4-Hydroxythiazole Inhibitors of 5-Lipoxygenase

Francis A. J. Kerdesky,* James H. Holms, Jimmie L. Moore, Randy L. Bell, Richard D. Dyer, George W. Carter, and Dee W. Brooks*

Immunosciences Research Area, Abbott Laboratories, Abbott Park, Illinois 60064. *Received October 23, 1990*

4-Hydroxythiazoles have been identified as potent inhibitors of 5-lipoxygenase in vitro exhibiting IC_{50}'s of less than 1 μM. An investigation of structure–activity relationships showed that the most potent inhibitors of this series are the 5-phenyl derivatives. The corresponding thiazolidin-4-one analogues were found to be relatively inactive. The 4-hydroxythiazoles were active inhibitors against 5-lipoxygenase in both intact rat polymorphonuclear leukocytes and human whole blood. The compounds were also selective inhibitors of 5-lipoxygenase, displaying only weak activity against other related enzymes, cyclooxygenase and 12- and 15-lipoxygenase.

The enzyme 5-lipoxygenase catalyzes the initial step in the metabolism of arachidonic acid leading to the leukotrienes, which have been implicated as important mediators of various human disorders.[1] Modulation of the activity of this enzyme provides a new therapeutic approach to treat leukotriene-mediated afflications and should offer an important means to further elucidate the role of leukotrienes in pathophysiological events.

During investigations to develop selective inhibitors of 5-lipoxygenase,[2] it was discovered that 5-methyl-2-phenyl-4-hydroxythiazole (**1**) had potent inhibitory activity (IC_{50} = 0.96 μM) against the RBL-1, 5-lipoxygenase enzyme (20000*g* supernatant), whereas, the closely related 2-phenylthiazolin-4-one (keto tautomer) (**2**) was relatively inactive (26% inhibition at 30 μM). Nuclear magnetic resonance (in DMSO-d_6 and $CDCl_3$) and infrared (KBr) spectrometric studies indicated that **1** existed entirely in the hydroxythiazole or enol form, while **2** existed as a mixture of keto and enol tautomers with the keto form predominant.[3] Several other related compounds were prepared and evaluated (Figure 1) to address the hypothesis that the 4-hydroxythiazole or enol form was necessary for potent inhibitory activity. Thiazolinone **3** constrained to the keto form by α-disubstitution was also inactive. Removal of the 4-hydroxy group as in thiazole **4** resulted in a compound with no inhibitory activity. Another pair of compounds **5** and **6** showed a similar phenomenon; that is, hydroxythiazole **5** was an inhibitor (IC_{50} = 3.9 μM) while thiazolidinone **6** was only marginally active (8% inhibition at 30 μM). These initial observations led us to propose that the 4-hydroxythiazole unit was a promising lead for the development of potent 5-lipoxygenase inhibitors.

Chemistry

The 4-hydroxythiazoles were prepared via two general synthetic routes[4] outlined in Scheme I. The first approach, Method A, involved the reaction of a nitrile with an α-mercaptoacetic acid derivative at 100 °C for several hours. The second approach, Method B, utilized the condensation of an α-halo ester with an appropriately substituted thioamide in toluene at 80 °C for several hours. Conventional methods of hydroxyl derivitization were used to provide analogues of the parent hydroxythiazoles.

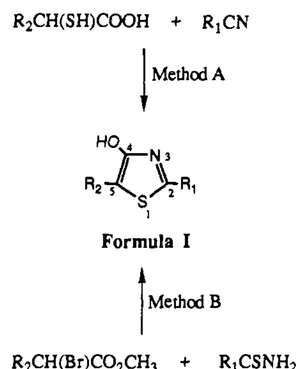
(1) Schewe, T.; Rapoport, S. M.; Kuhn, H. In *Advances in Enzymology*; Meister, E., Ed.; J. Wiley: New York, 1986; Vol. 58, pp 191–272.

(2) Summers, J. B.; Kim, K. H.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Stewart, A. O.; Dyer, R. D.; Carter, G. W. *J. Med. Chem.* **1990**, *33*, 992.

(3) The keto–enol equilibrium of substituted thiazoles has been studied: *Thiazole And Its Derivatives, Vol. 34, Part 2* of *The Chemistry of Heterocyclic Compounds*; Metzger, J. V., Ed.; J. Wiley: New York, 1979; pp 419–446 and references contained therein.

(4) *Comprehensive Heterocyclic Chemistry*; Potts, K. T. Ed.; Pergamon Press: Oxford, 1984; Vol. 6, p 235.

Scheme I



Evaluation of Compounds

The structure–activity relationships for the 4-hydroxythiazole system were investigated at the S, C_2, OH, and C_5 sites. The compounds were initially evaluated for inhibitory activity in a 5-lipoxygenase assay[5] utilizing the 20000*g* supernatant of sonicated homogenized rat basophilic leukemia cells.

Compounds with interesting activity in the broken cell 5-lipoxygenase assay were further evaluated against washed rat polymorphonuclear leukocytes stimulated to make LTB_4 by addition of the calcium ionophore A 23187 and against ionophore-stimulated human whole blood.

Heteroatom Replacements at S. Replacement of the sulfur atom with more electronegative atoms such as oxygen or nitrogen reduced inhibitory activity (Figure 2). For example, oxazole **8**, which exists primarily in the keto tautomeric form according to NMR and IR studies, had an IC_{50} of 8.1 μM, being about 16 times less potent than 4-hydroxythiazole **7** (IC_{50} = 0.53 μM). 4-Hydroxyimidazole **9** was essentially inactive at 32 μM. From this brief analysis the thiazole group was chosen as the template for further refinement of inhibitory activity.

Substituents at C_2. The effect of various substituents at C_2 of the 4-hydroxythiazole system represented by Formula I with respect to 5-lipoxygenase inhibitory activity was evaluated (Table I). The phenyl derivative **1** was the prototype and had an IC_{50} of 0.96 μM. Other heterocyclic groups at C_2 were examined and analogues such as 3-pyridyl (**5**), 2-thienyl (**10**), 2-furyl (**11**), 2-pyridyl (**12**), and 2-(6-methoxybenzothiazolyl) (**14**) exhibited IC_{50}'s in the 0.89–3.9 μM range. The 4-pyridyl (**13**), 3-quinolinyl (**15**), and 3-pyrazolyl (**16**) analogues were substantially less potent.

Compounds with polar substituents at C_2 as in the esters (**18** and **19**), carboxyl (**20**), amino (**21**), and hydrazino (**22**) analogues or a simple methyl derivative (**17**) were all inactive at 32 μM.

(5) Dyer, R. D.; Bornemier, D. A.; Haviv, F.; Carter, G. W. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1985**, *44*, 904.

0022-2623/91/1834-2158$02.50/0 © 1991 American Chemical Society

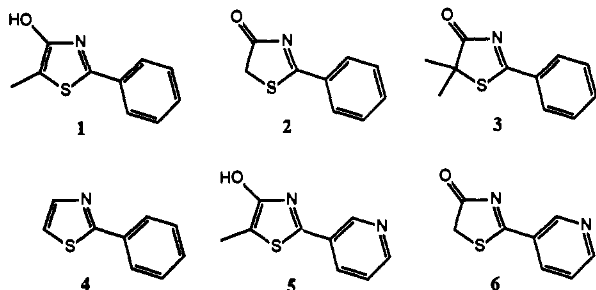


Figure 1.

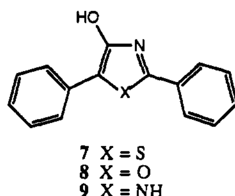


Figure 2.

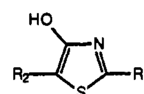
Substituted 2-Aryl Derivatives. Since compounds with a phenyl group at C_2, as in compound **1**, exhibited promising inhibitory potency, further examination of substituted phenyl derivatives was conducted. No apparent correlation was found to exist between biological activity [log $(1/IC_{50})$] and electronic (σ) or hydrophobic (π) constants. For example, the electron-donating methyl (**26**) and methoxy (**31**) analogues with IC_{50}'s of 0.63 and 1.1 μM had similar inhibitory activity as the electron-withdrawing nitrile (**27**) and nitro (**33**) analogues with IC_{50}'s of 0.70 and 1.6 μM. A variety of other substituents such as halogens (**23–25**), esters (**28–30**), keto (**32**), sulfonamide (**34**), trifluoromethyl (**35**), and trifluoromethyl thiol (**36**) led to only minor differences in inhibitory activity within a 0.35–2.7 μM range. A substantial reduction in inhibitory activity was observed in analogues with ionizable groups such as carboxamide (**37**), amino (**38**), and carboxyl (**39**). Incorporating another phenyl ring at the 2-aryl site as in **40** resulted in reduced activity. The position of the substituent on the phenyl ring was also studied. For example, *p*-fluorophenyl compound **23** exhibited activity similar to that of the corresponding *o*-fluoro (**41**) and the *m*-fluoro (**42**). With the exception of highly polar groups and biphenyl (**40**), the effect of substituents as well as their position on the phenyl ring generally did not greatly alter the inhibitory activity.

Modification of the 4-OH Site. The importance of the enolic form of 4-hydroxythiazoles for inhibitory activity was previously supported. To further evaluate the role of the hydroxy group the following modifications were tested (Table II). Since the initially prepared 4-hydroxythiazoles had rather limited solubility both in aqueous and organic solvents, modification of the hydroxy group was also hoped to enhance solubility. Replacement of the 4-hydroxy function with an amino group provided compound **43**, which was inactive. The methoxy (**44**) and phosphate (**45**) analogues were also relatively inactive.

Acyl derivatives retained 5-lipoxygenase inhibitory activity and some acetates were more potent than the corresponding hydroxy compounds. For example, acetates **61**, **62**, and **64** exhibited greater potency than the corresponding 4-hydroxy derivatives **60**, **39**, and **63**, respectively. Other esters such as succinate **47**, hexanoate **48**, and pivalate **49** provided potent inhibition. Carbamate derivatives **53–55** and carbonates **56–58** also showed good inhibitory activity; however, sulfonate **59** was inactive.

A structural modification where the hydroxy group was moved from C_4 to C_5 on the thiazole ring was also examined. As illustrated by 5-hydroxy analogue **50** compared to 4-hydroxy analogue **7**, this modification resulted in a

Table I. Inhibitory Activities of 4-Hydroxythiazoles of Formula I

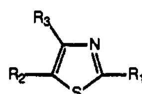


Formula I

no.	R_1	R_2	method[a]	in vitro 5-lo inhibn: IC_{50}, μM,[b] or % inhibn at μM concn
1	C_6H_5	CH_3	B	0.96 (0.8–1.1)
5	3-pyridyl	CH_3	A	3.9 (3.6–4.3)
7	C_6H_5	C_6H_5	B	0.53 (0.52–0.55)
10	2-thienyl	CH_3	A	1.4 (1.2–1.6)
11	2-furyl	CH_3	A	2.4 (2.2–2.6)
12	2-pyridyl	CH_3	A	2.1 (1.9–2.3)
13	4-pyridyl	CH_3	A	14 (13–14)
14	6-CH_3O-2-benzothiazolyl	CH_3	A	0.89 (0.71–1.1)
15	3-quinolinyl	CH_3	A	16 (14–18)
16	3-pyrazolyl	CH_3	A	31 (29–33)
17	CH_3	CH_3	B	NS at 32[c]
18	$CH_2CO_2CH_2CH_3$	CH_3	A	NS at 32[c]
19	$CO_2CH_2CH_3$	CH_3	A	NS at 32[c]
20	COOH	CH_3	A	NS at 32[c]
21	NH_2	CH_3	B	NS at 32[c]
22	$NHNH_2$	CH_3	B	NS at 32[c]
23	4-F-C_6H_4	CH_3	A	0.35 (0.28–0.43)
24	4-Br-C_6H_4	CH_3	A	0.51 (0.50–0.51)
25	4-Cl-C_6H_4	CH_3	A	0.57 (0.52–0.63)
26	4-CH_3-C_6H_4	CH_3	B	0.63 (0.62–0.64)
27	4-CN-C_6H_4	CH_3	A	0.70 (0.58–0.83)
28	4-$CO_2C_2H_5$-C_6H_4	CH_3	A	0.71 (0.60–0.85)
29	4-CO_2CH_3-C_6H_4	CH_3	A	0.88 (0.65–1.1)
30	4-$CO_2CH_2CH_2$-C_6H_5-C_6H_4	CH_3	A	0.98 (0.78–1.30)
31	4-OCH_3-C_6H_4	CH_3	B	1.10 (0.97–1.20)
32	4-$COCH_3$-C_6H_4	CH_3	A	1.40 (1.2–1.6)
33	4-NO_2-C_6H_4	CH_3	A	1.6 (1.4–1.8)
34	4-SO_2NH_2-C_6H_4	CH_3	A	2.2 (2.0–2.4)
35	4-CF_3-C_6H_4	CH_3	A	2.5 (2.2–2.7)
36	4-SCF_3-C_6H_4	CH_3	A	2.7 (2.5–2.9)
37	4-$CONH_2$-C_6H_4	CH_3	A	4.8 (3.9–6.1)
38	4-NH_2-C_6H_4	CH_3	A	15 (13–17)
39	4-COOH-C_6H_4	CH_3	A	30 (28–32)
40	4-C_6H_5-C_6H_4	CH_3	A	40% at 30
41	2-F-C_6H_4	CH_3	A	0.50 (0.48–0.52)
42	3-F-C_6H_4	CH_3	A	0.66 (0.56–0.76)
51	C_6H_5	$CH_2CH_2CH_3$	B	0.58 (0.55–0.62)
60	C_6H_5	CH_2CH_2-CH_2CH_3	B	18 (16–22)
63	4-C_6H_5-C_6H_4	C_6H_5	B	2.2 (2.0–2.4)
65	C_6H_5	CH_2CH_3	B	0.83 (0.73–0.92)
66	C_6H_5	CH_2CH_2-C_6H_5	B	0.69 (0.62–0.78)
67	C_6H_5	CH_2COOH	B	24% at 30
68	C_6H_5	$CH_2CO_2CH_3$	B	3.5 (2.7–4.6)
69	C_6H_5	CH_2CON-$(OH)CH_3$	B	4.4 (3.9–5.0)
70	C_6H_5	$CO_2C_2H_5$	B	17% at 30
17	CH_3	C_6H_5	B	0.7 (0.5–0.92)
72	4-F-C_6H_4	C_6H_5	B	0.5 (0.3–0.7)
73	4-CH_3-C_6H_4	C_6H_5	B	0.8 (0.6–1.3)
74	4-COOH-C_6H_4	C_6H_5	A	1.2 (0.92–1.5)
75	4-CH_3O-C_6H_4	C_6H_5	B	0.37 (0.36–0.38)
76	4-pyridyl	C_6H_5	B	0.54 (0.46–0.61)
77	3-pyridyl	C_6H_5	B	1.1 (0.8–1.4)

[a] See Experimental Section for methods. [b] IC_{50} with 95% confidence limits in parentheses or mean percent inhibition values for the in vitro inhibition of 5-lipoxygenase (5-lo) from the 20000*g* supernatant of RBl-1 cells. [c] Nonsignificant (NS) inhibition at concentration in μM.

Table II. Inhibitory Activities of 4-Substituted Thiazoles of Formula II



Formula II

no.	R_1	R_2	R_3	method[a]	in vitro 5-lo inhibn: IC_{50}, μM,[b] or % inhibn at μM concn
7	C_6H_5	C_6H_5	OH	B	0.53 (0.52–0.55)
43	C_6H_5	C_6H_5	NH_2		NS at 32[c]
44	C_6H_5	C_6H_5	OCH_3		NS at 32[c]
45	C_6H_5	C_6H_5	$(CH_3O)_2PO_2$		14% at 32
46	C_6H_5	C_6H_5	$OCOCH_3$	C	0.4 (0.3–0.54)
47	C_6H_5	C_6H_5	$OCOC_2H_4CO_2C_2H_5$	D	0.75 (0.69–0.80)
48	C_6H_5	C_6H_5	$OCOC_5H_{11}$	D	1.3 (1.2–1.4)
49	C_6H_5	C_6H_5	$OCOC_4H_9$	D	9.1 (8.5–1.0)
50	C_6H_5	OH	C_6H_5		6.9 (6.0–7.9)
51	C_6H_5	$CH_2CH_2CH_3$	OH	B	0.58 (0.55–0.62)
52	C_6H_5	$CH_2CH_2CH_3$	$OCOCH_3$	C	0.53 (0.48–0.59)
53	C_6H_5	$CH_2CH_2CH_3$	$OCONHCH_3$	E	8.8 (7.4–10.3)
54	C_6H_5	$CH_2CH_2CH_3$	$OCONHC_4H_9$	E	24 (22–26)
55	C_6H_5	$CH_2CH_2CH_3$	$OCONHC_6H_5$	E	0.46 (0.42–0.51)
56	C_6H_5	$CH_2CH_2CH_3$	$OCO_2C_2H_5$	F	0.91 (0.83–0.99)
57	C_6H_5	$CH_2CH_2CH_3$	$OCO_2CH_2C_6H_5$	F	2.8 (2.6–3.1)
58	C_6H_5	$CH_2CH_2CH_3$	$OCO_2C_3H_7$	F	3.3 (2.5–4.1)
59	C_6H_5	$CH_2CH_2CH_3$	OSO_2CH_3		NS at 32[c]
61	C_6H_5	$CH_2CH_2CH_2CH_3$	$OCOCH_3$	C	0.95 (0.81–1.1)
62	4-COOH-C_6H_4	CH_3	$OCOCH_3$	C	14 (12–16)
64	4-C_6H_5-C_6H_4	C_6H_5	$OCOCH_3$	C	1.4 (0.8–2.7)

[a] See Experimental Section for methods. [b] IC_{50} with 95% confidence limits in parentheses or mean percent inhibition values for the in vitro inhibition of 5-lipoxygenase (5-lo) from the 20000*g* supernatant of RBL-1 cells. [c] Nonsignificant (NS) inhibition at concentration in μM.

substantial loss in inhibitory potency.

Among the variations evaluated at the 4-OH site, the acetyl derivatives provided the best activity.[6]

Substitution at C_5. A similar pattern of substituent effects as observed for groups at C_2 was found for substitution at C_5. With respect to hydrocarbon chain length, propyl (**51**) was found to be superior to the methyl (**1**), ethyl (**65**), and butyl (**60**). Propyl (**51**) gave essentially the same activity as the more chemically stable phenyl (**7**). Attaching polar substituents to a hydrocarbon chain as in carboxy (**67**), carbomethoxy (**68**), and hydroxamyl (**69**) analogues resulted in substantial decreases in inhibitory activity. Activity, however, could be maintained by attaching a phenyl group to the hydrocarbon chain as in phenethyl analogue **66**. Direct attachment of an ester function as C_5, for example, compound **70**, was particularly detrimental to inhibitory potency. Substitution at C_5 with phenyl derivatives generally provided more potent inhibitors than their corresponding methyl analogues. In some cases, the difference in activity was quite dramatic. For instance, 2,5-dimethyl compound **17**, which was inactive (5% inhibition at 32 μM), was transformed into a potent inhibitor as 2-methyl-5-phenyl analogue **71** (IC_{50} = 0.7 μM). A similar phenomenon was observed for biphenyl compound **40** (40% inhibition at 30 μM); namely, the corresponding 5-phenyl analogue **63** provided potent activity (IC_{50} = 2.2 μM). 5-Phenyl compounds **75** and **77** were more potent inhibitors than the corresponding 5-methyl analogues **31** and **5**, respectively. 5-Phenyl acid **74** and pyridine **76** were ca. 30 times more active than their 5-methyl counterparts, compounds **39** and **13**. In this assay, further substitution on the 5-phenyl ring (comparing compounds **72**, **73**, **74**, or **75** with compound **7**) gave no substantial increase or decrease in activity. As a subgroup, the 5-phenyl derivatives were the most potent inhibitors with IC_{50}'s of 0.37–1.2 μM. Therefore 5-phenyl derivatives were considered as the preferred substitution at C_5 to provide potent 5-lipoxygenase inhibitory activity.

Table III. Inhibitory Activities of 4-Hydroxythiazoles in Intact Rat Polymorphonuclear Leukocytes

no.	5-LO IC_{50},[a] μM RBL-1	RPMNL
26	0.63 (0.62–0.64)	1.2 (1.1–1.3)
48	1.3 (1.2–1.4)	0.5 (0.4–0.6)
52	0.53 (0.48–0.59)	0.66 (0.53–0.82)
53	8.8 (7.4–10.3)	0.4 (0.2–0.6)
54	24 (22–26)	0.80 (0.76–0.85)
55	0.46 (0.42–0.50)	1.0 (0.9–1.1)
56	0.91 (0.83–0.99)	0.7 (0.6–1.1)
57	2.8 (2.6–3.1)	1.2 (1.2–1.3)
61	0.95 (0.81–1.1)	0.5 (0.5–0.6)
64	1.4 (0.8–2.7)	0.9 (0.8–1.0)
68	3.5 (2.7–4.6)	2.1 (1.6–2.9)
75	0.37 (0.36–0.38)	0.45 (0.35–0.55)

[a] IC_{50} with 95% confidence limits in parentheses for the inhibition of 5-lipoxygenase.

Reversibility of 5-Lipoxygenase Inhibition

The reversibility of the inhibition of the 5-lipoxygenase enzyme by the hydroxythiazoles was examined by incubating the enzyme with compound **75** followed by diluting the enzyme before the addition of substrate. A 6-fold dilution of a 0.3 μM initial mixture gave only 7% inhibition compared to 95% by the undiluted enzyme.

Activity in Other Enzyme Systems

Not only were the 4-hydroxythiazoles potent inhibitors in the broken-cell preparations but they were also active against 5-lipoxygenase in intact rat polymorphonuclear

(6) All of the hydroxyl protected analogues were stable to the conditions (pH, medium) of the assay; however, hydrolysis of the compounds may occur due to the complex nature of the contaminating proteins in the assay.

Table IV. Inhibitory Activities of 4-Hydroxythiazoles in Human Whole Blood

	5-LO IC_{50},[a] μM	
no.	RBL-1	HWBL
46	0.4 (0.3–0.59)	0.45 (0.38–0.55)
53	8.8 (7.4–10.3)	5.1 (4.4–6.0)
54	24 (22–26)	5.5 (4.9–6.2)
56	0.91 (0.83–0.99)	4.5 (3.1–6.1)
58	1.4 (0.8–2.7)	2.2 (2.0–2.5)
71	0.7 (0.5–0.92)	5.1 (4.6–5.8)
72	0.5 (0.3–0.96)	0.47 (0.43–0.50)
73	0.8 (0.6–1.3)	0.74 (0.65–0.85)
75	0.37 (0.36–0.38)	2.4 (1.9–2.9)
77	1.1 (0.8–1.4)	2.9 (2.7–3.1)

[a] IC_{50} with 95% confidence limits in parentheses for the inhibition of 5-lipoxygenase.

Table V. 4-Hydroxythiazoles and Inhibition of Related Enzymes

	5-lipoxygenase[a]	% inhibn at μM		
no.	IC_{50}, μM	cyclooxygenase[b]	15-lipoxygenase[c]	12-lipoxygenase[d]
1	0.96	32 at 30	44 at 10	51 at 100
7	0.53	47 at 30	50 at 100	12 at 30
29	0.88	6 at 30	52 at 10	0 at 100
66	0.69	11 at 100	34 at 100	3 at 100
72	0.50	20 at 100	16 at 100	0 at 100
75	0.37	25 at 100	22 at 100	6 at 100

[a] IC_{50} for the in vitro inhibition of 5-lipoxygenase from the 20000g supernatant of RBL-1 cells. [b] Mean percent inhibition values ± 2% SEM for the in vitro inhibition of sheep seminal vesicle cyclooxygenase. [c] Mean percent inhibition values ± 2% SEM for the in vitro inhibition of soybean 15-lipoxygenase. [d] Mean percent inhibition values ± 2% SEM for the in vitro inhibition of platelet 12-lipoxygenase.

leukocytes and human whole blood. In the intact rat polymorphonuclear leukocyte assay (Table III), a striking difference in potency was observed for compounds **53** and **54**. Their activity in the intact cell was more than 20 times that found in the broken cell, exhibiting IC_{50}'s of 0.4 and 0.8 μM, respectively. Regarding the human whole blood (Table IV), 4-hydroxythiazoles **46** and **72** were particularly active in this assay with IC_{50}'s of 0.45 and 0.47 μM, respectively. The 4-hydroxythiazoles were generally several fold less potent in the human whole blood compared to the activity obtained in the intact rat polymorphonuclear leukocyte assay. This may be the result of the compounds binding to plasma protein in the human whole blood assay. With respect to other lipoxygenases, the 4-hydroxythiazoles studied were found to be only weakly effective against sheep seminal vesicle cyclooxygenase, soybean 15-lipoxygenase, and platelet 12-lipoxygenase (Table V).

Activity Relative to Other Common Lipoxygenase Inhibitors

A comparison of the activity of standard inhibitors with a representative 4-hydroxythiazole assayed under the same conditions is shown in Table VI. For example, 4-hydroxythiazole **75** has a potency similar to that of the reference inhibitors quercetin,[7] NDGA,[8] and A-64077,[9] but is more active than BW-755C,[10] arachidonohydroxamic acid, 15-HETE,[11] Rev-5901,[12] and 5,6-DHA.[13]

Table VI. Comparison of 5-Lipoxygenase Inhibitory Activity with Common Reference Inhibitors

compound	IC_{50},[a] μM	compound	IC_{50},[a] μM
75	0.37 (0.36–0.38)	arachidonyl-hydroxamic acid	2.2 (2.0–2.4)
quercetin	0.3 (0.27–0.31)		
NDGA	0.4 (0.37–0.43)	15-HETE	7.3 (6.8–7.8)
A-64077	0.6 (0.5–0.6)	Rev-5901	>45
BW-755C	1.3 (1.2–1.5)	5,6-DHA	55 (46–64)

[a] IC_{50} with 95% confidence limits in parentheses for the in vitro inhibition of 5-lipoxygenase from the 20000g supernatant of RBL-1 cells.

Conclusion

Substituted 4-hydroxythiazoles have been identified as a novel series of 5-lipoxygenase inhibitors. Evaluation of a structure–activity relationship study has shown that 5-phenyl-4-hydroxythiazole analogues are especially potent. This new class of inhibitors appears to be selective for 5-lipoxygenase, being only weakly active against cyclooxygenase and 12- and 15-lipoxygenase.

Initial studies in vivo using a rat peritoneal anaphylaxis model have shown the hydroxythiazoles to be inactive when they are administered orally (100 mg/kg), probably due to a lack of absorption or solubility. Compound **7**, however, did exhibit significant activity when administered ip (85% inhibition of leukotriene biosynthesis at 10 mg/kg). The potential utility of these inhibitors appears to be as topical agents.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. ^1H NMR spectra were obtained on a General Electric QE-300 NMR instrument at 300 MHz and on a Varian T-60 NMR instrument at 60 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^1H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were recorded with an HP5985A spectrometer. Merck TLC plates were used for analytical TLC, and Merck Kieselgel 60 was used for column chromatography. Microanalyses were performed by the Abbott Analytical Department.

Method A. 2-(3-Pyridyl)-4-hydroxy-5-methylthiazole (5). Pyridine (2 g, 0.025 mol) was added to a mixture of thiolactic acid (10.6 g, 0.1 mol) and 2-cyanopyridine (10.4 g, 0.1 mol) at 23 °C under argon. The reaction mixture was then heated at 100 °C for 2 h. After cooling, the precipitate was collected and washed with absolute ethanol. Recrystallization from methanol afforded the product (14 g, 73%): mp 230 °C (MeOH); ^1H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H) 7.32–7.67 (m, 1 H), 8.00–8.30 (m, 1 H), 8.54–8.70 (m, 1 H), 8.98–9.10 (m, 1 H), 10.55 (s, 1 H); MS *m/e* 192 (M+). Anal. ($C_9H_8N_2OS$) C, H, N.

The following 4-hydroxythiazoles were prepared in a manner similar to that of **5** with the appropriately substituted nitrile or thiolactic acid derivative.

2-(2-Thienyl)-4-hydroxy-5-methylthiazole (10): 62% yield; mp 152–153 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 2.16 (s, 3 H), 7.08–7.28 (m, 1 H), 7.50–7.75 (m, 2 H), 10.32 (s, 1 H); MS *m/e* 197 (M+). Anal. ($C_8H_7NOS_2$) C, H, N.

(7) Hope, W. C.; Welton, A. F.; Fiedler-Nagy, C.; Batula-Bernardo, C.; Coffeg, J. W. *Biochem. Pharmacol.* **1983**, *32*, 367.
(8) Panganamala, R. V.; Miller, J. S.; Gwebu, E. T.; Sharma, H. M.; Cornwell, D. G. *Prostaglandins* **1977**, *14*, 261.
(9) Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J. B.; Dyer, R. D.; Bell, R. L.; Summers, J. B.; Brooks, D. W.; Gunn, B. P.; Rubin, P.; Kesterson, J. In *Leukotrienes and Prostanoids in Health and Disease. New Trends in Lipid Mediators Research*; Zor, U., Naor, Z., Danon, A., Eds.; Karger: Basel, 1989; VOl. 3, pp 50–55.
(10) Higgs, G. A.; Flower, R. J.; Vane, J. R. *Biochem. Pharmacol.* **1979**, *28*, 1959.
(11) Vanderhoek, J. K.; Bryant, R.; Bailey, J. M. *Biochem. Pharmacol.* **1982**, *31*, 3463.
(12) Musser, J. H.; Chakraborty, U. R.; Sciortino, S.; Gordon, R. J.; Khandwala, A.; Neiss, E. S.; Pruss, T. P.; Van Inwegen, R.; Weinryb, I.; Coutts, S. M. *J. Med. Chem.* **1987**, *30*, 96.
(13) Corey, E. J.; Monroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 1752.

2-(2-Furyl)-4-hydroxy-5-methylthiazole (11): 52% yield; mp 173–174 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3 H), 6.64–6.68 (m, 1 H), 6.86–6.89 (m, 1 H), 7.78–7.82 (m, 1 H), 10.46 (s 1 H); MS m/e 181 (M+). Anal. ($C_8H_7NO_2S$) C, H, N.

2-(2-Pyridyl)-4-hydroxy-5-methylthiazole (12): 72% yield; mp 201–202 °C (MeOH) (lit.[14] mp 198–202 °C); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.35–7.62 (m, 2 H), 8.05–8.35 (m, 2 H), 10.45 (s, 1 H); MS m/e 192 (M+). Anal. ($C_9H_8N_2OS$) C, H, N.

2-(4-Pyridyl)-4-hydroxy-5-methylthiazole (13): 55% yield; mp 223–224 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.28 (s, 3 H), 7.67–7.84 (m, 2 H), 8.67–8.85 (m, 2 H), 10.65 (s, 1 H); MS m/e 192 (M+). Anal. ($C_9H_8N_2OS$) C, H, N.

2-[2-(6-Methoxybenzothiazolyl)]-4-hydroxy-5-methylthiazole (14): 65% yield; mp 249–250 °C (EtOH) (lit.[14] mp 250–253 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3 H), 3.86 (s, 3 H), 7.11–7.17 (m, 1 H), 7.68–7.72 (m, 1 H), 7.90–7.96 (m, 1 H), 10.11 (s, 1 H); MS m/e 278 (M+). Anal. ($C_{12}H_{10}N_2O_2S_2$) C, H, N.

2-(3-Quinolinyl)-4-hydroxy-5-methylthiazole (15): 62% yield; mp 279–280 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3 H), 7.75–7.82 (m, 1 H), 7.60–7.68 (m, 1 H), 8.02–8.06 (s, 1 H), 8.10–8.15 (m, 1 H), 8.69–8.72 (m, 1 H), 9.32–9.35 (m, 1 H), 10.55 (s, 1 H); MS m/e 242 (M+). Anal. ($C_{13}H_{10}N_2O_5$) C, H, N.

2-(3-Pyrazolyl)-4-hydroxy-5-methylthiazole (16): 42% yield; mp 124–125 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.16 (s, 3 H), 8.00 (s, 1 H), 8.35 (s, 1 H), 9.02 (s, 1 H); MS m/e 181 (M+). Anal. ($C_7H_7N_3OS$) C, H, N.

2-(Carbethoxymethyl)-4-hydroxy-5-methylthiazole (18): 64% yield; mp 132–133 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.16 (t, 3 H, J = 7 Hz), 2.20 (s, 3 H), 4.08 (q, 2 H, J = 7 Hz), 5.51 (s, 2 H), 10.55 (s, 1 H); MS m/e 201 (M+). Anal. ($C_8H_{11}NO_3S$) C, H, N.

2-Carbethoxy-4-hydroxy-5-methylthiazole (19). The title compound was prepared from ethyl cyanoformate and thiolactic acid in 65% yield: mp 163–164 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.18 (t, 3 H, J = 7 Hz), 2.25 (s, 3 H), 4.35 (q, 2 H, J = 7 Hz), 8.87 (s, 1 H); MS m/e 187 (M+). Anal. ($C_7H_9NO_3S$) C, H, N.

2-Carboxy-4-hydroxy-5-methylthiazole (20). The title compound was prepared by treatment of 19 with LiOH in 85% yield: dec >170 °C; ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.32 (s, 3 H), 9.52 (br s, 1 H); MS m/e 159 (M+). Anal. ($C_5H_5NO_3S$) C, H, N.

2-(4-Fluorophenyl)-4-hydroxy-5-methylthiazole (23): 68% yield; mp 173–174 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 7.16–8.00 (m, 4 H), 10.0 (s, 1 H); MS m/e 209 (M+). Anal. ($C_{10}H_8FNOS$) C, H, N.

2-(4-Bromophenyl)-4-hydroxy-5-methylthiazole (24): 51% yield; mp 206–207 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.50–7.90 (m, 4 H), 10.32 (s, 1 H); MS m/e 269 (M+). Anal. ($C_{10}H_8BrNOS$) C, H, N.

2-(4-Chlorophenyl)-4-hydroxy-5-methylthiazole (25): 66% yield; mp 198–199 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 (s, 3 H), 7.48–7.54 (m, 2 H), 7.75–7.83 (m, 2 H), 10.40 (br s, 1 H); MS m/e 225 (M+). Anal. ($C_{10}H_8ClNOS$) C, H, N.

2-(4-Cyanophenyl)-4-hydroxy-5-methylthiazole (27): 62% yield; mp 220–221 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.26 (s, 3 H), 7.85–8.10 (m, 4 H), 10.55 (br s, 1 H); MS m/e 216 (M+). Anal. ($C_{11}H_8N_2OS$) C, H, N.

2-(4-Carbethoxyphenyl)-4-hydroxy-5-methylthiazole (28): 65% yield; mp 207–208 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.25 (t, 3 H, J = 7 Hz), 2.35 (s, 3 H), 4.32 (q, 2 H, J = 7 Hz), 7.85–8.15 (m, 4 H), 10.41 (br s, 1 H); MS m/e 263 (M+). Anal. ($C_{13}H_{13}NO_3S$) C, H, N.

2-(4-Carbomethoxyphenyl)-4-hydroxy-5-methylthiazole (29): 64% yield; mp 219–220 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.35 (s, 3 H), 3.80 (s, 3 H), 7.85–8.15 (m, 4 H), 10.41 (br s, 1 H); MS m/e 249 (M+). Anal. ($C_{12}H_{11}NO_3S$) C, H, N.

2-[4-[(Phenethyloxy)carbonyl]phenyl]-4-hydroxy-5-methylthiazole (30): 58% yield; mp 251–252 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 3.08 (t, 2 H, J = 7 Hz), 4.55 (t, 2 H, J = 7 Hz), 7.32–7.50 (m, 5 H), 7.95–8.05 (m, 4 H), 10.35 (br s, 1 H); MS m/e 339 (M+). Anal. ($C_{19}H_{17}NO_3S$) C, H, N.

2-(4-Acetylphenyl)-4-hydroxy-5-methylthiazole (32): 64% yield; mp 219–220 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 2.59 (s, 3 H), 7.89–7.95 (m, 2 H), 8.0–8.6 (m, 2 H), 10.50 (s, 1 H); MS m/e 233 (M+). Anal. ($C_{12}H_{11}NO_2S$) C, H, N.

2-(4-Nitrophenyl)-4-hydroxy-5-methylthiazole (33): 52% yield; mp 244–248 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.85–8.50 (m, 4 H), 10.41 (br s, 1 H); MS m/e 236 (M+). Anal. ($C_{10}H_8N_2O_3S$) C, H, N.

2-(4-Sulfamoylphenyl)-4-hydroxy-5-methylthiazole (34): 45% yield; mp 256–257 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 6.65 (s, 2 H), 7.32–7.66 (m, 2 H), 7.85–8.10 (m, 2 H); MS m/e 270 (M+). Anal. ($C_{10}H_{10}N_2O_3S_2$) C, H, N.

2-[4-(Trifluoromethyl)phenyl]-4-hydroxy-5-methylthiazole (35): 48% yield; mp 232–233 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 7.66–8.10 (m, 4 H), 10.50 (s, 1 H); MS m/e 259 (M+). Anal. ($C_{11}H_8F_3NOS$) C, H, N.

2-[4-[(Trifluoromethyl)thio]phenyl]-4-hydroxy-5-methylthiazole (36): 64% yield; mp 178–179 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 3.32 (br s, 1 H), 7.66–8.05 (m, 4 H), 9.75 (br s, 1 H); MS m/e 291 (M+). Anal. ($C_{11}H_8F_3NOS_2$) C, H, N.

2-(4-Carbamoylphenyl)-4-hydroxy-5-methylthiazole (37): 74% yield; mp 274–277 °C dec (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.21 (s, 3 H), 7.30–8.10 (m, 5 H), 10.15 (br s, 1 H); MS m/e 234 (M+). Anal. ($C_{11}H_{10}N_2O_2S$) C, H, N.

2-(4-Aminophenyl)-4-hydroxy-5-methylthiazole (38): 42% yield; mp 168–169 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (d, 3 H, J = 7 Hz), 4.35 (q, 1 H, J = 7 Hz), 6.63–6.72 (m, 4 H), 7.75–7.85 (m, 2 H); MS m/e 206 (M+). Anal. ($C_{10}H_{10}N_2OS$) C, H, N.

2-(4-Carboxyphenyl)-4-hydroxy-5-methylthiazole (39): 54% yield; mp 276 °C dec (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.88–7.94 (m, 2 H), 7.98–8.04 (m, 2 H), 10.49 (br s, 1 H), 12.07 (br s, 1 H); MS m/e 235 (M+). Anal. ($C_{11}H_9NO_3S$) C, H, N.

2-(4-Biphenylyl)-4-hydroxy-5-methylthiazole (40): 45% yield; mp 265–266 °C (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 2.16 (s, 3 H), 7.32–8.00 (m, 9 H), 10.25 (s, 1 H); MS m/e 267 (M+). Anal. ($C_{16}H_{13}NOS$) C, H, N.

2-(2-Fluorophenyl)-4-hydroxy-5-methylthiazole (41): 48% yield; mp 159–160 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.30–7.51 (m, 4 H), 8.05–8.15 (m, 1 H), 10.43 (br s, 1 H); MS m/e 209 (M+). Anal. ($C_{10}H_8FNOS$) C, H, N.

2-(3-Fluorophenyl)-4-hydroxy-5-methylthiazole (42): 44% yield; mp 162–163 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 7.23–7.31 (m, 1 H), 7.48–7.66 (m, 3 H), 10.45 (s, 1 H); MS m/e 209 (M+). Anal. ($C_{10}H_8FNOS$) C, H, N.

2-(4-Carboxyphenyl)-4-hydroxy-5-phenylthiazole (74): 35% yield; mp >300 °C dec (EtOH); ^{1}H NMR (60 MHz, DMSO-d_6) δ 7.32–8.15 (m, 9 H), 11.32 (br s, 1 H); MS m/e 297 (M+). Anal. ($C_{16}H_{11}NO_3S$) C, H, N.

Method B. 2-Phenyl-4-hydroxy-5-methylthiazole (1). Ethyl bromopropionate (3.96 g, 21.9 mmol) was added dropwise to a solution of thiobenzamide (3.00 g, 21.9 mmol) and pyridine (7 mL, 87.5 mmol) in toluene (200 mL) at 23 °C. The reaction mixture was heated to 80 °C for 2 h and allowed to cool to 23 °C. The precipitate was collected and recrystallized from ethanol to afford 3.3 g (81%) of product: mp 192–193 °C (EtOH) (lit.[15] mp 190–191 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 7.32–7.55 (m, 3 H), 7.75–7.82 (m, 2 H), 10.31 (s, 1 H); MS m/e 191 (M+). Anal. ($C_{10}H_9NOS$) C, H, N.

The following 4-hydroxythiazoles were prepared in a manner similar to that of 1 with the appropriately substituted benzamide or α-bromo ester.

2-Phenyl-4-thiazolinone (2): 42% yield; mp 107 °C (ether) (lit.[15] mp 106–108 °C); ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.70 (s, 2 H), 7.30–7.95 (m, 5 H); MS m/e 177 (M+). Anal. (C_9H_7NOS) C, H, N.

2,5-Diphenyl-4-hydroxythiazole (7): 68% yield; mp 212–213 °C (EtOH) (lit.[16] mp 215 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ

(14) Suzuki, N.; Goto, T. Agric. Biol. Chem. Jpn. 1972, 36, 2213.

(15) Jensen, K. A.; Crossland, I. Acta Chem. Scand. 1963, 17, 144.

7.22–7.30 (m, 2 H), 7.38–7.53 (m, 4 H), 7.82–7.87 (m, 2 H), 7.92–8.00 (m, 2 H); MS m/e 253 (M+). Anal. ($C_{15}H_{11}NOS$) C, H, N.

2,5-Dimethyl-4-hydroxythiazole (17): 48% yield; mp 101–103 °C; ^1H NMR (60 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 2.56 (s, 3 H), 8.65 (br s, 1 H); MS m/e 129 (M+). Anal. (C_5H_7NOS) C, H, N.

2-Amino-4-hydroxy-5-methylthiazole (21): 44% yield; mp 175–176 °C (EtOH); ^1H NMR (60 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 7.25–7.38 (m, 5 H), 9.85 (br s, 1 H), 8.55 (br s, 2 H); MS m/e 130 (M+). Anal. ($C_4H_6N_2OS$) C, H, N.

2-Hydrazino-5-methyl-4-thiazolinone (22): 58% yield; mp 242–243 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.50 (d, 3 H, J = 7 Hz), 4.53 (q, 1 H, J = 7 Hz), 5.82 (br s, 3 H), 11.05 (br s, 1 H); MS m/e 145 (M+). Anal. ($C_4H_7N_3OS$), C, H, N.

2-(4-Methylphenyl)-4-hydroxy-5-methylthiazole (26): 71% yield; mp 172–174 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 2.15 (s, 3 H), 2.25 (s, 3 H), 7.15–7.35 (m, 2 H), 7.55–7.85 (m, 2 H), 9.82 (s, 1 H); MS m/e 205 (M+). Anal. ($C_{11}H_{11}NOS$) C, H, N.

2-(4-Methoxyphenyl)-4-hydroxy-5-methylthiazole (31): 33% yield; mp 149–150 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 7.00–7.20 (m, 2 H), 7.67–7.97 (m, 2 H), 10.41 (br s, 1 H); MS m/e 221 (M+). Anal. ($C_{11}H_{11}NO_2S$) C, H, N.

2-Phenyl-4-hydroxy-5-propylthiazole (51): 56% yield; mp 86–87 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.92 (t, 3 H, J = 7 Hz), 1.50–1.65 (m, 2 H), 2.62 (t, 2 H, J = 7 Hz), 7.35–7.55 (m, 3 H), 7.75–7.83 (m, 2 H), 10.28 (s, 1 H); MS m/e 219 (M+). Anal. ($C_{12}H_{13}NOS$) C, H, N.

2-Phenyl-4-hydroxy-5-butylthiazole (60): 71% yield; mp 69–71 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, 3 H, J = 7 Hz), 1.28–1.41 (m, 2 H), 1.48–1.60 (m, 2 H), 2.63 (t, 2 H), J = 7 Hz), 7.40–7.50 (m, 3 H), 7.82–7.85 (m, 2 H), 10.35 (s, 1 H); MS m/e 233 (M+). Anal. ($C_{13}H_{15}NOS$) C, H, N.

2-(4-Biphenylyl)-4-hydroxy-5-phenylthiazole (63): 67% yield; mp 242–243 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 7.15–8.05 (m, 14 H), 11.25 (br s, 1 H); MS m/e 329 (M+). Anal. ($C_{21}H_{15}NOS$) C, H, N.

2-Phenyl-4-hydroxy-5-ethylthiazole (65): 52% yield; mp 175–177 °C dec (MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.18 (t, 3 H, J = 7 Hz), 2.66 (q, 2 H, J = 7 Hz), 7.40–7.50 (m, 3 H), 7.75–7.85 (m, 2 H), 9.52 (br s, 1 H); MS m/e 205 (M+). Anal. ($C_{11}H_{11}NOS$) C, H, N.

2-Phenyl-4-hydroxy-5-phenethylthiazole (66): 68% yield; mp 127–128 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 2.88 (s, 4 H), 7.21–7.90 (m, 10 H), 9.84 (br s, 1 H); MS m/e 281 (M+). Anal. ($C_{17}H_{15}NOS$) C, H, N.

2-Phenyl-4-hydroxy-5-(carboxymethyl)thiazole (67). The title compound was prepared by treatment of 68 with LiOH in 96% yield: mp 196 °C dec (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 3.65 (s, 2 H), 7.35–7.55 (m, 3 H), 7.72–7.89 (m, 2 H), 10.55 (br s, 1 H), 12.52 (br s, 1 H); MS m/e 235 (M+). Anal. ($C_{11}H_9NO_3S$) C, H, N.

2-Phenyl-4-hydroxy-5-(carbomethoxymethyl)thiazole (68): 62% yield; mp 114–116 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 3.65 (s, 2 H), 3.80 (s, 3 H), 7.35–7.55 (m, 3 H), 7.72–7.89 (m, 2 H), 10.50 (s, 1 H); MS m/e 249 (M+). Anal. ($C_{12}H_{11}NO_3S$) C, H, N.

2-Phenyl-4-hydroxy-5-[[(*N*-methyl-*N*-hydroxyamino)carbonyl]methyl]thiazole (69). The title compound was prepared from the corresponding acid chloride by treatment with methylhydroxyamine hydrochloride and triethylamine in 95% yield: mp 156–157 °C (ether); ^1H NMR (300 MHz, DMSO-d_6) δ 3.12 (s, 3 H), 3.80 (s, 2 H), 7.38–7.52 (m, 3 H), 7.75–7.86 (m, 2 H), 10.10 (br s, 1 H), 10.51 (s, 1 H); MS m/e 264 (M+). Anal. ($C_{12}H_{12}N_2O_3S$) C, H, N.

2-Phenyl-4-hydroxy-5-carbethoxythiazole (70): 62% yield; mp 91–92 °C (EtOH) (lit.[17] mp 91–92 °C); ^1H NMR (60 MHz, DMSO-d_6) δ 1.18 (t, 3 H, J = 7 Hz), 4.25 (q, 2 H, J = 7 Hz), 7.35–8.05 (m, 5 H); MS m/e 249 (M+). Anal. ($C_{12}H_{11}NO_3S$) C, H, N.

2-Methyl-4-hydroxy-5-phenylthiazole (71): 41% yield; mp 208–211 °C (EtOH) (lit.[18] 210–211 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 2.56 (s, 3 H), 7.13–7.20 (m, 1 H), 7.30–7.40 (m, 2 H), 7.59–7.65 (m, 4 H), 8.50 (br s, 1 H); MS m/e 191 (M+). Anal. ($C_{10}H_9NOS$) C, H, N.

2-(4-Fluorophenyl)-4-hydroxy-5-phenylthiazole (72): 52% yield; mp 231–233 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 7.20–8.05 (m, 9 H), 11.10 (br s, 1 H); MS m/e 271 (M+). Anal. ($C_{15}H_{10}FNOS$) C, H, N.

2-(4-Methylphenyl)-4-hydroxy-5-phenylthiazole (73): 71% yield; mp 252–255 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 2.32 (s, 3 H), 7.20–7.95 (m, 9 H), 10.75 (br s, 1 H); MS m/e 267 (M+). Anal. ($C_{16}H_{13}NOS$) C, H, N.

2-(4-Methoxyphenyl)-4-hydroxy-5-phenylthiazole (75): 52% yield; mp 218–220 °C (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 3.84 (s, 3 H), 7.0–8.0 (m, 9 H), 11.05 (br s, 1 H); MS m/e 283 (M+). Anal. ($C_{16}H_{13}NO_2S$) C, H, N.

2-(4-Pyridyl)-4-hydroxy-5-phenylthiazole (76): 44% yield; mp 280 °C dec (EtOH); ^1H NMR (60 MHz, DMSO-d_6) δ 7.15–7.95 (m, 9 H), 8.55 (br s, 1 H); MS m/e 254 (M+). Anal. ($C_{14}H_{10}N_2OS$) C, H, N.

2-(3-Pyridyl)-4-hydroxy-5-phenylthiazole (77): 41% yield; mp 273–276 °C (EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 7.20–7.30 (m, 1 H), 7.35–7.48 (m, 2 H), 7.52–7.80 (m, 3 H), 8.25–8.40 (m, 1 H), 8.63–8.80 (m, 1 H), 9.01–9.15 (m, 1 H), 10.20 (br s, 1 H); MS m/e 254 (M+). Anal. ($C_{14}H_{10}N_2OS$) C, H, N.

Preparation of Acetates. Method C. 2,5-Diphenyl-4-acetoxythiazole (46). The title compound was prepared by reacting hydroxythiazole (7) (2.53 g, 10 mmol) in methylene chloride (250 mL) with pyridine (0.8 g, 10 mmol) and acetic anhydride (1.5 g, 15 mmol) at 23 °C for 10 h. The reaction mixture was washed with water and dried ($MgSO_4$). Removal of solvent, followed by recrystallization of the crude residue provided the product (2.72 g, 92%): mp 101–103 °C (EtOAc/hexane); ^1H NMR (300 MHz, DMSO-d_6) δ 2.40 (s, 3 H), 7.38–7.62 (m, 8 H), 7.86–7.96 (m, 2 H); MS m/e 295 (M+). Anal. ($C_{17}H_{13}NO_2S$) C, H, N. The following compounds were prepared in a similar manner from the corresponding 4-hydroxythiazole as compound 46.

2-Phenyl-4-acetoxy-5-propylthiazole (52): 92% yield; colorless oil; ^1H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, 2 H, J = 7 Hz), 1.50–1.65 (m, 2 H), 2.28 (s, 3 H), 7.62 (t, 2 H, J = 71 Hz), 7.35–7.55 (m, 3 H), 7.75–7.83 (m, 2 H); MS m/e 261 (M+). Anal. ($C_{14}H_{15}NO_2S$) C, H, N.

2-Phenyl-4-acetoxy-5-butylthiazole (61): 81% yield; colorless oil; ^1H NMR (60 MHz, $CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 1.0–1.65 (m, 4 H), 2.20 (s, 3 H), 2.55 (t, 2 H, J = 7 Hz), 7.32–7.50 (m, 3 H), 7.80–8.00 (m, 2 H); MS m/e 275 (M+). Anal. ($C_{15}H_{17}NO_2S$) C, H, N.

2-(4-Carboxyphenyl)-4-acetoxy-5-methylthiazole (62): 91% yield; mp 227–230 °C (EtOH); ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 2.32 (s, 3 H), 7.84–8.20 (m, 4 H); MS m/e 277 (M+). Anal. ($C_{13}H_{11}NO_4S$) C, H, N.

2-(4-Biphenylyl)-4-acetoxy-5-phenylthiazole (64): 89% yield; mp 146–147 °C (EtOH); ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 7.30–8.05 (m, 14 H); MS m/e 371 (M+). Anal. ($C_{23}H_{17}NO_2S$) C, H, N.

Preparation of Esters. Method D. 2,5-Diphenyl-4-[(ethyloxysuccinyl)oxy]thiazole (47). The title compound was prepared by reacting compounds 7 (913 mg, 3.6 mmol) in methylene chloride (50 mL) with 4-(dimethylamino)pyridine (710 mg, 5.8 mmol) and ethyl succinyl chloride (924 mg, 5.61 mmol) at 23 °C under nitrogen for 2 h. The organic layer was washed with water and dried (Na_2SO_4). Removal of solvent, followed by recrystallization of the crude residue with EtOAc/hexane provided the product (1.34 g, 97%): mp 55–58 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (q, J = 7 Hz, 3 H), 2.73 (t, J = 7 Hz, 2 H), 2.98 (t, J = 7 Hz, 2 H), 4.15 (q, J = 7 Hz, 2 H), 7.45 (m, 6 H) 7.55 (m, 2 H), 7.92 (m, 2 H); MS m/e 381 (M+). Anal. ($C_{21}H_{19}NO_4S$) C, H, N.

The following compounds were prepared in a manner similar to that of compound 47 using the corresponding 4-hydroxythiazole and an appropriately substituted acid chloride.

2,5-Diphenyl-4-(hexanoyloxy)thiazole (48): 96% yield; mp 70–72 °C (EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.23–1.40 (m, 4 H), 1.65–1.80 (m, 2 H), 2.61 (t, 2 H, J

(16) Ferrey, M.; Robert, A.; Foucaud, A. *Synthesis* **1976**, 261.
(17) Duro, F. *Gazz. Chim. Ital.* **1963**, *93*, 215.
(18) Reeve, W.; Barrow, E. R. *J. Org. Chem.* **1975**, *40*, 1917.

= 7 Hz), 7.28–7.58 (m, 8 H), 7.88–7.96 (m, 2 H); MS *m/e* 351 (M+). Anal. ($C_{21}H_{21}NO_2S$) C, H, N.

2,5-Diphenyl-4-(trimethylacetoxy)thiazole (49): 85% yield; 134–136 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 7.40 (m, 6 H), 7.56 (m, 2 H), 7.92 (m, 2 H); MS *m/e* 337 (M+). Anal. ($C_{20}H_{19}NO_2S$) C, H, N.

Preparation of Carbamates. Method E. 2-Phenyl-4-[(*N*-methylcarbamyl)oxy]-5-propylthiazole (53). The title compound was prepared by reacting compound **51** (2.33 g, 10 mmol) in benzene (250 mL) with triethylamine (1.0 g, 10 mmol) and methyl isocyanate (0.65 mL, 10 mmol) at 23 °C under nitrogen for 20 h. The reaction mixture was washed with saturated aqueous NH_4Cl and water and dried ($MgSO_4$). The organic solvent was removed and the residue recrystallized from toluene to afford the product (2.4 g, 86%): mp 55–58 °C (toluene); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.90 (t, 3 H, *J* = 7 Hz), 1.67 (m, 2 H), 2.66 (t, 2 H, *J* = 7 Hz), 2.85 (d, 3 H, *J* = 7 Hz), 5.50 (br s, 1 H), 7.75 (m, 2 H), 7.40 (m, 3 H); MS *m/e* 276 (M+). Anal. ($C_{14}H_{16}N_2O_2S$) C, H, N.

The following compounds were prepared in a similar manner to that of compound **53** from the corresponding 4-hydroxythiazole and an appropriately substituted isocyanate.

2-Phenyl-4-[(*N*-*tert*-butylcarbamyl)oxy]-5-propylthiazole (54): 84% yield; mp 97–98 °C (benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3 H, *J* = 7 Hz), 1.21–1.45 (m, 2 H), 0.99 (s, 9 H), 2.55 (t, 2 H, *J* = 7 Hz), 7.05–7.10 (m, 1 H), 7.30–7.60 (m, 4 H); MS *m/e* 318 (M+). Anal. ($C_{17}H_{22}N_2O_2S$) C, H, N.

2-Phenyl-4-[(*N*-phenylcarbamyl)oxy]-5-propylthiazole (55): 65% yield; mp 104–105 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3 H, *J* = 7 Hz), 1.58–1.63 (m, 2 H), 2.61 (t, 2 H, *J* = 7 Hz), 7.05–7.16 (m, 1 H), 7.30–7.50 (m, 8 H), 7.80–7.90 (m, 2 H); MS *m/e* 338 (M+). Anal. ($C_{19}H_{18}N_2O_2S$) C, H, N.

Preparation of Carbonates. Method F. 2-Phenyl-4-[(ethoxycarbonyl)oxy]-5-propylthiazole (56). The title compound was prepared by reacting compound **51** (2.3 g, 10 mmol) and pyridine (0.9 mL, 10 mmol) in toluene (200 mL) with ethyl chloroformate (1 mL, 10 mmol) at 23 °C under nitrogen for 2 h. The organic solvent was washed with water and dried (Na_2SO_4). The organic solvent was removed and the crude residue chromatographed (silica gel, $CHCl_3$) to afford the product (2.1 g, 76%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, 3 H, *J* = 7 Hz), 1.40 (t, 3 H, *J* = 7 Hz), 1.62–1.76 (m, 2 H), 2.69 (t, 2 H, *J* = 7 Hz), 4.35 (q, 2 H, *J* = 7 Hz), 7.40 (m, 3 H), 7.87 (m, 2 H); MS *m/e* 291 (M+). Anal. ($C_{15}H_{17}NO_3S$) C, H, N.

The following compounds were prepared in a manner similar to that of compound **56** from the corresponding 4-hydroxythiazole and the appropriately substituted chloroformate.

2-Phenyl-4-[(benzoxycarbonyl)oxy]-5-propylthiazole (57): 88% yield; mp 62–64 °C (toluene); ^{1}H NMR (60 MHz, DMSO-d_6) δ 7.15–8.05 (m, 14 H), 11.25 (br s, 1 H); MS *m/e* 329 (M+). Anal. ($C_{20}H_{19}NO_3S$) C, H, N.

2-Phenyl-4-[(isopropoxycarbonyl)oxy]-5-propylthiazole (58): 96% yield; colorless oil; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (t, 2 H, *J* = 7 Hz), 1.25 (d, 6 H, *J* = 7 Hz), 1.60–1.87 (m, 2 H), 2.55 (t, 2 H, *J* = 7 Hz), 5.0 (m, 1 H), 7.30–7.50 (m, 3 H), 7.65–7.95 (m, 2 H); MS *m/e* 305 (M+). Anal. ($C_{16}H_{19}NO_3S$) C, H, N.

2,5-Diphenyl-4-oxazolinone (8). The title compound was prepared by the method of Rao and Filler.[19] 53% yield; mp 159–161 °C (lit.[19] mp 161 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.65 (s, 1 H), 7.28–7.70 (m, 8 H), 8.00–8.15 (m, 2 H); MS *m/e* 237 (M+). Anal. ($C_{15}H_{11}NO_2$) C, H, N.

2,5-Diphenyl-4-hydroxyimidazole (9). The title compound was prepared by the method of Jeffrey:[20] 21% yield; mp 162–164 °C (lit.[20] mp 162–164 °C); ^{1}H NMR (60 MHz, DMSO-d_6) δ 7.00–8.20 (m, 10 H), 11.8 (br s, 1 H); MS *m/e* 236 (M+). Anal. ($C_{15}H_{12}N_2O$) C, H, N.

2,5-Diphenyl-4-aminothiazole (43). The title compound was prepared by reacting α-cyanobenzyl benzenesulfonate (21 g, 80 mmol) in EtOH (200 mL) with thiobenzamide (11 g, 80 mmol) at 0 °C for 20 h. The yellow precipitate was collected and recrystallized from ethanol to afford the benzenesulfonate salt (12.8 g). The salt (12.8 g) was dissolved in concentrated NH_4OH/H_2O 1/1 (200 mL) and stirred for 1 h. The precipitate was collected and recrystallized from H_2O/EtOH to give the product (7.4 g, 38%): mp 92–94 °C (lit.[21] mp 103–104 °C); ^{1}H NMR (60 MHz, DMSO-d_6) δ 5.83 (br s, 2 H), 7.25–8.00 (m, 10 H); MS *m/e* 252 (M+). Anal. ($C_{15}H_{12}N_2S$) C, H, N.

2,5-Diphenyl-4-methoxythiazole (44). The title compound was prepared by reacting hydroxythiazole (**7**) (180 mg, 0.711 mmol) in ethanol (20 mL) at 0 °C with excess ethereal diazomethane. The reaction mixture was stirred for 2 h and the solvent removed. Recrystallization of the crude residue from EtOAc/hexane afforded the product (181 mg, 95%): mp 82–83 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 3 H), 7.18–7.25 (m, 1 H), 7.35–7.45 (m, 5 H), 7.70–7.82 (m, 2 H), 7.90–7.96 (m, 2 H); MS *m/e* 267 (M+). Anal. ($C_{16}H_{13}NOS$) C, H, N.

2,5-Diphenyl-4-[(dimethylphosphono)oxy]thiazole (45). Phosphorus oxychloride (4 mL) was added to compound **7** (2.5 g, 10 mmol) in benzene (40 mL) at 23 °C under nitrogen and the reaction stirred for 6 h. The benzene was removed and methanol (40 mL) added. The reaction mixture was stirred for 1 h and the solvent removed to afford a crude material. Recrystallization from ether gave the product (2.3 g, 66%): mp 98–99 °C (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 3.98 (s, 3 H), 7.30–7.50 (m, 6 H), 7.62–7.71 (m, 2 H), 7.88–7.95 (m, 2 H); MS *m/e* 361 (M+). Anal. ($C_{17}H_{16}NO_4PS$) C, H, N.

2,4-Diphenyl-5-hydroxythiazole (50). The title compound was prepared by reacting methyl thionobenzoate (3.86 g, 25 mmol) in ether (20 mL) with phenylglycine (4.22 g, 27 mmol) in 3 N NaOH (30 mL) at 23 °C under nitrogen for 18 h. The aqueous layer was separated and acidified slowly with 3 N HCl. A yellow precipitate formed and was collected. The yellow precipitate was then dissolved in acetic anhydride (25 mL) and heated at 100 °C for 1 h. After cooling to 23 °C, the acetic anhydride was removed in vacuo at 60 °C. The crude residue was dissolved in isopropyl alcohol/water 2/1 (60 mL) and lithium hydroxide (0.56 g, 13.6 mmol) added. After stirring at 23 °C for 4 h, water was added and the mixture extracted with methylene chloride. Chromatography (silica gel, CH_2Cl_2/pentane 3/1) afforded the product (2.6 g, 42%): mp 133–136 °C (EtOAc) (lit.[22] mp 134–135 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.30–7.60 (m, 8 H) 7.90–8.00 (m, 2 H); MS *m/e* 253 (M+). Anal. ($C_{15}H_{11}NOS$) C, H, N.

2-Phenyl-4-[(methylsulfonyl)oxy]-5-propylthiazole (59). The title compound was prepared by reacting compound **51** (650 mg, 2.96 mmol) in methylene chloride (20 mL) with triethylamine (0.42 mL, 3.00 mmol) and methanesulfonyl chloride (0.25 mL, 3.26 mmol) at 23 °C for 1 h. The reaction mixture was washed with water and dried (Na_2SO_4). Removal of solvent followed by recrystallization from ether afforded the product (550 mg 82%): mp 82–84 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.90 (t, 3 H, *J* = 7 Hz), 1.67 (m, 2 H), 2.80 (t, 2 H, *J* = 7 Hz), 3.50 (s, 3 H), 7.25–8.00 (m, 5 H); MS *m/e* 297 (M+). Anal. ($C_{13}H_{15}NO_3S_2$) C, H, N.

RBL-1 5-Lipoxygenase Assay. 5-Lipoxygenase activity was measured in the 20000*g* supernatant from homogenized rat basophilic leukemia (RBL-1) cells. Inhibitors or vehicle (2% Me_2SO) were preincubated for 20 min with the RBL-1 supernatant (7.5 × 10^6 cell equiv/mL) at 37 °C in pH 6.8 buffer (10 mM BES, 10 mM PIPES, 1 mM EDTA, 0.1 M NaCl, 0.7 mM $CaCl_2$) prior to initiating the 5-lipoxygenase reaction by addition of 66 μM [^{14}C]arachidonic acid. [^{3}H]-5-HETE added to the reaction mixture served as a recovery standard. Reactions were terminated by acidification to pH 3 and the mixtures were extracted with diethyl ether. The ether extracts were evaporated under nitrogen and the reaction products were separated from nonconverted substrate by thin-layer chromatography. Radioactivity comigrating with 5-HETE was measured by liquid scintillation counting and corrected for recovery of [^{3}H]-5-HETE. Inhibition was calculated as the percent reduction from control levels of [^{14}C]-5-HETE formation. Concentrations causing 50% inhibition (IC_{50}'s) and their 95% confidence limits were calculated as the 50% intercept and their fiducial limits from linear-regression analysis of percent inhibition vs log concentration plots.

(19) Rao, Y. S.; Filler, R. *J. Chem. Soc. Chem. Commun.* **1970**, 1622.
(20) Jeffery, E. A.; Johansen, O.; Meisters, A. *Aust. J. Chem.* **1978**, *31*, 79.
(21) Taylor, E.; Anderson, J.; Berchtold, G. *J. Amer. Chem. Soc.* **1955**, *77*, 5444.
(22) Barrett, G. C.; Khokhar, A. R. *J. Chem. Soc.* **1969**, *8*, 1117.

Inhibitory potencies against related enzymes were determined in assays similar to that described above,[23] 15-lipoxygenase from soybean (Sigma) or cycloxygenase from sheep seminal vesicles in place of the RBL-1 preparation.

Rat PMNL 5-Lipoxygenase Assay. Rat PMNL were obtained from the pleural cavity of nonfasted male rats (Sprague-Dawley, 200–250 g) injected intrapleurally with 200 μL of 0.05% (w/v) carrageenan. Cells were pooled and centrifuged for 15 min at 500*g*. The cell pellet was resuspended in PBS-H, washed by centrifugation, and then briefly resuspended in water for 25 s to lyse contaminating erythrocytes. The cells were washed two more times with PBS-H and suspended at a concentration of 2×10^7 cells/mL in 20 mM *N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid (Sigma Chemical Co., St. Louis, MO) in Earle's balanced salts (GIBCO Laboratories, Grand Island, NY), pH 7.0, containing 1 mg/mL BSA (EH-BSA). About 7.5×10^7 cells were recovered per rat and greater than 90% of the cells were polymorphonuclear leukocytes (PMNL) as determined by differential counting using Wright's stain. Test compounds or DMSO vehicle (final concentration 2%) were preincubated with cell suspensions (5×10^6 cells/250 μL) for 15 min at 37 °C. Cellular arachidonate metabolism was initiated by adding calcium ionophore A23187 (final concentration 8.3 μM) and terminated after 10 min by rapid cooling in an ice bath. Cell supernatants were extracted with two volumes of methanol and analyzed for LTB_4 content by HPLC.

Human Whole Blood 5-Lipoxygenase Assay. Heparinized (20 units/mL) human blood (0.7 mL) was preincubated with test compounds or vehicle for 15 min at 37 °C. Eicosanoid biosynthesis was initiated by adding calcium ionophore A23187 in DMSO (final concentration 50 μM) and terminated after 30 min by rapid cooling of the blood in an ice bath and centrifuging at 3 °C for 10 min at 2500*g*. The plasma was mixed with 4 volumes of methanol and allowed to stand for at least 2 h at 3 °C prior to centrifuging at 1800*g* for 30 min. The level of LTB_4 in aliquots of the methanol-plasma extract was analyzed by RIA (Amersham Corp., Arlington Heights, IL) or by EIA (Cayman Chemical Co., Ann Arbor, MI).

(23) Aharony, D.; Smith, J. B.; Silver, M. J. *Prostaglandins Med.* 1981, *6*, 237.

Acknowledgment. We wish to thank E. Otis, D. Bornemeier, and T. Clark for technical assistance.

Registry No. 1, 70547-26-1; 5, 131786-48-6; 7, 59484-42-3; 10, 131786-51-1; 11, 131786-50-0; 12, 131786-47-5; 13, 70547-50-1; 14, 39785-53-0; 15, 131786-49-7; 16, 133833-90-6; 17, 133833-91-7; 18, 133833-92-8; 19, 133833-93-9; 20, 133833-94-0; 21, 133833-95-1; 22, 133850-30-3; 23, 131786-53-3; 24, 131786-54-4; 25, 131786-55-5; 26, 131786-76-0; 27, 131786-64-6; 28, 131786-67-9; 29, 131786-61-3; 30, 131786-57-7; 31, 131786-75-9; 32, 131786-62-4; 33, 131786-56-6; 34, 133833-96-2; 35, 131786-60-2; 36, 131786-66-8; 37, 131786-58-8; 38, 133833-97-3; 39, 131786-63-5; 40, 131786-59-9; 41, 131786-68-0; 42, 131786-69-1; 43, 77077-60-2; 44, 133833-98-4; 45, 133833-99-5; 46, 65752-44-5; 47, 131786-91-9; 48, 131786-89-5; 49, 131786-90-8; 50, 133834-00-1; 51, 131786-77-1; 52, 131786-97-5; 53, 131786-93-1; 54, 131786-95-3; 55, 131786-96-4; 56, 131786-92-0; 57, 131786-94-2; 58, 133834-01-2; 59, 133834-02-3; 60, 131786-78-2; 61, 131787-05-8; 62, 131787-04-7; 63, 131786-84-0; 64, 131787-03-6; 65, 104223-98-5; 66, 131786-79-3; 67, 133834-03-4; 68, 131786-80-6; 69, 133011-84-4; 70, 70547-29-4; 71, 55073-97-7; 72, 131786-86-2; 73, 131786-85-1; 74, 131786-74-8; 75, 131786-83-9; 76, 131786-82-8; 77, 131786-81-7; thiolactic acid, 79-42-5; 3-cyanopyridine, 100-54-9; ethyl cyanoformate, 623-49-4; ethyl α-bromopropionate, 535-11-5; thiobenzamide, 2227-79-4; methyl isocyanate, 624-83-9; ethyl chloroformate, 541-41-3; α-cyanobenzyl benzenesulfonate, 22259-85-4; methyl thionobenzoate, 5873-86-9; phenyl glycine, 69-91-0; 5-lipoxygenase, 80619-02-9.

Synthesis of an (Iodovinyl)misonidazole Derivative for Hypoxia Imaging

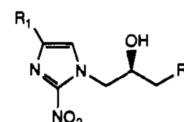
Joseph E. Biskupiak,* John R. Grierson, Janet S. Rasey, Gary V. Martin, and Kenneth A. Krohn

Departments of Radiology and Radiation Oncology, Imaging Research Laboratory, RC-05, University of Washington, Seattle, Washington 98195. *Received December 10, 1990*

Nitroimidazoles undergo a bioreduction in viable hypoxic tissue, resulting in trapping within these tissues, as demonstrated by misonidazole. A radioiodinated analogue of misonidazole (IVM, (*E*)-5-(2-Nitroimidazolyl)-4-hydroxy-1-iodopent-1-ene, 3) has been synthesized by halodestannylation, for evaluation as an imaging agent for hypoxia. A key step in the synthetic sequence involves the use of the Lewis acid $BF_3{\cdot}Et_2O$ to promote the nucleophilic ring opening of glycidyl tosylate with (*E*)-1-lithio-2-(tributylstannyl)ethylene. Direct comparison of IVM versus F-MISO (2) another misonidazole type hypoxic cell marker, in several in vitro cell culture studies, indicates that IVM behaves in analogous fashion to F-MISO and has promise as a hypoxia imaging agent for SPECT.

Our interest in misonidazole (MISO, 1) and its derivatives is due to the ability of viable hypoxic tissues, as might be found in ischemic heart and brain and the central regions of tumors, to metabolically trap these compounds following a bioreduction reaction.[1,2] This property was the impetus for the synthesis of ^{18}F-labeled fluoromisonidazole (F-MISO, 2) for in vivo nuclear imaging of hypoxic tissues by positron emission tomography (PET).[3-5] We now report the synthesis of an (iodovinyl)misonidazole derivative (IVM, 3) which has been labeled with ^{131}I and is being evaluated biologically as a hypoxia imaging agent.

Table I. Partition Coefficients



	R_1	R_2	partition coefficient
MISO (1)	H	OCH_3	0.41
F-MISO (2)	H	F	0.40
IVM (3)	H	CH=CHI	2.52
4-Br-MISO (4)	Br	OCH_3	2.87

The success of these efforts will directly lead to radiolabeling with ^{123}I, useful with more common nuclear imaging instrumentation, including single photon emission computed tomography (SPECT).

Chemistry Results and Discussion

In addition to the synthesis of F-MISO, other work in our laboratory involved the synthesis of [^{82}Br]-4-Br-MISO

(1) Chapman, J. D. *N. Eng. J. Med.* 1979, *301*, 1429.
(2) Rasey, J. S.; Grunbaum, Z.; Magee, S.; Nelson, N. J.; Olive, P. L.; Durand, R. E.; Krohn, K. A. *Radiat. Res.* 1987, *111*, 292.
(3) Grierson, J. R.; Link, J. M.; Mathis, C. A.; Rasey, J. S.; Krohn, K. A. *J. Nucl. Med.* 1989, *30*, 343.
(4) Koh, W.; Rasey, J. S.; Krohn, K. A. Radiation Research Society 37th Annual Meeting, March 18–23, 1989, Seattle, WA.
(5) Koh, W.; Rasey, J. S.; Grierson, J. R.; Link, J. M.; Woods, S. D.; Graham, M. M.; Lewellen, T. K.; Shields, A. F.; Modell, H. I.; Krohn, K. A. *J. Nucl. Med.* 1989, *30*, 789.

0022-2623/91/1834-2165$02.50/0 © 1991 American Chemical Society