Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): A Comparative QSAR Study

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1. Introduction

Inflammation. Inflammation is the process by which leukocytes and materials derived from the serum are directed to the site of tissue injury. As

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Alia S. Michaelidou received a B.S. from the School of Pharmacy, Aristotelian University of Thessaloniki, in 2000. Subsequently, she joined the Department of Pharmaceutical Chemistry, School of Pharmacy, as a postgraduate student to receive her Master degree in 2003, and she continues working toward her Ph.D.

Dimitra Hadjipavlou-Litina received a B.S. in pharmacy and a Ph.D. in pharmaceutical chemistry in 1990 for a synthetic and biological study of novel anti-inflammatory hydroxyamino and diamino ketones under Professor P. N. Kourounakis's supervision. From 1992 to 1993, she spent a postdoctoral year with Professor C. Hansch in the Chemistry Department, Pomona College, California. Currently she is an associate professor of pharmaceutical chemistry at the University of Thessaloniki, School of Pharmacy, Greece. Her research interests involve studies on anti-inflammatory and antioxidant agents (synthesis, design, and biological evaluation) and the relationships between structure and activity of various drug classes, as well as comparative QSAR, computer-assisted drug design (CADD), and cheminformatics.

the primary host defense mechanism against all forms of injury, the inflammatory reaction will be encountered on a continuous basis throughout the study of clinical medicine and surgery. Inflammation can best be defined as the vascular and cellular response of living tissue to injury. However, the reaction of blood vessels is its identifying feature. The inflammatory process serves to destroy, dilute, or wall-off the injurious agent as well as the tissue cells that may have been destroyed. A complex series of events are initiated, which, as far as possible, heal and reconstitute the damaged tissue. Repair is the process by which lost or destroyed cells are replaced by vital cells. However, under certain circumstances, inflammation and repair may become aberrant and harmful. In the skin, inflammation is characterized by local redness and swelling. Clotting factors, as well as factors that alter vascular permeability, aid in vasodilation and enhanced blood flow to the affected area, enhanced permeability of the capillaries, and increased migration of effector cells (leukocytes) from the circulatory system to the connective tissue.[1]

The inflammatory response can be divided into a series of overlapping stages: acute vascular, acute cellular, chronic cellular, and resolution. Acute inflammation is of relatively short duration, lasting for a few minutes, several hours, or 1−2 days. It is characterized by the exudation of fluids and plasma proteins (inflammatory edema) and by the emigration of leukocytes (predominantly neutrophils). Subacute inflammation usually is characterized by a decline in the vascular contribution (edema and hyperemia) and often by a change in the character of infiltrating leukocytes. The infiltrate becomes mixed with mononuclear cells (lymphocytes, macrophages, and maybe plasma cells) in reasonable numbers. This represents an intermediate time frame that can vay from a few days to a few weeks depending on the nature of the inciting stimulus. Leukocytic exudation refers to the massing of leukocytes, principally neutrophils and monocytes, at the site of inflammation. The phagocytic leukocytes engulf and destroy or at least weaken foreign invaders. The inflammatory process is designed to provide a rapid mechanism by which the host can respond to the invasion of foreign materials and return to homeostatic equilibrium. Excessive or inadequate activation of the system can have serious effects, as can the failure of inactivation mechanisms.[1]

In the 1970s, a scientific breakthrough occurred with the elucidation of the molecular mechanism of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Vane, Samuelson, and Bergstrom succeeded in showing that these anti-inflammatory substances block the biosynthesis of prostaglandins (PGs), which contribute to a variety of physiological and pathophysiological functions.[2,3]

NSAIDs are widely used for the treatment of pain, fever, and inflammation.[4] The worldwide NSAID market for both occasional and chronic users has been conservatively estimated at over 60 million people. All of the NSAIDs are approximately equivalent in terms of anti-inflammatory efficacy but also cause untoward side effects (e.g., gastrointestinal disorders) in a significant fraction of treated patients, and this frequently limits therapy.

The biosynthetic cascade of arachidonic acid[5] has been the object of intense research. Arachidonic acid liberated from phospholipids by various stimuli can be metabolized by the cyclooxygenase (COX) pathway to prostaglandins (PGs) and thromboxane A_2 or by lipoxygenase (LOX) pathways to hydroperoxyeicosatetraenoic acids (HPETEs), hydroxyeicosatetranoic acids (HETEs), and leukotrienes (LTs) (Figure 1).

Like aspirin, all other NSAIDs, such as ibuprofen, ketoprofen, and naproxen, develop their mode of action by blocking cyclooxygenase. Therapeutic effects and side effects of this class of anti-inflammatory drugs are closely related to their biochemical mechanism of action.

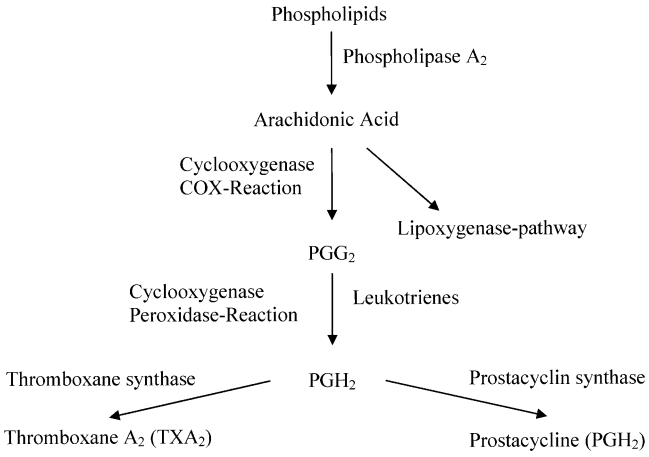


Figure 1. Biosynthesis of PGs.

Long-term NSAID users suffer from the following:
•a high incidence of GI irritation;
•the development of life-threatening GI ulcers and bleeding;[6−8]
•renal disorders and renal failure;[9−11]
•hypertensive effects;
•reduction in filtration of glomeruleric acid.

The inhibition of COX results in decreased production of thromboxane A2, which prolongs bleeding time and leads to inhibition of platelet aggregation. A severe side effect of NSAIDs is vasoconstriction with resultant asthmatic events.

Because of these problems, a major target of drug research is the development of NSAIDs with anti-inflammatory activity but without side effects. The use of QSAR has been increasingly helpful in toxicology and in the design and synthesis of new selective drugs. It has also provided useful insights in understanding many aspects of the chemical−biological interactions of NSAIDs.

2. Review of NSAID QSAR Studies from the Literature

In continuation of our previous research on reported QSAR studies of anti-inflammatories,[12] perusal of the literature enriched our findings with the following:

•Dearden and co-workers[13] found that in vivo anti-inflammatory activity of a series of aspirin derivatives in the rat is correlated with hydrophobicity and the shape of the substituent at the 4-position.

$$\log(1/\mathrm{ED}_{50}) = 2.285 + 1.031 \log P - 0.195 \log P^2 - 0.045L_4 - 0.244B_{2-4}$$

$$N = 28; \quad r = 0.966; \quad s = 0.113$$

•A detailed QSAR analysis of a series of 112 anti-inflammatory *N*-arylanthranilic acids[13] has been performed to determine which physicochemical parameters are responsible for their anti-inflammatory activity. The results indicate that anti-inflammatory activity, as measured by the anti-UV-erythema test, is modeled best by molecular shape parameters. The best QSAR obtained was

$$\log(1/\mathrm{MED}) = 1.601B_{1-2} + 0.576B_{1-3} - 1.187B_{3-4} + 0.522B_{1-6} - 1.681\mu(\mathrm{bond})2 - 0.208\mu(\mathrm{bond})5 - 0.265\mu(\mathrm{bond})6 - 0.226$$

$$N = 112; \quad r = 0.855; \quad r^2(\mathrm{adj}) = 0.716; \quad F = 40.33; \quad s = 0.511; \quad r(\mathrm{CV})^2 = 0.665$$

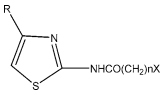
where B_1 and B_3 are Verloop substituent width parameters and μ is bond dipole.

•Kuchar and co-workers[14] studied the activity of arylalkanoic acids in vivo in the kaolin-induced rat paw edema assay. They showed that the potency of the compounds correlated with their hydrophobic and electronic properties:

$$\log I^k = 1.167\sum\pi - 0.278\sum\pi^2 + 0.289\sum\sigma - 1.237$$

$$N = 39; \quad r = 0.940; \quad s = 0.071; \quad F = 89.3$$

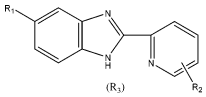
•For a group of thiazolyl N-substituted amides[15] tested as anti-inflammatory agents using the carrageenan-induced mouse paw edema assay, a parabolic dependence of activity CPE% on $c \log D_{7.4}$ and a linear dependence on surface tension were found.



$$\log \mathrm{CPE}\% = 0.107(\pm0.031)c \log D_{7.4} - 0.027(\pm0.007)(c \log D_{7.4})^2 + 0.043(\pm0.005)\mathrm{SURF} - 0.681\ (\pm0.284)$$

$$N = 13; \quad r = 0.945; \quad r^2 = 0.893; \quad s = 0.052; \quad \text{optimum for } c \log D_{7.4} = 1.98 \text{ (from 1.96 to 2.05)}; \quad F_{3,9} = 24.950; \quad p = 0.000$$

•For a series of 2-(2-pyridinyl)benzimidazoles, which were synthesized and evaluated for anti-inflammatory activity by the carrageenan-induced rat paw edema assay,[16] a linear equation was derived:[17]

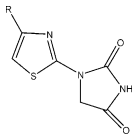


$$\log \mathrm{CPE}\% = 0.187\mathrm{Clog}\,P - 0.376\mathrm{MR}_{\mathrm{R}_1} + 0.334I_{-3} + 0.725I_{-\mathrm{H}} + 0.184$$

$$N = 32; \quad r = 0.861; \quad r^2 = 0.743; \quad s = 0.199; F_{4,27} = 19.27; \quad \alpha = 0.01$$

Clog P is the calculated lipophilicity of the whole molecule, whereas $\mathrm{MR}_{\mathrm{R}_1}$ is the molar refractivity for R_1 substituents. I_{-3} is an indicator variable taking the value of 1 for the presence of a methoxy group at R_1, and $I_{-\mathrm{H}}$ is an indicator variable indicating the possibility for hydrogen bonding.

•For a group of thiazolyl-hydantoins inducing anti-inflammatory activity on the carrageenan-induced paw edema assay,[17] the following QSAR was reported:[18]



$$\log \text{CPE\%} = 0.497\text{Clog}\,P - 0.817I_{-\text{p}} + 1.431$$

$$N = 6;\quad r = 0.92;\ r^2 = 0.831;\quad s = 0.159;\quad F_{2,3} = 7.44;\quad \alpha = 0.1$$

$I_{-\text{p}}$ is an indicator assigning a value of 1 for the presence of a para substituent.

Statistics. With each of the above QSARs, the following staristics are given: N is the number of data points, terms in parentheses are the 95% confidence limits for each term, r is the correlation coefficient between observed values of the dependent and the values predicted from the equation, r^2 is the squared correlation coefficient, s is the standard deviation, and the F-value is a measure of the level of statistical significance of the regression model.

3. Materials and Methods

Many thousands of compounds have been screened as nonsteroidal anti-inflammatory agents in industrial laboratories and a large number of active compounds with novel structures are undergoing clinical trials. The present article presents and analyzes comprehensively the QSARs of only nonsteroidal anti-inflammatory agents, NSAIDs. The biological activities used in the study are the inhibition of the carrageenan rat or mouse paw edema, the inhibition of the pleural inflammation induced in male rats by the intrapleular injection of the calcium ionophore A-23187, and the inhibition of induced adjuvant arthritis in rats.

The in vivo data usually refer to the molar concentration of compounds leading to a 50% inhibition and are expressed by ED_{50} values. Lipophilicity is a significant factor in the susceptibility of drugs to attack by the P-450 enzymes.[19]. In formulation of the QSAR, we have used only calculated log P values, using the CLOGP program.[20] The values of substituent constants (π, σ, E_s, MR, B_1, B_5, and L) have been taken from the literature,[21−26] and the QSAR regression analyses were executed with the C-QSAR program.[27] Multivariate linear/nonlinear regression models were used. This technique is simple and can produce equal or better models comparing to partial least-squares or neural network models. The equations were derived starting from a relatively small set of descriptors, and this research deals with relatively small sets of compounds, so the choice of linear or nonlinear multivariate regression analysis is reasonable and the most appropriate. The parameters used in this report have been discussed in detail along with their applications. Here we provide a brief definition. CMR is the calculated molar refractivity for the whole molecule. MR is calculated as we describe: $(n^2 - 1/n^2 + 2)(\text{MW}/d)$, when 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. MR values have been scaled by 0.1. MR can be used for a substituent or for the whole molecule. MgVol is the molar volume calculated by the methods of McGowan.

B_1, B_5, and L are Verloop's sterimol parameters for substituents. B_1 is a measure of the width of the first atom of a substituent, B_5 is an attempt to define the overall volume, and L is the substituent length. E_s is Taft's steric constant; Clog P is the 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. Clog P and CMR are for the neutral forms of partially ionized compounds.

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 is defined via equilibrium constants. Each regression equation includes 95% confidence limits for each term in parentheses, the correlation coefficient r between observed values of the dependent and the values calculated from the equation, the s standard deviation, q^2 square of cross-validated correlation coefficient (a measure of the quality of model, calculated as described by Cramer et al.[28]), which is often computed to test the stability of model, and the F-values for the individual term. All of the derived equations were obtained without outliers. The outliers are indicated in the corresponding tables with a footnote. The fitted values (calculated) given in tables were calculated by using the corresponding equations. All values given in tables for molecules indicated as outliers were predicted from the corresponding equation.

In Tables 1−56, we have collected several experimental data for several nonsteroidal anti-inflammatory molecules that we could find for sets large enough for a meaningful analysis. It is important to note that the results were obtained for each case from a different laboratory. Thus, it must be born in mind that the different qualities of testing in the various laboratories will have an effect that cannot be estimated.

4. Evaluation of New QSARs on NSAIDs—Results and Discussion

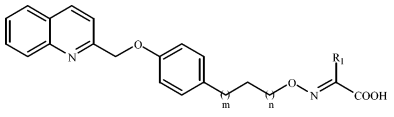
4.1. Heterocyclic Aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic Acids

A novel series of hetero-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic acids was studied as leukotriene biosynthesis inhibitors.[29] Compounds were tested in vivo for anti-inflammatory activity. Pleural inflammation was induced in male rats by the intrapleular injection of the calcium ionophore A-23187. RPI% values express the percent induced inhibition by the tested compounds at 3 mg/kg level.

4.1.1. Hetero-aryl-methoxy-phenyl-alkoxy-imino-methyl-carboxylic Acids

Table 1 presented a small group of four hetero-aryl-methoxy-phenyl-alkoxy-imino-methyl-carboxylic ac-

Table 1. Biological Data[29] and Physicochemical Parameters Used for Deriving Eq 1



no.	R_1	m	n	calcd log RPI%	Δlog RPI%	obsd log RPI%	CMR	Clog P
1	H	0	1	1.95	−0.09	1.86	12.59	−2.64
2	CH_3	0	1	1.41	0.11	1.52	13.06	−2.34
3	CH_3	1	0	1.41	0.07	1.48	13.06	−2.34
4	CH_3	2	0	0.87	−0.09	0.78	13.52	−2.34

ids, a subgroup from ref 29. From them, eq 1 was derived.

$$\log \mathrm{RPI\%} = -1.170(\pm 0.835)\mathrm{CMR} + 16.680(\pm 10.903) \quad (1)$$

$$n = 4;\quad r = 0.974;\quad r^2 = 0.948;\quad q^2 = 0.546;\quad s = 0.127;\quad F_{1,2} = 36.8;\quad \alpha = 0.05$$

Compounds do not contain any unusual substitution. The molecules do not appear to reach a hydrophobic surface for Clog P, $r = 0.665$. CMR represents the overall calculated molar refractivity. Its negative sign brings out a steric effect. The number of data points (four) is small, but the correlation is significant in terms of r and F.

4.1.2. Hetero-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic Acids

For another set of hetero-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic acids,[29] eq 2 was derived.

$$\log \mathrm{RPI\%} = 5.980(\pm 2.052)\mathrm{CMR} - 0.233(\pm 0.082)\mathrm{CMR}^2 - 36.636(\pm 12.789) \quad (2)$$

$$n = 11;\quad r = 0.931;\quad r^2 = 0.867;\quad q^2 = 0.678;\quad s = 0.194;\quad F_{2,8} = 35.878;\quad \alpha = 0.01$$

$$\mathrm{CMR_o} = 12.844(\pm 0.469);\ \mathrm{CMR\ vs\ Clog}\ P = 0.451$$

The biological activities are referred to the percent inhibition of the rat pleurisy inflammation. All the variation in the substituents is confined to the heterocyclic moieties, and no parametrization for them has been done. No correlation with a hydrophobic parameter was found ($r = 0.359$). Molar refractivity of the whole molecule in a parabolic model provides an optimum value $\mathrm{CMR_o} = 12.844$ (from 12.611 to 13.161). Two compounds, **6** and **11**, were omitted. Compound **3** has the lowest CMR value. Compound **6** is less active than predicted (Table 2).

4.1.3. 2-Benzothiazolyl/2-Quinolyl-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic Acids

More hetero-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic acids with a 2-benzothiazolyl- or a 2-quinolyl group were also studied for anti-inflammatory activity; ED_{50} values were used. We have formulated eq 3 from the data[29] in Table 3.

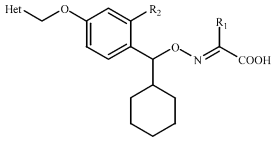
$$\log 1/\mathrm{ED_{50}} = 1.242(\pm 0.918)\mathrm{CMR} - 9.870(\pm 11.337) \quad (3)$$

$$n = 5;\quad r = 0.928;\quad r^2 = 0.861;\quad q^2 = 0.612;\quad s = 0.171;\quad F_{1,3} = 18.5;\quad \alpha = 0.05$$

Equation 3 ralationalizes 86% of the variance in log $1/\mathrm{ED_{50}}$. In terms of r^2, we found it necessary to omit two compounds (compounds **5** and **6**). They possess the first and the second highest CMR values within the dataset. Both have a halogen atom, Cl or Br, as a substituent at the R_2 position instead of a H. The effect of modifying the R_1 and R_2 substituents, as well as the lipophilicity, does not seem to be an important parameter. A much poorer correlation is derived with only Clog P ($r < 0.1$).

The problem with the confidence limits is to be expected. Since the difference among the experimental ED_{50} values is very low (5.15−6.002), a lack of precision in experimental techniques can occur.

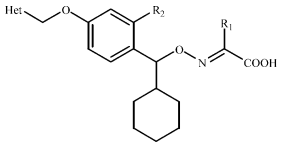
Table 2. Biological Data[29] and Physicochemical Parameters Used for Deriving Eq 2



no.	het	R_1	R_2	calcd log RPI%	Δlog RPI%	obsd log RPI%	CMR	
1	6-F-2-quinolyl	H	H	1.65	−0.06	1.59	12.14	
2	2-pyridyl	H	H	0.92	0.05	0.48	10.44	
3	pyrido[2,3-*b*]-2-thiazolyl	H	H	1.48	0.19	1.67	11.73	
4	2-methyl-4-thiazolyl	H	H	0.71	−0.11	0.60	10.71	
5	2-(4-chlorophenyl)-4-thiazolyl	H	H	1.73	−0.25	1.48	13.25	
6[a]	4-phenyl-2-thiazolyl	CH_3	H	1.74	−0.56	1.18	13.22	
7	4-(4-isopropylphenyl)-2-thiazolyl	H	H	1.37	−0.19	1.18	14.15	
8	4(4-isopropylphenyl)-2-thiazolyl	CH_3	H	1.04	0.19	1.23	14.62	
9	2-benzothiazolyl	CH_3	H	1.72	0.21	1.93	12.40	
10	2-benzothiazolyl	H	Cl	1.73	0.20	1.92	12.43	
11[a]	5-F-benzothiazolyl	CH_3	Cl	1.77	−0.43	1.34	12.91	
12	2-benzoxazolyl	H	H	1.29	−0.10	1.15	11.34	4.75
13	2-quinoxalyl	H	H	1.57	−0.12	1.45	11.92	4.61

[a] Data omitted from derived equation.

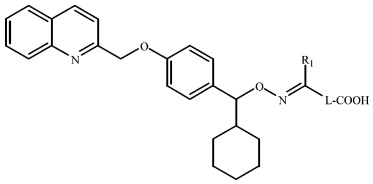
Table 3. Biological Data[29] and Physicochemical Parameters Used for Deriving Eq 3



no.	het	R_1	R_2	calcd log 1/ED_{50}	Δlog 1/ED_{50}	obsd log 1/ED_{50}	CMR	Clog *P*
1	2-quinolyl	H	H	5.29	−0.07	5.22	12.13	−2.44
2	2-quinolyl	CH_3	H	5.86	0.08	5.94	12.59	−2.08
3	6-F-2-quinolyl	CH_3	H	5.88	0.12	6.00	12.61	−1.64
4	2-benzothiazolyl	H	H	5.05	0.10	5.15	11.94	−1.94
5[a]	2-benzothiazolyl	CH_3	Cl	6.24	−0.98	5.26	12.89	−0.52
6[a]	2-benzothiazolyl	H	Br	6.01	−0.31	5.70	12.71	−0.74
7	5-F-2-benzothiazolyl	H	Cl	5.68	−0.23	5.45	12.44	−0.48

[a] Data omitted from derived equation.

Table 4. Biological Data[29] and Physicochemical Parameters Used for Deriving Eq 4



no.	*E/Z*	R_1	L	calcd log RPI%	Δlog RPI%	obsd log RPI%	Clog *P*
1		CH_2StBu	bond	1.65	0.02	1.67	9.06
2		Ph	bond	1.57	0.04	1.61	8.24
3		$PhCH_2CH_2$	bond	1.61	−0.02	1.59	8.10
4		4-OH-$PhCH_2$	bond	1.57	−0.04	1.53	9.15
5	*E*	2-thienyl	bond	1.74	0.04	1.78	7.89
6	*Z*	2-thienyl	bond	1.50	−0.04	1.46	7.89
7		CH_3	CH_2	1.90	−0.07	1.83	6.97
8	*Z*	CH_3	CH_2CH_2	1.71	0.08	1.79	7.32
9[a]		CH_3	$(CH_2)_5$	1.83	−1.13	0.70	8.62
10		H	Ph (1,4)	1.640	−0.03	1.61	8.05
11[a]		H	5-(2OH)Ph	1.73	−0.19	1.54	7.72
12[a]		1-cyclohexyl		1.88	0.93	0.95	6.27

[a] Data omitted from derived equation.

4.1.4. Hetero-aryl-methoxy-phenyl-alkoxy-imino-Substituted Alkyl-carboxylic Acids

For a series of hetero-aryl-methoxy-phenyl-alkoxy-imino-alkyl-carboxylic acids with substitution in the iminoxy linking group L, the anti-inflammatory activity was assayed by measuring the percent inhibition produced by the po administration of the compounds at 3 mg/kg of the calcium ionophore (A-23187)-induced rat pleurisy.[29] The RPI% values listed in Table 4 were used to formulate eq 4.

$$\log \text{RPI\%} = -0.176(\pm 0.068)\ \text{Clog}\ P + 1.209(\pm 0.177) \quad (4)$$

$$n = 9;\quad r = 0.918;\quad r^2 = 0.843;\quad q^2 = 0.554;\quad s = 0.053;\quad F_{1,7} = 37.1;\quad \alpha = 0.01$$

Hydrophilicity should be taken under consideration as an important variable for this dataset.

No term appears for R_1 or R_2 substitutuents. No parametrization for the examined *E* or *Z* isomers has been done. Three data points were rejected (compounds **9**, **11**, and **12**, Table 4). Compound **9** is less active than all others, whereas compound **12** is the only analogue with R_1 = a cyclohexyl group.

4.1.5. Symmetrical Bis(quinolyl-methoxy-phenyl) Alkyl-carboxylic Acids

Kolasa and co-workers[30] investigated symmetrical bis(quinolyl-methoxy-phenyl) alkyl-carboxylic acids as inhibitors of leukotriene biosynthesis. The compounds were tested in the ionophore-induced rat pleurisy model as possible anti-inflammatory agents. The percent inhibition RPI values at 3 mg/kg are listed in Table 5, and from them eq 5 was formulated.

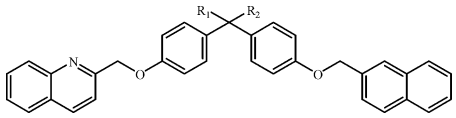
$$\log \text{RPI\%} = 8.561(\pm 1.999)\ \text{Clog}\ P - 0.642(\pm 0.150)\ \text{Clog}\ P^2 - 26.876(\pm 6.554) \quad (5)$$

$$n = 13;\quad r = 0.950;\quad r^2 = 0.902;\quad q^2 = 0.818;\quad s = 0.152;\quad F_{2,10} = 46.28;\quad \alpha = 0.01$$

$$\text{Clog}\ P_o = 6.673(\pm 0.108)\ \text{from 6.569 to 6.786}$$

Parabolic dependence on log *P* provides an optimum lipophilicity 6.673. Note that the calculated log *P* values for this set are high enough (from 5.11 to 7.39). The three outliers not included in this analysis are marked in Table 5. Compound **8** is a hydroxyl derivative, whereas compound **13** is the only derivative with a triple bond next to the −COOH group.

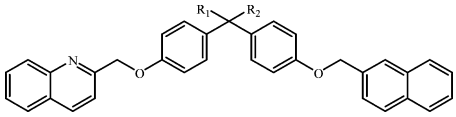
Table 5. Biological Data[30] and Physicochemical Parameters Used for Deriving Eq 5



no.	R_1	R_2	calcd log RPI%	Δlog RPI%	obsd log RPI%	Clog *P*
1[a]	H	ON=CHCOOH	0.70	0.87	1.57	5.43
2	H	ON=C(CH_3)CH=CHCOOH	1.58	−0.15	1.43	6.27
3	H	CH_2COOH	1.45	−0.22	1.23	6.07
4	H	C(CH_3)COO$^-$ Na$^+$	1.67	0.03	1.70	6.53
5	H	CH_2CH(CH_3)COOH	1.68	−0.05	1.63	6.76
6	Me	COOH	1.29	0.10	1.39	5.89
7	Me	$CH_2CH_2CH_2$COOH	1.37	0.14	1.51	7.38
8[a]	Me	$CH_2CH_2CH_2$OH	1.68	−0.83	0.85	6.81
9	H	$C(CH_3)_2CH_2$ON=CHCOOH	1.61	−0.17	1.43	7.03
10	Me	CH_2CH_2ON=C(CH_3)COOH	1.36	0	1.36	7.39
11	Me	$CH_2CH_2CH_2$ON=C(CH_3)COOH	0.70	−0.09	0.60	7.92
12	H	$C(CH_3)_2$CH=NOCH$_2$COO$^-$ Na$^+$	1.58	0.04	1.62	6.27
13[a]	OH	−C≡C−COOH	0.13	1.55	1.68	5.11
14	H	OH	0.26	0.04	0.30	5.18
15	2-thienyl	SCH$_2$COO$^-$ Na$^+$	1.62	0.28	1.90	6.99
16	OH	−C≡C−CH_2CH_2ON=(CH_3)COO$^-$ Na$^+$	1.53	0.07	1.60	6.18

[a] Data omitted from derived equation.

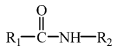
Table 6. Biological Data[30] and Physicochemical Parameters Used for Deriving Eq 6



no.	R_1	R_2	calcd log RPI%	Δlog RPI%	obsd log RPI%	CMR
1[a]	H	ON=CHCOOH	1.61	−0.05	1.57	16.64
2	H	ON=C(CH_3)CH=CHCOOH	1.44	−0.01	1.43	18.16
3	H	CH_2COOH	1.28	−0.05	1.23	15.99
4	H	CH_2CH(CH_3)COOH	1.68	−0.05	1.63	16.92
5	Me	COOH	1.28	0.11	1.39	15.99
6	Me	$CH_2CH_2CH_2$COOH	1.70	−0.19	1.51	17.38
7[a]	Me	$CH_2CH_2CH_2$OH	1.68	−0.83	0.85	16.88
8	H	$C(CH_3)_2CH_2$ON=CHCOOH	1.22	0.21	1.43	18.49
9	Me	CH_2CH_2ON=C(CH_3)COOH	1.22	0.14	1.36	18.49
10	Me	$CH_2CH_2CH_2$ON=C(CH_3)COOH	0.80	−0.20	0.60	18.96
11	OH	−C≡C−COOH	1.59	0.10	1.68	16.56
12	H	OH	0.32	−0.02	0.30	15.03

[a] Data omitted from derived equation.

Table 7. Biological Data[31] and Physicochemical Parameters Used for Deriving Eq 7



no.	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR	Clog *P*
1	3-C_5H_4N	1-morpholinyl	1.64	0.06	1.70	5.55	0.24
2	4-C_5H_4N	1,2,3,4-tetrahydroisoquinoline	1.18	0.05	1.23	7.44	1.38
3	4-C_5H_4N	Ph-CONH	1.31	−0.08	1.23	6.73	1.47
4	4-C_5H_4N	($CH_3CO)_2$N	1.73	−0.03	1.70	5.64	−1.01

Compound 13 is also the less lipophilic compound in terms of Clog *P* within the dataset.

In Table 6, we present a subgroup from the previous derivatives including only the acids and not the sodium salts. Equation 6 was derived.

$$\log \text{RPI\%} = 10.113(\pm 2.627)\text{CMR} - 0.294(\pm 0.077)\text{CMR}^2 - 85.272(\pm 22.402) \quad (6)$$

$$n = 11;\quad r = 0.954;\quad r^2 = 0.909;\quad q^2 = 0.804;\quad s = 0.147;\quad F_{2,8} = 3.624;\quad \alpha = 0.01$$

$$\text{CMR}_o = 17.202(\pm 0.152) \text{ from } 17.056 \text{ to } 17.361$$

4.2. N-Substituted 2(3,4)-Pyridyl Carboxylic Acid Hydrazines

In Table 7, a small number of N-substituted 2(3,4)-pyridyl carboxylic acid hydrazines is presented,[31] which were synthesized to investigate the effects that changes in functionality on the terminal hydrazine nitrogen have on analgesic and anti-inflammatory activities. The compounds were tested for anti-inflammatory activity using the carrageenan-induced mouse paw edema assay. The molar refractivity of the whole molecule plays a significant role.

$$\log \text{CPE\%} = -0.254(\pm 0.138)\text{CMR} + 3.121(\pm 0.863) \quad (7)$$

$$n = 4;\quad r = 0.946;\quad r^2 = 0.895;\quad q^2 = 0.436;\quad s = 0.108;\quad F_{1,2} = 17.217;\quad \alpha = 0.1$$

4.3. Arylidene 5-Phenyl-4-(*R*)-pyrrole-3-carbohydrazides

A group of arylidene 5-phenyl-4-(*R*)-pyrrole-3-carbohydrazides, which inhibit carrageenan-induced rat paw edema, was reported by Murineddu and coworkers.[32] For the data of Table 8, eq 8 is formulated using the molar refractivity of the whole molecule and E_s, Taft's steric parameter for the 4′ substituents.

$$\log \text{CPE\%} = 0.584(\pm 0.267)\text{CMR} - 0.161(\pm 0.117)E_{s_4} - 6.908(\pm 2.567) \quad (8)$$

$$n = 9;\quad r = 0.921;\quad r^2 = 0.848;\quad q^2 = 0.733;\quad s = 0.067;\quad F_{2,6} = 5.56;\quad \alpha = 0.05$$

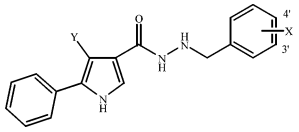
$$\text{CMR vs } E_{s_4} = 0.051$$

The negative coefficient with E_{s_4} brings out a positive steric effect by substituents in the 4′ positions. No role for a lipophilic or an electronic effect was found. All of the variation in the substituents is confirmed by the 4′ or 3′ positions of the aromatic ring. The correlation matrix for the CMR vs Clog *P* is 0.051. Compound **1** is omitted. It does not contain any unusual substituent, and it has a lower CMR value. Although the number of data points (nine) is small for the parameters, the correlation is significant in terms of *r* and *F*. CMR seems to be the most important parameter in the stepwise development ($r = 0.881$).

4.4. 9,10-Dihydro-9-oxo-2-acridine-alkanoic and 4-(2-Carboxy-phenyl)amino-benzene-alkanoic Acids

A small group of 9,10-dihydro-9-oxo-2-acridine-alkanoic and 4-(2-carboxy-phenyl)amino-benzene-alkanoic acids,[33] were evaluated by the carrageenan-induced rat paw edema assay, and the results are presented in Table 9. The general structure of the compounds corresponds to structures A, B, and C. From eq 9, a linear correlation between the biological activity and the overall molar refractivity was derived. Since MR is primarily a measure of gross bulk, which would be important in the intermolecular actions, we were concerned with the collinearity between CMR and Clog *P*. Overall, CMR and Clog *P* are reasonably orthogonal.

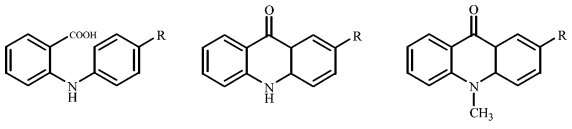
Table 8. Biological Data[32] and Physicochemical Parameters Used for Deriving Eq 8



no.	X	Y	calcd log CPE%	Δlog CPE%	obsd log CPE%	E_{s_4}	CMR	Clog *P*
1[a]	H	H	−0.99	0.68	−0.31	0.00	8.57	−0.53
2	4′-CH_3	H	−0.52	−0.05	−0.57	−1.24	9.22	−0.37
3	4′-C_2H_5	H	−0.24	0.06	−0.18	−1.31	9.68	0.40
4	4′-Cl	H	−0.55	0.03	−0.52	−0.97	9.24	−2.44
5	4′-CF_3	H	−0.31	0.00	−0.31	−2.40	9.26	−1.16
6	4′-OCH_3	H	−0.54	−0.05	−0.59	−0.55	9.37	−1.86
7	4′-NO_2	H	−0.47	0.09	−0.38	−1.01	9.36	−2.67
8	3′,4′-Cl_2	H	−0.26	0.04	−0.22	−0.97	9.74	−3.92
9	4′-CH_3	CH_3	−0.25	−0.09	−0.34	−1.24	9.68	−0.01
10	4′-Cl	CH_3	−0.28	−0.02	−0.30	−0.97	9.71	−1.65

[a] Data omitted from derived equation.

Table 9. Biological Data[33] and Physicochemical Parameters Used for Deriving Eq 9



A B C

no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR	Clog *P*
1(A_1)	−COOH	0.55	−0.24	0.30	6.87	4.20
2(A_2)	$-CH_2COOH$	1.26	−0.03	1.23	7.40	2.20
3(A_3)	$-CH(CH_3)COOH$	1.80	−0.12	1.68	7.80	3.92
4(B_1)	−COOH	0.34	−0.04	0.30	6.72	1.73
5(B_2)	$-CH_2COOH$	0.96	0.412	1.38	7.18	1.15
6(B_3)	$-CH(CH_3)COOH$	1.59	−0.59	1.00	7.65	1.46
7(C_1)[a]	−COOH	0.96	0.04	1.00	7.18	1.78
8(C_2)	$-CH_2COOH$	1.59	−0.02	1.57	7.65	1.20

[a] Data omitted from derived equation.

$$\log \text{CPE\%} = 1.354(\pm 0.602)\text{CMR} - 8.761(\pm 4.735) \quad (9)$$

$$n = 7;\ \ r = 0.933;\ \ r^2 = 0.870;\ \ q^2 = 0.782;\ \ s = 0.224;\ \ F_{1,5} = 33.466;\ \ \alpha = 0.01$$

The positive sign of the coefficient associated with the CMR term indicates than an increase in overall molar refractivity should result in stronger inhibition of edema. Lipophilicity and electronic factors are not found to play a definite role.

4.5. 1,2-Diarylimidazoles

A series of heteroaryl modified 1,2-diarylimidazoles has been synthesized and found to be potent and highly selective inhibitors of the human COX-2.[34] They have also exhibited excellent activity in the acute carrageenan-induced paw edema model of inflammation. The ED_{50} values were determined using a minimum of four dose points and using five rats per group (Table 10). We have evaluated eq 10 using the parabolic model of the Clog *P* values.

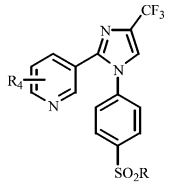
$$\log \text{CPE\%} = 2.490(\pm 0.827)\ \text{Clog}\ P - 0.498(\pm 0.176)\ \text{Clog}\ P^2 - 0.720(\pm 0.298)\sigma_{R_4} - 1.174(\pm 0.935) \quad (10)$$

$$n = 19;\ \ r = 0.936;\ \ r^2 = 0.877;\ \ q^2 = 2.224;\ \ s = 0.078;\ \ F_{3,15} = 35.83;\ \ \alpha = 0.01$$

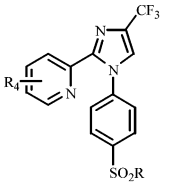
$$\text{Clog}\ P_o = 2.499(\pm 0.119)\ \text{from 2.403 to 2.642}$$

The parameters are reasonably orthogonal. In eq 10, the role of the overall lipophilicity seemed significant. The electronic substituent effect, σ_{R_4}, improves the correlation. Although no parametrization has been done for the R substituent, all the points fit well using Clog *P*. This fact shows that at this position, hydrophobic space is encountered. Only compound **6** was omitted. The biological activity is higher than it was expected. It is important to notice that eq 10 is high in terms of r^2 but its q^2 value is too high. The lack of diversity and the small differences between the experimental CPE% values are the main reasons.

Table 10. Biological Data[34] and Physicochemical Parameters Used for Deriving Eq 10



(A) for 1-11



(B) for 12-19

no.	R_4	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	σ_{R_4}
1	H	Me	1.91	0.09	2.00	2.04	0.00
2	2-Me	Me	2.06	−0.15	1.91	2.54	−0.17
3	6-Me	Me	2.03	−0.06	1.97	2.54	−0.17
4	5-Me	Me	1.96	−0.08	1.88	2.54	−0.07
5	6-OMe	Me	1.97	0.03	2.00	2.80	−0.27
6[a]	5-Br	Me	1.43	0.52	1.95	2.95	−0.39
7	H	NH_2	1.89	0.11	2.00	1.97	0.00
8	2-Me	NH_2	1.95	0.05	2.00	2.47	−0.17
9	6-Me	NH_2	2.04	−0.04	2.00	2.47	−0.17
10	5-Me	NH_2	1.97	0.01	1.98	2.47	−0.07
11	5-Br	NH_2	1.48	−0.06	1.42	2.88	−0.39
12	6-Me	Me	1.88	0.08	1.96	2.75	−0.07
13	5-Me	Me	1.95	0.03	1.98	2.75	−0.17
14	4-Me	Me	1.88	0.04	1.92	2.75	−0.07
15	3-Me	Me	2.05	−0.05	2.00	2.75	−0.17
16	6-Me	NH_2	1.91	0.09	2.00	2.68	−0.07
17	5-Me	NH_2	1.98	0.02	2.00	2.68	−0.17
18	4-Me	NH_2	1.91	−0.03	1.88	2.68	−0.07
19	3-Me	NH_2	2.06	−0.06	2.00	2.68	−0.17
20	H	NH_2	1.32	−0.04	1.28	1.38	0.00

[a] Data omitted from derived equation.

4.6. Dihydropyrimidines

Dihydropyrimidines are well-known calcium channel blockers. According to the literature[35] analogous derivatives are anti-inflammatories. Thus Bószing and co-workers[35] decided to synthesize the pyrimidothiazines and assay these compounds for the same profile. Acute anti-inflammatory activity was tested by inhibition of the carrageenan-induced paw edema in rats. ID_{30} values listed in Table 11, section a, were used to evaluate eq 11 for compounds **1**−**8**.

$$\log 1/\text{ED}_{30} = 0.674(\pm 0.449)E_{s_4} + 4.064(\pm 0.322) \quad (11)$$

$$n = 6;\ \ r = 0.901;\ \ r^2 = 0.813;\ \ q^2 = 0.518;\ \ s = 0.181;\ \ F_{1,4} = 17.30;\ \ \alpha = 0.05$$

E_{s_4} is a measure of a local steric effect of substituents 4 on the phenyl ring. Since the values of E_s constants are all negative, the positive coefficient with this term in eq 11 indicates a small negative effect of substituents. In other words, the smaller the substituent, the better the activity is. This might be due to polarizability of the 4-substituent.

For compound **6**, the E_s for $N(CH_3)_2$ is unknown. No parametrization for X and R′ groups has been performed; all compounds are well predicted.

For the subgroup **1**−**11**, Table 11, section b,[35] eq 12 was derived. All are alkoxy derivatives with the exception of compound **11**, which is an amide.

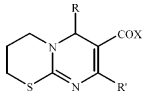
$$\log 1/\text{ID}_{30} = 0.341(\pm 0.207)\text{MR}_R + 0.946(\pm 0.353)\sum\pi_{2,3,5,6} + 2.489(\pm 0.709) \quad (12)$$

$$n = 9;\ \ r = 0.946;\ \ r^2 = 0.894;\ \ q^2 = 0.764;\ \ s = 0.132;\ \ F_{2,6} = 25.49;\ \ \alpha = 0.01$$

Compound **5** was rejected. It was found to be less active than expected. MR_R expresses the molar refractivity of the R group (the phenyl-substituted also). $\sum\pi_{2,3,5,6}$ is the sum of the lipophilic contribution of substituents on positions 2, 3, 5, and 6 of the phenyl ring. The correlation matrix did not show a collinearity problem (MR_R vs $\sum\pi_{2,3,5,6} = -0.193$).

No role for an electronic effect was found. An attempt was made to derive an equation for the whole dataset, but we did not get a significant correlation.

Table 11. Biological Data[35] and Physicochemical Parameters Used for Deriving Eqs 11 and 12



a. Equation 11

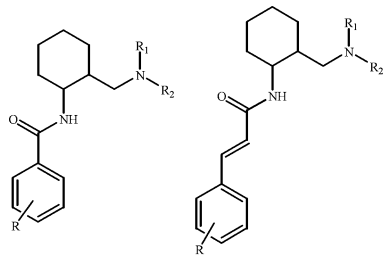
no.	X	R	R′	calcd log 1/ID_{30}	Δlog 1/ED_{30}	obsd log 1/ID_{30}	E_{s_4}
1	OCH_3	CH_3	CH_3			4.45	
2	OCH_3	C_6H_5	CH_3	4.06	−0.19	3.87	0
3	OCH_3	C_6H_4-2-OCH_3	CH_3	4.06	0.25	4.31	0
4	OCH_3	C_6H_4-4-CH_3	CH_3	3.23	−0.03	3.20	−1.24
5	OCH_3	C_6H_4-4-OCH_3	CH_3	3.69	0.01	3.70	−0.55
6	OCH_3	C_6H_4-4-$N(CH_3)_2$	CH_3			4.10	
7	OCH_3	C_6H_3-3,4-Cl_2	CH_3	3.41	0.12	3.53	−0.97
8	OCH_3	C_6H_2-3,4,5-OCH_3	CH_3	3.69	−0.14	3.55	−0.55

b. Equation 12

no.	X	R	R′	calcd log 1/ID_{30}	Δlog 1/ED_{30}	obsd log 1/ID_{30}	MR_R	$\pi_{2,3,5,6}$
1	OC_2H_5	C_2H_5	C_6H_5			3.22	1.03	
2	OC_2H_5	C_6H_5	CH_3	3.40	0.10	3.50	2.68	0
3	OC_2H_5	C_6H_4-3-NO_2	CH_3	3.35	0	3.35	3.30	−0.28
4	OC_2H_5	C_6H_4-4-OCH_3	CH_3	3.62	0.16	3.78	3.31	0
5[a]	OC_2H_5	C_6H_4-4-$N(CH_3)_2$	CH_3	3.85	0.69	4.54	3.99	0
6	OC_2H_5	C_6H_4-4-Br	CH_3	3.67	0.04	3.71	3.47	0
7	OC_2H_5	C_6H_3-2-F,6-Cl	CH_3	4.38	0.02	4.41	3.20	0.85
8	OC_2H_5	C_6H_3-3-NO_2,4-Cl	CH_3	3.52	0.08	3.60	3.79	−0.28
9	OC_2H_5	C_6H_2-3,4,5-OCH_3	C_6H_5	4.00	−0.06	3.94	4.54	−0.04
10	OC_2H_5	C_6H_4-4-NO_2	C_6H_5	3.62	−0.19	3.42	3.30	0
11	NHC_6H_5	C_6H_5	CH_3	3.40	−0.15	3.26	2.68	0

[a] Data omitted from derived equation.

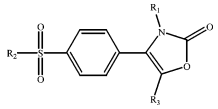
Table 12. Biological Data[36] and Physicochemical Parameters Used for Deriving Eq 13



No	R	NR_1R_2	calcd logCPE%	ΔlogCPE%	obsd logCPE%	$MR_{(NR1R2)}$
1	4-Cl	-$N(CH_2CH_3)_2$	1.68	-0.06	1.73	2.30
2	4-Cl		1.24	-0.01	1.23	2.12
3	4-Cl		1.62	0.04	1.65	2.28
4[a]	3,4,5-$(CH_3O)_3$	-$N(CH_2CH_3)_2$	1.68	-0.30	1.38	2.30
5[a]	3,4,5-$(CH_3O)_3$		1.24	0.37	1.61	2.12
6	3,4,5-$(CH_3O)_3$		1.62	0.04	1.65	2.28
7	4-Cl	-$N(CH_2CH_3)_2$	1.68	-0.04	1.63	2.30
8[a]	4-Cl		1.24	0.35	1.59	2.12
9	4-Cl		1.62	0.02	1.63	2.28
10	3,4,5-$(CH_3O)_3$	-$N(CH_2CH_3)_2$	1.68	-0.09	1.59	2.30

[a] Data omitted from derived equation.

Table 13. Biological Data[37] and Physicochemical Parameters Used for Deriving Eq 14



no.	R_1	R_2	R_3	calcd log CPE%	Δlog CPE%	obsd log CPE%	MR_{R_1}
1	C_6H_5	CH_3	H	1.43	−0.05	1.38	2.69
2	4-$CF_3C_6H_4$	CH_3	H	1.34	−0.02	1.32	3.20
3	4-$CH_3C_6H_4$	CH_3	H	1.35	0.08	1.43	3.15
4[a]	4-$CH_3CH_2C_6H_4$	CH_3	H	1.27	0.09	1.36	3.62
5	1-naphthyl	NH_2	H	1.13	−0.02	1.11	4.38
6	3-$CH_3C_6H_4$	NH_2	CH_3	1.35	0.01	1.36	3.15

[a] Data omitted from derived equation.

4.7. *N*-Cycloalkyl-benzamides, Cinnamides, and Indole-3-carboxamides

A series of substituted *N*-cycloalkyl-benzamides, cinnamides, and indole-3-carboxamides were synthesized and evaluated for their anti-inflammatory activities using the rat paw edema inhibition test.[36] From these data (Table 12), eq 13 was derived.

$$\log \text{CPE\%} = 2.458(\pm 0.910)\text{MR}_{\text{NR}_1\text{R}_2} - 3.979(\pm 2.068) \quad (13)$$

$$n = 7;\ \ r = 0.952;\ \ r^2 = 0.906;\ \ q^2 = -0.037;\ \ s = 0.055;\ \ F_{1,5} = 48.66;\ \ \alpha = 0.01$$

The subscript of NR_1R_2 with MR indicates that NR_1R_2 substituents are parametrized for this property. Since MR is primarily a measure of the bulk of the substituent, the positive coefficient with this term indicates that NR_1R_2 substituents are contacting a polar space and not a hydrophobic one. A Clog *P* or a π term does not improve the correlation, so the lipophilicity appears unimportant in this case. No parametrization has been made for the R substituent. However, these congeners are reasonably well fitted. Two data point compounds, **5** and **8**, have been omitted. Both have a pyrrolidine group at the NR_1R_2 position, and they do not contain any unusual substitution.

The large coefficient with MR brings out the sensitivity to steric effects. This dataset is not ideal for exploration of R (the usual overemphasis on halogens). The OCH_3 group has a π of −0.02, but this does not differ enough from O for H to make it interesting. Adding an indicator term for the benzamides or cinnamides does not seem to play a significant role and does not improve the equation. It is important to notice here that although eq 13 is high in terms of r^2, its q^2 value is low, indicating the possibilility of a chance correlation.

4.8. 3,4-Diaryloxazolones

Crespo and co-workers[37] prepared a series of 3,4-diaryloxazolones, which were evaluated for their ability to inhibit COX-2. The researchers carried out extensive structure−activity relationship work, and a number of potent and selective COX-2 inhibitors were identified. The replacement of the methyl sulfone group on the 4-phenyl-ring by a sulfonamide moiety resulted in compounds with better anti-inflammatory properties. From the data in Table 13 for the percent inhibition of carrageenan-induced rat paw edema at 3 mg/kg we have derived eq 14.

$$\log \text{CPE\%} = -0.177(\pm 0.147)\text{MR}_{\text{R}_1} + 1.909(\pm 0.494) \quad (14)$$

$$n = 5;\ \ r = 0.912;\ \ r^2 = 0.831;\ \ q^2 = -0.130;\ \ F_{1,3} = 15;\ \ \alpha = 0.05$$

In this equation, MR_{R_1} refers to R_1 substituents. MR represents the molar refractivity of substituents where $MR = (n^2 - 1)(n^2 + 2)(MW)/(d)$. Since the refractive index (n) of organic compounds varies little, MR is primarily a measure of volume (defined by mol wt/density) with a small component of polarizability. The negative term suggests steric hindrance.

Clog P/π cannot replace MR_{R1}. No parametrization has been done for R_2 or R_3. Compound 4 is not well predicted by our equation. Again a negative q^2 value was derived, indicating again the possibility of a chance correlation.

4.9. Indolyl Isoquinolines

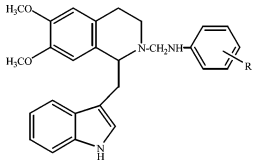
Several indolyl isoquinoline derivatives were synthesized and evaluated for their anti-inflammatory activity. These derivatives possessed 9.2−32.4% inhibition at a dose of 100 mg/kg ip against carrageenan-induced edema.[38] The CPE% values listed in Table 14 were used to formulate eq 15.

$$\log \text{CPE\%} = 1.189(\pm 0.695)\sum\sigma_{\text{R}} + 1.245(\pm 0.107) \quad (15)$$

$$n = 7;\ \ r = 0.892;\ \ r^2 = 0.795;\ \ q^2 = 0.632;\ \ s = 0.109;\ \ F_{1,5} = 19.49;\ \ \alpha = 0.01$$

No role for a hydrophobic parameter was found. The $\sum\sigma_R$ term would seem to imply a significant role for R substituents in the 2-, 3-, and 4-positions of the phenyl ring. In terms of r^2, we found it necessary to omit two compounds (compounds **3** and **8**, Table 14). Compound **3** does not contain any unusual moiety. In compound **8**, two methylene groups are inserted between −NH and Ar groups. Of course, compound **8** is more active than predicted, and it is a 3,4-disubstituted alkoxy derivative.

Table 14. Biological Data[38] and Physicochemical Parameters Used for Deriving Eq 15



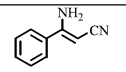
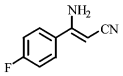
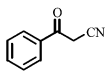
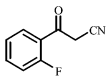
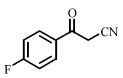
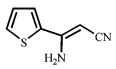
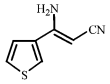
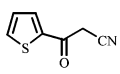
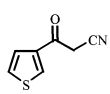
no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	$\sum\sigma$
1	C_6H_5	1.24	0.06	1.30	0.00
2	2-ClC_6H_4	1.52	−0.10	1.42	0.23
3[a]	3-ClC_6H_4	1.68	−0.38	1.31	0.37
4	4-ClC_6H_4	1.52	−0.03	1.49	0.23
5	4-FC_6H_4	1.32	0.19	1.51	0.06
6	2-$CH_3C_6H_4$	1.04	−0.08	0.96	−0.17
7	4-$CH_3C_6H_4$	1.04	−0.03	1.01	−0.17
8[a]	$-CH_2CH_2(3,4\text{-}OCH_3)C_6H_3$	1.07	0.38	1.45	−0.15
9	2-C_5H_4N	1.24	0.00	1.24	0.00

[a] Data omitted from derived equation.

4.10. Benzoylacetonitriles and β-Aminocinnamonitriles

The past decade has been witness to the development of many new chemical entities useful for the symptomatic treatment of rheumatoid arthritis. Benzoylacetonitriles and β-aminocinnamonitriles are shown to possess potent anti-inflammatory activity in the rat adjuvant arthritis model at an oral dose of 100 mg/kg.[39] From the data shown in Table 15, eq 16 was derived.

Table 15. Biological Data[39] and Physicochemical Parameters Used for Deriving Eq 16

No	Structure	calcd. logAPE%	ΔlogAPE%	obsd. logAPE%	MgVol
1		1.80	0.01	1.81	144.19
2		1.73	-0.01	1.72	162.18
3		1.80	0	1.80	145.17
4		1.73	-0.01	1.72	163.16
5		1.73	0.02	1.75	163.16
6[a]		1.77	-0.09	1.68	150.22
7		1.77	-0.02	1.75	150.22
8[a]		1.77	0.08	1.85	151.20
9[a]		1.77	-0.03	1.74	151.20

[a] Data omitted from derived equation.

$$\log \text{APE\%} = -0.004(\pm 0.002)\text{MgVol} + 2.380(\pm 0.322) \quad (16)$$

$$n = 6;\ \ r = 0.937;\ \ r^2 = 0.878;\ \ q^2 = 0.733;\ \ s = 0.015;\ \ F_{1,4} = 28;\ \ \alpha = 0.01$$

Biological activities were correlated with the molecular volume of the molecule. No correlation with a hydrophobic parameter was found. The negative sign with MgVol indicates that the steric interactions are unfavorable. Compounds **6**, **8**, and **9** (Table 15) were omitted. Of these, compound **6** presents the lowest inhibition, whereas compound **8** presents the highest, within the dataset. Compounds **8** and **9** are thienylacetonitriles, and both present the same MgVol values.

4.11. 4′,5-Disubstituted 3-Biphenylacetic Acids[40]

A series of 4′,5-disubstituted 3-biphenylacetic acids and several α-methyl derivatives were prepared as analogues of a new nonsteroidal anti-inflammatory agent, 4′-chloro-5-methoxy-3-biphenylacetic acid (DKA-9) and evaluated for anti-inflammatory activity on SLC-SD rats using carrageenan-induced rat paw edema. All compounds were administered orally in a dose of 50 mg/kg as a suspension in a 0.5% sodium carboxymethyl cellulose solution. We have formulated eq 17 from the data of the Table 16.

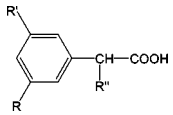
$$\log \text{CPE\%} = -0.465(\pm 0.152)\text{CMR} + 0.200(\pm 0.154)I_{4-\text{ClPh(R)}} + 0.294(\pm 0.120)\sum\pi + 3.910(\pm 1.058) \quad (17)$$

$$n = 17;\ \ r = 0.932;\ \ r^2 = 0.869;\ \ q^2 = 0.786;\ \ s = 0.123;\ \ F_{3,13} = 28.65;\ \ \alpha = 0.01$$

$$\text{Clog } P \text{ vs CMR} = 0.081$$

In eq 17, log CPE% values are the in vivo percent inhibition in the carrageenan paw edema. The major conclusion to be drawn from the above QSAR is that lipophilicity (expressed as the sum $\sum\pi$ of the lipophilic contributions π of groups R and R′ attached on the phenyl group) promotes anti-inflammatory activity. CMR refers to the overall molar refractivity. Since MR is primarily a measure of bulk, a negative term suggests steric hindrance. The indicator variable I_{-4} applies to the R = 4-Cl−Ph. The positive coefficient with I_{-4} means that the 4-Cl−Ph derivatives are correlated with higher activity on the rat paw edema. Equation 17 gave a good correlation between observed and calculated log CPE% values, the greatest deviations being noted for compounds **2** and **14**, Table 16. Compound **14** is the less active in the set without a Cl−Ph group in the substituent R, whereas compound **2** presents the highest CMR value compared to the rest. No parametrization has been done for substituent R″, although compounds **12**−**18** fit well the pattern of eq 17. For the derivatives

Table 16. Biological Data[40] and Physicochemical Parameters Used for Deriving Eq 17



no.	R	R′	R″	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR	I_{4-ClPh}	$\Sigma\pi$
1	Ph	NHAc	H	0.64	0.06	0.70	7.65	0	0.99
2[a]	4-MeOPh	NHAc	H	0.35	0.83	1.18	8.27	0	0.97
3	4-ClPh	NH_2	H	1.20	0.00	1.20	7.18	1	1.44
4	Ph	H	H	1.55	0.12	1.67	6.32	0	1.96
5	4-MeOPh	H	H	1.26	−0.22	1.04	6.93	0	1.94
6	4-ClPh	H	H	1.73	−0.09	1.64	6.81	1	2.67
7	Ph	Cl	H	1.53	−0.02	1.51	6.81	0	2.67
8	4-MeOPh	Cl	H	1.24	0.04	1.28	7.42	0	2.65
9	4-ClPh	Cl	H	1.71	−0.06	1.65	7.30	1	3.38
10	Ph	F	H	1.58	0.12	1.70	6.33	0	2.10
11	4-ClPh	F	H	1.76	−0.18	1.58	6.82	1	2.81
12	Ph	H	Me	1.33	−0.10	1.23	6.78	0	1.96
13	4-ClPh	H	Me	1.51	0.03	1.54	7.27	1	2.67
14[a]	Ph	Cl	Me	1.31	−0.71	0.60	7.27	0	2.67
15	4-MeOPh	Cl	Me	1.02	−0.12	0.90	7.89	0	2.65
16	4-ClPh	Cl	Me	1.49	0.12	1.61	7.76	1	3.38
17	Ph	F	Me	1.37	0.12	1.49	6.80	0	2.10
18	4-ClPh	F	Me	1.54	0.05	1.59	7.29	1	2.81
19	4-ClPh	Me	H	1.61	0.11	1.72	7.42	1	3.23

[a] Data omitted from derived equation.

of this set, there is no interrelationship between the independent variables.

4.12. Symmetrical Curcumin Derivatives.[41]

Curcumin is a well-known constituent of Indonesian traditional medicines and a frequently used food additive. A series of curcumin derivatives were prepared, and the inhibition of the carrageenan-induced edema by these derivatives was established. The log CPE% values listed in Table 17 were used to formulate eq 18.

$$\log \text{CPE\%} = 0.076(\pm 0.044)B_{5(4)} - 0.514(\pm 0.149)\sum\sigma + 1.400(\pm 0.103) \quad (18)$$

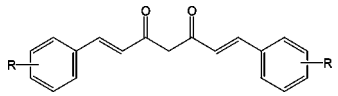
$$n = 14;\quad r = 0.930;\quad r^2 = 0.865;\quad q^2 = 0.763;\quad s = 0.059;\quad F_{2,11} = 35.32;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } B_{5(4)} = 0.066$$

$B_{5(4)}$ is the sterimol parameter for the 4-substituents, and it was found to be the most important term, followed by the $\sum\sigma$ for substituents on the phenyl ring, indicating a significant role for electron-donating groups. Since all the derivatives are symmetrical, the parameters used refer to one of the two rings. 4-Monosubstituted analogues showed higher inhibition, whereas disubstitution decreases the biological response. Both terms are orthogonal, whereas no role for lipophilicity was found. Two compounds (**14** and **16**) were omitted from the derivation of eq 18. Both present a double substitution with bulky alkyl groups.

Since steric reasons may cause complete loss of activity in these curcumin derivatives, we attempted to formulate an equation using a term capable of expressing the overall bulk of the molecules, for example, the molar refractivity. Thus, we derived eq 19 (using the same data, Table 18), which provides an optimum value of 12.827 for CMR.

Table 17. Biological Data[41] and Physicochemical Parameters Used for Deriving Eq 18



no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	$\Sigma\sigma$	B_{5MR}
1	H	1.48	0.00	1.48	0.00	1.00
2	4-OH	1.74	0.00	1.74	−0.37	1.93
3	3-OCH_3,4-OH	1.68	−0.03	1.64	−0.25	1.93
4	3-OCH_3	1.42	−0.09	1.32	0.12	1.00
5	3,4,5-tri-OCH_3	1.65	−0.01	1.64	−0.03	3.07
6	3,5-di-CH_3,4-OH	1.81	0.00	1.81	−0.51	1.93
7	3,5-di-C_2H_5,4-OH	1.81	0.06	1.87	−0.51	1.93
8	3,5-di-*i*-C_3H_7,4-OH	1.81	−0.07	1.74	−0.51	1.93
9	2-OCH_3	1.62	0.08	1.70	−0.27	1.00
10	4-Cl	1.42	0.03	1.45	0.23	1.80
11	4-OCH_3	1.77	−0.08	1.69	−0.27	3.07
12	4-CH_3	1.64	0.06	1.70	−0.17	2.04
13	3,4-DI-OCH_3	1.71	0.03	1.74	−0.15	3.07
14[a]	3,5-di-*i*-C_4H_9,4-OH	1.82	−0.46	1.36	−0.53	1.93
15	3,4-di-$C_6H_5CH_2O$	1.63	0.04	1.67	0.07	3.53
16[a]	3,5-di-OCH_3,4-OH	1.61	0.21	1.83	−0.13	1.93

[a] Data omitted from derived equation.

$$\log \text{CPE\%} = 0.750(\pm 0.276)\text{CMR} - 0.029(\pm 0.011)\text{CMR}^2 - 2.964(\pm 1.732) \quad (19)$$

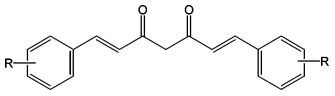
$$n = 12;\quad r = 0.901;\quad r^2 = 0.812;\quad q^2 = 0.669;\quad s = 0.076;\quad F_{2,9} = 38.94;\quad \alpha = 0.01$$

$$\text{CMR}_o = 12.827(\pm 0.423)\quad (12.388-13.234)$$

$$\text{Clog } P \text{ vs CMR} = 0.654$$

Four compounds are omitted (**2**, **4**, **5**, and **15**). Compound **15** presents the highest CMR value

Table 18. Biological Data[41] and Physicochemical Parameters Used for Deriving Eq 19



no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR	Clog *P*
1	H	1.43	0.04	1.48	9.08	3.89
2[a]	4-OH	1.50	0.24	1.74	9.38	2.55
3	3-OCH_3,4-OH	1.70	−0.06	1.68	10.62	2.25
4[a]	3-OCH_3	1.66	−0.34	1.42	10.31	3.72
5[a]	3,4,5-tri-OCH_3	1.84	−0.20	1.65	12.78	2.49
6	3,5-di-CH_3,4-OH	1.77	0.04	1.81	11.24	4.35
7	3,5-di-C_2H_5,4-OH	1.84	0.03	1.81	13.09	6.46
8	3,5-di-*i*-C_3H_7,4-OH	1.71	0.03	1.81	14.95	8.58
9	2-OCH_3	1.66	0.04	1.62	10.31	3.72
10	4-Cl	1.62	−0.17	1.42	10.06	5.31
11	4-OCH_3	1.66	0.03	1.77	10.31	3.72
12	4-CH_3	1.61	0.09	1.64	10.00	4.88
13	3,4-DI-OCH_3	1.80	−0.06	1.71	11.54	3.20
14	3,5-di-*i*-C_4H_9,4-OH	1.38	−0.02	1.82	16.80	10.70
15[a]	3,4-di-$C_6H_5CH_2O$	−0.40	2.07	1.63	21.59	10.53
16	3,5-di-OCH_3,4-OH	1.82	0.01	1.61	11.85	1.82

[a] Data omitted from derived equation.

(21.59) in the set. Compounds **4** and **5** have 3-OCH_3 groups (one or more), which are correlated with loss of activity. The correlation matrix for CMR vs Clog *P* is 0.654.

For some of the symmetrical curcumin derivatives, the ED_{50} values[41] concerning their anti-inflammatory activities have been established. From these data, indicated in Table 19, eq 20 was derived.

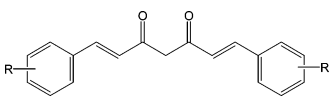
$$\log 1/ED_{50} = 0.005(\pm 0.002)\text{MgVol} + 1.963(\pm 0.811) \quad (20)$$

$$n = 7;\ \ r = 0.939;\ \ r^2 = 0.882;\ \ q^2 = 0.796;\ \ s = 0.107;\ \ F_{1,5} = 37.33;\ \ \alpha = 0.01$$

$$\text{Clog } P \text{ vs MgVol} = 0.504$$

Again the sterical hindrance as MgVol (molar volume) was found to be the most significant variable in terms of QSAR. Compound **5** presents the highest MgVol values, and it has been rejected from the derivation of the equation.

Table 19. Biological Data[41] and Physicochemical Parameters Used for Deriving Eq 20



no.	R	calcd log $1/ED_{50}$	Δlog $1/ED_{50}$	obsd log $1/ED_{50}$	MgVol
1	4-OH	3.58	0.05	3.63	308.35
2	3-OCH_3,4-OH	3.89	0.09	3.99	368.41
3[a]	3,5-di-CH_3,4-OH	3.87	0.58	4.45	364.47
4	3,5-di-C_2H_5,4-OH	4.17	0.11	4.28	420.59
5[a]	3,5-di-*i*-C_3H_7,4-OH	4.46	−0.55	3.91	476.71
6	4-OCH_3	3.72	−0.11	3.61	336.41
7	4-CH_3	3.56	0.02	3.58	304.41
8	3,4-DI-OCH_3	4.04	−0.14	3.90	396.47
9	3,5-di-OCH_3,4-OH	4.21	−0.02	4.18	428.47

[a] Data omitted from derived equation.

4.13. 2-[4(Thiazol)-2-yl)phenyl]propionic Acid Derivatives[42]

A series of 2-[4(thiazol)-2-yl)phenyl]propionic acid derivatives were prepared and tested as cyclooxygenase inhibitors. The potent inhibitors were tested for their ability to reduce carrageenan-induced inflammation of rat paw, and the in vivo results are given in Table 20. From them, we formulated eq 21.

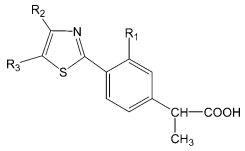
$$\log 1/ED_{40} = -2.333(\pm 1.581)\text{CMR} + 20.666(\pm 11.258) \quad (21)$$

$$n = 5;\ \ r = 0.938;\ \ r^2 = 0.880;\ \ q^2 = 0.709;\ \ s = 0.360;\ \ F_{1,3} = 22.03;\ \ \alpha = 0.05$$

$$\text{Clog } P \text{ vs CMR} = 0.106$$

In eq 21, CMR refers to the overall molar refractivity, and the negative coefficient suggests steric hindrance. Clog *P* cannot replace CMR. Substituting log *P* for MR in eq 21 gives a very poor fit indicating interaction in non-hydrophobic space (Clog *P* vs CMR = 0.106). The three outliers not included in this analysis are marked in Table 20.

Table 20. Biological Data[42] and Physicochemical Parameters Used for Deriving Eq 21



no.	R_1	R_2	R_3	calcd log $1/ED_{40}$	Δlog $1/ED_{40}$	obsd log $1/ED_{40}$	CMR
1[a]	H	H	H	5.78	−1.53	4.25	6.38
2	Cl	H	H	4.64	0.31	4.95	6.87
3	SMe	H	H	2.82	0.09	2.91	7.65
4	F	Me	H	4.67	0.22	4.88	6.86
5	F	H	Me	4.67	−0.46	4.21	6.86
6[a]	F	Me	Me	3.58	1.02	4.60	7.32
7[a]	Cl	Me	H	3.56	1.29	4.85	7.33
8	Cl	H	Me	3.56	−0.16	3.40	7.33

[a] Data omitted from derived equation.

4.14. 1,3,4-Substituted Oxadiazoles[43]

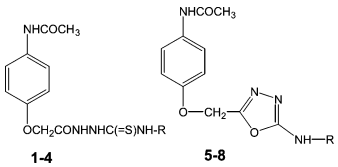
Various 5-[(acetamidophen-4-yl)oxy)-methyl]-2(para-substituted phenylamino)-1,3,4-oxadiazoles and thiosemicarbazides were synthesized and tested for anti-inflammatory activity (250 mg orally po) using the carrageenan-induced edema in rat paw. For these compounds (Table 21), eq 22 was formulated.

$$\log \text{CPE\%} = 0.224(\pm 0.126)\ \text{Clog } P + 1.143(\pm 0.274) \quad (22)$$

$$n = 6;\ \ r = 0.926;\ \ r^2 = 0.858;\ \ q^2 = 0.744;\ \ s = 0.060;\ \ F_{1,4} = 24.57;\ \ \alpha = 0.01$$

We were not able to formulate a QSAR with a bilinear model of Clog *P*. Equation 22 gave a satisfactory correlation between observed and calculated CPE% values, the greatest deviation being noted for

Table 21. Biological Data[43] and Physicochemical Parameters Used for Deriving Eq 22



no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*
1	C_6H_5	1.41	0.03	1.44	1.21
2	C_6H_4–CH_3-*p*	1.53	−0.01	1.52	1.71
3[a]	C_6H_4–OCH_3-*p*	1.40	0.27	1.67	1.13
4	C_6H_4–Br-*p*	1.61	−0.07	1.54	2.07
5	C_6H_5	1.68	−0.04	1.64	2.39
6	C_6H_5–CH_3-*p*	1.79	0.01	1.80	2.89
7	C_6H_4–OCH_3-*p*	1.67	0.08	1.75	2.33
8[a]	C_6H_4–Br-*p*	1.88	−0.21	1.68	3.29

[a] Data omitted from derived equation.

compounds **3** and **8**. Compound **8** is the one with the highest Clog *P* values in the set, whereas compound **3** is the one with the lowest.

4.15. 6-Acyl 3-Substituted 2(3*H*)-benzoxazolone Derivatives[44]

For eight new benzoxazolones, which were synthesized and further investigated as inhibitors of carrageenan- and arachidonic acid-induced mouse paw edema (CPE/AA) at 100 mg (oral administration), QSAR 23 was derived (Table 22, section a).

$$\log \text{CPE\%} = 0.020(\pm 0.009)\text{MgVol} - 7.570(\pm 3.845) \quad (23)$$

$$n = 6;\quad r = 0.954;\quad r^2 = 0.911;\quad q^2 = 0.860;\quad s = 0.209;\quad F_{1,4} = 40.96;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs MgVol} = 0.415$$

All of the variation in the substituents is confined to the ortho/para-position (R_1) of the phenyl ring and to the para-position (R_2) of the second phenyl ring, and no parametrization for them has been done, except the overall MgVol. No role for lipophilicity was found.

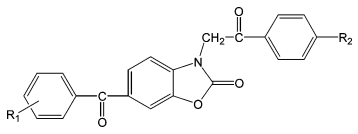
In contrast, QSAR 24 for the inhibition of arachidonic acid showed that overall lipophilicity is very important for the anti-inflammatory activity, and thus the phenyl rings with their substituents do appear to reach a hydrophobic surface (Table 22, section b).

$$\log \text{AA\%} = 0.409(\pm 0.092)\ \text{Clog } P - 0.471(\pm 0.436) \quad (24)$$

$$n = 8;\quad r = 0.975;\quad r^2 = 0.951;\quad q^2 = 0.918;\quad s = 0.049;\quad F_{1,6} = 121.28;\quad \alpha = 0.01$$

The same derivatives have been investigated as potent inhibitors of prostaglandin synthase, log-PGs%. From the results in Table 22, section c, eq 25

Table 22. Biological Data[44] and Physicochemical Parameters Used for Deriving Eqs 23, 24, and 25



a. Equation 23

no.	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	MgVol
1	*o*-Cl	H	0.33	−0.03	0.30	391.82
2	*o*-Cl	Cl	1.02	−0.24	0.78	426.26
3	*o*-Cl	Br	1.92	−0.08	1.84	470.71
4	*o*-Cl	NO_2	1.24	0.32	1.56	436.82
5[a]	*p*-Cl	H	0.33	0.90	1.23	391.82
6[a]	*p*-Cl	Cl	1.02	0.75	1.77	426.26
7	*p*-Cl	Br	1.92	−0.03	1.89	470.71
8	*p*-Cl	NO_2	1.24	0.07	1.30	436.82

b. Equation 24

no.	R_1	R_2	calcd log AA%	Δlog AA%	obsd log AA%	Clog *P*
1	*o*-Cl	H	1.28	0.00	1.28	4.29
2	*o*-Cl	Cl	1.61	−0.05	1.56	5.08
3	*o*-Cl	Br	1.67	−0.01	1.66	5.23
4	*o*-Cl	NO_2	1.24	−0.03	1.21	4.19
5	*p*-Cl	H	1.28	0.07	1.35	4.29
6	*p*-Cl	Cl	1.61	0.07	1.68	5.08
7	*p*-Cl	Br	1.67	−0.02	1.60	5.23
8	*p*-Cl	NO_2	1.24	−0.03	1.21	4.19

c. Equation 25

no.	R_1	R_2	calcd log PG%	Δlog PG%	obsd log PG%	MgVol
1	*o*-Cl	H	0.80	−0.03	0.77	391.82
2	*o*-Cl	Cl	0.50	0.21	0.71	426.26
3	*o*-Cl	Br	0.11	0.01	0.11	470.71
4	*o*-Cl	NO_2	0.41	−0.01	0.40	436.82
5[a]	*p*-Cl	H	0.80	−0.42	0.38	391.82
6	*p*-Cl	Cl	0.50	−0.14	0.36	426.26
7	*p*-Cl	Br	0.11	−0.03	0.08	470.71
8[a]	*p*-Cl	NO_2	0.41	0.30	0.71	436.82

[a] Data omitted from derived equation.

was derived, showing the importance of sterimol hindrance as MgVol.

$$\log \text{PGs\%} = -0.009(\pm 0.005)\text{MgVol} + 4.259(\pm 2.281) \quad (25)$$

$$n = 6;\quad r = 0.920;\quad r^2 = 0.847;\quad s = 0.126;\quad q^2 = 0.747;\quad F_{1,4} = 22.06;\quad \alpha = 0.01$$

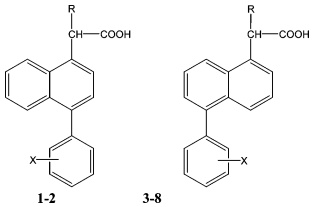
$$\text{Clog } P \text{ vs MgVol} = 0.411$$

The interrelationship of log CPE% vs log PGs% indicates $r = 0.778$, whereas log AA% and log PGs% gives $r = 0.455$. It seems that the PGs inhibition at the molecular level is correlated with the in vivo results (inhibition of CPE). Unfortunately the number of data points is small, and the correlation is not sharp enough to delineate the anti-inflammatory mechanism of action followed by the tested compounds.

4.16. 4- and 5-Aryl-1-naphthalene Acetic Acids[45]

Several 4- and 5-aryl-1-naphthalene acetic acids have been prepared, and their anti-inflammatory

Table 23. Biological Data[45] and Physicochemical Parameters Used for Deriving Eq 26



no.	X	R	calcd log AUVE%	Δlog AUVE%	obsd log AUVE%	MgVol
1	H	H	1.71	0.09	1.79	262.32
2	H	CH_3	1.33	−0.22	1.11	276.35
3	H	H	1.71	−0.07	1.63	262.32
4	*m*-F	H	1.23	0.07	1.30	280.31
5[a]	H	CH_3	1.33	−0.25	1.08	276.35
6	H	*d*-CH_3	1.33	0.14	1.48	276.35
7[a]	H	*l*-CH_3	1.33	−1.22	0.11	276.35
8	H	C_2H_5	0.96	−0.01	0.95	290.38

[a] Data omitted from derived equation.

activity has been investigated using the anti-UV-erythema test in albino guinea pigs. All agents were administered by gavage to depilated guinea pigs. Responses to treatment as the minimum effective dose (MED) are given in Table 23. From these data, eq 26 was derived.

$$\log \mathrm{AUVE}_{\mathrm{MED}} = -0.027(\pm 0.017)\mathrm{MgVol} + 8.666(\pm 4.631) \quad (26)$$

$$n = 6;\quad r = 0.909;\quad r^2 = 0.827;\quad q^2 = 0.705;\quad s = 0.147;\quad F_{1,4} = 19.08;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs MgVol} = 0.784$$

It is clear that the bulk of the molecule expressed as molecular volume decreases potency (e.g., compounds **2**, **4**, **7**, and **8**). The equation is not sharp in terms of $r = 0.909$. The number of data points is small, and we have to drop out two data points (compounds **5** and **7**, Table 23). Both present the same MgVol value. Compound **7**, the L-isomer, has the lowest potency in the dataset. No role for lipophilicity has been defined. However, Clog *P* versus MgVol = 0.784.

4.17. 5-Substituted 2,3-Dihydro-6′-mercapto-1,3-diphenyl-2-thioxo-4(3*H*)-pyrimidine and 6-Acylthio Derivatives[46]

Several substituted thioxo pyrimidines showed an anti-inflammatory activity in rats using the carrageenan-induced paw edema assay. Each compound was assayed orally at a dose of 50 mg/kg. We formulated eq 27.

$$\log \mathrm{CPE}\% = 0.135(\pm 0.088)\,\mathrm{Clog}\,P - 0.146(\pm 0.126)\mathrm{CMR} - 0.172(\pm 0.103)B_{5(4\mathrm{R}')} + 3.141(\pm 1.550) \quad (27)$$

$$n = 14;\quad r = 0.882;\quad r^2 = 0.777;\quad q^2 = 0.414;\quad s = 0.128;\quad F_{3,10} = 11.64;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs CMR} = 0.400;\quad \mathrm{Clog}\,P \text{ vs } B_{5(4\mathrm{R}')} = 0.013;\quad \mathrm{CMR} \text{ vs } B_{5(4\mathrm{R}')} = 0.127$$

The major conclusions to be drawn from the above QSAR are that lipophilicity promotes anti-inflammatory activity. Since MR is the measure of bulk, the negative with CMR suggests steric hindrance. $B_{5(4\mathrm{R}')}$ is the sterimol parameter for the largest width of substituent at position 4 at the phenyl ring, and it is found to be the most significant parameter followed by Clog *P* and CMR. The negative sign indicates that steric interactions at the 4R′ position of the aromatic ring are unfavorable. This is the most significant parameter. Another important point is that the two CMR and $B_{5(4\mathrm{R}')}$ parameters do not cover hydrophobic effect because there is no collinearity problem (Clog *P* vs CMR = 0.400, Clog *P* vs $B_{5(4\mathrm{R}')} = 0.013$).

The correlation is not exceedingly sharp. In terms of r^2, we found it necessary to omit three data points (Table 24, compounds **6**, **13**, and **16**). Their calculated values were found to be lower than the experimental values. Compound **6** is the most active in the set, whereas compound **16** presents the lowest Clog *P* value. No parametrization for the changes in *r* was done. However all derivatives fit the pattern of QSAR 27. The fact that Clog *P* has been used to model hydrophobicity implies that all the parts where substituents have been entered, hydrophobic contacts have been made. The existence of a linear only correlation between the log CPE% and log *P* suggests that the log *P* values were not great enough to establish the upper limit for the rate of membranes penetration.

4.18. Imidazo [1,2-*b*]Pyridazine-2-carboxylic Derivatives[47]

A series of imidazo-pyridazine-2-carboxylic acids, esters, and amides were synthesized and tested against carrageenan-induced edema in the rat paw for their anti-inflammatory activity.[47] The in vivo results, responses to 40 mg/kg (given orally), are shown in Table 25, sections a and b. Although the number of data points was small, we formulated eq 28.

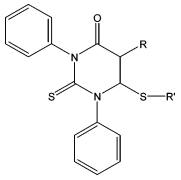
$$\log \mathrm{CPE}\% = -0.013(\pm 0.008)\mathrm{MgVol} + 0.578(\pm 0.332)\sum \pi_{\mathrm{RR'R''}} + 3.655(\pm 1.506) \quad (28)$$

$$n = 8;\quad r = 0.897;\quad r^2 = 0.804;\quad q^2 = 0.437;\quad s = 0.121;\quad F_{2,5} = 10.20;\quad \alpha = 0.05$$

$$\mathrm{Clog}\,P \text{ vs MgVol} = 0.940;\quad \mathrm{Clog}\,P \text{ vs } \sum\pi = 0.749;\quad \sum\pi \text{ vs MgVol} = 0.673$$

The above correlation is not a sharp one. It is an attempt to approach quantitatively those of the factors that affect the inhibition of carrageenan-induced paw edema. The lipophilic contribution of R, R′, and R″ groups (sum of π values, $\sum\pi$) promotes the inhibition. The negative sign with molar volume suggests steric hindrance. The correlation matrix for Clog *P* vs MgVol = 0.94 and $\sum\pi$ vs MgVol = 0.673 indicates collinearity problems. Three data points were omitted (compounds **2**, **3**, and **4**, Table 25, section a).

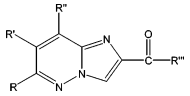
Table 24. Biological Data[46] and Physicochemical Parameters Used for Deriving Eq 27



no.	R	R′	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	CMR	$B_{5(4R')}$
1	C_6H_5	$COC(CH_3)_2OC_6H_4-Cl(4)$	1.50	0.15	1.65	8.45	16.94	1.80
2	C_6H_5	COC_6H_5	1.80	−0.11	1.70	7.45	14.90	1.00
3	C_6H_5	$COC_6H_4-CH_3(3)$	1.80	−0.04	1.76	7.95	15.36	1.00
4	C_6H_5	$COC_6H_4=CH_3(4)$	1.62	0.15	1.78	7.95	15.36	2.04
5	C_6H_5	$COC_6H_4-C(CH_3)_3(4)$	1.41	−0.15	1.26	9.28	16.75	3.17
6[a]	C_6H_5	$COC_6H_4-OCH_3$	1.39	0.45	1.85	7.69	15.52	3.07
7	C_6H_5	$COC_6H_4-OCOCH_3(2)$	1.60	−0.11	1.49	7.12	16.02	1.00
8	C_6H_5	$COC_6H_4-Cl(4)$	1.71	−0.01	1.70	8.27	15.39	1.80
9	$COOC_2H_5$	$COCH_2C_6H_5$	1.64	0.09	1.73	5.71	14.43	1.00
10	$COOC_2H_5$	$COC(CH_3)_2-O-C_6H_4-Cl(4)$	1.42	0.18	1.60	6.85	16.00	1.80
11	$COOC_2H_5$	$COCH=CHC_6H_5$	1.61	−0.06	1.56	6.33	15.17	1.00
12	$COOC_2H_5$	COC_6H_5	1.72	−0.06	1.66	5.85	13.97	1.00
13[a]	$COOC_2H_5$	$COC_6H_4-C(CH_3)_3(4)$	1.33	0.37	1.70	7.68	15.82	3.17
14	$COOC_2H_5$	$COC_6H_4-OCH_3(4)$	1.31	0.09	1.40	6.09	14.59	3.07
15	$COOC_2H_5$	$COC_6H_2-(OCH_3)_3(3,4,5)$	1.03	−0.13	0.90	5.35	15.82	3.07
16[a]	$COOC_2H_5$	$COC_6H_4-OCOCH_3(2)$	1.48	0.21	1.70	5.28	15.08	1.00
17	$COOC_2H_5$	$COC_6H_4-Cl(4)$	1.63	0.00	1.62	6.67	14.46	1.80

[a] Data omitted from derived equation.

Table 25. Biological Data[47] and Physicochemical Parameters Used for Deriving Eqs 28 and 29



a. Equation 28

no.	R	R′	R″	R‴	calcd log CPE%	Δlog CPE%	obsd log CPE%	MgVol	$\sum\pi_{RR'R''}$
1	H	H	H	OEt	1.15	−0.15	1.00	191.21	0.00
2[a]	Cl	H	H	OEt	1.11	0.42	1.53	225.65	0.71
3[a]	OMe	H	H	OEt	0.75	0.65	1.40	221.24	−0.02
4[a]	H	Me	H	OEt	1.29	0.40	1.69	205.24	0.56
5	H	H	Me	OEt	1.29	0.07	1.36	205.24	0.56
6	Cl	Me	H	OEt	1.25	0.01	1.26	239.68	1.27
7	Cl	H	Me	OEt	1.25	0.07	1.32	239.68	1.27
8	H	H	H	NH_2	1.23	0.09	1.62	162.17	0.00
9	OMe	H	H	NH_2	1.13	0.02	1.15	192.20	−0.02
10	Cl	Me	H	NH_2	1.63	0.06	1.69	210.64	1.27
11	Cl	H	Me	NH_2	1.63	−0.17	1.46	210.64	1.27

b. Equation 29

no.	R	R′	R″	calcd log CPE%	Δlog CPE%	obsd log CPE%	MR_R
1[a]	Cl	H	H	1.78	−0.04	1.74	0.60
2	OMe	H	H	1.77	0.00	1.77	0.79
3	H	Me	H	1.82	0.00	1.82	0.10
4	H	H	H	1.82	0.00	1.82	0.10
5	Cl	Me	H	1.78	−0.01	1.77	0.60
6	Cl	H	Me	1.78	0.01	1.79	0.60

[a] Data omitted from derived equation.

For the data of Table 25, section b, the formulated eq 29 is given below:

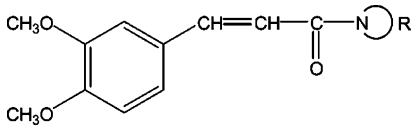
$$\log \text{CPE\%} = -0.073(\pm 0.046)\text{MR}_\text{R} + 1.826(\pm 0.024) \quad (29)$$

$$n = 5; \quad r = 0.947; \quad r^2 = 0.898; \quad q^2 = 0.808; \quad s = 0.009$$

$$\text{Clog } P \text{ vs } \text{MR}_\text{R} = 0.898$$

The most significant variable is the molar refractivity for R substituents with a negative sign indicating again the influence of the bulk. Of course, the interrelationship between MR_R vs Clog *P* is high (0.898). No parametrization for the changes at R′ and R‴ substituents has been done. However, they fit well eq 29. One data point was omitted (compound **1**). For the above equation, it was not possible to calculate the *F* values. The small number of data and the lack of diversity were two main reasons.

Table 26. Biological Data[48] and Physicochemical Parameters Used for Deriving Eqs 30 and 31



a. Equation 30

No	R	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	clog *P*
1	NMe_2	1.62	-0.02	1.59	1.36
2	NEt_2	1.67	-0.01	1.66	2.42
3	$N(nC_3H_7)_2$	1.73	0.06	1.78	3.48
4	$N(nC_4H_9)_2$	1.78	-0.06	1.72	4.53
5	$N(iC_5H_{11})_2$	1.82	0.02	1.84	5.15
6[a]		1.65	0.19	1.84	1.99
7[a]		1.68	0.21	1.89	2.55
8		1.62	0.02	1.64	1.42

b. Equation 31

	N	R	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	B_{1R}
	1	NMe_2	1.63	-0.04	1.59	1.35
	2	NEt_2	1.63	0.03	1.66	1.35
*	3	$N(nC_3H_7)_2$	1.63	0.15	1.78	1.35
	4	$N(nC_4H_9)_2$	.	.	1.72	.
	5	$N(iC_5H_{11})_2$	.	.	1.84	.
	6		1.86	-0.02	1.84	1.90
	7		1.87	0.02	1.89	1.91
	8		1.63	0.01	1.64	1.35

[a] Data omitted from derived equation.

4.19. 3,4-Dimethoxy Cinnamic Acid Tertiary Amides[48]

The anti-inflammatory activities of eight tertiary amides of cinnamic acid were determined by the carrageenan-induced paw edema test in mice using oral administration of 200 mg/kg. From the small number of data listed in Table 26, section a, we calculated eq 30.

$$\log \text{CPE\%} = 0.053(\pm 0.036)\ \text{Clog}\,P + 1.543(\pm 0.122) \quad (30)$$

$$n = 6;\quad r = 0.898;\quad r^2 = 0.806;\quad q^2 = 0.584;\quad s = 0.046;\quad F_{1,4} = 15.56;\quad \alpha = 0.05$$

Lipophilicity should be taken under consideration as an important variable for this dataset. In terms of r^2, this correlation is not a sharp one, and we had to drop out two compounds (**6** and **7**, Table 26, section a). Both have an alicyclic amine as substituent (R = pyrolidinyl for compound **6** and R = piperidinyl for compound **7**). It is important that compound **7** is the most active within the set; thus we reconsidered eq 30. Redoing eq 30, we derived the following eq 31.

$$\log \text{CPE\%} = 0.422(\pm 0.177)B_{1R} + 1.059(\pm 0.282) \quad (31)$$

$$n = 5;\quad r = 0.975;\quad r^2 = 0.951;\quad q^2 = 0.858;\quad s = 0.034;\quad F_{1,3} = 66;\quad \alpha = 0.01$$

$$\text{Clog}\,P \text{ vs } B_{1R} = 0.293$$

B_{1R} is the sterimol parameter of Verloop for the smallest width of R. It seems that as the smaller width of substituent increases the anti-inflammatory response increases too, for example, compound **5** (Table 26, section b), the most active analogue with the highest B_1 value in the set.

One point (compound **3**) was rejected from the derivation of this correlation. The main problem of this dataset is the small number of the data points, as well as some missing B_{1R} values for compounds **4** and **5**.

4.20. Imidazo-[2,1-*b*]benzothiazole Acids[49]

Twelve of the above-mentioned carboxylic or acetic acids were tested in vivo for their anti-inflammatory activity using the carrageenan-induced rat paw edema. The compounds were administered orally and the used dose was 150 μmol/kg (Table 27). Using the parabolic model, we found that CMR_{opt} for this set is 7.831 with a range of 7.694 to 7.958. Electronic factors are not found to play any definite role. It was found that larger CMR produced higher inhibition of carrageenan-induced rat paw edema.

$$\log \text{CPE\%} = 4.721(\pm 1.345)\text{CMR} - 0.301(\pm 0.085)\text{CMR}^2 - 16.715(\pm 5.234) \quad (32)$$

$$n = 10;\quad r = 0.954;\quad r^2 = 0.911;\quad q^2 = 0.849;\quad s = 0.108;\quad F_{2,7} = 35.82;\quad \alpha = 0.01$$

$$\text{CMR}_o = 7.831(\pm 0.132)\quad (7.694{-}7.958)$$

$$\text{Clog}\,P \text{ vs CMR} = 0.661$$

The two outliers (compounds **1** and **5**) not included in this analysis are marked in Table 27. Both present the two lower CMR values within the dataset.

4.21. Imidazolinyl-pyrazole Analogues[50]

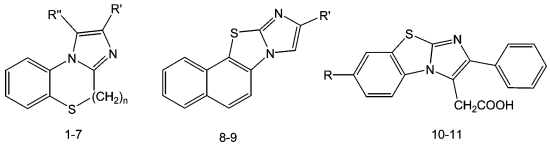
Derivatives with a pyrazole ring system often point out marked anti-inflammatory activities. Thus, some new imidazolinyl-pyrazoles were synthesized and evaluated for anti-inflammatory action using the carrageenan-induced rat paw edema in albino Wistar rats at 0.2 mmol/kg orally. The results are listed in Table 28, and they were used to develop eq 33.

$$\log \text{CPE\%} = 0.002(\pm 0.001)\text{MgVol} + 1.466(\pm 0.222) \quad (33)$$

$$n = 5;\quad r = 0.941;\quad r^2 = 0.885;\quad q^2 = 0.615;\quad s = 0.025;\quad F_{1,3} = 22.5;\quad \alpha = 0.05$$

$$\text{Clog}\,P \text{ vs MgVol} = 0.914$$

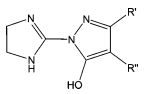
Table 27. Biological Data[49] and Physicochemical Parameters Used for Deriving Eq 32



no.	*n*	R′	R″	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	CMR
1[a]	0	COOH	H		0.46	1.27	1.73	3.06	5.74
2	1	COOH	H		1.01	0.04	1.04	2.55	6.24
3	2	COOH	H		1.39	0.10	1.49	2.88	6.70
4	0	C_6H_5	COOH		1.72	−0.08	1.63	4.16	8.26
5[a]	0	CH_2COOH	H		0.98	0.60	1.58	2.03	6.21
6	1	CH_2COOH	H		1.39	−0.16	1.23	1.51	6.70
7	2	CH_2COOH	H		1.64	−0.11	1.53	1.84	7.16
8		COOH			1.72	0.15	1.87	4.23	7.43
9		CH_2COOH			1.77	0.04	1.81	3.21	7.9
10				H	1.53	0.04	1.58	3.83	8.72
11				CF_3	1.18	−0.04	1.15	4.72	9.23
12				Br	0.94	0.02	0.95	4.70	9.50

[a] Data omitted from derived equation.

Table 28. Biological Data[50] and Physicochemical Parameters Used for Deriving Eq 33



no.	R	R′	calcd log CPE%	Δlog CPE%	obsd log CPE%	MgVol
1	Me	H	1.72	−0.02	1.7	166.21
2	Me	Me	1.74	0.03	1.77	180.24
3	Me	CH_2Ph	1.86	0.00	1.86	256.34
4	Ph	H	1.82	0.02	1.83	228.28
5	Ph	Me	1.84	−0.02	1.82	242.31
6[a]	Ph	CH_2Ph	1.96	−0.39	1.57	318.41

[a] Data omitted from derived equation.

Molecular volume is the most significant term. However, MgVol is highly correlated to Clog *P* (0.914). Equation 33 gave a good correlation between observed and calculated CPE% values, the greatest deviation being noted for compound **6**, Table 28, which presents the highest MgVol value compared to the rest.

4.22. *N*-[5*H*-[1]benzopyrano[4,3-α]pyrimidin-2-yl]-*N*-methyl Glycinamide[51]

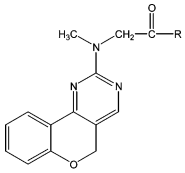
The title compounds were evaluated by the carrageenan-induced paw edema in albino rats using a dose of 50 mg/kg orally for anti-inflammatory activity. The percent inhibition values (Table 29) of all the derivatives were used in derivation of eq 34.

$$\log \text{CPE\%} = 0.148(\pm 0.094)B_{5R} + 1.036(\pm 0.331) \quad (34)$$

$$n = 7;\quad r = 0.852;\quad r^2 = 0.726;\quad q^2 = 0.560;$$
$$s = 0.100;\quad F_{1,5} = 13.1;\quad \alpha = 0.05$$
$$\text{Clog } P \text{ vs } B_{5R} = 0.371$$

The most important term is the sterimol parameter B_{5R} for the R substituents, which describes the largest width of the first atom of substituent R. The correlation is not sharp. One of the main reasons is the lack of variance in CPE% values (1.32−1.85) and the small number of data points (seven).

Table 29. Biological Data[51] and Physicochemical Parameters Used for Deriving Eq 34



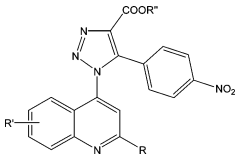
No	R	calcd. logCPE%	ΔLogCPE%	obsd. logCPE%	B_{5R}
1	OH	1.31	0.01	1.32	1.93
2	$NHCHMe_2$	1.71	-0.07	1.63	4.19
3	NMe_2	1.51	0.03	1.54	3.08
4	NEh_2	1.74	-0.01	1.73	4.39
5[a]		1.69	0.16	1.85	4.09
6		1.58	-0.13	1.45	3.49
7		1.57	0.01	1.58	3.42

[a] Data omitted from derived equation.

4.23. 1-[Quinolinyl(4)]-1,2,3-triazoles[52]

It is well-known that the triazole ring bears a number of pharmacological potentialities. Among them, the most often encountered property is anti-inflammatory activity. Savini and co-workers[52] were prompted to prepare new triazoles the chemical structures of which are related to that of triazolenaphthyridines and compounds with pentatomic nuclei containing nitrogen atoms.

Table 30. Biological Data[52] and Physicochemical Parameters Used for Deriving Eq 35



no.	R	R′	R″	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	$I_{ETHR''}$
1	H	7-CF_3	C_2H_5	1.62	0.03	1.66	5.60	1
2	Me	6,7,8-F	C_2H_5	1.62	0.06	1.68	5.50	1
3	Me	6,7-(OCH_2O)	C_2H_5	1.62	−0.09	1.53	5.65	1
4[a]	H	6-OCF_3	C_2H_5	1.62	−0.15	1.48	6.04	1
5	H	7-CF_3	H	1.44	0.02	1.46	4.07	0
6	Me	6-F	H	1.44	0.00	1.44	3.80	0
7	H	6-OCF_3	H	1.44	0.01	1.45	4.46	0
8	Me	6-OCF_3	H	1.44	−0.05	1.39	4.96	0
9[a]	Me	6-OCH_3	C_2H_5	1.62	−0.20	1.42	5.43	1
10[a]	Ph	6,7-(OCH_2O)	C_2H_5	1.62	−0.14	1.49	7.25	1
11	H	6,8-F	H	1.44	0.02	1.46	3.45	0

[a] Data omitted from derived equation.

The prepared compounds were submitted to biological tests for anti-inflammatory activity using the carrageenan-induced paw edema method and Wistar rats. The compounds were administered orally in a unique dosage (100 mg/kg) suspended in a 2% arabic gum−water solution. The results are shown as log CPE% in Table 30. For these data, it was not possible to derive a quantitative structure−activity relationship. One of the main reason was the lack of variance in CPE% values (1.39−1.68). Since the variety of substituents is limited, we tried to use an indicator variable to express the existence, the nature, and the attachment position of a functional group. Indicator variable $I_{EthR''}$ takes the values 1/0 for the presence of an ether group at R″. It seems that when such a group is attached on the quinolinyl ring, an increase in the inhibition of the carrageenan-induced paw edema is observed. However it is important to mention that $I_{EthR''}$ is significantly correlated to lipophilicity.

$$\log \text{CPE\%} = 0.183(\pm 0.095) I_{EthR''} + 1.440(\pm 0.058) \quad (35)$$

$$n = 8;\quad r = 0.887;\quad r^2 = 0.787;\quad q^2 = 0.554;\quad s = 0.053;\quad F_{1,6} = 22.24;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } I_{EtR''} = 0.737$$

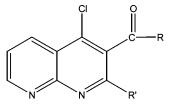
4.24. 1,8-Naphthyridene-3-carboxamides[53]

Preliminary results on the anti-inflammatory activity of 1,8-naphthyridene-3-carboxamide derivatives prompted Di Braccio and Roma[53] to synthesize and test some more new compounds. The carrageenan-induced rat paw edema test was used on rats with a dose of 100 mg/kg po. From these results (Table 31), eq 36 was derived.

$$\log \text{CPE\%} = 0.319(\pm 0.281)\ \text{Clog } P + 0.134(\pm 1.185) \quad (36)$$

$$n = 5;\quad r = 0.901;\quad r^2 = 0.813;\quad q^2 = 0.504;\quad s = 0.187;\quad F_{1,3} = 13.03;\quad \alpha = 0.05$$

Table 31. Biological Data[53] and Physicochemical Parameters Used for Deriving Eq 36



No	R	R'	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	clogP
1	$N(i\text{-}C_3H_7)_2$	Cl	1.06	-0.15	0.90	2.89
2	$N(C_4H_9)_2$	Cl	1.54	0.24	1.77	4.39
3	$N(C_2H_5)_2$	$NHCH_2CH{=}CH_2$	1.12	0.09	1.20	3.08
4	$N(C_2H_5)_2$	NH-i-C_4H_9	1.77	-0.13	1.64	5.14
5[a]	$N(C_2H_5)_2$		1.52	-0.48	1.04	4.34
6[a]	$N(C_4H_9)_2$	NH-i-C_3H_7	2.11	-0.86	1.26	6.20
7	$N(C_4H_9)_2$		1.73	-0.03	1.70	5.01
8[a]			1.10	0.44	1.54	3.03

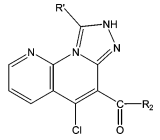
[a] Data omitted from derived equation.

Lipophilicity is the most important parameter, showing that at all the parts where substituents have been entered, hydrophobic contacts have been made. The three outliers not included in this analysis are shown in Table 31 (compounds **5**, **6**, and **8**), and one of them, compound **6**, had the highest Clog *P* value compared to the rest. Compound **8** is able to be omitted for steric reasons, but this dataset is too small to delineate the contribution of this property.

4.25. 1,8-Naphthyridene-3-carboxamides[54]

In continuation to their research, the previous researchers attempted to extend their investigation on the synthesis and biological evaluation of some new 1,8-naphthyridene-3-carboxamides. Unfortunately we could not derive a QSAR for these results (Table 32), except of a qualitative relationship (eq 37). It seems that the presence of a methyl group as the

Table 32. Biological Data[54] and Physicochemical Parameters Used for Deriving Eq 37



No	R_2	R′	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	clog *P*	I_{Me}
1	$N(C_2H_5)_2$	Me	1.45	0.00	1.45	1.11	1
2[a]	$N(C_2H_5)_2$	C_6H_5	0.58	0.88	1.46	2.94	0
3	$N(C_3H_7)_2$	C_6H_5	0.58	-0.28	0.30	4.00	0
4	$N(i\text{-}C_3H_7)_2$	H	0.58	0.26	0.85	1.46	0
5	$N(i\text{-}C_3H_7)_2$	Me	1.45	0.15	1.60	1.73	1
6	$N(i\text{-}C_3H_7)_2$	C_6H_5	0.58	0.02	0.60	3.56	0
7	$N(C_4H_9)_2$	Me	1.45	-0.15	1.30	3.22	1
8[a]		Me	1.45	-0.97	0.48	1.24	1
9[a]		C_6H_5	0.58	0.97	1.56	3.07	0

[a] Data omitted from derived equation.

R′ substituent increases the anti-inflammatory response.

$$\log \text{CPE\%} = 0.867(\pm 0.499) I_{\text{Me}} + 0.583(\pm 0.353) \quad (37)$$

$$n = 6; \quad r = 0.924; \quad r^2 = 0.853; \quad q^2 = 0.670; \quad s = 0.220; \quad F_{1,4} = 23.26; \quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } I_{\text{Me}} = 0.039$$

4.26. 6-Acyl-3-piperidinomethyl-2(*H*)-benzoxazolone Derivatives[55]

In continuation to their previous studies, Erol and his group[48] reported that some 2(3*H*)-benzoxazolone derivatives showed anti-inflammatory activities comparable to that of indomethacin. Carrageenan-induced mouse paw edema (CPE) was measured in female albino mice after oral administration of the compounds (100 mg/kg). Results (Table 33) are expressed as percent inhibition and led to the derivation of eq 38.

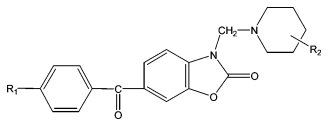
$$\log \text{CPE\%} = -1.032(\pm 0.276)\text{MR}_{\text{R}_1} + 1.924(\pm 0.186) \quad (38)$$

$$n = 12; \quad r = 0.935; \quad r^2 = 0.874; \quad q^2 = 0.836; \quad s = 0.105; \quad F_{1,10} = 69.72; \quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } \text{MR}_{\text{R}_1} = 0.058$$

MR_{R_1} (scaled by 0.1) is the molar refractivity of R_1 substituents, and it is the most significant parameter. The correlation matrix shows that MR_{R_1} and Clog *P* are reasonably independent vectors ($r = 0.058$). Thus we have assumed that substituents at the R_1 position interact in the non-hydrophobic space. Electronic effects referred to substituents in positions R_1 or R_2 do not improve the equation. Subtle steric changes rather than electronics are attenuating anti-inflammatory activity. No parametrization has been done for R_2. However all data fit significant to the reported

Table 33. Biological Data[55] and Physicochemical Parameters Used for Deriving Eq 38



no.	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	MR_{R_1}
1	H	H	1.82	0.05	1.86	3.66	0.10
2[a]	H	2-Me	1.82	−0.81	1.00	4.06	0.10
3	H	4-Me	1.82	0.01	1.83	4.06	0.10
4	2-Cl	H	1.30	−0.12	1.18	4.18	0.60
5	2-Cl	2-Me	1.30	−0.06	1.24	4.59	0.60
6[a]	2-Cl	4-Me	1.30	0.48	1.78	4.59	0.60
7	4-NO_2	H	1.16	−0.12	1.05	3.56	0.74
8	4-NO_2	2-Me	1.16	0.12	1.29	3.96	0.74
9	4-NO_2	4-Me	1.16	−0.08	1.09	3.96	0.74
10	4-MeO	H	1.11	0.08	1.19	3.88	0.79
11	4-MeO	2-Me	1.11	−0.08	1.03	4.39	0.79
12	4-MeO	4-Me	1.11	−0.01	1.10	4.39	0.79
13	4-MeO	4-C_6H_5	1.11	0.20	1.32	5.28	0.79
14[a]	4-MeO	4-CH_2−Ph	1.11	0.29	1.41	5.81	0.79
15	4-MeO	4-OH,4-Ph	1.11	0.00	1.12	3.65	0.79

[a] Data omitted from derived equation.

eq 38. Compounds **2**, **6**, and **14** are omitted from the correlation. Compound **2** presents the lowest percent inhibition compared to the rest, and substituent R_1 has a very low MR_{R_1} value (0.1). In contrast, the MR_{R_1} value for compound **14** is very high (0.79, Table 33). Compound **6** does not contain any unusual structural feature.

4.27. *O*-[2,6-Dicyclophenyl-1-amino]phenyl Acetic Acids[56]

Diclophenac is one of the most potent anti-inflammatory and analgesic drugs nowadays. Also, its amino acid conjugates improve the pharmacokinetics of drugs. Shalaby and Eraky[56] aimed to combine some amino acids with diclophenac in an attempt to prepare new derivatives having the potency of the parent drug and locking its undesirable effects. Anti-inflammatory activity was screened using the carrageenan-induced rat paw edema in male albino rats, which received 20 mg/kg of the tested compounds (solution in propylene glycol and water). We have evaluated eq 39 using the data listed at Table 34.

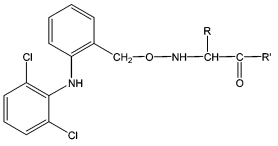
$$\log \text{CPE\%} = 1.042(\pm 0.540)\ \text{Clog } P - 0.076(\pm 0.043)\ \text{Clog } P^2 - 1.987(\pm 1.641) \quad (39)$$

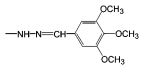
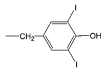
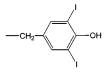
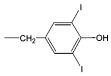
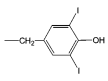
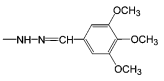
$$n = 9; \quad r = 0.939; \quad r^2 = 0.883; \quad q^2 = 0.641; \quad s = 0.070; \quad F_{2,6} = 252.5; \quad \alpha = 0.01$$

$$\text{Clog } P_{\text{o}} = 6.897(\pm 1.814) \quad (6.588-7.733)$$

In eq 39, the role of the overall lipophilicity seemed significant. Using the parabolic model, we found that Clog P_{o} for this set is 6.897 ranged from 6.588 to 7.733. Note that the calculated Clog *P* values may be somewhat high since they pertain to the unprotonated form. At pH 7.4, log *P* would be lower depending on the pK_{a} of the ionized group. No parametrization has been done for R and R′ substit-

Table 34. Biological Data[56] and Physicochemical Parameters Used for Deriving Eq 39



No	R	R'	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	clog *P*
1	H	OMe	1.26	0.04	1.30	4.76
2	H	OH	1.19	-0.06	1.13	4.54
3[a]	H	$NHNH_2$	0.62	0.46	1.08	3.29
4	H		1.42	0.1	1.43	5.32
5	$CHMe_2$	Ome	1.54	0.10	1.64	6.00
6[a]	$CHMe_2$	OH	1.51	-0.44	1.07	5.78
7	$CHMe_2$	$NHNH_2$	1.18	0	1.18	4.53
8		OMe	1.55	-0.09	1.46	7.77
9		OH	1.57	0.00	1.57	7.55
10		$NHNH_2$	1.58	-0.06	1.52	6.30
11			1.45	0.07	1.52	

[a] Data omitted from derived equation.

uents. This fact shows that at these positions, hydrophobic space is encountered. The two outliers (compounds **3** and **6**) not included in this analysis are marked in Table 34. Compound **3** is a hydrazide and presents the lowest Clog *P* value within the dataset, whereas compound **6** is the less active derivative compared to the rest.

4.28. 3,3′-Bi(1,3-thiazolidin-4-one) Derivatives[57]

Vigorita and co-workers[57] have reported bisthiazolidinonic structures, which usually exhibit stereoselective pharmacological properties, for example, anti-inflammatory, anti-pyretic, anti-histaminic, etc. Interestingly, the presence of sulfur atoms and the subsequent oxidation (SO_2) enhances the anti-inflammatory activity of all derivatives. The anti-inflammatory potency was explored by means of the carrageenan-induced edema test in rats (50 mg/kg orally). Independently of lipophilic and electronic features, disulfides and disulfones displayed interesting activity levels, which appear to be mainly linked to the disubstitution pattern on the benzenic rings. We have formulated eq 40 from the data in Table 35.

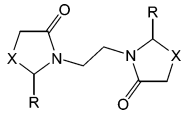
$$\log \mathrm{CPE\%} = 0.283(\pm 0.098)\,\mathrm{Clog}\,P + 0.826(\pm 0.372)B_{5(3)} - 1.650(\pm 1.136) \quad (40)$$

$$n = 12;\quad r = 0.911;\quad r^2 = 0.830;\quad q^2 = 0.711;\quad s = 0.207;\quad F_{2,9} = 22.02;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs } B_{5(3)} = 0.378$$

Hydrophobicity should be taken under consideration as an important variable in this dataset. No term appears for 4-substituents; one would expect an electronic term with them; however, there is so little variation in the 4-position that no effect can be assayed properly. All the points fit well using Clog *P*. $B_{5(3)}$, the sterimol parameter for the largest width of the first atom of group 3, points to a steric effect at this position. There is no collinearity problem between the used parameters (0.378). Four compounds are omitted, and for three of them, compounds **13**, **14**, and **16** (Table 35), the calculated biological activities are higher than the experimental ones; compounds **13** and **14** are di-Cl-substituted sulfones, and the $B_{5(3)}$ values for substituent 3 are the same (1.80). Compound **16** is also a disubstituted sulfone

Table 35. Biological Data[57] and Physicochemical Parameters Used for Deriving Eq 40



no.	X	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	$B_{5(3)}$
1	S	3-Br−Ph	1.37	−0.22	1.15	4.99	1.95
2	S	3-Br−Ph	1.37	0.21	1.58	4.99	1.95
3	S	3-CF_3−Ph	1.93	0.18	2.11	5.03	2.61
4	S	3-CF_3−Ph	1.93	−0.08	1.85	5.03	2.61
5	S	3,4-Cl_2−Ph	1.50	−0.24	1.26	5.88	1.80
6	S	3,4-Cl_2−Ph	1.50	0.23	1.73	5.88	1.80
7[a]	S	3,4-$(OMe)_2$−Ph	1.62	−0.42	1.19	2.58	3.07
8	S	3,4-$(OMe)_2$−Ph	1.62	0.03	1.65	2.58	3.07
9	SO_2	3-Br−Ph	0.70	0.20	0.90	2.61	1.95
10	SO_2	3-Br−Ph	0.70	−0.06	0.64	2.61	1.95
11	SO_2	3-CF_3−Ph	1.26	−0.13	1.12	2.65	2.61
12	SO_2	3-CF_3−Ph	1.06	−0.25	0.82	1.96	2.61
13[a]	SO_2	3,4-Cl_2−Ph	0.83	0.88	1.70	3.50	1.80
14[a]	SO_2	3,4-Cl_2−Ph	0.83	0.56	1.38	3.50	1.80
15	SO_2	3,4-$(OMe)_2$−Ph	0.94	0.13	1.07	0.20	3.07
16[a]	SO_2	3,4-$(OMe)_2$−Ph	0.94	0.88	1.82	0.20	3.07

[a] Data omitted from derived equation.

with the lowest Clog *P* value, whereas compound **7** is a thiazolidinyl derivative disubstituted, and the 3-substituant presents a high $B_{5(3)}$ value.

4.29. *N*-Pyridinyl-indole-3(alkyl)-carboxamides[58]

Duflos and co-investigators[58] reported the synthesis and biological evaluation of *N*-(4,6-dimethylpyridin-2-yl)heteroarylcarboxamides and acetamides as a novel type of nonacidic anti-inflammatory agents. It was also established that incorporation of amino acid residues, especially glycine and alanine, into 2-amino-4,6-dimethylpyridine led to potent systemic and topical inflammation inhibitors. The fact that indole constitutes the central core of numerous efficient LTD_4 antagonists or inhibitors of FLAP prompted the investigators to extend their research to the synthesis and biological activity of the title compounds. For the biological screening, the carrageenan-induced rat paw edema test was used after oral administration of 0.1 mM/kg of the tested compounds. For the reported compounds, eq 41 was evaluated.

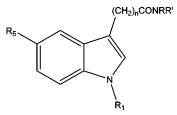
$$\log \mathrm{CPE\%} = -0.003(\pm 0.002)\mathrm{MgVol} + 2.554(\pm 0.625) \quad (41)$$

$$n = 6; \quad r = 0.904; \quad r^2 = 0.818; \quad q^2 = 0.559; \quad s = 0.124; \quad F_{1,4} = 17.8; \quad \alpha = 0.05$$

$$\mathrm{Clog}\,P \text{ vs } \mathrm{M_{Vol}} = 0.996$$

Compound **5** (Table 36), presenting the lowest MgVol value within the dataset, is omitted from the derivation of equation. The negative sign with MgVol indicates unfavorable steric effects.

Table 36. Biological Data[58] and Physicochemical Parameters Used for Deriving Eq 41

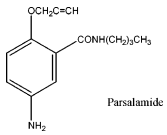


No	R_1	R_5	n	NRR'	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	MgVol
1	CH_3	Br	0		1.70	-0.18	1.52	330.20
2	4-FBn	Br	0		1.49	-0.03	1.46	410.26
3	4-FBn	Br	0		1.49	-0.06	1.43	410.26
4	4-FBn	Br	0		1.30	0.11	1.41	482.19
5[a]	H	H	1		1.90	-0.29	1.61	250.30
6	H	H	2		1.87	0.11	1.98	264.33
7	H	H	2		1.89	0.04	1.93	254.26

[a] Data omitted from derived equation.

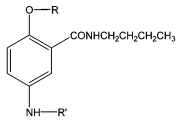
4.30. Substituted Benzamides[59]

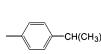
Parsalmide (Synovial) is a nonsteroidal anti-inflammatory drug with a peculiar basic structure that has been widely used to treat arthritic patients.



Caliendo et al.[59] synthesized a series of novel substituted benzamides related to parsalmide and have evaluated their activity in vivo in the carrageenan-induced rat paw edema assay using male Wistar rats and 100 mg/kg of the tested compounds orally suspended in carboxymethylcellulose 0.5%. The CPE% values listed in Table 37 were used to formulate eq 42.

Table 37. Biological Data[59] and Physicochemical Parameters Used for Deriving Eq 42



No	R	R'	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	L_R
1		H	1.66	0.23	1.89	6.17
2		H	1.60	0.19	1.80	6.28
3		H	1.31	0.08	1.40	6.87
4		H	0.89	-0.19	0.70	7.74
5		H	0.84	-0.14	0.70	7.84
6[a]		$COCH_3$	1.66	-0.52	1.14	6.17
7		$COCH_3$	1.60	-0.21	1.40	6.28
8		$COCH_3$	1.31	0.03	1.34	6.87
9		$COCH_3$	0.89	0.37	1.26	7.74
10		$COCH_3$	0.84	0.01	0.85	7.84
11[a]		SO_2CH_3	1.66	-0.96	0.70	6.17
12		SO_2CH_3	1.60	-0.26	1.34	6.28
13		SO_2CH_3	1.31	-0.08	1.23	6.87
14		SO_2CH_3	0.89	-0.04	0.85	7.74
15[a]		SO_2CH_3	0.84	0.39	1.23	7.84

[a] Data omitted from derived equation.

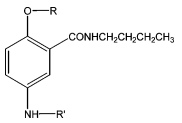
$$\log \mathrm{CPE\%}(100) = -0.493(\pm 0.196)L_R + 4.700(\pm 1.384) \quad (42)$$

$$n = 12; \quad r = 0.871; \quad r^2 = 0.759; \quad q^2 = 0.635; \quad s = 0.203; \quad F_{1,10} = 31.48; \quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs } L_R = 0.755$$

The most important single variable is L_R, the sterimol parameter for the length of the first atom of the substituent R. The negative coefficient indicates that steric interactions at the R substituent of the O− (of the aromatic ring) are unfavorable. At first, eq 42 seems strange because it contains no π or Clog *P*

Table 38. Biological Data[59] and Physicochemical Parameters Used for Deriving Eq 43



no.	R	R′	calcd log CPE%	Δlog CPE%	obsd log CPE%	$B_{5R'}$
1[a]	$CH_2C{\equiv}CH$	$COCH_3$	1.44	−0.33	1.11	3.13
2	$CH_2CH{=}C(CH_3)_2$	$COCH_3$	1.44	0.04	1.48	3.13
3	$CH_2C{\equiv}CH$	H	1.79	0.13	1.92	1.00
4	$CH_2CH{=}C(CH_3)_2$	H	1.79	−0.13	1.66	1.00
5	$CH_2C{\equiv}CH$	SO_2CH_3	1.43	−0.03	1.4	3.17
6	$CH_2CH{=}C(CH_3)_2$	SO_2CH_3	1.43	0.00	1.43	3.17

[a] Data omitted from derived equation.

term. The reason for this is apparent from the correlation matrix, where it is seen that L_R and Clog P are significantly collinear (0.755). Again, no existence for an electronic term was found. Although eq 42 is not sharp in terms of r, it is statistically significant. No parametrization for R′ substituents has been done. However, the CPE% values are well predicted. Three derivatives were omitted from the derivation of eq 42. They do not contain any unusual substitution moiety. For compounds **6** and **11**, the biological activities were higher than were expected. In contrast,, for compound **15** it was lower.

For a subgroup of substituted benzamides containing a 2-propynyloxy group, synthesized and tested by Galiendo's group,[59] eq 43 was derived.

$$\log \text{CPE\%}(100) = -0.165(\pm 0.147)B_{5R'} + 1.956(\pm 0.371) \quad (43)$$

$$n = 5;\ \ r = 0.900;\ \ q^2 = 0.264;\ \ r^2 = 0.810;\ \ s = 0.109;\ \ F_{1,3} = 12.67;\ \ \alpha = 0.05$$

$$\text{Clog } P \text{ vs } B_{5R'} = 0.045$$

The biological data and the physicochemical parameters used are given in Table 38. No role for lipophilicity was found. $B_{5R'}$, the sterimole parameter for the largest width of the first atom of substituent R′, is the most significant single parameter indicating an unfavorable steric effect. One compound (**1** in Table 38) was rejected from the derivation of the equation, and it was the least active compared to the rest.

4.31. Naphthalene Derivatives[60]

Feixas and co-workers[60] developed a series of selective COX-2 inhibitors that fit into the category of classical NSAIDs, such as zomepirac and indomethacin derivatives. These compounds were tested against carrageenan-induced rat paw edema (Table 39) by the administration of 30 mg/kg orally. These results led to the development of eq 44.

$$\log \text{CPE\%} = -0.353(\pm 0.264)\ \text{Clog } P - 0.350(\pm 0.157)E_{s_4} + 4.694(\pm 1.158) \quad (44)$$

$$n = 9;\ \ r = 0.940;\ \ r^2 = 0.883;\ \ q^2 = 0.728;\ \ s = 0.095;\ \ F_{2,6} = 22.61;\ \ \alpha = 0.01$$

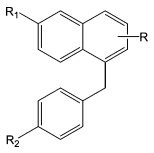
$$\text{Clog } P \text{ vs } E_{s_4} = 0.610$$

Hydrophilicity should be taken under consideration as an important variable for this dataset. No term appears for R/R_1 substituents. However, there is little variation in R/R_1 that the effect can be assayed properly. The negative sign with the E_{s_4} parameter of Taft indicates a positive steric effect for 4-substitutions (R_2), since E_s values are all negative. Two points (compounds **5** and **11**, Table 39) were omitted, of which compound **11** has the lowest Clog P value, whereas compound **5** is the only representative with R_1 = H.

4.32. 1-Methyl 5-Substituted (4(3*H*)-Oxo-1,2,3-benzothiazin-3-yl)-1*H*-pyrazole-4-acetic Acid Derivatives[61]

Heteroarylalcanoic acids are a well-established class of NSAIDs, for example, indomethacin and tolmetin, therapeutically useful in treatment of acute

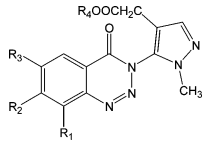
Table 39. Biological Data[60] and Physicochemical Parameters Used for Deriving Eq 44



no.	R	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog P	E_{s_4}
1	1-CH_2COOH	CH_3O	Cl	1.76	−0.04	1.72	5.29	−0.97
2	1-$CH(CH_3)COOH$	CH_3O	Cl	1.57	0.13	1.70	5.60	−0.97
3	1-$CH(CH_3)COOH$	CH_3O	F	1.74	−0.02	1.72	5.03	−0.46
4	1-$CH(CH_3)COOH$	CH_3S	Cl	1.17	0.04	1.20	6.24	−0.97
5[a]	1-$CH(CH_3)COOH$	H	F	1.69	−0.49	1.20	5.11	−0.46
6	1-$CH(CH_3)COOH$	CH_3O	2-Cl	1.23	−0.12	1.11	5.60	0.00
7	1-$CH(CH_3)COOH$	CH_3O	H	1.67	0.09	1.76	4.88	0.00
8	1-$CH(CH_3)COOH$	CH_3O	4-Me	1.79	−0.10	1.69	5.38	−1.24
9	1-$CH(CH_3)COOH$	CH_3O	4-Et	1.49	0.02	1.51	5.91	−1.31
10	1-$CH(CH_3)COOH$	CH_3O	4-*t*-Bu	1.51	0.00	1.51	6.71	−2.78
11[a]	1-$CH(CH_3)COOH$	CH_3O	4-MeO	1.91	−0.26	1.65	4.80	−0.55

[a] Data omitted from derived equation.

Table 40. Biological Data[61] and Physicochemical Parameters Used for Deriving Eq 45



no.	R_1	R_2	R_3	R_4	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	CMR
1	H	H	H	C_2H_5	1.84	−0.07	1.77	1.37	8.19
2	H	Cl	H	C_2H_5	1.75	−0.01	1.74	2.09	8.69
3	H	H	Cl	C_2H_5	1.75	0.02	1.77	2.09	8.69
4	CH_3	H	H	C_2H_5	1.76	−0.06	1.70	1.87	8.66
5	H	H	CH_3	C_2H_5	1.76	0.07	1.83	1.87	8.66
6	H	H	H	H	1.51	−0.02	1.49	0.44	7.27
7	H	Cl	H	H	1.77	−0.01	1.76	1.15	7.76
8	H	H	Cl	H	1.77	0.02	1.79	1.15	7.76
9[a]	CH_3	H	H	H	1.76	−0.28	1.48	0.94	7.73
10	H	H	CH_3	H	1.76	0.06	1.82	0.94	7.73

[a] Data omitted from derived equation.

as well as chronic inflammatory conditions. Daidone and co-workers[61] in their research program aimed to obtain new anti-inflammatory agents. All the new compounds were screened at 100 mg/kg orally using the carageenan-induced rat paw edema. From the data of Table 40, we have formulated eq 45.

$$\log \text{CPE\%} = 6.264(\pm 3.919)\text{CMR} - 0.382(\pm 0.242)\text{CMR}^2 - 23.815(\pm 15.780) \quad (45)$$

$$\text{CMR}_o = 8.192(\pm) \quad (8.075-8.640)$$

$$n = 9; \quad r = 0.879; \quad r^2 = 0.772; \quad q^2 = -0.810; \quad s = 0.056; \quad F_{2,4} = 10.26; \quad \alpha = 0.05$$

$$\text{Clog } P \text{ vs CMR} = 0.967$$

CMR is primarily a measure of bulk and of polarizability of the molecule. It seems that the bulk of the whole molecule plays a special role in increasing the inhibitory potency. From the correlation matrix, it is seen that CMR and Clog *P* are significantly collinear (0.967). For this set, the steric parameters are found to replace the hydrophobic effect. QSAR 45 is not exceedingly sharp. Compound **9**, which was omitted from the derivation of eq 45, is the least active compared to the rest. However eq 45 must not be taken under consideration due to its negative q^2 value.

4.33. *N*-[4-(Propyl)cyclohexyl]amides[62]

Generally, derivatives bearing a *tert*-butyl moiety showed a better pharmacological profile than the corresponding ethyl derivatives, indicating that the bulkiness of the alkyl chain has a positive influence on the pharmacological activity of some *N*-[4-(*tert*-butyl)]cyclohexyl and *N*-[4-(ethyl)cyclohexyl]-unsubstituted benzamides. Pau and co-workers[62] synthesized and pharmacologically investigated some *n*-propyl derivatives. The anti-inflammatory activity was studied by means of the carrageenan-induced rat paw edema assay at a dose of 300 mg/kg given orally. We tried to analyze the in vivo results to determine the most significant parameters that related to the activity. Thus, we have formulated the following equations (eqs 46 and 47).

$$\log \text{CPE\%}(300) = -0.134(\pm 0.093)\,\text{Clog } P + 2.476(\pm 0.491) \quad (46)$$

$$n = 5; \quad r = 0.935; \quad r^2 = 0.875; \quad q^2 = 0.462; \quad s = 0.028; \quad F_{1,3} = 25.5; \quad \alpha = 0.05$$

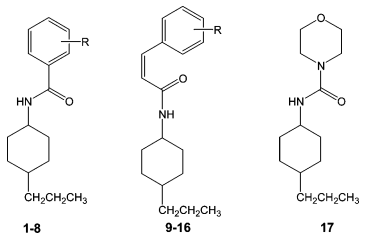
$$\log \text{CPE\%}(300) = 0.189(\pm 0.129)\sigma_{R(4)} + 1.715(\pm 0.047) \quad (47)$$

$$n = 6; \quad r = 0.897; \quad r^2 = 0.804; \quad q^2 = 0.392; \quad s = 0.033; \quad F_{1,4} = 19; \quad \alpha = 0.05$$

$$\text{Clog } P \text{ vs } \sigma_{R(4)} = 0.022$$

Hydrophilicity is taken under consideration in this QSAR 46. Three data points have to be omitted to have a significant r^2 term. Compound **1** is less active in the dataset representing the lower Clog *P* value, whereas compound **6** has the higher Clog *P* value. Compound **5** does not contain any unusual moiety (Table 41).

Table 41. Biological Data[62] and Physicochemical Parameters Used for Deriving Eq 46

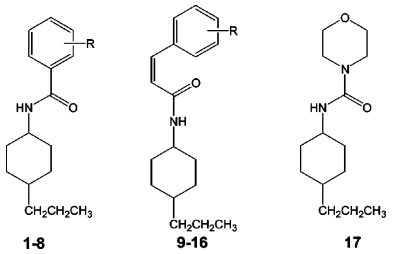


1-8 9-16 17

no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*
1[a]	4′-F	1.83	−0.21	1.62	4.81
2	2′,4′-Cl_2	1.76	0.00	1.76	5.34
3	4′-CH_3	1.81	−0.03	1.78	4.97
4	4′-NO_2	1.85	0.03	1.88	4.64
5[a]	4′-Cl	1.65	0.11	1.76	6.13
6[a]	2′,4′-Cl_2	1.56	0.14	1.70	6.84
7	H	1.75	−0.02	1.73	5.41
8	4′-CH_3	1.68	0.02	1.70	5.91

[a] Data omitted from derived equation.

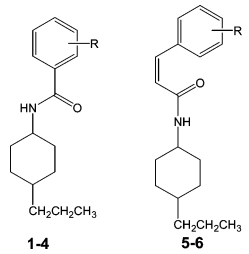
Table 42. Biological Data[62] and Physicochemical Parameters Used for Deriving Eq 47



no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	$\sigma_{R(4)}$
1[a]	4′-F	1.73	−0.10	1.62	0.06
2	2′,4′-Cl_2	1.76	0.00	1.76	0.23
3[a]	4′-CH_3	1.68	0.09	1.78	−0.17
4	4′-NO_2	1.86	0.02	1.88	0.78
5	4′-Cl	1.76	0.00	1.76	0.23
6	2′,4′-Cl_2	1.76	−0.06	1.70	0.23
7	H	1.72	0.02	1.73	0.00
8	4′-CH_3	1.68	0.02	1.70	−0.17

[a] Data omitted from derived equation.

Table 43. Biological Data[62] and Physicochemical Parameters Used for Deriving Eq 48



no.	R	calcd log 1/ED_{50}	Δlog 1/ED_{50}	obsd log 1/ED_{50}	$\sum\sigma_{(R)}$
1	2′,4′-Cl_2	3.76	−0.01	3.76	0.46
2[a]	4′-CH_3	3.62	0.10	3.72	−0.17
3	4′-NO_2	3.84	0.03	3.87	0.78
4	4′-Cl	3.71	−0.05	3.66	0.23
5	H	3.66	−0.03	3.62	0.00
6	4′-CH_3	3.62	0.06	3.68	−0.17

[a] Data omitted from derived equation.

From eq 47, it seems that electronic effects, as $\sigma_{R(4)}$ values (the Hammet's constant) are mostly significant. It is the first correlation in which an electronic parameter is referred, but the equation is not exceedingly sharp. Two points (compounds **1** and **3**, Table 42) have been omitted, of which compound **1** is the less active, whereas compound **3** due to the 4-CH_3 group has a low $\sigma_{R(4)}$ value.

In general, all the variation in the substituents is confined to the 2 or 4 positions on the phenyl ring. But the number of data points is small, and the range of substituents covered is narrow. Thus, there is a need for more derivatives to delineate the physicochemical parameters that relate significantly to the potency.

For the most potent derivatives, Pau and coworkers[62] determined their ED_{50} values. Using those (Table 43), we derived eq 48

$$\log 1/ED_{50}(300) = 0.234(\pm 0.230)\sum\sigma_{(R)} + 3.655(\pm 0.098) \quad (48)$$

$$n = 5;\ \ r = 0.882;\ \ r^2 = 0.778;\ \ q^2 = 0.130;\ \ s = 0.054;\ \ F_{1,3} = 10.33;\ \ \alpha = 0.10$$

$$\text{Clog } P \text{ vs } \sum\sigma_{(R)} = 0.160$$

in which again Hammet's constant, σ, as $\sum\sigma$ (the sum of the σ contribution of all the substituents for the 2 and 4 positions) was found most significant. Correlation is low in terms of r^2 and q^2. Compound **2**, having a 4-CH_3 group, was omitted from the derivation.

4.34. *N*-[4-(Alkyl)cyclohexyl]-Substituted Benzamides[63]

In continuation of their previous research, Pau and co-workers [63] synthesized two series of *N*-[4-(alkyl)-cyclohexyl]-substituted benzamides in which the methylic moiety in the 4-position of the cyclohexane was substituted by a *tert*-butylic or an ethylic group. Compounds were subjected to carrageenan-induced rat paw edema assay in vivo at a dose of 150 mg/kg given orally. Using the data in Table 44, we derived eq 49.

$$\log \text{CPE\%} = 0.303(\pm 0.142)\text{CMR} - 0.540(\pm 0.190)\text{MR}_\text{B} - 0.331(\pm 0.130)\sum\pi_\text{R} + 0.835(\pm 0.749) \quad (49)$$

$$n = 13;\ \ r = 0.942;\ \ r^2 = 0.887;\ \ q^2 = 0.768;\ \ s = 0.102;\ \ F_{3,9} = 23.45;\ \ \alpha = 0.01$$

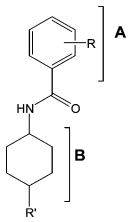
$$\text{Clog } P \text{ vs CMR} = 0.028;\ \ \text{Clog } P \text{ vs MR}_\text{B} = 0.057;\ \ \text{Clog } P \text{ vs } \sum\pi_\text{R} = 0.501;\ \ \text{CMR vs MR}_\text{B} = 0.666;\ \ \text{CMR vs } \sum\pi_\text{R} = 0.002;\ \ \text{MR}_\text{B} \text{ vs } \sum\pi_\text{R} = 0.000$$

CMR is the most significant term, followed by MR_B and $\sum\pi_R$. MR_B is the molar refractivity of group B (Table 44). The negative MR_B term suggests unfavorable steric effects from B substituents. The correlation matrix for CMR vs MR_B does indicate an interrelationship (0.666), but parameters $\sum\pi_R$ vs MR_B and $\sum\pi_R$ vs CMR are reasonably orthogonal.

Electronic effects referred to substituents R and R′ do not improve the equation. Subtle steric changes rather than electronics are influencing anti-inflammatory activity.

$\sum\pi$ is the sum of the π values for all the R substituents on the phenyl ring and is used as a measure of drug hydrophobicity. In the present case, the $\sum\pi$ coefficient shows that low hydrophobicity (high hydrophilicity) must be taken under consideration. It may be that in addition to the purely physical phenomena controlling partitioning, the more hydrophilic molecules may be more exposed to plasma proteins. The three outliers not included in this analysis are marked in Table 44. All have at least one halogen as a substituent at position 4, whereas compound **15** presents a second atom of −Cl at position 2. Compound **13** also presents a high $\sum\pi_R$ value.

Table 44. Biological Data[63] and Physicochemical Parameters Used for Deriving Eq 49



no.	R′	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR	MR_B	$\sum\pi_R$
1	CMe_3	3,4,5-$(CH_3O)_3$	1.45	−0.05	1.40	9.87	4.44	−0.06
2	CMe_3	4-Cl	1.52	0.07	1.59	8.51	3.08	0.71
3[a]	CMe_3	4-F	1.82	−0.54	1.28	8.03	2.60	0.14
4[a]	CMe_3	4-Br	1.40	0.17	1.57	8.79	3.37	0.86
5	CMe_3	2,4-Cl_2	1.11	−0.03	1.08	9.00	3.67	1.42
6	CMe_3	H	1.87	−0.01	1.86	8.02	2.59	0.00
7	CMe_3	4-CH_3	1.57	0.12	1.70	8.48	3.05	0.56
8	CMe_3	4-NO_2	1.82	−0.10	1.72	8.63	3.20	−0.28
9	CH_2CH_3	3,4,5-$(CH_3O)_3$	1.17	0.08	1.26	8.94	4.44	−0.06
10	CH_2CH_3	4-Cl	1.24	0.13	1.36	7.58	3.08	0.71
11	CH_2CH_3	4-F	1.54	−0.06	1.48	7.11	2.60	0.14
12	CH_2CH_3	4-Br	1.12	−0.17	0.95	7.87	3.37	0.86
13[a]	CH_2CH_3	2,4-Cl_2	0.83	0.76	1.59	8.07	3.67	1.42
14	CH_2CH_3	H	1.59	0.00	1.59	7.09	2.59	0.00
15	CH_2CH_3	4-CH_3	1.29	−0.04	1.26	7.55	3.05	0.56
16	CH_2CH_3	4-NO_2	1.54	0.06	1.59	7.70	3.20	−0.28

[a] Data omitted from derived equation.

4.35. 1-Methyl-4-(*N*-aroyl)-piperidinamides[64]

Pau and co-workers,[64] continuing their research, obtained new compounds by substituting the carbon in position 4 of the cyclohexane ring with a nitrogen atom. Furthermore, they tried to investigate the importance of the presence of the 4-(*N*-aroyl) moiety. The anti-inflammatory activity was studied by means of the carrageenan-induced rat paw edema assay (150 μmol/kg po).

The results from Table 45 were used to formulate eq 50.

$$\log \text{CPE\%} = -0.455(\pm 0.323)MR_{R(4)} - 0.360(\pm 0.184)E_{s_4} + 1.530(\pm 0.183) \quad (50)$$

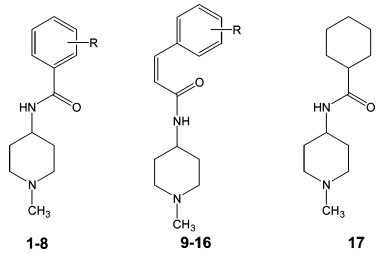
$$n = 14; \quad r = 0.809; \quad r^2 = 0.654; \quad q^2 = 0.298; \quad s = 0.145; \quad F_{2,11} = 10.41; \quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } MR_{R(4)} = 0.005; \quad \text{Clog } P \text{ vs } E_{s_4} = 0.307; \quad MR_{R(4)} \text{ vs } E_{s_4} = 0.208$$

E_{s_4} is the Taft steric constant for 4-substituents. Para substituents on the phenyl ring increase inhibitory potency, anti-inflammatory activity; MR_4 is the molar refractivity of substituents. The correlation matrix shows that MR_4, E_{s_4}, and Clog P/π are independent vectors. Thus, we have assumed that substituents at the 4 position interact in a non-hydrophobic space.

No parametrization has been done for substituents at position 2, 3, or 5, due to little variation in these positions. Although they are all well fit by eq 50, compounds **5** and **15** have been omitted. Compound **15** has the highest E_{s_4} value and the CPE% value is found to be higher than expected. Compound **5** is a disubstituted analogue.

Table 45. Biological Data[64] and Physicochemical Parameters Used for Deriving Eq 50



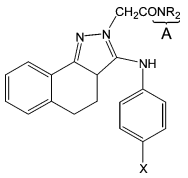
no.	R	calcd log CPE%	Δlog CPE%	obsd log CPE%	$MR_{R(4)}$	E_{s_4}
1	3′,4′,5′-$(OCH_3)_3$	0.97	−0.07	0.90	0.79	0.55
2	4′-Cl	1.61	0.09	1.70	0.60	−0.97
3	4′-F	1.66	−0.21	1.45	0.09	−0.46
4	4′-Br	1.55	−0.03	1.52	0.89	−1.16
5[a]	2′,4′-Cl_2	1.61	−0.53	1.08	0.60	−0.97
6	H	1.48	0.38	1.76	0.10	0.00
7	4′-CH_3	1.73	−0.20	1.53	0.56	−1.24
8	4′-NO_2	1.57	0.09	1.66	0.74	−1.01
9	3′,4′,5′-$(OCH_3)_3$	1.37	−0.07	1.30	0.79	−0.55
10	4′-Cl	1.61	−0.03	1.58	0.60	−0.97
11	4′-F	1.66	0.16	1.72	0.09	−0.46
12	4′-Br	1.55	0.09	1.66	0.89	−1.16
13	2′,4′-Cl_2	1.61	0.12	1.73	0.60	−0.97
14	H	1.48	0.10	1.38	0.10	0.00
15[a]	4′-CH_3	1.73	−0.73	1.00	0.56	−1.24
16	4′-NO_2	1.57	−0.04	1.53	0.74	−1.01

[a] Data omitted from derived equation.

4.36. N-Substituted 3-(Arylamino)-4,5-dihydro-2*H*-benz[*g*]indazol-2-yl Acetamides[65]

Previous work dealing with the biological activity of simple and complex pyrazole derivatives enabled Schenone and co-workers[65] to synthesize analogues bearing in position 2 of the benzindazole ring a

Table 46. Biological Data[65] and Physicochemical Parameters Used for Deriving Eqs 51 and 51a



a. Equation 51

no.	X	A	calcd log CPE%	Δlog CPE%	obsd log CPE%	MgVol
1	H	$NHCH(CH_3)_2$	1.57	−0.02	1.54	360.50
2[a]	H	$NH(CH_2)_2OCH_2CH_3$	1.63	0.09	1.72	390.53
3	H	$NHCH_2C_6H_5$	1.67	0.08	1.76	408.54
4[a]	H	morpholino	1.63	0.17	1.80	388.51
5	Cl	$NHCH(CH_3)_2$	1.64	−0.02	1.62	394.94
6	Cl	$NH(CH_2)_2OCH_2CH_3$	1.71	−0.01	1.7	424.97
7	Cl	$NHCH_2C_6H_5$	1.75	−0.03	1.72	442.98
8[a]	Cl	morpholino	1.71	−0.16	1.54	422.95
9	Br	$NH(CH_2)_2OCH_2CH_3$	1.81	−0.04	1.77	469.42
10	Br	morpholino	1.81	0.04	1.85	467.40

b. Equation 51a

no.	X	A	calcd log CPE%	Δlog CPE%	obsd log CPE%	L_A
1	H	$NHCH(CH_3)_2$	1.56	−0.02	1.54	4.83
2	H	$NHCH_2C_6H_5$	1.74	0.02	1.76	8.24
3[a]	H	morpholino	1.59	0.21	1.80	5.29
4	Cl	$NHCH(CH_3)_2$	1.56	0.06	1.62	4.83
5	Cl	$NHCH_2C_6H_5$	1.74	−0.01	1.72	8.24
6	Cl	morpholino	1.59	−0.04	1.54	5.29

[a] Data omitted from derived equation.

substituted acetamide moiety instead of an aryl group. Compounds were submitted to a preliminary screening for anti-inflammatory activity at a dose of 50 mg/kg orally using the carrageenan-induced rat paw edema assay. Equation 51 was derived from correlation of log CPE% values to the MgVol of the molecules.

$$\log \text{CPE\%} = 0.002(\pm 0.001)\text{MgVol} + 0.753(\pm 0.543) \quad (51)$$

$$n = 7;\quad r = 0.897;\quad r^2 = 0.805;\quad q^2 = 0.636;\quad s = 0.048;\quad F_{1,5} = 19.58;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs MgVol} = 0.244$$

The correlation is not a sharp one due to the lack of variance in CPE% values (1.54−1.85). Three data points were rejected, and two of them (compounds **4** and **8**, Table 46, section a) are morpholinic derivatives.

An attempt to evaluate another QSAR for the data in Table 46 led us to eq 51a. The most important single parameter is the length of substituent A (as marked in Table 46, section b).

$$\log \text{CPE\%} = 0.051(\pm 0.041)L_A + 1.320(\pm 0.263) \quad (51a)$$

$$n = 5;\quad r = 0.916;\quad r^2 = 0.840;\quad s = 0.046;\quad q^2 = 0.610;\quad F_{1,3} = 16.5;\quad \alpha = 0.05$$

Unfortunately, the number of data points used is small due to the missing values of L_A for compounds **2**, **6**, **9**, and **10** (Table 46, section b).

4.37. 5-Aroylamino Substituted 3-Nicotinoyl/Isonicotinoyl-1,3,4-thiadiazol-2(3*H*)-ones[66]

Within the framework of a research program on anti-inflammatory agents, Schenone and co-workers[66] focused on five-membered heterocyclic structures with three heteroatoms such as a thiadiazole ring. In particular, they have been concerned with whether thiadiazolones resembling the well-known pyrazolone analogues were endowed with anti-inflammatory activities. So they selected the nicotinoyl and isonicotinoyl moieties and aroylamino function to verify their possible influence on anti-inflammatory activity, which was evaluated by carrageenan-induced paw edema in rats (at 50 mg/kg po). Using the data of Table 47, we derived eq 52.

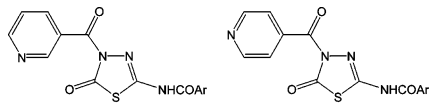
$$\log \text{CPE\%} = -0.100(\pm 0.046)\text{CMR} + 2.520(\pm 0.393) \quad (52)$$

$$n = 8;\quad r = 0.910;\quad r^2 = 0.829;\quad q^2 = 0.676;\quad s = 0.030;\quad F_{1,6} = 31.2;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs CMR} = 0.817$$

A negative sign with the overall molar refractivity assigns for steric hindrance. Two outliers are marked in Table 47, compounds **1** and **9**. Both contain no unusual substitution, except that compound **1** is the least active one in the set.

Table 47. Biological Data[66] and Physicochemical Parameters Used for Deriving Eq 52



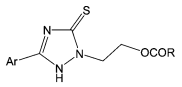
no.	Ar	calcd log CPE%	Δlog CPE%	obsd log CPE%	CMR
1[a]	C_6H_5	1.67	−0.16	1.51	8.47
2	C_6H_4-*p*-CH_3	1.62	0.03	1.65	8.93
3	C_6H_4-*p*-OCH_3	1.61	0.03	1.63	9.08
4	C_6H_4-*p*-Cl	1.62	−0.03	1.59	8.96
5	2-furyl	1.75	−0.02	1.73	7.68
6	C_6H_5	1.67	−0.04	1.63	8.47
7	C_6H_4-*p*-CH_3	1.62	0.01	1.63	8.93
8	C_6H_4-*p*-OCH_3	1.61	−0.02	1.59	9.08
9[a]	C_6H_4-*p*-Cl	1.62	0.13	1.75	8.96
10	2-furyl	1.75	0.03	1.78	7.68

[a] Data omitted from derived equation.

4.38. Esters from 5-Aroyl-1,2-dihydro-2-(2-hydroethyl)-3*H*-1,2,4-triazole-3-thiones[67]

Several examples of nonsteroidal anti-inflammatory drugs having a triazole structure have been recorded in the medicinal chemistry literature. Among them, 1,2,4-thiazololine thiones are of particular interest. Schenone and co-workers,[67] continuing their effort, synthesized some aliphatic and aromatic esters of the above thiones. Compounds were tested in vivo for anti-inflammatory activity by carrageenan-in-

Table 48. Biological Data[67] and Physicochemical Parameters Used for Deriving Eq 53



No	R	Ar	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	MR_{Ar}
1[a]	CH_3	C_6H_5	1.31	0.28	1.59	2.59
2	$CH(CH_3)_2$	C_6H_5	1.31	-0.08	1.23	2.59
3[a]		C_6H_5	1.31	0.14	1.45	2.59
4	$C_6H_2(OCH_3)_3$(3,4,5)	C_6H_5	1.31	0.06	1.36	2.59
5	CH_3	C_6H_4Cl(4)	1.60	-0.09	1.51	3.08
6	$CH(CH_3)_2$	C_6H_4Cl(4)	1.60	0.10	1.70	3.08
7		C_6H_4Cl(4)	1.60	0.04	1.63	3.08
8	$C_6H_2(OCH_3)_3$(3,4,5)	C_6H_4Cl(4)	1.60	0.06	1.65	3.08
9	CH_3	$C_6H_4OCH_3$(4)	1.67	-0.08	1.59	3.21
10[a]	$CH(CH_3)_2$	$C_6H_4OCH_3$(4)	1.67	-0.14	1.53	3.21
11		$C_6H_4OCH_3$(4)	1.67	0.04	1.71	3.21
12	$C_6H_2(OCH_3)_3$(3,4,5)	$C_6H_4OCH_3$(4)	1.67	-0.04	1.63	3.21

[a] Data omitted from derived equation.

duced paw edema in rats and the compounds were given at 50 mg/kg po.

We did not succeed in deriving a significant equation, since there was a lack of variation in CPE% (1.23−1.71) and a lack of variation in substitution R/Ar. The physicochemical properties for most of them are quite similar. Thus, we formulated eq 53, from the data in Table 48, in which there still is a problem with the confidence limits.

$$\log \mathrm{CPE\%} = 0.591(\pm 0.260)\mathrm{MR_{Ar}} - 0.224(\pm 0.787) \quad (53)$$

$$n = 9;\quad r = 0.897;\quad r^2 = 0.805;\quad q^2 = 0.638;\quad s = 0.077;\quad F_{1,7} = 28.5;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs } \mathrm{MR_{Ar}} = 0.030$$

No role for lipophilicity was found (0.030). MR_{Ar} as a measure of bulk and polarizability of substituents Ar suggests that Ar substituents interact in the hydrophobic space.

4.39. Benzodiazepines[68]

Grossi and co-workers[68] synthesized 1,5-benzodiazepines-5-amines, which were tested at 200 mg/kg po in vivo for their anti-inflammatory activity using the carrageenan-induced rat paw edema assay. It must be noted that these derivatives showed no affinity for the central and peripheral 1,4- and 1,5-benzodiazepine receptors and proved to affect inflammatory response in mice by inhibiting interleukin 6 and prostaglandin E_2 production.

From the data listed in Table 49, eq 54 was derived using the parabolic model for the overall molecular refractivity of the molecules.

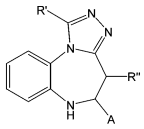
$$\log \mathrm{CPE\%} = 3.141(\pm 0.905)\mathrm{CMR} - 0.164(\pm 0.047)\mathrm{CMR}^2 - 13.208(4.263) \quad (54)$$

$$\mathrm{CMR_o} = 9.604(\pm)\quad (9.429-9.775)$$

$$n = 13;\quad r = 0.926;\quad r^2 = 0.858;\quad q^2 = 0.705;\quad s = 0.139;\quad F_{2,10} = 30.10;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs } \mathrm{CMR} = 0.715$$

Table 49. Biological Data[68] and Physicochemical Parameters Used for Deriving Eq 54



No	R'	A	R''	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	clog *P*	CMR
1	H	NEt_2	Cl	1.46	-0.08	1.38	1.10	8.00
2	C_6H_5	NMe_2	Cl	1.88	-0.03	1.85	2.14	9.59
3	H	NEt_2		1.87	-0.02	1.85	0.40	9.71
4	H	$N(C_4H_9)_2$		1.03	-0.25	0.78	3.80	11.88
5	H	$N(C_4H_9)_2$		1.25	0.07	1.32	2.52	11.57
6	C_6H_5	NMe_2		1.49	0.17	1.66	2.16	11.14
7	C_6H_5	NMe_2		1.22	0.10	1.32	2.72	11.60
8	H	NEt_2	H	1.16	-0.05	1.11	0.33	7.51
9	H	$N(C_4H_9)_2$	H	1.87	0.04	1.90	2.45	9.37
10	H		H	1.34	-0.04	1.30	0.38	7.80
11	H		H	1.14	0.24	1.38	-0.79	7.49
12	CH_3	NEt_2	H	1.44	-0.12	1.32	0.60	7.97
13	CH_3	$N(C_4H_9)_2$	H	1.87	-0.03	1.84	2.72	9.83

Molar refractivity has two components, molar volume and polarizability as derived by the interaction of light with the electrons. It seems that the bulk plays a special role in the biological response. No role for a π or a Clog *P* term was found. The reason for this is apparent from the correlation matrix, where it is seen that CMR and Clog *P* are significantly collinear (0.715).

4.40. Indanylidenes[69]

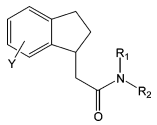
Back pain is often treated with nonsteroidal anti-inflammatory drugs, alone or in combination with other agents, including muscle relaxants. The design of rigid cyclic analogues derived from cinnamides has led to the discovery of a series of indanylidenes, which have been tested as anti-inflammatory agents at 20 mg/kg po using the carrageenan-induced pleurisy assay in rats.[70] In Table 50 is listed a set of indanylidenes. From these data, eq 55 was derived, which is not sharp in terms of r^2.

$$\log \mathrm{CPE\%} = -0.342(\pm 0.137)\,\mathrm{Clog}\,P - 1.507(\pm 0.418)\sum \mathrm{MR_Y} + 1.242(\pm 0.431)\sum \pi_Y + 0.367(\pm 0.198)B_{5Y_5} + 2.046(\pm 0.476) \quad (55)$$

$$n = 32;\quad r = 0.850;\quad r^2 = 0.723;\quad q^2 = 0.552;\quad s = 0.198;\quad F_{4,27} = 17.61;\quad \alpha = 0.01$$

$$\mathrm{Clog}\,P \text{ vs } \sum \mathrm{MR_Y} = 0.000;\ \mathrm{Clog}\,P \text{ vs } \sum \pi_Y = 0.099;\ \mathrm{Clog}\,P \text{ vs } B_{5Y_5} = 0.058;\ \sum \mathrm{MR_Y} \text{ vs } \sum \pi_Y = 0.487;\ \sum \mathrm{MR_Y} \text{ vs } B_{5Y_5} = 0.125;\quad \sum \pi_Y \text{ vs } B_{5Y_5} = 0.000$$

Table 50. Biological Data[69] and Physicochemical Parameters Used for Deriving Eq 55



no.	Y	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	Clog *P*	$\sum MR_Y$	$\sum\pi_Y$	B_{5Y_5}
1	6-Br	H	H	1.14	0.19	1.32	2.95	0.89	0.86	1.00
2	6-OMe	H	H	0.52	−0.04	0.48	2.00	0.79	−0.02	1.00
3	4-Me	H	H	1.37	−0.26	1.11	2.58	0.56	0.56	1.00
4	4-Cl	H	H	1.43	0.33	1.76	2.8	0.6	0.71	1.00
5	4-F	H	H	1.69	−0.16	1.53	2.23	0.09	0.14	1.00
6	5-Cl	H	H	1.72	−0.26	1.46	2.80	0.60	0.71	1.80
7	5-F	H	H	1.81	−0.19	1.62	2.23	0.09	0.14	1.35
8	5-OMe	H	H	1.28	0.12	1.4	2.00	0.79	−0.02	3.07
9	4,5-F_2	H	H	1.83	0.09	1.91	2.30	0.18	0.28	1.35
10	4,7-F_2	H	H	1.67	0.15	1.83	2.37	0.18	0.28	1.00
11	5,7-F_2	H	H	1.80	−0.06	1.74	2.37	0.18	0.28	1.35
12	6-Cl	H	CH_3	1.35	0.05	1.40	3.02	0.60	0.71	1.00
13[a]	6-Br	H	CH_3	1.06	0.67	1.72	3.17	0.89	0.86	1.00
14	6-F	H	CH_3	1.61	−0.03	1.58	2.45	0.09	0.14	1.00
15	5-Cl	H	CH_3	1.65	0.00	1.64	3.02	0.60	0.71	1.80
16	5-Br	H	*c*-C_3H_5	0.86	−0.26	0.6	3.76	0.89	0.86	1.00
17[a]	6-F	H	*c*-C_3H_5	1.41	−0.56	0.85t	3.04	0.09	0.14	1.00
18	4-Me	H	*c*-C_3H_5	1.10	−0.25	0.85	3.39	0.56	0.56	1.00
19	4-Cl	H	*c*-C_3H_5	1.15	0.29	1.45	3.61	0.60	0.71	1.00
20	4-F	H	*c*-C_3H_5	1.41	−0.15	1.26	3.04	0.09	0.14	1.00
21	5-Cl	H	*c*-C_3H_5	1.45	0.02	1.46	3.61	0.60	0.71	1.80
22	4,6-F_2	H	*c*-C_3H_5	1.4	0.05	1.45	3.18	0.18	0.28	1.00
23	4,5-F_2	H	*c*-C_3H_5	1.55	−0.12	1.43	3.11	0.18	0.28	1.35
24	5,6-F_2	H	*c*-C_3H_5	1.55	0.13	1.68	3.11	0.18	0.28	1.35
25	6-F	H	C_2H_5	1.43	0.37	1.80	2.98	0.09	0.14	1.00
26	6-F	H	Pr	1.25	0.31	1.56	3.51	0.09	0.14	1.00
27[a]	6-F	H	*i*-Pr	1.32	0.53	1.85	3.29	0.09	0.14	1.00
28	6-F	H	CH_2CH_2OH	1.82	0.07	1.89	1.84	0.09	0.14	1.00
29	6-F	H	*c*-C_5H_9	1.11	−0.06	1.04	3.92	0.09	0.14	1.00
30	6-F	H	CH_2-*c*-C_3H_5	1.28	0.05	1.32	3.43	0.09	0.14	1.00
31	6-F	H	CH_2Ph	1.00	−0.10	0.90	4.22	0.09	0.14	1.00
32	6-F	CH_3	C_2H_5	1.43	0.21	1.64	2.98	0.09	0.14	1.00
33	6-F	CH_3	OCH_3	1.33	−0.19	1.15	3.25	0.09	0.14	1.00
34	6-F	-$CH_2CH_2CH_2CH_2$-		1.43	−0.17	1.26	2.98	0.09	0.14	1.00
35	6-F	-$CH_2CH_2CH_2CH_2$-		1.62	−0.13	1.49	2.41	0.09	0.14	1.00

[a] Data omitted from derived equation.

Equation 55 is significantly improved by removing derivatives **13**, **17**, and **27**, which behave as outliers. Compounds **17** and **27** are 6-F-substituted derivatives and have low $\sum MR_Y$ and $\sum\pi_Y$ values.

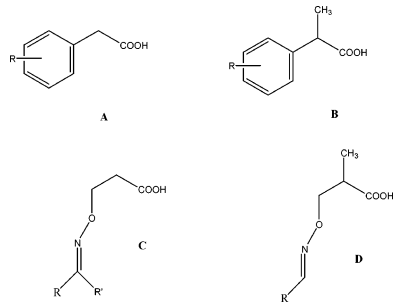
Hydrophilicity should be taken under consideration as an important variable for the molecules of this dataset. However, the lipophilic contribution π of substituents Y is important too. It seems that compounds reach a hydrophobic space through the Y moiety, but there is a limit for this hydrophobic interaction, since the overall hydrophobicity of the molecules must be low. The negative sign with MR_Y suggests steric hindrance.

For the 5-substituents especially, B_{5Y_5}, the largest width of the first atom, is significant. Adding a term in σ to eq 56 does not improve the correlation, so electronic effects appear unimportant. The parameters are reasonably orthogonal.

Although no parametrization has been done for R_2 substituents or for *E*/*Z* isomers, all the points are fit well by eq 55.

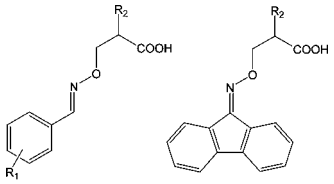
4.41. 3-(Arylmethylidene)aminoxy-2-methyl-propionic Acids[70a,b]

The NSAIDs more commonly used in the therapy of inflammatory conditions belong to the class of arylacetic (A) or arylpropionic (B) derivatives and



lack selectivity toward the two types of COX. Balsamo et al.,[70a] in previous papers,[70b,c] have described the synthesis and the anti-inflammatory properties,

Table 51. Biological Data[70] and Physicochemical Parameters Used for Deriving Eq 56



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no.	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	$B_{5R_{1(m)}}$	$B_{5R_{1(p)}}$
1	H	CH_3	1.74	−0.02	1.72	1.00	1.00
2[a]	H	CH_3	1.74	−0.26	1.48	1.00	1.00
3	H	H	1.74	0.08	1.82	1.00	1.00
4	*m*-Cl	CH_3	1.50	0.16	1.66	1.80	1.00
5	*m*-Cl	CH_3	1.50	−0.16	1.34	1.80	1.00
6	*m*-Cl	H	1.50	0.22	1.72	1.80	1.00
7	*m*-F	CH_3	1.63	0.00	1.63	1.35	1.00
8	*m*-F	CH_3	1.63	−0.03	1.60	1.35	1.00
9	*m*-F	H	1.63	−0.04	1.59	1.35	1.00
10	*m*-MeO	CH_3	1.14	0.07	1.20	3.07	1.00
11[a]	*m*-MeO	CH_3	1.14	0.28	1.41	3.07	1.00
12	*m*-MeO	H	1.14	−0.14	1.00	3.07	1.00
13	*p*-EtO	CH_3	1.00	0.20	1.20	1.00	3.36
14	*p*-EtO	CH_3	1.00	−0.05	0.95	1.00	3.36
15[a]	*p*-EtO	H	1.00	0.71	1.72	1.00	3.36
16	*p*-Me	CH_3	1.41	−0.21	1.20	1.00	2.04
17	*p*-Me	CH_3	1.41	0.03	1.45	1.00	2.04
18	*p*-CF_3	CH_3	1.24	−0.16	1.08	1.00	2.61
19	*p*-CF_3	CH_3	1.24	0.11	1.34	1.00	2.61
20	*p*-CF_3	H	1.24	−0.06	1.18	1.00	2.61

[a] Data omitted from derived equation.

evaluated by the carrageenan-induced edema test in rats, of a series of β-aminoxypropionic acids of type C, designed as analogues of arylacetic type A NSAIDs, on the basis of the hypothesis that a methylene aminoxy methyl moiety, $CNOCH_3$, may act as a bioequivalent of aryl groups in this class of drugs. Some of the new type C compounds have been shown to possess an appreciable anti-inflammatory activity. Thus, the researchers synthesized a series of N-substituted 3-aminoxy-2-methylpropionic acids of type D, which are the α-methyl-substituted homologues of compounds of type C and prepared both enantiomers of compounds of type D. Compounds were assayed for anti-inflammatory activity by means of the carrageenan-induced paw edema test in rats at a dose of 100 mg/kg po. These results were used for derivation of eq 56 (Table 51).

$$\log \text{CPE\%} = -0.289(\pm 0.126)B_{5R_{1(m)}} - 0.310(\pm 0.095)B_{5R_{1(p)}} + 2.335(\pm 0.307) \quad (56)$$

$$n = 17;\quad r = 0.887;\quad r^2 = 0.786;\quad q^2 = 0.674;\quad s = 0.136;\quad F_{2,14} = 25.74;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } B_{5R_{1(m)}} = 0.184;\quad \text{Clog } P \text{ vs } B_{5R_{1(p)}} = 0.308;\quad B_{5R_{1(m)}} \text{ vs } B_{5R_{1(p)}} = 0.275$$

The most important term is the sterimol parameter B_{5R} for the para substituent, followed by the B_5 for the meta substituents. Both terms have a negative sign indicating that steric interaction at the meta and para positions of the aromatic ring are unfavorable. No role for the electronic effect was found. Lipophilicity (π and Clog P) also seems to be unimportant.

Another important point is that the two B_{5R_m} and B_{5R_p} parameters do not cover a hydrophobic effect, and a collinearity problem does not exist. The presence/absence of a CH_3 group at position R_2 was not parametrized, although all points fit well (eq 56). Three points (compounds **2**, **11**, and **15**, Table 51) were not included in derivation of eq 56. For compounds **2** and **15**, the biological activities are lower than the calculated. All the rejected derivatives do not contain an unusual moiety.

4.42. N-Substituted Anthranilic Acids[71]

Mefenamic acid and meclofenamates, both *N*-phenylanthranilic acid derivatives, have been used as anti-inflammatory agents in therapy. A considerable amount of work has been done on the structural variation of this subclass of drugs broadly known as NSAIDs. It has been observed that the best known NSAIDs are acidic in nature. In view of this, the attention of Sharma and co-workers[71] has been directed to variation at the 2-position of anthranilic acid (2-amino-benzoic acids), by incorporating different acidic functional five-membered heterocyclic rings to synthesize new analogues with improved anti-inflammatory effects. Random screening of compounds was performed at 50 mg/kg po using carrageenan-induced rat paw edema. From theses results (Table 52), eq 57 was derived.

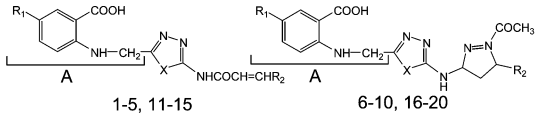
$$\log \text{CPE\%} = 0.002(\pm 0.001)\text{MgVol} - 0.194(\pm 0.083)\text{MR}_\text{A} + 0.247(\pm 0.085)\sigma_{4R_2} + 1.363(\pm 0.268) \quad (57)$$

$$n = 18;\quad r = 0.904;\quad r^2 = 0.817;\quad q^2 = 0.688;\quad s = 0.044;\quad F_{3,14} = 20.91;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs MgVol} = 0.221;\quad \text{Clog } P \text{ vs MR}_\text{A} = 0.023;\quad \text{Clog } P \text{ vs } \sigma_{4R_2} = 0.001;\quad \text{MgVol vs MR}_\text{A} = 0.487;\quad \text{MgVol vs } \sigma_{4R_2} = 0.080;\quad \text{MR}_\text{A} \text{ vs } \sigma_{4R_2} = 0.000$$

At first, no role for a lipophilic term was found. Instead, the molar volume seems to be important. Two compounds are rejected (**2** and **8**). Compound **8** has the higher MgVol. Molar refractivity for group A presents a positive sign, indicating that the larger and more polarizable the A-substituent is, the more it promotes the anti-inflammatory potency. The Hammet constant has been used to parametrize substituents at position 4 of substituents R_2. No parametrization has been done for the corresponding 2 substituents. However, they all fit eq 57. The nature of X also does not seem to play any role since no parametrization for this position of substitution has been done. The parameters are reasonably orthogonal.

Table 52. Biological Data[71] and Physicochemical Parameters Used for Deriving Eq 57



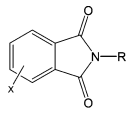
No	X	R_1	R_2	calcd. logCPE%	ΔlogCPE%	obsd. logCPE%	M_{Vol}	MR_A	σ_{4R2}
1	O	Br		1.51	0.01	1.51	443.28	4.85	0.00
2[a]	O	Br		1.51	0.09	1.61	473.31	4.85	-0.27
3	O	Br		1.53	0.06	1.59	489.31	4.85	-0.37
4	O	Br		1.41	-0.01	1.39	486.36	4.85	-0.83
5	O	Br		1.45	0.00	1.45	459.28	4.85	-0.37
6	O	Br		1.64	-0.04	1.60	499.36	4.85	0.00
7	O	Br		1.65	0.05	1.70	529.39	4.85	-0.27
8[a]	O	Br		1.85	-0.20	1.65	545.39	4.85	0.37
9	O	Br		1.54	-0.03	1.52	542.44	4.85	-0.83
10	O	Br		1.59	-0.03	1.56	515.36	4.85	-0.37
11	S	H		1.50	-0.02	1.48	380.46	4.07	0.00
12	S	H		1.51	0.05	1.56	410.49	4.07	-0.27
13	S	H		1.53	0.03	1.56	426.49	4.07	-0.37
14	S	H		1.40	-0.07	1.33	423.54	4.07	-0.83
15	S	H		1.45	0.02	1.47	396.46	4.07	-0.37
16	S	H		1.64	-0.04	1.60	436.54	4.07	0.00
17	S	H		1.65	0.03	1.68	466.57	4.07	-0.27
18	S	H		1.66	-0.04	1.62	482.57	4.07	-0.37
19	S	H		1.51	0.06	1.57	465.59	4.07	-0.83
20	S	H		1.59	0.00	1.59	452.54	4.07	-0.37

[a] Data omitted from derived equation.

4.43. *N*-Pyridinyl(alkyl)phthalamides[72]

Tumor necrosis factor-α (TNF_a) is a protein secreted by monocytes/macropages in response to many inflammatory stimuli. Excessive production of TNF_a has also been implicated in inflammatory processes and the pathogenesis of various human disorders. Drugs inhibiting the production or maturation of TNF_a may have excellent therapeutic potential constituting an interesting alternative to classical cyclooxygenase inhibitors in these pathologies. Collin and co workers[73] synthesized a new series of *N*-pyridinyl (alkyl)phthalamides and evaluated their in vitro activity in the inhibition of TNF_a. Eleven of these phthalamides were tested for their antiedematous effect in the phorbol-12-myristate-13-acetate (PMA)-induced mouse-ear edema. The tested compounds were administered orally at a dose of 0.4 mM/kg to male Swiss mice. The percentage of inhibition of the inflammatory reaction was determined for each animal by the comparison of ear edema in

Table 53. Biological Data[72] and Physicochemical Parameters Used for Deriving Eq 58



No	X	R	calcd. logPMAE%	ΔlogPMAE%	obsd. logPMAE%	$\Sigma\pi_X$
1	H		1.81	0.03	1.84	0.00
2	H		1.81	0.00	1.81	0.00
3	5-F		1.79	-0.05	1.75	0.14
4[a]	4,5,6,7-F_4		1.75	0.10	1.85	0.56
5	4-NO_2		1.84	0.08	1.92	-0.28
6	5-NO_2		1.84	-0.02	1.82	-0.28
7	4-NH_2		1.95	-0.05	1.90	-1.23
8	5-NH_2		1.95	0.02	1.97	-1.23
9	5-F		1.79	-0.02	1.77	0.14
10[a]	4,5,6,7-F_4		1.75	0.23	1.98	0.56
11[a]	4,5,6,7-F_4		1.75	0.15	1.90	0.56

[a] Data omitted from derived equation.

treated and nontreated animals. We formulated eq 58.

$$\log\text{PMAE\%}(0.4) = -0.113(\pm 0.074)\sum\pi_X + 1.810(\pm 0.047) \quad (58)$$

$$n = 8;\quad r = 0.835;\quad r^2 = 0.696;\quad q^2 = 0.432;\quad s = 0.046;\quad F_{1,6} = 13.38;\quad \alpha = 0.05$$

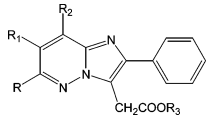
$$\text{Clog } P \text{ vs } \sum\pi_X = 0.734$$

It is not a sharp correlation, but it is an attempt to approach quantitatively the factors that effect the inhibition of mouse ear edema. The main reasons are (a) the lack of variance in PMAE% values (1.77−1.98), (b) the lack of variance in X and R substituents, and (c) the small number of data points (Table 53). $\Sigma\pi_X$, the sum of π lipophilic contribution for substituents X on the phenyl ring, is the most important parameter in the development of eq 58. However, the negative sign indicates that hydrophilicity (low lipophilicity) should be taken under consideration for this dataset. Three data points are omitted (**4**, **10**, and **11**).

4.44. 2-Phenylimidazo[1,2-*b*]pyridazine-3-acetic Derivatives

In continuation to previous studies,[73a−c] Sacchi and co-workers[74] synthesized a new series of 2-phenyl

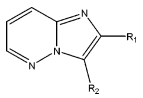
Table 54. Biological Data[74] and Physicochemical Parameters Used for Deriving Eq 59



no.	R	R_1	R_2	R_3	calcd log CPE%	Δlog CPE%	obsd log CPE%	$\sum MR_{(R+R_1+R_2)}$	B_{1R}
1[a]	H	H	H	C_2H_5	1.23	0.41	1.64	0.31	1.00
2	Cl	H	H	C_2H_5	1.35	−0.03	1.32	0.81	1.80
3	OMe	H	H	C_2H_5	1.72	0.05	1.77	0.99	1.35
4	H	Me	H	C_2H_5	1.67	0.04	1.71	0.77	1.00
5	H	H	Me	C_2H_5	1.67	−0.02	1.64	0.77	1.00
6	Cl	Me	H	C_2H_5	1.79	−0.15	1.64	1.27	1.80
7	Cl	H	Me	C_2H_5	1.79	−0.08	1.71	1.27	1.80
8[a]	H	H	H	H	1.23	0.59	1.82	0.31	1.00
9	Cl	H	H	H	1.35	0.03	1.38	0.81	1.80
10	OMe	H	H	H	1.72	0.08	1.81	0.99	1.35
11[a]	H	Me	H	H	1.67	−0.27	1.40	0.77	1.00
12	H	H	Me	H	1.67	−0.09	1.58	0.77	1.00
13	Cl	Me	H	H	1.79	0.09	1.88	1.27	1.80
14	Cl	H	Me	H	1.79	0.09	1.88	1.27	1.80

[a] Data omitted from derived equation.

derivatives with the replacement of the carboxylic moiety in position 3 by an acetic group.



The new molecules were tested in vivo at 40 mg/kg po using carrageenan-induced rat paw edema to study the anti-inflammatory activity. Equation 59 was derived from the datapoints listed at Table 54.

$$\log \text{CPE\%} = 0.950(\pm 0.380)\sum MR_{(R+R_1+R_2)} - 0.441(\pm 0.238)B_{1R} + 1.376(\pm 0.309) \quad (59)$$

$$n = 11;\quad r = 0.899;\quad r^2 = 0.808;\quad q^2 = 0.667;\quad s = 0.089;\quad F_{2,8} = 16.95;\quad \alpha = 0.01$$

$$\text{Clog } P \text{ vs } \sum MR_{(R+R_1+R_2)} = 0.175;\quad \text{Clog } P \text{ vs } B_{1R} = 0.141;\quad \sum MR_{(R+R_1+R_2)} \text{ vs } B_{1R} = 0.442$$

Sum of molar refractivity of substituents R, R_1, and R_2 ($\sum MR_{(R+R_1+R_2)}$), a measure of volume with a positive sign, indicates that the larger $\sum MR_{(R+R_1+R_2)}$ promotes the anti-inflammatory activity. B_{1R}, the sterimol parameter for the smallest width for the first atom of substituents R, has a negative sign indicating that steric interaction at the R substituent of the aromatic ring is unfavorable. Both parameters do not cover a lipophilic effect. No collinearity problem exists. Three compounds are omitted (**1**, **8**, and **11**), and for two of them (**1** and **8**, Table 54), the biological activities are higher than predicted. Also, these two derivatives have low $\sum MR_{(R+R_1+R_2)}$ and B_{1R} values for their substituents.

4.45. 1-(Pyrimidin-2-yl)-3-pyrazolin-5-ones and 2-(Pyrimidin-2-yl)-1,2,4,5,6,7-hexahydro-3*H*-indazol-3-ones[75]

The literature indicated that many pyrazole and indazole derivatives have found their clinical application of NSAIDs. Several related pyrazolidine-3,5-diones, pyrazolidi-3-ones, and pyrazolidi-5-ones are also available as NSAIDs. With regard to the anti-inflammatory indazoles, the literature survey indicated that some of them are clinically useful as topical NSAIDs. Thus, Badawey et al.[75] decided to investigate the possible anti-inflammatory activity of some related 1-(pyrimidin-2-yl)-2-pyrazolin-5-ones. The compounds were evaluated by the rat dextran-induced paw edema at 50 mg/kg po. Equation 60 was derived (Table 55).

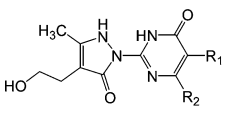
$$\log \text{CPE\%} = -0.696(\pm 0.399)\pi_{R_2} - 0.447(\pm 0.244)B_{5R_1} + 2.270(\pm 0.705) \quad (60)$$

$$n = 9;\quad r = 0.887;\quad r^2 = 0.786;\quad q^2 = 0.574;\quad s = 0.260;\quad F_{2,6} = 11.03;\quad \alpha = 0.01$$

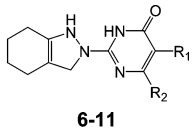
$$\text{Clog } P \text{ vs } \pi_{R_2} = 0.007;\quad \text{Clog } P \text{ vs } B_{5R_1} = 0.002;\quad \pi_{R_2} \text{ vs } B_{5R_1} = 0.552$$

Hydrophilicity as π_{R_2} values, the hydrophobic contribution of substituent R_2, should be taken under consideration as an important variable for this dataset. B_{5R_1} is the largest width for the first atom of substituents R_1, and it is the most significant parameter. The negative sign indicates an unfavorable steric effect at the R_1 position of the pyrimidinyl ring. No role for the nature of the pyrazolin/indazolinyl rings was found; no indicator assigned for the presence/absence of these rings was found to be significant. It is seen that B_{5R_1} and π_{R_2} are slightly collinear (0.552). Equation 60 is not a sharp one. The main reason is the difference between the experimental PE% values, which is very low (0.42−1.68); a lack of precision in experimental techniques can occur. Also, there are two parameters for nine data points, and two data points (**3** and **10**) are rejected. Both are most active compared to the rest, and compound **10** especially presents the highest B_{5R_1} value.

Table 55. Biological Data[75] and Physicochemical Parameters Used for Deriving Eq 60



1-5



6-11

no.	R_1	R_2	calcd log CPE%	Δlog CPE%	obsd log CPE%	π_{R_2}	B_{5R_1}
1	COOH	H	1.08	0.38	1.46	0.00	2.66
2	H	CH_3	1.43	0.16	1.60	0.56	1.00
3[a]	H	C_6H_5	0.46	1.19	1.65	1.96	1.00
4	n-C_4H_9	OH	0.71	−0.29	0.42	−0.67	4.54
5	C_6H_5	OH	1.35	−0.11	1.24	−0.67	3.11
6	COOEt	H	0.30	0.12	0.42	0.00	4.41
7	COOH	H	1.08	−0.06	1.02	0.00	2.66
8	H	CH_3	1.43	−0.31	1.12	0.56	1.00
9	H	C_6H_5	0.46	−0.04	0.42	1.96	1.00
10[a]	n-C_4H_9	OH	0.71	0.97	1.68	−0.67	4.54
11	C_6H_5	OH	1.35	0.15	1.50	−0.67	3.11

[a] Data omitted from derived equation.

5. Conclusion—Overview

The QSAR analysis presented here is an attempt to organize the knowledge about the anti-inflammatory agents. Since inflammation is a complex phenomenon involving interrelationships between humoral and cellular reactions through a number of inflammatory mediators, there is not much evidence on QSAR studies. The common mechanism of action of this broad class of drugs is believed to be the inhibition of the enzyme cyclooxygenase. Aspirin and other NSAIDs exhibit their effect by inhibiting COX enzymes and by blocking the synthesis of proinflammatory prostaglandins.[76,77] There is a high degree of conservation among the residues that line the COX active site, but subtle differences exist that are critical for selective binding of inhibitors. The central channel of COX-2 is larger than that of COX-1. This overall larger size may also reduce steric and ionic crowding by the charged Arg120 in COX-2 and thus preferentially increase binding of nonacidic NSAIDs by this isozyme.[78−81] The COX active site narrows at the top into a channel that opens to the surface near the dimer interface. The peroximal end of this channel appears to bind the ω end of arachidonate.

Recently Hansch and co-workers[82] reported their comparative QSAR studies on human COX-1 and COX-2 inhibitors. Many of the QSAR equations have linear log P terms. The role of lipohilicity is also brought out by equations that have parabolic Clog P terms. Sterimol parameters (B_1, B_5, and L) occur in many of these reported QSARs. For lipoxygenase (LOX), another enzyme that is implicated in the arachidonic acid cascade and inflammation, a QSAR study on LOX inhibitors has been published.[83a,b] Linear log P terms, as well as parabolic and bilinear equations with Clog P, have been reported.

We thought that it would be helpful to take these results into consideration and use them in our analysis of the anti-inflammatory QSAR. The equations generated by QSAR analysis are an indication of the properties of the substituent groups that make a particular molecule a better or worse inhibitor. This analysis yielded certain substituent properties that appear to have a significant effect on the anti-inflammatory capacity of the parent structure.

One of the most difficult problems in QSARs is the "outliers", the congeners that are "misfit" in the final equation. It could be associated with one of the following reasons:

- the mathematical model of the equation;
- outliers may be due to what seem to be congeners, but are not;
- compounds within a dataset may have different metabolic rates;
- poor quality of the experimental data;
- the used parameters may not be the best.

Forty-three datasets including in vivo results have been analyzed. A serious limitation to a QSAR study using in vivo data is the assumption that all the compounds have the same or similar oral pharmacokinetics, a factor dependent upon gastrointestinal absorption, drug metabolism, distribution, and total clearance. A solution to the problem is a pharmacokinetic analysis to be conducted on a small sample of selected compounds. In the development of a QSAR, four types of properties contribute: hydrophobic, electronic, steric, and polarizability. It is desirable to consider variation in these properties of substituents at each position of the parent structure in each series.

Inspection of the q^2 values suggests that in some cases "something else is going on". The negative or very low q^2 values in eqs 10, 13, 14, 43, 45, 47, 48, and 51 would clearly signal that these QSARs should either be discarded or examined more closely. They are intermediate QSARs, not believed to be "true" hypotheses. The low q^2 is a direct indication that these QSAR are less likely to have predictive character. It is assumed that these findings will help the corresponding researchers in their design and synthesis.

Our study shows that in 13 out of 60 cases Clog P plays a significant part in the QSAR of the anti-inflammatory agents. Also, in 4 out of 13 cases Clog P with a negative sign seems to be more important. Although it would be desirable to have more experimental values, log P calculated by the Clog P program is suitable for QSAR studies.

Although, the substituent variations are not nearly as good as they should be, it appears that many of the molecules must be interacting with a hydrophobic space in a nonspecific way (slope 0.6 $\pm$ 0.1). The nature of the hydrophobic binding surface is hard to picture. It has been observed[84] that entities binding to a more or less flat surface produce QSAR with log P or π coefficients of about 0.5, while engulfment into a crevice or pocket yields values of about 1.[85] It may be that the character of the surface is more significant than its shape. It is obvious that the substitution with chemical substituents that increase either the hydrophilicity or the hydrophobicity, associated with steric interactions due to the introduction of bulky substituents, produces potent anti-inflammatory compounds.

The existence of only linear correlation between activity and log P values was not great enough to establish the upper limit for the rate of penetration. Equations showing only a linear relationship of anti-inflammatory activity with log P may be interpreted as indicating a situation where the maximum activity had not been reached. The negative coefficient with Clog P indicates lack of hydrophobic terms.

The negative Clog P term in eqs 4, 44, 46, and 55 is significant and implies that activity could be improved by making less hydrophobic derivatives. Equations 12, 17, 28, and 55 have a linear $\sum\pi$ term that implies that activity could be increased by the use of more hydrophobic substituents. The role of hydrophobicity is also brought out by eqs 5, 10, and 39, which have parabolic Clog P terms with optimum Clog P values of 2.49. It is interesting to compare the Clog P values for two commercial drugs now on the market (rofecoxib (Vioxx) with 1.8 and celecoxib (Celebrex) with 4.4). The drugs appear to have comparable therapeutic value but the standard dose of rofecoxib is 12.5−25 mg/day, whereas that for celecoxib is 200 mg/day. It seems that this difference is due to bioavailability. A few years ago, it was found that a log P of ~2 should be ideal for general access to all parts of the body.[82] Thus, a principle of minimal hydrophobicity in drug design is suggested. It must be kept in mind that Clog P accounts for two things, hydrophobic interaction between ligands and the receptor and the random walk process in organisms from site of injection to the site of action. It is of interest that in a number of instances the COOH function is present and is well fit even though the Clog P values are for the neutral form. Hence, it would seem that these functions do not contact the COX enzyme.

Steric factors are obviously important. MgVol and CMR are two physicochemical parameters expressing the overall volume/size of the molecules. Altough MgVol is purely a prediction of the size of the molecule, CMR also represents the size with a correction for polazibality (as we have shown in the results section). Considering MgVol only, eq 16 has this term with a negative sign. Negative CMR appears in QSARs 1 and 7. In QSARs 2 and 6, we found parabolic correlations with CMR, which give optimum values of 12.82 and 17.20. The above 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.

Negative contribution for the molar refractivity of substituents was also found in eqs 14, 29, 38, 49, 55, and 57. It is commonly assumed in QSAR studies that when CMR/MR appears with positive sign, it indicates favorable polar interactions. The presence of steric terms suggest that a protein is involved. Thus, coefficients with steric terms may reflect the complex process of displacement of the ligand. The negative steric terms (CMR, MR, E_{s_4}) imply that the critical effects are occurring on (in) an active site on a macromolecule.

In the cases where no role for lipophilicity was found, for example, eqs 19, 25, 28, 29, 32, 33, 35, 41, 42, 45, 52, and 54, there was a considerable collinearity problem, an overlap between substituent bulk and hydrophobicity (a most common problem in drug development). This overlap sometimes makes it difficult to separate steric and hydrophobic effects. Clearly there are in the limit two kinds of surfaces in proteins as well as in enzymes, hydrophobic and hydrophilic, for which the three parameters log P, MgVol, and MR would appear to correlate ligand interactions when steric and electronic factors can be set aside.

Confusion arises in the role of heteroatoms, which confer different degrees of specificity terms in potency and in the quality of the biological response. The most common structural elements of clinically active drugs against inflammation appeared to be a nitrogen or a sulfur heteroatomic system bearing one or two phenyl rings and at least one carbonyl group. From our present review, the heterocycles confer different degrees of specificity in terms of potency and in the quality of the biological response, which have not been delineated.

For some structural features, eqs 35 and 37, we had to use indicator variables as a device to account for the effect of a specific feature that cannot be accounted for by a more specific parameter.

Electronic parameters, indicative of dipole−dipole or charge-dipole interactions, charge-transfer phenomena and hydrogen bond formation, are not found to govern anti-inflammatory activity. In eqs 10, 15, 18, 47, 48, 57, and 58, the activity was shown to have a significant dependence on Hammett's σ constant, which represents the effect of charge−charge or charge−dipole interactions of compounds.

Hansch and co-workers[84] were not able to define the major differences in the physicochemical properties of the molecules showing COX-2 inhibitory activity over COX-1, since they did not have inhibitory data for COX-1 for all of the sets reported for COX-2. At this point, it is not possible to obtain a definitive answer and to draw an conclusions or point out the difference on the basis of the limited information and QSAR reported here, as we also did not have inhibitory data for COX-1/-2 for all of the sets reported for in vivo anti-inflammatory activity. It will be helpful to explore derivatives with a wider spread in substituents to study the steric and electronic effects.

The only thing that can be said for sure now is that there is a similarity in terms of the requirement for hydrophobicity and size of the molecules for both COX-1 and COX-2 receptors.

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7. Note Added after ASAP Publication

This article was published ASAP on August 17, 2005. The corresponding author footnote and the

variables under eq 13 were added. The article was reposted on August 31, 2005

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