Synthesis and Endectocidal Activity of Novel 1-(Arylsulfonyl)-1-[(trifluoromethyl)sulfonyl]methane Derivatives

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We have recently synthesized a series of novel disulfonylmethane compounds that have shown anthelmintic and insecticidal (endectocidal) activity. Several analogues have shown activity against the internal nematode *Haemonchus contortus*. In sheep studies, these analogues have shown 100% control of this internal parasite at a 10 mg/kg rate. In vitro activity against the biting flies, *Stomoxys calcitrans* and *Haematobia irritans*, has been observed at rates as low as 25 and 2.3 ppm, respectively. Only marginal activity against the liver fluke *Fasciola hepatica* and *Trichostrongylus colubriformis* was seen. Respiratory control index values on rat liver mitochondria for this series suggested uncoupling of oxidative phosphorylation as a mechanism of action. Compound **1** is considered to be a promising agent for treatment of parasitized sheep.

Introduction

The search for a novel class of compounds for the treatment of parasitic nematodes and arthropods in domestic animals is of continuing interest. There are several broad-spectrum agents, representing a number of chemical classes, available for treatment of internal parasites of animals. Only the avermectins and milbemycins are used for the broad systemic control of both internal and external parasites.[1,2] Unfortunately, strains of nematodes and arthropods have shown resistance to commercially available anthelmintics and insecticides including the avermectins.[3−7] We have recently synthesized a series of novel 1-aryl-1-[(trifluoromethyl)-sulfonyl]methane compounds that have shown in vitro and in vivo anthelmintic activity against susceptible strains as well as an Ivermectin-resistant strain. They generally have shown good activity against the abomasal nematode *Haemonchus contortus* in sheep but were less effective against *Trichostrongylus colubriformis* and *Fasciola hepatica* (common liver fluke). This series has also demonstrated in vitro activity against the blood-feeding dipteral species *Stomoxys calcitrans* (stable fly), the adult of which attacks both domestic animals[8] and humans. The suspected mechanism of action of these disulfonylmethane compounds is oxidative phosphorylation uncoupling as they have been shown to uncouple rat liver mitochondria. Despite the potential nonselectivity of uncouplers, these disulfonylmethanes have shown a surprising margin of safety toward the host species. This paper describes the chemistry, structure−activity relationship, and biological activity of compound **1** and analogues.
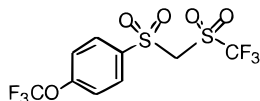

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Chemistry

Three synthetic routes were used for the synthesis of compound **1** and analogues. Scheme 1 was the most utilized method and is a modification of published procedures.[9] This synthetic pathway allowed for the greatest flexibility in varying groups on the phenyl ring. Chloromethyl trifluoromethyl sulfide was originally synthesized from dimethyl sulfide by chlorination with sulfuryl chloride, followed by fluorination with antimony trifluoride.[10] This was then used to synthesize the phenyl trifluoromethyl dithio intermediates by reaction with sodium salts of substituted benzenethiols. These intermediates were then oxidized to the corresponding disulfonylmethane compounds shown in Table 1. This required the use of strong oxidizing agents such as potassium permanganate or hydrogen peroxide in trifluoroacetic acid. Hydrogen peroxide in acetic acid would only oxidize the sulfur adjacent to the aryl ring.

Another method involved reaction of chloromethyl phenyl sulfide with potassium triflinate to give the sulfonyl sulfide intermediate, followed by oxidation to give the disulfonylmethane as shown in Scheme 1b. This method had less general application because of the difficulties in obtaining substituted phenyl sulfides and in the subsequent α-chlorination step.[11]

Scheme 1a shows the third method utilized in this series. It presented a more economical approach to structure **1**. The potassium salt of *p*-(trifluoromethoxy)-phenyl methyl sulfone was made using potassium bis-(trimethylsilyl)amide and then reacted with phenyltrifluoromethanesulfonimide to give **1** in good yield. Other trifluoromethanesulfonating agents have been used successfully, including triflic anhydride and *N*-trifylimidazolide. Trifyl fluoride also works well but is difficult to obtain commercially. Some of this work is also described in recent patent literature.[12]

Two synthetic approaches were used for the synthesis of the α-methyl compound **28**. Direct alkylation using dimethyl sulfate in DMF gave small amounts of product,
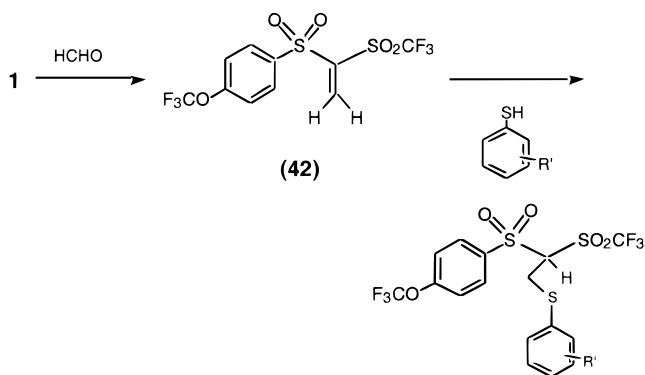
Scheme 1

Chart 1

(39)   (40)

(41)
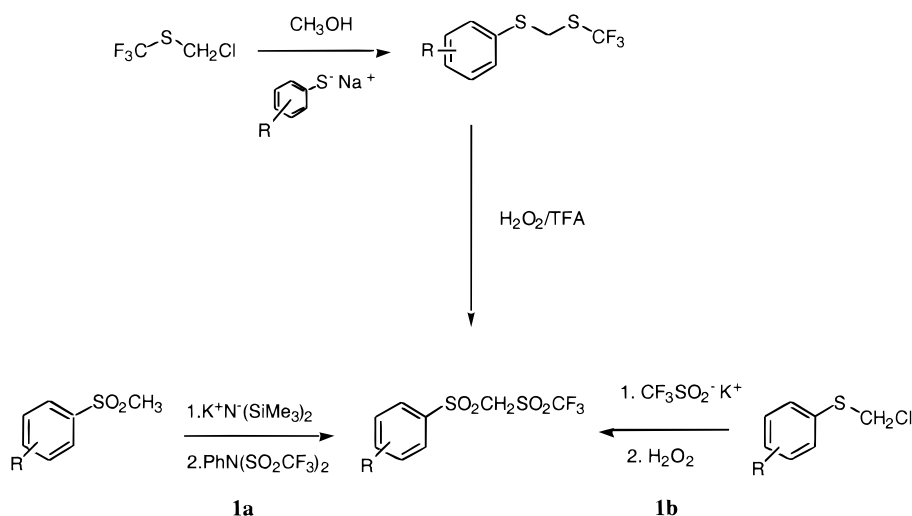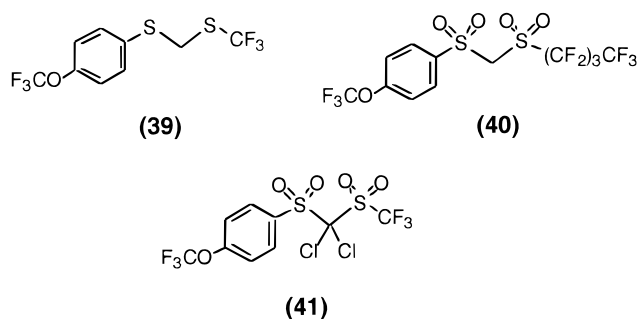
Scheme 2

(42)

but primarily the dimethyl compound.[13] An improved method involved reacting **1** with formaldehyde to obtain the corresponding vinyl compound **42**. This was followed by reduction with sodium borohydride to give the desired compound.

The α-chloro compound could not be synthesized by chlorination of **1**. Only the dichloro **41** (Chart 1) was obtained. However, an α-fluoro derivative (**27**) was obtained by electrophilic fluorination with 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Compound **42** was used as an intermediate for several derivatives (**35**−**38**). They were afforded by Michael-type additions to the double bond with various arylthio groups (Scheme 2). In addition, the α-ethyl (**32**) and α-benzyl (**33**) compounds were obtained in this fashion by reacting methylmagnesium bromide and phenylmag-

nesium bromide, respectively, with the analogous 4-chlorophenyl vinyl intermediate. The scheme used for each derivative is noted in Table 1.
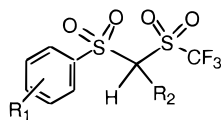
Biological Data and Structure−Activity Relationships

The compounds in Table 1 were tested for insecticidal activity using an in vitro adult stable fly (*S. calcitrans*) screen. Adult stable flies were fed serum containing titrated levels of the experimental compounds starting with 100 ppm. Percent mortality was determined after 24 and 48 h as compared to serum-only controls. Activity has shown a dependence on aryl group substitution. Compounds with 4- or 3,4-substitution on the phenyl ring gave the best activity. Lipophilic, electron-withdrawing groups in the para position generally gave good activity. Groups such as 4-chloro (**9**) or 4-CF$_3$ (**14**) were active at the 25−50 ppm rate. Better in vitro activity was seen with the 4-OCF$_3$ (**1**), 3,4-dichloro (**10**), 4-bromo (**11**), 4-OCF$_2$CF$_2$H (**23**), or their α-methyl derivatives (**28, 29**). Electron-donating groups such as methyl (**4**) and *tert*-butyl (**6**) did not compare favorably to the most active analogues. Strong electron-withdrawing groups with lesser lipophilic character such as cyano (**16**) or nitro (**17**) were not as active. Extending the perfluoroalkyl chain to four carbons (**40**) did not improve activity, regardless of the phenyl substitution.

Compound **1** was also tested in an assay (added to blood during in vitro feeding) and was highly toxic to buffalo fly (*Haematobia irritans exigua)* with an LC$_{50}$ = 2.3 ppm.[14] Surprisingly, very little larval blow fly (*Phormia regina*) activity was observed with this series. The flies were fed serum containing titrated levels of compound as described for stable fly.

Prior to testing in sheep, anthelmintic activity against *H. contortus* was determined using a Mongolian gerbil (*Meriones unguiculatus*) model, adapted from the model previously described by Conder.[15] Compounds were orally gavaged at 25 or 50 mg/kg, and the number of larvae present in the stomach of each gerbil was counted. Six compounds had greater than 90% activity at the 25 mg/kg dose (Table 2) and produced no obvious signs of toxicity. (Levamisole, administered at 10 mg/kg, gave 100% reduction of *Haemonchus* worms.) These results, as well as respiratory control index (RCI) values

Table 1

no.	R_1	R_2	formula[a]	mp[b] (°C)	ASF[c] (in vitro) (ppm)
1	4-OCF_3	H	$C_9H_6F_6O_5S_2$	112–114 (I,II)	25
2	H	H	$C_8H_7F_3O_4S_2$	71–73 (I,III) (e)	50
3	3,5-$(CF_3)_2$	H	$C_{10}H_5F_9O_4S_2$	110–111 (I)	50
4	4-CH_3	H	$C_9H_9F_3O_4S_2$	223–225 (I) (f)	>100
5	2,4-Cl_2	H	$C_8H_5Cl_2F_3O_4S_2$	93–95 (I)	>100
6	4-$C(CH_3)_3$	H	$C_{12}H_{15}F_3O_4S_2$	105–107 (I) (g)	>100
7	4-F	H	$C_8H_6F_4O_4S_2$	82–84 (I)	100
8	2,6-Cl_2	H	$C_8H_5Cl_2F_3O_4S_2$	77–79 (I)	>100
9	4-Cl	H	$C_8H_6ClF_3O_4S_2$	118–120 (I,II)	50
10	3,4-Cl_2	H	$C_8H_5ClF_3O_4S_2$	129–131 (I,II,III)	>100
11	4-Br	H	$C_8H_6BrF_3O_4S_2$	130–131 (I,II)	25
12	3-Cl, 4-F	H	$C_8H_5ClF_4O_4S_2$	109–111 (I)	100
13	2-Cl	H	$C_8H_6ClF_3O_4S_2$	101–102 (I)	>100
14	4-CF_3	H	$C_9H_6F_6O_4S_2$	119–122 (I)	50
15	3-CF_3	H	$C_9H_6F_6O_4S_2$	98–100 (I)	>100
16	4-CN	H	$C_9H_6F_3NO_4S_2$	134–136 (I)	>100
17	4-NO_2	H	$C_8H_6F_3NO_6S_2$	148–150 (I)	>100
18	4-OCH_3	H	$C_9H_9F_3O_5S_2$	116–118 (I)	>100
19	4-OSO_2CF_3	H	$C_9H_6F_6O_7S_3$	95–97 (I)	100
20	3-Cl, 4-SCF_2CF_2H	H	$C_{10}H_6ClF_7O_4S_3$	126–128 (I)	>100
21	4-$SC(CH_3)_3$	H	$C_{12}H_{15}F_3O_4S_3$	135–140 (I)	>100
22	4-$NHSO_2CF_3$	H	$C_9H_7F_6NO_6S_3$	163–165 (I)	100
23	4-OCF_2CF_2H	H	$C_{10}H_7F_7O_5S_2$	122–123 (I)	25
24	4-SCF_2CF_2H	H	$C_{10}H_7F_7O_4S_3$	112–114 (I)	>100
25	4-OH	H	$C_8H_7F_3O_5S_2$	99–101 (I) (h)	>100
26	4-OSO_2CH_3	H	$C_9H_9F_3O_7S_3$	111–112 (I)	>100
27	4-Cl	F	$C_8H_5ClF_4O_4S_2$	45–47 (j)	
28	4-OCF_3	CH_3	$C_{10}H_8F_6O_5S_2$	81–82 (j)	25
29	3,4-Cl_2	CH_3	$C_9H_7Cl_2F_3O_4S_2$	102–104 (j)	25
30	4-Cl	CH_3	$C_9H_8ClF_3O_4S_2$	112–113	50
31	4-Cl	SCH_3	$C_9H_8ClF_3O_4S_3$	142 dec (II) (j)	>100
32	4-Cl	CH_2CH_3	$C_{10}H_{10}ClF_3O_4S_2$	72–74 (j)	50
33	4-Cl	$C_6H_5CH_2$	$C_{15}H_{12}ClF_3O_4S_2$	91–92	>100
34	3,4-Cl_2	4-$CF_3C_6H_4CH_2$	$C_{16}H_{10}Cl_2F_6O_4S_2$	92 dec (j)	100
35	4-OCF_3	4-$FC_6H_4SCH_2$	$C_{16}H_{11}F_7O_5S_3$	76–77 (IV)	50
36	4-OCF_3	4-$OCF_3C_6H_4SCH_2$	$C_{17}H_{11}F_9O_6S_3$	130 dec (IV)	50
37	4-OCF_3	3-$FC_6H_4SCH_2$	$C_{16}H_{11}F_7O_5S_3$	48 dec (IV)	50
38	4-OCF_3	4-$ClC_6H_4SCH_2$	$C_{16}H_{11}ClF_6O_5S_3$	68–69 (IV)	50
39	4-OCF_3	H (Chart 1)	$C_9H_6F_6OS_2$		>100
40	4-OCF_3	H (Chart 1)	$C_{12}H_6F_{12}O_5S_2$	120–121 (II)	25
41	4-OCF_3	α,α-Cl_2	$C_9H_4Cl_2F_6O_5S_2$	103–104 (I)	>100

[a] Analytical results were within ±0.4% of the calculated values for all compounds. [b] Recrystallized from EtOH unless otherwise noted: (e) hexane, (f) iPrOH, (g) EtOH/H_2O, (h) benzene, (j) chromatographed only; (I) Scheme 1, (II) Scheme 1a, (III) Scheme 1b, (IV) Scheme 2. [c] Lowest concentration (ppm) of compounds in bovine serum vs adult stable fly giving >90% mortality.

(denoting oxidative phosphorylating potential) and stable fly results, were used to select compounds for sheep testing.

The endectocidal activity was determined by administering the compound intraruminally to parasitized sheep. Two sheep were each given a single injection of compound at a dosage of 10 mg/kg of body weight (BW). Blood samples were collected daily for 14 days posttreatment. Insecticidal activity against *S. calcitrans* was determined by 48-h exposure to posttreatment serum. Anthelmintic activity was determined by worm egg counts expressed as eggs per gram of feces (EPG) and by the number of worms present upon necropsy. At the 10 mg/kg dose, compound **1** gave 100% control of *H. contortus* and insecticidal activity was seen for 10 days posttreatment (Table 2). No adverse effects to the sheep were observed. It also gave 100% worm reduction at 5 mg/kg, but activity fell off below that rate. When **1** was administered in a single dose at 10 mg/kg to sheep

Table 2

no.	gerbil test (in vivo)[a,b]	*H. contortus* (sheep) (% reduction)[c]	adult stable fly (days of activity)[d]
1	100	100	10
9	100	100	3
10	100	100	1
14	100	100	0
28	100	100	6
35	100	100	6

[a] Expressed as percent reduction of *H. contortus* worms in gerbils dosed at 25 mg/kg of BW of compound by single oral gavage in DMSO/H_2O vehicle. [b] Gerbils dosed orally with Levamisole in DMSO/H_2O at 25 mg/kg gave 100% reduction of *H. contortus*. [c] Expressed as percent reduction of *H. contortus* worms in sheep dosed at 10 mg/kg of BW of compound by single ir injection in PEG 200 vehicle. Based on total worm counts at necropsy and compared to average nematode counts in untreated control group. [d] Number of days posttreatment in which >90% mortality of ASF was seen following exposure of insects to serum from sheep treated with 10 mg/kg of BW of compound by single ir injection in PEG 200 vehicle.

Table 3

no.	$pK_a{}^a$	$\log P^b$	RCI $IC_{50}{}^c$ (μM)
1	4.1	2.2	2950
6	5.1	2.4	2800
7	4.6	1.3	3150
9	4.4	1.9	4000
10	4.0	1.7	3987
14	4.0	1.0	5404
28	6.2	3.0	710
DNP^d	4.6	1.5	1000
Closantel			927

^{a} Determined in aqueous solution. ^{b} Partition coefficient determined by chromatographic techniques. ^{c} Uncoupler concentration (μM) that reduced the respiratory control index (RCI) by 50% of coupled rat liver mitochondria. ^{d} The oxidative phosphorylation uncouplers 2,4-dinitrophenol (DNP) and Closantel are included for comparative purposes.

infected with either *T. columbriformis* or the trematode *F. hepatica*, little effect was seen.

A beneficial feature of this series has been the low level of mammalian toxicity. In sheep, at rates up to 30 mg/kg for compound **1** and 40 mg/kg for other analogues such as **10**, no deaths have occurred and only minor transient toxicological effects to the host have been observed. These effects consisted of a slightly elevated body temperature and an increased respiratory rate that were seen for 1−2 h immediately posttreatment.

Several other analogues were tested in sheep and showed activity. The intermediate disulfide **39** was tested in sheep at 10 mg/kg. This compound gave similar results to **1**. The disulfide presumably was oxidized to the active compound **1** by the host animal, as is seen with certain benzimidazole anthelmintics.[16] The α-methyl analogue (**28**) also was quite active at 10 mg/kg. Compounds **9**, **10**, and **14** gave 100% control of *H. contortus* at that rate. The α,α-dichloro analogue (**41**) surprisingly gave 95% control of both *H. contortus* and stable fly at 10 mg/kg, presumably by in vivo chlorine reduction, even though it had no in vitro stable fly activity (Table 1).

Compound **1** was also administered to sheep infected with an Ivermectin-resistant strain of *H. contortus*.[17] The compound at 10 mg/kg BW effectively removed the resistant strain of *H. contortus* and again showed 100% efficacy against stable fly through day 10 posttreatment. These data, in addition to the mode of action and the unique class of chemistry, lead us to believe that this series will control Ivermectin-resistant *Haemonchus*. However, further studies at various rates with a larger number of sheep would be necessary for verification.

Mechanism of Action Studies

The mechanism of action of the disulfonylmethanes is thought to be through the uncoupling of oxidative phosphorylation. These proton ionophores disrupt mitochondrial pH gradients and the oxidative phosphorylation of ADP, thus disrupting energy production.[18−21] Several analogues have been evaluated for their ability to uncouple rat liver mitochondria, as measured by RCI values. These values were obtained by the methods described in the literature.[22−24] The effects of these compounds on RCIs indicated uncoupling ability about one-third as potent as that of 2,4-dinitrophenol (DNP) (Table 3). The structural requirements for protono-

phoric uncouplers have been studied extensively. Important features include strong electron-withdrawing groups, acidic protons, and optimal lipophilicity.[25−28] For this series, a pK_a between 4 and 6 appeared to be necessary. Log *P* values (octanol/water) as an indicator of lipophilicity ranged from 1.0 to 3.0 for active compounds. The acidity and lipophilicity of **1** (pK_a = 4.1, $\log P$ = 2.2) appeared to be the best balance for *H. contortus* and *S. calcitrans* activity. Traditional uncouplers such as DNP and CCCP have the acidic proton attached to oxygen or nitrogen. One unique feature of this series is the acidic proton is attached to carbon. We presume uncouplers of this type are not common because of the difficulty of finding structures with very acidic protons attached to carbon, yet having the prerequisite lipophilicity.

To date, compound **1** has been most active against hematophagous species, probably due to high serum binding ability. It also has the longest duration of activity in sheep testing (Table 2). This spectrum of activity against internal parasites appeared to be consistent with literature reports of other uncouplers, such as Rafoxanide and Closantel.[29−32]

Conclusions

These studies have demonstrated that the application of disulfonylmethanes can be an effective method of controlling certain internal and external parasites in domestic animals with a single dose. Future work will better define other routes of administration, dosing vehicles, etc., as well as effectiveness in other species of domestic and companion animals. Several analogues in this series were active against both fourth larval stage *H. contortus* in gerbils and adults in sheep. These compounds become systemic rapidly and are thought to bind to serum proteins. This would seem to suggest they require ingestion by the parasite for significant activity to occur. This accounts for the activity against adult stable fly, buffalo fly, and *H. contortus*. However, lack of activity against larval blow fly or *T. colubriformis* shows the relative narrow therapeutic spectrum of this class of compounds as compared with currently marketed endectocides.

Experimental Section

The benzenethiols and aryl methyl sulfones used as precursors were commercially available, as was chloromethyl trifluoromethyl sulfide. All commercially available chemicals and solvents were used without further purification. EM Science silica gel 60 was used for flash chromatography with the appropriate solvent. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All new compounds gave satisfactory NMR, elemental analysis, and mass spectrometry results. NMR chemical shifts are expressed in δ (ppm) values with tetramethylsilane as the internal standard. The following instrumentation was used: Varian Gemini-300 spectrometer, Mattson 3000 FTIR spectrometer, VG70SE field desorption mass spectrometer, Control Equipment Corp. 440 elemental analyzer.

[[4-(Trifluoromethoxy)phenyl]thio][(trifluoromethyl)-thio]methane (39) (Scheme 1). To a stirred solution of sodium methoxide (5.6 g, 0.103 mol) in 500 mL of methanol was added *p*-(trifluoromethoxy)benzenethiol (20 g, 0.103 mol) dropwise over 15 min. The reaction mixture was stirred for 30 min, and chloromethyl trifluoromethyl sulfide (17.1 g, 0.114 mol) was added dropwise over 10 min. The reaction mixture was refluxed for 18 h, poured into 500 mL of H_2O, and

extracted twice with ether (300 mL). The ether layer was washed with H_2O, dried over $MgSO_4$, and concentrated to give a yellow oil. The crude oil was purified on silica gel with hexane eluent to afford 26.3 g (83%) of **39** as a colorless oil: ^{1}H NMR (CHCl$_3$-d_1) δ 7.5 (d, 2 ArH), 7.2 (d, 2 ArH), 4.3 (s, 2 CH$_2$). Anal. (C$_9$H$_6$F$_6$OS$_2$) C, H.

[[4-(Trifluoromethoxy)phenyl]sulfonyl][(trifluoromethyl)sulfonyl]methane (1). To a solution of **39** (26.3 g, 0.085 mol) dissolved in 250 mL of TFA was added 50 mL of H_2O_2 (30%) dropwise over 1 h, keeping the temperature below 45 °C. The reaction mixture was stirred overnight at room temperature. The mixture was slowly heated to 70 °C and maintained there for a total of 8 h. The reaction mixture was cooled and poured into 500 mL of ice water. The resulting precipitate was filtered, washed with H_2O, dried, and recrystallized from EtOH to give 26.7 g (84%) of **1** as a white solid: mp 112–114 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.1 (d, 2 ArH), 7.45 (d, 2 ArH), 4.85 (s, 2 CH$_2$). Anal. (C$_9$H$_6$F$_6$O$_5$S$_2$) C, H.

[(4-Chlorophenyl)sulfonyl][(trifluoromethyl)sulfonyl]-methane (9) (Scheme 1a). Potassium bis(trimethylsilyl)-amide (22.0 g, 0.11 mol) was dissolved in THF (200 mL), and the solution was cooled to 0 °C. To this solution was added 4-chlorophenyl methyl sulfone (10.0 g, 0.0524 mol) as a solid in one portion. The white suspension was stirred for 20 min at 0 °C, and *N*-phenyltrifluoromethanesulfonimide (18.7 g, 0.0524 mol) was added as a solid in one portion. The suspension that formed was refluxed for 2 h, cooled, filtered, and rinsed with ether to give the potassium salt of **9** (13.8 g, 0.0382 mol, 73% yield) as a white solid. To obtain the free acid, the potassium salt (8.00 g, 22.2 mmol) was suspended in CH$_2$Cl$_2$ (150 mL), concentrated HCl (10 mL) was added in one portion, and the mixture was stirred for 18 h. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (100 mL). The combined organic extracts were dried, concentrated under reduced pressure, and recrystallized from EtOH to give 7.1 g (99%) of **9** as a white solid: mp 118–120 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.0 (d, 2 ArH), 7.65 (d, 2 ArH), 4.95 (s, 2 CH$_2$). Anal. (C$_8$H$_6$ClF$_3$O$_4$S$_2$) C, H.

(Phenylsulfonyl)[(trifluoromethyl)sulfonyl]methane (2) (Scheme 1b). To a solution of potassium triflinate (1.0 g, 0.0058 mol) in 6 mL of CH$_3$CN was added chloromethyl phenyl sulfide (0.77 g, 0.0048 mol) in one portion, and the reaction mixture was refluxed for 18 h. The reaction mixture was poured into 20 mL of H_2O and extracted with 20 mL of CH$_2$-Cl$_2$. The CH$_2$Cl$_2$ was evaporated to give a dark oil, which was dissolved in 5 mL of acetic acid; 3 mL of H_2O_2 (30%) was added dropwise over 10 min, and the solution was then heated to 75 °C for 1 h. The mixture was poured into 20 mL of H_2O and the solid collected, washed with H_2O, dried, and recrystallized from hexane to give 0.52 g (38%) of **2** as a white solid: mp 71–73 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 7.4–8.1 (m, 5 ArH), 4.9 (s, 2 CH$_2$). Anal. (C$_8$H$_7$F$_3$O$_4$S$_2$) C, H.

1-[[4-(Trifluoromethoxy)phenyl]sulfonyl]-1-[(trifluoromethyl)sulfonyl]ethene (42) (Scheme 2). A mixture of **1** (1.0 g, 0.0027 mol) and K$_2$CO$_3$ (0.45 g, 0.0033 mol) was stirred in 50 mL of H_2O for 10 min; then 6 mL of formaldehyde (37% solution in H_2O) was added dropwise. The reaction mixture was stirred overnight and filtered, the filtrate acidified, and a gummy solid collected. This material was dissolved in CH$_2$-Cl$_2$, dried over MgSO$_4$, evaporated to dryness, and purified on silica gel using EtOAc as eluent. The product obtained was recrystallized from benzene to afford 0.50 g (49%) of **42** as a white solid: mp 154–156 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.1 (d, 2 ArH), 7.7 (s, 1 H), 7.4 (d, 2 ArH), 7.2 (s, 1 H); FDMS *m/z* 384 Anal. (C$_{10}$H$_6$F$_6$O$_5$S$_2$) C, H: calcd, 31.25; found, 30.53.

1-[(4-Fluorophenyl)thio]-2-[[4-(trifluoromethoxy)-phenyl]sulfonyl]-2-[(trifluoromethyl)sulfonyl]ethane (35). To a solution of **42** (0.500 g, 0.0013 mol) in 25 mL of CH$_2$Cl$_2$ was added dropwise 4-fluorobenzenethiol (0.20 g, 0.0017 mol) in 5 mL of CH$_2$Cl$_2$. The reaction mixture was stirred for 18 h, the solvent evaporated, and the crude oil purified on silica gel using 20% EtOAc in hexane as the eluent. The purest fractions were combined, stirred in hexane/ether (90/10), and filtered to give 0.415 g (62%) of **35** as a white solid: mp 76–

77; ^{1}H NMR (CHCl$_3$-d_1) δ 8.0 (d, 2 ArH), 7.3–7.5 (m, 4 ArH), 7.1 (d, 2 ArH), 4.6 (t, 1H), 3.6–3.8 (m, 2 CH$_2$). Anal. (C$_{16}$H$_{11}$F$_7$O$_5$S$_3$) C, H.

1-[[4-(Trifluoromethoxy)phenyl]sulfonyl]-1-[(trifluoromethyl)sulfonyl]ethane (28). To a solution of **42** (5.7 g, 0.015 mol) in 150 mL of EtOH was added sodium borohydride (1.18 g, 0.031 mol) in three portions. The temperature rose to 35 °C spontaneously, and stirring continued for 4 h. An additional amount of sodium borohydride was added (200 mg), and the reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered, poured into 150 mL of H_2O, and acidified and the solid collected. This material was then purified on silical gel using CH$_2$Cl$_2$ as eluent to give 2.4 g (42%) of **28** as a white solid: mp 81–82 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.1 (d, 2 ArH), 7.5 (d, 2 ArH), 4.7 (q, 1H), 1.9 (d, 3 CH$_3$). Anal. (C$_{10}$H$_8$F$_6$O$_5$S$_2$) C, H.

[[4-(Trifluoromethoxy)phenyl]sulfonyl][(trifluoromethyl)sulfonyl]dichloromethane (41). To a stirred solution of **1** in 90 mL of acetic acid was added dropwise slowly at room temperature 20 mL of SO$_2$Cl$_2$ in 5 mL of acetic acid. The reaction mixture was stirred for 1 h and heated to 70 °C for 12 h. The mixture was poured into 250 mL of H_2O, and the resulting precipitate was collected and recrystallized from EtOH to give 3.1 g (88%) of **41** as a white solid: mp 103–104 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.2 (d, 2 ArH), 7.5 (d, 2 ArH). Anal. (C$_9$H$_4$Cl$_2$F$_6$O$_5$S$_2$) C, H.

[(4-Chlorophenyl)sulfonyl][(trifluoromethyl)sulfonyl]-fluoromethane (27). The potassium salt of **9** (0.107 g, 0.003 mol) was dissolved in acetonitrile (5 mL), and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.120 g, 0.0040 mol) was added as a solid in one portion. The mixture was stirred for 3 h and concentrated under reduced pressure. The residue was taken up in ether (50 mL) and washed with water (2 × 25 mL). The evaporated crude material was subjected to column chromatography on silica gel using CH$_2$Cl$_2$ and EtOAc as eluents to give 0.050 g (50%) of **27** as a white solid: mp 45–47 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.9–8.5 (m, 4H). Anal. (C$_8$H$_5$ClF$_4$O$_4$S$_2$) C, H.

1-[(4-Chlorophenyl)sulfonyl]-1-[(trifluoromethyl)sulfonyl]propane (32). Part A. To the potassium salt of **9** (0.25 g, 0.0007 mol) in 12 mL of H_2O was added 0.25 mL of 37% formaldehyde, and the mixture stirred for 30 min. The reaction mixture was acidified to pH 2, extracted with CH$_2$-Cl$_2$, dried, and evaporated. This material was chromatographed with ether to give 0.11 g of yellow oil which was used for part B.

Part B. The vinyl compound (0.11 g, 0.328 mmol) was dissolved in 10 mL of diethyl ether, and to this was added slowly dropwise (under N$_2$) 0.312 mL of 3.0 M methylmagnesium bromide. After 3 h, the reaction mixture was acidified and the ether layer was evaporated to a sticky yellow solid. This material was chromatographed with CH$_2$Cl$_2$ as eluent to give 0.067 g (59%) of **32** as a white solid: mp 72–74 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 7.95 (d, 2 ArH), 7.60 (d, 2 ArH), 4.44 (t, 1H), 2.38 (m, 2H), 1.34 (t, 3H). Anal. (C$_{10}$H$_{10}$ClF$_3$O$_4$S$_2$) C, H.

[(3,4-Dichlorophenyl)thio][(trifluoromethyl)thio]-methane (43). This compound was prepared by the general procedure of Scheme 1 using 3,4-dichlorobenzenethiol (2.0 g, 0.011 mol), sodium methoxide (0.64 g, 0.011 mol), and chloromethyl trifluoromethyl sulfide (2.0 g, 0.013 mol). The product was purified by chromatography on silica gel using hexane as the eluent to give 2.6 g (81%) of **43** as a clear oil: ^{1}H NMR (CHCl$_3$-d_1) δ 7.6 (s, 1 ArH), 7.45 (d, 1 ArH), 7.3 (d, 1 ArH), 4.3 (s, 2 CH$_2$). Anal. (C$_8$H$_5$Cl$_2$F$_3$S$_2$) C, H.

[(3,4-Dichlorophenyl)sulfonyl][(trifluoromethyl)thio]-methane (44). To a stirred solution of 3,4-dichlorophenyl bis-(sulfide) **(43)** (7.0 g, 0.024 mol) in 150 mL of acetic acid was added slowly dropwise 30% H_2O_2 (8.1 g, 0.071 mol), keeping the temperature below 30 °C. The solution was then stirred for 2 h and heated to 65 °C for 2 h. The reaction mixture was poured into H_2O and filtered, and the resulting solid was recrystallized from EtOH/H_2O to give 5.0 g (65%) of **44** as a white solid: mp 91–94 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.1 (s, 1 ArH), 7.8 (d, 2 ArH), 4.3 (s, 2H). Anal. (C$_8$H$_5$Cl$_2$F$_3$O$_2$S$_2$) C, H.

1-[(3,4-Dichlorophenyl)sulfonyl]-1-[(trifluoromethyl)-sulfonyl]-2-[4-(trifluoromethyl)phenyl]ethane (34). To a stirred solution of **44** (1.2 g, 0.0037 mol) in 50 mL of DMF was added slowly 60% NaH (0.160 g, 0.0040 mol) under N_2, and the mixture stirred for 30 min. Then *p*-(trifluoromethyl)-benzyl bromide (1.2 g, 0.0050 mol) was added dropwise, and the mixture stirred for 24 h. The reaction mixture was poured into 50 mL of H_2O and the gummy solid collected and dried. The product was slurried in hexane to obtain 0.64 g (36%) of light-yellow solid. This solid was dissolved in 20 mL of TFA, and 1.4 mL of 30% H_2O_2 was added slowly. The reaction mixture was stirred 1 h and heated to 70 °C for 3 h. The reaction mixture was poured into H_2O and the solid collected. The product was slurried in hexane to afford 0.390 g (57%) of **34** as a light-brown solid: mp 92 °C dec; ^{1}H NMR (CHCl$_3$-d_1) δ 7.95 (s, 1 ArH), 7.6–7.8 (m, 5 ArH), 7.4 (d, 1 ArH), 4.85 (t, 1H), 3.7 (m, 2H). Anal. ($C_{16}H_{10}Cl_2F_6O_4S_2$) C, H.

[(4-Hydroxyphenyl)sulfonyl][(trifluoromethyl)sulfonyl]-methane (25). To a stirred solution of **7** (5.0 g, 0.016 mol) in 200 mL of DMSO was added dropwise KOH (5.0 g, 0.089 mol) in 5 mL of H_2O. The reaction mixture was heated to 130 °C for 8 h and then stirred overnight at room temperature. The reaction mixture was cooled, a small amount of H_2O (20 mL) added, the mixture acidified, and the solid filtered. Recrystallization from benzene afforded 3.5 g (70%) of **25** as a white solid: mp 99–101 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 7.8 (d, 2 ArH), 7.0 (d, 2 ArH), 4.8 (s, 2 CH$_2$). Anal. ($C_8H_7F_3O_5S_2$) C, H.

[[4-(Tetrafluoroethoxy)phenyl]sulfonyl][(trifluoro-methyl)sulfonyl]methane (23). To a solution of 60% NaH (0.20 g, 0.005 mol) in 20 mL of DMF was added **25** (0.50 g, 0.0016 mol) portionwise. The mixture was stirred for 15 min, and then tetrafluoroethylene gas was bubbled slowly into the reaction mixture for 10 min. Stirring continued for 18 h. The reaction mixture was poured into 50 mL of H_2O and acidified, and the solid was collected. Slurring in hexane gave 0.45 g (68%) of **23** as a white solid: mp 122–123 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.1 (d, 2 ArH), 7.5 (d, 2 ArH), 6.0 (m, 1 CF$_2$H), 4.85 (s, 2 CH$_2$). Anal. ($C_{10}H_7F_7O_5S_2$) C, H.

[[4-(Trifluoromethoxy)phenyl]sulfonyl][(perfluoro-butyl)sulfonyl]methane (40). To 4-(trifluoromethoxy)phen-yl methyl sulfone (0.50 g, 0.0021 mol) in 10 mL of THF under N_2 was added dropwise at room temperature 0.5 M potassium bis(trimethylsilyl)amide in toluene (4.4 mL, 0.0021 mol). The solution was stirred for 30 min, and then perfluorobutane-sulfonyl fluoride (0.76 g, 0.0025 mol) in 2 mL of CH$_2$Cl$_2$ was added slowly. The solution darkened immediately, and stir-ring continued for 18 h. The mixture was poured into 30 mL of H_2O, acidified to pH 1, and extracted into EtOAc. The EtOAc layer was washed, dried, and evaporated to give a solid which was decolorized and recrystallized from iPrOH to give 0.40 g (36%) of **40** as a light-brown solid: mp 120–121 °C; ^{1}H NMR (CHCl$_3$-d_1) δ 8.15 (d, 2 ArH), 7.5 (d, 2 ArH), 4.85 (s, 2 CH$_2$). Anal. ($C_{12}H_6F_{12}O_5S_2$) C, H.

(Methylthio)methyl 4-Chlorophenyl Sulfone (45). (Methylthio)methyl 4-chlorophenyl sulfone was prepared ac-cording to the procedure of Ogura (Ogura et al. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3543). Methyl sulfoxide (9.25 g, 0.118 mol) and acetic anhydride (15.6 g, 0.153 mol) were heated at 80 °C for 24 h and cooled. Acetic acid (90 mL), sodium acetate (9.70 g, 0.118 mol), and sodium 4-chlorobenzenesulfinate (21.8 g, 0.110 mol) were sequentially added, and the mixture was heated at 100–120 °C for 24 h. The cooled mixture was concentrated under reduced pressure, and brine (150 mL) was added. The mixture was extracted with CH$_2$Cl$_2$ (5 × 75 mL), and the CH$_2$Cl$_2$ layers were concentrated under reduced pressure to give 27.8 g of an off-white crystalline solid. The crystals were suspended in ether (100 mL) and filtered to give 16.2 g (62%) of **45** as a white solid: mp 91.5–94.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (d, 2 ArH, J = 9 Hz), 7.76 (d, 2 ArH, J = 9 Hz), 4.52 (2H, s), 2.21(3H, s). Anal. ($C_8H_9ClO_2S_2$) C, H.

1-[(4-Chlorophenyl)sulfonyl]-1-[(trifluoromethyl)sul-fonyl](methylthio)methane (31). Compound **45** (0.50 g, 0.00211 mol) was dissolved in THF (10 mL) and cooled to 0 °C. Potassium bis(trimethylsilyl)amide (8.90 mL of 0.5 M

solution in toluene, 0.004 45 mol) was dropwise added via syringe. After 2 h at 0 °C, *N*-phenyltrifluoromethanesulfon-imide (0.755 g, 0.00211 mol) was added as a solid in one portion. After an additional 45 min the mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue extracted from water (50 mL) with CH$_2$Cl$_2$ (2 × 25 mL). The aqueous layer was acidified to pH 1 and extracted with CH$_2$Cl$_2$ (3 × 25 mL). The evaporated crude material was subjected to column chromatography on silica gel using CH$_2$Cl$_2$ and EtOAc as eluents to give 0.306 g (39%) of **31** as a hygroscopic pale-yellow oil which solidified on standing: mp 142 °C dec; ^{1}H NMR (acetone-d_6) δ 7.94 (d, 2 ArH, J = 9 Hz), 7.50 (d, 2 ArH, J = 9 Hz), 2.94 (s, 3H). Anal. ($C_9H_8ClF_3O_4S_3$) C, H.

Nematode Infection in Gerbils. Female, Mongolian gerbils (35 g) (*Meriones unguiculatus*) were continuously fed rodent meal containing 2% hydrocortisone for the entire 3-week experimental period. After a 1-week conditioning period necessary to obtain a nematode infection in a foreign host, the gerbils were infected with approximately 1000 exsheathed, *H. contortus* larvae. On day 9 postinfection, three gerbils were sacrificed to determine the presence of an adequate infection. Following verification of the presence of an infection, three gerbils per treatment were orally gavaged with each compound at 25 or 50 mg/kg. Compounds were dissolved in either DMSO or water. Three gerbils each were either treated with levamisole at 10 mg/kg or left untreated to serve as a positive or negative control. Thirteen days postinfection, the gerbils were sacrificed and the stomachs removed. The stomachs were opened longitudinally and the stomach and the stomach contents placed in a 50-mL conical tube with saline and vortexed. The contents contained in the 50-mL conical tube were then incubated at 35 °C for at least 1 h. Following incubation, iodine was added to the tubes to stain the contents and the number of worms per gerbil determined. Efficacy was determined by comparing the aver-age number of worms per treatment to the infected, nonmedi-cated controls and to the levamisole controls.

Experimentally Induced Nematode Infections in Sheep. Cross-bred ewes and wethers, approximately 3–6 months of age and 20–30 kg, were orally challenged (day 0) with approximately 6000 susceptible third stage larvae of either *H. contortus* or *T. colubriformis* in order to produce monospecific nematode infections. On the basis of total baseline fecal egg counts conducted on days 26–28 postinocu-lation, the lambs were randomly allocated to treatment groups and placed in individual metabolism crates. The experimental compounds were dissolved in PEG 200 and administered via intraruminal injection. Fecal samples were collected daily and eggs per gram (EPG) determined for each animal. The percent reduction in egg burden from control and from initial baseline egg counts was calculated. When eggs counts were reduced significantly, the sheep were necropsied and total worm counts (TWC) for *H. contortus* or *T. colubriformis* were calculated. The percent reduction in worm burden from controls was then calculated as:

$$\frac{\text{TWC(control)} - \text{TWC(treated)}}{\text{TWC(control)}} \times 100$$

Adult Stable Fly Screen. Dental wicks were saturated with serum containing titrated levels of experimental com-pounds starting at 100 ppm. The dental wicks were placed in Petri dishes along with 10 adult stable flies (*S. calcitrans*) previously chilled for easier handling. Percent mortality was determined after 24- and 48-h incubation at approximately 25 °C and 75–85% humidity when compared to a dish containing a wick with control serum only. When determining the insecticidal activity of compounds after treating sheep, whole blood drawn from sheep dosed with experimental compounds was allowed to separate for approximately 24 h. Dental wicks were soaked in the resulting serum and placed in Petri dishes with the adult stable flies. Percent mortality was determined after 24 or 48 h in comparison to a serum-only control.

Larval Blow Fly Procedure. Dental wicks saturated with bovine serum (collected from whole blood obtained at a local abattoir) and titrated levels of experimental compounds (starting at 100 ppm) were placed individually in test tubes. Several hundred larval blow fly (*Phormia regina*) were placed in each test tube, and a cotton ball was placed in the top to prevent them from crawling out of the tube. The tubes were incubated for up to 48 h at approximately 25 °C and 75−85% humidity. Efficacy was determined by visual inspection of each tube for larvae movement, and the data are reported as percent mortality as compared to a serum-only control.

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