previously described.[16,26] IC_{50} values were determined with log-phase cultures in 96-well microculture plates and are calculated as the nominal drug concentration required to reduce the cell density to 50% of control values, with eight control cultures on each microplate. For P388 cultures, drug was present throughout the growth period (72 h), and final cell densities were determined by using a minor modification of the MTT method of Mossman.[27] For AA8 and UV4 cultures, drug exposure was terminated after 18 h by washing three times with fresh medium. Cultures were grown for a further 72 h before determining cell density by staining with methylene blue.[28]

Acknowledgment. This work was supported by the Auckland Division of the Cancer Society of New Zealand, the Medical Research Council of New Zealand, and Pharmol Pacific Ltd. The authors thank Susan Pullen and Michael Chin for cytotoxicity testing and Lynden Wallis for preparation of the manuscript.

Registry No. 6·2HCl, 133041-48-2; 7·2HCl, 133041-49-3; 8·2HCl, 133041-50-6; 9·2HCl, 133041-51-7; 10·2HCl, 133041-52-8; 11·HCl, 133041-53-9; 12·HCl, 133041-54-0; 13·HCl, 133041-55-1; 14·HCl, 133041-56-2; 15·HCl, 133041-57-3; 16·HCl, 133041-58-4; 17·HCl, 133041-59-5; 18·2HCl, 133041-60-8; 19, 133041-62-0; **20**, 133041-64-2; **21**, 133041-66-4; **22**, 133041-68-6; **23**, 103-90-2; **24**, 350-46-9; **25**, 2687-40-3; **26**, 2687-41-4; **27**, 133041-69-7; **28**, 133041-70-0; **29**, 92961-98-3; **30**, 93538-06-8; 31, 462-06-6; **32**, 122-04-3; 33, 2195-47-3; 34, 133041-71-1; **35**, 133041-72-2; **36**, 133041-73-3; 37, 133041-74-4; 38, 133041-75-5; 39, 133041-76-6; **40**, 133041-77-7; 41, 133041-78-8; **42**, 133041-79-9; **43**, 133041-80-2; **44**, 133041-81-3; **45**, 100132-31-8; **46**, 133041-82-4; **47**, 133041-83-5; **48**, 133041-84-6; **49**, 133041-85-7; **50**, 133041-86-8; **51**, 133041-87-9; **52**, 16331-48-9; **53**, 2067-58-5; **54**, 133041-88-0; **55**, 133041-89-1; **56**, 133041-90-4; **57**, 7575-35-1; **58**, 133041-91-5; **59**, 15944-88-4; **60**, 133041-92-6; **61**, 133041-93-7; **62**, 133041-94-8; **63**, 133041-95-9; 4-chloroquinoline, 611-35-8.

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5-Lipoxygenase Inhibitors: The Synthesis and Structure–Activity Relationships of a Series of 1-Phenyl-3-pyrazolidinones[1]

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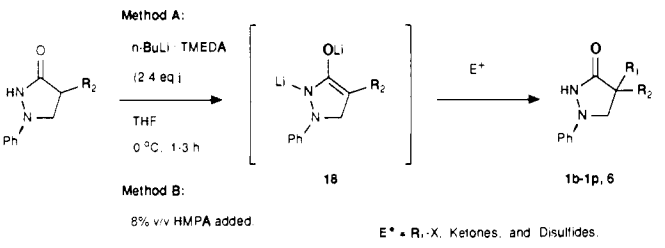
A series of analogues of the 5-lipoxygenase inhibitor 1-phenyl-3-pyrazolidinone (phenidone, **1a**) has been prepared via two complementary new synthetic methods. The reaction of various electrophiles with the dianion of **1a** or with an *N*-silylpyrazolidinone anion gave the desired 4-substituted pyrazolidinones (Scheme I and II). A new procedure was developed for the resolution of 4-substituted pyrazolidinones (Scheme V). A regression study on 21 compounds in this series showed a correlation of increased inhibitor potency (pIC_{50}) with increased compound lipophilicity (log *P*) and with an *N*-phenyl electronic effect as measured by the ^{13}C NMR chemical shift parameter CNMR1′ (R^2 = 0.79). The most potent 5-lipoxygenase inhibitor in this series was 4-(ethylthio)-1-phenyl-3-pyrazolidinone (**1n**) with an IC_{50} of 60 nM. Another member of this series, 4-(2-methoxyethyl)-1-phenyl-3-pyrazolidinone (**1f**, IC_{50} = 0.48 μM), although less potent than **1n**, was better tolerated in the whole animal relative to phenidone (**1a**) and also displayed good oral activity in two models of 5-lipoxygenase inhibition. On the basis of a structure–activity relationship study, a mechanism for the inhibition of 5-lipoxygenase by this class of inhibitors was proposed.

The identification of the leukotrienes (LTC_4, LTD_4, LTE_4) as mediators in the pathophysiology of allergic disease has attracted the interest of many laboratories to discover agents which either antagonize the leukotriene receptor(s)[2] or inhibit leukotriene biosynthesis.[3] Since 5-lipoxygenase (5-LO) oxidizes arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) in the first step of the leukotriene pathway in the arachidonic acid cascade, inhibitors of this enzyme should prevent leukotriene biosynthesis and therefore prove useful in the treatment of allergic asthma.

Phenidone (**1a**) and BW-755C were reported to inhibit 5-LO both in vitro[4,5] and orally ex vivo.[6] More recently the phenidone analogues A-53612 (**2a**)[7] and A-65260[8] have been reported to possess improved selectivity for 5-LO, compared to that of phenidone, as well as oral activity in the inhibition of leukotriene biosynthesis. We now report our findings in the chemistry and in the structure–activity

Scheme I. 4-Substituted Pyrazolidinones via the Dianion 18 (Methods A and B)



(1) Presented in part at the 199th National Meeting of the American Chemical Society, Boston, MA, April 22-27, 1990; MEDI 77.
(2) Musser, J. H.; Kubrak, D. M.; Chang, J.; DiZio, S. M.; Hite, M.; Hand, J. M.; Lewis, A. J. *J. Med. Chem.* **1987**, *30*, 400 and cited references.

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.
§ Department of Molecular Characterization.

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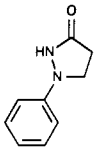
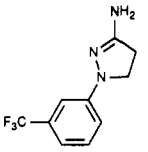
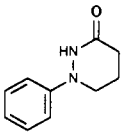
relationships (SAR) of a series of phenidone analogues.



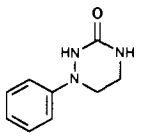
Phenidone (1a)



BW-755C



A-53612 (2a)



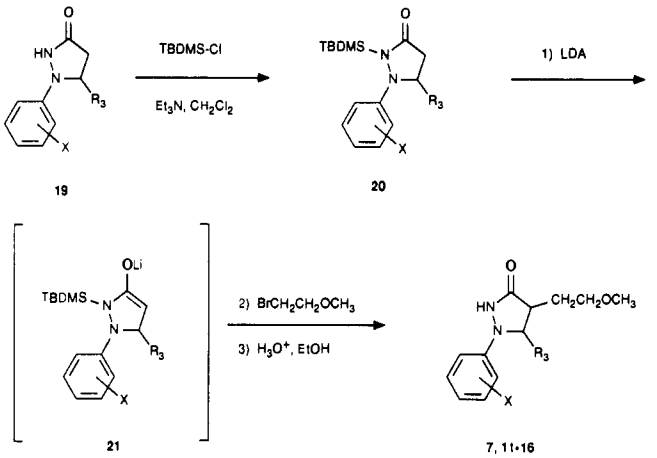
A-65260

Chemistry

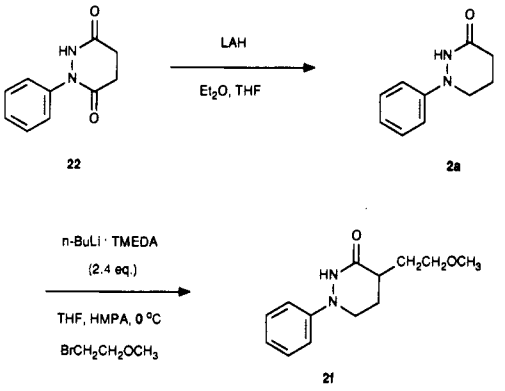
The formation of dianions from secondary amides[9] or carboxylic acids[10] has been known for some time. We have found that treatment of phenidone (**1a**) with 2.4 equiv of *n*-butyllithium·*N,N,N',N'*-tetramethylethylenediamine complex in tetrahydrofuran at 0 °C was necessary for the formation of the dianion **18** (R_2 = H, see Scheme I, method A). Quenching experiments of the dianion **18** with D_2O showed complete deuterium incorporation by NMR after reaction for 1 h at 0 °C. In the absence of TMEDA, no deuterium incorporation was detected at 0 °C and in ether after 4 h at room temperature only 50% conversion to the dianion was detected. Treatment of **18** with various electrophiles provided the desired 4-substituted pyrazolidinones (**1b–p**) in modest to good yields. 1-Phenyl-1*H*-pyrazol-3-ols **4** were the major products formed when poor alkylating agents were used. In some cases this could be obviated by the addition of 8% by volume of hexamethylphosphoramide (HMPA) (method B). For example, ethoxyethyl derivative **1g** was prepared in 63% yield in the presence of HMPA, while in the absence of HMPA a 22% yield of **1g** was obtained along with 1-phenyl-1*H*-pyrazol-3-ol **4**. This reaction was extended to the formation of dianion **18** (R_2 = CH_3)[11] which on treatment with bromomethyl methyl ether gave 4-methyl analogue **6**.

Attempts to form the dianion of 5-methyl- or 5,5-dimethyl-1-phenyl-3-pyrazolidinone, 1-(4-methylphenyl)-3-pyrazolidinone, or 1-(4-chlorophenyl)-3-pyrazolidinone[11] were unsuccessful. These compounds, however, were obtained via the anion formed from 2-(*tert*-butyldimethylsilyl)-3-pyrazolidinones **20** with lithium diisopropylamide in THF at −78 °C (see Scheme II, method C).[12] Treatment of anions **21** with 2-bromoethyl methyl ether at 0 °C or room temperature gave the desired trans-substituted 5-

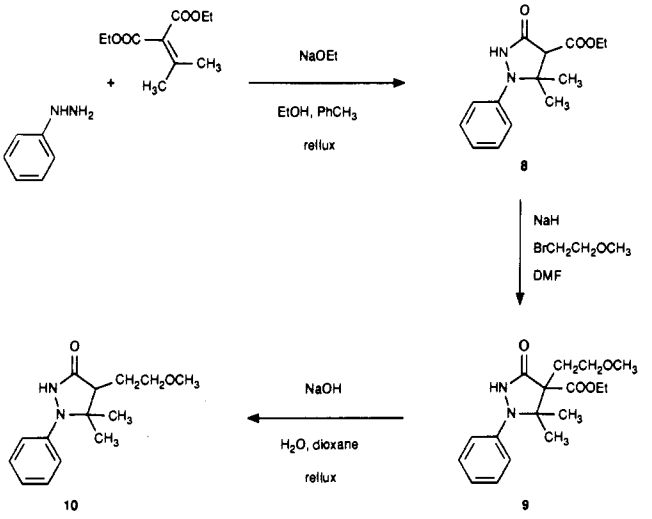
Scheme II. 4-(2-Methoxyethyl)pyrazolidinones via the *N*-Silylpyrazolidinone Anion **21** (Method C)



Scheme III. Synthesis of Pyridazinones **2a** and **2f**



Scheme IV. Synthesis of 4-(2-Methoxyethyl)-5,5-dimethylpyrazolidinone **10**



(3) Welton, A. F.; Holland, G. W.; Morgan, D. W.; O'Donnell, M. *Annual Reports in Medicinal Chemistry*; Academic Press: 1989; Vol. 24, Chapter 7, p 61.
(4) Blackwell, G. J.; Flower, R. J. *Prostaglandins* **1978**, *16*, 417.
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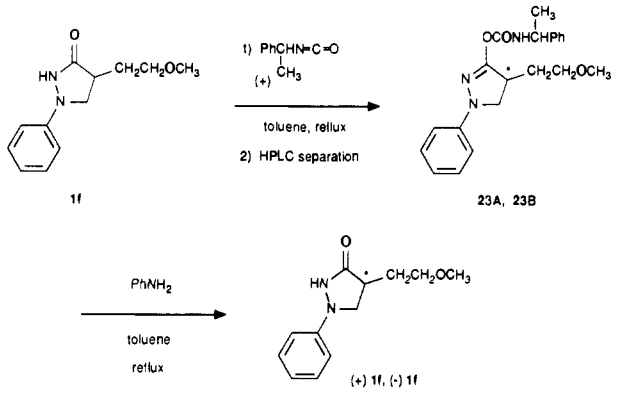
(11) The substituted 1-phenyl-3-pyrazolidinone starting materials **19** were prepared from substituted phenylhydrazines and ethyl acrylates by the following method. Bennett, G. B.; Houlihan, W. J.; Mason, R. B.; Roach, J. B., Jr. *J. Med. Chem.* **1976**, *19*, 715.
(12) Subsequent to our work a patent application disclosed the use of this method on similarly substituted 3-pyrazolidinones. Michno, D. M. Eur. Pat. Appl. EP 134,696, 1985; *Chem. Abstr.*, **1985**, *103*, 79403*k*.

Scheme V. Resolution of 4-(2-Methoxyethyl)-1-phenyl-3-pyrazolidinone (1f)



methyl analogue **7** and phenyl substituted derivatives **11–16**. The trans stereochemistry of 5-methyl analogue **7** was assigned by NOE difference experiments.

Pyridazinone **2a** was prepared by a literature procedure[13] through the reaction of phenylhydrazine with ethyl 4-chlorobutyrate in variable yields (10–27%). We have developed an improved two-step procedure (Scheme III). Condensation of phenylhydrazine with diethyl succinate gave pyridazin-3,6-dione **22**,[14] which on reduction with lithium aluminum hydride gave pyridazinone **2a** in 67% yield. The regioselectivity of the reduction reaction was confirmed by a NOESY experiment on **2a** which displayed a crosspeak between the *o*-phenyl and the pyridazinone ring C6 protons. The dianion formation from **2a** proceeded smoothly, which on alkylation (method B) gave the 4-substituted pyridazine **2f** in 50% yield.

Acetylation of 1-methyl-1-phenylhydrazine with acetic anhydride and triethylamine in methylene chloride yielded acethydrazide **3**.[15] Pyrazolidinones **1b** and **1f** were readily oxidized by *m*-chloroperbenzoic acid in methylene chloride to afford pyrazol-3-ols **4b** and **4f**. Pyrazolidinone **1b** was N-methylated with sodium hydride–methyl iodide in DMF to give *N*-methylpyrazolidinone **5**. 5,5-Dimethyl analogue **10** was prepared through the three-step procedure outlined in Scheme IV. The regiochemistry of the condensation reaction was confirmed by a NOESY experiment on **10** which showed a crosspeak between the *o*-phenyl and the C5 methyl protons.

We wished to determine the enantio preference for inhibition of 5-lipoxygenase; however, a method for the resolution of racemic pyrazolidinones had not been reported. The formation of diasteromeric salts with chiral bases was unsuccessful since the pyrazolidinones are weak acids.[16] We have found that adduct **23** can be formed in good yield by the thermal reaction of (*R*)-(+)-α-methylbenzylisocyanate with **1f** (see Scheme V). Preparative HPLC afforded the two diastereomers **23**, which on reaction with aniline in refluxing toluene gave the enantiomers (+)-**1f** and (−)-**1f**. We chose to trap the isocyanate generated in the thermal cleavage of the diastereomers **23** with aniline, a weak, poorly nucleophilic base, to avoid epimerization or pyrazolidinone ring cleavage. For example, attempted cleavage of the adduct **23** to **1f** with sodium hydroxide in methanol at 0 °C for 30 min only gave pyrazolidinone ring cleavage. The optical purity of (+)-**1f** and (−)-**1f** was determined by chiral HPLC analysis on a Chiralcel OD column eluted with 2-propanol–hexanes mixtures. The optical purities of (+)-**1f** and (−)-**1f** were 99% and 89%, although the optical rotations were +94.0° and −94.7°, respectively. The lower optical purity of (−)-**1f** is presumably due to incomplete separation of the diastereomers in the difficult preparative HPLC separation of diastereomers **23**.

The physical properties of **1b–p**, **2a,f**, **3**, **4b,f**, and **5–17** are outlined in Table I.

The X-ray crystal structure of (+)-**1f** was determined and is shown in Figure 1 in an arbitrary absolute configuration. The absolute configuration could not be determined due to the absence of significant anomalous ab-

Table I. Physical Properties

compd	% yield (method)	mp, °C	recrystn solvent[a]	formula[b]
1b	42 (A)	98–99	EA–C	$C_{11}H_{14}N_2O_2$
1c	50 (A)	82.5–83	T–H	$C_{12}H_{16}N_2O_2$
1d	20 (A)	94.5–96	T–H	$C_{13}H_{18}N_2O_2$
1e	43 (A)	81–83	T–C	$C_{13}H_{18}N_2O_3$
1f	63 (B)	73.5–75	T–H	$C_{12}H_{16}N_2O_2$
1g	63 (B)	74–75.5	EA–H	$C_{13}H_{18}N_2O_2$
1h	20 (A)	102–104	EA–H	$C_{11}H_{14}N_2O_2$
1i	29 (B)	83–84	B–H	$C_{13}H_{19}N_3O$
1j	70 (A)	112–115	C	$C_{12}H_{16}N_2O_2$
1k	52 (A)	124–129	EA–H	$C_{22}H_{20}N_2O_2$
1l	22 (B)	119–120.5	T–H	$C_{14}H_{14}N_2OS$
1m	47 (A)	115–117	EA–C	$C_{10}H_{12}N_2OS$
1n	41 (A)	73.5–74.5	EA–H	$C_{11}H_{14}N_2OS$
1o	29 (A)	112–113.5	EA–H	$C_{16}H_{16}N_2OS$
1p	37 (A)	131–133	EA–H	$C_{14}H_{13}N_3OS$
2a	67[c]	148.5–150.5	EA	$C_{10}H_{12}N_2O$
2f	50 (B)	70–72	EA–H	$C_{13}H_{18}N_2O_2$
3	63[d]	85–87	EA–H	$C_9H_{12}N_2O$
4b	65[c]	104–105.5	T–H	$C_{11}H_{12}N_2O_2$
4f	47[c]	91–93	Et	$C_{12}H_{14}N_2O_2$[e]
5	44[c]	(bp 154–155, 1.5 mmHg)	oil	$C_{12}H_{16}N_2O_2$
6	58 (A)	137–139	EA–H	$C_{12}H_{16}N_2O_2$
7	52 (C)	65–66.5	E–H	$C_{13}H_{18}N_2O_2$
8	64[c]	66–67	E–H	$C_{14}H_{18}N_2O_3$
9	41[c]	55–56	E–H	$C_{17}H_{24}N_2O_4$
10	64[c]	oil		$C_{14}H_{20}N_2O_2$
11	40 (C)	95–96.5	EA–H	$C_{12}H_{14}Cl_2N_2O_2$
12	36 (C)	98–99.5	EA–H	$C_{13}H_{15}F_3N_2O_2$
13	53 (C)	88–89	EA–E	$C_{12}H_{15}ClN_2O_2$
14	40 (C)	64.5–66	E	$C_{13}H_{18}N_2O_2$
15	54 (C)	129–131	EA	$C_{19}H_{22}N_2O_3$
16	45 (C)	59–60	E	$C_{13}H_{18}N_2O_3$
17	71[c]	144–146	A	$C_{12}H_{16}N_2O_3$

[a] A = acetonitrile, B = *tert*-butyl methyl ether, C = cyclohexane, E = ether, EA = ethyl acetate, Et = 95% ethanol, H = hexanes, T = toluene. [b] Carbon, hydrogen, and nitrogen analysis were within ±0.4% of the theoretical values. [c] See the Experimental Section. [d] Reference 15. [e] C: calcd, 65.43; found, 64.94.

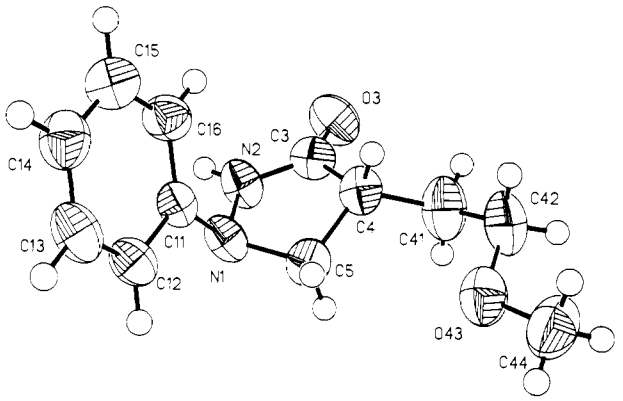


Figure 1. ORTEP drawing of **1f**.

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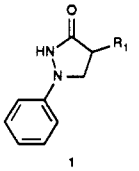
(14) Conrad, M.; Zart, A. *Chem. Ber.* **1906**, *39*, 2282.
(15) Fischer, E. *Justus Liebig Ann. Chem.* **1887**, *239*, 248.
(16) The pK_a of phenidone (**1a**) is 9.35. Lee, W. E.; Brown, E. R. *The Theory of the Photographic Process*, 4th ed., Macmillian: New York, 1977; Chapter 11, p 321.

Table II. C-4 Substituent Effects on 5-Lipoxygenase Inhibition



1

compd	R_1	5-LO inhibn:[a] IC_{50}, μM
phenidone (1a)	H	0.52 (0.43–0.64)
1b	CH_2OCH_3	0.59 (0.37–0.94)
1c	$CH_2OCH_2CH_3$	0.28 (0.24–0.33)
1d	$CH_2OCH_2CH_2CH_3$	0.26 (0.21–0.33)
1e	$CH_2OCH_2CH_2OCH_3$	0.52 (0.42–0.65)
1f	$CH_2CH_2OCH_3$	0.48 (0.41–0.56)
1f (+)	$CH_2CH_2OCH_3$	0.35 (0.29–0.41)
1f (–)	$CH_2CH_2OCH_3$	1.03 (0.85–1.24)
1g	$CH_2CH_2OCH_2CH_3$	0.15 (0.11–0.20)
1h	CH_2CH_2OH	>1[b]
1i	$CH_2CH_2N(CH_3)_2$	≫1[c]
1j	$C(OH)(CH_3)_2$	>1[b]
1k	$C(OH)Ph_2$	<1[d]
1l	CH_2-2-thienyl	0.14 (0.12–0.16)
1m	SCH_3	0.32 (0.20–0.52)
1n	SCH_2CH_3	0.06 (0.03–0.10)
1o	SCH_2Ph	0.18 (0.16–0.20)
1p	S-2-pyridinyl	0.12 (0.10–0.15)

[a] 95% confidence limits are in parentheses. [b] 20–35% inhibition at 1 μM. [c] <20% inhibition at 1 μM. [d] IC_{50} was not determined since 1k displayed poor in vivo activity.

sorption. The N1 nitrogen is largely sp^3 hybridized which was noted on examination of the bond angles. The bond angles for C11–N1–C5 and C11–N1–N2 were both 113°. Also, the C3–N2–N1–C11 dihedral angle was 107°, showing the phenyl to be substantially out of the pyrazolidinone ring plane. The lone pair of electrons on N1 are clearly accessible for electron-transfer reactions which we propose as being necessary for the inhibition of 5-LO by 1f. The importance of this property is described in the Discussion section of this paper.

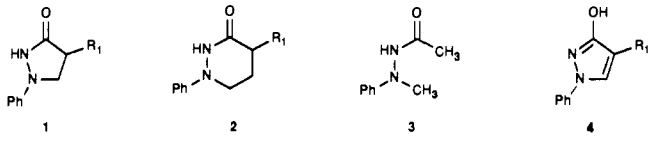
Results and Discussion

In Vitro 5-Lipoxygenase Inhibition. The inhibition of 5-LO in vitro was determined in a broken-cell assay, modified from that of Jakschik et al.[17] Homogenized rat basophils (RBL-1 cells) were incubated with test compound and then with [^{14}C]arachidonic acid. A chloroform extract was subjected to thin-layer chromatography and radiochromatographic scanning for the determination of LTB_4 and 5-HETE levels.

Substitution at the 4-position (see Table II) with alkoxyalkyl substituents gave analogues 1b–1g with potency equal to or better than that of phenidone. Additionally, compond 1f was shown to be better tolerated than phenidone in the rat (less severe overt effects upon acute administration of 300 mg/kg po). Increasing the polarity of the side chain by replacement of the methoxy in 1f with hydroxy or dimethylamino attenuated potency (see 1h and 1i). The incompatibility of the side-chain hydroxy with good inhibitory potency could be overcome by further increasing the side chain lipophilicity (see 1j and 1k).

Since the substrate for 5-lipoxygenase is arachidonic acid, a relatively lipophilic molecule, it follows that the lipophilicity of 5-lipoxygenase inhibitors should play a key role in improving the potency. In fact, this has been demonstrated in SAR studies of other 5-LO inhibitor classes.[18,19] Recently, Hammond and co-workers[20] showed that for a series of 2,3-dihydro-5-benzofuranols, 5-lipoxygenase inhibition correlated very well with calculated log P values. 4-Mercapto analogues 1m–1p further exemplify this correlation of inhibitory potency with lipophilicity. 4-Ethylthio analogue 1n, the most potent analogue in the series, is 9 times more potent than phenidone and is one of the most lipophilic compounds in this series as defined by calculated log P values.[21]

Table III. Ring Modification Effects on 5-Lipoxygenase Inhibition



1 2 3 4

compd	R_1	5-LO inhibn:[a] IC_{50}, μM
1a	H	0.52 (0.43–0.64)
1f	$CH_2CH_2OCH_3$	0.48 (0.41–0.56)
2a	H	0.53 (0.33–0.85)
2f	$CH_2CH_2OCH_3$	0.44 (0.24–0.80)
3		≫1[c]
4b	CH_2OCH_3	≫1[c]
4f	$CH_2CH_2OCH_3$	>1[b]

[a] 95% confidence limits are in parentheses. [b] 20–35% inhibition at 1 μM. [c] <20% inhibition at 1 μM.

Table IV. Pyrazolidinone Ring Substituent Effects on 5-Lipoxygenase Inhibition

1 5, 6, 7, 10

compd	substitution[c]	5-LO inhibn:[a] IC_{50}, μM
1b	$R_1 = CH_2OCH_3$	0.59 (0.37–0.94)
1f	$R_1 = CH_2CH_2OCH_3$	0.48 (0.41–0.56)
5	$R_1 = CH_2OCH_3$, $R_5 = CH_3$	≫1[b]
6	$R_1 = CH_2OCH_3$, $R_2 = CH_3$	0.67 (0.47–0.94)
7[d]	$R_1 = CH_2CH_2OCH_3$, $R_3 = CH_3$	0.50 (0.43–0.59)
10	$R_1 = CH_2CH_2OCH_3$, $R_3 = R_4 = CH_3$	≫1[b]

[a] 95% confidence limits are in parentheses. [b] <20% inhibition at 1 μM. [c] Unless otherwise indicated, R_2, R_3, R_4, R_5 = H. [d] Trans stereochemistry.

Modification of the pyrazolidinone ring in this series (Table III) did not enhance potency. The six-membered ring analogues 2a and 2f retained potency. The ring-opened derivative 3 was devoid of activity as were the oxidized ring system analogues 4b and 4f. N-Methyl derivative 5 was inactive (Table IV).

The steric effects of substitution at ring positions 4 and 5 were probed (Table IV). A methyl group at either the 4- or 5-position in the 4-(methoxyalkyl)pyrazolidinones 1b and 1f did not alter potency (see 6 and 7). However, the 5,5-dimethyl analogue 10 was inactive, indicating that

(17) Jakschik, B. A.; Sun, F. F.; Lee, L. H.; Steinhoff, M. M. *Biochem. Biophys. Res. Commun.* **1980**, *95*, 103.

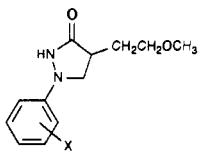
(18) Summers, J. B.; Mazdiyasni, H.; Holms, J. H.; Ratajczyk, J. D.; Dyer, R. D.; Carter, G. W. *J. Med. Chem.* **1987**, *30*, 574.

(19) Kees, K. L.; Musser, J. H.; Chang, J.; Skowronek, M.; Lewis, A. J. *J. Med. Chem.* **1986**, *29*, 2329.

(20) Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Luell, S.; MacIntyre, D. E. *J. Med. Chem.* **1989**, *32*, 1006.

(21) CLOGP3 version 3.54, MedChem Software Package, Daylight Chemical Information Systems, Claremont, CA, 1989.

Table V. Phenyl Substituent Effects on 5-Lipoxygenase Inhibition



compd	X	5-LO inhibn:[a] IC_{50}, μM	σ	log P
11	3,4-Cl_2	0.19 (0.14–0.26)	0.60	1.96
12	3-CF_3	0.22 (0.18–0.27)	0.43	1.41
13	4-Cl	0.25 (0.22–0.28)	0.23	1.24
1f	H	0.48 (0.41–0.56)	0	0.53
14	4-CH_3	1.08 (0.89–1.32)	−0.17	1.03
15	4-OCH_2Ph	0.5[b]	−0.17	2.22
16	4-OCH_3	1.46 (1.14–1.86)	−0.27	0.45
17	4-OH	5.13 (3.51–7.50)	−0.37	−0.14

[a] 95% confidence limits are in parentheses. [b] Approximate IC_{50} due to a steep dose–response curve.

certain steric requirements exist for enzyme inhibition. The 5,5-dimethyl substituents of **10** may not permit the phenyl to adopt the necessary orientation to inhibit the enzyme. A conformational change in **10** was detected in the ^{13}C NMR spectrum. The C1 of the phenyl that is attached to the pyrazolidinone (1′-position) in **10** is shielded by 12 ppm relative to **1f** and **7**, suggesting less π orbital overlap of the N1 nitrogen and the phenyl ring of **10**. Since the 4-methyl analogue **6** was equipotent with **1f**, it appears that steric effects at the 4-position do little to affect inhibition of the enzyme. Consistent with these observations was the weak enantiomeric preference for enzyme inhibition by **1f**. The (+)-**1f** enantiomer was only 3 times more potent than the (−)-**1f** enantiomer.

Phenyl substitution gave a group of compounds (Table V) with a range of IC_{50}'s from 0.19 to 5.13 μM. Potency increased with increasing electron-withdrawing capability and increasing lipophilicity as measured by the Hammett σ constants[22] and calculated log P values.[21] Analogous to a report on a series of phenyl substituted hydroxamic acids,[18] a trend exists between potency and σ and calculated log P values.

Due to this trend in the relationship between σ and potency, we sought a more reliable and an experimental measure of electronic effects. The examination of the carbonyl stretch bands in the infrared spectra or of the absorption peaks in the ultraviolet spectra of the ultraviolet spectra of the pyrazolidinones did not give useful results. Since, as we have discussed above, there was a relationship between inhibitor potency and the ^{13}C NMR shift of the C1 of the phenyl group of **1f**, **7**, **10**, we chose to examine the ^{13}C NMR chemical shifts as a measure of electron density and thus the electronic effects on inhibitor potency. Note that the Hammett σ constants have also been correlated with the ^{13}C NMR shifts of the para carbon in monosubstituted benzenes.[23] The use of this strategy was applied in the multiple linear regression study discussed below.

Multiple Linear Regression Studies. The relationship of structural features in this series of compounds with 5-lipoxygenase activity was investigated by multiple linear regression methods. A set of 22 compounds was initially selected for study from the compounds reported here: **1a–g**, **1l–p**, **2a**, **2f**, **6**, **7**, **11–14**, **16**, and **17**. These compounds had well characterized biological activity in the 5-lipoxygenase inhibition assay in vitro.

To describe the structural variation of these 22 compounds, six physicochemical parameters were used as independent variables in the regression analysis. The descriptors were the calculated log of the partition coefficient (log P) as calculated by the MedChem software package,[21] calculated molar refractivity (MR) (also calculated with the MedChem package), and the experimentally determined ^{13}C NMR shifts at the carbon centers C1′, C3, C4, and C5 in this series of compounds (CNMR1′, CNMR3, CNMR4, CNMR5). Table VI lists the values for these descriptors and some simple statistics for each. The log P descriptor has been shown to correlate with 5-LO activity by Hammond et al.[20] and its constituent fragment constant was used by Summers and co-workers.[24] log P is commonly used as a measure of the lipophilicity of the molecules in SAR studies. Molar refractivity varies with the bulk of the molecule and within a series can indicate the relative size of ring substituents. The ^{13}C shifts are an experimental observation of the atomic environments of the measured carbon atoms. The steric and electronic environment of an atom will influence the chemical shift of that atom. This observation has been explored by Jurs and co-workers[25] to explain shift behavior as a function of the atomic environments. We felt that these chemical shift values would be good indicators of changes in electronic effects. The carbons selected for observation follow the pattern of substitution within the series and may indirectly indicate the conformational properties of some of the compounds.

A variety of regression methods were used including stepwise, forward addition and backward elimination techniques to relate the structural descriptors to the biological activity.[26] The dependent variable, pIC_{50}, was the negative logarithm of the IC_{50} values listed in Tables II–V. The best model for the 22 member data set included two variables log P and CNMR1′. Examination of this model showed that one compound, **1o**, was an outlier having both a large residual, the difference between the actual values and the value predicted by the regression equation, and a large Cook's distance, a measure of the change in model coefficients due to removal of a data point. This compound has a significantly larger log P of 3.63 which is 1.1 log units greater than the next lower value within the set. Examination of the log P calculation for **1o** showed several approximations were used for substituent constants. For this reason, **1o** was eliminated from further considerations.

The remaining 21 compounds were then examined. The best model that could be found is

$$pIC_{50} = 0.90\ (\pm 0.19)\ \log P + 0.15\ (\pm 0.06)\mathrm{CNMR1}' - 24.19\ (\pm 8.67) \quad (1)$$

$$n = 21,\ R^2 = 0.79,\ s = 0.49,\ F(2,18) = 33.6,\ p = 0.001$$

The model indicates that two descriptors, log P and CNMR1′, can be used to explain 79% of the total variance of the biological activity. The F statistic was used to verify the significance of the model at a probability level of 0.001. The individual correlations of the descriptors to one an-

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(23) Spiesecke, H.; Schneider, W. G. *J. Chem. Phys.* **1961**, *35*, 731.
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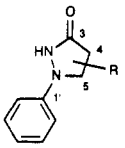
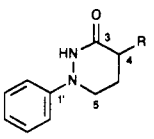
(25) Small, G. W.; Jurs, P. C. *Anal. Chem.* **1983**, *55*, 1121. Egolf, D. S.; Brockett, E. B.; Jurs, P. C. *Anal. Chem.* **1988**, *60*, 2700. Sutton, G. P.; Jurs, P. C. *Anal. Chem.* **1989**, *61*, 863.
(26) SAS Statistical System, Version 5, SAS Institute, Inc., Cary, NC, 1985.

Table VI. Descriptor Values and Statistics

compd	5-LO inhibn: IC_{50}, μM	log P	MR	CNMR1'[a]	CNMR3	CNMR4	CNMR5
1a	0.52	0.893	4.676	151.11	175.23	29.90	54.65
1b	0.59	0.891	5.756	151.37	174.37	41.21	58.34
1c	0.28	1.420	6.220	151.47	174.56	41.36	58.71
1d	0.26	1.949	6.684	151.65	174.72	41.18	59.17
1e	0.52	0.955	6.837	151.37	174.40	41.24	58.80
1f	0.48	0.530	6.220	151.34	176.88	38.04	61.27
1g	0.15	1.059	6.684	151.38	176.98	38.17	61.33
1l	0.14	2.476	7.460	151.32	175.51	42.26	60.47
1m	0.32	1.974	5.946	150.68	172.81	43.49	60.19
1n	0.06	2.503	6.410	150.96	173.54	42.26	61.28
1o	0.18	3.632	8.457	150.85	173.43	40.89	60.77
1p	0.12	2.157	7.782	151.01	172.69	42.48	62.19
2a	0.53	1.452	5.140	149.31	173.08	28.52	49.75
2f	0.44	1.089	6.684	149.38	175.93	35.73	49.39
6	0.67	1.410	6.220	151.66	176.77	45.98	62.75
7	0.50	1.049	6.684	151.56	176.16	47.31	67.80
11	0.19	1.956	7.203	150.84	177.12	38.42	61.22
12	0.22	1.413	6.731	151.74	177.20	38.40	61.06
13	0.25	1.243	6.712	149.96	176.93	38.17	61.30
14	1.08	1.029	6.684	149.25	176.97	37.90	61.87
16	1.46	0.449	6.837	145.10	176.94	37.67	62.27
17	5.13	−0.137	6.373	143.40	175.44	36.80	61.37
mean	0.64	1.426	6.563	150.30	175.34	39.42	59.81
stdev	1.05	0.819	0.804	2.11	1.55	4.39	4.05
min	0.06	−0.137	4.676	143.40	172.69	28.52	49.39
max	5.13	3.632	8.457	151.74	177.20	47.31	67.80

[a] The ^{13}C NMR spectra of the compounds were determined in $CDCl_3$.

Table VII. Pairwise Correlations (R^2)

	pIC_{50}	log P	MR	CNMR1'	CNMR3	CNMR4	CNMR5
pIC_{50}	1.000						
log P	0.702	1.000					
MR	0.093	0.098	1.000				
CNMR1'	0.522	0.331	0.000	1.000			
CNMR3	0.053	0.170	0.049	0.012	1.000		
CNMR4	0.063	0.113	0.270	0.117	0.001	1.000	
CNMR5	0.001	0.000	0.240	0.002	0.105	0.511	1.000

other and to the pIC_{50} is shown in Table VII. Independently, log P explains 70% of the pIC_{50} data spread while CNMR1' explains 52%. In Hammond's studies, the log P values were able to explain 81% of the variance. Figure 2 shows a plot of the experimental pIC_{50} versus calculated pIC_{50} using this model. The two compounds on the low end of the activity scale are **16** and **17**, which are the 4-methoxyphenyl and the 4-hydroxyphenyl analogues. These two are also the most hydrophilic compounds within the set. While these compounds influence the regression model, no statistical reasons were found for excluding these compounds from the evaluation. Figure 3 shows a residual plot for the model in eq 1 and shows no systematic variation within the regression model.

Ex Vivo and in Vivo 5-Lipoxygenase Inhibition. The inhibition of 5-LO ex vivo was assessed in the rat, in a modification of the method of Siegel et al.[27] Four hours after induction of pleural inflammation with carrageenan and 1 h after oral administration of test compound, neutrophils were harvested and stimulated with ionophore (A23187). Extracts were analyzed for LTB_4 by reverse-phase HPLC.

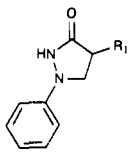
The inhibition of leukotriene-mediated bronchoconstriction in vivo was determined in the guinea pig, with a method modified from Ritchie et al.[28] Immunized guinea pigs were anesthetized and prepared for the monitoring of tracheal pressure. After pretreatment with test compound (po, 1 h prechallenge), naproxen, pyrilamine, and propranolol, the animals were challenged with antigen (ovalbumin) and their bronchoconstrictor responses determined.

In a preliminary rat tolerance test three analogues, **1b**, **1f**, and **1n**, were well-tolerated at 300 mg/kg po compared to phenidone. These analogues were tested for whole-animal activity in two models, the inhibition of leukotriene biosynthesis ex vivo and of leukotriene-mediated bronchoconstriction (see Table VIII). The three analogues (**1b**, **1f**, and **1n**) were less potent than phenidone (**1a**) in the ex vivo leukotriene biosynthesis inhibition model. These four compounds did inhibit leukotriene-mediated bronchoconstriction at similar ED_{50} values. A trend exists for decreasing potency in the ex vivo model with increasing lipophilicity for these four compounds. The oral toxicity of 4-(methoxyethyl)pyrazolidinone **1f** was investigated in

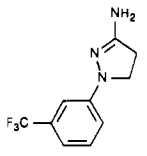
(27) Siegel, M. I.; McConnell, R. T.; Bonser, R. W.; Cuatrecasas, P. *Prostaglandins* 1981, *21*, 123.

(28) Ritchie, D. M.; Sierchio, J. N.; Capetola, R. J.; Rosenthale, M. E. *Agents Actions* 1981, *11*, 396.

Table VIII. Oral Activity of Pyrazolidinones



1



BW-755C

compd	R_1	5-LO inhibition[a] in vitro, IC_{50}, μM	5-LO inhibition[a] ex vivo, ED_{50}, mg/kg po	leukotriene-mediated[a] bronchoconstriction: ED_{50}, mg/kg po
phenidone (1a)	H	0.52 (0.43–0.64)	16 (14–18)	69 (42–114)
1b	CH_2OCH_3	0.59 (0.37–0.94)	29 (21–41)	25 (14–47)
1f	$CH_2CH_2OCH_3$	0.48 (0.41–0.56)	43 (34–53)	62 (39–97)
1n	SCH_2CH_3	0.06 (0.03–0.10)	95 (57–158)	92 (39–212)
BW-755C		5.0 (4.3–5.8)	>300[b]	~300

[a] 95% confidence limits are in parentheses. [b] The highest dose tested (300 mg/kg) produced weak inhibition (29%) accompanied by adverse side effects.

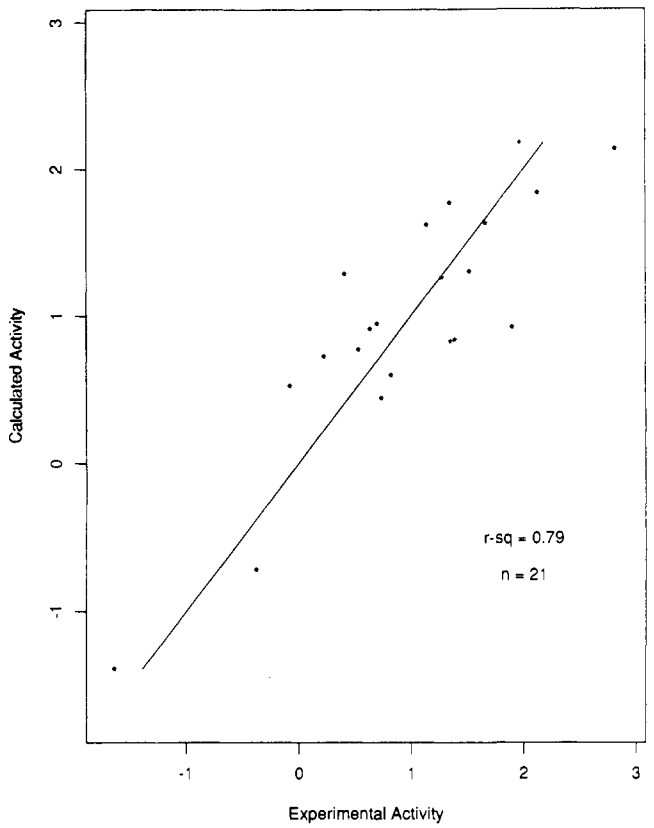


Figure 2. Plot of the experimental pIC_{50} versus the calculated pIC_{50} using the model eq 1.

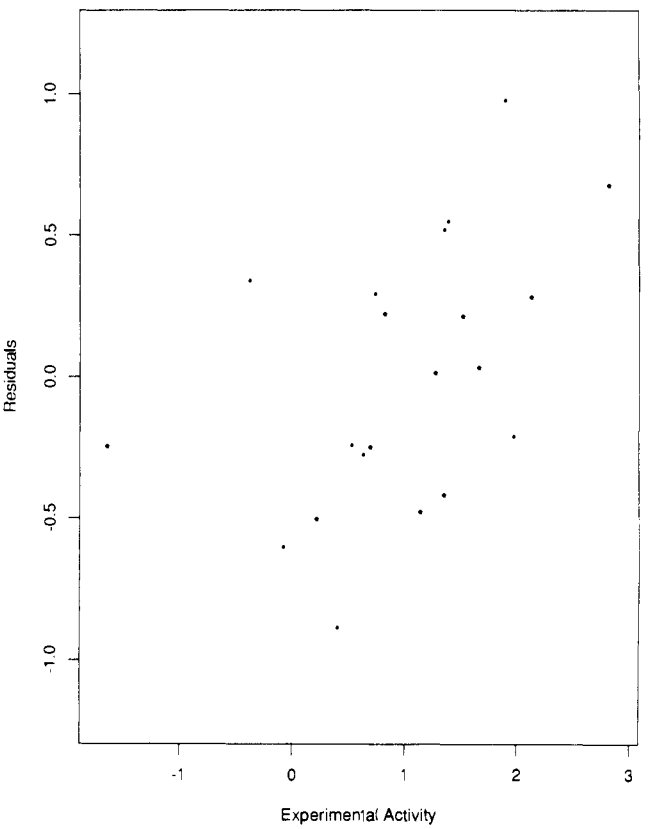


Figure 3. Regression residues plot.

rats. Dosages up to 675 mg/kg per day for 2 weeks resulted in hematologic effects. Dosage-related increases in methemoglobin and reticulocytes as well as decreases in red blood cell count were observed. In contrast, in vitro incubation in canine blood at a concentration of 1 mg/mL of phenidone and **1f** only produced moderate effects (a 26% and 11% increase of methemoglobin from baseline, respectively). The analogues **2a**, **3**, **14**, and **16** gave no effect at that concentration. These results are consistent with those reported by Brooks and co-workers.[8] They have postulated that methemoglobinemia caused by this class of compounds is due to in vivo enzymatic cleavage of the cyclic hydrazide to the phenylhydrazine which is the proposed toxic entity.

Hypothetical Mechanism of 5-Lipoxygenase Inhibition. The 5-LO catalyzed oxidation of arachidonic acid to 5-HPETE is not a simple process and a model for a

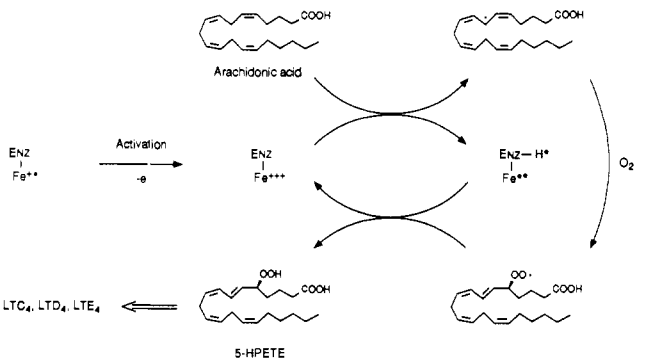


Figure 4. Hypothetical mechanism of 5-lipoxygenase.

mechanism of 5-LO has been proposed.[29,30] The mechanism for this transformation has been postulated to involve

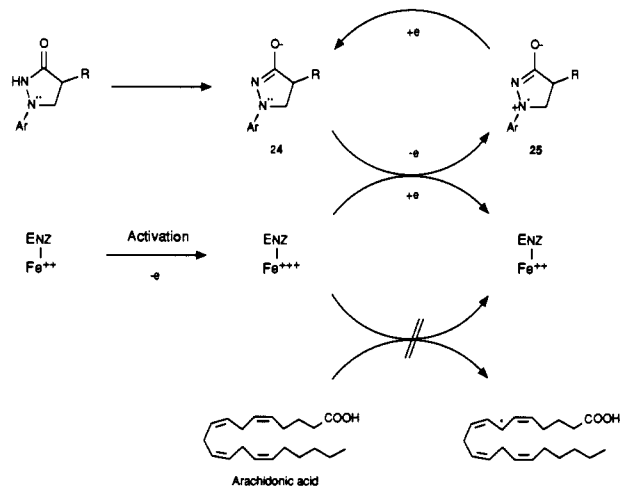


Figure 5. Proposed mechanism of 5-lipoxygenase inhibition.

initial oxidative activation of 5-LO by hydroperoxy fatty acids by the oxidation of iron(II) to iron(III) at the catalytic site of the enzyme.[31,32] This activated form of 5-LO may lead to the propagation of the free-radical process shown in Figure 4. The activated form of 5-LO oxidizes arachidonic acid to a radical species which is envisioned to be trapped by molecular oxygen to give 5-HPETE and completion of the catalytic cycle. In this oxidative process, 5-LO cycles between the iron(III) and iron(II) forms of the enzyme.

Phenidone (**1a**) is known to be a redox-active compound. The anion form of phenidone **24** is oxidized in solution by a one-electron reversible step to form a neutral free radical **25**. The free radical of phenidone has been shown to possess moderate stability and can be generated by the reaction of phenidone with potassium ferricyanide [iron(III)] as an oxidant.[16] The pyrazolidinones in this series can display the same redox properties as phenidone, and although this property is necessary for inhibitor activity, it is not the only requirement. Compound lipophilicity is another key property for good inhibitor potency in this series of compounds.

We therefore propose a possible mechanism for the inhibition of 5-LO by this class of compounds. At the catalytic site of the enzyme, we propose that the pyrazolidinone ring as anion **24** is oxidized to a lipophilic neutral radical species **25**, concomitant to the reduction of the activated form of 5-LO [iron(III)] to the inactive form of 5-LO [iron(II)], thereby preventing the oxidation of arachidonic acid to 5-HPETE (see Figure 5). This hypothesis is supported by the two important effects uncovered in our SAR study that are needed for potency of inhibition. First, we have shown that lipophilic effects outweigh both steric effects and enantiomeric preference for potency. If these compounds inhibited the enzyme by binding to the active site through hydrogen bonds, hydrophobic interactions, and/or chelation, then the steric effects on the SAR would have been pronounced. Secondly, the pyrazolidinones show a relationship between inhibition potency and electronic effects on the phenyl ring as measured by σ and CNMR1′. The ^{13}C NMR results (c.f. compounds **1f**, **7**, and **10**) point to the need for overlap of the phenyl ring π orbitals with the extended π orbital system of the pyrazolidinone ring for good inhibitor potency. This extended orbital system would stabilize a radical species thus contributing to the radical scavenger ability of the system and to the inactivation of 5-LO.

(29) Corey, E. J. *Stereochemistry of Organic and Bioorganic Transformations, Proceedings of the 17th Workshop Conference Hoechst*; VCH: Weinheim, 1987; p 1.
(30) Cashman, J. R. *Pharm. Res.* **1985**, 253.
(31) Rouzer, C. A.; Samuelsson, B. *FEBS Lett.* **1986**, *204*, 293.
(32) Egan, R. W.; Fluder, E. J.; Gale, P. H.; Brown, S. A. *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*; Raven Press: New York, 1987; Volume 17, p 69.

Summary

We have developed two new compelmentary synthetic methods (A and C) for the preparation of 4-substituted pyrazolidinones or tetrahydropyridazinones. Our method for the resolution of **1f** has potential for application to the resolution of these classes of compounds.

Our results in the SAR study have extended to this series the correlation of compound lipophilicity with inhibitor potency. A correlation of inhibitor potency with compound lipophilicity (log *P*) and the ^{13}C NMR shift of the C1 phenyl (CNMR1′ parameter) has been demonstrated. This SAR study revealed two factors that are important for efficient inhibition of 5-LO in vitro: (1) lipophilicity and (2) good radical-scavenging properties. Based on the data from this study, we have developed a model for the mechanism of inhibition of 5-LO by the pyrazolidinones via a lipophilic neutral radical species.

We have prepared an analogue (**1n**) which is a very potent inhibitor of 5-lipoxygenase. We have prepared a phenidone analogue (**1f**) with improved tolerance which retained in vivo activity relative to that of phenidone. The serious effects detected in the oral toxicology of **1f** have precluded **1f** from consideration as a drug candidate.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 467 spectrophotometer or on a Nicolet 10DX FTIR. NMR spectra were determined in the indicated solvent on a QE-300, an IBM NR/200 FTNMR, or a JEOL-FX270. ^{13}C NMR spectra were determined on a JEOL-FX270, and DEPT experiments were performed to aid in the signal assignments. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, and carbon, hydrogen, and nitrogen analyses were within ±0.4% of the theoretical values. Preparative HPLC was performed on a Waters Prep LC/System 500A.

Method B. 4-(2-Methoxyethyl)-1-phenyl-3-pyrazolidinone (1f). To a stirred solution of 20.0 g (123 mmol) of 1-phenyl-3-pyrazolidinone and 25 mL (170 mmol) of *N,N,N′,N′*-tetramethylethylenediamine in 500 mL of tetrahydrofuran at −78 °C and under nitrogen was added dropwise 114 mL (290 mmol) of a 2.58 M solution of *n*-butyllithium in hexanes. After completion of the addition, the reaction mixture was brought to 0 °C and stirred for 2.5 h. The clear yellow solution was cooled to −78 °C and 50 mL of hexamethylphosphoramide was added. A solution of 14 mL (150 mmol) of 2-bromoethyl methyl ether in 15 mL of tetrahydrofuran was added dropwise and stirring continued for 2 h at −78 °C. Saturated ammonium chloride was added and the mixture extracted with ether. The combined organic layers were washed with water and then saturated sodium chloride. The extract was dried over magnesium sulfate, filtered through a pad of Florisil, and concentrated to give 22.1 g of a yellow oil. Preparative HPLC of the crude product on silica gel eluted with 8% 2-propanol and 12% ethyl acetate in hexanes gave 17.0 g (63%) of **1f** as a light yellow solid.

An analytical sample was obtained by recrystallization from toluene–hexanes to give off-white crystals: mp 73.5–75 °C; IR (KBr) 1680, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (cm, 1 H), 2.12 (cm, 1 H), 2.82 (cm, 1 H), 3.29 (s, 3 H), 3.45 (cm, 2 H), 3.69 (t, 1 H), 4.10 (dd, 1 H), 7.04 (m, 3 H), 7.30 (m, 2 H), 8.75 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.87 (4-CH_2), 38.04 (4-CH), 58.36 (OCH_3), 61.27 (5-CH_2), 70.55 (OCH_2), 116.04 (2′-CH), 122.11 (4′-CH), 128.99 (3′-CH), 151.34 (1′-C), 176.88 (3-C). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

Method C. 4-(2-Methoxyethyl)-1-[4-(phenylmethoxy)-phenyl]-3-pyrazolidinone (15). To a stirred suspension of 34.07

g (127 mmol) of 1-[4-(phenylmethoxy)phenyl]-3-pyrazolidinone[11] and 21.05 g (140 mmol) of *tert*-butyldimethylsilyl chloride in 250 mL of methylene chloride at room temperature and under nitrogen was added dropwise a solution of 70 mL (500 mmol) of triethylamine in 100 mL of methylene chloride. After stirring overnight at room temperature, an additional 2.1 g (14 mmol) of *tert*-butyldimethylsilyl chloride was added and stirring was continued for another 3 h. The mixture was diluted to 1 L with ether, filtered and concentrated. The residue was dissolved in 400 mL of ether and filtered through a pad of Florisil and eluted with 400 mL of ether. Concentration of the eluents gave 45.4 g of the intermediate silylpyrazolidinone **20** as a solid and was used without purification.

To a stirred solution of LDA [prepared at −78 °C under nitrogen from 21.3 mL (152 mmol) of diisopropylamine and 56 mL (140 mmol) of 2.5 M *n*-butyllithium in hexanes in 500 mL of tetrahydrofuran] was added dropwise a solution of 45.4 g of the above silylpyrazolidinone **20** in 250 mL of tetrahydrofuran. After stirring at −78 °C for 45 min, 19.5 mL (207 mmol) of 2-bromoethyl methyl ether was added. The reaction mixture was brought to 0 °C, stirred for 1 h, and then poured onto a mixture of 750 mL of water and 750 mL of saturated sodium chloride. The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 500 mL). The combined organic layers were concentrated to give a light brown oil which was dissolved in 100 mL of ethanol and 1 L of methylene chloride containing a few drops of concentrated hydrochloric acid. The mixture was stirred under nitrogen for 30 min, neutralized with sodium bicarbonate, filtered, and concentrated to an orange solid. The crude product was triturated with a mixture of 200 mL of ether and 100 mL of ethyl acetate and filtered, and the solid recrystallized from 400 mL of ethyl acetate to give 22.2 g (54% overall) of **15** as a tan solid.

An analytical sample was obtained by recrystallization from ethyl acetate to give a white solid: mp 129–131 °C; IR (KBr) 3160, 1700, 1500 cm^{-1}; NMR (Me_2SO-d_6) δ 1.45 (cm, 1 H), 1.91 (cm, 1 H), 2.55 (cm, 1 H), 3.20 (s, 3 H), 3.35 (cm, 3 H), 3.90 (dd, 1 H), 5.04 (s, 2 H), 6.95 (s, 4 H), 7.41 (cm, 5 H), 10.05 (bs, 1 H). Anal. ($C_{19}H_{22}N_2O_3$) C, H, N.

1-(4-Hydroxyphenyl)-4-(2-methoxyethyl)-3-pyrazolidinone (17). Benzyl ether **15** (14.0 g, 43 mmol) was hydrogenated in four batches. For example, a mixture of 3.0 g (9.2 mmol) of **15** and 3.0 g of 10% palladium on carbon in 25 mL of ethanol and 200 mL of ethyl acetate was hydrogenated at 50 psi of hydrogen at room temperature for 2 h. The mixture was filtered, the catalyst was washed with 400 mL of ethyl acetate, and the filtrate was concentrated to afford the crude product as a pink oil. The crude products from the four batch reactions were crystallized from ethyl acetate and then recrystallized from acetonitrile to give 5.1 g (50%) of **17** as pink crystals. The mother liquors were concentrated, and the residue was purified by MPLC on silica gel (55 × 200 mm column) eluted with 50% ethyl acetate in hexanes, followed by ethyl acetate to give a pink solid which was recrystallized from acetonitrile to give 2.1 g (21%) of **17** as pink crystals. The total yield of **17** was 7.2 g (71%): mp 144–146 °C; IR (KBr) 3200, 1660, 1510 cm^{-1}; NMR (Me_2SO-d_6) δ 1.45 (cm, 1 H), 1.89 (cm, 1 H), 2.55 (cm, 1 H), 3.20 (s, 3 H), 3.35 (cm, 3 H), 3.85 (m, 1 H), 6.67 (cm, 2 H), 6.85 (cm, 2 H), 9.00 (bs, 1 H), 9.91 (bs, 1 H). Anal. ($C_{12}H_{16}N_2O_3$) C, H, N.

1-Phenyltetrahydro-3(2*H*)-pyridazinone (2a). To a stirred suspension of 6.05 (159 mmol) of lithium alumimum hydride in 350 mL of anhydrous ether and 350 mL of tetrahydrofuran at −15 °C and under nitrogen was added 20.2 g (100 mmol) of tetrahydro-1-phenyl-3,6-pyridazinedione (**22**)[14] in several portions over 15 min. The reaction mixture was allowed to come to 0 °C over 30 min and 30 mL of saturated ammonium chloride was added dropwise over 20 min. After drying with sodium sulfate, the mixture was filtered and concentrated, and the residue triturated with ether to give 14.5 g of a solid. The solid was dissolved in 50 mL of methylene chloride and filtered through a pad of silica gel by washing with 5% ethanol in methylene chloride. The filtrate was concentrated to afford an off-white solid which on recrystallization from ethyl acetate gave 12.5 g (67%) of **2a** as a white solid: mp 148.5–150 °C (lit.[33] mp 154–156 °C); IR (KBr) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.42 (t, 2 H), 3.71 (t, 2 H), 7.00 (cm, 3 H), 7.33 (cm, 2 H), 8.02 (bs, 1 H). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

4-(Methoxymethyl)-1-phenyl-1*H*-pyrazol-3-ol (4b). To a stirred solution of 15.0 g (73 mmol) of **1b** in 150 mL of methylene chloride at 0 °C and under nitrogen was added portionwise 15.0 g (87 mmol) of 3-chloroperoxybenzoic acid. The reaction was stirred at room temperature for 4 h, then diluted with ethyl acetate and neutralized with saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layers were washed with water (4×) and then saturated sodium chloride. The extract was dried over magnesium sulfate, filtered, and concentrated to give 17.7 g of a yellow solid. Recrystallization from toluene–hexanes gave 9.6 g (65%) of **4b** as yellow solid: mp 104–105 °C; IR (KBr) 3200–2600, 1540, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.42 (s, 3 H), 4.41 (s, 2 H), 7.27 (cm, 1 H), 7.49 (cm, 4 H), 7.72 (s, 1 H). Anal. ($C_{11}H_{12}N_2O_2$) C, H, N.

4-(Methoxymethyl)-2-methyl-1-phenyl-3-pyrazolidinone (5). To a stirred suspension of 3.4 g (141 mmol) of 60% sodium hydride in mineral oil in 180 mL of *N*,*N*-dimethylformamide at 0 °C and under nitrogen was added dropwise a solution of 17.0 g (82 mmol) of **1b** in 250 mL of *N*,*N*-dimethylformamide. After stirring at 0 °C for 1.5 h, a solution of 8.8 mL (141 mmol) of iodomethane in 40 mL of *N*,*N*-dimethylformamide was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, at room temperature for 1 h, and then heated on a steam bath for 16 h. After stirring at room temperature overnight, the reaction mixture was poured onto ice water and extracted with ether (2×) and ethyl acetate (1×). The combined organic layers were washed with water (6×) and saturated sodium chloride (1×), dried over magnesium sulfate, filtered, and concentrated to give 14 g of an orange oil. Vacuum distillation gave 7.9 (44%) of **5** as a pale yellow oil: bp 154–155 °C (1.5 mmHg); IR (film) 2900, 1700, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.00 (cm) and 3.04 (s) (4H), 3.32 (s, 3 H), 3.62 (cm, 2 H), 3.84 (m, 2 H), 6.92 (m, 2 H), 7.08 (m, 1 H), 7.36 (m, 2 H). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

4-(Methoxyethyl)-5-methyl-1-phenyl-3-pyrazolidinone (7). 2D-COSY and ^1H-^{13}C COSY experiments were used to make the chemical shifts assignments. In an NOE difference experiment, irradiation of the C5 methyl signal resulted in enhancements of protons at C4 and C5, which are consistent with the asignment of trans stereochemistry to **7**: NMR ($CDCl_3$) δ 1.43 (d, 3 H, 5-CH_3), 1.63 (m, 1 H, 4-CH_2), 1.89 (m, 1 H, 4-CH_2), 2.28 (m, 1 H, 4-H), 3.22 (s, 3 H, OCH_3), 3.40 (m, 2 H, OCH_2), 3.76 (m, 1 H, 5-H), 7.02 (m, 3 H, 2′,4′-H), 7.28 (m, 2 H, 3′-H), 8.94 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 21.16 (5-CH_3), 30.51 (4-CH_2), 47.31 (4-CH), 58.28 (OCH_3), 67.80 (5-CH), 70.13 (OCH_2), 116.39 (2′-CH), 122.51 (4′-CH), 129.10 (3′-CH), 151.56 (1′-C), 176.16 (3-C).

Ethyl 5,5-Dimethyl-3-oxo-1-phenyl-4-pyrazolidinecarboxylate (8). To 300 mL of absolute ethanol under nitrogen with stirring was added portionwise 11.8 g (0.51 mmol) of sodium and stirring continued until all the sodium was consumed. Then 45 mL (0.46 mol) of phenylhydrazine in 150 mL of toluene was added followed by 100 mL (0.51 mol) of diethyl isopropylidenemalonate in 150 mL of toluene. The mixture was refluxed for 4 h, cooled to room temperature, poured onto 1 L of ice water containing 29 mL (0.51 mol) of glacial acetic acid, and then extracted with ether (3 × 500 mL). The combined organic layers were washed with saturated sodium chloride, dried over sodium sulfate, filtered, concentrated to 200 mL, and diluted with hexanes to 1 L. Scratching afforded 59.6 g (45%) of **8** as light yellow crystals. The mother liquor was filtered through a silica gel column (42.5 × 300 mm) and gradient elution up to 30% ethyl acetate in hexanes afforded, after crystallization from hexanes, 25.9 g (19%) of **8** as light yellow crystals. The combined yield of **8** was 85.5 g (64%).

An analytical sample was obtained by recrystallization from ether–hexanes to give white needles: mp 66–67 °C; IR (KBr) 3200, 2975, 1720, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (cm, 9 H), 4.25 (q, 2 H), 5.00 (bs, 1 H), 7.11 (m, 1 H), 7.36 (m, 2 H), 7.85 (m, 2 H). Anal. ($C_{14}H_{18}N_2O_3$) C, H, N.

Ethyl 4-(2-Methoxyethyl)-5,5-dimethyl-3-oxo-1-phenyl-4-pyrazolidinecarboxylate (9). To a stirred suspension of 7.9 g (0.33 mol) of 97% sodium hydride in 350 mL of *N*,*N*-dimethylformamide at 0 °C and under nitrogen was added dropwise a solution of 72.1 g (0.275 mol) of **8** in 350 mL of *N*,*N*-di-

(33) Dowlatshahi, H. A. *Syn. Commun.* **1987**, *17*, 1253.

methylformamide. After stirring for 30 min at 0 °C, 28.4 mL (0.302 mol) of 2-bromoethyl methyl ether was added and the mixture stirred at 100 °C overnight. On cooling, the mixture was poured onto 1 L of saturated ammonium chloride and extracted with ether (3 × 400 mL). The combined organic layers were washed with saturated sodium chloride, dried over sodium sulfate, filtered through a 3-in. pad of silica gel, and concentrated to give 92.1 g of a yellow oil. MPLC on silica gel (50 × 1200 mm column) eluted with 5% ethyl acetate in hexanes, followed by 15% ethyl acetate in hexanes gave 36.0 g (41%) of 9 as a light yellow solid.

An analytical sample was obtained by recrystallization from hexanes to give a white solid: mp 55–56 °C; IR (KBr) 3200, 2975, 1730, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (m, 9 H), 2.12 (m, 2 H), 3.36 (s, 3 H), 3.56 (m, 1 H), 3.95 (m, 1 H), 4.30 (q, 2 H), 4.92 (bs, 1 H), 7.12 (m, 1 H), 7.36 (m, 2 H), 7.83 (m, 2 H). Anal. ($C_{17}H_{24}N_2O_4$) C, H, N.

4-(2-Methoxyethyl)-5,5-dimethyl-1-phenyl-3-pyrazolidinone (10). A stirred solution of 36.0 g (0.112 mol) of 9 and 5.4 g (0.13 mol) of sodium hydroxide in 200 mL of water and 500 mL of dioxane was refluxed for 3 h. An additional 2.7 g (0.067 mol) of sodium hydroxide was added and refluxing continued for 3 h. To the mixture was added 6 mL of 40% tetrabutylammonium hydroxide and refluxing continued overnight. On cooling, the mixture was concentrated and the residue acidified with 3 N hydrochloric acid and extracted with ether (3 × 500 mL). The combined organic layers were washed with saturated sodium chloride (2 × 100 mL), dried over sodium sulfate, filtered, and concentrated to give a yellow oil. MPLC on silica gel (50 × 1200 mm column) eluted with 20% ethyl acetate in hexanes, followed by 30% ethyl acetate in hexanes, gave an oil which on Kugelrohr distillation gave 17.7 g (64%) of 10 as a pale yellow oil: bp 140–145 °C (0.2 mmHg); IR (film) 3200, 2950, 1700, 1605, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.09 (s, 3 H), 1.30 (s, 3 H), 1.65 (cm, 1 H), 1.96 (cm, 1 H), 2.59 (dd, 1 H), 3.36 (s, 3 H), 3.62 (t, 2 H), 4.39 (bs, 1 H), 7.09 (t, 1 H), 7.30 (t, 2 H), 7.83 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.45 (5-CH_3), 25.00 (5-CH_3), 25.90 (4-CH_2), 51.91 (4-CH), 58.41 (OCH_3), 59.60 (5-C), 70.12 (OCH_2), 118.23 (2′-CH), 123.81 (4′-CH), 128.48 (3′-CH), 139.41 (1′-C), 174.32 (3-C). Anal. ($C_{14}H_{20}N_2O_2$) C, H, N.

Resolution of 4-(2-Methoxyethyl)-1-phenyl-3-pyrazolidinone (1f). 4,5-Dihydro-4-(2-methoxyethyl)-1-phenyl-1*H*-pyrazol-3-yl ((*R*)-1-Phenylethyl)carbamate (23A, 23B). A mixture of 3.34 g (15.2 mmol) of **1f**, 1.85 mL (19 mmol) of (*R*)-(+)-α-methylbenzyl isocyanate, and 110 mL of toluene was refluxed under nitrogen for 3 h. An additional 0.80 mL (8.2 mmol) of (*R*)-(+)-α-methylbenzyl isocyanate was added and refluxing was continued for 4 h. The reaction mixture was concentrated to give a pale yellow oil. Preparative HPLC of the crude product on silica gel eluted with 5% 2-propanol and 15% ethyl acetate in hexanes and recycling twice gave 1.28 g (23%) of **23A** as a colorless oil which eluted first, 1.13 g of a fraction enriched in **23A**, and 2.68 g of a fraction enriched in **23B**. These mixed fractions were separately subjected to preparative HPLC as before to give 0.77 g (14%) of **23A** as a colorless oil and 1.96 g (35%) of **23B** as a colorless oil. **23A**: IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.56 (d) and 1.61 (m) (4 H), 2.08 (m, 1 H), 2.99 (m, 1 H), 3.23 (s, 3 H), 3.37 (t, 2 H), 3.70 (t, 1 H), 3.97 (dd, 1 H), 5.06 (pentet, 1 H), 7.00 (cm, 3 H), 7.29 (m, 7 H), 8.45 (bd, 1 H). **23B**: IR (film) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (d) and 1.66 (m) (4 H), 2.11 (m, 1 H), 3.00 (m, 1 H), 3.26 (s, 3 H), 3.40 (t, 2 H), 3.76 (t, 1 H), 4.00 (m, 1 H), 5.09 (pentet, 1 H), 6.98 (cm, 3 H), 7.29 (cm, 7 H), 8.48 (bd, 1 H).

(-)-4-(2-Methoxyethyl)-1-phenyl-3-pyrazolidinone ((-)-1f). A stirred solution of 1.20 g (3.3 mmol) of **23A**, 0.91 mL (10 mmol) of aniline, and 75 mL of toluene was refluxed under nitrogen for 20 h. The reaction mixture was concentrated and the residue flash chromatographed on silica gel (50 mm × 8 in. column) eluted with 80% ethyl acetate in hexanes to give 0.71 g (98%) of yellow crystals. Recrystallization from toluene–hexanes and then from cyclohexane gave 288 mg (40%) of (-)-**1f** as white prisms: mp 69–71 °C; $[\alpha]^{25}$ -94.7° (c = 1, MeOH). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

(+)-4-(2-Methoxyethyl)-1-phenyl-3-pyrazolidinone ((+)-1f). A stirred solution of 1.59 g (4.3 mmol) of **23B**, 1.19 mL (13 mmol) of aniline, and 100 mL of toluene was refluxed under nitrogen for 14 h. The mixture was concentrated and the residue flash chromatographed on silica gel (50 mm × 8 in. column) eluted with 80% ethyl acetate in hexane to give 0.91 g (96%) of colorless crystals. Recrystallization from toluene–hexanes gave 0.20 g (21%) of (+)-**1f** as white prisms. The mother liquor was concentrated and the residue recrystallized from cyclohexane–hexanes and then from cyclohexane to give 0.36 g (38%) of (+)-**1f** as white prisms: mp 69–71 °C; $[\alpha]^{25}$ +94.0° (c = 1, MeOH). Anal. ($C_{12}H_{16}N_2O_2$) C, H, N.

X-ray Crystal Structure Analysis of (+)-1f. Suitable crystals were obtained by crystallization from toluene–hexanes. The sample of (+)-**1f** was a fragment of a monoclinic prism 0.36 × 0.48 × 0.52 mm of space group $P2_1$ (#4); $Z = 2$. The unit cell parameters are $a = 6.244$ (1) Å, $b = 7.656$ (1) Å, $c = 12.636$ (2) Å, $\beta = 101.99$ (1)°, $V = 590.9$ (1) Å. The calculated density is 1.240 g/cm^3. The data were collected on a Nicolet R3m diffractometer using Cu Kα radiation (graphite monochromator, λ = 1.54178 Å) in an ω scan mode (ω range, 2° + [$2\theta(K_{\alpha 1}) - 2\theta(K_{\alpha 2})$]; 2θ range, 3°–115°). A total of 1023 reflections were collected, of which 916 were unique and considered as observed [$I > 3\sigma(I)$]. Sheldrick's programs (SHELXTL; Rev. 5.1) were used for data reduction and all other calculations.

The observed systematic absences of reflections are compatible with those expected for the space groups $P2_1$ (#4) and $P2_1/m$ (#11). The space group $P2_1/m$ (#11) requires the presence of the enantiomer in the unit cell and it was known that it could not be present, thus only space group $P2_1$ was left for consideration. The evaluation of the effect of $Z = 2$ for $P2_1$ vs $Z = 4$ for $P2_1/m$ on the calculated density led to the choice of the same space group.

After direct phase determination four E maps were calculated. In the third map all 16 non-hydrogen atoms could be recognized. Atomic anisotropic temperature factors were refined for all non-hydrogen atoms. Hydrogen atoms were included in the refinement in calculated positions and with isotropic temperature factors. The refinement converged at $R = 5.38\%$; $R_w = 5.78\%$. A final Fourier difference map showed no features above 0.2 e/Å^3.

The absolute configuration of the compound remains unknown, because of the absence of significant anomalous absorption.

Inhibition of 5-Lipoxygenase in Vitro. Suspensions of rat basophils (RBL-1 cells) were homogenized, and preincubated with test compound or vehicle at 37 °C for 5 min. Radiolabeled arachidonic acid was added to each mixture for a 15-min incubation period (37 °C). After the reaction was stopped by the addition of formic acid, the products were extracted into chloroform. An aliquot of the extract was evaporated to dryness under nitrogen, then reconstituted with ether. The sample was then subjected to silica gel thin-layer chromatography. The heights of the peaks corresponding to LTB_4 and 5-HETE, determined by radiochromatographic scanning, were used for calculation of percent inhibition of 5-lipoxygenase. IC_{50} values and 95% confidence limits were computed from the linear portions of the concentration–response curves, with each concentration consisting of at least four incubations.

Inhibition of 5-Lipoxygenase ex Vivo. Pleural inflammation was induced in rats by injection of 0.25% (w/v) carrageenan solution. After 3 h, the test compound or vehicle was administered orally. Our hour later, each rat was sacrificed and the pleural exudate harvested. The exudate cells (>95% neutrophils) were stimulated with ionophore (A23187) for 15 min and the reaction was stopped with acetonitrile/methanol. Following a 30-min extraction period at room temperature, the sample was centrifuged (35000*g*, 5 °C) and the supernatant analyzed for LTB_4 by reverse-phase HPLC. ED_{50} values and 95% confidence limits were computed from the linear portions of the dose–response curves, with each dose administered to at least five animals.

Inhibition of Leukotriene-Mediated Bronchoconstriction in Vivo. Guinea pigs were immunized with 1 mg ovalbumin, and 3 mg alum used as an adjuvant. Two weeks later, each animal was anesthetized and prepared for the monitoring of tracheal pressure during mechanical ventilation. The guinea pig was pretreated iv with naproxen (10 mg/kg), pyrilamine (3 mg/kg), and propranolol (0.1 mg/kg), then challenged with ovalbumin (0.3 mg/kg iv). Test compound or vehicle was administered orally 1 h prior to challenge. Maximum increases in tracheal pressure occurring within 20 min postchallenge were used for assessment of percent inhibition. ED_{50} values and 95% confidence limits were computed from the linear portions of the dose–response curves,

with each dose administered to at least eight animals.

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Registry No. **1a**, 92-43-3; (±)-**1b**, 133043-49-9; (±)-**1c**, 133043-50-2; (±)-**1d**, 133043-51-3; (±)-**1e**, 133043-52-4; (±)-**1f**, 133043-53-5; (+)-**1f**, 133043-34-2; (-)-**1f**, 133043-35-3; (±)-**1g**, 133043-54-6; (±)-**1h**, 133043-55-7; (±)-**1i**, 133043-56-8; (±)-**1j**, 133043-57-9; (±)-**1k**, 133043-58-0; (±)-**1l**, 133043-59-1; (±)-**1m**, 133071-03-1; (±)-**1n**, 133043-60-4; (±)-**1o**, 133043-61-5; (±)-**1p**, 133043-62-6; **2a**, 7190-52-5; (±)-**2f**, 133043-63-7; **3**, 38604-68-1; **4b**, 133043-64-8; **4f**, 133043-65-9; (±)-**5**, 133043-36-4; (±)-**6**, 133043-37-5; (±)-**7**, 133043-38-6; (±)-**8**, 133043-39-7; (±)-**9**, 133043-40-0; (±)-**10**, 133043-41-1; (±)-**11**, 133043-42-2; (±)-**12**, 133043-43-3; (±)-**13**, 133043-44-4; (±)-**14**, 133043-45-5; (±)-**15**, 133043-46-6; (±)-**16**, 133043-47-7; (±)-**17**, 133043-48-8; **19** (R_3 = H, X = 4-OCH_2Ph), 6080-54-2; **20** (R_3 = H, X = 4-OCH_2Ph), 133043-66-0; **22**, 61446-43-3; HMPA, 680-31-9; 5-LO, 80619-02-9; (*R*)-(+)-$PhCH(CH_3)NCO$, 33375-06-3; $PhNH_2$, 62-53-3; $Br(CH_2)_2OCH_3$, 6482-24-2; TBDMS-Cl, 18162-48-6; Pd, 7440-05-3; $PhNHNH_2$, 100-63-0; $(CH_3)_2C{=}C(COOEt)_2$, 6802-75-1.

Supplementary Material Available: Tables listing crystal data, atomic coordinates, thermal parameters, bond lengths and angles, and a stereoview of **1f** (5 pages). Ordering information is given on any current masthead page.

The Synthesis and Potassium Channel Blocking Activity of Some (4-Methanesulfonamidophenoxy)propanolamines as Potential Class III Antiarrhythmic Agents

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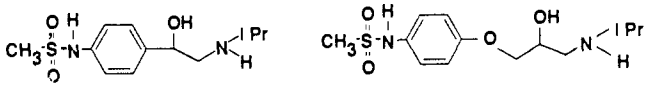
The synthesis of 22 (4-methanesulfonamidophenoxy)propanolamines and their testing on isolated guinea pig cardiac myocytes, on isolated preparations from guinea pig atria, and on rat blood pressure are described. Secondary amines in the series (**11a–f**) showed residual β-blocking activity, whereas incorporation of *N*-methyl phenylalkyl and 4-phenyl alicyclic amine groups abolished β-blocking activity but led to enhanced ability to block the channel conducting the delayed rectified potassium current, and hence produced an increase in the cardiac action potential duration (APD). Incorporation of hydrophobic Cl and CF_3 groups further enhanced potassium channel blocking activity. Compounds **8l** and **8m** produced a significant increase in APD at nanomolar concentrations, with no effect on cardiac muscle conduction velocity, and hence merit further investigation as Class III antiarrhythmic agents. Methylation of the methanesulfonamido group abolished channel-blocking activity; 4-carboxy and 3-methanesulfonamido analogues retained activity but at a reduced level.

Several years after its introduction as a β-blocking agent it was observed[1] that sotalol, **1**, produced a concentration-dependent increase of the cardiac action potential duration (APD) in a wide range of tissues, and it was this observation that prompted Vaughan Williams to designate a third category (class III) of antiarrhythmic agents.[2] This observation was not followed up immediately, but a resurgence of interest in sotalol (see ref 3 for a report on a recent symposium) occurred as a consequence of the increasing use of amiodarone (a compound that also increased cardiac APD) as an antiarrhythmic agent, and groups at Lilley,[4] Pfizer,[5] and Eisai[6] have recently reported results of searches for more potent class III agents.



1

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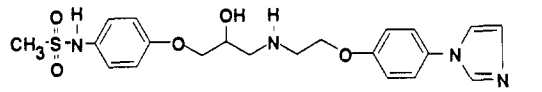

2

Recently a report has been published[7] by another group describing the development of a mixed function class II and class III antiarrhythmic agent **2** which, like ours, is based on an oxypropanolamine analogue of sotalol. The Berlex group sought to develop a mixed function compound on the grounds that a β-blocking (class II) action would reduce the possibility of a sympathetically mediated triggering of an arrhythmia, and that the increased cardiac refractory period produced by a class III agent would prevent a reentrant rhythm from becoming established. Our approach was quite different. There is a clinical need for a drug to reduce the likelihood of an arrhythmia developing in the recovery period immediately following a myocardial infarction. Chamberlain[8] has shown that during the 4 or 5 days following an infarction the risk of mortality is increased by the use of a β-blocking agent, as a consequence of an increased risk of heart failure. Under these circumstances the requirement is for a rapidly acting selective class III agent, devoid of class I or II actions. In general, as far as clinical use is concerned, the difficulty

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