1,3,4-Oxadiazole, 1,3,4-Thiadiazole, and 1,2,4-Triazole Analogs of the Fenamates: In Vitro Inhibition of Cyclooxygenase and 5-Lipoxygenase Activities

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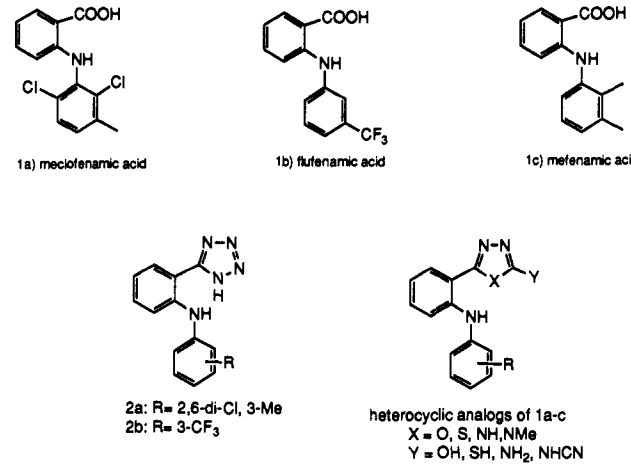
N-Arylanthranilic acids, known generically as the fenamates, are nonsteroidal antiinflammatory drugs (NSAIDs) that block the metabolism of arachidonic acid by the enzyme cyclooxygenase (CO). Substitution of the carboxylic acid functionality of several fenamates with acidic heterocycles provided dual inhibitors of CO and 5-lipoxygenase (5-LO) activities when tested in an intact rat basophilic leukemia (RBL-1) cell line. Compound **5b** (IC_{50} = 0.77 μM (5-LO), 0.27 μM (CO)) which contains an 1,3,4-oxadiazole-2-thione replacement and **10b** (IC_{50} = 0.87 μM (5-LO), 0.85 μM (CO)) which contains a 1,3,4-thiadiazole-2-thione are the most potent inhibitors of 5-LO and CO activities from these series. Both of these heterocyclic analogs of flufenamic acid are also active in carageenin-induced rat footpad edema (CFE), a model of acute inflammation. When dosed orally the ID_{50}s for **5b** and **10b** in CFE are 8.5 and 4.7 mg/kg, respectively.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are first line therapeutic agents for the treatment of arthritis. NSAIDs reduce the pain and swelling associated with arthritis by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins.[1] Since prostaglandins are cytoprotective, their decreased production is implicated in the formation of gastric ulcers, an undesirable side effect of the chronic use of NSAIDs.[2] Inhibiting CO may also increase the conversion of arachidonic acid to proinflammatory leukotrienes via the enzyme 5-lipoxygenase (5-LO). Leukotrienes, especially LTB_4, are implicated in the pathogenesis of inflammatory disease[3] and also of the acute gastric ulceration induced by NSAIDs.[4] It has been postulated that compounds that inhibit the activity of both CO and 5-LO would have improved efficacy and reduced side effects when compared to selective CO inhibitors.[5]

The fenamates are a class of NSAIDs that share as their common structural feature an *N*-arylanthranilic acid.[6] The fenamates are differentiated by their aryl substitutents as shown by meclofenamic acid (**1a**), flufenamic acid (**1b**), and mefenamic acid (**1c**).[7] These agents were originally found to be effective antiinflammatory agents as demonstrated by their activity in an anti-UV erythema model. It was later established that the mechanism of action of the fenamates is inhibition of CO.[8]

In 1968, Juby and co-workers reported the replacement of the carboxylic acid functionality of several fenamates with a 5-tetrazolyl group.[9] The resulting 5-(2-anilinophenyl)tetrazoles were tested in carageenin-induced rat footpad edema (CFE), a model of acute inflammation. The two most active 5-(2-anilinophenyl)tetrazoles were **2a** and **2b**; analogs of meclofenamic acid and flufenamic acid. Over 20 years after this account we found that while **2a**, as expected, inhibited the formation of $PGF_{2\alpha}$ from rat basophilic leukemia cells, it also inhibited LTB_4 production. Thus, replacement of the carboxylic acid functionality with a tetrazole not only retained the CO inhibitory activity of the parent but also introduced 5-LO inhibition.[10] Encouraged by this finding, we replaced the carboxylic acid group of several fenamates with additional heterocycles in the hope of obtaining additional inhibitors of cellular arachidonate metabolism. The heterocycles reported here are 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles which contain an acidic or basic functionality.[11]



Chemistry

The key intermediates in the preparation of the 1,3,4-oxadiazoles are hydrazides **3a–c**. These hydrazides are readily available via esterification of **1a–c** followed by treatment with hydrazine hydrate in methanol. Hydrazides **3a** and **3c** were converted to 1,3,4-oxadiazol-2-ones **4a** and **4c** by the addition of 1,1′-carbonyldiimidazole in the presence of triethylamine (Scheme I). The 1,3,4-oxadiazole-2-thiones **5a–c** were obtained by reaction of **3a–c** with carbon disulfide under basic conditions. The 2-amino-1,3,4-oxadiazoles **6a** and **6b** resulted from the action of cyanogen bromide and Na_2CO_3 on **3a** and **3b**.[12]

Preparation of the corresponding 1,3,4-thiadiazoles was not as direct. All attempts to transform hydrazides **3a–c**

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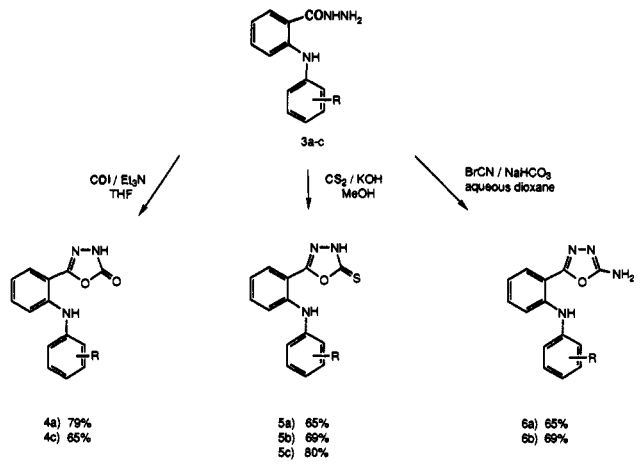
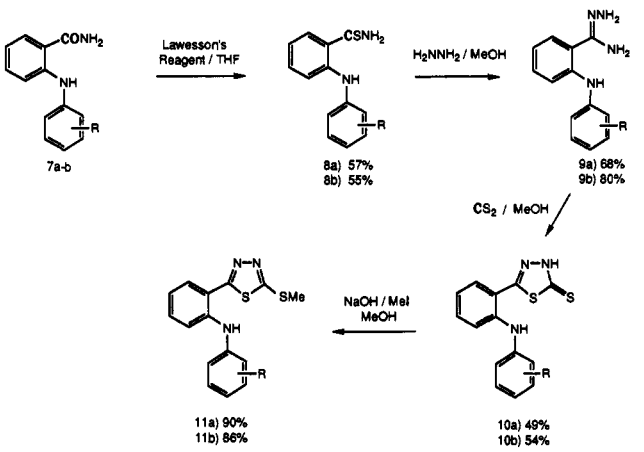
Scheme I



Scheme II



to their corresponding thiohydrazides failed. It was therefore necessary to convert amides **7a** and **7b** to the thioamides **8a** and **8b** with P_2S_5 or preferably with Lawesson's reagent in THF (Scheme II). The moderate yields reflect the unavoidable concomitant dehydration of **7a** and **7b** to the corresponding nitriles. Treatment of **8a** and **8b** with hydrazine and cyclization of the resultant unstable amidrazones **9a** and **9b** with carbon disulfide provided the 1,3,4-thiadiazole-2-thiones **10a** and **10b**.[13]

It was envisioned that the corresponding 1,3,4-thiadiazol-2-one derivatives could be prepared from the 1,3,4-thiadiazole-2-thiones by converting the exocyclic sulfur into a leaving group, followed by hydrolysis. The desired intermediates **11a** and **11b** were obtained via treatment of **10a** and **10b** with iodomethane under basic conditions with no alkylation on nitrogen observed. Since this route to **11a** and **11b** was rather long, an alternate synthesis was devised (Scheme III). Reaction of hydrazides **3a** and **3b** with KOH and carbon disulfide followed by addition of iodomethane gave intermediates **12a** and **12b** which were cyclized under acidic conditions to provide the desired 1,3,4-thiadiazoles **11a** and **11b** in moderate yield.[14] Oxidation of the exocyclic sulfur of **11a** and **11b** with mCPBA gave the corresponding sulfoxides **13a** and **13b**. In this instance the corresponding sulfones were too labile to be cleanly isolated. Flufenamic acid analog **13b** was transformed into 1,3,4-thiadiazol-2-one **15** in 40% yield via a two-step protocol of displacement of the sulfoxide by ethoxide followed by acid hydrolysis.

2-Amino-1,3,4-thiadiazoles **17a** and **17b** were prepared in two steps from the corresponding fenamate (Scheme IV). Meclofenamic acid (**1a**) was converted to the acid chloride then treated with thiosemicarbazide to yield intermediate **16a**. In the case of flufenamic acid (**1b**) since the corresponding acid chloride was not stable it was necessary to form the imidazolide derivative instead. Subsequent addition of thiosemicarbazide to the imidazolide gave the desired intermediate **16b**.[15] Dehydration of **16a** and **16b** with methanesulfonic acid led to 2-amino-1,3,4-thiadiazoles **17a** and **17b**.[16] When the thiosemicarbazides **16a** and **16b** were cyclized under basic conditions (NaOMe/MeOH), the 1,2,4-triazole-3-thiones **18a** and **18b**, isomeric to **17a** and **17b**, were obtained.[15]

2-Amino-1,3,4-oxadiazole **6b** was rearranged to triazole **19** upon treatment with ethanolic KOH (Scheme IV). Acid hydrolysis of the enol ether functionality of **19** provided 1,2,4-triazol-3-one **20**.[17] The 4-*N*-methyl-1,2,4-triazole-3-thione and 4-*N*-methyl-1,2,4-triazol-3-one analogs were readily prepared from hydrazides **3a** and **3b**. Reaction of **3a** and **3b** with methyl isocyanate gave the intermediates **21a** and **21b**. Treatment with base converted **21a** and **21b** to *N*-methyl-1,2,4-triazol-3-ones **22a** and **22b**.[18] In a similar fashion, *N*-methyl-1,2,4-triazole-3-thiones **24a** and **24b** were obtained from **3a** and **3b** via intermediates **23a** and **23b**.[19]

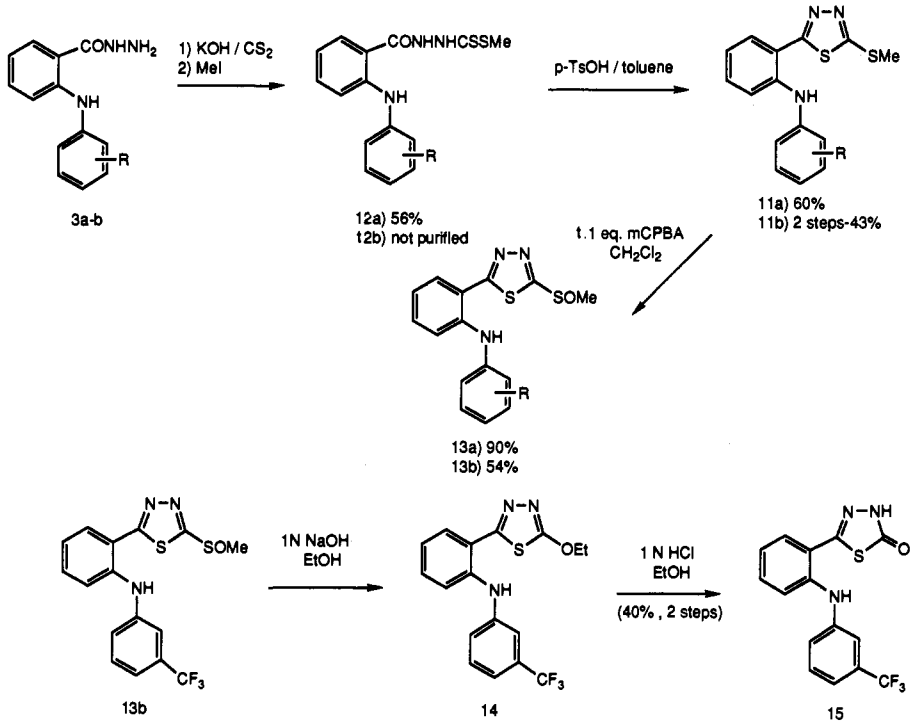
1,3,4-Oxadiazoles and thiadiazoles with a cyanamido group at the 2-position were prepared as bioisosteric replacements for the corresponding heterocycles with a 2-thione substituent.[20] To this end, the 1,3,4-oxadiazole-2-thiones **5a** and **5b** were alkylated exclusively on the sulfur to provide **25a** and **25b** (Scheme V). Oxidation of **25b** with an excess of m-CPBA under buffered conditions afforded sulfone **26**. Treatment of **26** with cyanamide in DMF in the presence of triethylamine gave 2-cyanamido-1,3,4-oxadiazole **27b**. In the meclofenamic acid series it was not possible to cleanly isolate 2-cyanamido-1,3,4-oxadiazole **27a** from the corresponding sulfoxide **28**. Fortunately, treatment of hydrazide **3a** with diphenyl cyanocarbonimidate gave, albeit in low yield, the desired **27a**.[21] Treatment of sulfoxides **13a** and **13b** with cyanamide under basic conditions provided the 2-cyanamido-1,3,4-thiadiazoles **29a** and **29b**.

Results and Discussion

Of the initial set of 1,3,4-oxadiazoles only those with an exocyclic sulfur at C-2 are potent balanced dual inhibitors of CO and 5-LO activities when tested in an intact rat basophilic leukemia (RBL-1) cell line. 1,3,4-Oxadiazole-2-thiones **5a–c** inhibit both CO and 5-LO activities at micromolar concentrations (Table I). The 1,3,4-oxadiazol-2-ones **4a** and **4c** are not active against either enzyme. The 2-amino-1,3,4-oxadiazoles **6a** and **6b** gave disparate results; **6a** is a weak inhibitor of cellular 5-LO activity and **6b**, while a dual inhibitor, is 4.5 times more potent against 5-LO. Due to the activity of the 1,3,4-oxadiazole-2-thiones **5a–c**, the analogous 1,3,4-thiadiazole-2-thiones **10a** and **10b** were synthesized. These analogs are also potent well-balanced dual inhibitors.

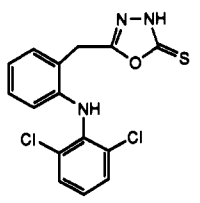
To complete the 1,3,4-thiadiazole series a 1,3,4-thiadiazol-2-one and two 2-amino-1,3,4-thiadiazoles were prepared. 1,3,4-Thiadiazol-2-one **15** is a weak inhibitor of cellular 5-LO activity. The 2-amino-1,3,4-thiadiazoles **17a** and **17b** are dual inhibitors but are 9–16 times more potent inhibitors of 5-LO activity than of CO activity. These results are consistent with those obtained for the oxo analogs **6a** and **6b**. Several 1,2,4-triazoles were also

Scheme III



synthesized and tested. These analogs include the 1,2,4-triazole-3-thiones **18a** and **18b**; 1,2,4-triazol-3-one **20**; *N*-methyl-1,2,4-triazol-3-ones **22a** and **22b**; and *N*-methyl-1,2,4-triazole-3-thiones **24a** and **24b**. Of these only **24b** has any *in vitro* activity.

To investigate the scope of the activity of compounds containing an 1,3,4-oxadiazole-2-thione, we prepared two additional analogs. In **30**, the heterocycle is separated from the anthranilic acid by a methylene unit. In **31**, the relationship of the heterocycle to the amino substituent is "meta", as opposed to the "ortho" pattern of the fenamates. Both **30** and **31** are selective inhibitors of cellular 5-LO activity.



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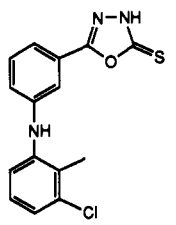

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The two most active compounds *in vitro* were tested in CFE. When dosed orally, the 1,3,4-oxadiazole-2-thione **5b** and the 1,3,4-thiadiazole-2-thione **10b** have respective ID_{50}s of 8.5 and 4.7 mg/kg. When these compounds and their chloline salts are tested orally in mycobacterium footpad edema (MFE), a 3-day subacute model of inflammation, they are inactive. Pharmacokinetic studies show that **5b** is rapidly absorbed but its plasma concentrations quickly decrease with time ($t_{1/2}$ = 2.3 h).[22] Since the exocyclic sulfur is most likely the primary site of metabolism, **5b** is thought to be converted to an inactive metabolite, namely **25b**. This compound does not inhibit either cellular CO or 5-LO activity *in vitro*.[23] By using a bioisosteric replacement for the exocyclic sulfur, and thereby removing that site of metabolism, we hoped to retain *in vitro* activity and gain *in vivo* activity. As a replacement for the thione we chose the cyanamido group.[20] The desired 2-cyanamido-1,3,4-oxadiazoles **27a** and **27b** and 1,3,4-thiadiazoles **29a** and **29b** are indeed inhibitors of both cellular CO and 5-LO activities. Unfortunately, this *in vitro* activity did not translate into *in vivo* activity.

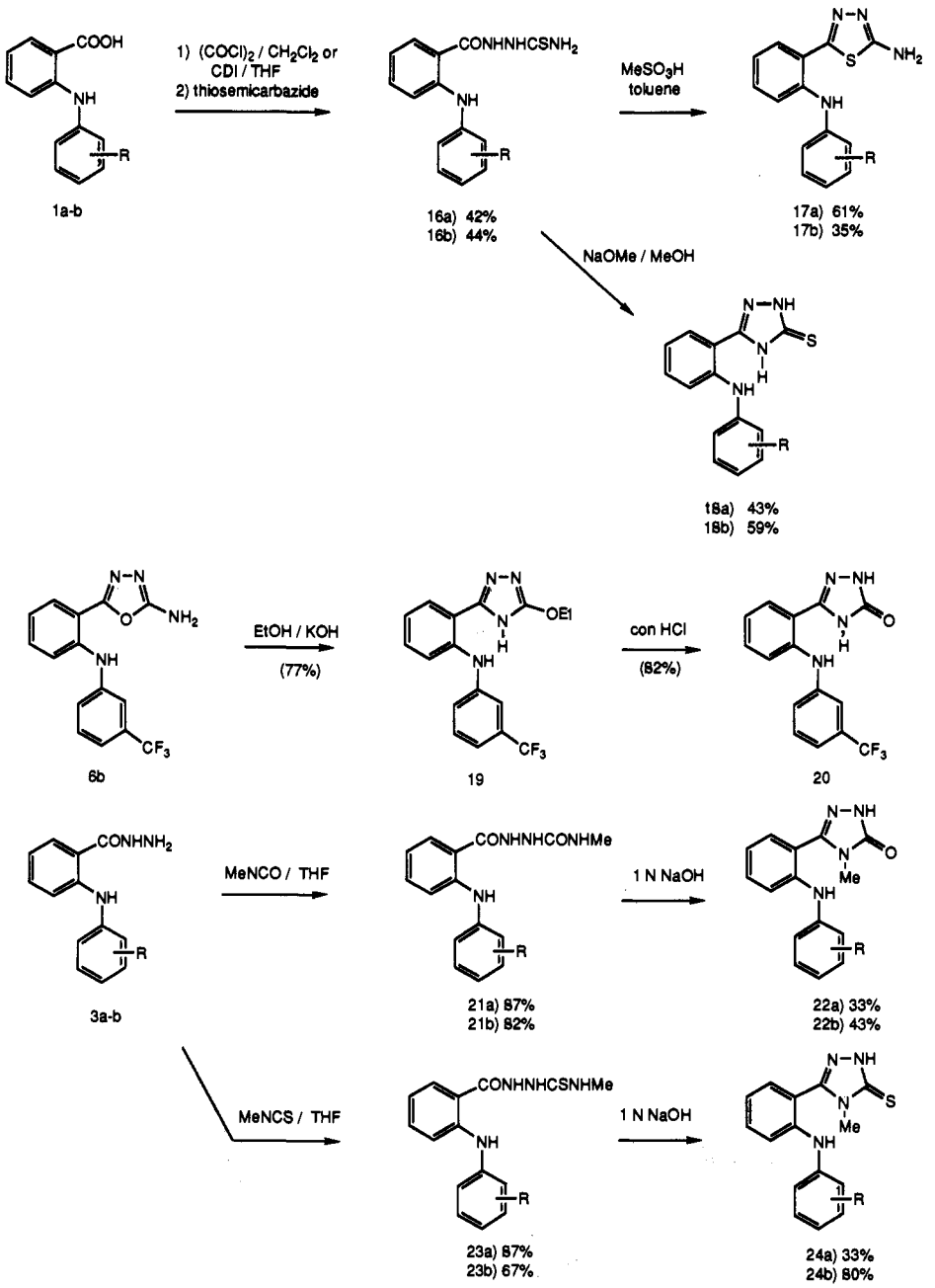
In summary, replacement of the carboxylic acid functionality of several fenamates with various acidic heterocycles gave compounds that were potent balanced dual inhibitors of CO and 5-LO activity *in vitro*. This work is being extended to other heterocyclic replacements in the hope of identifying substituted fenamates with sustained *in vivo* activity in animal models of inflammation.

Experimental Section

Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker AM 250 spectrometer, with chemical shifts reported in δ units relative to TMS. IR spectra were recorded on a Nicolet MX-1 FTIR spectrometer. Mass spectra were recorded on a Fisons TRIO-2A mass spectrometer. All new compounds yielded satisfactory IR and MS data. Elemental analyses were performed by the Parke-Davis Analytical Chemistry staff and were within ±0.4% of the theoretical values. Reactions were run under an atmosphere of nitrogen or argon. Flash chromatography was performed with E. Merck silica gel 60, 230–400 mesh.

Method A. Preparation of 1,3,4-Oxadiazol-2(3*H*)-ones. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-oxadiazol-2(3*H*)-one (4a). 1,1′-Carbonyldiimidazole (95 mg, 0.57 mmol) was added to a 0 °C solution of **3a** (127 mg, 0.41 mmol) and triethylamine (60 μL, 0.43 mmol) in 10 mL of tetrahydrofuran. After the reaction mixture was stirred at 0 °C for 5 h, additional triethylamine (40 μL) and 1,1′-carbonyldiimidazole (50 mg) were added, and the reaction mixture was allowed to warm to room temperature overnight. The volatiles were removed *in vacuo*, and the residue was dissolved in ether. The ether solution was washed consecutively with 1 N hydrochloric acid, saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resultant white solid was purified by chromatography, eluting with hexane–ethyl acetate (2:1), to give 109 mg (79%) of **4a**, mp 253–254 °C. ^{1}H NMR ($CDCl_3$–DMSO-d_6): δ 2.41 (s, 3H), 6.35 (d, J = 8 Hz, 1H), 6.86

Scheme IV



(t, J = 8 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.23 (t, J = 8.5 Hz, 1H), 7.33 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 8.30 (s, 1H), 12.00 (s, 1H). Anal. ($C_{15}H_{11}Cl_2N_3O_2$) C, H, N, Cl.

5-[2-[(2,3-Dimethylphenyl)amino]phenyl]-1,3,4-oxadiazol-2(3*H*)-one (4c). 4c was purified by chromatography, eluting with hexane–ethyl acetate (1:1), 85% yield, mp 239–241 °C. Anal. ($C_{16}H_{15}N_3O_2$) C, H, N.

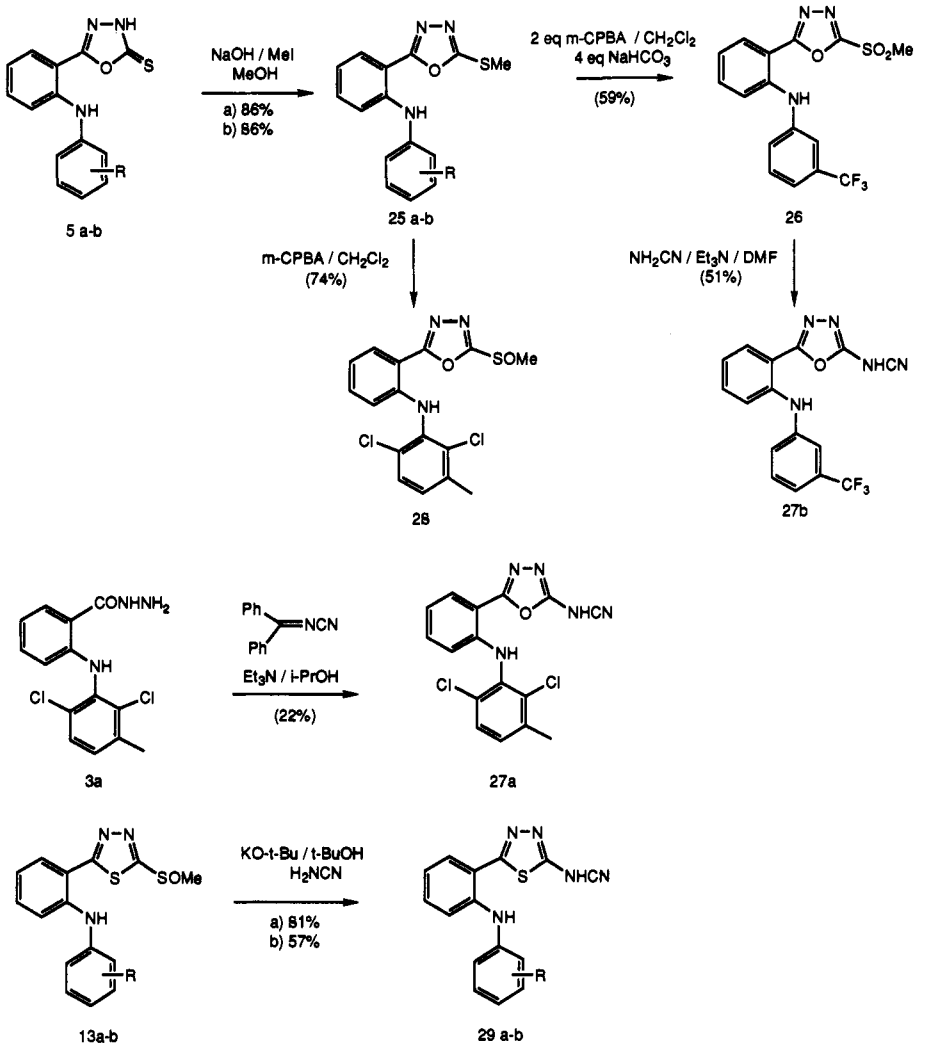
Method B. Preparation of 1,3,4-Oxadiazole-2(3*H*)-thiones. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (5a). **3a** (1.172 g, 3.78 mmol) was dissolved in 20 mL of methanol, and the solution was cooled to 0 °C. Carbon disulfide (520 μL, 8.82 mmol) was added, followed by potassium hydroxide (266 mg, 4.03 mmol). The solution was heated at reflux for 7 h and allowed to cool to room temperature overnight. The solution was concentrated *in vacuo* and the residue dissolved in water. The aqueous solution was acidified with 1 N hydrochloric acid, and the resulting solids were extracted into a 1:1 mixture of ether and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by chromatography, eluting with hexane–ethyl acetate (2:1), providing 864 mg (65%) of **5a**, mp 257–259 °C. ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H), 6.17 (d, J = 8.5 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 8 Hz, 1H), 7.04–7.12 (m, 2H), 7.66 (d, J = 8 Hz, 1H), 8.76 (s, 1H), 14.48 (s, 1H). Anal. ($C_{15}H_{11}Cl_2N_3OS$) C, H, N, Cl, S.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (5b). **5b** was purified by chromatograpy, eluting with ethyl acetate and hexane (1:1), 69% yield, mp 211–213 °C. Anal. ($C_{15}H_{10}F_3N_3OS$) C, H, N.

5-[2-[(2,3-Dimethylphenyl)amino]phenyl]-1,3,4-oxadiazole-2(3*H*)-thione (5c). **5c** was purified by chromatography, eluting with hexane–ethyl acetate (2:1), 80% yield, mp 242–244 °C dec. Anal. ($C_{16}H_{15}N_3OS$) C, H, N, S.

Method C. Preparation of 1,3,4-Oxadiazol-2-amines. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-oxadiazol-2-amine (6a). Sodium bicarbonate (524 mg, 6.23 mmol) in 15 mL of water was added to a room temperature solution of **3a** (1.936 g, 6.24 mmol) in 20 mL of dioxane. After the mixture was stirred at room temperature for 5 min cyanogen bromide (675 mg, 6.37 mmol) was added. After 3 h the tan precipitate was removed by filtration to provide 1.934 g. This material was stirred with ethyl acetate and then filtered and the solid dried *in vacuo* to yield 1.370 g (65%) of **6a**, mp 255–257 °C. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 6.28 (d, J = 7.5 Hz, 1H), 6.90 (t, J =

Scheme V



7.5 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.36–7.48 (complex m, 2H), 7.55 (d, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 9.08 (s, 1H, NH). Anal. ($C_{15}H_{12}Cl_2N_4O$) C, H, N, Cl.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-oxadiazol-2-amine (6b). 69% yield, mp 185–187 °C. Anal. ($C_{15}H_{11}F_3N_4O$) C, H, N.

Method D. Preparation of 1,3,4-Thiadiazole-2(3*H*)-thiones. 2-[(2,6-Dichloro-3-methylphenyl)amino]benzamide (7a). Oxalyl chloride (1.90 g, 14.8 mmol) was added dropwise to a 0 °C suspension of **1a** (2.00 g, 6.7 mmol) and dimethylformamide (530 μL, 6.7 mmol) in 100 mL of methylene chloride. The resulting clear yellow solution was stirred at 0 °C for 1 h and then added via cannula to 3.6 mL of ammonium hydroxide (29% aqueous solution) in tetrahydrofuran at room temperature. After 1 h the volatiles were removed, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The white solid was recrystallized from ethyl acetate and 2-propanol to give 1.30 g (69%) of **7a**, mp 185–187 °C. Anal. ($C_{14}H_{12}Cl_2N_2O$) C, H, N.

2-[(2,6-Dichloro-3-methylphenyl)amino]benzenethioamide (8a). Phosphorous pentasulfide (1.27 g, 5.60 mmol) was added to a colorless solution of **7a** (1.45 g, 4.90 mmol) in 20 mL of dioxane at room temperature, and the mixture was stirred overnight. The white solids were removed by filtration and washed with tetrahydrofuran. The solution was concentrated *in vacuo* and chromatographed, eluting with hexane–ethyl acetate (3:1), to give 310 mg (20%) of **8a** as a pale yellow solid, mp 134–136 °C. ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 3H), 6.24 (d, J = 8 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 7.15–7.32 (complex m, 3H), 7.46 (d, J = 8.5 Hz, 1H), 9.30 (s, 1H, NH), 9.72 (s, 1H, NH), 10.07 (s, 1H, NH). Anal. ($C_{14}H_{12}Cl_2N_2S$) C, H, N, Cl, S.

Alternative Preparation of 8a. Lawesson's reagent (2.67 g, 6.60 mmol) was added to a colorless solution of **7a** (2.83 g, 9.60 mmol) in 50 mL of tetrahydrofuran at room temperature. The resulting mixture was stirred under nitrogen for 3 days followed by heating at reflux for 2 h. The solution was concentrated *in vacuo* and chromatographed, eluting with hexane–ethyl acetate (gradient of 6:1 to 3:1), to provide 1.71 g (57%) of **8a**.

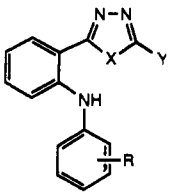
2-[[3-(Trifluoromethyl)phenyl]amino]benzenethioamide (8b). **8b** was purified by chromatography, eluting with hexane–ethyl acetate (gradient of 5:1 to 3:1), 55% yield, mp 106–108 °C. Anal. ($C_{14}H_{11}F_3N_2S$) C, H, N, S.

2-[(2,6-Dichloro-3-methylphenyl)amino]benzenecarboximidic Acid Hydrazide (9a). Hydrazine hydrate (430 μL) was added dropwise to a room temperature solution of **8a** (1.71 g, 5.48 mmol) in 30 mL of methanol. The solution was stirred at room temperature under nitrogen for 5 h and then concentrated *in vacuo* to half its original volume. This material was purified by chromatography, eluting with ethyl acetate–hexane (gradient of 1:1 to 3:1) to give 1.15 g (68%) of **9a** as a glassy pale yellow solid. Anal. ($C_{14}H_{14}Cl_2N_4$) C, H, N.

2-[[3-(Trifluoromethyl)phenyl]amino]benzenecarboximidic Acid Hydrazide (9b). 80% yield of a gummy tan solid that was used immediately in the next reaction.

5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-thiadiazole-2(3*H*)-thione (10a). Carbon disulfide (100 μL, 1.58 mmol) was added dropwise to a room temperature solution of **9a** (183 mg, 0.60 mmol) in 5 mL of methanol. The solution was stirred for 2 h and then concentrated. The residue was purified by chromatography, eluting with ethyl acetate–hexane (1:4), to give 107 mg (49%) of **10a** as a yellow solid, mp 250–252 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H), 6.35 (d, J = 8 Hz, 1H), 6.94 (t, J = 7 Hz, 1H), 7.27–7.36 (complex m, 2H), 7.50–7.54 (complex

Table I. 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, and 1,2,4-Triazole Analogs of the Fenamates



no.[a]	X	Y	method[b]	formula[c]	mp, °C	5-LO/CO[d]
1a	meclofenamic acid					24/0.10
4a	O	OH	A	$C_{15}H_{11}Cl_2N_3O_2$	253–254	N/N[e] at 16 μM
4c	O	OH	A	$C_{16}H_{15}N_3O_2$	239–141	N/N at 16 μM
5a	O	SH	B	$C_{15}H_{11}Cl_2N_3OS$	257–259	0.74/0.70
5b	O	SH	B	$C_{15}H_{10}F_3N_3OS$	211–213	0.77/0.27
5c	O	SH	B	$C_{16}H_{15}N_3OS$	242–244 dec	1.0/0.61
6a	O	NH_2	C	$C_{15}H_{12}Cl_2N_4O$	255–157	45%/N at 10 μM
6b	O	NH_2	C	$C_{15}H_{11}F_3N_4O$	185–187	0.68/7.1
10a	S	SH	D	$C_{15}H_{11}Cl_2N_3S_2$	250–252 dec	1.4/1.7
10b	S	SH	D	$C_{15}H_{10}F_3N_3S_2$	225–227	0.87/0.85
15	S	OH	E	$C_{16}H_{10}F_3N_3OS$	157–160	7.4/N at 10 μM
17a	S	NH_2	F	$C_{15}H_{12}Cl_2N_4S$	219–226	0.69/6.1
17b	S	NH_2	F	$C_{15}H_{11}F_3N_4S$	122–123	0.69/11
18a	NH	SH	G	$C_{16}H_{12}Cl_2N_4S$	300–305 dec	N/N at 16 μM
18b	NH	SH	G	$C_{16}H_{11}F_3N_4S$	275–279 dec	N at 16 μM/0.51
20	NH	OH	H	$C_{15}H_{11}F_3N_4O$	289–290	N/N at 10 μM
22a	NMe	OH	I	$C_{16}H_{14}Cl_2N_4O$	280–285 dec	N/N at 16 μM
22b	NMe	OH	I	$C_{16}H_{13}F_3N_4O$	178–180	N/N at 16 μM
24a	NMe	SH	J	$C_{16}H_{14}Cl_2N_4S$	218–220	86%/N at 16 μM
24b	NMe	SH	J	$C_{16}H_{13}F_3N_4S$	137–143	12/30
27a	O	NHCN	L	$C_{16}H_{11}Cl_2N_5O$	215 dec	0.89/0.25
27b	O	NHCN	K	$C_{16}H_{10}F_3N_5O$	234 dec	3.0/1.0
29a	S	NHCN	M	$C_{16}H_{11}Cl_2N_5S$	195 dec	0.29/1.9
29b	S	NHCN	M	$C_{16}H_{10}F_3N_5S$	177–180	1.7/2.6

[a] Analogs of meclofenamic acid (a) R = 2,6-di-Cl,3-Me; analogs of flufenamic acid (b) R = 3-CF_3; analogs of mefenamic acid (c) R = 2,3-di-Me. [b] See the Experimental Section for a description of the general methods. [c] Analyses for C, H, N within ±0.4% of theory. [d] Data reported as IC_{50} (μM) or the percent inhibition at the stated dose; 10 or 16 μM. IC_{50} calculated as the concentration of test compound causing 50% inhibition of LTB_4 (5-LO) or $PGF_{2\alpha}$ (CO) formation. The standard errors average 11% of the values shown for 5-LO and 8% for CO. [e] N = less than 40% inhibition at the screening dose.

m, 2H) 8.40 (s, 1H, NH), 14.79 (s, 1H, hetero-H). Anal. ($C_{15}H_{11}Cl_2N_3S_2$) C, H, N, Cl.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-thiadiazole-2(3*H*)-thione (10b). **10b** was purified by chromatography, eluting with ethyl acetate–hexane (1:4), 54% yield, mp 225–227 °C. Anal. ($C_{15}H_{10}F_3N_3S_2$) C, H, N, S.

2,6-Dichloro-3-methyl-*N*-[2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]benzenamine (11a). Carbon disulfide (200 μL, 3.32 mmol) was added to a 0 °C suspension of **3a** (1.010 g, 3.25 mmol) in 25 mL of methanol. Potassium hydroxide (220 mg, 3.34 mmol) was then added, and the reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 5 h. Iodomethane (220 μL, 3.53 mmol) was added and stirring continued overnight. The solution was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and then dried over magnesium sulfate. The residue was purified by flash chromatography, eluting with hexane–ethyl acetate (2:1), to provide 730 mg (56%) of **12**.

A solution of **12** (680 mg, 1.70 mmol) and *p*-toluenesulfonic acid (375 mg, 1.97 mmol) in 20 mL of toluene was heated at reflux for 2 h. The solution was concentrated *in vacuo* and purified by flash chromatography eluting with hexane–ethyl acetate (10:1). The solid was stirred with hexane and collected by filtration to give 387 mg (60%) of **11a**, mp 162–165 °C. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 2.83 (s, 3H), 6.34 (d, J = 8 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 8 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 9.56 (s, 1H, NH). Anal. ($C_{16}H_{13}Cl_2N_3S_2$) C, H, N, Cl, S.

3-(Trifluoromethyl)-*N*-[2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]benzenamine (11b). **11b** was purified by chromatography to give 43% yield from **3b**, mp 86–88 °C. Anal. ($C_{16}H_{12}F_3N_3S_2$) C, H, N.

Alternate Preparation of 2,6-Dichloro-3-methyl-*N*-[2-[5-(methylthio)-1,3,4-thiadiazol-2-yl]phenyl]benzenamine (11a). To a 0 °C suspension of **10a** (100 mg, 0.27 mmol) in 5 mL of methanol was added dropwise 1 N NaOH (280 μL, 0.28 mmol). After 10 min iodomethane (20 μL, 0.32 mmol) was added dropwise to the yellow solution. Stirring was continued at 0 °C for 5 min and then at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was chromatographed eluting with hexane–ethyl acetate (3:1) to provide 90 mg (90%) of **11a**.

2,6-Dichloro-3-methyl-*N*-[2-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl] phenyl]benzenamine (13a). To a 0 °C solution of **11a** (1.435 g, 3.75 mmol) in 50 mL of methylene chloride was added *m*-chloroperbenzoic acid (898 mg, 4.17 mmol). The reaction mixture was stirred at 0 °C for 1 h and then poured into methylene chloride and washed with saturated sodium bicarbonate followed by water. The organic layer was dried over magnesium sulfate and then concentrated *in vacuo*. Trituration with ethyl acetate followed by hexane provided 1.223 g of a pale yellow solid. The filtrate was concentrated and the residue purified by flash chromatography, eluting with hexane–ethyl acetate (3:1) to provide an additional 120 mg (90% total yield) of **13a**, mp 158–160 °C. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 3.20 (s, 3H), 6.40 (d, J = 7 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.32–7.38 (complex m, 2H), 7.54 (d, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 9.44 (s, 1H, NH). Anal. ($C_{16}H_{13}Cl_2N_3OS_2$) C, H, N, Cl.

3-(Trifluoromethyl)-*N*-[2-[5-(methylsulfinyl)-1,3,4-thiadiazol-2-yl]phenyl]benzenamine (13b). **13b** was purified by flash chromatography, eluting with a gradient of hexane–ethyl acetate (6:1 to 1:1), 54% yield, mp 125–126 °C. Anal. ($C_{16}H_{12}F_3N_3OS_2$) C, H, N, S.

Method E. Preparation of 1,3,4-Thiadiazol-3-ones. 5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-thiadiazol-2(3*H*)-one (15). To a bright yellow solution of **13b** (291 mg, 0.76 mmol) in 10 mL of ethanol was added 5 mL of 1 N NaOH. An initial bright red solution formed, followed by a thick tan precipitate. The mixture was stirred at room temperature overnight. The solid, **14**, was collected by filtration and the filtrate

extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give additional 14. The lots of 14 were combined, dissolved in ethanol, and treated with 10 mL of 1 N HCl. The solution was heated at reflux for 4 h and then cooled to room temperature. The resultant light yellow solid was collected by filtration. The filtrate was extracted with ethyl acetate, and then the organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The solids were combined and purified by flash chromatography eluting with hexane–ethyl acetate (3:1) to give 103 mg (40%) of **15**, mp 157–160 °C. ^{1}H NMR (DMSO-d_6): δ 7.10–7.15 (complex m, 3H), 7.23 (t, J = 7.5 Hz, 1H), 7.34–7.52 (complex m, 3H), 7.73 (d, J = 8 Hz, 1H), 8.55 (s, 1H, NH), 13.03 (s, 1H). Anal. ($C_{15}H_{10}F_3N_3OS$) C, H, N, S.

2-[(2,6-Dichloro-3-methylphenyl)amino]benzoic Acid 2-(Aminothioxomethyl)hydrazide (16a). Oxalyl chloride (2.85 g, 22.5 mmol) in 10 mL of methylene chloride was added dropwise to a 0 °C suspension of **1a** (3.17 g, 10.6 mmol) and dimethylformamide (830 μL, 10.6 mmol) in 50 mL of methylene chloride. The clear yellow solution was stirred at 0 °C for 15 min and then at room temperature for 30 min. The solution was then concentrated *in vacuo* to give a yellow solid. This solid was added in portions to a suspension of thiosemicarbazide (1.95 g, 2.1 mmol) in 20 mL of pyridine. The suspension was stirred at 0 °C for 30 min and then at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was concentrated and then slurried with equal volumes of ethyl acetate and hexane. The off-white solid was collected by filtration to give 1.66 g (42%) of **16a**. Anal. ($C_{15}H_{14}Cl_2N_4SO$) C, H, N, S.

2-[[3-(Trifluoromethyl)phenyl]amino]benzoic Acid 2-(Aminothioxomethyl)hydrazide (16b). 44% yield, converted directly to **17b**.

Method F. Preparation of 1,2,4-Triazole-3-thiones. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (17a). Sodium methoxide (734 mg, 13.59 mmol) was added to a solution of **16a** (1.466 g, 3.96 mmol) in 60 mL of methanol and the mixture heated at reflux overnight. An additional amount of sodium methoxide (702 mg, 13.00 mmol) was added, and heating at reflux was continued overnight. The volatiles were removed *in vacuo*, and the residue was dissolved in water. The aqueous solution was acidified to pH 4–5 with 10% hydrochloric acid. The resultant white solid was collected and chromatographed, eluting with hexane–ethyl acetate (1:2), to give 599 mg (43%) of **17a**, mp 300–305 °C. ^{1}H NMR (DMSO-d_6): δ 2.38 (s, 3H), 6.27 (d, J = 8 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 7.36 (d, J = 8 Hz, 1H), 7.53 (t, J = 8.5 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 8.74 (s, 1H, NH), 13.85 (s, 1H, NH). Anal. ($C_{15}H_{12}Cl_2N_4S$) C, H, N, Cl, S.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (17b). **17b** was purified by chromatography, eluting with ethyl acetate–hexane (2:1), 59% yield, mp 275–279 °C. Anal. ($C_{15}H_{11}F_3N_4S$) C, H, N, S.

Method G. Preparation of 1,3,4-Thiadiazol-2-amines. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-thiadiazol-2-amine (18a). Methanesulfonic acid (280 μL, 4.31 mmol) was added dropwise to a suspension of **16a** (1.008 g, 2.73 mmol) in 30 mL of toluene. The mixture was heated at reflux for 3 h and then allowed to cool to room temperature overnight. The tan solids were filtered off and suspended in 100 mL of ethyl acetate. This suspension was then stirred vigorously with 40 mL of 10% aqueous ammonium hydroxide, and the layers were separated. The ethyl acetate layer was washed with water and dried over magnesium sulfate. Filtration and concentration *in vacuo* followed by drying at 60 °C *in vacuo* overnight provided 561 mg (59%) of **18a**, mp 219–226 °C. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 6.25 (d, J = 8 Hz, 1H), 6.83 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.44–7.54 (m, 3H-Ar, 2H-NH$_2$), 9.80 (s, 1H, NH). Anal. ($C_{15}H_{12}Cl_2N_4S$) C, H, N, Cl, S.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-thiadiazol-2-amine (18b). **18b** was purified by chromatography, eluting with a gradient of hexane and ethyl acetate (1:1 to 1:3), 35% yield, mp 122–123 °C. Anal. ($C_{15}H_{11}F_3N_4S$) C, H, N, S.

Method H. Preparation of 1,2,4-Triazol-3-ones. 5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (20). To a room temperature suspension of **6b** (941 mg, 2.94 mmol) in 20 mL of ethanol was added 571 mg of potassium hydroxide. The solution was heated at reflux for 3 h, and an additional 100 mg of potassium hydroxide was added. After an additional 3.5 h of heating, the reaction mixture was allowed to cool to room temperature and neutralized with acetic acid. The solvents were removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexane–ethyl acetate (2:1) to provide 792 mg (77%) of **19**.

19 was suspended in 12 mL of concentrated HCl and heated at reflux for 4 h. The suspension was cooled to room temperature and collected by filtration, washing with water, to provide 597 mg (82%) of **20**. An analytical sample of **20** was obtained by recrystallization from ethyl acetate and ethanol, mp 289–290 °C. ^{1}H NMR (DMSO-d_6): δ 7.01 (m, 1H), 7.28 (d, J = 7 Hz, 1H), 7.35–7.60 (complex m, 6H), 7.69 (d, J = 8 Hz, 1H), 9.10 (s, 1H, NH), 11.83 (s, 1H, hetero-H), 12.03 (s, 1H, hetero-H). Anal. ($C_{15}H_{11}F_3N_4O$) C, H, N.

Method I. Preparation of 4-Methyl-1,2,4-triazol-3-ones. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (22a). Methyl isocyanate (190 μL, 3.22 mmol) was added dropwise to a room temperature solution of **3a** (889 mg, 2.86 mmol) in 11 mL of methanol. After the mixture was stirred at room temperature for 15 min, 100 mL of ether was added and the white solids were removed by filtration, washing with ether. The solid was dried to give 910 mg (87%) of **21a** that was not purified. A portion of **21a** (862 mg, 2.35 mmol) was suspended in 3 mL of water and treated with 3 mL of 1 N sodium hydroxide solution, and the resultant orange solution was heated at reflux overnight. An additional 2 mL of sodium hydroxide was added, and reflux was continued overnight. The mixture was cooled to room temperature, and the liquid decanted off and acidified with 1 N hydrochloric acid. The white solids were removed by filtration, washing with water. Flash chromatography eluting with hexane–ethyl acetate (2:1) gave 268 mg (33%) of **22a**, mp 280–285 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 3.16 (s, 3H), 6.19 (d, J = 8 Hz, 1H), 6.85 (t, J = 7 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.80 (s, 1H, NH), 11.88 (s, 1H, hetero-H). Anal. ($C_{16}H_{14}Cl_2N_4O$) C, H, N.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazol-3-one (22b). **22b** was purified by chromatography, eluting with hexane–ethyl acetate (1:1), 33% yield from **3b**, mp 178–180 °C. Anal. ($C_{16}H_{13}F_3N_4O$) C, H, F, N.

Method J. Preparation of 4-Methyl-1,2,4-triazole-3-thiones. 5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazole-3-thione (24a). Methyl isothiocyanate (331 mg, 4.52 mmol) was added dropwise to a room temperature solution of **3a** (1.083 g, 3.49 mmol) in 12 mL of tetrahydrofuran. After the mixture was stirred at room temperature overnight, the white solids were removed by filtration and dried to give 1.185 g (89%) of **23a**. This material was suspended in 5 mL of water and treated with 6.8 mL of 1 N sodium hydroxide solution. The resultant solution was heated at reflux for 1 h. The solution was cooled to room temperature and acidified with 1 N hydrochloric acid. The white solids were collected by filtration, washing with water. Flash chromatography, eluting with hexane–ethyl acetate (2:1), gave 843 mg (66%) of **24a**, mp 218–220 °C. ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 3.41 (s, 3H), 6.18 (d, J = 8.2 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 7.21–7.37 (complex m, 3H), 7.48 (d, J = 8.2 Hz, 1H), 7.72 (s, 1H), 13.85 (s, 1H, NH). Anal. ($C_{16}H_{14}Cl_2N_4S$) C, H, N, S.

5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-2,4-dihydro-4-methyl-3*H*-1,2,4-triazole-3-thione (24b). **3b** was converted to **23b** in 67% yield. Treatment of **23b** with base followed by chromatography, eluting with hexane–ethyl acetate (2:1), gave **24b** in 80% yield, mp 137–143 °C. Anal. ($C_{16}H_{13}F_3N_4S$) C, H, N, S.

2,6-Dichloro-3-methyl-*N*-[2-[5-(methylthio)-1,3,4-oxadiazol-2-yl]phenyl]benzenamine (25a). Five milliliters of 1.0 N sodium hydroxide was added dropwise to a room temperature suspension of **5a** (1.706 g, 4.85 mmol) in methanol. The clear pale yellow solution was stirred at room temperature for 10 min.

Iodomethane (320 μL, 5.13 mmol) was added dropwise, and stirring was continued for 6 h. The white solid was collected by filtration and dried *in vacuo* overnight at 60 °C to provide 1.530 g (86%) of **25a**, mp 170–171 °C. ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 3H), 2.80 (s, 3H), 6.34 (d, J = 8.5 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.29–7.42 (complex m, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 7 Hz, 1H), 8.94 (s, 1H, NH). Anal. ($C_{16}H_{13}Cl_2N_3OS$) C, H, N, Cl, S.

***N*-[2-[5-(Methylthio)-1,3,4-oxadiazol-2-yl]phenyl]-3-(trifluoromethyl)benzenamine (25b).** **25b** was purified by chromatography, eluting with hexane–ethyl acetate (4:1), 86% yield, mp 94–95 °C. Anal. ($C_{16}H_{12}F_3N_3OS$) C, H, N, S.

***N*-[2-[5-(Methylsulfonyl)-1,3,4-oxadiazol-2-yl]phenyl]-3-(trifluoromethyl)benzenamine (26).** To a 0 °C solution of **25b** (1.284 g, 3.65 mmol) in 60 mL of methylene chloride was added sodium bicarbonate (1.668 g, 19.85 mmol) followed by *m*-chloroperbenzoic acid (2.015 g, 9.37 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. Additional amounts of *m*-chloroperbenzoic acid (480 mg) and sodium bicarbonate (332 mg) were added, and stirring was continued for 6 h. The mixture was poured into methylene chloride and washed with saturated sodium bicarbonate and then water. The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with hexane–ethyl acetate (3:1) to provide 555 mg (40%) of **26**, mp 144–148 °C. ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 3H), 7.14 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.50–7.64 (complex m, 4H), 7.97 (d, J = 8 Hz, 1H), 8.94 (s, 1H, NH). Anal. ($C_{16}H_{12}F_3N_3O_3S$) C, H, N, S.

Method K. Preparation of 1,3,4-Oxadiazol-2-ylcyanamides. *N*-[5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-oxadiazol-2-yl]cyanamide (27b). To a solution of **26** (210 mg, 0.55 mmol) in 5 mL of dimethylformamide was added 1 mL of water followed by cyanamide (196 mg, 4.66 mmol) and triethylamine (100 μL, 0.72 mmol). The reaction mixture was stirred at 80 °C overnight. An additional amount of cyanamide (96 mg) was added and heating continued for 6 h. The mixture was poured into ether and extracted into 0.3 N sodium hydroxide. The aqueous layer was acidified with 1 N hydrochloric acid, and the resulting white solids were filtered off, washing with water. Recrystallization from acetonitrile provided 96 mg (51%) of **27b**, mp 234 °C dec. ^{1}H NMR (DMSO-d_6): δ 7.11 (t, J = 7 Hz, 1H), 7.30 (d, J = 7 Hz, 1H), 7.39–7.60 (complex m, 5H), 7.72 (d, J = 8 Hz, 1H), 8.43 (s, 1H, NH). Anal. ($C_{16}H_{10}F_3N_5O$) C, H, N, F.

2,6-Dichloro-3-methyl-*N*-[2-[5-(methylsulfinyl)-1,3,4-oxadiazol-2-yl]phenyl]benzenamine (28). To a 0 °C solution of **25a** (284 mg, 0.77 mmol) in 10 mL of methylene chloride was added *m*-chloroperbenzoic acid (132 mg, 0.77 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then an additional amount of *m*-chloroperbenzoic acid (33 mg) was added and stirring was continued for 1 h. The mixture was poured into methylene chloride and washed with saturated sodium bicarbonate and then water. The organic layer was dried over magnesium sulfate and then concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with hexane–ethyl acetate (1:1) to provide 220 mg (74%) of **28**, mp 146–149 °C. ^{1}H NMR (DMSO-d_6): δ 2.42 (s, 3H), 3.33 (s, 3H), 6.38 (d, J = 8.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.38–7.48 (complex m, 2H), 7.58 (d, J = 8 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H) , 8.97 (s, 1H, NH). Anal. ($C_{16}H_{13}Cl_2N_3O_2S$) C, H, N, Cl, S.

Method L. Preparation of 1,3,4-Oxadiazol-2-ylcyanamides. *N*-[5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-oxadiazol-2- yl]cyanamide (27a). To a suspension of **3a** (394 mg, 1.27 mmol) in 20 mL of 2-propanol was added triethylamine (200 μL, 1.43 mmol) followed by diphenyl cyanocarbonimidate (372 mg, 1.56 mmol). After 1.5 h the resultant yellow solution was concentrated *in vacuo*. The residue was dissolved in 10 mL of ethyl acetate and partitioned between water and a 1:1 mixture of ether and hexane. The aqueous layer was acidified with 1 N hydrochloric acid, and the resultant white solid was collected by filtration to provide 99 mg (22%) of **27a**, mp 235 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 6.31 (d, J = 8.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.32–7.42 (complex m, 2H), 7.55 (d, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H) 8.19 (s, 1H, NH). Anal. ($C_{16}H_{11}Cl_2N_5O$) C, H, N.

Method M. Preparation of 1,3,4-Thiadiazol-2-ylcyanamides. *N*-[5-[2-[(2,6-Dichloro-3-methylphenyl)amino]phenyl]-1,3,4-thiadiazol-2-yl]cyanamide (29a). Cyanamide (126 mg, 3.00 mmol) was added to a solution of potassium *tert*-butoxide (182 mg, 1.62 mmol) in 10 mL of *tert*-butyl alcohol. The reaction mixture was stirred at room temperature for 15 min. **13a** (406 mg, 1.02 mmol) was added, and the reaction mixture was heated at reflux for 15 min. Additional cyanamide (117 mg, 2.78 mmol) was added, and heating was continued for 2.5 h. After cooling, the reaction mixture was partitioned between ether and dilute sodium hydroxide. The organic layer was further washed with dilute base. The basic layers were combined and acidified with HCl. The thick white precipitate was collected by filtration, washing with water to provide 310 mg (81%) of **29a**, mp 195 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.39 (s, 3H), 6.39 (d, J = 8 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 7.28–7.41 (complex m, 2H), 7.52 (d, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 8.39 (s, 1H, NH). Anal. ($C_{16}H_{11}Cl_2N_5S$) C, H, N, S.

***N*-[5-[2-[[3-(Trifluoromethyl)phenyl]amino]phenyl]-1,3,4-thiadiazol-2-yl]cyanamide (29b).** **29b** was recrystallized from acetonitrile; 81% yield, mp undefined. Anal. ($C_{16}H_{10}F_3N_5S$-.25 H_2O) C, H, N, S.

Pharmacology. A. Whole Cell 5-Lipoxygenase (5-LO) and Cyclooxygenase (CO) Assays. Materials. The rat basophilic leukemia cell line (RBL-1) was obtained from the American Type Culture Collection (Rockville, MD). Radioimmunoassay (RIA) kits for LTB_4 and $PGF_{2\alpha}$ were obtained from Amersham (Arlington Heights, IL) and Seragen (Boston, MA), respectively. All tissue culture media were obtained from GIBCO (Grand Island, NY). **Method.** RBL-1 cells were grown at 37 °C in suspension culture in Eagle's minimum essential medium supplemented with 12% fetal bovine serum under 5% CO_2 in air. Cells were harvested by centrifugation, washed with cold phosphate buffered saline, pH 7.4 (PBS; NaCl, 7.1 g; Na_2HPO, 1.15 g; KH_2PO_4, 0.2 g; and KCl, 0.2 g/L), and suspended in PBS containing 1.0 mM calcium at a density of 2×10^6 cell/mL. Cells were incubated with and without test agent in 1% DMSO for 10 min at room temperature. Calcium ionophore A23187 (5 μM) was added, and incubations were continued for 7 min at 37 °C. The reaction was stopped by chilling the tubes on ice for 10 min. Cells were removed by centrifugation, and the supernatant was stored at −20 °C. Aliquots (100 μL) were analyzed for LTB_4 and $PGF_{2\alpha}$ by RIA according to the manufacturer's instructions. Product formation in the compound- and vehicle-treated incubations were compared to obtain percent inhibition. The IC_{50} values were determined by linear regression analysis of the percent inhibition *vs* log inhibitor concentration data.

B. Carrageenan Footpad Edema. Carrageenan solution (1% w/v) was prepared by dissolving 100 mg of carrageenan (Marine Colloidal Div., Springfield, NJ) in 10 mL of sterile saline (0.9%) solution (Travenol). Male Wistar rats were orally dosed with compound (in 10 mL/kg of 0.5% (hydroxypropyl)methylcellulose/0.2% Tween 80 or Labrafils) 1 h before carrageenan challenge. Foot paw edema was induced by injecting 0.10 mL of the carrageenan solution subcutaneously into the planter portion of the right hind paw of each rat under light anesthesia. Initial foot paw volume was measured immediately by mercury plethysmography (Buxco Electronics) following carrageenan challenge. Edema was measured 5 h after carrageenan administration. The swelling in each test group of animals was used to calculate the percent inhibition ± SEM of edema achieved by the compound at the test dose compared with the vehicle control group. Compounds were tested at doses of 1.0, 3.0, 10.0, and 30.0 mg/kg po, with 7–14 animals at each dose.

C. Mycobacterium Footpad Edema. *Mycobacterium butyricum* (5 mg/mL) was suspended in paraffin oil by sonication for 10 min in an ice bath. Footpad edema was induced on day 0 by injecting 0.1 mL of the *Mycobacterium* mixture into the left hindpaw of lightly anesthetized rats. Swelling in the injected hindpaw was determined by mercury plethamography 72 h after injection. Groups of rats were orally dosed with test compounds (suspended in 0.5% (hydroxypropyl)methylcellulose with 0.2% Tween-80) or vehicle 1 h before *Mycobacterium* injection and on

days 1 or 2. Inhibition of swelling was determined by comparing the change in hindpaw volume in compound- and vehicle-treated rats.

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(22) Unpublished results of Robert Guttendorf and Larry Andress of the Parke-Davis Pharmacokinetics and Drug Metabolism Department.
(23) Although a metabolism study of **10b** was not performed, we believe its inactivity in MFE is also due to the formation of an inactive metabolite.