *R* are favorable for improved selectivity. QSAR investigations on series 2 compounds revealed some interesting correlation of COX-2 inhibitory activity with calculated physicochemical properties of whole molecules. The positive log *P* confirms the hydrophobic interaction of series 2 compounds with COX-2 enzyme. The positive *MR* term indicates that an overall increase in size and polarizabilty of the molecules increases COX-2 inhibitory activity. The positive contribution of structural variable suggests biphenyl analogs are extremely potent COX-2 inhibitors.

Non steroidal anti-inflammatory drugs (NSAIDs) are still the most commonly prescribed drugs worldwide for the treatment of inflammatory diseases like rheumatoid arthritis, osteo arthritis, orthopedic injuries, post operative pain, acute mylagias, etc.[1] However NSAIDs increase the risk of peptic ulcers and renal insufficiency. NSAIDs act by inhibition of cyclooxygenase (COX), the enzyme involved in the biosynthesis of prostaglandins, prostacyclins and thromboxanes from arachidonic acid.[2] COX exists in two isoforms, COX-1 primarily responsible for cytoprotection and COX-2, the inducible form associated with inflammation.[3] Several strategies have been adopted to develop NSAIDs without their serious adverse effects. Following the hypothesis: inhibition of cyclooxygenase-1 (COX-1) accounts for the side effects whilst inhibition of cyclooxygenase-2 (COX-2) accounts for the therapeutic benefits of NSAIDs, the most promising approach emerged as the development of novel NSAIDs targeting selective COX-2 inhibition. Two diaryl heterocycles, celecoxib[4] and rofecoxib[5] are marketed in many countries as promising selective COX-2 inhibitors. Subsequently other selective COX-2 inhibitors valdecoxib,[6] parecoxib sodium,[7] and etoricoxib entered the market as second-generation inflammatory therapies. The investigations of selective COX-2 inhibitors in the treatment of colon cancer,[8] Parkinson's[9] and Alzheimer's[10] disease are the current highly interesting areas of research in this therapeutic area.

Since the last decade, ample QSAR studies of different heterocyclic ring systems as selective COX-2 inhibitors have been studied.[11,12] Recently Joo et al.[13] introduced 2,3-diaryl benzopyrans as a part of the vicinal diaryl heterocyclic family as a promising lead structure for selective COX-2 inhibition. Soon after this, the same research group reported a new series of selective COX-2 inhibitors containing the γ pyrone scaffold.[14] Caturla et al.[15] reported a new class of 2-phenylpyran-4-ones

Keywords: QSAR; COX-2; COX-1; Selectivity; 2-Phenylpyran-4-ones.
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as selective COX-2 inhibitors. The latter two series consist of 2-phenylpyran-4-one as a common template. In spite of spectacular development of molecular modeling and QSAR studies on vicinal diaryl heterocycles, this new lead structure has not been studied up to now. In our recent publication,[16] we reported the QSAR analysis of 2,3-diaryl benzopyran templates for the first time as selective COX-2 inhibitors. In a combined QSAR analysis, using semi-empirical, Austin Model-1 (AM1) calculations, we reported[17] the possible electronic and hydrophobic interactions of 2,3-diaryl benzopyrans/pyrans toward COX-2 binding site. Owing to our special interest in this pyran lead and in continuation with our previous work, we attempted to rationalize the title compounds in terms of physicochemical and structural requirements.

For QSAR analysis, the reported[15] 2-phenylpyran-4-ones were considered as series 1. It bifurcates as 6-methyl derivatives of 3-phenoxypyran-4-ones (subset A) and 3-phenylpyran-4-ones (subset B). Since series 1 compounds exhibit structural variations of substituents attached only to a single benzene ring in both the subsets, we adopted the classical Hansch approach using conventional 2D descriptors. Compounds of series 1 with various aromatic substituent constants and indicator variables are given in Table 1. The reported[14] 2,3-diaryl pyran-4-ones were considered as series 2. As series 2 compounds exhibit diverse structural variations mostly at the 3-aryl ring of central pyran-4-one ring, we attempted to calculate C$\log P$ and *CMR* for whole molecules using molecular modeling software. Recently, we reported[18] the significance of C$\log P$ and *CMR* of whole molecules of fused pyrazoles in explaining their selective COX-2 inhibition. A minor modification of –Cl and –H at 5-position and =O and =S at 4-position of pyran-4-one ring of series 2 is also identified. Compounds of series 2 are listed in Table 2.

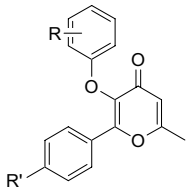
Upon considering $pIC_{50(COX\text{-}2\ HWB)}$, $pIC_{50(COX\text{-}1\ HWB)}$, log[COX-1/COX-2] as dependent variables and various aromatic substituent constants, indicator variables as independent variables, various statistically significant QSAR models for series 1 were developed. Linear regression analysis module of software Systat 10.2 was used for model building. The statistically significant QSAR models of series 1 are reported in Table 3.

Model 1 is developed for 23 compounds as 3-phenoxypyran-4-ones under subset A. It is a triparametric model, which shows the importance of electronic and steric factors for improved COX-2 inhibitory activity. The negative $\Sigma\sigma$ shows the need for electron donating groups at the phenoxy ring for better COX-2 inhibitory activity. The term $B1$ is a measure of width of the first atom of substituents and its contribution in model 1 denotes that the size of the first atom of 2 substituents of the phenoxy ring have positive effects on COX-2 inhibitory activity. I_{2F} is an indicator variable given a value of 1 for 2 fluoro substituents and 0 for others. Its positive coefficient suggests that 2 fluoro substitution is conducive to COX-2 inhibitory activity. Model 1 predicts a very high activity for compound **23** as compared to observed activity and thus was omitted as an outlier while deriving model 1a. The reason for outlying behavior is attributed to its basicity, as it is the only compound with an amino functional group among subset A. Model 1a is excellent as compared to model 1 in terms of all statistical parameters.

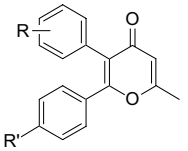
Correlation analysis of 13 compounds of 3-phenylpyran-4-ones under subset *B* resulted in models 2 and 3. The contribution of *R* in model 2 shows the importance of resonance effect of substituents among subset B compounds. Model 2 is insufficient as it explains only 54.0% variance in observed activity. The diparametric model 3 indicates the hydrophobic interactions of 3-phenylpyran-4-ones with COX-2 enzyme binding site. The positive contribution of indicator variable I_{4F} shows 4 fluoro substitution at the 3 phenyl ring of subset *B* compounds for improved COX-2 inhibitory activity. Stepwise deletion of outliers, compounds **30** and **36** (detected through high residual values) resulted in model 3a. The reason for outlying behavior is not immediately apparent. It explains 81.7% variance in observed activity and serves as a better model in describing 3-phenylpyran-4-ones.

In order to have a comparative study of both the subsets and to explore the selectivity of these analogs, both the subsets were combined together and a QSAR model was developed. An indicator variable I_{oPh} was included to account for the structural variation due to the combined analysis of both subsets. I_{oPh} was given 1 for compounds bearing a phenoxy ring at the 3 position of pyran-4-one and 0 for phenyl ring. Model 4 is developed for all 36 compounds with reported COX-2 inhibitory activity. It is an excellent model showing the importance of hydrophobic, electronic, steric and structural requirements among these novel congeners for improved COX-2 inhibitory activity. The negative contribution of $\Sigma\sigma$ shows the need for electron-donating groups at the 3-aryl ring for better COX-2 inhibitory activity. Since σ takes into account the electronic influence in terms of resonance (*R*) and field effect (*F*) described by Swain and Lupton, we attempted to correlate *R* and *F* with $pIC_{50(COX\text{-}2\ HWB)}$. However, we found no significant contribution of either resonance or field effect in model 4. The failure of contribution of *R* indicates that the resonance effect of the 3-aryl ring is not so important for these congeners. So the aromaticity of the 3-aryl ring is not a prime requisite to exhibit COX-2 inhibitory activity and hence could be suitably substituted by other nonaromatic cyclic systems. This is in good agreement with SAR data of Caturla et al., stating that among the several nonaromatic systems at the 3-position of pyran studied, cyclohexyl substitution offered good COX-2 inhibitory activity. However we could not derive much conclusion in this regard as these nonaromatic compounds were not included due to their unusual substitution pattern making them unsuitable for our conventional 2D QSAR work. The positive contribution of π_4 demonstrates the possible hydrophobic interactions of 4 substituents of the 3-aryl ring with the COX-2 binding site. Also, it is noteworthy to mention that steric effects play a major role in comparison to

Table 1. Compounds of series 1 with observed and predicted activity, aromatic substituent constants and indicator variables



Compounds **1-23** (subset A)



Compounds **24-36** (subset B)

Compd	Substitution		$pIC_{50(COX\text{-}2\ HWB)}$	$pIC_{50(COX\text{-}1\ HWB)}$	Sel[a]	I_{oPh}	$\Sigma\sigma$	$B1_2$	π_4	π_3	R	I_{2F}	$\Sigma\pi$	I_{4F}	Pre[b]
	R	R'													
1	4-F	SO_2CH_3	6.0088	—	—	1	0.06	1	0.14	—	—	0	—	—	6.0804
2	4-Cl	SO_2CH_3	6.4948	3.6840	2.8109	1	0.23	1	0.71	0	−0.15	0	—	—	6.0999
3	4-Br	SO_2CH_3	6.4437	3.9244	2.5185	1	0.23	1	0.86	0	−0.17	0	—	—	6.1485
4	4-I	SO_2CH_3	6.3872	—	—	1	0.18	1	1.12	—	—	0	—	—	6.2699
5	4-CF_3	SO_2CH_3	5.6108	—	—	1	0.54	1	0.88	—	—	0	—	—	6.0267
6	4-CF_3O	SO_2CH_3	5.8416	—	—	1	0.35	1	1.04	—	—	0	—	—	6.1858
7	4-NO_2	SO_2CH_3	5.3990	—	—	1	0.78	1	−0.28	—	—	0	—	—	5.5069
8	2,4-diF	SO_2CH_3	7.0969	4.6517	2.4456	1	0.12	1.35	0.14	0	−0.68	1	—	—	6.3280
9	3,4-diF	SO_2CH_3	5.3536	—	—	1	0.4	1	0.14	—	—	0	—	—	5.9030
10	3,4-diCl	SO_2CH_3	5.4711	—	—	1	0.6	1	0.71	—	—	0	—	—	5.9483
11	2-F, 4-Cl	SO_2CH_3	6.6990	4.7258	1.9731	1	0.29	1.35	0.71	0	−0.49	1	—	—	6.4084
12	2-F, 4-Br	SO_2CH_3	6.8239	4.6421	2.1818	1	0.29	1.35	0.86	0	−0.51	1	—	—	6.4438
13	2-Cl, 4-Br	SO_2CH_3	6.5086	4.4535	2.0531	1	0.46	1.8	0.86	0	−0.32	0	—	—	6.8831
14	4-F, 2-CH_3	SO_2CH_3	6.7447	4.6737	2.0719	1	−0.11	1.52	0.14	0	−0.47	0	—	—	6.6795
15	2-Cl, 4-CH_3	SO_2CH_3	6.6198	4.7799	1.8388	1	0.06	1.8	0.56	0	−0.28	0			7.0454
16	4-Cl, 2-CH_3	SO_2CH_3	6.7212	4.4365	2.2833	1	0.06	1.52	0.71	0	−0.28	0	—	—	6.7433
17	2-Cl, 4-CH_3O	SO_2CH_3	6.7447	4.8633	1.8808	1	−0.04	1.8	−0.02	0	−0.66	0	—	—	6.8917
18	H	SO_2CH_3	6.0000	—	—	1	0	1	0	—	—	0	—	—	6.0804
19	2-CH_3	SO_2CH_3	6.7695	4.6421	2.1271	1	−0.17	1.52	0	0	−0.13	0	—	—	6.6735
20	3-CH_3	SO_2CH_3	5.8697	—	1.8692	1	−0.07	1	0	0.56	—	0	—	—	6.1458
21	4-CH_3	SO_2CH_3	6.6778	4.4089	2.2695	1	−0.17	1	0.56	0	−0.13	0	—	—	6.3039
22	2-F, 4-CH_3	SO_2CH_3	7.2218	5.1611	2.0607	1	−0.11	1.35	0.56	0	−0.47	1	—	—	6.5994
23	4-NH_2	SO_2CH_3	5.8297	—	—	1	−0.66	1	−1.23	—	—	0	—	—	6.3955
24	H	SO_2CH_3	5.7352	—	—	0	0	1	0	—	0.00	—	0	0	5.6276
25	2-F	SO_2CH_3	5.8153	—	—	0	0.06	1.35	0	—	−0.34	—	0.14	0	5.9508
26	3-F	SO_2CH_3	5.4724	—	—	0	0.34	1	0	—	−0.34	—	0.14	0	5.4087
27	4-F	SO_2CH_3	5.9706	—	—	0	0.06	1	0.14	—	−0.34	—	0.14	1	5.6067
28	4-Cl	SO_2CH_3	5.6676	—	—	0	0.23	1	0.71	—	−0.15	—	0.71	0	5.6988
29	4-Br	SO_2CH_3	5.7619	—	—	0	0.23	1	0.86	—	−0.17	—	0.86	0	5.7367
30	4-CF_3	SO_2CH_3	5.1599	—	—	0	0.54	1	0.88	—	0.19	—	0.88	0	5.5998
31	4-CH_3	SO_2CH_3	5.6615	—	—	0	−0.17	1	0.56	—	−0.13	—	0.56	0	5.9660
32	3,4-diCl	SO_2CH_3	6.1675	4.4306	1.7324	0	0.6	1	0.71	0.71	−0.30	—	1.42	0	5.3434
33	2,4-diF	SO_2CH_3	5.9508	—	—	0	0.12	1.35	0.14	—	−0.68	—	0.28	1	5.9345

(*continued on next page*)

Table 1 (*continued*)

Compd	Substitution		$pIC_{50(COX\text{-}2\ HWB)}$	$pIC_{50(COX\text{-}1\ HWB)}$	Sel[a]	I_{oPh}	$\Sigma\sigma$	$B1_2$	π_4	π_3	R	I_{2F}	$\Sigma\pi$	I_{4F}	Pre[b]
	R	R'													
34	2-F, 4-Cl	SO_2CH_3	5.6882	—	—	0	0.29	1.35	0.71	—	−0.49	—	0.85	0	6.0358
35	4-SO_2CH_3	F	5.0101	—	—	0	0.72	1	−1.63	—	0.22	—	−1.63	0	4.2608
36	H	SO_2NH_2	5.1618	—	—	0	0	1	0	—	0.00	—	0	0	5.6924

[a] Sel = log[COX-1/COX-2].
[b] Pre = predicted activity through model 4.

electronic and hydrophobic effects as it is evident from a high coefficient of the $B1_2$ term. The contribution of the $B1_2$ term suggests that substituents at the 2 position of the 3-aryl ring appear to have positive steric effects towards the COX-2 binding site. This result is contradictory to similar findings by Hansch and co-workers[12] on 4,5-diaryl imidazoles, where the substituents at the 2 position of the 5-phenyl ring shows negative steric effects on COX-2 binding site. A similar negative steric effect is also encountered in the case of 3,4-diaryl oxazolones by Hansch and co-workers.[12] The positive contribution of the indicator variable, I_{oPh}, shows the demand for a 3-phenoxy ring of pyran-4-one rather than a 3-phenyl ring for improved COX-2 inhibitory activity.

Model 5 is developed for available COX-1 inhibitory activity data for the combined set. The correlation in model 5 is not satisfactory but the single parameter R explains 37.7% variance in COX-1 inhibitory activity. The contribution of R, resonance effect at the 3-aryl ring of pyran-4-one, suggests the demand for nonaromatic cyclic systems for decreased COX-1 inhibitory activity. This finding supplements the SAR data of Caturla et al. about the cyclohexyl derivative being a more selective COX-2 inhibitor among the compounds analyzed. Since the DW value is less than 1.4 (Table 3), there may be some indication of serial correlation in model 5.

Since it is not only the COX-2 inhibitory activity but also the selective inhibition of COX-2 over COX-1 that is of paramount importance in designing novel selective COX-2 inhibitors, Model 6 is derived to explore the selectivity requirements among these congeners. While deriving model 6, compound **20** was included in addition to the same 14 compounds as used for COX-1 modeling. This biparametric model derived for 15 compounds explains about 69.5% variance of selectivity for binding with COX-2 over COX-1. The negative contribution of the π_3 term indicates the need for more polar substituents at the 3 position of the 3-aryl ring of pyran-4-ones.

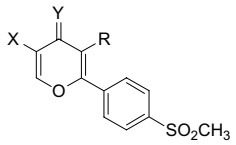
For series 2 compounds the best mono and biparamertic models generated are discussed below:

$$pIC_{50(COX\text{-}2\ MPM)} = 0.639(\pm 0.100)\log P + 1.438(\pm 0.238)$$

$$n = 18,\quad r = 0.848,\quad r^2 = 0.720,\quad s = 0.283,$$
$$F_{1,16} = 41.07,\quad q^2 = 0.6040,\quad p = 0.000,$$
$$DW = 2.655. \qquad (7)$$

Model 7 is developed for all reported 2,3-diaryl pyran-4-ones. It explains 72.0% variance in observed activity. The parameter $\log P$, as calculated from the ChemProp-Pro server of Chem3D software, is the logarithm of the partition coefficient of *n*-octanol/water. It is a measure of hydrophobicity of whole molecules. Calculated $\log P$ and other descriptors used in equations are given in Table 4. The fairly high positive coefficient of $\log P$ suggests that increasing hydrophobicity of the molecule

Table 2. Structures of 2,3-diaryl pyrans (series 2) and their COX-2 inhibitory activity



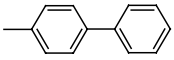
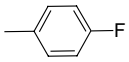
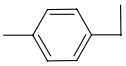
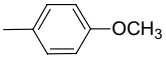
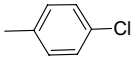
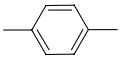
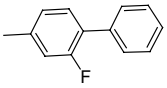
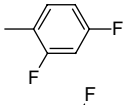
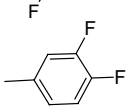
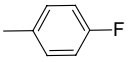
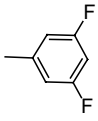
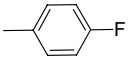
Compd	Substitution			pIC_{50}	Compd	Substitution			pIC_{50}
	R	X	Y			R	X	Y	
1		Cl	O	2.9662	**10**		Cl	O	4.0383
2		Cl	O	2.8302	**11**		Cl	O	3.1426
3		Cl	O	2.2000	**12**		Cl	O	2.1630
4		Cl	O	2.8460	**13**		Cl	O	3.1331
5		Cl	O	3.0287	**14**		Cl	O	2.7543
6		Cl	O	2.8487	**15**		Cl	O	4.0559
7		Cl	O	2.8582	**16**		Cl	O	2.1519
8		Cl	O	2.9084	**17**		H	O	2.6505
9		Cl	O	2.6301	**18**		Cl	S	3.0779

Table 3. QSAR models derived for series 1 compounds

Model no.	Equation	n	r	r^2	s	F	DW	p	q^2
1	$pIC_{50(COX\text{-}2\ HWB)} = -0.611(\pm0.224)\Sigma\sigma + 0.918(\pm0.237)B1_2 + 0.649(\pm 0.181)I_{2F} + 5.163(\pm0.302)$	23	0.839	0.704	0.324	15.04	1.519	0.000	0.519
1a	$pIC_{50(COX\text{-}2\ HWB)} = -1.057(\pm0.230)\Sigma\sigma + 0.726(\pm0.203)B1_2 + 0.619(\pm0.149)I_{2F} + 5.517(\pm0.271)$	22	0.897	0.804	0.265	24.69	1.685	0.000	0.741
2	$pIC_{50(COX\text{-}2\ HWB)} = -0.981(\pm0.273)R + 5.442(\pm0.086)$	13	0.735	0.540	0.244	12.91	1.554	0.004	0.366
3	$pIC_{50(COX\text{-}2\ HWB)} = 0.282(\pm0.102)\Sigma\pi + 0.429(\pm0.199)I_{4F} + 5.472(\pm0.086)$	13	0.730	0.533	0.258	5.70	1.678	0.022	0.356
3a	$pIC_{50(COX\text{-}2\ HWB)} = 0.315(\pm0.059)\Sigma\pi + 0.337(\pm0.113)I_{4F} + 5.558(\pm0.052)$	11	0.904	0.817	0.144	17.82	1.717	0.001	0.708
4	$pIC_{50(COX\text{-}2\ HWB)} = 0.294(\pm0.105)\pi_4 - 0.659(\pm0.211)\Sigma\sigma + 0.959(\pm0.234)B1_2 + 0.435(\pm0.127)I_{oPh} + 4.679(\pm0.280)$	36	0.832	0.692	0.346	17.40	2.277	0.000	0.560
5	$pIC_{50(COX\text{-}1\ HWB)} = -1.212(\pm0.450)R + 4.098(\pm0.181)$	14	0.614	0.377	0.305	7.27	0.915	0.019	—
6	$\log[COX\text{-}1/COX\text{-}2] = -1.088(\pm0.232)\pi_3 - 0.727(\pm0.171)B1_2 + 3.22(\pm0.246)$	15	0.834	0.695	0.172	13.67	1.798	0.001	0.554

increases the COX-2 inhibitory activity. This is in good agreement with the known hydrophobic binding pocket in the receptor-binding site of the COX-2 enzyme. At this point it is noteworthy to mention our attempts to derive a parabolic relationship between $\log P$ and COX-2 inhibitory activity. Unfortunately, the parabolic model derived is not statistically acceptable as the t value of the $\log P^2$ term being 0.208 makes it insignificant even at 95% confidence interval (tabulated t value is 2.120 at 95% level of significance for two-tailed

Table 4. Significant descriptors and predicted activities through derived QSAR models 7–10 for series 2 compounds

Compd	Descriptors				Predicted activity				
	C log *P*	*CMR*	I_{BP}	I_{Cl}	Model 7	Model 8	Model 8a	Model 9	Model 10
1	1.92	9.32	0	1	2.6422	2.6616	2.7072	2.7482	2.6539
2	2.08	9.34	0	1	2.7628	2.6805	2.7268	2.7573	2.7379
3	2.08	9.34	0	1	2.8040	2.7291	2.7773	2.7993	2.7803
4	2.08	9.34	0	1	2.7618	2.6793	2.7255	2.7562	2.7368
5	2.48	9.82	0	1	3.0224	2.9169	2.9685	2.7441	2.9008
6	2.48	9.82	0	1	3.0338	2.9275	2.9798	2.7561	2.9200
7	2.24	9.36	0	1	2.8686	2.6867	2.7331	2.7554	2.8073
8	2.24	9.36	0	1	2.8656	2.6829	2.7291	2.7521	2.8038
9	2.24	9.36	0	1	2.8821	2.7040	2.7511	2.7706	2.8234
10	3.59	11.84	1	1	3.6273	3.8170	3.9389	4.0559	3.9888
11	2.82	10.25	0	1	3.2542	3.1351	3.1938	2.7365	3.0397
12	1.79	9.94	0	1	2.6251	3.0347	—	2.8018	2.6694
13	1.85	9.13	0	1	2.5733	2.5369	2.5803	2.7371	2.6014
14	2.41	9.79	0	1	2.9908	2.9188	2.9710	2.7624	2.8949
15	3.75	11.85	1	1	3.7349	3.8154	3.9385	4.0383	4.1054
16	0.58	9.11	0	1	1.5640	2.6245	2.6705	2.8025	2.0162
17	2.04	8.85	0	0	2.7485	2.4228	2.4652	2.7693	2.7327
18	2.62	10.20	0	1	3.1175	3.1108	3.1686	2.7408	2.9586

test). The reason for this downfall is due to the narrow range of log *P* values of the series (0.5832 to 3.5955) studied.

$$\mathrm{pIC}_{50(\text{COX-2 MPM})} = 0.487(\pm 0.094)MR - 1.860(\pm 0.926)$$

$$n = 18, \quad r = 0.791, \quad r^2 = 0.625, \quad s = 0.327,$$
$$F_{1,16} = 26.67, \quad q^2 = 0.5497, \quad p = 0.000,$$
$$DW = 2.896. \tag{8}$$

Model 8 accounts for only 62.5% variance in observed activity. The term *MR*, as calculated from C log *P* server of Chem3D suite, is a measure of volume occupied by an atom or groups of atoms. Its calculation is based on the Lorentz–Lorentz equation, $MR = (n^2-1)/(n^2+2)MW/d$, where *n* is the index of refraction, *MW* represents molecular weight of the compound and *d* is the density. It is a measure of volume and polarizability of the whole molecule. The positive coefficient of *MR* indicates an overall increase in size of molecules for improved COX-2 inhibitory activity.

$$\mathrm{pIC}_{50(\text{COX-2 MPM})} = 0.499(\pm 0.074)MR - 1.928(\pm 0.729)$$

$$n = 17, \quad r = 0.866, \quad r^2 = 0.750, \quad s = 0.257,$$
$$F_{1,15} = 45.03, \quad q^2 = 0.6984, \quad p = 0.000,$$
$$DW = 2.685. \tag{8a}$$

Model 8a is developed for 17 compounds upon omitting compound **12** as an outlier from model 8. The overall statistics were improved. Even though the reason for the outlying behavior of compound **12** is not quite clear, it is the inactive member of the series with methoxyl substitution at the third aryl ring of pyran nucleus.

$$\mathrm{pIC}_{50(\text{COX-2 MPM})} = 1.285(\pm 0.239)I_{BP} + 2.762(\pm 0.080)$$

$$n = 18, \quad r = 0.803, \quad r^2 = 0.644, \quad s = 0.318,$$
$$F_{1,16} = 28.97, \quad q^2 = 0.5907, \quad p = 0.000,$$
$$DW = 2.469. \tag{9}$$

Model 9 is developed with an indicator variable, I_{BP}. I_{BP} assumes a value of 1 when biphenyl substitution occurs at the 3- position of the pyran-4-one structure and 0 for others. The positive contribution of I_{BP} suggests a biphenyl substitution for improved COX-2 inhibitory activity. This is consistent with the observation that the potent members of the series, compounds **10** and **15**, are biphenyls. The failure of contribution of indicator variable, I_{Cl}, (used in order to account for binary structural variation at the fifth position of pyran-4-one ring among the congeners) suggests the presence or absence of the chlorine atom at this position does not influence the COX-2 inhibitory activity.

$$\mathrm{pIC}_{50(\text{COX-2 MPM})} = 0.423(\pm 0.130)\log P + 0.627(\pm 0.277)I_{BP} + 1.864(\pm 0.284)$$

$$n = 18, \quad r = 0.889, \quad r^2 = 0.791, \quad s = 0.252,$$
$$F_{2,15} = 28.41, \quad q^2 = 0.7497, \quad p = 0.000,$$
$$DW = 2.796. \tag{10}$$

Model 10 is a biparametric equation developed by adding I_{BP} to model 7. The addition of this predictor variable is statistically significant above 95% confidence interval. The two descriptors of model 4 slightly suffer from the collinearity problem ($|r| = 0.53$). This indicates that both the properties to some extent tend to convey

the same phenomenon or in other words the highest activity of biphenyl analogs is attributed to their maximum hydrophobicity as compared to other derivatives. The log *P* values of most active compounds **10** and **15** are 3.59 and 3.75, respectively. The predictive ability of all our derived models are fairly good as discerned by the loo q^2.

In conclusion, our study brings important physicochemical and structural requirements among the recently reported novel derivatives of 2-phenylpyran-4-ones as selective COX-2 inhibitors. Investigations on 3-phenoxypyran-4-one subset A of series 1 revealed 2 fluoro substituents as crucial in governing COX-2 inhibitory activity. Hydrophobic and electronic interactions are primarily responsible for COX-2 binding. In contrast, 4 fluoro substituents are pivotal in improving the COX-2 inhibitory activity among 3-phenylpyran-4-ones under subset *B* of series 1. A combined QSAR analysis of series 1 shows electron-donating substituents around the 3-phenyl ring resulted in better COX-2 inhibitory activity. Hydrophobic substituents at the 4 position and substituents with a larger first atom at the 2 position are favorable for COX-2 inhibitory activity. Selective inhibition of COX-2 over COX-1 could be influenced by highly polar 3 substituents of pyran-4-ones. Also, 2 substituents seem to have negative steric effects on selective COX-2 binding. Relatively larger molecules with increased hydrophobicity are crucial in governing the COX-2 inhibitory activities among 2,3-diaryl pyran-4-ones of series 2 compounds. A bulkier hydrophobic ring substitution such as biphenyls seems to improve the activity considerably among series 2 analogs. Thus the results divulged here could further exploit this type of new lead for improved selective COX-2 inhibitory activity.

For series 1 compounds, COX-2 and COX-1 inhibitory activities were reported as IC_{50} in μM units using the whole blood assay method as described by Patrignani et al.[19] IC_{50} here denotes the micromolar concentration of compounds causing 50% of enzyme inhibition. The reported COX-2 and COX-1 IC_{50} data were converted to $-\log[IC_{50}]$ in molar units, $pIC_{50(COX\text{-}2\ HWB)}$ and $pIC_{50(COX\text{-}1\ HWB)}$, respectively. For COX-2 over COX-1 selectivity, the log of reported selectivity ratios, that is, log[COX-1/COX-2] was taken into consideration. Various aromatic substituent constants were derived from literature.[20,21] The parameters used for QSAR analysis include the hydrophobic parameter (π), molar refractivity (*MR*), Hammett electronic constant (σ), electronic field (*F*) and resonance (*R*) effects, Verloop's sterimol parameters viz., *B*1, *B*5 and *L*. For series 2 compounds, the COX-2 inhibitory activity data (IC_{50} in μg/ml) retained for the study was obtained from the mouse peritoneal macrophage method.[22] The reported IC_{50} data were converted to the negative logarithm, $pIC_{50(COX\text{-}2\ MPM)}$. C log *P* and *CMR* of whole molecules were calculated using ChemOffice 2001 molecular modeling software version 6.0, supplied by Cambridge Soft Corporation, USA. Based on the collinearity problem among the descriptors and their contribution towards the biological activity, different descriptors and/or a combination of descriptors were subjected to linear regressions using Systat 10.2 version. Parameters having intercorrelation above $lrl > 0.5$ and those that were insignificant at 95% confidence interval were not considered whilst deriving the QSAR models. The statistical quality of the models was gauged by the parameters like correlation coefficient (*r*) or squared correlation coefficient (r^2), standard error of estimate (*s*), variance ratio (*F*) and student's *t* test. The figure within the parentheses indicates the standard error of each regression coefficient and the constant. The level of significance of each regression term was assessed using *t*-test. In order to corroborate the validity of the derived QSAR models, leave-one-out (loo) method was used. Each compound is eliminated once, a model is derived from the remaining compounds and the eliminated compounds are predicted from this model. The same procedure is repeated after elimination of another compound until all the compounds have been eliminated once. Sum of squared prediction errors called predictive residual sum of squares (PRESS) statistic is calculated as the sum of squares of the differences between predicted and observed values of the activity. Standard deviation of prediction (Spress), the cross-validated correlation coefficient (q^2) and standard error of predictions (SDEP) were calculated for each model and taken as an estimate of the predictability of the models. A compound was considered as an outlier for deriving a particular model when the residual value exceeded twice the standard error of estimate of the model. Durbin–Watson (*DW*) test was used to check for serial correlation among residuals during regression analysis.[23]

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References and notes

1. Botting, J. H. *Drugs Today* **1999**, *35*, 225.
2. Vane, J. R. *Nature (London)* **1971**, *231*, 232.
3. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegeman, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isaksen, P.; Stalling, W. C. *Nature (London)* **1996**, *384*, 644.
4. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Doctor, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
5. Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y.; Gordon, R.; Guay, J.; Gresser, M.; Kargman, S.; Kennedy, B.; Leblanc, Y.; Leger, S.; Mancini, J.; O'Neill, G. P.; Ouellet, M.; Percival, M. D.; Perrier, H.; Riendeau, D.; Rodger, I. W.; Tagari,

P.; Therien, M.; Vickers, P.; Wong, E.; Xu, L.-J.; Young, R. N.; Zambani, R.; Boyce, S.; Rupniak, N.; Forest, M.; Visco, D.; Patrick, D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773.
6. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, D. J.; Shaffer, A. F.; Zhang, Y. Y.; Zweiefel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
7. Talley, J. J.; Bertenshaw, S. R.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Kellogg, M. S.; Koboldt, C. M.; Yuan, J.; Zhang, Y. Y.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 1661.
8. Oshima, M.; Dinchuk, J. E.; Kargman, S. L.; Oshima, H.; Hancock, B.; Kwong, E.; Trzaskos, J. M.; Evans, J. F.; Taketo, M. M. *Cell* **1996**, *87*, 803.
9. Teismann, P.; Tieu, K.; Choi, D. K.; Wu, D. C.; Naini, A.; Hunot, S.; Vila, M.; Jackson-Lewis, V.; Przedborski, S. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 5473.
10. Pasinetti, G. M. *Neurosignals* **2002**, *11*, 293.
11. Chavatte, P.; Yous, S.; Marot, C.; Baurin, N.; Lesieur, D. *J. Med. Chem.* **2001**, *44*, 3223.
12. Garg, R.; Kurup, A.; Mekapati, S. B.; Hansch, C. *Chem. Rev.* **2003**, *103*, 703.
13. Joo, Y. H.; Kim, J. K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413.
14. Joo, Y. H.; Kim, J. K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J. K.; Lim, K. M.; Chung, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2195.
15. Caturla, F.; Jimenez, J.-M.; Godessart, N.; Amat, M.; Cardenas, A.; Soca, L.; Beleta, J.; Ryder, H.; Crespo, M. I. *J. Med. Chem.* **2004**, *47*, 3874.
16. Prasanna, S.; Manivannan, E.; Chaturvedi, S. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4005.
17. Prasanna, S.; Manivannan, E.; Chaturvedi, S. C. *QSAR Comb. Sci.* **2004**, *23*, 621.
18. Prasanna, S.; Manivannan, E.; Chaturvedi, S. C. *Arch. Pharm. Med. Chem.* **2004**, *337*, 440.
19. Patrignani, P.; Panara, M. R.; Greco, A.; Fusco, O.; Natoli, C.; Iacobelli, S.; Chipollone, F.; Ganci, A.; Creminone, C.; Maclouf, J.; Patrono, C. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 1705.
20. Hansch, C.; Leo, A. *Substituents Constants for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1979.
21. Verloop, A. *In the Sterimol Approach to Drug Design*; Dekker: New York, 1987.
22. Mitchell, J. A.; Akarasereenont, P.; Thiermann, C.; Flower, R. J.; Vane, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 11693.
23. Durbin, J.; Watson, G. S. *Biometrika* **1951**, *38*, 159.