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A quantitative structure–activity relationship analysis of a series of 2'-(2,4-difluorophenoxy)-4'-substituted methanesulfonilides

WW Wilkerson

Du Pont Merck Pharmaceutical Company, Chemical and Physical Sciences Research, Experimental Station E353/347, PO Box 80353, Wilmington, DE 19880-0353, USA

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Summary — A series of antiinflammatory 2'-(2,4-difluorophenoxy)-4'-substituted methanesulfonilides was subjected to quantitative structure–activity relationship (QSAR) analysis. The result of the study showed that the oral antiinflammatory activity, as determined in the rat adjuvant arthritis model, was highly correlated with the electronic (σ_I) and steric (Sterimol B1) effects exhibited by the 4'-substitution (R). The relationship can be expressed by the following regression equation: log (% paw edema inhibition) = $1.073(0.304)\sigma_I + 1.019(0.259)B1 - 2.001(0.411)$.

antiinflammatory activity / structure–activity relationship / methanesulfonilide

Introduction

Extensive research efforts in our laboratories have been committed to finding novel non-steroidal compounds for the treatment of inflammatory diseases such as arthritis [1–6]. Because of our interest in various structural types and possible mechanisms of action of new potential treatments for inflammatory diseases, we chose to subject a set of the 2'-phenoxy-4'-substituted methanesulfonilides (**I**), as reported by Tsuji *et al* [7], (see also Nakamura *et al* [8]) to quantitative structure–activity relationship (QSAR) analysis (fig 1). These methanesulfonilides are analogues of nimesulide (**II**), which has been reported to have antiinflammatory-analgesic activity without gastrointestinal liability as determined in animal models [7, 9]. Tsuji *et al* [7] concluded that the best antiinflammatory activity was obtained when the R-group was 'electron-attracting'. We wanted to further understand the nature of this electronic effect, and the contribution to activity of other physiochemical properties such as lipophilicity and size. It is hoped that this study will contribute to a better understanding of the relationship between structure and antiinflammatory activity [10].

Method and data

The antiinflammatory data were taken from that of Tsuji *et al* [7], and the data were expressed as the 'per cent inhibition of adjuvant-induced paw edema in the rat caused by 10.0 mg/kg of drug (AA)'. For QSAR studies, we have converted the data to 'per cent paw edema inhibition per micromole of drug per kilogram of body weight (BA)'. The rat established adjuvant arthritis edema assay was a modification of that described by Winter *et al* [11–13]. Arrigoni-Martelli [14], and the references therein, have reported that the rat AA assay constitutes a delayed hypersensitivity response and may best represent autoimmune diseases (see also Shen [15]).

QSAR studies used the following parameters: substituent parameters π, MR, logMR, σ_p, σ_I, $\sigma_{res(0)}$, Taft E_s; the indicator variables for hydrogen bond acceptor (HBA) and donor (HBD); and the Sterimol parameters L1, B1, B2, B3, and B4 as reported [16–22]. We used logMR instead of MR in the regression analyses to bring the values in line with the numerical values of the other substituent parameters. Statistical methods were in accord with Havilcek and Crain [23] and Dowdy and Wearden [24]. The following statistical measures were used: n, the number of samples in the regression; r^2, coefficient of determination; r, correlation coefficient; se, standard error of the regression; and the F-ratio and the probability of finding a greater F-ratio were used to assess the statistical significance of the derived equations. In the regression equations, the numbers in parentheses are the standard error of the estimate for the derived coefficients.

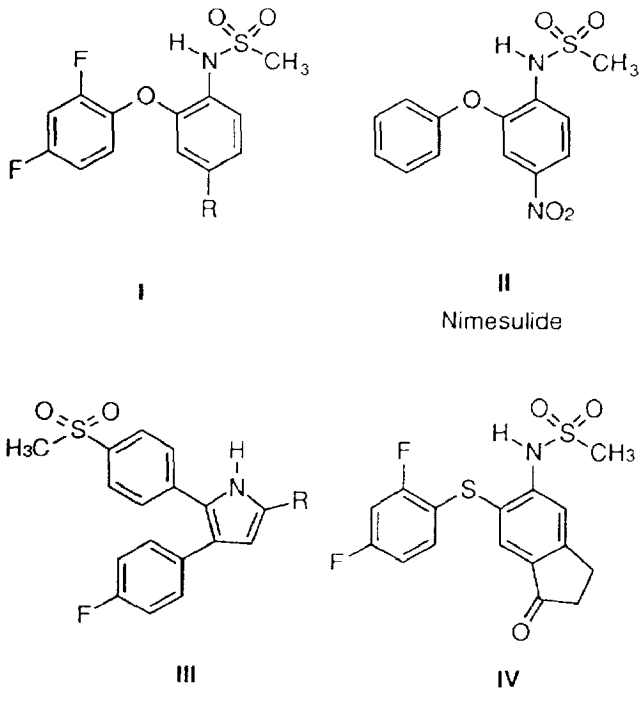


Fig 1. Analogues (**I**) of the antiinflammatory nimesulide (**II**), the antiinflammatory diaryl pyrroles (**III**), and the indanones (**IV**).

Discussion

The compounds in table I differed only in the nature of R, and except for **20** (R = H), were all *para*-substituted. The R-groups were classified as hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), or neither HBA nor HBD. Based on these observations, we attempted to understand the QSAR of this series of compounds by subjecting the compounds in tables I–II to multiple regression analysis using π, MR, logMR, σ_p, HBA and HBD. This analysis resulted in equation [1].

$$\log(BA) = 0.046(0.122)\pi + 0.489(0.365)\log MR + 0.842(0.314)\sigma_p + 0.111\ (0.292)HBA + 0.132(0.200)\ HBD - 0.801(0.265) \quad [1]$$

$n = 18$; $r = 0.780$; $se = 0.296$; $F = 3.728$; prob > F = 0.029

Statistically, equation [1] was considered to be a poor predictor of activity because of standard error in the coefficients and the F-ratio. The equation also violated the Topliss-Costello rule [25, 26]. Of the seven independent variables initially investigated, the greatest confidence was in σ_p (see table III). Single regression analysis using σ_p resulted in equation [2a]. Since $\sigma_p = \sigma_I + \sigma_R$, we made the substitution in equation [2a] to get equation [2b]. Clearly most of the electronic effect was inductive rather than resonance as shown in equations [2b–c].

$$\log(BA) = 0.852(0.264)\sigma_p - 0.205(0.108) \quad [2a]$$

n = 19; $r = 0.617$; $se = 0.314$; $F = 10.452$; prob > F = 0.005

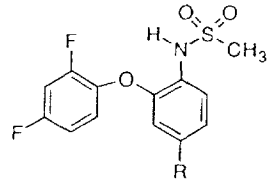
$$\log(BA) = 1.491(0.479)\sigma_I + 0.026(0.715)\sigma_R - 0.453(0.168) \quad [2b]$$

n = 14; $r = 0.751$; $se = 0.311$; $F = 7.103$; prob > F = 0.10

$$\log(BA) = 1.475(0.369)\sigma_I - 0.422(0.137) \quad [2c]$$

$n = 16$; $r = 0.730$; $se = 0.292$; $F = 15.941$; prob > F = 0.001

Table I. Structures and rat adjuvant arthritis data for compounds **1–20**.



Compound	*R*	*AA*[a]	*MW*	*BA*[b]	*log(BA)*
1	NO_2	100	344.292	3.44	0.537
2	CN	85	296.291	2.52	0.401
3	COMe	79	341.332	2.70	0.431
4	CONHMe	65	356.347	2.32	0.365
5	$CONH_2$	59	342.320	2.02	0.305
6	$CONMe_2$	59	370.374	2.19	0.339
7	CF_3	58	367.293	2.13	0.328
8	SO_2Me	58	377.380	2.19	0.340
9	CH=CHCOMe	55	367.370	2.02	0.305
10	SMe	49	345.381	1.69	0.228
11	CH=NOMe	48	356.347	1.71	0.233
12	CO_2Et	28	371.358	1.04	0.017
13	S-^{i}Pr	23	382.043	0.88	–0.056
14	CH=NOH	22	342.320	0.75	–0.123
15	SOMe	21	361.381	0.76	–0.120
16	COEt	20	355.359	0.71	–0.148
17	SH	20	331.354	0.66	–0.179
18	SEt	14	368.416	0.52	–0.288
19	Me	11	313.321	0.34	–0.463
20	H	3	299.294	0.09	–1.047

[a]Inhibition of paw edema in the rat adjuvant arthritis model at 10.0 mg/kg orally. [b]Per cent paw edema inhibition per micromole of drug per kilogram of body weight.

Table II. Aromatic substituents constants for compounds **1–20**.

Compound	*R*	*log(BA)*	π	*MR*	*logMR*	σ_p	*HBA*	*HBD*
1	NO_2	0.537	–0.28	7.36	0.867	0.78	1	0
2	CN	0.401	–0.57	6.33	0.801	0.66	1	0
3	COMe	0.431	–0.55	11.18	1.048	0.50	1	0
4	CONHMe	0.365	–1.27	14.57	1.163	0.36	1	1
5	$CONH_2$	0.305	–1.49	9.81	0.992	0.36	1	1
6	$CONMe_2$	0.339	–1.51				1	0
7	CF_3	0.328	0.88	5.02	0.701	0.54	0	0
8	SO_2Me	0.340	–1.63	13.49	1.130	0.72	1	0
9	CH=CHCOMe	0.305	–0.06	21.10	1.324	–0.01	1	0
10	SMe	0.228	0.61	13.82	1.141	0.00	1	0
11	CH=NOMe	0.233	0.40	15.73	1.197	0.30	1	0
12	CO_2Et	0.017	0.51	17.47	1.242	0.45	1	0
13	S-*i*Pr	–0.056		24.12	1.382	0.07	1	0
14	CH=NOH	–0.123	–0.38	10.28	1.012	0.10	1	1
15	SOMe	–0.120	–1.53	13.70	1.137	0.49	1	0
16	COEt	–0.148	0.06	15.83	1.199	0.48	1	0
17	SH	–0.179	0.39	9.22	0.965	0.15	0	1
18	SEt	–0.288	1.07	18.42	1.265	0.03	1	0
19	Me	–0.463	0.56	5.65	0.752	–0.17	0	0
20	H	–1.047	0.00	1.03	0.013	0.00	0	0

We were convinced that the lipophilicity and/or the size of the compounds must have some meaningful effect on activity. However, the data in table III did not indicate any significant contribution. Stepwise multiple regression analysis using σ_I, π and logMR produced equation [3a]. As can be seen in equations [3b–c], and their statistical characterization, logMR was a better (?) contributor to activity than π.

$$\log(BA) = 0.015(0.099)\pi + 0.430(0.268)\log MR + 1.326(0.433)\sigma_I - 0.797(0.255) \quad [3a]$$

$n = 14$; $r = 0.810$; $se = 0.290$; $F = 6.374$; prob > F = 0.011

$$\log(BA) = -0.026(0.097)\pi + 1.426(0.435)\sigma_I - 0.412(0.153) \quad [3b]$$

$n = 15$; $r = 0.730$; $se = 0.314$; $F = 6.862$; prob > F = 0.010

$$\log(BA) = 0.369(0.229)\log MR + 1.341(0.355)\sigma_I - 0.759(0.230) \quad [3c]$$

$n = 15$; $r = 0.803$; $se = 0.270$; $F = 10.859$; prob > F = 0.002

These results suggested that we investigate other size or steric parameters. We first investigated the Taft E_s parameter by adding it to equation [2c] to produce equation [3d]. Though the correlation was improved, the *se*, *F*-value and *n* associated with the equation were not acceptable.

$$\log(BA) = 0.049(0.054)E_s + 1.825(0.491)\sigma_I - 0.516(0.187) \quad [3d]$$

$n = 8$; $r = 0.857$; $se = 0.331$; $F = 6.911$; prob > F = 0.036

$$\log(BA) = 0.062(0.147)L1 + 1.411(0.425)B1 - 0.507(0.251)B2 + 0.255(0.167)B3 - 0.170(0.188)B4 + 0.813(0.352)\sigma_I - 1.984(0.449) \quad [3e]$$

$n = 16$; $r = 0.920$; $se = 0.209$; $F = 8.249$; prob > F = 0.003

Equation [3e] was a very good predictor of activity, but the equation contained six parameters that would suggest an *n* of 30 to avoid a chance correlation [25, 26]. The correlation matrix (table IV) also showed that L1 and B4, B1 and B2, and B3 and B4 were

Table III. Correlation matrix for the parameters in equation [1].

	log(BA)	π	*logMR*	σ_p	*HBA*	*HBD*
log(BA)	1.000	–0.311	0.527	0.617	0.557	0.041
π		1.000	–0.081	–0.473	–0.414	–0.327
logMR			1.000	0.114	0.703	0.065
σ_p				1.000	0.368	–0.149
HBA					1.000	–0.036
HBD						1.000

Table IV. Correlation matrix for the parameters in equation [3e].

	log(BA)	σ_I	*L1*	*B1*	*B2*	*B3*	*B4*
log(BA)	1.00	0.73	0.35	0.75	0.46	0.53	0.30
σ_I		1.00	0.12	0.48	0.43	0.37	0.07
L1			1.00	0.54	0.30	0.43	0.86
B1				1.00	0.78	0.63	0.59
B2					1.00	0.68	0.50
B3						1.00	0.70
							1.00

Table V. Correlation matrix for the parameters in equation [4a].

	log(BA)	σ_I	*B1*
log(BA)	1.000	0.730	0.753
σ_I		1.000	0.481
B1			1.000

highly cross-correlated. Of the five Sterimol parameters, B1 was best single predictor of activity. Parameter B1 represents the minimum width of substituent (see Martin [27] and references therein). When B1 was added to equation [2c], equation [4a] resulted, which we felt was the best predictor for this series of anti-inflammatory compounds based on the substituent constants evaluated. The cross-correlation matrix for equation [4a] is shown in table V.

$$\log(BA) = 0.967(0.324)\sigma_I + 0.866(0.266)B1 - 1.735(0.417) \quad [4a]$$

$n = 16$; $r = 0.862$; $se = 0.225$; $F = 18.733$; prob > F = 0.000

The addition of the hydrogen bonding indicator variables (HBA and HBD) to equation [4a] produced equation [5], which was not an improvement. Seventeen of the R-groups were HBA (1,0), four were classified as HBD (0,1) (SH), and three were neither (0,0). Generally, the more active compounds had R-groups that were hydrogen bond acceptors. These parameters were not considered essential to the QSAR calculations and were not considered further.

Table VI. Parameters for QSAR analysis for compounds **1–20**.

Compound	*R*	σ_I	*B1*	*Found log(BA)*	*Calcd log(BA) eq [4a]*	*Calcd log(BA) eq [4b]*	*Found AA*	*Calcd AA eq [4a]*	*Calcd AA eq [4b]*
1	NO_2	0.76	1.70	0.537	0.472	0.546	100	86	102
2	CN	0.53	1.60	0.401	0.163	0.198	85	49	53
3	COMe	0.30	1.90	0.431	0.200	0.257	79	46	53
5	$CONH_2$	0.28	1.60	0.305	–0.079	–0.070	59	24	25
6	$CONMe_2$	0.28	1.90	0.339	0.181	0.235	59	41	46
7	CF_3	0.40	1.98	0.328	0.366	0.445	58	63	76
8	SO_2Me	0.59	2.11	0.340	0.662	0.782	58	122	160
10	SMe	0.25	1.70	0.228	–0.022	–0.001	49	28	29
12	CO_2Et	0.21	1.90	0.017	0.113	0.160	28	35	39
13	S-*i*Pr	0.26	1.70	–0.056	–0.012	0.010	23	25	27
14	CH=NOH	0.20	1.60	–0.123	–0.157	–0.156	22	20	20
15	SOMe	0.49	1.60	–0.120	0.124	0.155	21	37	40
17	SH	0.26	1.70	–0.179	–0.012	0.010	20	29	31
18	SEt	0.25	1.70	–0.288	–0.022	–0.001	14	26	27
19	Me	–0.04	1.52	–0.463	–0.458	–0.495	11	11	10
20	H	0.00	1.00	–1.047	–0.869	–0.982	3	5	3

Equation [4a]: $\log(BA) = 0.967\sigma_I + 0.866B1 - 1.735$, $r^2 = 0.742$.

$\log(BA) = 0.171(0.150)HBA + 0.107(0.147)HBD + 0.853(0.351)\sigma_I + 0.823(0.273)B1 - 1.775(0.426)$ [5]

$n = 16$; $r = 0.833$; $se = 0.226$; $F = 9.689$; prob > F = 0.001

The found and calculated results using equation [4a] are shown in table VI. The analysis of the residuals from equation [4a] indicated that **8** (R = SO_2Me) was an outlier to the regression. When **8** was removed from the regression, equation [4b] resulted. The reason for the differences seen for **8** is not known, but it was observed that it had largest B1 value (2.11) in the data set.

$\log(BA) = 1.073(0.304)\sigma_I + 1.019(0.259)B1 - 2.001(0.411)$ [4b]

$n = 15$; $r = 0.889$; se = 0.207; $F = 22.619$; prob > F = 0.000

The graphs in figures 2 and 3, and equation [4b], clearly show that increasing the inductive effects of the R-group increases antiinflammatory activity. The primary result is the increase in the acidity (lower p*K*a) of the sulfonamide hydrogen which has been reported by Rufer *et al* [28] to be important in controlling antiinflammatory activity and gastrointestinal toxicity. These data show that increasing B1 also resulted in increased activity. Applying equation [4b] to hypothetical compounds not reported by Tsuji *et al* [7] using all aromatic substituents where both σ_I and B1 were reported [16–22], 17 hypothetical compounds were predicted to be more potent than **1** (see table VII). Of the 17, six were considered to be too chemically reactive to be considered as drugs (R' = $^+NMe_3$, CBr_3, SF_5, CCl_3, IO_2, SO_2F), and two were too large (R' = CPh_3 and P = OPh_2). The remaining nine are listed in table VIII along with comparison compounds **1** and **20**. Five of the nine hypothetical compounds are related to **8** (R = SO_2Me) in that the R'-group contains a sulfonyl (SO_2) and they all have B1 = 2.11. It is possible that a study of this series might explain why **8** was considered an outlier in equation [4a]. The synthesis and biological evaluation of the proposed compounds in table VIII should also be a test of the validity of equation [4b]. The primary interest in this test of equation [4] would be the evaluation of the compound where R' = SO_2CF_3 ($\sigma_I = 0.78$ and B1 = 9.68) and R' = ^{t}Bu (σ_I = –0.07 and B1 = 2.59). These two compounds have very different electronic and steric effects which should indicate which of the two parameters is more important to oral antiinflammatory activity as determined in the rat adjuvant arthritis model.

Table VII. Compounds not in the regression analysis[a].

	R	*AA*[b]	*MW*	*BA*[c]	*log(BA)*
	C(Me)=NOMe	81	370.374	3.00	0.477
	$C(Me)=NNHCONH_2$	70	398.387	2.79	0.445
	C(Me)=NOH	61	356.347	2.17	0.337
	$COCH_2SO_2Me$	36	419.418	1.51	0.179
	C(Me)=NOEt	17	384.401	0.65	–0.185
	$COCH_2SMe$	13	387.419	0.50	–0.298
	$CON(CH_2)_2NMe$	9	425.454	0.38	–0.417
	$C(Me)=NNHCSNH_2$	–3			
	CONH(OMe)	–9			
21	CO_2H	–13			
22	CHO	–16			
23	COPh	–30			

[a]Required parameters not available in the literature. [b]Inhibition of paw edema in the rat adjuvant arthritis model at 10.0 mg/kg orally. [c]Per cent paw edema inhibition per micromole of drug per kilogram of body weight.

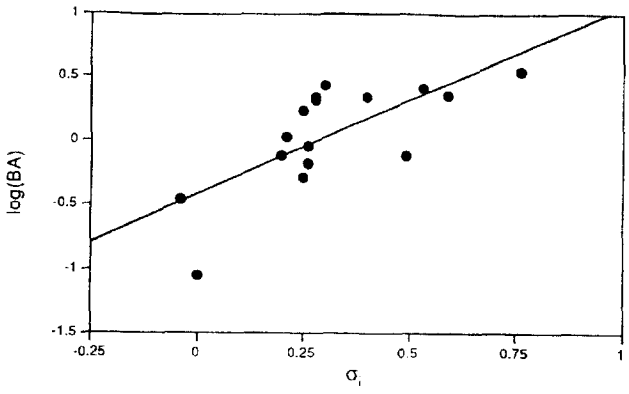


Fig 2. Activity (log BA) as a function of induction (σ_I). (●) $y = 1.475x - 0.422$; $r = 0.730$.

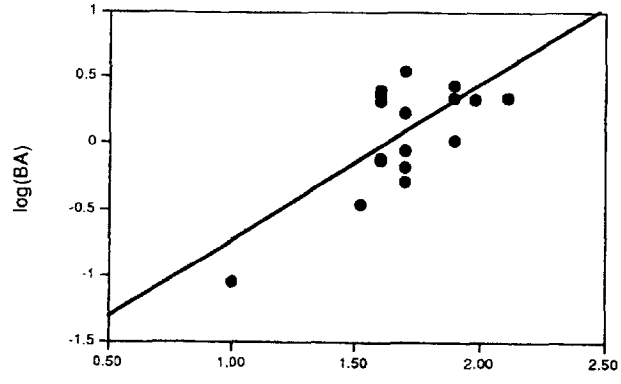
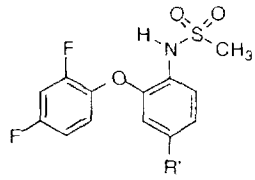


Fig 3. Activity (log BA) as a function of steric effects (Sterimol B1). (●) $y = 1.168x - 1.899$; $r = 0.691$.

Table VIII. Hypothetical 2'-(2,4-difluorophenoxy)-4'-substituted methanesulfonilides based on equation [4b].



R'	σ_I	*Sterimol B1*	*Calcd BA from eq [4]*[a]
(**1**)NO_2	0.76	1.70	3.52
(**20**) H	0.00	1.00	0.10
$C(Ph)_3$	0.25	4.84	1582.01
$SO_2(CF_3)$	0.78	2.11	9.68
SO_2Et	0.60	2.11	6.21
SO_2Ph	0.56	2.11	5.62
SO_2NH_2	0.46	2.11	4.39
I	0.39	2.19	4.15
C(=O)Ph	0.20	2.36	4.15
SO_2NMe_2	0.42	2.11	3.98
^{t}Bu	–0.07	2.59	3.66

[a]Per cent paw edema inhibition per micromole of drug per kilogram of body weight.

It was interesting to observe that the antiinflammatory activity (log BA) of the methanesulfonilides (**I**) in this study, as expressed in equation [4b], contained parameters for inductive (electronic) (σ_I) and steric effects (Sterimol B1) that were similar to the electronic ($\mathcal{F}$) and steric effects (MR) observed for the antiinflammatory diaryl pyrroles (**III**) as expressed in equation [6] below [2].

$$-\log(AA) = -4.415(0.515)\mathcal{F} - 0.187(0.021)MR + 2.789(0.390) \quad [6]$$

(Note that BA is expressed as '% paw edema inhibition/μM/kg' and AA is expressed as 'ED_{50} in μM/kg'.) In the absence of mechanism of action and pharmacokinetic data, the speculation is that these two sets of compounds may have the same site of action and/or may have similar absorption, distribution, and drug metabolism conditions.

The significance of B1 in equation [4b] may be questionable since there is 'little spread' in the values, and 12 of the 16 values in table VI range from 1.60 to 1.90 though the overall range was from 1.00 (R = H) to 2.11 (R = SO_2Me).

Additionally, there is a positive relationship between B1 and activity suggesting that an increase in substituent width results in increased activity when such steric factors often result in decreased activity. The absence of π in equation [4b] was also troubling since oral whole animal data would suggest that lipophilicity would be important for absorption and/or distribution of the drug. The π values for R ranged from –1.63 (R = SO_2Me) to +1.07 (R = SEt), a range comparable to other substituents investigated. Attempts to use other regressions to correlate activity with lipophilicity were also unsatisfactory: a parabolic relationship produced $r = 0.344$ ($se = 0.390$, $F_{2,16} = 1.075$); and a linear relationship produced $r = 0.344$ ($se = 0.379$, $F_{1,17} = 2.285$). Based on the size of the data set and the lack of a mechanism of action data, no definitive explanation could be made. It is possible, since the structural diversity of the data set is limited, that the pharmacokinetics is very similar and the major factors governing activity (electronic and steric) involve the interaction of the drug with the active site. As with the diarylpyrroles [2], oral antiinflammatory activity could be explained by electronic effects ($\mathcal{F}$) and steric effects (MR) (see equation [6]). However, recent studies on the diaryl pyrroles (**III**) show that oral antiinflammatory activity (–logAA) can also be explained by drug lipophilicity and dispersion, and the inhibition of cyclooxygenase-2 (COX-2) (Wilkerson, manuscript in preparation). Similar factors may be operating for the sulfonamides of this study. The B1 parameter was also addressed by Ford-Hutchinson *et al* [29] in their disclosure of a series of 5-methanesulfonamido-1-indanones (**IV**), which are orally active antiinflammatory COX-2 inhibitors.

Conclusion

The above studies have identified two parameters associated with the activity of this series of antiinflammatory sulfonamides, the electronic parameter σ_I and the steric parameter B1; the oral antiinflammatory was best described by equation [4b]. The QSAR results also suggest that other more potent analogues are possible. In the absence of mechanism of action information and pharmacokinetic data, care should be used in the application of this study. However, the compounds are orally active in a classical model of inflammation, and the extent of this activity can be explained by a regression equation with parameters that are consistent with previous reports [10].

Recently, a distinct prostaglandin endoperoxide synthase was found whose expression was induced by mitogens and inflammatory mediators and repressed by glucocorticoids [30–35]. There is about 60% amino-acid homology between prostaglandin endoperoxide synthase-1 and synthase-2. Both enzymes carry out the same cyclooxygenase and peroxidase activities [37], but the difference in amino-acid sequence allows the potential for selective inhibition [37, 38]. Because

of the reported gastrointestinal safety in laboratory animal models, it is possible that these 2'-(2,4-difluorophenoxy)-4'-substituted methanesulfonilides (**I**) [7], as well as the diaryl pyrroles (**III**) [2], may be acting as selective prostaglandin endoperoxide synthase inhibitors.

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