Cyclooxygenase (COX) Inhibitors: A Comparative QSAR Study

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I. Introduction

Cyclooxygenase (COX) or prostaglandin endoperoxide synthase (PGHS) catalyzes the first step in the biosynthesis of the prostaglandins (PGs) from the substrate arachidonic acid (AA).[1,2] COX enzyme possesses two distinct catalytic activities: (1) cyclooxygenase activity that catalyzes the oxidation of AA to produce hydroperoxy endoperoxide (PGG_2) and (2) peroxidase activity that reduces the hydroperoxide PGG_2 to the hydroxy endoperoxide (PGH_2). The PGH_2 is transformed by a range of enzymic and nonenzymic mechanisms into the primary prostanoids. In addition, arachidonic acid is a substrate for a variety of additional oxidative enzymes such as lipoxygenase, which generates biologically active lipids: hydroperoxyeicosatetraenoic acid (HPETE), hydroxyeicosatetraenoic acid (HETE), and leukotrienes (LTA_4, LTB_4, LTC_4, and LTE_4) (Figure 1).

A branched-chain radical mechanism (Figure 2) has been proposed to integrate the two catalytic activities performed by cyclooxygenase, which is a hemeprotein.[3,4] The first step of the reaction is

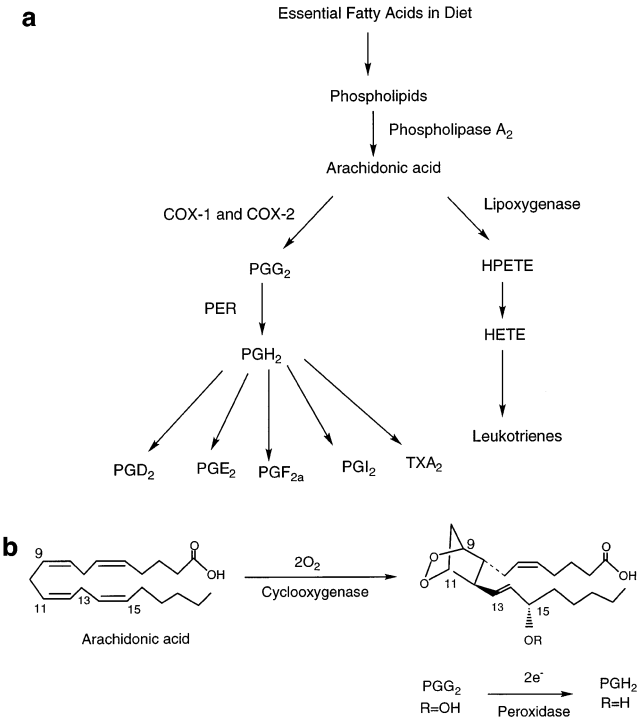

Figure 1. (a) Arachidonic acid cascade; (b) catalysis by cyclooxygenase.

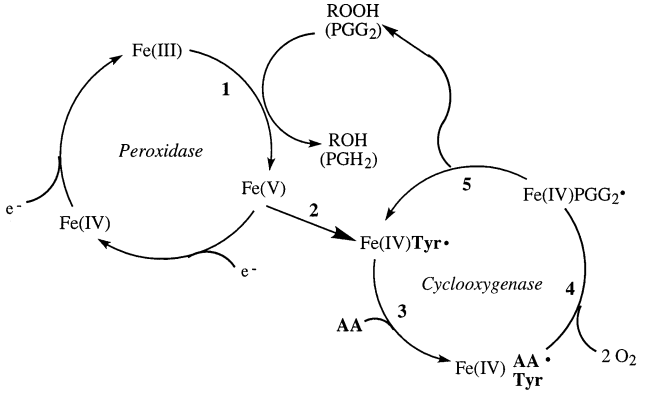

Figure 2. Proposed scheme for radical mechanism of cyclooxygenase activity.[5]

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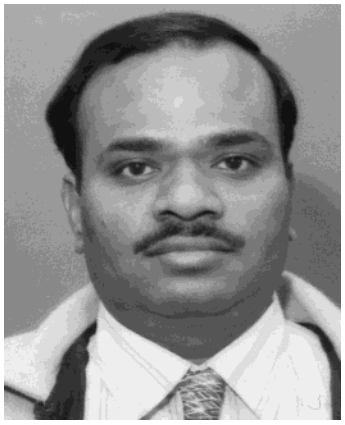
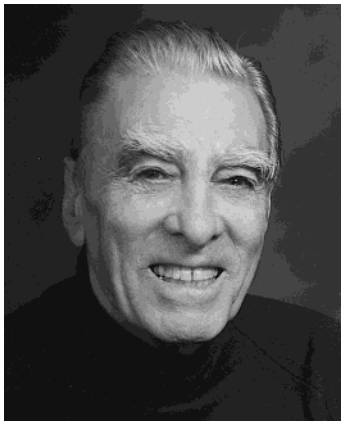
Alka Kurup received her undergraduate degree in pharmacy in 1981 from Birla Institute of Technology and Science in Pilani, India. In 1988, she received her Masters degree from the College of Pharmacy in Manipal, India. For two years she assumed Inchargeship and Quality Control of the Pharmacy Manufacturing Wing at Kasturba Medical College in Manipal. In 1991, she joined Birla Institute of Technology and Science as a faculty member in the Department of Pharmacy. She completed her Ph.D. degree in 1997 under the supervision of Professor S. P. Gupta with her thesis regarding QSAR studies of anticancer drugs. She joined Professor Hansch's group in July 1998 to pursue postdoctoral research. Currently, she is involved in building the C-QSAR database. Her research interests include QSAR and computer-aided drug design.



Suresh B. Mekapati was born in 1969 in India. He obtained a B.S. degree in pharmacy (1990) from Annamalai University, Chidambaram, and an M.S. degree in pharmacy from Birla Institute of Technology and Science, Pilani, India. He was a faculty member in the Pharmacy Department of Birla Institute of Technology and Science under the supervision of Professor S. P. Gupta. His doctoral work was on QSAR studies on anti-HIV agents. In February 2000 he joined Professor Hansch's laboratory at Pomona College to pursue postdoctoral research, and he is currently involved in building a C-QSAR database. His research interests include QSAR and computer-assisted drug design.



Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in organic chemistry from New York University in 1944. After working with the Du Pont Co., first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich, Switzerland, with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

oxidation of Fe(III) to Fe(V), which gets converted into Fe(IV)Tyr$^{\bullet}$ radical in the second step. In the third step this tyrosyl radical reacts with bound AA to form a fatty acid radical Fe(IV)Tyr/AA$^{\bullet}$, which then reacts with molecular oxygen and rearranges to form an Fe(IV)PGG_2 radical. Tyrosyl radical [Fe(IV)Tyr$^{\bullet}$] is regenerated and PGG_2 is released, which is reduced to PGH_2 using the electrons released in the first step.[5]

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit their effect by inhibiting COX enzymes and by blocking the synthesis of proinflammatory prostaglandins.[6,7] The use of NSAIDs for the treatment of inflammation and pain[1,8] is often accompanied by gastrointestinal ulceration,[9] bleeding,[10] and suppression of renal functions.[11,12]

In the late 1980s it was observed that the level of cellular COX protein increased after stimulation with interlukin-1, TNF alpha, or bacterial endotoxin. This increase could be blocked by administration of glucocorticoids. Needleman and coauthors postulated the existence of an inducible, second isoform of COX enzyme and hypothesized on its potential benefits.[13] Rosen et al.[14] reported that exposing sheep tracheal cells in culture to growth factors increased the ability of the cells to synthesize prostaglandins compared to that of freshly isolated cells. The appearance of a 4-kb mRNA gene, hybridized with COX-1 cDNA,

seems to be responsible for this increased activity.[14] There was no change in the 2.8 kb mRNA of COX-1 when the cells were exposed to growth factors. Rosen et al. proposed that a 4-kb mRNA coded for a COX protein and was the product of a distinct gene.[14] NSAIDs inhibited the expression of this inducible form of COX, not that of the basal COX. On the basis of these observations Fu et al. proposed the existence of separate pools of COX protein that were regulated independently.[15a] For more details readers are encouraged to see a recent paper by Marnett and DuBois.[15b] A year later, molecular cloning experiments identified a distinct isoform known as cyclooxygenase-2 (COX-2).[16]

It is now established that two distinct COX isoforms exist: the constitutive form (COX-1) expressed virtually in all tissues and the inducible form (COX-2) that is largely restricted to the brain and kidney. During normal physiology COX-2 levels are undetectable in most tissues. During periods of acute and chronic inflammation, however, the level of COX-2 is very often significantly higher. The association of COX-2 with inflammation led to the hypothesis that selective inhibitors of COX-2 might be anti-inflammatory without the side effects of the current NSAIDs.

In the present paper we have discussed in detail the QSAR studies on COX-2 inhibitors. We have also included QSAR studies on COX-1 inhibitors for comparison.

COX Structure. The crystal structures of sheep COX-1[17] and mouse and human COX-2 have been solved at 3−3.4 Å resolution.[18,19] There is a high degree of conservation (60% identical sequence in same species) among the residues that line the COX active site, but subtle differences exist that are critical for selective binding of inhibitors.

COX-2 is a homodimeric, glycosylated, monotopic membrane protein; the cyclooxygenase monomer has an approximate molecular weight of 72 kDa. The monomer is composed of three domains: the N-terminal EGF domain, the helical membrane binding domain, and the large catalytic domain. The catalytic domain, which is the largest of the three domains, contains both the cyclooxygenase and peroxidase active sites. The membrane-binding domain of COX-2 includes four helices (A−D, residues 75−115) that form a collar at the base of the catalytic domain. A single amino acid insertion of a proline residue at position 106 is observed in COX-2; it is referred to as residue 106a.[18]

The central channel of COX-2 is larger than that of COX-1 (17%). This difference in size is due to the change of some amino acid residues that increase the size and change the chemical environment of the binding pocket of NSAIDs. The most critical structural feature conferring sensitivity to inhibition by COX-2 is exchange of valine in COX-2 at positions 434 and 523 in place of isoleucine in COX-1. (It is important to note that the residues in COX-2 are given the same number as their equivalent amino acids in COX-1 for convenience; however, the exact amino acid residue number in COX-2 should be calculated by subtracting 14 from the COX-1 number.[18,20]) Also in COX-2, 17 amino acids are absent from the N terminus and 18 amino acids are inserted at the C terminus in comparison to COX-1.[21,22]

The change to the small Val523, one of the amino acids lining the binding site in COX-2, permits access to a pocket (or nook) near the mouth and adjacent to the hydrophobic central channel of the binding pocket, increasing the volume of the COX-2 binding site many times beyond that resulting from the loss of a single methyl group.[18] A second Val434 substitution in COX-2 present in the second shell of amino acids lining the active site increases the mobility of Phe518 that allows this amino acid to swing out of the way, further increasing access to the side chamber. The larger main channel and extra nook make the total binding site ∼25% larger in COX-2 than in COX-1. This extra size is essential for selective inhibition of COX-2. If access to this side chamber is restricted by switching valine back to isoleucine, COX-2 is no longer differentially sensitive to these inhibitors.[23,24]

The second essential amino acid change that results in the sensitivity of the drug toward COX-2 is the exchange of His513 in COX-1 for an arginine in COX-2. This arginine is within bonding distance of the sulfonamide moiety in the crystal structures of COX-2 with the diarylhetrocyclic inhibitor SC558.[19] In vitro mutagenesis experiments confirm its importance for time-dependent inhibition by this class of inhibitors.[25]

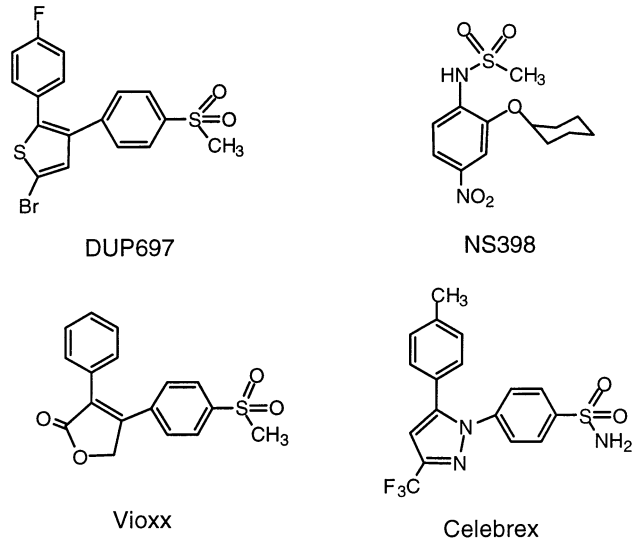
The overall larger size of the central channel of the COX-2-binding pocket may also preferentially reduce steric and ionic crowding by the charged Arg120 in COX-2 and thus preferentially increase binding of nonacidic NSAIDs by this isozyme.

The COX active site narrows at the top into a channel that opens to the surface near the dimer interface. The proximal end of this channel appears to bind the ω-end of arachidonate. Tyr385 is positioned near the top of the COX active site just below the heme prosthetic group. Tyr385 is converted to a tyrosyl radical during catalysis and appears to be responsible for oxidation of arachidonic acid.[3,5,26,27]

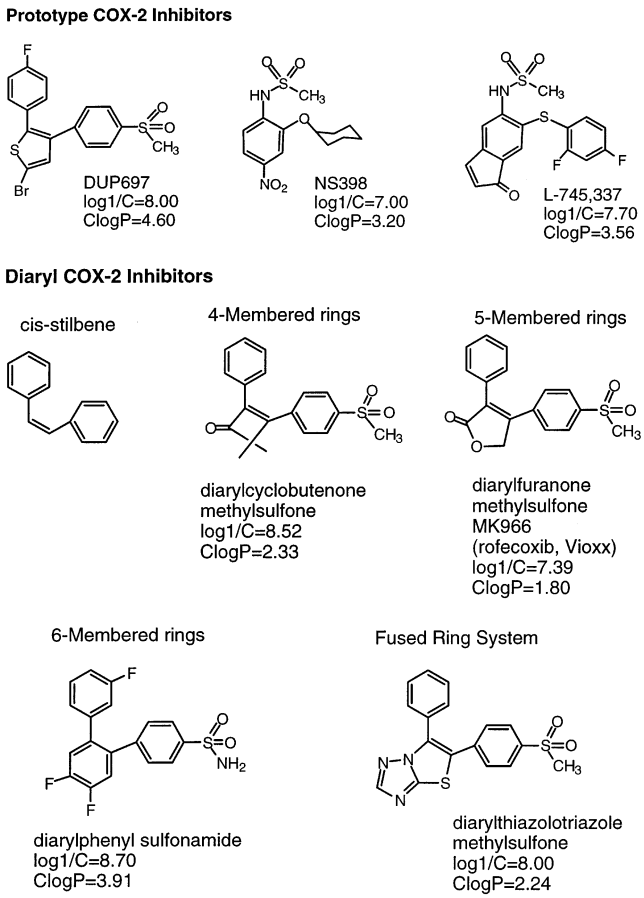
In 1995, Copeland et al.[20a,28] did kinetic experiments and reported that the selectivity occurs because COX-2 selective inhibitors inhibit COX-2 by a time-dependent slowly reversible mechanism, whereas they inhibit COX-1 by a freely reversible competitive mechanism. Time-dependent inhibition occurs when the freely reversible cyclooxygenase−inhibitor complexes undergo a conformational change to form a tightly bound complex. It is also important to note that there are many nonselective NSAIDs which are time-dependent for both COX-1 and COX-2.[20b] However, recent experiments[20c] proposed a time-dependent binding of diaryloxazole (SC2999), a selective COX-2 inhibitor, with both the isozymes with the difference that it binds to COX-2 in three distinct kinetic steps and COX-1 in two steps. See ref 20C for more details.

Development of COX-2 Selective Inhibitors. The first COX-2 selective compounds identified were DUP697[29] and NS398,[30] two NSAIDs already in development when COX-2 was discovered. These

compounds were shown to be 80 and 1000-fold selective, respectively, in animal models, tested for inhibition of recombinant human COX-2.[23,31] Although the development of NS398 and DUP697 was later discontinued, the structure of DUP697 was the starting point for the synthesis of the diaryl heterocyclic family of selective inhibitors, which include recently marketed celecoxib (SC58635, Celebrex)[32,59] and Rofecoxib (MK-966, Vioxx).[33]



The enormity of the COX-2 discovery is reflected in the unprecedented speed at which research laboratories have sought to validate its clinical implications. Several different major structural classes of COX-2 selective inhibitors have been identified[34,35] including the diaryl heterocyclics, acidic sulfonamides, and 2,6-di-*tert*-butylphenols, as well as the derivatives of nonselective inhibitors zomepirac, indomethacin, piroxicam, and aspirin. Some of them are shown in Figure 3. In a recent review Danhardt et al.[36] have described the current status of cyclooxygenase inhibitors in detail.



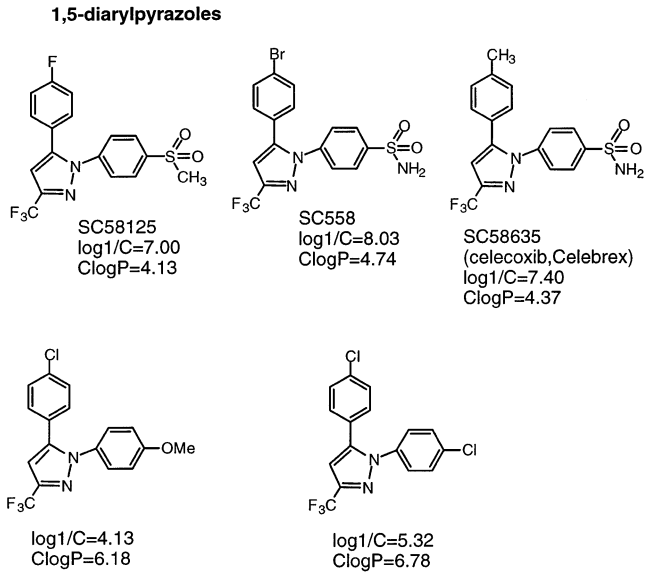


Figure 3. Structures of some of the COX-2 inhibitors.

The use of quantitative structure−activity relationships (QSAR) since its advent[37] has become increasingly helpful in understanding many aspects of chemical−biological interactions in drug and pesticide research as well as in many areas of toxicology. Getting a new QSAR no longer calls for rushing into print. Lateral support is required from as many points of view as possible.[38−46] The new subject of information science that depends so heavily on computers is in a rapid state of development. We have been working on its development in chemical−biological reactions for the past 30 years. Now we have a good start on an information database that contains over 18,000 QSAR, of which 9150 pertain to chemical−biological interactions; the remainder are for pure chemical reactions for comparison (C-QSAR Program, BioByte Corp., Claremont, CA).[47] We report here the comparative QSAR studies on human cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2) inhibitors.

II. Materials and Methods

All of the COX-1 and COX-2 inhibitory data have been collected from the literature (see individual data sets for respective references). It is expressed as IC_{50}, the molar concentration of the compound causing 50% inhibition of enzyme. All of the physicochemical parameters are autoloaded, and the C-QSAR regression analyses were executed with the C-QSAR program.[47] The utility of the QSAR program in comparative correlation analysis has been discussed.[48−50] When different QSAR are compared, however, it must be borne in mind that the different qualities of

testing in the various laboratories will have an effect that cannot be estimated.

The parameters used in this paper have been discussed in detail along with their applications.[48] Here we provide a brief definition. CMR is the calculated molar refractivity for the whole molecule. MR is calculated as follows: $(n^2 - 1/n^2 + 2)$ (MW/d), where n is the refractive index, MW is the molecular weight, and d is the density of a substance. MR is dependent on volume and polarizability. We have scaled our MR values by 0.1. MR can be used for a substituent or for the whole molecule. MgVol is the molar volume calculated by using the methods of McGowan.

B1, B5, and L are Verloop's sterimol parameters for substituents.[51] B1 is a measure of the width of the first atom of a substituent, B5 is an attempt to define the overall volume, and L is the substituent length. Es is Taft's steric constant.

ClogP is a calculated partition coefficient in octanol/water and is a measure of hydrophobicity. π is the hydrophobic parameter for substituents usually measured for substituents attached to benzene. ClogP and CMR are for the neutral form of partially ionized compounds.

σ, σ^-, and σ^+ are Hammett electronic parameters, which apply to substituent effects on aromatic systems. The normal σ for substituents on aromatic systems where strong resonance between substituent and reaction center does not occur is defined as $\sigma = \log K_X - \log K_H$, where K_H is the ionization constant for benzoic acid (normally in water or in 50% ethanol) and K_X is that for substituted benzoic acid. σ^- and σ^+ are employed when there is a strong resonance interaction between substituent and reaction center. Of these σ^- is defined using the ionization constants from phenols or anilines similar to σ: $\sigma^- = \log K_X - \log K_H$, where K refers to the ionization of anilines or phenols. Whereas σ and σ^- are defined via equilibrium constants, σ^+ is defined by the rate of solvolysis of cumene chlorides in 90% acetone/10% water. Taft's σ^* applies electronic effects in aliphatic systems. σ_I is a measure of the inductive effect of aliphatic substituents. The indicator variable I is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used.

In QSAR equations, n is the number of data points, r is the correlation coefficient, s is the standard deviation, q is a measure of the quality of fit and calculated as described by Cramer et al.,[52] and the data within the parentheses are for the 95% confidence intervals.

All of the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced. All of the sets were tested against recombinant human COX-1 and COX-2 enzymes except where mentioned.

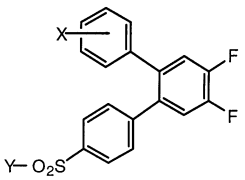
III. Results and Discussion

The QSAR have been divided into two groups according to the COX enzyme. Within each group we have tried to put together structurally analogous molecules for comparative study. The log 1/C range for each set of congeners is also listed with the QSAR.

A. QSAR of COX-2 Inhibitors

1. Terphenyls

*IC_{50} of 1-(X-phenyl)-2-(4-SO_2-Y-phenyl)-4,5-di-F-phenyl (**1**) (Table 1).*



1

$$\log 1/C = 1.12(\pm 0.20)\text{ClogP} - 0.83(\pm 0.27)\sigma^+_X - 1.06(\pm 0.24)\text{CMR} + 0.45(\pm 0.14)I_Y + 12.91(\pm 1.91) \quad (1)$$

$$n = 24,\ r^2 = 0.909,\ q^2 = 0.845,\ s = 0.164$$

outliers: X = 3-OCH_2O-4, Y = Me; X = 3-OCH_2O-4, Y = NH_2; X = 3,4-Me_2, Y = Me

range in log 1/C = 7.19−8.70

A novel series of terphenyl methyl sulfones and sulfonamides studied by Li et al.[53] were shown to be highly potent and selective COX-2 inhibitors. Equation 1 derived for the same shows steric, electronic, and hydrophobic interactions with the receptor. A

Table 1. IC_{50} Data for the Inhibition of COX-2 by Compound 1[53]

	substituent		log 1/C						
no.	X	Y	obsd	calcd (eq 1)	Δ	ClogP	I_Y	σ^+_X	CMR
1	4-F	Me	7.85	8.05	−0.19	4.67	0	−0.07	9.09
2	4-F	NH_2	8.40	8.41	−0.02	4.50	1	−0.07	9.00
3	3-Cl-4-F	Me	8.00	8.01	−0.01	5.38	0	0.30	9.59
4	3-Cl-4-F	NH_2	8.70	8.38	0.32	5.22	1	0.30	9.49
5	3-Me-4-F	Me	8.30	8.17	0.13	5.17	0	−0.14	9.56
6	3-Me-4-F	NH_2	8.70	8.54	0.16	5.00	1	−0.14	9.46
7	3-F-4-OMe	Me	7.68	7.53	0.15	4.52	0	−0.44	9.71
8	3-F-4-OMe	NH_2	7.89	7.91	−0.02	4.37	1	−0.44	9.62
9	3-Cl-4-OMe	Me	7.72	7.60	0.13	5.06	0	−0.41	10.19
10	3-Cl-4-OMe	NH_2	7.89	7.98	−0.09	4.91	1	−0.41	10.09
11	3,5-Cl_2-4-OMe	NH_2	7.68	7.74	−0.06	5.43	1	−0.04	10.58
12	3-Me-4-OMe	Me	7.89	7.88	0.01	4.96	0	−0.85	10.16
13	3-Me-4-OMe	NH_2	8.30	8.24	0.06	4.79	1	−0.85	10.06
14	3,4-$(OMe)_2$	Me	6.47	6.68	−0.21	4.17	0	−0.66	10.31
15	3,4-$(OMe)_2$	NH_2	7.19	7.07	0.12	4.02	1	−0.66	10.22
16	3-OCH_2O-4	Me[a]	7.92	6.88	1.04	3.73	0	−0.68	9.67
17	3-OCH_2O-4	NH_2[a]	8.40	7.27	1.13	3.58	1	−0.68	9.58
18	4-Me	Me	8.16	8.17	−0.01	5.03	0	−0.31	9.54
19	4-Me	NH_2	8.40	8.53	−0.13	4.86	1	−0.31	9.45
20	3-Cl-4-Me	Me	7.89	8.13	−0.25	5.74	0	0.06	10.03
21	3-Cl-4-Me	NH_2	8.52	8.50	0.02	5.57	1	0.06	9.94
22	3,4-Me_2	Me[a]	7.64	8.23	−0.59	5.47	0	−0.38	10.01
23	3,4-Me_2	NH_2	8.30	8.60	−0.30	5.31	1	−0.38	9.91
24	3-Me-4-Cl	Me	8.22	8.15	0.07	5.74	0	0.04	10.03
25	3-Me-4-Cl	NH_2	8.52	8.52	0.01	5.57	1	0.04	9.94
26	3-Cl-4-NMe_2	Me	8.10	7.91	0.19	5.31	0	−1.33	10.87
27	3-Cl-4-NMe_2	NH_2	8.22	8.29	−0.07	5.15	1	−1.33	10.77

[a] Data points not included in equation derivation.

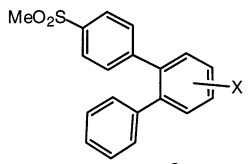
Table 2. IC_{50} Data for the Inhibition of COX-2 by Compound 2[54]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 2)	Δ	ClogP
1	H[a]	4.96	4.41	0.55	4.28
2	3-OH	3.83	4.04	−0.20	3.76
3	3-NH_2	3.71	3.63	0.08	3.19
4	4-NH_2	3.60	3.63	−0.03	3.19
5	3-NO_2	4.42	4.26	0.16	4.07
6	4-NO_2	4.36	4.26	0.10	4.07
7	3-COOMe	4.32	4.42	−0.10	4.29

[a] Data point not included in eqution derivation.

positive ClogP confirms the presence of a hydrophobic binding pocket in the receptor-binding site. The negative coefficient of σ^+ for X substituents shows that electron-donating X substituents favor activity via through-resonance. In our earlier work[41] we have found that a negative coefficient with σ^+ often correlates radical oxidation. CMR is calculated molar refractivity, which is a measure of the volume of the substituents, with a correction for the polarizability. From its negative coefficient in eq 1 it is evident that the COX-2 receptor has a limited tolerance to the bulk of the interacting molecules. It is of interest to note that there is a high mutual correlation between MgVol and CMR ($r^2 = 0.975$). Indicator variable I_Y was used with a value of 1 for Y = NH_2 and a value of 0 for Me. Its positive coefficient indicates that the presence of the NH_2 group at this position is conducive to the activity.

*IC_{50} of 1-(4-SO_2Me-phenyl)-2-phenyl-X-phenyl (**2**) (Table 2)*



2

$$\log 1/C = 0.72(\pm 0.40)\text{ClogP} + 1.35(\pm 1.51) \quad (2)$$

$$n = 6,\ r^2 = 0.861,\ q^2 = 0.737,\ s = 0.153$$

outlier: H

range in log 1/*C* = 3.60−4.96

This set of terphenyls was synthesized and studied by Pinto et al.[54] Equation 2 derived from their data shows a positive hydrophobic interaction of substituents with the receptor. A good correlation for this data set was also obtained with the Hammett constant σ ($\rho = 0.62$). However, σ and ClogP are mutually correlated ($r^2 = 0.746$), which makes it difficult to say whether these are truly hydrophobic or electronic interactions or both, as the small amount of data does not permit more detailed studies.

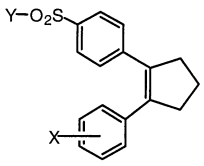
2. Cyclopentenes

*IC_{50} of 1-(X-phenyl)-2-(4-SO_2-Y-phenyl)-cyclopentene (**3**) (Table 3)*

Table 3. IC_{50} Data for the Inhibition of COX-2 by Compound 3[55]

	substituent		log 1/*C*						
no.	X	Y	obsd	calcd (eq 3)	Δ	σ^+_X	MgVol	$L_{X,3}$	$B1_{X,4}$
1	4-F	Me	7.59	7.65	−0.07	−0.07	2.32	2.06	1.35
2	4-F	NH_2	8.16	8.34	−0.18	−0.07	2.28	2.06	1.35
3	3,4-F_2	Me	7.29	7.14	0.15	0.27	2.33	2.65	1.35
4	3,4-F_2	NH_2	7.75	7.82	−0.08	0.27	2.29	2.65	1.35
5	3-Cl-4-F	Me	7.52	7.16	0.37	0.30	2.44	3.52	1.35
6	3-Cl-4-F	NH_2	8.00	7.84	0.16	0.30	2.40	3.52	1.35
7	3,4,5-F_3	NH_2	5.54	6.03	−0.49	0.61	2.31	2.65	1.35
8	4-Cl	Me	8.52	8.39	0.14	0.11	2.42	2.06	1.80
9	4-Cl	NH_2	8.52	9.07	−0.55	0.11	2.38	2.06	1.80
10	3,4-Cl_2	Me	8.00	7.89	0.11	0.48	2.54	3.52	1.80
11	3,4-Cl_2	NH_2	8.70	8.58	0.12	0.48	2.50	3.52	1.80
12	4-OMe	Me	8.30	7.76	0.54	−0.78	2.50	2.06	1.35
13	4-OMe	NH_2	8.70	8.44	0.26	−0.78	2.46	2.06	1.35
14	3-F-4-OMe	Me	6.92	7.25	−0.33	−0.44	2.52	2.65	1.35
15	3-F-4-OMe	Me	7.80	7.93	−0.14	−0.44	2.48	2.65	1.35
16	3-Cl-4-OMe	Me	6.85	7.27	−0.41	−0.41	2.62	3.52	1.35
17	3-Cl-4-OMe	NH_2	8.05	7.95	0.10	−0.41	2.58	3.52	1.35
18	3,5-Cl_2-4-OMe	Me[a]	7.77	3.59	4.18	−0.04	2.74	3.52	1.35
19	3,5-Cl_2-4-OMe	NH_2[a]	8.05	4.28	3.77	−0.04	2.70	3.52	1.35
20	4-NMe_2	Me	8.30	8.30	0.00	−1.33	2.80	3.52	1.35
21	3-Cl-4-NMe_2	NH_2	8.70	8.98	−0.29	−1.33	2.76	3.52	1.35
22	4-Me	Me	8.52	7.90	0.62	−0.31	2.44	2.06	1.52
23	4-CF_3	Me	6.06	6.37	−0.31	0.61	2.49	2.06	1.99
24	4-CF_3	NH_2	6.82	7.05	−0.23	0.61	2.45	2.06	1.99
25	3-F-4-CF_3	Me	6.12	5.85	0.27	0.95	2.51	2.65	1.99
26	3-F-4-CF_3	NH_2	6.77	6.54	0.23	0.95	2.47	2.65	1.99

[a] Data points not included in equation derivation.



3

$$\log 1/C = -4.42(\pm 0.82)\sigma^+_X - 16.66(\pm 3.71)\text{MgVol} + 2.18(\pm 0.53)L_{X,3} + 7.28(\pm 1.66)B1_{X,4} + 31.63(\pm 5.78) \quad (3)$$

$$n = 24,\ r^2 = 0.885,\ q^2 = 0.809,\ s = 0.341$$

outliers: X = 3,5-Cl_2−4-OMe, Y = Me; X = 3,5-Cl_2-4-OMe, Y = NH_2

range in log 1/*C* = 5.54−8.70

Equation 3 was derived for the data of Li et al.[55] From eq 3 it seems that electron-donating X substituents have a strong effect via through-resonance favoring receptor binding. Electron-donating groups will increase the electron density on the phenyl ring. Thus, the increased affinity of the derivatives with electron-donating groups could be due to an increased electronic interaction between enzyme and substrate analogues or radical reaction. MgVol is McGowan's volume, and its negative coefficient indicates that the larger molecules are unsuitable for good inhibitory activity. Here we found Verloop's sterimol parameter *L* and B1 significant. B1 is a steric parameter and a measure of the width of the first atom of the substituents, whereas *L* defines the length. A positive coefficient of B1 indicates that the 4-X substituents with the larger first atom are favorable. A positive *L*

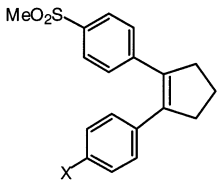
Table 4. IC_{50} Data for the Inhibition of COX-2 by Compound 4[56]

		log 1/C					
no.	substituent X	obsd	calcd (eq 4)	Δ	σ^+_X	$B1_X$	$B5_X$
1	4-F	7.59	7.39	0.19	−0.07	1.35	1.35
2	4-OMe	8.30	8.35	−0.05	−0.78	1.35	3.07
3	4-Cl	8.52	8.51	0.01	0.11	1.80	1.80
4	4-Me	8.52	8.61	−0.09	−0.31	1.52	2.04
5	H	5.65	5.38	0.27	0.00	1.00	1.00
6	4-CF_3	6.06	5.64	0.42	0.61	1.99	2.61
7	4-CN	4.11	4.59	−0.49	0.66	1.60	1.60
8	4-CH_2OH	5.50	6.04	−0.54	−0.04	1.52	2.70
9	4-CH_2OMe	5.18	4.91	0.27	−0.05	1.52	3.40
10	4-SMe[a]	6.66	9.27	−2.62	−0.60	1.70	3.26

[a] Data point not included in equation derivation.

indicates that the length of the X substituents at the 3-position is suitable for the activity. Li et al. reported that sulfonamide derivatives gave more potent but less selective COX-2 inhibitors with improved oral activity in the rat model. They found that potency of sulfonamide could be improved with incorporation of substituents at the 3-position of the second phenyl ring.

IC_{50} of 1-(4-X-phenyl)-2-(4-SO_2Me-phenyl)-cyclopentene ***(4)*** *(Table 4)*



4

$$\log 1/C = -5.43(\pm 1.29)\sigma^+_X + 6.34(\pm 2.06)B1_X - 1.68(\pm 0.63)B5_X + 0.72(\pm 2.52) \quad (4)$$

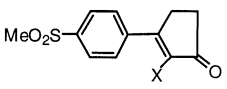
$$n = 9,\ r^2 = 0.959,\ q^2 = 0.858,\ s = 0.424$$

outlier: SMe

range in $\log 1/C = 4.11-8.52$

Reitz et al.[56] studied substituted diaryl cyclopentenes. Similar to eqs 1 and 3 we again observe a strong negative σ^+ term. It also suggests that electron-donating X substituents interact with the receptor via through-resonance, indicating a possible radical reaction. Verloop's sterimol steric parameters, B1 and B5 for the X substituents, are also found to be significant. B5 defines the overall volume. The positive coefficient of B1 indicates that the substituents with larger first atoms at the 4-X-position are favorable, whereas a negative B5 shows that the overall volume of these substituents would interfere with the binding of the molecules to the receptor. Therefore, bulkier X groups are detrimental to the activity.

*IC_{50} for COX-2 in CHO Cells by 2-X-3-(4-SO_2Me-phenyl)-2-cyclopenten-1-one (**5**) (Table 5)*



5

Table 5. IC_{50} Data for the Inhibition of COX-2 by Compound 5[57]

		log 1/C				
no.	substituent X	obsd	calcd (eq 5)	Δ	ClogP	MgVol
1	4-F-C_6H_4	7.72	7.70	0.02	2.25	2.33
2	C_6H_5	7.96	7.64	0.32	2.11	2.32
3	3-F-C_6H_4	7.85	7.70	0.15	2.25	2.33
4	3,4-F_2-C_6H_3	7.85	7.71	0.14	2.32	2.35
5	3,5-F_2-C_6H_3	7.82	7.77	0.05	2.39	2.35
6	3,5-Cl_2-C_6H_3	7.85	8.08	−0.23	3.53	2.56
7	3-Cl,4-F-C_6H_3	8.05	7.93	0.12	2.96	2.46
8	3-F,4-Cl-C_6H_3	7.82	7.93	−0.10	2.96	2.46
9	3,4,5-Cl_3-C_6H_2	8.22	8.10	0.13	4.01	2.68
10	3-pyridyl	6.77	6.48	0.29	0.61	2.27
11	5-Cl-3-pyridyl	7.06	6.78	0.29	1.41	2.40
12	5-Br-3-pyridyl	6.52	6.74	−0.21	1.56	2.45
13	4-Me-3-pyridyl	6.36	6.46	−0.10	1.11	2.41
14	4-methoxy-3-pyridyl	6.82	6.21	0.62	1.03	2.47
15	2-pyridyl	5.82	6.48	−0.67	0.61	2.27
16	4-Br-2-pyridyl	6.20	6.74	−0.54	1.56	2.45
17	4-Cl-2-pyridyl	6.72	6.78	−0.06	1.41	2.40
18	OC_6H_5	7.96	7.83	0.13	2.55	2.37
19	3,5-F_2-OC_6H_3	7.77	8.12	−0.35	3.02	2.41
20	CH═CH-(4-F-C_6H_5)[a]	6.76	7.63	−0.87	3.05	2.57
21	C≡C-C_6H_5[a]	8.22	7.14	1.08	2.26	2.51
22	C≡C-CMe_3[a]	6.82	7.53	−0.71	2.55	2.47

[a] Data points not included in equation derivation.

$$\log 1/C = 0.86(\pm 0.22)\text{ClogP} - 3.20(\pm 2.22)\text{MgVol} + 13.24(\pm 4.83) \quad (5)$$

$$n = 19,\ r^2 = 0.827,\ q^2 = 0.731,\ s = 0.328$$

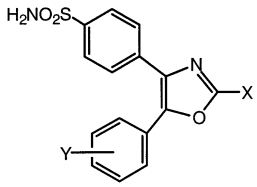
outliers: CH═CH-(4-F-C_6H_4); C≡C−C_6H_5; C≡C−CMe_3

range in $\log 1/C = 5.82-8.22$

Black et al.[57] published IC_{50} data for 2,3-diaryl cyclopentenones. These are believed to be highly selective COX-2 inhibitors. From the QSAR 5 we can see that the receptor has hydrophobic binding sites. However, as seen earlier (eq 3) there is a limitation for the overall volume of the ligand as there is a negative MgVol term in the equation. Black et al. reported that the pyridyl ring improves the activity. However, we could not detect a positive effect of pyridyl or phenyl derivatives.

3. Oxazoles

IC_{50} of 2-X-4-(4-SO_2NH_2-phenyl)-5-(Y-phenyl)-oxazole ***(6)*** *(Table 6)*



6

$$\log 1/C = 2.02(\pm 1.56)B1_X + 9.95(\pm 3.74)B5_{Y,4} - 2.18(\pm 0.84)(B5_{Y,4})^2 - 6.14(\pm 4.74) \quad (6)$$

Table 6. IC_{50} Data for the Inhibition of COX-2 by Compound 6[58]

	substituent		log 1/*C*				
no.	X	Y	obsd	calcd (eq 6)	Δ	$B1_X$	$B5_{Y,4}$
1	Me	H	4.65	4.70	−0.06	1.52	1.00
2	Me	4-Cl	8.22	7.79	0.43	1.52	1.80
3	Me	4-Br	8.00	8.06	−0.06	1.52	1.95
4	Me	3-F-4-OMe	7.27	6.97	0.30	1.52	3.07
5	CH_2OMe	4-Cl	7.40	7.79	−0.39	1.52	1.80
6	CH_2OMe	4-Br	7.82	8.06	−0.23	1.52	1.95
7	CH_2OH	H[a]	6.62	4.70	1.92	1.52	1.00
8	CF_2H	H[a]	7.70	5.09	2.61	1.71	1.00
9	CF_3	4-Cl	9.00	8.74	0.26	1.99	1.80
10	CF_3	3,4-Cl_2	8.70	8.74	−0.04	1.99	1.80
11	CF_3	3,4-F_2	7.40	7.34	0.06	1.99	1.35
12	CF_3	3-Cl-4-OMe	7.02	7.91	−0.89	1.99	3.07
13	CF_3	3-F-4-OMe	8.52	7.91	0.61	1.99	3.07

[a] Data points not included in equation derivation.

$$n = 11,\ r^2 = 0.875,\ q^2 = 0.684,\ s = 0.497$$

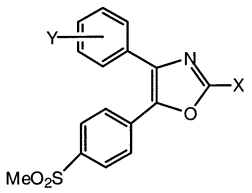
$$\text{outliers: X} = CH_2OH,\ \text{Y} = \text{H};\ \text{X} = CF_2H,\ \text{Y} = \text{H}$$

$$\text{optimum } B5_{Y,4} = 2.29(2.16-2.44)$$

$$\text{range in log } 1/C = 4.65-9.00$$

Talley et al.[58] synthesized and evaluated 2-substituted 4,5-diaryl oxazole derivatives for their ability to inhibit COX-2. A positive B1 for X substituents at the 2-position of the oxazole ring shows that these substituents have steric interactions with the receptor. Talley et al. also reported that the small substituents at the 2-position are generally well tolerated. A parabolic correlation for the Y substituents at the 4-position with B5 indicates that the substituents at this position favor activity initially and then are detrimental in a parabolic fashion with an optimum value of 2.29. This means that the activity first increases with an increase in the size of the substituents up to an optimum value of 2.29 and with further increase in size the activity decreases.

IC_{50} of 2-X-4-(Y-phenyl)-5-(4-SO_2Me-phenyl)-oxazole ***(7)*** *(Table 7)*



7

$$\log 1/C = -4.16\ (\pm 1.69)\sigma^+_Y + 0.32(\pm 0.26)\text{ClogP} + 5.95(\pm 0.79) \quad (7)$$

$$n = 7,\ r^2 = 0.948,\ q^2 = 0.802,\ s = 0.246$$

$$\text{outliers: X} = CMe_3,\ \text{Y} = 4-\text{F}$$

$$\text{range in log } 1/C = 6.25-8.70$$

One more set of congeners of 4,5-diaryloxazoles was reported by Talley et al.,[58] where SO_2Me replaces the SO_2NH_2 group in one of the phenyl rings. We observed a weak positive ClogP, indicating that the hydrophobicity of compounds may have a small effect on the activity. Electron-donating Y groups have a positive effect via through-resonance as evidenced by a negative coefficient of σ^+_Y conforming to our observations in QSAR 1, 3, and 4.

Table 7. IC_{50} Data for the Inhibition of COX-2 by Compound 7[58]

	substituent		log 1/*C*				
no.	X	Y	obsd	calcd (eq 7)	Δ	ClogP	σ^+_Y
1	Me	4-F	6.85	6.99	−0.14	2.31	−0.07
2	CH_2OH	H	6.25	6.23	0.02	0.86	0.00
3	CMe_3	4-F[a]	6.70	7.42	−0.72	3.64	−0.07
4	C_6H_5	4-F	7.40	7.58	−0.18	4.15	−0.07
5	$CH_2C_6H_5$	4-F	7.50	7.50	0.00	3.89	−0.07
6	$CH_2OCH_2C_6H_5$	H	7.07	6.94	0.14	3.06	0.00
7	CF_3	4-Me	8.70	8.34	0.36	3.41	−0.31
8	CF_3	3-F-4-OMe	8.52	8.73	−0.20	2.94	−0.44

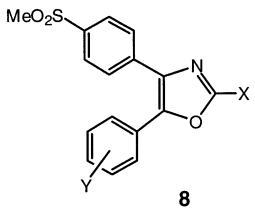
[a] Data point not included in equation derivation.

Table 8. IC_{50} Data for the Inhibition of COX-2 by Compound 8[58]

	substituent		log 1/*C*			
no.	X	Y	obsd	calcd (eq 8)	Δ	σ^+_Y
1	Me	4-F	6.85	7.25	−0.40	−0.07
2	CH_2OH	H[a]	5.71	7.01	−1.30	0.00
3	C_6H_5	4-F	7.40	7.25	0.15	−0.07
4	$CH_2C_6H_5$	4-F	7.50	7.25	0.25	−0.07
5	$CH_2OCH_2C_6H_5$	H	7.01	7.01	0.00	0.00
6	CF_3	3-F-4-OMe	8.52	8.52	0.00	−0.44

[a] Data point not included in equation derivation.

IC_{50} of 2-X-4-(4-SO_2Me-phenyl)-5-(Y-phenyl)-oxazole ***(8)*** *(Table 8)*



8

$$\log 1/C = -3.44(\pm 2.55)\sigma^+_Y + 7.01(\pm 0.52) \quad (8)$$

$$n = 5,\ r^2 = 0.860,\ q^2 = 0.764,\ s = 0.282$$

$$\text{outlier: X} = CH_2OH,\ \text{Y} = \text{H}$$

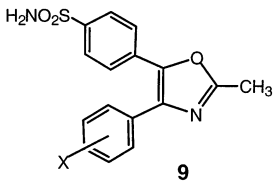
$$\text{range in log } 1/C = 5.71-8.52$$

This series was also studied by Talley et al.[58] Of course, this data set is too small and poorly designed to yield a satisfactory QSAR. σ^+ is highly collinear with $B5_{Y,4}$; however, we believe σ^+ is the parameter of importance. X substituents appear to have little effect on activity. Moreover, the data set being too small, it cannot be studied to see the effect of any other physicochemical property.

Table 9. IC_{50} Data for the Inhibition of COX-2 by Compound 9[58]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 9)	Δ	$B1_{X,4}$
1	H	7.57	7.44	0.13	1.00
2	4-F	8.05	7.88	0.17	1.35
3	4-Cl	8.52	8.45	0.07	1.80
4	4-Br	8.52	8.64	−0.12	1.95
5	3-F	7.21	7.44	−0.23	1.00

IC_{50} of 2-Me-4-(X-phenyl)-5-(4-SO_2NH_2-phenyl)-oxazole ***(9)*** *(Table 9)*



9

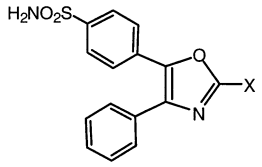
$$\log 1/C = 1.26(\pm 0.71)B1_{X,4} + 6.18(\pm 1.04) \quad (9)$$

$$n = 5,\ r^2 = 0.914,\ q^2 = 0.748,\ s = 0.197$$

$$\text{range in } \log 1/C = 7.21-8.52$$

In an attempt to explore more potent inhibitors of COX-2, Talley et al.[58] reported data on another series of 4,5-diaryl oxazoles. The 4-position X substituents show positive steric interaction. This set also has too few data points. However, the observation is the same as seen for QSAR 3 and 4.

IC_{50} of 2-X-4-phenyl-5-(4-SO_2NH_2-phenyl)-oxazole ***(10)*** *(Table 10)*



10

$$\log 1/C = 1.01(\pm 0.45)\text{ClogP} + 24.24(\pm 9.21)B1_X - 7.09(\pm 2.94)B1_X^2 - 14.97(\pm 7.18) \quad (10)$$

$$n = 17,\ r^2 = 0.862,\ q^2 = 0.767,\ s = 0.499$$

outliers: CH_2OH; SH; NH_2

$$\text{optimum B1} = 1.71\ (1.63-186)$$

$$\text{range in } \log 1/C = 4.10-8.40$$

In this series Talley et al.[58] explored the influence on the activity of various substituents at the 2-position of the oxazole ring of **10**. Equation 10 indicates a hydrophobic interaction of these substituents with the receptor. The B1 parabolic term shows that the increase in size first increases the activity up to an optimum = 1.71 and then decreases it. Probably the site where these substituents bind cannot accommodate larger substituents.

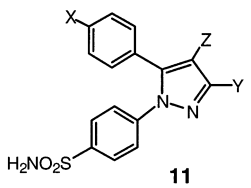
Table 10. IC_{50} Data for the Inhibition of COX-2 by Compound 10[58]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 10)	Δ	ClogP	$B1_X$
1	H	4.10	3.95	0.15	1.76	1.00
2	Me	7.57	7.54	0.03	2.03	1.52
3	CF_3	7.92	8.00	−0.08	2.79	1.99
4	CF_2H	8.30	7.72	0.58	1.95	1.71
5	Cl	8.40	8.26	0.14	2.55	1.80
6	CH_2OH[a]	7.46	6.22	1.24	0.72	1.52
7	CH_2OMe	7.77	7.04	0.73	1.54	1.52
8	CH_2COOH	6.54	6.53	0.00	1.03	1.52
9	SH[a]	6.34	8.37	−2.03	2.60	1.70
10	SMe	8.40	8.67	−0.28	2.90	1.70
11	SOMe	6.00	5.89	0.11	0.82	1.40
12	SO_2Me	6.43	6.57	−0.14	1.54	2.03
13	OH	6.31	6.91	−0.60	2.06	1.35
14	OMe	7.77	7.43	0.34	2.58	1.35
15	NH_2[a]	4.68	6.29	−1.61	1.44	1.35
16	NMe_2	7.20	7.33	−0.13	2.47	1.35
17	$CH{=}CH_2$	8.40	8.17	0.23	2.48	1.60
18	CCH	8.22	7.71	0.51	2.03	1.60
19	CCMe	7.70	8.24	−0.55	2.56	1.60
20	$CONH_2$	5.65	6.71	−1.05	1.26	1.50

[a] Data points not included in equation derivation.

4. Pyrazoles

*IC_{50} of 1-(4-SO_2NH_2-phenyl)-3-Y-4-Z-5-(X-phenyl)-pyrazole (**11**) (Table 11)*



11

$$\log 1/C = 1.27(\pm 0.29)\text{ClogP} + 0.46(\pm 0.16)\sigma^*_{Y+Z} - 0.85(\pm 0.54)I_{X,4} + 1.43(\pm 1.09) \quad (11)$$

$$n = 16,\ r^2 = 0.912,\ q^2 = 0.830,\ s = 0.444$$

outliers: X = H, Y = H, Z = F; X = 4-Cl, Y = H, Z = SO_2Me; X = 4-Cl, Y = COOMe, Z = Cl

$$\text{range in } \log 1/C = 4.33-8.77$$

In the landmark paper in which Penning et al.[59] reported Celecoxib (SC-58635), one of the COX-2 inhibitors now on the market, they also reported synthesis and IC_{50} data of several 1,5-diaryl pyrazoles. For one of the data sets eq 11 gave the best correlation. Hydrophobicity of the compounds is found to be important for better activity. σ^* is Taft's electronic parameter. Electron-attracting groups at the 3- and 4-positions of pyrazole ring seem to enhance the activity as evidenced by the presence of a positive σ^* term. The indicator variable $I_{X,4}$ was used with a value of 1 for X = 4-Cl, and its negative coefficient indicates that 4-Cl at this position is not conducive to the activity. According to Penning et al. substantial flexibility in functionality is allowed at the 3-position of the pyrazole ring. This position seems to be very tolerant of a variety of substituents

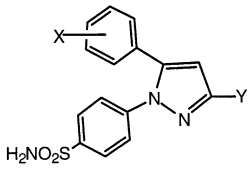
Table 11. IC_{50} Data for the Inhibition of COX-2 by Compound 11[59]

	substituent			log 1/C					
no.	X	Y	Z	obsd	calcd (eq 11)	Δ	ClogP	$\sigma^*_{(Y+Z)}$	$I_{X,4}$
1	4-Cl	CF_3	Cl	8.28	8.88	−0.60	4.74	4.94	1
2	H	CF_3	F	8.77	8.78	−0.01	3.90	5.19	0
3	4-Cl	CF_3	Me	7.66	7.12	0.54	4.43	2.00	1
4	4-Cl	CF_3	C_2H_5	7.55	7.75	−0.20	4.96	1.90	1
5	H	CF_3	OMe	7.10	7.25	−0.15	3.21	3.77	0
6	H	CF_3	OH	5.45	6.97	−1.52	3.14	3.37	0
7	H	H	Cl	7.31	7.15	0.16	3.26	3.43	0
8	4-Cl	H	Br	7.51	7.27	0.24	4.07	3.29	1
9	H	H	F[a]	5.33	6.86	−1.52	2.94	3.68	0
10	H	H	Me	4.33	5.10	−0.77	2.71	0.49	0
11	4-Me	H	CN	7.12	7.01	0.11	2.90	4.13	0
12	H	H	NO_2	6.54	6.44	0.10	2.08	5.15	0
13	4-Cl	H	SO_2Me[a]	4.70	5.35	−0.64	2.24	4.17	1
14	H	H	NH_2	4.53	4.31	0.21	1.87	1.11	0
15	H	Me	Cl	7.55	7.20	0.35	3.48	2.94	0
16	4-Cl	CH_2OH	Cl	6.47	5.86	0.61	2.88	3.50	1
17	4-Cl	CN	Cl	8.00	8.01	−0.01	3.46	6.58	1
18	4-Cl	COOMe	Cl[a]	6.80	8.35	−1.56	4.33	4.94	1
19	4-Cl	$CONH_2$	Cl	5.96	5.89	0.07	2.51	4.60	1

[a] Data points not included in equation derivation.

that show little steric interaction. X-phenyl substituents influence both in vivo potency and selectivity.

*IC_{50} of 1-(4-SO_2NH_2-phenyl)-3-Y-5-(X-phenyl)-pyrazole (**12**) (Table 12)*



12

$$\log 1/C = -1.24(\pm 0.41)\sigma^{+}_{X} - 0.99(\pm 0.98)I_{COOH} + 1.73(\pm 0.51)\text{ClogP} - 1.37(\pm 0.72)I_{CF3} + 1.24\ (\pm 1.77) \quad (12)$$

$$n = 23,\ r^2 = 0.852,\ q^2 = 0.761,\ s = 0.576$$

outliers: X = 4-C_2H_5, Y = CF_3; X = 4−CF_3, Y = CF_3; X = 4-OC_2H_5, Y = CF_3; X = 2-NMe_2, Y = CF_3

range in log 1/C = 4.03−8.33

Penning et al.[59] in this series reported a variation on the 3-position of pyrazoles and also on the 5-phenyl ring. Equation 12 reveals electronic and hydrophobic interactions. Electron-donating X substituents increase the activity via through-resonance. Hydrophobic interactions improve activity. The indicator variable I_{CF3} was used with a value of 1.0 for Y = CF_3. Its negative coefficient indicates that this group is detrimental to the activity. The negative coefficient of another indicator variable, I_{COOH} (with a value of 1 for X = 4-COOH), shows that the presence of this group also decreases the activity. This may be associated with its ClogP value, which is calculated for the neutral form of compounds.

Table 12. IC_{50} Data for the Inhibition of COX-2 by Compound 12[59]

	substitutent		log 1/C						
no.	X	Y	obsd	calcd (eq 12)	Δ	σ^{+}_{X}	I_{COOH}	I_{CF3}	ClogP
1	H	CF_3	7.50	6.56	0.94	0.00	0	1	3.87
2	2-F	CF_3	7.24	6.89	0.34	−0.07	0	1	4.01
3	3-F	CF_3	5.11	6.39	−1.27	0.34	0	1	4.01
4	4-F	CF_3	7.39	6.89	0.50	−0.07	0	1	4.01
5	2-Cl	CF_3	7.25	7.22	0.03	0.11	0	1	4.33
6	4-Cl	CF_3	8.00	7.65	0.34	0.11	0	1	4.59
7	4-Cl	CHF_2	8.00	7.72	0.28	0.11	0	0	3.83
8	2-Me	CF_3	7.16	7.29	−0.13	−0.31	0	1	4.07
9	3-Me	CF_3	6.96	7.51	−0.55	−0.07	0	1	4.37
10	4-Me	CF_3	7.40	7.81	−0.41	−0.31	0	1	4.37
11	4-Me	CHF_2	7.89	7.87	0.02	−0.31	0	0	3.62
12	4-C_2H_5	CF_3[a]	6.07	8.71	−2.64	−0.30	0	1	4.90
13	4-CF_3	CF_3[a]	5.09	7.33	−2.24	0.61	0	1	4.76
14	4-CN	CHF_2	4.53	4.85	−0.32	0.66	0	0	2.57
15	4-COOH	CHF_2	4.33	4.67	−0.34	0.42	1	0	2.86
16	4-NO_2	CF_3	5.58	5.14	0.44	0.79	0	1	3.62
17	2-OMe	CF_3	6.54	6.42	0.11	−0.78	0	1	3.23
18	4-OMe	CF_3	8.10	7.39	0.71	−0.78	0	1	3.79
19	4-OMe	CHF_2	7.82	7.45	0.37	−0.78	0	0	3.04
20	4-OC_2H_5	CF_3[a]	6.19	8.34	−2.15	−0.81	0	1	4.32
21	4-SMe	CF_3	8.05	8.27	−0.22	−0.60	0	1	4.43
22	4-NH_2	CF_3	6.47	6.07	0.39	−1.30	0	1	2.66
23	2-NMe_2	CF_3[a]	4.85	8.95	−4.11	−1.70	0	1	4.04
24	4-NHMe	CF_3	7.80	7.96	−0.17	−1.81	0	1	3.39
25	4-NMe_2	CF_3	8.33	8.95	−0.62	−1.70	0	1	4.04
26	4-CH_2OH	CF_3	4.03	4.82	−0.79	−0.04	0	1	2.84
27	4-COOH	CF_3	4.95	4.61	0.34	0.42	1	1	3.62

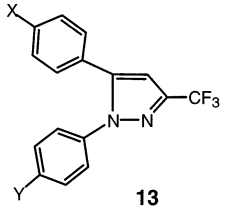
[a] Data points not included in equation derivation.

Table 13. IC_{50} Data for the Inhibition of COX-2 by Compound 13[59]

	substituent		log 1/C			
no.	X	Y	obsd	calcd (eq 13)	Δ	ClogP
1	4-F	4-SO_2Me	7.00	7.44	−0.44	4.21
2	4-F	4-SO_2NH_2	7.39	7.70	−0.31	3.89
3	4-SO_2NH_2	4-F[a]	8.00	7.71	0.29	3.88
4	4-OMe	4-SO_2NH_2	8.10	7.87	0.23	3.67
5	4-SO_2NH_2	4-OMe	8.17	7.90	0.27	3.64
6	4-Cl	4-Cl	5.32	5.24	0.08	6.95
7	4-OMe	4-OMe	6.13	6.51	−0.39	5.36
8	4-OMe	4-Cl	6.13	5.87	0.26	6.17
9	4-Cl	4-OMe[a]	4.13	5.88	−1.76	6.15

[a] Data point not included in equation derivation.

*IC_{50} of 3-CF_3-5-(X-phenyl)-1-(Y-phenyl)-pyrazole (**13**) (Table 13)*



13

$$\log 1/C = -0.80(\pm 0.25)\text{ClogP} + 10.08(\pm 1.20) \quad (13)$$

$$n = 8,\ r^2 = 0.910,\ q^2 = 0.858,\ s = 0.349$$

outlier: X = 4-SO_2NH_2, Y = 4-F

range in log 1/C = 4.13−8.17

Penning et al.[59] also explored variations on both of the phenyl rings attached to pyrazoles. In this

Table 14. IC_{50} Data for the Inhibition of COX-2 by Compound 14[60]

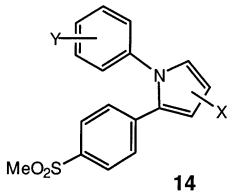
	substituent		log 1/C					
				calcd				
no.	X	Y	obsd	(eq 14)	Δ	ClogP	$MR_{X,4}$	$\sigma^{+}_{Y,4}$
1	5-Me	4-F	7.22	7.04	0.18	4.28	0.10	−0.07
2	5-Me	H	7.22	6.73	0.49	4.10	0.10	0.00
3	5-Me	4-CF_3	7.10	7.19	−0.09	5.07	0.10	0.61
4	5-Me	4-Me	7.40	7.71	−0.31	4.60	0.10	−0.31
5	5-Me	3,4-F_2	6.60	6.74	−0.14	4.37	0.10	0.27
6	H	4-F[a]	4.99	6.43	−1.44	3.79	0.10	−0.07
7	4-$COCF_3$-5-Me	4-F	6.92	6.41	0.51	4.42	1.12	−0.07
8	4-COMe-5-Me	4-F	5.79	5.73	0.07	3.86	1.12	−0.07
9	4-COC_6H_5-5-Me	4-F	5.99	6.18	−0.19	5.46	3.03	−0.07
10	4-SO_2CF_3-5-Me	4-F	7.22	6.98	0.25	4.99	1.29	−0.07
11	4-CHO-5-Me	4-F	5.49	6.05	−0.56	3.85	0.69	−0.07
12	4-CN-5-Me	4-F	6.13	6.21	−0.08	3.94	0.63	−0.07
13	4-Br-5-Me	4-F	7.70	7.49	0.21	5.16	0.89	−0.07
14	4-Cl-5-Me	4-F	7.30	7.53	−0.23	5.01	0.60	−0.07
15	4-CH_2NMe_2-5-Me	4-F[a]	4.00	5.39	−1.39	4.07	1.87	−0.07
16	4-CH_2OCOMe-5-Me	4-F[a]	6.33	5.55	0.78	4.05	1.65	−0.07
17	4-CH_2OH-5-Me	4-F	5.41	5.23	0.19	3.20	0.72	−0.07
18	4-(CH_2O-4-Cl-C_6H_4)-5-Me	4-F	7.52	7.28	0.24	6.77	3.68	−0.07
19	4-(CH_2O-3-Cl-C_6H_4)-5-Me	4-F	7.10	7.28	−0.18	6.77	3.68	−0.07
20	4-$CH(OH)CF_3$-5-Me	4-F	5.84	6.21	−0.37	4.26	1.13	−0.07
21	4-CH_2CF_3-5-Me	4-F	6.85	6.83	0.02	4.67	0.97	−0.07

[a] Data points not included in equation derivation.

equation we observed a negative ClogP term, showing that for this data set less hydrophobic molecules would have better activity.

5. Pyrroles

*IC_{50} of 1-(Y-phenyl)-2-(4-SO_2Me-phenyl)-X-pyrrole (**14**) (Table 14)*



14

$$\log 1/C = 1.22(\pm 0.30)\text{ClogP} - 0.78(\pm 0.25)MR_{X,4} - 1.18(\pm 0.97)\sigma^{+}_{Y} + 1.82(\pm 1.22) \quad (14)$$

$$n = 18,\ r^2 = 0.845,\ q^2 = 0.754,\ s = 0.320$$

outliers: X = H, Y = 4-F; X = 4-CH_2OCOMe-5-Me, Y = 4-F; X = 4-CH_2NMe_2-5-Me, Y = 4-F

range in $\log 1/C = 4.00-7.70$

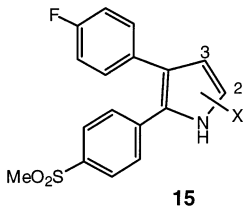
Substituted 1,2-diarylpyrroles studied by Khanna et al.[60] are selective inhibitors of the human COX-2 enzyme. Equation 14 shows that hydrophobic interactions are important for inhibition. Electron-donating Y substituents on *N*-phenyl enhance activity via through-resonance. From the negative term of $MR_{X,4}$ it is evident that the bulkier X groups at the 4-position have a steric interaction with the receptor resulting in decreased activity.

Table 15. IC_{50} Data for the Inhibition of COX-2 by Compound 15[61]

		log 1/C					
			calcd				
no.	substituent X	obsd	(eq 15)	Δ	σ_X	MgVol	E_{HOMO}
1	H	4.90	4.95	−0.05	0.00	2.23	−8.66
2	2-SCN	4.14	3.92	0.22	0.52	2.55	−9.01
3	2-SMe	4.46	4.22	0.25	0.00	2.54	−8.74
4	2-Br	4.40	4.41	−0.02	0.23	2.41	−8.79
5	2-$COCF_3$	3.53	3.71	−0.18	0.80	2.58	−9.18
6	2-I	4.04	4.24	−0.20	0.18	2.49	−8.81
7	2-SO_2Me	3.57	3.58	0.00	0.72	2.65	−9.16
8	2-Cl	4.38	4.54	−0.16	0.23	2.36	−8.74
9	1-Me-2-Br[a]	4.45	4.07	0.38	0.23	2.55	−8.73
10	2-CN	4.19	4.24	−0.06	0.66	2.39	−8.99
11	2-NO_2	4.20	4.14	0.06	0.78	2.41	−9.29
12	2,3-Cl_2	4.16	4.06	0.10	0.60	2.48	−8.92
13	2-Cl-3-Br	4.06	3.93	0.13	0.62	2.53	−9.04
14	1-COMe-2-Br	3.52	3.70	−0.18	0.23	2.71	−8.92
15	1-Me-2,3-Br_2[a]	4.25	3.46	0.80	0.62	2.72	−9.01
16	1-Me-2,3-Cl_2[a]	4.60	3.72	0.88	0.60	2.62	−8.88
17	1-Me	4.70	4.61	0.09	0.00	2.37	−8.60

[a] Data points not included in equation derivation.

*IC_{50} of 4-(4-F-phenyl)-5-(4-SO_2Me-phenyl)-X-pyrrole (**15**) (Table 15)*



15

$$\log 1/C = -0.50(\pm 0.35)\sigma_X - 2.40(\pm 0.83)\text{MgVol} - 10.31(\pm 2.00) \quad (15)$$

$$n = 14,\ r^2 = 0.872,\ q^2 = 0.781,\ s = 0.161$$

outliers: 1-Me-2-Br; 1-Me-2,3-Br_2; 1−Me-2,3-Cl_2

range in $\log 1/C = 3.53-4.90$

Wilkerson et al.[61] reported COX-2 inhibitory data for the derivatives of **15**, which gave eq 15. σ in eq 15 is the sum of substituents at the 2- and 3-positions of the pyrrole ring; its negative coefficient indicates that the electron-releasing X substituents at these positions enhance the activity. However, this is a weak term. The overall volume of the compounds was found to be detrimental for the activity (negative MgVol). Zoete et al.[62] reported E_{HOMO} (energy of the highest occupied molecular orbital) values for these substituents. It is interesting to compare the QSAR obtained with HOMO values to the one obtained with σ. The results are essentially the same.

$$\log 1/C = 1.26(\pm 0.71)E_{HOMO} - 1.62(\pm 1.02)\text{MgVol} + 19.39(\pm 5.17) \quad (15a)$$

$$n = 14,\ r^2 = 0.866,\ q^2 = 0.775,\ s = 0.167$$

6. Imidazoles

*IC_{50} of 1-(4-SO_2-Y-phenyl)-2-(X-phenyl)-4-Z-imidazole (**16**) (Table 16)*

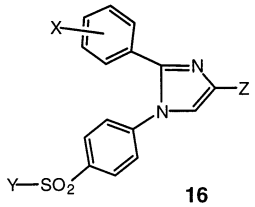
Table 16. IC_{50} Data for the Inhibition of COX-2 by Compound 16[63]

	substituent			log 1/*C*						
no.	X	Y	Z	obsd	calcd (eq 16)	Δ	ClogP	I_Y	MgVol	$L_{X,2}$
1	4-Cl	Me	CF_3	6.96	7.10	−0.04	4.41	0	2.49	2.06
2	4-F	Me	CF_3	7.00	6.76	0.24	3.84	0	2.39	2.06
3	H	Me	CF_3	6.92	6.68	0.24	3.69	0	2.37	2.06
4	4-Me	Me	CF_3	6.80	6.81	−0.01	4.19	0	2.51	2.06
5	4-OMe	Me	CF_3	6.24	6.32	−0.08	3.70	0	2.57	2.06
6	4-NHMe	Me	CF_3	5.83	6.00	−0.17	3.39	0	2.61	2.06
7	4-NMe_2	Me	CF_3	6.16	6.19	−0.04	3.97	0	2.75	2.06
8	4-SMe	Me	CF_3	6.80	6.58	0.21	4.29	0	2.67	2.06
9	4-SO_2Me	Me	CF_3	5.24	4.69	0.56	2.13	0	2.79	2.06
10	4-Cl	NH_2	CF_3	8.00	7.95	0.05	4.33	1	2.45	2.06
11	4-F	NH_2	CF_3	8.00	7.69	0.31	3.76	1	2.34	2.06
12	H	NH_2	CF_3	7.40	7.61	−0.22	3.62	1	2.33	2.06
13	4-Me	NH_2	CF_3	7.40	7.74	−0.35	4.12	1	2.47	2.06
14	3-Cl	Me	CF_3	7.22	7.01	0.21	4.41	0	2.49	2.06
15	3-F	Me	CF_3	6.92	6.76	0.16	3.84	0	2.39	2.06
16	3-Br	Me	CF_3	7.10	7.03	0.07	4.56	0	2.54	2.06
17	3-Me	Me	CF_3	7.22	6.81	0.41	4.19	0	2.51	2.06
18	3-CF_3	Me	CF_3	6.68	7.01	−0.34	4.58	0	2.56	2.06
19	3-OMe	Me	CF_3	6.46	6.32	0.14	3.70	0	2.57	2.06
20	3-SMe	Me	CF_3	6.46	6.58	−0.13	4.29	0	2.67	2.06
21	3-CH_2OMe	Me	CF_3[a]	4.17	5.90	−1.73	3.49	0	2.71	2.06
22	3-NMe_2	Me	CF_3	5.50	6.19	−0.70	3.97	0	2.75	2.06
23	3-NHMe	Me	CF_3	6.04	6.00	0.03	3.39	0	2.61	2.06
24	3-NH_2	Me	CF_3	5.23	5.68	−0.45	2.65	0	2.47	2.06
25	3-NO_2	Me	CF_3	6.24	6.16	0.08	3.44	0	2.54	2.06
26	3-Cl	NH_2	CF_3	8.10	7.95	0.15	4.33	1	2.45	2.06
27	3-F	NH_2	CF_3	7.52	7.70	−0.17	3.76	1	2.34	2.06
28	3-Br	NH_2	CF_3	8.16	7.97	0.19	4.48	1	2.50	2.06
29	3-Me	NH_2	CF_3	7.52	7.74	−0.22	4.12	1	2.47	2.06
30	2-Cl	Me	CF_3	6.05	5.51	0.53	4.16	0	2.49	3.52
31	2-F	Me	CF_3	6.40	6.23	0.17	3.84	0	2.39	2.65
32	2-Me	Me	CF_3	6.10	5.85	0.24	3.89	0	2.51	2.87
33	2-OMe	Me	CF_3	4.00	4.17	−0.17	3.14	0	2.57	3.98
34	2-F	NH_2	CF_3	7.00	7.17	−0.17	3.76	1	2.34	2.65
35	2-Me	NH_2	CF_3	6.70	6.79	−0.09	3.82	1	2.47	2.87
36	3-F-4-OMe	Me	CF_3	6.82	6.31	0.52	3.73	0	2.59	2.06
37	3-Cl-4-OMe	Me	CF_3	6.89	6.54	0.35	4.27	0	2.69	2.06
38	3-Cl-4-SMe	Me	CF_3	7.40	6.94	0.46	5.03	0	2.79	2.06
39	3-Cl-4-NMe_2	Me	CF_3	6.50	6.60	−0.11	4.78	0	2.87	2.06
40	3-F-4-NMe_2	Me	CF_3	6.48	6.35	0.13	4.21	0	2.77	2.06
41	3-Cl-4-NHMe	Me	CF_3	6.18	6.47	−0.29	4.28	0	2.73	2.06
42	3-Cl-4-Me	Me	CF_3	7.52	7.14	0.38	4.90	0	2.63	2.06
43	3-F-4-Me	Me	CF_3	6.96	6.89	0.07	4.33	0	2.53	2.06
44	3-Me-4-F	Me	CF_3	6.77	6.89	−0.12	4.33	0	2.53	2.06
45	3-Me-4-Cl	Me	CF_3	7.05	7.14	−0.10	4.90	0	2.63	2.06
46	3-OMe-4-Cl	Me	CF_3	6.60	6.54	0.07	4.27	0	2.69	2.06
47	3-NMe_2-4-Cl	Me	CF_3	5.98	6.60	−0.62	4.78	0	2.87	2.06
48	3,4-OCH_2O	Me	CF_3	6.77	6.43	0.34	3.73	0	2.52	2.06
49	3,4-F_2	Me	CF_3	6.92	6.78	0.14	3.91	0	2.40	2.06
50	3,4-Me_2	Me	CF_3	6.48	6.90	−0.42	4.64	0	2.65	2.06
51	3-Me-5-Cl	Me	CF_3	7.10	7.14	−0.04	4.90	0	2.63	2.06
52	3-Me-5-F	Me	CF_3	6.96	6.89	0.07	4.33	0	2.53	2.06
53	3-OMe-5-Cl	Me	CF_3	6.02	6.71	−0.70	4.50	0	2.69	2.06
54	3,5-Cl_2	Me	CF_3	6.77	7.34	−0.57	5.12	0	2.61	2.06
55	3-F-4-OMe	NH_2	CF_3	7.52	7.24	0.28	3.65	1	2.54	2.06
56	3-Cl-4-OMe	NH_2	CF_3	7.70	7.47	0.23	4.19	1	2.65	2.06
57	3-Br-4-OMe	NH_2	CF_3	7.52	7.49	0.03	4.34	1	2.70	2.06
58	3-Cl-4-SMe	NH_2	CF_3	8.00	7.88	0.13	4.96	1	2.75	2.06
59	3-Cl-4-Me	NH_2	CF_3	8.52	8.08	0.45	4.83	1	2.59	2.06
60	3-OMe-4-Cl	NH_2	CF_3	7.70	7.47	0.23	4.19	1	2.65	2.06
61	3,4-F_2	NH_2	CF_3	7.52	7.72	−0.20	3.84	1	2.36	2.06
62	3-Me-5-Cl	NH_2	CF_3	7.40	8.08	−0.68	4.83	1	2.59	2.06
63	3-Me-5-F	NH_2	CF_3	7.52	7.82	−0.30	4.26	1	2.49	2.06
64	3-OMe-5-F	NH_2	CF_3[a]	6.34	7.40	−1.06	3.85	1	2.54	2.06
65	3,5-F_2-4-OMe	Me	CF_3	6.77	6.25	0.52	3.70	0	2.60	2.06
66	3,5-Cl_2-4-OMe	Me	CF_3	6.85	6.71	0.15	4.78	0	2.81	2.06
67	3,5-Br_2-4-OMe	Me	CF_3	7.05	6.75	0.30	5.08	0	2.92	2.06
68	3,5-Me_2-4-OMe	Me	CF_3	6.14	6.58	−0.44	4.70	0	2.85	2.06
69	2,5-Me_2-4-OMe	Me	CF_3	4.91	5.62	−0.71	4.40	0	2.85	2.87
70	3,5-Cl_2-4-NMe_2	Me	CF_3	6.85	6.96	−0.10	5.53	0	3.00	2.06
71	3,5-F_2-4-OMe	NH_2	CF_3	7.52	7.19	0.34	3.62	1	2.56	2.06
72	4-Cl	Me	Me	6.62	6.53	0.09	3.66	0	2.44	2.06

Table 16 (Continued)

	substituent			log 1/C						
no.	X	Y	Z	obsd	calcd (eq 16)	Δ	ClogP	I_Y	MgVol	$L_{X,2}$
73	4-Cl	Me	CF_3	6.96	7.01	−0.05	4.41	0	2.49	2.06
74	4-Cl	Me	CHF_2	6.22	6.41	−0.19	3.59	0	2.47	2.06
75	4-Cl	Me	CH_2F	6.39	6.38	0.00	3.52	0	2.46	2.06
76	4-Cl	Me	CHO	5.80	6.22	−0.43	3.31	0	2.45	2.06
77	4-Cl	Me	CN	6.64	6.15	0.49	3.21	0	2.45	2.06
78	4-Cl	Me	$COOC_2H_5$	5.24	5.85	−0.60	3.63	0	2.79	2.06
79	4-Cl	Me	C_6H_5	6.62	7.10	−0.48	5.49	0	2.90	2.06
80	4-Cl	Me	$CH_2OC_6H_4$-4-Cl	7.52	6.85	0.67	5.94	0	3.23	2.06
81	4-Cl	Me	$CH_2SC_6H_4$-4-Cl	7.30	6.94	0.37	6.29	0	3.33	2.06
82	4-Cl	Me	CH_2OMe	5.43	5.80	−0.37	3.19	0	2.64	2.06
83	4-Cl	Me	CH_2OH	5.08	5.40	−0.32	2.36	0	2.50	2.06
84	4-Cl	Me	CH_2SMe	6.50	6.34	0.15	4.14	0	2.74	2.06
85	4-Cl	Me	CH_2CN	5.81	5.58	0.23	2.82	0	2.59	2.06

[a] Data point not included in equation derivation.



16

$$\log 1/C = 0.78(\pm 0.13)\text{ClogP} - 0.89(\pm 0.24)L_{X,2} + 0.92(\pm 0.19)I_Y - 1.84(\pm 0.54)\text{MgVol} + 10.00(\pm 1.32) \quad (16)$$

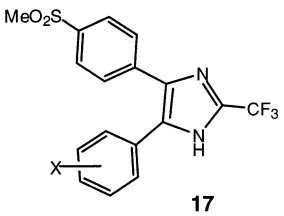
$$n = 83,\ r^2 = 0.833,\ q^2 = 0.802,\ s = 0.339$$

outliers: X = 3-CH_2OMe, Y = Me, Z = CF_3; X = 3-OMe-5-F, Y = NH_2, Z = CF_3

range in log 1/C = 4.00−8.52

The series of 1,2-diaryl imidazoles tested by Khanna et al.[63] are potent and selective inhibitors of human COX-2 enzyme. Equation 16 again emphasizes the importance of hydrophobic interactions of the ligand with the COX-2 receptor. The length of X substituents at the second position of the phenyl ring is detrimental to activity. Consistent with our observation from eq 1, Y = NH_2 group is found to be superior to Me, as confirmed by the presence of a positive I_Y term in eq 16, where it is used with a value of 1 for NH_2 and a value of 0 for Me. Khanna et al.[63] also reported that the compounds containing a sulfonamide group show superior in vivo activity as well as enhanced potency against the COX enzyme. However, they found that SO_2NH_2 reduces the selectivity for the COX-2 enzyme.

*IC_{50} of 2-CF_3-4-(4-SO_2Me-phenyl)-5-(X-phenyl)-imidazole (**17**) (Table 17)*



17

Table 17. IC_{50} Data for the Inhibition of COX-2 by Compound 17[64]

		log 1/C					
no.	sub-stituent X	obsd	calcd (eq 17)	Δ	ClogP	MgVol	$B1_{X,2}$
1	H	6.16	6.42	−0.26	3.09	2.37	1.00
2	2-F[a]	5.52	6.27	−0.75	3.24	2.39	1.35
3	3-F	6.62	6.55	0.07	3.24	2.39	1.00
4	4-F	6.72	6.55	0.18	3.24	2.39	1.00
5	2-Cl	5.89	5.89	−0.01	3.56	2.49	1.80
6	3-Cl	7.10	6.88	0.22	3.81	2.49	1.00
7	4-Cl[a]	6.43	6.88	−0.45	3.81	2.49	1.00
8	2-CH_3	5.75	5.64	0.10	3.29	2.51	1.52
9	3-CH_3	6.22	6.48	−0.27	3.59	2.51	1.00
10	4-CH_3	6.19	6.48	−0.29	3.59	2.51	1.00
11	3-OCH_3	5.62	5.50	0.12	3.10	2.57	1.00
12	4-OCH_3	5.54	5.50	0.04	3.10	2.57	1.00
13	3,4-Cl_2	7.40	7.17	0.23	4.40	2.61	1.00
14	2,4-F_2	6.26	6.40	−0.14	3.38	2.40	1.35
15	3,4-F_2	6.80	6.57	0.23	3.31	2.40	1.00
16	3-Cl-4-CH_3	6.64	6.85	−0.21	4.24	2.63	1.00
17	2-CH_3-3-F	5.77	5.77	0.00	3.44	2.53	1.52

[a] Data points not included in deriving equation.

$$\log 1/C = 1.45(\pm 0.40)\text{ClogP} - 4.67(\pm 1.84)\text{MgVol} - 0.78(\pm 0.48)B1_{X,2} + 13.79(\pm 3.94) \quad (17)$$

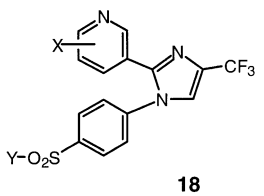
$$n = 15,\ r^2 = 0.885,\ q^2 = 0.798,\ s = 0.212$$

outliers: 2-F; 4-Cl

range in log 1/C = 5.52−7.40

Analogues of **17** were synthesized and tested against COX-2 by Barta et al.[64] QSAR 17 again shows that there are hydrophobic binding sites in the receptor. The negative coefficient of MgVol shows that the large molecules are detrimental to the activity. 2-X substituents appear to have negative steric effects on binding as evidenced by negative $B1_{X,2}$.

*IC_{50} for Purified COX-2 by 1-(4-SO_2-Y-phenyl)-2-(X-pyridin-3-yl)-4-CF_3-imidazole (**18**) (Table 18)*



18

Table 18. IC_{50} Data for the Inhibition of COX-2 by Compound 18[65]

	substituent		log 1/*C*					
no.	X	Y	obsd	calcd (eq 18)	Δ	ClogP	CMR	I_Y
1	H	Me	5.77	5.73	0.04	2.06	8.57	0
2	2-Me	Me[a]	5.02	4.62	0.40	2.26	9.03	0
3	6-Me	Me	5.75	5.62	0.12	2.56	9.03	0
4	5-Me	Me	5.75	5.62	0.12	2.56	9.03	0
5	4-Me	Me	4.27	4.62	−0.35	2.26	9.03	0
6	6-OMe	Me	5.92	6.10	−0.19	2.87	9.18	0
7	5-OMe	Me	4.43	4.77	−0.34	2.47	9.18	0
8	5-Br	Me	6.02	5.81	0.22	2.97	9.34	0
9	H	NH_2	6.36	6.49	−0.14	1.98	8.47	1
10	2-Me	NH_2	5.55	5.39	0.17	2.18	8.93	1
11	6-Me	NH_2	6.54	6.39	0.15	2.48	8.93	1
12	5-Me	NH_2	6.29	6.39	−0.09	2.48	8.93	1
13	4-Me	NH_2[a]	4.29	5.38	−1.09	2.18	8.93	1
14	5-Br	NH_2	6.47	6.57	−0.10	2.89	9.25	1

[a] Data points not included in equation derivation.

$$\log 1/C = 3.35(\pm 1.06)\text{ClogP} - 3.83(\pm 1.40)\text{CMR} + 0.64(\pm 0.36)I_Y + 32.32(\pm 10.34) \quad (18)$$

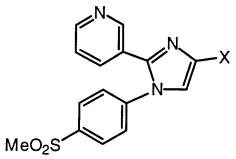
$$n = 13,\ r^2 = 0.906,\ q^2 = 0.809,\ s = 0.258$$

outlier: X = 4-Me, Y = NH_2

range in log 1/*C* = 4.29−6.47

Equation 18 derived from the data of Khanna et al.[65] is governed by hydrophobic and steric terms. It appears that the hydrophobic interactions are important. A negative CMR term shows that the large molecules are not suitable for the activity. ClogP and CMR are rather collinear ($r^2 = 0.751$). This may account for the unusually large coefficient with ClogP. The positive coefficient of the indicator variable I_Y with a value of 1 for Y = NH_2 shows that SO_2NH_2 is better for the activity than SO_2Me.

*IC_{50} of 1-(4-SO_2Me-phenyl)-2-(pyridin-3-yl)-4-X-imidazole (**19**) (Table 19)*



19

$$\log 1/C = 3.36(\pm 1.93)\text{B1}_X - 0.94(\pm 3.30) \quad (19)$$

$$n = 4,\ r^2 = 0.966,\ q^2 = 0.895,\ s = 0.159$$

outlier: CH_2OH

range in log 1/*C* = 3.03−5.77

Khanna et al.[65] studied variations on the 4-position of imidazoles in compound **19**. The positive $B1_X$ term indicates a positive effect of these substituents on the activity. There are too few data points for serious consideration of this QSAR.

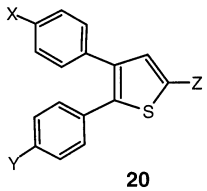
Table 19. IC_{50} Data for the Inhibition of COX-2 by Compound 19[65]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 19)	Δ	$B1_X$
1	CF_3	5.77	5.75	0.02	1.99
2	CHF_2	4.68	4.81	−0.13	1.71
3	CN	4.61	4.44	0.17	1.60
4	Me	4.10	4.17	−0.07	1.52
5	CH_2OH[a]	3.03	4.17	−1.14	1.52

[a] Data point not included in equation derivation.

7. Thiophenes

IC_{50} of 2-(4-Y-phenyl)-3-(4-X-phenyl)-5-Z-thiophene **(20)** *(Table 20)*



20

$$\log 1/C = 1.22(\pm 0.55)\text{ClogP} + 0.37(\pm 0.31)L_Z + 0.06(\pm 2.38) \quad (20)$$

$$n = 11,\ r^2 = 0.849,\ q^2 = 0.721,\ s = 0.448$$

outliers: X = SO_2NH_2, Y = F, Z = H;
X = SO_2NHMe, Y = F, Z = H

range in log 1/*C* = 5.14−8.30

Inhibition of COX-2 by substituted diaryl thiophenes was studied by Leblanc et al.[66] Equation 20 obtained from their data shows positive hydrophobic and weak steric interactions. It is evident from this equation that the hydrophobicity of the molecules is important for binding with the receptor. The length of the Z substituents at the 2-position of the thiophene ring is favorable to the activity.

Table 20. IC_{50} Data for the Inhibition of COX-2 by Compound 20[66]

	substituent			log 1/*C*				
no.	X	Y	Z	obsd	calcd (eq 20)	Δ	ClogP	L_Z
1	SO_2Me	F	Br	8.30	7.83	0.47	5.20	3.82
2	F	SO_2Me	Br	7.70	7.83	−0.13	5.20	3.82
3	SO_2Me	F	H	6.60	6.10	0.51	4.32	2.06
4	F	SO_2Me	H	5.37	6.10	−0.73	4.32	2.06
5	SO_2NH_2	F	H[a]	7.52	5.87	1.66	4.13	2.06
6	F	SO_2NH_2	H	6.17	5.87	0.31	4.13	2.06
7	SO_2NH_2	F	$CHMe_2$	8.00	8.37	−0.37	5.56	4.11
8	SO_2NH_2	F	COOMe	7.16	6.91	0.25	4.18	4.73
9	SO_2NH_2	F	CMe_2OH	6.39	6.22	0.17	3.80	4.11
10	F	SO_2NH_2	CMe_2OH	5.80	6.22	−0.42	3.80	4.11
11	SO_2NHMe	F	H[a]	5.14	6.63	−1.49	4.75	2.06
12	SO_2-NHCOMe	F	H	5.27	5.49	−0.22	3.82	2.06
13	SO_2Me	F	H	6.26	6.10	0.16	4.32	2.06

[a] Data points not included in equation derivation.

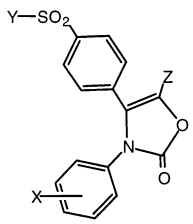
Table 21. IC_{50} Data for the Inhibition of COX-2 by Compound 21[67]

	substituent			log 1/*C*						
no.	X	Y	Z	obsd	calcd (eq 21)	Δ	$B5_{X,3}$	$B1_{X,4}$	$B1_{X,2}$	I_Y
1	H	Me	H	5.80	5.94	−0.15	1.00	1.00	1.00	1
2	2-F	Me	H[a]	6.18	5.73	0.45	1.00	1.00	1.35	1
3	4-F	Me	H	6.29	6.15	0.14	1.35	1.00	1.00	1
4	4-Cl	Me	H	6.50	6.41	0.08	1.80	1.00	1.00	1
5	4-Me	Me	H	6.32	6.25	0.07	1.52	1.00	1.00	1
6	4-C_2H_5	Me	H	6.16	6.25	−0.09	1.52	1.00	1.00	1
7	2,4-F_2	Me	H	5.87	5.93	−0.06	1.35	1.00	1.35	1
8	H	NH_2	H	5.62	5.61	0.01	1.00	1.00	1.00	0
9	2-F	NH_2	H	5.66	5.39	0.27	1.00	1.00	1.35	0
10	4-F	NH_2	H	5.82	5.81	0.01	1.35	1.00	1.00	0
11	2-Cl	NH_2	H	5.19	5.12	0.07	1.00	1.00	1.80	0
12	3-Cl	NH_2	H	5.82	5.99	−0.17	1.00	1.80	1.00	0
13	4-Cl	NH_2	H	5.92	6.08	−0.16	1.80	1.00	1.00	0
14	2-Me	NH_2	H	5.01	5.29	−0.27	1.00	1.00	1.52	0
15	3-Me	NH_2	H	6.29	6.10	0.19	1.00	2.04	1.00	0
16	4-Me	NH_2	H	6.10	5.91	0.19	1.52	1.00	1.00	0
17	4-C_2H_5	NH_2	H	5.81	5.91	−0.11	1.52	1.00	1.00	0
18	4-OMe	NH_2	H[a]	6.68	5.81	0.87	1.35	1.00	1.00	0
19	2,4-F_2	NH_2	H	5.64	5.60	0.04	1.35	1.00	1.35	0
20	3,4-Cl_2	NH_2	H	6.40	6.46	−0.06	1.80	1.80	1.00	0
21	4-OMe-3-F	NH_2	H	5.95	5.98	−0.03	1.35	1.35	1.00	0
22	4-OMe-3-Cl	NH_2	H	6.11	6.20	−0.09	1.35	1.80	1.00	0
23	H	NH_2	Me	5.75	5.61	0.14	1.00	1.00	1.00	0
24	4-F	NH_2	Me[a]	6.29	5.81	0.48	1.35	1.00	1.00	0
25	3-Me	NH_2	Me	6.03	6.10	−0.07	1.00	2.04	1.00	0
26	4-Me	NH_2	Me	5.77	5.91	−0.14	1.52	1.00	1.00	0
27	3,4-Cl_2	NH_2	Me	6.64	6.46	0.18	1.80	1.80	1.00	0

[a] Data points not included in equation derivation.

8. Oxazolones

*IC_{50} for COX-2 in Human Whole Blood by 3-(X-phenyl)-4-(4-SO_2-Y-phenyl)-5-Z-oxazol-2-one (**21**) (Table 21)*



21

$$\log 1/C = 0.48(\pm 0.20)B5_{X,3} + 0.59(\pm 0.25)B1_{X,4} - 0.61(\pm 0.36)B1_{X,2} + 0.34(\pm 0.17)I_Y + 5.15(\pm 0.73) \quad (21)$$

$$n = 24,\ r^2 = 0.868,\ q^2 = 0.786,\ s = 0.153$$

outliers: X = 2-F, Y = Me, Z = H; X = 4-OMe, Y = NH_2, Z = H; X = 4-F, Y = NH_2, Z = Me

range in log 1/*C* = 5.01−6.68

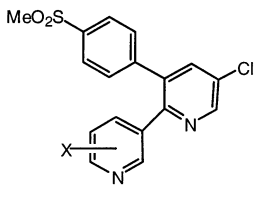
Diphenyl oxazolones were tested for their inhibitory activity against COX-2 in human whole blood by Puig et al.[67] X substituents on the 2-, 3-, and 4-positions of the phenyl ring show steric interactions. The size of the first atom of the 2-X substituent seems to have a negative effect on the activity, whereas the size of the 4-position substituents seems to have positive effects. Larger 3-position substituents favor activity, evident by the presence of a positive $B5_{X,3}$. Surprisingly, in this series we observed a favorable effect of SO_2Me over SO_2NH_2 as in this QSAR the indicator variable $I_Y = 1$ is for Y = Me, the positive coefficient of which indicates that the presence of the Me group attached to 4-SO_2- is good for the activity. This result does not agree well with our observation in QSAR 1 and 16. Puig et al.[67] also concluded that sulfonamides are better than methyl sulfones for COX-2 inhibition. We are unable to explain this finding.

Table 22. IC_{50} Data for the Inhibition of COX-2 by Compound 22[68]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 22)	Δ	ClogP
1	6-Me	5.88	5.96	−0.09	2.65
2	4-Me	6.08	5.96	0.12	2.65
3	3-Me	7.06	7.12	−0.06	2.95
4	2-Me	7.09	7.12	−0.03	2.95
5	2-C_2H_5	7.30	7.48	−0.17	3.48
6	2-cy-C_3H_5	7.80	7.56	0.23	3.39

9. Pyridines

*IC_{50} of 2-(X-pyridin-3-yl)-3-(4-SO_2Me-phenyl)-5-Cl-pyridine (**22**) (Table 22)*



22

$$\log 1/C = 25.48(\pm 21.49)\mathrm{ClogP} - 3.86(\pm 3.51)\mathrm{ClogP}^2 - 34.42(\pm 32.53) \quad (22)$$

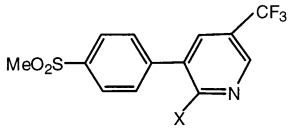
$$n = 6,\ r^2 = 0.960,\ q^2 = 0.814,\ s = 0.192$$

$$\text{optimum ClogP} = 3.29(3.16-5.71)$$

$$\text{range in } \log 1/C = 5.88-7.80$$

IC_{50} data of these congeners were reported by Friesen et al.[68] Our results indicate a parabolic correlation with hydrophobicity; that is, activity first increases with an increase in the hydrophobicity of the molecules up to an optimum value of ClogP = 3.29 and then with further increase in hydrophobicity it decreases. More data points are needed to study this set to obtain a reliable result.

*IC_{50} of 2-X-3-(4-SO_2Me-phenyl)-5-CF_3 -pyridine (**23**) (Table 23*)



23

$$\log 1/C = -1.15(\pm 0.54)\mathrm{CMR} + 17.29(\pm 5.27) \quad (23)$$

$$n = 7,\ r^2 = 0.857,\ q^2 = 0.747,\ s = 0.195$$

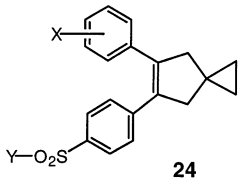
$$\text{outliers: } OCH_2CF_3;\ OCH(CF_3)_2;\ OCH_2CMe_2OH$$

$$\text{range in } \log 1/C = 5.33-6.85$$

Equation 23 derived from the results of Dube et al.[69] gave best correlation with CMR. The negative coefficient of CMR shows that the increase in the size and polarizability of the molecule decreases activity.

10. Fused Ring System

a. Spiroheptenes. *IC_{50} of 5-(X-phenyl)-6-(4-SO_2-Y-phenyl)-spiro[2.4]hept-5-ene (**24**) (Table 24*)



24

$$\log 1/C = 1.86(\pm 0.53)L_{X,4} - 5.47(\pm 1.26)\log(\beta \times 10^{L_{X,4}} + 1) + 0.43(\pm 0.20)I_Y + 3.47(\pm 1.49) \quad (24)$$

$$n = 27,\ r^2 = 0.842,\ q^2 = 0.775,\ s = 0.251$$

$$\text{outlier: } X = 2,4\text{-}Cl_2,\ Y = Me$$

$$\text{optimum } L_{X,4} = 3.36,\ \log \beta = -3.65$$

$$\text{range in } \log 1/C = 7.48-9.00$$

Huang et al.[70] reported COX-2 inhibitory data for 5,6-diarylspiro heptenes. The length of 4-X substituents seems to affect receptor binding in a bilinear fashion as evidenced by the L term. The activity increases initially up to an optimum of 3.36 and then decreases in a linear fashion with increase in length. In eq 24, the indicator variable I_Y is used with a value of unity for Y = NH_2 and a value of zero for Y = Me. Similar to eqs 1 and 16, here also its positive coefficient indicates that the NH_2 group is better for the activity than CH_3. Huang et al. suggested that the replacement of the methyl sulfone group on the 6-phenyl ring by a sulfonamide moiety results in compounds with superior in vivo pharmacological properties, although with lower COX-2 selectivity that can be enhanced by suitable substitution on the other ring.

Table 23. IC_{50} Data for the Inhibition of COX-2 by Compound 23[69]

		log 1/C			
no.	substituent X	obsd	calcd (eq 23)	Δ	CMR
1	OCH_2CF_3[a]	6.30	8.11	−1.81	7.96
2	$OCH(CF_3)_2$[a]	6.30	7.52	−1.22	8.47
3	OCH_2CMe_2OH[a]	6.00	6.92	−0.92	9.00
4	OCH_2-(1-OH-cy-C_5H_8)	5.85	6.05	−0.20	9.75
5	$OCH(CH_3)C(Me)_2OH$	6.34	6.38	−0.05	9.46
6	$OCH(CH_3)C(C_2H_5)_2OH$	5.33	5.32	0.01	10.39
7	O-(2-OH-2-Me-cy-C_5H_8)	5.85	6.05	−0.20	9.75
8	N-(2-C_2H_4OH-piperidine)	6.10	5.81	0.29	9.96
9	$SCH_2C(CH_3)_2OH$	6.16	6.17	−0.01	9.65
10	$SCH(CH_3)CH_2OH$	6.85	6.70	0.15	9.19

[a] Data points not included in equation derivation.

Table 24. IC_{50} Data for the Inhibition of COX-2 by Compound 24[70]

	substituent		log 1/C				
no.	X	Y	obsd	calcd (eq 24)	Δ	I_Y	$L_{X,4}$
1	4-F	Me	8.10	8.17	−0.07	0	2.65
2	4-F	NH_2	8.52	8.60	−0.08	1	2.65
3	4-Cl	Me	9.00	8.70	0.30	0	3.52
4	4-Cl	NH_2	9.00	9.13	−0.13	1	3.52
5	4-Me	Me	8.82	8.44	0.39	0	2.87
6	4-OMe	Me	8.30	8.16	0.15	0	3.98
7	4-OMe	NH_2	9.00	8.59	0.41	1	3.98
8	4-OCF_3	Me	6.87	6.67	0.20	0	4.57
9	4-OCF_3	NH_2	6.89	7.10	−0.21	1	4.57
10	4-CF_3	Me	8.70	8.73	−0.03	0	3.30
11	4-CF_3	NH_2	9.00	9.16	−0.16	1	3.30
12	3-F-4-OMe	Me	8.00	8.16	−0.16	0	3.98
13	3-F-4-OMe	NH_2	8.70	8.59	0.11	1	3.98
14	3-Cl-4-OMe	Me	7.77	8.16	−0.39	0	3.98
15	3-Cl-4-OMe	NH_2	8.70	8.59	0.11	1	3.98
16	3-Br-4-OMe	Me	7.89	8.16	−0.27	0	3.98
17	3-Br-4-OMe	NH_2	8.70	8.59	0.11	1	3.98
18	3-OCH_2O-4	Me	8.60	8.42	0.19	0	3.82
19	3,4-F_2	Me	8.48	8.17	0.31	0	2.65
20	3,4-F_2	NH_2	8.52	8.60	−0.08	1	2.65
21	3,4-Cl_2	Me	8.52	8.70	−0.17	0	3.52
22	3,4-Cl_2	NH_2	9.00	9.13	−0.13	1	3.52
23	3-Cl-4-F	Me	8.16	8.17	−0.01	0	2.65
24	3-Cl-4-F	NH_2	8.82	8.60	0.22	1	2.65
25	2,4-F_2	Me	7.66	8.17	−0.51	0	2.65
26	2,4-Cl_2	Me[a]	7.48	−9.24	16.72	0	3.52
27	3,5-Cl_2−4-OMe	Me	8.22	8.16	0.07	0	3.98
28	3,5-Cl_2-4-OMe	NH_2	8.40	8.59	−0.19	1	3.98

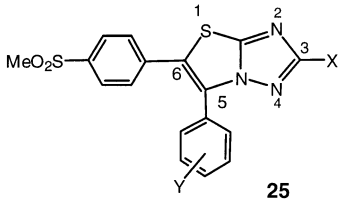
[a] Data point not included in equation derivation.

Table 25. IC_{50} Data for the Inhibition of COX-2 by Compound 25[71]

	substituent		log 1/*C*					
no.	X	Y	obsd	calcd (eq 25)	Δ	σ^*_X	σ^+_Y	$I_{Y,4}$
1	H	H	8.00	8.03	−0.03	0.49	0.00	0
2	Me	H	7.70	7.91	−0.21	0.00	0.00	0
3	C_2H_5	H	7.82	7.88	−0.06	−0.10	0.00	0
4	CF_3	H	8.52	8.43	0.10	2.00	0.00	0
5	$CH{=}CH_2$	H	8.22	8.01	0.21	0.40	0.00	0
6	$CHMe_2$	H	7.96	7.86	0.10	−0.19	0.00	0
7	H	3-F	7.66	7.64	0.02	0.49	0.34	0
8	H	4-F	7.44	7.58	−0.13	0.49	−0.07	1
9	H	3,4-F_2	7.32	7.19	0.13	0.49	0.27	1
10	H	3-OMe[a]	6.59	7.90	−1.31	0.49	0.12	0
11	Me	3-F[a]	6.82	7.51	−0.69	0.00	0.34	0
12	CF_3	3-F	7.89	8.03	−0.15	2.00	0.34	0
13	CF_3	3-Me	8.52	8.51	0.02	2.00	−0.07	0

[a] Data points not included in equation derivation.

b. Thiazolotriazoles. *IC_{50} of 3-X-5-(Y-phenyl)-6-(4-SO_2Me-phenyl)thiazolotriazole (**25**) (Table 25)*



25

$$\log 1/C = 0.26(\pm0.14)\sigma^*_X - 1.15(\pm0.74)\sigma^+_Y - 0.54(\pm0.29)I_{Y,4} + 7.91(\pm0.17) \quad (25)$$

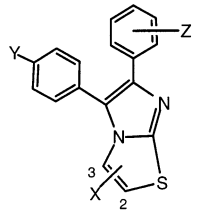
$$n = 11,\ r^2 = 0.890,\ q^2 = 0.658,\ s = 0.156$$

outliers: X = Me, Y = 3-F; X = H, Y = 3-OMe

range in log $1/C$ = 6.59−8.52

Diaryl thiazolotriazoles were synthesized and tested for their COX-2 inhibitory activity by Roy et al.[71] Best correlation is given by eq 25. In this QSAR electron-attracting X substituents were found to be weakly conducive to activity. Occurrence of $-\sigma^+_Y$ shows the importance of electron-donating Y substituents. They seem to promote activity via through-resonance. The indicator variable $I_{Y,4}$ was used with a value of 1 for 4-F substituents at the Y-position. Its negative coefficient shows the presence of this group is detrimental to activity.

c. Imidazothiazoles. *IC_{50} for COX-2 in CHO Cells by 5-(Y-phenyl)-6-(Z-phenyl)-imidazothiazole (**26**) (Table 26)*



26

$$\log 1/C = -0.74(\pm0.45)\mathrm{CMR} + 1.49(\pm1.28)B1_{Z,4} + 2.89(\pm1.16)B1_Y + 7.28(\pm5.54) \quad (26)$$

$$n = 13,\ r^2 = 0.854,\ q^2 = 0.710,\ s = 0.517$$

outliers: X = 2-Me, Y = H, Z = SO_2Me; X = 3-Me, Y = SO_2Me, Z = H; X = 2,3-Me_2, Y = SO_2Me, Z = H; X = 3-CH_2COOH, Y = SO_2Me, Z = H; X = 2,3-Cl_2, Y = SO_2Me, Z = 4−Cl

range in log $1/C$ = 5.30−7.92

Therien et al.[72] reported inhibitory activity of diarylimidazothiazoles. The negative CMR term shows that the larger molecules are unfavorable for the activity. Z substituents at the 4-position have positive steric interaction ($B1_{Z,4}$). $B1_Y$ is for the Y substituents. It appears that these substituents have a positive interaction with the receptor. The correlation is not very satisfactory because of the relatively large number of outliers. The reason for this is not clear.

Table 26. IC_{50} Data for the Inhibition of COX-2 by Compound 26[72]

	substituent			log 1/*C*					
no.	X	Y	Z	obsd	calcd (eq 26)	Δ	CMR	$B1_{Z,4}$	$B1_Y$
1	H	SO_2Me	H[a]	7.80	7.45	0.35	9.76	1.00	2.03
2	H	H	4-SMe	5.30	5.57	−0.27	9.70	1.70	1.00
3	H	H	4-SO_2Me	5.49	6.01	−0.52	9.76	2.03	1.00
4	H	SMe	H	6.38	6.54	−0.17	9.70	1.00	1.70
5	2-Me	H	4-SO_2Me[a]	6.85	5.67	1.19	10.23	2.03	1.00
6	H	SO_2Me	4-F	7.85	7.96	−0.10	9.78	1.35	2.03
7	H	SO_2Me	3,4-F_2	7.92	7.95	−0.03	9.79	1.35	2.03
8	2-Me	SO_2Me	H	7.92	7.11	0.82	10.23	1.00	2.03
9	3-Me	SO_2Me	H[a]	5.52	7.11	−1.58	10.23	1.00	2.03
10	2,3-Me_2	SO_2Me	H[a]	5.30	6.76	−1.46	10.69	1.00	2.03
11	2,3-Me_2	H	4-SO_2Me	5.30	5.33	−0.03	10.69	2.03	1.00
12	3-Me	H	4-SO_2Me	6.00	5.67	0.33	10.23	2.03	1.00
13	2-CH=CHCH=CH-3	SO_2Me	H	5.30	6.21	−0.90	11.45	1.00	2.03
14	2-CH=CHCH=CH-3	H	4-SO_2Me	5.30	4.77	0.53	11.45	2.03	1.00
15	3-$CH_2COOC_2H_5$	SO_2Me	H	6.05	5.94	0.10	11.81	1.00	2.03
16	3-CH_2COOH	SO_2Me	H[a]	5.30	6.63	−1.32	10.88	1.00	2.03
17	2-Cl	SO_2Me	4-Cl	7.80	7.92	−0.12	10.75	1.80	2.03
18	2,3-Cl_2	SO_2Me	4-Cl[a]	5.44	7.56	−1.11	11.24	1.80	2.03

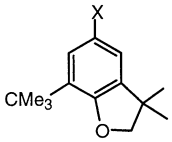
[a] Data points not included in equation derivation.

Table 27. IC_{50} Data for the Inhibition of COX-2 by Compound 27[73]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 27)	Δ	CMR	*I*
1	$CONHC_2H_5$	5.22	5.19	0.03	8.17	1
2	$CONHC_3H_7$	6.02	5.96	0.06	8.63	1
3	$CONHC_4H_9$	6.66	6.30	0.36	9.10	1
4	$CONHC_5H_{11}$	6.60	6.20	0.40	9.56	1
5	CONH-cy-C_3H_5	6.26	5.78	0.48	8.50	1
6	$CONH(CH_2)_2OMe$[a]	7.52	6.12	1.40	8.79	1
7	$CON(Me)C_2H_5$	5.35	5.96	−0.62	8.63	1
8	CON(Me)-cy-C_3H_5	6.00	6.24	−0.24	8.96	1
9	$CON(C_3H_7)$-cy-C_3H_5	5.40	5.87	−0.47	9.89	1
10	NHCOMe	5.46	5.45	0.00	7.71	0
11	NH-(2-COOH-C_6H_4)[a]	5.40	7.31	−1.91	9.91	0
12	3-(5,5-Me_2)isoxazolinyl[a]	6.70	7.78	−1.08	9.17	0
13	2-thienyl	7.16	7.50	−0.34	8.70	0
14	4-(2-guanidino)thiazolyl[a]	5.05	7.35	−2.30	9.88	0
15	6-imidazo[2.1-*b*]thiazolyl	7.82	7.59	0.24	9.66	0
16	3-methylene-γ-butyrolactonyl	8.46	7.72	0.74	8.98	0
17	5-methylene-2-imino-4-thiazolindinonyl	5.52	5.51	0.01	10.72	0
18	CO-2-thienyl	7.42	7.78	−0.36	9.19	0
19	CO-2-(N-Me-pyrrole)	7.35	7.78	−0.43	9.28	0
20	(E)-CH=CH-2-thienyl	7.46	7.31	0.14	9.90	0

[a] Data points not included in equation derivation.

d. Dihydrobenzofurans. *IC_{50} of 7-CMe_3-3,3-di-Me-5-X-2,3-dihydrobenzofuran (**27**) (Table 27*)



27

$$\log 1/C = 18.65(\pm 6.28)\mathrm{CMR} - 1.01(\pm 0.34)\mathrm{CMR}^2 - 1.47(\pm 0.50)I - 78.26(\pm 28.65) \quad (27)$$

$$n = 16,\ r^2 = 0.854,\ q^2 = 0.782,\ s = 0.431$$

outliers: $CONH(CH_2)_2OMe$; NH-(2-COOH-C_6H_4); 3-(5,5-Me_2)isoxazolinyl; 4-(2-guanidino)thiazolyl

optimum CMR = 9.22 (9.05−9.41)

range in log 1/*C* = 5.05−8.46

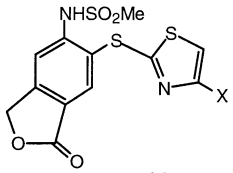
The compounds in this series have a variety of substituents at the 5-position of dihydrobenzofuran and were reported by Janusz et al.[73] The best prediction of their inhibitory activity is made with CMR. Its parabolic nature shows that the overall size of the compound initially increases the activity up to an optimum value of 9.22 and then decreases it. The indicator variable *I* was used with a value of 1 for the X = CO-N-alkyl group and a value of 0 for others. Its negative coefficient indicates that CO-N-alkyl groups do not favor the activity. CMR and ClogP are not collinear; hence, hydrophobicity does not play a significant role.

e. Benzofuranones. *IC_{50} for COX-2 in CHO Cells by 6-(4X-thiazol-2-yl)thio-5-$NHSO_2$Me-3H-isobenzofuran-3H-1-one (**28**) (Table 28*)

Table 28. IC_{50} Data for the Inhibition of COX-2 by Compound 28[74]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 28)	Δ	$\sigma_{I,X}$
1	H	7.57	7.75	−0.18	0.00
2	Me[a]	7.37	8.18	−0.81	−0.04
3	C_2H_5	7.89	7.86	0.03	−0.01
4	$CH=CH_2$	6.85	6.58	0.28	0.11
5	SMe	4.96	5.08	−0.12	0.25

[a] Data point not included in equation derivation.



28

$$\log 1/C = -10.69(\pm 5.15)\sigma_{I,X} + 7.75(\pm 0.70) \quad (28)$$

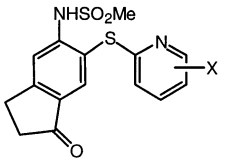
$$n = 4,\ r^2 = 0.976,\ q^2 = 0.828,\ s = 0.251$$

outlier: Me

range in log 1/*C* = 4.96−7.89

Ouimet et al.[74] explored variation in the thiazole ring of compound **28**. Equation 28 shows that the X substituents promote the activity in proportion to their field/inductive effect. These data are also too limited to draw any firm conclusions.

f. Benzocyclopentanones. *IC_{50} for COX-2 Expressed in CHO Cells by 1-($NHSO_2$Me)-2-[S-(X-pyridin-2-yl)]-benzocyclopentanone (**29**) (Table 29*)



29

Table 29. IC_{50} Data for the Inhibition of COX-2 by Compound 29[74]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 29)	Δ	σ_X
1	H	6.30	6.29	0.01	0.00
2	5-Me	6.19	6.23	−0.03	−0.07
3	3-Cl	6.66	6.62	0.04	0.37
4	3,5-Cl_2	6.92	6.95	−0.02	0.74

[a] Data points not included in equation derivation.

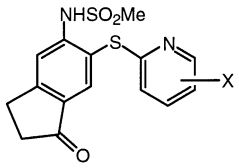
$$\log 1/C = 0.89(\pm 0.28)\sigma_X + 6.29(\pm 0.12) \quad (29)$$

$$n = 4,\ r^2 = 0.990,\ q^2 = 0.934,\ s = 0.042$$

$$\text{range in } \log 1/C = 6.19-6.92$$

A small set of analogues of benzocyclopentanone reported by Ouimet et al.[74] showed that electron-withdrawing X substituents favor inhibitory activity.

*IC_{50} for Purified Recombinant COX-2 by 1-(NHSO₂Me)-2-[S-(X-pyridin-2-yl)]-benzocyclopentanone (**30**) (Table 30)*



30

$$\log 1/C = 0.53(\pm 0.22)\sigma_X + 6.07(\pm 0.09) \quad (30)$$

$$n = 4,\ r^2 = 0.982,\ q^2 = 0.906,\ s = 0.033$$

$$\text{range in } \log 1/C = 6.00-6.44$$

Equation 30 gave the best correlation for the inhibitory data reported by Ouimet et al.[74] It shows that electron-withdrawing X substituents enhance activity. A QSAR based on only four data points cannot be taken seriously, but it is a starting point. It is of note that the range in activity is very narrow for this set.

Table 30. IC_{50} Data for the Inhibition of COX-2 by Compound 30[74]

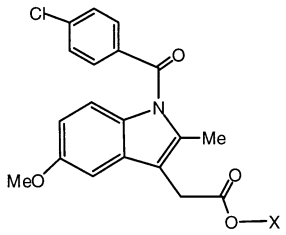
		log 1/*C*			
no.	substituent X	obsd	calcd (eq 30)	Δ	σ_X
1	H	6.09	6.07	0.02	0.00
2	5-Me	6.00	6.03	−0.03	−0.07
3	3-Cl	6.28	6.26	0.02	0.37
4	3,5-Cl_2	6.44	6.46	−0.01	0.74

Table 31. IC_{50} Data for the Inhibition of COX-2 by Compound 31[75]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 31)	Δ	ClogP
1	C_6H_5[a]	6.40	7.39	−0.99	6.11
2	α-naphthyl	5.30	5.27	0.03	7.28
3	$CH_2CH_2C_6H_5$[a]	7.40	6.66	0.74	6.68
4	4-SMe-C_6H_4	6.52	6.63	−0.11	6.70
5	2-SMe-C_6H_4	7.22	7.21	0.01	6.30
6	4-OMe-C_6H_4	7.40	7.32	0.08	6.19
7	4-NHCOMeC_6H_4	7.30	7.39	−0.09	5.28
8	4-F-C_6H_4	7.13	7.11	0.02	6.39
9	3-pyridyl	7.30	7.24	0.06	5.11

[a] Data points not included in equation derivation.

g. Indomethacin Analogues. *IC_{50} for Purified COX-2 by Aromatic Esters of Indomethacin (**31**) (Table 31)*



31

$$\log 1/C = 10.23(\pm 2.32)\text{ClogP} - 0.90(\pm 0.19)\text{ClogP}^2 - 21.57(\pm 7.04) \quad (31)$$

$$n = 7,\ r^2 = 0.991,\ q^2 = 0.937,\ s = 0.089$$

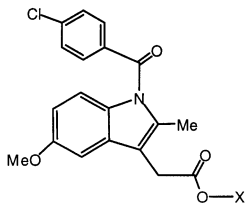
$$\text{outliers: } C_6H_5;\ CH_2CH_2C_6H_5$$

$$\text{optimum ClogP} = 5.69\ (5.55-5.79)$$

$$\text{range in } \log 1/C = 5.30-7.40$$

Aromatic esters of indomethacin reported by Kalgutkar et al.[75] showed potent COX-2 inhibitory activity. Equation 31 derived by us indicates that the activity first increases with increase in hydrophobicity and then decreases. The optimum ClogP value is 5.69.

*IC_{50} for Purified COX-2 by Aliphatic Esters of Indomethacin (**32**) (Table 32)*



32

$$\log 1/C = 1.72(\pm 0.91)\text{ClogP} - 0.12(\pm 0.07)\text{ClogP}^2 + 0.27(\pm 0.21)I + 0.92(\pm 2.77) \quad (32)$$

$$n = 15,\ r^2 = 0.846,\ q^2 = 0.690,\ s = 0.178$$

$$\text{outliers: } CH_2CH_2\text{-cy-}C_6H_{11};\ CH_2C{\equiv}C(CH_2)_3Me;\ CH_2CH_2NHCOOCMe_3$$

$$\text{optimum ClogP} = 7.13\ (6.66-8.72)$$

$$\text{range in } \log 1/C = 6.00-7.40$$

Kalgutkar et al.[75] also studied the inhibitory action of aliphatic esters of indomethacin. Equation 32 derived for the data also depicts parabolic correlation with ClogP similar to eq 31 with an optimum ClogP of 7.13. The indicator variable *I* was used with a

Table 32. IC_{50} Data for the Inhibition of COX-2 by Compound 32[75]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 32)	Δ	ClogP	*I*
1	H	6.13	6.02	0.11	4.18	0
2	Me	6.60	6.56	0.04	4.59	1
3	C_2H_5	7.00	6.85	0.15	5.12	1
4	C_3H_7	7.00	7.08	−0.08	5.64	1
5	$CHMe_2$	6.60	6.72	−0.12	5.42	0
6	C_4H_9	7.30	7.23	0.07	6.17	1
7	C_5H_{11}	7.30	7.32	−0.02	6.70	1
8	C_6H_{13}	7.22	7.34	−0.12	7.23	1
9	cy-C_6H_{11}	6.92	7.04	−0.12	6.62	0
10	CH_2CH_2-cy-C_6H_{11}[a]	6.00	7.02	−1.02	7.77	0
11	C_7H_{15}	7.40	7.30	0.10	7.76	1
12	$CH_2CH_2O(CH_2)_3Me$	7.22	6.95	0.28	6.12	0
13	*trans*-$CH_2CHCH(CH_2)_3Me$	7.30	7.06	0.24	7.48	0
14	$CH_2C{\equiv}C(CH_2)_3Me$[a]	6.60	7.06	−0.46	6.80	0
15	$CH(Me)CH_2C{\equiv}CC_2H_5$	6.92	7.03	−0.11	6.53	0
16	C_8H_{17}	7.05	7.19	−0.14	8.29	1
17	CH_2CH_2-N-morpholine	6.17	6.46	−0.29	4.88	0
18	$CH_2CH_2NHCOOCMe_3$[a]	7.35	6.85	0.49	5.80	0

[a] Data points not included in equation derivation.

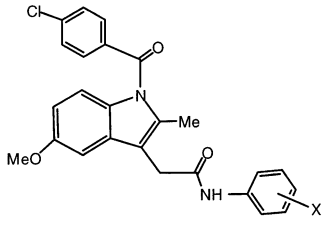
Table 33. IC_{50} Data for the Inhibition of COX-2 by Compound 33[75]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 33)	Δ	MgVol	$B5_{X,4}$
1	4-F	7.22	7.25	−0.03	3.20	1.35
2	4-Cl	7.26	7.10	0.16	3.30	1.80
3	4-SMe	6.92	6.99	−0.07	3.48	3.26
4	3-SMe	6.66	6.50	0.16	3.48	1.00
5	4-OMe	7.25	7.19	0.06	3.38	3.07
6	3-OC_2H_5	6.19	6.41	−0.22	3.52	1.00
7	4-NHCOMe	6.92	6.84	0.08	3.58	3.61
8	4-CH_2CO_2Me[a]	7.24	6.78	0.46	3.68	4.40
9	4-$CONH_2$	6.85	7.06	−0.21	3.44	3.07
10	4-C_6H_5	6.30	6.24	0.06	3.79	3.11

[a] Data point not included in equation derivation.

value of unity for straight-chain alkanes; it appears that these groups have an additive effect on the activity.

*IC_{50} for Purified COX-2 by Aromatic Amide Derivatives of Indomethacin (**33**) (Table 33*)



33

$$\log 1/C = -2.34(\pm 0.93)\mathrm{MgVol} + 0.22(\pm 0.15)B5_{X,4} + 14.50(\pm 3.09) \quad (33)$$

$$n = 9,\ r^2 = 0.871,\ q^2 = 0.698,\ s = 0.165$$

outliers: 4-CH_2CO_2Me

range in $\log 1/C = 6.19-7.26$

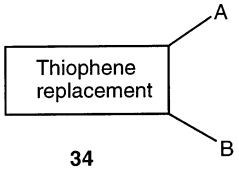
Aromatic amide derivatives of indomethacin were also studied by Kalgutkar et al.[75] Surprisingly, eq 33 derived for the data does not show any hydrophobic interaction. The negative MgVol (McGowan's volume) term indicates that the volume of the molecule is detrimental to activity. On the other hand, larger 4-X substituents in the phenyl ring seem to enhance the activity.

Table 34. IC_{50} Data for the Inhibition of COX-2 by Compound 34[76]

		log 1/*C*			
no.	compound	obsd	calcd (eq 34)	Δ	ClogP
1	2-Me-4B-5A-thiazole[a]	6.51	6.26	0.25	3.79
2	2-Me-4A-5-B-thiazole	6.51	6.26	0.25	3.79
3	4A-5B-1,2-thiazole	5.68	5.87	−0.19	3.44
4	4B-5A-1,2-thiazole	5.29	5.87	−0.58	3.44
5	4B-5A-1,2,3-thiadiazole	5.19	4.96	0.23	2.61
6	3A-4B-thiophene	6.33	6.61	−0.28	4.11
7	2A-3B-norbornene[b]	4.52	6.79	−2.27	4.27
8	2-Br-3B-4A-thiophene	7.52	7.26	0.26	4.69
9	2-CMe_2OH-3B-4A-thiophene[b]	5.23	5.91	−0.68	3.48
10	1A-5B-3-CF_3-pyrazole	6.70	7.01	−0.31	4.46
11	1B-5A-3-CF_3-pyrazole[b]	5.92	6.59	−0.67	4.09
12	1A-2B-cyclopentene	6.80	6.45	0.35	3.96

[a] A = 4-SO_2Me-C_6H_4; B = 4-F-C_6H_4. [b] Data points not included in equation derivation.

h. Thiophene Replacement. *IC_{50} of Diaryl Thiophene (**34**) (Table 34*)



34

A = 4-SO_2Me-C_6H_4; B = 4-F-C_6H_4

$$\log 1/C = 1.11(\pm 0.49)\mathrm{ClogP} + 2.07(\pm 1.90) \quad (34)$$

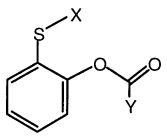
$$n = 9,\ r^2 = 0.802,\ q^2 = 0.654,\ s = 0.362$$

outliers: 2A,3B-norbornene;
2-CMe_2OH,3B,4A-thiophene;
1B,5A,3-CF_3-pyrazole

range in $\log 1/C = 4.52-7.52$

Equation 34 was derived from the data of Gauthier et al.[76] in which the thiophene ring of DUP 697 was replaced by various heterocycles. Positive hydrophobic interactions of ligand−receptor binding are evident from the equation. This is not a good QSAR, nor could one be expected considering the unusual nature of the substituents; nevertheless, it does point to the importance of hydrophobicity.

i. Phenylalkyl Sulfides. *IC_{50} of 1-S-X-2-(OCO-Y)-phenyl (**35**) (Table 35*)



35

Table 35. IC_{50} Data for the Inhibition of COX-2 by Compound 35[77]

	substituent		log 1/C						
no.	X	Y	obsd	calcd (eq 35)	Δ	ClogP	L_Y	I	I_{Ph}
1	Me	Me	3.60	3.94	−0.34	1.65	2.87	0	0
2	Me	C_2H_5	3.00	3.30	−0.30	2.18	4.11	0	0
3	Me	CF_3	3.59	3.91	−0.33	2.21	3.30	0	0
4	Me	CH_2Cl	3.44	3.25	0.20	1.76	3.89	0	0
5	Me	CH_2Br	3.29	3.17	0.12	1.90	4.09	0	0
6	C_2H_5	Me	3.70	4.21	−0.51	2.18	2.87	0	0
7	C_3H_7	Me	4.18	4.48	−0.30	2.71	2.87	0	0
8	C_4H_9	Me	4.47	4.74	−0.27	3.24	2.87	0	0
9	C_5H_{11}	Me	5.30	4.96	0.34	3.77	2.87	0	0
10	C_6H_{13}	Me	5.46	5.09	0.37	4.30	2.87	0	0
11	C_7H_{15}	Me	5.70	5.02	0.68	4.82	2.87	0	0
12	C_8H_{17}	Me	4.40	4.72	−0.32	5.35	2.87	0	0
13	C_9H_{17}	Me	4.40	4.28	0.12	5.88	2.87	0	0
14	cy-C_6H_{11}	Me	4.40	4.93	−0.53	3.68	2.87	0	0
15	cy-C_7H_{13}	Me[a]	4.40	−1.20	5.60	4.24	2.87	0	0
16	$CH_2C_6H_5$	Me	3.60	3.03	0.58	3.22	2.87	0	1
17	$CH_2CH_2C_6H_5$	Me[a]	4.00	−2.41	6.41	3.75	2.87	0	1
18	$CH_2CH_2CH_2C_6H_5$	Me	3.00	3.36	−0.36	4.13	2.87	0	1
19	$CH_2CH_2CH_2OC_6H_5$	Me	3.00	3.22	−0.22	3.66	2.87	0	1
20	$C_6H_{12}I$	Me	5.00	5.09	−0.09	4.54	2.87	0	0
21	$C_6H_{12}Br$	Me	4.92	5.07	−0.15	4.15	2.87	0	0
22	$C_5H_{10}Br$	Me	5.02	4.91	0.12	3.62	2.87	0	0
23	$C_5H_{10}COOH$	Me	4.30	4.30	0.00	2.35	2.87	0	0
24	C_4H_8COOH	Me	4.30	4.03	0.28	1.82	2.87	0	0
25	C_4H_8CN	Me	4.30	3.92	0.38	1.62	2.87	0	0
26	$(CH_2)_5OCOMe$	Me	4.30	4.49	−0.19	2.73	2.87	0	0
27	$C_5H_{10}OH$	Me	4.30	4.01	0.30	1.78	2.87	0	0
28	$CH_2CH_2OC_4H_9$	Me	5.16	4.54	0.62	2.82	2.87	0	0
29	$CH_2CH_2CH_2OC_3H_7$	Me	4.30	4.48	−0.18	2.71	2.87	0	0
30	$CH_2CH{=}CHC_4H_9$	Me	4.96	5.43	−0.47	4.54	2.87	1	0
31	CH_2CCH	Me	4.60	4.59	0.01	2.25	2.87	1	0
32	CH_2CCMe	Me	4.70	4.86	−0.16	2.78	2.87	1	0
33	$CH_2CCC_2H_5$	Me	5.30	5.12	0.19	3.31	2.87	1	0
34	$CH_2CCC_3H_7$	Me	5.52	5.33	0.19	3.84	2.87	1	0
35	$CH_2CCC_4H_9$	Me	6.10	5.44	0.66	4.37	2.87	1	0
36	$CH_2CH_2CCC_3H_7$	Me	5.19	5.32	−0.14	3.82	2.87	1	0
37	$CH(Me)CCC_4H_9$	Me	5.16	5.41	−0.25	4.68	2.87	1	0
38	$CH_2CCC_5H_{11}$	Me	5.16	5.34	−0.18	4.90	2.87	1	0
39	$CH_2CCC_4H_9$	C_2H_5	4.40	4.43	−0.03	4.90	4.11	1	0
40	$CH_2CCC_4H_9$	CH_2Br	4.59	4.52	0.06	4.62	4.09	1	0
41	$CH_2CCC_4H_9$	CH_2NH_2	4.40	4.29	0.11	3.35	4.02	1	0

[a] Data points not included in equation derivation.

$$\log 1/C = 0.52(\pm0.18)\text{ClogP} - 1.53(\pm0.82)\log(\beta \times 10^{\text{ClogP}} + 1) - 0.73(\pm0.28)L_Y + 0.34(\pm0.30)I - 1.71(\pm0.47)I_{Ph} + 5.19(\pm1.08) \quad (35)$$

$$n = 39,\ r^2 = 0.820,\ q^2 = 0.746,\ s = 0.358$$

outliers: X = cy-C_7H_{13}, Y = Me; X = $CH_2CH_2C_6H_5$, Y = Me

optimum ClogP = 4.4

range in log 1/C = 3.00−6.10

Kalgutkar et al.[77] evaluated phenylalkyl sulfides for their inhibitory action against COX-2. We found that hydrophobicity of molecules correlates with activity in a bilinear fashion. It first increases with an increase in hydrophobicity to an optimum ClogP of 4.4 and then decreases linearly. The length of Y substituents did not seem to favor interaction. The indicator variable I takes a value of unity for alkene and alkyne substituents, which appear to be conducive to the activity. Another indicator variable, I_{Ph}, was used for derivatives with X substituents containing a phenyl ring. Its negative coefficient indicates a negative effect of these substituents on the activity.

B. QSAR of COX-1 Inhibitors

1. Oxazoles

*IC_{50} of 2-Me-4-(X-phenyl)-5-(4-SO_2NH_2-phenyl)-oxazole (**9**) (Table 36)*

$$\log 1/C = 1.82(\pm0.53)\text{ClogP} + 0.94(\pm1.30) \quad (36)$$

$$n = 5,\ r^2 = 0.975,\ q^2 = 0.940,\ s = 0.130$$

range in log 1/C = 4.67−6.14

Talley et al.[58] also tested analogues of **9** for their COX-1 inhibitory activity. Hydrophobicity of the molecules seems to be important for the activity. It is important to note that ClogP is highly collinear with L ($r^2 = 0.95$). This data set also is too small for a more detailed study.

Table 36. IC_{50} Data for the Inhibition of COX-1 by Compound 9[58]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 36)	Δ	ClogP
1	H	4.67	4.62	0.05	2.03
2	4-F	4.98	4.89	0.09	2.18
3	4-Cl	6.01	5.92	0.09	2.75
4	4-Br	6.14	6.19	−0.05	2.90
5	3-F	4.72	4.89	−0.17	2.18

Table 37. IC_{50} Data for the Inhibition of COX-1 by Compound 10[58]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 37)	Δ	$B1_X$	π_X
1	Me	4.67	4.93	−0.26	1.52	0.56
2	CF_3	5.94	5.84	0.10	1.99	0.88
3	CF_2H	5.37	4.99	0.38	1.71	0.21
4	Cl	5.19	5.44	−0.26	1.80	0.71
5	CH_2OH	3.69	3.90	−0.21	1.52	−1.03
6	CH_2OMe	4.50	4.43	0.07	1.52	−0.21
7	CH_2COOH[a]	4.63	4.10	0.53	1.52	−0.72
8	SH[a]	5.76	5.09	0.67	1.70	0.39
9	SMe	5.13	5.23	−0.10	1.70	0.61
10	SO_2Me	4.27	4.26	0.01	2.03	−1.63
11	OMe	4.50	4.30	0.20	1.35	−0.02
12	NMe_2	4.47	4.43	0.04	1.35	0.18
13	$CH{=}CH_2$	5.07	5.22	−0.15	1.60	0.82
14	C≡CH	4.95	4.95	0.00	1.60	0.40
15	C≡CMe	5.04	5.21	0.19	1.60	0.81

[a] Data points not included in equation derivation.

*IC_{50} of 2-X-4-phenyl-5-(4-SO_2NH_2-phenyl)-oxazoles (**10**) (Table 37)*

$$\log 1/C = 1.48(\pm 0.65)B1_X + 0.65(\pm 0.18)\pi_X + 2.32(\pm 1.08) \quad (37)$$

$$n = 13,\ r^2 = 0.892,\ q^2 = 0.840,\ s = 0.211$$

$$\text{outliers: } CH_2COOH;\ SH$$

$$\text{range in } \log 1/C = 4.27-5.94$$

In this series Talley et al.[58] explored the influence of various substituents at the 2-position of the oxazole ring of **10**. Like eq 10 for COX-2 inhibition, eq 37 indicates a positive hydrophobic interaction of these substrate analogues with the enzyme, and here also the size of the first atom of the substituents is important for the inhibitory activity. The positive π_X shows that hydrophobic X substituents improve the activity.

*IC_{50} of 2-X-4-(4-SO_2NH_2-phenyl)-5-(Y-phenyl)-oxazole (**6**) (Table 38)*

$$\log 1/C = 0.82(\pm 0.35)\text{ClogP} + 1.67(\pm 1.39)B1_X - 0.97(\pm 0.52)L_{Y,3} + 2.19(\pm 1.67) \quad (38)$$

$$n = 13,\ r^2 = 0.883,\ q^2 = 0.781,\ s = 0.320$$

$$\text{range in } \log 1/C = 3.11-6.40$$

Talley et al.[58] also evaluated 2-substituted 4,5-diaryl oxazole derivatives on COX-1. Hydrophobicity of the compound is found to be important for the activity. Similar to eq 6 for COX-2 inhibition of analogues of **6**, here also a positive B1 for X substituents at the 2-position of the oxazole ring shows that the receptor has steric interactions with the ligands at this position and the length of Y substituents at the 3-position decreases activity. Talley et al.[58] also reported that small substituents at the 2-position are generally well tolerated for COX-2 also.

Table 38. IC_{50} Data for the Inhibition of COX-1 by Compound 6[58]

			log 1/*C*					
	substituent			calcd				
no.	X	Y	obsd	(eq 38)	Δ	ClogP	$B1_X$	$L_{Y,3}$
1	Me	H	4.00	4.39	−0.39	2.03	1.52	2.06
2	Me	4-Cl	5.16	4.98	0.18	2.75	1.52	2.06
3	Me	4-Br	4.83	5.10	−0.27	2.90	1.52	2.06
4	Me	3-F-4-OMe	4.10	3.85	0.26	2.07	1.52	2.65
5	CH_2OMe	4-Cl	4.82	4.58	0.24	2.26	1.52	2.06
6	CH_2OMe	4-Br	4.71	4.70	0.01	2.41	1.52	2.06
7	CH_2OH	H	3.11	3.32	−0.21	0.72	1.52	2.06
8	CF_2H	H	4.96	4.65	0.31	1.95	1.71	2.06
9	CF_3	4-Cl	6.40	6.38	0.01	3.50	1.99	2.06
10	CF_3	3,4-Cl_2	5.46	5.45	0.01	4.09	1.99	3.52
11	CF_3	3,4-F_2	4.93	5.40	−0.47	3.00	1.99	2.65
12	CF_3	3-Cl-4-OMe	4.76	8.85	−0.09	3.36	1.99	3.52
13	CF_3	3-F-4-OMe	5.66	5.25	0.41	2.82	1.99	2.65

Table 39. IC_{50} Data for the Inhibition of COX-1 by Compound 13[59]

			log 1/*C*				
	substituent			calcd			
no.	X	Y	obsd	(eq 39)	Δ	ClogP	$B5_X$
1	4-F	4-SO_2Me	4.59	4.78	−0.18	3.89	1.35
2	4-F	4-SO_2NH_2	5.76	5.96	−0.20	5.51	1.35
3	4-SO_2NH_2	4-F	7.10	6.48	0.62	3.88	3.05
4	4-OMe	4-SO_2NH_2	5.59	6.35	−0.76	3.67	3.07
5	4-SO_2NH_2	4-OMe	6.01	5.58	0.43	5.48	1.00
6	4-Cl	4-Cl	7.26	7.46	−0.20	6.95	1.80
7	4-OMe	4-OMe	8.30	7.58	0.72	5.36	3.07
8	4-OMe	4-Cl	7.75	8.17	−0.43	6.17	3.07
9	4-Cl	4-OMe[a]	8.16	6.88	1.28	6.15	1.80

[a] Data point not included in equation derivation.

2. Pyrazoles

IC_{50} of 3-CF_3-5-(X-phenyl)-1-(Y-phenyl)-pyrazole (**13**) *(Table 39)*

$$\log 1/C = 0.73(\pm 0.52)\text{ClogP} + 1.01(\pm 0.67)B5_X + 0.58(\pm 3.37) \quad (39)$$

$$n = 8,\ r^2 = 0.821,\ q^2 = 0.561,\ s = 0.626$$

$$\text{outlier: X} = \text{4-Cl, Y} = \text{4-OMe}$$

$$\text{range in } \log 1/C = 4.59-8.30$$

Congeners of **13** were tested for their COX-1 inhibition by Penning et al.[59] Here again hydrophobicity of the compounds is found to promote the inhibitory activity. A positive B5 of X substituents shows that the bulky group at this position favors the activity.

Table 40. IC_{50} Data for the Inhibition of COX-1 by Compound 17[64]

		log 1/*C*			
no.	substituent X	obsd	calcd (eq 40)	Δ	$L_{X,4}$
1	H	2.80	3.12	−0.32	2.06
2	3-Cl	3.27	3.12	0.15	2.06
3	4-Cl	5.00	4.95	0.05	3.52
4	4-CH_3	4.48	4.14	0.35	2.87
5	4-OCH_3	5.25	5.53	−0.27	3.98
6	3,4-Cl_2	5.00	4.95	0.05	3.52
7	3,4-F_2[a]	3.12	3.86	−0.74	2.65
8	3-Cl,4-CH_3	4.25	4.14	0.12	2.87
9	2-CH_3,3-F	3.00	3.12	−0.12	2.06

[a] Data point not included in equation derivation.

3. Imidazoles

*IC_{50} of 2-CF_3-4-(4-SO_2Me-phenyl)-5-(X-phenyl)-imidazole (**17**) (Table 40)*

$$\log 1/C = 1.25(\pm 0.30)L_{X,4} + 0.54(\pm 0.87) \quad (40)$$

$$n = 8,\ r^2 = 0.947,\ q^2 = 0.898,\ s = 0.242$$

outlier: 3,4-F_2

range in log $1/C = 2.80-5.25$

Analogues of **17** were tested by Barta et al.[64] for their inhibitory action against COX-1. $L_{X,4}$ terms suggest a positive steric interaction of these substituents with the COX-1 receptor.

4. Thiophenes

*IC_{50} of 2-(4-Y-phenyl)-3-(4-X-phenyl)-5-Z-thiophene (**20**) (Table 41)*

$$\log 1/C = 0.79(\pm 0.26)\mathrm{ClogP} - 1.27(\pm 0.63)\mathrm{CMR} - 1.48(\pm 0.67)\mathrm{Es}_Z + 12.52(\pm 5.59) \quad (41)$$

$$n = 12,\ r^2 = 0.902,\ q^2 = 0.800,\ s = 0.263$$

outliers: X = SO_2NH_2, Y = F, Z = H; X = F, Y = SO_2NH_2, Z = H; X = COOMe, Y = F, Z = H

range in log $1/C = 4.50-6.68$

Inhibition of COX-1 by substituted diaryl thiophenes was studied by Leblanc et al.[66] Equation 41 obtained from their data shows hydrophobic and steric interactions. It is evident from this equation that the hydrophobicity of the molecules is important for binding with the receptor. The CMR term indicates negative steric interaction of these molecules with the enzyme. The negative Es values of substituents indicate that the size of Z substituents promotes the activity.

5. Oxazolones

*IC_{50} for COX-1 in Human Whole Blood by 3-(X-phenyl)-4-(4-SO_2-Y-phenyl)-5-Z-oxazol-2-one (**21**) (Table 42)*

$$\log 1/C = -2.47(\pm 1.17)\mathrm{MgVol} + 0.80(\pm 0.25)B5_{X,3} + 0.51(\pm 0.15)L_{X,4} + 0.28(\pm 0.20)I_Y + 8.14\ (\pm 2.30) \quad (42)$$

$$n = 24,\ r^2 = 0.815,\ q^2 = 0.719,\ s = 0.177$$

outliers: X = 4-Cl, Y = Me, Z = H; X = 4-C_2H_5, Y = Me, Z = H; X = 4-OMe, Y = NH_2, Z = H

range in log $1/C$ =4.31−6.05

Diphenyl oxazolones were also studied for their inhibitory activity against COX-1 in human whole blood by Puig et al.[67] X substituents on the phenyl ring show positive steric interactions. The overall volume of the compounds seems to be detrimental to the activity as evidenced by the negative MgVol term. In this QSAR the indicator variable $I_Y = 1$ is for Y = Me. It is interesting to note a favorable effect of SO_2Me over SO_2NH_2, similar to QSAR 21, derived for COX-2 data of the same set of congeners.

Table 41. IC_{50} Data for the Inhibition of COX-1 by Compound 20[66]

	substituent			log 1/*C*					
no.	X	Y	Z	obsd	calcd (eq 41)	Δ	ClogP	CMR	Es_Z
1	SO_2Me	F	Br	6.22	6.11	0.11	5.20	9.65	−1.16
2	F	SO_2Me	Br	5.96	6.11	−0.15	5.20	9.65	−1.16
3	SO_2NH_2	F	H[a]	5.89	4.66	1.22	4.13	8.78	0.00
4	F	SO_2NH_2	H[a]	5.57	4.66	0.91	4.13	8.78	0.00
5	SO_2NH_2	F	$CHMe_2$	6.64	6.54	0.09	5.56	10.17	−1.71
6	F	SO_2NH_2	CMe_2OH	5.27	5.32	−0.06	3.80	10.32	−1.95
7	SO_2Me	F	H	4.50	4.69	−0.20	4.32	8.87	0.00
8	$CONH_2$	F	H	5.50	5.40	0.09	4.47	8.40	0.00
9	COMe	F	H	6.13	6.00	0.12	5.39	8.50	0.00
10	COOMe	F	H[a]	4.77	6.22	−1.45	5.90	8.65	0.00
11	CHO	F	H	6.01	6.53	−0.52	5.31	8.04	0.00
12	CN	F	H	6.68	6.61	0.07	5.37	8.01	0.00
13	CH2OH	F	H	6.46	6.05	0.40	4.89	0.15	0.00
14	SMe	F	H	6.47	6.49	−0.02	6.49	8.81	0.00
15	SOMe	F	H	4.82	4.77	0.05	4.37	8.84	0.00

[a] Data points not included in equation derivation.

Table 42. IC_{50} Data for the Inhibition of COX-1 by Compound 21[67]

	substituent			log 1/*C*						
no.	X	Y	Z	obsd	calcd (eq 42)	Δ	MgVol	$B5_{X,3}$	$L_{X,4}$	I_Y
1	H	Me	H	4.47	4.85	−0.38	2.19	1.00	2.06	1
2	2-F	Me	H	4.87	4.81	0.07	2.21	1.00	2.06	1
3	4-F	Me	H	5.29	5.11	0.19	2.21	1.00	2.65	1
4	4-Cl	Me	H[a]	4.87	5.29	−0.42	2.31	1.00	3.52	1
5	4-Me	Me	H	4.94	4.91	0.02	2.33	1.00	2.87	1
6	4-C_2H_5	Me	H[a]	4.37	5.19	−0.82	2.47	1.00	4.11	1
7	2,4-F_2	Me	H	5.16	5.06	0.10	2.23	1.00	2.65	1
8	H	NH_2	H	4.61	4.67	−0.06	2.15	1.00	2.06	0
9	2-F	NH_2	H	4.55	4.62	−0.07	2.17	1.00	2.06	0
10	4-F	NH_2	H	4.88	4.92	−0.04	2.17	1.00	2.65	0
11	2-Cl	NH_2	H	4.45	4.37	0.09	2.27	1.00	2.06	0
12	3-Cl	NH_2	H	4.97	5.01	−0.04	2.27	1.80	2.06	0
13	4-Cl	NH_2	H	5.16	5.11	0.05	2.27	1.00	3.52	0
14	2-Me	NH_2	H	4.54	4.32	0.22	2.29	1.00	2.06	0
15	3-Me	NH_2	H	5.18	5.15	0.03	2.29	2.04	2.06	0
16	4-Me	NH_2	H	4.96	4.73	0.23	2.29	1.00	2.87	0
17	4-C_2H_5	NH_2	H	4.98	5.01	−0.03	2.43	1.00	4.11	0
18	4-OMe	NH_2	H[a]	6.05	5.15	0.90	2.35	1.00	3.98	0
19	2,4-F_2	NH_2	H	4.82	4.88	−0.07	2.19	1.00	2.65	0
20	3,4-Cl_2	NH_2	H	5.82	5.45	0.38	2.40	1.80	3.52	0
21	4-OMe-3-F	NH_2	H	5.29	5.39	−0.09	2.37	1.35	3.98	0
22	4-OMe-3-Cl	NH_2	H	5.24	5.49	−0.25	2.47	1.80	3.98	0
23	H	NH_2	Me	4.31	4.32	−0.01	2.29	1.00	2.06	0
24	4-F	NH_2	Me	4.34	4.58	−0.24	2.31	1.00	2.65	0
25	3-Me	NH_2	Me	4.77	4.81	−0.03	2.43	2.04	2.06	0
26	4-Me	NH_2	Me	4.36	4.38	−0.02	2.43	1.00	2.87	0
27	3,4-Cl_2	NH_2	Me	5.06	5.10	−0.04	2.54	1.80	3.52	0

[a] Data points not included in equation derivation.

Table 43. IC_{50} Data for the Inhibition of COX-1 by Compound 27[73]

		log 1/*C*				
no.	substituent X	obsd	calcd (eq 43)	Δ	CMR	*I*
1	$CONHC_2H_5$	4.70	4.89	−0.19	8.17	1
2	$CONHC_3H_7$	6.26	5.55	0.71	8.63	1
3	$CONHC_4H_9$	5.60	5.83	−0.23	9.10	1
4	$CONHC_5H_{11}$	5.70	5.75	−0.05	9.56	1
5	CONH-cy-C_3H_5[a]	6.54	5.39	1.14	8.50	1
6	$CONH(CH_2)_2OMe$	6.00	5.68	0.32	8.79	1
7	$CON(Me)C_2H_5$	5.60	5.55	0.06	8.63	1
8	CON(Me)-cy-C_3H_5	6.30	5.79	−0.49	8.96	1
9	$CON(C_3H_7)$-cy-C_3H_5	5.35	5.48	−0.13	9.89	1
10	NHCOMe	5.46	5.39	0.07	7.71	0
11	NH-(2-COOH-C_6H_4)[a]	5.60	6.97	−1.37	9.91	0
12	3-(5,5-Me_2)isoxazolinyl	7.16	7.37	−0.21	9.17	0
13	2-thienyl	6.70	7.13	−0.43	8.70	0
14	4-(2-guanidino)thiazolyl[a]	4.82	7.01	−2.19	9.88	0
15	6-imidazo[2.1-*b*]thiazolyl	7.13	7.21	−0.08	9.66	0
16	3-methylene-γ-butyrolactonyl	7.35	7.32	0.03	8.98	0
17	5-methylene-2-imino-4-thiazolindinonyl	5.30	5.47	−0.16	10.72	0
18	CO-2-thienyl	7.35	7.37	−0.02	9.19	0
19	CO-2-(N-Me-pyrrole)	7.46	7.37	0.09	9.28	0
20	(*E*)-CH=CH-2-thienyl	7.70	6.98	0.72	0.72	0

[a] Data points not included in equation derivation.

6. Dihydrobenzofurans

*IC_{50} of 7-CMe_3-3,3-di-Me-5-X-2,3-dihydrobenzofuran (**27**) (Table 43)*

$$\log 1/C = 15.79(\pm 5.14)\mathrm{CMR} - 0.86(\pm 0.28)\mathrm{CMR}^2 - 1.52(\pm 0.40)\mathrm{I} - 65.47(\pm 23.53) \quad (43)$$

$$n = 17,\ r^2 = 0.880,\ q^2 = 0.792,\ s = 0.367$$

outliers: CONH-cy-C_3H_5; NH-(2-COOH-C_6H_4); 4-(2-guanidino)thiazolyl

optimum CMR = 9.23 (9.06−9.41)

range in log 1/*C* = 4.70−7.70

The compounds in this series have a variety of substituents at the 5-position of dihydrobenzofuran and were reported by Janusz et al.[73] The best prediction of their inhibitory activity against COX-1

is made with CMR. Its parabolic nature shows that the overall size of the compound influences the activity in a parabolic way up to an optimum value of 9.23. The negative coefficient of indicator variable *I*, used with a value of 1 for X = CO-N-alkyl group and a value of 0 for others, indicates that this group is not conducive to the activity. QSAR 43 is quite similar to QSAR 27 derived for COX-2 data for the same set. It seems that these compounds should be explored further for obtaining better selectivity between COX-2 and COX-1 inhibitors.

IV. Overview

In the development of a QSAR we mainly consider four types of properties: hydrophobic, electronic, steric, and polarizability. It is required to consider variation in these properties of substituents at each position of the parent structure in each series. The complexity of various chemical structures considered in this review makes this a difficult task. Those making various derivatives obviously did not have in mind getting good variation in the above properties. We hope our review will help others to design new structures that will help in clearly establishing the nature of receptor−ligand binding. In view of the information available about the structure of the cyclooxygenase receptor, the occurrence of hydrophobic, electronic, and steric effects in QSAR equations is summarized.

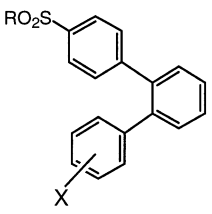
A. COX-2

An analysis of the COX-2 QSAR brings up a number of points of interest. Seventeen data sets have congeners that reach an inhibitory range between 10^{-8} and 10^{-9} M (log1/C = 8−9).

In a survey of our results one of the first observations to attract our attention was that eight QSAR contain a negative σ^+ term (eqs 1, 3, 4, 7, 8, 12, 14, and 25). All of these examples consist of quite active congeners with log1/C > 8 except one (eq 14), with log1/C = 7.70. Correlation with σ^+ is often a characteristic of radical reactions.[41]

It is noteworthy that in all of these examples except one (eq 12) an SO_2Me (R) group is located para to the stilbene-like double bond. In fact, most of the sets are based on this function. However, of the two commercial products, Vioxx contains SO_2Me, whereas Celebrex contains SO_2NH_2.

In all of these equations a striking feature of the parent structure is the presence of a *cis*-stilbene frame of following type:



where the best variations are X with $-\sigma^+$ values conjugated with an electron-attracting function. Our database contains a number of examples of stilbenes displaying radical reactions, of which the following are representative.

Addition of $^{\bullet}SCH_2COOH$ to trans-X-$C_6H_4CH{=}CHC_6H_5$[78]

$$\log k_{rel} = -0.40(\pm 0.18)\sigma^+ - 0.001(\pm 0.07) \quad (44)$$

$$n = 5,\ r^2 = 0.944,\ q^2 = 0.828,\ s = 0.041$$

outliers: X = 3,4-di-OMe

Oxidation of trans-X-$C_6H_4CH{=}CHC_6H_5$ with Perbenzoic Acid[79]

$$\log k = -0.92(\pm 0.08)\sigma^+ - 3.43(\pm 0.06) \quad (45)$$

$$n = 9,\ r^2 = 0.989,\ q^2 = 0.973,\ s = 0.075$$

Oxidation of trans-X-$C_6H_4CH{=}CHC_6H_5$ with Phthaloyl Peroxide in CCl_4[80]

$$\log k_2 = -1.75(\pm 0.25)\sigma^+ + 1.22(\pm 0.12) \quad (46)$$

$$n = 7,\ r^2 = 0.985,\ q^2 = 0.956,\ s = 0.123$$

Now considering sets with highly active compounds (log1/C > 7) without σ^+ terms we find the following QSAR: 6, 9−11, 13, 16−18, 20, 22, 24, 26−28, and 31−34. Many of the equations have linear logP terms that imply that activity could be increased by the use of more hydrophobic substituents. Of these 18 examples, 2 eqs, 9 and 28, are based on too few data points for serious consideration. Of the remaining 16 QSAR, 6, 24, 26, 27, and 33, do not contain a ClogP term. The others, 10, 11, 13, 16−18, 20, 22, 31, 32, and 34, contain ClogP term. All but one of the oxazoles do not contain significant logP term. The one that does, 10, depends heavily on the steric parameter B1. QSAR 24, like 27, contains a carbon with two attached carbons in the five-membered ring. QSAR 13, a pyrazole, is a bit of an enigma. The large value of the intercept shows the fundamental potency of this set of compounds. The negative ClogP term is very unusual and implies that activity could be improved by making less hydrophobic derivatives.

The role of hydrophobicity is also brought out by equations that have parabolic ClogP terms. Optimum ClogP values are as follows:

QSAR	optimum ClogP	confidence limit	range in log 1/C
22	3.3	3.2−5.7	5.9−7.8
31	5.7	5.5−5.8	5.3−7.4
32	7.1	6.7−8.7	6.0−7.4
35	4.4	3.8−4.8	3.0−6.1

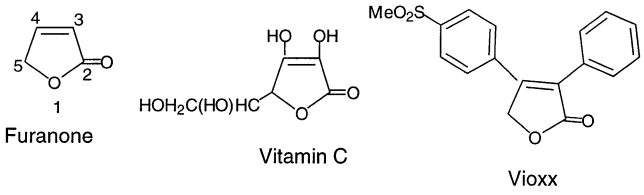
In the examples where a maximum is found in ClogP highest activities are not attained. The highest is eq 22, with a log 1/C of 7.8. It is of interest to compare ClogP values for the two commercial drugs now on the market. In Figure 3, Vioxx and Celebrex have values of 1.8 and 4.4. The drugs appear to have comparable therapeutic value, but the standard dose of Vioxx is 12.5−25.0 mg/day, whereas that for Celebrex is 200 mg/day. It seems likely that this difference is due to bioavailability. Some years ago we reviewed the evidence for optimum ClogP in CNS

agents and came to the conclusion that a logP of ~2 should be ideal for general access to all parts of the body. We suggested a principle of minimal hydrophobicity in drug design.[81]

It must be kept in mind that ClogP accounts for two things, hydrophobic interaction between ligand and receptor and the random walk process in organisms from site of injection to the site of action. Also, ClogP is for the neutral form of the compounds that may be partially ionized. If the degree of ionization is about the same for a set of congeners, one can overlook it. If not, using electronic terms, one can often obtain good correlation, where, for example, σ is associated with the degree of ionization and hence its effect on logP. Of course, the intercept cannot be compared with that from un-ionized compounds.

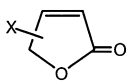
Although QSAR 1, 12, and 14 have σ^+ terms, they have rather low ρ values. Each of these QSAR contains a significant ClogP term. It is of course known that the COX-2 receptor contains a highly hydrophobic region. Equations 3, 4, and 8 do not contain ClogP terms, whereas eq 7 contains one of dubious value [note the confidence limits on this term; 0.32(±0.26)]. In summary, it would appear that activity could be strongly influenced by either a hydrophobic or an electronic interaction. Vioxx would appear to be heavily influenced by electronic interactions, whereas Celebrex (a pyrazole, QSAR 11 and 12) may be more influenced by hydrophobic contacts.

We found furanones of particular interest in our studies:



Vioxx is an important drug based on its ability to inhibit COX-2. Vitamin C is a well-known radical scavenger.[82] One wonders if Vioxx or other COX-2 inhibitors might operate by the same mechanism.

Another interesting aspect of the furanone system is its mutagenecity. Tuppurainen[83] studied mutagenecity by various substituted halogenated hydroxy furanones in the *Salmonella typhimurium* TA100 tester stain, for which QSAR 47 was obtained. Substituents X are 3,4-mono- or di-Cl, Br, OH, OMe, OC_2H_5, $CHCl_2$, $CHBr_2$, CH_2Cl.



$$\log\mathrm{RBR} = -13.9(\pm1.98)E_{\mathrm{LUMO}} - 1.43(\pm1.01)\mathrm{ClogP} \quad (47)$$

$$n = 22,\ r^2 = 0.920,\ q^2 = 0.895,\ s = 1.05$$

outliers: 3-Cl, 4-Me, 5-OC_2H_5; 3-Cl, 5-OH

It is clear that the electron-releasing substituents (e.g., OH and OMe) at the 3-position are most effective. Tuppurainen suggests that a one-electron reduction is involved.

The negative ClogP term in the QSAR was unexpected, but it is significant. Omitting this term yields a QSAR with r^2 of 0.883. These results help to explain why Vioxx would not be expected to be mutagenic or carcinogenic.

It is of interest that in a number of instances the COOH function is present and is well fit even though the ClogP values are for the neutral form. Hence, it would seem that these functions do not contact the enzyme.

Steric factors are obviously important. MgVol and CMR are two physicochemical parameters that are indicative of the overall volume/size of the molecules. Although MgVol is purely a prediction of the size of a molecule, CMR also more or less represents the same, with correction for polarizability as discussed under Materials and Methods.

Considering MgVol, only 6 QSAR (3, 5, 15−17, and 33) of 35 (for COX-2) have this term. Interestingly, all have negative coefficients. The overall range of MgVol for all of these sets is 2.23−3.79. Negative CMR appears in 4 QSAR (1, 18, 23, and 26). In QSAR 28 we found a parabolic correlation with CMR, which gives an optimum value of 9.22. If we look at the data set with negative CMR, the range of CMR is ≥9.

S. no.	QSAR	range in CMR
1	1	9.45−10.39
2	18	8.47−9.25
3	23	7.96−10.39
4	26	9.70−11.81

In data set 23 there are two molecules with CMR 7.96 and 8.47, and both are outliers (they do not fit in the QSAR derived for the best fit model). All other molecules in this set have CMR values >9. These two molecules probably do not give sufficient spread to the data set to give a parabolic correlation and could not fit in the QSAR. Both of these observations directly point to the fact that the receptor site cannot accommodate larger molecules. This should be kept in mind when new derivatives are synthesized.

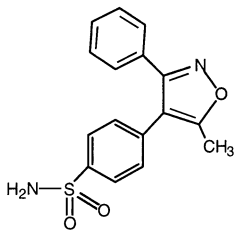
Sterimol parameters (B1, B5, and *L*) occur in many of the QSAR, sometimes positive, sometimes negative. Because the variation in the molecules is brought about by the presence of different groups in different positions of the parent molecule, the effect of a specific group is also brought out by steric interactions in addition to electronic effects or their contributions to the volume/size/hydrophobicity of the analogue. Steric terms (mainly Verloop's sterimol) appear in QSAR 3, 4, 6, 9, 10, 16, 17, 20, 21, 24, 26, 33, and 35. It is not easy to evaluate the role of these terms; still, wherever a negative coefficient is seen, one should consider reducing the size, length, width, or bulk of the substituent groups as per the QSAR model. However, an interesting feature, which surfaces when a QSAR with a substituted phenyl ring attached to the five-membered ring is considered, is the steric interaction of substituents of the fourth position, in particular. In QSAR 3, 4, 9, 21, and 26, B1 for the fourth-position substituents is positive. It appears that small substituents attached to the first

atom of the pharamacophore enhance activity by positive interaction with the receptor. Two QSAR, 6 and 24, where we found parabolic correlation with B5 and bilinear with *L*, respectively, indicate that this steric site is small, having an optimum for both volume (2.09) and length (3.36). QSAR 16 has negative $L_{X,2}$. QSAR 17 and 21 have negative $B1_{X,2}$. It appears that the substituents at the second position of the phenyl group rotate the phenyl ring out of the plane, resulting in poor binding of the substituents specifically at the fourth position. Hence, it is suggested that it would be better to explore molecules with substituents at position four for better activity.

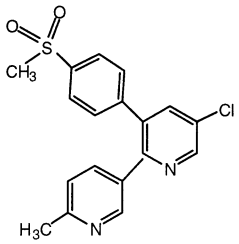
Indicator variables appear in a number of QSAR (1, 11, 12, 16, 18, 21, 24, 25, 27, 32, and 35). They have been used with a value of 1 or 0 for special effects with special features that are otherwise difficult to parametrize. Their occurrence in the QSAR points toward the importance of that specific feature for which they have been used.

A point to note is the presence of indicator variable I_Y in eqs 1, 16, 18, and 24 in the best-derived QSAR model, where it is used for the presence of a NH_2 group linked to the 4-SO_2- of one of the phenyl rings attached to the five-membered ring. Its presence seems to increase the activity in these sets. However, overall it is difficult to comment on the suitability of one over the other, as of 35 QSAR reported here, 10 have SO_2Me and 6 have SO_2NH_2 in the parent molecule. Of the two drugs approved as COX-2 inhibitors, Vioxx has SO_2Me (ClogP = 1.8) and Celebrex has SO_2NH_2 (ClogP = 4.4). We know that the molecules containing the SO_2Me group would be more hydrophobic than those containing SO_2NH_2. It appears to us that the presence of these two groups influences the inherent hydrophobicity of the molecules and affects their selectivity toward COX-2 and COX-1.

Here we would also like to mention two new COX-2 drugs: Valdecoxib (Pharmacia, Talley et al.[84])



Valdecoxib (Pharmacia)
log1/C=8.30
ClogP=1.83



Etoricoxib (Merck)
log1/C=6.08
ClogP=2.35

and Etoricoxib (Merck, Friesen et al.[68]) soon to be on the market. We find it very interesting that both of the new drugs have low ClogP values, although Valdecoxib containing the 4-SO_2NH_2 group showed a higher inhibitory activity than Etoricoxib, containing the 4-SO_2Me group, against human recombinant COX-2 enzyme.

We must point out that over the years we have found the optimum ClogP for cells always higher than that for animals.

B. COX-1

To find any major difference in the physicochemical properties of the molecules showing COX-2 inhibitory activity over COX-1, we derived QSAR for the available data. At this point it is not possible to obtain a definitive answer, as we did not have inhibitory data for COX-1 for all of the sets reported for COX-2.

We can clearly see that of the 8 QSAR for COX-1 (36−43), 4 have positive ClogP values (36, 38, 39, and 41). Interestingly, QSAR 13 for COX-2, derived from the same data set as QSAR 39, has a negative ClogP value. A negative MgVol term appears in QSAR 42. CMR is negative in QSAR 41 and gives a parabolic correlation in QSAR 43. It is surprising to find that the CMR optimum here also is 9.23 (for COX-2 = 9.22, QSAR 27).

Sterimol steric terms *L*, B1, and B5 also appear in QSAR 37−40 and 42. It is not possible to draw any conclusions or point out the difference on the basis of the limited information and QSAR reported here. It will be helpful to explore derivatives with a wider spread in substituents to study the steric and electronic effects. Interestingly, none of the QSAR show an electronic term. The only thing that can be said for sure now is there is similarity in terms of the requirement for hydrophobicity and size of the molecules for both COX-1 and COX-2 receptors.

One of the most difficult problems in QSAR is the problem of "congeners" that are "misfit" in the final equation. It could be associated with one of the following reasons: (1) The mathematical form of the equation may be off the mark. (2) Outliers may be due to what seem to be "congeners" but are not. (3) Members of a set may have different rates of metabolism. (4) The quality of the experimental data may be poor. (5) Finally, the parameters used may not be the best. Sometimes, experimentally obtained parameters are better than those calculated and vice versa.

Hence, one has to expect outliers that must not be forgotten for they are the leads to new understanding. To cover them up by including them in a QSAR, at the cost of lower r^2, can be more confusing than helpful.

Another serious problem is the quality of parameters, particularly that of logP and steric parameters. There are several programs, of varying quality, for calculating logP; few indeed take the time to experimentally determine new values. From our experience we believe that while ClogP may be in error in terms of absolute values, this may affect only the intercept of a QSAR.[50] The general value of our ClogP calculations is shown in the following equation:

$$\text{MlogP} = 0.975(\pm 0.003)\text{ClogP} + 0.049(\pm 0.007)$$

$$n = 12,107,\ r^2 = 0.973,\ s = 0.299$$

Steric parameters are much more difficult to define. Two approaches have been tried. We have tried to use measured or calculated values for the various substituents. The problem with this approach is that the shape of a receptor site is not known, except in rare examples.[85] The only guide is the

empirical quality of the QSAR. Another approach is CoMFA. Here one attempts, by trial and error, to place the members of a data set in a proper conformation from which steric interactions are estimated by exploring the outer surfaces of the sets of "congeners". Because the positions of the ligand are fixed, the "give" in the system has to be the receptor wall. However, we know from many examples that steric effects are often a linear function of the empirical parameters. That is, as substituent size increases, activity gradually falls or rises. This more or less uniform decline or increase in activity could be due to two effects: the receptor wall could give to some degree or the position of the ligands could gradually move, or possibly both mechanisms could operate. In our approach, we do not assume a perfectly uniform mode of binding. Thus, coefficients with steric terms may reflect the complex process of displacement of the ligand and/or the receptor wall.

Considerable work has been done using CoMFA methodology,[86,87] where three-dimensional pictures are used to discuss the results, not the numbers as we do in QSAR. These pictures are not precise enough to be compared with other results, in part because the terms used to formulate a regression-based model are based on principle components. Such terms will have different compositions from data set to data set so that comparison is possible only via pictures that are not easy to understand. Although termed QSAR, it is generally used as qualitative SAR. It is mainly qualitative or at best semiquantitative. It is not easy to compare our work with the CoMFA models. This is not to say that CoMFA cannot provide insight, but not the kind we are interested in for mechanistic comparison.

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