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QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDY ON SOME 5-LIPOXYGENASE INHIBITORS

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A quantitative structure-activity relationship (QSAR) study has been made on some lipoxygenase inhibitors belonging to the series of ω-phenylalkyl hydroxamic acids, ω-naphthylalkyl hydroxamic acids, eicosatetraenoic acids, and 1H-benzimidazole-4-ols. It was found that the hydrophobic character of the molecules and the size of their substituents selectively govern their lipoxygenase inhibitory activity. The enzyme active site possesses a non-heme ferric ion, a hydrophobic domain, and a carboxylic acid binding site. It was found that while the functional group of inhibitors must interact with the ferric ion, the substituent on one side of it would be involved in hydrophobic interaction and that on the other side in van der Waals interaction with the enzyme so leading to an enhancement in the inhibitory activity of the inhibitors.

KEY WORDS: 5-Lipoxygenase inhibitors, ω-phenylalkylhydroxamic acids, ω-naphthylalkyl hydroxamic acids, eicosatetraenoic acids, 1H-benzimidazole-4-ols, quantitative structure-activity relationship.

INTRODUCTION

The enzyme 5-lipoxygenase (5-LO) catalyzes the first step of a biochemical pathway in which arachidonic acid (AA) is converted into the leukotrienes (Scheme I). Leukotrienes were so called because of their initial discovery in leukocytes and their conjugated triene structure.[1] Numerous biochemical effects have been associated with the leukotrienes and they have been implicated as important mediators of inflammation and allergic reactions.[2] As the first dedicated enzyme in the biosynthetic cascade leading to these important mediators, 5-lipoxygenase clearly represents an exciting target for therapeutic intervention. Its inhibitors may be of great value in the treatment of inflammatory and allergic diseases.

In man, arachidonic acid is the most abundant precursor, and it is either derived from dietary linoleic acid or is ingested as a constituent of meat. Arachidonate is then esterified as a component of the phospholipids of cell membranes or is combined through ester linkages in other complex lipids. Thus the concentration of free arachidonic acid is very low, but it can be released from cellular stores by various hydrolases. Once released, it is rapidly metabolized to leukotrienes. As shown in Scheme I,

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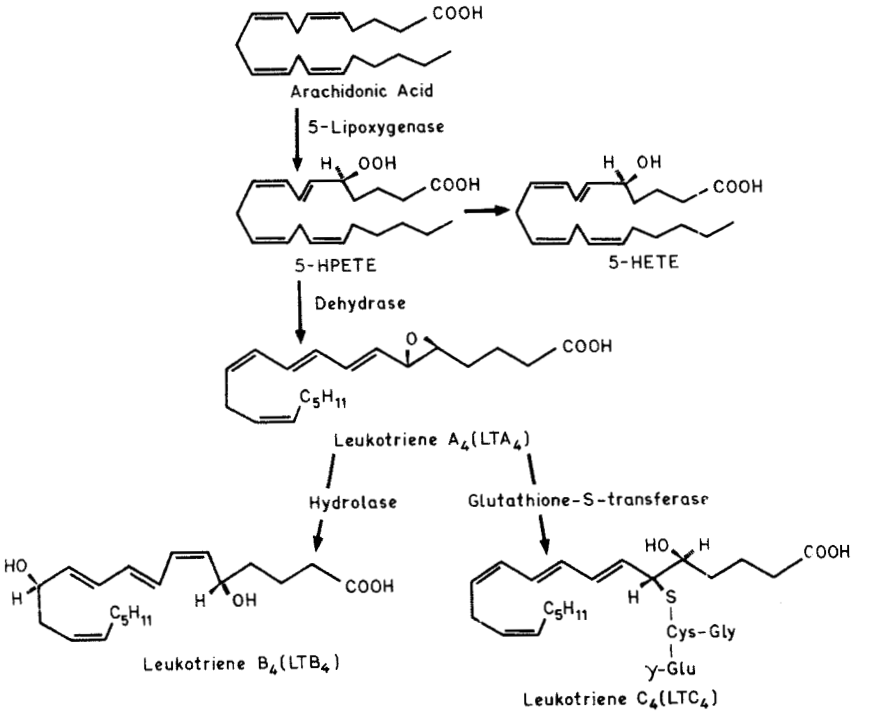
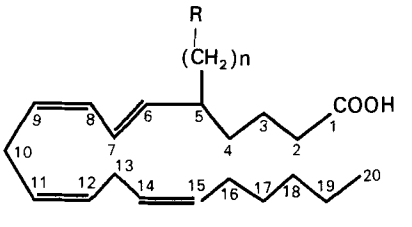


SCHEME I. The Arachidonic acid – leukotriene biosynthetic pathway.

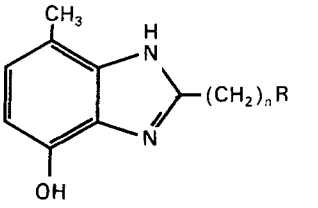
the first step of this metabolic reaction is the conversion of arachidonic acid to 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE) catalysed by 5-lipoxygenase. On the basis of the current knowledge of the enzymatic mechanisms of related lipoxygenases,[3] it is reasonable to assume that the reaction of oxygen with AA to form 5-HPETE requires a metal species, putatively iron, in the active site of the enzyme.

As summarized by Cashman,[4] the key structural features of the active site of 5-lipoxygenase are a non-heme ferric ion, a hydrophobic domain, and a carboxylic acid binding site. Beyond this, there is little information available about this enzyme. Based on this information, a group at Abbott Laboratories tried to find potent inhibitors of the enzyme.[5,6] Since hydroxamic acids (R-CONHOH) are known to form strong complexes with a variety of transition metals, hydroxamic acid containing molecules were considered as potential inhibitors of 5-lipoxygenase. Accordingly, Summers *et al.*[5] made a study on a series of ω-phenylalkyl and ω-naphthylalkyl hydroxamic acids.

It was found that when a hydroxamic acid group was positioned at C_5 of arachidonic acid, a potent inhibitor of 5-lipoxygenase was obtained.[7] Considering this premise, Kerdesky *et al.*[6] synthesized a series of eicosatetraenoic acids (**I**) in which various functional groups capable of interacting with iron or other functional groups in the active site of the enzyme were incorporated at the C_5 position and studied their 5-lipoxygenase inhibitory activity.



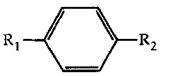
(I)



(II)

A series of 1H-benzimidazol-4-ols (II) were also studied[8] for their 5-lipoxygenase inhibitory activity, in which the hydroxyl group was found to be functional and the substituents at the 2-position were found to control the activity. The aim of the present study is to investigate the physicochemical properties of molecules that govern the activity of various types of 5-lipoxygenase inhibitors and to establish the nature of the interactions that take place beteen the inhibitors and the enzyme.

TABLE I
ω-Phenylalkyl Hydroxamic Acids and Their 5-Lipoxygenase Inhibitory Activities and Physicochemial Parameters.

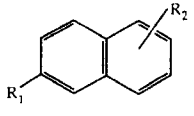


No.	R_1	R_2	$V_w(R_1)$ (10^2 Å^3)	$V_w(R_2)$ (10^2 Å^3)	log P	$-\log IC_{50}$ Obsd[a]	$-\log IC_{50}$ Calc. Eqn (2)	$-\log IC_{50}$ Calc Eqn (3)
1	H	CONHOH	0.056	0.442	−1.67	3.96	3.81	4.27
2	H	$CH_2CONHOH$	0.056	0.596	−2.03	3.52	4.12	4.19
3	H	$CH_2CH_2CONHOH$	0.056	0.750	−1.49	4.06	4.44	4.33
4	H	$CH_2CH_2CH_2CONHOH$	0.056	0.904	−0.95	4.57	4.75	4.59
5	H	CH=CHCONHOH(trans)	0.056	0.708	−2.04	4.92	4.35	4.19
6	H	CH=CHCONHOH(cis)	0.056	0.708	−2.04	4.51	4.35	4.19
7	H	C≡CCONHOH	0.056	0.675	−2.91	4.34	4.28	4.24
8	p-NO_2	CONHOH	0.276	0.442	−2.15	4.64	4.33	4.18
9	p-CN	CONHOH	0.268	0.442	−2.46	4.22	4.31	4.17
10	p-CF_3	CONHOH	0.383	0.442	−1.01	4.57	4.58	4.55
11	p-Br	CONHOH	0.287	0.442	−0.81	4.85	4.35	4.68
12	p-I	CONHOH	0.388	0.442	−0.55	4.82	4.59	4.86
13	p-C_6H_5	CONHOH	0.809	0.442	−0.13	5.39	5.58	5.22
14	p-CH_3	CONHOH	0.245	0.442	−1.14	4.19	4.25	4.48
15	p-OH	CONHOH	0.137	0.442	−2.56	3.72	4.00	4.18
16	m-C_6H_5	CONHOH	0.809	0.442	−0.13	5.22	5.58	5.22
17	p-(2,4,6-Trimethylphenyl)	CONHOH	1.271	0.442	1.45	6.54	6.67	7.26
18	p-(2,4,6-Trimethylphenyl)	$CON(CH_3)OH$	1.271	0.604	1.36	7.19	7.00	7.11
19	p-(1-Naphthyl)	CONHOH	1.253	0.442	0.99	6.75	6.62	6.55
20	p-(2-Naphthyl)	CONHOH	1.253	0.442	0.99	6.48	6.62	6.55
21	p-(2,4,6-Trimethylphenyl)	$CH=CHCON(CH_3)OH$	1.271	0.870	1.36	7.66	7.54	7.11

[a]Ref. 5

TABLE II

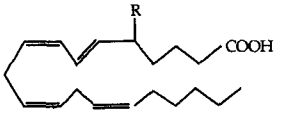
ω-Naphthylalkyl Hydroxamic Acids and Their 5-Lipoxygenase Inhibitory Activites and Physicochemical Parameters

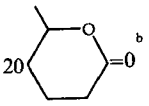
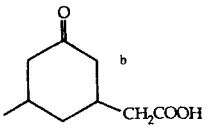
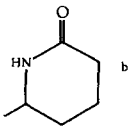


No.	R_1	R_2	$V_w(R_1)$ (10^2 Å^3)	$V_w(R_2)$ (10^2 Å^3)	log P	-log IC_{50} Obsd[a]	-log IC_{50} calc. Eqn. (8)
1	H	2-CONHOH	0.056	0.442	−0.55	4.85	5.30
2	H	2-CH_2CONHOH	0.056	0.596	−0.01	4.72	5.56
3	H	2-CH_2CH_2CONHOH	0.056	0.750	0.53	5.01	5.82
4	H	1-CONHOH	0.056	0.442	−0.55	4.37	4.34
5	H	1-CH_2CONHOH	0.056	0.596	−0.01	4.57	4.60
6	H	2-CON(CH_3)OH	0.056	0.604	−1.02	5.89	5.57
7	OCH_3	2-CONHOH	0.304	0.442	−0.61	5.09	5.30
8	$O(CH_2)_3CH_3$	2-CONHOH	0.766	0.442	1.01	5.70	5.30
9	$O(CH_2)_6CH_3$	2-CONHOH	1.228	0.442	2.75	5.19	5.30
10	$O(CH_2)_7CH_3$	2-CONHOH	1.382	0.442	3.29	5.15	5.30
11	$OCH_2CH_2CH{=}CH(CH_2)_4CH_3$(cis)	2-CONHOH	1.494	0.442	3.28	5.54	5.30
12	H	2-CH=CHCONHOH	0.056	0.708	−0.02	6.02	5.75
13	H	2-CH=CHCON(CH_3)OH	0.056	0.870	−0.36	7.00	6.02
14	H	2-CH=CHCON[$CH(CH_3)_2$]OH	0.056	1.128	0.74	7.09	6.46
15	H	2-CH=CHCON(c-C_6H_{11})OH	0.056	1.536	2.03	7.00	7.14
16	H	2-CH=CHCON(C_6H_5)OH	0.056	1.434	0.65	7.28	6.97
17	H	2-CH=C(CH_3)CON(CH_3)OH	0.056	1.080	0.17	6.33	6.37
18	H	2-C(CH_3)=CHCON(CH_3)OH	0.056	1.080	0.17	6.92	6.37
19	H	2-CH=C(C_6H_5)CON(CH_3)OH	0.056	1.588	1.18	6.30	7.23

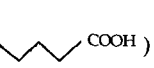
[a] Ref. 5

TABLE III
Eicosatetraenoic Acids and Their 5-Lipoxygenase Inhibitory Activities and Physicochemical Parameters



No.	R	V_w(CH(R)...COOH) (10^2 Å^3)	log P	−log IC_{50} Obsd[a]	−log IC_{50} Calc. Eqn. (12)
1	OH	0.760	5.48	4.11	4.51
2	CH_2OH	0.811	6.24	4.54	4.40
3	CH_2CH_2OH	1.068	6.78	4.66	4.32
4	$CH_2CH_2CH_2OH$	1.222	7.32	4.01	4.24
5	SH	0.873	6.89	5.12	4.93
6	CH_2SH	1.027	7.65	4.96	4.81
7	CH_2CH_2SH	1.181	8.19	4.60	4.73
8	$CH_2CH_2CH_2SH$	1.335	8.73	4.44	4.65
9	CONHOH	1.043	2.77	5.85	6.13
10	$CH_2CONHOH$	1.197	3.41	6.72	6.04
11	$CH_2CH_2CONHOH$	1.351	3.95	5.55	5.95
12	CH_2COOH	1.089	6.77	4.02	4.32
13	NH_2	0.791	6.38	4.60	4.38
14	NHOH	0.868	3.33	4.68	4.83
15	$OCOCH_3$	1.102	6.52	4.17	4.36
16	=O	0.713	5.01	4.74	4.58
17	=NOH	0.830	2.78	4.96	4.91
18	$=NNHCONH_2$	1.144	2.24	5.15	4.99
19	$=NNHCSNH_2$	1.260	−0.10	5.10	5.34
20		0.859	5.46	4.57	4.52
21		1.329	7.14	4.23	4.27
22		0.873	5.13	5.00	4.56

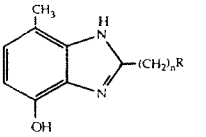
[a] Ref. 6

[b] They represent complete () group

MATERIALS AND METHODS

The ω-phenylalkyl and ω-naphthylalkyl hydroxamic acids studied by Summers *et al.*[5] have been arranged in two groups as shown in Tables I and II. Eicosatetraenoic acids

TABLE IV
1H-Benzimidazol-4-ols and Their 5-Lipoxygenase Inhibitory Activities and Physicochemical Parameters



No.	R	n	$V_w[(CH_2)_nR]$ (10^2 Å^3)	log P	$-\log IC_{50}$ Obsd[a]	$-\log IC_{50}$ Calc. Eqn. (14)
1	C_6H_5	0	0.809	2.79	5.92	5.75
2	C_6H_5	1	0.963	3.33	5.92	5.82
3	C_6H_5	1	0.963	3.33	5.89	5.82
4	C_6H_5	2	1.117	3.87	5.68	5.80
5	$4\text{-}CH_3C_6H_4$	1	1.117	3.86	5.60	5.80
6	$4\text{-}ClC_6H_4$	1	1.128	4.04	6.00	5.80
7	$4\text{-}CH_3OC_6H_4$	0	1.044	2.72	5.66	5.57
8	$4\text{-}CH_3OC_6H_4$	1	1.198	3.26	5.68	5.65
9	$4\text{-}CH_3OC_6H_4$	1	1.198	3.26	5.66	5.65
10	$3\text{-}CH_3OC_6H_4$	1	1.198	3.26	5.77	5.65
11	$2\text{-}CH_3OC_6H_4$	1	1.198	3.26	5.47	5.65
12	$4\text{-}C_2H_5OC_6H_4$	1	1.352	3.80	5.52	5.65
13	$4\text{-}OHC_6H_4$	1	1.031	2.44	5.16	5.45
14	$3,4\text{-}(CH_3O)_2C_6H_3$	1	1.433	2.78	5.28	5.35
15	$3,4,5\text{-}(CH_3O)_3C_6H_2$	1	1.668	2.31	5.01	4.97
16	$4\text{-}N(CH_3)_2C_6H_4$	0	1.232	3.17	5.89	5.61
17	$1\text{-}C_{10}H_7$	1	1.407	4.45	6.64	5.60
18	2-Furyl	0	0.616	1.99	5.48	5.46
19	2-Thienyl	1	0.725	2.97	5.68	5.87
20	3-Pyridyl	1	0.758	1.84	5.30	5.26

[a] Ref. 8

studied by Kerdesky *et al.*[6] are listed in Table III, and 1H-benzimidazol-4-ols studied by Buckle *et al.*[8] in Table IV. The *in vitro* 5-lipoxygenase inhibitory activity of these compounds was measured by respective authors using the 20000 (or 10000)g supernatant from homogenized rat basophilic leukemia (RBL-1) cells and reported in terms of IC_{50}, the molar concentration of inhibitor leading to 50% inhibition of the enzyme activity. The term pIC_{50} in the Tables refers to $(-\log IC_{50})$.

In our investigation, the hydrophobicity and molecular size of inhibitors are found to produce major effect on 5-lipoxygenase inhibition. To quantify these effects, we calculated, for all the inhibitors in Table I–IV, log P values as suggested by Hansch and Leo[9] and V_w values as suggested by Moriguchi *et al.*[10] The log P, where P is the octanol-water partition coefficient, is a measure of hydrophobic character of the molecule and characterizes the hydrophobic interaction of the latter with the receptor. In an *in vivo* experiment, it also characterizes the ability of the molecule to cross the cell membrane and reach the target. The parameter V_w is the van der Waals volume and represents the size of the substituent or of the whole molecule. It characterizes the dispersion interaction or sometimes steric effects between the drug molecule and the receptor. It has been found to be very useful in structure-activity relationship studies.[11]

To quantify the hydrophobic and molecular size effects on the inhibitory activity

of molecules, we derived quantitative correlations of activity with log P and V_w, using multiple regression analysis.[12]

RESULTS AND DISCUSSIONS

For ω-phenylalkyl hydroxamic acids as listed in Table I, the V_w of R_1-substituent was found to play a dominant role in the inhibitory activity of the compounds. The regression analysis has revealed a very significant correlation between the activity and $V_w(R_1)$ as shown by the equation,

$$pIC_{50} = 2.236(\pm 0.415)V_w(R_1) + 3.955$$
$$n = 21, \quad r = 0.933, \quad s = 0.437, \quad F_{1,19} = 127.07 \qquad (1)$$

where n is the number of data points, r is the correlation coefficient, s is the standard deviation, and F is the F-ratio between the variances of calculated and observed activities. The datum within parenthesis is the 95% confidence interval. This equation shows that size of the R_1-substituent alone can account for 87% of the variance in the activity ($r^2 = 0.87$). Though R_2-group represents the functional hydroxamic moiety with small variation, this small variation was sufficient to make a significant improvement in the correlation when accounted for by $V_w(R_2)$ (eqn. 2). The inhibitory activity of these compounds was, however, also found to be well correlated with the

$$pIC_{50} = 2.351(\pm 0.295)V_w(R_1) + 2.033(\pm 0.930)V_w(R_2) + 2.779$$
$$n = 21, \quad r = 0.970, \quad s = 0.305, \quad F_{2,18} = 141.35 \qquad (2)$$

hydrophobic character of molecules (eqn. 3), but the hydrophobic character of molecules was found to be a significant function of $V_w(R_1)$ (eqn. 4). The $V_w(R_2)$ was found to produce little effect on log P values of the compounds (eqn. 5). Thus since

$$pIC_{50} = 1.005(\pm 0.182)\log P + 0.214(\pm 0.110)(\log P)^2 + 5.350$$
$$n = 21, \quad r = 0.951, \quad s = 0.387, \quad F_{2,18} = 84.14 \qquad (3)$$
$$\log P = 2.659(\pm 0.510)V_w(R_1) - 2.159$$
$$n = 21, \quad r = 0.929, \quad s = 0.537, \quad F_{1,19} = 119.18 \qquad (4)$$
$$\log P = 2.719(\pm 0.507)V_w(R_1) + 1.062(\pm 1.598)V_w(R_2) - 2.773$$
$$n = 21, \quad r = 0.936, \quad s = 0.524, F_{2,18} = 63.54 \qquad (5)$$

$V_w(R_2)$ hardly affects the hydrophobic character of inhibitors but affects their activity, it may be concluded that lengthening of hydroxamic moiety might lead to a dispersion interaction with the enzyme near its active site containing ferric ion, while the R_1-substituent might be fully involved in the hydrophobic interaction with the hydrophobic region of the enzyme.

The V_w of the hydroxamic moiety-containing R_2 group in ω-naphthylalkyl hydroxamic acids (Table II) is found to play a major role in controlling 5-lipoxygenase inhibitory activity of molecules (eqn. 6) but has little effect on their hydrophobic character (eqn. 7). This is in total conformity with the results that were obtained for the comfounds in Table I, where there was only a small variation in the R_2-group. Thus this substantiates the view that the R_2-group would be involved in the dispersion

interaction with the enzyme. The position of the R_2-group in the naphthyl ring was also found to be determinative.

$$pIC_{50} = 1.866(\pm 0.755)V_w(R_2) + 4.311$$
$$n = 19,\ r = 0.785,\ s = 0.605,\ F_{1,17} = 17.20 \quad (6)$$

$$\log P = 0.116(\pm 1.674)V_w(R_2) + 0.575$$
$$n = 19,\ r = 0.036,\ s = 1.343,\ F_{1,17} = 0.02 \quad (7)$$

The 2-position appeared to be more effective than the 1-position. Hence, when a dummy parameter D with a value of unity for the 2-position and zero for the 1-position was introduced, a significant improvement in the correlation was obtained (eqn. 8). Equation (8) shows that any substituent at the 2-position will have approximately ten times more activity than at the 1-position.

$$pIC_{50} = 1.682(\pm 0.698)V_w(R_2) + 0.961(\pm 0.883)D + 3.597$$
$$n = 19,\ r = 0.843,\ s = 0.541,\ F_{2,16} = 19.72 \quad (8)$$

In this series of inhibitors, the V_w of the R_1 group was not found to have any significant effect on the activity (eqn. 9) as was also the case with log P (eqn. 10) which had significant correlation with $V_w(R_1)(r > 0.9)$. The direct mutual correlation between activity and log P was unimportant ($r = 0.06$). These results lead to the suggestion

$$pIC_{50} = 1.738(\pm 0.864)V_w(R_2) + 0.921(\pm 0.976)D + 0.079(\pm 0.679)V_w(R_1) + 3.564$$
$$n = 19,\ r = 0.844,\ s = 0.557,\ F_{3,15} = 12.40 \quad (9)$$

$$pIC_{50} = 1.679(\pm 0.722)V_w(R_2) + 0.998(\pm 0.944)D - 0.034(\pm 0.221)\log P + 3.589$$
$$n = 19,\ r = 0.845,\ s = 0.556,\ F_{3,15} = 12.45 \quad (10)$$

that although there was a small variation with the R_1-group (not to much reliance should be placed upon the implications of eqns. (9) and (10)) the hydrophobic site of the enzyme is not far from the iron moiety and is localized, so that any R_1-group falling outside the hydrophobic site in the inhibitor-enzyme complex will not affect the activity. It appears, therefore, that in this series of compounds the second ring of the naphthalene is sufficient to cover the hydrophobic region of the enzyme, while in case of ω-phenylalkyl hydroxamic acids (Table I), substituents of the size of trimethylphenyl would be required to fully cover the region and produce the optimum activity. If both the series are combined, a good correlation between the inhibition potency and log P and $V_w(R_2)$ is obtained (eqn. 11). The reason for obtaining only a moderately good correlation is due to the small variations in the R_2-group of ω-phenylakyl hydroxamic acid series and in the R_1-group of ω-napthylalkyl hydroxamic acid series. In eqn. (11), the log P and $V_w(R_2)$ are almost orthogonal to each other ($r = 0.20$).

$$pIC_{50} = 0.426(\pm 0.162)\log P - 0.103(\pm 0.079)(\log P)^2 + 1.311(\pm 0.753)V_w(R_2) + 4.831$$

$$n = 40, \quad r = 0.80, \quad s = 0.71, \quad F_{3,36} = 21.19 \qquad (11)$$

The conclusions drawn so far regarding the nature of the inhibitor-enzyme interaction is in good support of Summers *et al.*'s hypothesis.[5] Their hypothesis makes use of a simplistic graphical comparison of bound substrate with inhibitors using a hypothetical conformation of arachidonic acid when bound to 5-lipoxygenase.[5] In the course of the enzyme reaction, a cis, cis-1,4-diene is converted into a trans,cis-1,3-diene and it was proposed that the substrate should be bound with the enzyme in a "W"conformation at C_5-C_9. Since 5-lipoxygenase is believed to contain a catalytically important iron, such an atom was postulated to be in the vicinity of C_5 where oxidation occurs. Within this context of the hypothesis, inhibitors were aligned with the postulated bound arachidonic acid geometry such that the hydroxamate function in each compound was fixed in a position near the iron moiety. The remainder of the inhibitors structure was then matched as close as possible with the hypothetical enzyme-bound conformation of arachidonic acid.

The 5-lipoxygenase inhibitory activity of eicosatetraenoic acids (Table III), in which various functional groups capable of interacting with iron or other functional groups in the active site of the enzyme were incorporated at C_5, was found to be a significant function of the nature of substituted group. The hydrophobicity was observed to have a negative effect on potency. The best correlation equation obtained in this case was given by,

$$pIC_{50} = 1.215(\pm 0.429)D_1 + 0.621(\pm 0.423)D_2 - 0.148(\pm 0.079)\log P + 5.326$$
$$n = 22, \quad r = 0.896, \quad s = 0.306, \quad F_{3,18} = 24.45 \qquad (12)$$

where D_1 and D_2, the two dummy parameters, were used for groups containing $-NHOH$ and $-SH$ moieties, respectively. Equation (12) shows that the group containing NHOH or SH will produce about 17 times and about 4 times respectively greater activity than the other groups. Thus NHOH appears to produce the strongest interaction with the iron moiety of the enzyme. The negative effect of log P on activity may be interpreted as the consequence of an attempt by the molecule to interact with the hydrophobic area of the enzyme, leading to interference in the interaction of the functional group with the iron. The correlation of activity with log P alone was given by,

$$pIC_{50} = 5.658 - 0.158(\pm 0.111)\log P$$
$$n = 22, \quad r = 0.553, \quad s = 0.545, \quad F_{1,20} = 8.80 \qquad (13)$$

Equation (12) however provides no further information regarding the nature of the inhibitor-enzyme interaction.

For the 1H-benzimidazol-4-ols (Table IV), the inhibitory activity was found to be related with the hydrophobic character of the molecules and the V_w of the substituent as given by,

$$pIC_{50} = 1.260(\pm 0.896)\log P - 0.154(\pm 0.142)(\log P)^2 - 0.638(\pm 0.330)V_w + 3.952$$
$$n = 20, \quad r = 0.832, \quad s = 0.162, \quad F_{3,16} = 11.22 \qquad (14)$$

Equation (14) thus shows that this series of compounds will also be involved in the hydrophobic interaction with the enzyme, accounting for a major fraction of the

variance in the activity. However, this equation also suggests that there would be steric hindrance to this interaction due to the large bulky substituent since the coefficient of V_w is negative and there is no significant mutual correlation between the log P and V_w($r = 0.38$).

The overall picture that now emerges from this study concerning the nature of the inhibitor-enzyme interaction is that in addition to the primary interaction between the functional moiety of the inhibitor and the iron of the enzyme, there are also strong dispersion as well as hydrophobic interactions. A large functional group may also be involved in dispersion interactions and the groups on the other side of the molecule may be involved in the hydrophobic interaction which might be hindered if the group is sufficiently large. This study presents a clear picture of the nature of the active site present in the enzyme in that near the iron moiety a polarizable site can be expected and on the other side a hydrophobic region is established which is not far from the iron moiety and is localized.

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