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Quantitative structure-activity relationship study of benzylsulfanyl imidazoles as cytokine release inhibitors

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Abstract

Benzylsulfanyl imidazole derivatives (Figure 1) have shown their ability to inhibit the release of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) from peripheral blood mononuclear cells or human whole blood. Such anticytokine actions of these congeners are quantitatively studied using Fujita-Ban and Hansch type analyses. The Fujita-Ban study resulted in the contributions of different substituents and the parent moiety for the inhibitions of cytokines TNF-α and IL-1β. The substituents that have a higher positive contribution to the given activity, relative to substituents of the parent moiety at different positions were then used to obtain a trend for the active analogues. None of the substituents present at *X*, *Y*, 2-*R* and 3-*R*, appears to be advantageous over the substituents of the parent moiety for inhibition of both the cytokines. However, the substituents at 4-*R*, 5-*R* and 6-*R* help to improve the inhibitory actions of the compounds for both cytokines. The optimal activities seem to be manifested by compounds in which 4-*R*, 5-*R* and 6-*R* are substituted respectively by OH (or $SOCH_3$ and SO_2CH_3), Cl and OH for inhibition of TNF-α, whereas by $SOCH_3$ (or SO_2CH_3 and OH), H and OH for inhibition of IL-1β. The Hansch type analysis, on the other hand, revealed that the F-substituents of the X-position and a less bulky structural moiety such as $-S(CH_2)_2-$ at the Y-incision are advantageous in improving the inhibitory action towards TNF-α. Similarly, a less bulky/polar substituent present at 2-*R* and not having a hydrogen-bond donor property, while a more hydrophobic substituent at 3-*R* and hydrogen-bond acceptor substituent at 4-*R* are helpful in augmenting inhibitory activity of a compound. However, for inhibition of cytokine IL-1β, it emerged that the *X*-substituents that transmits a higher negative resonance effect, the *Y*-substituent that offers less molecular bulk are beneficial. The *R*-substituents, being more electron donors at the meta-position, less hydrophobic at the *para*-position and offering smaller refractivity (less bulky and or polar) at the *ortho*-position are likewise helpful in improving the activity of a compound.

Keywords: *Benzylsulfanyl imidazole derivatives, Cytokine inhibition activity, QSAR analysis, Fujita-Ban and Hansch approaches, Physicochemical properties, substituent selection in drug design*

Introduction

The antibody Inflizimab and the fusion protein Etanercept were successfully shown to have efficacy in the treatment of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) by reducing the synovial and circulating blood levels of tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine [1,2]. Therapeutic use of both of these antibodies on a large scale is, however, limited by high costs of therapy [3] and the disadvantages of protein drugs such as the lack of oral availability and a time-dependent loss of activity. Therefore, efforts in inflammation research were made to develop small molecular inhibitors of cytokine release [4,5]. One of the important drug target in this direction is provided by p38 MAP (mitogen–activated protein) kinase which is involved in the biosynthesis of pro-inflammatory cytokines interleukin-1β (IL-1β) and TNF-α [6]. Several small molecular inhibitors of p38 were shown to reduce effectively the release of both of these cytokines from human monocytes. Such compounds compete with ATP at the ATP binding site, which is located in the cleft between the two domains of p38 [7–9]. For a number of kinases, it has been found that upon binding of ATP, the triphosphate group is coordinated by one or two metal ions which are ligated by amino acids located in the phosphate binding ribbon [10].

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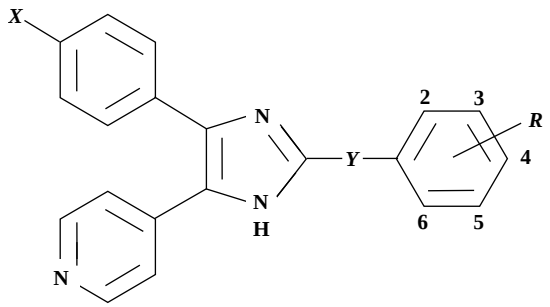

Figure 1. Structures of 2,4,5-trisubstituted imidazole derivatives.

Additionally, the phenolic functionality present on these inhibitors further enhances the interaction with this region of the enzyme. As a part of a research program to find novel and potent inhibitors of cytokine release, recently a series of benzylsulfanyl imidazoles differing in their respective substituents at the 2-position were prepared and tested on their ability to inhibit the release of TNF-α and IL-1β from peripheral blood mononuclear cells or human whole blood [11]. The structure-activity relationship (SAR) studies on these compounds were mainly concerned with the alteration of substituents at different positions of the parent moiety and provided no rationale to reduce the trial-and-error factors. Therefore, a quantitative SAR (QSAR) study on these congeners is carried out in the present communication so as to provide the rationale for drug-design and explore the possible mechanism of their interaction.

Materials and methods

The reported compounds [11] consisting of 2,4,5-imidazole derivatives are represented by a general structure, shown in Figure 1. These congeners with their biological effects are listed in Table I while the appropriate quantifying parameters of the different substituents used are given in Table II. The biological effects are expressed in terms of their ability to inhibit the release of tumor necrosis factor-α (TNF-α) and interleukin-β (IL-β) from peripheral blood mononuclear cells (PBMC) or human whole blood. Such effects, measured as the IC_{50} represents the concentration of a compound required to inhibit 50% of cytokine activity. For a given compound the same is expressed as $-\log IC_{50}$ on a molar basis in the present study.

Both the Fujita-Ban and the Hansch types of analyses were carried out on these compounds to derive a QSAR employing the method of multiple regression analysis (MRA). The Fujita-Ban analysis [12] based on an additivity principle is a non-parametric approach and requires, relatively, a larger data-set. In addition, the approach also requires certain group to occur two or more times at a given varying position in a molecule. The Hansch approach, on the other hand, is a parametric approach in which physicochemical or structural parameters are most commonly used as the correlative parameters. This method is generally used to increase the understanding of the mechanisms of action of a set of congeners and to direct drug design in a congeneric series as well as to attempt to predict biological activities quantitatively. In general, the approach is to set up the equations involving different combinations of the substituents constants, then to allow the correlative methods to aid in the selection of the 'best equation' justifying it statistically and avoiding chance correlations. For the present study, the most suitable quantifying parameters were found to be the

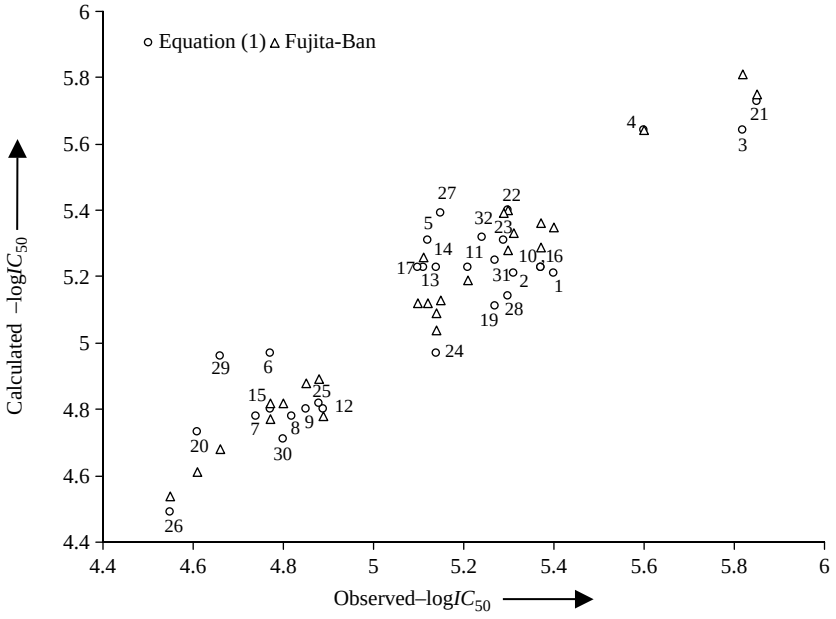

Figure 2. Plot of observed versus calculated $-\log IC_{50}$(TNF-α) values.

Table I. The cytokine release inhibitory activity of 2,4,5-trisubstituted imidazole derivatives (see Figure 1 for structure).

				$-\log IC_{50}$ (M)							
				TNF-α				IL-Iβ			
					Calcd				Calcd		
S. No.	X	Y	R	Obsd[a]	Eq(1)	F. B.	Prdctd	Obsd[a]	Eq(2)	F. B.	Prdctd
1	F	SCH_2	H	5.40	5.21	5.35	5.19	6.52	6.45	6.46	6.44
2	F	SCH_2	4-SCH_3	5.31	5.21	5.33	5.20	6.17	6.25	5.90	6.27
3	F	SCH_2	4-$SOCH_3$	5.82	5.64	5.81	5.61	6.60	6.94	6.79	7.00
4	F	SCH_2	4-SO_2CH_3	5.60	5.64	5.64	5.65	6.64	6.96	6.72	7.02
5	F	SCH_2	3-SCH_3	5.12	5.31	5.12	5.34	6.26	6.24	6.38	6.24
6	F	SCH_2	3-$SOCH_3$	4.77	4.97	4.77	5.04	5.85	5.75	5.80	5.72
7	F	SCH_2	2-SCH_3	4.74[b]	4.78	–	4.82	5.64[b]	5.81	–	5.97
8	F	SCH_2	2-$SOCH_3$	4.82[b]	4.78	–	4.74	6.00[b]	5.81	–	5.64
9	Cl	SCH_2	4-SCH_3	4.85	4.80	4.88	4.79	5.59	5.52	5.62	5.50
10	Cl	SCH_2	4-$SOCH_3$	5.37	5.23	5.36	5.21	6.59	6.21	6.51	6.16
11	Cl	SCH_2	4-SO_2CH_3	5.21	5.23	5.19	5.23	6.41	6.22	6.44	6.20
12	Br	SCH_2	4-SCH_3	4.89	4.80	4.78	4.78	5.52	5.59	5.39	5.61
13	Br	SCH_2	4-$SOCH_3$	5.11	5.23	5.26	5.25	6.15	6.28	6.28	6.30
14	Br	SCH_2	4-SO_2CH_3	5.14	5.23	5.09	5.25	6.19	6.30	6.21	6.31
15	H	SCH_2	4-SCH_3	4.77	4.80	4.82	4.81	4.40	4.94	4.77	5.25
16	H	SCH_2	4-$SOCH_3$	5.37	5.23	5.29	5.21	5.89	5.63	5.65	5.54
17	H	SCH_2	4-SO_2CH_3	5.10	5.23	5.12	5.25	5.72	5.64	5.59	5.62
18	F	SCH_2	4-OH	5.17[c]	–	–	–	6.43[c]	–	6.49	–
19	F	SCH_2	3-OH	5.27[b]	5.11	–	5.09	6.51[b]	6.28	–	6.27
20	F	SCH_2	2-OH	4.61	4.73	4.61	4.79	6.36	6.36	6.36	6.36
21	F	SCH_2	3-SCH_3, 4-OH	5.85	5.73	5.75	5.70	6.55	6.46	6.41	6.45
22	F	SCH_2	3-$SOCH_3$, 4-OH	5.30	5.40	5.40	5.45	5.74	5.96	5.83	6.03
23	F	SCH_2	3-SCH_3, 6-OH	5.29	5.31	5.39	5.31	6.32	5.24	6.39	6.24
24	F	SCH_2	3-$SOCH_3$, 6-OH	5.14	4.97	5.04	4.92	5.89	5.75	5.81	5.71
25	F	SCH_2	2-OH, 3-SCH_3, 5-Cl	4.88	4.82	4.89	4.78	6.19	6.15	6.15	6.15
26	F	SCH_2	2-OH, 3-$SOCH_3$, 5-Cl	4.55	4.49	4.54	4.43	5.52	5.66	5.56	5.70
27	F	$S(CH_2)_2$	4-$SOCH_3$	5.15	5.39	5.13	5.44	6.39	6.72	6.45	6.79
28	F	$S(CH_2)_3$	4-$SOCH_3$	5.30	5.14	5.28	5.01	6.66	6.51	6.59	6.43
29	F	$S(CH_2)_2$	H	4.66	4.96	4.68	5.01	6.19	6.21	6.13	6.23
30	F	$S(CH_2)_3$	H	4.80	4.71	4.82	4.64	6.19	6.01	6.26	5.90
31	F	CH_2CH_2	H	5.27[b]	5.25	–	5.25	6.82[b]	6.73	–	6.70
32	F	CH=CH	H	5.24[b]	5.32	–	5.34	6.89[b]	6.76	–	6.71

[a] Taken from Ref. 11; [b] Compound ignored in Fujita-Ban (F.B.) study; [c] 'Outlier' compound in present study.

hydrophobic (π), the electronic (σ), the resonance (R), the molar refraction (MR), the hydrogen—donor and –acceptor (HD and HA), the molecular weight (MW) and the van der Waals volume (V_W). Most of these parameters were taken from the literature [13], while the V_W was calculated using the method reported earlier [14–15]. In addition to these parameters the indicator variable, representing the presence or absence of certain structural characteristics, was also used. The final QSAR equations were further subjected to the validation test [16] by the leave-one-out (LOO) method. This method generates a number of modified data sets by eliminating one compound each time from the parent data set. In this way, one model is developed for each reduced data set and the response values of the eliminated observations are predicted from these models. The squared differences between predicted and actual values are added to give the predictive residual sum of squares, PRESS. Obviously, each observation of the parent data set contributes to PRESS. The cross-validated q^2 value is then calculated as (SSY-PRESS)/SSY, where SSY is obtained as the variance of the observed activities of compounds around their mean value. For a statistical reasonable QSAR model, q^2 should be greater than 0.6 and its value greater than 0.9 represents an excellent model.

Results and discussion

In formulation of the Fujita-Ban matrix, twenty-seven compounds of Table I were initially retained and compound 1 was taken as the parent congener. Five compounds (**7**, **8**, **19**, **31** and **32**) from this Table were, however, not included in the above training set as certain substituents in these five compounds occurred only once. The matrix consisting of 27 compounds (rows) and 15 substituents (including parent contribution) related to varying positions of the parent moiety (columns) is not documented here for the sake

Table II. QSAR parameters of the substituents in various positions in 2,4,5- trisubstituted imidazoles.

Position	Substituent	Parameter	
		R_X	I_X
X	H	0.00	0
	F	−0.34	1
	Cl	− 0.15	0
	Br	− 0.17	0
		$V_{WY}(10^{-2}Å^3)$	MW_Y
Y	SCH_2	0.410	0.460
	$S(CH_2)_2$	0.564	0.600
	$S(CH_2)_3$	0.718	0.740
		MR(2)	*HD*(2)
2-*R*	H	0.103	0
	OH	0.285	1
		$\pi(3)$	$\sigma(3)$
3-*R*	H	0.00	0.00
	SCH_3	0.61	0.15
	$SOCH_3$	− 1.58	0.52
		$\pi(4)$	HA(4)
4-*R*	H	0.00	0
	OH	− 0.67	1
	SCH_3	0.61	0
	$SOCH_3$	− 1.58	1
	SO_2CH_3	− 1.63	1

of brevity. The rows and columns of this matrix representing respectively the data-points and the independent variables while the activity values ($-\log IC_{50}$s for TNF-α and IL-1β; one at a time) being considered as the dependent variable were subjected to MRA. The resulting statistical parameters of the study corresponding to the inhibition of TNF-α were:

$$n = 27,\ r = 0.939,\ s = 0.178,\ F(15, 11) = 5.445$$

Here and in the follow up discussion *n*, *r*, *s* and *F* are respectively the number of data-points in the training set, multiple regression coefficient, standard error of estimate and *F*-ratio between the variances of calculated and observed activities. Except for the *r*-value, which accounts for 88% of variance ($r^2 = 0.882$), the remaining statistical parameters of the analysis are poorer to account for significant results. The abnormal behavior of certain compound present in the original data-set may be responsible for it. Compound **18** is such an identified compound whose calculated inhibition activity value (= 5.48) was found to be higher than the observed value. This is the only compound substituted singly with a polar 4-OH group at the benzylsulfanyl moiety. Though, a polar functionality is most favorable for the substituent of the 4-position in this aromatic ring, the presence of 4-OH group alone may, however, be least preferred. Perhaps the benzylsulfanyl ring with a 4-OH group is improperly oriented towards the receptor thereby leading it to participate weakly in the hydrogen bonding either through the hydrogen-donor or -acceptor property. As a result of such weak drug-receptor interaction, a smaller activity value is obtained for this congener. The data-point was, therefore, deleted further. In doing so, the corresponding row was removed from the Fujita-Ban matrix and the MRA of the remaining matrix lead to the results summarized in the first column of Table III. The data within the parentheses, associated to substituent contributions obtained, are the 95% confidence intervals. The much improved statistical parameters of the study are:

$$n = 26,\ r = 0.984,\ s = 0.096,\ F(15, 10) = 20.543$$

The r^2-value now accounts for 97% of the variance and the *F*-value stands significant at 99% level [$F_{15,10}(0.01) = 4.56$]. The calculated values of

Table III. Fujita-Ban contributions of substituents and parent moiety to the cytokine inhibitory activities of the title compounds.

Position	Substituent	Contribution to $-\log IC_{50}$ (M) for TNF-α ($n = 26$)	Contribution to $-\log IC_{50}$ (M) for IL-1β ($n = 27$)
Parent moiety	μ	5.352(± 0.13)	6.462(± 0.25)
X	H	−0.517(± 0.14)	−1.137(± 0.29)
	Br	−0.549(± 0.14)	−0.515(± 0.29)
	Cl	−0.449(± 0.14)	−0.279(± 0.29)
Y	$S(CH_2)_2$	−0.673(± 0.16)	−0.335(± 0.32)
	$S(CH_2)_3$	−0.531(± 0.16)	−0.200(± 0.32)
2-*R*	OH	−0.746(± 0.22)	−0.105(± 0.44)
3-*R*	SCH_3	−0.235(± 0.19)	−0.084(± 0.32)
	$SOCH_3$	−0.580(± 0.19)	−0.666(± 0.32)
4-*R*	OH	0.633(± 0.17)	0.030(± 0.29)
	SCH_3	−0.018(± 0.16)	−0.560(± 0.32)
	$SOCH_3$	0.455(± 0.13)	0.328(± 0.27)
	SO_2CH_3	0.290(± 0.16)	0.261(± 0.32)
5-*R*	Cl	0.516(± 0.28)	−0.126(± 0.53)
6-*R*	OH	0.270(± 0.17)	0.016(± 0.35)

$-\log IC_{50}$(TNF-α) for all the compounds in Table I are also in close agreement with the observed ones. Likewise, the Fujita-Ban matrix for 27 data-points and inhibition activity for cytokine IL-1β as the dependent variable on MRA revealed the following statistical parameters:

$$n = 27,\ r = 0.963,\ s = 0.203,\ F(15, 11) = 9.327$$

which accords to highly significant results. The r^2-value accounts for 93% of variance and *F*-value stands significant at 99% level [$F_{15,11}(0.01) = 4.25$]. The calculated activity values, listed in Table I, were in close agreement with the observed ones. The contributions of different substituents and that of the parent moiety obtained for the inhibitions of cytokines TNF-α and IL-1β are given in Table III. From this Table, the substituents that have a higher positive contribution to activity pertaining to either TNF-α or IL-1β, relative to substituents of the parent moiety at different positions may easily be obtained. None of the substituents present at *X*, *Y*, 2-*R* and 3-*R*, appears to be advantageous over the substituents of the parent moiety for inhibition of both the cytokines. However the substituents at 4-*R*, 5-*R* and 6-*R* contribute positively, certainly improve inhibitory actions of the compounds for both the cytokines. The appropriate substituents for varying positions, which have highest positive contribution to the parent moiety may be selected for the future design of more active analogues of the series. The optimal activities seem to be manifested by compounds in which 4-*R*, 5-*R* and 6-*R* are substituted respectively by OH (or $SOCH_3$ and SO_2CH_3), Cl and OH for inhibition of TNF-α, whereas by $SOCH_3$ (or SO_2CH_3 and OH), H and OH for inhibition of IL-1β.

It is important to note that the Fujita-Ban approach cannot extrapolate beyond the substituents of the training set whereas the Hansch approach, discussed below for the entire data-set, can do so. The earlier predicted 'outlier' compound **18** is still excluded in this approach. A number of physicochemical parameters for the *R*-substituents of the benzylsulfanyl moiety bonded at the 2-position of imidazole were selected in a systematic manner. A data-set consisting of substituent constants such as hydrophobicity, π, hydrogen-bond donor, *HD*, hydrogen-bond acceptor, *HA*, electronic (*meta* and *para*), σ, field, ***F***, resonance, ***R***, dipole moment, μ, Taft's steric, *Es*, molar refraction, *MR*, molecular weight, *MW* and van der Waals volume, *Vw* for each of five *R*-positions was considered for the compounds in Table I. Along with, a similar data-set for the *X*-substituents of the phenyl ring attached at the 4-position of imidazole was also considered but only *MR*, *MW*, *Vw* and the indicator variable, I_X were considered for structural features present in incision *Y*. In this way, a total number of 70 independent variables ($5 \times 11 + 11 + 4$) were then permuted appropriately for the varying positions and subjected to MRA. This resulted in a large number of QSAR equations, which were then subjected to different statistical tests. The correlation equation with a minimum number of independent variables having highest *r*- and *F*- values and lowest *s*-value was finally retained for further discussion. The most appropriate quantifying parameters that lead to most significant correlation equations are only included in Table II. The derived correlation for the compounds in Table I and parameters in Table II, is given by Equation (1)

$$\begin{aligned} &-\log IC_{50}(\text{TNF-}\alpha) \\ &= -0.341(\pm 0.15)MR(2) - 0.425(\pm 0.16)HD(2) \\ &\quad + 0.152(\pm 0.08)\pi(3) + 0.427(\pm 0.11)HA(4) \\ &\quad + 0.410(\pm 0.12)I_X - 1.639(\pm 0.58)V_{WY} + 5.511 \\ &n = 31,\ R = 0.914,\ s = 0.149, \\ &F(6, 24) = 20.175,\ q^2 = 0.732 \end{aligned} \tag{1}$$

where the indicator variable I_X highlights the presence of an F-substituent at the *X*-position in the phenyl ring. A value 1 or 0 for this variable indicates the presence or absence of an F-substituent in the *para*-position of the phenyl ring, bonded at the 4-position of imidazole. The statistical parameters obtained for Equation (1) indicated highly significant results and the equation as such reflected the parametric requirement of various substituents at different positions of imidazole inhibitors. The F-value given above, is significant at 99% level [$F_{6,24}(0.01) = 3.67$] and the r^2-value accounted for 84% of variance in the observed activity values. Additionally, the cross-validated index q^2 was calculated as discussed previously. The higher value obtained for this statistical index is in favor of a reasonable QSAR model. The variables used in obtaining Equation (1), possess poor inter-correlations (Table IV) amongst themselves and thus satisfy an important criterion of statistical significance, the mutual orthogonal condition or independency amongst descriptors. All calculated (Equation (1))

Table IV. Intercorrelation matrix amongst independent variables of Equation(1).

	MR(2)	*HD*(2)	π(3)	*HA*(4)	I_X	V_{WY}
MR(2)	1.000	0.086	0.047	0.253	0.204	0.102
HD(2)		1.000	0.096	0.260	0.209	0.105
π(3)			1.000	0.087	0.156	0.078
HA(4)				1.000	0.367	0.109
I_X					1.000	0.204
V_{WY}						1.000

and predicted (LOO model) values seems to be in close agreement with the observed ones. These are also listed in Table I for the sake of comparison with observed values. From Equation (1), it appeared that the presence of an F substituents in the *X*-position, accounted by the indicator variable I_X, is adding positively to the activity value. Such a substituent is, therefore, helpful in augmenting the activity value. The parameter V_{WY} contributes negatively to the activity value and the less bulky structural moieties such as $-SCH_2-$ and $-S(CH_2)_2-$ at the *Y*-incision are only advantageous in improving the inhibitory action. Further the negative coefficients obtained in association with *MR*(2) and *HD*(2) parameters indicate that a less bulky/polar substituent, present at 2-*R*, and have no hydrogen-bond donor property are also essential. Additionally, the positive regression coefficient of $\pi(3)$ and *HA*(4) variables suggest that the substituents with more hydrophobic nature and hydrogen-bond acceptor character, respectively at 3-*R* and at 4-*R*, are advantageous in improving the inhibitory activity of a compound. The plot of observed versus calculated $-\log IC_{50}$ using Equation 1 and the Fujita-Ban study is also given in Figure 2 to demonstrate the goodness of fit and to show systematic variation of observed versus calculated activities in the present congeneric series.

Following the approach of selecting variables described above, the MRA on the data related to the inhibition of cytokine IL-1β revealed the following correlation equation.

$$\begin{aligned} -\log IC_{50}(\text{IL-1}\beta) &= -3.876(\pm 0.67)\boldsymbol{R}_X - 0.499(\pm 0.23)MR(2) \\ &\quad - 1.342(\pm 0.43)\,\sigma(3) - 0.315(\pm 0.09)\pi(4) \\ &\quad - 1.565(\pm 0.77)MW_Y + 5.899 \\ n = 31,\ R = 0.915,\ s = 0.222, & \\ F(5,25) = 25.605,\ q^2 = 0.698 & \end{aligned} \tag{2}$$

This equation has also shown the importance of the parameters accounting for electronic, hydrophobic, molecular bulk and polarity of the substituents. The r^2-value accounted for 84% of variance in observed activity values and the F-value stood significant at 99% level $[F_{5,25}(0.01) = 3.86]$. This showed that the statistical parameters of Equation (2) account to a highly significant correlation. A reasonably high q^2-value is obtained through a cross-validation test by LOO procedure, also hinted at a satisfactory statistical model. Further, the independent variables used in deriving the above equation showed poor inter-correlations among themselves (Table V). The equation was, therefore, used to calculate the activity of all 31 compounds of the test data set. These values, listed in Table I, were found to be in close agreement with the observed values. The predicted values of all the compounds, obtained through the LOO approach, were also given in this Table for the sake of comparison. The derived regression coefficients of various descriptors in Equation (2) are all negative. It therefore follows that the *X*-substitutents that transmits a higher negative resonance effect, the *Y*-substituent that offers less molecular bulk are beneficial in raising the inhibitory action of a compound towards cytokine IL-1β. Similarly, the R-substituents, being more electron donors at the *meta*-position, less hydrophobic at the *para*-position and offering smaller refractivity (less bulky and or polar) at the *ortho*-position are also helpful in improving the activity of a compound. This strategy may, therefore, be followed for designing higher potency compounds for future synthesis.

These guidelines may, therefore, provide a basis for rationalizing substituent selection in the future designing of effective inhibitors of cytokine. The study may also help in proposing the possible mode of action of benzylsulfanyl imidazoles at the molecular level.

Table V. Intercorrelation matrix amongst independent variables of Equation (2).

	R_X	*MR*(2)	$\sigma(3)$	$\pi(4)$	MW_Y
R_X	1.000	0.190	0.311	0.281	0.096
MR(2)		1.000	0.094	0.187	0.052
$\sigma(3)$			1.000	0.203	0.084
$\pi(4)$				1.000	0.190
MW_Y					1.000

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References

[1] Van Assche G, Rutgeerts P. Expert Opin Investig Drugs 9 2000;103–111.
[2] Mikuls TR, Moreland LW. Expert Opin Pharmacother 2001;2:75–84.
[3] Yazdani C, McLaughlin T, Cummins G, Doyle J. Am J Manag Care 2001;7:419–426.
[4] Boehm JC, Adams JL. Expert Opin Ther Pat 2000;10:25–27.
[5] Foster ML, Halley F, Souness JE. Drug News Perspect 2000;13:488–497.
[6] Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, Green D, McNulty D, Blumenthal MJ, Heys JR, Landvatter SW, Strickler JE, McLaughlin MM, Siemens IR, Fisher SM, Livi GP, White JR, Adams JL, Young PR. Nature 1994;372: 739–746.

[7] Young PR, McLaughlin MM, Kumar S, Kassis S, Doyle ML, McNulty D, Gallaghar TF, Fisher S, McDonnell PC, Carr SA, Huddleston MJ, Seibel G, Porter TG, Livi GP, Adams JL, Lee JC. J Biol Chem 1997;272:12116–12121.
[8] Wilson KP, McCaffrey PG, Hsiao K, Pazhanisamy F, Galullo V, Bemis GW, Fitzgibbon MJ, Caron PR, Murcko MA, Su MS. Chem Biol 1997;4:423–431.
[9] Tong L, Pav S, White DM, Rogers S, Crane KM, Cywin CL, Brown ML, Pargellis CA. Nat Struct Biol 1997;4:311–316.
[10] Toledo LM, Lydon NB, Elbaum D. Curr Med Chem 1999;6: 775–805.
[11] Laufer SA, Striegel HG, Wagner GK. J Med Chem 2002;45: 4695–4705.
[12] Fujita T, Ban T. J Med Chem 1971;14:148–152.
[13] Hansch C, Leo AJ. Substituents constants for correlation analysis in chemistry and biology. New York: John Wiley; 1979.
[14] Bondi A. J Phys Chem 1964;68:441–451.
[15] Moriguchi I, Kanada Y, Komatsu K. Res Commun Chem Pathol Pharmacol 1976;24:1799–1806.
[16] Wold S. Quant Struct-Act Relat 1991;10:191–193 and references cited therein.