53023-42-0; $C_{16}H_{33}Br$, 112-82-3; $(CH_3)_2N(CH_2)_2OH$, 108-01-0; $(CH_3)_2N(CH_2)_3OH$, 3179-63-3; $(CH_3)_3N$, 75-50-3; $HOCH_2CH(OH)CH_2Br$, 34637-21-3; $Br(CH_2)_2OH$, 540-51-2; 1-naphthol, 90-15-3; (±)-1,2-*O*,*O*-isopropylidene-3-*O*-mesylglycerol, 34331-40-3; 1,2-(isopropylidenedioxy)-3-bromopropane, 34637-20-2; 2-heptadecyl-4-(bromomethyl)-1,3-dioxolane, 124581-84-6; *trans*-2-heptadecyl-4-(bromomethyl)-1,3-dioxolane, 124581-87-9; dihydropyran, 110-87-2.

Hydroxamic Acid Inhibitors of 5-Lipoxygenase: Quantitative Structure–Activity Relationships

James B. Summers,*,† Ki H. Kim,‡ Hormoz Mazdiyasni,† James H. Holms,† James D. Ratajczyk,† Andrew O. Stewart,† Richard D. Dyer,† and George W. Carter†

Immunosciences Research and Computer Assisted Molecular Design Areas, Abbott Laboratories, Abbott Park, Illinois 60064.
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An evaluation of the quantitative structure–activity relationships (QSAR) for more than 100 hydroxamic acids revealed that the primary physicochemical feature influencing the in vitro 5-lipoxygenase inhibitory potencies of these compounds is the hydrophobicity of the molecule. A significant correlation was observed between the octanol–water partition coefficient of the substituent attached to the carbonyl of the hydroxamate and in vitro inhibitory activity. This correlation held for hydroxamic acids of diverse structure and with potencies spanning 4 orders of magnitude. Although the hydrophobicity may be packaged in a variety of structural ways and still correlate with potency, the QSAR study revealed two major exceptions. Specifically, the hydrophobicity of portions of compounds in the immediate vicinity of the hydroxamic acid functionality does not appear to contribute to increased inhibition and the hydrophobicity of fragments beyond approximately 12 Å from the hydroxamate do not influence potency. The QSAR study also demonstrated that inhibitory activity was enhanced when there was an alkyl group on the hydroxamate nitrogen, when electron-withdrawing substituents were present and when the hydroxamate was conjugated to an aromatic system. These observations provide a simple description of the lipoxygenase–hydroxamic acid binding site.

The enzyme 5-lipoxygenase is the first dedicated enzyme in the biosynthetic pathway leading to the leukotrienes. Since leukotrienes have been implicated as important mediators in several diseases including asthma, arthritis, and psoriasis, inhibition of 5-lipoxygenase represents a potential new approach for therapeutic intervention in these diseases. Simple stable molecules containing the hydroxamic acid functionality have been shown to inhibit 5-lipoxygenase.[1-5] In fact, several hydroxamates are orally active inhibitors of the enzyme as determined by their ability to block the biosynthesis of leukotrienes in vivo.[2-4] The hydroxamic acid moiety is essential for the inhibition observed with these compounds. Molecules in which the hydroxamate has been replaced by related functional groups exhibit little or no 5-lipoxygenase inhibitory activity in vitro.[1]

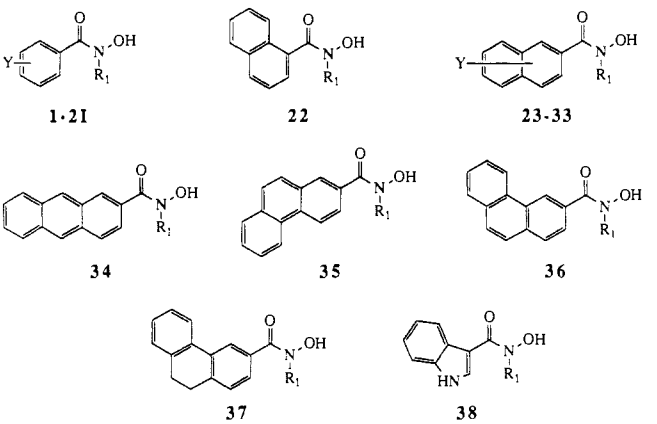
In this paper we report the in vitro 5-lipoxygenase inhibitory activities of many new "type A"[6] hydroxamic acids. We have combined these new compounds with those previously reported to study the influence of the structural features on their in vitro inhibitory potency. The results of a quantitative evaluation of structure–activity relationships (QSAR)[7] involving more than 100 hydroxamic acid of diverse structure are described.

Results and Discussion

Table I lists the 111 hydroxamic acids used in this QSAR study. The compounds have been classified into four groups on the basis of common structural features. The structure–activity relationships of each group are discussed below.

Group A: Arylhydroxamic Acids (Chart I). We have previously described the 5-lipoxygenase inhibitory properties of a series of para-substituted benzohydroxamic acids, **1–10**.[1] A highly significant correlation was noted between the hydrophobicity and electronic nature of the para substituent and the inhibitory potency of these compounds. This correlation is described in eq 1. The term

Chart I. Group A. Arylhydroxamic Acids



$$\log (1/IC_{50}) = 0.49(\pm 0.08)\pi + 0.45(\pm 0.17)\sigma_p + 3.10(\pm 0.20) \quad (1)$$

$$n = 10,\ s = 0.220,\ r = 0.945,\ F_{2,7} = 28.9,\ p < 0.0001$$

† Immunosciences Research Area.
‡ Computer Assisted Molecular Design Area.

(1) Summers, J. B.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Dyer, R. D.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 574.
(2) Summers, J. B.; Gunn, B. P.; Mazdiyasni, H.; Goetze, A. M.; Young, P. R.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 2121.
(3) Summers, J. B.; Gunn, B. P.; Martin, J. G.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Goetze, A. M.; Bouska, J. B.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 3.
(4) Summers, J. B.; Gunn, B. P.; Martin, J. G.; Martin, M. B.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1960.

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π refers to the Hansch hydrophobicity constant, determined as described in the Experimental Section, for the entire group attached to the carbonyl of the hydroxamate. The parameter σ_p refers to the Hammett electronic constant of the aryl substituent.[8] The IC_{50} is a measure of the in vitro 5-lipoxygenase inhibitory potency, n is the number of data points, s is the standard deviation from the regression equation, and r is the correlation coefficient. The values in parentheses are standard deviations of the coefficients. The positive coefficients for σ_p and π indicate that electron-withdrawing and lipophilic substituents increase inhibitory potency. The lipophilic descriptor alone explains more than 76% of the variance of the data and it is thus the most significant property affecting activity. The electronic descriptor accounts for about 13% of the variance. Attempts to correlate the inhibitory potency with a steric term such as MR did not result in a significant correlation.

In addition to the original para-substituted benzohydroxamates, Table I contains 28 other compounds in which an aryl ring system is directly attached to the hydroxamic acid functionality, **11–38**. Equation 2 describes

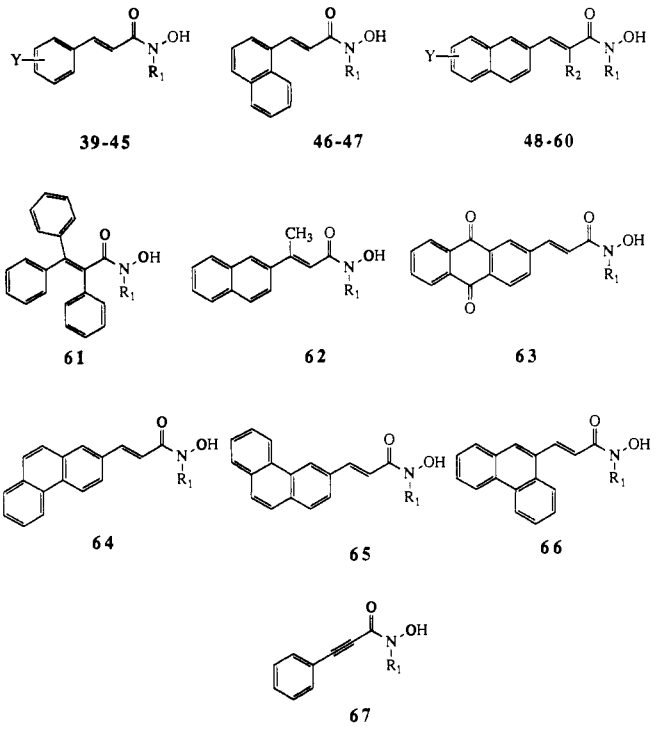
$$\log (1/IC_{50}) = 0.41(\pm0.06)\pi - 0.92(\pm0.25)I_{NH} + 4.51(\pm0.31) \quad (2)$$

$$n = 38,\ s = 0.500,\ r = 0.815,\ F_{2,35} = 37.5,\ p < 0.0001$$

the structure–activity relationships of all 38 arylhydroxamic acids. As with eq 1, π refers to the hydrophobicity constant of the entire aryl fragment. The parameter I_{NH} is an indicator variable having a value of 1 when the substituent on the hydroxamate nitrogen, R_1, is hydrogen and 0 when it is anything else (**11**, **13**, **15**, **24**, **30**).[9] This parameter accounts for the average 8-fold greater 5-lipoxygenase inhibitory activity observed among this group for *N*-methylhydroxamic acids relative to unsubstituted ones. The reason for this increase in potency is not clear, but it cannot be accounted for solely on the basis of the increased lipophilicity of the methyl group.

The electronic parameter, σ_p, has not been included in eq 2 as it was in eq 1, because the Hammett electronic parameters of many of the substituents in the expanded set have not been determined. On the basis of eq 1, an electronic term should improve the correlation, but this improvement is expected to be minor.

Chart II. Group B. Arylacrylohydroxamic Acids



Group A includes a wide variety of structures including benzohydroxamates with substituents at all positions, substituted and unsubstituted naphthohydroxamic acids, polynuclear aromatics, and a heterocyclic compound. Despite this rather diverse collection of structures, the dominant feature of the structure–activity relationship is the hydrophobicity of the aromatic ring system and its substituents. Although this hydrophobicity can be packaged in the form of many structural types, closer examination of the data suggested some generalizations about the possible boundaries of the hydrophobic binding region.

One such generalization is illuminated by hydroxamic acids **31–33**. These three compounds are outliers, exhibiting much less potency against 5-lipoxygenase than would be predicated on the basis of eq 2 (e.g., **31**: observed IC_{50} = 6.5 μM, calculated IC_{50} = 0.61). All three compounds have long alkoxy chains appended to a naphthyl ring. These alkoxy chains extend farther from the hydroxamate functionality than portions of any other molecule within group A. It must be that when these inhibitors are bound to 5-lipoxygenase, part of the alkoxy chain reaches beyond the hydrophobic binding areas of the enzyme. This portion may extend into regions (e.g. open solvent) where its lipophilicity cannot contribute to binding. If the values of π for **31–33**, as well as **29**, **30**, are adjusted so that only the lipophilicity of the first three carbons of the alkoxy chain are included (π') a much improved correlation is achieved. Equation 3 accounts for 89% of the variance in the data.

$$\log (1/IC_{50}) = 0.66(\pm0.04)\pi' - 0.83(\pm0.15)I_{NH} + 3.68(\pm0.21) \quad (3)$$

$$n = 38,\ s = 0.301,\ r = 0.942,\ F_{2,35} = 137.0,\ p < 0.0001$$

Limiting the lipophilicity to the first three carbons of the alkoxy chain produces the best correlation. It suggests that there may be a boundary to the binding region at about 12 Å from the hydroxamic acid moiety. Beyond this point hydrophobic groups do not enhance potency.

(5) Other examples of hydroxamic acid containing inhibitors of 5-lipoxygenase include: (a) Corey, E. J.; Cashman, J. R.; Kantner, S. S.; Wright, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 1503. (b) Kerdesky, F. A. J.; Schmidt, S. P.; Holms, J. H.; Dyer, R. D.; Carter, G. W.; Brooks, D. W. *J. Med. Chem.* **1987**, *30*, 1177. (c) Musser, J. H.; Kubrak, D. M.; Chang, J.; Lewis, A. J. *J. Med. Chem.* **1986**, *29*, 1429. (d) Sweeney, D.; Travis, J.; Gordon, R.; Coutts, S.; Jariwala, N.; Haung, F.; Carnathan, G. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1987**, *46*, 540. (e) Jackson, W. P.; Islip, P. J.; Kneen, G.; Pugh, A.; Wates, P. J. *J. Med. Chem.* **1988**, *31*, 499.

(6) The terms type A and type B hydroxamic acids are used as defined previously.[3] Type A hydroxamates have small substituents on the hydroxamic acid nitrogen and large groups appended to the carbonyl. The type B hydroxamates have the reverse substitution pattern.

(7) Martin, Y. C. *Quantitative Drug Design*; Marcel Dekker: New York, 1978.

(8) Values for σ_p are listed in ref 1 and were obtained from Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1208.

(9) Both *N*-methyl and *N*-unsubstituted hydroxamate of group A show a correlation with lipophilicity:

Unsubstituted: $\log (1/IC_{50}) = 0.40(\pm0.06)\pi + 3.63(\pm0.25)$

$n = 33,\ s = 0.529,\ r = 0.760,\ F_{1,31} = 8.64,\ p < 0.0001$

N-methyl: $\log (1/IC_{50}) = 0.56(\pm0.10)\pi + 3.90(\pm0.42)$

$n = 5,\ s = 0.293,\ r = 0.956,\ F_{1,3} = 31.8,\ p = 0.011$

Table I. In Vitro 5-Lipoxygenase Inhibitory Potencies and Parameters Used in the Derivation of Eq 1–18

no.	R_1	R_2	Y	π	π'	I_{NH}	I_{Big2}	I_I	IC_{50}[a]	log (1/IC_{50}) obsd	log (1/IC_{50}) calc[b]	Δ
				Group A								
1	H		4-NO_2	1.89	1.89	1	0	0	23 (21–26)	4.64	4.21	0.42
2	H		4-CN	1.58	1.58	1	0	0	61 (51–73)	4.21	4.04	0.18
3	H		4-CF_3	3.03	3.03	1	0	0	27 (24–29)	4.57	4.86	−0.30
4	H		4-Br	3.01	3.01	1	0	0	14 (12–16)	4.85	4.85	0.00
5	H		4-I	3.27	3.27	1	0	0	15 (14–16)	4.82	5.00	−0.18
6	H		4-C_6H_5	4.03	4.03	1	0	0	4.1 (3.7–4.7)	5.39	5.44	−0.05
7	H		4-CH_3	2.79	2.79	1	0	0	65 (57–74)	4.19	4.73	−0.54
8	H		4-OH	1.48	1.48	1	0	0	190 (160–230)	3.72	3.98	−0.26
9	H		4-NH_2	0.92	0.92	1	0	0	≥400	3.40	3.66	−0.26
10	H		H	2.14	2.14	1	0	0	110 (94–120)	3.95	4.36	−0.41
11	CH_3		H	2.14	2.14	0	0	0	14 (9.8–21)	4.85	5.52	−0.67
12	H		4-$CH_2CH(CH_3)_2$	4.25	3.85	1	0	0	6.0 (5.2–6.3)	5.22	5.33	−0.11
13	CH_3		4-OC_4H_9	3.65	3.65	0	0	0	0.49 (0.40–0.66)	6.31	6.38	−0.07
14	H		4-(2,4,6-$(CH_3)_3C_6H_2$)	5.98	5.98	1	0	0	0.29 (0.27–0.30)	6.54	6.55	−0.01
15	CH_3		4-(2,4,6-$(CH_3)_3C_6H_2$)	5.98	5.98	0	0	0	0.064 (0.054–0.074)	7.22	7.71	−0.49
16	H		4-(1-naphthyl)	5.20	5.20	1	0	0	0.18 (0.16–0.19)	6.74	6.11	0.64
17	H		4-(2-naphthyl)	5.20	5.20	1	0	0	0.33 (0.31–0.35)	6.48	6.11	0.38
18	H		4-(2-$NO_2C_6H_4$)	3.77	3.77	1	0	0	8.3 (7.8–8.8)	5.08	5.29	−0.21
19	H		3-C_6H_5	4.03	4.03	1	0	0	6.0 (5.2–6.8)	5.22	5.44	−0.22
20	H		3-COC_6H_5	3.21	3.21	1	0	0	7.9 (7.1–8.9)	5.10	4.97	0.13
21	H		2-OH	1.82	1.82	1	0	0	30 (25–35)	4.52	4.17	0.35
22	H			3.32	3.32	1	0	0	43 (37–53)	4.37	5.03	−0.66
23	H		H	3.32	3.32	1	0	0	14 (12–16)	4.85	5.03	−0.18
24	CH_3		H	3.32	3.32	0	0	0	1.3 (1.1–1.5)	5.89	6.19	−0.30
25	H		1-OH	2.99	2.99	1	0	0	3.6 (3.1–4.0)	5.44	4.84	0.60
26	H		3-OH	3.66	3.66	1	0	0	3.3 (3.2–3.5)	5.48	5.22	0.26
27	H		6-OCH_3	3.24	3.24	1	0	0	8.2 (6.8–9.6)	5.09	4.98	0.10
28	H		6-$OCH_2CH{=}CH_2$	3.75	3.75	1	0	0	4.6 (3.8–5.7)	5.34	5.28	0.06
29	H		6-OC_4H_9	4.82	4.29	1	0	0	2.0 (1.7–2.3)	5.70	5.59	0.11
30	CH_3		6-OC_4H_9	4.82	4.29	0	0	0	0.41 (0.36–0.45)	6.39	6.75	−0.36
31	H		6-OC_6H_{13}	6.41	4.29	1	0	0	6.5 (5.7–7.4)	5.19	5.59	−0.40
32	H		6-OC_7H_{15}	6.94	4.29	1	0	0	7.1 (5.6–9.9)	5.15	5.59	−0.44
33	H		6-$O(CH_2)_2CH{=}CH(CH_2)_4CH_3$	6.92	4.02	1	0	0	2.9 (2.6–3.2)	5.54	5.43	0.11
34	H			4.49	4.49	1	0	0	0.98 (0.91–1.0)	6.01	5.70	0.31
35	H			4.49	4.49	1	0	0	1.9 (1.6–2.2)	5.72	5.70	0.02
36	H			4.49	4.49	1	0	0	1.2 (1.1–1.4)	5.92	5.70	0.22
37	H			4.78	4.78	1	0	0	0.78 (0.66–0.91)	6.11	5.87	0.24
38	H			2.14	2.14	1	0	0	61 (56–67)	4.21	4.36	−0.15
				Group B								
39	H	H (trans)	H	2.87	2.87	1	0	0	12 (8–14)	4.92	4.77	0.15
40	H	H (cis)	H	2.87	1.44	1	1	0	31 (27–36)	4.51	3.96	0.55
41	CH_3	H	3-C_6H_5	4.75	4.75	0	0	0	0.070 (0.060–0.080)	7.15	7.01	0.15
42	CH_3	H	4-C_6H_5	4.75	4.75	0	0	0	0.13 (0.12–0.14)	6.89	7.01	−0.12
43	CH_3	H	4-(2,4,6-$(CH_3)_3C_6H_2$)	6.70	6.70	0	0	0	0.022 (0.018–0.026)	7.70	8.12	−0.42
44	CH_3	H	4-OC_4H_9	4.37	4.37	0	0	0	0.10 (0.08–0.12)	7.00	6.79	0.21
45	CH_3	H	4-$OCH_2C_6H_5$	4.53	4.53	0	0	0	0.11 (0.09–0.14)	6.96	6.88	0.08
46	CH_3	H	H	4.04	4.04	0	0	0	0.21 (0.17–0.25)	6.68	6.60	0.07
47	CH_3	H	4-NO_2	3.78	3.78	0	0	0	0.13 (0.11–0.15)	6.89	6.46	0.43
48	H	H	H	4.04	4.04	1	0	0	0.95 (0.77–1.1)	6.02	5.44	0.58
49	CH_3	H	H	4.04	4.04	0	0	0	0.10 (0.091–0.11)	7.00	6.60	0.40
50	$CH(CH_3)_2$	H	H	4.04	4.04	0	0	0	0.082 (0.040–0.15)	7.10	6.60	0.49
51	*c*-C_6H_{11}	H	H	4.04	4.04	0	0	0	0.10 (0.085–0.12)	7.00	6.60	0.40
52	C_6H_5	H	H	4.04	4.04	0	0	0	0.052 (0.040–0.069)	7.30	6.60	0.70
53	4-$CH_3C_6H_4$	H	H	4.04	4.04	0	0	0	0.28 (0.23–0.32)	6.55	6.60	−0.05
54	CH_3	H	3-NO_2	3.78	3.78	0	0	0	0.30 (0.24–0.37)	6.52	6.45	0.07
55	H	CH_3	H	4.57	4.57	1	0	0	1.8 (1.6–2.1)	5.74	5.74	0.00
56	CH_3	CH_3	H	4.57	4.57	0	0	0	0.47 (0.43–0.52)	6.33	6.90	−0.58
57	CH_3	C_6H_5	H	5.61	4.54	0	1	0	0.51 (0.44–0.59)	6.29	6.20	0.09
58	CH_3	4-FC_6H_4	H	5.75	4.54	0	1	0	0.95 (0.82–1.09)	6.02	6.20	−0.18
59	CH_3	4-ClC_6H_4	H	6.32	4.54	0	1	0	1.5 (1.3–1.7)	5.82	6.20	−0.37
60	CH_3	4-BrC_6H_4	H	6.47	4.54	0	1	0	1.8 (1.7–1.9)	5.74	6.20	−0.45
61	CH_3			5.87	3.02	0	1	0	2.7 (2.2–3.2)	5.57	5.33	0.24
62	CH_3			4.44	4.44	0	0	0	0.12 (0.10–0.14)	6.92	6.83	0.09
63	CH_3			3.44	3.44	0	0	0	0.16 (0.14–0.18)	6.80	6.26	0.53
64	CH_3			4.50	4.50	0	0	0	0.13 (0.10–0.16)	6.89	6.87	0.02
65	CH_3			4.50	4.50	0	0	0	0.10 (0.08–0.12)	7.00	6.87	0.14
66	CH_3			5.21	5.21	0	0	0	0.12 (0.08–0.15)	6.92	7.27	−0.35
67	H			2.41	2.41	1	0	0	46 (42–49)	4.34	4.51	−0.18
				Group C								
68	H	H	H	2.79	2.79	1	0	1	300 (250–300)	3.53	4.09	−0.56
69	H	H	4-OC_4H_9	4.30	4.30	1	0	1	27 (23–34)	4.57	4.95	−0.38
70	CH_3	H	4-OC_4H_9	4.30	4.30	0	0	1	0.72 (0.61–0.85)	6.14	6.11	0.03

Table I (Continued)

no.	R_1	R_2	Y	π	π'	I_{NH}	I_{Big2}	I_1	IC_{50}[a]	log (1/IC_{50}) obsd	log (1/IC_{50}) calc[b]	Δ
71	CH_3	CH_3	4-OC_4H_9	4.83	4.83	0	0	1	0.77 (0.70–0.88)	6.11	6.41	−0.30
72	CH_3	$CH(CH_3)_2$	4-OC_4H_9	5.75	4.83	0	1	1	0.85 (0.69–1.0)	6.07	5.72	0.35
73	H	CH_3	4-$CH_2CH(CH_3)_2$	5.43	5.03[c]	1	0	1	5.7 (5.3–6.1)	5.24	5.37	−0.12
74	CH_3	CH_3	4-$CH_2CH(CH_3)_2$	5.43	5.03[c]	0	0	1	0.29 (0.23–0.35)	6.54	6.53	0.01
75	$CH(CH_3)_2$	CH_3	4-$CH_2CH(CH_3)_2$	5.43	5.03[c]	0	0	1	0.43 (0.37–0.50)	6.37	6.53	−0.16
76	c-C_6H_{11}	CH_3	4-$CH_2CH(CH_3)_2$	5.43	5.03[c]	0	0	1	0.43 (0.37–0.51)	6.37	6.53	−0.16
77	C_6H_5	CH_3	4-$CH_2CH(CH_3)_2$	5.43	5.03[c]	0	0	1	0.38 (0.33–0.43)	6.42	6.53	−0.11
78	CH_3	H	4-$CH_2CH(CH_3)_2$	4.90	4.50[c]	0	0	1	0.39 (0.35–0.43)	6.41	6.23	0.18
79	CH_3	CH_2CH_3	4-$CH_2CH(CH_3)_2$	5.96	5.03[c]	0	1	1	0.56 (0.52–0.61)	6.25	5.84	0.41
80	CH_3	$(CH_3)_2$	4-$CH_2CH(CH_3)_2$	5.83	5.03[c]	0	1	1	0.76 (0.61–1.0)	6.12	5.84	0.28
81	CH_3	$CH(CH_3)_2$	4-$CH_2CH(CH_3)_2$	6.35	5.03[c]	0	1	1	1.6 (1.3–1.8)	5.80	5.84	−0.04
82	CH_3	$CH_2C_6H_5$	4-$CH_2CH(CH_3)_2$	6.99	5.03[c]	0	1	1	1.5 (1.3–1.7)	5.89	5.84	0.05
83	CH_3	CH_3	4-$OCH(CH_3)_2$	4.08	3.77[c]	0	0	1	3.7 (3.5–3.8)	5.43	5.81	−0.38
84	CH_3	CH_3	4-$OCH_2C_6H_5$	5.07	5.07	0	0	1	0.28 (0.27–0.28)	6.55	6.55	0.00
85	CH_3	H	4-C_6H_5	4.68	4.68	0	0	1	0.36 (0.31–0.41)	6.44	6.33	0.12
86	CH_3	H	2,4,6-$(CH_3)_3$	4.74	4.74	0	0	1	2.6 (2.2–3.0)	5.57	6.36	−0.79
87	CH_3	CH_3	3-COC_6H_5	3.67	3.67	0	0	1	0.83 (0.76–0.93)	6.08	5.75	0.33
88	H	H		3.97	3.97	1	0	1	27 (26–29)	4.57	4.76	−0.19
89	H	H	H	3.97	3.97	1	0	1	19 (16–21)	4.72	4.76	−0.04
90	CH_3	CH_3	H	4.49	3.94	0	0	1	0.59 (0.52–0.67)	6.23	5.90	0.33
91	H	H	6-OCH_3	3.88	3.88	1	0	1	22 (20–24)	4.66	4.71	−0.06
92	H	CH_3	6-OCH_3	4.41	4.41	1	0	1	6.5 (6.1–6.8)	5.19	5.02	0.17
93	CH_3	CH_3	6-OCH_3	4.41	4.41	0	0	1	0.41 (0.34–0.50)	6.39	6.18	0.21
94	H		H	3.32	3.32	1	0	1	87 (81–93)	4.06	4.39	−0.33
95	CH_3		4-OC_4H_9	4.83	4.83	0	0	1	0.31 (0.28–0.34)	6.51	6.41	0.10
96	CH_3		4-$CH_2CH(CH_3)_2$	5.43	5.03	0	0	1	0.45 (0.36–0.52)	6.35	6.53	−0.18
97	H		H	4.49	4.49	1	0	1	9.7 (8.5–11)	5.01	5.06	−0.05
98	CH_3		H	4.49	4.49	0	0	1	0.38 (0.29–0.47)	6.42	6.22	0.20
99	H		7-CH_3	5.14	5.14	1	0	1	2.9 (2.7–3.1)	5.54	5.43	0.11
100	CH_3			4.44	4.44	0	0	1	0.34 (0.30–0.40)	6.47	6.19	0.28
101	CH_3			4.76	4.63	0	1	1	5.3 (4.6–6.1)	5.28	5.61	−0.33
102	H			3.85	3.85	1	0	1	27 (25–29)	4.57	4.69	−0.13
					Group D							
103	H	H	4-OC_4H_9	3.74	3.74	1	0	1	5.3 (4.6–6.1)	5.28	4.63	0.65
104	CH_3	H	4-OC_4H_9	3.74	3.74	0	0	1	0.89 (0.68–1.1)	6.05	5.79	0.26
105	H	CH_3	4-OC_4H_9	4.27	4.27	1	0	1	8.0 (6.6–9.3)	5.10	4.93	0.17
106	CH_3	CH_3	4-OC_4H_9	4.27	4.27	0	0	1	1.3 (1.1–1.6)	5.89	6.09	−0.21
107	CH_3	C_6H_5	4-OC_4H_9	3.72	3.72	0	0	1	0.64 (0.56–0.71)	6.19	5.78	0.41
108	CH_3	CH_3	4-OC_4H_9	4.48	4.48	0	0	1	0.67 (0.50–0.61)	6.17	6.21	−0.04
109	CH_3	CH_3	4-NO_2	2.63	2.63	0	0	1	14 (12–16)	4.85	5.16	−0.31
110	CH_3			3.24	3.24	0	0	1	2.1 (1.6–2.6)	5.68	5.50	0.17
111	H			4.40	4.40	1	0	1	4.6 (3.8–5.7)	5.34	5.01	0.33

[a] In vitro RBL-1 5-lipoxygenase inhibitory potencies in units of μM. Values in parentheses represent 95% confidence limits. [b] Calculated according to eq 15. [c] Indicated values are those used in eq 7, 8, 10, and 12–18. The values for π' used in eq 9 are **73–77** and **79–82**, 5.43; **78**, 490; **83**, 4.08. In all other cases π'' is equal to π'.

Group B: Arylacrylohydroxamic Acids (Chart II). Group B includes 29 compounds (**39–67**) in which an unsaturated spacer unit connects the hydroxamate moiety with the aromatic ring. Equation 4 describes the relationship of the activity of compounds in group B with the parameters π and I_{NH} (as defined above). This equation provides only a crude description of the QSAR. In particular it fails to accurately predict the activity of compounds **40** and **57–61**. Equation 5 demonstrates how a superior correlation is achieved when these six compounds are excluded from group B.

$$\log (1/IC_{50}) = -0.09(\pm 0.12)\pi - 1.81(\pm 0.33)I_{NH} + 7.13(\pm 0.58) \quad (4)$$

$$n = 29,\ s = 0.571,\ r = 0.765,\ F_{2,26} = 18.3,\ p < 0.0001$$

$$\log (1/IC_{50}) = 0.36(\pm 0.09)\pi - 1.34(\pm 0.20)I_{NH} + 5.33(\pm 0.39) \quad (5)$$

$$n = 23,\ s = 0.301,\ r = 0.925,\ F_{2,20} = 59.0,\ p < 0.0001$$

Hydroxamic acids **57–61** are the only compounds of group B that have groups larger than methyl at R_2; the phenyl group of cis compound **40** extends into the region of space occupied by large R_2 substituents. These six compounds are less effective inhibitors of 5-lipoxygenase than analogous compounds with smaller groups at this position (e.g. compare **49**, IC_{50} = 0.1 μM, and **60**, IC_{50} = 1.8 μM).

Several methods of incorporating the effects of large R_2 substituents into the QSAR of group B were examined. Parameters describing the size of the R_2 substituent (e.g. MR) and higher order lipophilicity terms were studied, but no expression could be identified which produced a significant correlation for this small set of compounds. However, an improvement in the correlation was observed when the values of π were adjusted so as to omit the contribution of the hydrophobicity of all but the first carbon of the R_2 substituent. A comparison of the correlation of potency with π and the adjusted parameter, π', for compounds **40** and **57–61** are given in eqs 6 and 7, respectively. The parameter I_{NH} was dropped from these expressions since all but one of the compounds in the set is an *N*-methyl hydroxamate (I_{NH} = 0).

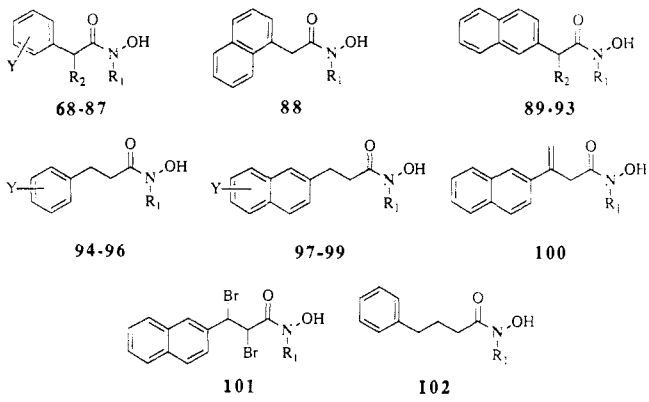
$$\log (1/IC_{50}) = 0.38(\pm 0.13)\pi + 3.55(\pm 0.73) \quad (6)$$

$$n = 6,\ s = 0.387,\ r = 0.827,\ F_{1,4} = 8.64,\ p = 0.04$$

$$\log (1/IC_{50}) = 0.44(\pm 0.09)\pi' + 3.99(\pm 0.35) \quad (7)$$

$$n = 6,\ s = 0.254,\ r = 0.929,\ F_{1,4} = 25.4,\ p = 0.007$$

Chart III. Group C. (Arylalkyl)hydroxamic Acids



The physical significance of this adjustment to the hydrophobicity parameter is unclear. It may reflect the existence of another boundary to the hydrophobic binding region. This is not unreasonable since the hydroxamate moiety is likely to interact with the enzyme in a relatively hydrophilic site. Large hydrophobic groups at R_2 might extend into this region. Thus only part of the hydrophobicity of the R_2 substituent would be expected to interact favorably with the enzyme and contribute to enhanced inhibition.

Comparison of the coefficients of π and π' in eqs 5 and 7 reveals that the potency of compounds with both small and large R_2 substituents exhibit similar dependency on lipophilicity. However, from the intercepts of these equations it can be seen that compounds with large R_2 substituents are less potent than compounds of similar lipophilicity with small R_2 groups. To account for this lower potency a new parameter, I_{Big2}, was introduced. I_{Big2} is an indicator variable having a value of 0 when R_2 is hydrogen or methyl and 1 for anything larger. Equation 8 describes the QSAR for the entire set of group B compounds when I_{Big2} is included.

$$\log (1/IC_{50}) = 0.36(\pm 0.07)\pi' - 1.46(\pm 0.18)I_{NH} - 0.98(\pm 0.15)I_{Big2} + 5.36(\pm 0.33) \quad (8)$$

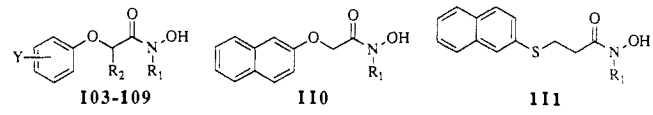
$$n = 29,\ s = 0.299,\ r = 0.944,\ F_{2,26} = 67.8,\ p < 0.0001$$

The coefficient of I_{Big2} indicates that the presence of a large R_2 substituent causes an approximate 10-fold loss in activity. The reason for this loss remains obscure, but it is tempting to speculate that these large groups interfere with the ability of the hydroxamic acid functionality to bind optimally with the enzyme.

The negative coefficient on the indicator variable I_{NH} in eq 8 again signifies that compounds with alkyl substituents at R_1 inhibit 5-lipoxygenase more effectively than unsubstituted hydroxamates. Four compounds in this set (**50–53**) have alkyl groups larger than methyl at R_1. These compounds are generally no more potent than analogous *N*-methyl hydroxamates. Apparently the added lipophilicity at R_1 does not greatly increase inhibitory activity. The failure of large R_1 substituents to enhance 5-lipoxygenase inhibition may be related to the failure of large R_2 substituent to affect potency. In both cases large hydrophobic groups are placed in the immediate vicinity of the hydrophilic hydroxamate moiety.

The carbonyl substituents of all but one of the 29 compounds in group B extends no more than 12 Å from the hydroxamate carbonyl. Only compound **45** extends slightly past the limit of the lipophilic binding domain (about 13 Å from the carbonyl) proposed above for group A compounds. However, adjusting the lipophilicity of this single compound slightly does not appreciably alter the correlation in eq 8.

Chart IV. Group D. [(Aryloxy)alkyl]hydroxamic Acids



Group C. (Arylalkyl)hydroxamic Acids (Chart III). Compounds of structural group C (**68–102**) have a saturated alkyl spacer unit between the aromatic ring system and the hydroxamate functionality. The relationship of structure to activity for the 35 compounds in this group is described by eq 9. The same parameters were used to

$$\log (1/IC_{50}) = 0.49(\pm 0.09)\pi' - 1.27(\pm 0.12)I_{NH} - 0.58(\pm 0.14)I_{Big2} + 3.94(\pm 0.42) \quad (9)$$

$$n = 35,\ s = 0.293,\ r = 0.939,\ F_{2,32} = 77.3,\ p < 0.0001$$

describe this set of compounds as were used for group B (eq 8). The I_{NH} term again indicates that a 19-fold average improvement in activity is achieved with alkyl substitution at R_1 and, as with group B, large alkyl substituents at R_1 improve potency no more than a simple methyl substituent. I_{Big2} has been included to indicate the presence of large substituents at R_2, and π has been adjusted as previously described to omit the hydrophobicity of all but the first carbon of R_2. The coefficient for I_{Big2} is slightly smaller than that found in eq 8.

Ten of the 35 compounds in group C have *p*-isobutyl groups as the Y substituent (**73–82**). Compound **83** has an isosteric *p*-isopropoxy substituent. Examination of the data revealed that these compounds were consistently less potent than predicted by eq 9. Several methods of accounting for this deviation were investigated. The best correlation was obtained when the hydrophobicity terms for these compounds were adjusted so that only one of the two methyls of the isobutyl was included. Accordingly the π' term for **73–83** was altered and used to derive eq 10. This expression better predicted the potency of the isobutyl compounds and provided a more significant correlation than eq 9.

$$\log (1/IC_{50}) = 0.61(\pm 0.09)\pi'' - 1.26(\pm 0.11)I_{NH} - 0.62(\pm 0.13)I_{Big2} + 3.43(\pm 0.43) \quad (10)$$

$$n = 35,\ s = 0.266,\ r = 0.950,\ F_{2,32} = 95.7,\ p < 0.0001$$

The physical significance of the adjustment to π for *p*-isobutyl-containing compounds is unknown. Perhaps one of the methyl groups extends beyond the boundary of the hydrophobic binding region or lies above a hydrophobic binding surface.

Group D: [(Aryloxy)alkyl]hydroxamic Acids (Chart IV). The fourth set of hydroxamates includes eight compounds (**104–111**) in which an ether linkage is used to connect an aromatic ring system to a hydroxamate-bearing alkyl chain. Equation 11 explains 73% of

$$\log (1/IC_{50}) = 0.57(\pm 0.21)\pi - 0.80(\pm 0.27)I_{NH} + 3.71(\pm 0.77) \quad (11)$$

$$n = 8,\ s = 0.319,\ r = 0.853,\ F_{2,5} = 6.69,\ p < 0.03$$

the variance in the data of this set. As with previous sets, compounds of greater lipophilicity are more potent inhibitors and methyl substitution on the hydroxamate nitrogen improves the inhibitory activity. One compound (**107**) contains a phenyl group at R_2. This large group does not appear to create a loss in activity and a I_{Big2} term does not significantly improve the correlation.

Table II. Correlation Matrix of Variables Used in Eq 12

	π'	I_{NH}	I_{Big2}	I_I
π'	1.00	−0.39	0.20	0.28
I_{NH}		1.00	−0.31	−0.24
I_{Big2}			1.00	0.10
I_I				1.00

Cumulative QSAR of Groups A–D. The structure–activity relationships described for the four structural groups above have several common features. Although the coefficients vary slightly, eq 2–11 demonstrate that the common physicochemical feature affecting the 5-lipoxygenase inhibitory potency of all 111 compounds is the lipophilicity of the molecules. The substitution on the hydroxamate nitrogen (I_{NH}) and at R_2 (I_{Big2}) are also important. Since there is similarity in the QSAR of all the compounds, eq 12 was derived to evaluate the overall

$$\log (1/IC_{50}) = 0.51(\pm0.05)\pi' - 1.07(\pm0.09)I_{NH} - 0.70(\pm0.15)I_{Big2} + 4.28(\pm0.21) \quad (12)$$

$$n = 111,\ s = 0.441,\ r = 0.884,\ F_{3,107} = 128.0,\ p < 0.0001$$

QSAR of the four groups. Further examination of the data revealed that eq 12 consistently predicted compounds in groups C and D to be less potent than analogous compounds in groups A and B. Equations 13 and 14 describe

$$\log (1/IC_{50}) = 0.55(\pm0.04)\pi' - 1.11(\pm0.10)I_{NH} - 0.59(\pm0.16)I_{Big2} + 4.36(\pm0.21) \quad (13)$$

$$n = 67,\ s = 0.369,\ r = 0.937,\ F_{3,63} = 150.7,\ p < 0.0001$$

$$\log (1/IC_{50}) = 0.58(\pm0.08)\pi' - 1.18(\pm0.10)I_{NH} - 0.58(\pm0.15)I_{Big2} + 3.60(\pm0.34) \quad (14)$$

$$n = 44,\ s = 0.294,\ r = 0.927,\ F_{3,40} = 81.4,\ p < 0.0001$$

the separate correlations for groups A and B, and C and D, respectively. Although the coefficients for each of the parameters in eqs 13 and 14 are quite similar, the intercepts are significantly different and consistent with the difference in potency observed. To account for this difference an additional parameter, I_I, was included to indicate whether the hydroxamic acid functionality is electronically insulated from the aromatic ring system. I_I is assigned a value of 0 when the hydroxamate is directly attached to the aryl ring or attached through an unsaturated spacer unit (groups A and B); I_I is given a value of 1 when the groups are insulated by one or more methylenes (groups C and D). Equation 15 describes the QSAR for compounds 1–111 with the I_I parameter included. This

$$\log (1/IC_{50}) = 0.57(\pm0.03)\pi' - 1.16(\pm0.07)I_{NH} - 0.69(\pm0.11)I_{Big2} - 0.64(\pm0.07)I_I + 4.30(\pm0.15) \quad (15)$$

$$n = 111,\ s = 0.323,\ r = 0.940,\ F_{4,106} = 201.8,\ p < 0.0001$$

equation is statistically significant above the 99.9% confidence limit as judged by the F statistic and explains 89% of the variance in the data. The stepwise derivation of this equation is given in eqs 16–18 and the correlation matrix for the variables is shown in Table II.

$$\log (1/IC_{50}) = 0.67(\pm0.06)\pi' + 3.04(\pm0.26) \quad (16)$$

$$n = 111,\ s = 0.652,\ r = 0.717,\ F_{1,109} = 115.6,\ p < 0.0001$$

$$\log (1/IC_{50}) = 0.48(\pm0.05)\pi' - 0.95(\pm0.10)I_{NH} + 4.23(\pm0.23) \quad (17)$$

$$n = 111,\ s = 0.483,\ r = 0.858,\ F_{2,108} = 150.5,\ p < 0.0001$$

$$\log (1/IC_{50}) = 0.55(\pm0.04)\pi' - 1.05(\pm0.08)I_{NH} - 0.64(\pm0.08)I_I + 4.25(\pm0.18) \quad (18)$$

$$n = 111,\ s = 0.379,\ r = 0.916,\ F_{3,107} = 185.9,\ p < 0.0001$$

The coefficient of the new parameter I_I in eq 15 indicates that presence of a saturated spacer units between the hydroxamate and the aryl ring system (groups C or D) results in about a 4-fold reduction in 5-lipoxygenase inhibitory activity relative to those with an unsaturated spacer (group B) or no spacer at all (group A). Whether this difference in potency is actually due to some sort of electronic interaction between the aromatic ring and the hydroxamate which influences inhibition or whether it is due to some other effect is unclear.

As with each of the individual structural groups, the negative coefficient for I_{NH} indicates that an *N*-alkylhydroxamic acid is on average about 15 times more potent than an N-unsubstituted analogue. The I_{Big2} term confirms that large groups near the hydroxamate result in reduced potency.

The most important physical property determining inhibitory potency is the lipophilicity of the molecule. The coefficient of 0.57 for π' suggests that a typical hydroxamic acid is about 57% desolvated when bound to 5-lipoxygenase. Hansch[10] has proposed that hydrophobicity coefficients of this magnitude may indicate that the inhibitor rests upon a surface or shallow trough of the enzyme.

Recently, Hammond et al.[11] have reported that there is a similar relationship between hydrophobicity and 5-lipoxygenase inhibitory potency for a set of more than 50 dihydrobenzofuran-containing compounds. It appears that hydrophobicity has a dominant effect on the 5-lipoxygenase inhibitory potency of many classes of compounds.

Summary

The 111 hydroxamic acids in Table I encompass a diverse set of type A[6] hydroxamic acid 5-lipoxygenase inhibitors. Among the structural types are benzo- and naphthohydroxamic acids with a variety of substituents, polycyclic aromatics, arylacrylohydroxamic acids, and arylalkylhydroxamic acids with branched or straight chain alkyl spacer units of one to three atoms. Compounds are included with π' values spanning 7 log units and potencies differing by more than 4 orders of magnitude. Despite this structural diversity, some common patterns of inhibition can be identified through QSAR and a rudimentary picture of how hydroxamic acid inhibitors and 5-lipoxygenase interact can be envisioned. The structure–activity relationships discussed here demonstrate that a wide variety of hydroxamates can inhibit this enzyme and the potency of the compounds is largely governed by the hydrophobicity of the molecule. The QSAR suggests that hydroxamic acids may interact with a large hydrophobic surface or trough on the enzyme. This hydrophobicity can be packaged in a variety of ways and still enhance inhibition. However, two major areas were identified where hydrophobicity does not appear to improve inhibitory activity. Large lipophilic substituents (R_1 and R_2) extremely close to the hydroxamate moiety may be encountering hydrophilic areas of the enzyme. Also, at distance relatively remote from the hydroxamate (greater than about 12 Å), portions of inhibitors may extend beyond the hydrophobic binding region of the enzyme. Other regions where hydrophobicity does not contribute are also possible.

This QSAR study also demonstrated that 5-lipoxygenase inhibitory activity is adversely affected by large groups at

(10) Hansch, C.; Klein, T. E. *Acc. Chem. Res.* **1986**, *19*, 392.
(11) Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Leull, S.; MacIntyre, D. E. *J. Med. Chem.* **1989**, *32*, 1006.

R_2 (I_{Big2}) and by spacer groups which electronically insulate the hydroxamic acid from the aromatic ring (I). Potency is improved by alkyl substitution on the hydroxamate nitrogen (I_{NH}).

We have previously proposed a graphical representation of the inhibitor binding region of 5-lipoxygenase.[1] That representation was useful in the identification of many potent inhibitors, but was based entirely on hypotheses for matching inhibitor geometry to a putative substrate conformation. The empirically derived view of the inhibitor binding site set forth by the present QSAR study goes beyond these simplistic hypotheses and provides a more general and reliable view of inhibitor–enzyme interaction. In this QSAR investigation, no attempt has been made to derive the conformation of the inhibitors or to describe the inhibitor enzyme interactions in detail. The parameters are crude and adjustments are somewhat arbitrary. Nonetheless, the equations presented here provide a highly significant description of the inhibitory potency of hydroxamic acids.

Experimental Section

Determination of π and π' Values. The program CLOGP[12] was used to calculate the hydrophobicity parameters in this investigation. The term π is the logarithm of the octanol–water partition coefficient calculated for a molecule corresponding to the fragment of the inhibitor attached to the hydroxamate carbonyl group. For example, the π value of 1.89 for *p*-nitrobenzohydroxamic acid (1), is the calculated partition coefficient for nitrobenzene. When portions of the carbonyl substituent were omitted to give π', values were calculated with the corresponding abbreviated molecule.

Determination of 5-Lipoxygenase Inhibitory Potencies. Adherent rat basophilic leukemia (RBL-1) cells were harvested by trypsinization, suspended (3.0×10^7 cells/mL) in buffer [10 mM *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 10 mM piperazine-*N,N'*-bis(2-ethanesulfonic acid) (PIPES), 1 mM ethylenediaminetetraacetic acid (EDTA), pH 6.8], and lysed by sonication. The lysate was centrifuged at 20000*g* for 20 min and the supernatant containing the 5-lipoxygenase activity was stored frozen until used.

Compounds were evaluated for 5-lipoxygenase activity in 100-μL incubations containing 12.5 μL of the RBL-1 20000*g* supernatant in assay buffer (10 mM BES, 10 mM PIPES, 1 mM EDTA, 0.7 mM $CaCl_2$, and 100 mM NaCl, pH 6.8). Compounds were dissolved in dimethyl sulfoxide, and preincubated with the enzyme for 20 min at 37 °C before initiation of the 5-lipoxygenase reaction by addition of 6.6 nmol of arachidonic acid and 25 nCi of [^{14}C]arachidonic acid (55.8 mCi/mmol) in 3 μL of aqueous NH_4OH (0.028%). As an internal recovery standard, 3 nCi of [^{3}H]5-HETE was added with the substrate. Reactions were terminated after 5 min by acidification with HCl to pH 3.5. Under these conditions the initial product of the reaction, 5-HPETE, was further converted to 5-HETE. The reducing agent triphenylphosphine (100 μg) was then added to convert any remaining 5-HPETE to 5-HETE, and the product was separated by TLC.

Table III. Summary of Physical Data for New Compounds

no.	formula[a]	mp, °C	no.	formula[a]	mp, °C
11	$C_6H_9NO_2$	oil[b]	64	$C_{16}H_{15}NO_2$	187–190
13	$C_{12}H_{17}NO_3$	76–77	65	$C_{16}H_{15}NO_2$	178–180
18	$C_{13}H_{10}N_2O_4$	oil	66	$C_{16}H_{15}NO_2$	170–173
19	$C_{13}H_{11}NO_2$	179–180	69	$C_{12}H_{17}NO_3$	161–162[e]
20	$C_{14}H_{11}NO_3$	149–151	70	$C_{13}H_{19}NO_3$	oil
25	$C_{11}H_9NO_3$	186–187 dec[c]	72	$C_{16}H_{25}NO_3$	oil
26	$C_{11}H_9NO_3$	195–196 dec[d]	76	$C_{19}H_{29}NO_2$	117–120
28	$C_{14}H_{13}NO_3$	178–180 dec	79	$C_{15}H_{23}NO_2$	65–66
30	$C_{16}H_{19}NO_3$	137–138	82	$C_{20}H_{25}NO_2$	oil
34	$C_{15}H_{11}NO_2$	185 dec	85	$C_{15}H_{15}NO_2$	138
35	$C_{15}H_{11}NO_2$	192	86	$C_{12}H_{17}NO_2$	135–137
36	$C_{15}H_{11}NO_2$	208–209 dec	87	$C_{17}H_{17}NO_3$	144–146
37	$C_{15}H_{13}NO_2$	160–163 dec	90	$C_{14}H_{15}NO_2$	117–118
38	$C_9H_6N_2O_2$	165 dec	91	$C_{13}H_{13}NO_3$	183–184
41	$C_{16}H_{15}NO_2$	143–145	92	$C_{14}H_{15}NO_3$	168–169
42	$C_{16}H_{15}NO_2$	oil	95	$C_{14}H_{21}NO_3$	64–65
44	$C_{14}H_{19}NO_3$	134–135	98	$C_{14}H_{15}NO_2$	91–93
45	$C_{17}H_{17}NO_3$	181–183	99	$C_{14}H_{15}NO_2$	182–183
46	$C_{14}H_{13}NO_2$	156–157	100	$C_{15}H_{15}NO_2$	121–123
47	$C_{14}H_{12}N_2O_4$	164–166	101	$C_{14}H_{13}Br_2NO_2$	129–131
53	$C_{20}H_{17}NO_2$	203–206	103	$C_{12}H_{17}NO_4$	138–140
54	$C_{14}H_{12}N_2O_4$	163–164	104	$C_{13}H_{19}NO_4$	151–152
55	$C_{14}H_{13}NO_2$	147–148	105	$C_{13}H_{19}NO_4$	113–115
56	$C_{15}H_{15}NO_2$	93–95	106	$C_{14}H_{21}NO_4$	149–150
58	$C_{20}H_{16}FNO_2$	132–134	107	$C_{19}H_{23}NO_4$	128–129.5
59	$C_{20}H_{16}ClNO_2$	140–142	108	$C_{16}H_{17}NO_3$	160
60	$C_{20}H_{16}BrNO_2$	118–120	109	$C_{10}H_{12}N_2O_5$	156–158
61	$C_{22}H_{19}NO_2$	195–197	110	$C_{13}H_{13}NO_3$	188–190 dec
63	$C_{16}H_{13}NO_4$	130 dec	111	$C_{13}H_{13}NO_2S$	118–119

[a] Elemental analysis data are within ±0.4% of the theoretical values. [b] Previously prepared.[13] [c] Literature[14] mp 188–192 °C. [d] Literature mp 206–207.5 °C;[15a] 191–192 °C.[15b] [e] Literature[16] mp 155 °C.

The acidified incubations were prepared for TLC analysis by addition of 20 μg each of 5-HETE and arachidonic acid to permit visualization of product and substrate on TLC plates and 150 μL of acetone to extract eicosanoids. Aliquots of acetone extracts were applied to silica gel impregnated glass-fiber TLC sheets which were developed with hexane–ethyl acetate–glacial acetic acid (85:15:0.25). Arachidonic acid and 5-HETE were located by brief exposure to iodine vapor, the reaction product was eluted, and radioactivity was measured with a liquid-scintillation counter. Product formation in the individual incubations was corrected for recovery of [^{3}H]5-HETE.

Synthesis. The detailed procedures for many of the compounds in this investigation have been previously reported.[1,2,4] Other hydroxamic acids were prepared from the corresponding carboxylic acid according to the methods described for **13** below. Melting point and analytical data for these new compounds are reported in Table III.

***N*-Hydroxy-*N*-methyl-4-butoxybenzamide (13).** 4-Butoxybenzoic acid (1.7 g, 8.75 mmol) and DMF (0.64 g, 8.75 mmol) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Oxalyl chloride (2.84 g, 21.8 mmol) was added slowly. Vigorous gas evolution was noted. After being stirred for 40 min, this solution was added to a solution of *N*-methylhydroxylamine (2.92 g, 35.0 mmol) and triethylamine (5.31 g, 52.6) in THF (50 mL)/H_2O (5 mL). After being stirred an additional 30 min, the mixture was poured into 2 N HCl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue was recrystallized from hexanes to give a white solid (1.5 g, 79%): ^{1}H NMR (Me_2SO-d_6) δ 0.93 (t, 3 H, J = 7.5 Hz), 1.33–1.50 (m, 2 H), 1.65–1.75 (m, 2 H), 3.23 (s, 3 H), 4.00 (t, 2 H, J = 6 Hz), 6.94 (d, 2 H, J = 9 Hz), 7.64 (d, 2 H, J = 9 Hz), 9.96 (s, 1 H); MS m/e 223, 177, 121. Anal. ($C_{12}H_{17}NO_3$) C, H, N.

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(12) CLOGP Program, MedChem Project, Pomona College, Claremont, CA.
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