Discovery of Novel *p*-Arylthio Cinnamides as Antagonists of Leukocyte Function-Associated Antigen-1/Intracellular Adhesion Molecule-1 Interaction. 1. Identification of an Additional Binding Pocket Based on an Anilino Diaryl Sulfide Lead

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The interaction between leukocyte function-associated antigen-1 (LFA-1), a member of the β_2-integrin family of adhesion molecules, and intracellular adhesion molecule ICAM-1 (cd54) is thought to play a critical role in the inflammatory process. On the basis of an anilino diaryl sulfide screening lead **1**, in combination with pharmacophore analysis of other screening hits, we have identified an adjacent binding pocket. Subsequently, a *p*-ethenylcarbonyl linker was discovered to be optimal for accessing this binding site. Solution-phase parallel synthesis enabled rapid optimization of the cinnamides for this pocket. In conjunction with fine-tuning of the diaryl substituents, we discovered a novel series of potent, nonpeptide inhibitors of LFA-1/ICAM-1 interaction, exemplified by A-286982 (**28h**), which has IC_{50} values of 44 and 35 nM in an LFA-1/ICAM-1 binding assay and LFA-1-mediated cellular adhesion assay, respectively.

Introduction

Inflammation results from a cascade of events that includes vasodilation accompanied by increased vascular permeability and exudation of fluid and plasma proteins. Inflammatory mediators (chemokines such as IL-8, MCP-1, MIP-1, RANTES, etc.) have chemotactic activity for leukocytes and attract the circulating leukocytes to localize and cross the vascular endothelium at a precise location. This leukocyte recruitment is accomplished by a process called cell adhesion.[1]

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue.[2] These steps are mediated by families of adhesion molecules such as integrins, Ig supergene family members, and selectins which are expressed on the surface of the circulating leukocytes and on the vascular endothelial cells. Leukocyte function-associated antigen-1 (LFA-1, also termed CD11a/CD18) belongs to a member of the β_2-integrin family of adhesion molecules, $\alpha_L\beta_2$. LFA-1 is thought to play a critical role in the inflammatory process by interacting with the intercellular adhesion molecule ICAM-1 (CD54), an immunoglobin expressed on endothelial cells, this interaction promotes the migration of leukocytes rapidly into surrounding tissue.[3] Thus, an agent which blocks the LFA-1/ICAM-1 interaction may suppress these early steps in the inflammatory response.[4] Consistent with this background, ICAM-1 knockout mice have numerous abnormalities in their inflammatory responses.[5]

To date, most of the agents designed for blocking the binding of LFA-1 to ICAM-1 have been monoclonal antibody based.[6,7] Several small molecules have been reported to prevent cell adhesion via inhibition of integrin activation, but they do not directly block association of the purified proteins.[8,9] More recently, three accounts of structurally diverse small molecules have been reported to prevent the binding of LFA-1 to ICAM-1.[10−12] Herein, we report the discovery of a series of *p*-arylthio cinnamides that inhibit LFA-1 from binding to ICAM-1, interrupting the endothelial cell−leukocyte adhesion process in vitro. These compounds are potentially useful for the prophylaxis or treatment of diseases in which leukocyte trafficking plays a role, notably acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection, and reperfusion injury.

Our process of discovery began with the identification of anilino diaryl sulfide **1** from screening a compound library. It has low-micromolar potency against the binding of LFA-1 to ICAM-1 (Scheme 1). Preliminary SAR studies indicated that both the sulfur atom and the anilino group are critical for the affinity of the compound. Alkylation and acylation of the anilino group generally attenuated the potency of the resulting compounds (data not shown). Replacement of the sulfide linkage with oxygen, carbonyl, and methylene groups also reduced the affinities of the compounds (data not shown). On the other hand, compound **2** was identified from the same screening and found to moderately antagonize the LFA-1/ICAM-1 interaction. Even though compounds **1** and **2** likely have very different bound conformations, it is intriguing to note the tolerance of an *N*,*N*-dimethylaminoethyl group on the phenothiazine template of **2**, which might indicate the existence of an additional binding pocket adjacent to the diaryl sulfide

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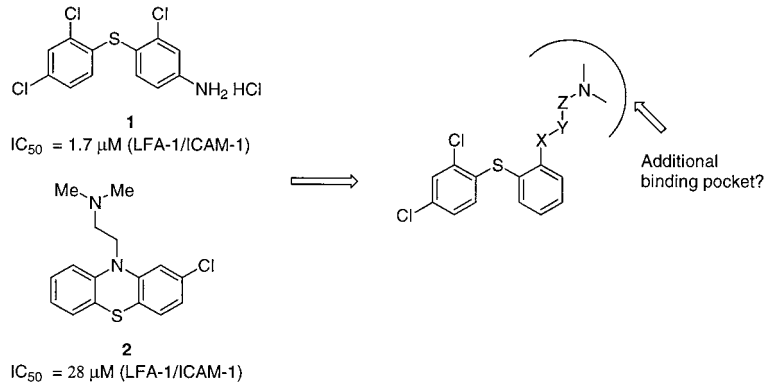
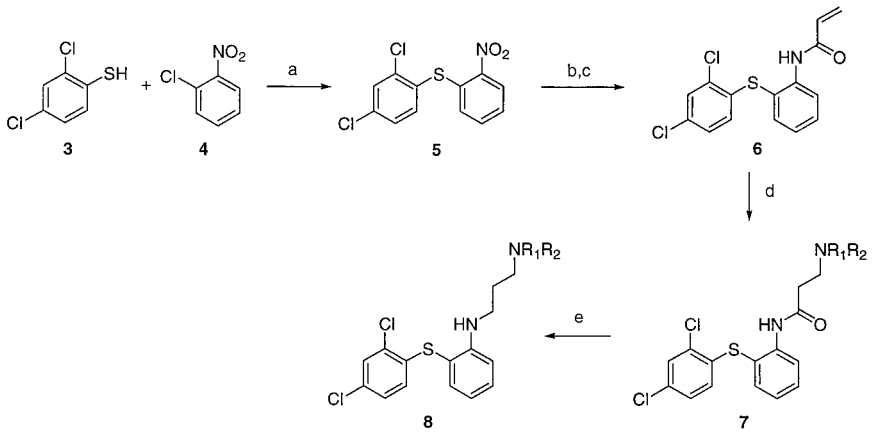
Scheme 1. Pharmacophore Analysis of Screening Leads of LFA-1/ICAM-1 Inhibitors



Scheme 2[a]



[a] Reagents and conditions: (a) K_2CO_3, DMF, 70 °C, 83%; (b) $SnCl_2$, EtOH, reflux; (c) acryloyl chloride, Et_3N, CH_2Cl_2, 65% two steps; (d) HNR_1R_2, MeOH, reflux, 55−90%; (e) LAH, THF, rt, 86%.

binding site. We decided to explore the tolerance of such *ortho* substituents on a more flexible template, such as diaryl sulfide **1**.

Chemistry

Scheme 2 describes the synthesis of a typical diaryl sulfide aniline compound **8** and the corresponding amide precursor **7**. Nucleophilic substitution of the 2-chloronitrobenzene (**4**) with 2,4-dichlorobenzenethiol (**3**) yielded the diaryl sulfide **5**. The nitro group of **5** was then reduced to the amine, which was subsequently acylated with acryloyl chloride. Michael addition of the resulting acrylamide **6** with secondary amines provided amides **7**. Lithium aluminum hydride reduction of the amide **7** offered *N*,*N*-dialkyl(aminopropyl)amino diaryl sulfide **8**.

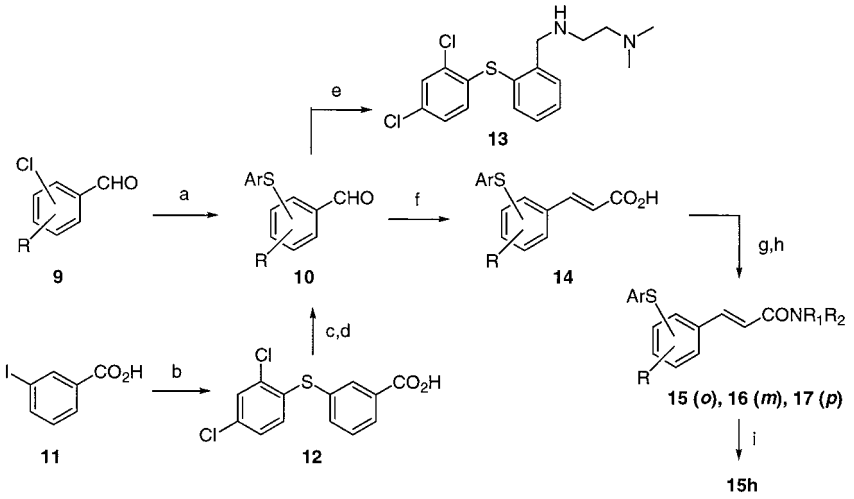
In a similar fashion, diaryl sulfide aldehydes (both *ortho*- and *para*-substituted) **10** were synthesized from substituted chlorobenzaldehydes **9** and substituted benzenethiols, such as **3** (Scheme 3). The *meta*-substituted aldehyde **10** can be prepared through an Ullman coupling[13] of benzenethiol **3** with 3-iodobenzoic acid (**11**), followed by borane reduction of the resulting acid **12** and oxidation of thus formed alcohol. The aldehydes **10** were converted to the corresponding cinnamic acids **14** using the Doebner modification of the Knoevenagel condensation with malonic acid.[14] Activation of acids as acid chlorides, followed by condensation with primary or secondary amines, provided the desired cinnamides **15**−**17**. The *o*-aldehyde **10** was also subjected to a standard reductive amination protocol to give amine **13**.

From bromide **18**, bis-cinnamide **19** was synthesized through palladium-catalyzed Heck reaction with acryloylmorpholine (Scheme 4). Buchwald coupling[15] of the same bromide with aminopropylmorpholine yielded the A-ring functionalized anilino compound **22**. Activation of the alcohol **20** as a bromide and displacement of which with secondary amines provided analogues **21** (Scheme 5). Similar Heck reaction of bromide **23** with acryloylmorpholine gave the mono-cinnamide **24** (Scheme 6). Subsequent homologation and amidation yielded the other series of bis-cinnamide **25**.

Alternatively, the order of assembly may be reversed to offer a greater flexibility for exploring the SAR of the A-ring (Scheme 7). 4-Chloro-3-nitrocinnamic acid (**26**) was coupled with a primary or secondary amine as described before to give the corresponding amide **27**. The chlorine of **27** can then be displaced with virtually any thiophenol to provide a library of analogues **28**. Functional groups on the A- and B-rings of the diaryl sulfide **28** can be further modified to produce new analogues, such as amine **29**. Sandmeyer reaction converted the amine **29** to bromide **30**, which can undergo Buchwald coupling to give the anilino analogue **31**.

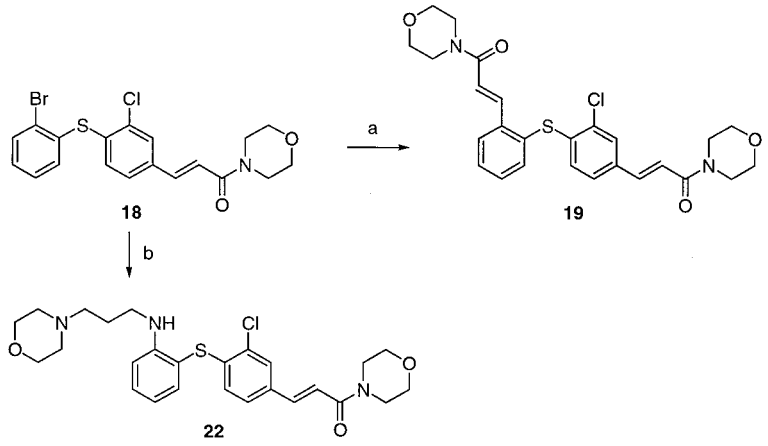
B-Ring-modified cinnamides, such as **34** and **35**, were prepared from diaryl sulfide **32** through the same palladium-mediated Heck coupling described for **18** (Scheme 8). The resultant aldehyde **33** can be oxidized to the carboxylic acid **34** with silver oxide,[16] and amidation of the resulting acid provided amide **35**.

Scheme 3[a]



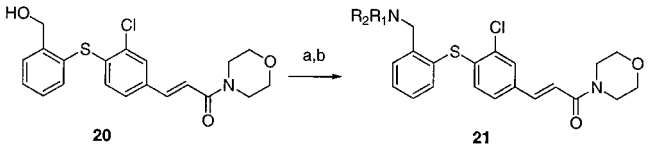
[a] Reagents and conditions: (a) K_2CO_3, DMF, 70 °C, ca. 85%; (b) KOH, H_2O, Cu, 2,4-dichlorothiophenol, reflux, 97%; (c) BH_3·THF, rt, 97%; (d) Swern oxidation, 47%; (e) *N*,*N*-dimethylethylenediamine, $NaBH_4$, MeOH, 95%; (f) malonic acid, cat. piperidine, pyr, 110 °C, 91%; (g) $(COCl)_2$, CH_2Cl_2, cat. DMF, rt; (h) HNR_1R_2, *i*-$PrNEt_2$, cat. DMAP, CH_2Cl_2, 90%; (i) 1 N NaOH, MeOH, 95%.

Scheme 4[a]



[a] Reagents and conditions: (a) acryloylmorpholine, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, DMF, 110 °C, 39%; (b) aminopropylmorpholine, $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, 18-C-6, toluene, 80 °C, 44%.

Scheme 5[a]



[a] Reagents and conditions: (a) PBr_3, LiBr, DMF; (b) HNR_1R_2, *i*-$PrNEt_2$, Ch_3CN, 87%.

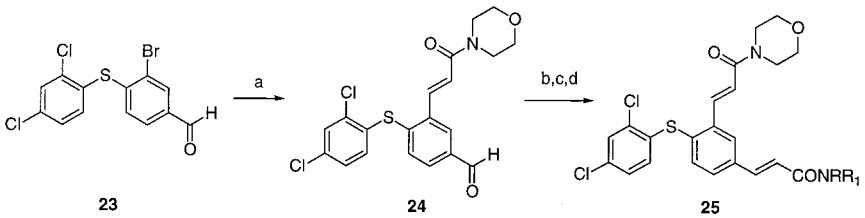
Structure−Activity Relationship Discussion

The primary biochemical assay measures the ability of the compound to block the interaction between the integrin LFA-1 and its adhesion partner ICAM-1 in a time-resolved fluorescent LFA-1/ICAM-1 biochemical interaction assay. Biologically relevant activity of the compounds can be confirmed using a cell-based adhesion assay, which measures the ability of a compound to block the adherence of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-1.

On the basis of the hypothesis that an additional binding pocket adjacent to the compound **1** binding site might be available, we decided to explore the tolerance of *ortho* substituents on the diaryl sulfide template **1**. A synthetic strategy of using Michael addition of secondary amines to the acrylamide **6** was devised to allow access to both the amido and anilino analogues sequentially. The acyclic dialkylaminoethyl amide analogues were much weaker inhibitors than **1**, with *N*,*N*-dimethylamine (**7a)** and *N*,*N*-di-*n*-propylamine (**7b)** analogues exhibiting IC_{50} values close to 100 μM, and *N*-methylbenzylamine (**7c**) analogue having an IC_{50} value greater than 100 μM (Table 1). For the cyclic amine analogues, five-membered pyrrolidine-derived compound **7d** did not showed any affinity, and six-membered morpholine (**7e**) and *N*-methylpiperazine (**7f**)-based analogues are well-tolerated, exhibiting only a 5−10-fold decrease of potency compared with the parent compound **1**. When the amide of **7e** was reduced to aniline **8**, more than an 85-fold boost of potency was observed to give a submicromolar inhibitor of LFA-1/ICAM-1 association. Notably, compound **13**, derived from changing the anilinopropyl linker of **8** to a methylaminoethyl and the morpholine to the less optimal dimethylamine, has a comparable IC_{50} value to that of compound **1**.

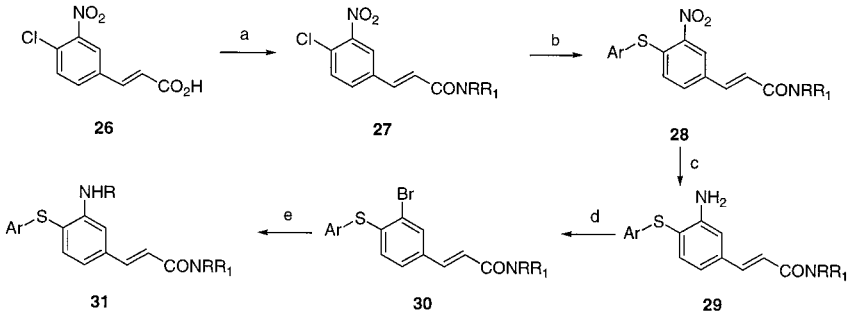
Once the existence of an additional binding space

Scheme 6[a]



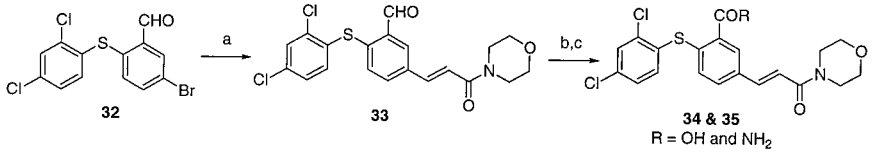
[a] Reagents and conditions: (a) acryloylmorpholine, $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, Et_3N, DMF, 110 °C, 77%; (b) malonic acid, cat. piperidine, pyr, 110 °C, 91%; (c) $(COCl)_2$, CH_2Cl_2, cat. DMF, rt; (d) $HNRR_1$, *i*-$PrNEt_2$, cat. DMAP, CH_2Cl_2, 90%.

Scheme 7[a]



[a] Reagents and conditions: (a) $HNRR_1$, EDAC, DMF, 92%; (b) K_2CO_3, DMF, rt, 89%; (c) $SnCl_2$, EtOH, reflux; (d) *tert*-butyl nitrite, $CuBr_2$, CH_3CN, 29%; (e) aminopropylmorpholine, $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, 18-C-6, toluene, 80 °C, 44%.

Scheme 8[a]

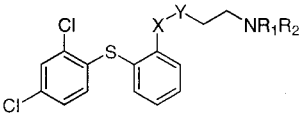


[a] Reagents and conditions: (a) acryloylmorpholine, $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, Et_3N, DMF, 110 °C, 77%; (b) Ag_2O, H_2O, 3 N NaOH, 71%; (c) EDAC, HOBT, NH_4Cl, Et_3N, DMF, 74%.

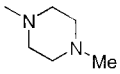
adjacent to where compound **1** binds was established by the improved potency exhibited by compound **8**, we started to search for different linkers and terminal amines to fill that portion of the binding pocket. Because of the availability of the intermediate aldehyde **10**, and the ease of synthesis and versatility for further manipulation, the ethenylcarbonyl group was examined as a three-atom linker between the aromatic ring and the terminal amino group. Interestingly, the *o*-cinnamic acid itself **14a** was almost equipotent as compound **1**, representing the first non-aniline-containing, low-micromolar inhibitor of the series (Table 2). The results from the first small set of amides prepared from acid **14a** were rather encouraging and offered direction for optimizing this series of LFA-1/ICAM-1 inhibitors. Hydrophobic amines, such as phenethylamine (**15a**), 2-aminobenzothiazole (**15b**), and phenoxybenzylbenzylamine (**15c**), yielded completely inactive analogues. In contrast, amidation of the cinnamic acid **14a** with 1-amino-6-hexanol yielded **15d**, an inhibitor slightly more potent than the acid **14a**. Prompted by this critical observation, other hydrophilic amino alcohols, amino acids, and aminoalkylamines were examined with this *o*-cinnamide template. Ethanolamine-derived cinnamide **15e** is slightly less potent than the hexanolamine analogue **15d**. Similarly, 2,3-dihydroxypropylamine (**15f**) and diethanolamine (**15g**) yielded analogues with comparable affinities to that of **15e**. Compared with alcohol **15e**, glycine-derived analogue **15h** showed essentially identical potency. When an amino group such as imidazole (**15i**) was appended to the terminus of the cinnamide, the potency of the resulting compound remained the same as **15d**. Neutral heterocyclic alkylamines, such as aminotetrahydrofurfuryl and aminopropylpyrrolidine, produced cinnamides (**15j**, **15k**) which are also potent LFA-1/ICAM-1 antagonists. Similar to **15g**, morpholine-derived tertiary cinnamide **15l** exhibited identical potency to **15d**.

Encouraged by the early success of the *o*-cinnamides, we surveyed the position preference of the cinnamide relative to the arylthio group using the above-mentioned preferred amines. In comparison to *o*-cinnamides, the corresponding *m*-cinnamides are generally less active against LFA-1/ICAM-1 interaction. The decrease of the potency ranges from 15-fold (morpholino analogue **16d**) to 3-fold (aminopropylpyrrolidinone analogue **16e**) and somewhere in between for amino alcohols **16a** and **16b** and aminoalkylamine derivative **16c** (Table 3). For the *p*-cinnamides, the reversed trend was observed. *p*-Cinnamic acid **14b** is equipotent to the *ortho* analogue **14a**. For the amino alcohols, such as ethanolamine (**17a**), 1-amino-6-hexanol (**17b**), and diethanolamine (**17c**), a trend of improvement over the corresponding *o*-cinnamides was observed. Imidazole analogue **17d** exhibited comparable affinity to **15i**, while aminopropylpyrrolidinone **17e** and morpholine **17f** showed approximately 3-fold improvement as well. Using the *p*-cinnamide template, the apparent preference of this

Table 1. Structure−Activity Relationships of *o*-*N*,*N*-Dialkylpropyl(oxo)amino Diaryl Sulfides and *N*,*N*-Dialkylethylaminomethyl Diaryl Sulfides



7,8,13

Compound	-NR_1R_2	-X-Y-	LFA-1/ICAM-1 IC_{50} (μM)[a]
7a	-NMe_2	-NHCO-	82
7b	-N-*n*Pr_2	-NHCO-	61
7c	-NBnMe	-NHCO-	>100
7d		-NHCO-	>10
7e		-NHCO-	12
7f		-NHCO-	33
8		-$NHCH_2$-	0.14 (0.10-0.20)
13	-NMe_2	-CH_2NH-	5.6 (5.1-6.1)

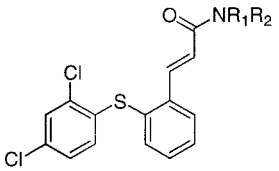
[a] IC_{50} calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 3.2×10^{-8} to 10^{-4} unless otherwise noted.

series of inhibitors for six-membered cyclic amine was briefly explored. The basic *N*-methylpiperazine (**17g**) and *N*-pyridylpiperazine (**17i**) analogues were slightly less potent than the morpholine analogue **17f**. *N*-Acetylpiperazine compound **17h** turned out to be 3-fold more potent than **17i**, the most active cinnamide examined so far.

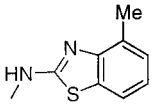
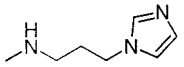
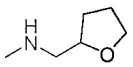
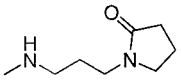
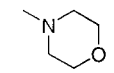
During this process of searching for an agent suitable for oral therapy of diseases related to inflammatory response, we had successfully eliminated the metabolically liable aniline group of **1**. The other potentially troublesome features of this series of compounds are the sulfide and cinnamide double bond. The pharmacokinetic behavior of the representative compound **17e** of this novel series of LFA-1/ICAM-1 inhibitors was examined, and the results were encouraging. In rats, compound **17e** was reasonably absorbed following 5 mg/kg oral administration and achieved good plasma drug level ($t_{1/2}$ = 1.8 h, C_{max} = 1.08 μg/mL, AUC = 3.26 μg·h/mL). The compound was not extensively metabolized based on the rat microsome metabolism studies (data not shown), suggesting the viability of both the sulfide and the cinnamide double bond as parts of the drug molecule. The calculated oral bioavailability (*F*) is 33%, which indicates that this series of compounds has the potential to be orally deliverable agents.

At this stage, it was still unclear whether the *p*-cinnamides bind to the same site as the *o*-cinnamides or if they interact with yet another binding pocket. The

Table 2. Structure−Activity Relationships of *o*-Cinnamido Diaryl Sulfides



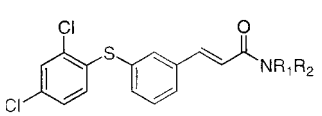
14a,15

Compound	-NR_1R_2	LFA-1/ICAM-1 IC_{50} (μM)[a]
14a	-OH	2.6 (2.5-2.7)
15a	-$NHCH_2CH_2Ph$	>100
15b		>100
15c	-NH(Bn)CH_2Ph-*p*-OPh	>100
15d	-$NH(CH_2)_6OH$	1.0 (0.6-1.8)
15e	-$NH(CH_2)_2OH$	3.3 (1.9-6.6)
15f	-$NHCH_2CHOHCH_2OH$	3.8 (2.1-4.5)
15g	-$N[(CH_2)_2OH]_2$	2.3 (2.3-3.2)
15h	-$NH(CH_2)CO_2H$	3.9 (1.9-9.4)
15i		0.96 (0.70-1.50)
15j		2.1
15k		1.6 (1.2-2.0)
15l		1.2 (0.60-2.9)

[a] IC_{50} calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 3.2×10^{-8} to 10^{-4} unless otherwise noted.

marginal potency increase realized by switching from *o*-cinnamides to *p*-cinnamides could be attributed to the better fitting of the compounds in the receptor or the presence of an additional chlorine on the *p*-cinnamides. To address this question, some hybrid molecules carrying both *o*- and *p*-cinnamides were synthesized, and results from this study are summarized in Table 4. When the *p*- and *o*-cinnamides were situated on the two opposing phenyl groups of the diaryl sulfide, exemplified with compound **19**, the resulting antagonist exhibited only a slight increase of affinity over *p*-cinnamide **17f**. At the onset of the project, we had also examined *o*-benzylamine **13** for filling this additional binding site. Naturally, we explored the combination of *o*-benzyl-

Table 3. Structure−Activity Relationships of *m*- and *p*-Cinnamido Diaryl Sulfides



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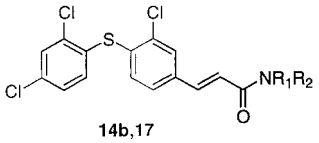
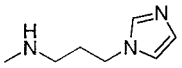
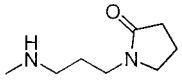
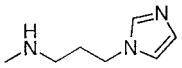
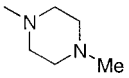
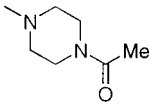
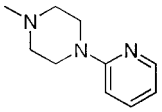


14b,17

Compound	-NR_1R_2	LFA-1/ICAM-1 IC_{50} (μM)[a]
16a	-$NH(CH_2)_6OH$	9.8
16b	-$N[(CH_2)_2OH]_2$	15
16c		7.0
16d		16.5 (16-17)
16e		4.5
14b	-OH	2.6 (2.3-2.9)
17a	-$NH(CH_2)_2OH$	0.92 (0.4-2.0)
17b	-$NH(CH_2)_6OH$	0.59 (0.5-0.7)
17c	-$N[(CH_2)_2OH]_2$	0.71 (0.3-1.8)
17c		1.4
17f		0.46 (0.40-0.50)
17g		1.1 (0.8-1.6)
17h		0.14 (0.1-0.2)
17i		0.75 (0.7-0.8)

[a] IC_{50} calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 3.2×10^{-8} to 10^{-4} unless otherwise noted.

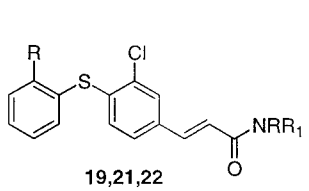
amines with *p*-cinnamides on the two opposing phenyl rings of the sulfide. Among the secondary amines explored, morpholine (**21a**), methylenedioxybenzylpiperazine (**21c**), and *N*-methylsarcocine (**21d**) derivatives are as active as the bis-cinnamide **19**, while *N*-formylpiperazine analogue **21b** is only marginally less active than **19**. Interestingly, combining the *o*-anilino substituent of **8** with *p*-cinnamide yielded the equally potent antagonist **22** against LFA-1/ICAM-1 interaction as **19**. The results from positioning both *o*- and *p*-cinnamides on the same aromatic ring turned out to be quite different. Fixing the *o*-cinnamide as morpholinamide, aminopropylpyrrolidinone as the *p*-cinnamide partner rendered virtually inactive compound **25a**, so did *N*-acetylpiperazine (**25b**) and morpholine (**25c**) analogues. The lack of synergy between *o*- and *p*-cinnamides appears to indicate the existence of only one additional binding pocket. We focused on the *p*-cinnamide as the lead structure for further optimization based on its better potency.

The three portions of the *p*-arylthio cinnamide were examined separately to identify optimal substituents for final assembly of a more potent inhibitor. Replacing the chlorine on the central phenyl ring (B-ring) of **17e** with a nitro group led to a small increase of the potency of the resulting compound **28a** (Table 5). On the basis of the existing SAR of the B- and C-rings (cinnamide portion), the A-ring (*p*-arylthio) substituents were then explored using compound **28b** (IC_{50} = 0.090 μM), an *N*-acetylpiperazine analogue, as the benchmark. The main focus was to examine hydrophobic benzenethiols as A-ring partners, along with some hydrophilic benzenethiols as wild cards. The results from this exercise seem to suggest that the binding pocket for the A-ring consists primarily of hydrophobic amino acid residues. 2,3-Dichlorobenzenethiol yielded inhibitor **28c** equipotent to the reference analogue **28b**, so did 2-chloro (**28d**) and 2-methyl (**28e**) benzenethiols. To fully take advantage of the hydrophobic interaction at the 2-position of the A-ring, different alkyl substituents were examined. An ethyl group (**28g**) was slightly better than the methyl group, and the isopropyl group in turn yielded a slightly more active analogue **28h** (A-286982). But the *tert*-butyl group offered compound **28i** with more than a 10-fold decrease in potency compared with **28h**. In contrast to the incremental improvement seen from **28c** to **28h**, the hydrophilic groups faired worse than the hydrophobic groups. 2-Aminobenzenethiol analogue **28f** is 6-fold less active than the 2-chloro compound **28e**. *N*,*N*-Dimethylaminobenzenethiol derivative **28k** is 7-fold less active than its analogous **28h**. 2-Formylbenzenethiol resulted in a very potent inhibitor **28j**, although 2-carboxamidobenzenethiol **28l** led to almost complete negation of all the affinity we have gained so far.

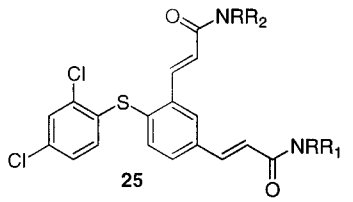
For the SAR of the B-ring, electron-donating groups, such as amino (**29**) and morpholinopropylamino (**31**), yielded much less active compounds. Other electron-withdrawing groups, such as bromine (**30**) and formyl (**33**), yielded analogues with similar potency as their chlorine counterpart. The negatively charged carboxylic acid (**34**) and neutral primary carboxamide group (**35**) replacing the chlorine of **17e** led to a complete loss of potency against LFA-1/ICAM-1 interaction.

To confirm the cellular relevancy of inhibiting LFA-1/ICAM-1 inaction in the primary assay, we devised a secondary assay using an IL-8-stimulated JY cell system. A selective panel of compounds were examined, and the results are shown in Table 6. In general, the IC_{50} values derived from the primary assay agree well with the data from the adhesion assay. For example, the most active compound in the group, **28h**, exhibited an IC_{50}

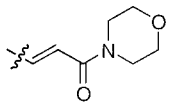
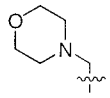
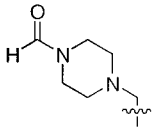
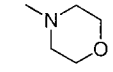
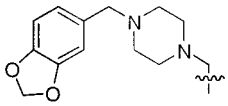
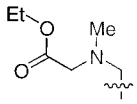
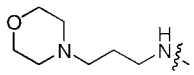
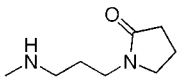
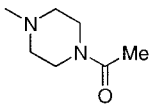
Table 4. Structure–Activity Relationships of Chimeras of *Ortho*- and *Para*-Disubstituted Cinnamido Diaryl Sulfides



19,21,22



25

Compound	R	-NRR$_1$	-NRR$_2$	LFA-1/ICAM-1 IC$_{50}$ (μM)[a]
19				0.18 (0.11-0.28)
21a				0.15 (0.11-0.21)
21b				0.42 (0.36-0.50)
21c				0.10 (0.070-0.15)
21d				0.26 (0.14-0.47)
22				0.18 (0.14-0.22)
25a				>20
25b				18 (16.8-19.3)
25c				> 20

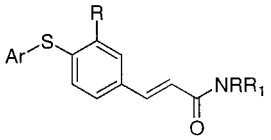
[a] IC$_{50}$ calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 6.4×10^{-9} to 2×10^{-5} unless otherwise noted.

value of 0.035 μM in the JY-8 cell adhesion assay versus 0.044 μM in the LFA-1/ICAM-1 biochemical assay.

Summary

A novel series of *p*-arylthio cinnamide-based inhibitors of LFA-1/ICAM-1 interaction has been identified, starting from an anilino diaryl sulfide screening lead, by mapping out additional binding space in close proximity to the one occupied by the original lead compound and by identifying the preferred linker to access that binding site. Rapid parallel optimization of the different portions of the lead structure and combination of the preferred structural features led to the identification of compound **28h**, a potent representative of this novel series of LFA-1/ICAM-1 interaction inhibitors. Studies of the mechanism of the inhibition for this

Table 5. Structure–Activity Relationships of A- and B-Ring Modification



28-31,33-35

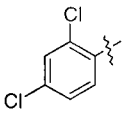
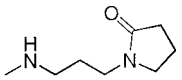
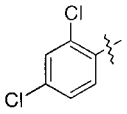
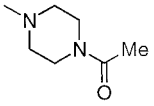
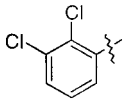
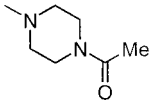
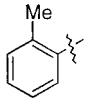
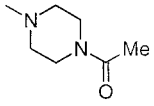
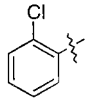
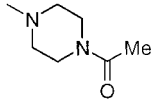
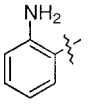
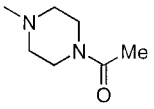
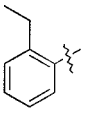
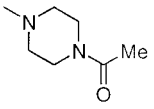
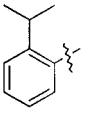
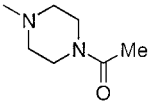
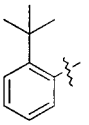
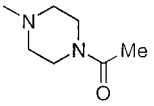
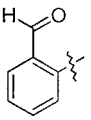
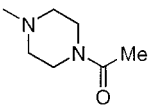
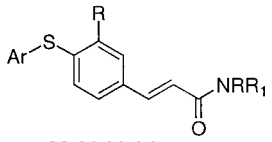
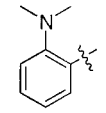
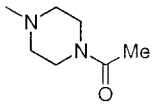
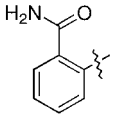
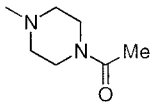
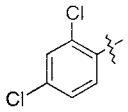
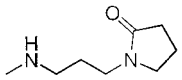
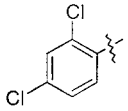
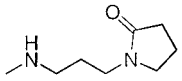
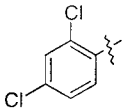
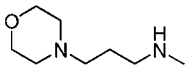
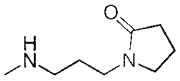
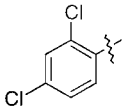
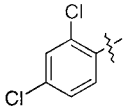
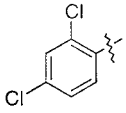
Compound	Ar	R	-NRR$_1$	LFA-1/ICAM-1 IC_{50} (μM)[a]
28a		NO_2		0.17 (0.1-0.3)
28b		NO_2		0.090
28c		NO_2		0.10 (0.10-0.11)
28d		NO_2		0.12 (0.080-0.15)
28e		NO_2		0.11 (0.08-0.16)
28f		NO_2		0.62 (0.86-0.44)
28g		NO_2		0.065 (0.060-0.070)
28h		NO_2		0.044 (0.030-0.060)
28i		NO_2		0.53 (0.47-0.59)
28j		NO_2		0.060 (0.050-0.080)

Table 5. (Continued)



28-31,33-35

Compound	Ar	R	-NRR$_1$	LFA-1/ICAM-1 IC$_{50}$ (μM)[a]
28k		NO_2		0.31 (0.29-0.33)
28l		NO_2		16.2
29		NH_2		19
30		Br		0.65 (0.61-0.70)
31				15.5 (14.9-16.1)
33		-CHO		0.61 (0.50-0.74)
34		-COOH		>20
35		$-CONH_2$		>20

[a] IC$_{50}$ calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 6.4×10^{-9} to 2×10^{-5} unless otherwise noted.

series of compounds against LFA-1/ICAM-1 interaction and further optimization of the pharmaceutical properties of this series of compounds will be reported in due course.

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

Table 6. Comparison of LFA-1/ICAM-1 Biochemical Assay and ICAM-1/JY-8 Cell Adhesion Assay

Compound	LFA-1/ICAM-1 IC_{50} (μM)	JY-8 Cell Adhesion IC_{50} (μM)[a]
15d	1.0 (0.6-1.8)	2.1
15l	1.2 (0.60-2.9)	5.3
17e	0.55 (0.4-0.7)	0.70 (0.60-0.80)
17h	0.14 (0.1-0.2)	0.24
19	0.18 (0.11-0.28)	0.19 (0.10-0.50)
21c	0.10 (0.070-0.15)	0.36 (0.20-0.70)
28a	0.17 (0.1-0.3)	0.14 (0.10-0.20)
28b	0.090	0.063 (0.02-0.2)
28g	0.065 (0.060-0.070)	0.10
28h	0.044 (0.030-0.060)	0.035

[a] IC_{50} calculated using a mean of at least two measurements (all duplicates) for 6 concentrations from 6.4×10^{-9} to 2×10^{-5} unless otherwise noted.

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% B in 20 min. The purified fractions were evaporated to dryness on a Savant SpeedVac.

2-[(2,4-Dichlorophenyl)thio]nitrobenzene (5). To a stirred solution of 2,4-dichlorothiophenol (2.0 g, 11.2 mmol) in 25 mL of anhydrous DMF was added potassium carbonate (3.09 g, 22.4 mmol), followed by 2-chloronitrobenzene (1.78 g, 11.3 mmol). The mixture was then heated under nitrogen atmosphere at 70 °C for 5 h. The reaction mixture was then allowed to cool to room temperature and partitioned between ether and water. The aqueous layer was extracted with ether once and the combined organic layer was washed with water and brine, dried over sodium sulfate and condensed in vacuuo to give 2.78 g (9.25 mmol, 83%) of the desired nitrobenzene as a light yellow solid.

2-[(2,4-Dichlorophenyl)thio](2-acrylamido)benzene (6). A mixture of compound **5** (1.5 g, 5.0 mmol) and $SnCl_2$ (4.74 g, 25 mmol) in 50 mL of anhydrous EtOH was refluxed under nitrogen atmosphere for 90 min. The reaction was then allowed to cool to room temperature, quenched with saturated $NaHCO_3$, extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, condensed in vacuuo to give 1.29 g of the crude aniline as a yellowish brown solid. The aniline was taken up in 20 mL of CH_2Cl_2, Et_3N (1.0 mL, 7.17 mmol) was added, followed by dropwise addition of acryloyl chloride (0.42 mL, 5.26 mmol). After stirring for 1 h at ambient temperature, the mixture was poured into 10 mL of 3 N aqueous HCl and extracted with 20 mL of EtOAc. The organic layer was then washed with brine, dried over $MgSO_4$, concentrated under reduced pressure to give the crude amide which was purified on a silica gel flash column eluted with 50% EtOAc in hexanes to give 1.05 g (3.24 mmol, 65% over two steps) of the acrylamide as a white solid.

2,4-Dichlorophenyl 2-(Morpholinoethylcarbonylamino)phenyl Sulfide (7e). The acrylamide **6** (100 mg, 0.31 mmol) was refluxed with morpholine (0.13 mL, 1.55 mmol) in 1.0 mL of MeOH for 16 h. After cooling to room temperature, the reaction mixture was purified on a preparative HPLC to give 114 mg of amide **7e** (0.28 mmol, 90% yield) as a light brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (br m, 4H), 2.52 (br m, 4H), 3.62 (br m, 4H), 6.53 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 2.4, 8.7 Hz, 1H), 7.17 (td, J = 0.9, 7.65 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.46−7.56 (m, 2H), 8.33 (d, J = 8.7 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 411, 413, 415. Anal. ($C_{19}H_{20}Cl_2N_2O_2S \cdot 0.06H_2O$) C, H, N.

2,4-Dichlorophenyl 2-(*N*,*N*-Dimethylaminoethylcarbonylamino)phenyl Sulfide (7a): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (br s, 6H), 2.47 (br m, 2H), 2.75 (br m, 2H), 6.44 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 2.1, 8.4 Hz, 1H), 7.10−7.23 (m, 2H), 7.39 (br m, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 369, 371, 373. Anal. ($C_{17}H_{18}Cl_2N_2OS$) C, H, N.

2,4-Dichlorophenyl 2-(*N*,*N*-Di-*n*-propylaminoethylcarbonylamino)phenyl Sulfide (7b): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 6.9 Hz, 3H), 1.01 (t, J = 6.9 Hz, 3H), 1.36 (br m, 2H), 1.53 (br m, 2H), 1.83 (br m, 2H), 2.39 (br m, 2H), 2.67 (br m,1H), 2.94 (br m, 1H), 3.12 (br m, 1H), 3.37 (br m, 1H), 6.44 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 2.1, 8.4 Hz, 1H), 7.10−7.23 (m, 2H), 7.39 (br m, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 425, 427, 429. Anal. ($C_{21}H_{26}Cl_2N_2OS \cdot 0.04H_2O$) C, H, N.

2,4-Dichlorophenyl 2-(*N*-Benzylmethylaminoethylcarbonylamino)phenyl Sulfide (7c): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3H), 2.45 (br m, 2H), 2.58 (br m, 2H), 3.56 (s, 2H), 6.47 (d, J = 8.4 Hz, 1H), 7.02 (dd, J = 2.7, 8.4 Hz, 1H), 7.11−7.46 (m, 7H), 7.51 (t, J = 8.4 Hz, 1H), 7.55 (dd, J = 1.9, 8.4 Hz, 1H), 8.40 (d, J = 7.5 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 445, 447, 449. Anal. ($C_{23}H_{22}Cl_2N_2OS \cdot 0.06H_2O$) C, H, N.

2,4-Dichlorophenyl 2-(1-Pyrrolinylethylcarbonylamino)phenyl Sulfide (7d): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66−1.90 (br m, 4H), 2.28−2.63 (br m, 6H), 2.63−2.83 (br m, 2H), 6.52 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 2.1, 8.7 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.43−7.53 (m, 2H), 8.41 (d, J = 8.1 Hz, 1H); MS (ESI) $(M + H)^+$ at m/z 395, 397, 399. Anal. ($C_{19}H_{20}N_2OSCl_2 \cdot 0.10H_2O$) C, H, N.

2,4-Dichlorophenyl 2-(4-Methyl-1-piperazinylethylcarbonylamino)phenyl Sulfide (7f): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28−2.97 (m, 15H), 6.53 (d, J = 8.7 Hz, 1H), 7.06 (dd, J = 2.4, 8.7 Hz, 1H), 7.17 (td, J = 0.9, 7.65 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.46−7.57 (m, 2H), 8.33 (d, J = 8.7 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 424, 426, 428. Anal. ($C_{20}H_{23}Cl_2N_3OS \cdot 0.17H_2O$) C, H, N.

2,4-Dichlorophenyl 2-(Morpholinopropylamino)phenyl Sulfide (8). To a stirred suspension of LAH (120 mg, 0.29 mmol) in 2.0 mL of anhydrous THF was added amide **7e** (22 mg, 0.58 mmol) in 1.0 mL of THF dropwise. After completion of the addition, the reaction mixture was stirred for 4 h at room temperature before it was quenched with 22 μL of H_2O, 22 μL of 3 N NaOH, and 66 μL of H_2O. The resulting mixture was filtered through Celite and condensed in vacuuo. The resulting residue was purified on a preparative HPLC to give 100 mg (0.25 mmol, 86% yield) of the diamine **8** as a light brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.94−2.10 (m, 2H), 2.58−2.81 (br m, 2H), 2.83−2.95 (m, 2H), 3.27 (t, J = 6.45 Hz, 1H), 3.44 (br d, J = 8.1 Hz, 2H), 3.87−4.07 (br m, 4H), 6.52 (d, J = 8.7 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 6.78 (td, J = 0.9, 7.5 Hz, 1H), 7.05 (dd, J = 2.4, 8.7 Hz, 1H), 7.39 (td, J = 1.8, 7.8 Hz, 2H), 7.49 (d, J = 1.8, 7.8 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 397, 399, 401. Anal. ($C_{19}H_{22}N_2OCl_2S \cdot 1.14TFA$) C, H, N.

3-[(2,4-Dichlorophenyl)thio]benzoic Acid (12). To a solution of KOH (1.6 g, 28.5 mmol) in 30 mL of H_2O was added Cu powder (133 mg, 0.45 mmol), 2,4-dichlorothiophenol (1.5 g, 8.38 mmol) and 3-iodobenzoic acid (2.0 g, 8.38 mmol) sequentially. The mixture was then refluxed for 9 h before it was allowed to cool to room temperature. The aqueous mixture

was then filtered through Celite, washed with hot H_2O, acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine, dried over Mg_2SO_4, condensed in vacuuo, and pumped to give 2.44 g (8.16 mmol, 97% yield) of the acid **12** as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.15 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 2.1, 8.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.66 (dd, J = 1.8, 7.8 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 1.8, 7.8 Hz, 1H), 13.2 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 298, 300.

3-[(2,4-Dichlorophenyl)thio]benzaldehyde (10m). To a stirred solution of acid **12** (1.4 g, 4.68 mmol) in THF was added 1.0 M of BH_3 in THF (9.4 mL, 9.36 mmol). The mixture was then stirred at room temperature for 1 h before it was quenched carefully with 3 N HCl. The biphasic mixture was extracted with Et_2O (2 × 25 mL), the combined organic layer was washed with brine, dried over Na_2SO_4, condensed in vacuuo to give 1.3 g (4.56 mmol, 97%) of the alcohol as a colorless oil. To a stirred solution of DMSO (1.74 mL, 24.6 mmol) in 30 mL of CH_2Cl_2 at −78 °C was dropped in $(COCl)_2$ (1.07 mL, 12.3 mmol) slowly. After 20 min, the alcohol (700 mg, 2.46 mmol) in 5 mL of CH_2Cl_2 was then added. After 30 min, Et_3N (6.9 mL, 49.2 mmol) was then added and the resulting mixture was then allowed to warm to room temperature gradually and stirred for 2 h. The mixture was then partitioned between Et_2O and 3N HCl. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and condensed in vacuuo. The residue was purified on a silica gel column eluted with 10% Et_2O in hexanes to give 330 mg (1.17 mmol, 47% yield) of the aldehyde **10m** as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, J = 8.4 Hz,1H), 7.18 (dd, J = 2.1, 8.4 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.58 (td, J = 1.8, 7.8 Hz, 1H), 7.80 (td, J = 1.8, 7.8 Hz, 1H), 7.82 (d, J = 1.8 Hz, 1H), 9.98 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 282, 284.

2,4-Dichlorophenyl 2-(*N*,*N*-Dimethylaminoethylaminomethyl)phenyl Sulfide (13). A mixture of the aldehyde **10** (100 mg, 0.35 mmol) prepared analogous to nitrobenzene **5** with *N*,*N*-dimethylethylenediamine (38.9 μL, 0.35 mmol) in 2.5 mL of MeOH was stirred at room temperature for 2 h before $NaBH_4$ (20.8 mg, 0.53 mmol) was added. The resulting mixture was stirred for an additional 2 h before it was quenched with saturated $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL), the organic layer was washed with brine, dried over Mg_2SO_4, condensed in vacuuo. The resulting residue was purified on a preparative HPLC to give 117 mg (0.33 mmol, 95% yield) of the diamine **13** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 6H), 2.42 (t, J = 6.15 Hz, 2H), 2.70 (t, J = 6.15 Hz, 2H), 3.89 (s, 2H), 6.65 (d, J = 8.7 Hz, 1H), 7.04 (dd, J = 2.4, 8.7 Hz, 1H), 7.30 (dd, J = 1.5, 7.2 Hz, 1H), 7.37−7.45 (m, 3H), 7.56 (dd, J = 1.5, 7.2 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 355, 357, 359. Anal. ($C_{17}H_{20}N_2Cl_2S$·2.13TFA) C, H, N.

***trans*-2-[(2,4-Dichlorophenyl)thio]cinnamic Acid (14a).** A mixture of the aldehyde **10** (1.50 g, 5.3 mmol), malonic acid (1.21 g, 11.6 mmol), and piperidine (78.6 μL, 0.80 mmol) in 8.0 mL of anhydrous pyridine was heated at 110 °C for 2 h during which the gas evolution ceased. After pyridine was removed under vacuum, water and 3 N aqueous HCl were then added with stirring. The desired cinnamic acid was collected through filtration, washed with cold water and dried in a vacuum oven overnight to give 1.56 g (4.8 mmol, 91%) of a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.57 (d, J = 15.9 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 7.34 (d, J = 2.7, 8.9 Hz, 1H), 7.47−7.60 (m, 3H), 7.74 (d, J = 2.7 Hz, 1H), 7.89 (d, J = 15.9 Hz, 1H), 8.00 (d, J = 6.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 342, 344, 346. Anal. ($C_{15}H_{10}O_2Cl_2S$·0.22H_2O) C, H, N.

***trans*-2-Chloro-4-[(2,4-dichlorophenyl)thio]cinnamic Acid (14b):** white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.62 (d, J = 15.9 Hz, 1H), 7.05 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.49 (dd, J = 2.7, 8.9 Hz, 1H), 7.55 (d, J = 15.9 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.85 (d, J = 2.7 Hz, 1H), 7.98 (s, 1H), 12.5 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 358, 360, 362, 364. Anal. ($C_{15}H_9O_2Cl_3S$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((6-Hydroxyhexylamino)carbonyl)ethenyl)phenyl Sulfide (15d). A suspension of the acid **14** (284 mg, 0.87 mmol) in 5 mL of methylene chloride was stirred with $(COCl)_2$ (84 μL, 0.97 mmol), and 1 drop of DMF under nitrogen atmosphere for 90 min. The solvent was then removed under vacuum and the residual $(COCl)_2$ was removed with benzene (2 × 2 mL) in vacuuo. To a separate flask, previously filled with 6-amino-1-hexanol (12 mg, 0.10 mmol), *i*-Pr_2NEt (22.8 μL, 0.13 mmol) and DMAP (1.1 mg, 0.008 mmol) in 2.0 mL of CH_2Cl_2, the acid chloride (30 mg, 0.087 mmol) in 1.0 mL of CH_2Cl_2 was then dropped in slowly. After 30 min, the reaction mixture was poured into 3 N aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, condensed under reduced pressure. The crude product was purified on a preparative HPLC to give 21.0 mg (0.051 mmol, 90%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31−1.48 (m, 4H), 1.48−1.70 (m, 4H), 3.37 (q, J = 6.7 Hz, 2H), 3.65 (t, J = 6.3 Hz, 2H), 5.63 (br s, 1H), 6.36 (d, J = 15.9 Hz, 1H), 6.71 (d, J = 9.3 Hz, 1H), 7.05 (dd, J = 2.4, 8.7 Hz, 1H), 7.31−7.49 (m, 4H), 7.65 (dd, J = 2.1, 7.5 Hz, 1H), 7.99 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 441, 443, 445. Anal. ($C_{21}H_{23}Cl_2NO_2S$·0.03H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((Phenethylamino)carbonyl)ethenyl)phenyl Sulfide (15a): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.88 (t, J = 7.2 Hz, 2H), 3.63 (q, J = 7.2 Hz, 2H), 5.60 (br s, 1H), 6.32 (d, J = 15.9 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 7.04 (dd, J = 2.7, 8.9 Hz, 1H), 7.18−7.50 (m, 8H), 7.64 (dd, J = 1.8, 7.5 Hz, 1H), 8.00 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 428, 430, 432. Anal. ($C_{23}H_{19}Cl_2NOS$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((4-Methylbenzothiazo-2-ylamino)carbonyl)ethenyl)phenyl Sulfide (15b): light brown solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 6.46 (d, J = 15.9 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 7.07 (dd, J = 2.7, 8.9 Hz, 1H), 7.26 (overlapping t, 1H), 7.32−7.51 (m, 5H), 7.70 (dd, J = 3.3, 5.7 Hz, 1H), 8.35 (d, J = 15.9 Hz, 1H), 9.95 (br s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 471, 473, 475. Anal. ($C_{23}H_{16}Cl_2N_2OS_2$·0.07H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((*N*-Benzyl(*p*-phenoxybenzyl)amino)carbonyl)ethenyl)phenyl Sulfide (15c): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.66 (s, 2H), 6.70 (br m, 1H), 6.90−7.16 (m, 4H), 7.06−7.21 (m, 4H), 7.21−7.47 (m, 8H), 7.53 (br m, 1H), 8.22 (br s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 597, 599, 601. Anal. ($C_{35}H_{27}Cl_2NO_2S$·0.04H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((2-Hydroxyethylamino)carbonyl)ethenyl)phenyl Sulfide (15e): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.55 (q, J = 5.3 Hz, 2H), 3.80 (t, J = 5.3 Hz, 2H), 6.08 (s, 1H), 6.39 (d, J = 15.9 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 7.06 (d, J = 2.7, 8.9 Hz, 1H), 7.32−7.47 (m, 4H), 7.65 (dd, J = 1.8, 8.9 Hz, 1H), 8.05 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 368, 370, 372. Anal. ($C_{17}H_{15}NO_2Cl_2S$·0.33H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((2,3-Dihydroxypropylamino)carbonyl)ethenyl)phenyl Sulfide (15f): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (br m, 2H), 3.53 (q, J = 5.5 Hz, 2H), 3.57−3.66 (m, 2H), 3.83 (p, J = 5.5 Hz, 1H), 6.08 (br m, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.75 (d, J = 8.9 Hz, 1H), 7.06 (dd, J = 2.7, 8.9 Hz, 1H), 7.32−7.48 (m, 4H), 7.65 (dd, J = 1.8, 8.9 Hz, 1H), 8.06 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 398, 401, 403. Anal. ($C_{18}H_{17}Cl_2NO_3S$·0.5H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((*N*,*N*-Diethanolamino)carbonyl)ethenyl)phenyl Sulfide (15g): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (br m, 2H), 3.60 (t, J = 4.8 Hz, 2H), 3.65 (t, J = 4.8 Hz, 2H), 3.73 (t, J = 4.8 Hz, 2H), 4.02 (t, J = 4.8 Hz, 2H), 6.72 (d, J = 8.9 Hz, 1H), 6.90 (d, J = 15.9 Hz, 1H), 7.05 (dd, J = 2.7, 8.9 Hz, 1H), 7.32−7.49 (m, 4H), 7.67 (d, J = 8.9 Hz, 1H), 8.08 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 412, 414, 416. Anal. ($C_{19}H_{19}NO_3Cl_2S$·0.24H_2O) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-(Glycinylcarbonyl)ethenyl)-phenyl Sulfide (15h): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.13 (br m, 1H), 4.22 (d, J = 4.8 Hz, 2H), 6.29 (t, J = 4.65 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 7.06 (dd, J = 2.7, 8.9 Hz, 1H), 7.33−7.47 (m, 4H), 7.67 (dd, J = 1.8, 8.9 Hz, 1H), 8.10 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 399, 401, 403. Anal. ($C_{17}H_{13}NO_3Cl_2S\cdot 0.09$TFA) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((3-(1-Imidazolyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (15i): white powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.88 (p, J = 7.7 Hz, 2H), 3.11 (q, J = 7.7 Hz, 2H), 3.97 (t, J = 7.7 Hz, 2H), 6.63 (d, J = 15.9 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 0.9 Hz, 1H), 7.17 (d, J = 0.9 Hz, 1H), 7.33 (dd, J = 2.7, 8.7 Hz, 1H), 7.46−7.65 (m, 4H), 7.72 (d, J = 2.7 Hz, 1H), 7.78 (d, J = 15.9 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 8.24 (t, J = 5.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 448, 450, 452. Anal. ($C_{21}H_{19}N_3OCl_2S\cdot 0.87H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((2-Tetrahydrofurylmethylamino)carbonyl)ethenyl)phenyl Sulfide (15j): white powder; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (p, J = 7.05 Hz, 2H), 1.50−1.66 (m, 2H), 3.18−3.31 (m, 1H), 3.63−3.93 (m, 3H), 4.01 (qd, J = 3.0, 6.9 Hz, 1H), 5.98 (m, 1H), 6.38 (d, J = 15.9 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 2.7, 8.9 Hz, 1H), 7.32−7.49 (m, 4H), 7.66 (d, J = 1.8, 8.9 Hz, 1H), 8.03 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 408, 410, 412. Anal. ($C_{20}H_{19}NO_2Cl_2S\cdot 0.50H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((3-(1-Pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (15l): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (quintet, J = 6.1 Hz, 2H), 2.07 (quintet, J = 7.8 Hz, 2H), 2.44 (t, J = 7.8 Hz, 2H), 3.30 (q, J = 6.1 Hz, 2H), 3.34−3.48 (m, 4H), 6.44 (d, J = 15.9 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 7.03 (dd, J = 2.7, 8.9 Hz, 1H), 7.07 (br t, 1H), 7.30−7.49 (m, 4H), 7.71 (dd, J = 1.8, 8.9 Hz, 1H), 8.06 (d, J = 15.9 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 449, 451, 453. Anal. ($C_{22}H_{22}Cl_2N_2O_2S\cdot 0.23H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((1-Morpholino)carbonyl)-ethenyl)phenyl Sulfide (15m): white powder; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.53 (br m, 2H), 3.55−3.62 (m, 4H), 3.67 (br m, 2H), 6.66 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 15.9 Hz, 1H), 7.33 (dd, J = 2.7, 8.9 Hz, 1H), 7.42−7.62 (m, 3H), 7.74 (d, J = 2.7 Hz, 1H), 7.85 (d, J = 15.9 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 394, 396, 398. Anal. ($C_{19}H_{17}Cl_2NO_2S\cdot 0.09H_2O$) C, H, N.

2,4-Dichlorophenyl 3-((*E*)-((6-Hydroxyhexylamino)-carbonyl)ethenyl)phenyl Sulfide (16a): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31−1.48 (m, 4H), 1.48−1.72 (m, 4H), 3.40 (q, J = 6.9 Hz, 2H), 3.65 (t, J = 6.9 Hz, 2H), 5.61 (br t, 1H), 6.36 (d, J = 15.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.13 (dd, J = 2.4, 8.7 Hz, 1H), 7.33−7.50 (m, 4H), 7.53 (s, 1H), 7.58 (d, J = 15.3 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 424, 426, 428. Anal. ($C_{21}H_{23}NO_2Cl_2S\cdot 0.05H_2O$) C, H, N.

2,4-Dichlorophenyl 3-((*E*)-((*N*,*N*-Diethanolamino)carbonyl)ethenyl)phenyl Sulfide (16b): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.61−3.74 (m, 4H), 3.88 (t, J = 4.8 Hz, 2H), 3.94 (t, J = 4.8 Hz, 2H), 6.93 (d, J = 15.3 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.13 (dd, J = 2.4, 8.7 Hz, 1H), 7.33−7.40 (m, 2H), 7.44 (d, J = 2.4 Hz, 1H), 7.48 (td, J = 1.8, 6.6 Hz, 1H), 7.53 (s, 1H), 7.63 (d, J = 15.3 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 412, 414, 416. Anal. ($C_{19}H_{19}NO_3Cl_2S\cdot 0.10H_2O$) C, H, N.

2,4-Dichlorophenyl 3-((*E*)-((3-(1-Imidazolyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (16c): white powder; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02−2.34 (m, 2H), 3.39 (q, J = 6.1 Hz, 2H), 4.15 (t, J = 6.1 Hz, 2H), 6.50 (d, J = 15.3 Hz, 1H), 6.57 (br s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.03 (s, 1H), 7.12 (dd, J = 2.4, 8.7 Hz, 1H), 7.15 (s, 1H), 7.31−7.39 (m, 2H), 7.43 (d, J = 2.4 Hz, 1H), 7.46 (td, J = 1.8, 6.6 Hz, 1H), 7.52 (s, 1H), 7.58 (d, J = 15.3 Hz, 1H), 8.28 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 432, 434, 436. Anal. ($C_{21}H_{19}N_3OCl_2S\cdot 0.50H_2O$) C, H, N.

2,4-Dichlorophenyl 3-((*E*)-((1-Morpholino)carbonyl)-ethenyl)phenyl Sulfide (16d): white powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.51−3.67 (m, 6H), 3.67−3.77 (m, 2H), 6.94 (d, J = 8.9 Hz, 1H), 7.35 (d, J = 15.3 Hz, 1H), 7.37 (dd, J = 2.7, 8.9 Hz, 1H), 7.40 (d, J = 15.3 Hz, 1H), 7.48 (s, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 2.7 Hz, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.98 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 394, 396, 398. Anal. ($C_{19}H_{17}NO_2Cl_2S$) C, H, N.

2,4-Dichlorophenyl 3-((*E*)-((3-(1-Pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (16e): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (quintet, J = 5.9 Hz, 2H), 2.08 (quintet, J = 7.6 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 3.33 (q, J = 5.9 Hz, 2H), 3.41 (q, J = 6.7 Hz, 4H), 3.33 (q, J = 5.9 Hz, 2H), 3.41 (q, J = 6.7 Hz, 4H), 6.45 (d, J = 15.3 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 7.12 (dd, J = 2.7, 8.9 Hz, 1H), 7.30−7.39 (m, 2H), 7.43 (d, J = 2.7 Hz, 1H), 7.50 (td, J = 1.8, 6.6 Hz, 1H), 7.56 (d, J = 15.3 Hz, 1H), 7.56 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 449, 451, 453. Anal. ($C_{22}H_{22}N_2O_2Cl_2S\cdot 0.25H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((2-hydroxyethylamino)carbonyl)ethenyl)phenyl Sulfide (17a): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.57 (q, J = 7.65 Hz, 2H), 3.71 (q, J = 7.65 Hz, 2H), 6.06 (br s, 1H), 6.40 (d, J = 15.3 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 7.22−7.30 (m, 4H), 7.49−7.60 (m, 1H), 7.55 (d, J = 15.3 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 402, 404, 406, 408. Anal. ($C_{17}H_{14}NO_2Cl_3S\cdot 0.25H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl Sulfide (17b): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 4H), 1.58 (m, 4H), 3.40 (q, J = 6.7 Hz, 2H), 3.65 (br m, 2H), 5.60 (br t, 1H), 6.35 (d, J = 15.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.22−7.30 (m, 4H), 7.49−7.60 (m, 1H), 7.55 (d, J = 15.3 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 458, 460, 462, 464. Anal. ($C_{21}H_{22}NO_2Cl_3S\cdot 0.27H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((bis(2-hydroxyethyl)amino)carbonyl)ethenyl)phenyl Sulfide (17c): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (br s, 2H), 3.67 (br m, 4H), 3.88 (t, J = 5.1 Hz, 2H), 3.94 (t, J = 5.1 Hz, 2H), 6.94 (d, J = 15.3 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.21−7.32 (m, 3H), 7.50−7.54 (m, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.58 (d, J = 15.3 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 446, 448, 450, 452. Anal. ($C_{19}H_{18}NO_3Cl_3S\cdot 1.09H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((3-(1-imidazolyl)-propylamino)carbonyl)ethenyl)phenyl Sulfide (17d): white powder; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09 (p, J = 6.75 Hz, 2H), 3.41 (q, J = 6.75 Hz, 2H), 4.05 (t, J = 6.75 Hz, 2H), 5.81 (br m, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.98 (br s, 1H), 7.10 (br s, 1H), 7.24 (s, 2H), 7.27 (overlapping m, 2H), 7.52 (m, 1H), 7.52 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 466, 468, 470. Anal. ($C_{21}H_{18}N_3OCl_3S\cdot 0.71H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (17e): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.74 (quintet, J = 6.0 Hz, 2H), 2.09 (quintet, J = 7.5 Hz, 2H), 2.45 (t, J = 8.25 Hz, 2H), 3.33 (q, J = 6.0 Hz, 2H), 3.42 (q, J = 8.25 Hz, 4H), 6.46 (d, J = 15.6 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.14−7.23 (m, 2H), 7.30 (dd, J = 2.4, 8.7 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.51 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 483, 485, 487, 489. Anal. ($C_{22}H_{21}N_2O_2Cl_3S\cdot 0.57H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((1-morpholino)-carbonyl)ethenyl)phenyl Sulfide (17f): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59−3.80 (m, 8H), 6.83 (d, J = 15.6 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.16−7.32 (m, 3H), 7.49−7.53 (m, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 15.6 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 428, 430, 432, 434. Anal. ($C_{19}H_{16}NO_2Cl_3S\cdot 0.46H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((4-methylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (17g): colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.51 (br m, 4H), 3.63−3.87 (br m, 4H), 6.85 (d, J = 15.6 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.19−7.25 (m, 2H), 7.27 (dd, J = 2.1, 8.7 Hz, 1H), 7.52 (t, J = 0.9 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.60 (d, J

= 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 441, 443, 445, 447. Anal. ($C_{20}H_{19}N_2OCl_3S \cdot 0.45H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (17h): white solid; ^{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. Anal. ($C_{21}H_{19}N_2O_2Cl_3S \cdot 0.85H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Chloro-4-((*E*)-((4-(2-pyridyl)piperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (17i): white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.59 (br m, 2H), 3.69 (br m, 2H), 3.78 (br m, 2H), 3.86 (br m, 2H), 6.64−6.72 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 7.22−7.25 (m, 2H), 7.31(dd, J = 2.4, 8.7 Hz, 1H), 7.49−7.57 (m, 2H), 7.61 (d, J = 15.6 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 8.19−8.24 (m, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 504, 506, 508, 510. Anal. ($C_{24}H_{20}N_3OCl_3S$) C, H, N.

2-Bromophenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (18). Prepared analogously to compound **15d**, substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluorobenzadehyde, and 6-amino-1-hexanol with morpholine: white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.50−3.66 (br m, 6H), 3.66−3.79 (br m, 2H), 7.05 (d, J = 8.7 Hz, 1H), 7.26 (dd, J = 2.1, 8.1 Hz, 1H), 7.33 (dd, J = 2.1, 8.1 Hz, 1H), 7.36 (d, J = 15.6 Hz, 1H), 7.39 (dd, J = 1.8, 12.0 Hz, 1H), 7.45 (dd, J = 1.8, 6.3 Hz, 1H), 7.48 (d, J = 15.6 Hz,1H), 7.64 (dd, J = 2.1, 8.7 Hz, 1H), 7.80 (dd, J = 2.8, 8.7 Hz, 1H), 8.09 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 438, 440, 442.

2-((*E*)-((1-Morpholino)carbonyl)ethenyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (19). A mixture of bromide **18** (80 mg, 0.18 mmol), acryloylmorpholine (33 mg, 0.23 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), P(*o*-tolyl)$_3$ (17 mg, 0.056 mmol), Et_3N (39 μL, 0.27 mmol), and anhydrous DMF (1.0 mL) in a pressure tube was flushed with nitrogen for 5 min before it capped and heated at 110 °C overnight. TLC indicated almost complete consumption of the starting bromide. The reaction mixture was then allowed to cool to room temperature, partitioned between EtOAc and water. The aqueous layer was extracted once with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4, condensed under reduced pressure. The crude product was purified on a preparative HPLC to give 35 mg (0.070 mmol, 39%) of compound **19** as a light brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.43−3.88 (m, 16H), 6.58 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 15.3 Hz, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.47−7.64 (m, 4H), 7.86 (d, J = 15.3 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at *m/z* 516, 518. Anal. ($C_{26}H_{27}N_2O_4ClS \cdot 0.46H_2O$) C, H, N.

2-(Hydroxymethyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (20). Prepared analogously to compound **18**, substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol: white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.50−3.62 (br m, 6H), 3.65−3.74 (br m, 2H), 4.54 (d, J = 5.7 Hz, 2H), 5.33 (t, J = 5.7 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 15.0 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 15.0 Hz, 1H), 7.43 (dd, J = 1.8, 8.7 Hz, 1H), 7.50 (dd, J = 2.1, 8.7 Hz, 1H), 7.55 (dd, J = 2.1, 7.8 Hz, 1H), 7.68 (dd, J = 1.5, 8.1 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 390, 392.

2-(1-Morpholinomethyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (21a). To a stirred solution of benzyl alcohol **20** (195 mg, 0.32 mmol) in 2.0 mL of anhydrous DMF was added LiBr (48 mg, 0.35 mmol). The mixture was then cooled in an ice−water bath, and PBr_3 (60 μL, 0.40 mmol) was dropped in slowly. The ice bath was then removed and the mixture was stirred at room temperature for 1 h. Water was then added, the mixture was then partitioned between EtOAc and aqueous $NaHCO_3$ and the aqueous layer was extracted with EtOAc once. The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated on a rotavap. The crude bromide (230 mg) was used directly for the alkylation without purification.

To a stirred solution of morpholine (10 μL, 0.11 mmol) in 0.5 mL of CH_3CN was added *i*-Pr_2NEt (23.7 μL, 0.14 mmol), followed by the bromide (40 mg, 0.091 mmol). The mixture was then stirred at room temperature for 2 h. Solvent was then removed and the crude product was purified with a preparative HPLC to give 36.3 mg (0.079 mmol, 87% yield) of compound **21a** as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.33 (br t, 4H), 3.45 (br t, 4H), 3.50−3.65 (m, 6H), 3.56 (s, 2H), 3.65−3.80 (br m, 2H), 6.74 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 15.3 Hz, 1H), 7.35−7.41 (m, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.46 (td, J = 2.4, 8.1 Hz, 1H), 7.52 (dd, J = 2.1, 8.7 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 459, 461. Anal. ($C_{24}H_{27}ClN_2O_3S \cdot 1.12TFA$) C, H, N.

2-(4-Formylpiperazin-1-ylmethyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (21b): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.20−2.32 (m, 6H), 2.74 (br m, 2H), 3.48 (s, 2H), 3.59 (m, 6H), 3.70 (br m, 2H), 6.74 (d, J = 8.7 Hz, 1H), 7.29 (d, J = 15.6 Hz, 1H), 7.35−7.41 (m, 2H), 7.42 (d, J = 15.6 Hz, 1H), 7.45−7.52 (m, 3H), 7.98 (d, J = 2.1, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 486, 488. Anal. ($C_{25}H_{28}ClN_3O_3S \cdot 0.34TFA$) C, H, N.

2-(4-(1,3-Benzodioxol-5-ylmethyl)piperazin-1-ylmethyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (21c): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.13−2.40 (br m, 8H), 3.28 (s, 2H), 3.49−3.64 (br m, 6H), 3.54 (s, 2H), 3.70 (br m, 2H), 5.97 (s, 2H), 6.69 (dd, J = 1.8, 8.1 Hz, 1H), 6.74 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 15.3 Hz, 1H), 7.33−7.38 (m, 2H), 7.38−7.50 (m, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 592, 594. Anal. ($C_{32}H_{34}ClN_3O_4S \cdot 1.07TFA$) C, H, N.

2-((*N*-Ethoxycarbonylmethyl-*N*-methylamino)methyl)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (21d): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.16 (t, J = 7.2 Hz, 3H), 2.27 (s, 2H), 3.30 (s, 2H), 3.51−3.66 (br m, 6H), 3.66−3.75 (br m, 2H), 3.78 (s, 2H), 4.05 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 8.7 Hz, 1H), 7.30 (d, J = 15.3 Hz, 1H), 7.33−7.38 (m, 2H), 7.42−7.50 (m, 2H), 7.43 (d, J = 15.3 Hz, 1H), 7.53 (dd, J = 2.1, 8.7 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at *m/z* 489, 491. Anal. ($C_{25}H_{29}ClN_2O_4S \cdot 0.42TFA$) C, H, N.

2-((3-(1-Morpholino)propyl)amino)phenyl 2-Chloro-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (22). A mixture of bromide **18** (60 mg, 0.14 mmol), aminopropylmorpholine (24 μL, 0.17 mmol), $Pd_2(dba)_3$ (1.2 mg, 0.0013 mmol), BINAP (2.5 mg, 0.004 mmol), NaO*t*-Bu (19 mg, 0.20 mmol), 18-crown-6 (50 mg, 0.20 mmol), and anhydrous toluene (1 mL) in a pressure tube was flushed with nitrogen for 3 min before it was capped and heated at 80 °C overnight. The reaction was then stopped and allowed to cool to room temperature. The reaction mixture was partitioned between EtOAc and water, and the aqueous layer was extracted once with EtOAc. The combined organic layer was then washed with water and brine, dried over Na_2SO_4, condensed under reduced pressure. The crude product was purified with a preparative HPLC to give 30 mg (0.062 mmol, 44%) of compound **22** as a light brown oil: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.62 (quintet, J = 6.5 Hz, 2H), 2.15−2.26 (m, 8H), 3.17 (q, J = 6.5 Hz, 2H), 3.22−3.76 (m, 12 H), 3.50 (t, J = 6.5 Hz, 2H), 5.72 (t, J = 5.7 Hz, 1H), 6.47 (d, J = 8.7 Hz, 1H), 6.68 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 15.6 Hz, 1H), 7.35−7.42 (m, 2H), 7.43 (d, J = 15.6 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H); MS (APCI) $(M + H)^+$ at *m/z* 502, 504. Anal. ($C_{26}H_{32}ClN_3O_3S \cdot 1.8TFA$) C, H, N.

3-Bromo-4-[(2,4-dichlorophenyl)thio]benzaldehyde (23). Prepared analogously to compound **5**, substituting 2-chloronitrobenzene with 3-bromo-4-fluorobenzaldehyde: white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.23 (d, J = 2.7 Hz, 1H), 7.27 (d, J = 2.7 Hz, 1H), 7.43 (dd, J = 2.7, 8.4 Hz, 1H), 7.80 (dd, J

= 2.1, 8.4 Hz, 1H), 8.42 (d, J = 2.1 Hz, 1H), 10.01 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 360, 362, 364.

2,4-Dichlorophenyl 2-((*E*)-((1-Morpholino)carbonyl)-ethenyl)-5-formylphenyl Sulfide (24). Prepared analogously to compound **19**, substituting bromide **18** with bromide **23** as the starting material: white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.52−3.65 (m, 6H), 3.68−3.77 (m, 2H), 7.28 (d, J = 2.7 Hz, 1H), 7.31 (d, J = 2.7 Hz, 1H), 7.42 (d, J = 15.3 Hz, 1H), 7.47 (dd, J = 2.7, 8.4 Hz, 1H), 7.84 (dd, J = 2.1, 8.4 Hz, 1H), 7.88 (d, J = 15.3 Hz, 1H), 8.48 (d, J = 2.1 Hz, 1H), 10.03 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 422, 424, 426.

2,4-Dichlorophenyl 2-((*E*)-((1-Morpholino)carbonyl)-ethenyl)-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylaminocarbonyl)ethenyl)phenyl Sulfide (25a): light brown solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.64 (quintet, J = 6.9 Hz, 2H), 1.92 (quintet, J = 7.5 Hz, 2H), 2.22 (t, J = 8.1 Hz, 2H), 3.11−3.25 (m, 4H), 3.43−3.57 (m, 2H), 3.60 (br m, 6H), 3.72 (br m, 2H), 6.75 (d, J = 15.6 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 7.36 (dd, J = 2.7, 8.9 Hz, 1H), 7.37 (d, J = 15.3 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 15.6 Hz, 1H), 7.66 (dd, J = 1.8, 8.9 Hz, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.85 (d, J = 15.6 Hz, 1H), 8.19 (t, J = 6.0 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 587, 589, 591. Anal. ($C_{29}H_{31}Cl_2N_3O_4S\cdot 0.08H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((1-Morpholino)carbonyl)-ethenyl)-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)-phenyl Sulfide (25b): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.05 (s, 3H), 3.33−3.82 (m, 16H), 6.72 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 2.7, 8.4 Hz, 1H), 7.36 (d, J = 15.1 Hz, 1H), 7.39 (d, J = 4.8 Hz, 1H), 7.47 (d, J = 15.1 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 15.1 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 15.1 Hz, 1H), 7.90 (dd, J = 1.8, 8.4 Hz, 1H), 8.37 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 574, 576, 578. Anal. ($C_{28}H_{29}Cl_2N_3O_4S\cdot 0.05H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((*E*)-((1-Morpholino)carbonyl)-ethenyl)-4-((*E*)-((1-morpholino)carbonyl)ethenyl)phenyl Sulfide (25c): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.39−3.83 (m, 16H), 6.77 (d, J = 8.7 Hz, 1H), 7.35 (dd, J = 2.4, 8.7 Hz, 1H), 7.35 (d, J = 15.6 Hz, 1H), 7.46 (d, J = 15.6 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 15.6 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.83 (d, J = 15.6 Hz, 1H), 7.89 (dd, J = 1.8, 8.7 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 550, 552, 554. Anal. ($C_{26}H_{26}Cl_2N_2O_4S\cdot 0.17H_2O$) C, H, N.

1-Chloro-2-nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)benzene (27). To a stirred solution of *trans*-4-chloro-3-nitrocinnamic acid **(26)** (1.50 g, 6.59 mmol) and 1-acetylpiperazine (0.89 g, 6.94 mmol) in 20 mL of DMF at room temperature was added EDAC (1.4 g, 7.30 mmol). The mixture was then stirred at room temperature for 2 h. TLC indicated the complete consumption of the acid. Water was then added to quench the reaction and to precipitate out the product. The light yellow cinnamide **27** was then collected through filtration, washed with cold water, dried in a vacuum oven overnight at 40 °C to give 2.04 g (6.03 mmol, 91.6%) of the amide as a light yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.17 (s, 3H), 3.52−3.60 (br m, 4H), 3.60−3.72 (br m, 2H), 3.72−3.86 (br m, 2H), 6.77 (d, J = 15.3 Hz, 1H), 7.47 (d, J = 15.3 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 2.4, 8.4 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 355, 357.

2,4-Dichlorophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28b). To a stirred solution of 4-chloro-3-nitrocinnamide **(27)** (275 mg, 0.814 mmol) in 1.0 mL of DMF was added potassium carbonate (169 mg, 1.22 mmol), followed by the dropwise addition of 2,4-dichlorothiophenol (146 mg, 0.815 mmol). The mixture was then stirred at room temperature for 60 min. Completion of the reaction was indicated by the TLC, and water was then added to precipitate the product. Filtration, washing with cold water, and drying in a vacuum oven afforded 350 mg (0.728 mmol, 89%) of compound **28b** as a light yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.05 (s, 3H), 3.42−3.50 (br m, 4H), 3.50−3.64 (br m, 2H), 3.64−3.79 (br m, 2H), 6.83 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 15.3 Hz, 1H), 7.55 (d, J = 15.3 Hz, 1H), 7.63 (dd, J = 2.7, 8.7 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 2.7 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 497, 499, 501. Anal. ($C_{21}H_{19}N_3O_4Cl_2S\cdot 0.82H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Nitro-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (28a): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.64 (quintet, J = 7.1 Hz, 2H), 1.91 (quintet, J = 7.5 Hz, 2H), 2.21 (t, J = 8.3 Hz, 2H), 3.15 (q, J = 6.3 Hz, 2H), 3.21 (dd, J = 9.9, 17.7 Hz, 2H), 3.32 (overlapping t, J = 8.4 Hz, 2H), 6.72 (d, J = 15.6 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 7.46 (d, J = 15.6 Hz, 1H), 7.63 (dd, J = 2.4, 8.1 Hz, 1H), 7.79 (dd, J = 2.4, 8.7 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 2.4 Hz, 1H), 8.18 (t, J = 6.0 Hz, 1H), 8.46 (d, J = 2.1 Hz, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 494, 496. Anal. ($C_{22}H_{21}Cl_2N_3O_4S\cdot 0.77H_2O$) C, H, N.

2,3-Dichlorophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28c): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.42−3.50 (br m, 4H), 3.50−3.64 (br m, 2H), 3.64−3.79 (br m, 2H), 6.88 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.55 (t, J = 7.65 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.78 (dd, J = 1.8, 8.1 Hz, 1H), 7.87 (dd, J = 1.8, 8.1 Hz, 1H), 7.95 (dd, J = 2.7, 9.0 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) $(M + NH_4)^+$ at m/z 497, 499, 501. Anal. ($C_{21}H_{19}Cl_2N_3O_4S\cdot 0.85H_2O$) C, H, N.

2-Methylphenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)-carbonyl)ethenyl)phenyl Sulfide (28d): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.03 (s, 3H), 2.29 (s, 3H), 3.47 (br m, 4H), 3.53 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.83 (br m, 1H), 6.64 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 15.0 Hz, 1H), 7.36−7.42 (m, 1H), 7.46−7.57 (m, 3H), 7.63 (d, J = 6.9 Hz, 1H), 7.89 (dd, J = 2.4, 9.0 Hz, 1H), 8.66 (d, J = 2.4 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 426. Anal. ($C_{22}H_{23}N_3O_4S\cdot 0.1H_2O$) C, H, N.

2-Chlorophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)-carbonyl)ethenyl)phenyl Sulfide (28e): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.73 (br m, 1H), 6.75 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 15.3 Hz, 1H), 7.54 (d, J = 15.3 Hz, 1H), 7.55 (dd, J = 1.8, 8.1 Hz, 1H), 7.64 (t, J = 1.8, 8.1 Hz, 1H), 7.76 (d, J = 1.8, 8.1 Hz, 1H), 7.82 (d, J = 1.8, 8.1 Hz, 1H), 7.93 (dd, J = 2.4, 9.0 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 446, 448, 450. Anal. ($C_{21}H_{20}ClN_3O_4S\cdot 0.03H_2O$) C, H, N.

2-Aminophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl-)carbonyl)ethenyl)phenyl Sulfide (28f): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 5.58 (s, 2H), 6.65 (td, J = 1.5, 15.0 Hz, 1H), 6.72 (dd, J = 1.5, 8.7 Hz, 1H), 7.00 (dd, J = 1.8, 8.7 Hz, 1H), 7.27 (t, J = 1.5, 8.6 Hz, 1H), 7.36 (dd, J = 1.5, 8.7 Hz, 1H), 7.39 (d, J = 15.3 Hz, 1H), 7.53 (d, J = 15.3 Hz, 1H), 7.89 (dd, J = 1.8, 8.7 Hz, 1H), 8.64 (d, J = 1.8 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 427. Anal. ($C_{21}H_{22}N_4O_4S\cdot 0.43H_2O$) C, H, N.

2-Ethylphenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)-carbonyl)ethenyl)phenyl Sulfide (28g): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.01 (t, J = 7.65 Hz, 3H), 2.04 (s, 3H), 2.69 (q, J = 7.65 Hz, 2H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.59 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 6.64 (d, J = 8.7 Hz, 1H), 7.38 (dd, J = 2.4, 7.5 Hz, 1H), 7.40 (d, J = 15.6 Hz, 1H), 7.50−7.61 (m, 3H), 7.53 (d, J = 15.6 Hz, 1H), 7.89 (dd, J = 2.4, 8.7 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H); MS (APCI) $(M + Cl)^-$ at m/z 474, 476. Anal. ($C_{23}H_{25}N_3O_4S\cdot 0.59H_2O$) C, H, N.

2-Isopropylphenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28h): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.05 (d, J = 6.9 Hz, 6H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.72 (br m, 1H), 6.64 (d, J = 8.4 Hz, 1H), 7.34−7.41 (m, 2H), 7.39 (d, J = 15.3 Hz, 1H), 7.52 (d, J = 15.3 Hz, 1H), 7.56−7.73 (m, 2H), 7.90 (dd, J = 2.1, 8.7 Hz, 1H),

8.64 (d, J = 2.1 Hz, 1H); MS (APCI) $(M + NH_4)^+$ at m/z 471. Anal. ($C_{24}H_{27}N_3O_4S \cdot 0.21H_2O$) C, H, N.

2-*tert*-Butylphenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28i): light yellow powder; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.46 (s, 9H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 6.68 (d, J = 8.7 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 15.3 Hz, 1H), 7.45−7.57 (m, 2H), 7.50 (d, J = 15.3 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 2.4, 8.7 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H); MS (APCI) $(M + NH_4)^+$ at m/z 485. Anal. ($C_{25}H_{29}N_3O_4S \cdot 0.07H_2O$) C, H, N.

2-Formylphenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28j): yellow solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 15.6 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.80 (td, J = 2.4, 7.5 Hz, 1H), 7.92 (dd, J = 2.1, 9.0 Hz, 1H), 8.04 (dd, J = 2.4, 7.5 Hz, 1H), 8.66 (d, J = 2.1 Hz, 1H), 10.29 (s, 1H); MS (APCI) $(M + Cl)^-$ at m/z 474, 476. Anal. ($C_{22}H_{21}N_3O_5S \cdot 0.33H_2O$) C, H, N.

2-Dimethylaminophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28k). To a stirred solution of aniline **28f** (21 mg, 0.049 mmol) in 1 mL of ethanol was added Me_2SO_4 (14.0 μL, 0.15 mmol) followed by saturated Na_2CO_3 (25 mL). The mixture was then refluxed for 1 day. The reaction mixture was allowed to cool to ambient temperature, partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was then purified on a preparative HPLC to give 10 mg of compound **28k** (0.022 mmol, 45% yield) as a light yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.83 (s, 3H), 3.32 (br s, 3H), 3.47−3.85 (m, 8H), 6.75 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 15.6 Hz, 1H), 7.40−7.51 (m, 3H), 7.64 (d, J = 15.6 Hz, 1H), 8.45 (d, J = 1.8 Hz, 1H); MS (APCI) $(M + H)^+$ at m/z 454. Anal. ($C_{23}H_{26}N_4O_4S \cdot 0.18H_2O$) C, H, N.

2-Carboxamidophenyl 2-Nitro-4-((*E*)-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl Sulfide (28l): yellow solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.04 (s, 3H), 3.43−3.80 (m, 8H), 6.93 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 15.6 Hz, 1H), 7.49−7.63 (m, 4H), 7.89 (dd, J = 2.1, 8.7 Hz, 1H), 7.93 (s, 1H), 8.59 (d, J = 2.1 Hz, 1H); MS (APCI) $(M + Cl)^-$ at m/z 489, 491. Anal. ($C_{22}H_{22}N_4O_5S \cdot 0.33H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Amino-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (29): yellow solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.65 (quintet, J = 7.0 Hz, 2H), 1.92 (quintet, J = 7.5 Hz, 2H), 2.22 (t, J = 7.5 Hz, 2H), 3.15 (q, J = 7.0 Hz, 2H), 3.21 (t, J = 7.5 Hz, 2H), 3.30−3.43 (t, J = 7.0 Hz, 2H), 5.63 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 15.6 Hz, 1H), 6.83 (dd, J = 1.8, 8.4 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 7.25−7.38 (m, 3H), 7.66 (d, J = 1.8 Hz, 1H), 8.20 (t, J = 5.85 Hz, 1H); MS (DCI) $(M + H)^+$ at m/z 464, 466, 468. Anal. ($C_{22}H_{23}Cl_2N_3O_2S \cdot 0.56TFA$) C, H, N.

2,4-Dichlorophenyl 2-Bromo-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl Sulfide (30). To a stirred solution of *tert*-butyl nitrite (57 μL, 0.48 mmol), $CuBr_2$ (87 mg, 0.39 mmol) in 2.0 mL of CH_3CN at room temperature was added a solution of aniline **29** (150 mg, 0.323 mmol) in 1.0 mL of CH_3CN. The dark green solution was then heated at 65 °C under nitrogen atmosphere for 90 min. The reaction mixture was then allowed to cool to room temperature, partitioned between EtOAc and 3 N HCl. The organic layer was then washed with brine, dried over Na_2SO_4, condensed in vacuuo. The crude product was then purified with a preparative HPLC to give 50 mg (0.094 mmol, 29%) of bromide **30** as a light brown solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.63 (quintet, J = 7.2 Hz, 2H), 1.91 (quintet, J = 8.4 Hz, 2H), 2.22 (t, J = 8.4 Hz, 2H), 3.09−3.47 (m, 6H), 6.67 (d, J = 15.3 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 15.3 Hz, 1H), 7.50 (dd, J = 2.4, 8.7 Hz, 1H), 7.57 (dd, J = 2.1, 8.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.96 (d, J = 2.1 Hz, 1H), 8.13 (t, J = 6.0 Hz, 1H); MS (ESI) $(M + H)^+$ at m/z 527, 529, 531, 533. Anal. ($C_{22}H_{21}BrCl_2N_2O_2S \cdot 0.18H_2O$) C, H, N.

2,4-Dichlorophenyl 2-((3-(1-Morpholino)propyl)amino)-4-((*E*)-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)-ethenyl)phenyl Sulfide (31): light brown solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.70−1.89 (m, 4H), 2.06 (quintet, J = 7.65 Hz, 4H), 2.24−2.50 (m, 8H), 3.23 (p, J = 6.0 Hz, 2H), 3.29−3.48 (m, 4H), 3.59−3.83 (m, 4H), 6.56 (d, J = 8.4 Hz, 1H), 6.77−6.90 (m, 2H), 7.02 (dd, J = 2.8, 8.4 Hz, 1H), 7.09−7.18 (m, 1H), 7.33−7.39 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H); MS (ESI) $(M + H)^+$ at m/z 591, 593, 595. Anal. ($C_{29}H_{36}Cl_2N_4O_3S \cdot 1.02TFA$) C, H, N.

5-Bromo-2-[(2,4-dichlorophenyl)thio]benzaldehyde (32). Prepared analogously to compound **5**, substituting 2-chloronitrobenzene with 5-bromo-2-fluorobenzaldehyde: white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.21 (d, J = 2.7 Hz, 1H), 7.25 (d, J = 2.7 Hz, 1H), 7.40 (dd, J = 2.7, 8.4 Hz, 1H), 7.76 (dd, J = 2.1, 8.4 Hz, 1H), 8.39 (d, J = 2.1 Hz, 1H), 9.99 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 360, 362, 364.

2,4-Dichlorophenyl 2-Formyl-4-((*E*)-((1-morpholino)-carbonyl)ethenyl)phenyl Sulfide (33): white solid; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.60 (br m, 6H), 3.71 (br m, 2H), 6.82 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 15.6 Hz, 1H), 7.54 (d, J = 15.6 Hz, 1H), 7.55 (dd, J = 2.4, 8.7 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.86 (dd, J = 2.4, 8.4 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H), 10.19 (s, 1H); MS (DCI/NH_3) $(M + H)^+$ at m/z 422, 424, 426. Anal. ($C_{20}H_{17}Cl_2NO_3S$) C, H, N.

2,4-Dichlorophenyl 2-Carboxy-4-((*E*)-((1-morpholino)-carbonyl)ethenyl)phenyl Sulfide (34). To a stirred suspension of the Ag_2O (110 mg, 0.47 mmol) in 2 mL of H_2O at room temperature was added the aldehyde **33** (100 mg, 0.24 mmol), followed by 3 N NaOH (0.16 mL, 0.47 mmol). The mixture was stirred overnight, then filtered through Celite, washed with 3 N NaOH and H_2O. The filtrate was acidified, the precipitates collected through filtration, dried in a vacuum oven to give 75 mg (0.17 mmol, 71%) of the acid **34** as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.50−3.62 (m, 6H), 3.62−3.73 (m, 2H), 6.50 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 15.0 Hz, 1H), 7.44 (d, J = 15.0 Hz, 1H), 7.51 (d, J = 2.8, 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 2.8 Hz, 1H), 8.11 (d, J = 1.8 Hz, 1H); MS (DCI) $(M + H)^+$ at m/z 438, 440, 442. Anal. ($C_{20}H_{17}Cl_2NO_4S \cdot 0.33H_2O$) C, H, N.

2,4-Dichlorophenyl 2-Carboxamido-4-((*E*)-((3-(1-morpholino)propylamino)carbonyl)ethenyl)phenyl Sulfide (35). A mixture of acid **34** (35 mg, 0.080 mmol), EDAC (21 mg, 0.112 mmol), HOBT (14 mg, 0.096 mmol), NH_4Cl (22 mg, 0.40 mmol), and Et_3N (28.5 μL, 0.20 mmol) in 2.0 mL of DMF was stirred at room temperature for overnight. Water was added to the reaction mixture, and the precipitates were collected through filtration, washed with H_2O, and dried in a vacuum oven to give 26 mg (0.059 mmol, 74% yield) of amide **35** as a white solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.48−3.66 (m, 6H), 3.66−3.78 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 15.6 Hz, 1H), 7.43−7.52 (m, 3H), 7.64 (dd, J = 2.4, 8.7 Hz, 1H), 7.79 (d, J = 2.7 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H); MS (ESI) $(M + H)^+$ at m/z 437, 439, 441. Anal. ($C_{20}H_{18}Cl_2N_2O_3S \cdot 0.72H_2O$) C, H, N.

ICAM-1/LFA-1 Biochemical Interaction Assay. In the biochemical assay, 100 μL of anti-LFA-1 antibody (ICOS Corp.) at a concentration of 5 μg/mL in Dulbecco's phosphate-buffered saline (D-PBS) was used to coat wells of a 96-well microtiter plate overnight at 4 °C. The wells were then washed twice with wash buffer (D-PBS without Ca^{2+} or Mg^{2+}, 0.05% Tween 20) and blocked by addition of 200 μL of D-PBS, 5% fish skin gelatin. Recombinant LFA-1 (100 μL of 0.7 μg/mL; ICOS Corp.) in D-PBS was then added to each well. Incubation continued for 1 h at room temperature and the wells were washed twice with wash buffer. Serial dilutions of compounds being assayed as ICAM-1/LFA-1 antagonists, prepared as 10 mM stock solutions in dimethyl sulfoxide (DMSO), were diluted in D-PBS, 2 mM $MgCl_2$, 1% fish skin gelatin and 50 μL of each dilution was added to duplicate wells. This was followed by addition of 50 μL of 0.8 μg/mL biotinylated recombinant ICAM-

1/Ig (ICOS Corp.) to the wells and the plates were incubated at room temperature for 1 h. The wells were then washed twice with wash buffer and 100 μL of europium-labeled streptavidin (Wallac Oy) diluted 1:100 in Delfia assay buffer (Wallac Oy) was added to the wells. Incubation proceeded for 1 h at room temperature. The wells were washed eight times with wash buffer and 100 μL of enhancement solution (Wallac Oy, cat. No. 1244-105) was added to each well. Incubation proceeded for 5 min with constant mixing. Time-resolved fluorimetry measurements were made using the Victor 1420 multilabel counter (Wallac Oy) and the percent inhibition of each candidate compound was calculated using the following equation: % inhibition = 100 × {1 − (average OD with compound minus background)/(average OD without compound minus background)}, where "background" refers to wells that are not coated with anti-LFA-1 antibody.

ICAM-1/JY-8 Cell Adhesion Assay. For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates were coated with 70 μL of recombinant ICAM-1/Ig (ICOS Corp.) at a concentration of 5 μg/mL in D-PBS without Ca^{2+} or Mg^{2+} overnight at 4 °C. The wells were then washed twice with D-PBS and blocked by addition of 200 μL of D-PBS, 5% fish skin gelatin by incubation for 1 h at room temperature. Fluorescent-tagged JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 50 μL at 2×10^6 cells/mL in RPMI 1640/1% fetal bovine serum) were added to the wells. For fluorescent labeling of JY-8 cells, 5×10^6 cells washed once in RPMI 1640 were resuspended in 1 mL of RPMI 1640 containing 2 μM Calceiun AM (MolecularProbes), incubated at 37 °C for 30 min, and washed once with RPMI 1640/1% fetal bovine serum. Dilutions of compounds to be assayed for ICAM-1/LFA-1 antagonistic activity were prepared in RPMI 1640/1% fetal bovine serum from 10 mM stock solutions in DMSO and 50 μL was added to duplicate wells. Microtiter plates were incubated for 45 min at room temperature and the wells were washed gently once with RPMI 1640/1% fetal bovine serum. Fluorescent intensity was measured in a fluorescent plate reader with an excitation wavelength at 485 nm and an emission wavelength at 530 nm. The percent inhibition of a candidate compound at a given concentration was calculated using the following equation: % inhibition = 100 × {1 − (average OD with compound)/(average OD without compound)}. These concentration/inhibition data were used to generate dose−response curves, from which IC_{50} values were derived.

Pharmacokinetic Analysis. The pharmacokinetic behavior of compounds was evaluated in male Sprague−Dawley rats. Briefly, the test compound was prepared as a 10 mg/mL solution in an ethanol:propylene glycol:D5W (20:30:50, by volume) vehicle containing 1 mol equiv of sodium hydroxide. Groups of rats (n = 4/group) received either a 10 mg/kg (1 mL/kg) intravenous dose administered as a slow bolus in the jugular vein or a 10 mg/kg (1 mL/kg) oral dose administered by gavage. Heparinized blood samples (~0.4 mL/sample) were obtained from a tail vein of each rat 0.1 (iv only), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h after dosing. The samples were analyzed by reverse-phase HPLC following liquid−liquid extraction from the plasma. Initial estimates of the pharmacokinetic parameters (e.g. the maximum concentration C_{max}) for NONLIN84[18] were obtained with the program CSTRIP.[19] Area under the curve (AUC) values were calculated by the trapezoidal rule over the time course of the study. The terminal-phase rate constant (β) was utilized in the extrapolation of the AUC from 12 h to infinity to provide an $AUC_{0-\infty}$ value and in the calculation of $t_{1/2}$ values. Assuming dose proportionality and correcting for the differences in dosing, a comparison of the AUC following oral dosing with that obtained following an intravenous dose provided an estimate of the bioavailability (F).

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