Discovery of Novel *p*-Arylthio Cinnamides as Antagonists of Leukocyte Function-Associated Antigen-1/Intercellular Adhesion Molecule-1 Interaction. 4. Structure−Activity Relationship of Substituents on the Benzene Ring of the Cinnamide

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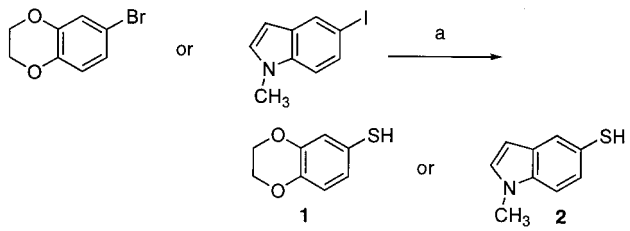
We have shown that *p*-arylthio cinnamides can inhibit the interaction of LFA-1 and ICAM-1, which is involved in cell adhesion and the inflammatory process. We now show that 2,3-disubstitution on the aryl portion of the cinnamide results in enhanced activity over mono substitution on the ring. The best 2,3-substituents were chlorine and trifluoromethyl groups. Compounds **39** and **40** which contain two CF_3 groups have IC_{50} values of 0.5 and 0.1 nM, respectively, in inhibiting JY8 cells expressing LFA-1 on their surface, from adhering to ICAM-1. The structure−activity relationship (SAR) was examined using an NMR based model of the LFA-1 I domain/compound **31** complex. One of our compounds (**38**) was able to reduce cell migration in two different in vivo experiments.

Introduction

Inflammation results from a cascade of events that ultimately leads to leukocyte migration to affected tissues. Early stages of this process involve leukocytes rolling, firmly adhering to, and subsequently crossing the vascular endothelium. The process of attaching to the vessel wall is mediated through interactions of leukocyte integrins including LFA-1 (lymphocyte function-associated antigen-1, CD11a/CD18, $\alpha_L\beta_2$) with counter-receptors on the endothelial cells. LFA-1 interacts with the immunoglobulin superfamily member intercellular adhesion molecule-1 (ICAM-1) on activated endothelium. The arrested leukocytes then transmigrate the vascular wall and move toward the lesion along a chemotactic gradient. The adhesive interaction between LFA-1 and ICAM-1 is thought to play a critical role in the inflammatory process, and a drug that would disrupt this event might be of use in the treatment of inflammatory diseases, autoimmune diseases, tumor metastasis, and reperfusion injury. We have discovered that appropriately substituted cinnamides block the interaction of LFA-1 and ICAM-1.[1−3]

Paper 1[1] of this series described the synthesis and activity of novel diarylsulfides including **22**, **30,** and **31**, while paper 2[2] of this series describes optimization studies leading to compound **24**. These compounds were moderately potent in inhibiting the interaction of LFA-1 and ICAM-1 with IC_{50}'s in the range of 30−1000 nM. Paper 2 also describes an NOE-based NMR model of the LFA-1 I domain and compound **31**. We hereby report the further exploration of the SAR of substituents on the aryl portion of the cinnamides and report a modification which provides a dramatic improvement in potency. The affinity of our compounds can be understood in terms of an NMR-based model of the LFA I domain and compound **31**. We also selected one compound (**38**) and performed in vivo experiments to show that this compound indeed slows cell migration into an area of inflammation.

Scheme 1. Synthesis of Thiols[a]



[a] Reagents: (a) 1. iPr_3Si-SH, KH, $(PPh_3)_4Pd$, THF, 2. CsF.

Chemistry

The cinnamic acids sulfides, which are key intermediates in our work, were synthesized by three different methods. In Scheme 2 the appropriate sufide aldehydes **4** were made by reacting a benzaldehyde with a fluoro or triflate in the 4 position, with a substituted benzenethiol. The resulting aldehydes were then converted to cinnamic acids by treatment with malonic acid. Alternatively, an aryl iodide such as **14** was reacted with methyl acrylate in a Heck reaction (Scheme 4). In another route to preparing the desired compounds, the 4-chloro-3-nitrocinnamide **11** and 2,4-difluorocinnamide **12** were treated with a substituted benzenethiol to give cinnamides **29**−**31** and **49** (Scheme 4), which were subsequently hydrolyzed. The cinnamic acids were coupled with amines under standard amide forming conditions to provide the desired analogues.

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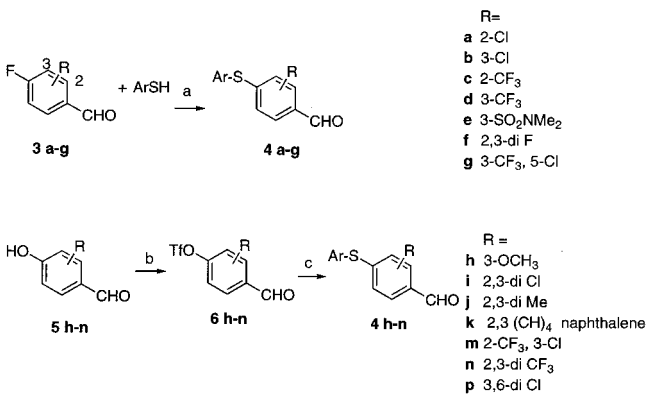
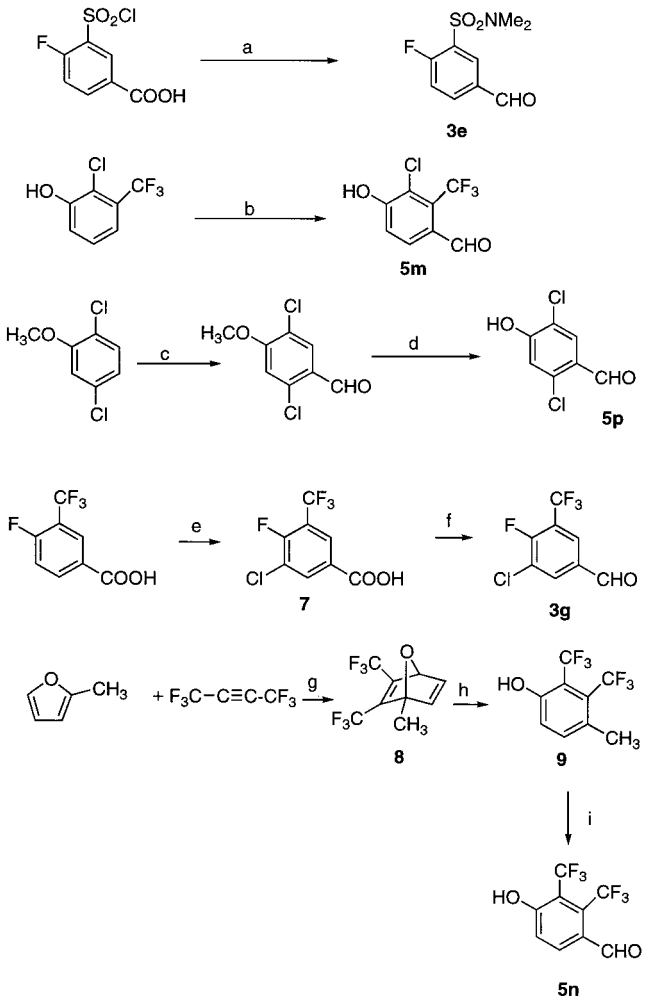
Scheme 2. Synthesis of Sulfides[a]



[a] Reagents: (a) K_2CO_3, DMF, 60 °C; (b) Tf_2O, pyridine; (c) iPr_2NEt, CH_3CN.

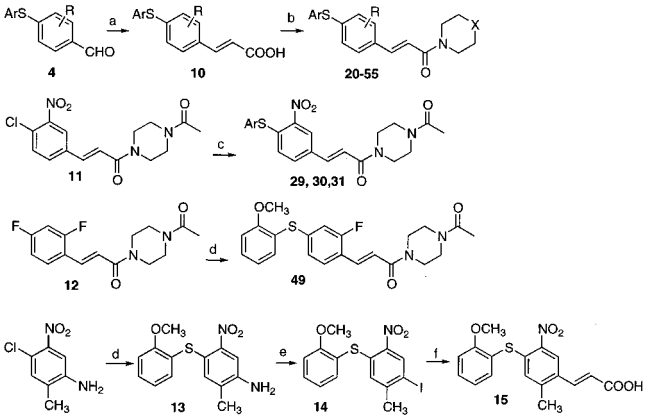
Scheme 3. Synthesis of Aldehydes[a]



[a] Reagents: (a) 1. Me_2NH, 2. BH_3 THF, 3. MnO_2; (b) $CHCl_3$, $Ca(OH)_2$; (c) Cl_2CHOMe, $TiCl_4$; (d) BBr_3; (e) sec-Bu Li, TMEDA, Cl_3CCCl_3; (f) 1. BH_3 THF, 2. MnO_2; (g) 120 °C, 15 h; (h) BF_3 Et_2O, 25 °C, 16 h; (i) 1. Br-C_6H_4-SO_2Cl, iPr_2NEt, 2. NBS, $(PhCO)_2O_2$, CCl_4, reflux, 13 h., 3. Me_3N-O, DMSO, 25 °C, 2 h.

The thiols we used were commercially available except for the benzodioxane (**1**) and indole (**2**). They were prepared from the appropriate aryl bromide by reacting with *i*-Pr_3Si-SH, K salt with Pd(0) catalyst and removing the *i*-Pr_3Si with CsF[4] (Scheme 1). The thiols were reacted with 4-fluorobenzaldehydes (Scheme 2) to give the sulfide aldehydes (**4**) which were reacted with malonic acid to give cinnamic acids and then coupled with the appropriate amine to give the target compounds.

Scheme 4. Synthesis of Cinnamides[a]



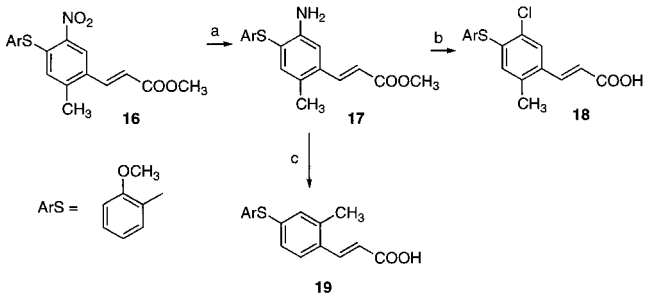
[a] Reagents: (a) malonic acid, pyridine, cat. piperidine, 110 °C; (b) 1. $(COCl)_2$, 2. amine, iPr_2NEt; (c) ArSH, K_2CO_3, DMF, 25 °C; (d) 2-methoxy-thiophenol, Cs_2CO_3; (e) 1. tBu-ONO, H_2SO_4, CH_3CN, 2. Kl, urea, 94%; (f) 1. methyl acrylate, $Pd(OAc)_2$, Et_3N 82%, 2. NaOH, EtOH.

All the 4-fluorobenzaldehydes were commercially available except **3e** and **3g** (Scheme 3). 4-Fluoro-3-chlorosulfonyl benzoic acid was reacted with dimethylamine to give the sulfonamide. The carboxylic acid was then reduced to the benzyl alcohol with borane and this was oxidized to 4-fluoro-3-dimethylaminosulfonyl benzaldehyde (**3e**).

We wished to make the 4-fluoro-2-chloro-3-triflouromethyl benzaldehyde starting with 3-trifluoromethyl-4-fluorobenzoic acid. Bennetau[5] had converted 3-chloro-4-fluorobenzoic acid to 2,3-dichloro-4-fluorobenzoic acid by dilithiating the acid with *sec*-butyllithium in the presence of TMEDA and then treating with hexachloroethane. We did this with 3-trifluoromethyl-4-fluorobenzoic acid. The resulting acid was converted to the aldehyde by reaction with borane followed by MnO_2 oxidation. Examination of the NMR spectrum of the aldehyde showed that the chlorination had taken place *ortho* to the fluorine to give 3-trifluoromethyl-4-fluoro-5-chlorobenzaldehyde (**3g**). The NMR spectrum of 3-trifluoromethyl-4-fluorobenzaldehyde (from Aldrich) has a double doublet ($J = 9$ Hz, $J = 9$ Hz) at 7.40 ppm for the 5 proton (ortho to the fluorine), a double doublet ($J = 9$ Hz, $J = 2$ Hz) at 8.18 ppm for the 2 proton, and a multiplet of 6 peaks at 8.13 ppm for the 6 proton. Our aldehyde has no peak at 7.40 ppm which shows that there is no proton in position 5. There are two double doublets ($J = 8$ Hz, $J = 2$ Hz) at 8.05 and 8.15 ppm for the 2 and 6 protons.

The triflates were synthesized from 4-hydroxybenzaldehydes (**5h**−**p**). The 2,3-dichloro (**5i**),[6] 2-trifluoromethyl-3-chloro (**4m**), and 2,3-dimethyl (**5j**)[7] benzaldehyes were made from the corresponding phenols by the Reimer-Tiemann reaction. 1-Naphthol gave **5k** by reaction[8] with dichloromethyl methyl ether. 2,5-Dichloroanisole and dichloromethyl methyl ether gave 2,5-dichloro-4-methoxybenzaldehyde, which was demethylated to the known **5p.**[9] 4-Methyl-2,3-di-(trifluoromethy)-phenol[10] was synthesized from 2-methyl furan and hexafluoro butyne as shown in Scheme 3. The methyl

Scheme 5. Interconversion of Cinnamides[a]



[a] Reagents: (a) Fe, NH_4Cl, EtOH, H_2O 97%; (b) 1. tBuONO, HBF_4, CH_3CN, 2. CuCl, $CuCl_2$ 68%; (c) 1. tBuONO, H_2SO_4, CH_3CN, 2. H_3PO_2 50%.

group was brominated with NBS and the resulting bromide oxidized to the aldehyde **5n** with Me_3N-O.[11]

2-Methyl-4-chloro-5-nitroaniline was a common starting material for the synthesis of the 3-NO_2-6-CH_3, (**53**), 3,6-di-Cl (**51**), and 2-CH_3 (**46**) cinnamides. It was reacted with 2-methoxybenzenethiol to give **13** (Scheme 4). The aniline was transformed to the iodo compound **14**, and this was reacted with methyl acrylate via a Heck reaction to get the cinnamic acid **15** and ester **16**. The nitro group in **16** was reduced to an amino (**17**) which was transformed to a chloro (**18**) and was also removed to give **19** (Scheme 5).

Structure−Activity Relationships

Two experiments were used to measure the activity of these compounds. In the biochemical interaction experiment, the wells are coated with LFA-1, and ICAM-1 is in solution. An active compound will block the ICAM-1 from binding to the LFA-1. In the cell adhesion assay, the ICAM-1 coats the wells and the JY8 cells expressing LFA-1 on their surface are added to the wells. An active compound prevents the cells from sticking to the wells.

Three compounds (**22**, **30**, and **31**) in Table 1 were described in our first paper. Compound **22** has a 3-chloro on the cinnamide (ring B), a 2,4-dichlorophenyl sulfide (ring A), and an *N*-acetyl piperazine amide. Compounds **30** and **31** have a 3-nitro on ring B with a 2,3-dichloro or 2-isopropyl on ring A and are also *N*-acetyl piperidine amides. These had moderate activity in both assays. Compound **24**, described in our second paper, in which ring A is a benzodioxane has better activity in the biochemical assay but showed no improvement in the cell adhesion assay. We also used the morpholine and the 4-carboxypiperidine amides in our series. Examination of Table 1 (compare **24**−**25**, **26**−**27**, **34**−**35**, and **42**−**43**) shows that interchanging these amides has little effect on the activity of these compounds. This is consistent with the results of our third paper.[3] A more dramatic SAR was seen when we varied the substituents on ring B.

Compounds with only hydrogens on ring B (**20** and **21**) were only weakly active. A 3-CF_3 on ring B (**26**−**28**) showed some improvement over chloro and nitro. Incorporating a sulfonamide in position 3 (**56**) greatly reduced activity. This was surprising since a sulfonamide is also an electron withdrawing group. The compounds with the electron donating 3-CH_3O (**32**) or the electronegative but electron donating 2-F (**49**) have very little activity.

An additional boost in potency of 7- to 20-fold came from adding a second chlorine to position 2 (**35**−**38**). The substitution on the A ring did not seem to make much of a difference. The 2,3-di-CF_3 compounds (**39**−**41**) were equally potent to the 2,3-dichloro compounds in the biochemical assay but gave another big boost in the cell adhesion assay when the A ring was 2′-methoxyphenyl (compare **35** to **40**) or a benzodioxane (compare **39** and **37**), but no boost when the A ring was a methylindole (compare **41** and **38**). Compound **40** was the most active compound in the cell adhesion assay with an IC_{50} of 0.1 nM. The 2-CF_3, 3-Cl compounds (**42**−**44**) were equipotent to the 2,3-dichloro compounds. We could not make the 2-Cl, 3-CF_3 compounds.

The 2,3 dimethyl compound **45** was 9 times less active than the corresponding 2,3-dichloro compound **34**. The 2,3-difluoro compound **48** was 12 times less active than the corresponding 2,3-dichloro compound **36**. The naphthalene compound **47** is 42 times less active than the corresponding 2,3-dichloro compound **37**. These last three comparisons show that the 2,3-substituents have to be electron withdrawing. The compounds with one chlorine, one CF_3, or one methyl in the 2 position rather than the 3 position (compounds **55**, **54**, and **46**) gave weak to inactive compounds, though no exact comparisons are available.

A dramatic effect occurs when a substituent was added to the other side of ring B. Compare the inactive 3-Cl-5-CF_3 compound **50** to the corresponding 3-Cl **(25)** and 3-CF_3 **(28)** compounds. Adding a second chlorine in the 6 position (**51**) or a methyl in the 6 position (**52**) gave inactive compounds. Adding a 6-methyl to a 3-nitro compound (**53**) also gave an inactive compound, although no exact comparisons are available.

NMR Model

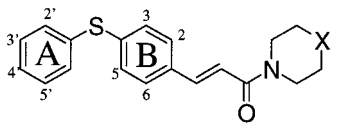
In an earlier paper[2] we reported an NOE based model of compound **31** with the LFA-1 I domain (Figure 1A). This model predicted a hydrophobic pocket next to the aryl portion of the cinnamides. The 2,3-dichloro compounds were synthesized (**35**, Figure 1C) and they were found to have higher affinity than **31**. The second chlorine fills the hydrophobic pocket in the model without altering the structure of the I domain. For instance, interactions of the 2-Cl with the side chain of I306 may account for the increase in potency relative to compound **31**.

Figure 1B shows a model of the inactive sulfonamide **56**. This inactivity was surprising since sulfonamide is also an electron withdrawing group. However, the loss of potency is explained by the modeling studies. The sulfonamide is larger than the nitro group of compound **31** or the chlorine group of **35**. As a result, the backbone of the C-terminal helix would have to move to accommodate the ligand compared to its position when bound to compound **31**. This indicates that compound **56** cannot fill the B ring pocket without changing the binding pocket or orientation of the ligand. This reorientation could explain the reduction in potency.

In Vivo Experiments

The demonstration that appropriately substituted cinnamides could block the interaction of LFA-1 and ICAM-1 in vitro suggested it would be worthwhile to

Table 1. Structure−Activity Relationships of Cinnamides in the Biochemical ICAM-1/LFA-1 Assay and in the ICAM-1/JY-8 Cell Adhesion Assay



cpd	A ring	B ring	X	biochemical IC_{50}, nM (*n*) (range)	cell adhesion IC_{50}, nM (*n*) (range)
20	2′,4′-di Cl	H	$NCOCH_3$	4300 (2) (3600−5100)	
21	2′,3′-di Cl	H	O	9100	
22	2′,4′-di Cl	3-Cl	$NCOCH_3$	140 (2) (100−200)	130 (7) (100−600)
23	2′-CH_3O	3-Cl	O	150 (2) (130−170)	40 (3) (6−100)
24	3′,4′-OCH_2CH_2O	3-Cl	$NCOCH_3$	40 (2) (30−60)	80 (3) (30−150)
25	3′,4′-OCH_2CH_2O	3-Cl	CH-COOH	145 (2) (140−150)	
26	3′,4′-OCH_2CH_2O	3-CF_3	O	30 (2) (30−30)	
27	3′,4′-OCH_2CH_2O	3-CF_3	$NCOCH_3$	55 (2) (50−60)	60 (3) (30−170)
28	3′,4′-OCH_2CH_2O	3-CF_3	CH-COOH	50 (2) (40−60)	
29	3′,4′-OCH_2CH_2O	3-NO_2	$NCOCH_3$	139 (2) (120−140)	
30	2′,3′-di Cl	3-NO_2	$NCOCH_3$	105 (2) (100−110)	100 (6) (30−300)
31	2′-$CHMe_2$	3-NO_2	$NCOCH_3$	44 (3) (30−60)	30 (3) (12−60)
32	2′-CH_3O	3-CH_3O	$NCOCH_3$	10700 (2) (10400−11300)	
33	3′,4′-OCH_2CH_2O	2,3-di Cl	$NCOCH_3$	7 (2) (6−9)	8 (2) (6−10)
34	2′-CH_3O	2,3-di Cl	O	10 (2) (6−13)	6 (1)
35	2′-CH_3O	2,3-di Cl	CH-COOH	8 (2) (6−12)	8 (3) (2−30)
36	2′-$CHMe_2$	2,3-di Cl	CH-COOH	10 (4) (6−19)	6 (8) (3−18)
37	3′,4′-OCH_2CH_2O	2,3-di Cl	CH-COOH	7 (2) (6−9)	6 (5) (2−9)
38	1-Me-5-indolyl	2,3-di Cl	CH-COOH	6 (3) (6−6)	4 (12) (1−10)
39	3′,4′-OCH_2CH_2O	2,3-di CF_3	CH-COOH	3 (4) (3−6)	0.5 (3) (0.08−1.0)
40	2′-CH_3O	2,3-di CF_3	CH-COOH	5 (2) (4−6)	0.1 (4) (0.03−0.5)
41	1-Me-5-indolyl	2,3-di CF_3	CH-COOH	5 (2) (5−5)	5 (3) (2−8)
42	2′-CH_3O	2-CF_3, 3-Cl	O	8 (3) (6−10)	5 (3) (3−10)
43	2′-CH_3O	2-CF_3, 3-Cl	CH-COOH	6 (3) (5−8)	4 (6) (2−9)
44	3,4′-OCH_2CH_2O	2-CF_3, 3-Cl	CH-COOH	5 (2) (4−7)	2 (2) (2−2)
45	2′-CH_3O	2,3-di CH_3	O	90 (2) (80−110)	
46	2′-CH_3O	2-CH_3	CH-COOH	>20000 (2)	
47	3′-4′-OCH_2CH_2O	1,4-naphthalene	CH-COOH	295 (2) (290−300)	
48	2′-$CHMe_2$	2,3-di F	CH-COOH	115 (2) (110−120)	
49	2′-CH_3O	2-F	$NCOCH_3$	3900 (3) (2500−11500)	
50	3′,4′-OCH_2CH_2O	3-Cl, 5-CF_3	CH-COOH	>20000 (2)	
51	2′-CH_3O	3,6-di Cl	CH-COOH	>20000 (2)	
52	2′-CH_3O	3-Cl, 6-CH_3	CH-COOH	>20000 (2)	
53	2′-CH_3O	3-NO_2, 6-CH_3	CH-COOH	>20000 (2)	
54	2′-CH_3O	2-CF_3	CH-COOH	265 (2) (260−270)	
55	2′-CH_3O	2-Cl	CH-COOH	1400 (2) (760−2620)	
56	2′-3′-di Cl	3-SO_2NMe_2	NCOCHe	3750 (2) (3700−3800)	

determine if an active compound could block in vivo cell trafficking.

Pharmacokinetic experiments showed that neutral compounds had very low plasma concentrations when administered orally to rats. This could be the result of their very low water solubility. The carboxylic acids had much greater water solubility and much improved pharmacokinetics[3]. The most dramatic case was with the carboxylic acid compound **38**. Its water solubility (at pH = 7.4) was >3000 μg/mL, and gave, in rats, an area under the curve (0−8 h, 5 mg/kg oral dose, $n = 3$) of 14. μg h/mL and an oral bioavailability of 60%. In contrast, the *N*-acetyl piperidine amide analogue (not in table) had a water solubility of 0.21 μg/mL, and an area under the curve (0−8 h, 5 mg/kg oral dose, $n = 3$) of <0.01 μg h/mL.

Compound **38** was tested in a murine model of allergen-induced pulmonary inflammation. ICAM-1 dependent eosinophil influx to the lung is a characteristic feature of this model.[13] As shown in Table 2, compared to the vehicle only control, compound **38** had a significant inhibitory effect on eosiniphilia in a dose dependent fashion at concentrations down to 1 mg/kg. Greater than 60% of eosinophil trafficking was inhibited at the 10 mg/kg concentration. Neutrophil trafficking was not affected because the neutrophil influx in the inhaled allergen model is not an ICAM-1 dependent event.[14] It is believed to be more of a VCAM dependent function. These results indicate that compound **38** is capable of inhibiting in vivo cell trafficking by blocking LFA-1/ICAM-1 interactions.

Compound **38** was also tested in a staphylococcus enterotoxin A (SEA)-induced neutrophil trafficking model in the rat. SEA stimulates macrophages to produce cytokines that are chemotactic for neutrophils.[15] In contrast to the inhaled allergen model, neutrophil influx is LFA-1/ICAM-1 dependent.[16] Results in Table 3 indicate that compound **38** can inhibit neutrophil migration in an apparent dose responsive manner with a significant inhibitory effect seen at the 100 mg/kg concentration. These results confirm that an inhibitor of LFA-1/ICAM-1 interactions can reduce the severity of an in vivo inflammatory reaction.

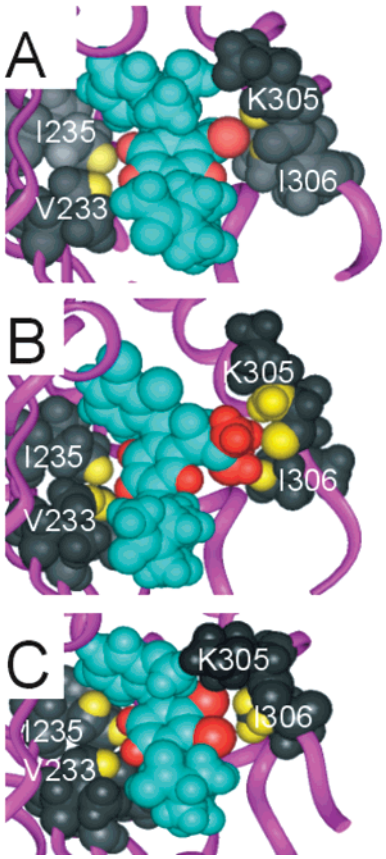


Figure 1. Interactions of *p*-arylthiocinnamide antagonists with the LFA domain. Highlighted in red are atoms on the B ring that interact with K305, I306, I235, and V233 whose selected side chain atoms are shown in yellow. (A) NOE based model of compound **31**.[2] (B) Model of compound **56** (see methods). (C) Model of compound **35** (see methods).

Table 2. Compound **38** Inhibits Allergen Induced Cell Influx in Mice

treatment	*N*	total cells (#/μL)	neutrophils (%)	eosinophils (%)
naive (− ctrl)	4	70 ± 10	2 ± 1	0 ± 0
vehicle (+ ctrl)	6	243 ± 25	31 ± 4	22 ± 1
38 (1 mpk)	7	291 ± 38	36 ± 3	14 ± 2[a]
38 (3 mpk)	7	147 ± 8[b]	31 ± 3	10 ± 2[b]
38 (10 mpk)	6	189 ± 26	30 ± 2	8 ± 2[b]

[a] Significantly different (p, 0.01 from positive control by 1-tail t-test. [b] Significantly different (p, 0.001) from positive control by 1-tail t-test.

Table 3. Compound **38** Inhibits SEA-Induced Neutrophil Trafficking in the Rat

treatment[a]	polymorphonuclear cells × 10^5
negative control (MC/PBS)	$2.87 \times 10^5 \pm 5.2 \times 10^4$ *b*
positive control (MC/SEA)	$10.46 \times 10^5 \pm 2.34 \times 10^5$ *b*
38 (50 mg/kg)	$7.48 \times 10^5 \pm 1.73 \times 10^5$ *b*
38 (100 mg/kg)	$4.88 \times 10^5 \pm 1.28 \times 10^5$ *b,c*

[a] Ten rats per treatment group. [b] Standard error. [c] $p < 0.052$.

Conclusion

4-Arylthio-cinnamides that contain a chlorine or a CF_3 in both the 2 and 3 positions are potent inhibitors of the interaction of LFA-1 and ICAM-1. The most potent compounds (**39** and **40**) contain two CF_3 groups and have IC_{50} values of 0.5 and 0.1 nM in inhibiting adhesion of cells expressing LFA-1 on their surface, to ICAM-1.

Experimental Section

General. Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. All reactions were performed under nitrogen atmosphere unless specifically noted. Flash chromatography was performed using silica gel (230−400 mesh) from E. M. Science. Proton NMR spectra were recorded on a General Electric QE300 instrument with Me_4Si as an internal standard and are reported as shift (multiplicity, coupling constants, proton counts). Mass spectral analyses were accomplished using different techniques, including desorption chemical ionization (DCI), atmospheric pressure chemical ionization (APCI), and electrospray ionization (ESI), as specified for individual compounds. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ, and are consistent with theoretical values to within 0.4% unless indicated. Preparative HPLC was performed on an automated Gilson HPLC system, using an YMC C-18 column, 75 × 30 mm i.d., S-5 μM, 120 Å, and a flow rate of 25 mL/min; λ = 214, 245 nm; mobile phase A, 0.05 M NH_4OAc or 0.1% TFA in H_2O, and mobile phase B, CH_3CN; linear gradient 20−100% of B in 20 min. The purified fractions were evaporated to dryness on a Savant SpeedVac.

See paper 1[1] for the ICAM-1/LFA-1 Biochemical Assay and ICAM-1/JY-8 Cell Adhesion Assay.

1-Methyl-5-iodoindole. To 75 g of 5-iodoindole (0.31 mol) in 750 mL of dry THF at −78 °C was added 14.85 g of NaH (60% in mineral oil, 0.37 mol). The suspension was stirred at −78 °C for 1 h, after which 28.8 mL of CH_3I (0.46 mol) was added. After the mixture was stirred at 25 °C for 16 h, ether was added, and the mixture was washed with NaCl and dried (Na_2SO_4), the ether was evaporated, and the solid was recrystallized from hexane to give 78.5 g of product (99% yield).

1-Methyl-*S*-triisopropylsilyl-5-indolethiol and 1-Methyl-5-indolethiol (2). KH (12.03 g 35%, in mineral oil, 0.105 mol) was washed with THF and then suspended in 75 mL of THF at 5 °C. Triisopropylsilylthiol (20.0 g, 0.105 mol) was added over 15 min with vigorous evolution of hydrogen gas. The mixture was stirred at 5 °C 1 h and then at 25 °C for 1 h. This solution was added to a solution of 24.5 g (1.91 mol) of 1-methyl-5-iodoindole and 2.2 g (1.91 mmol) of $(Ph_3P)_4Pd$ in 100 mL of THF. The yellow suspension was stirred 1 h at 70 °C. After cooling, ether was added, and the solution was washed with NaCl, dried (Na_2SO_4), and concentrated. The residue was chromatographed (silica gel, 3% EtOAc in hexane) to give 26.7 g (88%) of silylated compound. A solution of the thiol was made by treating a 10% solution of the silylated product in *N*-methyl pyrrolidinone (NMP) with 50% excess CsF.

1,4-Benzodioxane-6-thiol (1). 6-Bromo-1,4-benzodioxane was reacted with KS-Si(^{i}Pr)$_3$ and $(Ph_3P)_4Pd$ and then with CsF as described above to give a solution of **1**, which was used in the next step.

4-Fluoro-3-dimethylaminosulfonyl-benzoic Acid. 4-Fluoro-3-chlorosulfonyl-benzoic acid[12] (8.00 g), in 20 mL of THF was added to 60 mL of a cold 15% solution of dimethylamine in THF and stirred for 1 h at 25 °C. The THF was removed and the residue treated with water and HCl. The product was filtered, dissolved in $CHCl_3$, dried (Na_2SO_4), and concentrated. Ether and hexane were added to get 6.85 g of product, mp 205−207 °C.

4-Fluoro-3-dimethylaminosulfonylbenzyl Alcohol. The above-described acid (7.47 g, 30.24 mmol) was added in portions to 75 mL of 1 M BH_3 in THF with ice cooling. The resulting solution was stirred at 25 °C for 90 min. After cooling in ice, 10 mL of water was added slowly. The resulting solution was concentrated. The residue was dissolved in $CHCl_3$ and washed with dilute NaOH, dried (Na_2SO_4), and concentrated to give 6.89 g of product (98%).

4-Fluoro-3-dimethylaminosulfonylbenzaldehyde (3e). The above-described alcohol (7.00 g, 30.04 mmol) was dissolved in 140 mL of CH_2Cl_2 and stirred with 25 g of activated MnO_2 (Aldrich) for 16 h at 25 °C. The MnO_2 was filtered. The crude

product was chromatographed (SiO_2, 10% EtOAc, 90% CH_2Cl_2) to give 4.66 g (67% yield) of **3e**.

4-Hydroxy-2,3-dimethylbenzaldehyde (5j). 2,3-Dimethoxyphenol (15.0 g, 0.123 mol) was added to 44.83 g of Na_2CO_3 (0.423 mol) in 230 mL of water. $Ca(OH)_2$ (39.22 g, 0.530 mol) was added, and the mixture was stirred at 85 °C while $CHCl_3$ (29.37 g, 0.246 mol) was added slowly over a 30 min period. The mixture was heated for 2 h more at 85 °C. After cooling, EtOAc was added, and the mixture was acidified with HCl. The EtOAc was separated, dried ($MgSO_4$), and treated with charcoal. The solution was concentrated and the residue crystallized from ether to get 2.567 g; mp 160−171 °C, lit.[6] mp 171−172 °C; 14% yield.

3-Chloro-4-hydroxy-2-(trifluoromethyl)benzaldehyde (5m). $CHCl_3$ (6.7 g, 2.0 equiv) was added dropwise to a stirred mixture of $Ca(OH)_2$ (8.95 g, 120 mmol), K_2CO_3 (13.5 g, 98 mmol), 2-chloro-3-(trifluoromethyl)phenol (5.0 g, 22 mmol), and 50 mL of water at 65 °C over 2 h. The reaction mixture was cooled and acidified with concentrated HCl. The product was extracted into EtOAc and dried (Na_2SO_4). The crude product was purified by chromatography (silica gel, hexanes−EtOAc 3:2) to get 580 mg (10%) of product.

4-(4-Bromobenzenesulfonyloxy)-2,3-bis(trifluoromethyl)benzyl Bromide. 4-Methyl-2,3-bis(trifluoromethyl)phenol[9] (**9**) (10.0 g, 40 mmol) was treated with 4-bromobenzenesulfonyl chloride (11.0 g, 43 mmol) and *i*-Pr_2NEt (5.56 g, 43 mmol) in 100 mL of CH_2Cl_2 for 2 h. The solution was washed with NaCl and dried ($MgSO_4$). The solvent was evaporated and replaced by 100 mL of CCl_4. *N*-Bromosuccinimide (7.3 g, 40 mmol) and benzoyl peroxide (200 mg) were added, and the mixture was refluxed 13 h. After cooling, the solid was filtered and washed with CCl_4. The filtrate was concentrated to give the crude product, which was used in the next step.

4-Hydroxy-2,3-bis(trifluoromethyl)benzaldehyde (5n). The crude product described above was dissolved in 60 mL of DMSO and 20 mL of CH_2Cl_2. Trimethylamine *N*-oxide (12.0 g) was added, and the mixture was stirred at 25 °C for 2.5 h. The mixture was poured into 200 mL of cold NaCl solution and extracted with ether (3 × 100 mL). The ether was dried (Na_2SO_4) and concentrated. The product was purified by chromatography (SiO_2, hexanes−EtOAc 3:2) to get 3.00 g of **5n** and 4.0 g of recovered 4-(4-bromobenzenesulfonyloxy-2,3-bis(trifluoromethyl toluene.

4-(2-methoxyphenythio)-3-chlorobenzaldehyde (4b). 4-Fluoro-3-chlorobenzaldehyde (1.00 g, 6.31 mmol) and 2-methoxybenzenethiol (0.975 g, 6.95 mmol) were dissolved in 4 mL of DMF. Powdered K_2CO_3 (0.960 g, 6.96 mmol) was added in portions. The mixture was stirred at 25° for 15 min and at 55 °C for 1 h. After cooling, cold water, ether, and 0.5 mL of 50% NaOH were added. The ether phase was washed with dilute HCl, then NaCl, and dried (Na_2SO_4). The ether was evaporated, and hexane was added to get 1.471 g; mp 75−77 °C; 84% yield.

4-Methoxy-3,6-dichlorobenzaldehyde. 2,5-Dichloroanisole (3.54 g, 20 mmol) in 50 mL of CH_2Cl_2 was treated at 0 °C with 4.38 mL (40 mmol) of $TiCl_4$, followed by 2.30 g (20 mmol) of CH_3OCHCl_2 added slowly (30 min). After refluxing for 2 h, the mixture was cooled and poured onto HCl and ice. The product was dissolved in EtOAc , washed with water, aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). The solvent was removed to give 4.00 g (98% yield) of product.

4-Hyrdroxy-3,5-dichlorobenzaldehyde (5p). The above methoxybenzaldehyde was treated with 2 equiv of BBr_3 at 0 °C for 1 h, then cooled to −78 °C. Water was added to destroy the excess BBr_3. The CH_2Cl_2 solution was washed with NaCl solution, dried, and concentrated to give the title compound.

4-Fluoro-3-chloro-5-(trifluoromethyl)benzoic Acid (7). To a vigorously stirred solution of *s*-BuLi (20.34 mL of 1.3 M in cyclohexane) and TMEDA (4.0 mL, 3.04 mmol) cooled to −90 °C (liquid N_2, pentane/MeOH bath) was added 2.50 g (12.0 mmol) of 4-fluoro-3-(trifluoromethyl) benzoic acid in 80 mL of THF over a period of 30 min. After being stirred for 30 min at −90 °C, the solution was then treated with 11.4 g (48.0 mmol) of hexachloroethane in 100 mL of THF, and the reaction mixture was allowed to warm to 25 °C. Water was added slowly, and the solvents were evaporated. Water was added and the mixture extracted with ether. The aqueous solution was acidified with HCl and extracted with EtOAc, back washed with brine, dried (Na_2SO_4), and concentrated to give 2.2 g of crude product.

4-Fluoro-3-chloro-5-(trifluoromethyl)benzyl Alcohol. The above acid (1.4 g, 6.7 mmol) in 25 mL of THF was treated dropwise at 0 °C with 13.5 mL of 1 M BH_3 in THF. After being stirred at 25 °C for 2 h, the solution was treated with 3 N HCl at 0 °C. The mixture was extracted with EtOAc to get 1.30 g of crude benzyl alcohol used in the next step without purification.

4-Fluoro-3-chloro-5-(trifluoromethyl)benzaldehyde (3g). The above alcohol (200 mg) in 10 mL of CH_2Cl_2 was stirred overnight at room temperature with 750 mg of activated MnO_2. The MnO_2 was filtered, and the solution was concentrated. The residue was purified by chromatography (hexane: ethyl acetate 4:1). The fast moving fraction yielded 70 mg of desired product.

4-(1,4-Benzodioxane-6-thio)-3-chloro-5-(trifluoromethyl)benzaldehyde (4g). The fluoroaldehyde **3g** (70 mg, 0.31 mmol), 52 mg (0.31 mmol) of 1,4-benzodioxane-6-thiol (in solution), and 22 mg of K_2CO_3 were stirred in 3 mL of CH_3CN for 1 h at 25 °C. Water (10 mL) was added, and the mixture was extracted with ether. The ether was washed with dilute NaOH, water, and finally dilute HCl. The resulting solution was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2, hexanes−EtOAc 4:1) to get 110 mg (96%) of the desired product.

2-Methoxyphenyl 4-Amino-2-nitro-5-methylphenyl Sulfide (13). 2-Methoxybenzenethiol (4.2 mL, 34.4 mmol), 4-chloro-5-nitro-2-methylaniline (6.43 g, 34.4 mmol) and Cs_2CO_3 (22.8 g, 70.0 mmol) in 70 mL of DMF were stirred at 60 °C for 16 h. After cooling, water was added and the solid filtered to get 7.92 g (79%) of product.

2-Methoxyphenyl 4-Iodo-2-nitro-5-methylphenyl Sulfide (14). *tert*-Butyl nitrite (2.6 mL, 21.6 mmol) was added to a solution of 5.97 g (20.6 mmol) of **13** and 33 mL (1.6 equiv) of 3 N aqueous H_2SO_4 in 50 mL of CH_3CN, with ice cooling. After the mixture was stirred 1 h, a solution of KI (5.81 g, 35.0 mmol) and urea (0.247 g, 4.12 mmol) in 10 mL of water was added at 0 °C slowly. Gas evolution. After being stirred overnight, the mixture was filtered to give 7.43 g (90%) of product.

4-(2-Methoxyphenylthio)-2-methyl-5-nitrocinnamic Acid (15). A solution of 5.00 g (12.5 mmol) of **14**, methyl acrylate (3.4 mL, 37.5 mmol), Et_3N (5.2 mL, 37.5 mmol), and $Pd(OAc)_2$ (0.561 g, 2.5 mmol) was heated at 65 °C for 2 days in 100 mL of THF. The solvents were evaporated in a vacuum, and the residue was chromatographed without further treatment (SiO_2, hexane−EtOAc 1:1) to get 3.65 g (81%) of cinnamate ester. The cinnamate ester (400 mg, 1.11 mmol) in 4 mL of EtOH was hydrolyzed at room temperature with NaOH (1.5 mL of 2 M aqueous solution). After 24 h, the orange solution was acidified with 1 N HCl, and the resulting precipitate was filtered to give 360 mg (94%) of the title compound.

4-(2-Methoxyphenylthio)-3-chlorocinnamic Acid (10b). The benzaldehyde **4b** (Ar = 2-methoxyphenyl) (1.45 g, 5.22 mmol) and malonic acid (1.21 g, 11.63 mmol) in 4.2 mL of pyridine was treated with 90 mg of piperidine. The solution was heated in a 120 °C bath for 90 min. After cooling, dilute HCl was added. A goo resulted which crystallized upon adding 2 mL of ether. It was filtered and dried by dissolving in THF and treating with Na_2SO_4. The product was crystallized from heptane and ether (3:1) to get 1.452 g; mp 149−151 °C; 87% yield.

2-Methoxyphenyl 2-Chloro-4-[*E*-(1-morpholino-carbonyl)ethenyl)phenyl] Sulfide (23). The cinnamic acid described above (0.250 g) was refluxed with 2 mL of benzene and 1.5 mL of oxalyl chloride for 45 min. The solvents were evaporated and toluene added and evaporated three times to remove all of the excess oxalyl chloride. Morpholine (1 mL) was added to the resulting acid chloride in 2 mL of toluene

and the mixture stirred at 25° for 45 min. Toluene was added and the mixture washed with dilute HCl, water, and finally $KHCO_3$. After drying (Na_2SO_4) the solvent was evaporated and the residue crystallized from ether and hexane (1:2) to get 0.282 g; mp 162−164 °C; 93% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60−3.78 (m, 8H), 3.84 (s, 3H), 6.72 (d, J = 9 Hz, 1H), 6.78 (d, J = 16 Hz, 1H), 6.96−7.04 (m, 2H), 7.16 (dd, J = 9 Hz, 2 Hz, 1H), 7.40−7.46 (m, 2H), 7.55 (d, J = 2H, 1H), 7.58 (d, J = 16 Hz, 1H). Anal. ($C_{20}H_{20}ClNO_3S$) C, H, N.

2,4-Dichlorophenyl [4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (20) was prepared (method of compound **23**) using 2,4-dichlorobenzenethiol, 4-fluorobenzaldehyde, and *N*-acetyl piperazine as starting materials.. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 3.5−3.8 (m, 8H), 6.85 (d, J = 15 Hz, 1H), 7.10 (d, J = 9 Hz, 1H), 7.15 (dd, J = 9 Hz, 2 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.46 (d, J = 2 Hz, 1H), 7.50 (d, J = 8 Hz, 1H), 7.68 (d, J = 15 Hz, 1H). MS (DCI/NH_3) (M+H) = 435, 437, 452, 454. Anal. ($C_{21}H_{20}Cl_2N_2O_2S$ 0.5 H_2O) C, H, N.

2,3-Dichlorophenyl [4-*E*-((1-morpholino-carbonyl)ethenyl)phenyl] sulfide (21) was prepared (method of compound **23**) using 2,3-dichlorobenzenethiol, 4-fluorobenzaldehyde, and morpholine as starting materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.5−3.7 (m, 8H), 6.94 (dd, J = 8 Hz, 2 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.33 (d, J = 15 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.51 (d, J = 15 Hz, 1H), 7.54 (dd, J = 8 Hz, 2 Hz, 1H), 7.83 (d, J = 8 Hz, 2H). MS (DCI/NH_3) (M+H)$^+$ 394, 396, 398. Anal. ($C_{19}H_{17}Cl_2NO_2S$) C, H, N.

2,4-Dichlorophenyl [2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (22) was prepared (method of compound **23**) using 2,4-dichlorobenzenethiol, 4-fluoro-3-chlorobenzaldehyde, and *N*-acetyl piperazine as starting materials. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 3.50−3.58 (m, 2H), 3.58−3.85 (m, 6H), 6.85 (d, J = 15.3 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.24−7.36 (m, 3H), 7.54 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 15.3 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H). MS (DCI/NH_3) (M+H)$^+$ at m/z 486, 488, 490, 492.

1,4-Benzodioxan-6-yl [2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (24) was prepared (method of compound **23**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-fluoro-3-chlorobenzaldehyde, and *N*-acetylpiperazine as starting materials. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 3.44−3.57 (m, 2H), 3.57−3.86 (m, 6H), 4.25−4.35 (m, 4H), 6.75 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 15.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 2.1, 8.4 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.18 (dd, J = 2.1, 8.4 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H). MS (APCI$^+$) (M+H)$^+$ at m/z 459, 461.

1,4-Benzodioxan-6-yl [2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (25) was prepared (method of compound **23**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-fluoro-3-chlorobenzaldehyde, and 4-carbethoxy piperidine as starting materials. The resulting ethyl ester was hydrolyzed by stirring for 2 h in 1:1 ethanol water containing 4 equiv of NaOH, then evaporating the ethanol and acidifying with HCl. The resulting solid was dried by dissolving in $CHCl_3$, filtering from Na_2SO_4, and evaporating the $CHCl_3$ to give a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64−1.88 (br m, 2H), 1.95−2.09 (br m, 2H), 2.57−2.73 (m, 1H), 2.90−3.17 (m, 1H), 3.17−3.50 (m, 1H), 3.90−4.19 (m, 1H), 4.25−4.36 (m, 4H), 4.39−4.66 (m, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 15.3 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 2.4, 8.7 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.51 (s, 1H), 7.54 (d, J = 15.3 Hz, 1H). MS (ESI$^+$) (M+H)$^+$ at m/z 460, 462. Anal. ($C_{23}H_{22}ClNO_5S$) C, H, N.

1,4-Benzodioxan-6-yl [2-trifluoromethyl-4-(*E*-morpholin-1-yl-carbonyl)ethenyl)phenyl] sulfide (26) was prepared (method of compound **23**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-fluoro-3-trifluoromethylbenzaldehyde, and morpholine as starting materials. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (s, 1H), 7.62 (d, 1H, J = 15.6 Hz), 7.40 (dd, 1H, J = 1.8, 8.2 Hz), 7.04 (d, 1H, J = 2 Hz), 6.98−7.03 (m, 2H), 6.91 (d, 1H, J = 8 Hz), 6.81 (d, 1H, J = 15.3 Hz), 4.30 (m, 4H), 3.65−3.74 (br m, 8H). MS (ESI) m/z 452, 474, 925. Anal. ($C_{22}H_{20}F_3NO_4S$) C, H, N.

1,4-Benzodioxan-6-yl [2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (27) was prepared (method of compound **23**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-fluoro-3-trifluoromethylbenzaldehyde, and *N*-acetyl piperazine as starting materials. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 3.46−3.89 (m, 8H), 4.30 (dd, J = 2.1, 6.0 Hz, 4H), 6.84 (d, J = 15.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.97−7.10 (m, 3H), 7.42 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 15.0 Hz, 1H), 7.77 (s, 1H). MS (ESI$^+$) m/z 493 (M+H)$^+$. Anal. ($C_{24}H_{23}F_3N_2O_4S$) C, H, N.

1,4-Benzodioxan-6-yl [2-trifluoromethyl-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (28) was prepared (methods of compounds **23** and **25**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-fluoro-3-trifluoromethylbenzaldehyde, and 4-carbethoxypiperidine as starting materials. The product is a white solid, mp 88 °C (dec). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.40 (m, 2H), 1.98 (m, 2H), 2.95 (m, 1H), 3.15 (m, 1H), 3.45 (m, 1H), 4.20 (m, 2H), 4.35 (m, 4H), 7.00 (m, 4H), 7.20 (m, 2H), 7.90 (m, 1H), 8.20 (m, 1H), 12.30 (s, 1H). MS (APCI) m/z 494 (M+H)$^+$. Anal.($C_{24}H_{22}F_3NO_5S\cdot 0.3H_2O$) C, H, N.

1,4-Benzodioxan-6-yl [2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (29). To a solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 1 equiv of the nitro chloro cinnamide **11**[1] was added along with 1.5 equiv of K_2CO_3. After the mixture was stirred 1 h at 25 °C, water was added to precipitate the product as a light-yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.41−3.80 (m, 8H), 4.28−4.38 (m, 4H), 6.86 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 2.1, 8.4 Hz, 1H),7.15 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 15.6 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.91 (dd, J = 1.8, 8.4 Hz, 1H), 8.62 (d, J = 1.8 Hz, 1H). MS (APCI$^+$) (M+H)$^+$ at m/z 470. Anal. ($C_{23}H_{23}N_3O_6S\cdot 0.17H_2O$) C, H, N.

2,3-Dichlorophenyl [2-nitro-4-(*E*-((4-Acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (30) and 2-Isopropylphenyl [2-Nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)-ethenyl)phenyl] Sulfide (31). See paper 1.[1]

2,3-Dichlorophenyl [2-dimethylaminosulfonyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (56) was prepared (method of compound **23**) using 2,3-dichlorobenzenethiol, benzaldehyde **3e**, and *N*-acetyl piperazine as starting materials The product has mp 205−207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H), 2.95 (2, 6H), 3.5−3.8 (broad m, 8H), 6.88 (d, J = 9 Hz, 1H), 6.92 (d, J = 16 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 7.41 (m, 1H), 7.45 (dd, J = 8 Hz, 2 Hz, 1H), 7.55 (dd, J = 8 Hz, 2 Hz, 1H), 7.65 (d, J = 16 Hz, 1H), 8.20 (s, 1H). Anal. ($C_{23}H_{25}Cl_2N_3O_4S_2$) C, H, N.

4-Trifluoromethanesulfonyloxy-2,3-dichlorobenzaldehyde (6i). 4-Hydroxy-2,3-dichlorobenzaldehyde (**5i**)[5] (9.10 g, 47.64 mmol) was dissolved in 50 mL of pyridine, and 15.63 g (55.42 mmol) of $(CF_3SO_2)_2O$ was added with cooling. The mixture was stirred at 25 °C for 1 h and then poured onto ice, ether, and 100 mL of concentrated HCl. The ether was separated and washed with dilute HCl, dried (Na_2SO_4), and concentrated. The residue was dissolved in heptane and filtered from some insoluble material. The heptane was evaporated giving 8.74 g (57% yield) of **6i** as a yellow oil which solidified in the freezer.

4-(2-Methoxyphenylthio)-2,3-dichlorobenzaldehyde (4i, Ar = 2-methoxyphenyl). The 4-trifloxybenzaldehyde **6i** (2.85 g, 8.82 mmol) and 2-methoxybenzenethiol (2.47 g, 17.64 mmol) were dissolved in 7 mL of CH_3CN. With cooling, 2.85 g (22.62 mmol) of ^{i}Pr$_2$NEt was added, whereupon a solid formed. The mixture was stirred at 25 °C 15 min and then at 50 °C for 3 min. Five more milliliters of CH_3CN was added, and the mix was cooled in ice. A solid which formed was filtered. Yield 2.063 g; mp 138−139 °C; 75% yield.

4-(2-Methoxyphenylthio)-2,3-dimethylbenzaldehyde (4j, Ar = 2-methoxyphenyl). 4-Hydroxy-2,3-dimethyl benzaldehyde (**5j**) was converted to the 4-triflate by the method used with **6i**. The triflate (3.29 g, 11.67 mmol), 2-methoxyben-

zenethiol (3.29 g, 23.5 mmol) and $^{i}Pr_2NEt$ (3.73 g, 29.14 mmol) were dissolved in 8 mL of CH_3CN. In contrast to the fast reaction with the 2,3-dichloro analogue, this reaction needed heating at 95 °C for 18 h to go to completion. After cooling, toluene was added and then washed with dilute HCl, water, and then NaOH. The product was purified by chromatography (SiO_2, CH_2Cl_2) to get 1.311 g (59% yield) of **4i** mp 102−104 °C. Also isolated (first off the column) was the disulfide of 2-methoxybenzenethiol (1.311 g).

4-(2-Methoxyphenylthio)-3-methoxybenzaldehyde (4h, Ar = 2-methoxyphenyl). Vanillin was converted to the 4-triflate by the method used with **6i**. This triflate (4.50 g, 19.05 mmol), 2-methoxybenzenethiol (6.43 g, 45.92 mmol), and $^{i}Pr_2NEt$ (5.00 g, 39.06 mmol) were heated for 5 h at 85 °C in 13 mL of CH_3CN. The mixture was cooled, and ether was added and extracted with dilute HCl, water, and then dilute NaOH. After drying (Na_2SO_4 + charcoal), the solution was concentrated, and the product was chromatographed (SiO_2, CH_2Cl_2) to get 2.78 g (64% yield) of product. The disulfide of 2-methoxybenzene thiol (faster moving) was also collected.

(2-Methoxyphenyl) [2,3-Dichloro-4(*E*-[(morpholin-1-yl)-carbonyl]ethenyl)phenyl] Sulfide (34). Aldehyde **4i** was converted to cinnamic acid and then the amide **34** by reaction with morpholine, using the methods used to prepare **10b** and **23**, giving a white solid, mp 161−162 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 3.83 (s, 3H), 6.55 (d, J = 9 Hz, 1H), 6.70 (broad d, J = 15 Hz, 1H), 6.99−7.05 (m, 2H), 7.26 (d, J = 9 Hz, 1H), 7.43−7.50 (m, 2H), 8.07 (broad d, J = 15 Hz, 1H) Anal. ($C_{20}H_{19}Cl_2NO_3S$) C, H, N.

(2-Methoxyphenyl) [2-methoxy-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (32) was prepared from the cinnamic acid derivative of aldehyde **4h** (Ar = 2-methoxyphenyl) and *N*-acetylpiperazine using the method of compound **23**. Product has mp 141−143 °C. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.15 (s, 3H), 3.5−3.8 (br m, 8H), 3.84 (s, 3H), 3.94 (s, 3H), 6.78 (d, J = 15 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 6.90−7.03 (m, 4H), 7.30 (dd, J = 8 Hz, 2 Hz, 1H), 7.32−7.39 (m, 1H), 7.65 (d, J = 15 Hz, 1H). Anal. ($C_{23}H_{26}N_2O_4S$) C, H, N.

(1,4-Benzodioxan-6-yl) [2,3-dichloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide (33) was prepared (method of compound **34**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-trifloxy-2,3-dichlorobenzaldehyde, and *N*-acetyl piperazine as starting materials. The product is a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 3.50−3.94 (m, 8H), 4.26−4.40 (m, 4H), 6.61 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 15.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 2.4, 8.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 15.6 Hz, 1H). MS (ESI$^+$) $(M+Na)^+$ at m/z 515, 517, 519. Anal. ($C_{23}H_{22}Cl_2N_2O_4S$ 0.52 CH_2Cl_2) C, H, N.

(2-Methoxyphenyl)-[2,3-dichloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide (35) was prepared (methods of compounds **34** and **25**) using 2-methoxybenzenethiol, 4-trifloxy-2,3-dichlorobenzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 1.66−1.83 (m, 2H), 1.95−2.09 (m, 2H), 2.57−2.69 (m, 1H), 2.94−3.08 (m, 1), 3.15−3.31 (m, 1H), 3.72 (s, 3H), 3.90−4.05 (m, 1H), 4.41−4.55 (m, 1H), 6.55 (d, J = 9 Hz, 1H), 6.73 (d, J = 15 Hz, 1H), 7.00−7.05 (m, 2H), 7.27 (d, J = 8 Hz, 1H), 7.44−7.50 (m, 2H), 7.92 (d, J = 15 Hz, 1H). Anal. ($C_{22}H_{21}Cl_2NO_4S$) C, H, N.

(2-Isopropylphenyl) [2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (36) was prepared (methods of compounds **34** and **25**) using 2-isopropylbenzenethiol, 4-trifloxy-2,3-dichlorobenzaldehyde, and 4-carbethoxypiperidine as starting materials. The sodium salt was prepared as follows. The acid was dissolved in methanol. One equivalent of NaOH was carefully weighed out and dissolved in methanol. The solutions of acid and NaOH were mixed, and the methanol was evaporated in a vacuum. Toluene was added and then evaporated to remove all of the methanol. Ether was added and the mixture stirred to give the sodium salt as a white powder. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.16 (d, J = 7.2 Hz, 6H), 1.33−1.53 (m, 2H), 1.64−1.78 (m, 2H), 1.97−2.10 (m, 1H), 2.88 (brt, J = 10.5 Hz, 1H), 3.15 (brt, J = 10.5 Hz, 1H), 3.97 (br d, J = 13.2 Hz, 1H), 4.11 (br d, J = 13.2 Hz, 1H), 6.41 (d, J = 9.0 Hz, 1H), 7.22 (d, J = 15.6 Hz, 1H), 7.31−7.42 (m, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.56−7.64 (m, 2H), 7.71 (d, J = 15.6 Hz, 1H), 7.85 (d, J = 9.0 Hz, 1H). MS (ESI$^+$) $(M+H)^+$ at m/z 478, 480, 482. Anal. Na salt ($C_{24}H_{24}Cl_2NO_3SNa$ 0.95 H_2O) C, H, N.

(1,4-Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (37) was prepared (methods of compounds **34**, **25**, and **36**) using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-trifloxy-2,3-dichlorobenzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.33−1.55 (m, 2H), 1.62−1.78 (m, 2H), 1.93−2.07 (m, 1H), 2.90 (br t, J = 10.5 Hz, 1H), 3.16 (brt, J = 10.5 Hz, 1H), 3.96 (br d, J = 13.5 Hz, 1H), 4.09 (br d, J = 13.5 Hz, 1H), 4.26−4.42 (m, 4H), 6.60 (d, J = 9.0 Hz, 1H), 7.04−7.08 (m, 2H), 7.13 (d, J = 1.5 Hz, 1H), 7.22 (d, J = 15.3 Hz, 1H), 7.70 (d, J = 15.3 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H). MS (ESI$^+$) $(M+H)^+$ at m/z 516, 518, 520. Anal. Na salt ($C_{23}H_{20}Cl_2NNaO_5S\cdot0.36Et_2O$): C, H, N.

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (38) was prepared (methods of compounds **34**, **25**, and **36**) using the solution of 1-methyl-5-indolethiol in NMP prepared above, 4-trifloxy-2,3-dichlorobenzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.31−1.53 (m, 2H), 1.62−1.76 (m, 2H), 1.94−2.09 (m, 1H), 2.88 (brt, J = 10.5 Hz, 1H), 3.13 (brt, J = 10.5 Hz, 1H), 3.86 (s, 3H), 3.93 (br d, J = 13.2 Hz, 1H), 4.09 (br d, J = 13.2 Hz, 1H), 6.41 (d, J = 8.7 Hz, 1H), 6.53 (dd, J = 0.9, 3.0 Hz, 1H), 7.04 (d, J = 15.3 Hz, 1H), 7.32 (dd, J = 2.1, 8.7 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 15.3 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 2.1 Hz, 1H). MS (ESI$^+$) $(M+H)^+$ at m/z 489, 491, 493. Anal. Na salt ($C_{24}H_{21}Cl_2N_2NaO_3S$), C, H, N.

(2-Methoxyphenyl) [2,3-Bis(trifluoromethyl)-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (40). 4-Hydroxy-2,3-bis(trifluoromethyl)benzaldehyde (**5n**) was converted to the 4-triflate **6n** by the same methods used to prepare the 2,3-dichloro analogue **6i**. This triflate was reacted with 2-methoxybenzenethiol by the same method used to prepare the 2,3-dichloro analogue (**4i**, Ar = 2-methoxyphenyl) to give 4-(2-methoxyphenylthio)-2,3-bis(trifluoromethyl)-benzaldehyde (**4n**, Ar = 2-methoxyphenyl). Reaction of **4n** with malonic acid gave the cinnamic acid **10**, which was converted to the acid chloride. This was reacted with 4-carbethoxypiperidine and the resulting ester hydrolyzed to give the desired product (methods of compound **23** and **25**). ^{1}H NMR (CD_3OD, 300 MHz) δ 1.65 (br s, 2H), 1.94−2.03 (m, 2H), 2.57−2.67 (m, 1H), 2.95−3.05 (m, 1H), 3.23−3.32 (m, 1H), 3.75 (s, 3H), 4.12 (br s, 1H), 4.40 (br s, 1H), 7.00 (d, J = 15 Hz, 1H), 7.03−7.20 (m, 3H), 7.47−7.53 (m, 2H), 7.68 (d, J = 9 Hz, 1H), 7.77 (dd, J = 15 Hz, 1H). MS (ESI) m/z 534 $(M+H)^+$. Anal. ($C_{24}H_{21}NF_6O_4S$) C, H, N.

(1,4-Benzodioxan-6yl) [2,3-bis(trifluoromethyl)-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (39) was prepared (method of compound **40**) using a solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-trifloxy-2,3-bis(trifluoromethyl)benzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.65(br s, 2H),1.93−2.04 (m, 2H), 2.57−2.65 (m, 1H), 2.95−3.05 (m, 1H), 3.25 (m, 1H), 4.12 (m, 1H), 4.28 (m, 4H), 4.41 (m, 1H), 6.92−7.03 (m, 4H), 7.25 (d, J = 9 Hz, 1H), 7.72 (d, J = 9 Hz, 1H), 7.72−7.81 (m, 1H). MS (ESI) m/e 562 $(M+H)^+$. Anal. ($C_{25}H_{21}NO_5F_6S$) C, H, N.

(1-Methylindol-5-yl) [2,3-bis(trifluoromethyl)-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (41) was prepared (method of **40**) using the solution of 1-methylindole-5-thiol in NMP prepared above, 4-trifloxy-2,3-bis(trifluoromethyl)benzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.52−1.68 (m, 2H), 1.92−2.03 (m, 2H), 2.55−2.65 (m, 1H), 2.93−3.04 (m, 1H), 3.20−3.28 3.84 (s, 3H), (m, 1H), 4.01−4.12 (m,

1H), 4.32−4.43 (m, 1H), 6.52 (dd, J = 4 Hz, 2 Hz, 1H), 7.04 (d, J = 15 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.25−7.30 (m, 2H), 7.50 (d, J = 8 Hz, 1H), 7.61 (d, J = 9 Hz, 1H), 7.70−7.80 (octet, J = 15 Hz, 4 Hz, 1H), 7.82 (d, J = 2 Hz, 1H). Anal. ($C_{26}H_{22}F_6N_2O_3S$). C, H, N.

(2-Methoxyphenyl) [2-Chloro-3-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (42). 4-Hydroxy-3-chloro-2-trifluoromethylbenzaldehyde (**5m**) was converted to the 4-triflate **6m** by the same methods used to prepare the 2,3-dichloro analogue **6i**. This triflate was reacted with 2-methoxybenzenethiol by the same method used to prepare the 2,3-dichloro analogue (**4i**, Ar = 2-methoxyphenyl) to give 4-(2-methoxyphenylthio)-2-chloro-3-(trifluoromethy)-benzaldehyde (**4m**, Ar = 2-methoxyphenyl). Reaction of **4m** with malonic acid gave the cinnamic acid **10** which was converted to the acid chloride. This was reacted with morpholine to give the desired product (method of compound **23**). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.56−3.62 (br m, 2H), 3.67−3.77 (br m, 6H), 3.85 (s, 3H), 6.45 (d, J = 15 Hz, 1H), 6.73 (d, J = 9 Hz, 1H), 7.03 (d, J = 9 Hz, 2H), 7.09 (t, J = 9 Hz, 1H), 7.52 (d, J = 9 Hz, 2H), 2.93 (dd, J = 6 Hz, 1H). MS (DCI/NH_3) m/z 458 $(M+H)^+$. Anal. ($C_{21}H_{19}ClF_3NO_3S$) C, H, N.

(2-Methoxyphenyl) [2-chloro-3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (43) was prepared (methods of compounds **42** and **25**) by using 2-methoxybenzenethiol, 4-trifloxy-3-chloro-2-(trifluoromethyl)benzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (DMSO, 300 MHz) δ 1.37−1.52 (br. 2H), 1.78−1.86 (br. 2H), 2.45−2.55 (m, 1H), 2.83 (t, J = 12 Hz, 1H), 3.17 (t, J = 13.5 Hz, 1H), 3.80 (s, 3H), 4.07 (d, J = 12 Hz, 1H), 4.26 (d, J = 13.5 Hz, 1H), 6.75 (d, J = 9 Hz, 1H), 6.98 (d, J = 15 Hz, 1H), 7.11(t, J = 9 Hz, 1H), 7.26 (d, J = 9 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 9 Hz, 2H), 7.70 (dd, J = 4.5 Hz, 1H). MS (DCI/NH_3) m/e 500 $(M+H)^+$. Anal. ($C_{23}H_{21}ClF_3NO_4S$) C, H, N.

1,4-Benzodioxan-6-yl [2-chloro-3-trifluoromethyl4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (44) was prepared (methods of compounds **42** and **25**) by using the solution of 1,4-benzodioxane-6-thiol in NMP prepared above, 4-trifloxy-3-chloro-2-(trifluoromethyl)benzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.55−1.70 (m, 2H), 1.93−2.04 (m, 2H), 2.55−2.67 (m, 1H), 2.92−3.04 (m, 1H), 3.22−3.31 (m, 1H), 4.05−4.15 (m, 1H), 4.26−4.37 (m, 4H), 4.35−4.46 (m, 1H), 6.85 (d, J = 15 Hz, 1H), 6.89 (d, J = 8 Hz, 1H), 6.95−7.08 (m, 3H), 7.41 (d, J = 8 Hz, 1H), 7.84 (octet, J = 15 Hz, 4 Hz, 1H). Anal. ($C_{24}H_{21}ClF_3NO_5S$) C, H, N.

(2-Methoxyphenyl)-[2,3-dimethyl-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] Sulfide (45). 4-(2-Methoxyphenylthio)-2,3-dimethylbenzaldehyde (**4j**) was converted to the cinnamic acid with malonic acid (method of compound **10b**), and this was converted to the acid chloride with $(COCl)_2$ and reacted with morpholine to give the title compound. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 2.39 (s, 3H), 2.42 (s, 3H), 3.60−3.80 (m, 8H), 3.90 (s, 3H), 6.69 (d, J = 15 Hz, 1H), 6.82−6.94 (m, 3H), 7.05 (d, J = 9 Hz, 1H), 7.20−7.30 (m, 2H), 8.06 (d, J = 5 Hz, 1H). Anal.($C_{22}H_{25}NO_3S$) C, H, N.

(1,4-Benzodioxan-6-yl) [4-(*E*-((4-Carboxypiperidin-1-yl)carbonyl)ethenyl)naphthyl] Sulfide (47). 4-Hydroxy-1-naphthaldehyde[7] was converted to the triflate by the method used to prepare **6i**. This was reacted with a solution of 1,4-benzodioxane-6-thiol in NMP prepared above, by the method used to prepare **4j** (Ar = 2-methoxyphenyl) to give 4-(1,4-benzodioxane-6-thio)-1-naphthaldehyde (**4k**, Ar = 1,4-benzodioxane-6-yl). This was converted to the cinnamic acid with malonic acid. The cinnamic acid was converted to the acid chloride with oxalyl chloride, which was reacted with 4-carbethoxypiperidine, and the resulting ester was hydrolyzed with NaOH to give the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.50 (br s, 2H), 1.83−1.92 (m, 2H), 2.5−2.6 (m, 1H), 2.85−2.95 (m, 1H), 3.18−3.29 (m, 1H), 4.22 (br s, 5H), 4.30−4.38 (m, 1H), 6.87−6.92 (m, 3H), 7.38 (d, J = 15 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.64−7.70 (m, 2H), 7.93 (d, J = 7.5 Hz, 1H), 8.20−8.45 (m, 3H). MS(ESI$^+$) m/z 476 $(M+H)^+$. Anal. ($C_{27}H_{25}NO_5S\cdot0.67H_2O$) C, H, N.

(2-Isopropylphenyl) [2,3-Difluoro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (48). 2,3,4-Trifluorocinnamic acid (Aldrich) was converted to the methyl ester. This compound was reacted with 1 equiv of 2-isopropylbenzenethiol, and 2.5 equiv of K_2CO_3 in CH_3CN at 25 °C for 16 h. The product was purified by chromatography (hexanes−EtOAc 5:1) to get methyl 4-(2-isopropylthio) 2,3-difluoro cinnamate in 27% yield. This was hydrolyzed to the acid with NaOH, coupled with 4-carbethoxypiperidine, and then hydrolyzed with NaOH to the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.18 (d, J = 6.8 Hz, 6H); 1.30−1.91 (br m, 4H); 2.50−3.50 (br m, 4H); 4.02−4.34 (br m, 2H); 6.62−6.72 (m, 1H); 7.23−7.73 (m, 7H). MS (APCI) $(M+H)^+$ at m/z 446. Anal. ($C_{24}H_{25}F_2NO_3S$) C, H, N.

(2-Methoxyphenyl) [3-Fluoro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (49). 2,4-Difluorocinnamic acid and *N*-acetyl piperazine were coupled to form the cinnamide **12**. This was reacted with 2-methoxybenzenethiol by the method of compound **48** to give the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.02 (s, 3H), 3.45−3.75 (br m, 8H), 3.80 (s, 3H), 6.90 (dd, J = 10 Hz, 2 Hz, 1H), 6.98 (dd, J = 8 Hz, 2 Hz, 1H), 7.02 (t, J = 7 Hz, 1H), 7.18 (d, J = 7 Hz, 1H), 7.25 (d, J = 15 Hz, 1H), 7.38 (d, J = 7 Hz, 1H), 7.47 (dt, J = 8 Hz, 2 Hz, 7.55 (d, J = 15 Hz, 1H), 7.86 (t, J = 8 Hz, 1H). Anal. ($C_{22}H_{23}FN_2O_3S$) C, H, N.

1,4-Benzodioxan-6-yl [2-Chloro-6-trifluoromethyl-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] Sulfide (50). The aldehyde **4g** was converted to the cimnnamic acid **10g** (Ar = 1,4-benzodioxane) by reaction with malonic acid (see compound **10b**, Ar = 2-methoxypheny), and then coupling with 4-carbethoxypiperidine, and finally hyrolysis with NaOH to give the title compound. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.55−1.70 (m, 2H), 1.93−2.04 (m, 2H), 2.55−2.67 (m, 1H), 2.92−3.04 (m, 1H), 3.22−3.31 (m, 1H), 4.25−4.35 (m, 1H), 4.36−4.47 (m, 4H), 4.55−4.66 (m, 1H), 6.58 (d, J = 2 Hz, 1H), 6.63 (dd, J = 2 Hz, 9 Hz, 1H), 6.75 (d, J = 9 Hz, 1H), 7.37 (d, J = 15 Hz, 1H), 7.52 (d, J = 15 Hz, 1H), 8.02 (d, J = 2 Hz, 1H), 8.10 (d, J = 2 Hz). Anal. ($C_{24}H_{21}ClF_3NO_5S$) C, H, N.

(2-Methoxyphenyl) [2,5-Dichloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] Sulfide (51). 4-Hydroxy-3,6-dichlorobenzaldehyde (**5p**) was converted to the 4-triflate (**6p**) by the method used with the 2,3-dichloro analogue (**5i**), and then this was reacted with 2-methoxybenzenethiol to give **4p** (Ar = 2-methoxyphenyl) and then on to the title compound also using the same method used to make the 2,3-dichloro analogue **35**. ^{1}H NMR (CD_3OD, 300 MHz) δ 1.57−1.67 (m, 2H), 1.93−2.07 (m, 2H), 2.58−2.69 (m, 1H), 2.95−3.06 (m, 1H), 3.32−3.4 1 (m, 1H), 3.82 (s, 3H), 4.25−4.35 (m, 1H), 4.36−4.45−4.56 (m, 1H), 6.55 (s, 1H), 7.08 (t, J = 8 Hz, 1H), 7.18 (, J = 9 Hz, 1H), 7.22 (d, J = 15 Hz, 1H), 7.49−7.59 (m, 1H), 7.80 (d, J = 15 Hz, 1H), 7.94 (s, 1H). Anal. ($C_{22}H_{21}Cl_2NO_4S$) C, H, N.

(2-Methoxyphenyl) [2-Nitro-5-methyl-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] Sulfide (53). 4-(2-Methoxyphenylthio)-2-methyl-5-nitrocinnamic acid **(15)** and 4-carbethoxypiperidine were converted to the title compound (methods of compounds **23** and **25**); mp 206−208 °C. ^{1}H NMR (DMSO-d_6, 300 MHZ) δ 1.35−1.45 (m, 2H), 1.80−1.90 (m, 2H), 2.39 (s, 3H), 2.45−2.55 (m, 1H), 2.75−2.85 (m,1H), 3.05−3.15 (m, 1H), 3.60−3.70 (m, 1H), 3.77 (s, 3H), 4.15−4.25 (m, 1H), 6.47 (d, J = 15 Hz, 1H), 6.89 (s, 1H), 7,11 (t, J = 7 Hz, 1H), 7.24 (d, J = 8 Hz, 1H), 7.47−7.62 (m, 3H), 8.14 (s, 1H). Anal. ($C_{23}H_{24}N_2O_6S$), C, H, N.

(2-Methoxyphenyl) [2-Chloro-5-methyl-4-(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] Sulfide (52). The ethyl ester of cinnamic acid **16** (3.12 g, 8.70 mmol) was added to powdered iron (2.43 g, 43.5 mmol) and NH_4Cl (0.558 g, 10.4 mmol) in 20 mL of water and 20 mL of ethanol and heated at 105 °C for 1 h. The mixture was filtered and the solid washed with EtOAc. The filtrate was washed with brine and dried ($MgSO_4$) and the solvents evaporated to give 2.76 g of the amino compound, methyl ester intermediate (**17**). This

compound (330 mg, 1.00 mmol), in 15 mL of CH_3CN containing 0.19 mL (1.30 mmol) of 60% HBF_4, was treated with *tert*-butyl nitrite (0.155 mL, 1.30 mmol) at 0 °C. After 2 h, 45 mL of saturated NH_4Cl was added. And the mixture was extracted with EtOAc. The EtOAc was washed with NH_4Cl, water, and brine and dried ($MgSO_4$), and the solvents were evaporated. The product was purified by chromatography (SiO_2, hexanes−EtOAc 7:3) to get 0.236 g (68%) of the methyl ester of **18**. This was hydrolyzed to **18** with NaOH in water−ethanol. The cinnamic acid **18** and 4-carbethoxypiperidine were converted to the title compound (methods of compounds **23** and **25**). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.35−1.45 (m, 2H), 1.80−1.89 (m, 2H), 2.38 (s, 3H), 2.75−2.85 (m, 1H), 3.05−3.15 (m, 1H), 3.50−3670 (m, 1H), 3.84 (s, 3H), 3.95−4.05 (m, 1H), 4.22−4.31 (m, 1H), 6.76 (d, J = 7 Hz, 1H), 6.93 (t, J = 8 Hz, 1H), 6.99 (d, J = 15 Hz, 1H), 7.11 (d, J = 9 Hz, 1H), (t, J = 7 Hz, 1H), 7.54 (s, 1H), 7.58 (d, J = 15 Hz, 1H), 7.71 (s, 1H). Anal. ($C_{23}H_{24}ClNO_4S\cdot 0.25H_2O$) C, H, N.

(2-Methoxyphenyl) [3 -Methyl-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] Sulfide (46). The amino cinnamate intermediate **17** in the synthesis of **52** (1.95 g, 5.92 mmol) in 25 mL of CH_3CN containing 3.16 mL of 3 M aqueous H_2SO_4, 9.47 mmol) was treated with 0.820 mL of *tert*-butyl nitrite (6.22 mmol) at 0 °C. After 30 min, a 50% aqueous solution of hypophosphorus acid (H_3PO_2, 12.3 mL, 118 mmol) was added. The mixture was stirred at 25 °C for 16 h. The product was purified by chromatography (SiO_2, hexane−ETOAc 85:15) to get 0.905 (49%) of methyl ester of the cinnamic acid **19**. This was hydrolyzed to **19** (LiOH) which was coupled with 4-carbethoxypiperidine and the resulting ester hydrolyzed to the title compound (methods of compounds **23** and **35**). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.35−1.45 (m, 2H), 1.80−1.89 (m, 2H), 2.37 (s, 3H), 2.78−2.88 (m, 1H), 3.15−3.25 (m, 1H), 3.50−3.60 (m, 1H), 3.82 (s, 3H), 4.15−4.22 (m, 1H), 4.32−4.41 (m, 1H), 6.83−6.92 (m, 2H), 7.08 (d, J = 8 Hz, 1H), 7.15−7.28 (m, 3H), 7.22 (d, J = 15 Hz, 1H), 7.66 (d, J = 15 Hz, 1H), 7.88 (s, 1H). Anal. ($C_{23}H_{25}NO_4S$ 0.5 H_2O) C, H, N.

(2-Methoxyphenyl) [3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (54) was prepared (methods of compounds **23** and **25**) using 2-methoxybenzenethiol, 4-fluoro-2-(trifluoromethyl)benzaldehyde, and 4-carbethoxypiperidine as starting materials. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.40−1.55 (m, 2H), 1.80−1.90 (m, 2H), 2.80−2.92 (m, 1H), 3.14−3.26 (m, 2H), 3.79 (s, 3H), 4.11−4.30 (m, 2H), 7.04 (dt, J = 8 Hz, 2 Hz, 1H), 7.19 (dd, J = 8 Hz, 1H), 7.33 (d, J = 15, 1H), 7.36−7.41 (m, 2H), 7.49 (dt, J = 8 Hz, 2 Hz, 1H), 7.65 (octet, J = 15 Hz, 2 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), MS (APCI) (M+ H) 466 Anal. ($C_{23}H_{22}F_3NO_4S$) C, H, N.

(2-Methoxyphenyl) [3-chloro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide (55) was prepared (methods of compounds **23** and **25**) using 2-methoxybenzenethiol, 4-fluoro-2-chlorobenzaldehyde, and 4-carbethoxypiperidine as staring materials. The reaction between 2-methoxybenzenethiol and 4-fluoro-2-chloro-benzaldehyde was carried out at 25 °C instead of at 55 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.35−1.50 (m, 2H), 1.84−1.93 (m, 2H), 2.50−2.60 (m, 1H), 2.80−2.90 (m, 1H), 3.15−3.25 (m, 1H), 4.10−4.20 (m, 1H), 4.22−4.35 (m 1H), 7.02 (t, J = 8 Hz, 1H), 7.10 (dd, J = 8 Hz, 1 Hz),7.15 (d, J = 2 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 7.26 (d, J = 15 Hz, 1H), 7.35 (d, J = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.70 (d, J = 15 Hz, 1H), 7.96 (d, J = 8 Hz, 1H). Anal. ($C_{22}H_{22}ClNO_4S$ 0.5 H_2O) C, H, N.

In Vivo Cell Trafficking Models. The in vivo efficacy of compound **38** was evaluated in two separate rodent cell trafficking models. In the first model, eosinophil migration into the lung was induced by inhaled allergen. The dosing vehicle was 1.7% dextrose in water. On day 0 mice were sensitized with ovalbumin (OA) adsorbed to aluminum hydroxide (AlOH) intraperitoneally (ip) and boosted on day 6 with OA-AlOH ip and OA in PBS intranasally. Mice were aerosol challenged twice on day 20 with OA in PBS, and compound **38** was administered orally at −1 h and +7 h relative to the first aerosol challenge. Lungs from sacrificed animals were lavaged 24 h later for the determination of total cell number using a particle counter (Coulter Corp.) and percent leukocytes using Diff-Quik differential stains (Dade AG).

In the second model of in vivo trafficking, neutrophil migration in the rat was induced by injection of Staphlococcus Enterotoxin A (SEA) (Sigma S-9399) in an air pouch. The dosing vehicle was 0.2% methylcellulose (MC) in phosphate buffered saline (PBS). Animals were injected subcutaneously with 20 cm^3 sterile air on day 0 and again on day 3 to induce an air pouch. On day 6, compound **38** was administered orally, and 1 h later SEA was injected into the air pouch. Four hours later, animals were sacrificed, the air pouches lavaged, cytospins collected, and differential cell counts determined with Wright Giemsa staining.

NMR modeling. Procedures used to generate the NOE based model of compound **31** bound to the LFA-1 I domain are described in ref 2. A model of compound **56** bound to LFA-1 I domain was obtained by positioning the compound near the C-terminus of the I domain followed by energy minimization with XPLOR as described in ref 2. Nineteen intermolecular and one intraligand distance restraints were used that mimic the NOEs observed for the complex of LFA-1 and compound **31**. The six lowest energy structures out of 100 calculations were selected for a comparison with the compound **31**/LFA-1 complex. Similarly, the binding of compound **35** was modeled using 19 intermolecular and one intraligand distance restraints. The seven lowest energy structures out of 100 calculations were selected for a comparison with the compound **31**/LFA-1 complex.

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